

Treatment Alternatives for Chronic Hepatitis B Virus Infection: A Cost-Effectiveness Analysis

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Background: Treatment options for chronic hepatitis B virus (HBV) infection have disparate risks and benefits. Interferon has clinically significant side effects, and lamivudine is associated with viral resistance. In contrast, adefovir is safe and has lower viral resistance but is more expensive. The most cost-effective approach is uncertain.

Objective: To determine whether and under what circumstances the improved efficacy of adefovir offsets its increased cost compared with lamivudine or interferon.

Design: Cost-utility analysis stratified by hepatitis B e antigen (HBeAg) status.

Data Sources: Systematic review of MEDLINE from 1970 to 2005.

Target Population: Patients with chronic HBV infection, elevated aminotransferase levels, and no cirrhosis.

Time Horizon: Lifetime.

Perspective: Third-party payer.

Interventions: 1) No HBV treatment ("do nothing" strategy), 2) interferon monotherapy, 3) lamivudine monotherapy, 4) adefovir monotherapy, or 5) lamivudine with crossover to adefovir upon resistance ("adefovir salvage" strategy).

Outcome Measure: Incremental cost per quality-adjusted life-year (QALY) gained.

Results of Base-Case Analysis: The "do nothing" strategy was least effective yet least expensive. Compared with the "do nothing" strategy, using interferon cost an incremental \$6337 to gain 1 additional QALY. Compared with interferon, the adefovir salvage strategy cost an incremental \$8446 per QALY gained. Both the lamivudine and adefovir monotherapy strategies were more expensive yet less effective than the alternative strategies and were therefore dominated.

Results of Sensitivity Analysis: In sensitivity analysis, interferon was most cost-effective in health care systems with tight budgetary constraints and a high prevalence of HBeAg-negative patients.

Limitations: These results apply only to patients with chronic HBV infection, elevated aminotransferase levels, and no clinical or histologic evidence of cirrhosis. They do not apply to alternative populations.

Conclusions: Neither lamivudine nor adefovir monotherapy is cost-effective in chronic HBV infection. However, a hybrid salvage strategy reserving adefovir only for lamivudine-associated viral resistance may be highly cost-effective across most health care settings. Interferon therapy may still be preferred in health care systems with limited resources, especially in those serving populations with a high prevalence of HBeAg-negative HBV.

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Chronic hepatitis B virus (HBV) infection is a prevalent and expensive condition, affecting 350 million people worldwide and 1.25 million people in the United States (1) at a cost of more than \$700 million annually (2). Chronic HBV infection can progress to cirrhosis, liver failure, and hepatocellular carcinoma and is a major cause of morbidity and mortality (1, 3). Traditional therapy for chronic HBV infection with either interferon- α 2b (interferon) or lamivudine is difficult and has limited long-term efficacy (4). Interferon has clinically significant side effects and results in durable virologic response in only 15% to 30% of patients (5–8). Lamivudine is easy to administer and is associated with minimal side effects (9–11), but it has a higher rate of viral resistance (12), lower durable response rate (9–11), and greater need for prolonged therapy (9, 11) compared with interferon. The efficacy of both interferon and lamivudine is even more limited in patients with hepatitis B e antigen–negative (HBeAg–negative) disease (4). This burgeoning population now accounts for more than half of patients with HBV in the United States (13) and up to 80% of patients with HBV in Asia (14, 15).

Data from 2 randomized, controlled trials indicate that

adefovir is efficacious in HBeAg–positive and HBeAg–negative patients (16, 17). Adefovir has a low risk for side effects and viral resistance (18) compared with interferon and lamivudine, but it is more expensive (19). Therefore, the improved therapeutic benefits of adefovir in chronic HBV infection may offset its increased cost compared with interferon and lamivudine, therapies that are less effective yet less expensive.

The most effective and cost-effective therapeutic approach to chronic HBV infection must be established.

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Context

Because current treatment options for chronic hepatitis B virus (HBV) infection have varying effects and costs, choosing among them is often difficult.

Contribution

Using a third-party payer perspective and lifetime horizon, this cost–utility analysis found that monotherapy with interferon but not lamivudine or adefovir was cost-effective. A salvage strategy that used adefovir only in case of lamivudine-associated viral resistance also seemed cost-effective.

Cautions

The findings apply only to patients with persistently elevated aminotransferase levels and no cirrhosis. The authors did not model the cost-effectiveness of nucleoside analogue salvage after interferon therapy failure.

—The Editors

Given the uncertainty on how best to initiate therapy in HBV, this information may assist clinicians in everyday clinical decision making. We therefore performed an economic analysis to estimate the cost-effectiveness of 5 competing strategies for managing chronic HBV infection in patients with elevated liver enzyme levels and no evidence of cirrhosis—the most prevalent and clinically relevant presentation of chronic HBV infection in the primary care setting. We sought to determine whether and under what circumstances the improved therapeutic benefits of adefovir offset its increased cost compared with lamivudine or interferon in managing chronic HBV infection.

METHODS**Decision Model Framework****Model Overview**

Using decision analysis software (DATA, version 4.0, TreeAge Software, Inc., Williamstown, Massachusetts), we evaluated a hypothetical cohort of patients 40 years of age with chronic HBV infection, elevated aminotransferase levels, and no clinical or histologic evidence of cirrhosis. To emulate the case mix in clinical practice in the United States (13), we assumed that 55% of the cohort was HBeAg-negative. We subsequently varied this estimate between 0% and 100% in our sensitivity analysis. Patients entered the hypothetical model without previous treatment for HBV infection and received 1 of 5 competing strategies for managing chronic HBV infection: 1) no pharmacologic treatment of chronic HBV infection (“do nothing” strategy), 2) interferon monotherapy, 3) lamivudine monotherapy, 4) adefovir monotherapy, or 5) lamivudine with crossover to adefovir upon development of viral resistance (“adefovir salvage” strategy).

Because the clinical course, prognosis, and response to

therapy vary in patients with HBeAg-positive and HBeAg-negative HBV (4), we stratified our analysis by HBeAg status and assigned separate probability estimates for each group. Patients entering the model received either no treatment (“do nothing” strategy) or active treatment for chronic HBV infection. We then followed the cohort over a lifetime horizon through a series of Markov cycles governing patient transitions between relevant health states. The Appendix (available at www.annals.org) describes the model structure in detail.

Competing Strategies

“Do Nothing” Strategy. In this strategy, which served as the referent case for our analysis, we assumed that patients were followed clinically but did not receive pharmacologic therapy for chronic HBV infection. Patients followed the natural history of chronic HBV infection according to their HBeAg status. We further assumed that all patients received regular ongoing care, including hepatocellular cancer screening, and that patients developing cirrhosis were managed for complications, as outlined by published management guidelines (4, 20). We assumed that a proportion of patients with cirrhosis became eligible for liver transplantation and that a subgroup of these patients subsequently underwent liver transplantation at the rate reported by the United Network for Organ Sharing (21).

Interferon Monotherapy Strategy. Patients in this strategy received up-front active therapy with interferon, 10 million units subcutaneously 3 times per week. We assumed that HBeAg-positive and HBeAg-negative patients received 4 and 12 months of treatment, respectively, as suggested by published guidelines (4, 20). Patients without virologic response did not receive additional HBV therapy and followed the natural history of chronic HBV infection.

