Supplementary materials for

Cost-effectiveness of screening and treatment or vaccination of hepatitis B in six high-risk populations in the US

November 12, 2018

Technical Supplement – Detailed Methods and Additional Results

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I. Modelling

1. Model assumptions

Modelling natural history: Key assumptions

1. Patients entered the model in one of two ways:
    a. To reflect the current population distribution of chronic hepatitis B at diagnosis, patients *started* the simulation in one of seven CHB health states:
        i. Immune tolerant (after perinatal transmission)
            1. Perinatal infection and immune tolerant state were built into the model for completeness of the natural history and to allow for full calibration of the model. This study does not analyze perinatal infection.
        ii. Inactive HBeAg *negative.* This group can be:
            1. Non-cirrhotic
            2. Cirrhotic
        iii. Active HBeAg *positive* chronic hepatitis B. This group can be:
            1. Non-cirrhotic
            2. Cirrhotic
        iv. Active HBeAg *negative* chronic hepatitis B. This group can be:
            1. Non-cirrhotic
            2. Cirrhotic
    b. New infections (perinatal and horizontal adult exposures) could *enter* via the initial exposure and acute hepatitis B state, and may progress to the states above. Detail below.
2. Adult patients who acquired hepatitis B while in the model through transmission entered the acute hepatitis B state and transitioned into either chronic hepatitis B, immune active phase (HBeAg+), or achieve hepatitis B surface antigen (HBsAg) clearance. Asymptomatic and symptomatic acute hepatitis, fulminant hepatitis (amongst symptomatic patients), and death and liver transplant from fulminant hepatitis was modeled in this state.
3. Perinatal transmissions of hepatitis B did not enter the acute hepatitis state; these patients entered the immune tolerant or surface antigen clearance state.
4. Horizontal transmission for children under 5 was not be modeled.
5. Immune tolerant patients experienced annual progression to immune active phase of chronic hepatitis B into the non-cirrhotic, HBeAg *positive* and HBsAg positive state.
6. Progression from immune tolerant phase to active phase was age-specific so that all patients enter active hepatitis B before 40 years of age. This was based on epidemiological findings that majority of patients will transition into active hepatitis B between the ages of 20 and 40, based on genotype of hepatitis B virus.[1,2]
7. Patients in HBeAg *positive* status with active disease, both non-cirrhotic and cirrhotic, were able to transition to active corresponding HBeAg *negative* states.
8. HBeAg+ can jump to inactive state without going through the HBeAg- active state.
9. Inactive states were HBeAg- (with suppressed HBV DNA (<2000 IU/ml) and normal liver enzymes) and Anti-HBe.
10. Patients in active HBeAg *positive* and HBeAg *negative* states (both non-cirrhotic and cirrhotic), can transition into HBeAg *negative,* anti-HBe (inactive stat in which antibodies to HBeAg have developed) state.
11. Patients who seroconvert to anti-HBe and are in the *inactive* state were able to experience reactivation of HBeAg *negative* and HBeAg *positive* active hepatitis.

12. Cirrhosis regression in natural history was not be modeled for patients who achieved anti-HBs.
13. Cirrhosis regression in natural history was not be modeled for HBeAg+ and HBeAg- who entered inactive states.
14. Non-cirrhotic patients who achieved HBsAg clearance/anti-HBs status were allowed to progress to cirrhosis, in sensitivity analyses.
15. Inactive chronic hepatitis B state in this model were marked by anti-HBe positive with normal ALT and low DNA levels.
16. Chronic hepatitis B patients who achieve inactive state were eligible for HBsAg seroconversion to anti-HBs (used interchangeably with HBsAg seroclearance and "resolved").
17. Patients who seroconverted to anti-HBs (i.e. enter the resolved state) did not experience reactivation of chronic hepatitis B (not modeled).
18. Reoccurrence of hepatitis B in patients who underwent liver transplantation was not be modeled.
19. Patients were able to transmit the virus, on an annual basis, to a susceptible individual, adjusted for a given population, in any state except after seroconversion of HBsAg to anti-HBs (or resolved) state.
20. For perinatal infections, risk for infection and establishment of chronic hepatitis B were stratified according to mother's HBeAg status as *negative* or *positive*.
21. Patients could develop hepatocellular carcinoma from any state except initial exposure/acute hepatitis states, resolved, and post-liver transplant.
22. The model did not distinguish between patient sex or hepatitis B virus genotype, although these factors can influence clinical outcomes.
23. Patients experienced age-specific background mortality based on US life tables.
24. Hepatitis B related excess mortality was modeled in active and inactive hepatitis B states, non-cirrhotic and cirrhotic.
25. Hepatitis B related mortality for advanced states (fulminant failure, liver failure, liver carcinoma, liver transplantation and post-liver transplant) was also be modeled. Background mortality in these states will not be portrayed.

<u>Modelling treatment: Key assumptions</u>

26. The model included treatment naïve and lamivudine-experienced patients.
27. Treatment was only initiated in active CHB (HBeAg- or HBeAg+). Treatment was not be modeled in immune tolerant phase, decompensated cirrhosis or liver cancer.
28. Lamivudine experienced or resistance patients, if retreated, were eligible only for tenofovir therapy, due to evidence of developing high levels of resistance with entecavir therapy.[3]
29. Entecavir experienced or resistance patients, if retreated, were eligible for only tenofovir switch.
30. Patients who experienced tenofovir resistance will go into natural history of CHB and were not allowed retreatment.
31. Treatment of CHB occurred in the immune active phases, depending on the status of DNA, ALT, and histological disease. It increased the transition from active phases to the inactive phase, and indirectly to resolved disease.
32. Treatment, depending on drug and duration, increased transition of HBeAg *positive* / HBsAg positive, both non-cirrhotic and cirrhotic, to HBeAg *negative* / HBsAg positive. Transition probabilities for HBeAg seroconversion with treatment were varied over time (higher in the first year).
33. Transition probabilities for drug resistance were varied over the first five years for each treated patient, remaining constant in subsequent years.

34. Transition probabilities for viral suppression (lower DNA) were varied over time. In the Markov this is represented as transition to HBeAg negative state and inactive disease.
35. Transition probabilities for HBsAg seroconversion were varied over time, dependent on treatment.
36. For all HBeAg- and cirrhotic HBeAg+ patients, treatment was modeled to continue until HBsAg loss.
37. For non-cirrhotic HBeAg+, treatment was continued for 12 months after achieving inactive disease (i.e. seroconversion to anti-HBe), regardless of HBsAg status. Once in the inactive state, patients followed the natural history. And those who experienced reactivation of CHB to HBeAg+ or HBeAg- states, if retreated, were eligible for tenofovir therapy.
38. Patients who discontinued treatment (either tenofovir or entecavir) entered natural history. These patients, if retreated, were eligible for tenofovir treatment only.
39. Cirrhosis regression in treatment was modeled for patients who achieved anti-HBs.
40. Cirrhosis regression in treatment was modeled for HBeAg+ and HBeAg- who entered inactive states.

Modelling prevention: Key assumptions

41. For susceptible high-risk adults, prevention with hepatitis B vaccine was modeled, taking into consideration the probability of completing one, two or all three doses of the series.
42. Data for completing vaccine series was derived from population specific literature when possible. Assumptions, based on other high-risk populations, was used when population-specific data were unavailable.

Modelling screening and linkage to care: Key assumptions

43. High risk, high prevalence populations were modeled for targeted screening and linkage to care.
44. 'Care' in the model will consist of treatment (for those with active CHB) or vaccination for susceptible adults.
45. Three screening and linkage options were modeled: 1) screen and treat; 2) screen and vaccinate; and 3) screen and treat or vaccinate.
46. For each screening and linkage option, population and program specific inputs were used. When population specific program inputs for screening and linkage were not available, data from other hepatitis B programs or other disease (such as hepatitis C) screen and linkage programs was used.
47. The model took into account the probability of false negatives and false positives with screening tests and allocated costs and patient disposition accordingly.

Transmission: Key assumptions

48. Within population transmission based on annual incidence rates of acute hepatitis B in high-risk populations were modeled for susceptible adult patients.
49. Populations did not interact with each other in this model.

2. Markov structure

Markov tree and stages: Figure 4 below is a detailed portrayal of the Markov disease state structure. It shows the natural history of acute HBV infection and chronic hepatitis B Markov with transitions from source to target states. It uses mainly *annual* transition probabilities between health states.

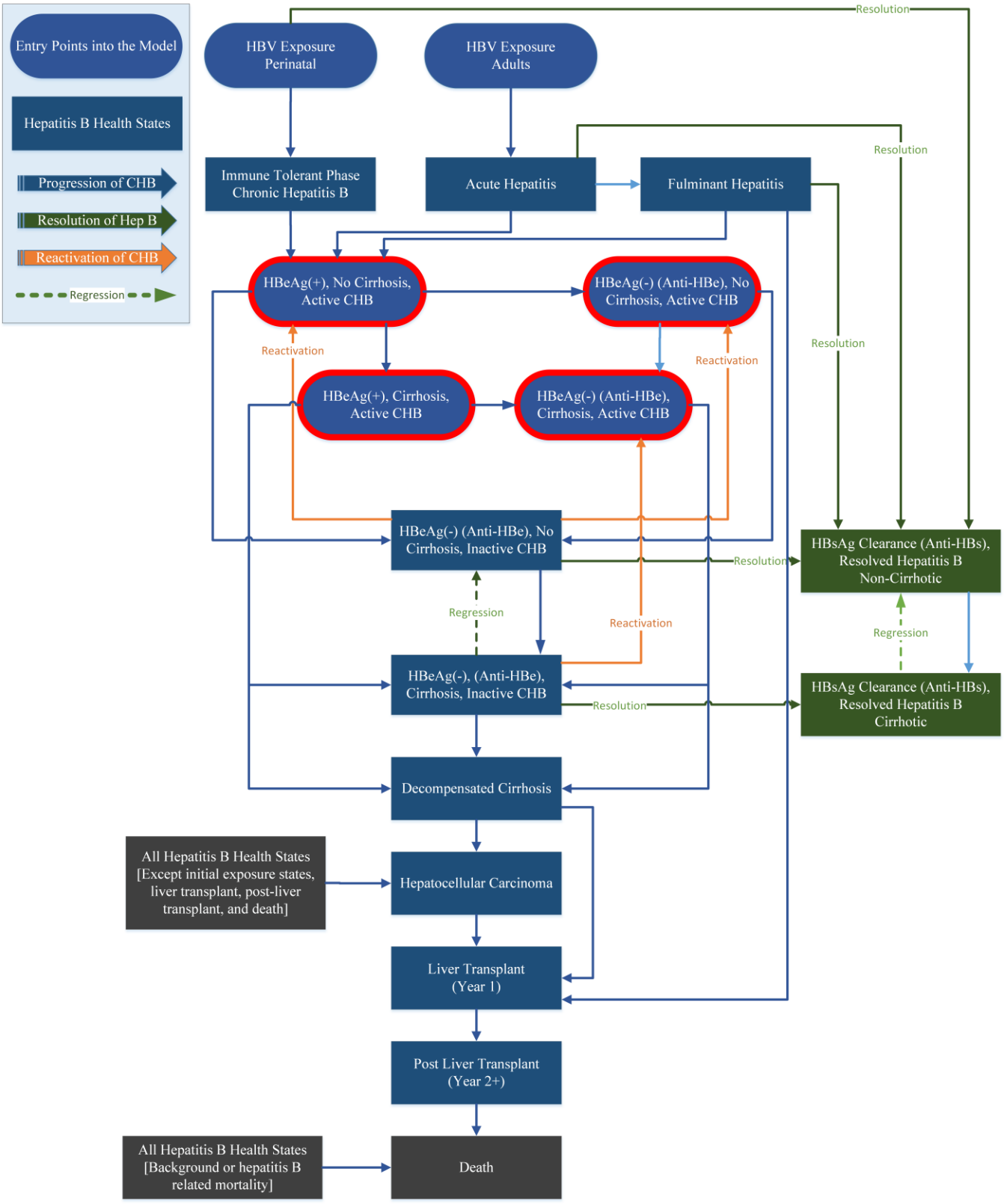

Figure S1: Markov state diagram of natural history of acute and chronic hepatitis B

Supplement Figure 1 description: *The figure depicts the natural history of hepatitis B virus infection from initial exposure and infection (acute HBV) to development of chronic hepatitis B (CHB) health states (blue boxes). The*

diagram flows from top (initial exposure, initial health states) to bottom (advanced liver diseases and death). The blue arrows show progression from a health state of lower severity to higher severity. Solid green arrows depict resolution of HBV infection, defined as hepatitis B surface antigen clearance and/or development of antibody to the surface antigen (green boxes). Dashed green arrows show the potential for regression of liver cirrhosis to a non-cirrhotic state from inactive hepatitis B or resolved states. Orange arrows show reactivation of hepatitis B from inactive (HBeAg- and anti-HBe) states to either HBeAg- or HBeAg+ active hepatitis B. The ovals with red outline indicate health states in which treatment can initiate for patients with chronic hepatitis B.

3. Model structure – simplified graphics

To illustrate how the hepatitis B model was operationalized, in addition to **Figure 1** in the main paper, simplified figures of the model's tree structure are produced below for reference.

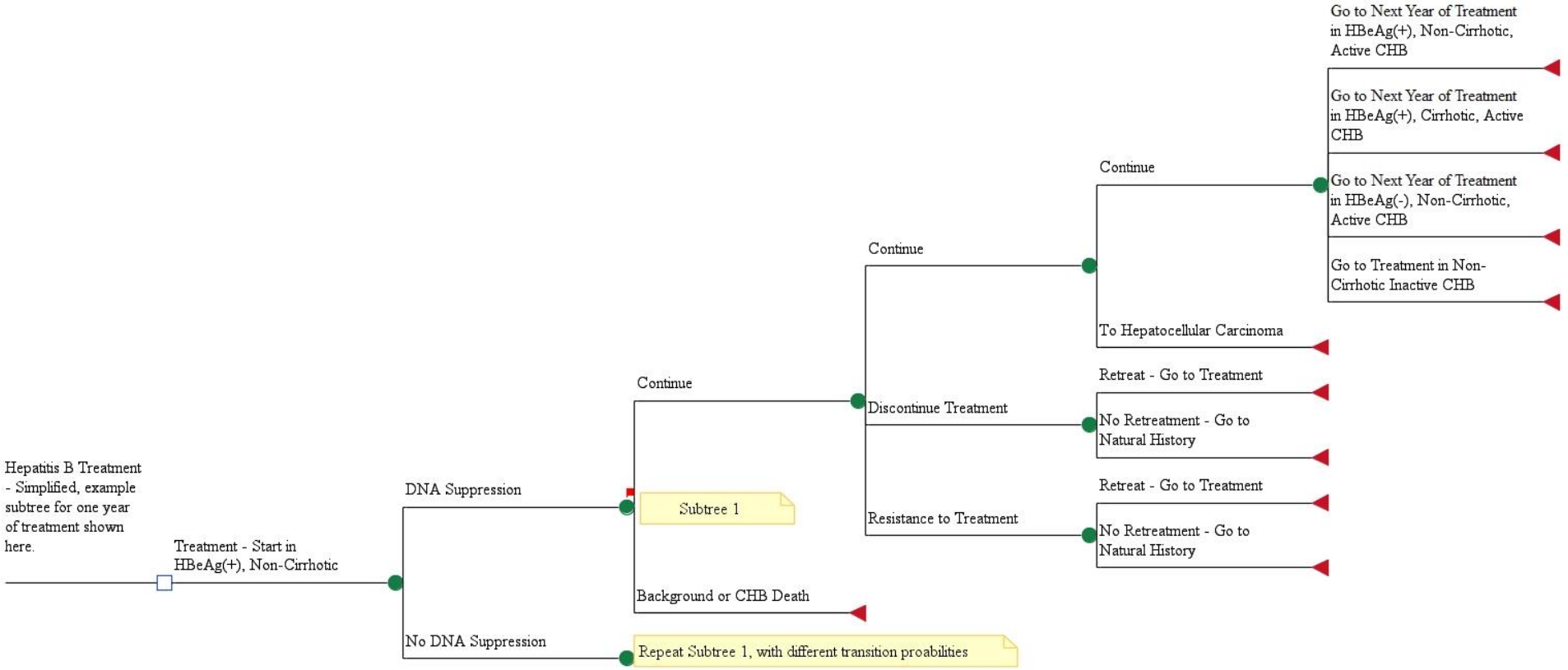

Figure S2: Simplified treatment model tree structure

Caption: The figure shows how the patients progress through the treatment model by using a simplified visualization of year 1 of treatment. Patients progress through the model to either achieve DNA suppression or not, depending on treatment selected and year of treatment, followed by CHB related and background death, discontinuation, development of resistance, and hepatocellular carcinoma. Patients then transition into HBeAg- state, inactive CHB state, cirrhosis or next year of treatment in the same state. In the model, the probabilities for many of the outcomes differ depending which year treatment the patients are in and whether or not DNA suppression has been successful.

