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Tenofovir is superior to entecavir for achieving complete viral suppression in hbeag-positive chronic hepatitis b patients with high hbv dna

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SUMMARY

Background—Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are the two first-line antiviral therapies for chronic hepatitis B (CHB); however, there are limited studies directly comparing their effectiveness.

Aims—To compare the effectiveness of ETV and TDF in nucleos(t)-ide-naïve CHB patients with high hepatitis B virus (HBV) DNA levels, defined as serum HBV DNA greater than 6 $\log_{10}$ IU mL^{-1}.

Methods—We performed a retrospective multicenter cohort study of adult CHB patients who were seen between 2009 and 2012 at four Northern California community gastroenterology and hepatology clinics.

Results—We identified 59 consecutive patients treated with TDF and 216 patients treated with ETV. Pretreatment characteristics were similar between the two groups. Among HBeAg-negative patients, there was no significant difference in viral suppression rates between ETV and TDF (p = 0.72). In contrast, among HBeAg-positive patients, those treated with TDF achieved viral suppression significantly more rapidly than those treated with ETV ($p < 0.0001$); the Kaplan-Meier estimated probability of complete suppression was 18% vs. 11% at 6 months, 51% vs. 28%

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AUTHORSHIP

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Effect of entecavir (ETV) dosage on viral suppression in hepatitis B e antigen (HBeAg) positive patients.

Fig. S2. Effect of entecavir (ETV) dosage on viral suppression in hepatitis B e antigen (HBeAg) negative patients.

at 12 months, and 72% vs. 39% at 18 months, respectively. Multivariate Cox proportional hazards analysis indicated that treatment with TDF compared to ETV was a significant predictor of viral suppression but only for HBeAg-positive patients (HR = 2.59; 95% CI 1.58–4.22; $p < 0.001$).

Conclusions—TDF is significantly more effective than ETV for achieving complete viral suppression in HBeAg-positive, nucleos(t)-ide-naïve chronic hepatitis B patients with HBV DNA greater than 6 $\log_{10}$ IU mL^{-1}.

INTRODUCTION

Hepatitis B virus (HBV) infection is a significant global health problem. About two billion people worldwide have been exposed to HBV, among which an estimated 400 million are chronically infected. For patients with chronic hepatitis B (CHB), the lifetime risk of developing cirrhosis or hepatocellular carcinoma (HCC) is 15–40% [1]; and each year, CHB alone causes 1 million deaths worldwide [2]. The risk of developing cirrhosis and HCC has been shown to increase with increasing serum HBV DNA levels [3, 4]. In one large study, over 30% of patients with HBV DNA greater than 5.3 $\log_{10}$ IU mL^{-1} (6 $\log_{10}$ copies mL^{-1}) developed cirrhosis within 12 years [4]. In addition, patients who are positive for the hepatitis B e antigen (HBeAg) have increased risk for HCC [5]. Thus, achieving sustained suppression of HBV replication with anti-HBV therapy may be critical in preventing cirrhosis and HCC, especially for HBeAg-positive patients with high HBV DNA levels.

Currently, seven antiviral therapies have been approved for CHB in the United States, including two interferons (interferon alfa and pegylated interferon alfa) and five nucleos(t)ide analogs (lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxil fumarate). Among these, entecavir (Bristol-Myers Squibb, New York, NY, USA) and tenofovir disoproxil fumarate (Gilead Sciences, Foster City, CA, USA) are the first-line options [6, 7]. Entecavir (ETV) is a carbocyclic analog of 2’-deoxyguanosine, and tenofovir disoproxil fumarate (TDF) is an analog of 2’-deoxyadenosine monophosphate. ETV was approved by the U.S. Food and Drug Administration in March 2005, and TDF was approved for treatment of CHB in August 2008. Both ETV and TDF selectively inhibit HBV viral replication with potent activity [8, 9] and low rates or absence of long-term resistance [10–12]. However, there are few studies to date that directly compare their effectiveness.

The current study aimed to compare the effectiveness of ETV and TDF for achieving complete viral suppression in CHB patients with high HBV DNA levels and who had not previously been treated with any nucleos(t)ide analog or interferon. The study also evaluated the rates of normalization of alanine aminotransferase (ALT) and HBeAg seroconversion. HBeAg-positive and HBeAg-negative patient subgroups were studied separately.

MATERIALS AND METHODS

We performed a retrospective cohort study of adult CHB patients who were seen between 2009 and 2012 at four Northern California community gastroenterology and hepatology clinics. The TDF cohort consisted of consecutive patients treated with 300 mg TDF daily, and the ETV cohort consisted of patients treated with 0.5 or 1.0 mg ETV daily. Both ETV doses were included in the study in order to present an accurate representation of a real-life

cohort, and also because previous research has suggested no significant differences in effectiveness between the two doses [13, 14]. All patients were identified via electronic query of all CHB patient records at these treatment centers using ICD-9 diagnosis codes, and data was abstracted via individual record review using a case report form.

