

Evaluation of the Cost-Effectiveness of Entecavir Versus Lamivudine in Hepatitis BeAg-Positive Chronic Hepatitis B Patients

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ABSTRACT

BACKGROUND: As new treatment options for chronic hepatitis B virus (HBV) become available, evaluations of cost-effectiveness become important. Entecavir is a deoxyguanine nucleoside analogue approved by the U.S. Food and Drug Administration in March 2005 for HBV infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (alanine aminotransferase or aspartate aminotransferase) or histologically active disease. Entecavir has demonstrated greater suppression of viral replication compared with lamivudine, but also has a relatively higher drug acquisition cost in the United States.

OBJECTIVE: To estimate the long-term health and economic impact of treating HBV with entecavir versus lamivudine in patients who are positive for hepatitis B e antigen (HBeAg) based on the efficacy and safety results of the Phase 3, double-blind, randomized controlled trial, Benefits of Entecavir for Hepatitis B Liver Disease (BEHoLD).

METHODS: A decision tree model was developed to evaluate the cost-effectiveness of entecavir compared with lamivudine in suppressing HBV DNA to an undetectable level. Risks for compensated cirrhosis (CC), decompensated cirrhosis (DC), and hepatocellular carcinoma (HCC) were derived from the published Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV, 2006) study, a longitudinal (mean follow-up: 11.4 years) cohort study of community residents who were seropositive for the hepatitis B surface antigen; 85% of REVEAL-HBV participants were HBeAg-negative. To estimate future risks of CC, DC, and HCC, the REVEAL-HBV study's multivariate-adjusted relative risks of CC, DC, and HCC for 5 HBV DNA (viral load level) categories were applied to posttreatment HBV DNA levels obtained from the BEHoLD trial of 709 HBeAg-positive HBV patients treated with entecavir (n = 354) or lamivudine (n = 355). Entecavir and lamivudine were assigned annual costs of \$7,365 and \$2,604, respectively, based on the wholesale acquisition cost. Life expectancy for DC and HCC was estimated by the declining exponential approximation of life expectancy method. Other model parameter values, such as utilities and event medical costs, were derived from published sources. The joint uncertainty of projected event time distribution and treatment failure rates beyond the trial period were considered using probabilistic sensitivity analyses (PSA) with 1,000 replicates. The analytic perspective was that of a U.S. third-party payer responsible for all direct health care expenditures.

RESULTS: In the BEHoLD clinical trial (A1463022), subjects were predominantly male (75%), Asian (57%), or white (40%) with a mean age of 35 years. Entecavir was superior to lamivudine in the proportion of subjects who achieved undetectable HBV DNA (<300 copies per mL) by polymerase-chain reaction assay at week 48 (69.1% vs. 39.8%, respectively) ($P < 0.001$). In the REVEAL-HBV study after statistical adjustment for age, gender, cigarette smoking, and alcohol consumption, rates of CC, DC, and HCC were associated with higher HBV DNA levels (e.g., compared with the reference category [< 300 copies per mL], adjusted hazard ratios for HCC were 1.2, 2.9, 9.5, and 15.2 for serum HBV DNA levels of 300-9,999, 10,000-99,999, 100,000-999,999, and ≥ 1 million copies per mL, respectively). In the reference case, for a hypothetical cohort of 1,000 HBV patients aged 35 years, 52 weeks of entecavir treatment compared with lamivudine treatment avoided 71 cases of CC, 8 DC cases, and 42 HCC cases within 10 years, resulting in a 0.728 quality-adjusted life-year (QALY)

gain at an incremental cost of \$2,350, with a 3% annual discount. The incremental cost of using entecavir was \$3,230 per QALY gained (95% confidence interval [CI], \$2,312-\$4,528), with 99.3% of PSA-derived estimates below \$5,000 per QALY. Results were robust and most sensitive to efficacy, drug cost, and treatment duration.

CONCLUSIONS: Assuming that (1) the efficacy of entecavir after 1 year is sustainable and (2) liver disease risk levels from the REVEAL-HBV study population (a primarily HBeAg-negative group) adequately represent risk for a treated HBeAg-positive patient group, entecavir given for up to 10 years would be highly cost-effective in HBeAg-positive patients.

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What is already known about this subject

- Chronic hepatitis B virus (HBV) infection is a complex disease, with 15%-40% of infected persons progressing to severe liver disease including cirrhosis, liver failure, and liver cancer. Manifestations of HBV usually occur late in life, resulting in substantial life years lost as well as a negative economic impact among individuals during the most productive decades of life. About 1.25 million HBV-infected people live in the United States, and most of the chronically infected persons in the United States are of Asian descent.
- Current analyses of the cost-effectiveness of HBV drugs have been based on a disease progression paradigm focused heavily on the ability to achieve hepatitis B e antigen (HBeAg) seroconversion (to HBeAg-negative status and HBe antibody) following treatment intervention. However, recent evidence suggests that the incidence of liver cirrhosis and hepatocellular carcinoma (HCC), as well as the risk of progression to liver cirrhosis and HCC in HBV patients, are strongly linked to the level of circulating virus independent of HBeAg status. A cost-effectiveness analysis of HBV therapies based on this paradigm of disease progression to cirrhosis and HCC does not exist in the literature.

What this study adds

- This study is the first to evaluate the cost-effectiveness of HBV antiviral therapy based on an ability to suppress viral replication. Our decision tree model indicates that initiating therapy in HBeAg-positive HBV patients with entecavir (both short-term and long-term use) would be very cost-effective at \$3,176 per quality-adjusted life-year (QALY) gained (95% CI, \$2,202-\$4,482), with 99.3% of PSA-derived estimates below \$5,000 per QALY.

Note: Two commentaries and an editorial on the subject of this article appear on pages 61-64, 65-69, and 83-85 of this issue.

Chronic hepatitis B (CHB) virus infection is defined by the presence of hepatitis B viral surface antigen (HBsAg) in the blood for >6 months. Besides HBsAg, other antigens are detected in the blood, such as hepatitis B e antigen (HBeAg). However, HBeAg may be absent after several decades of infection as hepatitis B mutants, which do not secrete HBeAg, replace the hepatitis B wild types. HBeAg-negative CHB infection is defined by no detectable HBeAg, but evidence of viral replication as indicated by the presence of viral deoxyribonucleic acid (HBV DNA) in the blood.

