New Drug

Telbivudine for the Management of Chronic Hepatitis B Virus Infection

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ABSTRACT

Background: Telbivudine (LdT) is an L-nucleoside that is structurally related to lamivudine. It is highly selective for hepatitis B virus (HBV) and inhibits viral DNA synthesis. LdT was approved by the US Food and Drug Administration on October 25, 2006, for the treatment of chronic HBV infection in adults who have active viral replication and either elevations in liver transaminases or signs of active liver disease on histologic examination.

Objective: This article reviews the pharmacology, pharmacokinetics, and therapeutic efficacy of LdT. Potential drug interactions and adverse events associated with the use of LdT are also reviewed.

Methods: Relevant publications were identified from searches of MEDLINE (1996–June 2007), the Cochrane Library, and BIOSIS (1993–June 2007). Search terms included, but were not limited to, *telbivudine*, *β-L-thymidine*, *LdT*, *pharmacology*, *pharmacokinetics*, *adverse events*, *resistance*, *drug interactions*, *hepatitis B*, and *therapeutic use*. Additional publications were identified from the reference lists of the identified papers, meeting abstracts, and correspondence with the manufacturer of LdT.

Results: After 52 weeks of therapy in the Phase III GLOBE study, HBV resistance (breakthrough and resistance mutations) to LdT occurred in 3% of patients who were hepatitis B e antigen (HBeAg) positive and 2% of patients who were HBeAg negative. After 104 weeks of therapy, 17.8% to 21.6% of HBeAg-positive and 7.3% to 8.6% of HBeAg-negative LdT-treated patients had a rebound in HBV DNA associated with breakthrough and resistance mutations. After 24 weeks of treatment, the risk of resistance was greater in patients with HBV DNA titers >3 $\log_{10}$ copies/mL than in those with lower numbers of copies. LdT is not active against lamivudine-resistant HBV. The proportion of HBeAg-positive patients with undetectable HBV DNA (by polymerase chain reaction assay) after 104 weeks of therapy in the GLOBE study was significantly greater with LdT compared with lamivudine (56% vs 39%, respectively; $P < 0.05$). After 104 weeks of therapy, the corresponding proportions of HBeAg-negative patients with undetectable HBV DNA were 82% and 57% ($P < 0.05$). Patients who failed lamivudine therapy in the GLOBE study showed cross-resistance to LdT. The most common adverse events associated with LdT are upper respiratory tract infection (14%–17%), fatigue and malaise (12%–14%), nasopharyngitis (11%–15%), headache (11%–12%), and abdominal pain (6%–12%). Grade 3/4 adverse events included elevations in serum creatine kinase, which were more common in patients receiving LdT than in those receiving lamivudine (9% vs 3%, respectively). Elevations in creatine kinase are typically asymptomatic; however, myopathy has been reported in 3 of 680 patients receiving LdT.

Conclusions: LdT joins the increasing number of antiviral agents for the management of chronic HBV infection. Questions concerning the optimal length of therapy and long-term efficacy await the results of ongoing clinical trials. Concerns about increasing resistance over time may relegate LdT to second-line status in the management of chronic HBV infection. The role of LdT in combination therapy is under investigation. (*Clin Ther*. 2007;29:2635–2653) Copyright © 2007 Excerpta Medica, Inc.

Key words: telbivudine, hepatitis B, pharmacokinetics, therapeutic use, adverse events.

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INTRODUCTION

Although more than a quarter century has elapsed since the availability of an effective vaccine to prevent hepatitis B virus (HBV) infection, the virus continues to play an important role in human disease.[1] Approximately 360 million people worldwide and 1.25 million people in the United States have chronic HBV infection.[2,3] These patients are at risk for cirrhosis of the liver, liver failure, and hepatocellular carcinoma. It is estimated that between 500,000 and 700,000 people die annually from HBV-related disease such as cirrhosis or hepatocellular carcinoma.[2]

Active disease is defined as documented viral replication (HBV DNA), persistent elevations in serum alanine transaminase (ALT), or abnormal liver histology.[4] Until recently, approved agents for the management of active chronic HBV infection included α-interferons (peginterferon alfa-2a and unmodified interferon alfa-2b), lamivudine (an L-nucleoside), adefovir (an acyclic nucleoside phosphonate), and entecavir (a deoxyguanosine analogue).[5–15] The advantages of α-interferon therapy include lack of HBV resistance and a defined duration of therapy,[5] but their use is limited by high cost (average wholesale price for 1 year of treatment with peginterferon alfa-2a, $22,893), need for parenteral administration, and frequent adverse events (56% incidence of fatigue/asthenia and 18% incidence of depression).[5,6,16,17] The acquisition cost of lamivudine (average wholesale price for 1 year, $3287) is less than that of the α-interferons,[16] but lamivudine is associated with time-dependent development of resistance. Resistance rates of ~14% to 24% are noted in the first year of lamivudine therapy, increasing to 69% to 71% after 4 to 5 years of therapy.[11–14,18–21] The incidence of lamivudine resistance in individuals coinfected with HBV and HIV is reported to be 20% per year of therapy.[22] Adefovir is effective against lamivudine-resistant virus, and adefovir-resistant virus remains sensitive to lamivudine and entecavir.[5,15] Reported rates of adefovir resistance after 1, 2, 3, 4, and 5 years of therapy are 0%, 3%, 11%, 18%, and 29%, respectively.[15] Rates of entecavir resistance vary depending on whether patients are lamivudine naive or harbor lamivudine-resistant mutants at baseline.[23,24] Genotypic resistance was observed in 3 of 673 treatment-naive patients receiving entecavir therapy over 3 years, and virologic rebound due to entecavir resistance was reported in patients with existing lamivudine-resistant mutants at rates of 1%, 10%, 16%, and 15% after 1, 2, 3, and 4 years of therapy, respectively.[24] Development of resistance may be followed by hepatitis flares and occasionally by severe hepatic failure.[25,26] The likelihood of achieving a complete response (loss of hepatitis B surface antigen [HBsAg] and seroconversion to anti-HBs Ag status) with existing therapies is small (<2% of patients receiving nucleotide therapy after 1 year), and prolonged treatment is needed to suppress HBV and prevent complications of uncontrolled HBV replication.[4,25] New medications are required to address the need for chronic therapy.

Telbivudine (LdT)* was approved by the US Food and Drug Administration on October 25, 2006, for the treatment of active chronic HBV infection in adults (age ≥16 years).[27] As of April 30, 2007, 17 additional countries had approved LdT for the treatment of active chronic HBV infection. This review summarizes the pharmacology and pharmacokinetics, drug interactions, therapeutic efficacy, and adverse effects of LdT in the management of adult patients with chronic HBV infection.

METHODS

Relevant publications were identified from searches of MEDLINE (1996–June 2007), the Cochrane Library, and BIOSIS (1993–June 2007). Search terms included, but were not limited to, *telbivudine*, *β-L-thymidine*, *LdT*, *pharmacology*, *pharmacokinetics*, *adverse events*, *resistance*, *drug interactions*, *hepatitis B*, and *therapeutic use*. Additional publications were identified from the reference lists of the identified papers, meeting abstracts, and correspondence with the manufacturer of LdT.

CHEMISTRY

LdT is a synthetic thymidine nucleoside analogue (L-nucleoside) with the chemical name 1-(2-deoxy-β-L-ribofuranosyl)-5-methyluracil.[27] Its molecular formula and weight are $C_{10}H_{14}N_2O_5$ and 242.23, respectively. LdT is only slightly soluble in water. The chemical structure of LdT is shown in **Figure 1**.

MECHANISM OF ACTION

LdT is efficiently phosphorylated by human cellular kinases to the active triphosphate form.[28,29] The intracellular half-life of the triphosphate metabolite is

*Trademark: Tyzeka™ (Idenix Pharmaceuticals, Cambridge, Massachusetts, and Novartis Pharmaceuticals, East Hanover, New Jersey).

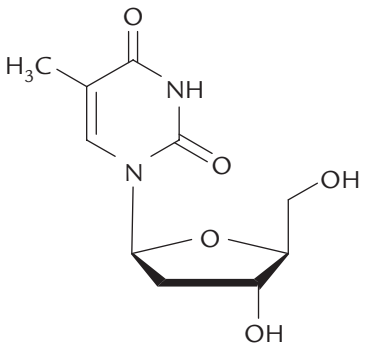

Figure 1. Chemical structure of telbivudine.

~15 hours.[29] LdT acts through blockade of viral reverse-transcriptase activity, which prevents reverse transcribing of HBV pregenomic mRNA, and inhibition of DNA-dependent DNA synthesis, which terminates viral DNA synthesis.[27,30] LdT inhibits first-strand HBV DNA replication (mean [SD] 50% effective concentration [EC_{50}], 1.3 [1.6] µmol/L) and second-strand replication (EC_{50}, 0.2 [0.2] µmol/L), but appears to preferentially inhibit second (+) strand synthesis.[27,30] Like lamivudine, LdT does not inhibit HBV DNA priming.[30] In an in vitro model, the HBV DNA polymerase bound preferentially to LdT triphosphate, and the active moiety did not affect human DNA polymerase (α, β, γ), mitochondrial function, or morphology.[31]

SPECTRUM OF ACTIVITY

LdT is highly selective for HBV and lacks activity against other viruses, including HIV-1 (EC_{50} >200 µmol/L), herpes simplex virus types 1 and 2, influenza A and B viruses, varicella zoster virus, and others.[27,31] The mean (SD) EC_{50} using HBV-producing human HepG2 2.215 cells was 0.19 (0.09) µmol/L.[31]

The effect of combining LdT and adefovir on wild-type HBV has been studied under in vitro conditions using the Bliss independence and Loewe additivity models.[32] These mathematical models are used to quantify the effects of compounds when used in combination. The combination showed additive activity in both the Bliss independence and Loewe additivity models. The combination did not induce cytotoxicity, and no antagonism was noted at the concentrations studied. In an in vitro model,[27] LdT did not antagonize the anti-HIV activity of didanosine, emtricitabine, abacavir, zidovudine, tenofovir, lamivudine, or stavudine.

TELBIVUDINE AND HBV RESISTANCE

Lamivudine-Resistant HBV

Resistance to lamivudine occurs through mutations in the HBV polymerase.[33] Mutations occurring during lamivudine use are commonly termed the YMDD (tyrosine [Y]–methionine [M]–aspartate [D]–aspartate [D]) motif. The mutations occur in the C domain of the reverse transcriptase (rt) of the HBV DNA polymerase.[33] Methionine is the only residue that changes as a result of lamivudine therapy: methionine 204 changes to isoleucine or valine (rtM204I/V). Compensatory mutations often accompany lamivudine-resistant mutations (ie, rtL180M + rtM204V).[33] Yang et al[34] investigated the susceptibility of 11 anti-HBV agents, including LdT, against stable cell lines expressing wild-type HBV or the 4 major lamivudine-resistant HBV patterns (rtL180M + rtM204V, rtV173L + rtL180M + rtM204V, rtM204I, and rtL180M + rtM204I). The mean (SD) EC_{50} for wild-type HBV was 0.7 (0.32) µM. Greater than 300-fold resistance to LdT (wild-type EC_{50}/mutant EC_{50}) was noted for all 4 lamivudine-resistant mutants. As would be expected, high cross-resistance was observed for the other L-nucleoside agents studied (emtricitabine, clevudine, and torcitabine). Adefovir and tenofovir (acyclic phosphonate nucleotides) maintained activity against lamivudine-resistant strains.

