ORIGINAL ARTICLE

Tenofovir Disoproxil Fumarate versus Adefovir Dipivoxil for Chronic Hepatitis B

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ABSTRACT

BACKGROUND

Tenofovir disoproxil fumarate (DF) is a nucleotide analogue and a potent inhibitor of human immunodeficiency virus type 1 reverse transcriptase and hepatitis B virus (HBV) polymerase.

METHODS

In two double-blind, phase 3 studies, we randomly assigned patients with hepatitis B e antigen (HBeAg)–negative or HBeAg-positive chronic HBV infection to receive tenofovir DF or adefovir dipivoxil (ratio, 2:1) once daily for 48 weeks. The primary efficacy end point was a plasma HBV DNA level of less than 400 copies per milliliter (69 IU per milliliter) and histologic improvement (i.e., a reduction in the Knodell necroinflammation score of 2 or more points without worsening fibrosis) at week 48. Secondary end points included viral suppression (i.e., an HBV DNA level of <400 copies per milliliter), histologic improvement, serologic response, normalization of alanine aminotransferase levels, and development of resistance mutations.

RESULTS

At week 48, in both studies, a significantly higher proportion of patients receiving tenofovir DF than of those receiving adefovir dipivoxil had reached the primary end point ($P<0.001$). Viral suppression occurred in more HBeAg-negative patients receiving tenofovir DF than patients receiving adefovir dipivoxil (93% vs. 63%, $P<0.001$) and in more HBeAg-positive patients receiving tenofovir DF than patients receiving adefovir dipivoxil (76% vs. 13%, $P<0.001$). Significantly more HBeAg-positive patients treated with tenofovir DF than those treated with adefovir dipivoxil had normalized alanine aminotransferase levels (68% vs. 54%, $P=0.03$) and loss of hepatitis B surface antigen (3% vs. 0%, $P=0.02$). At week 48, amino acid substitutions within HBV DNA polymerase associated with phenotypic resistance to tenofovir DF or other drugs to treat HBV infection had not developed in any of the patients. Tenofovir DF produced a similar HBV DNA response in patients who had previously received lamivudine and in those who had not. The safety profile was similar for the two treatments in both studies.

CONCLUSIONS

Among patients with chronic HBV infection, tenofovir DF at a daily dose of 300 mg had superior antiviral efficacy with a similar safety profile as compared with adefovir dipivoxil at a daily dose of 10 mg through week 48. (ClinicalTrials.gov numbers, NCT00116805 and NCT00117676.)

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The investigators who enrolled participants in this trial are listed in the Appendix.

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Chronic hepatitis B virus (HBV) infection is a major health problem.[1-3] Since most patients with chronic HBV infection require long-term therapy,[4-6] there is a need for new drugs with potent antiviral activity and established long-term safety, as well as a proven low rate of HBV antiviral resistance, a high genetic barrier (i.e., requiring more than one amino acid substitution to confer resistance to HBV treatment), or both.

The ultimate goal of treatment of chronic HBV infection is to prevent liver complications. This goal is seldom achieved through hepatitis B surface antigen (HBsAg) loss and seroconversion, which are associated with sustained immunologic and virologic control of the virus. In hepatitis B e antigen (HBeAg)–positive chronic HBV infection, HBeAg loss and seroconversion are associated with a reduction in HBV DNA levels but they are not curative, and the emergence of precore escape mutations may lead to active HBeAg-negative, chronic hepatitis with attendant long-term complications.[7] Maintenance of viral suppression with oral therapy is often the best that can be achieved. Viral suppression maintained by treatment with lamivudine has been shown to reduce the progression of the disease to decompensation and the development of hepatocellular carcinoma in patients with cirrhosis.[8]

Seven drugs are licensed for the treatment of chronic HBV infection: lamivudine,[9] interferon alfa,[10,11] adefovir dipivoxil,[12] peginterferon alfa-2a,[13] entecavir,[14] telbivudine,[15] and tenofovir disoproxil fumarate (DF). Interferons are not recommended for use in patients with decompensation or immunosuppression; they may have treatment-limiting side effects, and they require parenteral administration. Oral nucleosides, although potent, have been limited by the development of resistance mutations in the HBV polymerase–reverse transcriptase.[16,17]

Tenofovir DF, the oral prodrug of tenofovir, is a nucleotide analogue that inhibits viral polymerases by direct binding, and after incorporation into DNA, by termination of the DNA chain due to the absence of a requisite 3′ hydroxyl on the tenofovir molecule.[18]

Tenofovir DF is currently approved in the United States and more than 50 other countries for the treatment of human immunodeficiency virus type 1 (HIV-1), and it was recently approved for the treatment of chronic HBV infection in the United States, Canada, Europe, Australia, and Turkey.

Tenofovir is a potent and selective inhibitor of HBV DNA polymerase–reverse transcriptase in vitro.[19] It remains active against lamivudine-resistant HBV,[20-23] and it has known activity against HBV both in patients with HBV monoinfection[24-26] and in patients with HIV-1 and HBV coinfection.[27-29] Two phase 3 studies were designed to compare the safety and efficacy of tenofovir DF at a dose of 300 mg with adefovir dipivoxil at a dose of 10 mg, administered once daily, in HBeAg-negative patients (Study 102) or HBeAg-positive patients (Study 103).

METHODS

STUDY DESIGN

With the use of a central, interactive voice-response system (ClinPhone), we randomly assigned patients in a 2:1 ratio to receive tenofovir DF or adefovir dipivoxil. The treatment assignments were stratified according to serum alanine aminotransferase level (<4 times the upper limit of the normal range or ≥4 times the upper limit of the normal range) in Study 103 and according to previous treatment with lamivudine or emtricitabine (<12 weeks or ≥12 weeks) in Study 102. In both studies, treatment assignments were also stratified according to geographic region (Europe, North America, or Australia and New Zealand). Within each stratum, treatment groups were balanced by permuted blocks of size 6. Patients were enrolled at 106 clinical sites in 15 countries across North America (31 sites), Europe (60 sites), and the Asia-Pacific region (15 sites).

