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A Simulation Shows That Early Treatment Of Chronic Hepatitis B Infection Can Cut Deaths And Be Cost-Effective

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ABSTRACT Chronic hepatitis B affects between 800,000 and two million people in the United States and causes 4,000 deaths each year. Yet the costs and benefits of treatment have not been fully evaluated. Using a model that simulates disease progression, we compare treatment programs for hepatitis B that start at an early stage of the disease to treatment that begins at a late stage. Our analysis concludes that early hepatitis B care can improve health, reduce premature deaths, and prevent expensive complications, making it highly cost-effective in the long term. Our results demonstrate the importance of screening for hepatitis B among at-risk groups and then linking screening to treatment. They also illustrate how predictive models can be used to evaluate strategies for improving access to care.

Chronic hepatitis B is a major cause of cirrhosis of the liver and of “primary” liver cancer, or cancer in which the liver is the primary tumor site. At any given time, the virus affects between 800,000 and two million people in the United States.^{1–4} Infection is concentrated among people born in Asia, sub-Saharan Africa, Eastern Europe, South America, and the Caribbean. This disparity is particularly severe in Asian populations within the United States, among whom the infection rate is estimated to be 10–15 percent, compared to the general population infection rate of less than 0.5 percent.^{5,6} Although universal infant vaccination has reduced the number of new infections that occur in the United States, the number of cases of chronic hepatitis B has increased in recent years as a result of immigration from countries where the virus is endemic.^{5,7}

Hepatitis B And Public Health

Chronic hepatitis B infection has a long latent, or clinically silent, phase, during which it causes few or no symptoms. It is frequently undiag-

nosed until symptoms of late-stage complications develop, many years after infection. An estimated 15–40 percent of infected people will eventually develop complications, the most common and deadliest of which are primary liver cancer (hepatocellular carcinoma) and end-stage liver disease.⁶ When these complications are diagnosed, they require very expensive treatments and are most often fatal. Hepatitis B infection is responsible for 4,000 US deaths each year. The total direct and indirect annual cost burden of the disease in the United States is estimated to be as high as \$1 billion.^{4,8}

Hepatitis B infection thus represents a serious public health issue. It remains so despite the fact that new treatments have become available that reduce the amount of virus in the blood (“viral load”) more effectively, can be administered for a longer period without the development of resistance, and could avert serious outcomes.^{9–14} In current clinical practice guidelines, viral load is used as a predictor of health outcome, a criterion for starting antiviral treatment, and a marker of treatment effectiveness.¹⁵ The risk for cirrhosis and primary liver cancer increases significantly as viral load levels increase.^{15–17} Therefore, mon-

itoring infected people for early cirrhosis or hepatocellular carcinoma, along with intervention as needed to keep hepatitis B virus levels low or undetectable, could reduce illness and death.^{18–21}

MANAGING THE DISEASE Recent assessments of best practices in the clinical management of hepatitis B have emphasized the need for appropriate treatment as a way to prevent long-term complications.^{18,19} In January 2010 the Institute of Medicine recommended working to improve access to screening and treatment, highlighting the lack of access to care among key at-risk groups and the need for more investigation of the cost and cost-effectiveness of treatment programs.²²

SCREENING AND TREATMENT As yet, there has been no systematic assessment of whether providing improved access to screening and treatment would be cost-effective. Therefore, we believe that it is timely to examine the costs and benefits of providing comprehensive care for this illness. In this article we describe a model that simulated, over twenty years, a group of people with chronic hepatitis B infection, whose health status depended on the timing of the medical intervention they received. Our analysis compared the health outcomes, costs, and cost-effectiveness of providing comprehensive early treatment and care for people with chronic hepatitis B compared with a standard population that received care only at late stages of the disease.

Given that access to appropriate early treatment and care for chronic hepatitis B is likely to correlate with the availability of comprehensive health insurance, we also examined strategies for providing expanded care to populations that do not currently have access. Many infected people have little or no health insurance and are ineligible for publicly subsidized insurance such as Medicaid. Although this problem will be somewhat alleviated by the implementation of the Affordable Care Act, care for some of these patients will remain fragmented and difficult to obtain as a result of underinsurance or socio-cultural barriers to care. Improving access for this population could prevent disability and premature death and could provide an important policy model for future efforts to improve health and reduce costs by providing early-stage care for chronic diseases.

