

# Treatment of Hepatitis B e Antigen–Positive Chronic Hepatitis with Telbivudine or Adefovir

## A Randomized Trial

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**Background:** The efficacy of nucleoside and nucleotide analogues for hepatitis B has been linked to the magnitude and durability of hepatitis B virus (HBV) suppression.

**Objective:** To compare the antiviral efficacy of telbivudine and adefovir dipivoxil, and the effects of switching from adefovir to telbivudine, in hepatitis B e antigen (HBeAg)–positive patients with chronic hepatitis B.

**Design:** Randomized, controlled, open-label trial.

**Setting:** 16 outpatient clinics.

**Patients:** 135 treatment-naive, HBeAg-positive adults with chronic hepatitis B.

**Intervention:** Patients were randomly assigned in a 1:1:1 ratio to 52 weeks of telbivudine (group A) or adefovir (group B), or 24 weeks of adefovir and then telbivudine for the remaining 28 weeks (group C). One hundred thirty-one patients completed 52 weeks of treatment.

**Measurements:** The primary efficacy comparison was serum HBV DNA reduction at week 24, with a secondary comparison at week 52.

**Results:** At week 24, mean HBV DNA reduction was greater in group A than in pooled groups B and C (–6.30 vs. –4.97 log<sub>10</sub> copies/mL; difference, –1.33 log<sub>10</sub> copies/mL [95% CI, –1.99 to

–0.66 log<sub>10</sub> copies/mL];  $P < 0.001$ ), and more patients in group A were polymerase chain reaction–negative (39% vs. 12%; odds ratio, 4.46 [CI, 1.86 to 10.72];  $P = 0.001$ ). At week 52, the mean residual HBV DNA level was lower in group A and group C than in group B (3.01 log<sub>10</sub> copies/mL [group A] and 3.02 log<sub>10</sub> copies/mL [group C] vs. 4.00 log<sub>10</sub> copies/mL [group B]; difference, –0.99 log<sub>10</sub> copies/mL [CI, –1.67 to –0.32 log<sub>10</sub> copies/mL] and –0.98 log<sub>10</sub> copies/mL [CI, –1.64 to –0.32 log<sub>10</sub> copies/mL];  $P = 0.004$ ). Adverse events were similar across groups; the most common were upper respiratory symptoms, headache, back pain, and diarrhea.

**Limitations:** The trial was open-label and was not of sufficient size or duration to compare clinical outcomes and long-term efficacy.

**Conclusion:** Telbivudine demonstrated greater and more consistent HBV DNA suppression than adefovir after 24 weeks of treatment. After 52 weeks, HBV DNA suppression was greater in patients who had received continuous telbivudine or were switched to telbivudine after 24 weeks than in those who received continuous adefovir.

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In chronic hepatitis B virus (HBV) carriers, elevated serum HBV DNA levels have been associated with increased risk for end-stage complications, such as cirrhosis and hepatocellular carcinoma (1–4). Corresponding evidence supports the concept that antiviral therapy can ameliorate liver injury and reduce or delay the progression of cirrhosis and the incidence of hepatocellular carcinoma (5–9). Effectively maintained viral suppression has been correlated with these effects (5, 10). Recent studies further suggest that, with direct-acting anti-HBV nucleosides and nucleotides, therapeutic efficacy and the emergence of resistance are related to the degree of viral suppression achieved early in the course of treatment (11–18). Specifically, achieving low serum HBV DNA levels in the first 6 to 12 months—preferably levels undetectable by polymerase chain reaction (PCR) assay—has been associated with greater subsequent efficacy and less resistance, with observations now extending to treatment periods beyond 2 years. Maximizing early viral suppression is therefore emerging as an important therapeutic goal for patients with hepatitis B.

Telbivudine and adefovir are approved for use in the United States and elsewhere (8, 19–22). Telbivudine, a thymidine nucleoside analogue, had greater antiviral efficacy than lamivudine in phase IIb and III trials (22, 23). Adefovir, an adenosine nucleotide analogue, had greater efficacy than placebo in phase III trials (8, 21). Telbivudine and adefovir have not been compared directly, although HBV DNA reductions after 1 year of telbivudine in phase

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**Context**

Optimal regimens for suppressing virus in chronic hepatitis B infection are unclear.

**Contribution**

In this 52-week open label trial, 135 adults with hepatitis B e antigen–positive chronic hepatitis B were randomly assigned to telbivudine, adefovir, or adefovir for 24 weeks followed by telbivudine for 28 weeks. The telbivudine and the adefovir-to-telbivudine groups experienced similar reductions in viral levels that were greater than those in the adefovir group.

**Caution**

The small trial did not establish long-term drug resistance or effects on clinical outcomes.

**Implication**

Telbivudine and switching from adefovir to telbivudine suppressed viral levels more than adefovir in adults with chronic hepatitis B.

—The Editors

III trials seemed greater than those reported with adefovir in similar patient populations (8, 21, 22).

We compared the degree of telbivudine- and adefovir-induced viral suppression after 24 and 52 weeks of treatment to assess the relative antiviral efficacy and safety of these agents. Because trial data (8, 22) suggest that the clinical antiviral effects of telbivudine may be greater than those of adefovir, we also assessed antiviral efficacy and safety in patients switched to telbivudine after receiving adefovir treatment for 24 weeks. Finally, we evaluated potential relationships between the degree of viral suppression achieved after 6 months of therapy and subsequent efficacy outcomes at 1 year.

