Received: 30 January 2023 | Revised: 21 April 2023 | Accepted: 13 May 2023

DOI: 10.1111/jvh.13843

JOURNAL OF VIRAL HEPATITIS JVH WILEY

ORIGINAL ARTICLE

Cost-effectiveness of treating all hepatitis B–positive individuals in the United States

Devin Razavi-Shearer | Chris Estes | Ivane Gamkrelidze | Homie Razavi

Center for Disease Analysis Foundation, Lafayette, Colorado, USA

Correspondence
Homie Razavi, Center for Disease Analysis Foundation, Lafayette, Colorado, USA.
Email: hrazavi@cdafound.org

Funding information
Gilead Sciences

Abstract

Chronic hepatitis B virus (HBV) infection is a leading cause of liver disease and related mortality globally. However, most of the infected individuals in the United States remain undiagnosed and untreated. There is a need to understand more completely the economic and disease burden impact of removing treatment restrictions and increasing diagnosis and treatment. The PRoGReSs model, a dynamic HBV model that tracks the infected population by year, disease stage, and gender, was used to quantify the disease and economic burden of chronic HBV infection in the United States from 2020 to 2050 based on four scenarios: a status quo (base) scenario and three treat-all scenarios, in which screening, diagnosis, and treatment were maximized at different annual treatment price levels of $5382, $2000 and $750. Compared to the base scenario, the treat-all scenarios would avert 71,100 acute and 11,100 chronic incident cases of HBV, and 169,000 liver-related deaths from 2020 to 2050. At an annual treatment cost of $2000, treating all HBV infections would be highly cost-effective, and at $750 would be cost saving and would achieve a positive return on investment before 2050. Maximizing the diagnosed and treated HBV population in the United States would avert a significant number of cases of advanced liver disease and related mortality. Such interventions can also be cost-effective compared to the status quo strategy, and cost saving at a treatment price threshold of $750 annually, above the current lowest annual treatment cost of $362.

KEYWORDS
cost-effectiveness, economic impact, hepatitis B virus, test and treat all, treatment

1 | INTRODUCTION

Chronic hepatitis B virus (HBV) infection leads to cirrhosis, hepatocellular carcinoma (HCC), and liver-related death. Globally, one death every 38 s is attributed to HBV.[1] Antiviral treatment of HBV infection has been shown to lead to regression of cirrhosis and reduction of HCC incidence.[2,3] The American Association for the Study of Liver guidelines[4] limits treatment of individuals with HBV cirrhosis or those with a high viral load and alanine transaminase (ALT) levels two times the upper limit of normal. These guidelines

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ALT, alanine transaminase; HIV, human immunodeficiency virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e-antigen; DALY, disability-adjusted life year; GNI, gross national income; U.S., United States.

focus on preventing liver disease rather than treating HBV as an infectious disPGease. Yet, there is ample evidence that treating all HBV-infected individuals will reduce disease progression further. As long as 10 years ago, there have been recommendations to treat HBV infections earlier,[5] and more recent studies[6,7] comparing treated individuals monoinfected with HBV with a matched cohort of treated patients coinfected with human immunodeficiency virus (HIV)/HBV found a 60% lower HCC incidence in the latter group, which initiated treatment upon diagnosis. These data suggest that removing existing treatment restrictions would lead to a further reduction in disease progression.

In the United States (U.S.), an estimated 0.32% (95% confidence interval, 0.24%–0.41%) of individuals 15 years or older were infected with HBV, based on a national serosurvey of the years 2013–2018.[8] Prevalence was significantly greater among the foreign-born population [1.24% (0.92–1.66)] compared to the U.S.-born population [0.12% (0.07–0.20)]. A recent analysis[9] used all available immigration data to model U.S. HBV prevalence adjusted for the cumulative and continued impact of immigration. It estimated a prevalence of 0.55% (0.41–0.77) among all ages in 2020, corresponding to 1.8 million (1.3–2.6 million) infections. It also found that 76% of all chronic infections were among immigrants, and the results projected an increasing number of HBV-related liver-related deaths as well as an increase in the number of patients with HCC and cirrhosis under the current practice guidelines.[9]

The objective of our study was to assess the cost-effectiveness of removing the current treatment guidelines in the United States and treating all diagnosed those infected with HBV similar to the current practice for the treatment of HBV/HIV coinfected individuals.

2 | METHODS

2.1 | Disease burden modelling

A dynamic Markov model (ProGReSs) was used to track the U.S. HBV-infected population by disease stage, gender, and age, and forecast disease progression, all-cause mortality, liver-related deaths, and the impact of HBV treatment on disease progression and transmission.[10] The model also took into consideration individuals with high and low viral loads because the former group has a faster disease progression rate. A full description of the model mechanisms and inputs can be found in the Supplementary Materials.