A high HBV DNA level was defined as serum HBV DNA greater than 6 $\log_{10}$ IU mL^{-1} (1,000,000 IU mL^{-1}), or approximately 6.7 $\log_{10}$ copies mL^{-1}. Patients were eligible for inclusion in the study if they had a baseline serum HBV DNA level greater than 6 $\log_{10}$ IU mL^{-1}, were treated for at least six months, and were at least 18 years of age at the start of treatment. Patients were excluded if they had evidence of co-infection with the hepatitis C virus, hepatitis D virus, or HIV; a history of chemotherapy, radiation, or immunosuppressive therapy; or any prior exposure to nucleos(t)-ide analogs or interferon therapy.

Complete viral suppression was defined as undetectable serum HBV DNA (< 60 IU mL^{-1} or < 300 copies mL^{-1}, or below the lower limit of quantification of the PCR assay). An ALT level of ≤ 30 U L^{-1} for a male patient and ≤ 19 U L^{-1} for a female patient was considered normal.

All statistical analysis was performed using Stata/IC ver. 12.1 (StataCorp LP, College Station, TX). Categorical variables were described as a proportion (%), and continuous variables were described as a mean ± standard deviation or median (range). Follow-up times were calculated from treatment initiation to last date of follow-up, non-adherence, or change in therapy. Categorical variables were evaluated using the chi-squared test, and continuous variables were evaluated using the Student's *t*-test if normally distributed and nonparametric methods if not. Independent predictors of viral suppression were determined using univariate and multivariate Cox proportional hazards models inclusive of age, gender, weight, baseline HBV DNA level, baseline ALT, and ETV vs. TDF. Kaplan–Meier survival analysis was used to estimate probabilities of complete viral suppression, ALT normalization, and seroconversion. Survival functions describing these variables were compared using the log-rank test. For all statistical tests, a two-sided *p* value of less than 0.05 was considered significant.

The study was approved by the Administrative Panel for the Protection of Human Subjects at Stanford University.

RESULTS

Patient Population

We identified a total of 275 patients eligible for inclusion in the study, of which 59 were treated with TDF and 216 were treated with ETV. Over 90% of the patients in the total cohort were Asian. Of the total cohort, 174 were HBeAg-positive, and 101 were HBeAg-negative. Within the HBeAg-positive group, there were 39 consecutive TDF patients and 135 ETV patients; and within the HBeAg-negative group, there were 20 consecutive TDF patients and 81 ETV patients. Pretreatment characteristics were similar among both HBeAg-positive and HBeAg-negative groups (Table 1).

Virologic Response

To analyze suppression of HBV DNA, a Kaplan-Meier plot was used to visualize the estimated probability for achieving complete viral suppression as a function of treatment time for each of the four subgroups (Fig. 1). In this plot, a steeper rise in the Kaplan-Meier curve represents more effective viral suppression. For HBeAg-positive patients (shown as bold lines), the TDF curve was consistently higher than the ETV curve, suggesting that those treated with TDF achieved viral suppression significantly more rapidly than those treated with ETV. This was supported by the log-rank test ($p < 0.0001$). The estimated probability of achieving complete suppression was 18% vs. 11% at 6 months, 51% vs. 28% at 12 months, and 72% vs. 39% at 18 months, respectively (Table 3). In contrast, for HBeAg-negative patients, there was no significant difference in viral suppression rates between TDF and ETV ($p = 0.72$).

Predictors of Viral Suppression

For HBeAg-positive patients, univariate and multivariate Cox proportional hazards analysis inclusive of age, gender, weight, baseline ALT, baseline HBV DNA, and ETV vs. TDF indicated that treatment with TDF compared to ETV was a significant predictor of viral suppression (HR = 2.59; 95% CI 1.58–4.22; $p < 0.001$). In addition, baseline HBV DNA level was a significant negative predictor for viral suppression (HR = 0.47; 95% CI 0.35–0.62; $p < 0.001$) (Table 2). This was supported by Kaplan-Meier analysis on HBeAg-positive patients restricted to those with HBV DNA > 8 $\log_{10}$ IU mL^{-1} (Fig. 3), which further indicated that TDF patients achieved complete viral suppression faster than ETV patients ($p < 0.0001$).

For HBeAg-negative patients, treatment with ETV compared to TDF was a not significant predictor of viral suppression (HR = 1.02; 95% CI 0.59–1.76; $p = 0.94$), in contrast to the HBeAg-positive patients. However, higher baseline HBV DNA was still a significant negative predictor for viral suppression (HR = 0.60; 95% CI 0.41–0.89; $p = 0.01$) (Table 2).

Both univariate and multivariate Cox models indicated that age, weight, and baseline ALT level were not significant predictors of viral suppression in either HBeAg-positive or HBeAg-negative patients. In addition, HBeAg-negative patients on the whole (ETV and TDF combined) achieved viral suppression faster than HBeAg-positive patients ($p < 0.0001$), with estimated probabilities of 44% vs. 13% at 6 months, 80% vs. 33% at 12 months, and 93% vs. 46% at 18 months, respectively. The mean baseline HBV DNA was 7.81 ± 0.72 $\log_{10}$ IU mL^{-1} for HBeAg-positive patients and 6.83 ± 0.60 $\log_{10}$ IU mL^{-1} for HBeAg-negative patients.