**METHODS****Design Overview**

In this open-label trial, we randomly assigned hepatitis B e antigen (HBeAg)–positive patients with chronic hepatitis B to receive telbivudine or adefovir for 52 weeks (groups A and B, respectively) or adefovir for 24 weeks and then telbivudine for the remaining 28 weeks of the study (group C), evaluating the results at weeks 24 and 52. Screening began on 21 October 2004, and the last patient's last visit was on 16 August 2006. The study was conducted in compliance with the Declaration of Helsinki and in accordance with good clinical practice guidelines and applicable local regulations. All patients provided written informed consent, and all participating institutions received ethics committee approval. There was no data safety monitoring board.

**Setting and Participants**

We conducted this trial at 16 outpatient gastroenterology clinics at academic centers in Hong Kong, Australia, Canada, France, Korea, Singapore, Taiwan, Thailand, and the United States. Study investigators recruited participants from among their clinic patients after reviewing medical records and completing screening procedures to assess eligibility. Eligible patients were men or women with chronic hepatitis B 18 to 70 years of age, with no history or signs of hepatic decompensation, positivity for serum hepatitis B surface antigen (HBsAg), positivity for serum HBeAg, serum alanine aminotransferase (ALT) level between 1.3 and 10 times the upper limit of normal, and serum HBV DNA levels of at least  $6 \log_{10}$  copies/mL. We excluded patients who were pregnant, breastfeeding, or co-infected with hepatitis C or D virus or HIV; had other known causes of liver disease, a history or signs of pancreatitis or hepatocellular carcinoma, or potentially confounding concomitant medical conditions; had ever been treated for hepatitis B with nucleoside or nucleotide analogues or had received interferon or other immunomodulatory agents within 12 months of screening; or had used alcohol or illicit drugs in the past 2 years. Patients with elevated serum creatinine levels, hemoglobin levels less than 110 g/L for men or less than 100 g/L for women, an absolute neutrophil count less than  $2 \times 10^9$  cells/L, platelet counts less than  $100 \times 10^9$  cells/L,  $\alpha$ -fetoprotein levels greater than 50  $\mu$ g/L, serum amylase or lipase levels at least 1.5 times the upper limit of normal, a prothrombin time prolonged by more than 3 seconds above the upper limit of normal, albumin levels less than 34 g/L, or total bilirubin levels at least 2 times the upper limit of normal were also excluded.

**Randomization and Interventions**

A centralized computer-generated process assigned eligible patients to each of the 3 treatment groups by using block randomization with block sizes of 3, implemented with an automated voice-response system. Eligible patients were randomly assigned in a 1:1:1 ratio to receive 600 mg (3 tablets) of telbivudine per day for 52 weeks (group A), 10 mg (1 tablet) of adefovir dipivoxil per day for 52 weeks (group B), or 10 mg of adefovir per day for 24 weeks followed by 600 mg of telbivudine per day for the remaining 28 weeks (group C). This design compared responses to telbivudine and adefovir at week 24, consistent with the primary study goal, and provided 3 treatment comparisons at week 52 (group A vs. group B vs. group C), as appropriate to secondary goals. Patients completing this study were offered enrollment in a follow-up study of continuing treatment with telbivudine if indicated.

Telbivudine was supplied by Idenix Pharmaceuticals, Cambridge, Massachusetts, and adefovir (Hepsera, Gilead Sciences, Foster City, California) was purchased commercially. The brittle nature of adefovir tablets precluded treatment blinding by routine overencapsulation. Investigators

were blinded to HBV serologic data from baseline until week 52.

### Outcomes and Follow-up

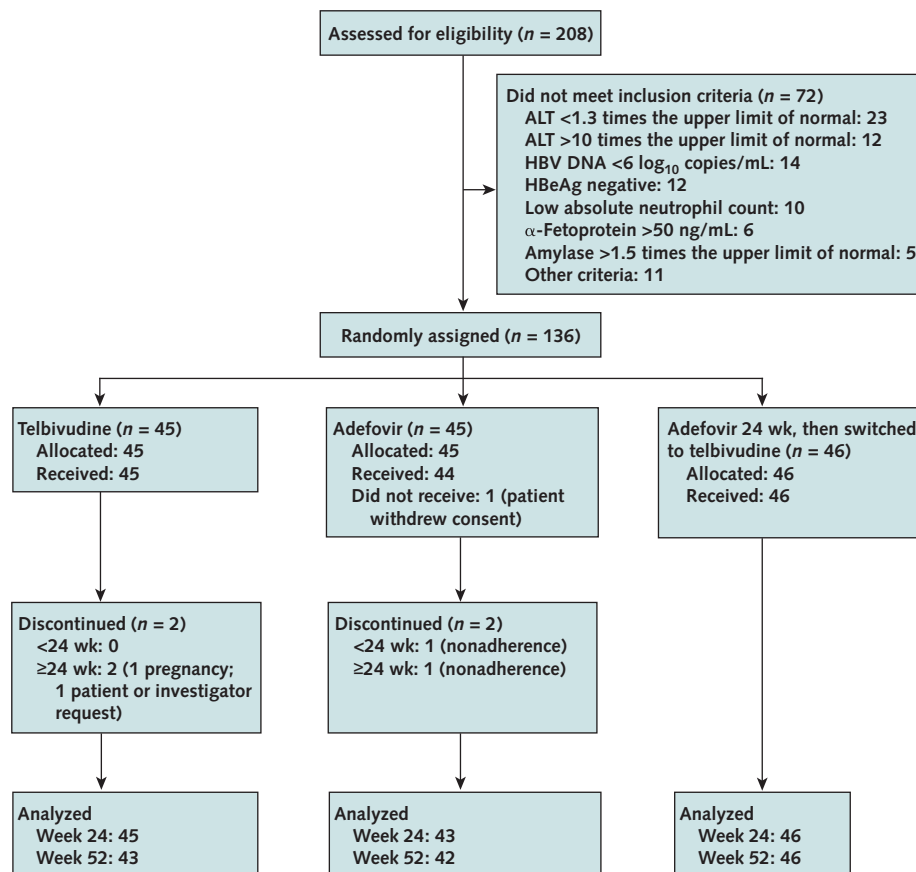
Routine laboratory values, including HBV DNA levels, were obtained along with clinical status at screening; baseline; and weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, and 52. Other HBV serologic markers were measured beginning at week 12. A central reference laboratory (Quintiles Transnational, Research Triangle Park, North Carolina) conducted all laboratory-based assessments (HBV markers, serum chemistries, hematology, and urinalyses). Staff at Quintiles Transnational collected clinical data and entered them into a database in accordance with standardized data management and quality assurance procedures. Adherence was evaluated at each study visit; evaluation methods included pill counts and discussions with study participants.