These inputs included the vaccination schedules of the general population, both childhood and adolescents.[11,12] The screening rates of pregnant women and the coverage of hepatitis B immunoglobulin (HBIG) and timely birth dose of the HBV vaccine of infants born to HBV-positive mothers was assumed to be flat from 1984 to 1993 (no annual data available), and then annual published numbers were utilized from 1994 to 2017.[13-15] The antiviral treatment of pregnant women, to prevent mother-to-child transmission, was assumed to increase from 39% in 2007 to 44.8% by 2020, utilizing annual screening rates to adjust these estimates.[14,16,17] Based on recent data, it was estimated that there are 300,000 individuals diagnosed with chronic hepatitis B in the US, 13,900 chronic cases diagnosed annually, and 143,500 individuals on antiviral treatment.[10,18,19,20]

A status quo (base) scenario was compared to intervention scenarios during which screening, diagnosis, and treatment are expanded to all chronically infected individuals (treat-all scenario). Model inputs were based on published data shown in Table 1.[9]

2.2 | Scenarios

HBV disease burden and economic impacts were assessed under four scenarios. A base scenario and three treat-all scenarios were modelled for 2020–2050 in order to better evaluate the long term impacts and costs of HBV. The treat-all scenarios were designed to consider the effect of maximizing screening, diagnosis, and treatment at three levels of annual treatment price—$5382, $2000, and $750—and were compared to the base scenario at a $5382 annual treatment price. The latter two prices were back-calculated to determine the annual price of HBV treatment that would make the treat-all scenario highly cost-effective (at $2000) and cost saving (at $750).

2.3 | Cost-effectiveness analysis

Cost data were applied to disease burden forecasts to determine the economic impact of each scenario (Table 1).[24,25] Direct costs included healthcare, screening, prophylaxis, diagnostic, and treatment costs. Screening (hepatitis B surface antigen [HBsAg] and anti-HBs) and diagnostic costs were based on published Medicare and Medicaid laboratory fee and physician fee schedules.[24,25] Diagnostic costs for hepatitis B e-antigen (HBeAg) and hepatitis B DNA (quantitative) were not included for the treat-all scenarios because it was assumed these diagnostics are not required when treatment is expanded to all chronic infections. Compared to the base scenario, it was also assumed that only treated individuals with cirrhosis in the treat-all scenario would receive abdominal echocardiography and alpha-fetoprotein serum tests. Healthcare costs by disease stage were based on published estimates (Table 1), and it was assumed conservatively that costs for no cirrhosis were negligible and thus not included. Costs were inflated to December 2021 U.S. dollars based on the consumer price index for healthcare.[28] Annual costs for HBV medication under the base scenario were estimated at $5382 ($362–$12,310) based on drug sales data.[19] However, this does not include all the discounts and rebates which will result in a lower net price. The net prices of HBV medicine in the US are not publicly available.

Disability-adjusted life years (DALYs)[29] were calculated based on years of life lost as a result of premature mortality and years lived with disability among chronically infected individuals in decompensated cirrhosis, HCC, and liver transplant disease stages. Economic outcomes were analysed to 2050, including the cost per DALY averted and return on investment. These outputs were considered in the context of two thresholds: one gross national income (GNI) per capita of $65,850[23] and a highly cost-effective threshold of $20,000.

TABLE 1 Disease burden and economic model inputs.

Disease Burden Inputs	Year	Value (source)
HBsAg+ prevalence	2010	0.53%[9]
% HBeAg+	2014	21%[16]
Viral load ≥20,000 IU/mL among HBeAg+	2002–2008	90%[21]
Viral load ≥20,000 IU/mL among HBeAg−	2002–2008	13%[21]
Total diagnosed, *n*	2015	300,000[10]
Newly diagnosed, *n*	2019	13,859[18]
Treated annually, *n*	2020	143,537[19]
Economic Impact Inputs	Item	Value; 95% CI (source)
Disability weight	Decompensated cirrhosis	0.178[22]
	HCC	0.466[22]
	Liver transplant	0.024[22]
Cost-effectiveness thresholds	Gross national income per capita	65,850[23]
	Highly cost-effective	20,000
Screening and lab costs per test (2021 USD)	Hepatitis B surface antigen	10.33[24]
	Hepatitis B surface antibody	10.74[24]
	Hepatitis B e-Antigen	11.53[24]
	Hepatitis B DNA, quantitative	42.84[24]
	Hepatic function panel	8.17[24]
	Echo exam of abdomen	93.17[25]
	HAV, HCV, HDV	45.14[24]
	Alpha-fetoprotein	16.77[24]
Annual HBV treatment cost (2021 USD)	Base scenario	5382[19]
	Treat-all scenarios	5382, 2000, 750
Annual health state costs (2021 USD)	Compensated cirrhosis	2076; 1558–4776[26]
	Decompensated cirrhosis	35,464; 33,284–37,646[27]
	HCC	56,569; 50,769–62,362[27]
	Liver transplant	224,574; 207,095–242,049[27]
	Post liver transplant	48,910; 39,965–57,885[27]

Abbreviations: CI, confidence interval; HAV, hepatitis A virus; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; USD, U.S. dollars.

2.4 | Uncertainty analysis

An uncertainty analysis was conducted to measure the impact of uncertainty for key model outputs. Inputs for uncertainty included low and high estimates for healthcare costs, prevalence, and the proportion of individuals with high viral load by HBeAg status. These inputs were used to generate 95% uncertainty intervals around model outputs for direct costs, DALYs, and cost-effectiveness.

3 | RESULTS

3.1 | Disease burden

Under the base scenario, the number of annual, newly diagnosed individuals would average 13,900 for 2020–2050, and there would be 430,000 new diagnoses during this time. The total diagnosed prevalent population would peak at 379,000 individuals in 2035 (Figure 1). Approximately 143,000 individuals were estimated to be on antiviral treatment each year from 2020 to 2050.

