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Reduced Incidence of Hepatocellular Carcinoma in Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis B Treated With Tenofovir—A Propensity Score–Matched Study

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(See the Editorial Commentary by Kaplan on pages 1–2.)

Background. The effect of newer oral anti–hepatitis B virus (HBV) medication, tenofovir disoproxil (TDF), on liver-related outcomes among Asians is limited. We examined the effect of TDF on the incidence of hepatocellular carcinoma (HCC) in an Asian population with chronic hepatitis B (CHB).

Methods. This was a retrospective cohort study of 6914 adults with chronic HBV monoinfection and no history of transplantation who were recruited from 6 US referral, community medical centers and a community based Taiwan cohort for a total of 774 patients who received TDF and 6140 who were not treated. Propensity score matching (PSM) for age, sex, HBV e antigen status, HBV DNA level, alanine aminotransferase (ALT) level, baseline cirrhosis status, and follow-up time was performed to balance the groups, resulting in 591 treated individuals and 591 untreated individuals. Kaplan-Meier analysis was used to estimate the cumulative risk of HCC. Cox proportional hazards models were run to estimate the HCC risk between groups.

Results. The 8-year cumulative HCC incidence was significantly higher in the PSM untreated group (20.13% vs 4.69%; $P < .0001$). Cirrhosis was a significant predictor for HCC (adjusted hazard ratio [aHR], 5.36; 95% confidence interval [CI], 2.73–10.51; $P < .001$). On multivariate analysis adjusted for age, sex, HBV DNA level, ALT level, and study site, TDF was associated with a 77% reduction in the risk of HCC (aHR, 0.23; 95% CI, .56–.92) in patients with cirrhosis and a 73% reduction (aHR, 0.27; 95% CI, .07–.98) in patients without cirrhosis.

Conclusions. Among cirrhotic and noncirrhotic Asian patients with CHB, TDF therapy was significantly associated with a reduction in the 8-year HCC cumulative incidence rate.

Keywords. End-stage liver disease; hepatitis B; liver cancer; reduction; tenofovir; treatment.

Chronic hepatitis B (CHB) affects approximately 250 million people worldwide [1]. While mostly endemic to Asia and Africa, CHB is also prevalent in the United States among many immigrant groups and has been estimated by the National Health and Nutrition Examination Survey (NHANES) to affect approximately 800 000–1 400 000 persons [2]. However, this number is likely an underestimation, owing to underrepresentation of immigrant populations within the NHANES database [3]. Such findings are concerning as CHB is a progressive disease and can lead to adverse outcomes, including cirrhosis, hepatocellular carcinoma (HCC), liver transplantation, and death [1].

Fortunately, antiviral treatment of CHB has been shown to decrease the risk of HCC, especially if treatment is started at the earlier stages of CHB [4, 5]. Since CHB is currently a noncurable chronic disease, the indicated therapy is medication that provides long-term suppression of hepatitis B virus (HBV) replication without developing resistance to treatment [2, 3]. Thus, the current recommended therapy is the use of nucleos(t)ide analogues that have high barriers to resistance and include entecavir (ETV), tenofovir disoproxil (TDF), or tenofovir alafenamide (TAF) [4, 6–11]. For patients with mild or moderate CHB, pegylated interferon alfa treatment may be considered; however, pegylated interferon alfa has a substantial side effect profile that prevents it from being frequently used. Furthermore, combination therapy is not recommended because it has not been shown to be beneficial and may exacerbate the potential for resistance [6, 7].

Of these new drugs, ETV has been the most studied as treatment for CHB [4, 11–15]. Recently, TDF has received attention and is now undergoing extensive study, especially within the Asian population. One reason for this increased attention may be its more recent approval: TDF was approved in 2008 in the

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United States (compared with 2005 for ETV), in 2012 in most Asian countries, and in 2014 in Japan [16].

The few studies on TDF have been published in combination with ETV [17–19]. Nevertheless, in regard to decreasing the incidence of HCC, data are more limited and conflicting, especially in regard to treatment effect for patients without cirrhosis [20–23]. To our knowledge, there has been no study directly comparing HCC incidence in CHB patients treated with TDF with well-matched untreated patients with and without cirrhosis. Therefore, the purpose of this study was to compare the incidence rate of HCC development in a real-world cohort of cirrhotic and noncirrhotic patients with CHB who were treated with TDF vs those who were not treated with any antiviral medications.