### Outcomes and Measurements

Serum HBV DNA levels were assessed at each study visit by using the COBAS Amplicor PCR assay (Roche

Molecular Systems, Branchburg, New Jersey), which has a lower limit of detection of 300 copies/mL. The primary treatment comparison was HBV DNA reduction from baseline values at week 24, with a secondary comparison at week 52. Other secondary efficacy measures included comparisons of mean residual HBV DNA levels, proportions of patients with HBV DNA who were PCR-negative or had HBV DNA values less than 5, 4, or 3 log<sub>10</sub> copies/mL; serum ALT normalization; HBeAg loss and seroconversion; HBsAg loss and seroconversion; and primary treatment failure. Primary treatment failure was defined as completion of at least 24 weeks of treatment without achieving 2 consecutive serum HBV DNA values less than 5 log<sub>10</sub> copies/mL, the minimal response threshold recommended by treatment guidelines when the study was designed (24, 25). After study completion, suboptimal response was defined for exploratory analyses as a serum HBV DNA level of 3 log<sub>10</sub> copies/mL or greater at week 24, consistent with reports of greater resistance and poorer

Figure 1. Study flow diagram.



Primary exclusion criteria are listed; some patients met more than 1 exclusion criterion. One patient assigned to adefovir withdrew before initiation of treatment; thus, the intention-to-treat sample was 135 patients, of whom 45, 44, and 46 were assigned to receive telbivudine, adefovir, or adefovir for 24 weeks and then telbivudine for the remaining 28 weeks, respectively. One adefovir recipient withdrew before the week-24 analysis; 1 additional adefovir recipient and 2 telbivudine recipients withdrew before the week-52 analysis. ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus.

Table 1. Baseline Characteristics\*

Characteristic	Telbivudine (Group A) (n = 45)	Adefovir (Group B) (n = 44)	Adefovir to Telbivudine (Group C) (n = 46)	Pooled Groups B and C (n = 90)
Mean age (range), y	34 (18–60)	30 (19–47)	33 (18–53)	32 (18–53)
Men, n (%)	35 (78)	40 (91)	27 (59)	67 (74)
Mean body weight ( $\pm$ SE), kg	68 $\pm$ 2.0	69 $\pm$ 1.8	63 $\pm$ 1.7	66 $\pm$ 1.3
Ethnicity, n (%)				
Asian	42 (93)	39 (89)	43 (94)	82 (91)
White	3 (7)	1 (2)	1 (2)	2 (2)
Other	0	4 (9)	2 (4)	6 (6.7)
Mean serum HBV DNA value ( $\pm$ SE), $\log_{10}$ copies/mL	9.57 $\pm$ 0.26	9.98 $\pm$ 0.23	9.47 $\pm$ 0.29	9.72 $\pm$ 0.19
Serum ALT level, U/L				
Median (range)	133 (47–750)	144 (43–854)	110 (50–455)	119 (43–854)
Mean ( $\pm$ SE)	183 $\pm$ 23.6	199 $\pm$ 25.7	138 $\pm$ 12.8	168 $\pm$ 14.4

\* ALT = alanine aminotransferase; HBV = hepatitis B virus.

efficacy outcomes for patients with this level of residual viremia (11, 17, 18).

### Viral Breakthrough and Resistance

Viral breakthrough was defined as an on-treatment increase in HBV DNA over 2 consecutive determinations of greater than 1  $\log_{10}$  from nadir, or a single determination at week 52, consistent with recent recommendations (26, 27). Resistance (viral breakthrough with documented resistance mutations) was identified by PCR amplification of HBV DNA from sera of patients with viral breakthrough at week 52, followed by automated DNA sequencing of the entire 344-codon reverse transcriptase domain of the HBV polymerase gene at an independent reference laboratory (Delft Diagnostic Laboratory, Delft, the Netherlands).

### Adverse Events

At all study visits, we evaluated clinical adverse events, regardless of drug attributability, and discontinuation of study treatment for any reason; confirmed serum creatinine level elevations of 44.2  $\mu$ mol/L or greater ( $\geq$ 0.5 mg/dL) from baseline; and conducted graded assessments of laboratory abnormalities. Adverse event evaluations included spontaneous patient reports, open-ended questioning by the investigator, and physical examinations. They were documented on case report forms that included investigator assessments of possible cause and drug attributability. We used standard, recommended, open-ended questions to elicit adverse event information rather than checklists or targeted questionnaires. Staff at Quintiles Transnational monitored each study site at 6- to 8-week intervals to ensure complete data entry into case report forms, including adverse events, and to verify source data.