Acute HBV infections were projected to decrease 79%—from 7500 in 2020 to 1500 in 2050—largely as a result of an overall decrease in unvaccinated adults (Figure 2). Despite this decrease, 119,000 acute and 19,700 chronic infections would still occur during the study time frame because of infections in the paediatric population (children <12 years) and new infections in those who either did not receive or were not eligible for adolescent vaccination. Annual liver-related deaths under the base scenario would increase until 2045, when this value would peak at 11,900 deaths, then would decline thereafter. The total number of liver-related deaths during the study period was estimated to be 324,000. Total chronic infections would decline by 19%—from 1835,000 in 2020 to 1,487,000 in 2050.

Under the treat-all scenarios, the number of annual, newly diagnosed individuals would increase from 13,900 in 2020 to a peak

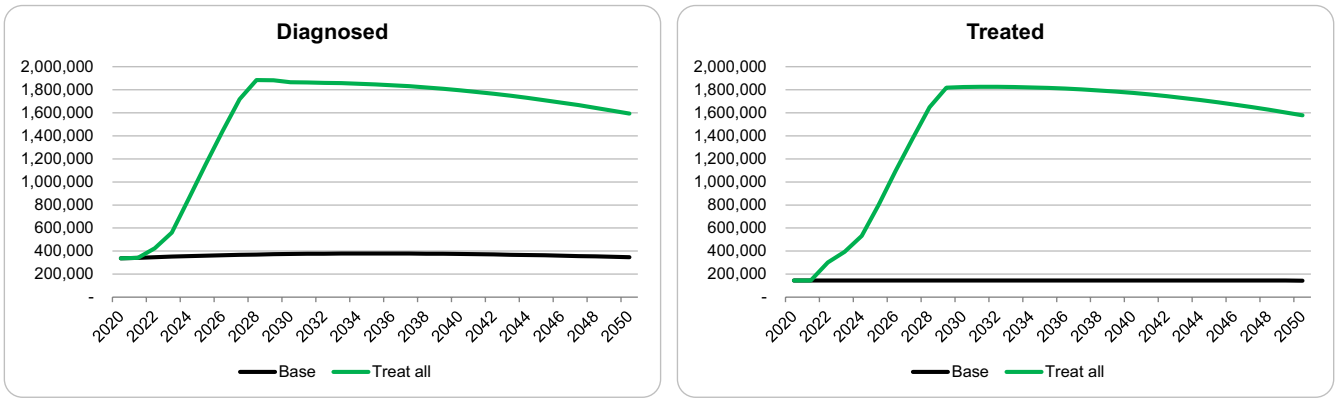

FIGURE 1 Diagnosed and treated populations by scenario: United States, 2020–2050.

of 300,000 in 2025 and then would decline to 12,300 by 2050. The projected number of cumulative new diagnoses was 2,075,000 during the study period. The total number of prevalent diagnosed cases would peak at 1,855,000 in 2028 (Figure 1). The number of individuals on antiviral therapy annually would increase from 142,000 in 2020 to a peak of 1,822,000 in 2032, before declining to 1,577,000 by 2050. Under these scenarios, new acute infections were forecasted to decline 99%—from 7500 in 2020 to 50 in 2050—as result of the stipulated treatment. The projected numbers of new acute and new chronic infections during the study period were 47,900 and 8600, respectively. The treat-all scenarios would prevent 71,100 acute and 11,100 chronic cases compared to the base scenario. Of these incident cases averted, 6200 of the acute (13%) and 5500 (73%) of the chronic cases were estimated have been cases of mother to child transmission that did not occur due to the universal and high treatment levels.

Under the treat-all scenarios, the number of liver deaths would decline 59%—from 8000 in 2020 to 3200 in 2050. Cumulative liver deaths from 2020 to 2050 were projected at 155,000, which is a reduction of 52% (169,000 fewer deaths) from the base scenario. The total number of chronically infected individuals would decline by 13% under the treat-all scenarios—from 1835,000 cases in 2020 to 1,604,000 cases in 2050. The total percentage of cases in 2050 was 8% greater compared to the base scenario because of the potential reduced mortality among this population.

3.2 | Direct costs

Direct costs included healthcare, screening, diagnostic, and treatment costs. Both annual costs and cumulative costs for the study period were compared between the treat-all scenarios and the base scenario (Figure 3). Under the base scenario, annual direct costs were forecasted to decrease 48% (from $1888 million [1788–2088 million] to $982 million [860–1179]), with peak annual costs occurring in 2020. Between 2020 and 2050, it was projected that the United States would spend $44,822 million (40,920–51,994 million) cumulatively in direct medical costs associated with HBV. Of this, 64% ($28,490 million) was classified as healthcare costs (cost of treating cirrhosis, HCC, and liver transplantation) and 36% ($15,981 million) was categorized as laboratory and treatment costs.

Under the $5382 treat-all scenario, annual direct costs would be 89% greater in 2050 ($3457 million [2886–4316 million]) compared to 2020 ($1827 million [1727–2026 million]), and peak costs would occur in 2029 ($7691 million [6884–8039 million]), because more individuals would need to be screened and treated (Figure 3). Cumulative costs were estimated at $157,294 million (140,267–178,092 million), with 87% of cumulative costs being treatment and laboratory costs; 11%, healthcare costs; and the remainder, screening and prophylaxes costs.

Under the $2000 treat-all scenario, annual direct costs would be 21% less in 2050 ($1445 million [1197–1835 million]) compared to 2020 ($1826 million [1727–2025 million]), and peak costs would occur in 2026 ($3357 million [3019–3531 million]) (Figure 3). Cumulative costs were estimated at $74,857 million (66,639–86,767 million), with 73% of cumulative costs classified as treatment and laboratory costs, 24% as healthcare costs, and the remainder as screening and prophylaxes costs.