METHODS

This was a retrospective cohort study with 6914 patients (774 patients with CHB who were treated with TDF and 6140 patients who received no treatment) who were seen at a large university medical center, a community gastroenterology clinic, and 4 community primary care centers from 2000 to 2016 in the US in addition to the community-based REVEAL-HBV cohort from Taiwan [21]. Patients were identified via an *International Classification of Diseases, Ninth Revision,* query for CHB (codes 070.2–070.3), and individual chart review was performed to confirm CHB and HCC diagnoses (code 155.0) and collect clinical, laboratory, and imaging data for the study. The inclusion criteria included adults aged ≥18 years with CHB confirmed by positivity for HBV surface antigen and/or detectable HBV DNA or HBV e antigen (HBeAg). Patients were excluded if they were coinfected with human immunodeficiency virus, hepatitis C virus, hepatitis D virus; had received a liver transplant; had HCC diagnosed within 1 year of presentation or a history of HCC; or received treatment with TDF in combination with other therapies (Figure 1). The primary study end point was incident HCC.

Definitions

CHB was determined by positivity for HBV surface antigen and/or detectable HBV DNA or HBeAg. Cirrhosis was determined by the presence of clinical, radiologic, endoscopic, or laboratory evidence of cirrhosis and/or portal hypertension (defined as a nodular contour on imaging, thrombocytopenia with a platelet count of <120 K/μL, splenomegaly, or the presence of varices) or symptoms of clinical hepatic decompensation (ie, ascites, hepatic encephalopathy, jaundice, or variceal hemorrhage). The noncirrhotic group was determined as those with a fibrosis stage of ≤3.

Statistical Analysis

When comparing the groups, the groups were unbalanced, with treated patients having more-advanced disease, as expected; therefore, we chose to use propensity score matching (PSM) to balance the groups. The propensity scores were estimated for all patients already treated with TDF using multiple logistic regression analysis. Variables used in the PSM model included age, sex, HBeAg status, HBV DNA level, alanine aminotransferase (ALT) level, baseline cirrhosis status, and follow-up time. Caliper matching on the propensity scores was performed, and pairs were matched to within a range of 0.2 standard deviations of the logit of the propensity scores [24].

Standard descriptive and comparative statistics were performed for all demographic and clinical variables. Categorical variables were described using proportions and evaluated using the χ^2 test. Continuous variables were described as means ± standard deviations or medians (with interquartile ranges [IQRs]) and evaluated using Student's *t* test if normal distribution was observed. When assumptions of normality were not met, continuous variables were evaluated using the Mann-Whitney *U* test. The Kaplan-Meier method was used to estimate the cumulative risks of HCC by treatment groups. The log-rank test was used to compare the differences of HCC cumulative risks between the treated and untreated group. Cox proportional hazards regression was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the risk of HCC in patients treated with TDF as compared to those without treatment. Patients were censored at incident HCC, liver transplantation, or loss to follow-up. We also conducted subanalyses on patients with cirrhosis (66 per group) and noncirrhotic patients (504 per group). Each subanalysis was conducted using PSM on the aforementioned variables. Statistical significance was defined using a 2-tailed *P* value of <.05.

The study was approved by the institutional review board at Stanford University (Stanford, CA) and Academia Sinica (Taipei, Taiwan). All statistical analyses were conducted using Stata 14.2 (College Station, TX).

RESULTS

Demographic Characteristics

The initial untreated study cohort (n = 6140) was older (45.70 ± 11.48 vs. 44.94 ± 13.46, *P* = .087), had fewer patients with cirrhosis (1.82% vs 11.24%, *P* < .001) and lower liver enzyme levels [ALT median 17 (10–30) vs ALT 45 (30–73), *P* < .001] when compared to the treated cohort (n = 774), respectively (Table 1). Within the treated cohort, 19.9% had a history of prior treatment with antiviral therapy.

After PSM, there were 591 patients per group (untreated vs treated), with no significant demographic differences; the average age was 44.84 ± 13.09 years, 59.31% were men, and 95.43% were Asian. The average follow-up duration (±SD) was 42.01 ± 34.48 months (Table 2). Within the treated cirrhotic group, 34.85% of patients received prior treatment, while only 19.64% of the noncirrhotic treated patients did.