### Statistical Analysis

With a target sample size of 120 patients and a 1:2 ratio of assignment to telbivudine or adefovir during the first 24 weeks, we estimated that our study had 98% power to detect a difference of 1.5  $\log_{10}$  copies/mL in HBV DNA reduction at week 24, the primary efficacy comparison.

This anticipated difference was based on previous clinical studies of these agents (8, 11). The analyses presented are based on data available at each time point, consistent with the low rate of patient discontinuation; no missing data were imputed. All end points and comparisons were pre-defined except for exploratory evaluations of suboptimal responders and relationships between week-24 viral load and subsequent efficacy responses. For continuous variables, such as HBV DNA reduction, we used analyses of variance to compare treatment results. For categorical variables, we used logistic regression; we present the odds ratios. Our exploratory analyses of relationships between viral load at week 24 and subsequent efficacy outcomes were based on the Fisher exact test. All analyses were tested at a 2-sided  $\alpha$  level of 0.05. We analyzed the results at weeks 24 and 52 by using unadjusted models and models adjusted for baseline covariates (HBV DNA level, age, body mass index, sex, and study site). We analyzed data by using SAS for Windows, release 8.02 (SAS Institute, Cary, North Carolina).

### Role of the Funding Source

Idenix Pharmaceuticals and Novartis Pharmaceuticals provided funding for this study. The study protocol and statistical analysis plan were designed by the sponsors in conjunction with the academic investigators. The protocol was submitted to the U.S. Food and Drug Administration, and the study was conducted under an Investigational New Drug authorization from the U.S. Food and Drug Administration. Quintiles Transnational conducted data management and site monitoring and provided the study data to the study statistician, an employee of Idenix Pharmaceuticals, who completed preprogrammed data analyses.

## RESULTS

### Baseline Patient Characteristics

Of the 208 patients screened, 72 were excluded and 136 were enrolled (Figure 1). One patient assigned to



adefovir withdrew before the start of treatment. Of the remaining 135 patients, 45 received telbivudine (group A), 44 received adefovir (group B), and 46 received adefovir for 24 weeks and then telbivudine for the remaining 28 weeks (group C). Adherence to study medication was considered good ( $\geq 80\%$ ) for at least 95% of patients in each treatment group at each study visit, and no unplanned crossovers occurred. Treatment groups were well matched at baseline for the primary analysis at week 24 (group A and pooled groups B and C) and the final analysis at week 52 (groups A, B, and C) (Table 1). More than 90% of the enrolled patients were ethnically Asian, and baseline HBV DNA and ALT levels were similar across treatment groups.

**Results at Week 24: Primary Treatment Comparison**

We observed a consistent separation of mean serum HBV DNA levels according to treatment beginning at week 2 (Figure 2, top). At week 24, the reduction in mean serum HBV DNA level from baseline in group A differed from that in pooled groups B and C ( $-6.30$  vs.  $-4.97$   $\log_{10}$  copies/mL; difference,  $-1.33$   $\log_{10}$  copies/mL [95% CI,  $-1.99$  to  $-0.66$   $\log_{10}$  copies/mL];  $P < 0.001$ ), as did the proportion of patients whose serum HBV DNA levels were undetectable by PCR (39% vs. 12%; odds ratio, 4.46 [CI, 1.86 to 10.72];  $P = 0.001$ ) (Table 2). Serum HBV DNA levels remained at or above 5  $\log_{10}$  copies/mL in more adefovir recipients than telbivudine recipients (42% vs. 5%; odds ratio, 0.07 [CI, 0.02 to 0.29];  $P < 0.001$ ). Similarly, group A and pooled groups B and C differed in the proportions of patients with HBV DNA levels that remained at or above 3  $\log_{10}$  copies/mL (50% vs. 78%;  $P = 0.003$ ) and 4  $\log_{10}$  copies/mL (32% vs. 61%;  $P = 0.003$ ). Rates of ALT normalization were similar (Table 2). Comparisons of all week-24 results, adjusted for baseline covariates, generally concur with the unadjusted results.

