National Task Force on Hepatitis B

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Meeting Notes

Date: Wednesday, April 16, 2025 (generally, the 2nd Wednesday of the quarterly month unless otherwise noted)
Time: 3PM ET / 2PM CT / 1PM MT / 12PM PT / 9 AM Hawaii
Email: administrator@hepbtaskforce.org

Zoom Meeting link: https://us02web.zoom.us/j/81255351755?pwd=y1ve5Bx77MaQeA25Lw5vzoeIq2UBSt.1
Meeting ID: 812 5535 1755; Passcode: 316125

Attendance (at or after 3:05PM) are as follows:

- ✓ Amy Trang, PhD, Administrator for the National Task Force on Hepatitis B (DC, MD, VA)
- ✓ Binh Tran, PharmD, APHF and Hep B Free LA (San Diego and Los Angeles, CA)
- ✓ Brett Lown, Dynavax
- ✓ Khaled Salama, VIP (New York, NY)
- ✓ Arina, AbbVie
- ✓ Dan Saltman, MD, (Hawaii)
- ✓ Thaddeus Pham, Viral Hepatitis Prevention Coordinator, Hawaii State Department of Health
- ✓ Scott Suckow, Liver Coalition of San Diego (CA)

Total Number of attendees: 8

Note: There may be some members missing from this list of attendees; please excuse any omission.

Agenda:

1) Welcome Task Force members
2) Note any changes to the previous meeting's notes
3) Program / Project updates from Hep B Task Force members across the country
4) Discussion:
    a. Federal Funding Impacts

Meeting format:

- Open discussions and resource sharing to assist members with their local work
- Note: majority of those on the call for this meeting was engaged in collaborative discussions, so not everyone's name was specifically mentioned in the notes.

Notes:

Zoom AI Companion and Microsoft Copilot were used to create Meeting Summary for the Quarterly National Task Force on Hepatitis B Discussion Forum.

Quick recap

At around 3PM Eastern Time, the web-based version of Zoom experienced a nationwide system interruption. Members who were able to login to the call were doing so through the Zoom App, which also was later affected after 3PM Eastern Time. It was agreed upon members on the call that the distribution of these meeting notes would be done early next week to allow for other members to share their updates and/or resources via email to be incorporated into the notes and/or quarterly e-newsletter.

The meeting discussion focused on member updates and sharing of any impacts being experienced due to federal funding cuts. Programs such as ECHO are continuing around the country as they are not funded through federal grants. While support for provider education continues, it's important to note the concerns some members have in regard to screening, testing, and linkage to care / treatment services because of threats of potential cuts in insurance benefits such as Medicaid or continued insurance coverage for those who are losing their jobs. It is important for providers to be aware of any insurance interruptions if they are treating patients and link them to patient assistance programs that they might be eligible to apply.

The group acknowledged that the community should prepare for worst-case scenarios, emphasizing the importance of community connections in times of uncertainty. There was an emphasis on the significance of building personal working relationships to ensure continuity of care for patients, especially at the community-based level.

Next steps

- Amy to coordinate with other members to include any additional news and resources to share via quarterly e-newsletter.

Advocacy Efforts

Hep B United is leading Virtual Advocacy Day to be held on Wednesday, April 30, 2025. Link to register: Hep B United Virtual Advocacy Day 2025.

Hawaii also has ongoing projects and the potential for new initiatives in hep B advocacy.

Richard So, Executive Director of SF Hep B Free – Bay Area, wasn't able to logon due to the Zoom system outage, but emailed during the call: "I was hoping to let folks know of the new advocacy work we are doing to help spin up hep B advocacy around the nation starting with Hep B Free LA and iHep B Free Arizona. We are rebranding as Hep B Free to allow for a bigger scope and serving as technical consultants and providing a replicable high quality digital platform that new and existing groups can use to center their advocacy and not reinvent the wheel. SF Hep B Free is currently using the platform for our own website at sfhepbfree.org. We are excited to continue partnering and see how the task force has collaborate or support."

Vaccination and Prevention

Brett Lown from Dynavax shared that they are planning a webinar focusing on Hepatitis B vaccination and identifying barriers to prevention. He mentioned that while funding from government sources is limited, they are open to grant

requests from organizations seeking support for educational initiatives. Those interested should email: grants@dynavax.com. Unfortunately, Brett is not directly involved with that process and could not provide additional information.

Upcoming Conferences and Training Resources

Please join a **Liver Disease ECHO session on April 22 at 8:00 AM Alaska time, 12pm (noon) ET**, for an update on what's new in hepatitis B and an update on the status of the CDC Division of Viral Hepatitis and Viral Hepatitis Laboratory. **This ECHO is run by the Alaska Native Tribal Health Consortium.** You can register at https://echo.zoom.us/meeting/register/tJUvdeytqT4vGtzmN4TyvItMlNRlZW7U38EU. Once you register, you will receive another link to access the meeting.

Check the Task Force website for additional upcoming conferences and training resources.

Articles and other resources to share:

Dr. Samuel So, Executive Director of the Asian Liver Center at Stanford University School of Medicine, shared the manuscript on CEA of universal HDV screening that was published today ahead of print. He notes, "Although the prevalence of viremic HDV is low in some Asian populations like Chinese, we did find a one time universal HDV screening among adults with chronic HBV infection and treatment of patients with viremic HDV even with peg interferon is potentially cost-effective in the US." Article is attached at the end of these notes.

He also shared a cost-effectiveness analysis that was just published on monitoring and the addition of HCC surveillance in patients with inactive CHB who did not require antiviral treatment. Article is attached at the end of these notes.

Dr. Binh Tran was recognized for her work in the California Pharmacist Spring 2025 - Flipbook - Page 23. Dr. Tran has been a long-time member of the National Task Force on the Hepatitis B and a community champion!

Dr. Robert Gish shared: Hepatitis B: Update 2025 and beyond via YouTube.

Note: Other members who emailed that they could not join did not have any updates to share, but had hoped to have the opportunity to engage in the quarterly discussion and indicated that they look forward to the meeting notes.

This document is an edited transcript of a quarterly meeting of the National Task Force on Hepatitis B, led by Amy Trang, who serves as the administrator for the task force. The meeting format has been updated to an open discussion forum, allowing participants to introduce themselves and share their experiences related to hepatitis B and related health issues.

Clinical Infectious Diseases

MAJOR ARTICLE

Cost-Effectiveness of One-time Universal Testing for Hepatitis D among Adults living with Chronic Hepatitis B in the United States

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Background: Chronic hepatitis D virus (HDV) infection increases the risk of liver-related deaths in adults with chronic hepatitis B (CHB). In the US, only an estimated 12.9% of adults with CHB have received an HDV antibody test. The aim of this study is to calculate the cost-effectiveness of one-time universal HDV testing of hepatitis B surface antigen (HBsAg)-positive adults living in the US.

Methods: A Markov model was used to calculate the costs, health impact, and cost-effectiveness of universal testing of HBsAg- positive adults with an HDV antibody test and, when positive, an HDV RNA test for chronic HDV infection. We assumed 50% of the HDV RNA positive patients would receive the current recommended treatment with pegylated interferon (PEG-IFN) for 48 weeks. With a 30% response rate. We also modelled the potential impact of hypothetical indefinite HDV antiviral therapy with a higher response rate to assess the annual cost threshold to be considered cost-effective.

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Results: Universal HDV testing of adults with CHB could avert 100 HDV-related deaths and an additional 30 cases of cirrhosis and 50 cases of hepatocellular carcinoma, and potentially result in a gain of 1,500 QALYs per 100,000 HBsAg-positive individuals screened. At a willingness to pay threshold of $50,000/QALY, the annual drug costs for a hypothetical indefinite therapy with a 50% or 70% treatment response rate would need to cost ≤ $13,027 and $14,104, respectively.

Conclusion: One-time HDV testing for all HBsAg-positive adults and treatment of chronic HDV infection with PEG-INF is potentially cost effective in the US.

Key words: Delta hepatitis, HDV, screening, testing, viral hepatitis, cost-effectiveness

Key points summarized: One-time testing of adults with chronic hepatitis B infection for hepatitis delta in the United States is likely cost-effective and will result in better health outcomes compared to current practice.