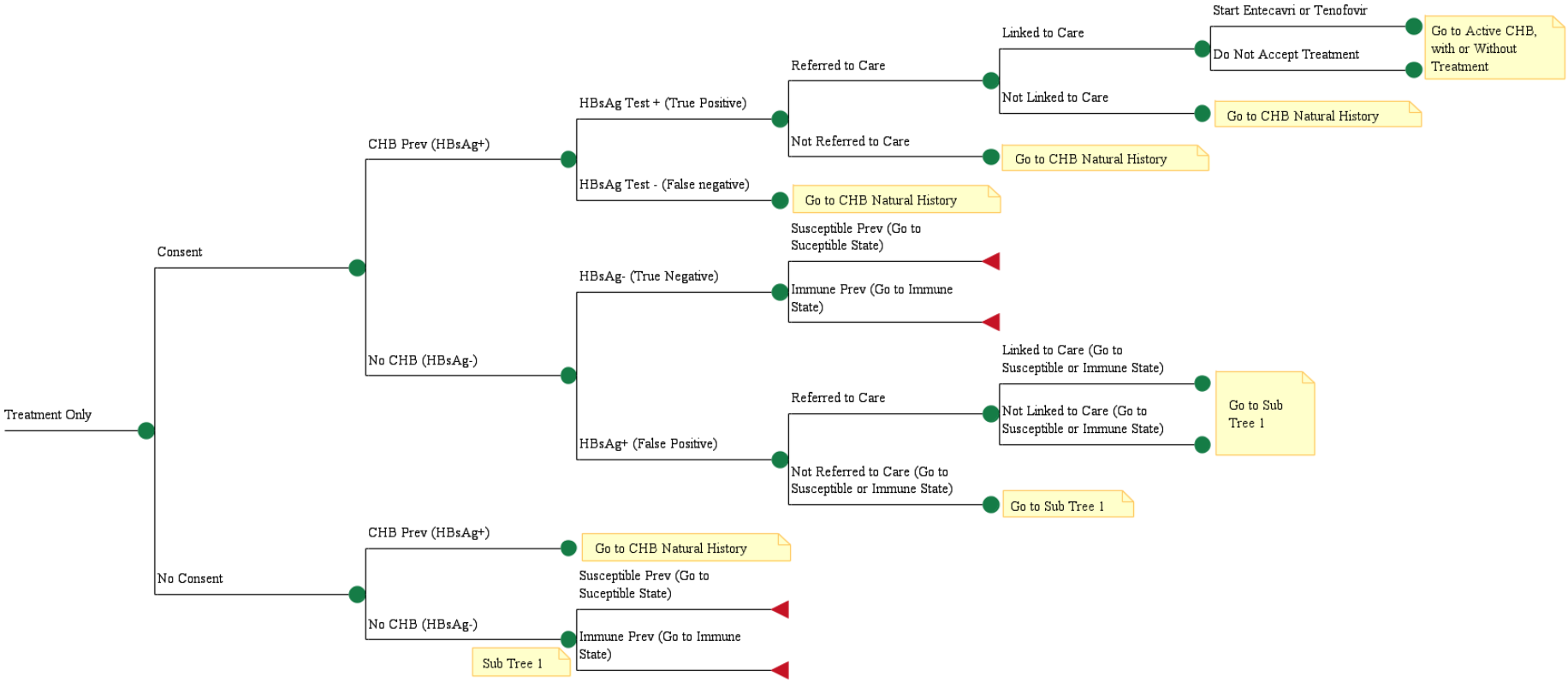

Figure S3: Simplified screen and treat (treatment only) model tree structure

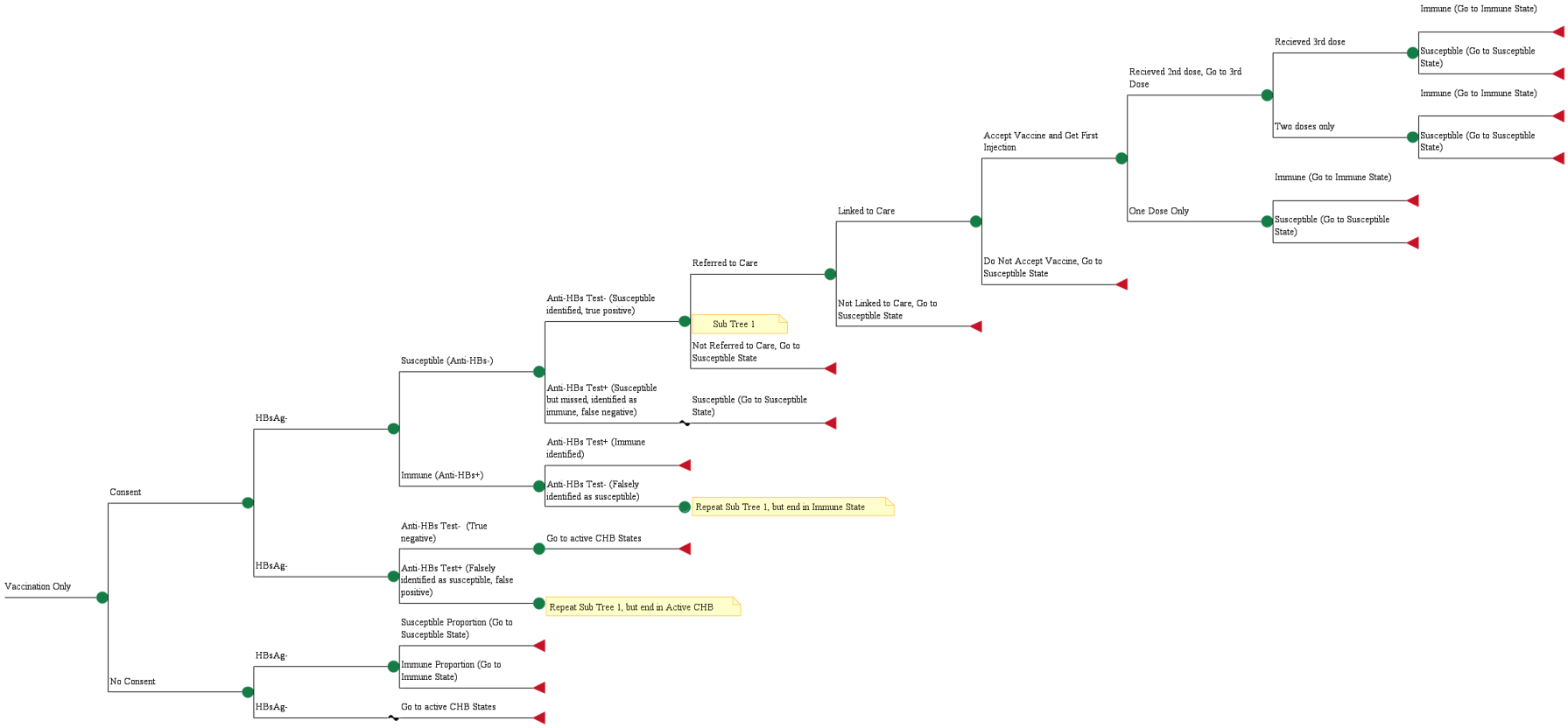

Figure S4: Simplified screen and vaccinate (vaccination only) model tree structure

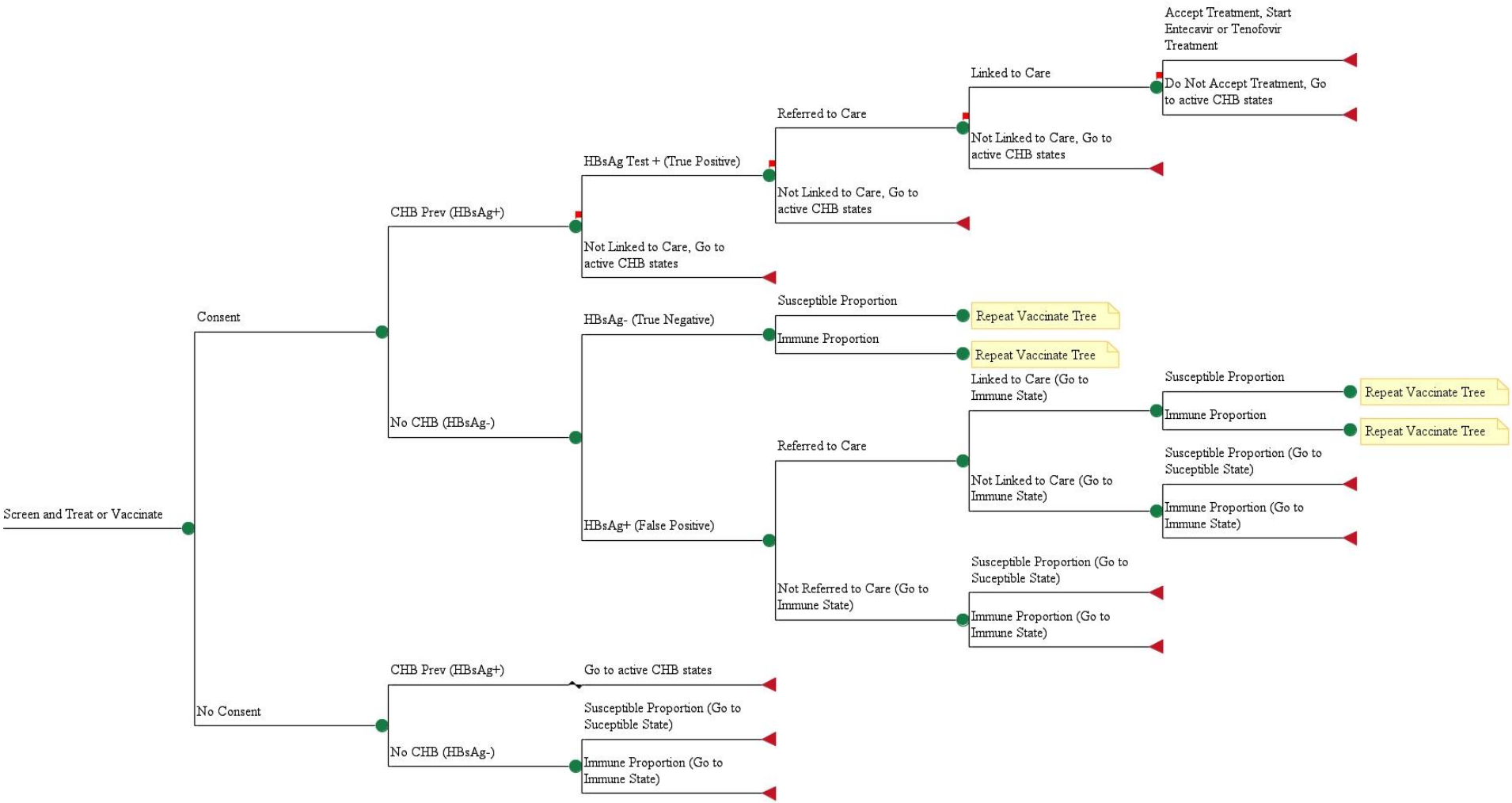

Figure S5: Simplified screen and treat or vaccinate (inclusive) model tree structure

II. Model Inputs

Below, input values for the model are listed by category. Multiple sources were used to collect data on input parameters. We conducted literature reviews of published primary and economic analyses of hepatitis B. The annual probabilities, patient distribution proportions, costs, utilities, and effectiveness of drugs and prevention methods are extracted from literature, including previously published cost-effectiveness studies. When annual transition probabilities for natural history were unavailable or refinement of estimates was indicated, data were extracted from primary studies and annual probabilities calculated. Expert estimates will be used for input parameters when necessary.

For calculation of annual probabilities from results over longer time periods, we followed established methods[4] as provided by the following equations:

Equation 1: $r = -\frac{1}{t}\ln(1-p)$

Equation 2: $p = 1 - e^{-rt}$

where r = rate or risk; t = time; and p = cumulative proportion or probability

1. Distribution of patients entering the model

A. Distribution of patients in immune tolerant, inactive and active (HBeAg positive and negative) states was determined from primary literature.[5] There are, however, limited data to inform status of cirrhosis in immune active and inactive phases. Thus, based on a previous economic analysis, it was assumed that, in the initial entry cohort, 5% of patients in each of the immune active phases (HBeAg- and HBeAg+) and the inactive phase are cirrhotic.[6] The number of patients in any given state were dynamically adjusted over time based on the transition probabilities listed in the next section.

Table S1: Distribution of patients entering the model, by health state

Markov entry state	Base-case (%)	Lower Limit (%)	Upper Limit (%)	Ref
Immune Tolerant Phase	5.74	4.31	7.18	5
Immune Active Phase (HBeAg+)				
HBeAg+, Non-Cirrhotic	21.02	15.77	26.28	5
HBeAg+, Cirrhotic*	1.11	0.83	1.38	5
Immune Active Phase (HBeAg-)^				
HBeAg-, Non-Cirrhotic	31.12	23.34	38.90	5
HBeAg-, Cirrhotic*	1.64	1.23	2.05	5
Immune Inactive Phase^				
HBeAg-, Inactive CHB, Non-Cirrhotic	37.40	28.05	46.75	5
HBeAg-, Inactive CHB, Cirrhotic*	1.97	1.48	2.46	5

*Prevalence of cirrhosis was assumed to be 5% amongst each of the three phases; distribution of cirrhotic patients calculated by authors based on the absolute numbers provided in the study.
^Distribution of patients in the immune active HBeAg- and in the HBeAg- inactive phase were calculated by the authors from the study data. Immune active HBeAg- patients were defined as those with detectable DNA and elevated ALT (> 1 x Upper Normal Limit), as reported in the study.
HBeAg+/-: Hepatitis B e-antigen positive or negative; CHB: Chronic Hepatitis B; Ref: Reference

2. Transition probabilities for acute and chronic hepatitis B Markov health states: natural history and with treatment

A. Natural history

Probabilities for initial exposure and acute hepatitis in perinatal and adult horizontal infection were collected from literature and previously published economic analyses.[6-16] We also collected and meta-analyzed primary data when there was wide variability in published estimates or refinement was needed, for example on the probability of mother to infant transmission by HBeAg status.[17-31] Similarly, mortality from fulminant hepatitis B was aggregated from primary literature.[32-37] Wide variability in point estimates on annual probability of HBsAg clearance was observed[6,9,11,12,38] so we calculated annual probability of clearing HBsAg by combining primary literature.[38-52] There was a dearth of data in published economic evaluations on development of hepatocellular carcinoma following HBsAg clearance, thus we calculated annual probabilities from primary studies.[45,49-53] Similar steps were taken to collect and refine data for development of cirrhosis[54,55] and hepatocellular carcinoma[55] based on cirrhosis status in inactive phase of chronic hepatitis B.

B. Development of HCC in Africa Born populations

Evidence suggests that for sub-Saharan Africa born Black population, there is a higher incidence of hepatocellular carcinoma at a younger age.[56-61] Although there is substantial heterogeneity in the data, for this study, we assumed that the annual incidence of HCC in this population to be 1.5 times higher (with a range of 1 to 2.5) than baseline rates used in the model for other populations. This increase in annual probability of HCC is applied to all hepatitis B health states from which HCC can develop.

C. Development of chronic hepatitis B in people who inject drugs

Evidence also suggests that PWIDs may have twice the risk of developing chronic hepatitis from exposure than the general population.[62] In this model, we simulated the transition from acute to chronic hepatitis for PWIDs to be 10% (varied from 5 to 15%), compared the 5% for other populations.

Literature generally did not distinguish probabilities between active HBeAg negative vs positive hepatitis B, so we assumed the probabilities to be equivalent. When confidence intervals were unavailable for input parameters we used +/- 25% of the base case estimate to portray uncertainty.