Lamivudine Monotherapy Strategy. Patients in this strategy received up-front lamivudine, 100 mg orally once daily. Lamivudine therapy was discontinued 6 months after a virologic response. Patients without virologic response, including those developing viral resistance, continued to receive long-term lamivudine therapy as recommended by published guidelines (4, 20). We then assigned patients to receive lifetime lamivudine therapy and discontinued therapy if patients developed a subsequent virologic response.

Adefovir Monotherapy Strategy. Patients in this strategy received up-front adefovir, 10 mg orally once daily. Adefovir therapy was discontinued 6 months after a virologic response. Patients without virologic response, including those developing viral resistance, continued to receive long-term adefovir therapy as recommended by published guidelines (20). We then assigned patients to receive lifetime adefovir therapy and discontinued therapy if patients developed a subsequent virologic response.

Adefovir Salvage Strategy (Lamivudine to Adefovir Crossover). A relevant therapeutic alternative available to clini-

Table 1. Base-Case Probability Estimates*

Variable (Reference)	Base-Case Estimate (Range in Sensitivity Analysis)
Natural history variables, %	
Probability of HBeAg-negative chronic HBV (13)	55 (0–100)
Probability of HBeAg-positive chronic HBV (13)	45 (0–100)
Annual rate of progression from chronic hepatitis to hepatocellular cancer (22–44)	1.5 (0–10)
Annual rate of progression to compensated cirrhosis in HBeAg-negative patients (26, 45–50)	4.6 (0.5–15)
Annual rate of progression to compensated cirrhosis in HBeAg-positive patients (29, 47, 48, 51–56)	3.0 (0.5–11)
Annual rate of mortality in compensated cirrhosis (27, 34, 44, 50, 57–63)	4.9 (2–14)
Annual rate of progression from compensated to decompensated cirrhosis (7, 50, 60, 62–65)	7.3 (3.5–10)
Probability of developing ascites in cirrhosis (7, 60, 62, 66)	68 (50–90)
Probability of developing variceal bleeding in cirrhosis (29, 44, 60, 62, 66)	14.6 (7–30)
Probability of developing overt encephalopathy in cirrhosis (60, 62)	10 (5–30)
Annual rate of mortality in decompensated cirrhosis (44, 50, 57, 58, 62, 66)	19 (6–25)
Annual rate of progression from cirrhosis to hepatocellular cancer (29, 33, 34, 40, 60, 62, 66–68)	3.4 (1–12)
Annual rate of mortality in hepatocellular cancer (69–71)	43.3 (20–60)
Annual probability of receiving a liver transplant in decompensated cirrhosis (21)	25 (0–40)
Annual probability of receiving a liver transplant in hepatocellular cancer (21)	30 (0–40)
Annual rate of mortality after successful transplantation (adjusted to account for decreasing mortality over time from transplantation) (21)	6.9 (2–12)
Utility estimates	
Utility of chronic HBV without cirrhosis (72)	0.99 (0.8–1.0)
Utility of compensated cirrhosis (73)	0.80 (0.7–0.9)
Utility of decompensated cirrhosis (73)	0.6 (0.5–0.7)
Utility of liver transplantation (73)	0.86 (0.7–0.9)
Utility of hepatocellular cancer (73)	0.73 (0.5–0.8)
Utility of durable virologic response (72)	1.0 (0.9–1.0)

* HBeAg = hepatitis B e antigen; HBV = hepatitis B virus.

cians is a hybrid strategy of up-front lamivudine followed by adefovir salvage if lamivudine-related viral resistance develops. We assumed that patients in this strategy initially received lamivudine as described in the lamivudine monotherapy strategy. We then crossed patients over to adefovir when they developed viral resistance, and we subsequently managed patients as described in the adefovir monotherapy strategy. Patients without viral resistance continued to receive lamivudine. Therefore, we reserved adefovir therapy only for patients developing viral resistance while they were receiving lamivudine therapy.

Tables 1 and 2 and the Appendix (available at www.annals.org) describe the probability estimates governing all 5 strategies.

Model Assumptions

The Appendix (available at www.annals.org) contains information about our key model assumptions, including base-case patient characteristics, survival assumptions, definition of virologic response, relationship between virologic response or resistance and subsequent health, and effect of treatment-related adverse events.

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 HBV infection (Tables 1 and 2). To derive these estimates, we systematically reviewed MEDLINE to identify relevant English-language studies published from January 1970 to February 2005. The Appendix (available at www.annals.org) describes our systematic review methods.

Outcomes

Because the main objective of cost-effectiveness analysis is to permit comparisons among different interventions in medicine, and because quality-adjusted life-years (QALYs) are the exchange currency that allows these comparisons to be made, we adopted QALYs as our main outcome (120). Our analysis reports the incremental cost per QALY gained among the competing strategies, along with the respective 2.5th and 97.5th percentiles around the point estimates as generated by a Monte Carlo analysis of 1000 trials (see Sensitivity Analyses section for details).

Utilities

We incorporated a wide range of relevant health state utilities in our model. Table 1 contains the specific utility estimates, and the Appendix (available at www.annals.org) describes these estimates in detail.

Cost Estimates

We conducted our analysis from the perspective of a third-party payer and incorporated the direct health care costs for many therapies, physician visits, diagnostic tests, and complications of chronic liver disease (Table 3). We obtained costs for physician services and procedures from the 2004 American Medical Association Current Procedural Terminology codebook and the 2004 Medicare Fee Schedule (121) and derived our base-case pharmaceutical costs from the average wholesale prices listed in the 2004 Red Book (19). Because large buying consortiums can often obtain prices lower than the average wholesale prices, we performed a sensitivity analysis by using the acquisition costs of the Veterans Administration as a proxy for the discounts achieved by large third-party

Table 2. Base-Case Treatment-Related Probability Estimates*

Variable (Reference)	Base-Case Estimate (Range Tested)	
	HBeAg-Positive Patients	HBeAg-Negative Patients
"Do nothing" strategy		
Probability of spontaneous virologic response (6, 16, 17, 23, 29, 37, 38, 51–55, 57, 74–93)	6.9 (2–23)	1.6 (0–11)
Interferon monotherapy strategy		
Probability of developing adverse events during interferon course (94)	26 (10–40)	26 (10–40)
Probability of adequate adherence to interferon course given adverse events (94)	64 (50–75)	64 (50–75)
Probability of adequate adherence to interferon course given no adverse events (94)	90 (60–100)	90 (60–100)
Probability of durable virologic response in adherent patient receiving interferon (50, 54, 55, 87, 91–97)	33 (20–40)	20 (10–30)
Probability of durable virologic response in nonadherent patient receiving interferon (94)	7 (3–10)	0 (0–5)
Duration of treatment course (4, 20)	4 mo	12 mo
Lamivudine monotherapy strategy		
Probability of durable virologic response after initial 18 months of therapy (9–11, 85, 86, 88–90, 98–113)	20 (15–20)	10 (0–15)
Yearly probability of developing resistance while receiving long-term lamivudine (60, 85, 86, 90, 98, 101–111)	23 (15–32)	23 (15–32)
Yearly probability of durable virologic response while receiving long-term lamivudine without resistance (9, 86, 110)	24 (10–30)	10 (0–15)
Yearly probability of durable virologic response while receiving long-term lamivudine despite resistance (86, 99, 104, 114–117)	4.5 (1–20)	0 (0–3)
Adefovir-based strategies		
Probability of durable virologic response after initial 18 months of therapy (16, 17)	12 (10–20)	10 (0–15)†
Yearly probability of developing resistance while receiving long-term adefovir (18)	1.3 (0–3)	1.3 (0–3)
Yearly probability of durable virologic response while receiving long-term adefovir without resistance (16, 118)	17.5 (5–20)	10 (0–10)†
Yearly probability of durable virologic response following crossover from lamivudine to adefovir (119)	12 (5–20)	10 (0–10)

* All values are percentages, unless otherwise indicated. HBeAg = hepatitis B e antigen.