INTRODUCTION

Hepatitis delta virus (HDV) is the smallest known virus infecting mammals and requires the hepatitis B surface antigen to infect hepatocytes (1). Superinfection, or HDV infection in a person already living with chronic HBV infection, can lead to chronic HDV infection in 90% of individuals. Chronic HDV accelerates the course of hepatitis and can result in cirrhosis in 60%-90% of patients. The risk of hepatocellular carcinoma (HCC) is three times higher among patients with both HDV and HBV compared with patients with HBV mono-infection (2).

The most effective way to control HDV is to prevent HBV infection with hepatitis B vaccination since HDV is dependent on HBV for entry into hepatocytes and propagation. Although there is no U.S. Food and Drug Administration (FDA)-approved treatment specifically for HDV infection, the American Association for the Study of Liver Diseases (AASLD) recommends patients with chronic HDV (HDV RNA positive) who have elevated alanine aminotransferase (ALT) or compensated cirrhosis receive treatment with pegylated interferon (PEG-IFN) (3, 4). Although PEG-IFN is reported to have only a 30% response rate with an estimated 8% relapse rate per year, patients who achieved a combined virologic and biochemical response (undetectable or at least a 2-$\log_{10}$ decrease in HDV RNA and normalization of ALT) at 24 weeks after PEG-IFN therapy had improved event-free survival (4). However, interferon therapy is associated with many side effects (5). Recent progress in HDV research has given rise to several new investigational drugs that may be more effective and have fewer side effects than interferon (3, 4). Bulevirtide, a drug given daily by subcutaneous injection that blocks the entry of HDV into hepatocytes, was approved for HDV treatment by the European Medicines Agency (6).

Studies assessing the prevalence of exposure to HDV (HDV antibody positive) in the US among HBsAg-positive adults report widely varying results, with HDV antibody positivity ranging from 2 to 6% and as high as 41% among Mongolians living in Los Angeles (7-10). A recent meta-

analysis estimates a 3.8% HDV prevalence among HBsAg-positive persons in the US (11). A global HDV prevalence meta-analysis by Stockdale et al. (12) estimated that 64% of anti-HDV positive adults are HDV RNA positive. Taken together these estimates imply that as many as 2.4% (3.8% anti-HDV x 64.2% RNA-positive) of the estimated 660,000 to 1.6 million HBsAg-positive adults in the US are living with chronic HDV infection (13, 14). However, the current AASLD recommendation for HDV testing is limited to persons at high risk of HDV (defined as persons who inject drugs, those with HIV and/or HCV infection, men who have sex with men, those with a history of sexually transmitted infections or multiple sexual partners, immigrants from areas with high HDV endemicity, or those who have HBV DNA < 2,000 IU/mL but elevated ALT) (15). The testing rate for HDV is very low, with an estimated 12.9% (range 6.7-19.7%) of HBsAg-positive adults having been screened for HDV antibody (16).

Recently, universal HBV screening in the US was found to be highly cost-effective (17), prompting the CDC to updated its guidelines to recommend one-time hepatitis B screening for all adults ≥ 18 years (18). The aim of this study is to calculate the cost-effectiveness of one-time hepatitis D testing among HBsAg-positive adults in the US.

METHODS

Overview

We developed a Markov model to simulate long-term outcomes of chronic hepatitis B (CHB) patients with HDV infection. We summarized health outcomes using quality-adjusted life years (QALYs), computed direct medical costs, and assessed cost-effectiveness using incremental cost per-QALY ratios, over a lifetime horizon. A threshold of ≤$50,000 per QALY is generally considered cost-effective in the US (19).

Natural history model

The natural history model included progression rates for cirrhosis, HCC, and liver-related death. Disease progression rates of untreated chronic HDV were derived from cohort studies and meta-analyses of HDV patients (Appendix Table 1 and Appendix Figure 1). Patients in the model can be diagnosed depending on one of two strategies, described below. Diagnosed patients may start treatment, which reduces disease progression risks compared to those among untreated patients. The model captures mortality from HBV, HDV, or other causes. Mortality rates from causes other than HBV or HDV were based on life tables from US vital statistics (20). We simulated a hypothetical cohort of diagnosed HBsAg-positive patients starting from age 45 years. Model transitions were simulated in one-year time steps. The model was implemented in TreeAge Pro 2023.

Screening scenarios

We compared two main screening scenarios: status quo levels of testing and universal one-time testing. For the status quo, we assumed that 12.9% of the cohort had been screened for exposure to HDV with an anti-HDV test, based on current screening rates. For the universal testing scenario, we assumed that 100% of the cohort was screened for exposure (Figure 1). In both scenarios, people who tested positive for anti-HDV were then tested for HDV RNA. If the HDV RNA test was negative the person did not have chronic HDV and those HBsAg-positive individuals followed the CHB care model, adapted from our previous studies (17). In this model, we assumed 3.8% of the HBsAg-positive individuals screened for exposure would test positive for anti-HDV (11), 64.2% of the anti-HDV positive individuals would test positive for HDV RNA meaning a diagnosis of chronic HDV infection (12), and 30% would have cirrhosis (21). In this study, we assumed only 50% of the HDV RNA positive patients would receive HDV treatment based on having compensated cirrhosis or an elevated ALT and no contraindication for PEG-IFN. Key input variables are shown in Table 1.

Hdv treatment

We analyzed treatment with pegylated interferon (PEG-IFN) for 48 weeks with 29% combined response rate (5) and 8% relapse rate per year (22). In a secondary analysis, we considered a hypothetical HDV antiviral treatment taken indefinitely with either a 50% or 70% initial combined response rate. Combined response is defined as a virological and biochemical response, with HDV RNA undetectable or decreased by > 2 $\log_{10}$ from baseline and normal ALT levels.

Assumptions

Diagnosis of HDV infection consisted of a one-time anti-HDV test followed when positive by an HDV RNA test. We assumed anti-HDV-negative and HDV RNA-negative patients would have the same disease progression rate and would receive the same monitoring as for patients with CHB mono-infection (17). The AASLD guideline recommendation is that Nucleoside Analogs (NAs) are indicated when control of HBV replication is appropriate (15). We assumed that patients with cirrhosis would receive NAs tenofovir or entecavir, which are first-line treatment for HBV, regardless of whether they receive HDV treatment. We assumed HDV RNA positive patients who did not receive HDV treatment and treatment non-responders and relapsers would follow HDV natural history disease progression estimates and would receive monitoring with an annual HDV RNA test and biannual liver ultrasound for liver cancer surveillance in addition to routine CHB monitoring and treatment.

We did not include an annual rescreening test for those at ongoing risk of exposure to HDV, since the rate of acquiring HDV in the US is unknown. In this model, we assumed only 50% of the HDV RNA positive patients (70% of whom have elevated ALT and 30% of whom have compensated cirrhosis) would receive HDV treatment.

Costs and Utilities

We included a Medicare reimbursement cost of $18.16 (23) for a total anti-HDV test, followed by a HDV RNA test. We also used the Medicare reimbursement cost of $42.84 for an HDV RNA test but varied this up to $300 in sensitivity analyses. We assumed HDV testing is performed as part of routine monitoring of patients with CHB. For patients receiving PEG-IFN treatment, we assumed the patient would receive additional monitoring that would include complete blood count, liver function tests, TSH (thyroid stimulating hormone) test, complete metabolic panel, quantitative HDV RNA test, HBV DNA test, HBsAg test, and monthly clinic visits during the 48-week treatment period (Table 1). The 48-week drug cost was $49,031 for PEG-IFN (24). All costs were adjusted to 2024 USD using the Medical Consumer Price Index (CPI) calculator. We included age-specific, per-person background medical costs using recently published US estimates (25). All costs and QALYs were discounted at 3% per year. The analysis was performed from the health care system perspective. We used EQ-5D utility assessments by Woo et al. (26) and included age adjustments from Parikh et al. (27). We added a disutility of 0.05 for all HDV health states, except for treatment utilities with the more effective hypothetical treatments, that could improve health-related quality of life measured by EQ-5D VAS (28). We added a lower utility for PEG-IFN treatment due to its low tolerance rate (29). Medical management costs such as cirrhosis, decompensated cirrhosis, HCC and LT are all included in the model. Key input variables related to costs and utilities are shown in Table 1.