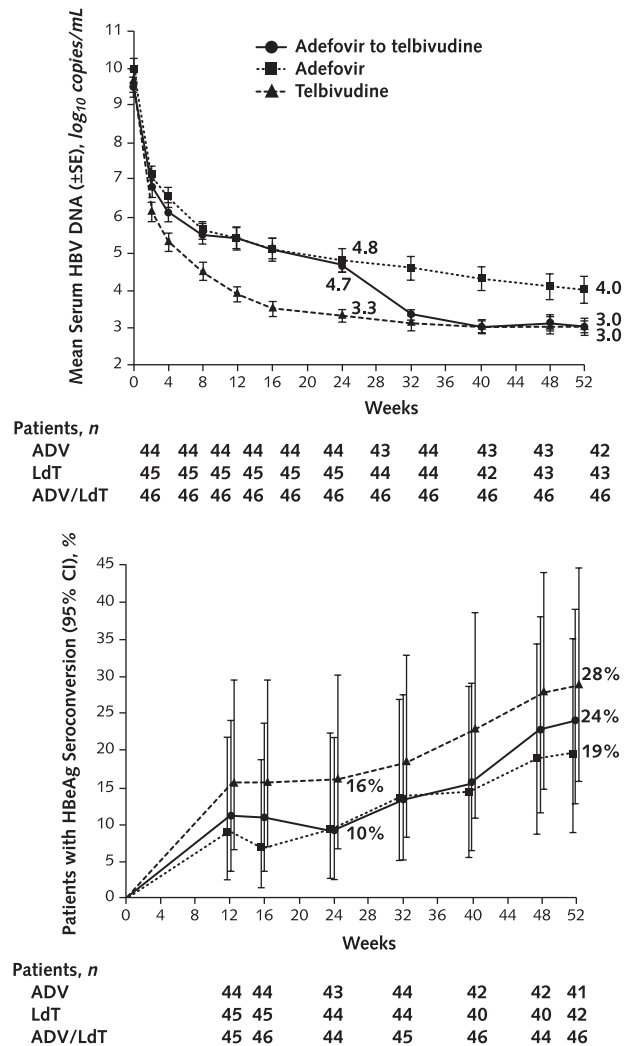
**Results at Week 52**

In patients switched from adefovir to telbivudine at week 24 (group C), mean HBV DNA levels rapidly decreased by approximately 1.4  $\log_{10}$  copies/mL after week 24; within 8 weeks, they were nearly identical to levels in group A (Figure 2, top). A corresponding increase in HBeAg seroconversion was evident in group C (Figure 2, bottom), although the differences were not statistically significant. At week 52, mean residual HBV DNA levels in groups A and C differed from those in group B (3.01  $\log_{10}$  copies/mL and 3.02  $\log_{10}$  copies/mL, respectively, vs. 4.00  $\log_{10}$  copies/mL; difference,  $-0.99$   $\log_{10}$  copies/mL [CI,  $-1.67$  to  $-0.32$   $\log_{10}$  copies/mL] and  $-0.98$   $\log_{10}$  copies/mL [CI,  $-1.64$  to  $-0.32$   $\log_{10}$  copies/mL];  $P = 0.004$ ) (Table 3). Reductions of mean serum HBV DNA levels were greater in groups A and C ( $-6.56$  and  $-6.44$   $\log_{10}$  copies/mL, respectively) than in group B ( $-5.99$   $\log_{10}$  copies/mL; differences,  $-0.57$   $\log_{10}$  copies/mL [CI,  $-1.41$  to  $0.27$   $\log_{10}$  copies/mL] [ $P = 0.18$ ] and  $-0.45$   $\log_{10}$  copies/mL [CI,  $-1.28$  to  $0.38$   $\log_{10}$  cop-

ies/mL] [ $P = 0.28$ ]). These differences were statistically significant after adjustment for baseline covariates (Table 3). More patients in groups A and C than in group B were PCR-negative at week 52, although these differences did not reach statistical significance (60% and 54% vs. 40%;  $P = 0.07$  and  $0.20$ , respectively). The rate of primary treatment failure (HBV DNA levels remaining  $> 5$   $\log_{10}$  copies/mL through week 52) in group B (29%) also differed from that in group A (2%; odds ratio, 0.06 [CI, 0.01 to 0.48];  $P = 0.008$ ) and in group C (11%; odds ratio, 0.30 [CI, 0.10 to 0.96];  $P = 0.042$ ).

Loss of HBeAg was more common in group A than in pooled groups B and C at week 24, and was more common in groups A and C at week 52 (30% and 26%, respec-

**Figure 2. Changes in serum hepatitis B virus (HBV) markers from baseline to week 52.**



Top. Mean serum HBV DNA levels. Bottom. Proportion of patients with hepatitis B e antigen (HBeAg) seroconversion. ADV = adefovir; ADV/LdT = adefovir to telbivudine; LdT = telbivudine.

**Table 2. Efficacy Results at Week 24 of Treatment\***

Variable	Telbivudine (Group A) (n = 44)	Adefovir (Groups B and C) (n = 89)	Unadjusted Effect (95% CI)†	P Value	Adjusted Effect (95% CI)‡	P Value
Change from baseline in mean HBV DNA level (±SE), log <sub>10</sub> copies/mL	-6.30 ± 0.21	-4.97 ± 0.21	-1.33 (-1.99 to -0.66)	<0.001	-1.46 (-2.01 to -0.91)	<0.001
HBV DNA PCR-negative, %	39	12	4.46 (1.86 to 10.72)	0.001	6.03 (2.20 to 16.52)	0.001
HBV DNA level >5 log <sub>10</sub> copies/mL, %	5	42	0.07 (0.02 to 0.29)	<0.001	0.07 (0.02 to 0.29)	<0.001
ALT normalization, %	58	61	0.89 (0.42 to 1.87)	0.76	0.91 (0.41 to 2.04)	0.83
Loss of HBeAg, %	16	11	1.49 (0.53 to 4.24)	0.45	1.81 (0.56 to 5.85)	0.32
HBeAg seroconversion, %	16	10	1.68 (0.58 to 4.86)	0.34	2.30 (0.69 to 7.70)	0.18

\* Summary statistics are presented for the 44 and 89 patients in the telbivudine and adefovir groups, respectively, with data available at week 24. ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; PCR = polymerase chain reaction.

† For continuous variables, the difference in least-squares means is presented; for categorical response variables, the odds ratio is presented.

‡ Results adjusted for baseline covariates (baseline HBV DNA level, age, body mass index, sex, and study site), on the basis of analysis of variance for continuous variables or logistic regression for categorical variables.

tively) than in group B (21%), although intergroup differences were not statistically significant (Tables 2 and 3). Hepatitis B e antigen seroconversion followed the same pattern. No patient experienced HBsAg loss or seroconversion. At week 52, ALT normalization occurred in 79% of patients in group A and 85% of patients in group C, compared with 85% of those in group B (P = 0.45 and 0.98, respectively).