† No data supporting base-case estimate. The estimate is an assumption. See Appendix (available at www.annals.org) for details.

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 (122). We discounted all costs at a rate of 3% per year (120).

Sensitivity Analyses

Tables 1 and 2 list our base-case probability estimates with respective ranges. To test the influence of all variables on the model results, we performed a multivariable sensitivity analysis (“tornado analysis” [124]) and rank-ordered

Table 3. Base-Case Cost Estimates*

Variable	Base-Case Estimate (Range in Sensitivity Analysis), \$	Study, Year (Reference)
Drug costs		
Cost per month of interferon treatment	750 (500–1000)	Red Book, 2004 (19)
Cost per month of lamivudine treatment	158 (50–500)	Red Book, 2004 (19)
Cost per month of adefovir treatment	528 (100–1000)	Red Book, 2004 (19)
Nondrug costs of treatment period		
Cost per physician visit	52 (25–100)	AMA CPT Code Book, 2004 (121)
Cost per set of laboratory tests	80 (50–150)	AMA CPT Code Book, 2004 (121)
Cost per abdominal ultrasonography	150 (50–250)	AMA CPT Code Book, 2004 (121)
Costs of developing cirrhosis†		
Cost per year of compensated cirrhosis	964 (500–5000)	Bennett et al., 1997 (122)
Cost of first year after variceal hemorrhage (assuming survival)	22 444 (10 000–30 000)	Bennett et al., 1997 (122)
Cost per subsequent year after variceal hemorrhage	4393 (2000–10 000)	Bennett et al., 1997 (122)
Cost per year of ascites	4058 (1000–10 000)	Bennett et al., 1997 (122)
Cost of first year of encephalopathy	14 406 (5000–25 000)	Bennett et al., 1997 (122)
Cost per subsequent year after encephalopathy	3337 (1000–10 000)	Bennett et al., 1997 (122)
Cost of liver transplantation	127 499 (50 000–150 000)	Bennett et al., 1997 (122)
Cost per year of follow-up care after liver transplantation	22 266 (10 000–50 000)	Bennett et al., 1997 (122)
Cost of hepatocellular cancer	38 715 (20 000–75 000)	Bennett et al., 1997 (122)

* AMA = American Medical Association; CPT = Current Procedural Terminology.

† All cost estimates were updated to 2004 U.S. dollars by using the medical care component of the Consumer Price Index (123).

the most influential variables. We then performed 1-way sensitivity analyses on the most influential variables. We conducted a Monte Carlo simulation, assuming that all variables followed a triangular distribution (123) with base-case, minimum, and maximum values from Tables 1 and 2. We simulated 1000 trials and plotted the results on cost-effectiveness acceptability curves stratified by willingness-to-pay thresholds (125). We analyzed the base-case cohort (55% HBeAg-negative) to find the 2.5th and 97.5th percentiles for our estimate of incremental cost per QALY gained among competing strategies.

Role of Funding Source

No funding was received for this study.

RESULTS

Base-Case Results

The “do nothing” strategy was the least expensive yet least effective strategy of the 5 competing strategies. Compared with doing nothing, using interferon cost an incremental \$6337 to gain 1 additional QALY (2.5th and 97.5th percentiles, \$4123 and \$8992, respectively). Compared with interferon, the adefovir salvage strategy cost an incremental \$8446 per QALY gained (2.5th and 97.5th percentiles, \$6031 and \$11 542, respectively). Both the lamivudine and adefovir monotherapy strategies were more expensive yet less effective than the alternative strategies and were therefore dominated. Our base-case analysis revealed that the restricted use of adefovir as salvage therapy was more cost-effectiveness than both lamivudine and adefovir monotherapies.

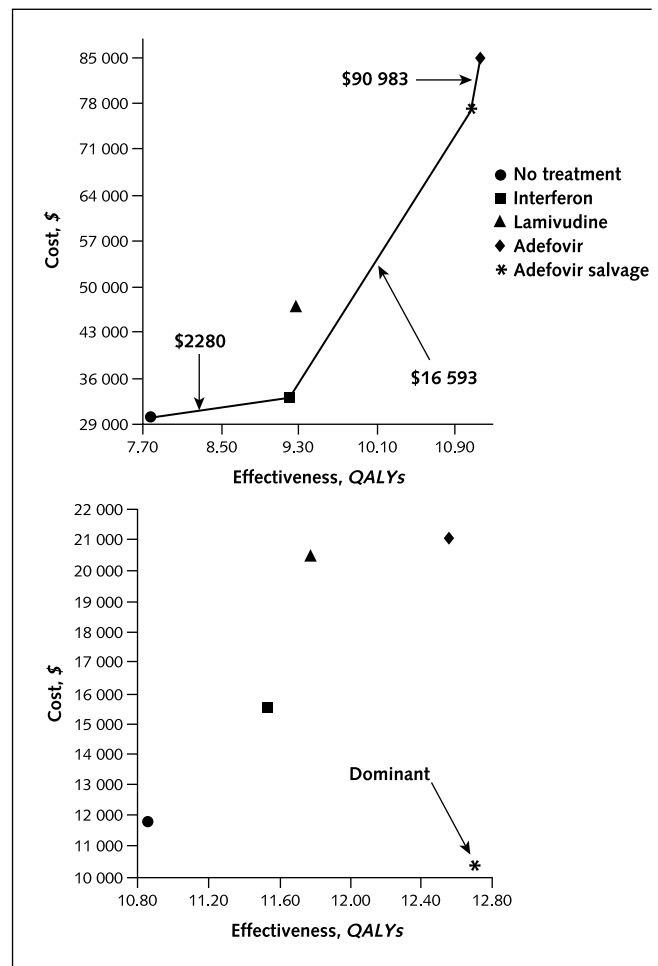
Results Stratified by HBeAg Status

Because individual patients are either HBeAg-positive or HBeAg-negative, we performed 2 separate analyses stratified by HBeAg status. Figure 1 displays these results.

HBeAg-Negative Cohort

Compared with the base-case analysis, which assumed that only 55% of the cohort was HBeAg-negative, in the HBeAg-negative cohort analysis, all the strategies became more expensive and less effective, thereby reflecting the difficulties and expense of treating HBeAg-negative patients (Figure 1, top). Therapy with interferon became more cost-effective in this cohort compared with the base-case analysis. Specifically, compared with the “do nothing” strategy, the incremental cost of using interferon decreased from \$6337 per QALY gained in the base-case analysis to \$2280 per QALY gained in the HBeAg-negative cohort. Compared with interferon, the adefovir salvage strategy cost an incremental \$16 593 per QALY gained. In contrast, the use of up-front adefovir showed diminishing returns, costing an incremental \$90 983 per QALY gained, compared with the adefovir salvage strategy. Finally, the lamivudine monotherapy strategy was dominated and was not cost-effective in HBeAg-negative patients.

Figure 1. Results of cost-effectiveness analysis stratified by hepatitis B e antigen (HBeAg) status.



