

Treatment Alternatives for Hepatitis B Cirrhosis: A Cost-Effectiveness Analysis

Fasiha Kanwal, M.D., M.S.H.S.,¹⁻⁴ Mary Farid, D.O.,^{1,3} Paul Martin, M.D.,⁶ Gary Chen, M.D.,⁶ Ian M. Gralnek, M.D., M.S.H.S.,^{2,3} Gareth S. Dulai, M.D., M.S.H.S.,^{2,3} and Brennan M. R. Spiegel, M.D., M.S.H.S.¹⁻⁴
¹Division of Gastroenterology, VA Greater Los Angeles Healthcare System, Los Angeles, California; ²Division of Digestive Diseases, David Geffen School of Medicine at UCLA, Los Angeles, California; ³UCLA/VA Center for Outcomes Research and Education (CORE), Los Angeles, California; ⁴CURE Digestive Diseases Research Center, Los Angeles, California; ⁵Mount Sinai School of Medicine, New York, New York; and ⁶Cedars Sinai Medical Center, Los Angeles, California

BACKGROUND: Hepatitis B virus (HBV) patients with cirrhosis are at risk for developing costly, morbid, or mortal events, and therefore need highly effective therapies. Lamivudine is effective but is limited by viral resistance. In contrast, adefovir and entecavir have lower viral resistance, but are more expensive. The most cost-effective approach is uncertain.

METHODS: We evaluated the cost-effectiveness of six strategies in HBV cirrhosis: (1) No HBV treatment (“do nothing”), (2) lamivudine monotherapy, (3) adefovir monotherapy, (4) lamivudine with crossover to adefovir on resistance (“adefovir salvage”), (5) entecavir monotherapy, or (6) lamivudine with crossover to entecavir on resistance (“entecavir salvage”). The primary outcome was the incremental cost per quality-adjusted life-year (QALY) gained.

RESULTS: The “do nothing” strategy was least effective yet least expensive. Compared with “do nothing,” using adefovir cost an incremental \$19,731. Entecavir was more effective yet more expensive than adefovir, and cost an incremental \$25,626 per QALY gained versus adefovir. Selecting between entecavir versus adefovir was highly dependent on the third-party payer’s “willingness-to-pay” (e.g., 45% and 60% of patients fall within budget if willing-to-pay \$10K and \$50K per QALY gained for entecavir, respectively). Both lamivudine monotherapy and the “salvage” strategies were not cost-effective. However, between the two salvage strategies, “adefovir salvage” was more effective and less expensive than “entecavir salvage.”

CONCLUSION: Both entecavir and adefovir are cost-effective in patients with HBV cirrhosis. Choosing between adefovir and entecavir is highly dependent on available budgets. In patients with HBV cirrhosis with previous lamivudine resistance, “adefovir salvage” appears more effective and less expensive than “entecavir salvage.”

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BACKGROUND

Chronic hepatitis B virus (HBV) infection is the leading cause of cirrhosis worldwide (1). The traditional cornerstone of treatment in HBV cirrhosis is lamivudine (2–4)—an agent favored because it is effective, easy to administer, and associated with few adverse effects (5–7). However, these benefits of lamivudine are counterbalanced by a high rate of viral resistance with prolonged therapy (8). Viral resistance has significant consequences in HBV patients with cirrhosis, because this subgroup is highly vulnerable with limited reserve of liver function (9, 10). Specifically, in comparison to HBV patients without cirrhosis, patients with cirrhosis are more likely to experience costly, morbid, or mortal events as a con-

sequence of lamivudine resistance in comparison to HBV patients without cirrhosis (11).

More recently, adefovir dipivoxil and entecavir have been approved for HBV therapy. Both agents are effective in HBV, have infrequent side effects, and have a lower incidence of viral resistance on prolonged therapy (12–15)—a major advantage over lamivudine. However, both adefovir and entecavir are more expensive than lamivudine (16–18). Therefore, there is a trade-off between the superior therapeutic benefits of these newer agents and their greater cost compared with lamivudine, which is less effective yet less expensive.

Although we have previously shown that the new antiviral agents are unlikely to be cost-effective as initial therapy in HBV patients without cirrhosis (19), they may nonetheless

have a health economic advantage in HBV patients with cirrhosis. This advantage not only arises because patients with HBV cirrhosis are at risk for developing resource intensive and life-threatening complications of liver disease, but also because they are more likely to develop these complications in the near term. Because health economic theory dictates that common and early events are weighted more heavily than late and rare events (20), the use of expensive yet effective therapies is likely to be more cost-effective in patients with cirrhosis than those with less advanced disease.

It is important to establish the most effective and cost-effective therapeutic approach to HBV cirrhosis, especially in light of the increasing availability of new agents. Given the uncertainty regarding how best to use the available agents in this growing patient population, data from cost-effectiveness analyses may assist clinicians in everyday clinical decision making. We therefore performed an economic analysis to estimate the cost-effectiveness of competing strategies for the management of cirrhosis as a result of chronic HBV with active viral replication. We specifically sought to determine whether and under what circumstances the greater therapeutic benefits of newer antiviral agents, such as adefovir and entecavir, offset their greater cost *versus* lamivudine in the management of chronic hepatitis B cirrhosis.

METHODS

Decision Model Framework

MODEL OVERVIEW. Using decision analysis software (DATA 4.0, TreeAge Software, Inc., Williamstown, MA), we evaluated a hypothetical cohort of 50-yr-old patients with chronic HBV cirrhosis and active viral replication. In order to emulate the case mix in clinical practice, we assumed that 50% of the cohort had compensated cirrhosis (*i.e.*, Child's Class A) and the remainder had decompensated cirrhosis (*i.e.*, Child's Class B or C). We subsequently varied the prevalence of decompensated cirrhosis between 0% and 100% in the sensitivity analysis, as described below. Patients entered the hypothetical model without previous treatment for HBV and received one of six competing strategies for the management of chronic HBV: (1) no pharmacological treatment of chronic HBV ("do nothing" strategy); (2) lamivudine monotherapy; (3) adefovir monotherapy; (4) lamivudine with crossover to adefovir on development of resistance ("adefovir salvage" strategy); (5) entecavir monotherapy; or (6) lamivudine with crossover to entecavir on development of resistance ("entecavir salvage" strategy).