HBeAg Seroconversion

Among HBeAg-positive patients, 20 of 135 (15%) of those treated with ETV achieved HBeAg seroconversion, with a median seroconversion time of 21.6 months. By comparison, 2 of 39 (5%) HBeAg-positive TDF patients seroconverted, with a median time of 20.7 months. TDF patients had significantly shorter median follow-up times than ETV patients (14.9 vs. 27.9 months, $p < 0.0001$).

Effects of ETV Dosage

A sub-analysis of ETV patients was also performed to analyze the relationship between drug dosage and viral suppression. Among the HBeAg-negative ETV patients, 62 were treated with 0.5 mg daily, 6 initiated treatment with 0.5 mg daily but later increased their dosage to 1.0 mg daily, and 13 were treated with 1.0 mg daily. Baseline HBV DNA was 6.78 ± 0.52 $\log_{10}$ IU mL^{-1}, 7.15 ± 0.92 $\log_{10}$ IU mL^{-1}, and 6.90 ± 0.65 $\log_{10}$ IU mL^{-1}, respectively. Among the HBeAg-positive ETV patients, 66 were treated with 0.5 mg daily, 38 initiated treatment with 0.5 mg daily but later increased their dosage to 1.0 mg daily, and 31 were treated with 1.0 mg daily. Baseline HBV DNA was 7.66 ± 0.70 $\log_{10}$ IU mL^{-1}, 7.91 ± 0.70 $\log_{10}$ IU mL^{-1}, and 8.05 ± 0.82 $\log_{10}$ IU mL^{-1}, respectively. There were significant differences in the rates of complete viral suppression between patients treated with different dosages among HBeAg-positive patients (Fig. S1) but not among HBeAg-negative patients (Fig. S2). In particular, patients who increased dosage had the lowest probability of viral suppression, followed by those treated with 1.0 mg daily. Patients who remained on 0.5 mg daily had the highest probability of viral suppression.

Biochemical Response

Kaplan-Meier analysis (Fig. 2) and the log-rank test indicated no significant difference in ALT normalization rates between the TDF and ETV patients in either the HBeAg-positive ($p = 0.44$) or HBeAg-negative ($p = 0.76$) groups.

DISCUSSION

The primary concern for CHB patients is the risk of developing cirrhosis, decompensated liver disease, and hepatocellular carcinoma. The necroinflammatory response in the liver resulting from persistent HBV virema is a major risk factor for these life-threatening complications. Chen et al. [3] and Iloeje et al. [4] have shown in large, long-term studies that the higher the serum HBV DNA level, the higher the risk for cirrhosis and HCC. Thus, the primary goal of antiviral therapy is complete suppression of viral replication, which may delay or prevent progression of liver disease [15]. Effective suppression is particularly important in patients with higher HBV DNA levels.

This study investigates the complete viral suppression rates of ETV and TDF in patients with high HBV DNA levels, defined as a baseline HBV DNA greater than 6 $\log_{10}$ IU mL^{-1}, or 6.7 $\log_{10}$ copies mL^{-1}. We found that among HBeAg-positive patients, TDF is significantly more effective than ETV for achieving complete viral suppression. Among HBeAg-negative patients, however, there was no significant difference in viral suppression between the two drugs.

A recent study by Lok et al. [16] suggested that ETV plus TDF combination therapy is superior to ETV alone for achieving complete viral suppression in HBeAg-positive patients with high baseline HBV DNA. Our results suggest that TDF alone is superior to ETV for achieving complete viral suppression for at least some of these patients. Although the present study does not directly compare TDF to combination therapy, this finding is significant given the high cost of both ETV and TDF; as of 2010, the cost of a 30-day supply

in the U.S. is $941 for ETV and $853 for TDF [17]. The ability to treat HBeAg-positive patients with high HBV DNA levels with TDF alone offers a substantial cost savings over combination therapy, especially when antiviral therapy is often long-term or life-long in the majority of patients with CHB.

Previous studies by Dogan et al. [18] and Guzelbulut et al. [19] reported no significant difference in viral suppression rates between ETV and TDF after 48 weeks of therapy. Maratea et al. [20] also suggested no significant difference between ETV and TDF through an indirect comparison. Our results indicate that among HBeAg-negative patients with high HBV DNA levels, ETV and TDF are similarly effective, in agreement with the previous findings. However, among HBeAg-positive patients with high HBV DNA levels, our data suggests that TDF is significantly more effective than ETV. This result is consistent with meta-analyses by Dakin et al. [21], Wiens et al. [22], and Woo et al. [23], which concluded that among the five approved nucleos(t)ide analog therapies for CHB, TDF is associated with the highest probability of achieving undetectable HBV DNA at 12 months of treatment for HBeAg-positive patients overall.