LdT remained active against the lamivudine-resistant mutant rtM204V in cell culture.[35] However, given the rare appearance of this mutation in the clinical setting, the preceding finding is unlikely to have any clinical significance.

Telbivudine-Resistant Mutants

The Phase III GLOBE trial compared the efficacy and safety profiles of LdT and lamivudine in the management of treatment-naive patients with compensated chronic HBV infection. Standring et al[36] reported the patterns of resistance seen at 48 weeks in patients who received LdT or lamivudine treatment in the GLOBE trial. Resistance was defined per protocol as virologic breakthrough (increase in HBV DNA from <5 to >5 $\log_{10}$ copies/mL or an increase in HBV DNA to within 1 log of baseline) or HBV DNA 1 log above the lowest concentration with resistance mutations. Treatment breakthrough reflected genotypic resistance in most cases (75/99 lamivudine-treated patients and 28/32 LdT-treated patients). The wild-type HBV genotype was responsible for the remaining breakthrough events. Ten of these 28 LdT-treated patients

had the M204I resistance pattern alone, and 17 harbored the mixed M204I + rtL80I/V mutant. In the lamivudine group, 45%, 33%, and 21% expressed the rtM204I, rtM204V + rtL180M, and rtM204I/V mixed patterns, respectively. In vitro testing indicated that the rtM204I and rtM204I + rtL80I mutants remained sensitive to adefovir and tenofovir.

Lai et al[37] reported the patterns of resistance seen at year 2 in patients who received LdT or lamivudine treatment in the GLOBE trial. In hepatitis B e antigen (HBeAg)–positive patients, resistance rates as defined per protocol and using the 1 log–above criterion were 17.8% and 21.6%, respectively, for LdT and 30.1% and 35.0% for lamivudine ($P < 0.001$, LdT vs lamivudine for both criteria). In HBeAg-negative patients, resistance rates as defined per protocol and using the 1 log–above criterion were 7.3% and 8.6% for LdT and 16.6% and 21.9% for lamivudine ($P < 0.001$, LdT vs lamivudine for both criteria). Approximately 80% of resistance was observed in patients with a 24-week HBV DNA concentration >3 $\log_{10}$ copies/mL. Among patients with an undetectable HBV DNA concentration on the polymerase chain reaction (PCR) assay after 24 weeks of LdT therapy, rates of LdT resistance were 4% and 2% in HBeAg-positive and HBeAg-negative patients, respectively.

Telbivudine and Adefovir Resistance

In an in vitro model,[38] adefovir was active against LdT-resistant mutants, and LdT remained active against an adefovir mutant strain (N236T). In the presence of the adefovir-resistant mutant rtA181V, there was a 3- to 5-fold decrease in LdT susceptibility.[5]

PHARMACOKINETICS

The pharmacokinetics of LdT are summarized in **Table I**. Sex and race do not affect LdT pharmacokinetics.[27,39] The pharmacokinetics of LdT have not been studied in children or the elderly.[27]

Absorption

LdT is quickly absorbed orally, and T_{max} is reached at 1.5 to 4.0 hours after administration.[27,39–42] In dose-ranging studies, C_{max} and $AUC_{0–\infty}$ increased in proportion to the dose.[39,42] With a 600-mg dose of LdT, mean (SD) steady-state C_{max} and $AUC_{0–\infty}$ were 3.7 (1.2) μg/mL and 37.9 (11.1) μg · h/mL, respectively.[27,39] LdT can be administered with or without food.[41]

Distribution

The apparent total Vd of LdT is greater than total body water (range, 1291.4–2144.3 L).[27,39] Protein binding is minimal (3.3%).[27,39]

Metabolism

No metabolites of LdT were noted during metabolic investigations in humans.[27] LdT does not appear to be a substrate for cytochrome P450 (CYP) isozymes.[27,40]

Elimination

After administration of a 600-mg dose, LdT was eliminated in the urine (42%) and feces (49.6%).[27,40] Samples were collected over 7 days after dosing. In healthy Chinese subjects, renal clearance varied between 4.6 and 9.5 L/h, with a mean (SD) of 6.6 (1.5) L/h, or 110 mL/min.[39] Renal clearance in these subjects was similar to that reported in the prescribing information (mean [SD], 7.6 [2.9] L/h).[27] As would be expected, renal clearance decreases as creatinine clearance (CrCl) decreases, reaching a mean of 0.7 (0.4) L/h when the CrCl decreases to <30 mL/min.[27] Hemodialysis for up to 4 hours decreased LdT plasma concentrations by 23%.[27] Apparent total plasma clearance of LdT varied from 16.3 to 29.7 L/h.[39]

The pharmacokinetic profile of LdT is biphasic, with the terminal phase beginning ~32 hours after attainment of C_{max}.[39] In patients with normal kidney function, the $t_{1/2}$ varies from a mean of 39.4 to 49.1 hours.[27,39] Earlier studies reported a shorter mean $t_{1/2}$ because of insufficient sampling times.[41,42] Steady-state conditions occur after 5 to 7 days of administration.[27,39]

In an open-label, parallel-group study, Zhou et al[40] studied the pharmacokinetics of a single 600-mg oral dose of LdT in subjects with normal liver function and mild to severe liver impairment (Child–Pugh class A–C). No significant differences in C_{max}, T_{max}, $t_{1/2}$, apparent total clearance (Cl/F), or $AUC_{0–\infty}$ were noted between those with normal liver function and those with hepatic impairment. However, a nonsignificant decrease in Cl/F (the 90% CI around the geometric mean ratios included unity) and a nonsignificant increase in $AUC_{0–\infty}$ were observed in patients with moderate to severe liver disease compared with healthy volunteers. These changes may be attributed to the differences in body weight and kidney function between groups, as patients with severe hepatic impairment had lower mean body weight than patients in the other groups (74 vs 79 kg, respectively), and those with moderate

Table I. Pharmacokinetics of telbivudine. Data are mean (SD), unless otherwise noted.

Condition	Dose, mg	No. of Patients	C_{max}, μg/mL	T_{max}, Median, h	$t_{1/2}$, h	Cl/F, L/h	Vd, L	AUC, μg · h/mL
Single dose[39]*	200	10	1.8 (0.4)	2.5	43.3 (15.2)	16.3 (3.6)	1305.9 (504.5)	12.8 (2.9)
	400	10	2.6 (0.9)	2.0	49.1 (14.4)	18.3 (3.8)	1291.4 (513.4)	22.9 (5.7)
	600	12	3.7 (1.2)	2.0	39.4 (12.1)	24.8 (7.3)	1344.0 (370.8)	26.4 (8.9)
	800	10	3.5 (1.0)	2.5	46.7 (20.8)	29.7 (8.1)	2144.3 (1497.8)	28.8 (7.9)
Multiple dose	600	12	3.7 (1.2)	2.0	48.8 (10.5)	24.4 (7.3)	1703.1 (528.9)	37.9 (11.1)
Liver function (Child–Pugh)[40]†								
Healthy	600	6	2.8 (0.8)	2.5	28.5 (18.7)	27.6 (5.5)	ND	22.5 (4.5)
Class A	600	6	3.5 (1.7)	2.5	23.3 (4.1)	27.4 (11.1)	ND	24.7 (8.8)
Class B	600	6	3.7 (2.1)	3.0	24.0 (13.7)	22.7 (8.3)	ND	32.2 (19.6)
Class C	600	6	3.4 (2.1)	4.0	23.1 (4.4)	20.0 (7.0)	ND	35.9 (21.8)

Cl/F = total clearance; ND = not done.
* Healthy Chinese subjects.
† Single dose.

and severe hepatic impairment had a larger SD for body weight (20.9 and 19.9, respectively) compared with those in the other groups (mild: 7.7; normal: 12.1). When the Cl/F was adjusted for body weight, the geometric mean ratios were closer to unity and the CIs were narrower in the groups with impaired hepatic function compared with subjects with normal hepatic function. Two patients with moderate to severe hepatic impairment had a CrCl close to the cutoff value of <50 mL/min. Given the small number of patients in each group (n = 6), this degree of renal impairment may have affected the observed decrease in Cl/F and increase in $AUC_{0-\infty}$. These data indicated that dose adjustment of LdT is not necessary in patients with liver impairment and normal kidney function.

DRUG INTERACTIONS

The risk of emerging resistance to single-agent therapy for chronic HBV infection has increased researchers' interest in the role of combination therapy.[43] Studies have evaluated the effects of combination therapy on the pharmacokinetic characteristics of therapeutic agents. The potential for interaction between LdT and lamivudine and adefovir was evaluated in 2 Phase I studies, each of which enrolled healthy subjects and had an open-label, multiple-dose, parallel-group design.[44] In one study in healthy adults, subjects (8 per group) received LdT 200 mg (given as two 100-mg tablets) and lamivudine 100 mg/d, either alone or in combination. In the other study, healthy adults (8 per group) received LdT 600 mg (given as three 200-mg tablets) and adefovir 10 mg/d, either alone or in combination. Pharmacokinetic parameters were assessed after a single dose and at steady state. Neither drug affected the pharmacokinetic parameters of the other when the drugs were used in combination. The mean (SD) AUC over the 24-hour dosing interval (AUC_τ) for LdT 200 mg alone and in combination with lamivudine was 8.9 (2.0) and 9.4 (1.5) μg · h/mL, respectively. The AUC_τ of LdT 600 mg alone and in combination with adefovir was 27.5 (5.3) and 27.3 (6.2) μg · h/mL, respectively. The pharmacokinetics of LdT at the currently approved dosage of 600 mg/d administered in combination with lamivudine have not been studied; however, a clinical trial of LdT combined with lamivudine reported no increased incidence of adverse events.[45]

In 2 separate studies, Zhou et al[46] evaluated the pharmacokinetics of LdT combined with either peginterferon alfa-2a or cyclosporine in healthy subjects. The dose of LdT was 600 mg/d in both studies. In the first study (N = 18), LdT was administered as 14 daily doses, beginning on day 15 of the study, between the first and second doses of peginterferon alfa-2a, which were administered as 180-μg SC injections on days 1 and 22. In the second study (N = 20), the total daily cyclosporine dose was 4 mg/kg administered in 2 equal

doses every 12 hours. Patients were divided into 2 parallel groups: in group 1, LdT was added to cyclosporine on day 5 for 5 days; in group 2, cyclosporine was added to LdT on day 6 for 4 days. LdT did not affect the pharmacokinetics of either drug, nor did either drug affect the pharmacokinetics of LdT. In the first study, the mean (SD) AUC for LdT alone and with peginterferon alfa-2a was 27.8 (6.7) and 28.3 (6.5) μg · h/mL, respectively. In the second study, the AUC for LdT alone and with cyclosporine was 29.0 (6.6) and 28.2 (4.9) μg · h/mL, respectively.