Because cirrhosis is a heterogeneous condition comprising patients with varying disease severity, we stratified our analysis by two groups: compensated *versus* decompensated cirrhosis. Furthermore, because the clinical course, outcomes, and resource usage vary in these two groups, we assigned separate probability estimates for compensated and decompensated cirrhosis (20–23). Patients entering the model either received no treatment ("do nothing") or active treatment for chronic HBV, as described below. We then followed the co-

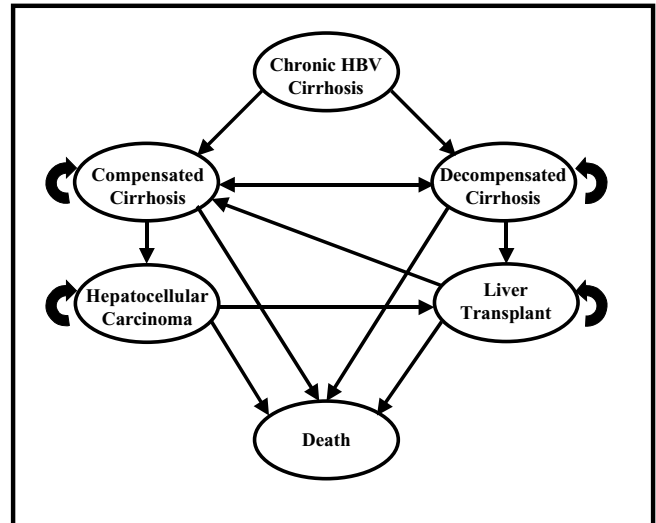


Figure 1. Markov state diagram. The base-case patient has chronic HBV infection, clinical cirrhosis, active viral replication, and no previous treatment for hepatitis B. The clinician treats with one of four competing strategies: (1) "do nothing," (2) lamivudine monotherapy, (3) adefovir monotherapy, and (4) "adefovir salvage" (see text for details). Within each strategy patients are stratified by stage of liver disease (*i.e.*, compensated *vs* decompensated). During each 1-yr cycle individual patients either remain in their assigned health state (recursive arrow) or progress to a new health state (straight arrow). Transition rates between health states were derived from a systematic review of the literature (Tables 1 and 2). Refer to the Technical Appendix for additional information.

hort over a lifetime horizon through a series of Markov cycles governing patient transitions between relevant health states (Fig. 1). Patients entered the model with either baseline compensated or decompensated cirrhosis. During each 1-yr cycle, individual patients either remained in their assigned health state (recursive arrow) or progressed to a new health state (straight arrow). Patients with compensated cirrhosis could develop decompensated cirrhosis (including variceal hemorrhage, ascites, or encephalopathy). In addition, patients with decompensated cirrhosis were eligible to regress back to compensated cirrhosis (double-headed arrow). Following recompensation, patients were eligible to decompensate a second time. This rate of subsequent decompensation was higher than the initial rate (not depicted in the model—see Appendix for details). Hepatocellular carcinoma could develop at any stage of cirrhosis. Patients with either decompensated cirrhosis or hepatocellular carcinoma were eligible to receive liver transplantation. Following liver transplantation, patients could develop recurrent HBV cirrhosis. These transition rates varied depending on both the treatment strategy employed and the presence or absence of underlying viral resistance (see Tables 1 and 2 and Appendix for details).

COMPETING STRATEGIES.

1. "*Do Nothing*" Strategy: In this strategy, which served as the referent case for our analysis, we assumed that patients

Table 1. Base-Case Natural History Estimates for Chronic Hepatitis B

Variable	Base-Case Estimate (%)	Range in Sensitivity Analysis (%)
Natural history variables		
Probability of decompensated cirrhosis (21)	50	0–100
Annual rate of mortality in compensated cirrhosis (21–31)	4.9	2–14
Annual rate of progression from compensated to decompensated cirrhosis (21, 23, 29, 31–34)	7.3	3.5–10
Probability of developing ascites in cirrhosis (21, 30, 32, 35)	68	50–90
Probability of developing variceal bleed in cirrhosis (21, 26, 29, 35, 36)	14.6	7–30
Probability of developing overt encephalopathy in cirrhosis (21, 29)	10	5–30
Annual rate of recompensation in decompensated cirrhosis (37–39)	8	0–16
Annual rate of decomposition following initial recompensation (40, 41)	20	10–40
Annual rate of mortality in decompensated cirrhosis (21–23, 26, 27, 35)	19	6–25
Annual rate of progression from cirrhosis to hepatocellular carcinoma (21, 25, 29, 35, 36, 42–45)	3.4	1–12
Annual rate of mortality in hepatocellular carcinoma (46–48)	43.3	20–60
Annual rate of receiving a liver transplant in decompensated cirrhosis (49)	25	0–40
Annual rate of receiving a liver transplant in hepatocellular carcinoma (49)	30	0–40
Annual rate of development of recurrent HBV following successful transplant (assuming patients on lamivudine and HBIG therapy posttransplant) (50–64)	4.7	0–13
Annual rate of progression to decompensated cirrhosis in patients with recurrent HBV following successful transplant (52, 56, 65)	24	16–43
Annual rate of progression to decompensated cirrhosis in patients without recurrent HBV following successful transplant (52, 56, 66)	7	5–13
Annual rate of receiving a second liver transplant in patients with recurrent HBV	13	5–20
Annual rate of receiving a second liver transplant in patients without recurrent HBV	1	1–10
Annual rate of mortality following successful transplant in patients with HBV recurrence (adjusted to account for decreasing mortality over time from transplant) (52, 66–70)	18.8	4–20
Annual rate of mortality following successful transplant in patients with recurrent HBV (adjusted to account for decreasing mortality over time from transplant) (52, 66, 67)	5.4	2–12

were followed clinically but did not receive pharmacological therapy for chronic hepatitis B. Patients were subjected to the natural history of hepatitis B cirrhosis conditional on their stage of liver disease. We further assumed that all patients received regular ongoing care, including management of cirrhosis-related complications and hepatocellular carcinoma surveillance, as outlined by published management guidelines (2–4). We assumed that a proportion of patients with decompensation became eligible for liver transplantation, and further assumed that a subgroup of these patients subsequently received a liver transplantation at the rate reported by the United Network of Organ Sharing (49). We assumed that all transplanted patients received prophylaxis against recurrent hepatitis B with a combination of monthly hepatitis B immune globulin (HBIG) and daily lamivudine for an indefinite period, as recommended by current management guidelines (2–7).