Both HBeAg-positive and HBeAg-negative infection can potentially result in progressive liver disease and affect about 350 million people worldwide, 1.25 million of whom live in the United States.¹ Hepatitis B virus (HBV) patients are at increased risk of developing liver cirrhosis and hepatocellular carcinoma (HCC). Although most patients will not develop hepatic complications from CHB, 15%-40% will eventually develop serious sequelae during their lifetime.²

Even in countries such as the United States where the prevalence of HBV is relatively low ($\leq 1\%$ of the population), the burden of illness and health care costs associated with the disease are substantial. In the United States, health costs associated with HBV were estimated at \$500 million annually (expressed in 1997 U.S. dollars).³ Other studies have found that the average cost per hospitalization for a HBV patient with cirrhosis is \$14,063 and that the cost of a liver transplant is an estimated \$89,076 (expressed in 1999 U.S. dollars).⁴ In determining the value of new medicines to treat HBV, drug acquisition costs must be balanced against the expected benefits in future morbidity, mortality, and costs avoided from disease progression.

Six drugs are currently approved for treating CHB virus infection in the United States. Interferons, including alfa-2b, recombinant (Intron-A), and peginterferon alfa-2a (Pegasys), are associated with several side effects and cannot be used in patients with decompensated liver disease. Additionally, many patients cannot tolerate the adverse events associated with interferons, resulting in treatment discontinuation.⁵⁻¹⁰ Lamivudine (Epivir) was the first oral antiviral agent approved by the U.S. Food and Drug Administration (FDA) for HBV in November 1995, and provided a well-tolerated, effective option for patients.¹¹ However, the occurrence of drug-resistant HBV mutants became a major limitation with lamivudine therapy.¹²⁻¹⁴

Adefovir dipivoxil (Hepsera) was approved by the FDA for HBV in September 2002.¹⁵ Adefovir is generally well tolerated^{16,17} and effective against lamivudine-resistant hepatitis B strains.^{18,19} However, with adefovir therapy, only about 21% of HBeAg-positive patients and 50% of HBeAg-negative patients achieve a viral load <300 copies per mL after 1 year of therapy, making adefovir the nucleoside analogue with the slowest viral kinetics of the approved agents. Additionally, the level of viral response after 1 year of adefovir therapy predicts the risk of future resistance, and the 5-year risk of resistance with adefovir therapy is 29%.²⁰

Entecavir (Baraclude), a deoxyguanine nucleoside analogue, is a selective inhibitor of the replication of HBV. Entecavir was approved by the FDA in March 2005²¹ and is currently the most potent antiviral agent for HBV treatment, suppressing viral replication to <300 copies per mL in approximately 87% of treatment-naïve patients after 96 weeks of therapy. Throughout 96 weeks, no patient experienced a virologic breakthrough due to entecavir resistance.²² Telbivudine (Tyzeka) is the most recent antiviral drug for treating HBV, approved by the FDA in October 2006.²³ Based on registrational studies, telbivudine's initial antiviral effect is better than that of lamivudine; however, its utility is limited by viral resistance that continues even through the second year of therapy.²⁴ No head-to-head clinical trials have investigated the safety and efficacy of telbivudine versus entecavir.

Our study aims to evaluate the cost-effectiveness of entecavir compared with lamivudine in chronic HBeAg-positive infection by using a statistical model that applied (1) community cohort study data on risks of HBV disease sequelae to (2) randomized clinical trial data on outcomes for HBV-treated patients.