In addition, we found no significant difference in ALT normalization between ETV and TDF for both HBeAg-positive and HBeAg-negative patients, as previously reported [18, 19].

For HBeAg-positive ETV patients, we observed a 15% (20/135) seroconversion rate, compared to 5% (2/39) of HBeAg-positive TDF patients. However, we could not conclude that ETV is more effective than TDF in inducing seroconversion because the median follow-up time for HBeAg-positive TDF patients was only 14.9 months, which is less than the median seroconversion time for HBeAg-positive ETV patients (by comparison, the median follow-up time for HBeAg-positive ETV patients was 27.9 months). This was likely because TDF is a newer therapy for CHB than ETV. Thus, these seroconversion rates were effectively conservative estimates, due to the fact that some patients were lost to follow-up, and their HBeAg status became unknown. It is possible that with longer follow-up times, HBeAg seroconversion could have been observed in a greater number of TDF patients. In addition, because this was a real-life study and not a clinical trial, other factors such as possible non-adherence may have contributed to lower rates of seroconversion than those reported in clinical trials.

Among HBeAg-positive patients, cumulative viral suppression rates were lower than previously reported viral suppression rates for both ETV and TDF. Chang et al. reported that in a phase 3, double-blind trial including 314 HBeAg-positive patients on ETV, 67% completely suppressed the virus after 48 weeks [24], and comparable numbers have been reported in other studies [16, 25–31]. In this study, however, the estimated probability of viral suppression for HBeAg-positive ETV patients at 48 weeks was only 25%. Likewise, Marcellin et al. reported that in two phase 3, double-blind studies, 76% of HBeAg-positive patients treated with TDF completely suppressed the virus at 48 weeks [32], while in this study, the estimated probability of viral suppression at 48 weeks was only 40%. A likely cause of this discrepancy was the restriction to highly viremic patients in this study, as high virema at baseline can result in slower decline of HBV DNA levels [33]. This hypothesis

was supported by our multivariate Cox proportional hazards analysis, which indicated that higher baseline viral load was a significant negative predictor for viral suppression. Moreover, TDF viral suppression rates in our study were similar to those reported in Gordon et al. [33], which focused on patients with HBV DNA > 8.3 $\log_{10}$ IU mL^{-1} (9 $\log_{10}$ copies mL^{-1}). Finally, possible unreported or unrecognized non-adherence during routine clinical care may have contributed to lower viral suppression rates than those reported in clinical trials, in which adherence is much more closely monitored.

Sub-analysis of the ETV patients indicated that ETV dosage was significantly correlated with viral suppression for HBeAg-positive patients. HBeAg-positive patients treated with 0.5 mg ETV daily had the highest probability of viral suppression, followed by those treated with 1.0 mg daily. Those who increased dosage from 0.5 mg to 1.0 mg daily had the lowest probability of viral suppression. This correlation, however, should not be interpreted as a difference in effectiveness between the doses. Rather, it reflects the fact that that baseline clinical characteristics may have influenced dosage decision; patients treated with 1.0 mg ETV had higher HBV DNA than those treated with 0.5 mg ETV (7.66 ± 0.70 $\log_{10}$ IU mL^{-1} vs. 8.05 ± 0.82 $\log_{10}$ IU mL^{-1}, $p = 0.02$). Likewise, the fact that those who increased dosage had the lowest probability of viral suppression may reflect a low effectiveness of increased dosage on patients who experience suboptimal response on 0.5 mg ETV daily. This interpretation is consistent with Ha et al. [13, 14], which found no significant difference in viral suppression rates between ETV 0.5 mg and 1.0 mg daily in ETV partial responders.

The definition of a high HBV DNA level varies from study to study; several studies have defined 7–9 $\log_{10}$ IU mL^{-1} [16, 31, 33] as high HBV DNA, while some have used 5.3 $\log_{10}$ IU mL^{-1} (6 $\log_{10}$ copies mL^{-1}) [3, 4]. In this study, we used 6 $\log_{10}$ IU mL^{-1} based on clinical observations in our practice that patients with HBV DNA levels of above about 6 $\log_{10}$ IU mL^{-1} do not have high rates of viral suppression after one year of treatment. We focused only on patients with high HBV DNA because previous studies [3, 4] indicate that these patients have increased risk for development of cirrhosis and HCC. In addition, since both ETV and TDF are potent anti-HBV medications, their performance would be better compared in more difficult-to-treat patients such as those with higher HBV DNA levels. An analysis of HBsAg levels and HBV genotypes was not performed because this data was only available for a minority of patients.

Limitations of the current study include the relatively small size and shorter follow-up times of the TDF cohort, as well as the retrospective design. In addition, this study evaluated only viral suppression, ALT normalization, and HBeAg seroconversion but neglected other treatment parameters such as adverse events (rare for both ETV and TDF), histological improvement (impractical in a real-life setting), and loss of hepatitis B surface antigen (a rare endpoint requiring much longer follow-up times). Nevertheless, this study is significant because there are few studies to date that directly compare ETV and TDF in CHB patients, and even fewer that have focused specifically on patients with high HBV DNA levels. In addition, the primary study endpoint was complete viral suppression, which is an objective measurement.