2. *Lamivudine Monotherapy Strategy*: Patients in this strategy received up-front lamivudine 100 mg orally once daily for an indefinite period, as recommended for cirrhosis by current management guidelines (2–4). Patients developing viral resistance continued receiving long-term lamivudine as recommended by published guidelines. Transplanted patients received prophylaxis with a combination of monthly HBIG and daily lamivudine for an indefinite period.
3. *Adefovir Monotherapy Strategy*: Patients in this strategy received up-front adefovir 10 mg orally once daily for an indefinite period, as recommended for cirrhosis by current

management guidelines (3, 4). Patients developing viral resistance continued receiving long-term adefovir. Transplanted patients received prophylaxis with a combination of monthly HBIG and daily adefovir for an indefinite period.

4. *Adefovir Salvage Strategy (Lamivudine to Adefovir Crossover)*: A relevant therapeutic alternative available to clinicians is a hybrid strategy of up-front lamivudine followed by “adefovir salvage” in case of developing lamivudine-related viral resistance. We assumed that patients in this strategy initially received lamivudine as described in the “lamivudine monotherapy strategy,” above. Patients were then crossed over to adefovir on developing viral resistance, and were subsequently managed as described in the “adefovir monotherapy strategy,” above. Patients without viral resistance remained on lamivudine. Therefore, adefovir was only reserved for patients developing viral resistance on lamivudine.
5. *Entecavir Monotherapy Strategy*: Patients in this strategy received up-front adefovir 0.5 mg orally once daily for an indefinite period, as recommended for cirrhosis by current management guidelines (3, 4). Patients developing viral resistance continued receiving long-term adefovir. Transplanted patients received prophylaxis with a combination of monthly HBIG and daily adefovir for an indefinite period.
6. *Entecavir Salvage Strategy (Lamivudine to Entecavir Crossover)*: We assumed that patients in this strategy initially received lamivudine as described in the “lamivudine

Table 2. Base-Case Treatment-Related Probability Estimates

Variable	Base-Case Estimate (%)	Range in Sensitivity Analysis (%)
Lamivudine variables		
Annual rate of developing resistance on long-term lamivudine (71–85)	23	15–32
Annual rate of progression from compensated to decompensated cirrhosis with lamivudine resistance (5, 7, 10, 11, 38, 86, 87)	8	3.5–10
Annual rate of progression from compensated to decompensated cirrhosis without lamivudine resistance (5, 11, 38, 86, 87)	2	1–10
Annual rate of recompensation in decompensated cirrhosis with lamivudine resistance*	8	10–25
Annual rate of recompensation in decompensated cirrhosis without lamivudine resistance (7, 38, 87)	35	10–50
Annual rate of decomposition following initial recompensation in decompensated cirrhosis with lamivudine resistance*	25	10–40
Annual rate of decomposition following initial recompensation in decompensated cirrhosis without lamivudine resistance (7)	4	1–10
Annual rate of progression from cirrhosis to hepatocellular carcinoma (7, 87)	1.5	1–10
Recurrent HBV following successful transplant with lamivudine resistance (5, 50, 70, 88)	80	50–100
Annual rate of developing recurrent HBV following successful transplant without lamivudine resistance (88)	4.7	0–40
Adefovir variables		
Annual rate of developing resistance on long-term adefovir (89)		
Year 1	0	0–3
Year 2	2	1–4
Year 3	5	3–8
Year 4	8	4–12
Annual rate of developing severe renal side effects (13, 88, 90, 91)	2	1–10
Annual rate of progression from compensated to decompensated cirrhosis with adefovir resistance*	8	3.5–10
Annual rate of progression from compensated to decompensated cirrhosis without adefovir resistance (14, 91, 92)	2	1–10
Annual rate of recompensation in decompensated cirrhosis with adefovir resistance*	8	10–25
Annual rate of recompensation in decompensated cirrhosis without adefovir resistance (14, 93)	33	10–50
Annual rate of decomposition following initial recompensation in decompensated cirrhosis with adefovir resistance*	25	10–40
Annual rate of decomposition following initial recompensation in decompensated cirrhosis without adefovir resistance (91)	4	1–10
Annual rate of progression from cirrhosis to hepatocellular carcinoma (93)	1.5	1–10
Annual rate of development of recurrent HBV following successful transplant with adefovir resistance*	80	50–100
Annual rate of development of recurrent HBV following successful transplant without adefovir resistance*	4.7	0–40
Entecavir variables		
Annual rate of developing resistance on long-term entecavir		
Treatment-naïve patients (years 1–2)	0	0–10
Treatment-naïve patients (years 3–10)	1	0–10
Lamivudine-resistant patients	7	3–14
Annual rate of progression from compensated to decompensated cirrhosis without entecavir resistance*	2	1–10
Annual rate of progression from compensated to decompensated cirrhosis with entecavir resistance*	8	3.5–10
Annual rate of recompensation in decompensated cirrhosis with entecavir resistance*	8	10–25
Annual rate of recompensation in decompensated cirrhosis without entecavir resistance*	35	10–50
Annual rate of progression from cirrhosis to hepatocellular carcinoma*	4.7	0–40

*This estimate is an assumption. Please refer to Technical Appendix for details.

monotherapy strategy,” above. Patients were then crossed over to entecavir on developing viral resistance, and were subsequently managed as described in the “entecavir monotherapy strategy,” above. Patients without viral resistance remained on lamivudine. Therefore, entecavir was only reserved for patients developing viral resistance on lamivudine.