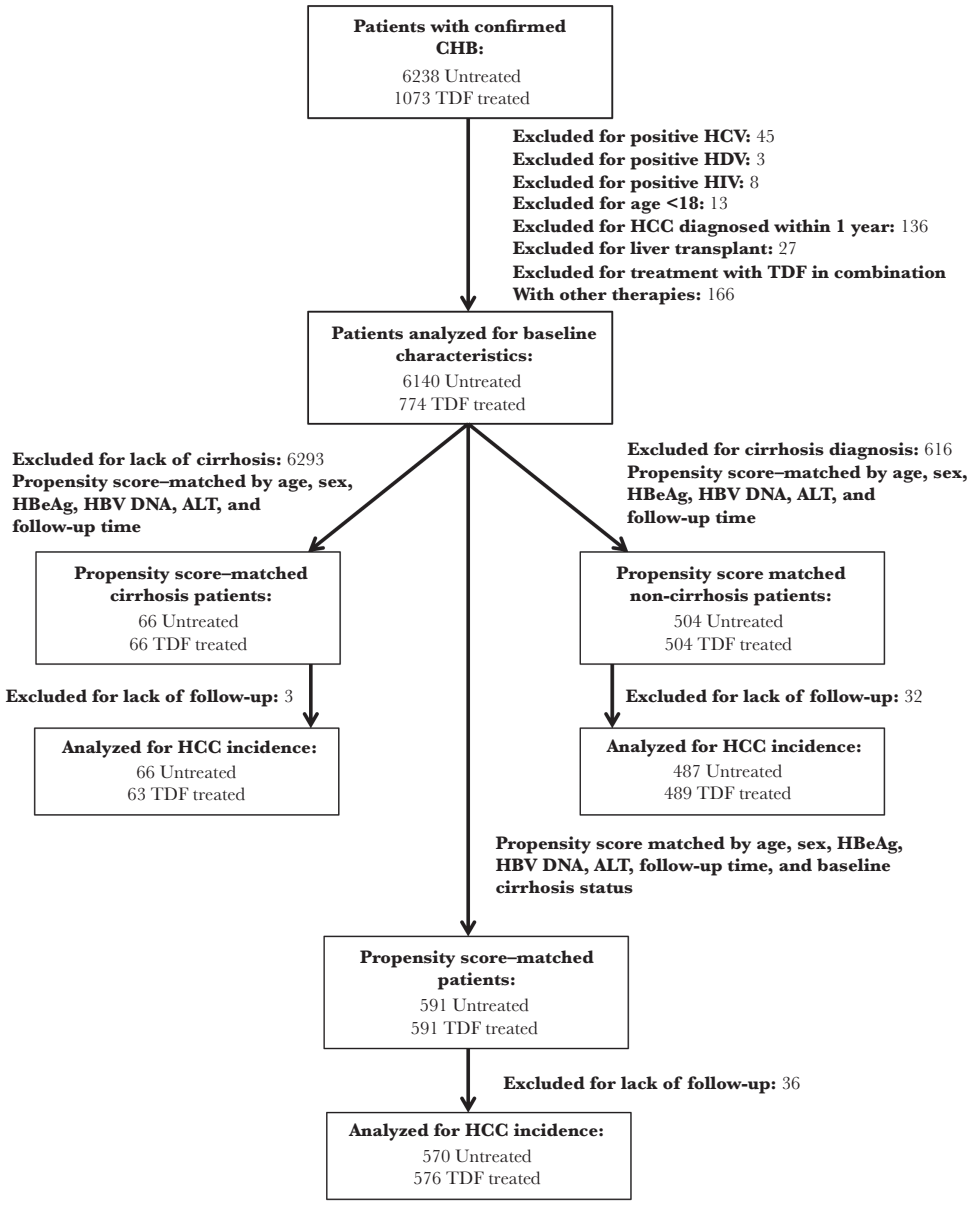

Figure 1. Flow of untreated and tenofovir disoproxil fumarate (TDF)–treated patients with chronic hepatitis B (CHB) through the study. ALT, alanine aminotransferase; HBeAg, hepatitis B virus e antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus.