Patients were recruited from May 2005 through June 2006 and were treated with medication in a double-blind study for 48 weeks. Patients underwent two liver biopsies: one pretreatment biopsy performed within 6 months before screening and the other biopsy performed between weeks 44 and 48. Patients returned to the clinic every 4 weeks for laboratory assessments of serum chemical and hematologic values, liver function, and HBV DNA levels and for documentation of any adverse events. Hepatitis B serologic markers (HBeAg and HBsAg) were assessed every 12 weeks. Covance Laboratories and affiliates conducted the laboratory tests. Patients who completed 48 weeks of treatment and underwent the second liver biopsy

were given the option to begin treatment with open-label tenofovir DF for up to 7 more years. Blinding of the original treatment assignment was maintained. Patients who discontinued double-blind treatment were followed after treatment for 24 weeks or until the initiation of an alternative hepatitis B therapy.

Resistance surveillance included genotypic analysis of the HBV polymerase in all patients at baseline, in patients with viremia who had an HBV DNA level of 400 copies per milliliter (69 IU per milliliter) or more at week 48 (or at the time that treatment was discontinued, in the case of patients who did not complete 48 weeks of treatment), and in patients with virologic breakthrough (i.e., a confirmed HBV DNA level of ≥400 copies per milliliter after a documented level of less than 400 copies per milliliter or a confirmed $\log_{10}$ increase of 1.0 or more from the nadir level). The population-based dideoxy sequencing assay used has a viral-load requirement of 400 copies per milliliter or more. Resistance surveillance testing was conducted by Gilead Sciences.

During double-blind treatment, an external independent data monitoring committee reviewed the safety results five times. The study was conducted in accordance with international scientific and ethical standards, including but not limited to the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. The study was approved by independent ethics committees or institutional review boards at the study sites. Written informed consent was obtained from all patients before any procedures were performed.

The studies were designed by Gilead Sciences in collaboration with their scientific advisors, and the primary end point was negotiated with the Food and Drug Administration. Clinical data were collected and monitored by ICON Clinical Research (in North America, Western Europe, and the Asia-Pacific region) and Quintiles (in Eastern Europe). Data from case-report forms were entered into the database by ICON Clinical Research (Dublin), and the data were unblinded for statistical analysis after the database was locked. Gilead Sciences performed all statistical analyses and wrote the manuscript in collaboration with the lead academic authors. The academic authors vouch for the veracity and completeness of the reported data and data analyses.

STUDY POPULATION

The studies enrolled patients 18 to 69 years of age who had HBeAg-negative or HBeAg-positive chronic hepatitis B with compensated liver disease and pretreatment liver-biopsy specimens that showed a Knodell necroinflammatory score of 3 or more (on a scale of 0 to 18, with higher scores indicating more severe chronic hepatitis). All patients had been HBsAg-positive for at least 6 months before screening. In Study 102, patients had alanine aminotransferase levels that were more than 1 time and less than 10 times the upper limit of the normal range and HBV DNA levels that were higher than 10^5 copies per milliliter. Patients either had received less than 12 weeks of treatment with any nucleoside or nucleotide or had received lamivudine or emtricitabine for at least 12 weeks (the lamivudine-treatment subgroup). In Study 103, patients had alanine aminotransferase levels that were more than 2 times and less than 10 times the upper limit of the normal range and HBV DNA levels of more than 10^6 copies per milliliter; these patients had received less than 12 weeks of treatment with any nucleoside or nucleotide. Key exclusion criteria were coinfection with HIV-1 or hepatitis C or D virus, evidence of hepatocellular carcinoma, a creatinine clearance of less than 70 ml per minute, a hemoglobin level of less than 8 g per deciliter, a neutrophil count of less than 1000 per cubic millimeter, and liver decompensation or failure.

END POINTS

The primary efficacy end point at week 48 was defined as the combination of an HBV DNA level of less than 400 copies per milliliter and histologic improvement (i.e., a reduction of 2 or more points in the Knodell necroinflammatory score without an increase in fibrosis). HBV DNA was measured with the use of the Roche Cobas TaqMan polymerase-chain-reaction assay, which has a lower limit of quantitation of 169 copies per milliliter (29 IU per milliliter). Since the viral-load requirement for the population-based dideoxy sequencing assay used for resistance surveillance was 400 copies per milliliter, this was the threshold level for the primary end point. Paired liver-biopsy slides (i.e., a specimen from the first biopsy, performed before treatment, and a specimen from the second biopsy, performed during treatment) were evaluated by one independent

central pathologist, who remained unaware of both the assigned treatment and the biopsy sequence; biopsy slides were scored according to the Knodell schema.[30]

Secondary end points included HBV DNA and alanine aminotransferase levels over time and the proportion of patients with HBV DNA levels of less than 400 copies per milliliter, normalized alanine aminotransferase levels, histologic improvement, HBeAg and HBsAg loss and seroconversion, and resistance mutations in HBV polymerase.

SAFETY ANALYSIS

The safety analyses included all patients who received at least one dose of a study drug and all events that occurred during double-blind treatment. Adverse events, serious adverse events, laboratory abnormalities, discontinuation of the study drug due to adverse events, and deaths were evaluated. In this protocol, alanine aminotransferase flares, were considered to be serious adverse events. Flares were defined as an alanine aminotransferase level that was more than twice the baseline level and more than 10 times the upper limit of the normal range, with or without associated symptoms, or a confirmed elevation in the alanine aminotransferase level with confirmed changes outside the normal range in other laboratory values that were suggestive of worsening hepatic function (i.e., a total bilirubin level ≥2 mg per deciliter [34 μmol per liter] above the baseline value, a prothrombin time ≥2 seconds higher than the baseline value or an international normalized ratio ≥0.5 over baseline, or a serum albumin level ≥1 g per deciliter below the baseline value).

RESISTANCE SURVEILLANCE AND BASELINE GENOTYPING

Phylogenetic mapping of individual HBsAg nucleotide sequences was used to determine the viral genotype (A through H) at baseline. At week 48, changes in the HBV polymerase–reverse-transcriptase region from baseline were identified in patients with either persistent viremia or virologic breakthrough. Changes in the amino acid sequence of the HBV polymerase–reverse-transcriptase domain were further evaluated to determine whether these substitutions occurred at polymorphic or conserved sites. All conserved site substitutions were phenotypically assessed with in vitro cell-culture assays to measure susceptibility to tenofovir. Polymorphic changes were also phenotyped if they occurred in more than one patient.