In summary, TDF is significantly more effective than ETV for achieving complete viral suppression in HBeAg-positive, nucleos(t)-ide-naïve hepatitis B patients with HBV DNA greater than 6 $\log_{10}$ IU mL^{-1}. In contrast, for HBeAg-negative patients with HBV DNA greater than 6 $\log_{10}$ IU mL^{-1}, we observed no significant difference in rates of viral suppression between ETV and TDF. These results may be of interest to clinicians in informing decisions to select treatment for HBeAg-positive CHB patients with high HBV DNA levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Declaration of personal interests: Huy N. Trinh has served as a speaker for Vertex and Bristol-Myers Squibb, consultant for Bristol-Myers Squibb, advisory board member for Gilead Sciences Inc. and Bristol-Myers Squibb, has received funding from Gilead Science Inc. and Roche, and owns stock and shares in Gilead Sciences Inc. Mindie H. Nguyen has served as a consultant for Bristol-Myers Squibb, Novartis Pharmaceuticals, Gilead Sciences Inc., Bayer, and Onyx Pharmaceuticals and has received research funding from Bristol-Myers Squibb, Novartis Pharmaceuticals, Gilead Sciences, and Roche Laboratories.

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ABBREVIATIONS

ETV	Entecavir
TDF	Tenofovir disoproxil fumarate
CHB	Chronic hepatitis B
HBV	Hepatitis B virus
ALT	Alanine aminotransferase
HBeAg	Hepatitis B e antigen
HCC	Hepatocellular carcinoma

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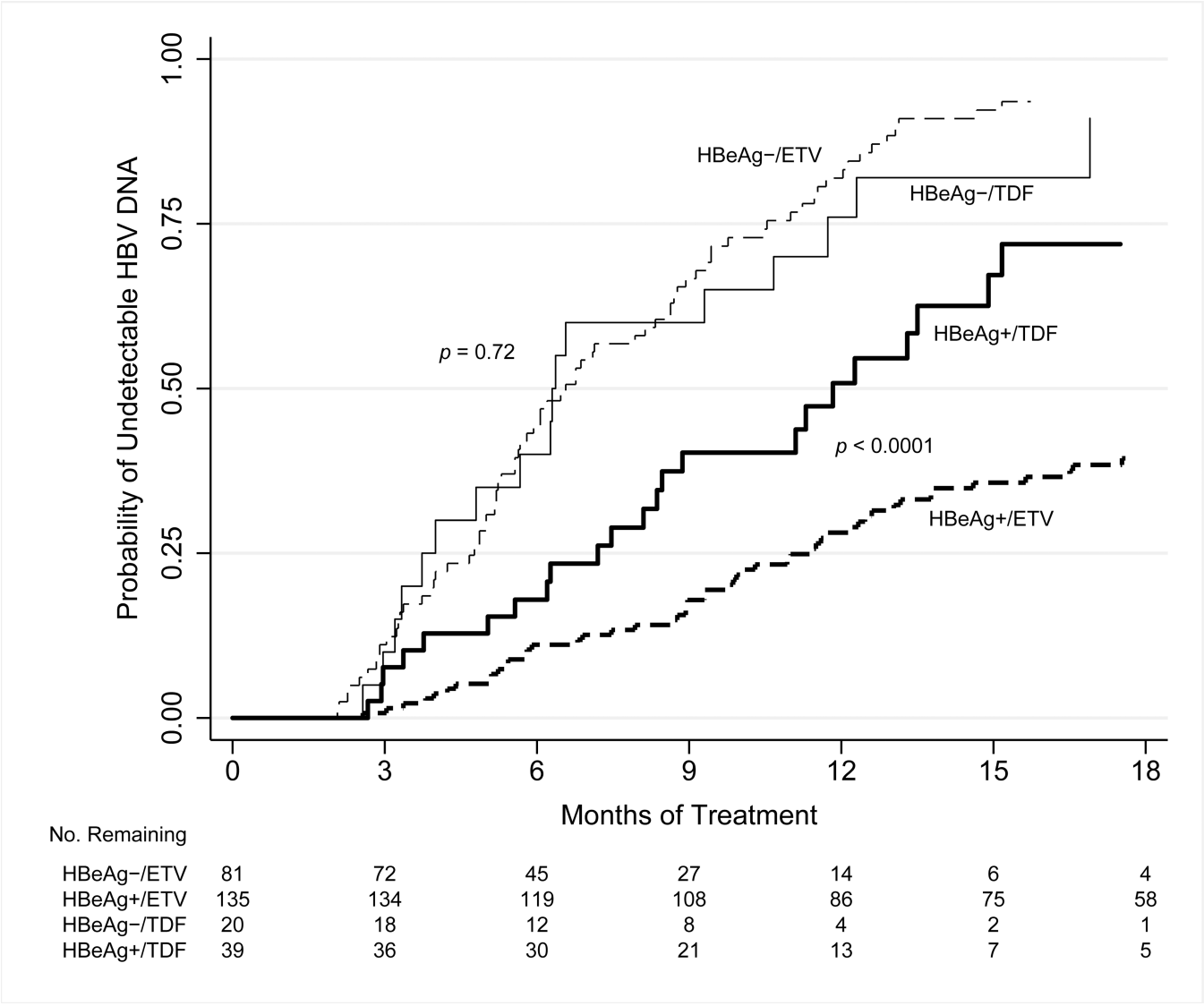

Fig. 1.