Sensitivity analysis

We conducted one-way sensitivity analyses to determine the parameters that had the greatest impact on the results. Sensitivity analyses were performed with anti-HDV prevalence ranging from 1.0% to 10%, prevalence of HDV RNA among anti-HDV patients ranging from 20% to 100%, treatment rates ranging from 20% to 100%, and proportion of patients with cirrhosis who received treatment ranging from 30% to 50%. The costs of the HDV RNA test and the hypothetical more effective treatments were varied in cost-effectiveness threshold analyses. Finally, we conducted a probabilistic sensitivity analysis to evaluate the impact of overall parameter uncertainty and outcomes.

RESULTS

One-time HDV testing and treatment with PEG-IFN

Compared to current practice, where only 12.9% of adults with CHB infection in the US are screened for HDV, one-time universal testing of adults with CHB and subsequent treatment of 50% of the HDV RNA positive patients with PEG-IFN could potentially avert 100 HDV-related deaths and an additional 30 cases of cirrhosis and 50 cases of HCC, per 100,000 HBsAg-positive individuals screened. Compared to current practice, universal testing and treatment with PEG-IFN

has an ICER of $22,333/QALY, resulting in a gain of 1,500 QALYs and an averted $33.5 million in lifetime healthcare costs to treat HDV-related liver complications per 100,000 HBsAg-positive individuals screened. (Table 2).

For an estimated prevalence of 0.2%, or 660,000 HBsAg-postive adults as reported by Bixler et al. (13), and assuming 50% are diagnosed or aware of their HBV status (13), universal HDV testing could avert 330 HDV-related deaths and an additional 99 cases of cirrhosis and 66 cases of HCC. If the prevalence of CHB is 0.65% or 1.6 million as reported by Lim et al. (14), and assuming 50% are diagnosed, universal testing could avert 240 cases of cirrhosis, 160 HCC, and 800 HDV-related deaths.

Estimated health impact and cost threshold for hypothetical indefinite new therapies

Universal HDV testing and treatment of 50% of the HDV RNA-positive patients with hypothetical indefinite duration HDV antiviral therapy with a 50% or 70% combined virologic and biochemical response could avert 71% and 74% of HDV-related deaths, respectively, assuming a best case scenario of perfect treatment compliance and no drug resistance (Appendix Table 2-4). At a willingness to pay (WTP) threshold of $50,000/QALY, the annual drug cost of the indefinite therapy with a 50% or 70% combined response rate would need to be ≤$13,027 and ≤ $14,104, respectively (Figure 2). The hypothetical indefinite therapy with a 50% or 70% combined response would be cost-saving if the annual drug cost is ≤ $1,757 and ≤$1,729, respectively (Appendix Figure 2). If the WTP threshold is $100,000/QALY, the annual drug cost of indefinite therapy with a 50% or 70% combined response rate would need to be ≤ $24,377 and ≤ 26,559, respectively (Appendix Figure 3 and 4).

Sensitivity analysis

The results of one-way sensitivity analyses are summarized in Appendix Figure 5. The model was sensitive to certain parameters such as the proportion of HDV RNA positive patients that received HDV treatment, anti-HDV prevalence, HDV RNA prevalence, and the annual cost of the hypothetical therapies. We ran separate sensitivity analyses for each of these variables and for each treatment strategy. Varying the anti-HDV prevalence between 1 and 10% had a small impact on the ICER (Appendix Figure 6). If anti-HDV prevalence is only 1%, universal testing and treatment with PEG-IFN would still be cost-effective at an ICER of $22,333/QALY. Varying the HDV RNA prevalence between 20% and 100% similarly had a small impact on the ICER (Appendix Figure 7). Varying the proportion of HDV RNA-positive patients who received treatment (fraction treated) from 20%-100% did not have a large impact on the ICER (Appendix Figure 8), and varying the portion of patients who received treatment with cirrhosis from 30% to 50% reduced the ICER slightly to $19,587/QALY. The sensitivity analysis of hypothetical drug response rate is presented in appendix figure 9. The probabilistic sensitivity analysis showed a > 99% likelihood that universal screening strategies would be cost-effective at a WTP threshold of $50,000/QALY (Appendix Figure 10).

DISCUSSION

With an estimated anti-HDV positivity rate of 3.8% and an HDV RNA positivity rate of 64.2% among the estimated 660,00-1.6 million people living with CHB in the US, chronic HDV may affect 16,000 to 40,000 of Americans (11, 12, 30). Many adults with chronic HDV likely have not been diagnosed since only a small fraction of HBsAg-positive adults in the US (~13%) have been tested for HDV, given that testing is currently recommended by the AASLD only for persons at increased risk of HDV infection (4, 15). The reported low HDV risk-based testing rate is not surprising since most primary care clinicians would likely not remember a long list of risk factors that are often not collected or documented in the health records, and many may not be aware of the recommendations for HDV testing. Universal anti-HDV testing of people with CHB is recommended by the European Association for the Study of the Liver (EASL), the Asian Pacific Association for the Study of the Liver, and the updated 2024 World Health Organization Guidelines (3). With the recognition that chronic HDV is underdiagnosed and with emerging new therapies, many US experts are advocating for universal HDV testing among HBsAg-positive persons (30, 31). This study found one-time universal HDV testing among HBsAg-positive persons, and treatment of an estimated 50% of persons with chronic HDV with elevated ALT or compensated cirrhosis with PEG-IFN in the US cost $22,333/QALY. At a willingness to pay of $50,000/QALY, the annual drug costs for a hypothetical indefinite HDV antiviral therapy with 50% or 70% combined response rate would need to cost ≤ $13,027 and ≤ $14,104, respectively. Since many HBV infected individuals are unaware of their infection, there is a missed opportunity for significant improvements, including the diagnosis of HDV infections, if HBV infection ascertainment is not achieved. The potential benefits are substantial if more individuals become aware of their HBV status.

There are a number of limitations in this study. The natural history of chronic HDV infection is not well studied. In the model, disease progression rates in patients with chronic HDV are based on estimates from available published studies. Our model also assumes standard background mortality, but risk factors for HDV co-infection are correlated with behaviors that limit life-expectancy. To the extent individuals with HDV have higher background mortality, we may overestimate long-term health gains. A limitation in our study is the estimated proportion of 64% anti-HDV positive adults testing positive for HDV RNA, which was taken from a meta-analysis by Stockdale et al. (12) which may not be representative of CHB among persons in the US. Knowing this limitation we ran a sensitivity analysis around the proportion of anti-HDV positive adults testing positive for HDV RNA that ranged from 20% to 100%. We assume patients who are anti-HDV positive but HDV RNA negative have resolved infection and would not require further HDV RNA monitoring and would have disease progression rates similar to CHB patients without HDV. Currently there are no FDA approved anti-HDV and HDV RNA assays and the sensitivity and specificity of the current tests are variable and are not assessed in the study. We assumed 50% of the HDV RNA positive adults would not receive treatment because they either have normal ALT or decompensated cirrhosis. But treatment rates are uncertain, particularly if

individuals are reluctant to take PEG-IFN or the prescribed treatment. However, treatment rates of 20% to 100% were assessed in sensitivity analysis and universal testing was still cost-effective. Although patients on bulevirtide have a 50% initial combined virologic and biochemical response rate, it would likely have to be taken long-term since most patients may relapse after stopping treatment. It is unclear whether a combination of new therapies with or without PEG-IFN will prove to be more effective (3). Another limitation of our study is that it does not include out of pocket costs to patients.

In 2023, CDC recommended a one-time universal screening of all adults for HBV infection (18). A national recommendation for universal testing for HDV among persons with HBV would require a call to action to raise clinician and public awareness.

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Potential conflicts of interest: The authors: No reported conflicts of interest.

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Disclaimer*:* The findings and conclusions in this report are those of the authors and do not necessarily reflect the official position of the Centers for Disease Control and Prevention, or the authors' affiliated institutions.