Clinical Probability Estimates

Our base-case model incorporated a wide range of estimates governing relevant clinical probabilities in the management and natural history of chronic hepatitis B cirrhosis (Tables 1 and 2). Our efficacy end points included clinical outcomes most relevant to patients with HBV cirrhosis, *i.e.*, progression from compensated to decompensated cirrhosis,

Table 3. Utility Estimates for Chronic Hepatitis B Cirrhosis Health States

Utility Estimates		
Utility of compensated cirrhosis (94)	0.80	0.7–0.9
Utility of decompensated cirrhosis (94)	0.6	0.5–0.7
Utility of liver transplant (94)	0.86	0.7–0.9
Utility of hepatocellular carcinoma (94)	0.73	0.5–0.8

regression from decompensated to compensated cirrhosis, progression to hepatocellular cancer, progression to liver transplantation, and progression to cirrhosis and subsequent complications related to recurrent HBV postliver transplantation. We have used similar probability estimates in previous decision analysis in hepatitis B (19). We performed a systematic review of MEDLINE in order to derive these estimates. Refer to the Technical Appendix for a detailed description of our systematic review methodology.

Outcomes

Because the main objective of cost-effectiveness analysis is to permit comparisons between different interventions in medicine, and because quality-adjusted life-years (QALYs) are the exchange currency to allow for these comparisons to be made, we adopted QALYs as our main outcome (20). Our analysis reports the incremental cost per QALY gained between the competing strategies.

Utilities

We incorporated a wide range of relevant health-state utilities in our model. Refer to Table 3 for the specific utility estimates, and to the Technical Appendix for a detailed description of these estimates.

Cost Estimates

We conducted our analysis from the perspective of a third-party payer and incorporated the direct health-care costs for a range of therapies, physician visits, diagnostic tests, and complications of chronic liver disease (Table 4). We obtained costs for physician services and procedures from the 2005 American Medical Association Current Procedural Terminology codebook and the 2005 Medicare Fee Schedule, and derived our base-case pharmaceutical costs from the average wholesale prices (AWPs) listed in the 2006 Red Book (16, 95). Because large buying consortiums are often capable of obtaining prices lower than the Red Book AWPs, we performed a sensitivity analysis using the acquisition costs of the Veteran's Administration (VA) as a proxy for the discounts achieved by large third-party payers. We obtained cost estimates for cirrhosis and related health states from a published study of detailed itemized inpatient and outpatient direct costs incurred by patients with cirrhosis (96). As these costs were originally generated in 1997, we updated all the cost estimates to 2005 dollars using the medical care component of the consumer price index (97). We discounted all costs at a rate of 3% per yr (20).

Sensitivity Analyses

BASE-CASE SENSITIVITY ANALYSES. Table 1 lists our base-case probability estimates with the plausible range of values for each estimate. To test the influence of all variables on the model results, we performed a multivariable sensitivity analysis ("tornado analysis") and rank-ordered the most influential variables (98). We then performed one-way sensitivity analyses on the most influential variables.

Whereas one-way sensitivity analyses provide information regarding the robustness of a model, they are inadequate to simulate real-world conditions. To acknowledge the reality that each individual carries a unique composition of clinical probabilities, we conducted a probabilistic (Monte Carlo) simulation under the assumption that all variables were triangular in distribution (98). The triangular distribution assumes that a parameter's base-case value is most likely to occur and that the minimum and maximum values are least likely to occur. The probability of observing a value between the base-case and extreme value is linearly interpolated. We simulated 2,000 trials and plotted the results on cost-effectiveness acceptability curves stratified by willingness-to-pay thresholds (99). We analyzed the base-case cohort to find the 2.5th and

Table 4. Base-Case Cost Estimates

Variable	Base-Case Estimate (%)	Range in Sensitivity Analysis (%)
Drug costs		
Cost per month of lamivudine (16)	158	50–500
Cost per month of adefovir (16)	595	100–1,000
Cost per month of entecavir (17, 18)	720	100–1,000
Cost per 5 mL injection of HBIG (16)	684	200–1,000
Nondrug costs of treatment period		
Cost per physician visit (95)	52	25–100
Cost per set of laboratory tests (95)	80	50–150
Cost per abdominal ultrasound (95)	150	50–250
Costs of cirrhosis care*		
Cost per year of compensated cirrhosis (96)	964	500–5,000
Cost of first year following variceal hemorrhage (assuming survival) (96)	22,444	10K–30K
Cost per subsequent year following variceal hemorrhage (95)	4,393	2K–10K
Cost per year of ascites (96)	4,058	1K–10K
Cost of first year of encephalopathy (96)	14,406	5K–25K
Cost per subsequent year following encephalopathy (96)	3,337	1K–10K
Cost of liver transplantation (96)	127,499	50K–150K
Cost per year of follow-up care postliver transplant (96)	22,266	10K–50K
Cost of hepatocellular carcinoma (96)	38,715	20K–75K

References supporting each base-case estimate in parentheses following variable.

HBIG = hepatitis B immunoglobulin.

*All cost estimates were updated to 2004 dollars using the medical care component of the consumer price index (97).

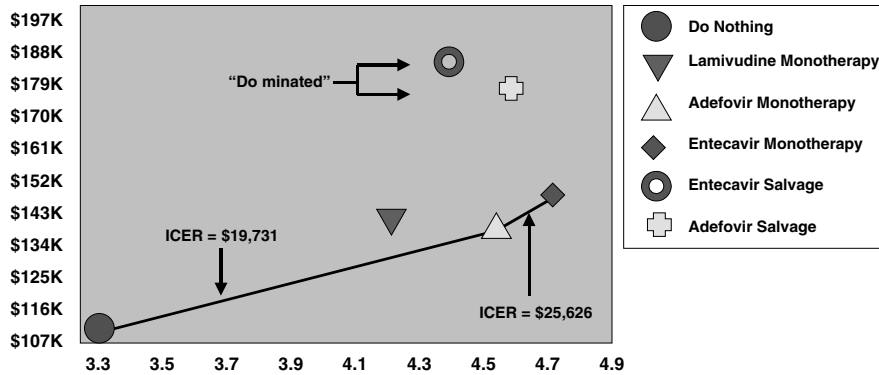


Figure 2. Base-case cost-utility results. The base-case analysis assumes that half of the patients have decompensated cirrhosis and half have compensated cirrhosis. The vertical axis below displays the lifetime cumulative cost, and the horizontal axis displays the QALYs gained. The “do nothing” strategy is located at the origin and is the least effective yet least expensive of the six competing strategies. Each diagonal line represents the incremental cost-effectiveness ratio (ICER) between the connected strategies. The ICER between strategies represents the additional cost that must be expended to gain one additional QALY when adopting the more expensive of the two compared strategies. For example, the use of entecavir monotherapy instead of adefovir monotherapy cost an additional \$26,626 to gain one additional QALY. The “adefovir salvage,” “entecavir salvage,” and lamivudine monotherapy strategies are “dominated” (*i.e.*, more expensive yet less effective than alternatives) because they fall above and to the left of the border that outlines the other three strategies that compose the “cost-effectiveness frontier.”