Under the $750 treat-all scenario, annual direct costs would be 62% less in 2050 [$701 million (573–916 million)] compared to 2020 ($1826 million [1727–2025 million]), and peak costs would occur in 2022 ($2554 million [2448–2779 million]) (Figure 3). Cumulative costs were estimated at $44,389 million (39,374–53,009 million), with 55% of cumulative costs classified as treatment and laboratory costs, 40% as healthcare costs, and the remainder as screening and prophylaxes costs.

A sensitivity analysis was conducted for cumulative direct costs under the base scenario for 2020 to 2050 (Figure 4). The uncertainty in healthcare cost for treating advanced liver disease was the top driver of uncertainty in this analysis.

3.3 | Disability-adjusted life years

Under the base scenario in 2020, there would be an estimated 134,000 annual DALYs (125,000–149,000) incurred as a result of HBV, and this value would increase by 27% to 137,000 annual DALYs (171,000–221,000) by 2050 (Figure 2). This increase would be, primarily, the result of the effects of liver-related disability and

FIGURE 2 Disease burden and disability-adjusted life years (DALYs) by scenario: United States, 2020–2050.

deaths in the current chronically infected population. Total cumulative DALYs were estimated at 5,141,000 (4,413,000–6,211,000) under the base scenario.

Under the treat-all scenarios, annual DALYs would decrease by 66%—from 134,000 (125,000–149,000) in 2020 to 46,000 (35,000–62,100) in 2050 because more individuals would be treated (Figure 2). Cumulative DALYs under the treat-all scenarios were estimated at 2,446,000 (2,070,000–3,066,000)—52% less than base. The treat-all scenarios would avert 2,695,000 DALYs (2,343,000–3,145,000 DALYs) in 2020 to 2050 compared to the base scenario. Under all scenarios, approximately 3% of all DALYs would be incurred as a result of years lived with disability; 97% would be incurred as a result of years of life lost (liver-related deaths).

3.4 | Cost-effectiveness

Cost per DALY averted for the treat-all scenarios was compared to two threshold values: U.S. GNI per capita ($65,850)[23] and a highly cost-effective threshold of $20,000. Under the $5382 treat-all scenario, annual cost per DALY averted would be less than the GNI per capita level from 2037 onward, making the treat-all scenario cost-effective even at the current average annual HBV treatment cost in the United States. This scenario does not achieve an overall positive return on investment by 2050 (Figure 3). Cost per DALY averted was estimated at $41,700 (40,100–42,200) (Table 2).

Under the $2000 treat-all scenario, the annual cost per DALY averted would be less than the GNI per capita starting in 2025 and