STATISTICAL ANALYSIS

The primary end point was a composite of HBV DNA suppression and histologic improvement. The population for analysis included all patients who were randomly assigned to treatment and who received at least one dose of study medication; no patient was excluded from the analysis because of a protocol deviation. In Study 102, we calculated that the planned sample size of 300 patients (200 in the tenofovir DF group and 100 in the adefovir dipivoxil group) would provide at least 85% power to detect an absolute difference of 19% in the proportion of patients with a complete response at week 48, on the basis of a two-sided significance level of 0.05 and assuming a complete response rate of 28% in the adefovir dipivoxil group. In Study 103, we calculated that the planned sample size of 240 patients (160 in the tenofovir DF group and 80 in the adefovir dipivoxil group) would provide at least 85% power to detect an absolute difference of 13% in the proportion of patients with a complete response at week 48, on the basis of a two-sided significance level of 0.05 and assuming an 18% response rate in the adefovir dipivoxil group.

The difference between treatment groups was evaluated with the use of a two-sided 95% confidence interval stratified according to the baseline level of alanine aminotransferase (in Study 102, a value that was less than or equal to twice the upper limit of the normal range vs. a value that was more than twice the upper limit; in Study 103, a value that was less than or equal to four times the upper limit of the normal range vs. a value that was more than four times the upper limit). For the intention-to-treat analysis, patients who did not have paired liver-biopsy specimens that could be evaluated or who did not undergo HBV DNA assessment were considered not to have had treatment responses.

Finally, observed data (on-treatment analysis) for the HBV DNA and alanine aminotransferase levels over time as well as the proportion of patients with an HBV DNA level of less than 400 copies per milliliter were analyzed.

To assess whether the treatment effect was consistent among the different patient subpopu-

lations, we evaluated the primary end point and its components in 10 integrated subgroup analyses based on prespecified definitions and performed with data pooled from Study 102 and Study 103. Subgroups were defined according to age, sex, race or ethnic group, baseline HBV DNA level, baseline alanine aminotransferase level in relation to the upper limit of the normal range, normal baseline alanine aminotransferase level versus abnormal level, Knodell necroinflammatory score at screening, Knodell fibrosis score at screening, baseline genotype, and receipt or nonreceipt of previous treatment with lamivudine or emtricitabine. In addition to the response within each subgroup, the heterogeneity of the response across subgroups was evaluated with the use of a logistic-regression model for each subgroup studied. Independent terms in the model included treatment, subgroup, and interaction between treatment and subgroup. If the interaction was not significant at the 0.01 level (after adjustment for multiple comparisons), then it was concluded that there was homogeneity of response across the categories of the subgroup. In addition, forest plots were constructed to compare treatment effects across the subgroups.

Demographic and baseline characteristics were compared with the use of a two-sided Mantel–Haenszel test for categorical data and a Wilcoxon rank-sum test for continuous data, with a significance level of 0.05. All reported P values are two-sided and have not been adjusted for multiple testing. No interim analyses were performed other than summary tabulations of safety data for review by the independent data monitoring committee.

RESULTS

STUDY POPULATION

In Study 102, among the 846 patients with HBeAg-negative infection who were screened, 382 patients underwent randomization and 375 patients received at least one dose of the assigned study drug (250 patients received tenofovir DF and 125 patients received adefovir dipivoxil). Most patients who did not meet the eligibility criteria had a low alanine aminotransferase level (31%), a low HBV DNA level (40%), or both, or they had exclusionary serologic findings — that is, coinfection, a positive test for HBeAg, or a negative test for antibodies against HBeAg (anti-HBe antibodies) (14%). Six patients receiving tenofovir DF (2%) and four receiving adefovir dipivoxil (3%) withdrew from the study before week 48. Five patients discontinued tenofovir DF because of adverse events, and one patient was lost to follow-up; no patients discontinued tenofovir DF before week 48 because of lack of efficacy.

In Study 103, among the 603 patients with HBeAg-positive infection who were screened, 272 patients underwent randomization and 266 patients received at least one dose of the assigned study drug (176 patients received tenofovir DF and 90 received adefovir dipivoxil). Most patients who did not meet eligibility criteria had a low alanine aminotransferase level (54%), a low HBV DNA level (12%), or both or they had exclusionary serologic findings (20%). Ten patients who received tenofovir DF (6%) and five patients who received adefovir dipivoxil (6%) discontinued treatment before week 48; most withdrew consent or were lost to follow-up. No patients discontinued tenofovir DF because of adverse events or lack of efficacy. Diagrams showing screening, enrollment, and treatment of patients in both studies are included in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

In both studies, the two treatment groups were well balanced with respect to baseline demographic and clinical characteristics (Table 1). Overall, 20% of the patients had cirrhosis at baseline. Patients enrolled in Study 102 were generally older than those in Study 103 (mean age, 44 years vs. 34 years). HBV DNA levels were about 2 $\log_{10}$ copies per milliliter lower in the patients in Study 102, who were HBeAg-negative, than in the patients in Study 103, who were HBeAg-positive; 18% of the HBeAg-negative patients had previously received lamivudine. A total of 347 of 375 patients in Study 102 (93%) and 236 of 266 patients (89%) in Study 103 completed 48 weeks of treatment and had paired biopsy specimens that could be evaluated and HBV DNA results.

HISTOLOGIC AND VIROLOGIC RESPONSE

In both studies, a significantly greater proportion of patients who received tenofovir DF than patients who received adefovir dipivoxil reached the primary end point of both an HBV DNA level of less than 400 copies per milliliter and histologic improvement (71% vs. 49% among HBeAg-negative patients and 67% vs. 12% among HBeAg-