Zhou et al[47] also investigated the potential for an interaction between LdT and tenofovir in 16 healthy volunteers.[47] Pharmacokinetic parameters at steady state were comparable for both medications when administered separately or concurrently.

The prescribing information states that LdT does not affect the CYP enzyme system and should not interact with agents metabolized by these enzymes.[27]

CLINICAL EFFICACY

Phase II Trials

In a double-blind study by Lai et al,[48] adult (age ≥18 years) Asian patients with chronic compensated HBV infection (HBeAg positive) were randomized in a 6:1 ratio to receive LdT 25, 50, 100, 200, 400, or 800 mg/d or placebo. Patients were treated for 4 weeks and monitored for an additional 12 weeks. Eligible patients had markers of chronic HBV infection and had to be free of antiviral or immunosuppressive therapy for 6 months before the trial. Additional exclusion criteria included, but were not limited to, HIV, hepatitis C, or hepatitis delta virus infection; pregnancy; previous nucleoside anti-HBV therapy; or active abuse of illegal drugs or alcohol. A virologic response was defined as a reduction in HBV DNA of ≥2 $\log_{10}$ copies/mL from baseline at 4 weeks, as determined by PCR assay (COBAS AMPLICOR PCR assay for HBV DNA, Roche Diagnostics, Branchburg, New Jersey) with a lower limit of detection of 300 genomic copies/mL. E_{max} (predicted maximal effect) modeling, which approximates the dose of a drug required to achieve a desired outcome, and viral dynamic modeling were used to further assess the dose-response effect of LdT on HBV infection.

The study population ranged in age from 20 to 64 years.[48] Of the 6 patients in the LdT 25-, 50-, 100-, 200-, 400-, and 800-mg and placebo groups, a respective 83%, 50%, 83%, 67%, 67%, 100%, and 86% were male. HBV DNA and serum ALT concentrations were comparable between study groups at baseline. Efficacy data were available for 42 patients. At week 4, the mean reductions from baseline in serum HBV DNA were 2.50, 2.68, 3.19, 2.89, 3.63, and 3.75 $\log_{10}$ copies/mL for the LdT 25-, 50-, 100-, 200-, 400-, and 800-mg groups, respectively, compared with a decrease of 0.13 $\log_{10}$ copies/mL in the placebo group. One patient in the LdT 25-mg group failed to achieve a virologic response; therefore, 97% of patients receiving LdT achieved a virologic response, compared with 0% of placebo recipients ($P < 0.001$). The authors suggested that the lower virologic response to LdT 200 mg compared with LdT 100 mg was the result of numerically lower baseline HBV DNA concentrations in the 200-mg group (P not provided). After discontinuation of LdT, serum HBV DNA concentrations began to rise toward baseline values, but the increase was slower in the LdT 400- and 800-mg groups (P not provided).

E_{max} modeling indicated that the 400- and 800-mg doses of LdT produced "near-maximal" reductions in viral load.[48] In a review of viral dynamics, all LdT doses studied were associated with a rapid decline in HBV DNA viral load of ~2 $\log_{10}$ copies/mL during the first week of drug administration. Modeling of viral dynamics revealed 2 phases of reduction in viral load with LdT therapy. The first phase occurred during the first week of the study. During the second phase, the decay in viral load was slower than in the first phase and appeared to be dose related.

LdT was well tolerated, and no major dose-limiting toxicities were noted.[48] Grade 1 and 2 changes in mean transaminase levels were reported at similar rates in the LdT and placebo groups. Two patients (1 each in the LdT 50- and 100-mg groups) had a transient grade-3 increase in transaminases after discontinuation of LdT.

This study found that LdT (25–800 mg/d) administered for 4 weeks was associated with significant reductions in HBV DNA compared with placebo, with no serious adverse events.[48] Based on the results of this study, LdT daily doses of 400 and 600 mg were chosen for further clinical investigation.

To expand on the previous findings, Lai et al[45] conducted a randomized, double-blind trial of the efficacy and safety profile of 5 therapeutic regimens (LdT 400 mg/d, 600 mg/d, LdT 400 mg/d + lamivudine 100 mg/d, LdT 600 mg/d + lamivudine 100 mg/d, and lamivudine 100 mg/d) in adults with chronic HBV infection (HBeAg positive) and compensated liver disease. The duration of treatment was 52 weeks, with the

option of participating in a continuation study for an additional year. Eligible patients were aged ≥18 years, had markers of chronic HBV infection (serum HBV DNA >6 $\log_{10}$ copies/mL and serum ALT concentrations between 1.3 and 10 times the upper limit of normal [ULN]), and had received no interferon therapy for 12 months before the trial. Exclusion criteria included, but were not limited to, HIV, hepatitis C virus, or hepatitis delta virus infection; pregnancy; previous nucleoside or nucleotide anti-HBV therapy; and abuse of illegal drugs or alcohol in the past 2 years.

The primary efficacy end points of the study were reduction in serum HBV DNA from baseline, area under the curve minus baseline (AUCMB) HBV DNA, and proportion of patients achieving HBV DNA concentrations <5, <4, and <3 $\log_{10}$ copies/mL or <200 copies/mL.[45] HBV DNA concentrations were determined by PCR assay (COBAS AMPLICOR MONITOR PCR assay, Roche Molecular Systems, Branchburg, New Jersey; lower limit of detection, 200 genomic copies/mL). The AUCMB analysis was performed from weeks 1 to 12 and from baseline to the end of the study (52 weeks). Secondary end points included ALT normalization, loss of serum HBeAg with seroconversion (detection of antibody to HBeAg), and loss of hepatitis B surface antigen with seroconversion. Composite end points included virologic response (HBV DNA <5 $\log_{10}$ copies/mL and HBeAg loss) and therapeutic response (ALT normalization or HBeAg loss and HBV DNA concentrations <5 $\log_{10}$ copies/mL). Virologic breakthrough was defined by HBV DNA concentrations that did not decrease to <5 $\log_{10}$ copies/mL and increased during therapy to within 1 $\log_{10}$ of baseline values on ≥2 occasions; and by HBV DNA concentrations that rose to >5 $\log_{10}$ copies/mL during treatment on ≥2 occasions after having decreased to <5 $\log_{10}$ copies/mL.

The study population was mainly Asian (80%–90%) and ranged in age from 18 to 68 years.[45] The numbers of patients in the LdT 400, LdT 600, LdT 400 + lamivudine, LdT 600 + lamivudine, and lamivudine groups were 22 (74% male), 22 (86% male), 21 (90% male), 20 (80% male), and 19 (84% male), respectively. One hundred four patients were included in the intent-to-treat analysis. Baseline demographic characteristics and HBV DNA concentrations were comparable between groups. Because statistical analysis indicated that the efficacy results for the groups were independent of each other, data were pooled for the 2 LdT monotherapy groups and for the 2 combination-therapy groups. The median changes in HBV DNA concentrations at 52 weeks were –4.66, –6.34, and –6.06 $\log_{10}$ copies/mL for the lamivudine, pooled LdT monotherapy, and pooled LdT + lamivudine groups, respectively (P = NS) (**Table II**). The AUCMB values for the pooled data sets at 0 to 52 weeks were –4.42 for the lamivudine group, –5.55 for the pooled LdT monotherapy group, and –5.80 for the pooled LdT + lamivudine group (P < 0.05, LdT monotherapy and combination therapy vs lamivudine only). The proportions of the lamivudine group, pooled LdT monotherapy group, and pooled LdT + lamivudine group who achieved target HBV DNA concentrations were 58%, 89%, and 78%, respectively, for <5 $\log_{10}$ copies/mL; 53%, 82%, and 78% for <4 $\log_{10}$ copies/mL; and 47%, 75%, and 59% for <3 $\log_{10}$ copies/mL (P values not reported). The proportions of patients with undetectable HBV DNA were 32% for the lamivudine group, 61% for the pooled LdT monotherapy group (P < 0.05, LdT vs lamivudine), and 49% for the pooled LdT + lamivudine groups (P = NS vs lamivudine).

In the lamivudine group, 63% of patients achieved normal ALT concentrations, compared with 86% of the pooled LdT monotherapy group (P < 0.05 vs lamivudine) and 78% of the pooled LdT + lamivudine group (P = NS vs lamivudine) (**Table II**).[45] Loss of HBeAg and seroconversion did not differ significantly between the lamivudine group and the pooled LdT monotherapy or pooled LdT + lamivudine group, nor did the proportions of patients achieving a virologic or therapeutic response. Patients in all treatment groups remained HBsAg positive over 52 weeks. After 48 weeks of therapy, viral breakthrough occurred in 3 of 19 patients treated with lamivudine (15.8%). Two patients harbored the rtM204I mutant, and 1 harbored the rtL180M + rtM204V mutant. In the pooled LdT monotherapy group, viral breakthrough occurred in 2 of 44 patients (4.5%); the rtM204I mutant was present in both patients. In the pooled LdT + lamivudine group, viral breakthrough occurred in 5 of 41 patients (12.2%). Three patients had the rtM204I mutant, 1 had wild-type virus, and 1 harbored the rtL180M + rtM204V mutant.

Interestingly, although the combination of LdT + lamivudine was associated with a statistically significant mean reduction in HBV DNA concentrations from baseline compared with lamivudine alone (P < 0.05), it

Table II. Phase IIb studies of telbivudine (LdT) for hepatitis B virus (HBV) infection.

Authors/ Regimens	Decrease in HBV DNA, Median, Log_{10} Copies/mL	Undetectable HBV DNA, %	ALT Normalization, %	Virologic Response, %	Therapeutic Response, %	Viral Breakthrough, %
Lai et al (1 y)[45]						
LAM 100 mg/d	–4.66	32	63	26	53	15.8
LdT 400/600 mg/d (pooled)	–6.34	61*	86*	32	77	4.5
LdT 400/600 mg/d (pooled) + LAM 100 mg/d	–6.06	49	78	20	63	12.2
Lai et al (2 y)[49]						
LAM 200 mg/d	–3.9†	32	47	NR	NR	21.1
LdT 600 mg/d‡	–5.2†	71*	81*	NR	NR	4.5*

ALT = alanine transaminase; virologic response = HBV DNA <5 log_{10} copies/mL + hepatitis B e antigen (HBeAg) loss; therapeutic response = HBV DNA <5 log_{10} copies/mL and HBeAg loss or ALT normalization; LAM = lamivudine; NR = not reported.
* $P < 0.05$ versus LAM.
† Mean.
‡ Given either as monotherapy or in combination with LAM 100 mg/d.

was not significantly different from LdT alone.[45] The occurrence of viral breakthrough also was similar between the lamivudine and pooled LdT + lamivudine group. Given that both medications are L-nucleosides, one might speculate that the lack of a significant benefit from combination therapy relative to LdT alone was due to the similarity in their mechanism of action, with some competition occurring for sites of action.

