Exposure to tenofovir alafenamide and tenofovir disoproxil fumarate and the risk of hepatocellular carcinoma

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Conclusions

- Long-term treatment with tenofovir alafenamide (TAF) was associated with a significantly lower risk of hepatocellular carcinoma (HCC) compared to tenofovir disoproxil fumarate (TDF), showing an approximate 70% risk reduction.
- Early alanine aminotransferase (ALT) normalization at Week 24 emerged as an independent predictor of reduced HCC risk, particularly among patients receiving TAF.
- Propensity score adjusted analysis supported the robustness of these findings, accounting for heterogeneity across study populations and designs.
- While these results are compelling, differences in trial design and patient characteristics warrant further validation in real-world cohorts.

Plain Language Summary

- Hepatitis B virus (HBV) is a condition that can lead to long-term liver damage and, in some cases, liver cancer.
- Over an 8-year period, we compared two treatments for HBV, tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF), to see if one lowers the risk of liver cancer more than the other.
- We found that the risk of liver cancer was around 70% lower in patients receiving TAF versus those receiving TDF.
- We also found that having normal liver enzyme levels at 6 months further reduced the risk of liver cancer, which happened more often for patients receiving TAF than TDF.
- Our findings suggest that long-term use of TAF may reduce liver cancer risk in patients with HBV infection more than TDF, however, further research is needed to confirm this.

Introduction

- Chronic HBV infection is a leading cause of HCC worldwide.[1]
- Long-term antiviral therapy with nucleos(t)ide analogs has been shown to reduce HCC risk in patients with chronic hepatitis HBV infection.[2,3]
- Some studies have suggested that tenofovir-based therapies are more effective than entecavir in reducing HCC risk.[4]
- TAF and TDF are both prodrugs of tenofovir, which differ in their pharmacokinetic, safety, and efficacy profile; notably, TAF has been associated with earlier and higher rates of ALT normalization compared to TDF.[5,6]
- Given these differences and the widespread use of both agents, evaluating long-term HCC risk associated with cumulative exposure to TAF versus TDF is clinically important.

Objective

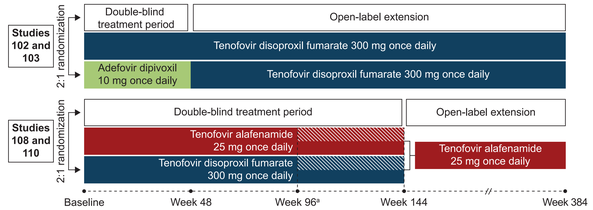
- This analysis assessed HCC incidence by cumulative exposure to TAF versus TDF, using pooled data from four phase 3 trials with up to 8 years of follow-up, to explore potential differences in long-term risk.

Methods

- To examine the association between TAF/TDF exposure and HCC incidence, data were pooled from four pivotal phase 3 trials: Study 102 (NCT00117676); Study 103 (NCT00116805); Study 108 (NCT01940341 and NCT02836249); and Study 110 (NCT01940471 and NCT02836236).[6–10]
  - Study designs of the included trials are shown in **Figure 1**.
- HCC was a predefined adverse event of interest and HCC surveillance was done as part of routine care; biannual hepatic ultrasonography was conducted in Studies 108 and 110 after Week 96.
- HCC risk factors were evaluated using Cox proportional hazards analysis, including a propensity score adjusted model.
- The outcome variable in these analyses was HCCs occurring after 48 weeks of treatment initiation or switching (adefovir dipivoxil to TDF).
- Exposure to TAF vs TDF was the main predictor variable.
  - Exposure was captured by the total TAF exposure time/(total TAF exposure time + total TDF exposure time), with values ranging between 0 (TDF only) and 1 (TAF only).
- Cumulative incidence of HCC by time of exposure to each drug is also reported using Kaplan-Meier analysis.

Methods (continued)

Figure 1. Study Designs



Time intervals are not drawn to scale. [a]Shaded areas represent patients who rolled over to open-label tenofovir alafenamide at Week 96, before a protocol amendment was implemented to increase the double-blind treatment duration to Week 144 and open-label extension duration to Week 384 (Year 8).

Results

- In total, 2,273 patients were included in the pooled analysis: 641 patients from Studies 102/103 and 1,632 patients from Studies 108/110.
- By Year 8, 46 (2%) patients had developed HCC: 20 patients from Studies 102/103 and 26 patients from Studies 108/110.
  - Nine cases occurred within the first 48 weeks and were excluded from modeling.
- Baseline characteristics are presented in **Table 1**.