The results presented assume that the entire cohort is HBeAg-negative (top) or HBeAg-positive (bottom). The vertical axes display the lifetime cumulative cost, and the horizontal axes display the quality-adjusted life-years (QALYs) gained. The “do nothing” strategy is the least expensive of the 5 competing strategies in both analyses. When the cohort is entirely HBeAg-negative (top), the lamivudine strategy is dominated as it falls above and to the left of the concave border that outlines the 4 competing strategies composing the cost-effectiveness frontier. When the cohort is entirely HBeAg-positive (bottom), the adefovir salvage strategy becomes the dominant strategy because it is the most effective and least expensive of the 5 competing strategies.

HBeAg-Positive Cohort

The adefovir salvage strategy was more effective and less expensive than the 4 competing strategies and became the dominant strategy in the HBeAg-positive cohort (Figure 1, bottom).

Base-Case Sensitivity Analyses

Tornado analysis revealed that the model was sensitive to 6 variables. Table 4 displays the results of 1-way sensitivity analyses for these variables in decreasing order of influence and lists the thresholds where the cost-effectiveness order among the strategies changed. The remaining estimates did not affect the model when varied over a wide range. The results of our sensitivity analysis using Veterans

Table 4. Results of 1-Way Sensitivity Analyses*

Variable	Base-Case Estimate	Threshold	Comment
Cost per month of adefovir, \$	528	120	If cost falls below threshold, then adefovir monotherapy is more cost-effective than adefovir salvage
Cost per month of lamivudine, \$	158	627	If cost exceeds threshold, then adefovir monotherapy is more cost-effective than adefovir salvage
Cost per month of interferon, \$	750	2400	If cost exceeds threshold, then interferon becomes less effective and more expensive than adefovir salvage (that is, dominated)
Annual incidence of viral resistance on lamivudine, %	23	10	If incidence falls below threshold, then lamivudine monotherapy becomes cost-effective
Annual incidence of viral resistance on adefovir, %	1.3	14	If incidence exceeds threshold, then lamivudine becomes more cost-effective than both adefovir monotherapy and adefovir salvage
Annual incidence of cirrhosis in HBeAg-negative patients with viral resistance, %	4.9	0.3	If incidence falls below threshold, then lamivudine becomes more cost-effective than both adefovir monotherapy and adefovir salvage

* HBeAg = hepatitis B e antigen.

Administration acquisition costs for pharmaceuticals did not qualitatively differ from those of our base-case analysis (results not shown).

Monte Carlo Analyses

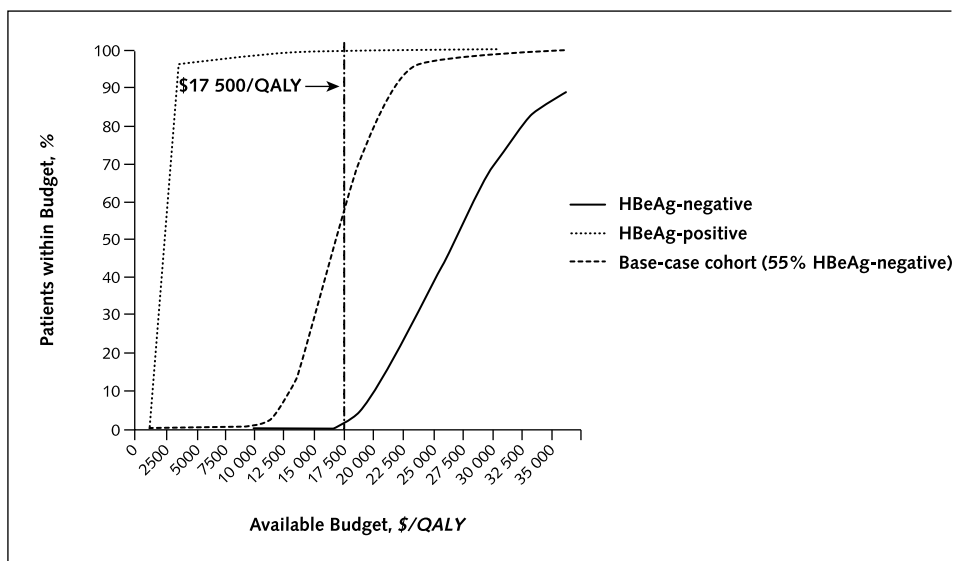
Together, the results indicate that of the 4 active therapy strategies, the interferon and adefovir salvage strategies were potentially cost-effective. To determine which comparator to use under different budgetary restraints, we performed 3 Monte Carlo analyses to compare interferon and adefovir salvage across a range of willingness-to-pay thresholds. Figure 2 displays cost-effectiveness acceptability curves reflecting 1000 hypothetical patients in each of 3 populations: 1) the base-case

cohort (55% HBeAg-negative), 2) the HBeAg-negative cohort, and 3) the HBeAg-positive cohort. The curves reveal that the use of the adefovir salvage strategy instead of interferon is most cost-effective in HBeAg-positive patients. In contrast, interferon is most cost-effective in health care systems with tight budgetary constraints (that is, low willingness to pay) and high prevalence of HBeAg-negative patients.

DISCUSSION

Interferon, lamivudine, and adefovir are the 3 agents currently approved for treating chronic HBV infection.

Figure 2. Cost-effectiveness acceptability curves of the adefovir salvage strategy versus interferon monotherapy arranged by hepatitis B e antigen (HBeAg) status.



The horizontal axis displays the willingness-to-pay budgetary thresholds to gain 1 additional quality-adjusted life-year (QALY) when using the adefovir salvage strategy instead of interferon, and the vertical axis displays the percentage of 1000 patients that fall within the available budget. There are 3 curves: 1) curve assuming that cohort is 55% HBeAg-negative (base-case analysis) (dashed line); 2) curve assuming that cohort is HBeAg-negative (solid line); and 3) curve assuming that cohort is HBeAg-positive (dotted line). For example, if a third-party payer had a budget of \$17 500 per QALY gained to substitute adefovir salvage for interferon (vertical line), more than 99% of the HBeAg-positive cohort would fall within the budget, whereas only 2% and 60% of the HBeAg-negative and base-case cohorts, respectively, would fall within the budget. In contrast, the adefovir salvage strategy becomes cost-effective for close to 90% of all patients in health care systems willing to pay at least \$35 000 per QALY, regardless of HBeAg status.

The cost-effectiveness of these therapies has not been previously evaluated. We therefore performed a comprehensive decision analysis to identify the most cost-effective therapeutic approach under varying clinical and budgetary conditions. Our analysis has 3 key findings. First, the use of up-front adefovir in HBV is unlikely to be cost-effective under any circumstance. We found that adefovir monotherapy is less effective yet more expensive than competing strategies in HBeAg-positive patients and has an incremental cost of more than \$90 000 per QALY gained in HBeAg-negative patients, a value that exceeds the cost of many commonly accepted medical interventions (126). Second, our data reveal that continuing lamivudine therapy in patients who develop viral resistance is not cost-effective, regardless of HBeAg status. Third, despite our finding that lamivudine is not cost-effective in the setting of viral resistance, our analysis reveals that up-front lamivudine may be highly cost-effective, assuming that patients developing viral resistance cross over to adefovir instead of continuing long-term lamivudine therapy. The adefovir salvage strategy seems highly cost-effective across a range of health care budgets, from the most liberal to the most conservative (Figure 2).