Incidence Rates of HCC Development in Cirrhotic and Noncirrhotic Patients

Overall, the 8-year cumulative incidence of HCC was significantly higher in the untreated group at 20.13% (95% CI, 13.99%–28.49%) vs 4.69% (95% CI, 2.38%–9.10%; $P < .0001$) in the treated group. There were 38 newly developed HCC cases after 1123 person-years of follow-up among patients who did not receive antivirals. On the other hand, only 10 newly developed HCC cases occurred after 2070 person-years of follow-up among patients who received TDF. The rate was 20.48 cases per 1000 person-years (95% CI, 14.91–28.15) for the untreated group, compared with 4.83 cases per 1000 person-years (95% CI, 2.60–8.98) for the treated group (Figure 2A). It is important to note that the viral loads were suppressed in all patients receiving TDF at the time of HCC diagnosis.

Predictors for HCC Development in Cirrhotic and Noncirrhotic Patients

The most significant variable predicting HCC was cirrhosis (adjusted HR [aHR], 5.36; 95% CI, 2.73–10.51; $P < .001$), followed by sex (aHR, 2.28; 95% CI, 1.04–4.96; $P = .038$) and age (aHR, 1.37; 95% CI, 1.20–1.58; $P < .001$). Overall, TDF therapy was significantly associated with a 66% reduction in the risk of HCC (aHR, .34; 95% CI, .16–.71; $P = .005$; Table 3). TDF therapy remained significantly associated with HCC risk reduction after treatment site was also added to the model. Notably, patients seen at a specialty clinic were less likely than those seen at a

Table 1. Baseline Characteristics of Study Subjects With Chronic Hepatitis B, by Tenofovir Disoproxil Fumarate (TDF) Treatment Status

Characteristic	Untreated (n = 6140)	TDF Treated (n = 774)	*P*
Age, y	45.70 ± 11.48	44.94 ± 13.46	.087[a]
Male sex	57.81	59.56	.35[b]
Asian ethnicity	98.26	93.93	<.001[b]
Baseline cirrhosis	1.82	11.24	<.001[b]
Duration of follow-up, mo	129.30 ± 84.23	39.65 ± 31.47	<.001[a]
HBeAg positivity (n = 6293)	14.92	32.02	<.001[b]
Log_{10} HBV DNA level, IU/mL (n = 6175)	3.48 ± 1.91	4.48 ± 2.33	<.001[a]
ALT level, U/L (n = 6319)	17 (10–30)	45 (30–73)	<.001[c]
Prior treatment with other antiviral therapy	…	19.90	

Values are mean ± SD, percentage of patients, or median (interquartile range).

Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus.

[a]By Student's *t* test.

[b]By the χ^2 test.

[c]By the Mann-Whitney *U* test.

Table 2. Characteristics of 1182 Propensity Score–Matched Patients With Chronic Hepatitis B, by Tenofovir Disoproxil Fumarate (TDF) Treatment Status

Characteristic	Untreated (n = 591)	TDF Treated (n = 591)	*P*
Age, y	44.59 ± 12.71	45.10 ± 13.36	.50[a]
Male sex	59.05	59.56	.86[b]
Asian ethnicity	96.62	94.25	.051[b]
Baseline cirrhosis	8.46	8.29	.92[b]
HBeAg positivity	29.61	28.09	.56[b]
Log_{10} HBV DNA level, IU/mL	4.52 ± 2.22	4.37 ± 2.25	.23[a]
ALT level, U/L	31 (19–51)	44 (30 - 71)	.30[c]
Follow-up duration, mo	40.32 ± 36.68	43.71 ± 32.07	.091[a]
Propensity score	0.30 ± 0.17	0.30 ± 0.17	.63[a]

Values are mean ± SD, percentage of patients, or median (interquartile range).

Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus.

[a]By Student's *t* test.

[b]By the χ^2 test.

[c]By the Mann-Whitney *U* test.

community or primary care site to receive a diagnosis of HCC (aHR, 0.45; 95% CI, .21–.97; *P* = .040; Supplementary Table 1).