97.5th percentiles for our estimate of incremental cost per QALY gained among competing strategies.

RESULTS

Base-Case Results

The results of our base-case analysis are displayed in Figure 2. The “do nothing” strategy was the least expensive yet least effective of the four competing strategies. Compared with doing nothing, using adefovir monotherapy cost an incremental \$19,731 to gain one additional QALY (2.5th and 97.5th percentiles, \$14,342 and \$24,224). Compared with adefovir, entecavir monotherapy cost an incremental \$25,626 per QALY-gained (2.5th and 97.5th percentiles, \$19,637 and \$31,184). Therefore, entecavir monotherapy was more effective yet more expensive than adefovir monotherapy. Both the

lamivudine monotherapy and “salvage” strategies (*i.e.*, “adefovir salvage” and “entecavir salvage”) were more expensive yet less effective than competing strategies, and were therefore “dominated,” suggesting that initial therapy with low-resistance therapies (*e.g.*, adefovir or entecavir) is more cost-effective than reserving these therapies for the development of lamivudine resistance.

Base-Case Sensitivity Analyses

Tornado analysis revealed that the model was sensitive to six variables. Table 5 displays the results of one-way sensitivity analyses for these variables in decreasing order of influence, and lists the thresholds in which the cost-effectiveness order between the strategies changed. The remaining variables did not impact the model when varied over a wide range. In particular, the results were qualitatively similar regardless

Table 5. Results of One-Way Sensitivity Analyses

Variable	Base-Case Estimate	Threshold	Comment
Cost per month of adefovir	\$595	\$660	If cost is more than threshold, then entecavir monotherapy is dominant strategy
Cost per month of entecavir	\$720	\$670	If cost is more than threshold, then entecavir monotherapy is dominant strategy
Annual rate of progression from compensated to decompensated cirrhosis with lamivudine resistance	8%	3.5%	If incidence is less than threshold, then lamivudine becomes cost-effective
Annual rate of progression from compensated to decompensated cirrhosis with entecavir (no resistance)	2%	1.3%	If incidence is less than threshold, then entecavir monotherapy is dominant strategy
Annual rate of progression from compensated to decompensated cirrhosis with adefovir (no resistance)	2%	3.5%	If incidence is more than threshold, then entecavir monotherapy is dominant strategy
Annual rate of progression from compensated to decompensated cirrhosis with adefovir resistance	8%	15%	If incidence is more than threshold, then entecavir monotherapy is dominant strategy

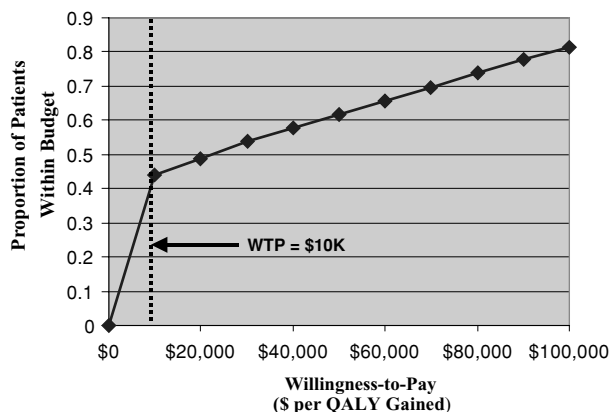


Figure 3. Cost-effectiveness acceptability curves of “entecavir monotherapy” versus “adefovir monotherapy.” The horizontal axis displays the willingness-to-pay budgetary thresholds to gain one additional QALY when using entecavir *in lieu* of adefovir, and the vertical axis displays the percentage of 2,000 patients who fall within the available budget. For example, if a third-party payer had a budget of \$10,000 per QALY-gained to substitute entecavir versus adefovir (vertical broken line), then only 45% of the cohort would fall within the budget. In contrast, entecavir becomes cost-effective for over 60% of patients in health-care systems willing to pay at least \$50,000 per QALY gained.

of the ratio of patients with compensated versus decompensated cirrhosis. Similarly, the results of our sensitivity analysis employing VA acquisition costs for pharmaceuticals were qualitatively similar to our base-case results (results not shown).

Our results suggest that of the five active therapeutic strategies, both the entecavir and adefovir monotherapy strategies were potentially cost-effective. To help determine whether to use adefovir or entecavir under different budgetary restraints, we performed a Monte Carlo analysis with 2,000 simulations to compare entecavir and adefovir monotherapy across a range of willingness-to-pay thresholds (Fig. 3). The analysis revealed that the decision to pay more money for better effectiveness depended highly on the available budget. For example, if a third-party payer was only willing to spend an additional \$10,000 per QALY gained for entecavir, then 45% of patients would fall within the budget. In contrast, if a third-party payer was willing to pay \$50,000 per QALY gained, then 60% of patients would fall within the budget.

DISCUSSION

The most cost-effective strategy in the management of HBV cirrhosis remains unclear. We performed a comprehensive decision analysis to identify the most cost-effective therapeutic approach under varying clinical and budgetary conditions. Our analysis has four key findings. First, we found that the newer generation of antiviral therapies in HBV, including adefovir and entecavir, are cost-effective in patients with HBV

cirrhosis and should be preferred over lamivudine monotherapy. Second, of the competing new-generation antiviral therapies, entecavir appears to be more effective yet more expensive than adefovir. Specifically, compared with adefovir, treating with up-front entecavir cost an additional \$25,626 to gain one additional QALY—a value that falls well within the range of many commonly accepted medical interventions (Table 6). Third, selecting between adefovir and entecavir is highly dependent on available budgets and “willingness to pay” (Fig. 3). For third-party payers willing to pay \$50,000 per QALY gained for entecavir, most (>60%) patients receiving entecavir will fall within the budget. In contrast, entecavir is generally not cost-effective for third-party payers willing to pay less than \$25,000 per QALY gained. Fourth, our analysis found that initiating up-front lamivudine with crossover to adefovir or entecavir as “salvage” on emergence of viral resistance is not cost-effective in HBV patients with cirrhosis. However, when faced with a patient who has already developed lamivudine resistance, using “adefovir salvage” appears more effective and less expensive than “entecavir salvage” on the basis of current viral resistance data (12, 100, 109).