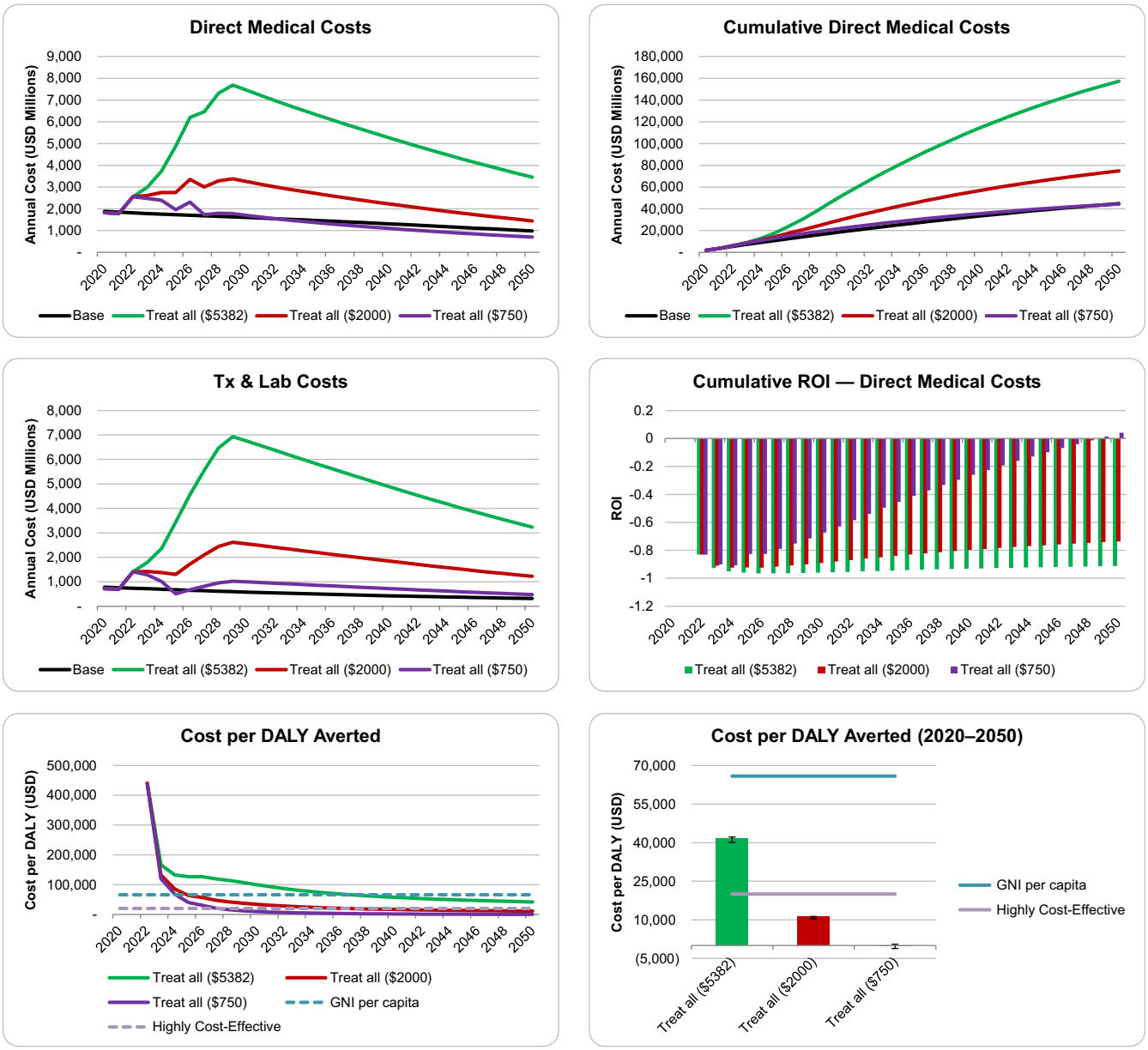

FIGURE 3 Economic outcomes by scenario: United States, 2020–2050. DALY = disability-adjusted life year; GNI = gross national income; ROI = return on investment; Tx = treatment; USD = U.S. dollar.

would become highly cost-effective after 2037 (Figure 3). The cost per DALY averted was estimated at $11,100 (10,400–11,300) (Table 2).

Under the $750 treat-all scenario, the annual cost per DALY averted would be less than the GNI per capita starting in 2025 (cost-effective), would become highly cost-effective after 2028, and would be cost saving from 2032 onward. This scenario would achieve an overall positive return on investment beginning in 2049 (Figure 3), and the cost per DALY averted was estimated at −$160 (−1100 to 480) (Table 2).

4 | DISCUSSION

The current analysis demonstrates there are significant health and economic benefits that justify expanding screening, diagnosis, and treatment of individuals infected with HBV in the United States. Our results show that dramatically increased rates of screening, diagnosis, and treatment would result in a 99% reduction in annual new infections by 2050, and would prevent 11,100 new chronic infections and avert 169,000 deaths. We evaluated three treat-all scenarios against a status quo base scenario. The analysis of cost per DALY averted showed all three scenarios were cost-effective, even though they require expanding screening and treatment. If the average price of HBV treatments can be negotiated to less than $2000 per year, then this treat-all scenario is highly cost-effective. At an annual treatment cost of $750, this treat-all strategy is cost saving; the cumulative healthcare costs between now and 2050 would be less than what the U.S. healthcare system spends under the current base scenario. These prices are achievable since the lowest annual HBV treatment cost is already $362.

