Tenofovir-based antiviral therapy reduces long-term incidence of hepatocellular carcinoma in chronic hepatitis B

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Conclusions

- Over the course of up to 8 years of tenofovir-based treatment, a total of 46 of 2,273 (2%) patients with CHB, enrolled across four phase 3 trials, developed HCC
- Factors such as older age, male sex, lower baseline platelet count, reduced baseline albumin, lower baseline ALT, and lack of early ALT normalization by Week 24 were predictors of HCC development by multivariate logistic regression analysis
- Utilizing the REACH-B model, the standard incidence ratio for the development of HCC (comparing observed cases under various tenofovir-based treatment regimens against predicted cases based on the model) demonstrated a significant reduction at Year 8, underscoring the beneficial impact of antiviral therapy on the risk for HCC
- The outcomes derived from two additional predictive models (aMAP and mPAGE-B) indicated that most patients initially classified as low risk for HCC at baseline remained in the same category at Year 8 (98% and 97%, respectively). Conversely, a considerable proportion of patients initially deemed high risk had shifted to a lower risk category by Year 8 of treatment (72% and 53%, respectively)
- These conclusions, drawn from analyses of two large and well-characterized global cohorts of CHB patients under long-term treatment, offer further substantiation that tenofovir-based therapies can effectively reduce the risk of HCC
  - In this pooled analysis, TAF was shown to be similar to TDF in reducing HCC risk by multiple validated assessment methods

Plain Language Summary

- This study looked at hepatitis B patients in four clinical trials who were receiving antiviral treatments
- Infection with hepatitis B virus, especially over a long period of time, increases the risk of developing liver cancer, or HCC
- Over a period of 8 years, we accounted for how many patients developed HCC while taking antiviral treatment containing tenofovir, and, using an established HCC prediction model, compared this amount to how many patients would be expected to develop HCC
- Overall, we found that long-term antiviral treatment significantly reduces the risk of HCC in patients with hepatitis B

Background and Aims

- Hepatitis B virus (HBV) infection is the leading cause of hepatocellular carcinoma (HCC) worldwide[1,2]
- Treatment with oral nucleos(t)ide analogs (NAs) has been shown to reduce the risk of HCC[3]
- Utilizing validated risk prediction algorithms, we previously demonstrated a reduction in the risk of HCC after up to 5 years of tenofovir-based treatment among chronic hepatitis B (CHB) patients participating in phase 3 studies of tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF)[3]
- In the present analysis, we aimed to pool data across these global cohorts to assess the impact of antiviral treatment through up to 8 years

Methods

- Pooled analysis of data across four recently completed phase 3, randomized, clinical trials:[4-8]
  - Hepatitis B e antigen (HBeAg)-positive CHB: TDF (GS-US-174-0103 [Study 103]; NCT00116805) and TAF (GS-US-320-0110 [Study 110]; NCT01940471)
  - HBeAg-negative CHB: TDF (GS-US-174-0102 [Study 102]; NCT00117676) and TAF (GS-US-320-0108 [Study 108]; NCT01940034)

References: **1**. Hsu Y-C, et al. *Nat. Rev. Gastroenterol. Hepatol.* 2023;20:524–37. **2**. Kim WR, et al. *Cancer.* 2015;121:3631–38. **3**. Lim Y-S, et al. *JHEP Rep.* 2023. **4**. Heathcote EJ, et al. *Gastroenterology.* 2011;140:132–43. **5**. Marcellin P, et al. *NEJM.* 2008;359:2442–55. **6**. Buti M, et al. *Lancet Gastroenterol. Hepatol.* 2016;1:196–206. **7**. Chan HLY, et al. *Lancet Gastroenterol. Hepatol.* 2016;1:185–95. **8**. Hou J, et al. *J. Clin. Transl. Hepatol.* 2021;9:324–34. **9**. Yang H-I, et al. *Lancet Oncol.* 2011;12(6):568–74. **10**. Kim JH, et al. *J Hepatol.* 2018;68(5):1066–73. **11**. Fan R, et al. *J Hepatol.* 2020;73(6):1368–78.

