Tenofovir Disoproxil Fumarate (TDF), Emtricitabine/TDF, and Entecavir in Patients with Decompensated Chronic Hepatitis B Liver Disease

Yun-Fan Liaw,[1] I-Shyan Sheen,[1] Chuan-Mo Lee,[2] Ulus Salih Akarca,[3] George V. Papatheodoridis,[4] Florence Suet-Hing Wong,[5] Ting-Tsung Chang,[6] Andrzej Horban,[7] Chia Wang,[8] Peter Kwan,[9] Maria Buti,[10] Martin Prieto,[11] Thomas Berg,[12] Kathryn Kitrinos,[13] Ken Peschell,[13] Elsa Mondou,[13] David Frederick,[13] Franck Rousseau,[13] and Eugene R. Schiff[14]

Data are limited on the safety and effectiveness of oral antivirals other than lamivudine and adefovir dipivoxil for treatment of chronic hepatitis B (CHB) in patients with decompensated liver disease. This Phase 2, double-blind study randomized 112 patients with CHB and decompensated liver disease to receive either tenofovir disoproxil fumarate (TDF; n = 45), emtricitabine (FTC)/TDF (fixed-dose combination; n = 45), or entecavir (ETV; n = 22). The primary endpoint was safety; more specifically, tolerability failure (adverse events resulting in permanent treatment discontinuation) and confirmed serum creatinine increase ≥0.5 mg/dL from baseline or confirmed serum phosphorus <2 mg/dL. Patients with insufficient viral suppression (e.g., confirmed HBV DNA ≥400 copies/mL at week 8 or 24) could begin open-label FTC/TDF but were considered failures in this interim week 48 analysis for efficacy endpoints. Tolerability failure was infrequent across arms: 6.7% TDF, 4.4% FTC/TDF, and 9.1% ETV ($P = 0.622$) as were confirmed renal parameters meeting threshold 8.9%, 6.7%, and 4.5% ($P = 1.000$), respectively. Six patients died (none considered related to study drug) and six received liver transplants (none had HBV recurrence). The adverse event and laboratory profiles were consistent with advanced liver disease and complications, with no unexpected safety signals. At week 48, HBV DNA was <400 copies/mL (69 IU/mL) in 70.5% (TDF), 87.8% (FTC/TDF), and 72.7% (ETV) of patients. Proportions with normal alanine aminotransferase were: 57% (TDF), 76% (FTC/TDF), and 55% (ETV). Hepatitis B e antigen (HBeAg) loss/seroconversion occurred in 21%/21% (TDF), 27%/13% (FTC/TDF), and 0%/0% (ETV). Child-Turcotte-Pugh and Modification for End-stage Liver Disease scores improved in all groups. *Conclusion:* All treatments were well tolerated in patients with decompensated liver disease due to CHB with improvement in virologic, biochemical, and clinical parameters. (HEPATOLOGY 2011;53:62-72)

Chronic hepatitis B virus (HBV) infection affects 400 million people worldwide, producing substantial morbidity and mortality.[1] About one million people die annually from complications of chronic hepatitis B (CHB).[2] Cirrhosis, liver failure, and/or hepatocellular carcinoma (HCC) are expected to develop in 15%-40% of patients with CHB.[2] In cirrhotic patients the 5-year probability of decompensation is

Abbreviations: ADV, adefovir dipivoxil; AE, adverse event; ALT, alanine aminotransferase; CHB, chronic hepatitis B; Cl_{cr}, calculated serum creatinine clearance; CTP, Child-Turcotte-Pugh; ETV, entecavir; FTC, emtricitabine; HBeAg, hebatitis B e antigen; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; WBC, white blood cell.

From the [1]Liver Research unit, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan; [2]Department of Internal Medicine, Chang Gung Memorial Hospital, Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan; [3]Ege Universitesi Tip Fakultesi Hastanesi. Izmir, Turkey; [4]Ippokration General Hospital of Athens, Athens, Greece; [5]Toronto General Hospital, Toronto, ON, Canada; [6]National Chen Kun University Hospital, Tainan, Taiwan; [7]Hospital of Infectious Diseases, Warsaw, Poland; [8]Virginia Mason Medical Center, Seattle, WA, USA; [9]The Gordon and Leslie Diamond Centre, Vancouver, BC, Canada; [10]Hospital General Universitari Vall d'Hebron, Barcelona, Spain; [11]Hospital La Fe, Valencia, Spain; [12]Charite Campus Virchow-Klinikum, Berlin, Germany; [13]Gilead Sciences, Durham, NC, USA; and [14]University of Miami School of Medicine, Miami, FL, USA.

Received July 16, 2010; accepted August 19, 2010.

15%-20%, with higher risk associated with viral replication. The 5-year survival rate is 14%-35% for decompensated cirrhosis.[3]

There are seven approved drugs for the treatment of CHB (lamivudine, adefovir dipivoxil [ADV], entecavir [ETV], telbivudine, tenofovir disoproxil fumarate [TDF], as well as pegylated and standard interferon-α). Current clinical practice guidelines[4-6] advocate sustained HBV DNA suppression to reduce sequelae. TDF and ETV are recommended oral first-line therapies for CHB. ETV (0.5 mg dose) is superior to lamivudine in treatment-naïve hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients,[7,8] and ETV resistance is extremely low.[9] However, ETV is less efficacious in lamivudine-refractory patients even at 1.0 mg daily, with the reported resistance rate at 5 years of 51%.[10] TDF is superior to ADV in HBeAg-negative and HBeAg-positive treatment-naïve patients.[11] Additionally, TDF demonstrated potent antiviral efficacy (92% complete suppression through week 96) in a subset of lamivudine-experienced HBeAg-positive patients,[12] and in patients with suboptimal response to ADV (most with prior lamivudine experience): 89% <400 copies/mL at 96 weeks.[13] There has been no development of resistance to tenofovir through 144 weeks of therapy.[14]

Present treatment guidelines advocate oral antivirals in decompensated CHB patients.[3-5] Studies with lamivudine[15-17] and ADV[18,19] have demonstrated improved clinical outcomes (decreased mortality and improved liver function) in decompensated CHB patients. Notably, lamivudine resistance mutations emerging during lamivudine treatment can negate therapeutic benefit, resulting in increased Child-Turcotte-Pugh (CTP) scores.[17] In an open-label compassionate use trial, ADV benefited pre- and posttransplant patients with lamivudine-resistant CHB including decompensated cirrhotics,[18,19] in terms of HBV DNA suppression and CTP score improvement. Consistent with outcomes in lamivudine-treated patients, the majority of deaths in the trial occurred during the first 6 months, particularly in patients extremely ill at entry. Although no ADV mutations occurred after 48 weeks of therapy, increasing rates of resistance accrue over time in patients with compensated liver disease.[20]

TDF and ETV seem to possess optimal characteristics for treatment of decompensated CHB, although ETV resistance emerges more rapidly in lamivudine-refractory than in treatment-naïve patients. An ETV (0.5 mg) trial in 144 compensated and 55 decompensated treatment-naïve patients showed that HBV DNA suppression at 1 year was comparable between groups and most decompensated patients had improved CTP scores, generally within 6 months of treatment.[21] Another study compared ETV (1.0 mg) to ADV (10 mg/day) in decompensated CHB patients (34% with lamivudine resistance).[22] Preliminary results demonstrated ETV was superior to ADV with respect to reduction in HBV DNA, although overall 1-year patient survival rates were nearly identical (84% ETV, 83% ADV).