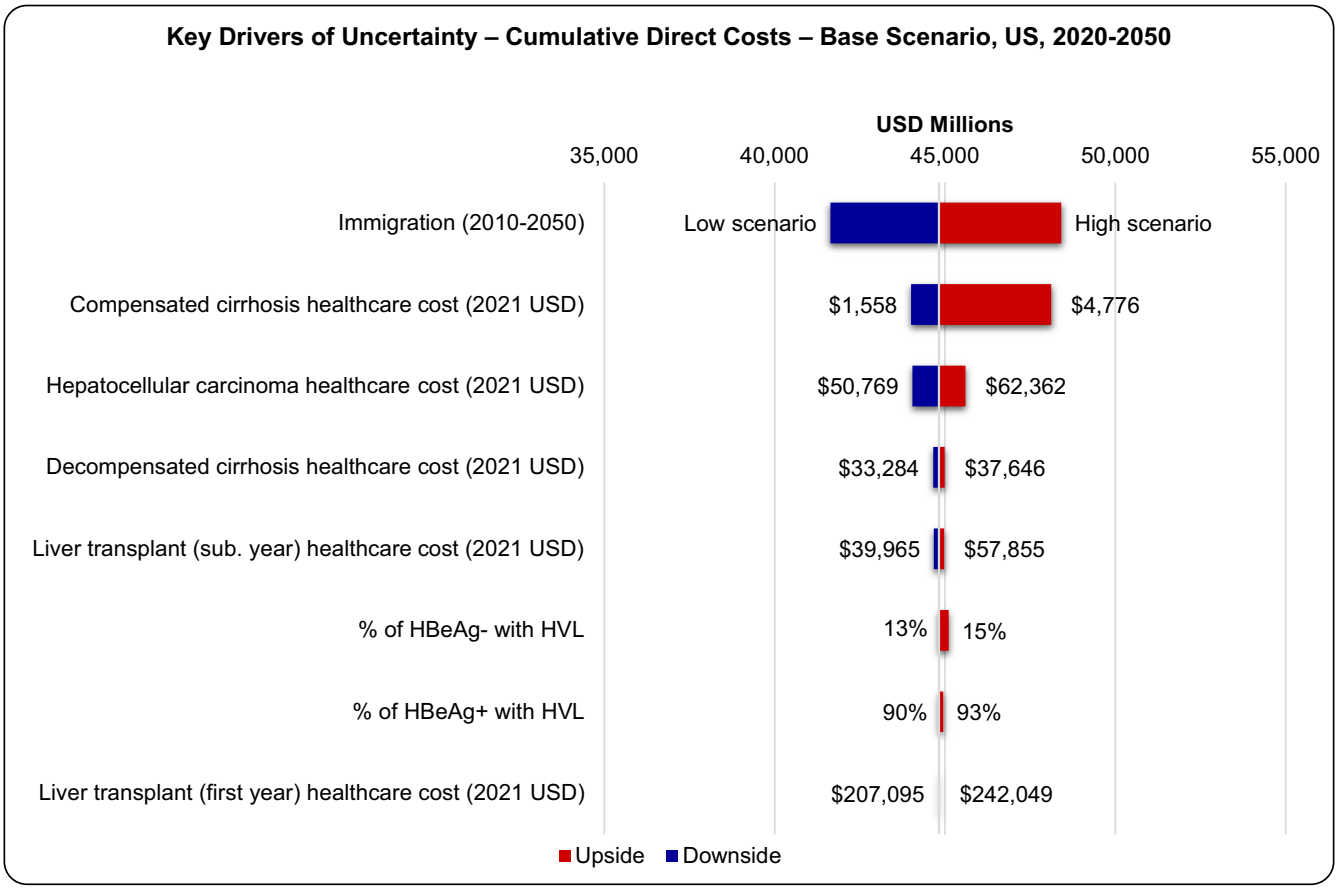

FIGURE 4 Key drivers of uncertainty for direct costs using the base scenario for the United States, 2050. HBeAg−, hepatitis B e-antigen negative; HBeAg+, hepatitis B e-antigen positive; HVL, high viral load; USD, U.S. dollars.

TABLE 2 Cumulative economic outputs by scenario: United States, 2020–2050.

Scenario	Cumulative direct costs (USD millions)	Cumulative DALYs	Cumulative DALYs averted	Cost per DALY averted (USD millions)
Base	44,822 (40,920–51,994)	5,141,000 (4,413,000–6,211,000)	—	—
Treat all, $5382	157,294 (140,267–178,092)	2,446,000 (2,070,000–3,066,000)	2,695,000 (2,343,000–3,145,000)	41,700 (40,100–42,200)
Treat all, $2000	74,857 (66,639–86,767)	2,446,000 (2,070,000–3,066,000)	2,695,000 (2,343,000–3,145,000)	11,100 (10,400–11,300)
Treat all, $750	44,389 (39,374–53,009)	2,446,000 (2,070,000–3,066,000)	2,695,000 (2,343,000–3,145,000)	−160 (−1100 to 480)

Abbreviations: DALYs, disability-adjusted life years; USD, U.S. dollars.

Antiviral therapy for HBV has been shown to reduce viral load significantly in individuals infected with HBV, with the majority achieving HBV DNA levels of <400 copies/mL after 48 weeks of therapy,[30,31] and there are continued viral declines over longer periods of therapy.[32,33] Likewise, 48 weeks of therapy reduces markers for liver inflammation,[30,31] and long-term therapy can produce regression of fibrosis and cirrhosis,[2] and reduce the incidence of HCC significantly.[3,34,35] Our model shows that individuals with a low viral load are also less likely to transmit HBV, resulting in fewer acute and chronic new HBV infections under the treat-all scenarios (Figure 2).

Individuals with immune-active chronic infection generally have HBV DNA levels >20,000 IU/mL, but this is an arbitrary cut-off that fluctuates throughout the course of disease. Individuals with chronic infection, including cirrhosis and liver cancer, can have HBV DNA levels below the cut-off value.[4,36] Therefore, it is impossible to define a single HBV DNA cut-off value to distinguish inactive carriers from HBeAg-negative individuals infected with chronic hepatitis. Clinicians are encouraged to consider other factors, including age, disease duration, disease stage, and the presence of elevated ALT levels, defined as ALT >35 U/L for males and >25 U/L for females.[4] However, ALT may not be consistently predictive of liver injury, and

a substantial portion of individuals with persistently normal ALT levels may experience significant inflammation and fibrosis, especially people age 40 years and older.[37] The current guidelines make the treatment of HBV too complicated for the average general practitioner. Although primary care guidance is more streamlined than the guidelines of the American Association for the Study of Liver Diseases, it still requires a large number of tests and follow-up.[38]

The U.S. Preventive Services Task Force recommends a one time screening for all adults,[39] screening adolescents at increased risk of infection[40] and pregnant women.[41] Previous analyses have estimated that one-time universal screening of adults combined with antiviral therapy would avert cases of advanced disease and would be cost-effective using current treatment guidelines.[42] Our analysis shows that expanding treatment to all HBV infections is also cost-effective and cost saving if the price of antivirals is lower.

For an HBV elimination program to be feasible in the United States, it is critical that primary healthcare providers be able to provide treatment for all nonadvanced cases. This is of particular importance because immigrants, who are more likely to be infected with HBV, are often under- or uninsured and face language barriers, which lead to challenges in following up with specialists.

There were several limitations with this study. Our model likely underestimates the cost of disease burden because it does not account for HIV/HBV, HBV/hepatitis C virus, and HBV/hepatitis D virus coinfections, all of which can lead to faster disease progression. Although HCC can still develop after HBsAg clearance,[43,44] the current model does not account for the small number of older individuals who are chronically infected and who clear HBsAg.[45-48] This study did not consider additional costs, such as the cost of transportation to and from appointments nor staff time. Although our analysis quantified DALYs, only direct costs were considered. There would be even greater cost-effectiveness when including increased work productivity as a function of reducing DALYs.

5 | CONCLUSION

Our analysis demonstrates that an expansion of efforts to diagnose and treat individuals chronically infected with HBV would avert a significant number of cases of advanced liver disease and related mortality. Such efforts would be cost-effective, and a reduced average treatment price ($750 annually) would result in cost savings and a positive return on investment.