The fact that our analysis identified a hybrid strategy (that is, adefovir salvage) as the preferred approach under most clinical and economic circumstances is consistent with the results from cost-effectiveness analyses evaluating hybrid strategies in other areas of medicine. For example, in the primary care management of patients with uninvestigated dyspepsia, the combination of *Helicobacter pylori* “test and treat” and empirical proton-pump inhibitor therapy dominates the use of either therapy alone if patients cross over to proton-pump inhibitor therapy when “test and treat” fails (127). In the management of patients with chronic arthritis, the combination of naproxen and a cyclooxygenase-2 selective inhibitor is more cost-effective than either therapy alone if patients cross over to a cyclooxygenase-2 inhibitor when naproxen therapy fails (128). In these examples, expensive yet effective therapies are reserved for when less effective yet less expensive first-line therapies fail. The net result is to maximize cost-effectiveness by targeting resource-intensive therapies to patients who are most in need and most likely to benefit. This approach is not only economically prudent but is also effective, since multiplying sequential therapies in a rational order often provides more benefit than relying on any single therapy alone. In our analysis, we found that reserving adefovir for patients who developed viral resistance while receiving up-front lamivudine was more cost-effective than using either lamivudine or adefovir alone. This hybrid strategy represents a potentially high-yield therapeutic niche for adefovir in managing patients with chronic HBV infection.

Although we found that the adefovir salvage strategy may be cost-effective, our analysis also reveals that interferon remains an important therapy in several health eco-

nom circumstances. Interferon may save costs by avoiding prolonged therapy; the typical therapeutic course lasts only 4 months for HBeAg-positive patients and 12 months for HBeAg-negative patients. Interferon also remains effective in many patients since viral resistance is nonexistent. In contrast, nucleoside analogues like lamivudine and adefovir require a minimum of 12 months of therapy in HBeAg-positive patients and up to a lifetime of therapy in HBeAg-negative patients. Moreover, viral resistance is a frequent problem in patients receiving lamivudine and, although rare, occurs in patients receiving adefovir. For these reasons, our analysis indicates that interferon is particularly cost-effective in HBeAg-negative patients (Figure 1). Moreover, interferon is preferred over adefovir salvage in health care systems with tight budgetary constraints and high proportions of HBeAg-negative patients (Figure 2). Therefore, interferon may be the most cost-effective therapy in urban hospitals serving large immigrant populations, that is, settings where HBeAg-negative patients are highly prevalent (13) and health care budgets are often restricted.

Our analysis has several strengths. First, to our knowledge, our study is the first decision analysis to compare all 3 currently approved agents for chronic HBV infection. Previous models have focused on either the cost-effectiveness of interferon versus the “do nothing” strategy or that of lamivudine versus interferon. However, no model has examined the role of the adefovir or adefovir salvage strategies. Second, our model acknowledges the increasing prevalence of HBeAg-negative chronic HBV infection. Whereas previous models have focused primarily on HBeAg-positive patients, our model is stratified by HBeAg status and accounts for the fact that clinical course, prognosis, and response to therapy differ in patients with HBeAg-positive versus HBeAg-negative disease. This approach increases the generalizability of our findings in light of data reporting that more than half of patients with HBV in the United States and 80% of patients with HBV in Asia are HBeAg-negative (14, 15). Third, our model attempts to reflect the everyday challenges in managing chronic HBV infection. Specifically, we account for non-adherence to medical therapy, nonadherence to physician follow-up visits, virologic recurrence after initially successful HBV therapy, various treatment durations according to HBeAg status, and poor availability of donor organs for eligible patients. By acknowledging these practical issues, our analysis is more likely to reflect the health economic consequences of everyday practice.

Our analysis has several limitations. First, several of our estimates are based on studies of varying design, patient population, follow-up, and quality. However, we 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 virus infection (not HBV) (73) and utilities for noncirrhosis health states in HBV that were derived from expert opinion (not patients) (72). However, it is reasonable to assume that a patient who develops cirrhosis or related complications would have the same quality-of-life decrement regardless of whether their cirrhosis resulted from HBV or hepatitis C virus infection. Moreover, our results did not change despite varying our utility estimates over a wide range in several forms of sensitivity analysis. Third, we did not evaluate the potential strategy of up-front treatment with interferon followed by crossover to lamivudine or adefovir in case of interferon treatment failure. Although this approach is a relevant variant of the strategies modeled in our analysis, our systematic review identified only 1 study on the use of lamivudine in HBeAg-positive patients when interferon therapy failed (85) and no studies on the use of lamivudine in HBeAg-negative patients when interferon therapy failed. Moreover, whether the effect of nucleoside analogue therapy on histologic or clinical progression differs in patients in whom previous interferon treatment failed versus treatment-naïve patients remains unclear. Although modeling this strategy would be entirely conjectural given our current knowledge, the use of nucleoside analogue salvage after interferon therapy failure may be a cost-effective strategy and should be researched further, especially in light of recent data reporting that pegylated interferon achieves a durable virologic response with a low incidence of adverse effects in both HBeAg-negative (112) and HBeAg-positive patients (113, 129). Finally, our analysis applies only to a narrow patient population. Specifically, our hypothetical cohort has chronic HBV infection, persistently elevated liver enzyme levels, and no clinical or histologic evidence of cirrhosis. Therefore, our results may not apply to alternative populations, including those with intermittently elevated liver enzyme levels, compensated cirrhosis, or decompensated cirrhosis, or those who undergo liver transplantation. However, because our base-case cohort reflects the most common and clinically relevant presentation of chronic HBV infection in the United States, we believe that our data apply to most patients with HBV and are especially relevant to the community-based practice setting.

In conclusion, our analysis reveals that the use of either lamivudine or adefovir monotherapy is not cost-effective in managing chronic HBV infection. Of the active therapeutic strategies currently available for chronic HBV infection, only interferon monotherapy and adefovir salvage therapy are potentially cost-effective. Whereas adefovir salvage is likely to be highly cost-effective across most health care settings independent of HBeAg status, interferon may be preferred in health care systems with limited resources, especially in those serving populations with a high prevalence of HBeAg-negative HBV. Future research should prospectively measure the cost-effectiveness of these

competing management strategies in representative samples of community-based patients with chronic HBV infection.

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APPENDIX

Model Structure

Appendix Figure 1 depicts a truncated version of our decision tree. Appendix Figure 2 depicts the Markov model governing patient transitions between health states. During each 1-year cycle, individual patients either remain in their assigned health state or progress to a new health state. There are 2 submodels: precirrhosis health states and cirrhosis health states. We derived the transition rates between health states from a systematic review of the literature (described in Systematic Review Results section of this Appendix).

Precirrhosis Health States

Patients enter the model with chronic HBV infection. Patients in the “do nothing” strategy do not receive treatment and instead follow the natural history of chronic HBV infection. Over a lifetime horizon, these patients may develop compensated cirrhosis (in which case they enter the cirrhosis health states submodel), develop hepatocellular cancer directly without progressing through cirrhosis, or remain with chronic HBV infection until death. Patients achieving virologic response (either spontaneously or after treatment) do not develop cirrhosis and have a normal life expectancy, as supported by evolving natural history data (6, 55, 97, 130). Additional assumptions about the natural history of chronic HBV infection are described in the Model Assumptions and Systematic Review Results sections of this Appendix.