The present study was undertaken primarily to obtain safety data using a TDF-containing regimen (TDF monotherapy or the combination of emtricitabine [FTC] plus TDF) in decompensated CHB patients to explore treatment options for this difficult-to-manage population. Tenofovir is principally eliminated by the kidney, and there have been reports of renal impairment, including cases of acute renal failure and Fanconi syndrome with the use of TDF,[23] with the majority of cases reported in the human immunodeficiency virus (HIV) population. Cirrhotic patients with decompensation are prone to renal dysfunction,[24] and renal failure is a common posttransplantation complication.[25] The combination of FTC/TDF, which is approved for HIV-1 infection[26] but not for CHB, was also evaluated. Both TDF and FTC have activity against HBV,[11,27] and in vitro data indicate that tenofovir has a synergistic effect with FTC.[28] ETV was also evaluated to provide a safety comparator arm that did not contain TDF. This is a 168-week trial and results through the first 48 weeks of treatment are presented.

Patients and Methods

Study Patients. Patients were 18 to 69 years, with HBV DNA $\geq 10^3$ copies/mL (Roche COBAS TaqMan assay), a CTP score of 7-12 (inclusive) or prior CTP score ≥ 7 and CTP ≤ 12 at screen, alanine aminotransferase (ALT) <10 times upper limit of normal (ULN), calculated serum creatinine clearance (Cl_{cr}; Cockcroft-

Address reprint requests to: Elsa Mondou, Gilead Sciences Inc., 4 University Place, 4611 University Drive, Durham, NC 27707. E-mail: elsa.mondou@gilead.com; fax: 919-493-5925.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.23952

Potential conflict of interest: Nothing to report.

Additional supporting information may be found in the online version of this article.

Gault[29]) ≥50 mL/min, hemoglobin ≥7.5 g/dL, total white blood cell (WBC) count ≥1,500/mm,^{3} platelet count ≥30,000/mm,^{3} α-fetoprotein ≤20 ng/mL, and no evidence of HCC. Patients were excluded for HIV, HCV, or HDV-positive serologies, prior TDF or ETV exposure, ADV exposure ≥24 months, current Grade 2 or higher hepatic encephalopathy, history (within 60 days) of variceal bleeding, hepatorenal syndrome, Grade 3 or 4 hepatic encephalopathy, or spontaneous bacterial peritonitis, solid organ or bone marrow transplant, or use of hepatotoxic or nephrotoxic drugs including those affecting renal tubular secretion.

Study Objective. The primary study objective was to evaluate and compare the safety/tolerability of TDF, FTC/TDF, and ETV in the treatment of CHB patients with decompensated liver disease. Secondary objectives included the relative efficacy of TDF, FTC/TDF, and ETV, and incidence and patterns of drug resistance mutations in HBV DNA polymerase.

Study Design. This was a Phase 2, double-blind, multicenter, randomized trial conducted at 39 sites in Europe (17 sites), Canada (4), Singapore (4), Taiwan (5), and the United States (9). Eligible patients were randomized in a 2:2:1 ratio using a central, interactive voice response system to: (1) TDF 300 mg; (2) FTC 200 mg/TDF 300 mg; or (3) ETV 0.5 mg or 1 mg. Randomization was stratified by CTP score (≤9 or 10-12) and prior lamivudine exposure: <6 months lamivudine exposure and no history of lamivudine resistance mutations (blind ETV dose 0.5 mg) or ≥6 months lamivudine exposure and/or a history of lamivudine resistance mutations (blind ETV dose 1.0 mg). All patients began their randomly assigned treatment at baseline: patients on therapy switched from their existing treatment without interruption.

Serum chemistry, hematology, prothrombin time (PT), international normalized ratio (INR), urinalysis, and plasma HBV DNA were collected every 4 weeks through week 48. Adverse events (AEs) and concomitant medications were recorded every 4 weeks. A complete physical examination was performed every 12 weeks. Serum α-fetoprotein was measured at baseline, weeks 24 and 48. HBV serologies were evaluated at screening, baseline, and every 12 weeks through week 48. Covance Laboratories conducted the laboratory tests.

Because this trial enrolled patients with decompensated liver disease, it was necessary to provide early intervention strategies if profound viral suppression was not expeditiously achieved. Patients with a <2 $\log_{10}$ copies/mL decrease in HBV DNA at week 8 (and greater than entry value) could, at the investigator's discretion, initiate open-label FTC/TDF fixed-dose combination and continue in the study, or remain on blinded therapy. Patients with a virologic breakthrough (≥1 $\log_{10}$ copies/mL increase from nadir on two consecutive determinations or consecutive HBV DNA ≥400 copies/mL after being <400 copies/mL) or who had plasma HBV DNA levels remaining >400 copies/mL (confirmed) at or after 24 weeks of treatment also could switch to open-label FTC/TDF and continue in the study, or remain on blinded therapy.

For patients with a confirmed (two consecutive visits) CL_{cr} <50 mL/min dosing was adjusted from daily to every other day until the CL_{cr} returned to ≥50 mL/min. Patients whose CL_{cr} decreased to <30 mL/min were to be permanently discontinued from the study. It is acknowledged that any estimate of CL_{cr} has limitations though the Cockcroft-Gault equation utilizing ideal body weight was employed in accordance with product labeling for dose adjustment.

The protocol was approved by each investigator's Independent Ethics Committee or Institutional Review Board before study initiation. Written informed consent was obtained from all patients. This trial was conducted in accordance with international scientific and ethical standards, including the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. The trial was funded in full by Gilead Sciences (Durham, NC; clinicaltrials.gov identifier NCT00298363). An external independent multidisciplinary data monitoring committee reviewed the safety for the study four times prior to the last patient completing 48 weeks of treatment.