Study Data And Methods

We constructed a model of chronic hepatitis B care that was based on current clinical decision-making algorithms. Our model included a fixed population of people with chronic hepatitis B in a finite number of discrete health states, called

Markov states. Markov-state transition models provide a more realistic approximation of outcomes and costs than static models can provide. Transition rates from one state to another were informed by a literature search on the natural history, epidemiology, and treatment of hepatitis B.^{6,16–20,23–28}

The model projected and compared outcomes, costs, and quality-of-life estimates over twenty years by running repeated simulations. Simulations were randomly selected for two different scenarios: (1) the late care group, in which people received no treatment (and accrued no costs) until they became seriously ill with hepatocellular carcinoma or decompensated cirrhosis (a condition in which liver scarring is severe enough to result in serious symptoms, including liver failure); and (2) the early care group, in which all individuals were monitored, and any meeting criteria for drug treatment received it. All hepatitis B-related costs were included.

More detailed information on model assumptions and specifications can be found in the online Appendix.²⁹

INITIAL HEALTH STATES People in the model were initially divided into one of several discrete health states. These states equated to baseline health states found among people newly diagnosed with chronic hepatitis B infection in large-scale community screening campaigns. These broad community samples more accurately reflect the conditions in the population than do those from cases referred to specialists, which are typically more advanced.^{30,31}

The health states were categorized by four viral-load ranges for people who did not yet show signs of disease and by four major complications. The complications we considered were cirrhosis that was “compensated,” in which the person had sustained liver damage but did not yet show symptoms and could recover with treatment; decompensated or late-stage cirrhosis accompanied by other medical complications; hepatocellular carcinoma, or liver cancer; and post-liver transplant, representing the lifetime management required by patients who received a new liver.

TREATMENT ASSUMPTIONS AND TRANSITION PROBABILITIES People in the model moved among the health states each year according to probabilities of transition that were drawn from published reports. Transition probabilities depended on whether patients were receiving treatment. Patients with a higher viral load were more likely to transition to complications.¹⁶ Some of these patients might also progress to death from non-hepatitis B causes, at rates based on overall mortality for a given age group in the general population.³²

In the early care scenario, patients received antiviral drugs in accordance with a simplified program of treatment that combined recommendations from several recently published guidelines, which describe when treatment with antiviral drugs should begin (based on viral-load ranges), how to manage resistance to drugs, and what further treatments are needed for complications.^{19,33} People can transition to healthier states, a much more likely outcome for those in this scenario than among late care individuals who do not receive drug treatment.^{15,16,25,26}

Because of the wide variety of antiviral drugs currently used to treat chronic hepatitis B, we used theoretical drugs with rates of response that could be reasonably expected from the best treatment available today. This theoretical treatment profile included a first-line drug with a high barrier to resistance and a second drug for those who did not respond to the first drug.^{34–37}

We assumed that no individuals had received treatment for their infection at the onset of the simulation. Drug resistance was assumed to be limited to those who failed the first-line treatment. We also assumed that those eligible would receive the indicated care. This was a necessary simplification because availability is no guarantee of adherence to interventions, even among people who have adequate health coverage and particularly those with chronic, often asymptomatic conditions such as hepatitis B.

Early diagnosis of hepatocellular carcinoma increases one's eligibility for life-extending treatments and procedures.^{20,27,38} Thus, the model assumed that patients with hepatocellular carcinoma in the early care group were more likely than those in late care to be diagnosed early and to qualify for either a transplant or one of the other measures.³⁹ People whose immune systems successfully cleared their infection, permanently eliminating the hepatitis B surface antigen from their blood, and people who died remained permanently in those states for the rest of the time the model ran.