HCC Development in Patients With Cirrhosis

Cirrhotic patients treated and untreated after PSM (66 per group) had an average age (±SD) of 53.81 ± 12.20 years; 73.00% were male, and 93.94% were Asian, with an average follow-up duration (±SD) of 43.19 ± 36.93 months (Supplementary Table 2). The 8-year cumulative incidence of HCC was significantly higher in the untreated group: 69.67% (95% CI, 52.22%–85.44%) versus 12.71% (95% CI, 4.14%–35.41%; *P* < .0001; Figure 2B). After 202 person-years of follow-up, there were 26 HCC cases that occurred among patients with cirrhosis and without treatment, and among patients who received TDF treatment, 3 cases of HCC occurred after 240 person-years of follow-up, yielding rates of 128.44 cases per 1000 person-years (95% CI, 87.45–188.65) and 12.47 cases per 1000 person-years (95% CI, 4.02–38.65), respectively. On multivariate analysis, TDF therapy was significantly associated with a 77% reduction in the risk of HCC (aHR, 0.23; 95% CI, .56–.92; *P* = .038; Table 4).

HCC Development in Patients Without Cirrhosis

For the noncirrhotic group (504 per group), the average age (±SD) was 43.63 ± 12.78 years, 56.25% were male, and 95.93% were Asian, with an average follow-up duration (±SD) of 42.17 ± 34.18 months (Supplementary Table 3). The 8-year cumulative incidence for HCC was significantly higher for the untreated group compared to the treated group- 5.81% (95% CI, 2.99–11.11) vs. 1.36% (95% CI, .42–4.31; *P* = 0.029; Figure 2C). After 1607 person-years of follow-up, there were 10 newly developed HCC cases among those without antiviral treatment, giving an incidence of 6.22 cases per 1000 person-years (95% CI, 3.35–11.56). Among patients treated with TDF, 3 cases of HCC were diagnosed after 1769 person-years of follow-up, with an incidence rate of 1.70 cases per 1000 person-years (95% CI, .55–5.26). TDF therapy was associated with a 73% reduction (aHR, 0.27; 95% CI, .07–.98; *P* = .047) in the risk of developing HCC (Table 5).

Prior Exposure to Antiviral Therapy

On univariate analysis for predictors of HCC in the overall propensity score–matched cohort, other antiviral treatment prior to TDF was not significantly associated with a risk of HCC (unadjusted HR, 1.32; 95% CI, .34–5.10; *P* = .69). In the propensity score–matched cohort of patients without cirrhosis, antiviral history prior to TDF was also not significantly associated with the risk of HCC (unadjusted HR, 1.08; 95% CI, .11–10.36; *P* = .95). Similarly, in the propensity score–matched cohort of 132 patients with cirrhosis, 29 developed HCC (26 were untreated, and 3 were treated with TDF), and of the 3 patients who received TDF and developed HCC, none had a history of antiviral therapy prior to TDF treatment (Table 1 and Supplementary Tables 2 and 3).

Death Data

There were 28 deaths, of which 17 were in the untreated group, and 11 were in the TDF group. In the untreated group, 5 deaths (29.41%) were attributed to HCC; 2 (11.76%), to other liver-related complications; 3 (17.65%), to other non–liver-related cancers; and 7 (41.18%), to other non–liver-related complications. In the TDF group, 3 deaths (27.27%) were attributed to HCC; 4 (36.36%), to other liver-related complications; 2 (18.18%), to other non–liver-related cancers; and 2 (18.18%), to other non–liver-related complications. There was no significant difference between the 2 groups in regard to cause of death (*P* = .407). The average duration of follow-up (±SD) experienced by patients