311 *Table S2: Annual Transition Probabilities - Natural History of Acute and Chronic Hepatitis B (without treatment)*

Source State	Target State	Base Case (%)	Lower Limit (%)	Upper Limit (%)	Reference
HBV exposure, perinatal					
HBV Exposure, Perinatal, HBeAg+ mother	Neonatal Infection	87.0	73.3	97.0	17-23,25-31
HBV Exposure, Perinatal, HBeAg- mother	Neonatal Infection	14.0	6.0	24.0	17-21,23,24,27,28,30
Neonatal Infection	Immune Tolerant Phase	90.0	85.0	95.0	63
Immune Tolerant Phase	HBeAg+, Active CHB, No Cirrhosis	Age-Dependent[1]			Calculated
HBV exposure, adult					
HBV Exposure, Adult	Acute Hepatitis, Adult	100.0	95.0	100.0	Assumption
Acute Hepatitis, Adult	Acute Hepatitis, Adult, Symptomatic	30.0	20.0	40.0	16
Acute Hepatitis, Adult	Acute Hepatitis, Adult, Asymptomatic	1 – Symptomatic Hepatitis			16
Acute Hepatitis, Adult, Symptomatic	Fulminant Hepatitis[2]	4.0	3.0	5.0	8,16
Fulminant Hepatitis	HBeAg+, Active CHB, No Cirrhosis	7.1	5.3	8.9	9,11
Fulminant Hepatitis	HBsAg Clearance (Resolved)	1 – HBeAg+, Active CHB			Calculated
Fulminant Hepatitis	Liver Transplant	1.70	1.69	4.50	64
Fulminant Hepatitis	Death, Hepatitis B related	67.0	50.3	83.8	32-36
Acute Hepatitis, Adult, Asymptomatic[3]	HBeAg+, Active CHB, No Cirrhosis	5.0	1.0	10.0	15,65,66
Acute Hepatitis, Adult, Asymptomatic	HBsAg Clearance (Resolved)	1 – HBeAg+, Active CHB			15
Acute Hepatitis, Adult, Symptomatic[3]	HBeAg+, Active CHB, No Cirrhosis	5.0	1.0	10.0	15,65,66
Acute Hepatitis, Adult, Symptomatic	HBsAg Clearance (Resolved)	1 – HBeAg+, Active CHB			15
CHB, HBeAg+					
HBeAg+, Active CHB, Non-Cirrhotic	HBeAg+, Active CHB, Cirrhotic	2.4	0.7	3.8	12,15
HBeAg+, Active CHB, Non-Cirrhotic	HBeAg-, Active CHB, Non-Cirrhotic	1.9	1.0	3.8	12
HBeAg+, Active CHB, Cirrhotic	HBeAg-, Active CHB, Cirrhotic	1.9	1.0	3.8	12
HBeAg+, Active CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	9.5	7.1	11.9	16
HBeAg+, Active CHB, Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic	9.5	7.1	11.9	16
CHB, HBeAg-					
HBeAg-, Active CHB, Non-Cirrhotic	HBeAg-, Active CHB, Cirrhotic	4.6	0.5	15.0	12,15
HBeAg-, Active CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	1.6	0.0	11.0	12
HBeAg-, Active CHB, Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic	1.6	0.0	11.0	12
HBeAg-, Inactive CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic	0.6	0.4	0.7	54,55
Reactivation of CHB					
HBeAg-, Inactive CHB, Non-Cirrhotic	HBeAg+, Active CHB, Non-Cirrhotic	0.200	0.185	0.300	67
HBeAg-, Inactive CHB, Non-Cirrhotic	HBeAg-, Active CHB, Non-Cirrhotic	1.6	1.2	2.0	67
HBeAg-, Inactive CHB, Cirrhotic	HBeAg-, Active CHB, Cirrhotic	0.7	0.5	0.9	67
Progression to DC					
HBeAg+, Active CHB, Cirrhotic	Decompensated Cirrhosis	5.0	2.3	9.5	6,15
HBeAg-, Active CHB, Cirrhotic	Decompensated Cirrhosis	5.0	2.3	9.5	51,53
HBeAg-, Inactive CHB, Cirrhotic	Decompensated Cirrhosis	0.0	0.0	0.1	Assumption
Progression to HCC[4]					
Immune Tolerant Phase	Hepatocellular Carcinoma	0.060	0.045	0.075	68
HBeAg+, non-cirrhotic, Active CHB	Hepatocellular Carcinoma	0.5	0.2	0.7	6,8,16
HBeAg+, Active CHB, Cirrhotic	Hepatocellular Carcinoma	2.4	0.2	8.1	6,8,16
HBeAg-, Active CHB, Non-Cirrhotic	Hepatocellular Carcinoma	0.5	0.2	0.7	6,8,16
HBeAg-, Active CHB, Cirrhotic	Hepatocellular Carcinoma	2.4	0.2	8.1	6,8,16
HBeAg-, Inactive CHB, Non-Cirrhotic	Hepatocellular Carcinoma	0.100	0.075	0.125	55
HBeAg-, Inactive CHB, Cirrhotic	Hepatocellular Carcinoma	1.1	0.9	1.4	55
Decompensated Cirrhosis	Hepatocellular Carcinoma	6.3	3.0	7.0	15
Anti-HBs	Hepatocellular Carcinoma	0.7	0.5	0.9	45,49-53
Progression to Liver Transplant					
Decompensated Cirrhosis	Liver Transplant	1.70	1.69	4.50	64
Hepatocellular Carcinoma	Liver Transplant	1.70	1.69	4.50	64
CHB related mortality					
Immune Tolerant Phase	Death	0.7	0.0	0.9	9,14

HBeAg+, non-cirrhotic, Active CHB	Death	1.0	0.3	2.8	[15]
HBeAg+, Active CHB, Cirrhotic	Death	3.0	1.3	4.8	[15]
HBeAg-, Active CHB, Non-Cirrhotic	Death	1.0	0.3	2.8	[15]
HBeAg-, Active CHB, Cirrhotic	Death	3.0	1.3	4.8	[15]
HBeAg-, Inactive CHB, Non-Cirrhotic	Death	0.7	0.4	0.9	[15]
HBeAg-, Inactive CHB, Cirrhotic	Death	0.7	0.4	0.9	Assumption
Decompensated Cirrhosis	Death	12.9	10.3	15.5	[69]
Hepatocellular Carcinoma	Death	42.7	34.2	51.2	[69]
Anti-HBs	Death	0.0	0.0	0.9	[6]
Liver transplant related mortality					
Liver Transplant	Death	10.7	9.0	13.0	[69]
Post Liver Transplant	Death	4.9	3.9	5.9	[69]
Clearance of HBsAg					
HBeAg-, Inactive CHB, Non-Cirrhotic	Anti-HBs, Non-Cirrhotic	0.8	0.6	0.9	[38-52]
HBeAg-, Inactive CHB, Cirrhotic	Anti-HBs, Cirrhotic	0.8	0.6	0.9	[38-52]
Regression of Cirrhosis					
HBeAg-, Inactive CHB, Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	0.0	0.0	0.5	Assumption
Anti-HBs, Cirrhotic	Anti-HBs, Non-Cirrhotic	0.0	0.0	0.5	Assumption
Progression of cirrhosis post-HBs Clearance					
Anti-HBs, Non-Cirrhotic	Anti-HBs, Cirrhotic	0.0	0.0	0.5	Assumption

1: Model calibrated to match natural history data. See Section III of Supplement for details.
2: Development of fulminant hepatitis applied only to patients who develop symptomatic acute hepatitis (i.e. 4% risk of fulminant hepatitis among 30% who develop acute hepatitis in base-case)
3: Double for PWID
4: 1.5x baseline for Africa born Blacks
HBeAg+/-: Hepatitis B e-antigen positive or negative; HBV: Hepatitis B Virus; CHB: Chronic Hepatitis B; HBs – Hepatitis B Surface Antigen ; Anti-HBs – Antibody to Hepatitis B Surface Antigen;

3. Screening and linkage to care inputs

The following section details the strategies for screening and linking to care (treatment or vaccination) by various populations of interest to this model. The data for prevalence of active hepatitis B and susceptibility are also shown for each population.

A. Prevalence of chronic hepatitis B, by subgroup

The table below shows the data for prevalence of chronic hepatitis B (HBsAg+) in adults (age 18 and over) within selected populations.

Table S3: Populations with high prevalence of chronic hepatitis B

Populations with high prevalence of chronic hepatitis B	**Group level prevalence of chronic hepatitis B**			**Ref**
	Base Case (%)	**Lower Limit (%)**	**Upper Limit (%)**	
Foreign born Asian and Pacific Islanders	7.9	5.9^	9.9^	[70]
Incarcerated persons	1.4	0.3	3.1	[71]
People who inject drugs	11.8	3.5	20	[72]
Men who have sex with men	2.3	1.7	2.9	[73]
Africa born	9.7	7.3^	12^	[74]
Refugees	6.3*	4.7^	7.9^	[75]

^Author selected to be +/- 25% of base-case value.
*Calculated from study data based on refugees screened between 2011 and 2014
Ref: Reference

B. Proportion of persons susceptible to hepatitis B, by subgroup

The table below shows the proportion of adult (age 18 and over) populations that are expected to be susceptible to hepatitis B virus. This is excluding individuals who are positive for HBsAg (i.e. CHB) and have natural or vaccine induced immunity.

Table S4: Proportion of persons susceptible to hepatitis B, by subgroup

	Group level susceptibility to hepatitis B virus			
Populations at high risk of hepatitis B	**Base Case (%)***	**Lower Limit (%)^**	**Upper Limit (%)^**	**Ref**
Foreign born Asian and Pacific Islanders	41	31	51	[76]
Incarcerated persons	53	40	66	[77,78]
People who inject drugs	44	33	55	[79]
Men who have sex with men	62	47	78	[73]
Africa born	48	36	61	[76]
Refugees	55	41	69	[80]

*Calculated from study data. All values rounded to the nearest whole number.
^Author selected to be +/- 25% of base-case value. All values rounded to the nearest whole number.
Ref: Reference

C. Screening tests for hepatitis B

Numerous types of hepatitis B surface antigen and surface antibody tests are available, most are highly specific and sensitive.[81,82] For the purposes of screening patients in this model, HBsAg and anti-HBs assay tests will be modeled using the specificity and sensitivity as described in the table below. HBsAg test is used to detect acute and chronic hepatitis B infection. Anti-HBs is used to detect presence of immunity, either due to resolved past infection or vaccine-induced immunity.

Table S5: Specificity and Sensitivity of hepatitis B screening tests

Test	**Specificity**	**Sensitivity**	**Lower Limit^**	**Upper Limit^**	**Ref.**
Hepatitis B Surface Antigen (HBsAg)*	99.97%	99.80%	0.95	1	[83]
Hepatitis B Surface Antibody Test (Anti-HBs)	97.90%	99.80%	0.95	1	[15,81]

*ARCHITECT HBsAg qualitative test (Abbott Laboratories, North Chicago, IL, USA)
^Same limits for both specificity and sensitivity
Ref: Reference

D. Screening strategies and associated efficacy, by population

The goal of screening strategies is to identify hepatitis B susceptible persons or non-treated/managed hepatitis B infected patients and connect them to care.[84] Care in the model is modeled by either vaccination of susceptible persons or treatment of those with chronic hepatitis B. The table below shows the various screening strategies that were modeled to either link patients to treatment or to vaccination (**Table 28**).

As a comparator, a no intervention strategy (no screening and no linkage to care) was modeled for each population. In the no intervention strategy individuals with active chronic hepatitis B progresses through the natural history model. Those susceptible to hepatitis B enter a 'susceptible' stage in the model, through which persons can become infected with hepatitis B according to a population specific annual incidence rate. Among those who become infected, they progress to acute or chronic hepatitis B, per natural history probabilities discussed above. Those with prior immunity (either natural or due to vaccination) enter the immune state of the model.

Much of the data for screening and linkage to care comes from two major initiatives, Hepatitis Testing and Linkage to Care (HepTLC) and San Francisco Hepatitis B Free (SFHBF).[70,74,75,85-90] Evidence for effectiveness of screening and linkage to care is not available for all populations; in such circumstances the best available evidence from related screening programs was used. For example, due to lack of evidence showing screening and linking the refugee population to vaccination, this model uses the data from the SFHBF and assumptions were varied in sensitivity analyses. Other exceptions are noted below in the tables as appropriate.

Interventions specific to each modeled population for screening and treatment and screening and vaccination are discussed below. The efficacies of each program by population are shown in **Tables 29 and 30**:

1. *Foreign born persons: Asia and Pacific Islanders (APIs)*

For Asian and Pacific Islander (APIs) foreign born persons, three strategies for linkage to treatment and two strategies for linkage to vaccination were modelled. Strategies for linkage to treatment include: 1) no screening and no care; 2) screening and linkage to care based on the data from HepTLC; and 3) screening and linkage to care based on the data from SFHBF program. Strategies for vaccination (for susceptible individuals) included: 1) no screening and no vaccination; and 2) screening and vaccination based on the San Francisco Hepatitis B Free program.

A. Linkage to treatment of APIs:

Intervention 1: This strategy modeled the efficacy according to the HepTLC program. The HepTLC strategy focused on community based, testing and linking to treatment populations born in moderate to high prevalence countries (=>2% HBsAg).[90] The HepTLC program recruited foreign born persons through community-based programs and partnering with medical providers to conduct screening. Components of the program used various methods to reach and link patients to care, including patient navigators, however, detailed data on the effectiveness of such efforts are not available.[74] But data on effectiveness of linkage to care for Asia and Africa born populations are available.[90]

Intervention 2: Standalone testing and vaccination sites with treatment referral and community outreach.[70] San Francisco Hepatitis B Free program established seven testing and vaccination sites for susceptible individuals and referral for medical care for those with chronic hepatitis B.[70] Majority (80%) of the individuals covered by the program were Asian/Pacific Islanders, of whom 66% were foreign born.[70] The data in the table below for linkage to medical care and vaccination are from the entire cohort in the program, but are adopted for foreign born Asian/Pacific Islanders for the purposes on this analysis.

B. Linkage to vaccination of APIs:

Intervention: Using data from San Francisco Hepatitis B Free initiative, for those identified as susceptible, the model used the vaccination rates shown in the table below.[70] Those vaccinated enter the immune state in the model. If patients only receive one or two doses, a subset experience protection (according to probabilities discussed in a later section) while others go into the 'susceptible' stage.[9]

2. *Foreign born persons: Africa Born Persons*

For Africa born persons, two strategies for linkage to treatment and two strategies for linkage to vaccination were modelled. Strategies for linkage to treatment include: 1) no screening and no care; and 2) screening and linkage to care based on the data from HepTLC program.[74] Due to the lack of direct evidence for vaccination strategies in this population, strategies for vaccination (for those found to susceptible) include: 1) no screening and no vaccination; and 2) screening and vaccination based on the San Francisco Hepatitis B Free program.[70]

A. Linkage to treatment of Africa born persons:

Intervention: This strategy modeled the efficacy according to the HepTLC program. Program described above.[74]

B. Linkage to vaccination of Africa born persons:

Intervention: Reliable data specific to screening and linking Africa born persons who are susceptible to hepatitis B was not identified. Thus for this population data from the San Francisco Hepatitis B Free initiative was used to simulate the possible effects of a screening and vaccination program (described above).[70] Assumptions were varied in sensitivity analyses.

3. *Foreign born persons: Refugees*

For recently immigrated to the US refugee population, two strategies for screening and linkage to treatment and 2 strategies for screening and linkage to vaccination were modeled. Strategies for linkage to treatment include: 1) no screening and no care; and 2) screening and linkage to care based on the data from HepTLC program.[75] Due to the lack of direct evidence for vaccination strategies in this population, strategies for vaccination (for those found to susceptible) included: 1) no screening and no vaccination; and 2) screening and vaccination based on the San Francisco Hepatitis B Free program.[70]

A. Linkage to treatment of Refugees:

Intervention: The HepTLC strategy includes supplementation of the existing Minnesota Department of Public Health's programs for screening refugees and linking the infected person to health care.[75] The HepTLC begin supplementing Minnesota's existing program in 2012, which has shown an increase in linkage to care.[75]

B. Linkage to vaccination of Refugees:

Intervention: Data specific to screening and linking refugees who are susceptible to hepatitis B has not been identified. Thus for this population data from the San Francisco Hepatitis B Free initiative (program described above) was used to simulate the possible effects of a screening and vaccination program.[70] Assumptions were varied in sensitivity analyses.

4. *Incarcerated persons*

For incarcerated persons, two strategies for linkage to treatment and two strategies for linkage to vaccination were modelled. Strategies for linkage to treatment included: 1) no screening and no care; and 2) a universally offered screening and treatment. Strategies for vaccination included: 1) no screening and no vaccination; and 2) screening and vaccination based on the available population specific evidence. The model does not explicitly model

individuals who are released and re-enter their respective communities. Release may result in lower follow up with treatment and reduce the chance of completing vaccination series.

A. Linkage to treatment for Incarcerated Persons:

Intervention: This includes offering universal screening to incarcerated population. Among those that accept screening, universal treatment was offered and linked to care.

B. Linkage to vaccination for Incarcerated Persons:

Intervention: Universal screen and vaccine offer. Data based on prison programs screening and offering vaccination was used, as shown is table below. Those vaccinated enter the immune state in the model. If patients only receive one or two doses, a subset experience protection (according to probabilities discussed in a later section) while others go into the 'susceptible' stage.

5. *Persons who inject drugs*

For persons who inject drugs (PWID), two strategies for linkage to treatment and two strategies for linkage to vaccination were modelled. Strategies for linkage to treatment included: 1) no screening and no care; and 2) a screening and treatment at syringe service programs.[79] In this model, we assume a program in which the syringe service site works in collaboration with local health care providers to link to care. Local provider network may include community health centers, opioid substance treatment clinics, and primary care providers. Strategies for vaccination (for susceptible individuals) included: 1) no screening and no vaccination; and 2) screening and vaccination based on the available population specific evidence.[79] Incentive pay to recruit patients for screening and to encourage patients to complete the vaccine series was modeled.[79]

A. Linkage to treatment for PWIDs:

Intervention: This includes offering universal screening to PWIDs presenting at syringe exchange programs. Among those that accept screening, treatment was offered and linked to care. Syringe service sites are uniquely positioned to screen and help link target population to care.[91,92] Experience from other screening programs with the PWID has shown significant challenges in successful linkage to care for this population, with treatment uptake between 2 to 10%.[93,94] Population specific data for screening and linkage to treatment at syringe exchange sites for hepatitis B was not available, thus the data for referring to and linking to care data form hepatitis C programs or assumptions as identified in the table below are used.[74,93,94]

B. Linkage to vaccination for PWIDs:

Intervention: Universal screen and vaccine offer was provided to PWIDs presenting at syringe service programs. The participants who accept and return for vaccination were offered compensation. Those vaccinated enter the immune state in the model. If patients only receive one or two doses, a subset experience protection (according to probabilities discussed in a later section) while others go into the 'susceptible' stage.

6. *Men who have sex with men*

For men who have sex with men (MSM), two strategies for linkage to treatment and two strategies for linkage to vaccination were modelled. Strategies for linkage to treatment included: 1) no screening and no care; and 2) a screening and treatment at sexually transmitted infections (STI) clinics based on assumed data. Strategies for vaccination (for

susceptible individuals) included: 1) no screening and no vaccination; and 2) screening and vaccination based on data from STI clinics.

A. Linkage to treatment for MSMs:

Intervention: This includes offering universal screening to MSMs presenting at STI clinics. Among those that accept screening, treatment was offered and men were linked to care. Population specific data for screening and linkage to treatment at STI clinics was not available, thus the data for referring to and linking to care are assumed based on other available data.[74]

B. Linkage to vaccination:

Intervention: Universal screen and vaccine offer was provided to MSMs presenting at STI clinics.[95] Those vaccinated enter the immune state in the model. If patients only receive one or two doses, a subset experience protection (according to probabilities discussed in a later section) while others go into the 'susceptible' stage.