Methods

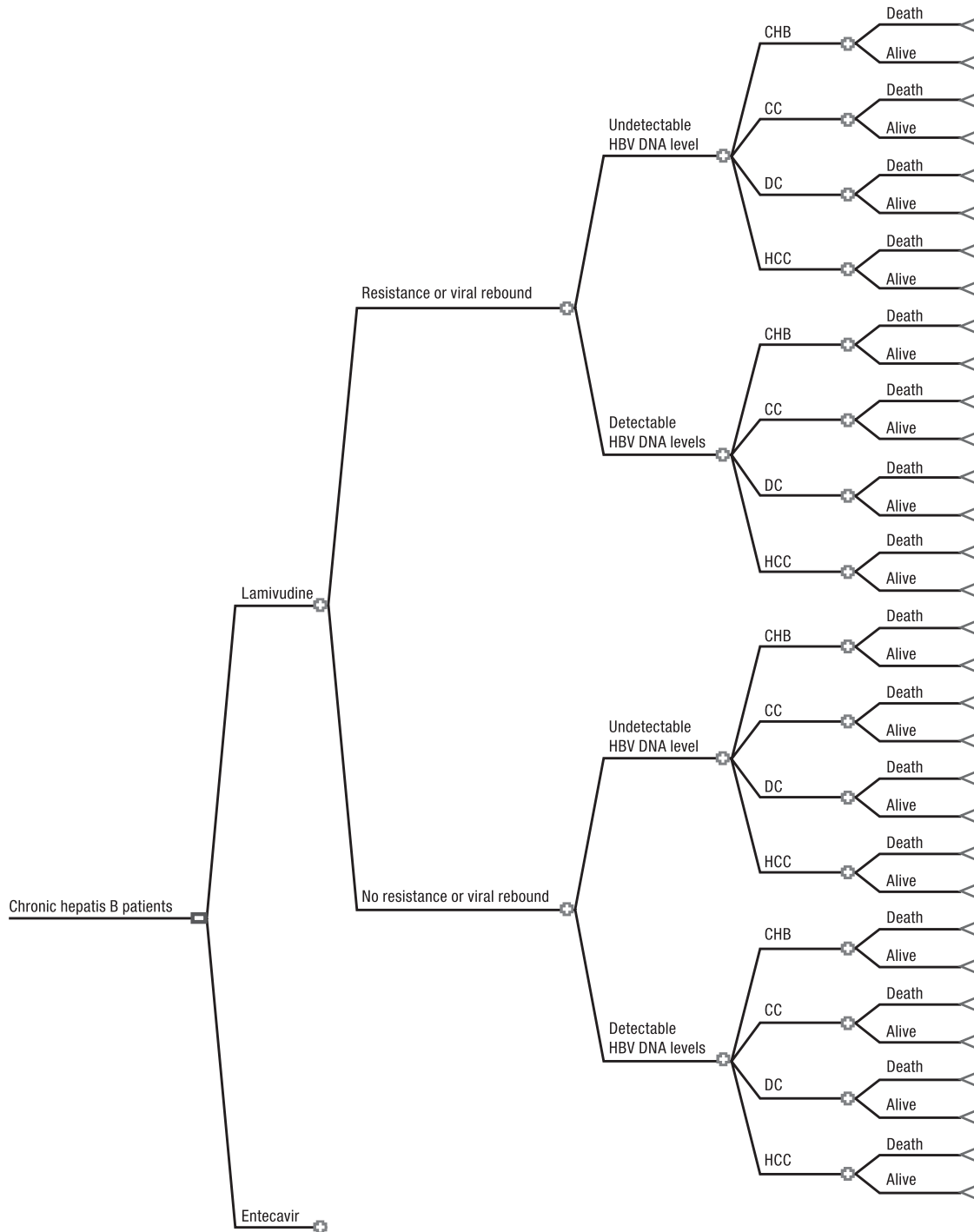
Overview of Modeling Structure

A decision tree model with a fixed 10-year window was developed to evaluate the cost-effectiveness of initiating therapy with entecavir in nucleos(t)ide-naïve HBeAg-positive HBV patients compared with a strategy of initiating therapy with lamivudine and adding adefovir to rescue patients once they developed drug resistance. The model was based on the ability of each strategy to achieve HBV DNA suppression to an undetectable level. An illustrative conceptual model framework is shown in Figure 1.

A hypothetical cohort of 1,000 HBV patients received either lamivudine or entecavir at model entry. Because patients might develop viral resistance with continued drug use or experience viral rebound after treatment cessation, their HBV DNA values were updated annually to incorporate first-year trial efficacy results as well as the impacts from subsequent development of viral resistance or viral rebound after treatment cessation. The decision model consisted of 5 disease stages: CHB (HBV without cirrhosis and HCC as entry point), compensated cirrhosis, decompensated cirrhosis, HCC, and death. Based on the pattern and rates of observed liver complications from the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study,^{25,26} the majority of patients developing HCC were from the cirrhosis health state, but the decision model was modified to allow some HBV patients to progress to a HCC health state directly without passing through the compensated cirrhosis health state. However, all patients experiencing decompensated cirrhosis had to progress through the compensated cirrhosis health state. The base case model assumed treatment for 1 year, and sensitivity analyses allowed drug treatment for up to 10 years. Any

FIGURE 1 Illustrative Model Diagram of 10-Year Disease Progression

This modified tree model projects disease risks based on current HBV DNA levels.



The entecavir arm follows the same pathways as the lamivudine arm.

CHB=chronic hepatitis B; CC=compensated cirrhosis; DC=decompensated cirrhosis; HBV=hepatitis B virus; HCC=hepatocellular carcinoma.

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TABLE 1 Reference Case Model Parameters, Inputs, Data Sources, and Methodology

	Entecavir 0.5 mg	Lamivudine 100 mg	Source	Methodology
Estimated relative risk by serum HBV DNA levels (copies/mL)				
< 300 (undetectable)	1.0 for cirrhosis, DC, and HCC		REVEAL-HBV ^{25,28,29}	Cox proportional hazards models were used with adjustment for gender, age, and habits of cigarette smoking and alcohol drinking.
300-9,999	1.4 for cirrhosis (2.7 for DC), 1.2 for HCC		REVEAL-HBV ^{25,28,29}	
10,000-99,999	2.5 for cirrhosis (2.7 for DC), 2.9 for HCC		REVEAL-HBV ^{25,28,29}	
100,000-999,999	5.9 for cirrhosis (5.9 for DC), 9.5 for HCC		REVEAL-HBV ^{25,28,29}	
≥ 1 million	9.8 for cirrhosis (19.3 for DC), 15.2 for HCC		REVEAL-HBV ^{25,28,29}	
Proportion of patients with HBV DNA levels (copies/mL)				
< 300 (undetectable)	69.1%	39.8%	BEHoLD ²⁷	Measured postrandomization at week 48.
300-9,999	24.7%	18.2%	BEHoLD ²⁷	
10,000-99,999	4.4%	11.7%	BEHoLD ²⁷	
100,000-999,999	0.6%	9.3%	BEHoLD ²⁷	
≥ 1 million	1.2%	21.0%	BEHoLD ²⁷	
Annual incidence rates with undetectable HBV DNA				
CC		0.34%	REVEAL-HBV ^{25,26}	Estimated based on 873 patients with undetectable HBV DNA at study entry.
DC		0.02%	REVEAL-HBV ^{25,26}	
HCC		0.11%	REVEAL-HBV ^{25,26}	
Annual mortality rate				
DC		14.4%	Reference 33	Life expectancy estimated based on the DEALE method.
HCC		23.3%	Reference 32	
Average time to event from study entry (years)				
CC		8	REVEAL-HBV ^{25,26}	Estimated based on actual patient-level data.
DC		9	REVEAL-HBV ^{25,26}	
HCC		7	REVEAL-HBV ^{25,26}	
Annual medical costs				
CC		\$1,130	Reference 36	Reimbursed cost (not provider-submitted charges) from U.S. third-party payers. Published cost estimates were inflated to year 2006 values using the medical component of the Consumer Price Index.
DC		\$15,095	Reference 37	
HCC		\$9,923	Reference 37	
Utilities				
CHB		0.81	Reference 34	Survey of a U.S. sample of 100 uninfected individuals using standard gamble method.
CC		0.82	Reference 34	
DC		0.36	Reference 34	
HCC		0.41	Reference 34	
Study drugs				
Daily cost/patient	\$20.52	\$7.61	Reference 35	Officially published figures.
Actual days of use/patient/year	359	342	BEHoLD ²⁷	Estimated based on number of days of drug use recorded in the trial.

All costs are expressed in 2006 U.S. dollars.

BEHoLD=Benefits of Entecavir for Hepatitis B Liver Disease; CHB=chronic hepatitis B; CC=compensated cirrhosis; DEALE=declining exponential approximation of life expectancy; DC=decompensated cirrhosis; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; REVEAL-HBV=Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus.

patient developing resistance was rescued by a strategy of adding adefovir to the current drug therapy.