As noted, patients participating in the study by Lai et al[45] were given the opportunity to continue therapy for an additional year, and 90 of 99 patients (90.9%) volunteered to continue.[49] Patients who had received lamivudine continued the 100-mg/d dose, those who had received LdT 400 or 600 mg/d continued at 600 mg/d, and those who had received combination therapy with LdT 400 or 600 mg/d + lamivudine 100 mg/d continued at LdT 600 mg/d + lamivudine 100 mg/d. Results of the LdT-alone and LdT + lamivudine groups were pooled for efficacy comparisons with the lamivudine-alone group (**Table II**). The mean decreases in HBV DNA from baseline were –3.9 and –5.2 log_{10} copies/mL for the lamivudine and pooled LdT groups, respectively. Thirty-two percent of lamivudine recipients and 71% of pooled LdT recipients had undetectable HBV DNA at 2 years ($P < 0.05$). ALT concentrations were normalized in 47% of lamivudine patients and 81% of LdT patients ($P < 0.05$). Viral breakthrough (ALT elevations and increased HBV DNA concentrations) occurred at a higher rate in the lamivudine group than in the pooled LdT group (21.1% vs 4.5%, respectively; $P < 0.05$). The rate of HBeAg seroconversion did not differ significantly between the lamivudine and pooled LdT groups (21% and 38%). As in the first year of treatment, the combination of LdT + lamivudine was associated with a better response compared with lamivudine alone (*P* not reported); however, the response in any outcome category was no better for the combination-therapy group than for LdT alone. Based on the results of this study, the 600-mg daily dose of LdT was adopted for further clinical study.

Phase III Trials

The multinational GLOBE trial was the major Phase III trial investigating the efficacy and safety profile of LdT 600 mg/d (n = 680) compared with lamivudine 100 mg/d (n = 687) in the management of treatment-naive patients with compensated chronic HBV infection.[37,50,51] Eligible patients had stable chronic HBV infection (HBeAg positive or negative), were HBsAg positive, had a baseline HBV DNA

>6 $\log_{10}$ copies/mL (COBAS AMPLICOR PCR assay), had a baseline ALT concentration 1.3 to 10 times the ULN, and had a prestudy liver biopsy indicating chronic HBV infection. The primary efficacy end point was a therapeutic response, defined as an HBV DNA concentration $\leq 10^5$ copies/mL and ALT normalization or disappearance of HBeAg. The antiviral effect was evaluated in terms of the reduction from baseline in HBV DNA concentrations and the rate of PCR-undetectable HBV DNA. Additional efficacy markers included the rate of ALT normalization, percentage of HBeAg loss and seroconversion, and response on liver histology (52 weeks only). Baseline characteristics (HBV genotype, age, sex, and ethnicity) were analyzed for virologic response.

The data presented here represent intention-to-treat analyses conducted after 52 and 104 weeks of therapy.[37] Seventy-seven percent of the patients were men. Nine hundred twenty-one patients were HBeAg positive (458 LdT, 463 lamivudine), and 446 were HBeAg negative (222 LdT, 224 lamivudine). The mean age of HBeAg-positive and HBeAg-negative patients was 32 and 43 years, respectively. Among HBeAg-positive patients, 82% were Asian, 12% white, and 2% black; among HBeAg-negative patients, 65% were Asian, 23% white, and 1% black.

Week-52 results for HBeAg-positive patients in the GLOBE study are presented in **Figure 2**.[50] Seventy-five percent of patients receiving LdT had a therapeutic response, compared with 67% of patients receiving lamivudine ($P < 0.01$). The decrease in HBV DNA from baseline was 6.5 and 5.5 $\log_{10}$ copies/mL for LdT and lamivudine, respectively ($P < 0.01$). The proportions of patients with undetectable HBV DNA were 60% in the LdT group and 40% in the lamivudine group ($P < 0.01$). The proportions with normalization of ALT concentrations were similar in the 2 groups (77% and 75%, respectively), as were the proportions with HBeAg loss (26% and 23%) and seroconversion (22% and 21%).[37,50] Sixty-five percent of LdT-treated patients had an improvement in liver histology (criteria not described), compared with 56% of lamivudine-treated patients ($P < 0.01$). Primary treatment failure, defined as plasma HBV DNA concentrations consistently ≥ 5 $\log_{10}$ copies/mL, occurred in a respective 5% and 13% of LdT and lamivudine recipients ($P < 0.01$). HBV resistance to therapy (breakthrough and resistance mutations) occurred in 3% and 8% of the 2 treatment groups ($P < 0.01$).[37]

Week-52 results for HBeAg-negative patients in the GLOBE study are presented in **Figure 3**.[50] The proportions achieving a therapeutic response were comparable in the LdT and lamivudine groups (75% and 77%, respectively). The decrease in HBV DNA from baseline was 5.2 and 4.4 $\log_{10}$ copies/mL in the respective groups ($P < 0.01$). The proportions of patients achieving undetectable HBV DNA were 88% and 71% ($P < 0.01$). The corresponding proportions achieving normalization of ALT during therapy were 74% and 79%. The incidence of histologic response was 67% in the LdT group and 66% in the lamivudine group. Primary treatment failure (as defined in the previous paragraph) occurred in <1% of LdT patients and 3% of lamivudine patients.[50] HBV resistance to therapy occurred in 2% and 9% of the 2 groups ($P < 0.01$).

In the analysis of baseline characteristics for virologic response to therapy after 52 weeks, the response to LdT was comparable for all baseline characteristics (P = NS) and numerically higher than the response to lamivudine.[52]

Week-104 results for HBeAg-positive patients in the GLOBE study are presented in **Figure 2**.[37,51] Sixty-four percent of patients receiving LdT had a therapeutic response, compared with 48% of patients receiving lamivudine ($P < 0.05$). The decrease from baseline in HBV DNA was 5.7 and 4.4 $\log_{10}$ copies/mL for LdT and lamivudine, respectively ($P < 0.05$). The proportions of patients with undetectable HBV DNA were a respective 56% and 39% ($P < 0.05$), and the proportions with ALT normalization were 70% and 62% ($P < 0.05$). The proportions of patients with HBeAg loss (34% and 29%) and seroconversion (29% and 24%) were similar in the 2 groups.[51] Primary treatment failure, defined as plasma HBV DNA never falling below 5 $\log_{10}$ copies/mL, occurred in 4% and 12% of patients in the 2 groups ($P < 0.001$).[37] Overall treatment failure in the LdT group was 6.8%, compared with 18.8% in the lamivudine group ($P < 0.001$).[37]

Virologic breakthrough resistance as a cause of treatment failure was reviewed after 104 weeks of therapy.[37] Virologic breakthrough resistance was defined per protocol as a return of HBV DNA to >5 $\log_{10}$ copies/mL; alternatively, it was defined as an increase within 1 $\log_{10}$ copy/mL of the baseline value, or a 1 $\log_{10}$-copy/mL increase in viral load above the lowest measured concentration. Per-protocol resistance was noted in 17.8% and 30.1% of LdT and lamivudine recipients, respectively ($P < 0.001$). Using the cri-

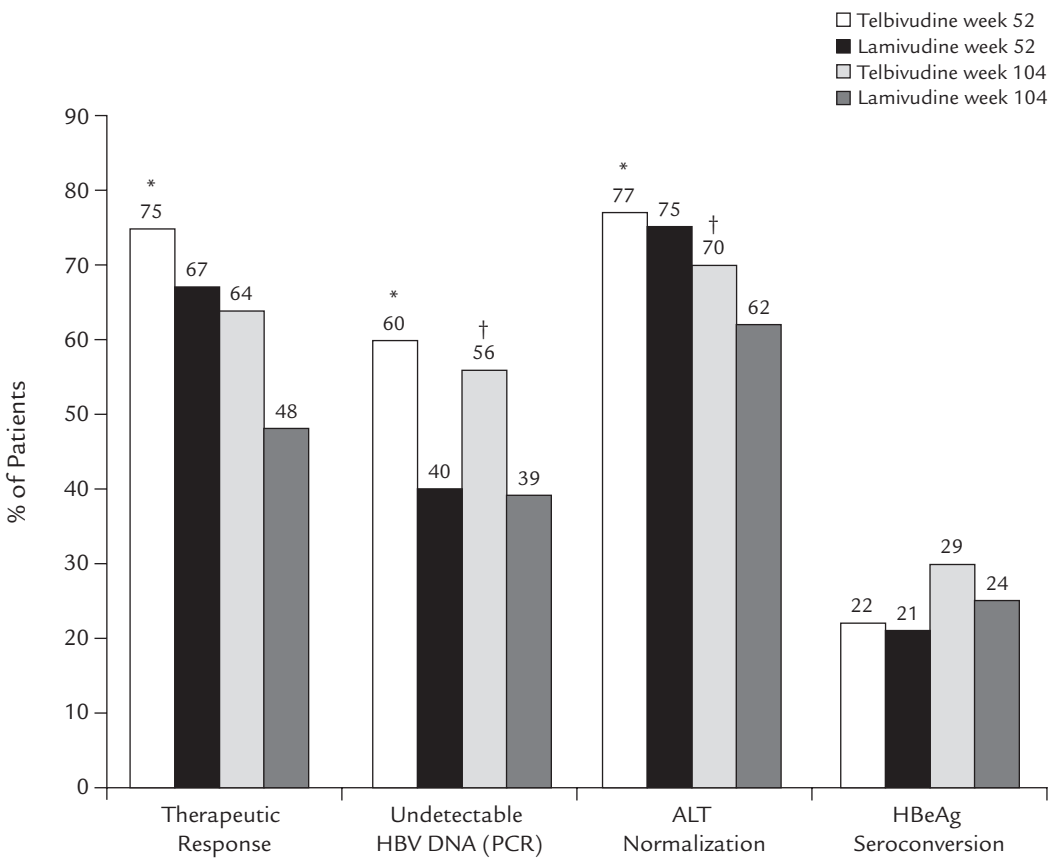

Figure 2. Responses at weeks 52 and 104 in hepatitis B e antigen (HBeAg)–positive patients in the GLOBE study.[37] *$P < 0.01$, telbivudine versus lamivudine; †$P < 0.05$, telbivudine versus lamivudine. Therapeutic response = hepatitis B virus (HBV) DNA concentrations $<10^5$ copies/mL and alanine transaminase (ALT) normalization or disappearance of HBeAg; PCR = polymerase chain reaction.

terion of an increase within 1 $\log_{10}$ copy/mL of baseline, 21.6% of LdT and 35.0% of lamivudine recipients had virologic breakthrough ($P < 0.001$).

