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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). This response was developed according to principles of evidence-based medicine and only contains prospective and retrospective studies (N≥10,000).

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Summary

Clinical Data: Incidence and Risk of HCC With TAF

A pooled analysis of data from four phase 3 studies (102, 103, 108, and 110; N=2273) found that TAF exposure was associated with a 70% reduction in risk of HCC compared with TDF exposure (HR, 0.3; 95% CI: 0.13–0.71; *P*<0.01). Based on a multivariate analysis, male sex, older age, Asian race, and not achieving ALT normalization at Week 24 were each significantly associated with HCC (each, *P*≤0.01).[1]

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).[2]

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).[3,4]

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

In a review of data from the Korean NHIS claims database that compared the risk of HCC development with TAF vs TDF in TN patients with CHB (n=19,013 each), TAF was associated with an overall significantly lower incidence of HCC than TDF (*P*<0.0001).[5]

Clinical Data: Incidence and Risk of HCC With TAF

Pooled Analysis of Studies 102, 103, 108, and 110[1]

Study designs

A pooled analysis of data from four phase 3 studies (Studies 102, 103, 108, and 110) with up to 8 years of follow-up was conducted to assess the incidence of HCC (N=2273). In Studies 102 and 103, participants were randomly assigned in a 2:1 ratio to either TDF 300 mg once daily or adefovir dipivoxil 10 mg once daily for 48 weeks in the double-blind phase, followed by open-label TDF through Year 8. In Studies 108 and 110, participants were randomly assigned in a 2:1 ratio to either TAF 25 mg once daily or TDF 300 mg once daily for 96 weeks, followed by open-label TAF through Year 8. Risk factors associated with HCC and the cumulative incidence of HCC by exposure to TAF vs TDF were assessed.

Results

By Year 8, HCC had developed in 46 participants (2%; Studies 102/103, n=20; Studies 108/110, n=26); 9 participants developed HCC within the first 48 weeks of treatment and were excluded from analyses. In a univariate analysis, a significantly reduced risk of HCC was associated with exposure to TAF (HR, 0.41; 95% CI: 0.2–0.83; *P*=0.01) and ALT normalization (defined as ALT ≤25 U/L for females and ≤35 U/L for males) at Week 24 (HR, 0.29; 95% CI: 0.13–0.67; *P*<0.01). In a multivariate analysis, exposure to TAF was associated with a 70% reduction in risk of HCC compared with exposure to TDF, whereas male sex, older age, Asian race, and not reaching ALT normalization at Week 24 were each associated with an increased risk of HCC (Table 1). The results of a propensity score-adjusted multivariate analysis were consistent with results of the multivariate analysis.

Table 1. Pooled Analysis of Studies 102, 103, 108, and 110: Multivariate Cox Regression Analysis of HCC Risk (Kim et al)[1]

Risk Factor	HR (95% CI)	*P*-Value
Sex, male vs female	4.14 (1.57–10.93)	<0.01
Age, years	1.09 (1.05–1.13)	<0.01
Asian, yes vs no	3.19 (1.32–7.72)	0.01
ALT normalization at Week 24,[a] yes vs no	0.29 (0.13–0.68)	<0.01
Exposure, time on TAF vs TDF	0.3 (0.13–0.71)	<0.01

[a]ALT upper limit of normal defined as 25 U/L for females and 35 U/L for males.
Note: An HR <1 indicates a reduced risk of HCC, and an HR >1 indicates an increased risk of HCC.

With up to 8 years of treatment, the cumulative incidence of HCC was significantly lower with TAF than with TDF treatment (*P*<0.01). Furthermore, participants who received TAF and achieved ALT normalization at Week 24 had the lowest cumulative incidence of HCC, and participants who received TDF and did not achieve ALT normalization at Week 24 had the highest incidence of HCC.

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.[2,6-8]

Global cohort

Analysis of HCC incidence and risk[6]

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.