Table S6: Screening and linkage to care (treatment or vaccination) strategies modeled, by population

Population/Strategy	Link to Treatment Strategies	Link to Vaccination Strategies	Link to Treatment or Vaccination Strategies
Asia and Pacific Islanders			
Program 1	No screening and care	No screening and care	No screening and care
Program 2	Community outreach/clinic partnership*	Community outreach/clinic referral	Community outreach/clinic referral
Program 3	Community outreach/clinic referral^		
Africa born			
Program 1	No screening and care	No screening and care	No screening and care
Program 2	Community outreach/clinic partnership	Community outreach/clinic referral	Community outreach/clinic referral
Refugees			
Program 1	No screening and care	No screening and care	No screening and care
Program 2	Community outreach/clinic partnership	Community outreach/clinic referral	Community outreach/clinic referral
Incarcerated			
Program 1	No screening and care	No screening and care	No screening and care
Program 2	Universal screening offer	Universal screening offer	Universal screening offer
PWID			
Program 1	No screening and care	No screening and care	No screening and care
Program 2	Syringe services programs	Syringe services programs	Syringe services programs
MSMs			
Program 1	No screening and care	No screening and care	No screening and care
Program 2	STI Clinics	STI Clinics	STI Clinics

*Based on Hepatitis Testing and Linkage to Care initiative (HepTLC)
^Based on San Francisco Hepatitis B Free initiative (SFHBF)
#When multiple options were available (clinic referral or partnership), most effective of the screening programs was used in this strategy
PWID = People who inject drugs; MSM = Men who have sex with men; STI = Sexually Transmitted Infections

493 *Table S7: Screening program effectiveness of referral and linkage to treatment, by population*

Population and Intervention	Base-Case (%)	Lower Limit (%)*	Upper Limit (%)*	Ref
All Populations and Interventions				
Acceptance of Screening for HBsAg	70.0	40.0	100.0	[15]
Accept anti-viral treatment	75.0	50.0	100.0	
Asian and Pacific Islander Population / HepTLC				
Refer to Medical Care[1]	98.0	73.5	100.0	[74]
Linked to Medical Care[1,2]	45.6	34.2	57.0	[74]
Asian and Pacific Islander Population / SFHBF				
Refer to Medical Care	100.0	73.5	100.0	[70]
Linked to Medical Care[3]	69.0	52.0	86.0	[70]
Africa Born Population / HepTLC				
Refer to Medical Care[1]	98.0	73.5	100.0	[74]
Linked to Medical Care[1,2]	71.9	54.0	90.0	[74]
Refugee Population / HepTLC				
Refer to Medical Care[4]	98.0	73.5	100.0	[74]
Linked to Medical Care	93.1	70.0	100.0	[75]
Incarcerated Population / Universal Screening				
Refer to Medical Care[5]	100.0	75.0	100.0	Assumption
Linked to Medical Care[5]	90.0	67.5	100.0	Assumption
Persons Who Inject Drugs / Needle Exchange Clinics				
Refer to Medical Care[6]	75.0	56.0	94.0	Assumption
Linked to Medical Care[6]	8.6	6.0	40.0	[94]
Accept Treatment[6]	6.0	1.6	40.0	[93,94]
Men who Have Sex with Men / STI Clinics				
Refer to Medical Care[6]	98.0	73.5	100.0	[74]
Linked to Medical Care[6]	45.6	34.2	57.0	[74]

*Author selected ranges of +/- 25% of base-case value.
HBsAg= Hepatitis B Surface Antigen; HepTLC = Hepatitis Testing and Linkage to Care initiative; SFHBF = San Francisco Hepatitis B Free initiative; STI = Sexually Transmitted Infections; Ref = References

1: Author calculated from study data.
2: Attended 1st medical appointment.
3: The paper refers to patients "enrolled in follow-up clinical care;" authors assume this entails successful linkage to a medical professional for anti-viral treatment.
4: The paper does not specifically state the rate of referral thus 98% referral rate, based on other HepTLC data, was assumed.
5: It is assumed that due the nature of incarceration, all patients positive for HBsAg will be referred to care and 90% will be successfully linked and initiate treatment.
6: Population specific data for referral and linkage to treatment in syringe exchange sites not available; data from hepatitis C literature used to assume linkage to care and acceptance of treatment. Base-case values subjected to wide author-selected sensitivity ranges.

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Table S8: Screening program effectiveness of referral and linkage to vaccination, by population

Population and Intervention	Base-Case (%)	Lower Limit (%)*	Upper Limit (%)*	Ref
All Populations and Interventions				
Acceptance of Screening for Anti-HBs	70.0	40.0	100.0	[15]
Asian and Pacific Islander Population / SFHBF				
Refer to Medical Care	100.0	73.5	100.0	[70]
Linked to Medical Care[1]	69.0	52.0	86.0	[70]
Accept and receive 1st dose of vaccine	52.0	39.0	65.0	[70]
2nd dose of vaccine received[2]	50.0	25.0	75.0	Assumption
3rd dose of vaccine received	49.0	44.0	74.0	[70]
Africa Born Population / SFHBF				
Refer to Medical Care	100.0	73.5	100.0	[70]
Linked to Medical Care[1]	69.0	52.0	86.0	[70]
Accept and receive 1st dose of vaccine	52.0	39.0	65.0	[70]
2nd dose of vaccine received[2]	50.0	25.0	75.0	Assumption
3rd dose of vaccine received	49.0	44.0	74.0	[70]
Refugee Population / SFHBF				
Refer to Medical Care	100.0	73.5	100.0	[70]
Linked to Medical Care[1]	69.0	52.0	86.0	[70]
Accept and receive 1st dose of vaccine	52.0	39.0	65.0	[70]
2nd dose of vaccine received[2]	50.0	25.0	75.0	Assumption
3rd dose of vaccine received	49.0	44.0	74.0	[70]
Incarcerated Population / Universal Screening				
Refer to Medical Care[3]	100.0	75.0	100.0	Assumption
Linked to Medical Care[3]	90.0	67.5	100.0	Assumption
Accept and receive 1st dose of vaccine	70.0	40.0	100	[77,78]
2nd dose of vaccine received[4]	65.0	49.0	81.0	Assumption
3rd dose of vaccine received[4]	60.0	45.0	75.0	Assumption
Persons Who Inject Drugs / Needle Exchange Clinics				
Refer to Medical Care[5]	98.0	73.5	100.0	[74]
Linked to Medical Care[5]	45.6	34.2	57.0	[74]
Accept and receive 1st dose of vaccine	69.0	52.0	86.0	[79]
2nd dose of vaccine received	53.0	40.0	67.0	[79]
3rd dose of vaccine received	40.0	30.0	50.0	[79]
Men who Have Sex with Men / STI Clinics				
Refer to Medical Care[5]	98.0	73.5	100.0	[74]
Linked to Medical Care[5]	45.6	34.2	57.0	[74]
Accept and receive 1st dose of vaccine	62.6	47.0	78.0	[95]
2nd dose of vaccine received	50.8	38.0	64.0	[95]
3rd dose of vaccine received	35.0	26.0	43.0	[95]

*Author selected ranges of +/- 25% of base-case value.
HBsAg= Hepatitis B Surface Antigen; HepTLC = Hepatitis Testing and Linkage to Care initiative; SFHBF = San Francisco Hepatitis B Free initiative; STI = Sexually Transmitted Infections; Ref = References

1: The paper refers to patients "enrolled in follow-up clinical care;" authors assume this entails successful linkage to a medical professional for anti-viral treatment.
2: Data for completion of two doses not presented in paper; consistent with literature, authors assumed a reduction in completion in second dose compared to first.
3: It is assumed that due the nature of incarceration, all patients positive for HBsAg will be referred to care and 90% will be successfully linked and initiate treatment.
4: Given that the incarcerated individuals will be stationary with scheduled care, it is assumed that vaccine completion rates, once accepted will be high. A reduction in second and third dose completion is modeled for patients who may choose not to complete the series.
5: Population specific data for referral and linkage to treatment not available; HepTLC data used for referral and link to care.

4. Transition probabilities and risk reduction with chronic hepatitis B treatment

A. Chronic hepatitis B with treatment

The goals of treatment of chronic hepatitis B with anti-viral medicines is to increase the probability of transitioning from active hepatitis B to inactive state by reducing DNA replication and normalizing ALT levels, as well as to increase seroconversion rate of HBeAg+ to HBeAg-.[96,97] The desired outcome of HBsAg clearance is rare with therapy.[96,98] As a result of lower levels of HBV DNA and seroconversion to HBeAg-, other benefits of therapy include reduction in incidence of cirrhosis, hepatic decompensation, and hepatocellular carcinoma.[99-105] Transition to inactive hepatitis B, including HBeAg seroconversion is higher in the first year of nucelos(t)ide treatment, but continues with ongoing therapy, albeit at a decreased rate.[106]

In this study, success of therapy is defined transitioning to inactive state of hepatitis B. For HBeAg+ patients this entails undetectable DNA, normal ALT and HBeAg loss in a given year of treatment. For HBeAg- patients, treatment success will be indicated by undetectable DNA and ALT normalization after 1 year of therapy. For entecavir and tenofovir, in both treatment naïve and lamivudine-experienced patients, data on efficacy (transitioning from active to inactive states and loss of HBsAg), were collected from clinical trials, follow up post-market studies, and other published literature including economic studies.[6,107-119] Clinical data show that response to therapy is higher in the first year of treatment (Table S9) compared to subsequent years (Table S10). Annual probabilities for efficacy and resistance were calculated using data from clinical trials and post-market studies per the methods described above.

517 *Table S9: Transition probabilities with anti-viral treatment, year 1*

Source State	Target State	Base-Case (%)	Lower Limit (%)	Upper Limit (%)	Ref
Tenofovir, Treatment Naïve, Year 1					
HBeAg+, Active CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	21.0	10.5	31.5	[107]
HBeAg+, Active CHB, Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic	21.0	10.5	31.5	[107]
HBeAg-, Active CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	76.0	38.0	100.0	[107]
HBeAg-, Active CHB, Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic	76.0	38.0	100.0	[107]
HBeAg-, Inactive CHB, Non-Cirrhotic	Anti-HBs, Non-Cirrhotic	1.80	0.90	2.70	[107]
HBeAg-, Inactive CHB, Cirrhotic	Anti-HBs, Cirrhotic	1.80	0.90	2.70	[107]
Discontinuation rate[1]		3.50	1.75	5.25	[109]
Tenofovir, Treatment Experienced, Year 1					
HBeAg+, Active CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	21.0	10.5	31.5	[107]
HBeAg+, Active CHB, Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic	21.0	10.5	31.5	[107]
HBeAg-, Active CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	76.0	38.0	100.0	[107]
HBeAg-, Active CHB, Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic	76.0	38.0	100.0	[107]
HBeAg-, Inactive CHB, Non-Cirrhotic	Anti-HBs, Non-Cirrhotic	1.0	0.8	1.3	[107]
HBeAg-, Inactive CHB, Cirrhotic	Anti-HBs, Cirrhotic	1.0	0.8	1.3	[107]
Discontinuation rate[1]		3.50	1.75	5.25	[109]
Entecavir, Treatment Naïve, Year 1					
HBeAg+, Active CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	22.0	16.5	27.5	[120]
HBeAg+, Active CHB, Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic	22.0	16.5	27.5	[120]
HBeAg-, Active CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	78.0	58.5	97.5	[119]
HBeAg-, Active CHB, Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic	78.0	58.5	97.5	[119]
HBeAg-, Inactive CHB, Non-Cirrhotic	Anti-HBs, Non-Cirrhotic	1.0	0.8	1.3	[120]
HBeAg-, Inactive CHB, Cirrhotic	Anti-HBs, Cirrhotic	1.0	0.8	1.3	[120]
Discontinuation rate[1]		5.2	3.9	6.5	[111]

HBeAg+/-= Hepatitis B eAntigen positive or negative; Anti-HBs = Antibody of Hepatitis B Surface Antigen; CHB = Chronic Hepatitis B; Ref = References

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Table S10: Annual probabilities with anti-viral treatment, year 2+

Source State	Target State	Base-Case (%)	Lower Limit (%)	Upper Limit (%)	Ref
Tenofovir, Treatment Naïve, Year 2+					
HBeAg+, Active CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	11.40	5.70	17.09	109
HBeAg+, Active CHB, Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic	17.60	8.78	26.33	109
HBeAg-, Active CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	13.80	6.90	20.69	117
HBeAg-, Active CHB, Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic	13.80	6.90	20.69	117
HBeAg-, Inactive CHB, Non-Cirrhotic	Anti-HBs, Non-Cirrhotic	1.00	0.50	1.50	109
HBeAg-, Inactive CHB, Cirrhotic	Anti-HBs, Cirrhotic	1.00	0.50	1.50	109
Discontinuation rate[1]		3.50	1.75	5.25	109
Tenofovir, Treatment Experienced, Year 2+					
HBeAg+, Active CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	11.40	5.70	17.09	109
HBeAg+, Active CHB, Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic	17.60	8.78	26.33	109
HBeAg-, Active CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	13.80	6.90	20.69	117
HBeAg-, Active CHB, Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic	13.80	6.90	20.69	117
HBeAg-, Inactive CHB, Non-Cirrhotic	Anti-HBs, Non-Cirrhotic	1.00	0.50	1.50	109
HBeAg-, Inactive CHB, Cirrhotic	Anti-HBs, Cirrhotic	1.00	0.50	1.50	109
Discontinuation rate[1]		3.50	1.75	5.25	109
Entecavir, Treatment Naïve, Year 2+					
HBeAg+, Active CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	5.20	2.60	7.79	111
HBeAg+, Active CHB, Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic	5.20	2.60	7.79	111
HBeAg-, Active CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	5.20	2.60	7.79	111
HBeAg-, Active CHB, Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic	5.20	2.60	7.79	111
HBeAg-, Inactive CHB, Non-Cirrhotic	Anti-HBs, Non-Cirrhotic	0.70	0.33	0.98	111
HBeAg-, Inactive CHB, Cirrhotic	Anti-HBs, Cirrhotic	0.70	0.33	0.98	111
Discontinuation rate[1]		5.20	2.58	7.74	111

1: for PWIDs modeled as 2x baseline
HBeAg+/-= Hepatitis B eAntigen positive or negative; Anti-HBs = Antibody of Hepatitis B Surface Antigen; CHB = Chronic Hepatitis B; Ref = References

B. Resistance to nucleos(t)ide therapies

Clinical evidence indicates that it is possible to develop resistance to nucleos(t)ide therapies leading to treatment failure, which may result in progression liver disease due to CHB.[121] With the exception of tenofovir, resistance to other anti-viral drugs has been seen observed in clinical trials and long-term post-market studies.[3,116,117,122-125] The risk of developing resistance increases with increase duration of therapy, as observed with lamivudine and entecavir.[3,108,115,116,126] Furthermore, risk of cross-resistance is higher for patients who may have failed another nucleos(t)ide therapy and response to another anti-viral with a prior treatment failure.[3,110] For this model, based on the available clinical data, annual probability of developing resistance, based on treatment naïve or experienced status was portrayed. When applicable, the risk of developing resistance will increase per year for the first five years of therapy, followed by constant annual probability equal to year 5 of treatment. [3,6,117,123,124,127]

Table S11: Annual probabilities for developing resistance to nucleos(t)ide therapies

Therapy (patient population)	Year of Treatment	Annual probability of resistance			
		Base Case (%)	Lower Limit (%)	Upper Limit (%)	Ref
Entecavir (Treatment Naïve, HBeAg+ and - patients, cirrhotic and non-cirrhotic)	1	0.4	0.0	0.9	3,6,123
	2	0.4	0.0	0.9	3,6,123
	3	0.7	0.0	2.0	3,6,123
	4	0.8	0.0	2.5	3,6,123
	5+	0.8	0.0	2.5	3,6,123
Tenofovir (Treatment Naïve, HBeAg+ and - patients, cirrhotic and non-cirrhotic)*	1	0.0	0.0	1.0	117,124,127
	2	0.0	0.0	1.2	117,124,127
	3	0.0	0.0	1.4	117,124,127
	4	0.0	0.0	1.6	117,124,127
	5+	0.0	0.0	1.8	117,124,127
Tenofovir (in treatment experienced, lamivudine resistant patients, HBeAg+ and - patients, cirrhotic and non-cirrhotic)*	1	0.0	0.0	1.2	117,124,127
	2	0.0	0.0	1.4	117,124,127
	3	0.0	0.0	1.6	117,124,127
	4	0.0	0.0	1.8	117,124,127
	5+	0.0	0.0	2.0	117,124,127

*Author assumed upper limit for annual probability to develop resistance associated variants (RAV).
HBeAg+/-= Hepatitis B eAntigen positive or negative; Ref = References

C. Retreatment after discontinuation or RAV development

Patients may discontinue therapy for any reason according to the treatment-specific annual probabilities listed above. Patients may also develop resistance forcing them to stop a given therapy. For the base-case scenario, we assumed that up to 75% of the patients who discontinue therapy may be retreated annually. If patients develop resistance to entecavir, up to 75% may be retreated with tenofovir. If patients develop resistance to tenofovir (although not yet reported), they will enter natural history model.