Safety Assessments. The coprimary endpoints in the study were safety-related: tolerability failures and confirmed (two consecutive visits) increases in serum creatinine ≥0.5 mg/dL above baseline or serum phosphorus values <2.0 mg/dL. Safety analyses through 48 weeks included all patients who received at least one dose of a study drug. AEs, serious adverse events (SAEs), laboratory abnormalities, deaths, and discontinuation of the study drug due to AEs were evaluated.

Efficacy Assessments. Secondary efficacy endpoints included plasma HBV DNA, ALT, and HBeAg/HBsAg loss and seroconversion, as well as CTP and model for endstage liver disease (MELD) scores.

Resistance Surveillance. Hepatitis B virus genotype (A-H) and identifiable drug resistance mutations in HBV polymerase/reverse transcriptase (pol/RT) were determined at baseline by population sequencing (detects mutations present at ≥25% of the population). Postbaseline genotypic analysis was attempted for viremic patients (HBV DNA ≥400 copies/mL) at week 48 (or the last visit after Week 24 for early

discontinuations), and for patients with virologic breakthrough. Additionally, the last available on-treatment sample before switching from blinded therapy to open-label FTC/TDF was evaluated. Amino acid substitutions in the HBV pol/RT domain were evaluated to determine if they occurred at polymorphic or conserved sites. Conserved site substitutions were phenotypically assessed in cell culture assays to measure *in vitro* tenofovir susceptibility. Phenotyping was also performed for viruses isolated from patients with virologic breakthrough. Resistance surveillance testing was conducted by Gilead Sciences.

Statistical Methods. The planned study enrollment was 40 TDF, 40 FTC/TDF, 20 ETV, for a total of 100 randomized patients. Demographic and baseline measurements were summarized using standard descriptive methods by treatment group and overall.

For each of the two coprimary endpoints, the number and percentage of patients achieving the endpoint were summarized. Proportions were calculated for the TDF, FTC/TDF, and ETV treatment groups, and for the TDF and FTC/TDF groups combined, and the difference in proportions between the TDF-containing arms (combined) and the ETV arm was evaluated using Fisher's exact test. All categorical secondary endpoints were summarized by number and percentage of patients that achieved the endpoint. For each endpoint, a 95% confidence interval (CI) around the point estimate (mean for continuous and percentage for categorical endpoints) was constructed for each treatment group.

For all efficacy endpoints, unless otherwise stated, a noncompleter/switch = failure analysis was performed. Specifically, patients who discontinued the study or switched to open-label FTC/TDF were considered as failures for categorical endpoints. Additionally, patients who underwent orthotopic liver transplantation were censored from efficacy analyses at the time of transplant, apart from surveillance for HBV recurrence posttransplant.

Results

Study Patients. Enrollment began April 4 2006; the last patient completed week 48 on 05 December 2008. In all, 112 patients were randomized and treated. Forty-five patients were randomized to receive TDF, 45 to FTC/TDF, and 22 to ETV. In the ETV group 9 of 22 patients were in the stratum designated for 1.0 mg daily dosing ($\geq$6 months of lamivudine exposure and/or a history of HBV with lamivudine resistance mutations). Eighty-eight patients completed 48 weeks of double-blinded treatment, 10 switched to open-label FTC/TDF prior to week 48 (1 based on Week 8 and 9 based on the week 24 criteria) and completed 48 weeks of treatment, and 14 patients discontinued double-blind study drug prior to Week 48 (8 TDF, 3 FTC/TDF, and 3 ETV). Patient disposition is displayed in Supporting Information Fig. 1.

Baseline demographic and disease characteristics were similarly distributed between the three treatment groups (Table 1). There were no statistically significant differences between groups. The median baseline CTP score was 7 in all groups, and the interquartile range (IQR; Q1, Q3) ranged from 6 to 9. A total of 18 patients (6, 9, and 3 on TDF, FTC/TDF, and ETV, respectively) had CTP scores >9 at screening. The median MELD score was 11.0, 13, and 10.5 for TDF, TDF/FTC, ETV, and the IQR ranged from 9-17; 12 subjects had a MELD score $\geq$20. At baseline, lamivudine-associated resistance mutations (rtM204V/I $\pm$ rtL180M) were detected in 21 patients (8 TDF, 10 FTC/TDF, and 3 ETV).

Safety. Overall, seven patients (all on blinded study medication) met the protocol-defined criteria for tolerability failure (Table 2): three in the TDF group, two in the FTC/TDF group, and two in the ETV group. Six discontinued the study drug because of an AE and one interrupted study drug and never resumed (denoted as *Tolerability Failures [TF] 1 through 7* by treatment). Four patients (TF 1-4) died within 30 days of the last dose of study drug: liver failure secondary to cirrhosis and sepsis (TF1; FTC/TDF), endstage liver disease (TF2; TDF), disease deterioration/exacerbation of hepatitis B (TF3; ETV), and septic shock (TF4; ETV). None of these AEs was considered related to study drug. TF5 (TDF) discontinued with renal failure (considered unrelated to study drug) that developed immediately following liver transplantation commencing before TDF was restarted. TF6 (FTC/TDF) was discontinued for an allergic reaction (Grade 2 allergy considered related to study drug) with severe skin itching, headache, runny nose, and insomnia after the first dose. The allergic reaction resolved 1 day after the last (second) dose. TF7 (TDF) interrupted the study drug because of hepatic encephalopathy and hepatorenal syndrome (considered unrelated to study drug) and never resumed; the patient died on study day 12, 2 days after the last dose of study drug.

Patients who met the protocol-defined criteria for confirmed changes in renal parameters are shown in Table 2 (including combined TDF and FTC/TDF groups). Eight patients (four TDF, three FTC/TDF, and one ETV) had either a confirmed change from baseline in serum creatinine of $\geq$0.5 mg/dL or phosphorus <2.0