In each 1-year Markov cycle (Appendix Figure 2), patients receiving therapy for HBV may either achieve a virologic response, develop viral resistance, or continue to receive long-term therapy (without virologic response or resistance). We further assumed that patients achieving initial virologic response may subsequently relapse (108, 109, 112), in which case they re-enter the original state of chronic HBV infection. Patients with viral resistance maintained during long-term therapy are eligible to achieve virologic response, as depicted by the double-headed arrow in the precirrhosis submodel in Appendix Figure 2. Additional assumptions about the relationship between these health states and future health are described in the Model Assumptions section of this Appendix.

Cirrhosis Health States

Patients enter the model with compensated cirrhosis. Patients with compensated cirrhosis may develop decompensated cirrhosis (including ascites, variceal hemorrhage, or encephalopathy). Hepatocellular cancer or death may develop at any stage of cirrhosis. Patients with decompensated cirrhosis and hepatocellular cancer are eligible for liver transplantation.

Model Assumptions

Base-Case Patient Characteristics

To reflect the cohorts described in primary treatment trials and to simulate the most common presentation of chronic HBV infection in primary care, we assumed that our base-case patients had chronic HBV infection with persistently elevated aminotransferase levels, no symptoms or signs of cirrhosis, and no con-

traindications to treatment. Liver biopsy specimens revealed no evidence of cirrhosis, although early fibrosis (that is, grade 1 to 2) was not an exclusion criterion. In accordance with recent U.S. prevalence data, we assumed that 55% of the base-case cohort had HBeAg-negative HBV (13). However, because the prevalence of HBeAg-negative HBV is higher in endemic regions, such as Asia and southern Europe (14, 15), and is also higher in recent U.S. immigrant populations (13), we performed a sensitivity analysis in which we ranged this estimate between 0% and 100%. The average age of 37 669 adult patients in 149 studies included in our systematic review was 40.5 years (see the Systematic Review Results section in this Appendix for details of review). We therefore assumed that our base-case patients were 40 years of age. Because the primary studies included patients of many ages, we varied this estimate between 25 and 65 years in our sensitivity analysis.

Effect of Chronic HBV Infection on Survival

Survival in chronic HBV infection depends on the clinical stage of the disease. Most patients with chronic HBV infection do not progress to cirrhosis and instead remain seropositive without clinically significant histologic progression. Data indicate that survival in these patients does not differ from that in matched controls without chronic HBV infection (standardized mortality ratio, 1.1 [95% CI, 0.99 to 1.22]) (32). However, as depicted in Appendix Figure 2, we assumed that patients with chronic HBV infection without cirrhosis were nonetheless eligible to develop hepatocellular cancer and related complications. We therefore assumed that patients with chronic HBV infection who never progressed to cirrhosis or hepatocellular cancer had a normal lifespan of an additional 39 years, in accordance with U.S. population life tables for persons 40 years of age (131). Patients who developed hepatocellular cancer, cirrhosis, or both were subjected to disease-specific mortality rates, as described in the Systematic Review Results section of this Appendix.

Definition of Virologic Response

Virologic response in chronic HBV infection has several definitions. Definitions variably include normalization of liver enzyme levels, loss of HBeAg, seroconversion from HBeAg to HBV e antibody, suppression of HBV DNA, or improvement of histologic stage on liver biopsy. The American Association for the Study of Liver Diseases endorses HBeAg seroconversion as the most reliable marker of long-term and sustained virologic response in HBeAg-positive patients (4), and we therefore adopted this definition for virologic response in our model. Because HBeAg seroconversion is not relevant in HBeAg-negative patients, the treatment goal in this subgroup is to fully suppress HBV replication while maintaining normal serum aminotransferase levels (4). In light of this treatment goal in HBeAg-negative patients, and given the association between HBV suppression and histologic improvement (17, 90, 105, 112), we adopted complete HBV suppression with normal aminotransferase levels as evidence of virologic response in the HBeAg-negative subgroup. We assumed that patients achieved a durable response if they had continuous virologic response without active therapy

(that is, HBV did not recur after antiviral therapy was discontinued).

Relationship between Virologic Response and Subsequent Health

We assumed that patients with therapy-induced virologic response did not develop subsequent complications of chronic HBV infection and had a normal lifespan of an additional 39 years in accordance with U.S. life table estimates (131). This assumption is supported by several natural history and long-term efficacy studies indicating that patients with durable virologic response, either spontaneous or occurring after therapy, have low rates of progression to cirrhosis (0% to 0.5% per year) and longer survival than that of patients without virologic response (6, 55, 97, 104, 130). For example, Niederau and colleagues (6), in a survival analysis comparing long-term follow-up of patients treated with interferon, found 100% survival in patients achieving a durable virologic response versus 80% survival in patients without treatment response over 7 years. However, we also assumed that a subset of these patients relapsed despite initial virologic response, as suggested by natural history data (9, 10, 108, 109, 112). Patients without an initial virologic response or those with subsequent recurrence were at risk for developing cirrhosis. Refer to the Systematic Review Results section of this Appendix for our estimates of progression rates to cirrhosis (55, 97, 104, 130).

Relationship between Viral Resistance and Subsequent Health

We assumed that viral resistance occurred at a rate of 23.0% and 1.3% per year in patients receiving lamivudine (60, 85, 86, 90, 98, 101–111) and adefovir (18), respectively. We further assumed that patients developing viral resistance followed the natural history of chronic HBV infection, as suggested by evolving natural history data (114, 132, 133). Specifically, despite earlier data to the contrary (9), recent studies indicate that patients with resistant HBV strains with the tyrosine, methionine, aspartate, aspartate (YMDD) mutation may also develop clinical and histologic progression of their disease (114, 132, 133).

Effect of Treatment-Related Adverse Events

Data from randomized, placebo-controlled trials in chronic HBV infection indicate that minimal adverse events occur with lamivudine and adefovir and that the rate of adverse events is similar between each agent and placebo (16, 17, 89, 98). However, interferon is associated with more adverse events than placebo, including flu-like symptoms, arthralgias, psychiatric symptoms, thyroid abnormalities, and blood dyscrasias (94). Because these adverse events negatively affect adherence, we accounted for these events in the model. Specifically, we assumed that 26% of patients receiving interferon developed a clinically significant adverse event, and we further assumed that 36% of these patients discontinued therapy prematurely (94). In contrast, we assumed that 90% of patients without adverse events adhered to therapy (94). We assumed that nonadherent patients achieved placebo response rates. Furthermore, we accounted for the additional

costs engendered by interferon-related adverse events, including additional physician visits and laboratory-monitoring costs. Patients who became nonadherent ceased to accrue drug costs upon discontinuation.

Additional Model Assumptions

To capture the full range of downstream costs generated by each strategy, we included ongoing cost of care associated with HBV, including physician visits, laboratory tests, hepatocellular cancer screening, and treatment-related costs for complications of cirrhosis, in the model (Table 3). Similarly, to emulate clinical reality, our model reflected common challenges to the care of HBV, including nonadherence to medical therapy (especially interferon), decreased therapeutic efficacy of antiviral therapy in HBeAg-negative patients, nonadherence to physician follow-up visits, virologic recurrence after successful HBV therapy, and poor availability of donor organs for eligible patients (Tables 1 and 2).

Systematic Review Methods

We conducted a structured search of MEDLINE to identify relevant English-language studies published from January 1970 to February 2005. In addition, we reviewed published abstracts from 3 major subspecialty journals and the bibliographies of key review articles for references that our search strategy did not capture. We targeted studies that addressed either the natural history of chronic HBV infection or the efficacy of interferon, lamivudine, or adefovir in treating chronic HBV infection. The keywords and search strings used to perform the systematic review are available from the authors on request.