Table 1. Demographic and Baseline Characteristics of the Study Patients.*

Characteristic	HBeAg-Positive Patients		HBeAg-Negative Patients	
	Tenofovir DF (N=176)	Adefovir Dipivoxil (N=90)	Tenofovir DF (N=250)	Adefovir Dipivoxil (N=125)
Mean age — yr	34±11	34±12	44±10.6	43±10.0
Race — no. (%)†				
White	92 (52)	46 (51)	161 (64)	81 (65)
Asian	64 (36)	32 (36)	63 (25)	30 (24)
Black	13 (7)	5 (6)	8 (3)	4 (3)
Other	7 (4)	7 (8)	18 (7)	10 (8)
Male sex — no. (%)	119 (68)	64 (71)	193 (77)	97 (78)
Geographic region — no. (%)				
Europe	97 (55)	49 (54)	158 (63)	76 (61)
North America	47 (27)	24 (27)	53 (21)	29 (23)
Australia or New Zealand	32 (18)	17 (19)	39 (16)	20 (16)
Mean Knodell necroinflammatory score‡	8.3±2.14	8.3±2.27	7.8±2.44	7.9±2.18
Knodell fibrosis score — no./total no. (%)				
0	0/172 (0)	0/87 (0)	0/250 (0)	1/125 (1)
1	77/172 (45)	33/87 (38)	107/250 (43)	51/125 (41)
3	61/172 (35)	37/87 (43)	96/250 (38)	48/125 (38)
4	34/172 (20)	17/87 (20)	47/250 (19)	25/125 (20)
Missing data	4/176 (2)	3/90 (3)	0/250 (0)	0/125 (0)
Mean Knodell fibrosis score	2.3±1.23	2.4±1.19	2.3±1.21	2.4±1.23
Mean HBV DNA — $\log_{10}$ copies/ml	8.64±1.076	8.88±0.930	6.86±1.31	6.98±1.27
Alanine aminotransferase§				
Mean — IU/ml	142±102.81	155±121.49	127.5±101.21	163.6±146.02
<2× ULN — no. (%)	39 (22)	16 (18)	95 (38)	38 (30)
2 to <5× ULN — no. (%)	105 (60)	55 (61)	117 (47)	54 (43)
≥5× ULN — no. (%)	32 (18)	19 (21)	38 (15)	33 (26)
Previous treatment with lamivudine or emtricitabine — no. (%)				
No	168 (95)	89 (99)	207 (83)	102 (82)
Yes	8 (5)	1 (1)	43 (17)	23 (18)
Previous treatment with interferon — no. (%)				
No	146 (83)	77 (86)	208 (83)	102 (82)
Yes	30 (17)	13 (14)	42 (17)	23 (18)
HBV genotype — no./total no. (%)				
A	41/173 (24)	18/88 (20)	28/243 (12)	14/125 (11)
B	25/173 (14)	10/88 (11)	22/243 (9)	17/125 (14)
C	43/173 (25)	26/88 (30)	29/243 (12)	12/125 (10)
D	55/173 (32)	31/88 (35)	156/243 (64)	79/125 (63)
E, F, G, H	9/173 (5)	3/88 (3)	8/243 (3)	3/125 (2)
Other or unknown	3/176 (2)	2/90 (2)	7/250 (3)	0

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding. Only the mean alanine aminotransferase level at baseline in the HBeAg-positive patients differed significantly between the treatment groups (i.e., $P<0.05$). HBeAg denotes hepatitis B e antigen, and HBV hepatitis B virus.

† Race was self-reported.

‡ The Knodell necroinflammatory score ranges from 0 to 18, with higher scores indicating more severe chronic hepatitis. The Knodell fibrosis score ranges from 0 to 4, with a score of 4 indicating cirrhosis.

§ The upper limit of the normal range (ULN) for alanine aminotransferase was 34 IU per milliliter for women and 43 IU per milliliter for men.

positive patients (Table 2). Histologic improvement was similar between treatment groups; most patients had reduced necroinflammation, and few patients had worsening fibrosis.

Among the HBeAg-negative patients, 93% of all the patients who received tenofovir DF had a plasma HBV DNA level of less than 400 copies per milliliter by week 48 (intention-to-treat analysis), and 97% of whose who were receiving tenofovir DF at week 48 had an HBV DNA level of less than 400 copies per milliliter (observed data) (Table 2). At week 24, a total of 85% of the patients who received tenofovir DF had HBV DNA suppression below this level (Fig. 1A). The change in the level of HBV DNA was characterized by a precipitous decrease by week 4. At week 12, the mean HBV DNA level was 3 $\log_{10}$ copies per milliliter as compared with a baseline HBV DNA level of approximately 7 $\log_{10}$ copies per milliliter (Fig. 2A). Patients with lower baseline HBV DNA levels had undetectable levels of HBV DNA sooner than did patients with higher baseline levels (Fig. 3A and 3B).

Among HBeAg-positive patients, 76% of patients who received tenofovir DF had an HBV DNA level of less than 400 copies per milliliter at week 48, and 49% of patients who received tenofovir DF had an HBV DNA level of less than 400 copies per milliliter at week 24. With the use of observed data, 83% of the patients receiving tenofovir DF treatment at week 48 had an HBV DNA level of less than 400 copies per milliliter (Fig. 1B and Table 2). HBV DNA suppression was characterized by a rapid 4.5-log reduction in the HBV DNA level by week 12, with complete viral suppression in increasing numbers of patients over time (Fig. 2B).

An evaluation of the treatment response in subgroups defined by baseline characteristics showed no significant interactions at the 0.01 alpha level. Among patients treated with tenofovir DF, 90% of patients who had received lamivudine versus 88% of those who had not received lamivudine had HBV DNA suppression to less than 400 copies per milliliter (see the forest plots in the Supplementary Appendix).

BIOCHEMICAL AND SEROLOGIC RESPONSE

At baseline, 94% of patients in Study 102 and 97% of patients in Study 103 had elevated alanine aminotransferase levels (>34 IU per milliliter in women and >43 IU per milliliter in men). In Study 102 (HBeAg-negative patients), similar proportions of patients in the two treatment groups had normalized alanine aminotransferase levels at week 48, whereas in Study 103 (HBeAg-positive patients), a significantly greater proportion of patients in the tenofovir DF group had normalized alanine aminotransferase levels (68% vs. 54%, $P=0.03$). Overall, at week 48, patients who received tenofovir DF had a mean alanine aminotransferase level of approximately 35 IU per milliliter (Table 2). In Study 103, similar proportions of patients in the tenofovir DF group and the adefovir dipivoxil group had HBeAg seroconversion (21% and 18%, respectively, $P=0.36$), and significantly more patients in the tenofovir DF group had HBsAg loss (3% vs. 0%, $P=0.02$) (Table 2). Two patients with HBsAg loss also had seroconversion to antibodies against hepatitis B surface antigen (anti-HBs antibodies). All five patients who lost HBsAg were white (three men and two women), and they ranged in age from 24 to 44 years; two patients were infected with HBV genotype A, and three patients infected with HBV genotype D. Four of the five patients had bridging fibrosis or cirrhosis at study entry. None of the patients who were HBeAg-seronegative at baseline (i.e., all the patients in Study 102) had HBsAg loss or seroconversion.