Table S12: Proportion of patients retreated on an annual basis after discontinuation of therapy or development of resistance

	Base-Case (%)	Lower Limit (%)	Upper Limit (%)	Reference
Discontinuation of Therapy				
Entecavir	75	25	100	Assumption
Tenofovir	75	25	100	Assumption
Development of Resistance Associated Variant (RAV)				
Entecavir	75	25	100	Assumption

D. Probability of DNA suppression, reduction in advanced liver disease and regression of cirrhosis with treatment

One of the key outcomes of treatment with anti-viral drugs is a marked reduction in DNA level of hepatitis B virus. A reduction in hepatitis B virus DNA has been linked to a reduction in development of advanced liver disease chronic hepatitis B, particularly hepatocellular carcinoma and cirrhosis.[68,128-131] Clinical studies for both tenofovir and entecavir have shown a reduction in hepatitis B virus DNA levels within the first year of treatment.[107,119,120] As seen in Table S13, the DNA reduction is dependent on HBeAg status; less HBeAg positive patients experience a DNA reduction

554 than HBeAg negative patients. And a greater number of tenofovir patients, in clinical studies,
555 reached undecteable DNA levels than did entecavir patients. Proportion of patients experiencing
556 DNA reduction in treatment year 2 and beyond were reduced by approximately 40% based on a
557 previously published estimate, which was varied widely in sensitivity analyses (Table S13).[6] During
558 long term (5 to 6 years) follow up of patients in clinical trials, treatment has also been shown to
559 reverse cirrhosis at high rates; we used data from clinical trials to estimate annual regression rates
560 from cirrhosis to no cirrhosis in inactive and anti-HBs states.[132,133]
561
562 Table S14 shows the relative risk reductions for progression to cirrhosis, decompensated cirrhosis,
563 and hepatocellular carcinoma in patients who achieve DNA suppression with treatment.[6] The annual
564 probability of regression from cirrhosis is also listed.[6] Patients who do not achieve DNA suppression
565 (per ratios listed in Table S13), will experience annual natural history transition probabilities.

566 *Table S13: Proportion of patients with suppressed hepatitis B DNA in the first year of treatment and subsequent years*

Treatment	Base-case (%)	Lower-Limit (%)	Upper-Limit (%)	Reference
Year 1 of treatment				
Tenofovir				
HBeAg(+)^	76.00	57.00	95.00	[107]
HBeAg(-)^	93.00	70.00	1.00	[107]
Entecavir				
HBeAg(+)^	67.00	5.00	84.00	[120]
HBeAg(-)^	90.00	68.00	1.00	[119]
Year 2+ of treatment				
Ratio of year 1 probability	62.99	47.24	78.74	[6]
^Author selected lower and upper limits of +/-25%. HBeAg+/-= Hepatitis B eAntigen positive or negative				

567

568 *Table S14: Risk reduction of advanced liver disease with suppressed hepatitis B virus DNA with treatment*

Source State	Target State	Base Case	Lower Limit	Upper Limit	Ref
Progression to Cirrhosis					
HBeAg+, Active CHB, Non-Cirrhotic	HBeAg+, Active CHB, Cirrhotic	0.55 (0.38-0.78)[1]			97
HBeAg-, Active CHB, Non-Cirrhotic	HBeAg-, Active CHB, Cirrhotic				97
HBeAg-, Inactive CHB, Non-Cirrhotic	HBeAg-, Inactive CHB, Cirrhotic				97
Progression to Decompensated Cirrhosis					
HBeAg+, Active CHB, Cirrhotic	Decompensated Cirrhosis	0.45 (0.22-0.89)[1]			97
HBeAg-, Active CHB, Cirrhotic	Decompensated Cirrhosis				97
HBeAg-, Inactive CHB, Cirrhotic	Decompensated Cirrhosis				Assumption
Progression to Hepatocellular Carcinoma					
HBeAg+, Active CHB, Non-Cirrhotic	Hepatocellular Carcinoma	0.5209 (0.391-0.651)[1]			6
HBeAg-, Active CHB, Non-Cirrhotic	Hepatocellular Carcinoma				6
HBeAg-, Inactive CHB, Non-Cirrhotic	Hepatocellular Carcinoma				6
HBeAg+, Active CHB, Cirrhotic	Hepatocellular Carcinoma	0.54 (0.41-0.72)[1]			97
HBeAg-, Active CHB, Cirrhotic	Hepatocellular Carcinoma				97
HBeAg-, Inactive CHB, Cirrhotic	Hepatocellular Carcinoma				97
CHB related mortality					
HBeAg+, Active CHB, Non-Cirrhotic	Death	0.1695 (0.0469-0.6098)[1]			6
HBeAg-, Active CHB, Non-Cirrhotic	Death				6
HBeAg-, Inactive CHB, Non-Cirrhotic	Death				6
HBeAg+, Active CHB, Cirrhotic	Death	0.68 (0.00-0.90)[1,2]			97
HBeAg-, Active CHB, Cirrhotic	Death				97
HBeAg-, Inactive CHB, Cirrhotic	Death				97
Regression of Cirrhosis					
HBeAg-, Inactive CHB, Cirrhotic	HBeAg-, Inactive CHB, Non-Cirrhotic	0.24	0.18	0.30	132,133
Anti-HBs, Cirrhotic	Anti-HBs, Non-Cirrhotic	0.24	0.18	0.30	132,133

1: Relative risk reduction compared to natural history probability with detectable DNA
2: Author selected range
HBeAg+/-= Hepatitis B eAntigen positive or negative; Anti-HBs = Antibody of Hepatitis B Surface Antigen; CHB = Chronic Hepatitis B; Ref = References

569

5. Transmission probabilities

Annual incidence of acute hepatitis B for each of the high-risk population groups was determined from published literature, when available. For Africa born and refugee population, due to lack of quality and reliable data on annual incidence of acute hepatitis B, we used a rate equivalent of high-risk Asian Pacific Islander population.

Table S15: Annual incidence of horizontal acute infection amongst susceptible adults within a population

Source population	Susceptible population	Base-Case (%) annual incidence of acute hepatitis B	Lower limit (%)	Upper limit (%)	Ref
FB API[1]	FB API	0.64	0.47	0.81*	[134]
Incarcerated	Incarcerated	2.31[2]	0.82	3.80	[77]
PWID	PWID	10.00	8.30	12.20	[135,136]
MSM	MSM	0.96	0.85	1.10	[137]
Africa Born	Africa Born	0.64	0.47	0.81*	Assumption[3]
Refugee	Refugee	0.64	0.47	0.81*	Assumption[3]

*Author selected upper range; the source had listed the range as 0.47 to 0.61, in which the upper range is lower than the base-case value. Authors adjusted the upper range value by the same factor as lower range value from base-case value.
1: Incidence rate for high-risk Asian Pacific Islander population used.
2: Calculated mean from min and max range.
3: Due to lack of quality population specific data, the annual incidence is assumed to be higher than the general population incidence rate and equivalent of high-risk Asian Pacific Islander population.
FB = Foreign Born; API = Asian Pacific Islander; PWID = People who inject drugs; MSM = Men who have sex with men; Ref = Reference

6. Prevention

A. Hepatitis B vaccine

Two vaccines are available, however, since there is no difference in doses, efficacy or adverse events, we modeled "vaccine" intervention. The cost of the vaccines may differ and was modeled accordingly using a range to cover the uncertainty. Immunity due to vaccination was assumed to continue for life without the need for boosters.[138,139] Due to their rare occurrence, adverse events to the vaccine were not modeled.[16]

B. Vaccination effectiveness by number of doses

Vaccine efficacy varies by number of doses a patient receives, as presented in the table below.

Table S16: Hepatitis B vaccine effectiveness rates among those completing the 3-dose series, by number of doses

Number of Doses	Base-Case (%)	Lower Limit (%)	Upper Limit (%)	Ref
Efficacy with 1 Dose	14.50	13.78^	15.23^	[9]
Efficacy with 2 Doses	81.00	79.50	82.90	[9]
Efficacy with 3 Doses	98.10	93.12^	1.00^	[9]

^Author calculated for +/- 25% of base-case value
Ref = Reference

7. Health related quality of life: Natural history and treatment

Health related quality of life was estimated using health state utility values based on a literature review of published primary studies and economic evaluation of hepatitis B.[6,7,9,10,12,13,15,16,140-148] The utility values vary widely in literature. Thus, whenever possible we relied on primary studies conducted in hepatitis B-infected individuals.[141,147] For perinatal exposure and asymptomatic acute hepatitis states, we assumed no loss of quality of life and patients would not be aware of their status nor would they feel physical symptoms.

Table S17: Health state utilities

Health State	Base case	Lower Limit	Upper Limit	Ref
Susceptible	0.99	0.98	1.00	15
Immune	0.99	0.98	1.00	15
HBV Exposure, Perinatal	0.99	0.97	1.00	Assumption*
Acute Hepatitis, Adult, asymptomatic	0.99	0.95	1.00	Assumption*
Acute Hepatitis, Adult, symptomatic	0.70	0.63	0.77	142
Fulminant Hepatitis	0.37	0.333	0.407	140
Immune Tolerant Phase	0.95	0.84	1.00	146
HBeAg+, Active CHB, Non-Cirrhotic	0.670	0.603	0.737	141
HBeAg+, Active CHB, Cirrhotic	0.660	0.594	0.726	141
HBeAg-, Active CHB, Non-Cirrhotic	0.670	0.603	0.737	141
HBeAg-, Active CHB, Cirrhotic	0.660	0.594	0.726	141
HBeAg-, Inactive CHB, Non-Cirrhotic	0.850	0.765	0.935	6
HBeAg-, Inactive CHB, Cirrhotic	0.850	0.765	0.935	6
Decompensated Cirrhosis	0.370	0.333	0.407	141
Hepatocellular Carcinoma	0.430	0.387	0.473	141
Liver Transplant	0.570	0.513	0.627	141
Post Liver Transplant	0.640	0.576	0.704	141
Anti-HBs, Non-Cirrhotic	0.860	0.774	0.946	6
Anti-HBs, Cirrhotic	0.860	0.774	0.946	6
*It is assumed that if patients are not aware of their infection and are not symptomatic, there would be minimal to no loss of quality of life, thus we used a utility of 0.99 to indicate near perfect health. HBeAg+/-= Hepatitis B eAntigen positive or negative; Anti-HBs = Antibody of Hepatitis B Surface Antigen; CHB = Chronic Hepatitis B; Ref = References				

8. Utility loss with anti-viral treatment

Utility loss due to adverse events with entecavir and tenofovir was calculated by weighting the frequency of adverse events from clinical trials with the disutility weights for common and serious side-effects.[107,119,120] The disutility weights are adjusted under the assumption that most patients will experience adverse at most 25% of the time.

Table S18: Annual utility loss due to treatment

Drug	Base Case (annual)*	Lower Limit*	Upper Limit*	Ref
Entecavir	-0.029	-0.043	0.000	111,119,120,149
Tenofovir	-0.031	-0.047	0.000	107,109
* (-) represents utility loss; it does not imply a negative utility. Ref = Reference				

9. Cost Inputs

A. Healthcare costs

Costs related to medical management of acute and chronic hepatitis B through its natural history were collected from economic evaluations of the disease.[7,8,10,11,16,69,150-153] When data for specific health states were not available, we relied on educated and expert assumptions. For example, costs of managing initial exposure in infants and asymptomatic acute infection in adults were assumed to be zero. The reason is that in majority of patients with initial exposure, the acute infection is asymptomatic; and if patients are not aware of their status, no medical care will be sought. Cost of managing patients in inactive phase of hepatitis B was assumed to be half of the costs in active state. Cost of managing patients following HBeAg clearance (or development of anti-HBe), was assumed to be half of the costs of managing patients in inactive phase. HBeAg cleared patients are still at risk of developing advanced liver diseases, including hepatocellular carcinoma, as such require continuous monitoring.[45,49-53] Costs in literature are not segregated between active HBeAg positive and negative states; in this model we assumed that the costs of management in the active phase were same, regardless of HBeAg status.

Further, for advanced liver disease, we assumed that cost of management would not differ significantly that those established for advanced liver disease in hepatitis C. Advanced liver disease in this context is considered to be cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and liver transplant (including post-liver transplant). Therefore, we used the data for management of advanced liver conditions from a recent hepatitis C economic evaluation.[69]

When available, confidence intervals around point estimates of costs from published sources were used. When not available we used values of +/- 50% of the base-case estimate; however, for active and inactive non-cirrhotic and cirrhotic states, as well as HBs cleared states, we used an interval of 50% to 300% to compensate for the variation in the point estimates observed in the literature.[7,10,11,16]

Table S19: Hepatitis B health state costs (annual except as noted with E for episode)

Health State	Base Case ($/year)	Lower Limit	Upper Limit	Ref
HBV Exposure, Perinatal	0	0	622	Assumption*
Acute Hepatitis, Adult, asymptomatic	0	0	622	Assumption*
Acute Hepatitis, Adult, symptomatic	357	185	622	[16]
Fulminant Hepatitis (E)	17,309	17,362	46,489	[16]
Immune Tolerant Phase	520	265	1,059	[151]
HBeAg+, Active CHB, Non-Cirrhotic	1,293	647	3,880	[152]
HBeAg+, Active CHB, Cirrhotic	2,714	1,357	8,141	[69]
HBeAg-, Active CHB, Non-Cirrhotic	1,293	647	3,880	[152]
HBeAg-, Active CHB, Cirrhotic	2,714	1,357	8,141	[69]
HBeAg-, Inactive CHB, Non-Cirrhotic	647	323	1,940	Assumption^
HBeAg-, Inactive CHB, Cirrhotic	1,357	678	4,070	Assumption^
Decompensated Cirrhosis	32,134	30,159	34,111	[69]
Hepatocellular Carcinoma	51,258	46,002	56,507	[69]
Liver Transplant (E)	203,489	187,651	219,323	[69]
Post Liver Transplant	44,318	36,213	52,423	[69]
Anti-HBs, Non-Cirrhotic	323	162	970	Assumption&
Anti-HBs, Cirrhotic	678	339	2,035	Assumption&

*Assumed that with initial asymptomatic exposure when patients are unaware of infection status, there would be no healthcare associated costs.
^Assumed to be 50% of the costs in active phase of chronic hepatitis B.
&Assumed to be 50% of the costs in inactive phase of chronic hepatitis B.
HBeAg+/-= Hepatitis B eAntigen positive or negative; Anti-HBs = Antibody of Hepatitis B Surface Antigen; CHB = Chronic Hepatitis B; Ref = Reference

B. Diagnostic, and monitoring tests for hepatitis B

1. Initial diagnostic tests, frequency of testing and related costs

If HBsAg is positive, patients will be referred for medical management, which will initiate with number of baseline tests as shown in the table below. The cost of the tests was determined using clinical laboratory and physician fee schedules of Centers for Medicare and Medicaid Services.[154,155]

Table S20: Initial diagnostic tests, frequency of testing and related costs

Tests for Initial Evaluation	Base Case ($/unit)	Lower Limit	Upper Limit	Ref
Hepatitis B e-Antigen (HBeAg)	15.70	7.85	23.55	154
Hepatitis B e-Antigen Antibody (anti-HBe)	15.76	7.88	23.64	154
Hepatitis B Surface Antibody (anti-HBs)	14.63	7.32	21.95	154
Hepatitis B Core Antigen (anti-HBc)	16.41	8.21	24.62	154
IgM Antibody to Hepatitis B Core Antigen (IgM anti-HBc)^	16.04	8.02	24.06	154
Hepatitis B DNA Quantification	58.35	29.18	87.53	154
Liver Function Tests	11.13	5.57	16.70	154
Complete Blood Count	10.59	5.30	15.89	154
Hepatitis C Virus	19.44	9.72	29.16	154
Hepatitis D virus	23.38	11.69	35.07	154
Human immunodeficiency virus	18.67	9.34	28.01	154
Renal function panel	11.83	5.92	17.75	154
Alpha-fetoprotein serum (age >40, clinical decision <40)	22.85	11.43	34.28	154
Ultrasound (Right Upper Quadrant ultrasound)	101.31	50.66	151.97	155
^Patients presenting with acute hepatitis only HBeAg= Hepatitis B eAntigen; Anti-HBs = Antibody to Hepatitis B Surface Antigen; Anti-HBc = Antibody to Hepatitis B Core Antigen; IgM = Immunoglobulin M; CHB = Chronic Hepatitis B; Ref = References				

2. Tests for monitoring for patients with or without ongoing treatment, frequency of testing and related costs

Patients who are linked to care, and are being treated with antiviral drugs will be monitored using the following tests at regular intervals. Patients who are not undergoing treatment or have completed treatment but remain in care will be monitored at regular intervals using the indicated tests.