Three reviewers assessed the generated titles for relevancy and rejected titles that fulfilled the following explicit exclusion criteria: 1) not written in English; 2) not about human participants; 3) not related to chronic viral hepatitis; or 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 with the remaining titles and excluded abstracts for the following reasons: 1) fulfilled 1 or more of the title exclusion criteria; 2) did not pertain to 1 or more of the natural history estimates (prevalence of HBeAg-positive and HBeAg-negative HBV, progression rate to compensated cirrhosis, progression rate to decompensated cirrhosis, progression rate to hepatocellular cancer, health state-specific mortality rates, or natural virologic response rates); 3) did not pertain to 1 of the treatment efficacy estimates (virologic response, virologic relapse, resistance, treatment-related adverse events, or treatment-specific adherence); or 4) were limited to a pediatric population. The reviewers then assessed the relevancy of all manuscripts corresponding with the remaining abstracts and included manuscripts if they had data pertaining to the probability estimates required for the model (Tables 1 and 2). We relied on summary estimates derived from published systematic reviews and meta-analyses where available.

For each study, we converted all available data into annual probability estimates for use in the Markov model. We calculated these annual estimates by using the standard transformation for-

mula: $P = 1 - e^{-rt}$, where P is the probability, e is the base of the natural logarithm, r is the event rate, and t is the time interval (134). We then combined all the data across studies by calculating a weighted mean and 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 represents the weighted mean for the corresponding probability estimate.

Systematic Review Results

The search strategy identified 4811 titles, 150 of which met our explicit inclusion criteria (Appendix Figure 3). Of these studies, 91 addressed natural history estimates, 33 addressed lamivudine efficacy estimates, 15 addressed interferon efficacy estimates, and 11 addressed adefovir efficacy estimates.

Natural History Estimates

Spontaneous Virologic Response. Some patients with chronic HBV infection achieve spontaneous virologic response as part of the disease's natural history. Our review indicated that the annual rate of achieving virologic response in patients with HBeAg-positive HBV (defined as seroconversion to anti-HBe) was 8.3% (6, 16, 23, 29, 37, 38, 51–55, 57, 74–89). However, the range around this point estimate was wide (range, 1.7% to 23.0% per year). When we limited our review to results of randomized, controlled trials, we calculated a rate of 6.9% per year with a range of only 4.0% to 10.1% per year. Because we derived most of our efficacy estimates from randomized, controlled trials, we opted to use the latter estimate for our base-case assumption about spontaneous virologic response in HBeAg-positive patients. However, to test the full range of observed data, we conducted a sensitivity analysis between 1.7% and 23.0% per year. In HBeAg-negative patients, our review found an annual spontaneous virologic response rate (defined as persistent HBV DNA suppression and normalization of aminotransferase level) of 2.7% (range, 0% to 11.7%) (17, 57, 90–93). With the exception of 1 outlying study (92), all studies reported a rate less than 6% per year and 3 studies (17, 91, 93) reported a rate of 0% per year. When we removed the outlying study, the annual rate was 1.6%. We adopted this estimate for our base-case assumption on spontaneous virologic response in HBeAg-negative patients and conducted a sensitivity analysis across the full range of observed data.

Progression to Cirrhosis and Hepatocellular Cancer in Chronic HBV Infection. We found that the annual rate of developing cirrhosis in patients with chronic HBV infection varies by HBeAg status. Specifically, the annual rate of progression in HBeAg-positive and HBeAg-negative patients was 3% (29, 47, 48, 51–56) and 4.9% (27, 34, 44, 57–63), respectively. With the exception of 2 small studies reporting annual rates exceeding 15% (22 and 24 patients, respectively [47, 49]), no clear outliers in the data pertained to annual progression rates to cirrhosis in HBeAg-negative patients (range, 0.5% to 9.3% per year). We did not find any outliers in the data pertaining to HBeAg-positive patients (range, 0% to 11.5% per year). Our review found 23 studies reporting data on the incidence of hepatocellular cancer

in chronic HBV infection (22–44). The annual rate of hepatocellular cancer was 1.5% (range, 0% to 10.6%).

Complications of Cirrhosis in Chronic HBV Infection. Our analysis found an annual rate of progression from compensated to decompensated cirrhosis in HBV of 7.3% (range, 3.4% to 10.0%) (7, 50, 60, 62–65). Among patients with decompensated cirrhosis, the probability of developing ascites, variceal hemorrhage, and overt encephalopathy was 68.0% (7, 60, 62, 66), 14.6% (29, 44, 60, 62, 66), and 10.0% (60, 62), respectively. After developing cirrhosis, patients with HBV developed hepatocellular cancer at a rate of 3.4% per year (range, 0.8% to 12.0% per year) (29, 33, 34, 40, 60, 62, 66–68). The annual mortality rates in compensated and decompensated cirrhosis were 4.9% (27, 34, 44, 50, 57–63) and 19.0% (44, 50, 57, 58, 62, 66), respectively.

Treatment Efficacy Estimates

Interferon Efficacy Estimates. A previous meta-analysis in HBeAg-positive patients revealed that 33% of patients achieve seroconversion after interferon therapy (94), and we adopted this estimate for our base-case analysis. Our analysis identified 5 studies reporting data on virologic response in HBeAg-negative patients (50, 91–93, 97); the durable response rate was 20%.

Lamivudine Efficacy Estimates. We found that although more than 90% of patients achieved initial virologic or biochemical suppression while receiving lamivudine therapy (9–11, 85, 86, 88, 89, 98–113), only 20% of HBeAg-positive patients (9–11, 85, 86, 88, 89, 98–103) and 10% of HBeAg-negative patients (108, 109) achieved a durable virologic response after the initial 18 months of therapy. Our review indicated that 23% of patients developed viral resistance annually (that is, developed the YMDD mutation) regardless of HBeAg status (60, 85, 86, 90, 98, 101–111). In our model, patients without virologic response, including those developing viral resistance, continued to receive long-term lamivudine therapy, as recommended by published guidelines. In these patients, the rate of subsequent durable virologic response differs between those with and without viral resistance. Our review showed that 24% of HBeAg-positive patients without viral resistance who were maintained with long-term lamivudine therapy developed durable virologic response annually (9, 86) compared with only 4.5% of patients with viral resistance (86, 99, 104, 114–117). Among HBeAg-negative patients, 10% of those without viral resistance who were maintained with long-term lamivudine therapy developed durable virologic response annually (110) compared with 0% of those with viral resistance (104).