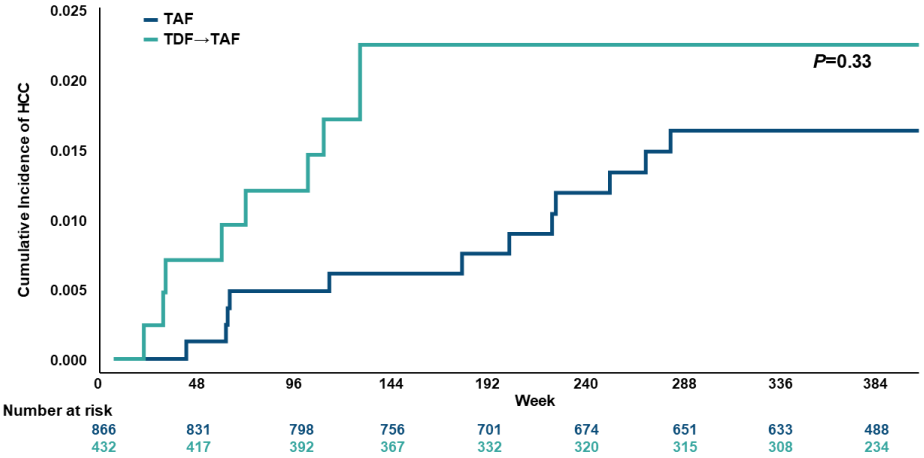
Through Week 384, 21 cases of HCC were reported. Participants who developed HCC, relative to those who did not develop HCC (n=1277), were significantly older (median, 54 vs 39 years, respectively; *P*<0.0001), were more likely to be male (86% vs 63%; *P*=0.03), had higher rates of cirrhosis at baseline (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 2). 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 2. Studies 108 and 110 Post Hoc Analysis: HCC Cases Through Week 384 by Treatment and Study Period[6]

	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.

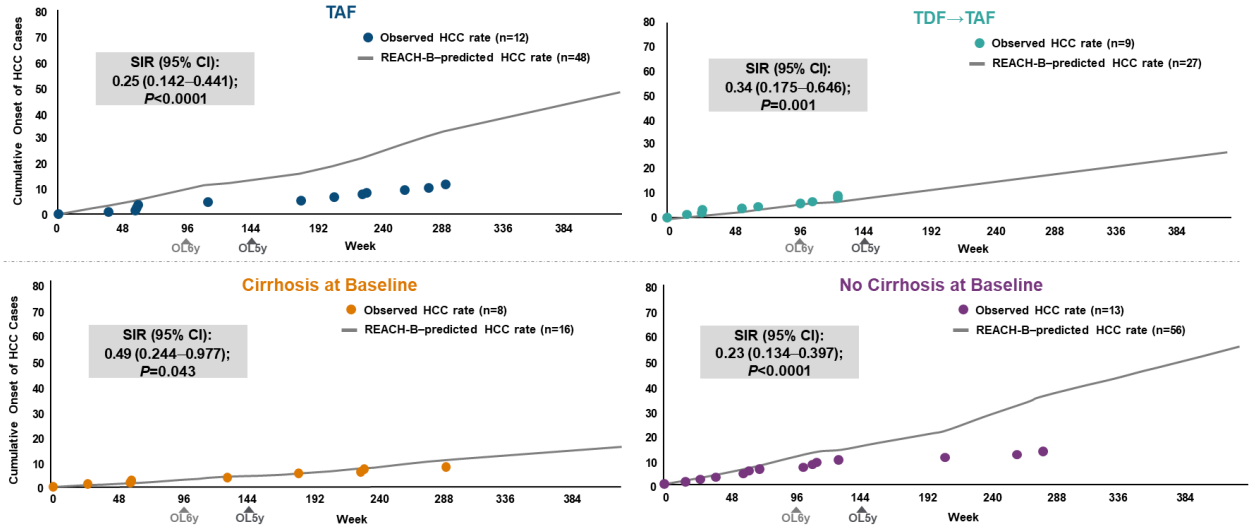
Figure 1. Studies 108 and 110 Post Hoc Analysis: Cumulative Incidence of HCC Through Week 384[6]



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 participant characteristics to predict the risk of HCC in CHB.[9] 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[6]



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%).