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Methods (cont'd)

- **Studies 102 and 103** — HBeAg-negative (Study 102) and HBeAg-positive (Study 103) patients with CHB randomized 2:1 to receive double-blind (DB) TDF or adefovir dipivoxil (ADV) for 48 weeks, followed by open-label (OL) TDF (i.e., TDF or ADV→TDF) through Week 384 (Year 8)[4,5]
  - 641 patients from Studies 102/103 were included in this pooled analysis
- **Studies 108 and 110** — HBeAg-negative (Study 108) and HBeAg-positive (Study 110) patients with CHB randomized 2:1 to receive DB TAF or TDF for 96 or 144 weeks, followed by OL TAF (i.e., TAF or TDF→TAF, respectively) through Week 384 (Year 8)[6-8]
  - 1,632 patients from Studies 108/110 were included in this pooled analysis: 1,298 from a global cohort[6,7] and 334 from a China cohort[8]
- The presence of HCC was assessed by local standards of care; in Studies 108/110 beginning at Week 96, hepatic ultrasonography was introduced to be performed on all patients every 6 months to enrich HCC surveillance
- Cumulative HCC incidence by treatment group was assessed across these studies over 8 years
- Baseline and on-treatment factors associated with HCC development were assessed by multivariate analysis using a Cox proportional hazards model; stepwise selection was used to determine factors to be included in the final model
- HCC risk was estimated using three validated models: Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B), age-Male-ALBI-Platelets (aMAP), and modified Platelet Age GEnder-HBV (mPAGE-B) to assess the predicted risk for HCC development[9–11]
  - Using the REACH-B model, the standard incidence ratios (SIR) for HCC (observed cases vs. model-predicted rates) with 95% CIs (calculated by Poisson regression), were determined overall and by cirrhosis status
  - Using the aMAP and mPAGE-B prediction tools, scores were calculated at baseline and by visit with shifts from baseline HCC risk categories (low, medium, high) determined over 8 years

Results

Table 1. Cumulative HCC Incidence and Onset

	Studies 102/103		Studies 108/110		
	TDF (n=426)	ADV→TDF (n=215)	TAF (n=1,093)	TDF→TAF (n=539)	Total (N=2,273)
Incidence, n (%)	16 (3.8)	4 (1.9)	14 (1.3)	12 (2.2)	46 (2.0)
Median time to HCC onset, days (Q1, Q3)	770 (330, 1,214)	1,650 (1,481, 1,962)	1,356 (401, 1,723)	702 (279, 1,107)	855 (388, 1,534)

ADV, adefovir dipivoxil; HCC, hepatocellular carcinoma; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Studies 102/103 reported a cumulative HCC incidence of 3.1% (n=20/641; **Table 1**)
- Studies 108/110 reported a cumulative HCC incidence of 1.6% (n=26/1,632; **Table 1**)

Table 2. Baseline Characteristics of Patients With vs. Without HCC

	HCC (n=46)	No HCC (n=2,227)	Total (N=2,273)	P-value
Median age, years, (Q1, Q3)	52 (46, 59)	39 (31, 49)	39 (31, 49)	<0.0001
Male, n (%)	40 (87)	1,496 (67)	1,536 (68)	0.0046
Race, n (%)				
Asian	35 (76)	1,508 (68)	1,543 (68)	0.3429
Black or African American	2 (4)	41 (2)	43 (2)	
Native Hawaiian or Pacific Islander	0	22 (1)	22 (1)	
White	8 (17)	626 (28)	634 (28)	
Other	1 (2)	30 (1)	31 (1)	
HBeAg-negative, n (%)	28 (61)	940 (42)	968 (43)	0.0113
Median HBV DNA, log_{10} IU/mL (Q1, Q3)	6.5 (5.6, 7.4)	7.2 (5.7, 8.0)	7.2 (5.7, 8.0)	0.0228
HBV DNA categories, n (%)				
≤6 log_{10} IU/mL	16 (35)	689 (31)	705 (31)	0.0431
>6–≤7 log_{10} IU/mL	11 (24)	338 (15)	349 (15)	
>7–≤8 log_{10} IU/mL	13 (28)	496 (22)	509 (22)	
>8 log_{10} IU/mL	6 (13)	704 (32)	710 (31)	
Median ALT, U/L, (Q1, Q3)	75 (61, 100)	88 (59, 144)	88 (59, 143)	0.0547
HBV genotype group, n (%)				
A	0	188 (8)	188 (8)	0.0574
B	7 (15)	438 (20)	445 (20)	
C	26 (57)	909 (41)	935 (41)	
D	10 (22)	636 (29)	646 (28)	
Other	2 (4)	41 (2)	43 (2)	
Unknown	1 (2)	15 (1)	16 (1)	
Median platelet count, 10^3/mm^3 (Q1, Q3)	149 (109, 185)	195 (161, 234)	194 (160, 233)	<0.0001
Cirrhosis[a], n (%)	16 (35)	291 (13)	307 (14)	<0.0001

[a] Defined as Ishak Fibrosis score of 5 or 6 for Studies 102/103 or FibroTest score ≥0.75 for Studies 108/110.
ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; Q, quartile.