Adefovir Efficacy Estimates. We found that fewer patients achieved initial virologic or biochemical suppression while receiving adefovir therapy compared with lamivudine therapy (60% to 70% vs. 90%) (16, 17, 118, 119). However, in patients who received long-term adefovir therapy, more than 80% achieved biochemical suppression (normalization of aminotransferase levels) (118). Our review found that 12% of HBeAg-positive patients achieved seroconversion after the initial course of adefovir therapy (16) and that the seroconversion was durable in more than 90% of patients (135). We did not find any studies that

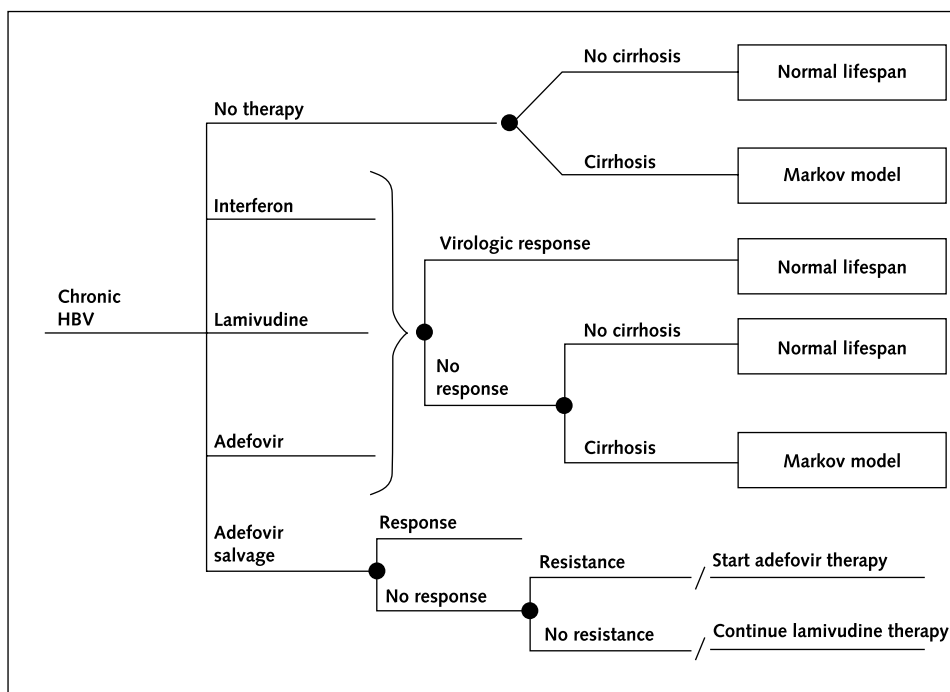
report data on the long-term durability of virologic response in HBeAg-negative patients receiving adefovir. Without data, we assumed that the rate of durable virologic response was the same between lamivudine and adefovir, and we therefore set the rate for adefovir at 10% per year in HBeAg-negative patients. Our review found that 1.3% of patients developed viral resistance annually regardless of HBeAg status (18). We found that 17.5% of HBeAg-positive patients without viral resistance who were maintained with long-term adefovir therapy developed durable virologic response annually (118). Among HBeAg-negative patients, 15.1% developed virologic suppression annually while receiving long-term adefovir therapy (136). However, without long-term durability data on this response, we assumed that the annual durable response rate among HBeAg-negative patients receiving long-term adefovir therapy was similar to the corresponding estimate for long-term lamivudine therapy (that is, 10%). We based the annual rate of durable virologic response after crossover from lamivudine to adefovir on data reported by Buti and colleagues (119). Because these rates were the same as those reported in previous randomized, controlled trials of adefovir, we assumed that the efficacy of adefovir was the same regardless of whether patients had previously developed lamivudine resistance.

Utility Estimates

Patients with chronic viral hepatitis experience many health states that may diminish their health-related quality of life. Sev-

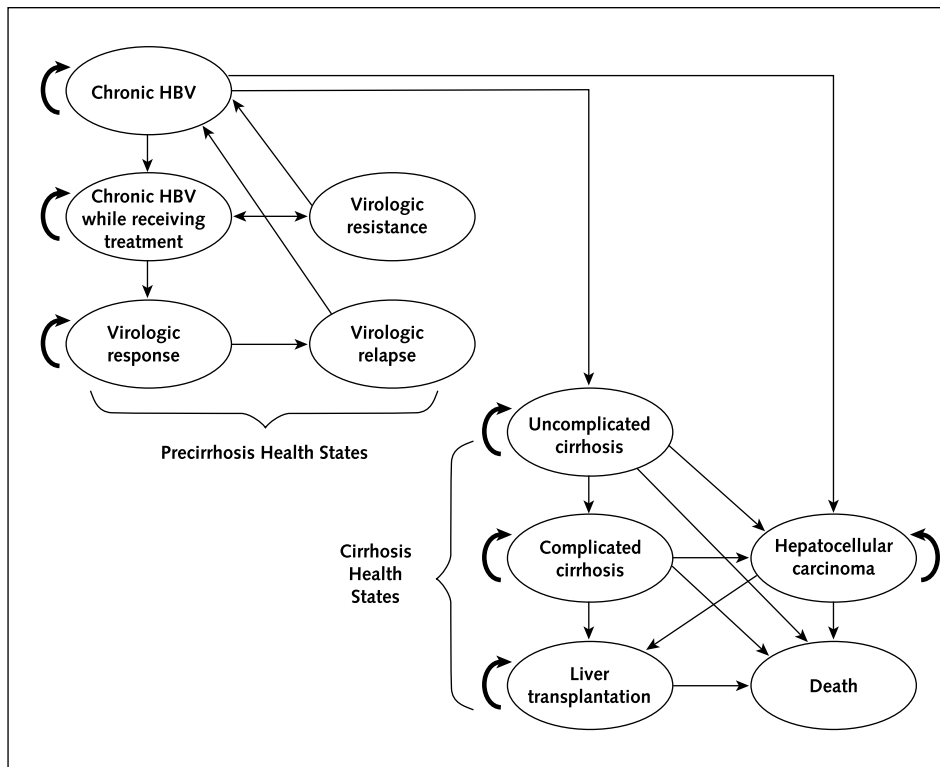
eral studies in hepatitis C virus have measured patient health preferences, or utilities, for complications of chronic liver disease, including compensated cirrhosis, decompensated cirrhosis, hepatocellular cancer, and liver transplantation (73, 137). There are no similar studies in HBV. However, both hepatitis C virus and HBV lead to cirrhosis and related complications, and no a priori reason suggests that the quality-of-life decrement engendered by these health states would vary by underlying cause. 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 have the same quality-of-life decrement independent of the cause. We therefore adopted previously established utilities for cirrhosis and related complications that were derived by using standard-gamble elicitations in patients with chronic hepatitis C virus infection (73). Specifically, we assumed utilities of 0.82 for compensated cirrhosis, 0.60 for decompensated cirrhosis, 0.86 after successful liver transplantation, and 0.73 for hepatocellular cancer (73). 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. **Table 1** 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 year, as recommended by the National Panel on Cost-Effectiveness in Health and Medicine (120).

Appendix Figure 1. Truncated decision model.



The base-case patient has chronic hepatitis B virus (*HBV*) infection, elevated aminotransferase levels, no clinical or histologic evidence of cirrhosis, and no previous treatment for *HBV* infection. The clinician treats with 1 of 5 competing strategies. Within each strategy, patients are stratified by hepatitis B e antigen status (not depicted). In all strategies, patients are eligible to develop cirrhosis, in which case they enter a Markov model governing the downstream events of cirrhosis. See text for details about specific assumptions governing patient management and probability estimates for individual branch points.

Appendix Figure 2. Markov state diagram.



Patients enter the model with chronic hepatitis B virus (HBV) infection. During each 1-year cycle, individual patients either remain in their assigned health state (*curved arrow*) or progress to a new health state (*straight arrow*). Patients may develop cirrhosis, in which case they move from the precirrrosis submodel to the cirrhosis submodel. Transition rates between health states were derived from a systematic review of the literature (Table 2). Refer to the Appendix for additional information.

Appendix Figure 3. Results of literature search.