Table 1. Baseline and Disease Characteristics

Demographics and Baseline Characteristics*	TDF (*N*=45)	FTC/TDF (*N*=45)	ETV (*N*=22)	*P*-value‡
Sex, *n* (%)				
Male	37 (82.2%)	40 (88.9%)	17 (77.3%)	0.444
Baseline age (yrs)				
Median	52	50	54	0.297
Q1, Q3	48, 57	42, 58	47, 58	
Race, *n* (%)				
Asian	23 (51.1%)	24 (53.3%)	13 (59.1%)	0.830
White	19 (42.2%)	20 (44.4%)	8 (36.4%)	
Other	3 (6.7%)	1 (2.2%)	1 (4.5%)	
Baseline HBV DNA (log_{10} copies/mL)				
Median	5.70	6.28	5.93	0.877
Q1, Q3	4.9, 6.6	4.5, 7.3	4.2, 7.4	
Baseline ALT (I/U)				
Median	48	54	52	0.596
Q1, Q3	31, 73	34, 98	41, 66	
Baseline ALT above ULN,* *n* (%)				
Yes	27 (60.0%)	27 (60.0%)	17 (77.3%)	0.330
Baseline HbeAg,† *n* (%)				
Negative	31 (68.9%)	27 (60.0%)	15 (68.2%)	0.661
Baseline CTP score				
Median	7	7	7	0.377
Q1, Q3	6, 8	6, 9	6, 8	
Baseline MELD score				
Median	11	13	10.5	0.133
Q1, Q3	9, 14	10, 17	9, 13	
Previous CHB treatment experience, *n* (%)				
Lamivudine ≥6 months	19 (42.2%)	17 (37.8%)	8 (36.4%)	0.906
ADV	9 (20.0%)	10 (22.2%)	5 (22.7%)	1.000
Baseline HBV viral genotype, *n* (%)				
A	8 (17.8%)	8 (17.8%)	4 (18.2%)	0.859
B	9 (20.0%)	13 (28.9%)	6 (27.3%)	
C	10 (22.2%)	11 (24.4%)	5 (22.7%)	
D	15 (33.3%)	10 (22.2%)	4 (18.2%)	
E	1 (2.2%)	0	0	
F	0	1 (2.2%)	1 (4.5%)	
G	0	1 (2.2%)	0	
Unable to genotype	2 (4.4%)	1 (2.2%)	2 (9.1%)	

Q1, Q3 = interquartile range.

*ULN for ALT: 43 U/L for males and 34 U/L for females.

†Borderline values considered as positive for all serology markers.

‡*P*-values for categorical data from an exact test; *P*-values for continuous data from a Kruskal-Wallis test.

mg/dL during the first 48 weeks of the study. One patient in the TDF group had both, along with confirmed CL_{cr} <50 mL/min. This patient discontinued at the investigator's discretion due to overall poor health and noncompliance, with ongoing SAEs of hepatic encephalopathy and bacterial peritonitis. Six patients

Table 2. Summary of Coprimary Safety Endpoints at Week 48

Endpoint	TDF (*N*=45)	FTC/TDF (*N*=45)	TDF or FTC/TDF (*N*=90)	ETV (*N*=22)	P-value‡TDF and FTC/TDF Combinedvs. ETV
Tolerability failure*	3 (6.7%)	2 (4.4%)	5 (5.6%)	2 (9.1%)	0.622
Confirmed increase in serum Creatinine of ≥0.5 mg/dL from Baseline or confirmed phosphorus of <2.0 mg/dL	4 (8.9%)†	3 (6.7%)	7 (7.8%)†	1 (4.5%)	1.000
Confirmed increase in Creatinine of 0.5 mg/dL from baseline	4 (8.9%)†	1 (2.2%)	5 (5.6%)†	1 (4.5%)	1.000
Confirmed phosphorus of <2.0 mg/dL	1 (2.2%)	2 (4.4%)	3 (3.3%)	0	1.000
Confirmed increase in Creatinine of 0.5 mg/dL from baseline and confirmed phosphorus of <2.0 mg/dL	1 (2.2%)	0	1 (1.1%)	0	1.000

*Tolerability failure, defined as permanent discontinuation of study drug due to a treatment-emergent AE; any patient who temporarily discontinued study due to an AE but did not restart study drug was considered a tolerability failure. Six patients discontinued due to an AE (one discontinuation due to an AE was considered related to study drug) and one patient temporarily discontinued study drug and did not restart.

†Includes the only patient achieving a co-primary endpoint after beginning open-label FTC/TDF.

‡*P*-values are from a two-sided Fisher's exact test.

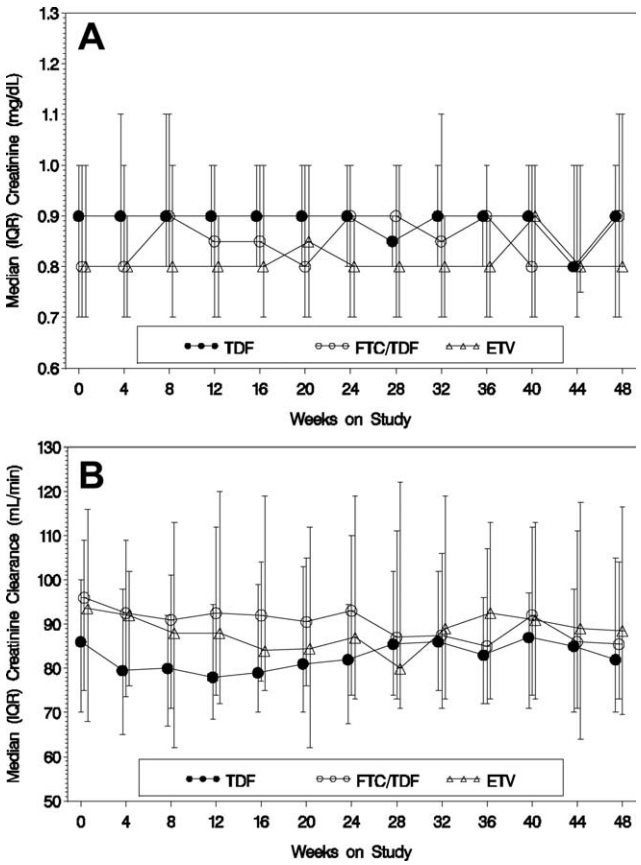

Fig. 1. (A) Median (IQR) serum creatinine (mg/dL) over time. (B) Median (IQR) calculated creatinine clearance (mL/min) over time.

had confirmed ≥0.5 mg/dL increases from baseline in serum creatinine (all also had confirmed CL_{cr}< 50 mL/min). All confirmed increases in serum creatinine occurred within the first 24 weeks of treatment and were associated with evident clinical deterioration related to endstage decompensated liver disease. Three patients had confirmed serum phosphorus values <2.0 mg/dL, including one in the TDF group and two in the FTC/TDF group; the patient in the TDF group also had a confirmed creatinine increase and Cl_{cr} <50 mL/min. Three additional patients (one ETV and two FTC/TDF) had a confirmed CL_{cr} <50 mL/min without confirmed 0.5 mg/dL increase in serum creatinine. There were no statistically significant differences between the combined TDF and FTC/TDF groups compared to the ETV group for any renal parameter examined ($P = 1.000$ for all comparisons). Overall treatment group medians (IQR) for serum creatinine and CL_{cr} by study visit are presented in Fig. 1A,B, respectively, and were generally stable throughout the 48-week treatment period in all groups.