- Patients who developed HCC (n=46) were significantly older, more likely to be male, HBeAg-negative, and cirrhotic, and had lower median HBV DNA levels and platelet counts than those who did not (n=2,227) (**Table 2**)
- The higher proportion of the observed HCC cases occurred in the moderate HBV DNA tiers between >6 to ≥7 log_{10} IU/mL

Results (cont'd)

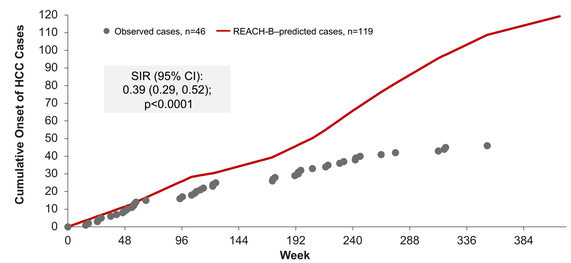
Table 3. Baseline and On-Treatment Factors Associated with HCC Development (Multivariate Analysis)

Predictor	Hazard ratio	95% CI	P-value
Sex, male	4.561	1.742, 11.942	0.0020
Age, years	1.074	1.041, 1.108	<0.0001
Baseline ALT, U/L	0.994	0.988, 0.999	0.0232
Baseline platelet count, x10^3/uL	0.985	0.979, 0.992	<0.0001
Baseline albumin, g/L	0.974	0.957, 0.990	0.0020
No ALT normalization at Week 24	2.237	1.113, 4.494	0.0238

ALT, alanine aminotransferase; CI, confidence interval; HCC, hepatocellular carcinoma.

- Multivariate Cox regression found that male sex, older age, lower baseline alanine aminotransferase (ALT), platelet count, and albumin, and lack of ALT normalization at Week 24 were significant predictors of HCC risk **(Table 3)**

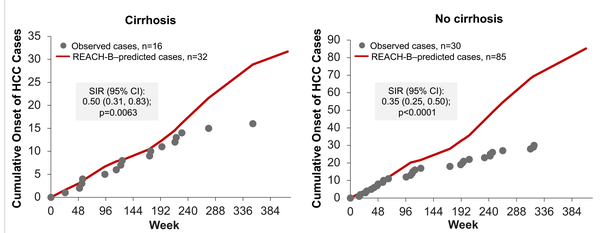
Figure 1. Observed vs. Predicted HCC Cases over 8 Years by REACH-B Analysis, Overall



SIR is Standardized Incidence Ratio of observed cases/predicted cases as determined by REACH-B.
CI, confidence interval; HCC, hepatocellular carcinoma; REACH-B, Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; SIR, standardized incidence ratio.

- Based on the SIR, observed HCC incidence with treatment overall was 61% lower compared to incidence predicted by REACH-B **(Figure 1)**
- Studies 102/103 reported an SIR of 0.65 overall (95% CI: 0.42, 1.01; p=0.0528)
  - TDF arm: SIR=0.79 (95% CI: 0.49, 1.29; p=0.3530)
  - ADV→TDF arm: SIR=0.37 (95% CI: 0.14, 1.00; p=0.0501)
- Studies 108/110 reported an SIR of 0.29 overall (95% CI: 0.20, 0.43; p<0.0001)
  - TAF arm: SIR=0.25 (95% CI: 0.15, 0.42; p<0.0001)
  - TDF→TAF arm: SIR=0.37 (95% CI: 0.21, 0.66; p=0.0006)

Figure 2. Observed vs. Predicted HCC Cases by REACH-B Analysis over 8 Years, by Baseline Cirrhosis Status



SIR is Standardized Incidence Ratio of observed cases/predicted cases as determined by REACH-B.
CI, confidence interval; HCC, hepatocellular carcinoma; REACH-B, Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; SIR, standardized incidence ratio.