Kaplan-Meier analysis of complete viral suppression rates in patients with baseline HBV DNA greater than 6 $\log_{10}$ IU/mL and treated with either entecavir (ETV) or tenofovir (TDF), by hepatitis B e antigen (HBeAg) status.

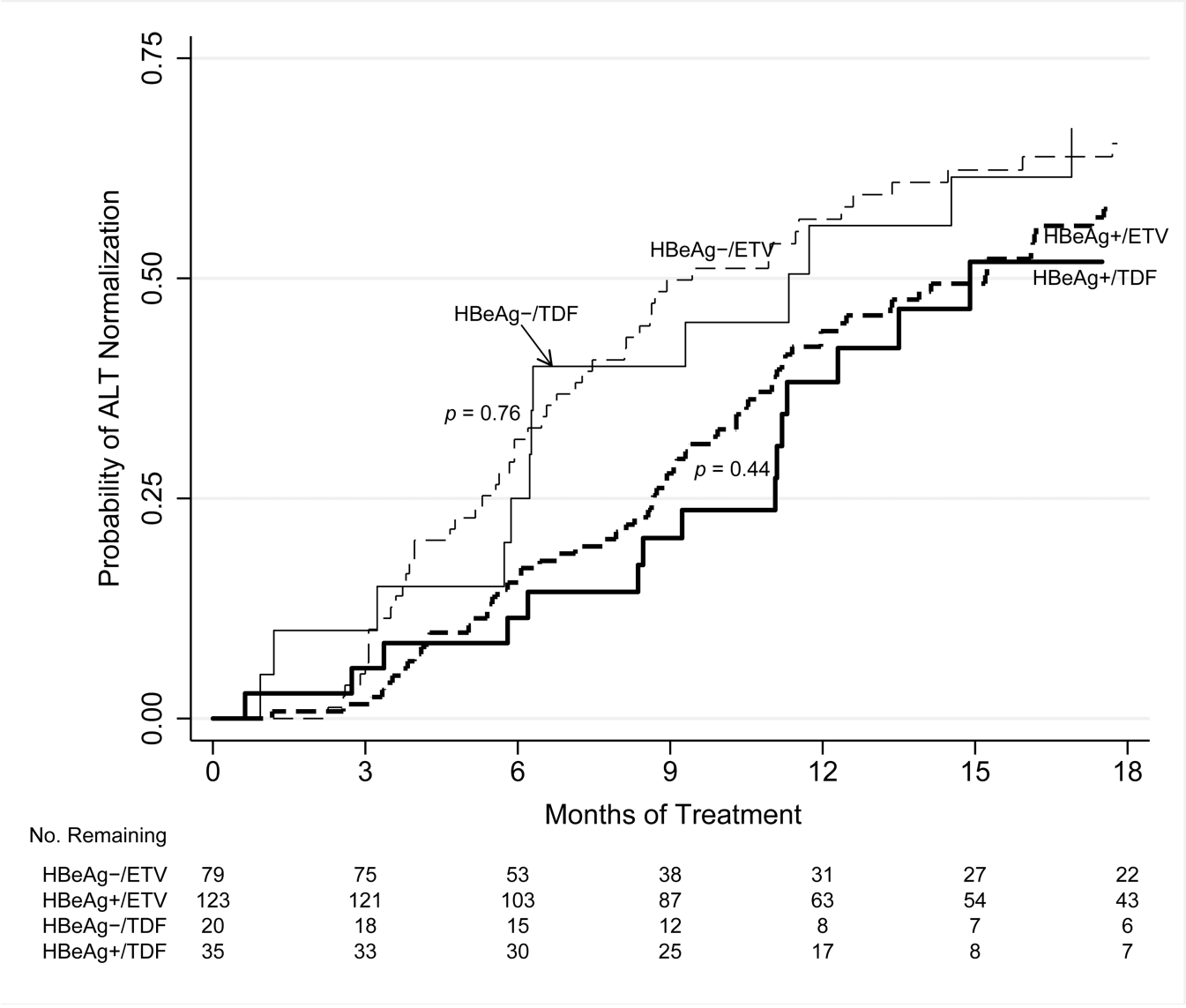

Fig. 2.

Kaplan-Meier analysis of alanine aminotransferase (ALT) normalization rates in patients with baseline HBV DNA greater than 6 $\log_{10}$ IU/mL and treated with either entecavir (ETV) or tenofovir (TDF), by hepatitis B e antigen (HBeAg) status.