These results are consistent with our *a priori* hypothesis that expensive yet effective therapies are more cost-effective in patients with cirrhosis than those without cirrhosis. This hypothesis is supported by the health economic theory that early and frequent events are weighted more heavily than late and rare events (20). In the case of cirrhosis—a health state plagued by the specter of impending clinical complications—patients may develop resource-intensive, morbid, or mortal complications in short order. In contrast, most HBV patients without cirrhosis either never develop complications

Table 6. League Table* of Incremental Cost per QALY of Common Medical Therapies

Medical Intervention	Incremental Cost/QALY	Reference
Primary angioplasty vs thrombolysis in patients with acute myocardial infarction	\$13,100	101
Entecavir monotherapy vs adefovir monotherapy in HBV cirrhosis	\$25,626	Present analysis
Pegylated interferon plus ribavirin vs nonpegylated interferon plus ribavirin in the treatment of hepatitis C	\$15,000–\$55,000	46
Initiating prophylactic gancyclovir for cytomegalovirus retinitis vs no prophylaxis in HIV-infected patients with a CD4 lymphocyte count <100 cells/mm ³	\$80,000	102
Using a COX-2 selective inhibitor vs naproxen in patients with chronic arthritis	\$275,809	103

*League Table is a valid method of comparing the incremental cost/QALY ratios of medical interventions (104).

of chronic liver disease or else develop complications after a 10–20-yr lead period. Although antiviral resistance is never a goal of therapy in either group of patients, the development of resistance has less severe health economic consequences in noncirrhotics than cirrhotics, because patients with cirrhosis can ill afford the emergence of viral resistance and subsequent viral flares (11). Taken together, these factors strengthen the argument for employing effective therapies in cirrhosis, not only to improve effectiveness, but also to improve cost-effectiveness.

This analysis has several strengths. First, this is the only study to date that compares all of the currently approved agents for chronic HBV cirrhosis, and in particular incorporates the most recent data for entecavir. In light of the increasing availability of newer agents, coupled with the attendant uncertainty regarding how best to select between these agents, our model helps to direct clinical decision making in a cost-conscious environment. Second, our model acknowledges the heterogeneity in liver disease severity seen in clinical practice. Specifically, we stratified our analyses by the stage of liver disease, and accounted for the variations in clinical course, prognosis, and response to therapy between patients with compensated *versus* decompensated cirrhosis. This approach increases the generalizability of our findings. Third, our model attempts to reflect the everyday challenges in the management of patients with HBV cirrhosis. For example, we account for noncompliance with medical therapy, noncompliance with physician follow-up visits, renal side effects of adefovir, development of clinical recompensation in patients with initially decompensated cirrhosis, development of second decompensation among patients with previous recompensation, poor availability of donor organs for eligible patients, immune prophylaxis after liver transplantation, and HBV recurrence following liver transplantation. By acknowledging these practical issues, our analysis is more likely to reflect the health economic consequences of everyday practice.

There are several limitations to our analysis. First, several of our estimates are derived from studies of varying design, patient population, follow-up time, and quality. However, we have attempted to guard against inaccurate base-case results by systematically reviewing the literature, calculating weighted means to account for study sample size, and relying on preexisting meta-analyses when available. Second, our estimates of patient health preferences may be limited because we adopted utilities for cirrhosis and related complications resulting from hepatitis C, not HBV. However, it is reasonable to assume that a patient developing cirrhosis or related complications should suffer similar quality-of-life decrement regardless of whether their cirrhosis resulted from hepatitis B or hepatitis C. Moreover, our results did not change despite varying our utility estimates over a wide range in multiple forms of sensitivity analysis. Third, we did not evaluate the potential strategy of up-front treatment with interferon. Although this approach is a relevant strategy in patients with histological cirrhosis, its role in clinically significant cirrho-

sis has been limited given the risk of causing (sometimes fatal) disease flare-ups (11). Because practice guidelines recommend against the use of interferon in patients with clinical cirrhosis (3, 4), we did not model interferon monotherapy in this analysis. Last, our analysis only applies to a narrow patient population. Specifically, our hypothetical cohort has HBV-related clinical cirrhosis, evidence of viral replication, and no contraindications to therapy. Therefore, our results may not be applicable to alternative populations, including those without viral replication, those with histological (but not clinical) cirrhosis, and postliver transplantation. However, because our base-case cohort reflects the most common and clinically relevant presentation of patients with HBV cirrhosis, we believe our data are applicable to most patients with HBV cirrhosis, and are especially relevant to the community-based practice settings.

In conclusion, our analysis reveals that both adefovir and entecavir are cost-effective in the management of HBV cirrhosis, and these agents should be preferred over lamivudine as first-line therapy in this vulnerable subgroup of patients. Selecting between adefovir and entecavir is highly dependent on budgetary restraints and willingness to pay. Among patients with HBV cirrhosis who have previously developed lamivudine resistance, “adefovir salvage” appears more cost-effective than “entecavir salvage.” As our knowledge about resistance patterns of these agents becomes better refined with longer term follow-up, these cost-effectiveness data may ultimately change with time. Therefore, future research should aim to prospectively measure the accrued cost and effectiveness of these competing management strategies in patients with HBV cirrhosis, and should specifically measure the impact of viral resistance patterns on health economic outcomes.

TECHNICAL APPENDIX

Systematic Review Methodology

We conducted a structured search of MEDLINE to identify relevant English language studies from January 1970 to March 2006. In addition, we reviewed the bibliographies of key review articles for references not captured by our search strategy. We targeted studies that address either the natural history of HBV cirrhosis, including the posttransplantation course, or the efficacy of lamivudine, adefovir, or entecavir in the treatment of both pre- and posttransplantation HBV. The keywords and search strings used to perform the systematic review are available from the authors on request.