Table 3 presents a summary of AEs, SAEs, discontinuations due to AEs, and deaths. AEs during double-blind treatment occurred in 82.2%, 93.3%, and 77.3% of TDF, FTC/TDF, and ETV patients, respectively. The percentages of patients with AEs and SAEs considered related to study drug and with AEs causing permanent discontinuation or death were low and similar among the treatment groups. Most AEs occurring in at least 5% of patients were comparable across groups (Table 4) and were consistent with decompensated liver disease. Two patients had Grade 3 or 4 AEs that were considered related to study drug: Grade 3 abdominal pain (TDF) that resolved after temporary dose interruption (9 days; the patient discontinued 6 days later due to noncompliance) and Grade 3 psoriasis (ETV) ≈2 months after switching to open-label FTC/TDF; this event was ongoing at week 48. SAEs were reported in 24.4%, 42.2%, and 22.7% of patients in the TDF, FTC/TDF, and ETV groups, respectively. Gastrointestinal disorders, infections and infestations, and hepatobiliary disorders were the most frequently reported SAEs. Two SAEs (abdominal pain [TDF] and allergic reaction [FTC/TDF] in one patient each) were considered related to study drug. Nearly all patients who had SAEs were hospitalized as a prerequisite for seriousness; 4.4%-4.5% of patients in each double-blind treatment arm had a treatment-emergent SAE of ascites, and variceal hemorrhage and hepatic encephalopathy SAEs occurred in 3% and 4% of patients in the TDF-containing arms, respectively.

Grades 3 or 4 laboratory abnormalities (Table 5) occurred with similar frequency in the three treatment groups. In general, these abnormalities were consistent

Table 3. Overall Summary of Treatment-Emergent Adverse Events

Adverse Event Category, *n* (%)*	DB TDF (*N*=45)	DB FTC/TDF (*N*=45)	DB ETV (*N*=22)	Total OL FTC/TDF (N=10)
Any AE	37 (82.2%)	42 (93.3%)	17 (77.3%)	4 (40.0%)
Study drug-related AE	8 (17.8%)	7 (15.6%)	2 (9.1%)	2 (20.0%)
Grade 3 or 4 AE	14 (31.1%)	9 (20.0%)	5 (22.7%)	1 (10.0%)
Grade 3 or 4 study drug-related AE	1 (2.2%)	0	0	1 (10.0%)
Any SAE	11 (24.4%)	19 (42.2%)	5 (22.7%)	2 (20.0%)
Study drug-related SAE	1 (2.2%)	1 (2.2%)	0	0
Death	2 (4.4%)	2 (4.4%)	2 (9.1%)	0

DB = double blind; OL = open label.

*Patients are counted once only for each category at the maximum severity.

Table 4. Common and Treatment-Related Treatment Emergent Clinical Adverse Events

Variable	DB TDF (*N*=45)	DB FTC/TDF (*N*=45)	DB ETV (*N*=22)	Total OL FTC/TDF (*N*=10)
Grade 2, 3, or 4 adverse events (reported in at least 5% of treated patients; *n* [%])	23 (51.1%)	23 (51.1%)	8 (36.4%)	4 (40.0%)
Ascites	4 (8.9%)	2 (4.4%)	4 (18.2%)	1 (10.0%)
Abdominal pain	4 (8.9%)	1 (2.2%)	2 (9.1%)	0
Nausea	4 (8.9%)	1 (2.2%)	0	0
Vomiting	3 (6.7%)	1 (2.2%)	0	0
Diarrhea	1 (2.2%)	0	2 (9.1%)	1 (10.0%)
Abdominal pain upper	1 (2.2%)	0	0	1 (10.0%)
Duodenal ulcer	0	0	2 (9.1%)	0
Hiatus hernia	0	0	0	1 (10.0%)
Sepsis	1 (2.2%)	3 (6.7%)	0	0
Bronchitis	0	0	0	1 (10.0%)
Influenza	0	0	0	1 (10.0%)
Hepatic encephalopathy	3 (6.7%)	1 (2.2%)	1 (4.5%)	0
Chronic hepatic failure	0	2 (4.4%)	2 (9.1%)	0
Depression	1 (2.2%)	0	0	1 (10.0%)
Diabetes mellitus	3 (6.7%)	1 (2.2%)	0	0
Psoriasis	0	0	0	1 (10.0%)
Rash pruritic	0	0	0	1 (10.0%)
Hypotension	4 (8.9%)	0	0	0
Hepatic neoplasm malignant	3 (6.7%)	1 (2.2%)	1 (4.5%)	0
Calculus ureteric	0	0	0	1 (10.0%)
Cough	0	0	1 (4.5%)	1 (10.0%)
Any treatment-related adverse event	8 (17.8%)	7 (15.6%)	2 (9.1%)	2 (20.0%)
Rash	2 (4.4%)	2 (4.4%)	1 (4.5%)	1 (10.0%)
Pruritus	1 (2.2%)	1 (2.2%)	0	0
Psoriasis	0	0	0	1 (10.0%)
Rash pruritic	0	0	0	1 (10.0%)
Nausea	3 (6.7%)	1 (2.2%)	0	0
Abdominal distension	1 (2.2%)	0	0	0
Abdominal pain	1 (2.2%)	0	0	0
Diarrhea	0	0	0	1 (10.0%)
Vomiting	0	1 (2.2%)	0	0
Blood creatine phosphokinase increased	1 (2.2%)	2 (4.4%)	0	0
Blood amylase increased	1 (2.2%)	0	0	0
Glucose urine present	0	1 (2.2%)	0	0
Lipase increased	1 (2.2%)	0	0	0
Asthenia	1 (2.2%)	0	1 (4.5%)	0
Hypersensitivity	0	1 (2.2%)	0	0
Hyperamylasemia	0	1 (2.2%)	0	0
Myalgia	1 (2.2%)	0	0	0
Dizziness	1 (2.2%)	0	0	0
Gynecomastia	0	1 (2.2%)	0	0

DB = double blind; OL = open label.
Events coded using MedDRA version 10.
Patients are counted only once for each preferred term at the maximum severity.

with the decompensated liver disease. There were no reports of lactic acidosis, although lactate levels were not mandated in the protocol.

There were a total of six deaths, all of which were considered unrelated to study drug. Five deaths were due to disease progression and occurred in patients with endstage cirrhosis who were eligible to receive liver transplants. These deaths occurred on days 12, 12, 29, 64, and 119 of the study. One death (day 122) was attributed to septic shock from *Vibrio vulnificus* after being bitten by a fish.

Eight patients had dose reductions to every other day: three TDF (6.7%); four FTC/TDF (8.9%); one ETV (4.5%); three received liver transplants, two died, one discontinued, and of the remaining two patients, one maintained on every other day dosing through Week 48 and the other resumed daily dosing.