Data on treatment efficacy were obtained from a randomized, controlled, double-blind, Phase 3 registrational trial (Benefits

of Entecavir for Hepatitis B Liver Disease [BEHoLD]).²⁷ Using the week-48 HBV DNA data from this trial, future disease progression was projected based on observed rates from the aforementioned REVEAL-HBV study. Progressions to compensated

cirrhosis, decompensated cirrhosis, and HCC were modeled separately, and we subsequently estimated the cost consequences and life year impacts from the modeled progression. All model assumptions and data inputs used in the reference case analysis are presented in Table 1.

This decision tree model structure was chosen instead of a state transition or patient-level simulation model to capture chronic disease progression because of lack of data access and reliable details for estimating the disease state transition rates for HBV DNA levels over time. The decision tree model with a fixed-time window made our model as simple as possible while still retaining sufficient structure to specify the assumed relationship between inputs and outcomes.

The study perspective was that of a U.S. third-party payer responsible for all direct health care expenditures. The cost-effectiveness of entecavir compared with lamivudine was expressed as the incremental cost per life-year gained or quality-adjusted life-years (QALYs) gained. Indirect medical costs and lost productivity were not included in the analyses. A 3% discount rate was applied to both costs and life-year projections beyond the model base year.

Statistical software (SAS, SAS Institute, Cary, NC) was used for patient-level data analyses, and an Excel spreadsheet-based model using Visual Basic for Applications (Microsoft Corporation, Redmond, WA) was created for all modeling and simulation executions.

Efficacy and Safety Data From the BEHoLD Phase 3 Clinical Trial

We obtained efficacy and safety data from a randomized Phase 3 trial of HBeAg-positive subjects (BEHoLD-A1463022 trial).²⁷ Briefly, this was a randomized, double-blind, double-dummy study of entecavir 0.5 mg given once daily for 52 weeks compared with lamivudine 100 mg once daily. A total of 709 eligible subjects were randomized (1:1) to receive either entecavir (n=354) or lamivudine (n=355). Subjects who had previously received a nucleoside analogue active against hepatitis B, interferon alfa, or thymosin alfa within 24 weeks prior to randomization were excluded. Any subject with a prior exposure to lamivudine lasting >12 weeks was also excluded. Response to treatment was assessed based on a primary endpoint of histologic improvement and other secondary efficacy endpoints, including our primary study endpoint of interest—serum HBV DNA by polymerase-chain reaction (PCR) assay at the week-48 visit.

Entecavir was well tolerated, with a safety profile comparable with that of lamivudine 100 mg. The most frequent adverse events in the entecavir group were headache, upper respiratory tract infection, nasopharyngitis, upper abdominal pain, fatigue, and pyrexia, all of which occurred with comparable frequency in the lamivudine group. As a result, the risk and costs of drug-related adverse events were not included in the analysis.

All intent-to-treat patients were considered in this analysis. All patients with missing HBV DNA data at either baseline or week 48 (n=45) were treated as missing and excluded in the primary analyses. An alternative imputation method, using Last Observation Carried Forward or treating noncompleters as failures, was also implemented, but it had minimal impact on our modeling results. The study period ranged from a patient's randomization to the end of blinded treatment or week 48, whichever came first.

Data on Disease Progression Risk

Data on risk of disease progression based on the level of viral load was derived from the REVEAL-HBV study.^{25,26} This prospective cohort study was conducted as part of a community-based cancer screening program in Taiwan and designed to evaluate the relationship between baseline (cohort entry) risk factors and progression to cirrhosis and HCC.

In brief, of 4,115 REVEAL-HBV participants who were HBsAg-seropositive, free of HCC at cohort entry, and followed until June 30, 2004, 3,653 participants (88.8%) were determined to be seronegative for anti-hepatitis C virus (HCV) antibody and were thus included in the analyses of cirrhosis and HCC risk in HBV patients. During a mean follow-up time of 11.4 years and 41,779 person-years, 365 subjects (10.0%) were newly diagnosed with cirrhosis, 31 of whom (0.8%) were determined to have decompensated cirrhosis events; there were 164 incident cases of HCC (4.5%). Adjusted relative risks for liver cirrhosis and HCC for each of 5 defined serum HBV DNA levels were estimated using Cox proportional hazards models, with adjustment for gender, age, and habits of cigarette smoking and alcohol drinking.^{25,28}

Two steps were followed to apply the REVEAL-HBV results to the 709 subjects from the BEHoLD randomized clinical trial to project future events over a 10-year period. First, everyone with a week-48 posttreatment HBV DNA level <300 copies per mL was assigned the baseline event rate for participants with undetectable viral loads observed from the REVEAL-HBV cohort study. The risks of liver events for subjects with HBV DNA in the higher categories were then estimated based on the adjusted hazard ratio associated with that viral load category in the REVEAL-HBV study cohort. To stratify all cirrhosis events into compensated and decompensated cirrhosis so as to assign respective medical costs and QALYs, we further developed a submodel for predicting decompensated cirrhosis, and then subtracted this predicted number from the total cirrhosis estimate to derive the number of compensated cirrhosis events.²⁹

Life Year Gain and Utility Estimates

Age- and gender-specific life expectancy estimates for HBV and compensated cirrhosis were based on data from National Vital Statistics Reports.³⁰ Life expectancy for decompensated cirrhosis or HCC was estimated based on the declining exponential

approximation of life method: inverse of annual event mortality.³¹ Annual mortality was set at 23.3% for HCC³² and 14.4% for decompensated cirrhosis.³³ To avoid double-counting life years lost for those patients with multiple events, we assumed that (1) all patients with decompensated cirrhosis had a prior compensated cirrhosis, and 72% of patients with HCC had a prior compensated cirrhosis, and (2) if patients had both HCC and compensated cirrhosis or both decompensated cirrhosis and compensated cirrhosis, only life expectancy for HCC or decompensated cirrhosis was assigned. These assumptions were based on the final REVEAL-HBV study sample, in which all patients with decompensated cirrhosis had prior compensated cirrhosis, and 72% of patients with HCC had prior compensated cirrhosis, but no one was observed to experience both decompensated cirrhosis and HCC.