Three reviewers (FK, MF, BS) assessed the generated titles for relevancy and only rejected titles that fulfilled the following explicit exclusion criteria: (1) not written in English, (2) not concerning human subjects, (3) not related to chronic viral hepatitis, and (4) solely related to cholestatic liver diseases, autoimmune liver diseases, or metabolic liver diseases. The reviewers then individually assessed the relevancy of all abstracts corresponding to the remaining titles and excluded abstracts for the following reasons: (1) fulfilled

one or more of the title exclusion criteria, (2) did not pertain to one or more of the following estimates: progression rate to decompensated cirrhosis, progression rate to hepatocellular carcinoma, health state-specific mortality rate, progression rate to recompensated cirrhosis, annual rate of viral resistance on therapy, or posttransplantation recurrence of HBV and subsequent consequences, and (3) were solely limited to the pediatric population. The reviewers then assessed the relevancy of all manuscripts corresponding to the remaining abstracts, and included manuscripts if they had data pertaining to the probability estimates required for the model (Tables 1 and 2). Where available, we relied on summary estimates derived from published systematic reviews and meta-analyses.

For each study, we converted all available data into annual probability estimates for use in the Markov model. We calculated these annual estimates using the standard transformation formula $p = 1 - e^{-rt}$, where p is the probability, e is the base of the natural logarithm, r is the event rate, and t is the time interval (105). We then combined all the data across studies by calculating a weighted mean using study sample size as the weight. We also recorded the range of values reported in the literature, and conducted sensitivity analyses to span this range. Each estimate reported in Tables 1 and 2 (and discussed below) represents the weighted mean for the corresponding probability estimate.

Systematic Review Results

The search strategy identified 4,771 titles, of which 192 met our explicit inclusion criteria. Of these, 91 addressed natural history estimates, 83 addressed efficacy of the antiviral agents in pretransplant HBV (50 addressed lamivudine efficacy estimates, 20 addressed adefovir efficacy estimates, 8 addressed entecavir efficacy estimates), and 23 addressed efficacy of the antiviral agents in posttransplant HBV.

NATURAL HISTORY ESTIMATES

1. *Progression to Decompensated Cirrhosis*: Our analysis found an annual rate of progression from compensated to decompensated cirrhosis in HBV of 7.3% (range 3.4–10% per yr) (21, 23, 29, 31–34). Among those patients with decompensated cirrhosis, the probability of developing ascites, variceal hemorrhage, and overt encephalopathy was 68% (21, 30, 32, 35), 14.6% (21, 26, 29, 35, 36), and 10% (21, 29), respectively. The annual mortality rates in compensated and decompensated cirrhosis were 4.9% (21–31) and 19% (21–23, 26, 27, 35), respectively.
2. *Regression from Decompensated to Compensated Cirrhosis*: Our review found that 8% of patients with decompensated cirrhosis regressed back to compensated cirrhosis, *i.e.*, recompensated (range 0–16%) (37–39). In our model, we assumed that these recompensated patients could then decompensate for the second time.
3. *Progression to Hepatocellular Carcinoma*: Patients with HBV cirrhosis developed hepatocellular carcinoma at a rate of 3.4% per yr (range 0.8–12% per yr) (21, 25, 29,

35, 36, 42–45). The annual mortality rate in hepatocellular carcinoma was 43.3% (46–48).

4. *Progression to Cirrhosis and Subsequent Complications with Recurrent HBV*: We assumed that all patients received prophylaxis against recurrent HBV (see “Methods” section). We found that only 4.7% of patients receiving a combination of HBIG and lamivudine developed recurrent HBV per yr (range 0–13%) (50–64). We did not find any studies reporting the HBV recurrence rate in patients receiving prophylaxis with a combination of HBIG and adefovir. In the absence of data, we assumed that the rate of HBV recurrence was the same between protocols using lamivudine and adefovir, and therefore set the rate for HBIG and adefovir at 4.7% per yr.

Treatment Efficacy Estimates

1. *Lamivudine Efficacy Estimates*: Our review indicated that 23% of patients developed viral resistance annually (*i.e.*, development of YMDD mutation) on lamivudine therapy (71–85). In our model, the disease progression rates and response to treatment differ between those with and without viral resistance. Our review showed that 2% of cirrhotic patients without viral resistance who were maintained on long-term lamivudine developed decompensation annually (5, 11, 38, 86, 87) *versus* 8% of patients with viral resistance (5, 7, 10, 11, 38, 86, 87). We found that 35% of patients with decompensated cirrhosis (*i.e.*, Child class B or C) without viral resistance regressed to compensated cirrhosis (*i.e.*, Child class A) (7, 38, 87), and that only a few patients developed second decompensation on long-term therapy (7). We did not find data regarding the rate of regression from decompensated to compensated cirrhosis in patients with viral resistance on long-term lamivudine. In the absence of data, we adopted the rate of 8% per yr observed in natural history studies.
2. *Adefovir Efficacy Estimates*: We found several studies that report data on the efficacy of adefovir among cirrhotic patients with preexisting lamivudine resistance (*i.e.*, “adefoviral salvage” strategy). However, we did not find any data on the efficacy of adefovir monotherapy among treatment-naïve patients with cirrhosis. In the absence of these data, we assumed that the efficacy of adefovir among cirrhotics was the same regardless of whether or not patients had previously developed lamivudine resistance. This assumption has face validity because the annual rate of durable virologic response on adefovir is the same independent of previous lamivudine resistance (106–108). Our review found that the annual rate of viral resistance during year 1, 2, 3, and 4 was 0%, 2%, 5%, and 8%, respectively (with a cumulative rate of 18% over 4 yr) (89). We found that 2% of cirrhotic patients developed decompensation annually (14, 91, 92), and that 33% of patients with decompensated cirrhosis regressed to compensated cirrhosis annually in the absence of viral resistance on long-term adefovir (14, 93). Our review did not find data on the rates of disease progression and regression in patients with adefovir

resistance. We therefore assumed that these rates were similar to the corresponding estimates in patients with viral resistance on long-term lamivudine.