Efficacy. Measures of efficacy were not statistically evaluated, but are descriptively summarized (Table 6). Approximately half of the patients in each treatment group had HBV DNA suppression <400 copies/mL by week 12 (51.2% TDF, 46.5% FTC/TDF, and

Table 5. Grade 3/4 Treatment-Emergent Laboratory Abnormalities

Variable	DB TDF (*N*=45)	DB FTC/TDF (*N*=45)	DB ETV (*N*=22)	Total OL FTC/TDF (*N*=10)
Grade 3 and 4 laboratory abnormalities (*n* [%])	21 (46.7%)	23 (51.1%)	10 (45.5%)	3 (30.0%)
Chemistry				
Hyperglycemia	5 (11.1%)	2 (4.4%)	2 (9.1%)	0
Serum amylase	2 (4.4%)	3 (6.7%)	0	0
Albumin	1 (2.2%)	2 (4.4%)	1 (4.5%)	0
Creatinine	1 (2.2%)	1 (2.2%)	1 (4.5%)	0
Creatine kinase	1 (2.2%)	1 (2.2%)	0	0
Serum lipase	1 (2.2%)	1 (2.2%)	0	0
Hyperuricemia	1 (2.2%)	0	0	0
Electrolytes				
Hyponatremia	1 (2.2%)	1 (2.2%)	1 (4.5%)	0
Hyperkalemia	1 (2.2%)	0	0	0
Hypernatremia	0	1 (2.2%)	0	0
Hypokalemia	0	1 (2.2%)	0	0
Serum bicarbonate	1 (2.2%)	0	0	0
Hematology				
Platelets	9 (20.0%)	8 (17.8%)	3 (13.6%)	1 (10.0%)
WBC	5 (11.1%)	5 (11.1%)	1 (4.5%)	0
Neutrophils	0	1 (2.2%)	1 (4.5%)	0
Hemoglobin	0	1 (2.2%)	0	0
Liver				
Total bilirubin	9 (20.0%)	9 (20.0%)	2 (9.1%)	0
AST (SGOT)	5 (11.1%)	4 (8.9%)	0	0
ALT (SGPT)	5 (11.1%)	2 (4.4%)	0	0
Prothrombin time	4 (8.9%)	3 (6.7%)	0	0
Alkaline phosphatase	0	0	0	1 (10.0%)
Urinalysis				
Urine glucose	6 (13.3%)	3 (6.7%)	4 (18.2%)	1 (10.0%)

DB = double blind; OL = open label.

Patients are counted only once for each laboratory test at the maximum severity.

Table 6. Efficacy Results at Week 48

	TDF (*N*=45)	FTC/TDF (*N*=45)	ETV (*N*=22)
HBV DNA < 400 copies/mL,* (69 IU/mL) *n/N* (%)†	31/44 (70.5%)	36/41 (87.8%)	16/22 (72.7%)
95% confidence interval	57.0%, 83.9%	77.8%, 97.8%	54.1%, 91.3%
Median (IQR) change from baseline in HBV DNA (log_{10} copies/mL)*,‡	−3.11 (-4.1, -2.4)	-3.92 (-5.2, -2.2)	-3.40 (-5.0, -1.3)
Normal ALT§, *n/N* (%)†	25/44 (56.8%)	31/41 (75.6%)	12/22 (54.5%)
95% Confidence Interval	42.2%, 71.5%	62.5%, 88.8%	33.7%, 75.4%
Normalized ALT,§ *n/N* (%)†	12/26 (46.2%)	16/25 (64.0%)	7/17 (41.2%)
95% confidence interval	27.0%, 65.3%	45.2%, 82.8%	17.8%, 64.6%
Median (IQR) change from baseline in serum ALT (U/L)‡	−7.0 (−42.0, 1.0)	−16.5 (−64.5, −2.5	−25.5 (−44.5, −5.5)
CTP Score† ≥ 2 point decrease‖ (*n/N*; %)	7/27 (25.9%)	12/25 (48.0%)	5/12 (41.7%)
95% confidence interval	9.4%, 42.5%	28.4%, 67.6%	13.8%, 69.6%
CTP Score† ≥ 2 point increase (*n/N*; %)	0/43	1/38 (2.6%)	0/22
95% confidence interval		0.0%, 7.7%	
Median (IQR) change from baseline in MELD score‡	−2.0 (−12, 3)	−2.0 (−18, 4)	−2.0 (−10, 1)
HBeAg loss,¶ *n/N* (%)†	3/14 (21.4%)	4/15 (26.7%)	0/7
95% confidence interval	(0.0%, 42.9%)	(4.3%, 49.0%)	
HbeAg seroconversion,¶ *n/N* (%)†	3/ 14 (21.4%)	2/ 15 (13.3%)	0/7
95% confidence interval	(0.0%, 42.9%)	(0.0%, 30.5%)	
HBV recurrence after liver transplantation	0/2	0/4	–

Patients who underwent liver transplantation (2 TDF, 4 FTC/TDF) are censored from the analysis of secondary efficacy endpoints. One patient randomized to TDF underwent liver transplant after switching to open-label FTC/TDF and is thus considered a failure in the efficacy analyses and is included in the TDF group denominator.

IQR = interquartile range.

*Taqman assay LLQ =169 copies/mL (29 IU/mL).

†Noncompleter/Switch = Failure.

‡Data after a patient switched to open-label FTC/TDF are excluded from the analysis.

§Normal ALT value defined as ALT value at or below ULN (43 U/L for males; 34 U/L for females). Normalized ALT defined as ALT value at or below ULN for patients with baseline ALT above ULN.

‖For patients with CTP scores ≥7 at baseline; because the minimum CTP score is 5, only these patients were evaluable for analyses of ≥2-point decrease in CTP score.

¶For patients with positive HBeAg at baseline.

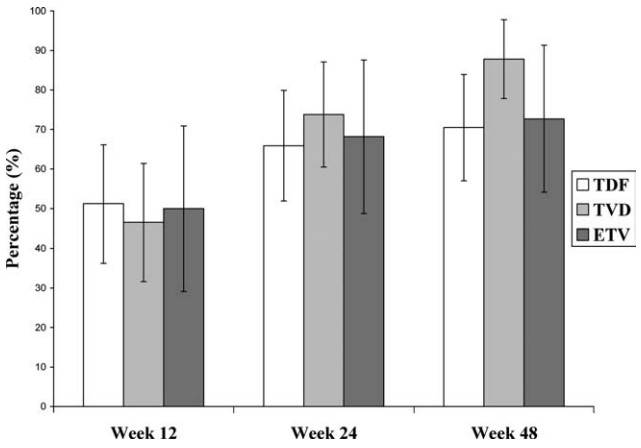

Fig. 2. Percentage of patients with HBV DNA <400 copies/mL (95% CI) at weeks 12, 24, and 48.