FUNDING INFORMATION

This analysis was funded by an investigator-initiated research grant from Gilead Sciences (IN-US-320-6057). The funders had no role in study design, data collection, data analysis, data interpretation, or preparation of the manuscript.

CONFLICT OF INTEREST STATEMENT

DRS, CE, IG, and HR are all employees of CDA Foundation which received research grants from Gilead, Assembly Biosciences, AbbVie, Boehringer Ingelheim, Intercept, Merck, Novartis, Pfizer, and Roche. HR is a member of advisory boards for Gilead, AbbVie, Abbott, Merck, Janssen, Roche, and VBI Vaccines. All proceeds were donated to CDA Foundation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Polaris Observatory at https://cdafound.org/premium-dashboard/.

REFERENCES

1. World Health Organization. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Accountability for the global health sector strategies 2016–2021: actions for impact. Geneva, Switzerland: World Health Organization; 2021 15 July 2021. Report No: ISBN: 978-92-4-002707-7.
2. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet*. 2013;381(9865):468-475.
3. Kim WR, Loomba R, Berg T, et al. Impact of long-term tenofovir disoproxil fumarate on incidence of hepatocellular carcinoma in patients with chronic hepatitis B. *Cancer*. 2015;121:3631-3638.
4. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic Hepatitis B: AASLD 2018 Hepatitis B guidance. *Clin Liver Dis (Hoboken)*. 2018;12(1):33-34.
5. Zoulim F, Mason WS. Reasons to consider earlier treatment of chronic HBV infections. *Gut*. 2012;61(3):333-336.
6. Lui G, Yip T, Yuen B, et al. HIV infection and the risk of hepatocellular carcinoma in patients with Hepatitis B virus (HBV) Co-infection: a propensity score-matched cohort study. *Open Forum Infect Dis*. 2019;6(Supplement_2):S188-S.
7. Naggie S, McQuaid TL, Ramroth T, et al. Risk of HCC in patients with HBV infection with and without HIV co-infection: a US administrative claims analysis. *Hepatology*. 2020;72:494A.
8. Roberts H, Jiles R, Harris AM, Gupta N, Teshale E. Incidence and prevalence of sexually transmitted hepatitis B, United States, 2013–2018. *Sex Transm Dis*. 2021;48(4):305-309.
9. Razavi-Shearer D, Gamkrelidze I, Pan CQ, et al. The Impact of Immigration on Hepatitis B Burden in the United States: A Modeling Study. *Lancet Regional Health - Americas*. 2023;22:100516. [in press].
10. Razavi-Shearer D, Gamkrelidze I, Nguyen MH, et al. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol*. 2018;3(6):383-403.
11. Lu PJ, Yankey D, Jeyarajah J, et al. Hepatitis B vaccination among adolescents 13-17 years, United States, 2006-2012. *Vaccine*. 2015;33(15):1855-1864.
12. WHO/UNICEF. Reported official target population, number of doses administered and official coverage. http://www.who.int/immunization/monitoring_surveillance/data/en/2020 [updated 2020-Oct-14]. Available from: http://www.who.int/immunization/monitoring_surveillance/data/en/
13. Smith EA, Jacques-Carroll L, Walker TY, Sirotkin B, Murphy TV. The national perinatal hepatitis B prevention program, 1994-2008. *Pediatrics*. 2012;129(4):609-616.
14. Koneru A, Fenlon N, Schillie S, Williams C, Weng MK, Nelson N. National perinatal hepatitis B prevention program: 2009-2017. *Pediatrics*. 2021;147(3):e20201823.
15. Centers for Disease Control and Prevention. Hepatitis B vaccination–United States, 1982–2002. *MMWR Morb Mortal Wkly Rep*. 2002;51(25):549-563.
16. Kubo A, Shlager L, Marks AR, et al. Prevention of vertical transmission of hepatitis B: an observational study. *Ann Intern Med*. 2014;160(12):828-835.