COST-EFFECTIVENESS ASSUMPTIONS Costs for drugs were estimated based on current wholesale costs and Medicaid reimbursement rates; other costs were based on a literature review (Exhibit 1).^{20,21,24,38–43} The perspective of the cost analysis was that of the US public health system; the costs tallied represented the total cost of care for a given individual and did not distinguish among different payers. We noted that many uninsured people have some access to medical services and that some costs of major complications would probably be covered by patients themselves. These out-of-pocket expenses could be considered a part of the societal perspective of our analysis.

On the other hand, this evaluation did not incorporate indirect costs, such as lost wages due to illness or death, even though each healthy life-year gained was associated with an economic gain to society as a whole. All costs were adjusted to 2008 dollars where possible. To arrive at a number representing the present value of future costs, we used the standard discount rate of 3 percent per year.⁴⁴

The effectiveness of providing early care was measured in quality-adjusted life-years (QALYs), a unit that both captures the life-years gained by a particular intervention and evaluates the quality of life experienced in each disease state. We gave perfect health a value of 1, and death a value of 0. Each disease state in the model had a QALY value between 0 and 1 (Exhibit 2) that was based on values obtained by the standard gamble methodology in hepatitis C patients.^{24,45} A gain in QALYs therefore represented a reduction in both the morbidity and the mortality associated with hepatitis B.

Average QALYs were determined for both scenarios at five, ten, fifteen, and twenty years from initial diagnosis. Cost-effectiveness models typically include health and cost effects that accumulate after the intervention is stopped. However, our approach allowed us to report what could be achieved at the end of each five-year period. Indirect costs, such as those associated with wage losses due to illness or death, were not calculated. The QALYs gained by coverage were not assigned a specific dollar value. Results were presented as dollars per QALY gained, representing the additional cost to the health system for each additional QALY achieved by a given intervention, and were also discounted at 3 percent per year.

Results

Our results showed that providing early care helps prevent long-term health problems even within a short time frame. Because most serious outcomes of hepatitis B infection usually take years to manifest, the health benefits associated with averting these problems increase over time.

As shown in Exhibit 3, the proportion of patients with resolved infections or low viral loads was 52.5 percent in the late care scenario and 80.0 percent in the early care scenario after just five years of treatment or lack of treatment, according to the rules of the scenario. Meanwhile, the proportion of patients facing serious complications—decompensated cirrhosis, hepatocellular carcinoma, or transplant—fell from 1.2 percent at three years to 0.7 percent after twenty years in early care. This proportion was higher in late care than early care after just three years

EXHIBIT 1**Costs Used In Model Calculations, Study Of Health Outcomes, Costs, And Cost-Effectiveness Of Providing Comprehensive Early Treatment And Care For People With Hepatitis B**

Item	Cost, \$ (range in sensitivity analysis)
Outpatient visit	80 (60–100)
Diagnostic and monitoring tests	
Hepatitis B virology	178 (100–250)
Alpha-fetoprotein	20 (10–30)
Standard lab tests	30 (15–45)
Detailed lab tests	250 (150–350)
Abdominal ultrasound	200 (100–300)
Drug treatment (per year)	
Initial treatment	5,000 (1,000–7,000)
Salvage treatment	6,000 (1,500–8,000)
Decompensated cirrhosis (per year)	30,571 (10,000–50,000)
HCC procedures (composite)	11,175 (8,500–20,000)
HCC remission monitoring (per year)	4,500 (3,000–6,000)
HCC relapse/terminal care (per year)	45,323 (30,000–60,000)
Liver transplant	137,918 (100,000–150,000)
Post-liver transplant care (per year)	24,065 (10,000–40,000)

SOURCES Notes 20, 21, 24, 39, 40, 43, and 44 in text. **NOTE** HCC is hepatocellular carcinoma.

and grew continually, despite extensive attrition from mortality.

Over twenty years, the average annual incidence, or number of new cases, of hepatocellular carcinoma—one of the most severe and expensive complications of chronic hepatitis B—was 572 per 100,000 chronically infected people in the late care scenario, versus just 194 per 100,000 in early care.

Providing early care also greatly reduced mortality rates (Exhibit 4). After just five years, according to the model, cumulative mortality for these identical populations diverged greatly: Rates per 100,000 were 2,094 in late care, versus 1,628 in early care. After twenty years the cumulative mortality rates were, respectively, 20,730 and 11,606 per 100,000.