50.0% ETV), and 70.5%, 87.8%, and 72.7% had HBV DNA suppression <400 copies/mL at Week 48 (Fig. 2). If data are included from patients who switched to open-label FTC/TDF 76.7%, 87.8%, and 85.7% of patients in the TDF, FTC/TDF, and ETV groups, respectively, had HBV DNA <400 copies/mL. The mean (SD) $\log_{10}$ copies/mL decrease from baseline in HBV DNA at week 48 was −3.30 (1.516) in the TDF group, −3.72 (1.769) in the FTC/TDF group, and −3.24 (1.919) in the ETV group. At week 48 the percentages of patients with normalized ALT were 46%, 64%, and 41% in the TDF, FTC/TDF, and ETV groups, respectively. The median serum ALT values over time were similar across the groups. Seven patients achieved HBeAg loss at week 48 (three TDF and four FTC/TDF) and five of these patients seroconverted to anti-HBe. No HBeAg loss or seroconversion occurred in the ETV group. No patient achieved HBsAg loss by week 48.

At week 48, 24/64 (37.5%) patients achieved a ≥2 point decrease in CTP score and one patient had a ≥2 point increase in CTP score. Two-point increases in CTP score were infrequent and occurred sporadically in all treatment groups with no apparent time or treatment relationship. In all three groups the Week 48 median change from baseline in MELD score was −2 and the median MELD score was 8.

Six patients (two on blinded TDF [one open-label FTC/TDF switch prior to transplant] and four on blinded FTC/TDF) received liver transplants during the first 48 weeks of the study. Five completed 48 weeks of study treatment and one discontinued due to a posttransplant complication. All liver transplants were preplanned (all referred for transplantation prior to the screening visit). All six patients had HBV DNA <169 copies/mL at their last on-study visit and none were HBsAg seropositive (i.e., none experienced recurrence of HBV infection).

Resistance Surveillance. Thirteen patients (eight TDF, two FTC/TDF, and three ETV) qualified for genotypic testing based on viremia through 48 weeks. Two (TDF) developed conserved site changes in HBV pol/RT (rtS85P and rtV27A) in the context of virologic breakthrough. The rtS85P change was found to be replication-incompetent, whereas the rtV27A did not confer phenotypic resistance to tenofovir in vitro. Three ETV patients qualified for genotypic testing (all subsequently switched to open-label FTC/TDF); two had lamivudine resistance mutations (rtL180M and/or rtM204I) at baseline. After switching to open-label FTC/TDF, all three patients achieved undetectable HBV DNA levels (<400 copies/mL). Overall, no patient was found to develop resistance to any study drug.

Discussion

These results provide the first report of the safety and efficacy of TDF in patients with decompensated liver disease due to CHB. This analysis evaluated the comparative safety of two TDF-containing regimens (TDF and FTC/TDF) and ETV through 48 weeks, and assessed the relative efficacy of these regimens in a decompensated CHB population with few viable treatment options. For both coprimary safety endpoints (tolerability failures and confirmed changes in renal parameters), there were no statistically significant differences between the combined TDF and FTC/TDF groups and the ETV group. Most protocol-specified safety events were associated with clinical deterioration considered unrelated to the study drugs. Through 48 weeks, tolerability failures were similarly infrequent in patients treated with TDF or FTC/TDF. Only one patient was discontinued for an AE that represented actual intolerance to the study drug (Grade 2 allergy considered related to FTC/TDF). The percentages of patients with confirmed changes in serum creatinine and/or serum phosphorus were not significantly different among patients who received TDF compared to ETV, suggesting similar renal safety. All confirmed increases in serum creatinine were associated with evident clinical deterioration based on severely compromised hepatic function and sequelae. The observed rate of confirmed 0.5 mg/dL increases in serum creatinine in the ETV group (4.5%) is much lower than the 17% rate reported in a similar patient population.[22]

Although the study was not designed to detect differences in efficacy among the three treatment regimens, standard CHB efficacy assessments (e.g., viral

suppression, normalization of ALT, HBeAg/HBsAg loss, and seroconversion) were generally improved at 48 weeks in the majority of patients in each treatment group, as were measures of severity of liver disease and dysfunction (CTP and MELD scores). As anticipated, each treatment arm produced reductions in serum HBV DNA and normalization of ALT levels consistent with results obtained in CHB patients without decompensation.[7,8,11] Substantial reductions in serum HBV DNA levels were noted in each arm by week 12 and continued through week 48. The rates of HBeAg loss/seroconversion were higher in the TDF and FTC/TDF groups compared to the ETV group, where no patient achieved either of these endpoints. No patient was found to develop resistance to any study drug through 48 weeks; however, two out of three ETV patients with baseline lamivudine resistance switched to open-label FTC/TDF due to insufficient viral suppression at week 24 (all three had HBV DNA <400 copies/mL at week 48).

With respect to clinical outcomes related to efficacy, all three treatment regimens were associated with comparable improvements in CTP and MELD scores at week 48, and none of the six patients undergoing liver transplantation had recurrence of CHB. The ETV group produced results consistent with prior reports.[21,22]

Six deaths, two in each randomized treatment group, were all considered unrelated to study drug and reflective of endstage liver disease (except one case of septic shock due to *V. vulnificus*). All occurred within 6 months of entry, which is consistent with mortality patterns for other studies of ADV,[19] lamivudine,[16] and ETV[21] in decompensated CHB patients.

Since the initiation of the present study, lactic acidosis has been reported in decompensated CHB patients treated with ETV.[30] Of 16 ETV-treated patients, lactic acidosis occurred between 4 and 240 days after start of ETV treatment in five patients (all with MELD scores >20). Four patients experienced resolution of lactic acidosis after interruption or stoppage of ETV treatment, and one died. Liaw et al.[22] reported one AE of lactic acidosis (without supporting lactate levels) in an ETV-treated patient that resolved (based on subsequent lactate measurements) with continued ETV treatment. Shim et al.[21] evaluated ETV in decompensated and noncompensated CHB patients and did not report any cases of lactic acidosis, but as noted in an accompanying editorial,[31] their report did not contain renal, metabolic, or safety laboratory results. In the present study, which measured lactate only if required for toxicity management, no AEs of lactic acidosis were reported.