Table 1. Key input variables for the model

Variable	Base Case	Range	Reference
Age/birth cohort	45 yrs	18-70yrs	
Male-to-female prevalence ratio	58:42		Patel et al. 2019 (9)
CHB adults receiving anti-HDV screening (current status)	12.9%	5%-20%	Nathani 2023 (16)
Anti-HDV positivity among HBsAg-positive adults	3.8%	1.0%-10.0%	Wong et al. 2024 (11, 32)
Proportion of anti-HDV positive adults testing positive for HDV RNA	64.2%	20-100%	Stockdale et al. 2020 (12)
Percent of anti-HDV-positive persons with cirrhosis	30.0%	10-50%	Kamal et al. 2022 (21)
Percent HDV viremic patients receiving HDV treatment (elevated ALT or with compensated cirrhosis)	50.0%	20-100%	assumption
Combined virologic and biochemical response rate with PEG-IFN alfa-2a therapy	29.0%	24-34%	Abdrakhman et al. 2022 (5)
Combined virologic and biochemical response rate with hypothetical drug therapy	50.0%	50-90%	assumption
Relapse rate for PEG-IFN alfa-2a per year	8.0%	8-10%	Mentha et al. 2020 (33)
Costs of Testing			

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Anti-HDV test	$18.16	$17-82	Medicare reimbursement (23)
HDV RNA test	$42.84	$35-300	Medicare reimbursement (23)
Annual medical management costs			
Cirrhosis	$5,964	$202-$7,096	Liu et al. 2012 (34)
Decompensated cirrhosis	$15,795	$4,901-$37,081	Liu et al. 2012 (34)
Liver Transplantation 1st year	$215,162	$167,163-$250,746	Liu et al. 2012 (34)
Liver Transplantation 2nd year	$26,860	$23,958-$35,937	Liu et al. 2012 (34)
Costs of PEG-IFN treatment x 48 weeks			
PEG-IFN alpha-2a 180µg/week (48 weeks) drug cost	$49,031	$49,031-60,000	Redbook [33]
Cost of monitoring and clinic visits for 48 weeks of HDV treatment*	$1,276	$873-1309	Medicare reimbursement (23)
Liver function test and complete blood count with platelet count	$86.74 x 4		Medicare reimbursement (23)
TSH (thyroid-stimulating hormone) test	$16.80 x 4		Medicare reimbursement [16]
HDV RNA test	$42.84 x 4		Medicare reimbursement (23)
HBV DNA test	$59 x 4		Medicare reimbursement (23)

HBsAg test	$10.33 x 4		Medicare reimbursement (23)
Clinic visits	$74 x8		Medicare reimbursement (23)
CBC (complete blood count)	$7.77 x 12		Medicare reimbursement (23)
CMP (complete metabolic panel)	$10.56 x 4		Medicare reimbursement (23)
Costs of longterm monitoring of HDV RNA positive patients**	$250		Medicare reimbursement (23)
Health State Utilities			
Disutility HDV infection	0.05		assumption
Utility for PEG-IFN treatment	0.77		Wong et al. 2000 (29)

* 48 weeks treatment with hypothetical drug with fewer side effects: same monitoring as PEG-IFN treatment but without TSH testing, and decreased frequency for: CBC x 4 and clinic visit x4

** The long-term monitoring costs include: biannual CBC, CMP, HDV RNA, HBV DNA, abdominal ultrasound, and annual HBsAg

Table 2. Costs, cost-effectiveness, and health impact of universal HDV testing and treatment of 50% of HDV RNA positive patients with PEG-IFN for an estimated 100,000 population with CHB compared with the current screening rate of 12.9%

Scenario	**Cost (millions)**	**QALYs**	**ICER***	**HDV Cirrhosis cases**	**HDV Decompensated Cirrhosis cases**	**HDV HCC cases**	**HDV deaths**
Natural History	$19,089	2,039,100	-	390	230	650	1,060
Current Practice	$19,094	2,039,300	-	390	230	640	1,050
Screen All	$19,127	2,040,800	$22,333	360	210	590	950

Abbreviations: HCC: Hepatocellular Carcinoma, HDV: Hepatitis D Virus, ICER: Incremental Cost-Effectiveness Ratio, QALY: Quality-Adjusted Life-year
* ICER is compared to current practice

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FIGURE LEGENDS

Figure 1: Decision tree for anti-HDV testing and treatment vs. no testing among HBsAg-positive adults that are aware of their infection

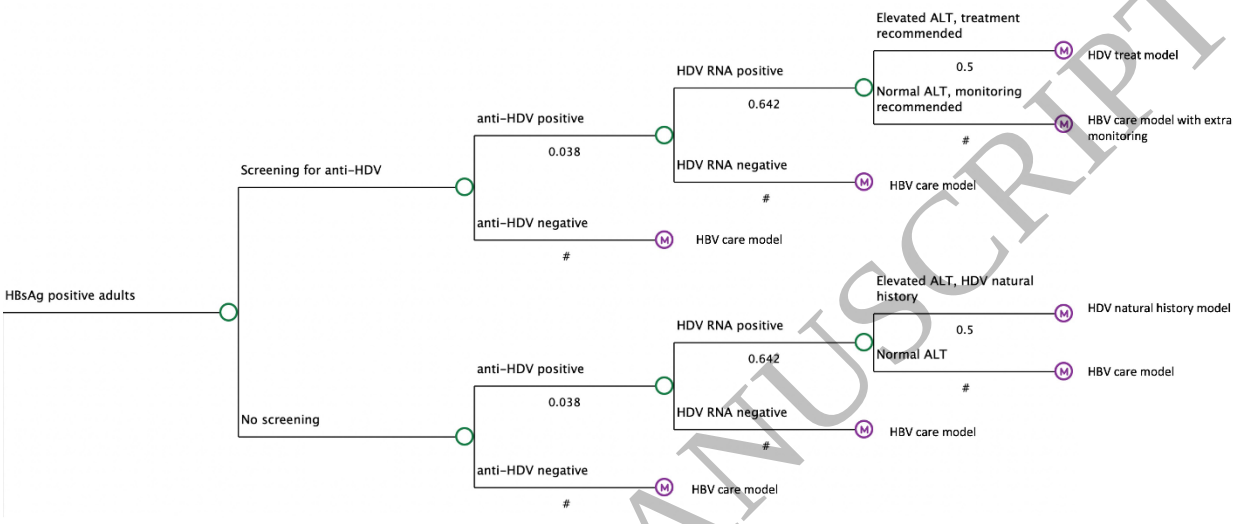
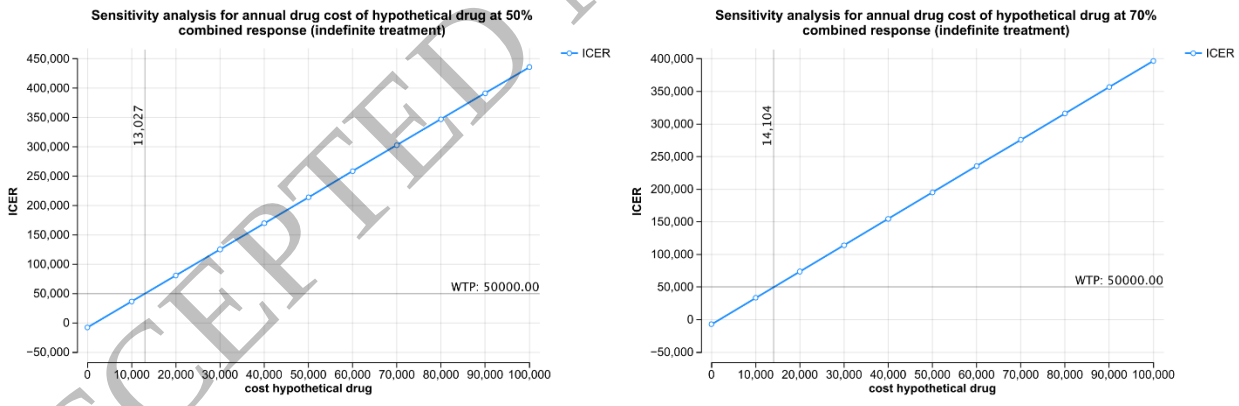