Exploratory analyses indicated that for the 78% of adefovir recipients with suboptimal response at week 24 (HBV DNA level ≥3 log<sub>10</sub> copies/mL), those in group C displayed an additional reduction of 2.1 log<sub>10</sub> copies/mL in mean HBV DNA between weeks 24 and 52, compared with 0.8 log<sub>10</sub> copies/mL for patients in group B. Patients with a suboptimal response to adefovir who switched to telbivudine also had greater HBeAg seroconversion at week 52 than those who continued receiving adefovir (19% vs. 9%; P = 0.20), and a higher proportion was HBV DNA PCR-negative (42% vs. 24%; P = 0.11), although these differences were not statistically significant. Viral load was suppressed to less than 6 log<sub>10</sub> copies/mL by week 52 in all patients in group C, whereas levels remained above this

threshold in 27% of those in group B, remaining as high as 8.9 log<sub>10</sub> copies/mL.

**Relationship between Week-24 Viral Load and Week-52 Efficacy Responses**

At week 24, serum HBV DNA levels were less than 3 log<sub>10</sub> copies/mL in more patients in group A than in pooled groups B and C (50% vs. 22%; P < 0.001). Among patients who received 52 weeks of telbivudine or adefovir (groups A and B), those with HBV DNA level <3 log<sub>10</sub> copies/mL at week 24 showed the highest rates of efficacy responses at week 52 (Table 4). In groups A and B combined, HBV DNA was undetectable at week 52 in 94% of patients with an HBV DNA level less than 3 log<sub>10</sub> copies/mL at week 24, versus 25% of patients with a viral load of 3 log<sub>10</sub> copies/mL or greater at week 24 (P < 0.001). Similarly, HBeAg seroconversion and ALT normalization at week 52 were observed in 44% and 94%, respectively, of patients with viral load <3 log<sub>10</sub> copies/mL at week 24, compared with 11% and 75% of patients with HBV DNA levels of 3 log<sub>10</sub> copies/mL or greater at week 24 (P = 0.001 and 0.04, respectively).

**Table 3. Efficacy Results at Week 52 of Treatment\***

Variable	Telbivudine (Group A)	Adefovir (Group B)	Adefovir to Telbivudine (Group C)	Group A vs. Group B			
				Unadjusted Effect (95% CI)†	P Value	Adjusted Effect (95% CI)‡	P Value
Change from baseline in mean HBV DNA, log <sub>10</sub> copies/mL	-6.56	-5.99	-6.44	-0.57 (-1.41 to 0.27)	0.18	-0.84 (-1.49 to -0.19)	0.012
HBV DNA PCR-negative, %	60	40	54	2.25 (0.94 to 5.36)	0.067	1.89 (0.72 to 4.94)	0.20
Mean HBV DNA level, log <sub>10</sub> copies/mL	3.01	4.00	3.02	-0.99 (-1.67 to -0.32)	0.004	-0.84 (-1.49 to -0.19)	0.012
ALT normalization, %	79	85	85	0.65 (0.21 to 2.02)	0.45	0.61 (0.18 to 2.08)	0.43
Loss of HBeAg, %	30	21	26	1.59 (0.59 to 4.25)	0.36	1.42 (0.50 to 4.07)	0.51
HBeAg seroconversion, %	28	19	24	1.65 (0.59 to 4.56)	0.34	1.49 (0.51 to 4.39)	0.47
Primary treatment failure, %	2	29	11	0.06 (0.01 to 0.48)	0.008	0.05 (0 to 0.45)	0.008

\* Summary statistics are presented for the 43, 42, and 46 patients in the telbivudine, adefovir, and adefovir-to-telbivudine groups, respectively, with data available at week 52. ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; PCR = polymerase chain reaction.

† For continuous variables, the difference in least-squares means is presented; for categorical response variables, the odds ratio is presented.

‡ Results adjusted for baseline covariates (baseline HBV DNA level, age, body mass index, sex, and study site), on the basis of analysis of variance for continuous variables or logistic regression for categorical variables.

### Viral Breakthrough and Resistance

Viral breakthrough, defined as a confirmed increase in serum HBV DNA levels of more than 1 log above the nadir value, occurred in 4 adefovir recipients and 3 telbivudine recipients. No breakthroughs occurred in the adefovir-to-telbivudine group. All breakthroughs occurred after week 24 in patients with serum HBV DNA levels that remained at 3 log<sub>10</sub> copies/mL or greater at week 24. No codon A181V/T or N236T signature resistance mutations were detected in adefovir recipients with viral breakthrough (27). The signature M204I telbivudine resistance mutation was detected at week 52 in the 3 telbivudine recipients with breakthrough; 1 of these was accompanied by an L80V secondary change (28).

In the study protocol, viral breakthrough was defined as an increase of serum HBV DNA to 5 log<sub>10</sub> copies/mL or greater after a decrease to below that level. During the study, this definition was superseded by the more widely accepted definition that pertains to the data reported here (27). Breakthrough per protocol occurred in 2, 1, and 0 patients in groups A, B, and C, respectively. All 3 patients were also included in the primary resistance analysis reported here.