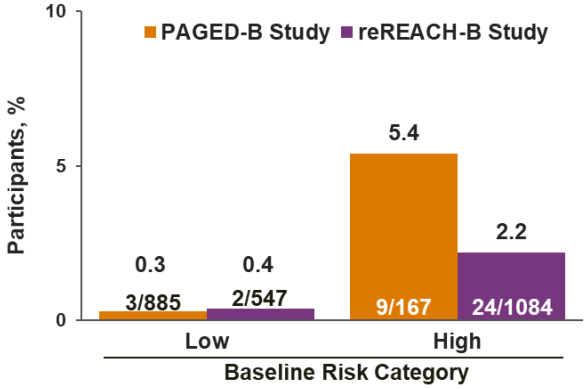
Pooled global and Chinese cohorts

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.[2,10]

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 g/dL; *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).[2]

Figure 3. Studies 108 and 110 Post Hoc Analysis: Incidence of HCC Through Week 384[2,10]



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).[2,10]

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).[10]

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).[2]

Figure 4. Studies 108 and 110 Post Hoc Analysis: Risk Category Shifts at Week 384[2,10]

Baseline

Week 384 n (%)	PAGED-B Study: Low Risk (n=885)	PAGED-B Study: High Risk (n=167)	reREACH-B Study: Low Risk (n=547)	reREACH-B Study: High Risk (n=1084)
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

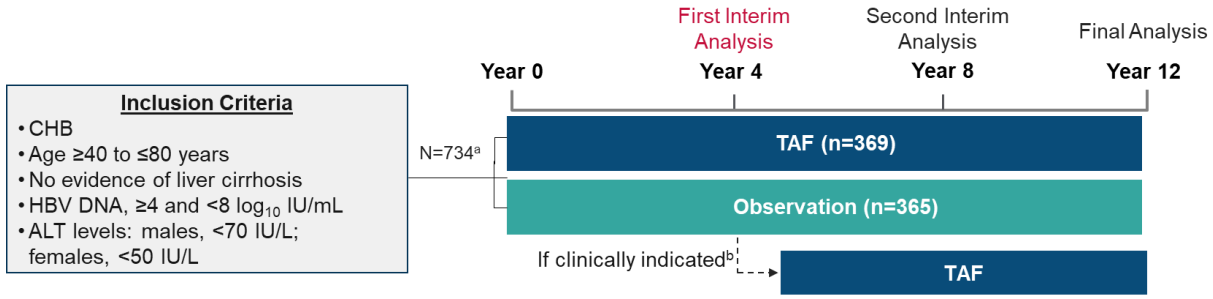
Note: Green cells indicate a decrease in risk category and pink cells indicate an increase in risk category.

ATTENTION Study: TAF Beyond Treatment Indications

Study design and demographics[3,4]

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 include death, HCC, liver transplantation, or decompensation (Child-Pugh score ≥7, ascites, or varices).

Figure 5. ATTENTION Study: Study Design[4]



[a]; The planned overall N=780; as of the interim analysis data cutoff, 734 participants underwent randomization.
[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 3. ATTENTION Study: Baseline Demographics and Disease Characteristics[4]

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)

Key Demographics and Characteristics	TAF (n=369)	Observation (n=365)
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[4]

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 4]; decompensation, n=1; death, n=1).
Three participants in the observation group who experienced primary outcome events (HCC, n=2 [see Table 4]; 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 PY 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 4. ATTENTION Study: Characteristics of Participants With HCC Development[4]

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[4]