17. Harris AM, Isenhour C, Schillie S, Vellozzi C. Hepatitis B virus testing and care among pregnant women using commercial claims data, United States, 2011-2014. *Infect Dis Obstet Gynecol*. 2018;2018:4107329.
18. Centers for Disease Control and Prevention. Viral Hepatitis Surveillance Report, 2019. 2021. https://www.cdc.gov/hepatitis/statistics/SurveillanceRpts.htm Accessed 12 Mar 2022.
19. IQVIA. IQVIA GPM National Audit for HBV/antivirals market, January 2019–December 2020. 2021.
20. Spradling PR, Rupp L, Moorman AC, et al. Hepatitis B and C virus infection among 1.2 million persons with access to care: factors associated with testing and infection prevalence. *Clin Infect Dis*. 2012;55(8):1047-1055.
21. Wiseman E, Fraser MA, Holden S, et al. Perinatal transmission of hepatitis B virus: an Australian experience. *Med J Aust*. 2009;190(9):489-492.
22. Global Burden of Disease Collaborative Network. *Global Burden of Disease Study 2015 (GBD 2015) Disability Weights*. Institute for Health Metrics and Evaluation (IHME); 2016.
23. The World Bank. GNI per capita, Atlas method (current US$). 2021 Available from: https://data.worldbank.org/indicator/NY.GNP.PCAP.PP.CD?locations=KR
24. U.S. Centers for Medicare & Medicaid Services. Clinical Laboratory Fee Schedule Files (21CLABQ1 CY 2021 Q1 Release) Baltimore, MD. 2021 Available from: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Clinical-Laboratory-Fee-Schedule-Files
25. U.S. Centers for Medicare & Medicaid Services. Physician Fee Schedule Baltimore, MD. 2021 Available from: https://www.cms.gov/medicare/physician-fee-schedule/search
26. Eckman MH, Ward JW, Sherman KE. Cost effectiveness of universal screening for Hepatitis C virus infection in the era of direct-acting, pangenotypic treatment regimens. *Clin Gastroenterol Hepatol*. 2019;17(5):930-939 e9.
27. Chahal HS, Peters MG, Harris AM, McCabe D, Volberding P, Kahn JG. Cost-effectiveness of Hepatitis B virus infection screening and treatment or vaccination in 6 high-risk populations in the United States. *Open Forum Infect Dis*. 2019;6(1):ofy353.
28. Bureau of Labor Statistics, United States Department of Labor. CPI for All Urban Consumers (CPI-U) Washington,D.C: United States Department of Labor. 2021 Available from: https://www.bls.gov/data/#prices
29. World Health Organization. *WHO Methods and Data Sources for Global Burden of Disease Estimates 2000–2019*. Department of Data and Analytics Division of Data, Analytics and Delivery for Impact, WHO. 2020. Global Health Estimates Technical Paper WHO/DDI/DNA/GHE/2020.3.
30. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med*. 2008;359(23):2442-2455.
31. Heathcote EJ, Marcellin P, Buti M, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology*. 2011;140(1):132-143.
32. Marcellin P, Wong DK, Sievert W, et al. Ten-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B virus infection. *Liver Int*. 2019;39(10):1868-1875.
33. Buti M, Tsai N, Petersen J, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. *Dig Dis Sci*. 2015;60(5):1457-1464.
34. Nguyen MH, Yang HI, Le A, et al. Reduced incidence of hepatocellular carcinoma in cirrhotic and noncirrhotic patients with chronic Hepatitis B treated with tenofovir-a propensity score-matched study. *J Infect Dis*. 2019;219(1):10-18.
35. Papatheodoridis GV, Idilman R, Dalekos GN, et al. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. *Hepatology*. 2017;66(5):1444-1453.
36. Chu CJ, Hussain M, Lok AS. Quantitative serum HBV DNA levels during different stages of chronic hepatitis B infection. *Hepatology*. 2002;36(6):1408-1415.
37. Lai M, Hyatt BJ, Nasser I, Curry M, Afdhal NH. The clinical significance of persistently normal ALT in chronic hepatitis B infection. *J Hepatol*. 2007;47(6):760-767.
38. Workgroup HPC. Hepatitis B Management: Guidance for the Primary Care Provider. 2020 Febuary 25, 2020.
39. Conners, E. E., Panagiotakopoulos, L., Hofmeister, M. G., Spradling, P. R., Hagan, L. M., Harris, A. M., Rogers-Brown, J. S., Wester, C., Nelson, N. P., Rapposelli, K., Sandul, A. L., Choi, E., Coffin, C., Marks, K., Thomas, D. L., & Wang, S. H. (2023). Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations — United States, 2023. *MMWR Recommendations and Reports*, 72(1), 1–25. https://doi.org/10.15585/mmwr.rr7201a1
40. Krist AH, Davidson KW, Mangione CM, et al. Screening for Hepatitis B virus infection in adolescents and adults: US preventive services task force recommendation statement. *Jama*. 2020;324(23):2415-2422.
41. Owens DK, Davidson KW, Krist AH, et al. Screening for Hepatitis B virus infection in pregnant women: US preventive services task force reaffirmation recommendation Statement. *Jama*. 2019;322(4):349-354.
42. Toy M, Hutton D, Harris AM, Nelson N, Salomon JA, So S. Cost-effectiveness of 1-time universal screening for chronic Hepatitis B infection in adults in the United States. *Clin Infect Dis*. 2022;74(2):210-217.
43. Adachi H, Kaneko S, Matsushita E, Inagaki Y, Unoura M, Kobayashi K. Clearance of HBsAg in seven patients with chronic hepatitis B. *Hepatology*. 1992;16(6):1334-1337.
44. Ahn SH, Park YN, Park JY, et al. Long-term clinical and histological outcomes in patients with spontaneous hepatitis B surface antigen seroclearance. *J Hepatol*. 2005;42(2):188-194.
45. Chen CJ, Yang HI. Natural history of chronic hepatitis B REVEALed. *J Gastroenterol Hepatol*. 2011;26(4):628-638.
46. Chu CM, Liaw YF. HBsAg seroclearance in asymptomatic carriers of high endemic areas: appreciably high rates during a long-term follow-up. *Hepatology*. 2007;45(5):1187-1192.
47. Gigi E, Lalla T, Orphanou E, Sinakos E, Vrettou E, Raptopoulou-Gigi M. Long term follow-up of a large cohort of inactive HBsAg (+)/HBeAg (–)/anti-HBe (+) carriers in Greece. *J Gastrointestin Liver Dis*. 2007;16(1):19-22.
48. Zacharakis GH, Koskinas J, Kotsiou S, et al. Natural history of chronic HBV infection: a cohort study with up to 12 years follow-up in North Greece (part of the Interreg I-II/EC-project). *J Med Virol*. 2005;77(2):173-179.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Razavi-Shearer D, Estes C, Gamkrelidze I, Razavi H. Cost-effectiveness of treating all hepatitis B–positive individuals in the United States. *J Viral Hepat*. 2023;00:1-9. doi:10.1111/jvh.13843