### Adverse Events

No drug-attributed serious adverse events were reported, no patients discontinued the study because of adverse events (1 patient withdrew after becoming pregnant), and no deaths occurred. Serious adverse events not attributed to study medications included a metacarpal fracture, transient elevation of ALT level, and hospitalizations for tonsillitis and a thyroid nodule. Clinical adverse events were similar in the 3 treatment groups (Table 5). Single cases of mild (grade 1) myopathy and persistent myalgia with creatine kinase elevations were reported in telbivudine recipients after 52 and 41 weeks, respectively; treatment was continued without dose modification. The serum creatinine level was elevated (>114.9 μmol/L [ $>1.3$  mg/dL]) in 1 adefovir recipient from weeks 24 to 52; the maximum

elevation was 53 μmol/L (0.6 mg/dL) above the baseline value at week 32. Creatinine levels returned to within the normal range after week 52, concomitant with switching to telbivudine in the follow-up study. Grades 3 and 4 neutropenia were observed in 1 patient in group A and 1 patient in group C. Retesting 6 days later indicated that both conditions had resolved without dose reduction or treatment interruption.

### DISCUSSION

In this study, telbivudine showed greater antiviral effects than adefovir dipivoxil after 24 weeks of treatment in HBeAg-positive patients with chronic hepatitis B. At week 24, 3 times as many telbivudine-treated patients (group A) as adefovir-treated patients (pooled groups B and C) were PCR-negative. Conversely, HBV DNA levels remained above 5 log<sub>10</sub> copies/mL in 42% of group B versus 5% of group A, suggesting more consistent antiviral suppression with telbivudine. Adefovir recipients randomly assigned to switch to telbivudine at week 24 (group C) showed a rapid, approximately 1-log incremental reduction of serum HBV DNA levels within 2 months. At 1 year, the difference in reduction of serum HBV DNA level, as assessed by residual HBV DNA levels, differed significantly when patients in groups A and C were compared with those in group B. Other measures at 1 year also consistently favored telbivudine over adefovir, although differences were not statistically significant. The incidence of viral breakthrough was similar for telbivudine and adefovir at 1 year, although resistance mutations were detected only with continuous telbivudine therapy (group A). Adverse event frequencies were similar in the 3 treatment groups; however, the occurrence of myopathy in a telbivudine recipient suggests that any persistent, unexplained muscle-related symptoms should be evaluated promptly.

Direct comparative studies are the most effective way to define the role of available agents for hepatitis B in clinical practice. A search of MEDLINE through March 2007 and hepatology conference abstracts from 2006 and 2007 identified several such studies. Phase III trials for both telbivudine and entecavir demonstrated greater antiviral efficacy at 1 year with less resistance (no resistance with entecavir) compared with lamivudine (9, 22, 23, 29, 30). A recent trial demonstrated greater antiviral effects with entecavir than with adefovir after 1 year (31).

Although all available agents have demonstrated greater antiviral efficacy than either placebo or lamivudine in phase III studies, a substantial proportion of patients receiving these agents did not achieve optimal viral suppression (7–9, 21, 29, 32). In a placebo-controlled, phase III study, the serum HBV DNA level was reduced by less than 2.2 log<sub>10</sub> copies/mL after 48 weeks in 25% of adefovir recipients (33). However, few studies have explored the effects of switching therapies as the basis for a rational strategy to improve efficacy outcomes. A small trial in

Table 3—Continued

Group C vs. Group B			
Unadjusted Effect (95% CI)†	P Value	Adjusted Effect (95% CI)‡	P Value
−0.45 (−1.28 to 0.38)	0.28	−0.74 (−1.41 to −0.08)	0.029
1.75 (0.75 to 4.08)	0.20	1.19 (0.44 to 3.22)	0.73
−0.98 (−1.64 to −0.32)	0.004	−0.74 (−1.41 to −0.08)	0.029
0.98 (0.30 to 3.21)	0.98	0.87 (0.24 to 3.19)	0.84
1.29 (0.48 to 3.48)	0.61	0.84 (0.27 to 2.57)	0.75
1.34 (0.48 to 3.73)	0.58	0.89 (0.28 to 2.82)	0.85
0.30 (0.10 to 0.96)	0.042	0.40 (0.10 to 1.68)	0.21

**Table 4. Effect of Viral Load at Week 24 on Efficacy Outcomes at Week 52\***

Serum HBV DNA at Week 24	Response at Week 52						P Value†
	<3 log <sub>10</sub> copies/mL			≥3 log <sub>10</sub> copies/mL			
	Adefovir	Telbivudine	Total	Adefovir	Telbivudine	Total	
Serum HBV DNA PCR-negative, n (%)	9/10 (90)	21/22 (95)	30/32 (94)	8/32 (25)	5/21 (24)	13/53 (25)	<0.001
HBeAg seroconversion, n (%)	5/10 (50)	9/22 (41)	14/32 (44)	3/32 (9)	3/21 (14)	6/53 (11)	0.001
ALT normalization, n (%)	9/10 (90)	20/21 (95)	29/31 (94)	25/30 (83)	13/21 (62)	38/51 (75)	0.04

\* ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; PCR = polymerase chain reaction.

† For the results in adefovir and telbivudine groups combined.

HBeAg-negative patients with suboptimal response to adefovir showed enhanced antiviral effects after switching to a combination of tenofovir and emtricitabine (34). In lamivudine-resistant patients, several studies have shown that viral suppression can be restored by adding or switching to adefovir or tenofovir, nucleotide analogues with complementary resistance profiles (35–37). Related studies suggest that in lamivudine-resistant patients, tenofovir or a higher dosage of adefovir (20 mg/d) may provide greater viral suppression than standard adefovir treatment, with potential benefits for patients with suboptimal responses to adefovir salvage therapy (38, 39). However, adefovir dosages greater than 10 mg/d have been associated with a higher incidence of nephrotoxicity (8, 40).