All trial patients were assigned a baseline utility of 0.81 at entry, meaning that 1 year of life in a person with HBV would be equivalent to 0.81 years of healthy life, and faced a sudden decline in the utility value—in other words, a tariff—as they developed liver complications.³⁴ To adjust for the health-related quality of life associated with different health states, the relative value, or utility, of each health state was rated compared with a year in perfect health. We used the ratings of HBV-associated health states elicited from a representative sample of 100 uninfected individuals in the United States using a visual analogue scale and weighted using the standard gamble method.³⁴ In this study, probability wheels with 2-color pie charts for the relative probabilities of perfect health and death were used as props for the standard gamble, and a feeling thermometer was used for the visual analogue scale. As a result, we assigned an estimated utility weight of 0.82 for compensated cirrhosis, 0.36 for decompensated cirrhosis, and 0.41 for HCC (Table 1).

Cost Estimates

Two cost components were considered in the analyses: study drug costs and medical costs of HBV-related complications. The medical component of the Consumer Price Index (2006 Bureau of Labor Statistics data) was used to adjust all costs to 2006 values.

In the base case analysis, it was assumed that the duration of drug treatment was 1 year; we also considered longer-term drug treatment in the sensitivity analyses. Drug compliance was estimated based on the actual usage of study drugs recorded on the clinical trial Case Report Forms. Total costs of study drugs were estimated by the wholesale acquisition cost (WAC) per day multiplied by the mean number of days of drug use (359 for entecavir, 342 for lamivudine) observed in the trial.³⁵ Annual drug costs were \$7,365 for entecavir 0.5 mg and \$2,604 for lamivudine 100 mg.

Annual medical costs updated to 2006 U.S. dollars were \$1,130 for compensated cirrhosis,³⁶ \$15,095 for decompensated cirrhosis, and \$9,923 for HCC.³⁷ The annual medical cost was

applied to a patient from the time an event occurred until that patient died. Costs of clinical trial outpatient physician visits and laboratory tests were excluded from cost estimates because we assumed that they would be equivalent in both groups.

Modeling Assumptions

In the REVEAL-HBV cohort, the average times to event from study entry were 8 years for compensated cirrhosis, 9 years for decompensated cirrhosis, and 7 years for HCC, with times ranging from 1 to 14 years. To appropriately discount the subsequent medical costs and life years lost after all of these events had occurred, in the reference case analysis we deterministically assigned these averages (at 8, 9, and 10 years) to the trial patients who later developed a compensated cirrhosis, decompensated cirrhosis or HCC event during the follow-up period, while we also modeled time to event probabilistically later in the sensitivity analyses.

Distributions of subjects to different HBV DNA levels beyond the first year after entecavir or lamivudine treatment cessation were assumed based on HBV DNA data observed at week-24 postdosing in those BEHoLD patients with a protocol-defined “response” (defined as HBV DNA <0.7 MEq per mL and loss of HBeAg at week 48). This was the only and best data source available to allow us to estimate viral rebound rates for both entecavir and lamivudine. This assumption is essential because viral rebound is an important phenomenon accompanying cessation of therapy, and rebound will occur in a significant proportion of patients. For entecavir, 37% had <300 copies per mL, 40% had between 300 and 10⁴ copies per mL, 11% had between 10⁴ and 10⁵ copies per mL, 1% had between 10⁵ and 10⁶ copies per mL, and 11% had >10⁶ copies per mL. For lamivudine, these percentages were 34%, 26%, 12%, 5%, and 23%, respectively. The number of events was first projected based on the observed first-year HBV DNA data and then repeated for each year based on rebound-adjusted viral data from years 2-10. An average of these projections was used for our final estimate of the number of liver cirrhosis or HCC events.

Sensitivity Analyses

To investigate the robustness of the model findings, we ran univariate sensitivity analyses (with a change of ±10% for continuous variables and use of the closest alternative category for categorical variables) on the following variables: age, gender, discount rate, efficacy, drug price, and event medical costs. We also ran sensitivity analyses on the 4 input parameters based on their available alternative values: utility, hepatic flares (defined as an elevation in serum alanine aminotransferase [ALT] to a level >2 times the patient's stable baseline and >10 times the upper limit of normal), length of treatment, and lamivudine resistance.

Because utility scores have rarely been measured for HBV patients, utilities for liver complications used in our study relied on a single but large sample survey of HBV patients. To test the

impact of varying utility scores for liver complications on our cost-effectiveness results, a different set of published utility tariff values was also used³⁸; these values were not chosen for reference case analyses because their utility scores were primarily derived from surveys on hepatitis C patients.

We also considered inclusion of severe hepatic flares in the sensitivity analyses, assuming the same medical costs as in the treatment of decompensated cirrhosis, and a 2% annual event rate that was estimated among lamivudine-resistant patients from the trial. Although clinically significant, hepatic flares were not considered in the primary analysis because their incidence rate was very low and thus not economically important.

To evaluate whether entecavir was also cost-effective for longer-term use, we modeled entecavir and lamivudine treatment for 3, 5, and 10 years, conservatively assuming that the trial efficacy observed for entecavir in the first year would be sustained beyond the trial period without any incremental benefit. In the long-term analysis, we assumed that as long as patients were taking lamivudine, additional patients would develop treatment resistance each year. Assumed cumulative lamivudine viral resistance rates from year 1 to year 5 were 14%, 38%, 49%, 66%, and 69%,³⁹ with 69% beyond 5 years. We assumed that patients developing lamivudine resistance would be treated with the addition of adefovir to lamivudine therapy to reflect recent clinical practice in the management of lamivudine-resistant patients, while also assuming that medication efficacy would not worsen. Annual treatment cost for a once-daily adefovir 10 mg tablet was \$6,975 based on WAC in 2006 dollars. The add-on adefovir strategy therefore includes both adefovir and lamivudine costs. In a separate sensitivity analysis, we also assumed that lamivudine-resistant patients could switch to adefovir monotherapy. We assumed no treatment resistance for entecavir therapy for the first 2 years and 0.7% for the third year. Patients developing entecavir resistance were treated by adding adefovir for the remaining years in the sensitivity analysis based on the long-term trial data.