COSTS AND COST-EFFECTIVENESS Costs for late

care increased steadily from a cumulative average of \$1,100 per person after three years to \$10,735 after twenty years (see the Appendix).²⁹ Early care did not become cost saving over this time frame, but the annual cost of care decreased from year to year in the early care scenario, whereas it increased in the late care scenario.

We used cost-effectiveness analysis to evaluate the health gains resulting from the additional spending associated with expanding coverage. For early care compared to late care, the cost per QALY gained decreased dramatically, from \$68,300 after five years to \$5,184 after twenty years. In general, interventions that cost less than \$50,000 per QALY gained are considered cost-effective in the United States. Thus, even after roughly five years, the early care scenario could be considered quite cost-effective. Cost-

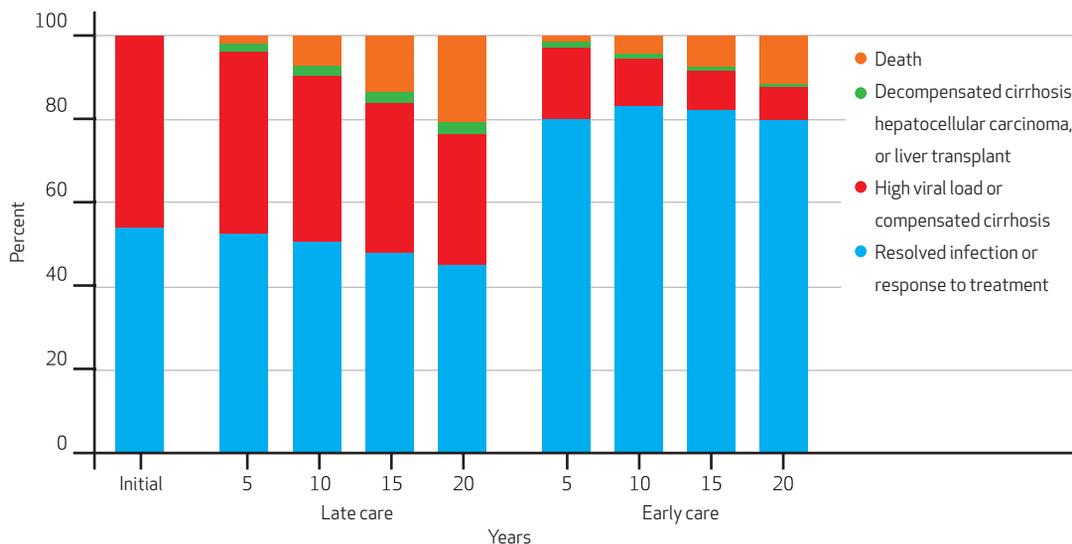
EXHIBIT 2**Annual Quality-Of-Life Values Assigned For Each Health State, Among People With Hepatitis B**

Health state	Quality-of-life value (range in sensitivity analysis)
s-antigen-negative, e-antigen-negative, or treatment response	1 (0.85–1)
Hepatitis B infection, no cirrhosis	0.99 (0.60–1)
Compensated cirrhosis	0.80 (0.70–0.90)
Decompensated cirrhosis	0.60 (0.50–0.70)
HCC remission	0.73 (0.60–0.80)
HCC failure	0.60 (0.50–0.70)
Post-liver transplant	0.86 (0.80–0.90)
Death	0

SOURCE Note 45 in text. **NOTES** A value of 1 represents a state equivalent to full health (and full quality of life). A value of 0 represents death. All intervening values are estimates of the quality of life associated with a given health state. HCC is hepatocellular carcinoma.

EXHIBIT 3

Distribution Of Health States Among People With Hepatitis B, By Years After Diagnosis



SOURCE Authors' model results.