Limitations of this study include an open-label design and reduced statistical power after the primary analysis at week 24, due to reduced group sizes associated with division of the study population into 3 comparator groups. In addition, the study was not of sufficient duration to evaluate long-term clinical outcomes. Because the patients were all HBeAg-positive and nucleoside- and nucleotide-naïve and were primarily Asian, the extent to which conclusions may be generalized to other patient populations with hepatitis B is uncertain. The open-ended approach that was used to elicit adverse event information may have resulted in variable or incomplete reporting of events. In analysis of variance models, observations of nondetectable HBV DNA were handled by single-value imputation (150 copies/mL); consequently, any variability of actual values for these data may not be accurately reflected in variability estimates, confidence limits, and P values.

In this trial, we randomly assigned some adefovir recipients to switch to telbivudine at 24 weeks. In clinical practice, however, treatment modification is generally considered only for patients with suboptimal antiviral responses (41). Adefovir recipients with suboptimal antiviral responses at week 24 achieved a substantial incremental decrease in viral load after switching to telbivudine, suggesting that treatment modification can be considered as early as week 24. Recent studies (42, 43) suggest that adding adefovir to ongoing lamivudine therapy in patients with resistance may reduce subsequent adefovir resistance, compared with switching to adefovir monotherapy, and may improve viral suppression in patients with high viral load. The same advantages may also apply to patients without a resistant virus, although this has not been prospectively evaluated (44). The M204I and M204V mutations both confer resistance to lamivudine, whereas M204I is the primary basis of telbivudine resistance (28, 29). These mutations reduce susceptibility to other L-nucleoside analogues, but not to the acyclic phosphonates adefovir and tenofovir. These findings suggest that there may be benefits of combining telbivudine with these agents, analogous to those reported for lamivudine and adefovir (28). Studies are needed to refine the definition of suboptimal early response as a basis for therapeutic decisions, to confirm that the benefits of treatment modification persist in the long

**Table 5. Clinical Adverse Events\***

Event	Telbivudine Group (n = 45)	Adefovir Group (n = 44)	Adefovir-to-Telbivudine Group (n = 46)
Total	76	61	67
Upper respiratory tract infection	11	11	13
Headache	11	7	13
Back pain	13	7	7
Diarrhea	13	2	11
Influenza	11	7	9
Upper abdominal pain	7	5	11
Nasopharyngitis	2	11	4
Cough	2	0	13
Arthralgia	4	5	4
Fatigue	4	0	9
Dizziness	2	0	9
Malaise	7	0	4
Nausea	4	5	2
Pharyngolaryngeal pain	2	7	2
Abdominal pain	4	2	0
Epigastric discomfort	4	0	2
Gastritis	7	0	0
Hepatic steatosis	4	2	0
Mouth ulceration	0	5	2
Myalgia	2	0	4
Toothache	4	2	0
Hepatitis B	0	5	0
Hordeolum	4	0	0
Allergic rhinitis	0	5	0

\* Number of events occurring in ≥4% of patients in any treatment group through week 52, regardless of attributability to study drug. Patients are counted once for each type of adverse event.



term, and to compare the effects of adding telbivudine versus switching to telbivudine monotherapy in patients with a suboptimal response to adefovir.

Antiviral resistance is a serious concern with longer-term nucleoside and nucleotide therapy for hepatitis B and a relevant consideration in choice of therapy (45). The cumulative incidence of lamivudine resistance approaches 70% after 4 years; adefovir resistance was observed in 29% of HBeAg-negative patients after 5 years, and in 16 of 38 HBeAg-positive patients with virologic failure after 110 to 279 weeks (40, 46). On the basis of an analysis of 120 of the 663 nucleoside-naïve patients from phase III trials (47), cumulative resistance to entecavir was 0.8% at 4 years. Preliminary data suggest that the cumulative incidence of telbivudine resistance in HBeAg-positive patients approaches 20% as therapy is extended to 2 years (23). In this study, the association of HBV DNA levels at 24 weeks with efficacy outcomes and viral breakthrough at 1 year for both telbivudine and adefovir are consistent with previous analyses of telbivudine, adefovir, and lamivudine (11–18). These findings suggest that greater early (24-week) HBV DNA reduction may be associated with reduced risk for subsequent telbivudine resistance (18, 23). Such considerations highlight the importance of regular viral load monitoring to support early intervention in patients with suboptimal virologic responses, with the goal of avoiding resistance and maintaining viral suppression (12, 14, 17, 18).

The multiple agents now available for treating chronic hepatitis B provide the basis for improved control of HBV replication. Data from this study support the concept that maximizing viral suppression early in the course of therapy is linked to improved efficacy responses and less resistance, suggesting that agents providing the greatest viral suppression may be preferable as initial therapy. Data from this and previous studies indicate that telbivudine may provide greater viral suppression than adefovir and lamivudine. With regular monitoring to ensure that responses are maintained, telbivudine may have an important role in treatment regimens for patients with chronic hepatitis B (22, 23).

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**Reproducible Research Statement:** A synopsis of the protocol is available to interested readers by contacting 877-889-9352. Statistical code and data are not available.

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In addition to the authors, investigators in this trial included Dr. Darrell Crawford, Princess Alexandra Hospital, Woolloomgatta, Queensland, Australia; Dr. Seng-Gee Lim, National University Hospital, Singapore; Dr. Anuchit Chutaputti, Phramongkutklao Hospital, Bangkok, Thailand; and Dr. Thierry Poynard, Groupe Hospitalier Pitié-Salpêtrière, Paris, France.