Figure 2: Sensitivity analysis for annual drug cost of hypothetical indefinite therapy with (A) a 50% combined response (B) 70% combined response at a willingness to pay threshold of $50,000



Abbreviations: ICER, incremental cost-effectiveness ratio; WTP, willingness to pay

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PLOS ONE

RESEARCH ARTICLE

Cost-effectiveness of monitoring and liver cancer surveillance among patients with inactive chronic hepatitis B

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Abstract

Patients with chronic hepatitis B infection (CHB) have an increased risk for death from liver cirrhosis and hepatocellular carcinoma (HCC). In the United States, only an estimated 37% of adults with chronic hepatitis B diagnosis without cirrhosis receive monitoring with at least an annual alanine transaminase (ALT) and hepatitis B deoxyribonucleic acid (DNA), and an estimated 59% receive antiviral treatment when they develop active hepatitis or cirrhosis. A Markov model was used to calculate the costs, health impact and cost-effectiveness of increased monitoring of adults with HBeAg negative inactive or HBeAg positive immune tolerant CHB who have no cirrhosis or significant fibrosis and are not recommended by the current American Association for the Study of Liver Diseases (AASLD) clinical practice guidelines to receive antiviral treatment, and to assess whether the addition of HCC surveillance would be cost-effective. For every 100,000 adults with CHB who were initially not recommended for treatment, if the monitoring rate increased from the current 37% to 90% and treatment rate increased from 59% to 80%, 4,600 cases of cirrhosis, 2,450 cases of HCC and 4,700 HBV-related deaths would be averted with a gain of 45,000 QALYs and a savings of $180 million in lifetime health care costs. At a willingness to pay threshold of $100,000/QALY, the addition of HCC surveillance with the standard recommended biannual liver ultrasound and alfa fetoprotein levels is likely cost-effective if the HCC risk $\geq$ 0.55%/year. Regular monitoring of persons with inactive or immune tolerant CHB who are initially not recommended to receive antiviral treatment in the United States is cost-saving. The addition of HCC surveillance with biannual US and AFP would be cost-effective for individuals with HCC incidence $\geq$ 0.55%/year.

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Introduction

In the United States, there are an estimated 1.25 to 2.4 million HBsAg-positive persons living with chronic hepatitis B (CHB) infection [1, 2]. Most of them have no or few symptoms and less than 50% are aware of their infection [3]. A significant proportion of adults tested positive for HBsAg are initially not recommended for antiviral treatment according to the AASLD clinical practice guidelines because they have HBeAg negative inactive CHB (anti-HBe positive, persistently normal ALT, HBV DNA $<$ 2,000 IU/mL, and with no or minimal liver necroinflammation or fibrosis) or HBeAg positive immune tolerant HBV infection (normal or minimally elevated ALT, very high HBV DNA, and minimal liver inflammation and no fibrosis) [4]. Although antiviral treatment is not currently recommended for inactive or immune tolerant CHB, AASLD recommends regular monitoring of ALT and HBV DNA levels to determine whether an indication for treatment has developed, and HBeAg testing is also recommended in HBeAg positive patients to assess when they would become e antigen negative [4]. Despite these recommendations, reported monitoring of ALT and HBV DNA among adults with CHB remains low [5]. The estimated monitoring rate of adults in the U.S. with CHB with at least an annual ALT and HBV DNA in individuals without cirrhosis is only 37%, with an estimated 59% receiving antiviral treatment when they become eligible for treatment [3].

The AASLD also recommends HBsAg positive individuals with an annual HCC risk greater than 0.2% per year to receive hepatocellular carcinoma (HCC) surveillance with biannual liver ultrasound with or without blood levels of alfa-fetoprotein (AFP). Despite this recommendation, only 36% of CHB without cirrhosis undergo HCC surveillance [5]. The recommended threshold for HCC surveillance was largely based on an unpublished cost-effectiveness study from 1999 that reported HCC surveillance with biannual ultrasound and AFP in a cohort of hepatitis B carriers $\geq$ age 30 years with an annual HCC incidence $\geq$ 0.2% would prolong life by 3 months and would be cost-effective at a willingness to pay at $50,000/life year gained [6, 7]. Although recent studies reported HCC surveillance in patients with cirrhosis is likely cost-effective, the cost-effectiveness of HCC surveillance in non-cirrhotic chronic hepatitis B patients in the U.S. have not been re-examined.

The aim of this study is to assess 1) the current population level costs, cost-effectiveness and health impact of monitoring of HBsAg-positive persons who are currently not on antiviral treatment, and 2) the threshold in HCC incidence for surveillance to be cost-effective in the United States.

Methods

A Markov model was developed using TreeAge Pro 2023 to simulate long-term outcomes including cirrhosis, HCC, and CHB-related death as patients with HBeAg negative inactive CHB and HBeAg positive immune tolerant CHB move through various health states (Fig 1). Once patients enter the HBeAg positive immune active or HBeAg negative active CHB or cirrhosis health state they become candidates for treatment following the latest 2018 AASLD clinical practice guidelines [4]. Individuals who receive treatment for active CHB and cirrhosis have a lower risk of developing liver-related complications such as HCC and cirrhosis following disease progression rates derived from cohort studies and meta-analyses of HBV mono-infected patients (S1 and S2 Tables in S1 File). Without monitoring and antiviral treatment, patients follow the disease natural history. The natural history of CHB and disease progression rates were derived from recent cohort studies and meta-analyses mainly from North America for HBV mono-infected patients (S1 Table in S1 File). Disease progression rates were assumed to be 50% lower among women compared to men, based on recent sex-specific studies [8–10]. Treatment effectiveness estimates were expressed as reductions in disease progression risks for

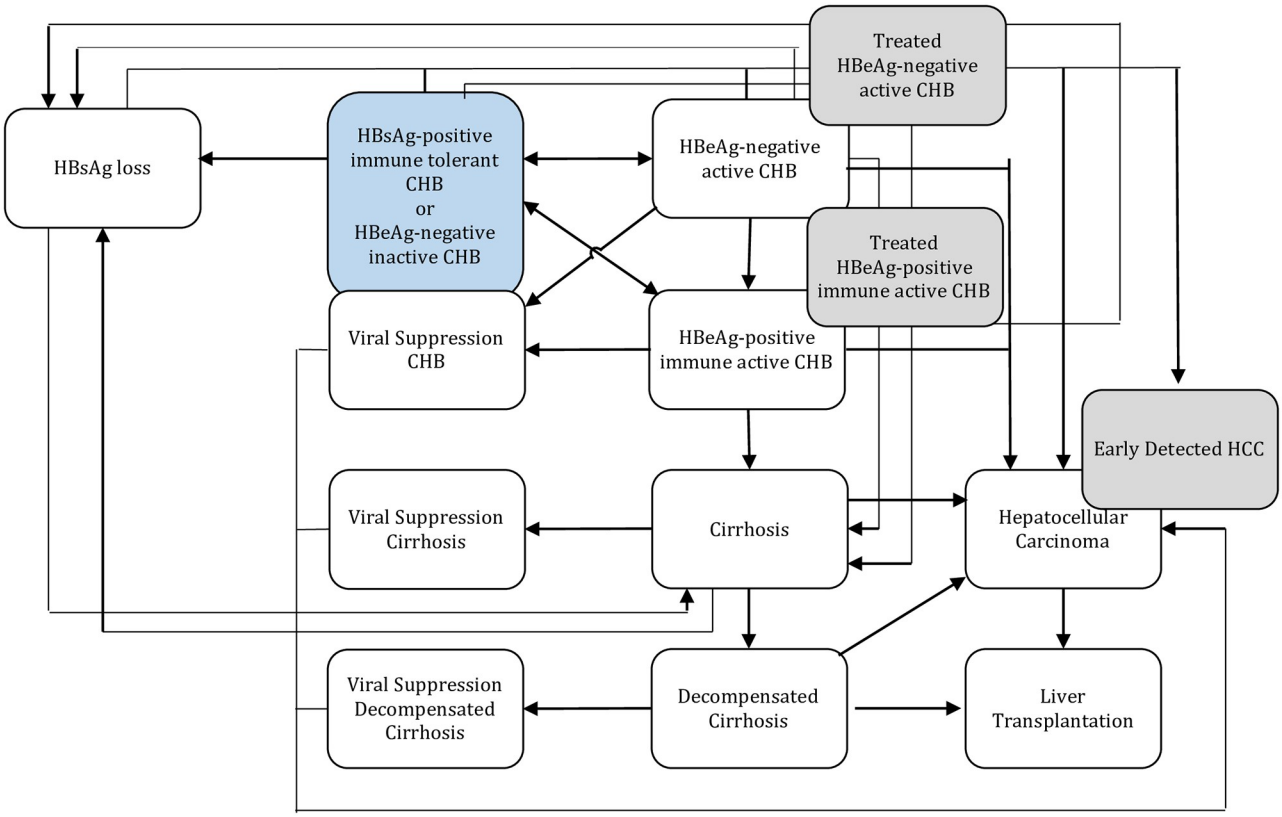

Fig 1. Markov schematic.