To evaluate uncertainty with respect to model parameters, probabilistic sensitivity analyses (PSA) with 1,000 iterations were conducted for the following 2 key parameters for which the greatest uncertainty existed: (1) viral rebound rates after treatment cessation, which were modeled using a beta distribution with values for shape parameters alpha (entecavir 44.1; lamivudine 37.6) and beta (entecavir 25.9; lamivudine 19.4) derived from the reported mean and standard deviation of viral rebound rates, and (2) time to the first event, which was modeled using a gamma distribution with the sample mean (survival years, compensated cirrhosis 7.6; decompensated cirrhosis 8.6; HCC 7.1) and standard deviation (compensated cirrhosis 3.95; decompensated cirrhosis 2.77; HCC 3.53) observed from the REVEAL-HBV cohort. We did not consider other parameters, such as event costs, in the PSA because their variance data were not reported; thus, the underlying property of their probability distributions could not be determined.

TABLE 2 Baseline Demographics and HBV Characteristics (BMS-AI463022)

Characteristic	ETV 0.5 mg (N = 354)	LVD 100 mg (N = 355)
Age, years		
Mean [SD]	35 [13]	35 [13]
Gender, n (%)		
Male	274 (77)	261 (74)
Female	80 (23)	94 (26)
Race, n (%)		
Asian	204 (58)	202 (57)
White	140 (40)	141 (40)
Other	10 (2)	12 (3)
HBV DNA by PCR, log ₁₀ copies per mL		
Mean [SD]	9.62 [2.01]	9.69 [1.99]
HBV surface antigen, n (%)		
Positive	354 (100)	355 (100)
HBV e antigen, n (%)		
Positive	348 (98)	351 (99)
ALT, U per L		
Mean [SD]	140.5 [114.33]	146.3 [132.27]
Knodell necroinflammatory score		
Mean [SD]	7.8 [2.98]	7.7 [2.99]
Ishak fibrosis score		
Mean [SD]	2.3 [1.27]	2.3 [1.29]

Chang TT et al. for the BEHoLD AI463022 Study Group (2006).²⁷

ALT = alanine aminotransferase; ETV = entecavir; HBV = hepatitis B virus; LVD = lamivudine; PCR = polymerase-chain reaction.

Results

Patient characteristics were balanced between the 2 treatment groups in the BEHoLD AI463022 study (Table 2). The majority of treated subjects were predominantly male (75%) and either Asian (57%) or white (40%), with a mean age of 35 years. Distribution of baseline histology scores was balanced between groups. Mean baseline Knodell necroinflammatory scores were balanced between the 2 groups (entecavir 7.8, lamivudine 7.7). Mean baseline fibrosis scores using the Ishak scoring system suggested mild to moderate fibrosis for both groups (2.3, both groups). No evidence of decompensated HBV disease was apparent in these subjects based on baseline laboratory tests related to HBV disease.

Mean baseline serum HBV DNA by PCR assay was 9.62 log₁₀ copies per mL for entecavir and 9.69 log₁₀ copies per mL for lamivudine. All BEHoLD subjects had detectable serum HBsAg, and all subjects were HbeAg-positive. Baseline laboratory tests related to HBV disease characteristics (albumin, total bilirubin, prothrombin time, and international normalized ratio) were

TABLE 3 Cost-Effectiveness Results for Entecavir Versus Lamivudine

	Entecavir 0.5 mg	Lamivudine 100 mg	Difference
Number of CHB patients at entry	1,000	1,000	
Duration of treatment (year)	1	1	
Total discounted drug costs	\$7,364,799	\$2,603,508	\$4,761,291
Projected liver complication in 10 years			
Compensated cirrhosis	78	149	71
Decompensated cirrhosis	8	16	8
Hepatocellular carcinoma	34	76	42
Total discounted medical costs	\$2,252,523	\$4,663,540	-\$2,411,017
Discounted life-year lost	682	1,499	817
Discounted QALY lost	608	1,336	728
Cost per life-year saved	\$2,877		
Cost per QALY saved	\$3,230		

CHB=chronic hepatitis B; QALY=quality-adjusted life-years.

comparable between groups. Mean (standard deviation) baseline ALT was 140.5 (114.33) U per L and 146.3 (132.27) U per L for entecavir and lamivudine, respectively.

Entecavir was superior to lamivudine for the portion of subjects who achieved undetectable HBV DNA (<300 copies per mL) by PCR assay at week 48. At the end of the 48-week trial period, 69.1% of patients in the entecavir arm and 39.8% of patients in the lamivudine arm reached the defined undetectable HBV DNA level (Table 1).

Of the 3,653 participants in the REVEAL-HBV cohort study, 565 (15.5%) were HbeAg-positive. Of the HBeAg-positive patients, 92.6% had HBV DNA levels >100,000 copies per mL, and 1.4% had HBV DNA levels <300 copies per mL. Annual incidence rates of compensated cirrhosis, decompensated cirrhosis, and HCC for subjects with undetectable (<300 copies per mL) hepatitis B viral load were 0.34%, 0.02%, and 0.11%, respectively (Table 1). In the Cox proportional hazards models adjusting for sex, age, cigarette smoking, and alcohol consumption, hepatitis B viral load was a strong independent predictor of liver cirrhosis and HCC events. Incidence of cirrhosis and HCC events increased with the serum HBV DNA level at study entry in a dose-response relationship.

Estimated clinical and economic outcomes are reported in Table 3. Among a hypothetical cohort of 1,000 patients, we projected 71 fewer cases of compensated cirrhosis, 8 fewer cases of decompensated cirrhosis, and 42 fewer HCC events in the entecavir arm compared with the lamivudine arm. These avoided events would translate into medical cost offsets of approximately \$2.4 million and a gain of 817 life years over a period of 10 years.

On a per-person basis, 1 year of entecavir therapy gained 0.728 QALYs at an incremental cost of \$2,350, with a 3% annual

discount. Compared with lamivudine, entecavir cost an incremental \$3,230 per QALY gained (95% confidence interval [CI], \$2,312-\$4,528).