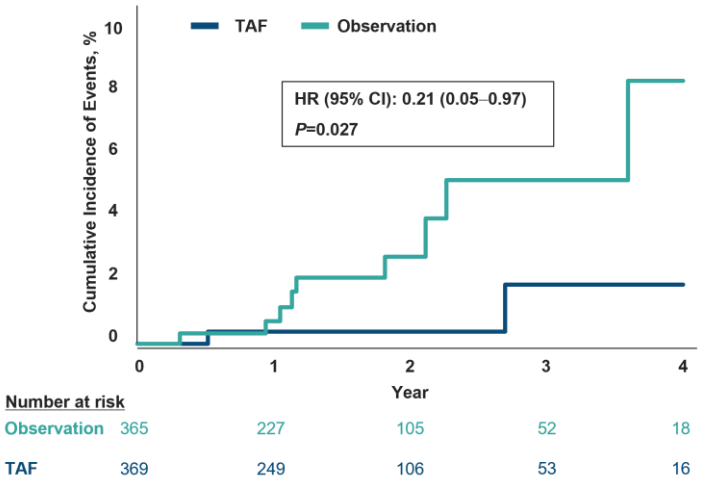


Figure 7. ATTENTION Study: Cumulative Incidence of Primary Outcome Events (Excluding Events From First Year of Follow-Up)[4]

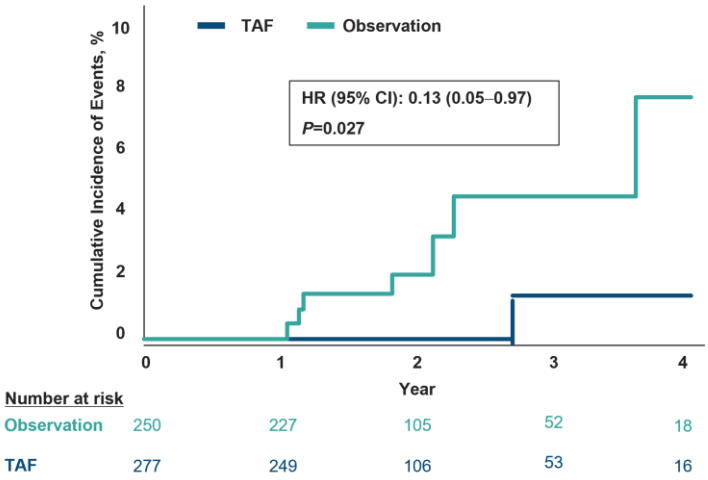
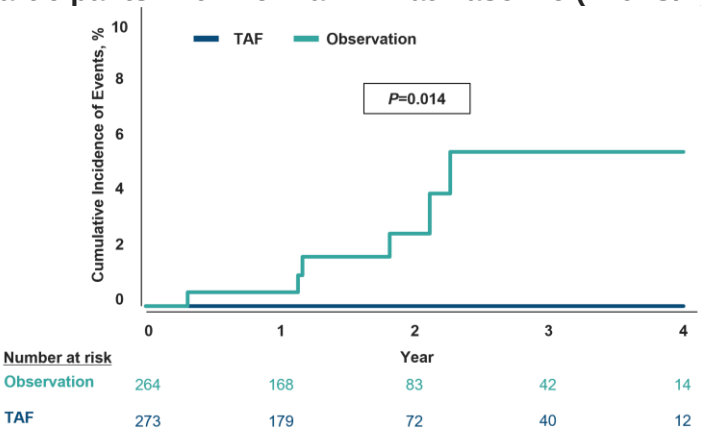


Figure 8. ATTENTION Study: Cumulative Incidence of Primary Outcome Events in Participants With Normal ALT at Baseline (<40 IU/L)[4]



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

Korean NHIS Claims Database: HCC Risk With TAF vs TDF in TN Patients[5]

Study design and demographics

A study was conducted using data from the Korean NHIS claims database to evaluate the risk of HCC in TN patients with CHB who received ≥6 months of TAF or TDF between 2017 and 2022 (index date: initial prescription date). Patients were PS-matched (1:1) to account for confounding effects. The primary outcome was the incidence of HCC, with death and liver transplantation considered as competing events. Patients were followed until the first occurrence of one of the following: death, liver transplantation, or the last prescription of TAF or TDF. Those who underwent solid organ transplantation or developed an extrahepatic malignancy were censored at the time those events occurred. Censoring also occurred at the last follow-up date (December 31, 2022).