In summary, both TDF-containing regimens were well tolerated in these decompensated CHB patients, with no significant differences compared to ETV with respect to tolerability failures or confirmed changes in renal parameters. Most AEs and laboratory abnormalities were consistent with decompensated cirrhosis, with few AEs considered related to study drugs. Each group also showed good efficacy responses (virologic, biochemical, clinical), although the study was not designed to assess comparative efficacy. These data demonstrate the safety of these treatments through 48 weeks in patients with decompensated CHB and evident therapeutic benefit in all groups.

Acknowledgment: In addition to the authors, the following investigators participated in the study: Canada: F. Anderson, R. Myers; France: D, Botta-Fridlund; Germany: C. Eisenbach, J. Encke, M. Schuchmann, W. Boecher; Italy: P. Burro, P. Toniutto; Poland: R. Flisiak, W. Halota; Singapore: E. Teo, S-G. Lim, C. Tan, W. Yang; Spain: T. Casanovas, R. Banares, A. Mas; Taiwan: I-S Sheen, Y-C. Chao, S-S. Yang; Turkey: O. Ozdogan, N. Tozun; United States: R. Brown, R. Gish, S-H. Han, D. Dieterich, S. Cohen, N. Shah, D. Moonka, V. Rustgi. The GS-US-174-0108 Study Team also included Gilead Sciences personnel: C. Cosentino, J. Somerville, E. Dixon, J. Quinn, Andrea Snow-Lampart.

References

1. McMahon BJ. Epidemiology and natural history of hepatitis B. Semin Liv Dis 2005;25(S1):3-8.
2. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepatitis 2004;11:97-107.
3. Liaw YF, Chu CM. Hepatitis B virus infection. Lancet 2009;373: 582-592.
4. Liaw YF, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, et al., for the Chronic Hepatitis B Guideline Workshop Party of the Asian-Pacific Association for the Study of the Liver. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. Hepatol Int 2008;2:263-283.
5. Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. HEPATOLOGY 2009;50:1-36.
6. EASL clinical practice guidelines: management of chronic hepatitis B. J Hepatol 2009;50:227-242.
7. Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao Y-C, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006;354:1001-1010.
8. Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006;354:1011-1020.
9. Tenney DJ, Rose RE, Baldick CJ, Pokornowski KA, Eggers BJ, Fang J, et al. Longterm monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. HEPATOLOGY 2009;49:1503-1514.
10. Baraclude® (entecavir) tablets. US Prescribing Information. Princeton, NJ: Bristol-Myers Squibb; November 2009.
11. Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008;359:2442-2455.

12. Manns M, Jeffers L, Dalekos G, Berg T, Trepo C, Roberts S, et al. Safety and efficacy of 96 weeks of tenofovir disoproxil fumarate therapy in lamivudine experienced patients. J Hepatol 2009;50(S1):S335-336.
13. Berg, T, Moller B, Trinh H, Chan S, Marcellin P, Suarez E, et al. Tenofovir disoproxil fumarate (TDF) versus emtricitabine plus TDF (FTC/TDF) for treatment of chronic hepatitis b (CHB) in patients with persistent viral replication receiving adefovir dipivoxil. J Hepatol 2009;50(S1):S328.
14. Snow-Lampart A, Chappell BJ, Curtis M, Zhu Y, Heathcote EJ, Marcellin P, et al. Resistance surveillance for up to 144 weeks in HBeAg+ and HBeAg- patients treated with tenofovir DF showed no relationship between virologic breakthrough and emergence of genotypic changes in HBV polymerase [Abstract]. HEPATOLOGY 2009;50:532A.
15. Yao FY, Bass NM. Lamivudine treatment in patients with severely decompensated cirrhosis due to replicating hepatitis B infection. J Hepatol 2000;33:301-307.
16. Fontana RJ, Hann H-W, Perrillo RP, Vierling JM, Wright T, Rakela J, et al. Determinants of early mortality in patients with decompensated chronic hepatitis B treated with antiviral therapy. Gastroenterology 2002;123:719-727.
17. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521-1531.
18. Schiff ER, Lai CL, Hadziyannis S, Neuhaus P, Terrault N, Columbo M, et al. Adefovir dipivoxil therapy for lamivudine-resistant hepatitis B in pre- and post-liver transplantation patients. HEPATOLOGY 2003;38:1419-1427.
19. Schiff ER, Lai CL, Hadziyannis S, Neuhaus P, Terrault N, Columbo M, et al. Adefovir dipivoxil for wait-listed and post-liver transplantation patients with lamivudine-resistant hepatitis B: final long-term results. Liver Transplant 2007;13:349-360.
20. Hepsera® (adefovir dipivoxil) Tablets. US Prescribing Information. Foster City, CA: Gilead Sciences; October 2009.
21. Shim JH, Lee HC, Kim KM, Lim YS, Chung YH, Lee YS, et al. Efficacy of entecavir in treatment-naive patients with hepatitis B virus-related decompensated cirrhosis. J Hepatol 2010;52:176-182.
22. Liaw YF, Raptopoulou-Gigi M, Cheinquer H, Sarin SK, Tanwandee T, Leung N, et al. Efficacy, safety of entecavir versus adefovir in chronic hepatitis B patients with evidence of hepatic decompensation [Abstract]. HEPATOLOGY 2009;50:505A.
23. Viread® (tenofovir disoproxil fumarate) tablets. US Prescribing Information. Foster City, CA: Gilead Sciences; October 2009.
24. Sherman M, Shafran S, Burak K, Doucette K, Wong W, Girgrah N, et al. Management of chronic hepatitis B: Consensus guidelines. Can J Gastroenterol 2007;21(SupplC):5C-24C.
25. Murray KF, Carithers RL Jr. AASLD practice guidelines: evaluation of the patient for liver transplantation. HEPATOLOGY 2005;41:1407-1432.
26. Truvada® (emtricitabine and tenofovir disoproxil fumarate) Tablets. US Prescribing Information. Foster City, CA: Gilead Sciences; November 2009.
27. Lim SG, Ng TM, Kung N, Krastev Z, Volfova M, Husa P, et al. A double-blind placebo-controlled study of emtricitabine in chronic hepatitis B. Arch Intern Med 2006;166:49-56.
28. Zhu Y, Curtis M, Qi X, Miller MD, Borroto-Esoda K. Anti-hepatitis B virus activity in vitro of combinations of tenofovir with nucleoside/nucleotide analogues. Antivir Chem Chemother 2009;19:165-176.
29. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
30. Lange CM, Bojunga J, Hofmann WP, Wunder K, Mihm U, Zeuzem S, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. HEPATOLOGY 2009;50:2001-2009.
31. Fontana RJ. Entecavir in decompensated HBV cirrhosis: the future is looking brighter. HEPATOLOGY 2010;52:147-149.