Week-104 results for HBeAg-negative patients in the GLOBE study are presented in **Figure 3**.[37,51] Seventy-eight percent of patients in the LdT group achieved a therapeutic response, compared with 66% of patients in the lamivudine group ($P < 0.05$). The decrease from baseline in HBV DNA was 5.0 and 4.2 $\log_{10}$ copies/mL for LdT and lamivudine, respectively ($P < 0.05$). The proportions of patients achieving undetectable HBV DNA concentrations were a respective 82% and 57% ($P < 0.05$). Comparable proportions of patients in the 2 groups achieved normalization of ALT during therapy (78% and 70%). Primary treatment failure (as defined previously) occurred in 0% and 3% of patients ($P < 0.01$).[37,51] Overall treatment failure was 0.9% in the LdT group, compared with 7.6% in the lamivudine group ($P < 0.001$).[37]

Virologic breakthrough resistance (as defined previously) as a cause of treatment failure was reviewed after 104 weeks of therapy in HBeAg-negative patients.[37] Per-protocol resistance was noted in 7.3% and 16.6% of the LdT and lamivudine groups, respectively ($P < 0.001$). Using the criterion of an increase within 1 $\log_{10}$ copy/mL of baseline, 8.6% and 21.9% of the 2 groups had virologic breakthrough ($P < 0.001$).

Patients enrolled in the GLOBE trial were offered the opportunity to discontinue treatment after 1 year of therapy if they had HBV DNA concentrations of <5 $\log_{10}$ copies/mL and had a loss of HBeAg for at least 24 weeks.[53] Thirty-nine patients in the LdT group and 20 in the lamivudine group discontinued therapy; at the time the abstract was prepared, they had been fol-

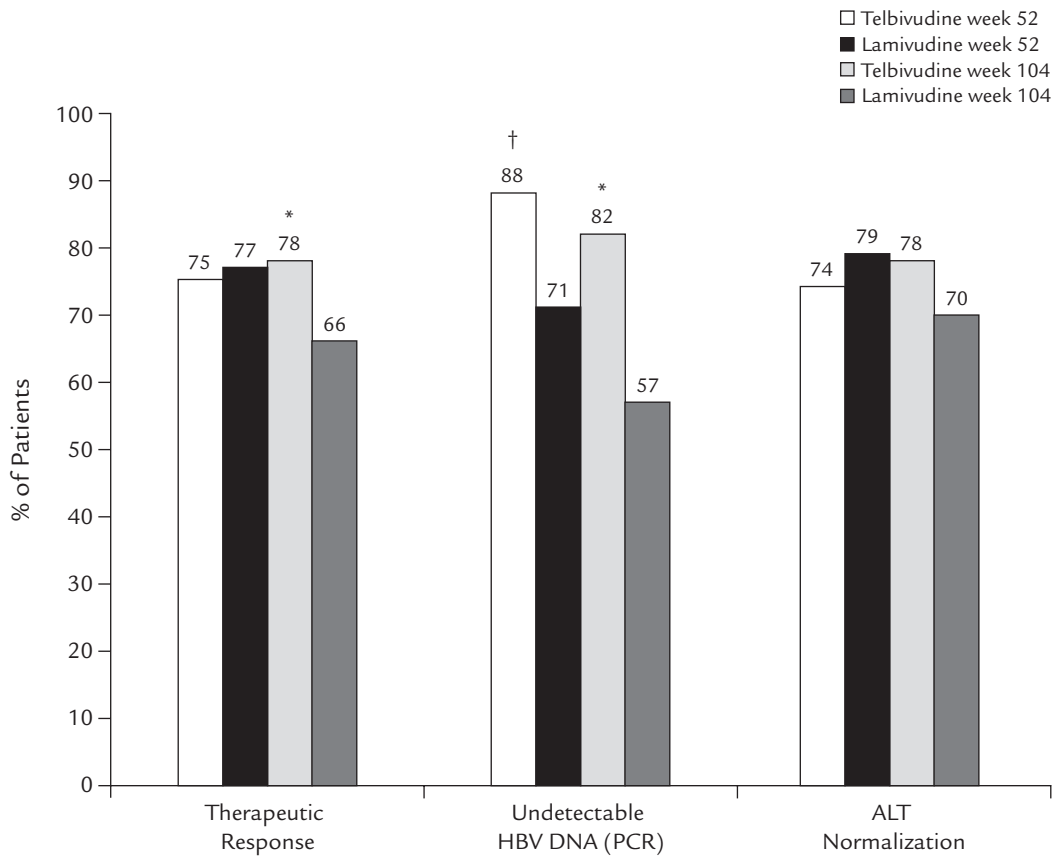

Figure 3. Responses at weeks 52 and 104 in hepatitis B e antigen (HBeAg)–negative patients in the GLOBE study.[37] *$P < 0.05$, telbivudine versus lamivudine; †$P < 0.01$, telbivudine versus lamivudine. Therapeutic response = hepatitis B virus (HBV) DNA concentrations $<10^5$ copies/mL and alanine transaminase (ALT) normalization; PCR = polymerase chain reaction.

lowed for a median of 35.2 weeks from discontinuation (range, 4–59 weeks) in the LdT group and 29.1 weeks from discontinuation (range, 0–53 weeks) in the lamivudine group. The rates of sustained loss of HBeAg and seroconversion were 84% and 83%, respectively, in the LdT group and 89% and 88% in the lamivudine group. Although the numbers of patients were low, the results suggested that therapeutic benefit could be maintained for a median of 33 weeks after discontinuation of LdT and lamivudine therapy.

Jia et al[54] reported the results of a 2-year, randomized, double-blind, Phase III trial comparing LdT with lamivudine in Chinese adults with chronic HBV infection. Inclusion criteria were the same as in the GLOBE study, except that liver biopsy was not required. Analysis was by intention to treat. The primary end point was the degree of HBV DNA suppression. Primary treatment failure was defined as the serum HBV DNA concentration never falling below 5 $\log_{10}$ copies/mL. Baseline parameters were comparable between groups. Two hundred ninety patients were HBeAg positive and 42 were HBeAg negative; the responses to therapy for these patients were combined.

The decrease from baseline in HBV DNA was 5.30 and 3.97 $\log_{10}$ copies/mL for LdT and lamivudine, respectively ($P < 0.05$).[54] The proportions of patients achieving undetectable HBV DNA were 63% and 39% ($P < 0.05$), and the proportions achieving ALT normalization during therapy were 78% and 63% ($P < 0.05$). A therapeutic response occurred in 71% and 45% of the 2 groups ($P < 0.05$). The proportions of HBeAg-positive patients with seroconversion were similar in the LdT (30%) and lamivudine (20%) groups. Primary treatment failure (as defined previ-

ously) occurred in 3% and 15% of the respective treatment groups ($P < 0.001$).

The GLOBE study was sufficiently large to provide information on the comparative efficacy and safety profile of LdT and lamivudine in patients with chronic HBV infection (HBeAg positive or negative).[37,50,51] In HBeAg-positive patients at week 104, LdT was significantly better than lamivudine on a number of efficacy parameters, including therapeutic response, rate of undetectable HBV DNA, and rate of ALT normalization (all, $P < 0.05$).[37,51] The incidence, severity, and types of adverse events with LdT were comparable to those with lamivudine. Because most of the patients in the GLOBE study were Asian or white, the ability to generalize the findings to other patient populations is limited.[37] The increase over time in viral breakthrough during LdT therapy is a concern.[36,37] Given that all patients had compensated HBV liver disease, the utility of LdT in patients with decompensated chronic HBV infection and cirrhosis is unknown.[37] Patients are currently being enrolled for a comparative study of LdT and lamivudine in adults with decompensated chronic HBV infection and cirrhosis.[55] The study by Jia et al[54] had a similar design and outcomes to the GLOBE study and provided more information concerning the efficacy of LdT in HBeAg-positive Chinese patients.

Predictors of Response to Therapy

In the Phase IIb study discussed earlier, Lai et al[45] investigated the efficacy and safety profile of LdT alone, the combination of LdT + lamivudine, and lamivudine alone. As part of this study, observed HBV DNA responses were pooled, regardless of treatment regimen, to determine whether an early response to therapy (week 24) could predict clinical results at week 52. Patients were divided into 4 groups according to their response to therapy at week 24: group 1 (undetectable HBV DNA); group 2 (detectable HBV DNA <3 $\log_{10}$ copies/mL); group 3 (HBV DNA 3–4 $\log_{10}$ copies/mL); and group 4 (HBV DNA >4 $\log_{10}$ copies/mL). Analysis of the response to therapy at the end of 52 weeks found that in group 1, HBV DNA concentrations remained undetectable in 100% of patients, 90% had normalization of ALT, and no patients had viral breakthrough (as defined in the study by Lai et al). At 52 weeks, 62% of patients in group 2 had undetectable HBV DNA and 88% had normalization of ALT. None of the patients in group 2 had viral breakthrough, whereas 19% to 26% of patients in groups 3 and 4 at 24 weeks had viral breakthrough after 52 weeks ($P < 0.05$).

Building upon the previous small study, Zeuzem et al[56] analyzed the results of the GLOBE trial to determine whether an early response to LdT or lamivudine therapy at week 24 could predict clinical results after 52 weeks. The response to therapy was analyzed based on serum HBV DNA concentrations obtained by PCR assay (COBAS AMPLICOR PCR assay; lower limit of detection, 300 genomic copies/mL) at 24 weeks of therapy, and patients were stratified using the same categories described in the preceding paragraph. When the responses in HBeAg-positive patients receiving LdT or lamivudine were combined, 41% of patients in group 1 had seroconversion at 52 weeks, whereas 26%, 13%, and 4% of HBeAg-positive patients in groups 2, 3, and 4, respectively, had seroconversion at this time point. Ninety-one percent of patients in group 1 had undetectable HBV DNA at week 52, compared with 69%, 30%, and 5% in groups 2, 3, and 4. In HBeAg-negative patients, 94%, 67%, 43%, and 10% in groups 1, 2, 3, and 4 had undetectable HBV DNA concentrations at week 52.

To further evaluate the utility of the response to therapy at 24 weeks, positive predictive value (PPV) and negative predictive value (NPV) were determined.[56] For HBeAg-positive patients who had undetectable concentrations of HBV DNA at 24 and 52 weeks, the PPV in patients receiving LdT and lamivudine was 95% and 84%, respectively. For HBeAg-negative patients in the same category, the corresponding PPV values were 96% and 81%. For HBeAg-positive patients who had detectable concentrations of HBV DNA at 24 and 52 weeks, the NPV was 66% and 79%; in HBeAg-negative patients in the same category, the NPV was 43% and 72%.