Univariate sensitivity analyses demonstrated that our findings are robust to individual variables and are most sensitive to efficacy, drug costs, and treatment duration. Assuming alternative utility scores derived from a hepatitis C patient survey study of 0.99 for HBV, 0.80 for compensated cirrhosis, 0.60 for decompensated cirrhosis, and 0.73 for HCC, the incremental cost per QALY gained was \$2,752, a more favorable result.³⁹ A sensitivity analysis showed that inclusion of severe hepatic flares in our modeling assumption had very little impact on our economic results due to a very low event rate observed in the trial, even though this is a costly and clinically important event.

Cost-effectiveness acceptability curves are shown in Figure 2. The cost-effectiveness results are robust, with 98.4% of simulation-derived incremental cost-effectiveness ratio (ICER) estimates below \$5,000/QALY. Longer-term modeling, assuming that the treatment-resistant patients would use add-on adefovir, showed that 3, 5, or 10 years of entecavir would still be cost-effective, yielding incremental costs per QALY of \$9,966, \$11,685, and \$12,233, respectively, with 100% of PSA-derived ICER estimates below \$50,000/QALY. Alternatively, in a separate sensitivity analysis assuming that lamivudine-resistant patients would switch to adefovir monotherapy, ICERs were higher, ranging from \$11,582 (3 years) to \$20,662 (10 years), primarily due to the relatively lower cost of adefovir monotherapy.

Discussion

Despite the development of safe and effective HBV vaccines that have been available since 1982, HBV infection remains a global problem. In the United States, HBV infection remains more prevalent in certain groups such as immigrants from endemic areas, men who have sex with men, injecting drug users, and persons with multiple sex partners. As long as these underlying sources of HBV remain, these subgroups would maintain a reservoir of this infectious virus. Patients with HBV should be actively counseled regarding lifestyle modifications and prevention of transmission. These steps are important because HBV can be transmitted by percutaneous and sexual exposure as well as by close person-to-person contact, presumably through open cuts and sores. It should be noted that carriers with high HBV DNA levels are more likely to be infectious.²

Major health risks and economic impacts associated with HBV infection seem to be driven primarily by the development of HCC and complications of decompensated cirrhosis. HBV infection is a complex disease that can manifest in a variety of ways. The heterogeneous nature of the disease with its slow and variable progression to distinct endpoints of liver failure, cirrhosis, HCC, and death means that it is often diagnosed late in life. Current management options for liver complications remain limited partly because of a paucity of sensitive methods for early

diagnosis, resulting in the diagnosis of HBV for most patients late in the disease course. Liver transplantation remains the only effective therapy for late complications like decompensated cirrhosis and HCC.

Therefore, the benefits of early treatment for HBV in suppressing viral load and reducing consequent risk of cirrhosis and HCC can be substantial. A consensus seems to have been reached that antiviral therapy, especially if started early, can delay the progression and reduce the severity of liver disease due to HBV.^{40,41} An evaluation of the cost-effectiveness of such treatments would be quite informative to decision makers.

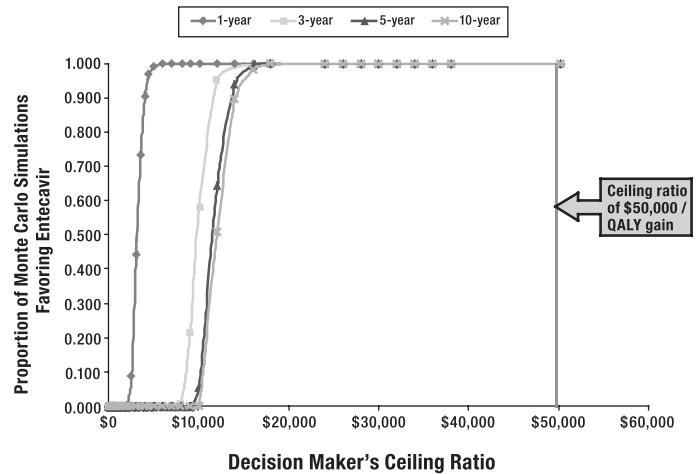
A number of factors can increase the rate of liver disease progression in patients infected with hepatitis B, including coinfection with HCV.⁴²⁻⁴⁴ We limited our analysis to patients without HCV coinfection to better delineate the natural history of hepatitis B alone, thus making our results generalizable only to monoinfected patients. Coinfection with human immunodeficiency virus (HIV) is also an important variable in HBV treatment, but for a reason unrelated to liver disease progression. The Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents (October 2006) were modified in April 2007, to clarify that entecavir should not be used for the treatment of HBV infection without concomitant treatment for HIV in patients coinfecting with HBV and HIV.⁴⁵

In the present analysis extrapolated from observed HBV DNA efficacy results, we estimated that in patients initiating lamivudine therapy, 15% would progress to compensated cirrhosis within 10 years, 1.6% to decompensated cirrhosis, and 7.6% to HCC. For patients initiating entecavir therapy, 7.8% would progress to compensated cirrhosis within 10 years, 0.8% to decompensated cirrhosis, and 3.4% to HCC. These estimates are well within the range of published figures.⁴⁰

Compared with lamivudine, the incremental cost per QALY gain ranges from \$3,230 for 1 year of entecavir treatment to \$12,233 for 10 years of entecavir treatment. These estimated cost-effectiveness ratios fall well within the range that is traditionally considered acceptable in cost-effectiveness analyses of new health technologies.⁴⁶⁻⁴⁸

Although the clinical benefits of reducing viral load have been demonstrated in recent literature,^{25,26} to the best of our knowledge, very few economic analyses have been conducted based on the endpoint of antiviral therapy-induced suppression of viral replication. HBeAg seroconversion (loss of HBeAg and presence of anti-HBeAg antibody) was uniformly thought to be a good outcome for patients, but recent data have shown that many patients who have undergone HBeAg seroconversion continue to develop severe complications (including HCC).⁴⁹ HBeAg loss and seroconversion are important clinical endpoints, but the risk of disease progression even when these endpoints are met still depends on the degree of ongoing viral replication in the host. Besides the REVEAL-HBV study, several studies have demonstrated a dose

FIGURE 2 CE Acceptability Curves by Entecavir Treatment Duration



CE=cost effectiveness; QALY=quality-adjusted life-year.

relationship between hepatitis B viral load and hepatic complications, with higher hepatitis B viral load associated with progressive liver disease, including the development of cirrhosis and HCC.^{25,26,50-52}