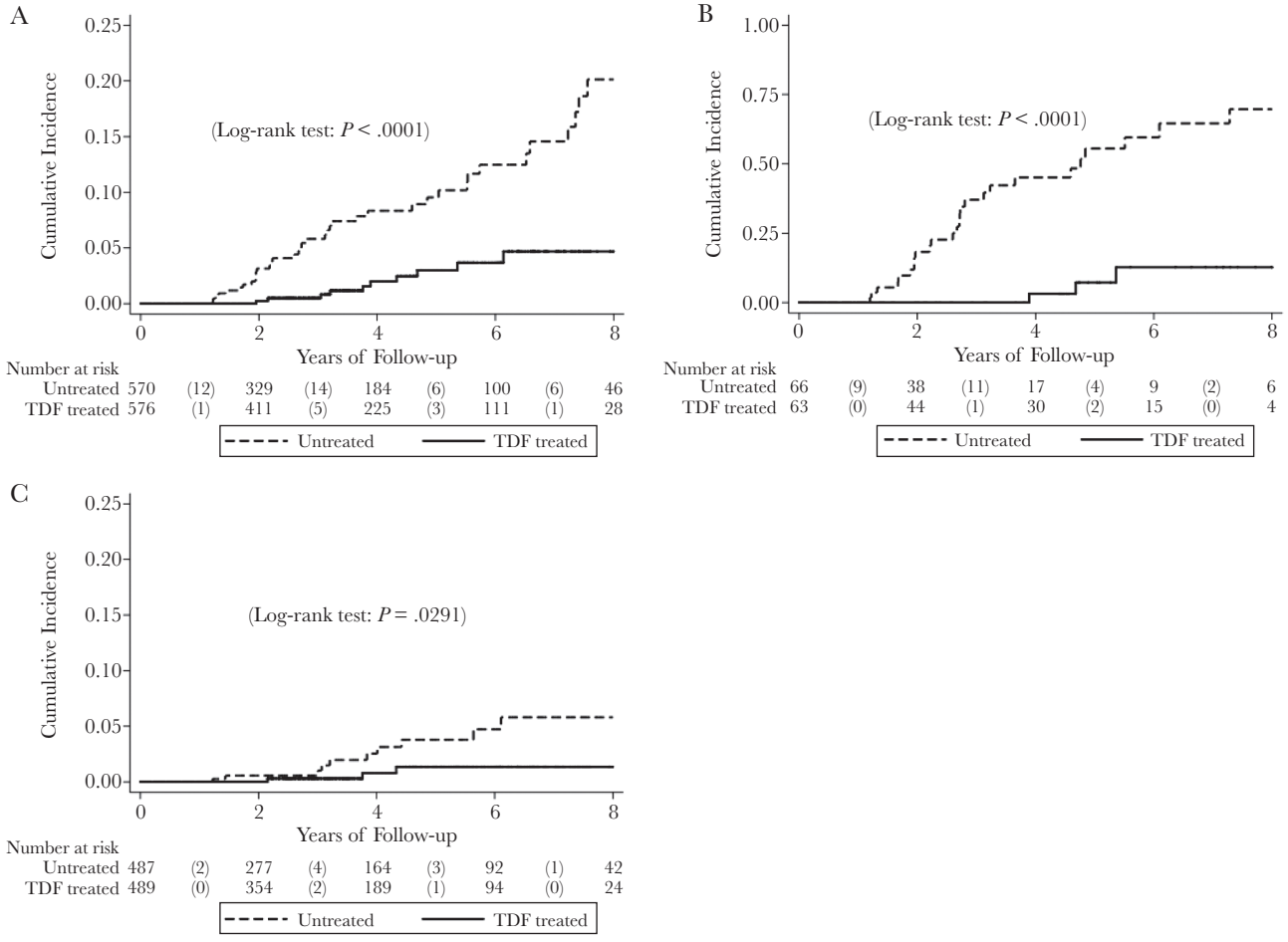

Figure 2. Cumulative incidence of hepatocellular carcinoma among propensity score–matched untreated and tenofovir disoproxil fumarate (TDF)–treated patients with chronic hepatitis B (CHB), overall (*A*), among patients with liver cirrhosis (*B*), and among patients without liver cirrhosis (*C*).

who died was 7.08 ± 4.58 years in the untreated group and 8.98 ± 7.56 years in the treated group ($P = .41$).

DISCUSSION

We believe that our study provides further insight into the importance of using TDF to treat Asian patients with chronic HBV infection. Our PSM models revealed that TDF was associated with an approximately 70% reduction in the development of HCC, compared with patients who were not treated. In fact, we demonstrated that Asian patients with CHB, a patient population most affected with CHB-associated HCC, benefitted significantly with TDF therapy whether cirrhosis was present or not, a finding that has not been consistently found by prior well-controlled studies of nucleoside analogs. In fact, after PSM, we found that the overall 8-year HCC incidence rate was 4.69% for those who were treated with TDF, compared with 20.13% for

Table 3. Treatment Reduced the Risk of Hepatocellular Carcinoma (HCC) Among Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis B, After Adjustment for Risk Factors

Risk Factor	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age (per 5-y interval)	1.33 (1.20–1.47)	<.001	1.37 (1.20–1.58)	<.001
Male sex	3.23 (1.51–6.91)	.002	2.28 (1.04–4.96)	.038
ALT level (per U/L)	0.997 (.99–1.003)	.35	0.997 (.99–1.003)	.33
Cirrhosis	11.41 (6.18–21.06)	<.001	5.36 (2.73–10.51)	<.001
Log_{10} HBV DNA level (per IU/mL)	1.18 (1.05–1.33)	.006	1.17 (.99–1.36)	.055
TDF treatment	0.23 (.12–.47)	<.001	0.34 (.16–.71)	.005

Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for HCC risk.

Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus; TDF, tenofovir disoproxil fumarate.

Table 4. Treatment Reduced the Risk of Hepatocellular Carcinoma (HCC) Among Cirrhotic Patients With Chronic Hepatitis B, After Adjustment for Risk Factors

Risk Factor	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age (per 5-y interval)	1.13 (.97–1.31)	.13	1.13 (.88–1.46)	.34
Male sex	1.19 (.45–3.12)	.73	1.01 (.37–2.77)	.99
ALT level (per U/L)	0.98 (.97–.99)	.029	0.99 (.99–1.00)	.16
HBeAg positivity	1.03 (.47–2.25)	.94	…	
Log_{10} HBV DNA level (per IU/mL)	1.02 (.87–1.20)	.83	0.97 (.80–1.17)	.73
TDF treatment	0.09 (.03–.30)	<.001	0.23 (.56–.92)	.038
Recruitment location				
Community/primary care clinic	Reference		Reference	
Specialty clinic	0.10 (.04–.27)	<.001	0.21 (.06–.68)	.009

Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for HCC risk.

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B virus e antigen; HBV, hepatitis B virus; TDF, tenofovir disoproxil fumarate.

those who were not treated, and these findings were similar for patients with and those without cirrhosis (12.71% among treated vs 69.67% among untreated cirrhotic patients and 1.36% among treated vs 5.81% among untreated noncirrhotic patients). The lower incidence rates were also confirmed in our PSM multivariate models, which showed that patients with CHB, regardless of the presence or absence of cirrhosis, had a 73%–77% lower risk of developing HCC. Also, patients seen at specialty clinics were less likely to develop HCC when compared to patients seen at community or primary care offices. Furthermore, when we controlled for treatment site, the reduction in HCC risk for those treated with TDF remained significant, suggesting that TDF therapy is strongly associated with a decreased risk such that treatment with TDF should be highly recommended in those eligible, regardless of treatment site. The lower risk seen in specialty practices could be due to higher treatment rates, as well as to selection for more motivated and adherent patients in specialty clinics.

We also found that cirrhosis was the strongest predictor for HCC. In fact, like Buti et al, we found that patients with cirrhosis were >5 times more likely to develop HCC [25]. In addition, both studies found a reduction in HCC following treatment with TDF. In fact, our study helps to confirm the suggestion by Buti et al that a reduction in HCC risk may be due to histologic improvement and the prevention of cirrhosis development and/or progression following treatment with TDF [25].

Our study results also expand the generalization of Buti et al's findings, which were reported from clinical trial data, to real-world clinical practice. Furthermore, we expand the generalization to the Asian population, as 95% of our study population was Asian as compared to only 25% of Buti et al's population. This is an important expansion of Buti et al's study, as HBV is more prevalent in the Asian population, and thus makes our findings especially relevant and encouraging for the treatment of HBV in this population. Specifically, we demonstrated that TDF therapy resulted in a 77% risk reduction in patients with cirrhosis (aHR, 0.23; $P = .038$) and a 73% risk reduction in noncirrhotic patients (aHR, 0.27; $P = .047$).

Of importance, in contrast to prior studies in which treatment was not consistently found to be beneficial in patients with a lower risk profile, such as those without cirrhosis, we found that TDF therapy was beneficial in noncirrhotic patients,

Table 5. Treatment Reduced the Risk of Hepatocellular Carcinoma (HCC) Among Noncirrhotic Patients With Chronic Hepatitis B, After Adjustment for Risk Factors

Risk Factor	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age (per 5-y interval)	1.18 (.98–1.43)	.086	1.14 (.93–1.40)	.21
Male sex	1.30 (.42–3.97)	.65	0.80 (.27–2.36)	.69
ALT level (per U/L)	0.999 (.99–1.01)	.77	1.0001 (.99–1.003)	.99
HBeAg positivity	1.34 (.46–3.92)	.60	…	
Log_{10} HBV DNA level (per IU/mL)	1.07 (.85–1.35)	.55	1.12 (.89–1.41)	.33
TDF treatment	0.26 (.07–.96)	.042	0.27 (.07–.98)	.047
Recruitment location				
Community/primary care clinic	Reference		Reference	
Specialty clinic	0.22 (.07–.71)	.012	0.18 (.06–.59)	.005

Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for HCC risk.