RESISTANCE SURVEILLANCE

No genotypic substitutions in polymerase–reverse transcriptase associated with decreased sensitivity to tenofovir were detected among patients who received tenofovir DF and were evaluated at week 48 in either Study 102 or 103. Among the 426 patients receiving tenofovir DF, 39 patients (8 patients in Study 102 and 31 patients in Study 103) had viremia (an HBV DNA level ≥400 copies per milliliter); 10 had virologic breakthrough and 29 did not. Fifteen patients had polymorphic site changes, 2 had conserved site changes, 11 had no change, and 10 could not be genotyped. One additional patient, who discontinued treatment early, had virus with polymorphic site changes. The two conserved site changes occurred without virologic breakthrough; phenotypic evaluation showed either full susceptibility to tenofovir DF or a nonviable, nonreplicative virus in cell culture. Of the 10 patients with virologic breakthrough, 7 had no changes, and 3 had polymorphic changes but not the same changes. Successful phenotyping in 6 of these 10 patients showed full phenotypic suscep-

Table 2. Efficacy Results at 48 Weeks.*

Variable	HBeAg-Positive Patients				HBeAg-Negative Patients			
	Tenofovir DF (N=176)	Adefovir Dipivoxil (N=90)	P Value	Stratum-Adjusted Relative Difference % (95% CI)†	Tenofovir DF (N=250)	Adefovir Dipivoxil (N=125)	P Value	Stratum-Adjusted Relative Difference % (95% CI)†
Primary end point								
HBV DNA <400 copies/ml and histologic improvement — no./total no. (%)‡¶								
Yes	117/176 (66)	11/90 (12)	<0.001	54.1 (44.6 to 63.6)	177/250 (71)	61/125 (49)	<0.001	23.5 (13.2 to 33.8)
No	39/176 (22)	68/90 (76)			57/250 (23)	52/125 (42)		
Missing data	20/176 (11)	11/90 (12)			16/250 (6)	12/125 (10)		
Secondary end points								
Histologic response — no./total no. (%)§¶	131/176 (74)	61/90 (68)	0.32	5.8 (–5.6 to 17.2)	181/250 (72)	86/125 (69)	0.29	5.2 (–4.5 to 14.9)
Reduced necroinflammation	137/176 (78)	64/90 (71)	0.27	6.2 (–4.8 to 17.3)	194/250 (78)	93/125 (74)	0.27	5.1 (–3.9 to 14.1)
Worsened fibrosis	3/176 (2)	3/90 (3)	0.36	–1.9 (–5.9 to 2.1)	16/250 (6)	11/125 (9)	0.96	–0.2 (–5.4 to 5.1)
Mean Knodell necroinflammatory score at week 48	4.7±2.02	5.2±1.96	0.06	–0.50 (–1.03 to 0.02)	4.4±1.82	4.4±1.81	0.78	–0.06 (–0.47 to 0.35)
HBV DNA — no. (%)								
<400 copies/ml, intention-to-treat analysis¶	134/176 (76)	12/90 (13)	<0.001	63.1 (53.8 to 72.3)	233/250 (93)	79/125 (63)	<0.001	30.3 (21.3 to 39.2)
<400 copies/ml, observed data	133/160 (83)	12/84 (14)	<0.001	68.8 (59.4 to 78.3)	233/241 (97)	79/117 (68)	<0.001	29.2 (20.4 to 37.9)
Alanine aminotransferase level								
Normalized level — no. (%)‖	115/169 (68)	49/90 (54)	0.03	13.6 (1.1 to 26.1)	180/236 (76)	91/118 (77)	0.86	–0.8 (–10.2 to 8.5)
Mean level — IU/ml	36.4±23.34	45.7±34.69	0.028	–9.31 (–17.61 to –1.02)	33.7±15.22	34.6±22.66	0.69	–0.93 (–5.48 to 3.63)
Serologic findings — no. (%)								
HBeAg seroconversion	32/153 (21)	14/80 (18)	0.36	4.7 (–5.5 to 14.9)	—	—		
HBsAg loss	5/158 (3.2)	0/82 (0)	0.02	10.9 (1.9 to 19.9)	0/250 (0)	0/125 (0)		

* Plus–minus values are means ±SD. CI denotes confidence interval, HBeAg hepatitis B e antigen, and HBV hepatitis B virus.
† The difference and confidence intervals are adjusted for baseline ALT stratum (i.e., baseline ALT ≤4× upper limit of the normal range (ULN), >4× ULN in HBeAg-positive patients and baseline ALT ≤2× ULN, >2× ULN in HBeAg-negative patients).
‡ A complete response was a composite end point defined as a histologic response and an HBV DNA level below 400 copies per milliliter.
§ Histologic improvement is defined as at least a two-point reduction in the Knodell necroinflammatory score and no worsening in the Knodell fibrosis score. The Knodell necroinflammatory score can range from 0 to 18, with higher scores indicating more severe chronic hepatitis. The Knodell fibrosis score can range from 0 to 4, with higher scores indicating more fibrosis.
¶ For this intention-to-treat analysis, missing data were considered equal to treatment failure. For observed data, only values that were not missing were analyzed.
‖ The population for analysis of ALT normalization included only patients with ALT values above the ULN at baseline (the ULN for ALT was 34 IU per milliliter for women and 43 IU per milliliter for men).