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treatment naïve patients (S2 Table in S1 File). We assumed effective antiviral suppression would reduce liver cancer risks in cirrhotic and non-cirrhotic patients by 50% and 70% respectively, compared with natural history [11, 12]. Disease progression between health states, conditional on treatment, age (where available) and sex was simulated in one-year cycles. Causes of death that were not related to CHB were included in the model, based on age-specific mortality rates from life tables in the National Statistics Report [13]. Annual probabilities of receiving a liver transplant for CHB-related decompensated cirrhosis and HCC (1.2% and 7%, respectively) were calculated based on data from Organ Procurement and Transplantation Network [14]. If progression rates were reported, these were transformed into annual probabilities using a standard formula ($P = 1\text{-}e^{-rt}$), where P is the probability and r is the annualized progression rate.

We ran the model for representative ages of 25, 35, 45, 55, 65, and 75 to represent the age groups of 18–29, 30–39, 40–49, 50–59, 60–69, 70+. We then weighted these results by U.S. Census data by age and aggregated across age cohorts to create a hypothetical cohort of 100,000 adults. Key input variables are shown in Table 1.

Scenarios

Three scenarios were analyzed in the model. 1). *Current practice (CP)* with 37% of CHB patients who are initially not eligible for treatment receiving monitoring with biannual ALT and annual HBV DNA [3] and 59% who become treatment eligible receiving antiviral treatment. 2). *Increased monitoring and treatment (increased M&T)* where the percentage of

Table 1. Key input variables.

Variable	Base Case	Range	References
Age/birth cohort	≥18 yrs	18–70 yrs	
Male to female ratio of positive HBsAg population	58:42		Patel et al. 2019 [15]
Percent receiving monitoring (current practice)	37%	20%-60%	Spradling et al. 2016 [16]
Percent receiving treatment if eligible (current practice)	59%	10%-90%	Spradling et al. 2016 [16]
Reduction in mortality risk with HCC surveillance	38%		Mittal et al. 2016 [17]
Linkage to and Treatment Costs			
Antiviral drug costs per year[a]	$387	$325-$16,464[b]	Redbook (May, 2024) [18]
Total annual monitoring costs (without HCC surveillance cost)‡	$221	$111–332	Medicare reimbursement
Clinic visit x 2	$74	$37-$111	Medicare reimbursement
ALT x 2	$7	$4-$11	Medicare reimbursement
HBV DNA x 1	$59	$29-$88	Medicare reimbursement
HBeAg	$11.53	$10–13	Medicare reimbursement
Total annual HCC surveillance costs[c]	$296	$100-$554	Medicare reimbursement
Ultrasound x 2	$125 x2	($62-$187)x2	Medicare reimbursement
AFP x 2	$23 x 2	($12-$35)x2	Medicare reimbursement
Annual Disease Management Costs[d]			
Chronic Hepatitis B	$2,002	$202-$7,816	Liu et al. 2012 [19]
Cirrhosis	$5,964	$202-$7,096	Liu et al. 2012 [19]
Decompensated cirrhosis	$15,795	$4,901-$37,081	Liu et al. 2012 [19]
Symptom detected HCC	$99,207	$77,076-$115,614	Parikh et al. 2020 [20]
Screen detected HCC non-cirrhosis	$41,360	$32,134-$48,200	Parikh et al. 2020 [20]
Screen detected HCC cirrhosis	$87,789	$68,205-$102,307	Parikh et al. 2020 [20]
Liver Transplantation 1st year	$215,162	$167,163-$250,746	Liu et al. 2012 [19]
Liver Transplantation 2nd year	$26,860	$23,958-$35,937	Liu et al. 2012 [19]
Health State Utilities			
Active CHB	0.91	(0.80–0.92)	Woo et al. (EQ-5D) [21]
Cirrhosis	0.88	(0.78–0.88)	Woo et al. (EQ-5D) [21]
Inactive CHB	1.00	(0.90–1.00	Assumption
Decompensated cirrhosis	0.73	(0.49–0.82)	Woo et al. (EQ-5D) [21]
Symptom detected HCC	0.67	(0.54–0.80)	Parikh et al. 2020 [20]
Screen detected HCC non-cirrhosis	0.81	(0.65–0.85)	Woo et al. (EQ-5D) [21]
Screen detected HCC cirrhosis	0.70	(0.66–0.84)	Parikh et al. 2020 [20]
Liver Transplantation	0.84	(0.72–0.84)	Woo et al. (EQ-5D) [21]
HBsAg seroclearance	1.00	(0.95–1.00)	Assumption
Viral suppression	1.00	(0.95–1.00)	Assumption

[a]Assuming 60% on generic TDF and 40% on generic ETV [22].

[b]This is the range for one-way sensitivity analysis, but for the probabilistic sensitivity analysis, it varies from $325 to $16,460.

[c]Annual monitoring is the total cost including 2x clinic visit, 2x ALT and 1x HBV DNA level as recommended by AASLD [23]. Annual HCC surveillance cost includes a scenario with a clinical visit and 2x US and 2x AFP, a scenario with 1x US and 2x AFP, and a scenario with 2x US and no AFP.

[d]Adjusted to 2024 USD using the Medical Consumer Price Index (CPI) calculator [24].

Abbreviations: AFP, alpha fetoprotein; ALT, alanine aminotransferase; CBC, complete blood count; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; LFT, liver function tests; OPTN, Organ Procurement and Transplantation Network.

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patients receiving monitoring and treatment increased to 90% and 80%, respectively. 3). *M&T plus HCC surveillance*, with increased monitoring and treatment of 90% and 80%, respectively, and 3 different HCC surveillance strategies to assess at what HCC incidence would the addition of HCC surveillance would be cost-effective: biannual liver ultrasound+AFP

recommended by AASLD, biannual ultrasound recommended by the European Association for the Study of the Liver (EASL) and an annual ultrasound+biannual AFP which likely reflects the reality in most clinical practice. When we evaluate these different surveillance strategies, we assume they have equivalent reductions in liver cancer-related mortality but have different costs (Table 1).

In each scenario, we assumed among patients who received monitoring and treatment, adherence was 90%, and patients who did not receive monitoring followed the natural history. In the HCC surveillance scenarios, we assumed 70% of the patients received HCC surveillance.