The frequency of tests is determined by clinical experience; the cost of the tests was determined using clinical laboratory and physician fee schedules of Centers for Medicare and Medicaid Services.[154,155]

Table S21: Tests for monitoring treatment, frequency of testing and related costs

Test for monitoring	No treatment (#/year)	With treatment (#/year)	Base Case ($/unit)	Lower Limit	Upper Limit	Ref
Hepatitis B e-Antigen (HBeAg)	0	2	15.70	7.85	23.55	[154]
Hepatitis B e-Antigen Antibody (anti-HBe)	0	2	15.76	7.88	23.64	[154]
Hepatitis B Surface Antigen^	0	1	14.07	7.04	21.11	[154]
Hepatitis B Surface Antibody (anti-HBs)*	0	1	14.63	7.32	21.95	[154]
Hepatitis B DNA Quantification	2	4	58.35	29.18	87.53	[154]
Liver Function Tests	2	4	11.13	5.57	16.70	[154]
Complete Blood Count	0	1	10.59	5.30	15.89	[154]
Renal function panel	0	4	11.83	5.92	17.75	[154]
Bone density scan/DEXA (Tenofovir therapy)	0	Q3 years	45.37	22.69	68.06	[155]
Alpha-Fetoprotein Serum	2	2	22.85	11.43	34.28	[154]
Ultrasound (RUQ ultrasound)	2	2	101.31	50.66	151.97	[155]

^Seroconverted patients only
*One time only test, only on HBsAg loss
HBeAg= Hepatitis B eAntigen; anti-HBe= Antibody to Hepatitis B eAntigen; Anti-HBs = Antibody to Hepatitis B Surface Antigen; Anti-HBc = Antibody to Hepatitis B Core Antigen; IgM = Immunoglobulin M; CHB = Chronic Hepatitis B; RUQ = Right Upper Quadrant; Q3 years = Every 3 Years; Ref = References

C. Costs of screening strategies

The model takes into account total cost per person for administration of a given strategy, plus cost of screening tests, vaccines and medicines according to costs listed elsewhere in this document. The administration costs include human resources to manage the program, cost to administer the initial screening test, and advertising (e.g. printed materials/flyers and other adverts) for recruiting, as applicable, by each type of program. However, if program specific costs were not available we used per person costs per screening from similar program categories reported in literature.[89] The modeled programs can be generally categorized into the following categories: 1) community clinic program (for incarcerated persons and MSM outreach via prison clinics and sexually transmitted infection clinics, respectively); 2) community outreach program (for PWID outreach via syringe exchange sites); 3) Community outreach and partnership program (for outreach and linkage to care via HepTLC program); and 4) community outreach and clinic program (San Francisco Hepatitis B Free program). From the published program costs, we subtracted the cost of the hepatitis B screening tests to estimate the administrative costs of the program. The administrative costs were then adjusted to 2016 dollars using the medical component of the Consumer Price Index (**Table 31**). To test the potential uncertainty in our estimates program costs, the values were varied widely from 75% to 300% of the base-case values.

Total cost for each modeled program include administrative costs (as reported in table below), cost of initial screening test (either HBsAg or anti-HBs), cost of full set of tests when referred to care, cost of vaccine or treatment, and cost of lifetime management of hepatitis B, with or without treatment or vaccination.

673 *Table S22: Administrative costs of screening programs*

Cost Component by Screening Program[1]	Base-Case (USD, Cost/person)	Lower Limit (USD)^	Upper Limit (USD)^	Ref
Vaccine Administration				
All programs	16	12	48	134
Program Administration				
HepTLC[2]	178	134	534	89
SFHBF[3]	140	105	420	89
Prison based clinic[4]	27	20	81	89
Syringe Exchange Sites[5]	97	73	291	89
Incentive Pay[6]	15	10	45	79
STI Clinics[4]	27	20	81	89

^Author selected ranges of 75% to 300% of base-case.
HepTLC = Hepatitis Testing and Linkage to Care initiative; SFHBF = San Francisco Hepatitis B Free initiative; STI = Sexually Transmitted Infections; USD = United States Dollars; Ref = References

1: All cost inflation adjusted to 2016 using medical component of Consumer Price Index. Costs rounded to the nearest whole dollar.
2: Community outreach and partnership model costs applied
3: Community outreach and clinic model costs applied, author calculated from study data by adding separate costs of community outreach and clinic model.
4: Clinic model costs applied
5: Community outreach model costs applied
6: Incentive pay applied to the first screening visit for screened patients; and for each subsequent vaccine visit for patients requiring vaccination.

674

675 ## D. Treatment and vaccines related costs

676 ### *1. Treatment (drug) costs*

677 Wholesale acquisition price (WAC) form Red Book Online is used for cost of drugs.[156] The base-case cost
678 will be set at 80% of listed WAC price with confidence bounds of 50% to 100% for sensitivity analyses.
679 The 80% of WAC for base-case is selected because it is likely that most, if not all payers, receive
680 discounts from the listed retail cost.[157] The upper bound of the sensitivity analyses is equal to the retail
681 cost listed in RedBook as it is unlikely that payers would acquire the drugs for a price greater than the
682 WAC. Other prices, such as discounted prices for certain payers may also be modeled in scenario
683 analyses.
684

685 *Table S23: Cost of treatments*

Drug	**Dose/day**	**Base Case ($/month)** †	**Lower Limit**‡	**Upper Limit**‡	**Ref**
Entecavir	0.5 mg	560	350	700	156
Tenofovir	300 mg	798	499	998	156

†80% of Wholesale Acquisition Cost (WAC) monthly cost from RedBook online.
‡Lower limit is set at 50% of WAC monthly cost from RedBook online; upper limit is set equal to the WAC monthly cost from RedBook online.
Ref = References

686

2. Vaccination costs

Costs for adult and pediatric vaccine formulations will be modeled as this model will be analyzing strategies to prevent hepatitis B infections in high-risk adult populations through immunization and in infants through vaccination and post-exposure prophylaxis.

Table S24: Cost of hepatitis B vaccines

Vaccine	# of injections	Base Case ($/unit) †	Lower Limit‡	Upper Limit ‡	Ref
Adult	3	42.00	26.25	52.50	[156]
†80% of Wholesale Acquisition Cost (WAC) monthly cost from RedBook online. ‡Lower limit is set at 50% of WAC monthly cost from RedBook online; upper limit is set equal to the WAC monthly cost from RedBook online. Ref = References					

3. Annual cost of treatment related adverse events

Annual cost of medical management of adverse events are calculated by weighting the frequency of common and serious adverse events observed in clinical trials[107,109,111,119,120,149] to which published costs of similar adverse events were applied.[158]

Table S25:Annual cost of medical management of treatment related adverse events

Drug	**Base case ($/year)** †	**Lower Limit**‡	**Upper Limit**‡	**Ref**
Entecavir	658	329	987	Calculated
Tenofovir	732	366	1,098	Calculated
†Based on cost of serious adverse events of $2,801 and cost of common adverse events of $534. Costs are weighted by frequency of serious and common adverse events and summed to calculate the costs in the table. ‡The lower and upper bounds for sensitivity analyses are set at 50%-150% of base case value. Ref = References				

10. Sensitivity analyses methods

A. One-way sensitivity analyses

In one-way sensitivity analyses, each input is varied across the lower and upper limits, one-by-one and results noted in terms of the effect on the cost-effectiveness ratio. In other words, the base-case value is substituted with the lower value of the input estimate and the model is run to get an ICER; same is done for the upper limit. The inputs that have the greatest impact on the ICER, relative to the base-case scenario, are considered to be the most sensitivity for model results. These are then presented in a tornado-diagram – a graph that orders the input values from the most sensitive to the least sensitive from top to bottom.

B. Probabilistic (multi-way) sensitivity analyses

In probabilistic analyses, all variables are simultaneously varied using defined distributions for each variable and the model is run to get an ICER. In our model, we conducted 10,000 simulations. We use normal distribution (with mean and standard deviation) for costs and triangular distributions (with a mode, lower and upper limits) for probabilities and proportions. The results are presented in cost-effectiveness acceptability curves for each strategy, by population, indicating at what dollar threshold is a given strategy consider to be 'acceptable.' For triangular distributions in this model, the base-case (point-estimate) value is the triangular mode, and lower and upper limits of the input values are the lower/upper limits of the triangular distribution, respectively.

III. Model Calibration and Validation

1. Calibration and Validation of Natural History Model

The chronic hepatitis B natural history Markov model was calibrated using epidemiology data for transitioning from immune tolerant phase to active chronic hepatitis B and for outcomes of three major complications of CHB – cirrhosis, hepatocellular carcinoma, and liver decompensation. REVEAL-HBV, a large longitudinal study in Taiwan on hepatitis B, provided data for the 48-year cumulative incidence of cirrhosis and hepatocellular carcinoma (HCC) in patients with chronic hepatitis B; [128] and for decompensation 5-year cumulative probability data provided by American Association for the Study of Liver Diseases (AASLD) was used. To validate, epidemiology data was matched with model outcomes; to do this the natural history model was run for 100,000 trials (using microsimulations) for 48-year or 5-year time-horizons, depending on outcome of interest.

1. Progression to active chronic hepatitis B from immune tolerant phase
   Based on available data and expert hepatologist input, the model was calibrated to ensure that majority of the patients in the immune tolerant phase would transition into active, non-cirrhotic, chronic hepatitis B by age 40. **Table 40** lists the probabilities used to meet this target. The calibration was based on epidemiological findings that majority of patients will transition into active hepatitis B between the ages of 20 and 40, based on genotype of hepatitis B virus.[1,2] In our model, 50% of patients transition into active CHB by age 21, and 100% transition to active CHB by age 37 (**Supplement A, Figure 5**).

Table S26: Age dependent transitions from Immune Tolerant to Immune Active Phase

Age	Transition to CHB (%)	Age	Transition to CHB (%)	Age	Transition to CHB (%)
0	0.00	19	8.21	38	46.11
1	0.00	20	9.40	39	48.95
2	0.01	21	10.67	40	51.87
3	0.04	22	12.04	41	54.87
4	0.10	23	13.50	42	57.93
5	0.19	24	15.05	43	61.07
6	0.33	25	16.69	44	64.28
7	0.51	26	18.43	45	67.56
8	0.75	27	20.25	46	70.90
9	1.05	28	22.17	47	74.31
10	1.42	29	24.18	48	77.78
11	1.85	30	26.27	49	81.32
12	2.36	31	28.45	50	84.91
13	2.95	32	30.72	51	88.56
14	3.61	33	33.08	52	92.26
15	4.36	34	35.52	53	96.02
16	5.19	35	38.05	54	99.84
17	6.11	36	40.65	55	100.00
18	7.12	37	43.34	56+	100.00

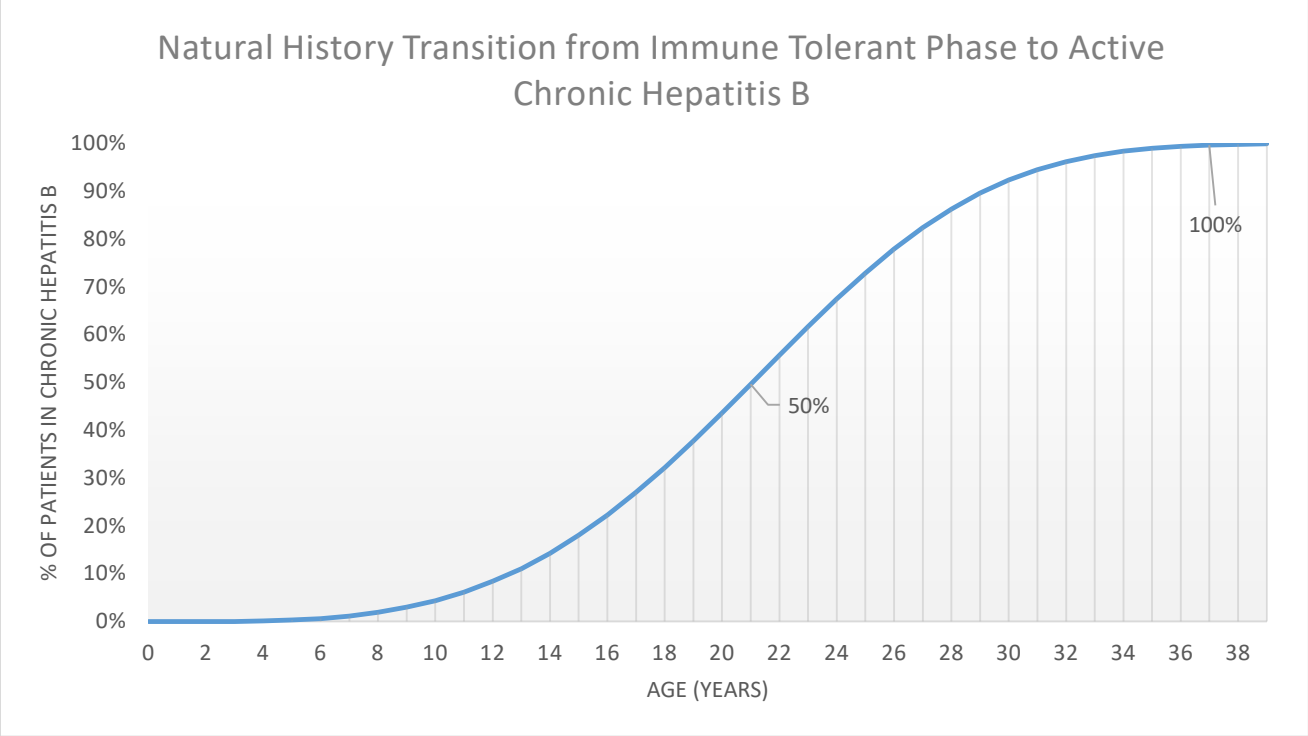

Figure S6: Percent of patients transitioning from immune tolerant phase to chronic hepatitis B

2. Development of cirrhosis and HCC:

As seen in

744 **Table** S27, REVEAL-HBV data are very closely related to model outcomes of cirrhosis and HCC. In the
745 REVEAL-HBV study, the cumulative probability of cirrhosis and hepatocellular carcinoma over a 48-year
746 period were 41.5 and 21.7, respectively. In this model, the cumulative probabilities after 25,000
747 simulations, over a 48-year period were 42 and 22 for cirrhosis and HCC respectively.

748 Further, **Supplement Table S28 and Figure S7** show the model outcomes for cirrhosis and HCC in 5-year
749 increments. Figure S8 shows graphs of cumulative probability of cirrhosis and liver cancer from the
750 REVEAL-HBV study. The cumulative probability curves of HCC in the REVEAL study indicates slower
751 development at earlier ages and increased incidence at older ages (**Figure 8a**). This trend is not
752 replicated by the model, which is parameterized for annual incidence regardless of age or other factors
753 that may affect development of HCC.[129] Given the lack of data to fit an exponential model, we opted to
754 use a linear approach to approximating incidence of HCC. This approach is consistent with previous
755 published economic evaluation studies.[6,12,15,159] Comparatively, with the cumulative probability line in
756 the REVEAL-HBV (**Figure 8**) and line produced by this model (**Figure 7**), it is observed that development
757 of cirrhosis seems to follow a linear progression (**Figure 8b**).

758

Table S27: CHB natural history model validation for cirrhosis and HCC with REVEAL-HBV study

REVEAL-HBV Data (Chen 2011)		This Model
Location	Taiwan	Inputs and Results
N	3653	N/A
Age	30 to 65 years	30 years (starting age)
HBeAg+	565 (15.5)	15.5
HBeAg-	3088 (84.5)	84.5
Time Horizon	Calculated over 48 years	48-year model run
Cumulative Probabilities (outcomes)		
Cirrhosis	41.50	42
Liver Cancer	21.70	22
HBeAg-/+= Hepatitis B eAntigen negative or positive		

Table S28: Results of 25,000 natural history model simulations over varying time-horizons

CHB Complication	Number of Years after Entry into Natural History Model and Model Outcomes										
	5-years	10	15	20	25	30	35	40	45	48*	50
Compensated Cirrhosis	10	18	25	29	33	36	38	40	42	42	42
Hepatocellular Carcinoma	3	6	9	12	14	16	18	19	21	22	22
*Corresponds to REVEAL-HBV study data for cumulative probabilities. CHB = Chronic Hepatitis B											

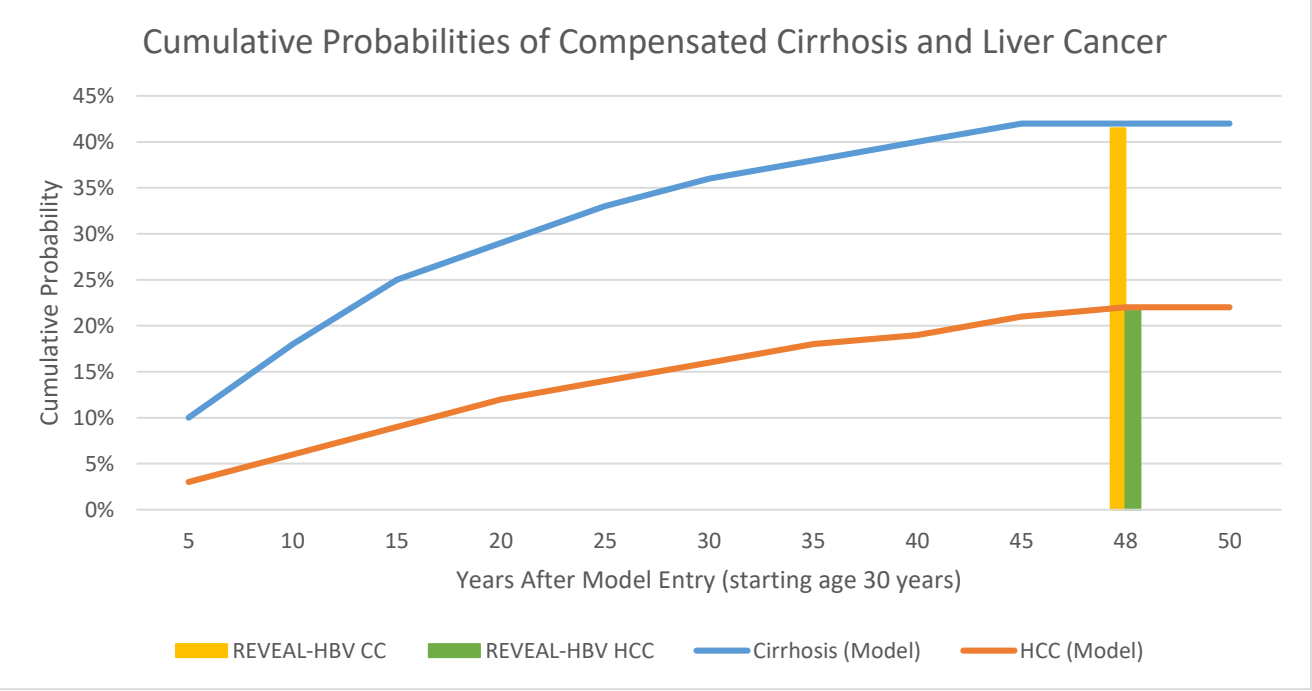

Figure S7: Cumulative probabilities of cirrhosis and HCC in the natural history model and epidemiology data

Supplement Figure 7 caption: The figure shows results of the natural history model in five-year increments. The results were generated using 25,000 microsimulations of the model. Cirrhosis cumulative probability is show in

blue line, with the height of the yellow vertical bar (41.5) showing epidemiology data from REVEAL-HBV. The orange line shows the cumulative probability of developing liver cancer, with the height of the green bar (21.7) indicating cumulative probability from the REVEAL-HBV study.