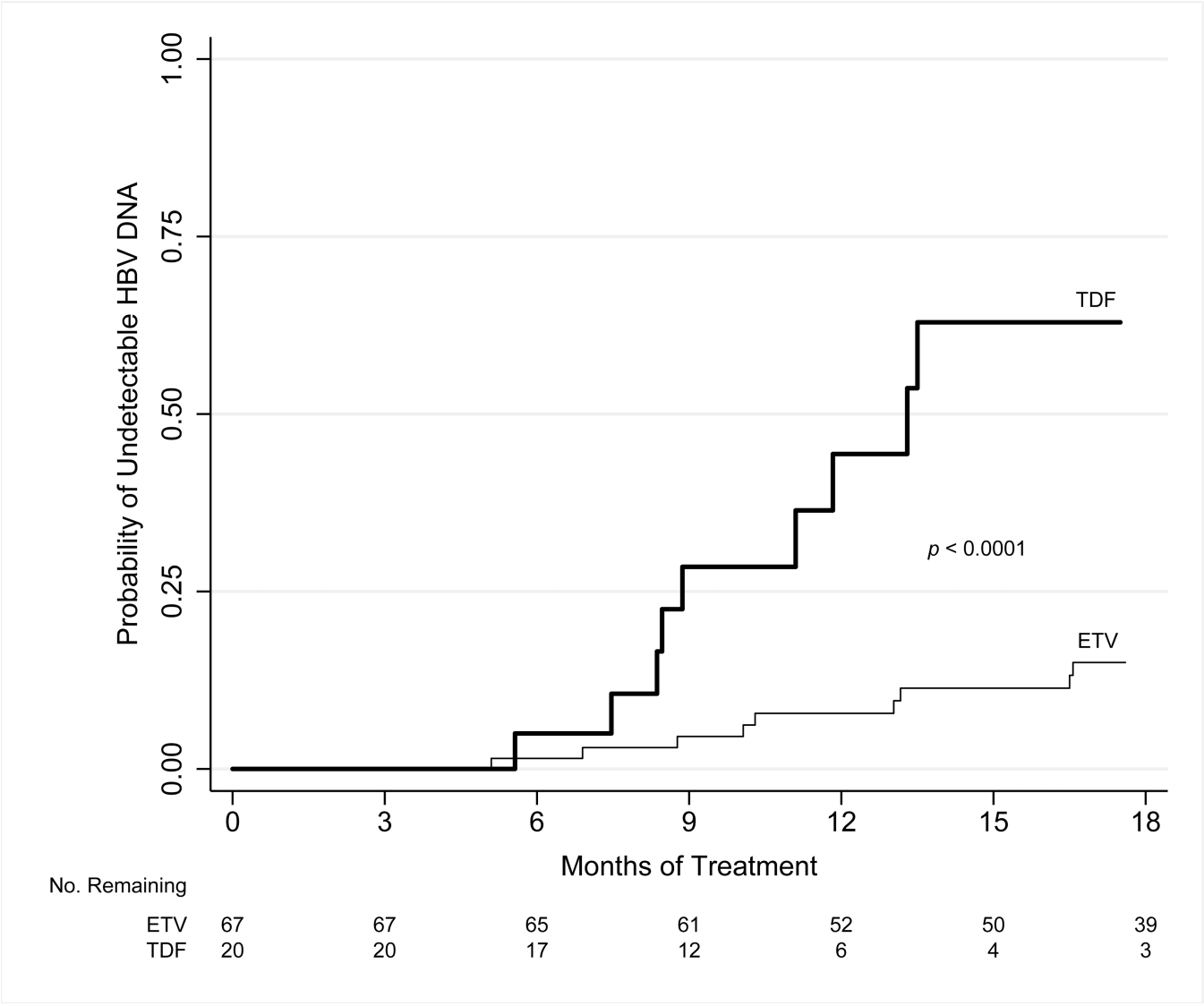

Fig. 3.

Complete viral suppression in hepatitis B e antigen (HBeAg)-positive patients with HBV DNA greater than 8 $\log_{10}$ IU/mL at baseline. The difference between TDF and ETV is greater in this subpopulation of patients with especially high HBV DNA levels, which is consistent with the conclusion that baseline HBV DNA is a significant negative predictor for viral suppression.

Table 1

Baseline patient characteristics for CHB patients with high HBV DNA treated with ETV (*n* = 216) and TDF (*n* = 59) between 2009 and 2012, by HBeAg status