- Observed HCC incidence was significantly reduced among patients with and without cirrhosis **(Figure 2)**. However, observed HCC cases diverged from predicted cases more rapidly for patients without cirrhosis (~Week 96) than for patients with cirrhosis (~Week 240)

Table 4. Baseline Characteristics by HCC Risk Category

	Low risk	Medium risk	High risk
aMAP, n/N (%)	**1,434/2,269 (63)**	**716/2,269 (32)**	**119/2,269 (5)**
Treatment arm, n (%)			
TDF	265 (19)	138 (19)	20 (17)
ADV→TDF	136 (10)	70 (10)	9 (8)
TAF	708 (49)	333 (47)	51 (43)
TDF→TAF	325 (23)	175 (24)	39 (33)
Mean baseline aMAP score (range)	42.9 (20.4, 50.0)	54.1 (50.0, 60.0)	62.8 (60.0, 72.6)
HCC cases during study period, n (%)	9 (1)	18 (3)	19 (16)
mPAGE-B, n/N (%)	**1,251/2,269 (55)**	**810/2,269 (36)**	**208/2,269 (9)**
Treatment arm, n (%)			
TDF	231 (19)	146 (18)	46 (22)
ADV→TDF	119 (10)	76 (9)	20 (10)
TAF	622 (50)	390 (48)	80 (39)
TDF→TAF	279 (22)	198 (24)	62 (30)
Mean baseline mPAGE-B score (range)	5.5 (0.0, 8.0)	10.2 (9.0, 12.0)	13.9 (13.0, 18.0)
HCC cases during study period, n (%)	8 (1)	17 (2)	21 (10)

aMAP, age–Male–ALBI–Platelets; ADV, adefovir dipivoxil; HCC, hepatocellular carcinoma; mPAGE-B, modified Platelet Age GEnder-HBV; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 5. Shifts in HCC Risk from Baseline to Year 8 (Week 384), Pooled Analysis Using aMAP Model

		Baseline		
	n (%)[a]	Low risk (n=1,434)	Medium risk (n=716)	High risk (n=119)
Year 8	Low risk	880 (98)	225 (43)	2 (3)
	Medium risk	22 (2)	298 (57)	52 (69)
	High risk	0	4 (1)	21 (28)
	Missing[b], n	532	189	44

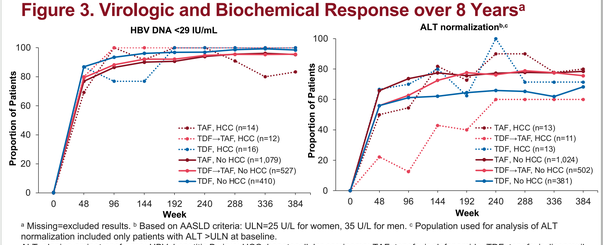
Table 6. Shifts in HCC Risk from Baseline to Year 8 (Week 384), Pooled Analysis Using mPAGE-B Model

		Baseline		
	n (%)[a]	Low risk (n=1,251)	Medium risk (n=810)	High risk (n=208)
Year 8	Low risk	749 (97)	157 (26)	3 (2)
	Medium risk	26 (3)	427 (72)	69 (51)
	High risk	0	10 (2)	64 (47)
	Missing[b], n	476	216	72

[a] The denominator for the percentage was the number of patients with non-missing values at both baseline and each post-baseline visit for each baseline category.
[b] The total number of patients with missing data for either the baseline or any postbaseline category.
aMAP, age–Male–ALBI–Platelets; mPAGE-B, modified Platelet Age GEnder-HBV.

- Most patients who were low- or medium-risk at baseline either remained at those risk categories or shifted to a lower risk group by Week 384. Of the patients who were high-risk at baseline, most shifted to medium or low-risk by Week 384 **(Tables 4–6)**

Figure 3. Virologic and Biochemical Response over 8 Years[a]



[a] Missing=excluded results. [b] Based on AASLD criteria: ULN=25 U/L for women, 35 U/L for men. [c] Population used for analysis of ALT normalization included only patients with ALT >ULN at baseline.
ALT, alanine aminotransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

- Rates of HBV DNA suppression were generally similar, regardless of HCC status or treatment group; whereas lower rates of ALT normalization were observed in the first 48 (TAF) to 192 (TDF→TAF) weeks of treatment in patients with HCC **(Figure 3)**
- A significantly greater proportion of patients with HCC had persistently abnormal ALT by AASLD criteria compared to those without HCC: 17% versus 8%, respectively (p=0.0148)