The likelihood of viral breakthrough at week 52 of therapy was lower for patients in group 1 than for those in groups 2, 3, or 4.[56] Viral breakthrough among HBeAg-positive patients occurred in 1% of group 1, 4% of group 2, 9% of group 3, and 14% of group 4. Among HBeAg-negative patients, the corresponding proportions of viral breakthrough were 0%, 7%, 17%, and 44%. Again, PPV and NPV were determined to evaluate the utility of the 24-week response to therapy and its association with viral resistance at week 52. For HBeAg-positive patients who had undetectable concentrations of HBV DNA at 24 weeks and no resistance at 52 weeks, the PPV was 99.5% and

98.5% in those receiving LdT and lamivudine, respectively. For HBeAg-negative patients in the same category, the PPV was 100% for those receiving LdT and 99.2% for those receiving lamivudine. Among HBeAg-positive patients who had detectable concentrations of HBV DNA at 24 weeks with resistance at 52 weeks, the NPV was 5.3% and 14.6% for LdT and lamivudine, respectively. Among HBeAg-negative patients in the same category, the NPV was 9.5% for LdT and 25.9% for lamivudine.

DiBisceglie et al[57] analyzed the results of the GLOBE trial to determine whether an early response to therapy with LdT or lamivudine at week 24 could predict clinical results at 104 weeks, as it appeared to do at week 52. The response to therapy was analyzed using the same criteria as mentioned previously. When the responses of the HBeAg-positive patients receiving LdT or lamivudine were combined, 45% of patients who were categorized as being in group 1 at week 24 had seroconversion at 104 weeks, compared with 38%, 19%, and 6% of HBeAg-positive patients in groups 2, 3, and 4, respectively. Seventy-seven percent of patients in group 1 were HBV DNA negative at week 104, compared with 58%, 32%, and 12% of groups 2, 3, and 4, respectively. Among HBeAg-negative patients who had undetectable HBV DNA concentrations at 24 weeks, 74%, 66%, 40%, and 10% of groups 1, 2, 3, and 4, respectively, had undetectable concentrations at week 104.

Marcellin et al[58] performed a subgroup analysis of a randomized, active-controlled comparison of therapeutic outcomes with continued LdT therapy, a switch from adefovir to LdT therapy, and continued adefovir therapy (see Switch Studies section).[59] The study population included 135 patients with compensated HBeAg-positive chronic HBV infection, baseline HBV DNA concentrations >6 $\log_{10}$ copies/mL, and serum ALT concentrations between 1.3 and 10 times the ULN. The primary goal of the subgroup analysis was to determine whether an early antiviral response to LdT or adefovir could predict the response at 52 weeks. Patients' responses at 52 weeks were reviewed according to whether HBV DNA concentrations were >3 or <3 $\log_{10}$ copies/mL at week 24. Serum HBV DNA concentrations were <3 $\log_{10}$ copies/mL in 49% of patients receiving LdT and 22% of patients receiving adefovir at week 24 ($P < 0.01$). When the 24-week results for these patients were pooled, 94% had undetectable HBV DNA concentrations, 44% had HBeAg seroconversion, and 94% had achieved normalization of ALT. Among patients with HBV DNA concentrations >3 $\log_{10}$ copies/mL at week 24, 23% had undetectable HBV DNA concentrations, 11% had HBeAg seroconversion, and 71% achieved normalization of ALT at 52 weeks. Viral breakthrough occurred exclusively in patients with 24-week HBV DNA concentrations >4 $\log_{10}$ copies/mL.

The results of these studies suggest that an early virologic response to therapy, defined as HBV DNA concentrations ranging from undetectable to <3 $\log_{10}$ copies/mL, may be of value in predicting subsequent therapeutic outcomes. The early response to therapy may be used to predict viral breakthrough. The incidence of treatment failure increased with higher 24-week HBV DNA concentrations and was particularly high in patients with HBV DNA concentrations >4 $\log_{10}$ copies/mL.[56,58] DiBisceglie et al[57] recommended that patients with HBV DNA concentrations >4 $\log_{10}$ copies/mL after 24 weeks of therapy be considered for treatment intensification.

Switch Studies

Two studies available only in abstract form evaluated the therapeutic effects of switching from lamivudine or adefovir to LdT after a defined interval compared with continuing lamivudine or adefovir therapy.[59–62] In the study by Safadi et al,[60] patients with compensated HBV infection (HBeAg positive or negative) with HBV DNA concentrations >3 $\log_{10}$ copies/mL after 3 to 12 months of lamivudine therapy were randomly assigned to 1 of 2 study groups. Group 1 received LdT 600 mg/d (n = 122) and group 2 continued therapy with lamivudine 100 mg/d (n = 124), both for 1 year. At week 24, LdT patients had a mean decrease in HBV DNA concentrations of 1.9 $\log_{10}$ copies/mL, compared with a decrease of 0.9 $\log_{10}$ copies/mL in the lamivudine group ($P = 0.002$) (**Table III**). Eighty percent of LdT recipients and 56% of lamivudine recipients had HBV DNA concentrations <5 $\log_{10}$ copies/mL ($P < 0.001$). The other efficacy parameters—percentages with undetectable HBV DNA, HBeAg loss, and ALT normalization—were comparable between groups at week 24.

Heathcote et al[59] reported the initial (week-24) results from a randomized, open-label trial comparing the efficacy and tolerability of LdT and adefovir in treatment-naive patients with compensated chronic HBV infection (HBeAg positive), baseline serum HBV DNA concentrations >6 $\log_{10}$ copies/mL, and baseline serum ALT concentrations 1.3 to 10 times the ULN. Patients

Table III. Week-24 results from switch studies of telbivudine (LdT) for hepatitis B virus (HBV) infection.

Authors/Regimens	Decrease in HBV DNA, Mean, Log_{10} Copies/mL	Undetectable HBV DNA, %*	Loss of HBeAg, %	ALT Normalization, %
Safadi et al[60]				
Switched from previous LAM to LdT	–1.9†	40	10	49
Continued LAM	–0.9	31	9	68
Heathcote et al[59]				
LdT	–6.3‡	38.6‡	16	61.4
ADF	–5.0	12.4	10	62.9

HBeAg = hepatitis B e antigen; ALT = alanine transaminase; LAM = lamivudine; ADF = adefovir.
* Lower limit of detection for the polymerase chain reaction assay, ≤300 copies/mL.
† $P = 0.002$, LdT versus LAM.
‡ $P < 0.01$, LdT versus ADF.

were initially randomized to receive LdT 600 mg/d (n = 45 [78% male; 93% Asian; mean age, 34 years) or adefovir 10 mg/d (n = 90 [74% male; 91% Asian; mean age, 32 years) for 24 weeks. After 24 weeks of therapy, 50% of patients receiving adefovir were randomly switched to LdT, and the other 50% continued adefovir. The primary end point was the reduction in HBV DNA concentrations at 24 weeks; secondary end points were antiviral effect and safety profile, evaluated at weeks 24 and 52. At week 24, the mean decreases in HBV DNA concentrations were –6.30 and –4.97 $\log_{10}$ copies/mL for LdT and adefovir, respectively ($P < 0.01$) (**Table III**). HBV DNA concentrations were undetectable in 38.6% and 12.4% of patients in the 2 groups ($P < 0.01$). Other measures of the response, including HBeAg loss and normalization of serum ALT, were similar between treatment groups. Both treatments were well tolerated.

Bzowej et al[61] reported 52-week results from the preceding study, comparing the antiviral responses to continued LdT therapy, adefovir switched to LdT therapy, and continued adefovir therapy. The continued LdT and switch groups had a greater decrease in HBV DNA concentrations compared with the continued adefovir group at 52 weeks (*P* not reported). Fifty-eight percent of the continued LdT group and 54% of the switch group had undetectable HBV DNA concentrations, compared with 39% of the continued adefovir group (*P* not reported). Loss of HBeAg occurred in 31%, 26%, and 21% of the continued LdT, switch, and continued adefovir groups, respectively. By 16 weeks after the switch from adefovir to LdT, the mean viral load was comparable to that in the continued LdT group.

Upon completion of that 52-week study,[59,61] patients could enroll in a 24-week extension trial in which they would receive LdT 600 mg/d.[62] The response to the switch from adefovir to LdT was reviewed in those patients who had a less-than-ideal response while receiving adefovir (HBV DNA concentrations >3 $\log_{10}$ copies/mL at 24 or 52 weeks). Patients who had HBV DNA concentrations >3.0 $\log_{10}$ copies/mL after 24 weeks of adefovir therapy (78% of those receiving adefovir) and were switched to LdT had a mean reduction in HBV DNA of 2.1 $\log_{10}$ copies/mL at week 52, whereas patients who remained on adefovir over the same period had a decrease of 0.9 $\log_{10}$ copies/mL. Patients who had HBV DNA concentrations >3.0 $\log_{10}$ copies/mL after 52 weeks of adefovir therapy and were switched to LdT had a decrease in HBV DNA concentrations of 2.1 $\log_{10}$ copies/mL at week 76. In those who continued LdT therapy, rates of undetectable HBV DNA were 39% at 24 weeks, 60% at 52 weeks, and 72% at 76 weeks.

The results of these preliminary studies indicate that patients receiving lamivudine or adefovir may experience improved virologic outcomes when switched to LdT. Studies are needed to assess the role of LdT as

a rescue option for patients with chronic HBV infection whose initial therapy fails.

Salvage Therapy and Ongoing Studies

Patients enrolled in the GLOBE study who had viral breakthrough during LdT therapy (increase in HBV DNA of >1 $\log_{10}$ copy/mL from nadir) were offered salvage therapy with adefovir (n = 17) or the combination LdT + adefovir (n = 5).[63] The abstract presents information for 21 of the 22 patients who received ≥16 weeks of salvage therapy. At 16 weeks after the initiation of salvage therapy, mean (SD) HBV DNA concentrations decreased by 4.1 (2.1) $\log_{10}$ copies/mL ($P < 0.001$), and ALT concentrations decreased by a mean of 93 IU/L ($P = 0.03$). In patients who received combination salvage therapy, the mean (SD) reduction in HBV DNA concentrations was 5.1 (1.5) $\log_{10}$ copies/mL ($P < 0.001$), and ALT concentrations decreased by 104 IU/L ($P = 0.03$). Although the number of patients receiving salvage therapy was small, these results indicate that adefovir with or without continued LdT may be effective in patients who experience viral breakthrough while receiving LdT.