Table 1. Baseline Characteristics

	HCC (n=46)	No HCC (n=2,227)	*p*-value[a]	Total (N=2,273)
Age (years), mean (SD)	51 (10.1)	40 (11.7)	<0.01	40 (11.8)
Sex, male, n (%)	40 (87.0)	1,496 (67.2)	<0.01	1,536 (67.6)
Race, n (%)				
White	8 (17.4)	626 (28.1)	0.34	634 (27.9)
Asian	35 (76.1)	1,508 (67.7)		1,543 (67.9)
Other	3 (6.5)	93 (4.2)		96 (4.2)
Baseline BMI (kg/m²), mean (SD)	25.6 (4.0)	24.4 (4.2)	0.03	24.4 (4.2)
HBV-DNA (log_{10} IU/mL), mean (SD)	6.5 (1.2)	6.8 (1.6)	0.02	6.8 (1.6)
HBV-DNA categories (log_{10} IU/mL), n (%)				
≤6 log_{10} IU/mL	16 (34.8)	689 (30.9)	0.43	705 (31.0)
>6–≤7 log_{10} IU/mL	11 (23.9)	338 (15.2)		349 (15.4)
>7–≤8 log_{10} IU/mL	13 (28.3)	496 (22.3)		509 (22.4)
>8 log_{10} IU/mL	6 (13.0)	704 (31.6)		710 (31.2)
HBeAg positive, n (%)	18 (39.1)	1,287 (57.8)	0.01	1,305 (57.4)
FIB4,[b] n (%)				
>3.25	15 (32.6)	167 (7.5)	<0.01	182 (8.0)
>1.45–≤3.25	19 (41.3)	689 (31.0)		708 (31.2)
≤1.45	12 (26.1)	1,366 (61.5)		1,378 (60.8)
FIB4,[b] mean (SD)	2.9 (2.0)	1.6 (1.4)	<0.01	1.6 (1.4)
HBV genotype group, n (%)				
A	0	188 (8.4)	0.06	188 (8.3)
B	7 (15.2)	438 (19.7)		445 (19.6)
C	26 (56.5)	909 (40.8)		935 (41.1)
D	10 (21.7)	636 (28.6)		646 (28.4)
Other/Unknown	3 (6.5)	56 (2.5)		59 (2.6)
Cirrhosis at baseline,[c,d] n (%)	16 (34.8)	291 (13.3)	<0.01	307 (13.8)
Platelet (10^3/mm^3),[e] mean (SD)	150 (48.0)	199 (57.4)	<0.01	198 (57.6)
ALT (U/L), mean (SD)	90 (55.7)	124 (119.7)	0.05	124 (118.8)
ALT > ULN (U/L),[f] n (%)	43 (93.5)	2,138 (96.0)	0.14	2,181 (96.0)
Baseline albumin (g/dL), mean (SD)	4.0 (0.4)	4.3 (0.4)	<0.01	4.3 (0.4)

[a]*p*-values were determined using the Cochran-Mantel-Haenszel test and the 2-sided Wilcoxon rank sum test for categorical data and continuous data, respectively; [b]5 patients from the No HCC group had missing data; [c]Cirrhosis was defined as a FibroTest score ≥0.75 for Studies 108 and 110 or Ishak Fibrosis score of 5 or 6 for Studies 102 and 103; [d]45 patients had indeterminate or unknown cirrhosis status at baseline; [e]4patients in the No HCC group had missing data; [f]AASLD criteria were used for defining ULN: 25 U/L for females and 35 U/L for males.[11] ALT: alanine aminotransferase; BMI: body mass index; DNA: deoxyribonucleic acid; FIB4: Fibrosis-4 index; HBeAg: hepatitis B e-antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; IU: International Units; SD: standard deviation; ULN: upper limit of normal.