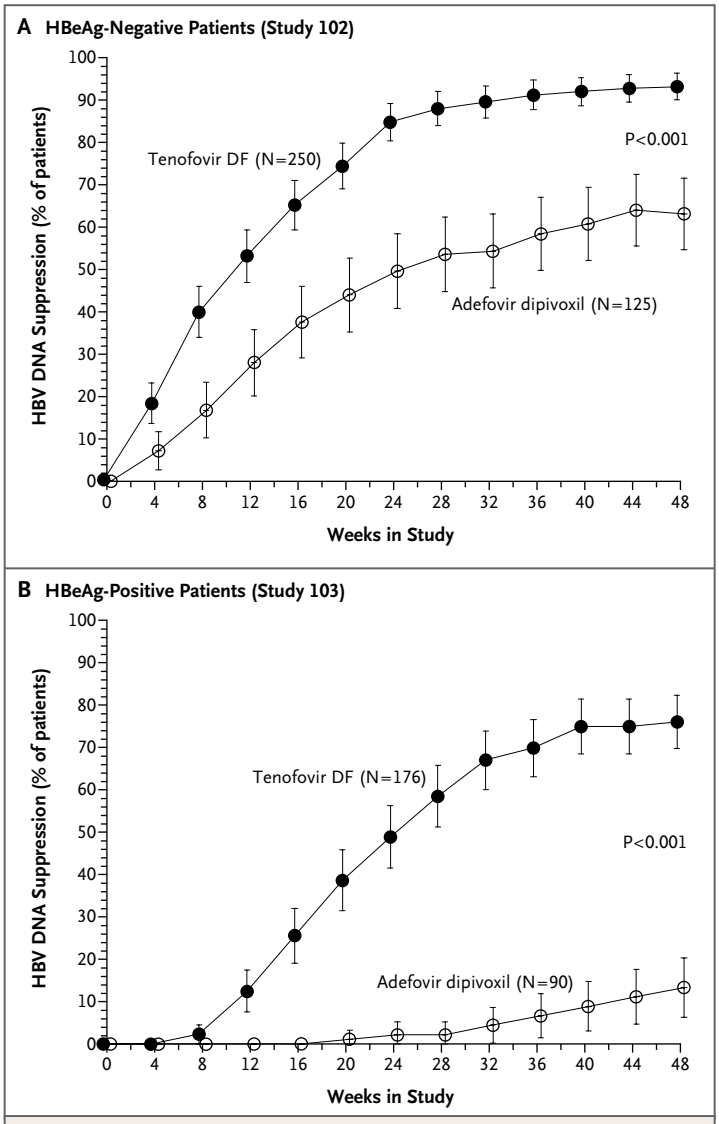

Figure 1. Suppression of HBV DNA Levels during the 48-Week Study Period.
Viral suppression was defined as an HBV DNA level of less than 400 copies per milliliter. Panel A shows the proportion of HBeAg-negative patients with viral suppression (Study 102), and Panel B shows the proportion of HBeAg-positive patients with viral suppression (Study 103). The difference, standard error of the difference, and confidence intervals were stratum-adjusted. P values correspond to a z-test of the null hypothesis that the stratum-adjusted difference is zero. I bars denote 95% confidence intervals.

tibility to tenofovir in vitro. Phenotypic analysis for the remaining four patients could not to be performed because of a low viral load that did not allow for amplification and cloning of the full-length HBV genome. A documented history of nonadherence to treatment, serum tenofovir DF levels below the level of quantitation (10 ng per milliliter), or both — findings that suggested nonadherence — may have contributed to virologic breakthrough in at least two thirds of these patients.

Among the 215 patients who were randomly assigned to receive adefovir dipivoxil, the rtN236T mutation developed in 1 patient, and the rtA181T mutation developed in 3 patients. Clonal analysis of the patients' baseline HBV revealed the presence of quasi-species with the rtA181T mutation (0.2 to 11.3%) and the rtM204I mutation (1.2 to 16.1%), indicating previous exposure to lamivudine or infection with a lamivudine-resistant virus. These results are consistent with previous studies that showed a higher rate of adefovir-dipivoxil resistance in patients with lamivudine-resistant virus.[31,32]

SAFETY

The safety profiles observed in both studies were consistent with the known safety profiles for tenofovir DF in patients with HIV infection and for the safety profiles for adefovir dipivoxil in patients with HBV infection.[33,34] Nausea was the only adverse event that consistently occurred more frequently in the group of patients who received tenofovir DF than in the group of patients who received adefovir dipivoxil. Among the cases of nausea that were considered to be related to tenofovir DF, nausea was mild except for one case of grade 2 (moderate) nausea (Table 3).

In both studies, similar proportions of patients in the two treatment groups had a serious adverse event, and few events were considered to be related to the study drug (Table 3). Overall, the only serious clinical adverse event reported in more than one patient was hepatocellular carcinoma (in three patients in Study 102), which is a known complication of chronic HBV infection. No deaths were reported during either study. The following five adverse events led to discontinuation of tenofovir DF in Study 102 and occurred in one patient each: anorexia, bladder neoplasm, fatigue, cervical carcinoma, and feeling hot. No patient in Study 103 discontinued tenofovir DF because of an adverse event.

The frequency of alanine aminotransferase flares during treatment was similar in the two groups (Table 3). Nearly all alanine aminotransferase flares occurred within the first 8 weeks after the start of treatment with tenofovir DF, were limited to increases in aminotransferase levels that were greater than 10 times the upper

limit of the normal range and twice the baseline level, with continued and profound decreases in the HBV DNA level, and resolved within 4 to 8 weeks without interruption or discontinuation of treatment. Grade 4 alanine aminotransferase flares were associated with HBeAg loss or seroconversion in 63% of patients, one of whom eventually had seroconversion to anti-HBs antibodies.

There was no evidence of compromised renal function or renal tubular dysfunction in any patient who received tenofovir DF (Table 3). None of the patients who received tenofovir DF had a confirmed increase from baseline in the serum creatinine level of 0.5 mg per deciliter (44.2 μmol per liter) or more or a confirmed calculated creatinine clearance of less than 50 milliliters per minute (Table 3). In Study 103, there was a confirmed increase in the serum creatinine level of 0.5 mg per deciliter above baseline in one patient who received adefovir dipivoxil.

DISCUSSION

In patients with compensated chronic HBV infection, tenofovir DF was superior to adefovir dipivoxil with respect to the primary end point of antiviral efficacy. Viral suppression occurred in approximately 80% of HBeAg-positive patients and 95% of HBeAg-negative patients who received tenofovir DF, and almost three fourths of the patients had histologic improvement. In both studies, histologic improvement was similar in the two treatment groups at 48 weeks. Multiple reports have shown that maintenance of viral suppression is a key determinant of therapeutic outcomes for patients with chronic HBV infection[8,35-37]; these reports include a review of 26 prospective clinical trials showing that a sustained HBV DNA response was correlated with serologic, histologic, or biochemical responses.[38]

HBsAg loss or seroconversion heralds durable immune control of the virus. In the phase 3 study involving HBeAg-positive patients, the proportion of patients with loss of HBsAg during the 48-week treatment period was significantly higher in the tenofovir DF group than in the adefovir dipivoxil group. In the absence of HBsAg loss, long-term treatment with oral therapies is often required to maintain viral suppression. Consequently, well-tolerated, potent therapies that offer a strong genetic barrier against the development of resistance are desirable, since antiviral resistance and poor adherence are key risk factors for treatment failure and subsequent reversal of clinical improvement.[39-43] The high proportion of patients who received tenofovir DF and had viral suppression portends a potential long-term advantage in preventing the emergence of resistance and attendant loss of response. No genotypic