	HBeAg-negative			HBeAg-positive		
	ETV (*n* = 81)	**TDF (*n* = 20)**	***p*-value**	**ETV (*n* = 135)**	**TDF (*n* = 39)**	***p*-value**
Age (years)	50.7 ± 13.2	49.0 ± 8.9	0.59	38.6 ± 10.7	37.4 ± 9.5	0.54
Male	56 (69%)	17 (85%)	0.16	78 (58%)	17 (44%)	0.12
Weight (lbs)	139.6 ± 26.1	147.9 ± 18.7	0.19	136.6 ± 25.5	128.1 ± 20.6	0.06
Cirrhosis	9 (11%)	0 (0%)	0.12	8 (6%)	4 (10%)	0.35
HCC	2 (2%)	0 (0%)	0.48	1 (1%)	0 (0%)	0.59
HBV DNA (IU mL^{-1})	6.83 ± 0.57	6.84 ± 0.69	0.94	7.82 ± 0.74	7.76 ± 0.66	0.64
ALT (U L^{-1})	97 (20–1237)	75 (42–1405)	0.57	62 (17–1077)	67 (6–208)	0.64
Follow-up Time (months)	36.9 (5.8–74.2)	18.4 (10.7–27.9)	0.0001	27.9 (5.8–80.2)	14.9 (5.6–35.0)	<0.0001
History of Alcohol Use	33 (41%)	5 (25%)	0.19	28 (21%)	12 (31%)	0.19
History of Smoking	21 (26%)	6 (30%)	0.71	23 (17%)	7 (18%)	0.89
Family History of HBV	19 (23%)	4 (20%)	0.74	53 (39%)	14 (36%)	0.70
Family History of HCC	8 (10%)	1 (5%)	0.49	21(16%)	5 (13%)	0.67
Family History of Liver-related Death	5 (6%)	1 (5%)	0.84	19 (14%)	4 (10%)	0.54
Diabetes Mellitus	11 (14%)	1 (5%)	0.29	2 (1%)	2 (5%)	0.18
Hypertension	23 (28%)	4 (20%)	0.45	18 (13%)	4 (10%)	0.61
Creatinine (mg dL^{-1})	1.0 ± 0.3	0.9 ± 0.1	0.17	1 ± 0.8	0.7 ± 0.2	0.08
Platelets (thous μL^{-1})	217.9 ± 135.3	202.8 ± 39.2	0.72	226.2 ± 58.9	204.4 ± 58.6	0.09

Abbreviation: HBeAg, Hepatitis B e antigen; TDF, tenofovir disoproxil fumarate; ETV, entecavir; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; ALT, alanine aminotransferase.

Table 2

Univariate and multivariate Cox proportional hazards analysis for complete suppression of HBV DNA, by HBeAg status

HBeAg-positive						
Predictors	**Univariate**			**Multivariate**		
	HR	**95% CI**	***p***	**HR**	**95% CI**	***p***
TDF (*n* = 39) (vs. ETV (*n* = 135))	2.69	1.67–4.32	<0.001	2.59	1.58–4.22	<0.001
Age (years)	1.00	0.98–1.02	0.77	0.99	0.97–1.01	0.27
Weight (lbs)	1.00	0.99–1.01	0.86	1.00	0.99–1.01	0.86
Male	0.94	0.63–1.42	0.77	0.90	0.54–1.52	0.71
Baseline HBV DNA ($\log_{10}$ IU mL^{-1})	0.51	0.40–0.66	<0.001	0.47	0.35–0.62	<0.001
Baseline ALT (U L^{-1})	1.00	1.00–1.00	0.15	1.00	1.00–1.00	0.01

HBeAg-negative						
Predictors	**Univariate**			**Multivariate**		
	HR	**95% CI**	***p***	**HR**	**95% CI**	***p***
TDF (*n* = 20) (vs. ETV (*n* = 81))	0.91	0.54–1.52	0.72	1.02	0.59–1.76	0.94
Age (years)	1.01	1.00–1.03	0.16	1.01	0.99–1.03	0.29
Weight (lbs)	0.99	0.99–1.00	0.13	1.00	0.99–1.01	0.91
Male	0.48	0.30–0.76	0.002	0.53	0.28–0.99	0.05
Baseline HBV DNA ($\log_{10}$ IU mL^{-1})	0.64	0.44–0.92	0.02	0.60	0.41–0.89	0.01
Baseline ALT (U L^{-1})	1.00	1.00–1.00	0.66	1.00	1.00–1.00	0.86

Abbreviation: HBeAg, Hepatitis B e antigen; TDF, tenofovir disoproxil fumarate; ETV, entecavir; HBV, hepatitis B virus; ALT, alanine aminotransferase.

Table 3

Kaplan-Meier estimated probabilities (95% CI) of complete viral suppression, by HBeAg status

HBeAg Status	Treatment	Months					
		3	6	9	12	15	18
HBeAg-negative	ETV (*n* = 81)	11% (6–20)	44% (34–56)	67% (56–77)	82% (73–89)	92% (85–97)	94% (87–98)
	TDF (*n* = 20)	10% (3–34)	40% (22–64)	60% (40–81)	76% (56–92)	82% (62–95)	91% (70–99)
HBeAg-positive	ETV (*n* = 135)	0% (0–5)	11% (7–18)	18% (12–26)	28% (21–37)	36% (28–45)	39% (31–49)
	TDF (*n* = 39)	8% (3–22)	18% (9–34)	40% (26–58)	51% (35–68)	67% (50–83)	72% (54–87)

Abbreviation: HBeAg, Hepatitis B e antigen; TDF, tenofovir disoproxil fumarate; ETV, entecavir.