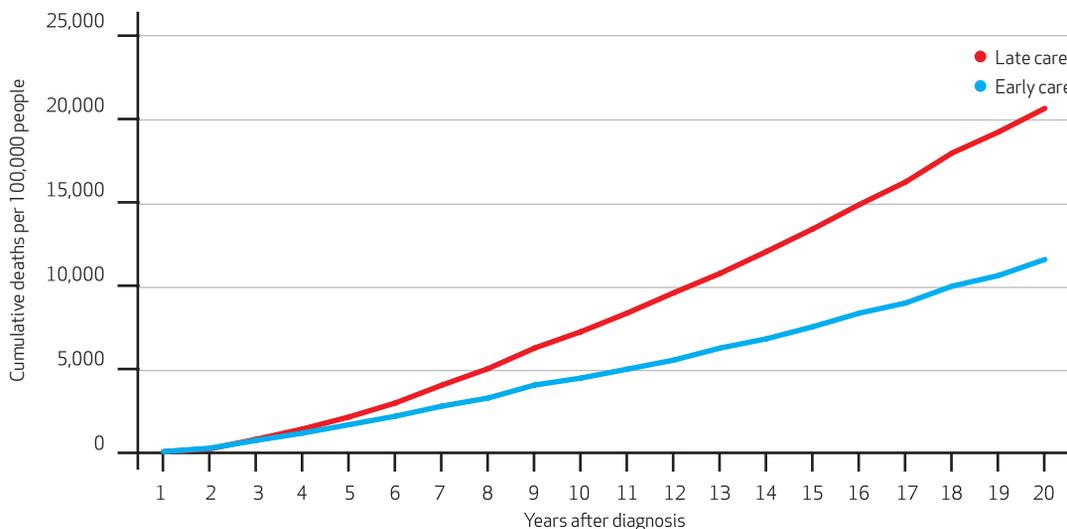
effectiveness results are summarized in Exhibit 5.

SENSITIVITY ANALYSIS To test the sensitivity of the results to key assumptions made in the model, including those for which evidence was mixed or controversial, we performed a one-way sensitivity analysis. Only four variables led to a significant (more than 30 percent) change in the baseline cost-effectiveness, but none changed

the final cost-effectiveness result by more than a few thousand dollars. All values comparing early care and late care remained highly cost-effective. These results suggest that the model, although somewhat sensitive to certain inputs, robustly captured a rough measure of overall cost-effectiveness. More details on the sensitivity analysis are available in the Appendix.²⁹

EXHIBIT 4

Cumulative Deaths Per 100,000 People With Hepatitis B, By Years After Diagnosis



SOURCE Authors' model results.

EXHIBIT 5

Incremental Cost-Effectiveness Ratios, Study Of Health Outcomes, Costs, And Cost-Effectiveness Of Providing Comprehensive Early Treatment And Care For People With Hepatitis B

Model run time (years)	Average QALYs gained in early care (versus late care) per person	Additional cost of early care (versus late care) per person (\$)	Incremental cost-effectiveness ratio (\$ per QALY)
5	0.05	3,415	68,300
10	0.22	4,291	19,505
15	0.47	4,495	9,564
20	0.79	4,096	5,184

SOURCE Authors' analysis. **NOTES** Values represent additional costs and gained QALYs in early care versus late care at four different time endpoints. Incremental cost-effectiveness improved over time. QALY is quality-adjusted life-year.

Discussion

This study demonstrates that the implementation of current clinical guidelines for the treatment of chronic hepatitis B infection (prior to the manifestation of late-stage complications) would be expensive but would decrease morbidity, save lives, and be cost-effective over as short a period as ten years. In addition to generating substantial health status gains, our results indicate that providing appropriate early care for chronic hepatitis B can be highly cost-effective compared to providing treatment only for serious hepatitis B-related illnesses, as money spent on early-stage treatment helps prevent expensive complications.

This investment in early-stage treatment would probably have much greater cost-effectiveness or even cost savings, given that each healthy life-year gained is associated with a substantial indirect benefit to society as a whole in the form of increased social and economic productivity.

By making it possible to evaluate a wide variety of treatment scenarios among different target populations, this model provides a tool for evaluating changes in both treatment recommendations and health care coverage policy options. We believe that it could serve as a useful tool for investigating the potential impact of future policy decisions by public and private entities regarding hepatitis B-related coverage. The model's dynamic nature means that it can be easily updated with data on the epidemiological impact and costs of interventions for early-stage disease or for major complications as new information becomes available.