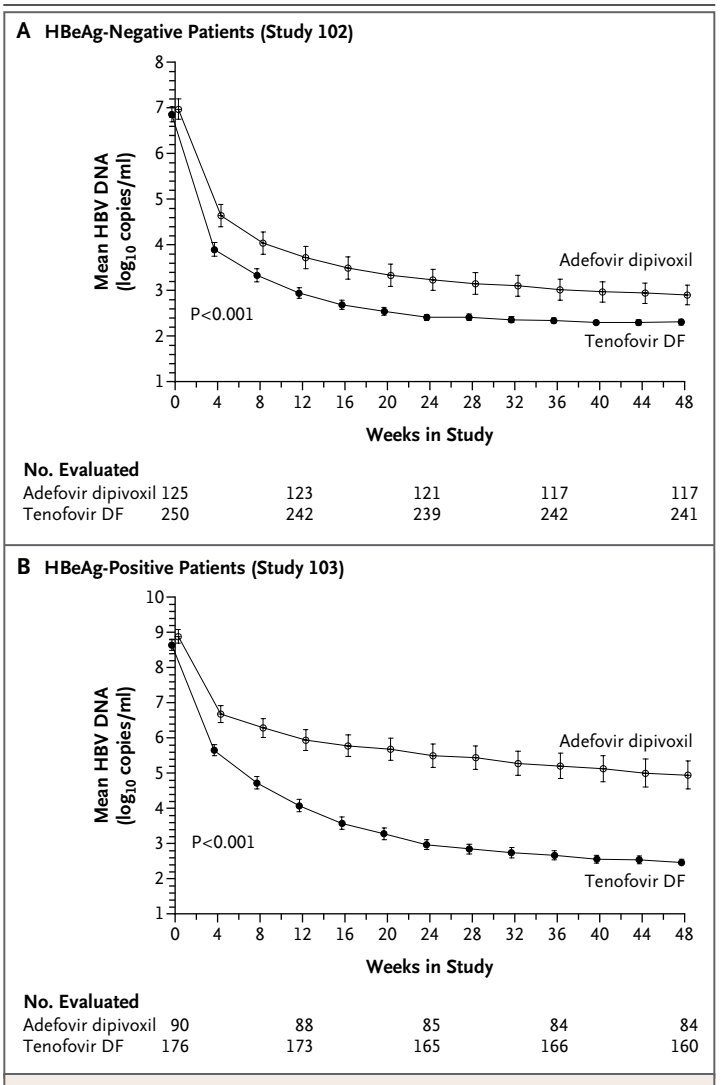

Figure 2. Mean Plasma HBV DNA Levels.

The mean HBV DNA levels ($\log_{10}$ copies per milliliter) were plotted over time. Panel A shows that the mean HBV DNA level at week 48 was 2.31 (0.466) for tenofovir DF and 2.91 (1.201) for adefovir dipivoxil in HBeAg-negative patients (Study 102). Panel B shows that the mean HBV DNA at week 48 was 2.46 (0.575) for tenofovir DF and 4.95 (1.851) for adefovir dipivoxil in HBeAg-positive patients (Study 103). The difference, standard error of the difference, and confidence intervals are stratum-adjusted. P values correspond to a z-test of the null hypothesis that the stratum-adjusted difference is zero. I bars indicate 95% confidence intervals.

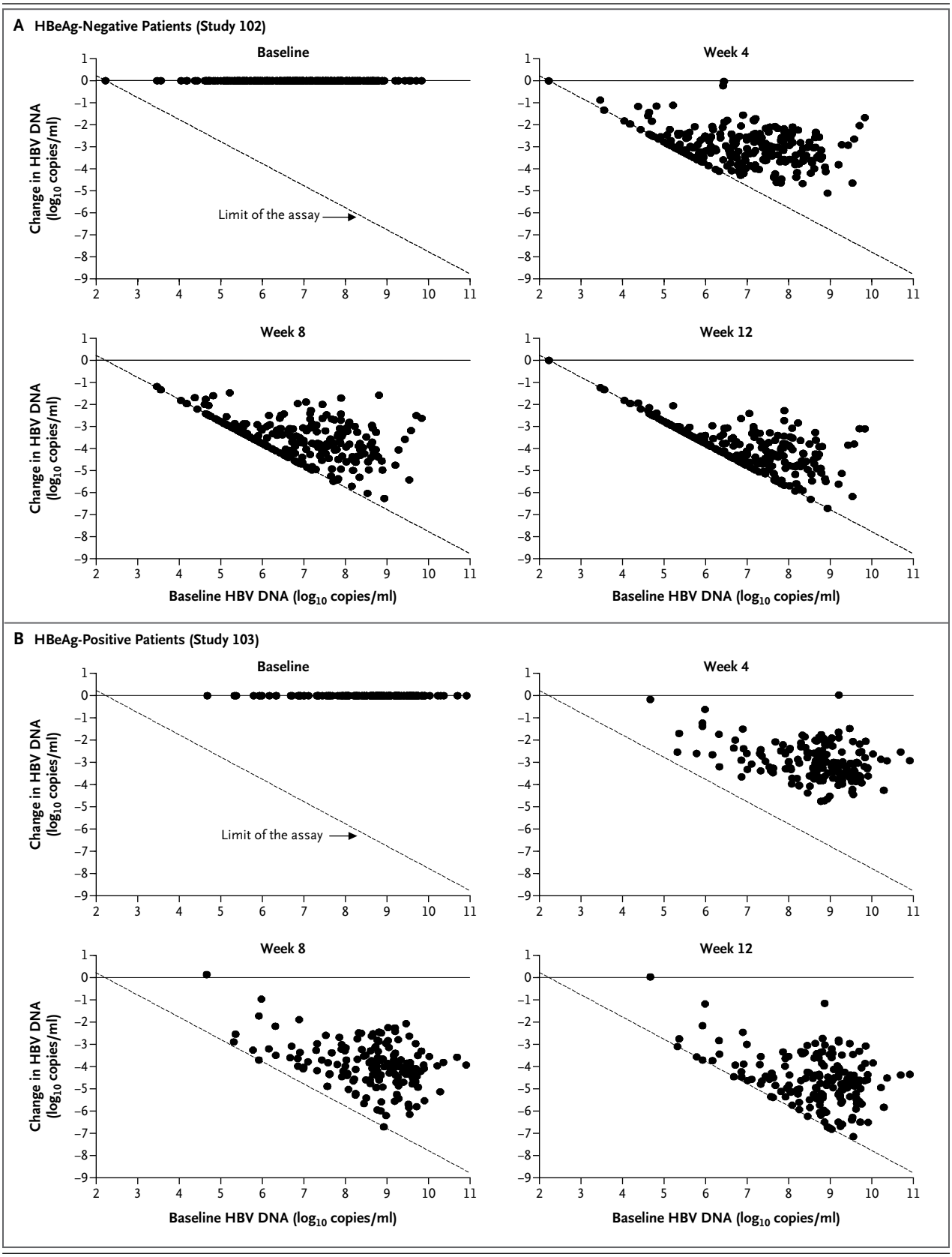

Figure 3 (facing page). Reduction in HBV DNA from Baseline through Week 12 in Patients Receiving Tenofovir DF.