Costs and utilities

The costs of annual monitoring for HBeAg negative inactive CHB ($221) was based on the Medicare reimbursement costs for bi-annual clinic visits, bi-annual blood tests for ALT and an annual HBV DNA (Table 1). The costs of annual monitoring for the estimated 26% [25] of CHB patients who are HBeAg positive would include an additional HBeAg test ($11.53). The cost of HCC surveillance was based on Medicare reimbursement of $125 for a single liver ultrasound and $23 for a single AFP test. The estimated annual medical management costs of surveillance-detected HCC (assuming 60% were early stage and 40% were intermediate or late stage HCC) among non-cirrhotic patients was $40,167 and $85,256 among cirrhotic patients, as derived from Parikh et al. [20]. The estimated annual medical management costs of symptom detected HCC was $96,345. We assume patients who meet treatment eligibility will be prescribed generic tenofovir disoproxil fumarate (TDF) or generic entecavir in the United States. Although the lowest price for generic TDF at $325 per year [26], we used an annual antiviral drug cost of $387 assuming 60% of the patients will be dispensed generic TDF and 40% generic ETV ($480 per year) [22]. Other medical management costs for CHB, cirrhosis, decompensated cirrhosis, and liver cancer were obtained from Liu et al. [19]. Medical management costs were adjusted for inflation using the US consumer price index to reflect 2024 US dollars [24]. We assumed patients who achieved HBsAg loss would continue to incur annual costs for long-term CHB monitoring. We added age-specific per person background medical costs to our analysis using a recently published US catalogue [27]. All costs and QALYs were discounted at a rate of 3% per year. The analysis was performed from the health care system perspective. We used EQ5D utility assessments calculated by Woo et al. [21] based on a Canadian CHB patient sample and included age adjustments from Parikh et al. [20]. All key input variables related to costs and utilities are shown in Table 1.

Sensitivity analysis

One-way sensitivity analysis was used to determine the parameters that had the greatest impact on the results. We also reported the findings when only monitoring was increased without an increase in treatment, and an increase in treatment rate without an increase in monitoring, and adherence to monitoring and treatment from 60% to 90%. In the base case, when we define a percentage of monitoring, we mean that a certain percentage of the population is monitored regularly for the rest of their lives and the rest of the population receives no monitoring for the rest of their lives. However, in an alternative sensitivity analysis scenario, we alter this definition so that we assume that all individuals are receiving monitoring, but at irregular rates. Under this alternative scenario, the definition of the percentage of monitoring is the fraction of the population receiving monitoring in any particular year, and this may not be the same individuals necessarily monitored each year. To assess the cost-effectiveness of HCC surveillance among patients with inactive and immune tolerant CHB, annual HCC incidence from 0.1% to 1.0% was examined. Finally, we conducted a probabilistic sensitivity

Table 2. Cost-effectiveness and health outcomes of increased monitoring of adults with HBeAg-negative inactive CHB and HBeAg-positive immune tolerant CHB to 90% and increased antiviral treatment to 80% when they become treatment eligible compared to current practice for a population of 100,000 adults with inactive or immune tolerant CHB.

Scenario	Cost	QALYs	ICER	Cirrhosis	Decompensated Cirrhosis	HCC	HBV Deaths
Current Practice (CP)	$18,275,900,000	1,891,800	-	17,210	2,090	8,470	12,100
Increased M&T	$18,257,900,000	1,936,900	Cost-saving	12,620	590	6,020	7,400
Difference	-$18,000,000	+45,100	-$399	-4,590	-1,500	-2,450	-4,700

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analysis varying all parameter values across specified distributions to evaluate the impact of overall parameter uncertainty on outcomes.

Results

Increasing monitoring and treatment

Compared to current practice, where an estimated 37% of persons with inactive or immune tolerant CHB are monitored and 59% receiving antiviral therapy when they become treatment eligible, increased monitoring to 90% and treatment to 80% (*increased M&T*) would be cost-saving (Table 2). In the current practice scenario, among the cohort of adults with inactive or immune active CHB, an estimated 17.21% would develop cirrhosis, 2.09% would develop decompensated cirrhosis, 8.47% would develop HCC, and 12.10% would die from CHB-related causes. For every 100,000 persons with inactive or immune active CHB, increasing monitoring to 90% and antiviral treatment for eligible individuals to 80% would save $180 million in lifetime health care costs, add 45,100 QALYs and would avert 4,590 cases of cirrhosis, 1,500 cases of decompensated cirrhosis, 2,450 cases of HCC, and 4,700 HBV related deaths. The decomposition of the total costs is presented in S1 Fig.

HCC surveillance

Adding HCC surveillance to increased monitoring and treatment in the cohort of inactive or immune tolerant CHB patients regardless of annual HCC risk would not be cost-effective ($266,728/QALY compared with current practice). At a willingness to pay at $100,000 per QALY, the incremental cost-effectiveness ratio (ICER) for increased M&T plus the AASLD recommended HCC surveillance strategy with biannual US and AFP ($296/year) would become cost-effective at HCC incidence $\geq$ 0.55%/year (Fig 2A). The ICER for HCC surveillance strategy with an annual ultrasound and biannual AFP ($171/year), would become cost-effective at HCC incidence $\geq$ 0.30%/year (Fig 2B). The ICER for the European Association for the Study of the Liver (EASL) recommended HCC surveillance strategy (biannual US without AFP ($250/year) would become cost-effective at HCC incidence $\geq$ 0.39%/year (Fig 2C).

Sensitivity analysis

In the scenario where the definition of the percent monitoring assumes all individuals with inactive and immune tolerant CHB potentially could be monitored, but not the same individuals regularly receiving monitoring each year, increasing the monitoring to 90% is considered cost-effective at $24,951 per QALY gained, but no longer cost-saving (S3 Table in S1 File). Under this assumption, outcomes for the status quo intervention are better because all people eventually get exposed to monitoring and enter treatment when an indication for treatment has developed, albeit at a slower rate. Increasing the monitoring rate increased the likelihood that patients who developed active hepatitis or cirrhosis would receive treatment. Although