Ensuring true universal access to care would be the most effective and efficient way to improve long-term health outcomes of people with chronic hepatitis B. However, even with the March 2010 enactment of the Affordable Care Act, access to adequate chronic disease management may remain fragmented and challenging for the population most affected by chronic hepatitis B, which includes many recent immigrants

and other socially vulnerable people.

Although the health reform law when fully phased in will expand Medicaid eligibility, many people will still not qualify. Even with newly available subsidies, they might not be able to afford to purchase a private health insurance policy that provides adequately for their needs as they face a complicated chronic illness. Health insurance companies have wide discretion in the services they provide, and they might not necessarily elect to pay for the early treatment of hepatitis B without estimates of the costs and benefits of such care.

Our model assumed knowledge of hepatitis B infection at the outset. However, it is estimated that fewer than one-third of infected people are aware of their infection, and many who are diagnosed do not have their care managed appropriately.²² Even with improved access to health services, the thousands of US residents who do not know of their infection would essentially continue to live out a late care scenario.

To achieve the benefits of early care, it is critical that people be screened for hepatitis B infection. Although virtually all pregnant women in the United States receive this screening, there is no comprehensive source of screening for other at-risk groups, although scattered community-based screening programs exist.^{31,46} A recent study indicated that universal screening of at-risk populations, along with targeted vaccination and access to treatment, could be highly cost-effective public health measures.⁴⁷ The Centers for Disease Control and Prevention (CDC) has recently issued broader and more forceful recommendations for routine hepatitis B screening to include a wider range of at-risk groups and referral to care for those who are infected.⁸

We anticipate that greater attention to hepatitis B screening will help highlight the need for improved access to treatment. Given that screening is likely to become more widespread, we anticipate a parallel need for better access to treatment, if only to prevent an ethically untenable

scenario in which people are informed of their hepatitis B infection status but have no way to obtain care.

The federal government has recognized and taken account of similar issues in the past. One example is when a screening program for breast and cervical cancer undertaken by the CDC led to diagnoses of cancer in many uninsured patients who then lacked access to treatment. In response, the Breast and Cervical Cancer Prevention and Treatment Act of 2000 allowed states to expand Medicaid coverage for women screened through this program regardless of additional costs—an option that was being implemented by all fifty states within three years of the law's passage.⁴⁸ The results from our model demonstrate the critical importance of linking hepatitis B screening to access to care and treatment, in order to achieve maximal health gains.

Because we now have a better understanding of the natural history of chronic hepatitis B infection and have newer, more potent and effective treatments, we have the opportunity to reduce long-term morbidity and mortality from this infection. Obtaining the greatest benefits and cost savings from a societal perspective can come about only by expanding access to care and coverage for chronic hepatitis B, increasing the possibility of adequate disease management through early-stage treatment.

Our model predicts that this improvement in access would not only decrease morbidity and save lives but would also be highly cost-effective in the long term. The model provides a potential tool for evaluating the impact, costs, and benefits of strategies to achieve these goals, and it could be used to optimize approaches aimed at correcting this long-standing health disparity. ■

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 - 29 To access the Appendix, click on the Appendix link in the box to the right of the article online.
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This paper on the benefits and cost savings of early screening and treatment for chronic hepatitis B grew out of two intersecting interests in the Division of Pediatric Infectious Diseases at the New York University (NYU) School of Medicine: improving the health of Asian Americans in New York City and making the increasingly effective treatments for hepatitis B more accessible.

Chronic hepatitis B disproportionately affects immigrants from countries without broad childhood immunization programs. Many of those infected, says lead author Sarah Post, are not aware of their illness, which complicates the prospects of reaching them with screening and treatment. But if widespread screening is implemented, widespread treatment should also be made available. "It's not really ethical to do one without the other," she says.

Post was a project associate in the Division of Pediatric Infectious Diseases when the research was conducted. Prior to that, she worked at the International AIDS Vaccine Initiative, encouraging pharmaceutical companies to invest in research leading to HIV vaccinations. She is currently a medical student at the University of Pennsylvania School of Medicine.

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