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

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
Cirrhosis, n (%)		3445 (18.1)	3418 (18)
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: Treatment 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

Patients were followed for a median (95% CI) of 3.27 (1.89–4.57) years. In both the PS-matched cohort and the entire cohort (N=54,185), TAF was associated with a significantly lower annual 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<0.001; entire cohort, 7.5/1000 PY vs 10.3/1000 PY; SHR, 0.74; 95% CI: 0.66–0.83; P<0.001). By year, patients receiving TAF had lower cumulative rates of HCC (Table 6).

Table 6. Cumulative HCC Incidence by Year (Yang et al)[5]

Incidence, % (95% CI)	TAF (n=19,013)	TDF (n=19,013)
Year 1	0.58 (0.48–0.7)	0.75 (0.63–0.88)
Year 2	1.56 (1.37–1.76)	1.97 (1.77–2.2)
Year 3	2.33 (2.08–2.59)	3.05 (2.77–3.34)
Year 5	3.77 (3.19–4.41)	4.87 (4.43–5.34)

In a multivariate analysis, TAF was associated with a lower incidence of HCC than TDF across various factors associated with HCC development (Table 7). In a subgroup analysis according to the calendar year of the index date, TAF was also associated with a lower risk of HCC than TDF was across all years.

Table 7. Multivariate Analysis of Select Factors Associated With HCC Development (Yang et al)[5]

Variable (Reference)		SHR (95% CI)	*P*-Value
TAF (TDF)		0.76 (0.67–0.85)	<0.001
Age (18–39 years)	40–49 years	4.13 (3.15–5.42)	<0.001
	50–59 years	8.06 (6.18–10.51)	<0.001
	60–69 years	11.63 (8.78–15.39)	<0.001
	≥70 years	15.32 (10.96–21.41)	<0.001
Cirrhosis (none)		2.94 (2.65–3.27)	<0.001
Male sex (female)		2.48 (2.17–2.83)	<0.001
Laboratory values	GGT ≥60 U/L (<60 U/L)	2.06 (1.77–2.4)	<0.001
	AST ≥40 U/L (<40 U/L)	1.67 (1.38–2.02)	<0.001
Smoking status (never)	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 (<25 kg/m^2)		1.15 (1.01–1.31)	0.03
Dyslipidemia (none)		0.81 (0.73–0.91)	<0.001

In a subgroup analysis, the risk of HCC development was lower with TAF than with TDF, regardless of cirrhosis status (Table 8). In multivariate analysis, the protective effect of TAF vs TDF was observed in the cirrhosis subgroup (SHR, 0.78; 95% CI: 0.66–0.92; *P*=0.003) and the non-cirrhosis subgroup (SHR, 0.73; 95% CI: 0.62–0.86; *P*<0.001). Similarly, the following risk factors were associated with a higher risk of HCC, regardless of cirrhosis status: older age, male sex, GGT ≥60 U/L, AST ≥40 U/L, and current history of smoking.

Table 8. Subgroup Analysis of HCC Development According to Cirrhosis Status (Yang et al)[5]

		Patients, n	Events, n	PY	Events/1000 PY	SHR (95% CI)	*P*-Value
Cirrhosis	**TAF**	3445	197	9260	21.3	0.77 (0.64–0.92)	0.005
	TDF	3418	273	10,070	27.1	1 (reference)	–
No cirrhosis	**TAF**	15,568	187	41,847	4.5	0.74 (0.62–0.89)	0.002
	TDF	15,595	282	45,946	6.1	1 (reference)	–

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Abbreviations

aMAP=age, male, albumin-bilirubin, and platelets prediction tool
CHB=chronic hepatitis B
GGT=γ-glutamyltransferase
HBeAg=hepatitis B envelope antigen
HCC=hepatocellular carcinoma
HR=hazard ratio
mPAGE-B=modified platelets, age, gender, hepatitis B scores prediction tool
NHIS=National Health Insurance Service
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

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