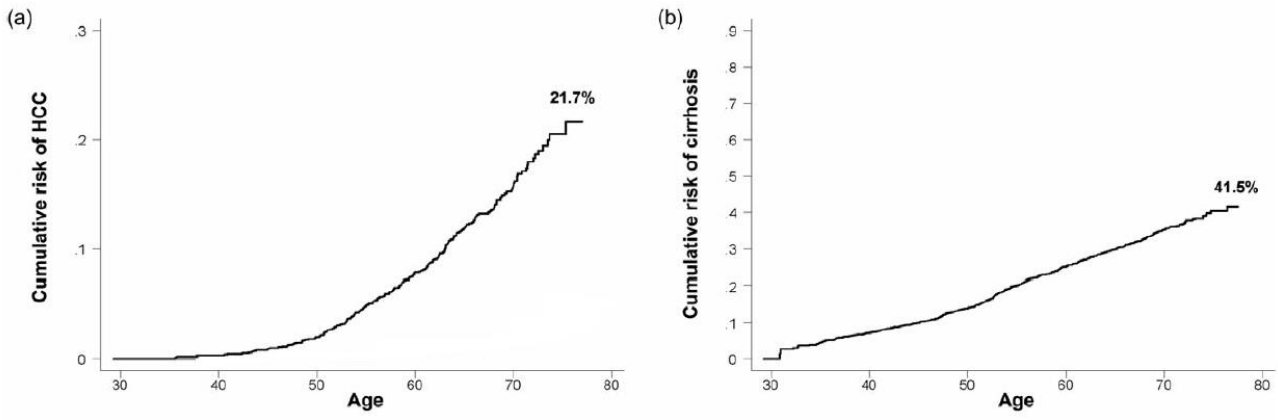

Figure S8: Cumulative probabilities graphs from REVEAL-HBV study

Supplement Figure 8 caption: reproduced from Chen, et al. 2011 (REVEAL-HBV) with slight modification to remove a non-relevant line from the graph (a). The graphs show cumulative probability of hepatocellular carcinoma (HCC, graph (a)) and cirrhosis (graph (b)).

3. Development of liver decompensation:

   The natural history model was validated for decompensated cirrhosis by matching epidemiology data with cumulative probability of incidence of decompensation amongst CHB cirrhotic patients.

   Epidemiology data: amongst patients with cirrhosis, the cumulative probability of develop liver decompensation is 20.[97] We ran the model with a cirrhotic cohort of 50 HBeAg(+) and 50 HBeAg(-) for 25,000 simulations for a time-horizon of 5 years. The model result was 18 cumulative probability of decompensation over a 5-year period, closely correlated with epidemiological data.

Conclusion of model validation: Overall, the model predictions of the outcome of the three major CHB complications (cirrhosis, hepatocellular carcinoma and liver decompensation) are closely aligned with the epidemiological data. And transition of patients from immune tolerant to immune active phase is depicted appropriately according to natural history data.

2. Validation of Treatment Model

To determine how our treatment model compares with the calibrated natural history model, we ran 100,000 microsimulations to determine clinical outcomes for an active chronic hepatitis B prevalent cohort. Data from observational and clinical trials show that chronic hepatitis B outcomes of cirrhosis, decompensation, hepatocellular carcinoma and death can be reduced, but not completely eliminated, with anti-viral therapy.[97,160-168] The estimates of percent reduction in outcomes, however, are not well defined with wide ranges reported in literature from no difference to 30 to 80% reduction in cirrhosis, decompensation and liver cancer.[97,163,165] When available, we used data published by American Association for the Study of Liver Disease to model relative risk reductions in development of cirrhosis, decompensation, hepatocellular carcinoma, and CHB related death.[97] In other instances, data from a previously published hepatitis B economic evaluation were used.[6]

We compared treatment with tenofovir with no intervention to determine the *reduction of key clinical outcomes* with treatment. For the purposes of validation test, we assumed complete adherence to treatment and complete suppression of HBV DNA. Relevant cohort and treatment characteristics for the validation test are shown in the **Supplement Table 29** below. The clinical outcomes measured were development of 1) compensated cirrhosis; 2) decompensated cirrhosis; 3) hepatocellular carcinoma from all CHB health states; 4) hepatocellular from cirrhotic states only; 5) liver transplantation; 6) death attributed to chronic hepatitis B from all health states; 7) death in compensated cirrhosis, attributed to chronic hepatitis B; 8) death from advanced liver disease (decompensated cirrhosis and hepatocellular carcinoma); and 9) death from decompensated cirrhosis, hepatocellular carcinoma, liver transplantation and post-liver transplantation.

Table S29: Treatment validation test cohort and treatment characteristics

Cohort Characteristics	**Base-case**
Model horizon	Life-time
Cohort Age	30 Years
Distribution in Active CHB States	
Immune Tolerant Phase	5.74
Immune Active Phase (eAg+)	
HBeAg+, Non-Cirrhotic	21.02
HBeAg+, Cirrhotic*	1.11
Immune Active Phase (eAg-)	
HBeAg-, Non-Cirrhotic	31.12
HBeAg-, Cirrhotic*	1.64
Immune Inactive Phase	
HBeAg-, Inactive CHB, Non-Cirrhotic	37.40
HBeAg-, Inactive CHB, Cirrhotic*	1.97
Treatment Characteristics	
Hepatitis B virus DNA suppression	100%
Adherence to therapy	100%
Development of resistance to tenofovir therapy	0%
HBeAg-/+= Hepatitis B eAntigen negative or positive; CHB = Chronic Hepatitis B	

Supplement Figure 9 below shows the outcomes of the model, represented as percent reduction in clinical outcomes with tenofovir treatment compared to no treatment. Overall, the model predicts appropriate levels of reduction in all key clinical outcomes. Reduction in development of cirrhosis, decompensation and hepatocellular carcinoma ranges from 33% to 67%, in general congruence with reported data and patterns. For example, Papatheodoridis, et al. reported an overall treatment related reduction of liver cancer of approximately 30%, our model predicts a reduction of 33% (light gray box in the figure below).[163] It has also been observed that reduction in hepatocellular carcinoma with treatment is higher in patients with cirrhosis.[97,162] In our model patients with cirrhosis experienced 46% increased reduction in liver cancer compared to overall reduction of 33%.

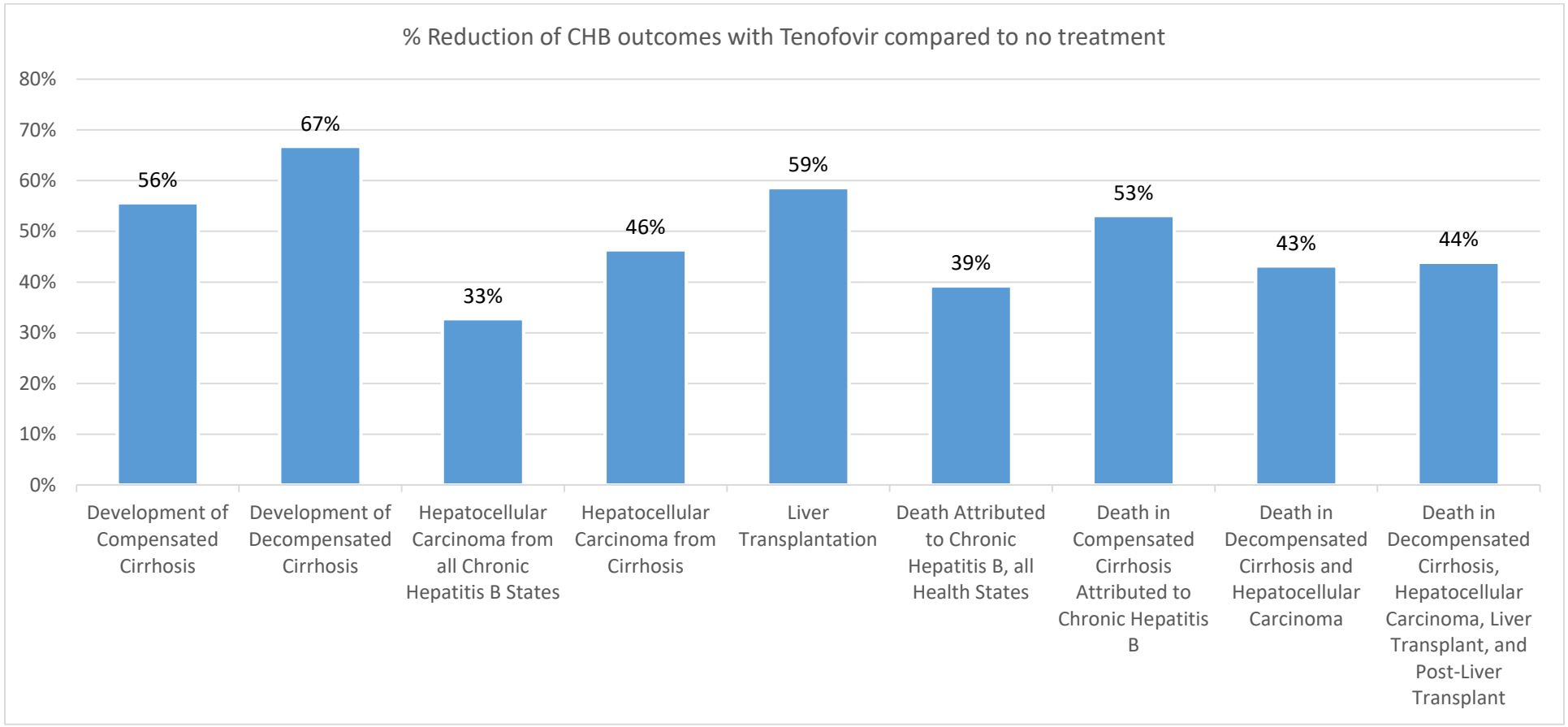

Figure S9: Percent reduction of key clinical outcomes of chronic hepatitis B with treatment

Supplement Figure 9 caption: The figure shows percent reduction of key clinical outcomes measured by the model for treatment with tenofovir compare to no treatment.

IV. Additional Base-Case Results

1. Results by strategy and program for each study population

a. Screen and Vaccinate

Table S30: Base-case results for screen and vaccinate strategy by program, by population

Strategy, by Population	Cost (USD)	Incremental Cost (USD)	QALYs	Incremental QALYs	ICER (USD/QALY)	Drug Costs (USD)	Health Care Costs (USD)	Screening Costs^ (USD)	Life Years
Asian and Pacific Islanders									
No Intervention	$3,902	-	23.780	-	-	$0	$3,902	$0	24.369
Community Outreach/Clinic Referral	$4,001	$99	23.787	0.007	13,397	$0	$3,876	$125	24.373
Africa Born Black Population									
No Intervention	$4,928	-	23.551	-	-	$0	$4,928	$0	24.205
Community Outreach/Clinic Referral	$5,024	$96	23.559	0.009	11,086	$0	$4,897	$127	24.210
Incarcerated Persons									
Universal Screening	$999	-	24.415	-	-	$0	$932	$67	24.755
No Intervention	$1,105	$106	24.365	-0.050	Dominated	$0	$1,105	$0	24.726
Refugee Population									
No Intervention	$3,183	-	23.934	-	-	$0	$3,183	$0	24.463
Community Outreach/Clinic Referral	$3,278	$95	23.944	0.010	9,453	$0	$3,147	$130	24.468
People Who Inject Drugs									
No Intervention	$6,924	-	23.070	-	-	$0	$6,924	$0	23.950
Syringe services programs	$6,974	$50	23.078	0.008	6,438	$0	$6,894	$80	23.954
Men Who Have Sex With Men									
No Intervention	$1,354	-	24.325	-	-	$0	$1,354	$0	24.701
STI Clinics	$1,361	$8	24.336	0.011	695	$0	$1,316	$46	24.707

USD: United States Dollar; QALYs: Quality-Adjusted Life-Years; ICER: Incremental Cost-Effectiveness Ratio; STI: Sexually Transmitted Infections
^Screening costs include vaccination costs.

b. Screen and Treat with Tenofovir

Table S31: Base-case results for screen and treat (with tenofovir) strategy by program, by population

Strategy, by Population	Cost (USD)	Incremental Cost (USD)	QALYs	Incremental QALYs	ICER (USD/QALY)	Drug Costs (USD)	Health Care Costs (USD)	Screening Costs^ (USD)	Life Years
Asian and Pacific Islanders									
No Intervention	$3,902	-	23.780	-	-	$0	$3,902	$0	24.369
Community Outreach/Clinic Partnership	$4,911	$1,009	23.827	0.048	21,159	$1,006	$3,762	$143	24.413
Community Outreach/Clinic Referral	$5,360	$449	23.853	0.026	17,314	$1,553	$3,686	$121	24.437
Africa Born Black Population									
No Intervention	$4,928	-	23.551	-	-	$0	$4,928	$0	24.205
Community Outreach/Clinic Partnership	$6,739	$1,811	23.646	0.096	18,947	$1,927	$4,662	$151	24.296
Incarcerated Persons									
No Intervention	$1,105	-	24.365	-	-	$0	$1,105	$0	24.726
Universal Screening	$1,446	$341	24.382	0.017	20,032	$359	$1,055	$32	24.742
Refugee Population									
No Intervention	$3,183	-	23.934	-	-	$0	$3,183	$0	24.463
Community Outreach/Clinic Partnership	$4,746	$1,563	24.011	0.078	20,066	$1,642	$2,955	$148	24.535
People Who Inject Drugs									
No Intervention	$6,924	-	23.070	-	-	$0	$6,924	$0	23.950
Syringe services programs	$7,016	$92	23.071	0.001	96,657	$15	$6,922	$80	23.951
Men Who Have Sex With Men									
No Intervention	$1,354	-	24.325	-	-	$0	$1,354	$0	24.701
STI Clinics	$1,637	$283	24.338	0.014	20,412	$293	$1,313	$31	24.713

USD: United States Dollar; QALYs: Quality-Adjusted Life-Years; ICER: Incremental Cost-Effectiveness Ratio; STI: Sexually Transmitted Infections
^Screening costs include vaccination costs.

c. Screen and Treat with Entecavir

Table S32: Base-case results for screen and treat (with entecavir) strategy by program, by population

Strategy, by Population	Cost (USD)	Incremental Cost (USD)	QALYs	Incremental QALYs	ICER (USD/QALY)	Drug Costs (USD)	Health Care Costs (USD)	Screening Costs^ (USD)	Life Years
Asian and Pacific Islanders									
No Intervention	$3,902	$0	23.780	0.000	$0	$0	$3,902	$0	24.369
Community Outreach/Clinic Partnership	$4,586	$685	23.819	0.039	$17,587	$652	$3,792	$143	24.406
Community Outreach/Clinic Referral	$4,859	$273	23.840	0.021	$12,878	$1,007	$3,732	$121	24.426
Africa Born Black Population									
No Intervention	$4,928	$0	23.551	0.000	$0	$0	$4,928	$0	24.205
Community Outreach/Clinic Partnership	$6,114	$1,186	23.629	0.078	$15,169	$1,245	$4,718	$151	24.281
Incarcerated Persons									
No Intervention	$1,105	$0	24.365	0.000	$0	$0	$1,105	$0	24.726
Universal Screening	$1,330	$225	24.378	0.014	$16,207	$233	$1,066	$32	24.740
Refugee Population									
No Intervention	$3,183	$0	23.934	0.000	$0	$0	$3,183	$0	24.463
Community Outreach/Clinic Partnership	$4,216	$1,033	23.997	0.064	$16,248	$1,065	$3,003	$148	24.523
People Who Inject Drugs									
No Intervention	$6,924	$0	23.070	0.000	$0	$0	$6,924	$0	23.950
Syringe services programs	$7,013	$89	23.071	0.001	$90,881	$11	$6,923	$80	23.951
Men Who Have Sex With Men									
No Intervention	$1,354	$0	24.325	0.000	$0	$0	$1,354	$0	24.701
STI Clinics	$1,543	$189	24.336	0.011	$16,672	$190	$1,322	$31	24.711

USD: United States Dollar; QALYs: Quality-Adjusted Life-Years; ICER: Incremental Cost-Effectiveness Ratio; STI: Sexually Transmitted Infections
^Screening costs include vaccination costs.

d. Screen and Treat (with Tenofovir) or Vaccinate

Table S33: Base-case results for screen and vaccinate or treat (with tenofovir) strategy by program, by population