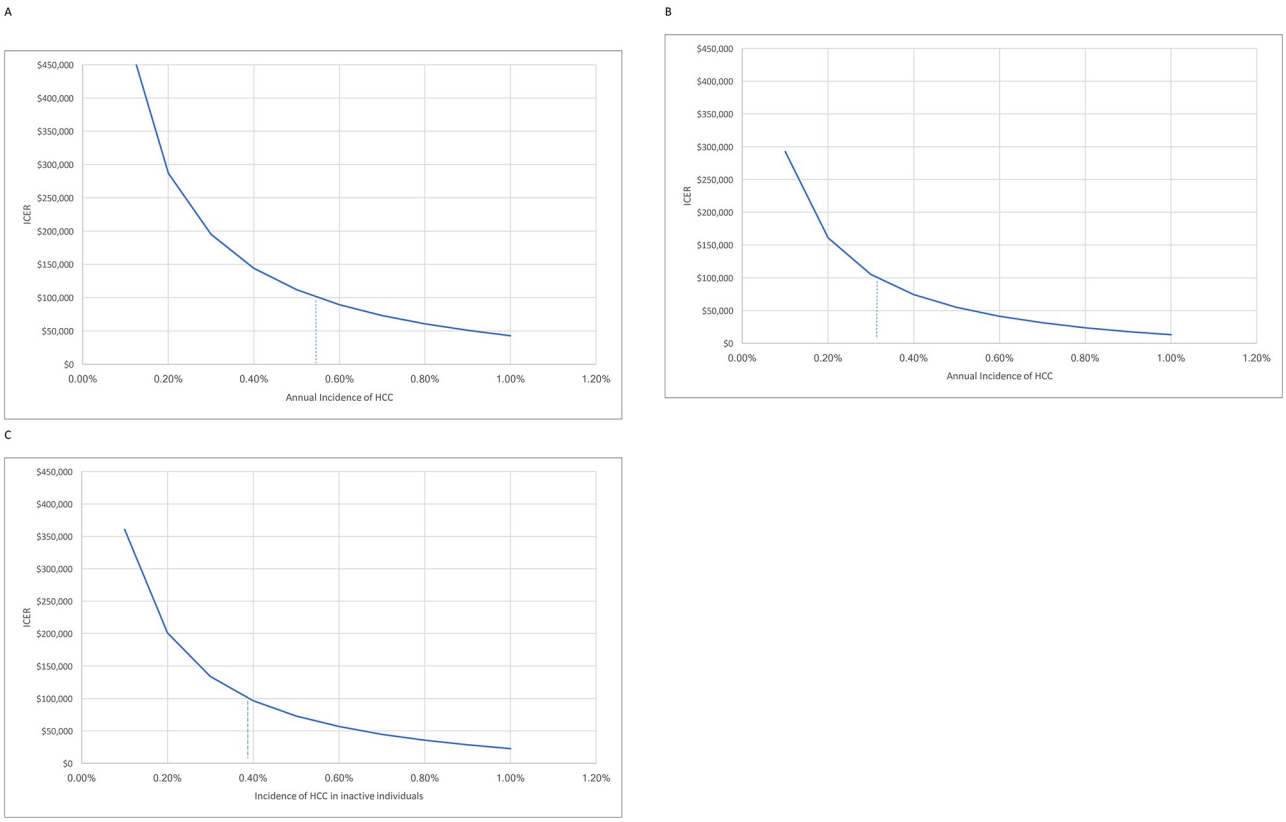

Fig 2. **A**. Cost-effectiveness based on incidence of HCC in individuals not currently on antiviral treatment with biannual liver ultrasound and AFP (AASLD guidelines). * At a willingness to pay at $100,000 per QALY, HCC surveillance with biannual liver ultrasound and AFP would be cost-effective if HCC risk is $\geq$ 0.55%/year in HBsAg-postive individuals who are not currently on antiviral treatment. **B**. Cost-Effectiveness based on incidence of HCC in individuals not currently on antiviral treatment with annual liver ultrasound and biannual AFP. * At a willingness to pay at $100,000 per QALY, HCC surveillance with annual liver ultrasound and biannual AFP would be cost-effective if HCC risk is $\geq$ 0.3%/year in HBsAg-postive individuals who are not currently on antiviral treatment. **C**. Cost-Effectiveness based on incidence of HCC in individuals not currently on antiviral treatment with biannual liver ultrasound (EASL guidelines). * At a willingness to pay at $100,000 per QALY, HCC surveillance with biannual liver ultrasound redwould be cost-effective if HCC risk is $\geq$ 0.39%/year in HBsAg-postive individuals who are not currently on antiviral treatment.

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the incremental benefits under this assumption are lower, the increased M&T strategy would still be highly cost-effective.

The probabilistic sensitivity analysis which varies all parameters simultaneously shows a > 99% likelihood that the increased M&T strategy would be cost-effective at a willingness to pay threshold of $100,000/QALY (S2 Fig). S3 Fig shows the results of one-way sensitivity analysis summarized using a tornado plot. The model was sensitive to a few parameters like discount rate on utility, HCC incidence, cost of antiviral therapy and utility of inactive CHB. Increasing monitoring has more health gains compared to increasing treatment alone (S4A and S4B Table in S1 File). For adults with HCC incidence $\geq$ 0.55%/year, increased M&T plus AASLD recommended HCC surveillance with US+AFP every 6 months yields 20,602,000 life years, which compared to the M&T scenario alone, HCC surveillance has an additional 400 life years gain for a 100,000 population (S5 Table in S1 File).

Discussion

Although adults with immune tolerant CHB or inactive CHB are not recommended by the current AASLD clinical practice guidelines to receive antiviral therapy, this study found

regular monitoring with biannual blood tests for disease activity and antiviral treatment when treatment becomes indicated would be highly cost-effective.

The cost-effectiveness of HCC surveillance among non-cirrhotic CHB patients have not been re-examined since 1999 when Collier, Krahn and Sherman, in an unpublished study, reported HCC surveillance with biannual liver ultrasound and AFP would be cost-effective (at a willingness to pay at $50,000 per life year gained) in HBV carriers over 30 years of age with an annual HCC risk of 0.2% or greater and would prolong life by 90 days. AASLD has adopted this threshold and recommends HCC surveillance with biannual ultrasound and AFP for patients with CHB with an annual HCC risk of 0.2% or greater. Accordingly, AASLD recommends HCC surveillance for CHB patients with cirrhosis, Asian male over 40 years, Asian female over 50 years (with estimated HCC incidence 3–8%/yr, 0.4–0.6%/yr, and 0.3–0.6%, respectively), as well as CHB patients with family history of HCC and African and North American Black.

The current study found at a willingness to pay at $100,000/QALY, HCC surveillance with biannual liver ultrasound and AFP in adults with CHB would not be cost-effective at a willingness to pay at $100,000/QALY unless the annual HCC risk is $\geq$ 0.55% which is 2.75 times higher than the threshold which was reported by Collier and adopted by AASLD. HCC surveillance with biannual ultrasound alone that is recommended by EASL would become cost-effective for patients with annual HCC incidence $\geq$ 0.40%.

Although EASL recommend only biannual liver ultrasound without AFP for HCC surveillance, a meta-analysis showed the addition of AFP measurements can increase the sensitivity of detecting early stage HCC to 63% compared with 45% with ultrasound alone [28]. Recent studies also found a rising AFP level on serial measurements improved the sensitivity of AFP to detect HCC to 77.1% - 87.5% in patients with cirrhosis or advanced fibrosis [29]. In clinical practice, many providers found compliance among adults with CHB to obtain more than one ultrasound a year is poor. There is no evidence that there is a survival difference between HCC diagnosed with annual or biannual liver ultrasound [30, 31]. In this study, we found an alternate HCC surveillance strategy with an annual liver ultrasound and biannual AFP would be cost-effective for CHB patients with an annual HCC risk as low as 0.3%.

In a meta-analysis of 59 studies reported between 2014 and 2019, biannual HCC surveillance in patients with liver cirrhosis is generally associated with improved detection at an earlier stage, increased chance for potentially curative treatment and prolonged survival [32]. Whether HCC surveillance leads to an overall decrease in patient mortality remains an ongoing debate because of the lack of clinical trial studies. Although the risk of HCC is greatest in patients with cirrhosis, patients with CHB without cirrhosis can also develop HCC especially if there is a family history of a first degree relative with HCC.

Our study could be used as additional evidence to inform updated guidelines. With that said, our estimates of the precise threshold for initiating HCC surveillance among adults with inactive and immune tolerant CHB are uncertain and dependent upon assumptions about the benefits of early HCC treatment. To the extent that surveillance may lead to early, inexpensive treatment and reduce the need for increasing use of expensive immunotherapies to treat late stage HCC, surveillance may become more cost-effective.

Our study has a few limitations. We have obtained the 37% of CHB patients receiving at least an annual ALT and HBV DNA and 59% percent receiving treatment if eligible from the The Chronic Hepatitis Cohort Study (CHeCS) study by Spradling et al. [16]. This study might not be generalizable for the CHB population in the United States, since the CHeCS study attempts to link to care in their system all those found to have CHB. Also, each of the large health research centers and hospitals that participated in the CHeCS study have liver specialists that are experts at managing CHB. Other studies based on insurance claims data reported 36%

-50% of CHB patients without cirrhosis received at least an annual ALT and HBV DNA or HBeAg [22, 33]. Wong et al found only 37.3% of treatment eligible CHB patients in four large safety-net health systems received antiviral treatment [34]. We also made assumptions related to the proportions of patients in the late and early stages of liver disease for HCC. Another limitation of our study was the general lack of data, especially in monitoring and HCC surveillance among adults with inactive or immune tolerant CHB. We tried to address this limitation by running sensitivity analyses.

The current study found regular monitoring of the thousands of adults diagnosed with inactive or immune tolerant CHB in the United States who are initially not recommended for treatment and subsequently receive antiviral therapy when indicated is cost-saving. The addition of HCC surveillance with the standard recommendation for biannual ultrasound and AFP would be cost-effective if the HCC risk is $\geq$ 0.55% per year such as patients with cirrhosis who have an estimated HCC incidence of over 3%/yr. A possible alternate lower cost HCC surveillance strategy consisting of only an annual ultrasound and biannual AFP would be cost-effective and could be considered for patients who have a lower HCC risk ($\geq$ 0.3%/yr) including Asian men over 40 years and Asian women over 50 years.

Supporting information

S1 File.
(DOCX)

S1 Fig. Decomposition of total costs. * "All other costs" are age-specific background medical costs (non-HBV-related, such as for heart disease).
(JPG)

S2 Fig. Cost-effectiveness acceptability curve. This figure shows the probability that each strategy might be cost-effective (Y-axis) at particular values of willingness-to-pay for QALYs (X-axis). Because the CP plus M&T strategy is highly likely to lead to both savings in costs and improvement in QALYs, it is highly likely that CP plus M&T is cost-effective, regardless of the willingness to pay for QALYs.
(JPG)

S3 Fig. Tornado diagram.
(JPG)

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