Additional studies are being conducted to investigate the utility of combining LdT with adefovir, peginterferon alfa-2a, and valtorcitabine for the management of chronic HBV infection.[64–67] Comparisons of LdT with entecavir are also under way.[68]

ADVERSE EVENTS

The most common adverse events attributed to LdT during clinical trials were upper respiratory tract infection (14%–17%), nasopharyngitis (11%–15%), headache (11%–12%), fatigue and malaise (12%–14%), abdominal pain (6%–12%), increase in blood levels of creatine kinase (9%–12%), cough (7%–8%), nausea and vomiting (7%), diarrhea (7%), and influenza or influenzalike symptoms (7%).[27,37] Adverse events were generally mild to moderate in severity. Approximately 0.6% of LdT-treated patients required discontinuation of medication because of adverse drug events, lack of effect, or disease progression, compared with 2% of lamivudine-treated patients.[27] Adverse events of moderate to severe intensity (grades 2–4) occurred in 22% of patients in the GLOBE trial.[27] Those reactions included muscle-related symptoms (2%), fatigue/malaise (1%), headache (1%), arthralgia (<1%), abdominal pain (<1%), diarrhea or loose stools (<1%), gastritis (<1%), and cough (<1%).

Grade 3 or 4 laboratory abnormalities may include creatine kinase ≥7.0 times the ULN, which occurred in 9% of LdT-treated patients and 3% of lamivudine-treated patients in the GLOBE trial.[27] Most creatine kinase elevations were asymptomatic, but the return to baseline values after drug discontinuation took longer in the LdT group than in the lamivudine group.[27] Symptoms may include diffuse myalgias, muscle tenderness, or muscle weakness. Three of 680 patients experienced myopathy with muscle weakness while receiving LdT therapy.[27] LdT therapy should be discontinued if myopathy is detected. Other grade 3 or 4 laboratory abnormalities included elevations in ALT >3.0 times baseline (4%) and bilirubin >5.0 times the ULN (<1%), and hematologic abnormalities (absolute neutrophil count ≤749/mm^3 in 2%; platelet count ≤49,999/mm^3 in <1%).[27] Moderate to severe ALT flares (ALT >500 IU/mL or ALT flare with bilirubin 2 times the ULN) occurred in 2.8% of LdT-treated patients and 8.4% of lamivudine-treated patients from week 24 to week 104.[37]

The package insert for LdT contains a black box warning concerning the risk of lactic acidosis and severe hepatomegaly with steatosis.[27] This condition is a class effect,[69] and the literature search identified no reported cases. In addition, patients who stop LdT therapy should be monitored for several months for flares of HBV infection. Readers are encouraged to review the LdT package insert for further discussion of adverse events.[27]

DOSAGE AND ADMINISTRATION

The primary goal of therapy in patients with chronic HBV infection is sustained suppression of virus production and prevention of complications due to uncontrolled disease. LdT is indicated for use in adult patients with chronic HBV infection and can be taken without regard to meals.[27,41] The recommended dose for the management of chronic HBV infection is one 600-mg tablet daily.[27]

Because LdT is eliminated by the kidney, dose adjustment is necessary when the CrCl is <50 mL/min.[27] No dose adjustment is recommended for patients with a CrCl ≥50 mL/min; those with a CrCl of 30 to 49 mL/min should receive LdT 600 mg once every 48 hours; those with a CrCl <30 mL/min without need for hemodialysis should receive LdT 600 mg every 72 hours; and those with end-stage kidney disease requiring hemodialysis should receive LdT 600 mg every 96 hours

after the completion of dialysis.[27] A 4-hour hemodialysis session has been shown to remove 23% of a dose of LdT.[27] Dose adjustment is not required in patients with moderate to severe liver impairment alone.[27,40] Given the nature of chronic HBV infection, the ideal duration of LdT administration has not been determined.[27]

LdT has not been studied during pregnancy. It is classified as Pregnancy Category B, and women should not breastfeed if they are taking this medication.[27] The drug should be used during pregnancy only after a careful review of the risks and benefits. The reader is encouraged to review the package insert for additional dosing information.[27]

PHARMACOECONOMIC CONSIDERATIONS

Wong and Pauker[70] used a Markov cohort simulation to assess the cost-effectiveness of LdT as applied to the GLOBE study. LdT reduced the 10-year relative risk of cirrhosis by 33% in HBeAg-positive patients and by 18% in HBeAg-negative patients. The model projected a life extension of 3.8 years in those who were HBeAg positive and 0.8 year in those who were HBeAg negative. LdT was found to have a favorable incremental cost-effectiveness ratio (adjusted for age and sex) in both treatment groups.

Based on average wholesale price, LdT is less costly than adefovir or entecavir in the management of chronic HBV infection. A 30-day supply of the standard doses of LdT (600 mg/d), entecavir (0.5- or 1-mg tablet daily), and adefovir (10 mg/d) cost ~$584.40, $768.40, and $688.08, respectively.[16]

CONCLUSIONS

LdT belongs to the same class of drugs (L-nucleosides) as lamivudine and is highly selective for HBV. Phase III studies in treatment-naive patients have reported significant benefits for LdT compared with lamivudine in the management of patients with chronic HBV infection. LdT should not be used in patients harboring lamivudine-resistant mutants because of cross-resistance. Head-to-head studies comparing LdT with other active medications are beginning to be published, and additional trials are enrolling patients. The GLOBE study found an increase in viral resistance and breakthrough with continued use of LdT, although resistance rates were lower with LdT than with lamivudine. Further study is needed to define the overall risk of resistance with continued use. Until this issue is resolved, LdT is likely to be relegated to second-line status after use of peginterferon alfa-2a, adefovir, and entecavir. LdT may have a role in combination therapy (although not with other L-nucleosides such as lamivudine), but studies are only beginning to be conducted. Adverse events with LdT are similar in character, severity, and incidence to those with lamivudine of placebo, with the exception of a greater risk for elevations in creatine kinase concentrations. Patients receiving LdT should be counseled to look for symptoms of myopathy and to report these to their health care provider.

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REFERENCES

1. Poland GA, Jacobson RM. Clinical practice: Prevention of hepatitis B with the hepatitis B vaccine. *N Engl J Med*. 2004;351:2832–2838.
2. Hepatitis B vaccines [World Health Organization (WHO) Web site]. *Wkly Epidemiol Rec*. 2004;79:253–264. http://www.who.int/wer/2004/en/wer7928.pdf. Accessed December 4, 2007.
3. Alter MJ, Mast EE. The epidemiology of viral hepatitis in the United States. *Gastroenterol Clin North Am*. 1994; 23:437–455.
4. Hoofnagle JH, Doo E, Liang TJ, et al. Management of hepatitis B: Summary of a clinical research workshop. *Hepatology*. 2007;45:1056–1075.
5. Lok AS, McMahon BJ. Chronic hepatitis B: Update of recommendations. *Hepatology*. 2004;39:857–861.
6. Cooksley WG, Piratvisuth T, Lee SD, et al. Peginterferon alpha-2a (40 kDa): An advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. *J Viral Hepat*. 2003;10:298–305.
7. Marcellin P, Lau GK, Bonino F, et al, for the Peginterferon Alfa-2a HBeAg-Negative Chronic Hepatitis B Study Group. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med*. 2004;351:1206–1217.
8. Chan HL, Leung NW, Hui AY, et al. A randomized, controlled trial of combination therapy for chronic hepatitis B: Comparing pegylated interferon-alpha2b and lamivudine with lamivudine alone. *Ann Intern Med*. 2005;142: 240–250.
9. Janssen HL, van Zonneveld M, Senturk H, et al, for the HBV 99-01 Study Group and the Rotterdam Foundation for Liver Research. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic

hepatitis B: A randomised trial. *Lancet*. 2005;365:123–129.
10. Lau GK, Piratvisuth T, Luo KX, et al, for the Peginterferon Alfa-2a HBeAg-Positive Chronic Hepatitis B Study Group. Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2005;352:2682–2695.
11. Lai CL, Chien RN, Leung NW, et al, for the Asia Hepatitis Lamivudine Study Group. A one-year trial of lamivudine for chronic hepatitis B. *N Engl J Med*. 1998;339:61–68.
12. Liaw YF, Leung NW, Chang TT, et al, for the Asia Hepatitis Lamivudine Study Group. Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. *Gastroenterology*. 2000;119:172–180.
13. Leung NW, Lai CL, Chang TT, et al, for the Asia Hepatitis Lamivudine Study Group. Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: Results after 3 years of therapy. *Hepatology*. 2001;33:1527–1532.
14. Gaia S, Marzano A, Smedile A, et al. Four years of treatment with lamivudine: Clinical and virological evaluations in HBe antigen-negative chronic hepatitis B. *Aliment Pharmacol Ther*. 2004;20:281–287.
15. Delaney WE IV. Progress in the treatment of chronic hepatitis B: Long-term experience with adefovir dipivoxil. *J Antimicrob Chemother*. 2007;59:827–832.
16. *Red Book*. Montvale, NJ: Thomson Healthcare Inc; 2007.
17. Pegasys (peginterferon alfa-2a) [prescribing information]. Nutley, NJ: Hoffman-LaRoche Inc; 2007.
18. Lai CL, Dienstag J, Schiff E, et al. Prevalence and clinical correlates of YMDD variants during lamivudine therapy for patients with chronic hepatitis B. *Clin Infect Dis*. 2003;36:687–696.
19. Guan R, Lai CL, Liaw YF, et al. Efficacy and safety of 5 years lamivudine treatment of Chinese patients with chronic hepatitis B. *J Gastroenterol Hepatol*. 2001;16(Suppl 1):44. Abstract A60.
20. Moskovitz DN, Osiowy C, Giles E, et al. Response to long-term lamivudine treatment (up to 5 years) in patients with severe chronic hepatitis B, role of genotype and drug resistance. *J Viral Hepat*. 2005;12:398–404.
21. Lok AS, Lai CL, Leung N, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology*. 2003;125:1714–1722.
22. Thio CL. Hepatitis B in the human immunodeficiency virus-infected patient: Epidemiology, natural history, and treatment. *Semin Liver Dis*. 2003;23:125–136.
23. Colonno RJ, Rose R, Bladick CJ, et al. Entecavir resistance is rare in nucleoside naive patients with hepatitis B. *Hepatology*. 2006;44:1656–1665.
24. Colonno RT, Rose RE, Pokornowski K, et al. Four year assessment of ETV resistance in nucleoside-naive and lamivudine refractory patients. *J Hepatol*. 2007;46(Suppl 1):S294. Abstract 781.
25. Lok AS, McMahon BJ, for the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines Committee. Chronic hepatitis B: Update of recommendations. *Hepatology*. 2004;39:857–861.
26. Ide T, Kumashiro R, Kuwahara R, et al. Clinical course of patients with chronic hepatitis B with viral breakthrough during long-term lamivudine treatment. *J Gastroenterol*. 2005;40:625–630.
27. Tyzeka (telbivudine) tablets [prescribing information]. Cambridge, Mass: Idenix Pharmaceuticals, Inc; and East Hanover, NJ: Novartis Pharmaceuticals Corporation; October 2006.
28. Golitsina N, Danehy F, Fellows R, et al. Telbivudine phosphorylation by three enzymes: Implications for anti-hepatitis B virus activity in vitro and in the clinic. *Hepatology*. 2006;44(Suppl 1):561A. Abstract 1000.
29. Hernandez-Santiago B, Placidi L, Cretton-Scott E, et al. Pharmacology of beta-L-thymidine and beta-L-2′-deoxycytidine in HepG2 cells and primary human hepatocytes: Relevance to chemotherapeutic efficacy against hepatitis B virus. *Antimicrob Agents Chemother*. 2002;46:1728–1733.
30. Seifer M, Patty A, Dukhan D, et al. Telbivudine (LDT) preferentially inhibits second (+) strand HBV DNA synthesis. *J Hepatol*. 2005;42(Suppl 2):151. Abstract 412.
31. Bryant ML, Bridges EG, Placidi L, et al. Antiviral L-nucleosides specific for hepatitis B virus infection. *Antimicrob Agents Chemother*. 2001;45:229–235.
32. Delaney WE IV, Yang H, Miller MD, et al. Combinations of adefovir with nucleoside analogs produce additive antiviral effects against hepatitis B virus in vitro. *Antimicrob Agents Chemother*. 2004;48:3702–3710.
33. Stuyver LJ, Locarnini SA, Lok A, et al. Nomenclature for antiviral-resistant human hepatitis B virus mutations in the polymerase region. *Hepatology*. 2001;33:751–757.
34. Yang H, Qi X, Sabogal A, et al. Cross-resistance testing of next-generation nucleoside and nucleotide analogues against lamivudine-resistant HBV. *Antivir Ther*. 2005;10:625–633.
35. Bartholomeusz A, Yuen L, Locarnini S, et al. Understanding HBV resistance to telbivudine: Molecular modeling and database mining. *J Hepatol*. 2007;46(Suppl 1):S185. Abstract 486.
36. Standring DN, Patty A, Chapron C, et al. Resistance determination in patients experiencing virologic breakthrough following telbivudine or lamivudine therapy in the International GLOBE trial. *Gastroenterology*. 2007;132(Suppl 2):A-766. Abstract 1781.
37. Lai CL, Gane E, Hsu CW, et al. Two-year results from the GLOBE trial in patients with hepatitis B: Greater clinical and antiviral efficacy for telbivudine (LdT) vs lamivudine. Presented at: 57th Annual Meeting of the American Association for the Study of Liver Disease; October 27–31, 2006; Boston, Mass. http://www.natap.org/2006/AASLD/AASL