The plots show the kinetics of HBV DNA viral suppression in HBeAg-negative patients (Study 102) (Panel A) and HBeAg-positive patients (Study 103) (Panel B) receiving tenofovir DF. Each dot represents an individual patient. The diagonal line represents the lower limit of quantification of the Roche Cobas TaqMan assay (169 copies per milliliter [29 IU per milliliter]).

substitutions in polymerase–reverse transcriptase associated with either decreased sensitivity to tenofovir or known resistance to other anti-HBV therapies were detected in either the HBeAg-negative patients or the HBeAg-positive patients after 48 weeks of treatment, but resistance patterns with long-term treatment are not known. In an effort to define the resistance profile for tenofovir DF, resistance surveillance will continue for at least 7 more years.

Table 3. Clinical Adverse Events and Laboratory Abnormalities.

Variable	Tenofovir DF (N=426)	Adefovir Dipivoxil (N=215)
	no. (%)	
Adverse events*		
Any adverse event	317 (74)	158 (73)
Headache	55 (13)	30 (14)
Nasopharyngitis	42 (10)	24 (11)
Nausea	40 (9)	6 (3)
Fatigue	36 (8)	16 (7)
Upper abdominal pain	30 (7)	11 (5)
Back pain	30 (7)	10 (5)
Diarrhea	28 (7)	11 (5)
Dizziness	24 (6)	7 (3)
Procedural pain	16 (4)	12 (6)
Pharyngolaryngeal pain	15 (4)	11 (5)
Upper respiratory tract infection	13 (3)	11 (5)
Grade 2–4 adverse events	128 (30)	68 (32)
Serious adverse events	27 (6)	14 (7)
Serious adverse events considered to be related to study drug†	7 (2)	5 (2)
ALT flare‡	6 (1)	4 (2)
Thrombocytopenia	1 (<1)	0 (0)
Toxic myopathy	0 (0)	1 (<1)
Adverse event leading to discontinuation of study drug	5 (1)	3 (1)
Laboratory abnormalities		
Grade 3 ALT (>5–10× ULN) and 2×baseline value§	13 (3)	2 (1)
Grade 4 ALT (>10× ULN) and 2×baseline value§	11 (3)	4 (2)
Confirmed serum creatinine increase of ≥0.5 mg/dl above baseline value	0	1 (<1)
Confirmed creatinine clearance <50 ml/min	0	0

* Individual adverse events occurring in more than 5% of patients are listed separately. ALT denotes alanine aminotransferase, and ULN upper limit of the normal range.
† Serious adverse events that were considered while investigators were unaware of treatment assignments to be related to a study drug and occurring in any patient are listed separately.
‡ An ALT flare included increased ALT, aspartate aminotransferase, or both, and hepatitis B infection.
§ The severity of this laboratory abnormality was graded according to criteria adapted from the Division of AIDS, National Institute of Allergy and Infectious Diseases.

No safety signals were observed for tenofovir DF in patients with chronic HBV infection. Although renal events have been observed with the use of tenofovir DF in patients with HIV infection, predominantly in patients with preexisting renal disease, no renal toxic effects were observed during 48 weeks of treatment with tenofovir DF in patients with chronic HBV infection who had preserved renal function at baseline. In these studies of tenofovir DF for chronic HBV infection, there were insufficient data to characterize exacerbation after treatment. However, there is a known risk after discontinuation of any oral anti-HBV treatment, and monitoring of liver-function tests for several months is required. Alanine aminotransferase flares during treatment with tenofovir DF were infrequent, transient, and associated with continuous and profound decreases in the HBV DNA level. Seroconversion to anti-HBe antibodies in a majority of these patients suggested enhanced immunologic activity against HBV that coincided with a treatment-induced reduction in the viral load. Treatment with nucleoside analogues also can result in lactic acidosis and hepatomegaly with steatosis, but no patients in these studies had these adverse events.

In these 48-week phase 3 studies, tenofovir DF was shown to be a potent therapy for the treatment of HBeAg-negative and HBeAg-positive chronic HBV infection. Tenofovir DF was just as effective in suppressing HBV DNA levels in patients who had not received treatment as in patients who had previously received lamivudine. In light of its favorable long-term safety record in patients with HIV-1 infection, tenofovir DF should be considered for the treatment of chronic HBV infection.

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APPENDIX

In addition to the authors, the following investigators participated in the two studies: **Australia** — W. Cheng, D. Crawford, P. Desmond, J. George, P. Gow, I. Kronborg, M. Ngu, S. Roberts, J. Sasadeusz, W. Sievert, S. Strasser; **Bulgaria** — R. Balabanska; **Canada** — F. Anderson, R. Myers, M. Sherman; **Czech Republic** — P. Husa, J. Sperl, P. Urbanek, M. Volfova; **France** — K. Barange, Y. Benhamou, J. Bronowicki, C. Hezode, F. Habersetzer, P. Mathurin, C. Trepo, J. Zarski; **Germany** — T. Berg, W. Boecher, P. Gerken, T. Heintges, H. Hinrichsen, D. Huppe, S. Kaiser, S. Mauss, B. Moller, G. Teuber, R. Zachoval, S. Zeuzem; **Greece** — G. Dalekos, S. Hadziyannis, G. Kitis; **Italy** — P. Andreone, M. Rizzetto; **New Zealand** — C. Moyes, N. Stace; **Poland** — M. Beniowski, A. Gladysz, W. Halota, A. Horban, W. Kryczka, T. Mach; **Spain** — J. Calleja, T. Casanovas, J. Enriquez, M. Prieto; **Turkey** — U. Akarka, S. Gurel, S. Ozenirler, H. Senturk, N. Tozun; **United Kingdom** — G. Dusheiko, D. Mutimer, R. Williams; **United States** — N. Afdahl, M. Bennett, N. Bzowej, S. Chan, A. DiBisceglie, P. Gaglio, N. Gitlin, S. Gordon, K. Hu, I. Jacobson, L. Jeffers, A. Lok, P. Martin, T. Min, T. Nguyen, P. Pockros, N. Ravendhran, R. Rubin, V. Rustgi, M. Tong, H. Tsai, C. Wang, Z. Younossi.

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