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B virus e antigen; HBV, hepatitis B virus; TDF, tenofovir disoproxil fumarate.

resulting in a 73% reduction in the risk of developing HCC for patients with CHB without cirrhosis [26–28]. The difference in our results may be due to the higher potency of TDF and the absence of viral resistance associated with the long-term use of TDF. Nevertheless, since antiviral therapy with TDF can significantly reduce the risk of HCC development by 73%–77% (dependent on the status of cirrhosis), early diagnosis and appropriate antiviral therapy become key in reaching these outcomes.

And finally, in the United States, the results of this study are significant because HCC is now the leading cause of primary liver cancer, the fifth most common cancer in men, and the eighth most common cancer in women [29]. As opposed to the majority of other cancers, incidence and death rates have been increasing for liver cancer in the United States over the past 2 decades. In fact, liver cancer has the second lowest 5-year relative survival for cases diagnosed in 2006–2012, at 18.1%, with only pancreatic cancer having a lower survival rate, at 8.5% [29]. Therefore, our finding that TDF is associated with a reduction in the risk of developing HCC in patients with CHB, a leading cause of HCC, is encouraging but will require further study, especially in other ethnicities [30].

There are some limitations to this study. First, this was a retrospective study, but we reviewed every medical chart individually in detail and used objective criteria to determine CHB, cirrhosis, and HCC status, which included laboratory results, radiology reports, biopsy results when available, and physician notes. Second, TDF was not approved until 2008, so some patients who received TDF were censored, owing to study closure, before the 8-year cumulative incidence of HCC could be evaluated in them. However, the trend of an extended time to HCC development noted in our analysis was very favorable as compared to that in the untreated group. Fourth, several laboratory results that are associated with the development of HCC (eg, albumin level and platelet count) were unavailable, so there may be an underestimation of the risk for HCC in both groups. Notably, these study results are not generalizable to individuals of non–Asian ethnicity. However, since CHB is endemic within the Asian population, these findings are especially relevant for treatment of CHB in this population of mixed Asian ethnicities predominantly infected with HBV genotype C, the main genotype for East Asians in general. We encourage other studies to be conducted with an emphasis on African Americans, as this is another population at high risk for CHB [31]. Finally, the strength of this study is that our investigation is the first large, controlled study that directly compares the HCC incidence in tenofovir-treated patients with untreated propensity score–matched HBV-infected controls.

In summary, the use of TDF in Asian patients with CHB significantly reduced the risk of developing HCC, regardless of the status of cirrhosis. Although HCC may still develop in Asian patients with CHB treated with TDF, the 8-year incidence rate was much lower than that in the untreated group, even in the absence of cirrhosis. Therefore, our findings confirm that TDF for Asian patients with CHB is an appropriate and beneficial treatment for cirrhotic and noncirrhotic patients with CHB and active disease. We encourage further research in patients of other ethnicities at risk for CHB to determine how these findings relate to them.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. M. H. N. was responsible for concept development, study design, data collection, data analysis and interpretation, drafting the manuscript, and supervising the study. H.-I. Y. was responsible for the study design, data analysis and data collection, data interpretation, and critical review of the manuscript. A. L. Was responsible for data collection, data analysis and interpretation, and drafting the manuscript. L. H. was responsible for data analysis and interpretation and drafting the manuscript. N. N. was responsible for data analysis and interpretation and critical review of the manuscript. M.-H. L. was responsible for data interpretation and critical review of the manuscript. J. Z. Was responsible for data collection and critical review of the manuscript. Ch. W. was responsible for data collection and critical review of the manuscript. Cl. W. was responsible for data collection and critical review of the manuscript. H. T. was responsible for data collection and critical review of the manuscript.

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