3. *Entecavir Efficacy Estimates*: There are no long-term data currently available regarding the clinical efficacy or antiviral resistance patterns of entecavir. In the absence of entecavir data regarding our efficacy end points (*i.e.*, clinical outcomes most relevant to patients with HBV cirrhosis including progression to decompensated cirrhosis, regression from decompensated to compensated cirrhosis, progression to hepatocellular cancer, or progression to liver transplantation) we relied on histological improvement as the best surrogate of improved long-term clinical outcomes. Our analysis stratifies patients into those with *versus* without viral resistance, and uses separate clinical efficacy estimates for both strata. Using this approach, our review revealed that, as compared with adefovir and entecavir, lamivudine use is associated with the highest rate of histological improvement. There are no peer-reviewed data available on the rate of fibrosis reduction with entecavir use. The data for the adefovir and lamivudine show that, as compared with adefovir, lamivudine use resulted in a greater reduction in the fibrosis scores among patients without evidence of viral resistance. In a recent independent systematic review, Dienstag *et al.* found no differences in the degree of histological improvements (including both necroinflammation and fibrosis score improvements) among studies reporting entecavir and lamivudine use in HBV, even after adjusting for lamivudine resistance (15). Based on these data, we assumed that entecavir had equal efficacy to lamivudine (12, 110–114). Short-term data indicate that the annual incidence of viral resistance with entecavir is 0% in treatment-naïve patients (12, 109), and 7% in patients with previous lamivudine resistance (100), and we used these estimates for the entecavir monotherapy and “entecavir salvage” strategy, respectively. Specifically, we assumed that there was *no* viral resistance from entecavir during the first 2 yr of therapy. Furthermore, we assumed that the rate of subsequent viral resistance with entecavir remained minimal, and never exceeded 1% over the entire course of therapy—an assumption that likely underestimates what will happen as longer term data are collected with entecavir (based on the experience of other antiviral agents, which are uniformly associated with increasing resistance over time).
4. *Progression to Cirrhosis and Subsequent Complications with Recurrent HBV*: We assumed that all patients received prophylaxis against recurrent HBV following liver transplantation (see “Methods” section). We further assumed that the rates of recurrent HBV varied depending on the presence or absence of pretransplant viral resistance. We found that less than 5% of patients without pretransplant viral resistance who subsequently received posttransplant HBIG and lamivudine developed recurrent HBV per yr (range 0–13%) (88). We did not find any studies that report the rate of HBV recurrence

in patients receiving prophylaxis with a combination of HBIG and adefovir. In the absence of data, we assumed that the rate of HBV recurrence was the same between protocols using lamivudine and adefovir, and therefore set the rate for HBIG and adefovir at 4.7% per yr. We assumed that 80% of patients with pretransplant viral resistance subsequently developed HBV recurrence post-transplant if continued on the same agent post-OLT (5, 50, 70, 88). In contrast to the patients in the lamivudine or adefovir monotherapy strategy, those in the “adefovir salvage” strategy (*i.e.*, patients with lamivudine resistance who cross over to adefovir pre-OLT) developed recurrent HBV at low rates. In a recent study, Marzano *et al.* reported that none of their 11 patients who were started on adefovir on development of lamivudine resistance experienced viral recurrence during the 3-yr study follow-up (88). Because the rate reported by Marzano *et al.* may underrepresent the true HBV recurrence rate because of the small number of patients, we set the corresponding rate to 4.7%—rate adopted for HBV recurrence without pre-OLT viral resistance (see above). Our review found that 24% of patients with recurrent HBV following liver transplantation developed graft failure per yr (range 16–43%) (52, 56, 65). In contrast, only 7% of patients without recurrent HBV developed graft failure per yr (range 5–13%) (52, 56, 66). The annual mortality rates in patients with and without recurrent HBV were 18.8% (52, 66–70) and 5.4% (52, 66, 67), respectively.

Utility Estimates

Patients with chronic viral hepatitis experience a wide range of health states that may diminish their health-related quality of life. Several studies in hepatitis C have measured patient health preferences, or utilities, for complications of chronic liver disease, including compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and liver transplantation (94, 115). There are no similar studies in HBV. However, both hepatitis C and HBV lead to cirrhosis and related complications, and there is no *a priori* reason to believe that the quality-of-life decrement engendered by these health states would vary by underlying etiology. In other words, cirrhosis is the end result of a common pathway shared by both forms of viral hepatitis, and a patient developing cirrhosis should suffer the same quality-of-life decrement independent of the etiology of cirrhosis in the first place. We therefore adopted previously established utilities for cirrhosis and related complications that were derived using standard gamble elicitation in patients with chronic hepatitis C (94). Specifically, we assumed a utility of 0.82 for compensated cirrhosis, 0.60 for decompensated cirrhosis, 0.86 following successful liver transplant, and 0.73 for hepatocellular carcinoma (94). Because our base-case utility estimates are unlikely to be precisely reproduced in varying populations, we varied each estimate over a wide range in sensitivity analysis as described below. Table 3 provides the full list of utilities and the range tested in sensitivity analysis around each point estimate. We discounted all utilities at a rate of 3% per yr as

recommended by the National Panel on Cost-Effectiveness in Health and Medicine (20).

STUDY HIGHLIGHTS

What Is Current Knowledge

- It is controversial whether the improved efficacy of the new-generation antiviral agents for hepatitis B, including adefovir and entecavir, offsets the cost *versus* lamivudine for the management of hepatitis B patients with cirrhosis.

What Is New Here

- Both adefovir and entecavir seem to be cost-effective in hepatitis B patients with cirrhosis.
- Of the new agents, entecavir appears more effective yet more expensive than adefovir. Selecting between these agents completely depends upon the available health care budget and willingness-to pay.
- In patients with pre-existing lamivudine resistance, it appears more cost-effective to start with adefovir than entecavir, since entecavir is associated with higher viral resistance than adefovir in the face of previous lamivudine resistance.

Reprint requests and correspondence: Brennan M. R. Spiegel, M.D., M.S.H.S., VA Greater Los Angeles Healthcare System, David Geffen School of Medicine at UCLA, UCLA/VA Center for outcomes Research and Education (CORE), 11301 Wilshire Boulevard, Building 115, Room 215E, Los Angeles, CA 90073.

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CONFLICT OF INTEREST

Guarantor of the article: Fasiha Kanwal

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