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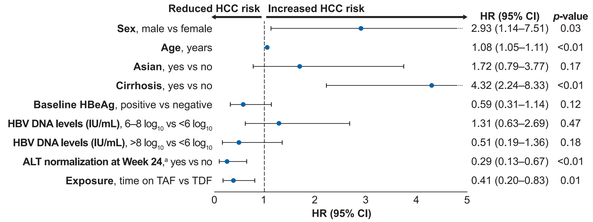
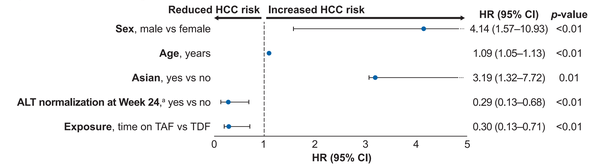
Results (continued)

Figure 2. HCC Risk Factors

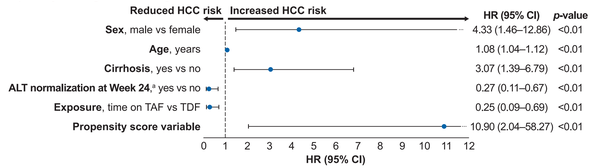
A) Univariate analysis



B) Multivariate analysis



C) Propensity score-adjusted model



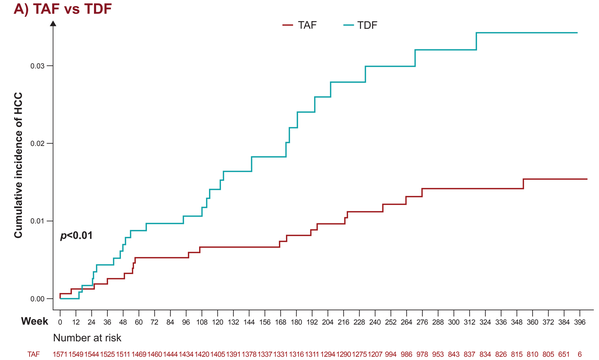
An initial multivariate analysis was conducted using all parameters, then was re-run for the multivariate model (and propensity score matched analysis) using only parameters found to be significant predictors of HCC; therefore, parameters without data were not found to be significant. *p*-values were determined using Chi-squared tests. [a]AASLD criteria were used for defining ULN: 25 U/L for females and 35 U/L for males.[11] ALT: alanine aminotransferase; CI: confidence interval; DNA: deoxyribonucleic acid; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HR: hazard ratio; IU: International Unit; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; ULN: upper limit of normal.

- In the univariate model, ALT normalization at Week 24 and exposure to TAF versus TDF were significantly associated with reduced HCC risk (**Figure 2A**).
  - Conversely, male sex, older age and presence of cirrhosis were significantly associated with an increased risk of HCC.
- In the final multivariate analysis, exposure to TAF was significantly associated with a 70% reduction in HCC risk compared to TDF (**Figure 2B**).
  - ALT normalization at Week 24 was also significantly associated with decreased HCC risk.
- In the propensity score-adjusted multivariate model, which accounted for heterogeneity across study populations and designs, results were consistent with those of the multivariate Cox regression analysis (**Figure 2C**).
  - The propensity score variable was significant, thereby further confirming the observed association between TAF vs TDF exposure and reduced HCC risk.

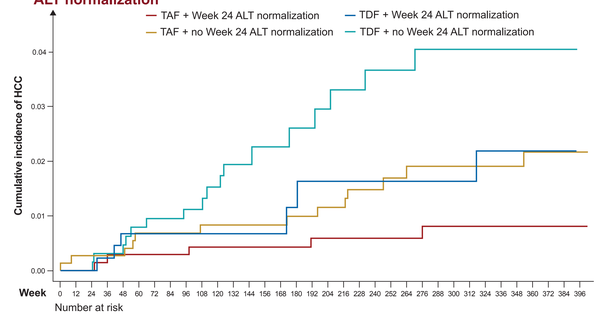
Results (continued)

Figure 3. Cumulative HCC Incidence

A) TAF vs TDF



B) TAF with/without Week 24 ALT normalization vs TDF with/without Week 24 ALT normalization



The total number of patients at risk exceeds the pooled number in our analysis, as some patients may have switched treatments during the study period.
ALT: alanine aminotransferase; HCC: hepatocellular carcinoma; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

- The cumulative incidence of HCC was significantly lower with TAF compared with TDF up to 8 years of treatment (**Figure 3A**).
- Further, patients receiving TAF who achieved ALT normalization at Week 24 had the lowest cumulative incidence of HCC, whereas patients receiving TDF who did not achieve ALT normalization at Week 24 had the highest incidence of HCC (**Figure 3B**).