D_18.htm. Accessed December 5, 2007.
38. Standring DN, Seifer M, Patty A, et al. HBV resistance determination from the telbivudine GLOBE registration trial. *J Hepatol*. 2006;44(Suppl 2): S191. Abstract 514.
39. Hu P, Jiang J, Wang H, et al. Single-dose and multiple-dose pharmacokinetics and safety of telbivudine after oral administration in healthy Chinese subjects. *J Clin Pharmacol*. 2006;46:999–1007.
40. Zhou XJ, Marbury TC, Alcorn HW, et al. Pharmacokinetics of telbivudine in subjects with various degrees of hepatic impairment. *Antimicrob Agents Chemother*. 2006;50:1721–1726.
41. Zhou XJ, Lloyd DM, Chao GC, Brown NA. Absence of food effect on the pharmacokinetics of telbivudine following oral administration in healthy subjects. *J Clin Pharmacol*. 2006;46:275–281.
42. Zhou XJ, Lim SG, Lloyd DM, et al. Pharmacokinetics of telbivudine following oral administration of escalating single and multiple doses in patients with chronic hepatitis B infection: Pharmacodynamic implications. *Antimicrob Agents Chemother*. 2006;50:874–879.
43. Borgia G, Gentile I. Treating chronic hepatitis B: Today and tomorrow. *Curr Med Chem*. 2006;13:2839–2855.
44. Zhou XJ, Fielman BA, Lloyd DM, et al. Pharmacokinetics of telbivudine in healthy subjects and absence of drug interaction with lamivudine or adefovir dipivoxil. *Antimicrob Agents Chemother*. 2006;50:2309–2315.
45. Lai CL, Leung N, Teo EK, et al, for the Telbivudine Phase II Investigator Group. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. *Gastroenterology*. 2005;129:528–536.
46. Zhou XJ, Fielman B, Dubuc-Patrick G, et al. Absence of pharmacokinetic drug-drug interaction between telbivudine and peginterferon alpha-2a or cyclosporine in healthy subjects. *J Hepatol*. 2006;44(Suppl 2):S194. Abstract 522.
47. Zhou X, Pietropaolo K, Becker M, et al. Absence of pharmacokinetic drug-drug interaction between telbivudine and tenofovir. *Gastroenterology*. 2007; 132(Suppl 2):A-766. Abstract S1782.
48. Lai CL, Lim SG, Brown NA, et al. A dose-finding study of once-daily oral telbivudine in HBeAg-positive patients with chronic hepatitis B virus infection. *Hepatology*. 2004;40:719–726.
49. Lai CL, Leung N, Teo EK, et al. Phase IIb extended-treatment trial of telbivudine (LdT) vs. lamivudine vs. combination treatment in hepatitis B patients: Two-year results. *Gastroenterology*. 2005;128(Suppl 2): A-692. Abstract 320.
50. Bzowej N, Lai CL, Gane E, et al. Phase III comparison of telbivudine vs. lamivudine in patients with chronic hepatitis B: Efficacy, safety, and predictors of response at 1 year. *Gastroenterology*. 2006;130(Suppl 2): A-765–A-766. Abstract 482.
51. Lai CL, Gane E, Hsu CW, et al. Two-year results from the GLOBE trial in patients with hepatitis B: Greater clinical and antiviral efficacy for telbivudine (LDT) vs. lamivudine. *Hepatology*. 2006;44(Suppl 1):222A. Abstract 91.
52. Thongsawat S, Lai CL, Gane E, et al. Telbivudine displays consistent antiviral efficacy across patient subgroups for the treatment of chronic hepatitis B: Results from the GLOBE study. *J Hepatol*. 2006;44(Suppl 2): S49. Abstract 110.
53. Poynard T, Chutaputti A, Hwang SG, et al. Sustained off-treatment HBeAg response in telbivudine and lamivudine treated HBeAg-positive patients from the GLOBE study. *J Hepatol*. 2007;46(Suppl 1):S27. Abstract 58.
54. Jia JD, Hou JL, Yin YK, et al. Two-year results of a phase III comparative trial of telbivudine vs. lamivudine in Chinese patients. *J Hepatol*. 2007;46 (Suppl 1):S189. Abstract 497.
55. Telbivudine versus lamivudine in adults with decompensated chronic hepatitis B and evidence of cirrhosis [ClinicalTrials.gov Web site]. http://www.clinicaltrials.gov/ct/show/NCT00076336?order=13. Accessed June 15, 2007.
56. Zeuzem S, Lai CL, Gane E, et al, for the GLOBE Study Group. Optimal virologic and clinical efficacy at one year is associated with maximal early HBV suppression in nucleoside-treated hepatitis B patients. Presented at: 41st Meeting of the European Association for the Study of Liver Diseases; April 26–30, 2006; Vienna, Austria. http://www.natap.org/2006/EASL/EASL_26.htm. Accessed December 5, 2007.
57. DiBisceglie A, Lai CL, Gane E, et al. Telbivudine GLOBE trial: Maximal early HBV suppression is predictive of optimal two-year efficacy in nucleoside-treated hepatitis B patients. *Hepatology*. 2006;44(Suppl 1): 230A–231A. Abstract 112.
58. Marcellin P, Chan HL, Lai CL, et al. In hepatitis B patients treated with either adefovir or telbivudine, maximal early HBV suppression at 24 weeks predicts optimal one-year efficacy. *J Hepatol*. 2007;46(Suppl 1):S193. Abstract 508.
59. Heathcote EJ, Chan HL-Y, Lai C-L, et al, for the 018 Study Group. A comparative trial of telbivudine and adefovir dipivoxil for treatment of HBeAg-positive, compensated chronic hepatitis B: 24 Week results. Presented at: Digestive Disease Week; May 20–25, 2006; Los Angeles, Calif. http://www.hivandhepatitis.com/2006icr/ddw/pdf/Heathcote.pdf. Accessed December 5, 2007.
60. Safadi R, Xie Q, Chen Y, et al. A randomized trial of switching to telbivudine versus continued lamivudine in adults with chronic hepatitis B: Results of the primary analysis at week 24. *J Hepatol*. 2007;46(Suppl 1): S196–S197. Abstract 516.
61. Bzowej N, Chan HL, Lai CL, et al. A randomized trial of telbivudine (LDT) vs. adefovir for HBeAg-positive chronic hepatitis B: Final week 52 re-

sults. *Hepatology*. 2006;44(Suppl 1): 563A. Abstract 1005.
62. Marcellin P, Chan HL, Lai CL, et al. 76 Week follow up of HBeAg-positive chronic hepatitis B patients treated with telbivudine, adefovir or switched from adefovir to telbivudine. *J Hepatol*. 2007;46(Suppl 1):S55. Abstract 124.
63. Gane E, Lai CL, Min A, et al. Adefovir salvage therapy for virologic breakthrough in telbivudine-treated patients from the GLOBE study. *J Hepatol*. 2007;46(Suppl 1):S187–S188. Abstract 493.
64. Study of combination therapy with LdT plus adefovir versus adefovir alone [ClinicalTrials.gov Web site]. http://www.clinicaltrials.gov/ct/show/NCT00376259?order=7. Accessed June 15, 2007.
65. Trial of telbivudine combination therapy vs. continued adefovir monotherapy [ClinicalTrials.gov Web site]. http://www.clinicaltrials.gov/ct/show/NCT00409019?order=5. Accessed June 15, 2007.
66. Efficacy and safety of telbivudine in treatment naïve patients with HBeAg-positive chronic hepatitis B (CHB) [ClinicalTrials.gov Web site]. http://www.clinicaltrials.gov/ct/show/NCT00412750?order=2. Accessed June 5, 2007.
67. Telbivudine versus the combination of telbivudine and valtorcitabine in patients with chronic hepatitis B [ClinicalTrials.gov Web site]. http://clinicaltrials.gov/ct/show/NCT00128544?order=1. Accessed June 5, 2007.
68. An extension to viral kinetics study of telbivudine and entecavir in adults with chronic hepatitis B [ClinicalTrials.gov Web site]. http://www.clinicaltrials.gov/ct/show/NCT00467545?order=1. Accessed June 7, 2007.
69. Gerschenson M, Brinkman K. Mitochondrial dysfunction in AIDS and its treatment. *Mitochondrion*. 2004;4:763–777.
70. Wong JB, Pauker SG. Cost-effectiveness of telbivudine versus lamivudine for chronic hepatitis B. *J Hepatol*. 2007;46(Suppl 1):S199. Abstract 522.

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