A key question arises when interpreting our findings: Is it appropriate to assume that patients treated down to an undetectable viral load (BEHoLD patients with HBV DNA <300 copies per mL at study endpoint) have risks of disease progression and hepatic complications that approximate the risks for community residents with an undetectable viral load (REVEAL-HBV)? This hypothesis is supported by evidence from a large meta-analysis of 26 prospective studies totaling 3,428 study subjects (2,524 HBeAg-positive at baseline) in whom the level of viral replication and the change in viral replication were significantly correlated with several outcomes including histological grading, and change in histological grading, serological and biochemical response.⁵³ An Italian study published in 2004 showed that in 656 HBeAg-negative CHB subjects treated with lamivudine, patients who developed resistance as determined by viral breakthrough and rebound had a worse outcome in all parameters, including mortality, when compared with those whose viral load was effectively suppressed by lamivudine.⁵⁴ This study was conducted in patients with e antigen-negative disease in which immune-induced HBeAg seroconversion is not an option; therefore, the benefit of therapy is from the direct antiviral effect of the drug. Indeed, a decrease in viral load through antiviral therapy has been associated with histologic improvement,^{26,27,55-61} increased survival of patients with decompensated liver disease from

hepatitis B,⁶²⁻⁷⁰ and improved clinical outcome in patients with HBV reactivation following chemotherapy.^{50,52,71-81}

Our analyses are conservative in the following aspects. First, longer-term clinical trial data consistently showed substantially better suppression of viral DNA levels with entecavir at week 96 for HBeAg-positive treatment-naïve subjects undergoing 2 years of entecavir treatment.²² These results were recently published in a peer-reviewed journal and therefore were not included in our current analysis. Second, we modeled HBV DNA reduction efficacy only at the end of follow-up, even though viral load reduction can be observed as soon as the first 6 months after randomization; this process may have underestimated the benefits of entecavir therapy that suppresses viral load to a very low level in a relatively short time period. Third, due to the limitation of the observation period in the REVEAL-HBV study, we were able to project events only up to 10 years; however, because the average age of trial patients was only 35 years, we could expect more events to be observed beyond 10 years. Fourth, we did not include indirect medical costs, caregiver support cost, and lost productivity in our study; however, we believe that these indirect disease burdens could be very significant and costly to U.S. society and individual patients.

Limitations

First and foremost among study limitations was the application of data on hepatic outcomes from a prospective cohort study (REVEAL-HBV) of community residents, all of whom were seropositive for HBsAg but only 15% of whom were seropositive for HBeAg, to clinical trial (BEHoLD) data for 715 patients with HBeAg-positive CHB. Of the 873 REVEAL-HBV participants with undetectable viral load at study entry whose outcomes were used in our model to indicate baseline risks of cirrhosis and HCC, only 0.9% (n=8) were HBeAg-positive. Additionally, only 4% (n=24) of the REVEAL-HBV study's 565 HBeAg-positive participants had HBV DNA <10,000 copies per mL. Thus, the present pharmacoeconomic model's assumed dose-response relationship between HBV disease sequelae and viral load for HBeAg-positive patients was based almost entirely on community residents who were HBeAg-negative.

Second, reliable long-term treatment rebound rates after treatment discontinuation are not yet available for either entecavir or lamivudine. In the BEHoLD results, 6 patients (2%) in the entecavir group and 63 patients (18%) in the lamivudine group experienced virologic rebound during the first year of drug administration. Among patients with a protocol-defined response, only 37% in the entecavir group and 34% in the lamivudine group had a sustained response 6 months after discontinuation of treatment. The optimal duration of entecavir or lamivudine administration in HBV patients requires further study.

Third, the appropriateness of extrapolation of the BEHoLD clinical trial results and REVEAL-HBV data to non-Asian

populations is unknown. The REVEAL-HBV epidemiologic data that provided the disease progression rates were derived from a Chinese patient population. Inherent environmental and genetic factors in the cohort may not be seen in other populations. However, REVEAL-HBV is the largest study of HBV-infected persons to examine detailed information on viral factors. Its results have been replicated in a second study that was also conducted in Chinese patients.⁸² The relationship between viral load and liver disease outcome has been found in other studies around the world including West Africa, China, and Japan, but primarily in Asians.^{42,44}

Fourth, potential cost-effectiveness for entecavir compared with other drugs, such as adefovir or interferon, was not evaluated due to lack of head-to-head randomized trial data at the time of this study. Future studies should explore the cost-effectiveness of other treatment strategies.

Fifth, although we accounted for the actual compliance rate in the BEHoLD clinical trial, we would expect the compliance rate in real-world practice to be much lower. However, there is no reason to believe that compliance rates between entecavir and lamivudine will differ based on their dosage form (oral), frequency of administration (once daily), and side effect profiles.

Sixth, we did not consider those patients with lamivudine-resistant virus who require larger doses of entecavir. Finally, we did not evaluate the cost-effectiveness of entecavir in patients coinfecting with HBV and HIV. Patients in our analysis were assumed to be naïve to antiretroviral treatment and not to be coinfecting with HIV, even though $\leq 10\%$ of all HIV-infected persons are coinfecting with HBV.⁸³ As we have noted, the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents no longer recommends entecavir in patients coinfecting with HBV and HIV who are not receiving simultaneous HIV drug treatment;⁴⁵ entecavir's package labeling has been changed accordingly.²¹

Conclusion

Based on published data for a Chinese population outside the United States, our modeling consistently demonstrated that a strategy of initiating therapy with entecavir in HBeAg-positive HBV patients (both short-term and long-term use up to 10 years) will be cost-effective and therefore economically attractive to U.S. health care payers assuming that (1) the efficacy of entecavir after 1 year is sustainable and (2) liver disease risk levels from the REVEAL-HBV study population (a primarily HBeAg-negative group) adequately represent risk for a treated HBeAg-positive patient group. While eradication of hepatitis B is rarely achieved using current treatment options, the availability of entecavir as part of an early treatment strategy is economically attractive for current HBV patients without coinfection with either HCV or HIV.

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DISCLOSURES

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Evaluation of the Cost-Effectiveness of Entecavir Versus Lamivudine in Hepatitis BeAg-Positive Chronic Hepatitis B Patients

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