Strategy, by Population	Cost (USD)	Incremental Cost (USD)	QALYs	Incremental QALYs	ICER (USD/QALY)	Drug Costs (USD)	Health Care Costs (USD)	Screening Costs^ (USD)	Life Years
Asian and Pacific Islanders									
No Intervention	$3,902	-	23.780	-	-	$0	$3,902	$0	24.369
Community Outreach/Clinic Referral	$5,361	$1,459	23.861	0.081	18,009	$1,553	$3,661	$148	24.441
Africa Born Black Population									
No Intervention	$4,928	-	23.551	-	-	$0	$4,928	$0	24.205
Community Outreach/Clinic Referral	$6,676	$1,748	23.653	0.102	17,089	$1,887	$4,636	$153	24.299
Incarcerated Persons									
No Intervention	$1,105	-	24.365	-	-	$0	$1,105	$0	24.726
Universal Screening	$1,321	$216	24.432	0.067	3,203	$359	$882	$80	24.770
Refugee Population									
No Intervention	$3,183	-	23.934	-	-	$0	$3,183	$0	24.463
Community Outreach/Clinic Referral	$4,716	$1,534	24.021	0.088	17,432	$1,642	$2,920	$154	24.540
People Who Inject Drugs									
No Intervention	$6,924	-	23.070	-	-	$0	$6,924	$0	23.950
Syringe services programs	$7,144	$220	23.090	0.020	11,160	$184	$6,869	$91	23.966
Men Who Have Sex With Men									
No Intervention	$1,354	-	24.325	-	-	$0	$1,354	$0	24.701
STI Clinics	$1,626	$272	24.349	0.025	10,954	$293	$1,275	$58	24.719

USD: United States Dollar; QALYs: Quality-Adjusted Life-Years; ICER: Incremental Cost-Effectiveness Ratio; STI: Sexually Transmitted Infections
^Screening costs include vaccination costs.

e. Screen and Treat (with Entecavir) or Vaccinate

Table S34: Base-case results for screen and vaccinate or treat strategy by program, by population

Strategy, by Population	Cost (USD)	Incremental Cost (USD)	QALYs	Incremental QALYs	ICER (USD/QALY)	Drug Costs (USD)	Health Care Costs (USD)	Screening Costs^ (USD)	Life Years
Asian and Pacific Islanders									
No Intervention	$3,902	$0	23.780	0.000	$0	$0	$3,902	$0	24.369
Community Outreach/Clinic Referral	$4,860	$958	23.847	0.068	$14,198	$1,007	$3,706	$148	24.430
Africa Born Black Population									
No Intervention	$4,928	$0	23.551	0	$0	$0	$4,928	$0	24.205
Community Outreach/Clinic Referral	$6,064	$1,136	23.636	0.085	$13,323	$1,220	$4,691	$153	24.285
Incarcerated Persons									
No Intervention	$1,105	$0	24.365	0	$0	$0	$1,105	$0	24.726
Universal Screening	$1,205	$100	24.429	0.064	$1,558	$233	$892	$80	24.768
Refugee Population									
No Intervention	$3,183	$0	23.934	0	$0	$0	$3,183	$0	24.463
Community Outreach/Clinic Referral	$4,186	$1,004	24.007	0.074	$13,626	$1,065	$2,968	$154	24.529
People Who Inject Drugs									
No Intervention	$6,924	$0	23.070	0	$0	$0	$6,924	$0	23.950
Syringe services programs	$7,109	$185	23.090	0.020	$9,194	$131	$6,886	$91	23.968
Men Who Have Sex With Men									
No Intervention	$1,354	$0	24.325	0	$0	$0	$1,354	$0	24.701
STI Clinics	$1,531	$178	24.347	0.022	$7,970	$190	$1,284	$58	24.717

USD: United States Dollar; QALYs: Quality-Adjusted Life-Years; ICER: Incremental Cost-Effectiveness Ratio; STI: Sexually Transmitted Infections
^Screening costs include vaccination costs.

2. Results by comparative broad strategies for each study population

a. Primary base-case results with drug (with tenofovir), health and screening costs plus life years

Table S35: Base-case results for screening and linkage to care (tenofovir treatment) strategies, by population

Strategy*, by Population	Cost (USD)	Incremental Cost (USD)	QALYs	Incremental QALYs	ICER (USD/QALY)	Drug Costs (USD)	Health Care Costs (USD)	Screening Costs^ (USD)	Life Years
Asian and Pacific Islanders									
No Intervention	$3,902	-	23.780	-	-	$0	$3,902	$0	24.369
Vaccination Only	$4,001	$99	23.787	0.007	13,397	$0	$3,876	$125	24.373
Treatment Only	$5,360	$1,359	23.853	0.066	20,519	$1,553	$3,686	$121	24.437
Inclusive	$5,361	$1	23.861	0.007	129	$1,553	$3,661	$148	24.441
Africa Born Black Population									
No Intervention	$4,928	-	23.551	-	-	$0	$4,928	$0	24.205
Vaccination Only	$5,024	$96	23.559	0.009	11,086	$0	$4,897	$127	24.210
Inclusive	$6,676	$1,652	23.653	0.094	17,645	$1,887	$4,636	$153	24.299
Treatment Only	$6,739	$63	23.646	-0.007	Dominated	$1,927	$4,662	$151	24.296
Incarcerated Persons									
Vaccination Only	$999	-	24.415	-	-	$0	$932	$67	24.755
No Intervention	$1,105	$106	24.365	-0.050	Dominated	$0	$1,105	$0	24.726
Inclusive	$1,321	$322	24.432	0.017	18,922	$359	$882	$80	24.770
Treatment Only	$1,446	$125	24.382	-0.050	Dominated	$359	$1,055	$32	24.742
Refugee Population									
No Intervention	$3,183	-	23.934	-	-	$0	$3,183	$0	24.463
Vaccination Only	$3,278	$95	23.944	0.010	9,453	$0	$3,147	$130	24.468
Inclusive	$4,716	$1,438	24.021	0.078	18,465	$1,642	$2,920	$154	24.540
Treatment Only	$4,746	$29	24.011	-0.010	Dominated	$1,642	$2,955	$148	24.535
People Who Inject Drugs									
No Intervention	$6,924	-	23.070	-	-	$0	$6,924	$0	23.950
Vaccination Only	$6,974	$50	23.078	0.008	6,438	$0	$6,894	$80	23.954
Inclusive	$6,999	$24	23.079	0.001	25,551	$15	$6,892	$91	23.955
Treatment Only	$7,016	$18	23.071	-0.008	Dominated	$15	$6,922	$80	23.951
Men Who Have Sex With Men									
No Intervention	$1,354	-	24.325	-	-	$0	$1,354	$0	24.701
Vaccination Only	$1,361	$8	24.336	0.011	695	$0	$1,316	$46	24.707
Inclusive	$1,626	$264	24.349	0.014	19,052	$293	$1,275	$58	24.719
Treatment Only	$1,637	$11	24.338	-0.011	Dominated	$293	$1,313	$31	24.713

*Specific screen and linkage to care programs for each broad strategy are shown in **Table S6**.
USD: United States Dollar; QALYs: Quality-Adjusted Life-Years
^Screening costs include vaccination costs.

b. Base-case results with drug (with entecavir), health and screening costs plus life years

Table S36: Base-case results for screening and linkage to care (entecavir treatment) strategies, by population

Strategy*, by Population	Cost (USD)	Incremental Cost (USD)	QALYs	Incremental QALYs	ICER (USD/QALY)	Drug Costs (USD)	Health Care Costs (USD)	Screening Costs^ (USD)	Life Years
Asian and Pacific Islanders									
No Intervention	$3,902	-	23.780	0.000	-	-	$3,902	-	24.369
Vaccination Only	$4,001	$99	23.787	0.007	$13,397	-	$3,876	$125	24.373
Treatment Only	$4,859	$858	23.840	0.053	$16,283	$1,007	$3,732	$121	24.426
Inclusive	$4,860	$1	23.847	0.007	$129	$1,007	$3,706	$148	24.430
Africa Born Black Population									
No Intervention	$4,928	-	23.551	0.000	-	-	$4,928	-	24.205
Vaccination Only	$5,024	$96	23.559	0.009	$11,086	-	$4,897	$127	24.210
Inclusive	$6,064	$1,039	23.636	0.077	$13,577	$1,220	$4,691	$153	24.285
Treatment Only	$6,114	$50	23.629	-0.007	Dominated	$1,245	$4,718	$151	24.281
Incarcerated Persons									
Vaccination Only	$999	-	24.415	0.000	-	-	$932	$67	24.755
No Intervention	$1,105	$106	24.365	-0.050	Dominated	-	$1,105	-	24.726
Inclusive	$1,205	$206	24.429	0.014	$14,847	$233	$892	$80	24.768
Treatment Only	$1,330	$125	24.378	-0.050	Dominated	$233	$1,066	$32	24.740
Refugee Population									
No Intervention	$3,183	-	23.934	0.000	-	-	$3,183	-	24.463
Vaccination Only	$3,278	$95	23.944	0.010	$9,453	-	$3,147	$130	24.468
Inclusive	$4,186	$909	24.007	0.064	$14,288	$1,065	$2,968	$154	24.529
Treatment Only	$4,216	$29	23.997	-0.010	Dominated	$1,065	$3,003	$148	24.523
People Who Inject Drugs									
No Intervention	$6,924	-	23.070	0.000	-	-	$6,924	-	23.950
Vaccination Only	$6,974	$50	23.078	0.008	$6,438	-	$6,894	$80	23.954
Inclusive	$6,996	$21	23.079	0.001	$21,897	$11	$6,894	$91	23.955
Treatment Only	$7,013	$18	23.071	-0.008	Dominated	$11	$6,923	$80	23.951
Men Who Have Sex With Men									
No Intervention	$1,354	-	24.325	0.000	-	-	$1,354	-	24.701
Vaccination Only	$1,361	$8	24.336	0.011	$695	-	$1,316	$46	24.707
Inclusive	$1,531	$170	24.347	0.011	$15,006	$190	$1,284	$58	24.717
Treatment Only	$1,543	$11	24.336	-0.011	Dominated	$190	$1,322	$31	24.711

*Specific screen and linkage to care programs for each broad strategy are shown in **Table S6.**
USD: United States Dollar; QALYs: Quality-Adjusted Life-Years
^Screening costs include vaccination costs.

V. Scenario Analysis

1. Improved screening and linkage to care – ICER Calculations

This scenario assumes 90% consent to screening, followed by 100% referral rate for those found susceptible or infected, followed by 90% successful linkage to treatment. Acceptance of treatment is modeled at 90% and acceptance of 1st, 2nd and 3rd dose of vaccine at 80% for each dose.

See Tables S37 and S38 on the next two pages.

a. Tenofovir based treatment and retreatment

Table S37: Scenario analysis - Improved screening and linkage to care, using tenofovir based treatment and retreatment - ICER Calculations

Strategy*, by Population	Cost (USD)	Incremental Cost (USD)	QALYs	Incremental QALYs	ICER (USD/QALY)	Drug Costs (USD)	Health Care Costs (USD)	Screening Costs^ (USD)	Life Years
Asian and Pacific Islanders									
No Intervention	$3,902	$0	23.780	0.000	-	$0	$3,902	$0	24.369
Vaccination Only	$4,016	$114	23.799	0.020	5,777	$0	$3,833	$183	24.380
Inclusive	$6,742	$2,726	23.948	0.148	18,394	$3,125	$3,400	$217	24.517
Treatment Only	$6,754	$12	23.928	-0.020	Dominated	$3,125	$3,468	$160	24.506
Africa Born Black Population									
No Intervention	$4,928	$0	23.551	0.000	-	$0	$4,928	$0	24.205
Vaccination Only	$5,035	$107	23.574	0.023	4,589	$0	$4,845	$189	24.218
Inclusive	$8,346	$3,312	23.762	0.188	17,578	$3,798	$4,320	$228	24.397
Treatment Only	$8,400	$54	23.739	-0.023	Dominated	$3,798	$4,403	$200	24.384
Incarcerated Persons									
Vaccination Only	$928	$0	24.444	0.000	-	$0	$830	$97	24.771
No Intervention	$1,105	$177	24.365	-0.080	Dominated	$0	$1,105	$0	24.726
Inclusive	$1,421	$494	24.471	0.026	18,795	$554	$754	$114	24.796
Treatment Only	$1,623	$201	24.391	-0.080	Dominated	$554	$1,028	$41	24.751
Refugee Population									
No Intervention	$3,183	$0	23.934	0.000	-	$0	$3,183	$0	24.463
Vaccination Only	$3,287	$104	23.961	0.027	3,866	$0	$3,089	$198	24.478
Inclusive	$5,470	$2,183	24.079	0.119	18,416	$2,500	$2,742	$228	24.587
Treatment Only	$5,526	$56	24.052	-0.027	Dominated	$2,500	$2,836	$190	24.572
People Who Inject Drugs									
Vaccination Only	$6,271	$0	23.281	0.000	-	$0	$6,126	$146	24.070
No Intervention	$6,924	$653	23.070	-0.211	Dominated	$0	$6,924	$0	23.950
Inclusive	$9,724	$3,453	23.538	0.257	13,449	$3,959	$5,574	$190	24.325
Treatment Only	$10,465	$740	23.327	-0.211	Dominated	$3,959	$6,373	$132	24.204
Men Who Have Sex With Men									
Vaccination Only	$1,302	$0	24.370	0.000	-	$0	$1,195	$107	24.726
No Intervention	$1,354	$52	24.325	-0.046	Dominated	$0	$1,354	$0	24.701
Inclusive	$2,105	$803	24.413	0.043	18,604	$910	$1,069	$126	24.766
Treatment Only	$2,181	$76	24.368	-0.046	Dominated	$910	$1,228	$43	24.740

*Specific screen and linkage to care programs for each broad strategy are shown in Table S6.
USD: United States Dollar; QALYs: Quality-Adjusted Life-Years; ^Screening costs include vaccination costs.

b. Entecavir based treatment and tenofovir retreatment

Table S38: Scenario analysis - Improved screening and linkage to care, using entecavir based treatment and retreatment - ICER Calculations

Strategy*, by Population	Cost (USD)	Incremental Cost (USD)	QALYs	Incremental QALYs	ICER (USD/QALY)	Drug Costs (USD)	Health Care Costs (USD)	Screening Costs^ (USD)	Life Years
Asian and Pacific Islanders									
No Intervention	$3,902	$0	23.780	0.000	$0	$0	$3,902	-	24.369
Vaccination Only	$4,016	$114	23.799	0.020	$5,777	$0	$3,833	$183	24.380
Inclusive	$5,734	$1,718	23.920	0.121	$14,201	$2,026	$3,491	$217	24.495
Treatment Only	$5,746	$12	23.901	-0.020	Dominated	$2,026	$3,559	$160	24.484
Africa Born Black Population									
No Intervention	$4,928	$0	23.551	0.000	$0	$0	$4,928	-	24.205
Vaccination Only	$5,035	$107	23.574	0.023	$4,589	$0	$4,845	$189	24.218
Inclusive	$7,114	$2,079	23.728	0.154	$13,495	$2,454	$4,431	$228	24.368
Treatment Only	$7,168	$54	23.705	-0.023	Dominated	$2,454	$4,514	$200	24.355
Incarcerated Persons									
Vaccination Only	$928	$0	24.444	0.000	$0	$0	$830	$97	24.771
No Intervention	$1,105	$177	24.365	-0.080	Dominated	$0	$1,105	-	24.726
Inclusive	$1,243	$315	24.466	0.021	$14,692	$359	$770	$114	24.792
Treatment Only	$1,444	$201	24.386	-0.080	Dominated	$359	$1,044	$41	24.747
Refugee Population									
No Intervention	$3,183	$0	23.934	0.000	$0	$0	$3,183	-	24.463
Vaccination Only	$3,287	$104	23.961	0.027	$3,866	$0	$3,089	$198	24.478
Inclusive	$4,664	$1,377	24.057	0.097	$14,227	$1,621	$2,815	$228	24.569
Treatment Only	$4,720	$56	24.030	-0.027	Dominated	$1,621	$2,909	$190	24.555
People Who Inject Drugs									
Vaccination Only	$6,271	$0	23.281	0.000	$0	$0	$6,126	$146	24.070
No Intervention	$6,924	$653	23.070	-0.211	Dominated	$0	$6,924	-	23.950
Inclusive	$8,962	$2,691	23.546	0.265	$10,165	$2,831	$5,941	$190	24.361
Treatment Only	$9,702	$740	23.335	-0.211	Dominated	$2,831	$6,739	$132	24.240
Men Who Have Sex With Men									
Vaccination Only	$1,302	$0	24.370	0.000	$0	$0	$1,195	$107	24.726
No Intervention	$1,354	$52	24.325	-0.046	Dominated	$0	$1,354	-	24.701
Inclusive	$1,811	$509	24.405	0.035	$14,458	$590	$1,096	$126	24.759
Treatment Only	$1,887	$76	24.360	-0.046	Dominated	$590	$1,254	$43	24.734

*Specific screen and linkage to care programs for each broad strategy are shown in Table S6.
USD: United States Dollar; QALYs: Quality-Adjusted Life-Years
^Screening costs include vaccination costs.

2. Improved screening and linkage to care - Clinical Outcomes

a. Short-, intermediate-, and long-term clinical outcomes

Results of 1 million simulations with base-case values to determine the percent reduction in clinical outcomes with a program that screens and treats or vaccinates compared to no intervention.

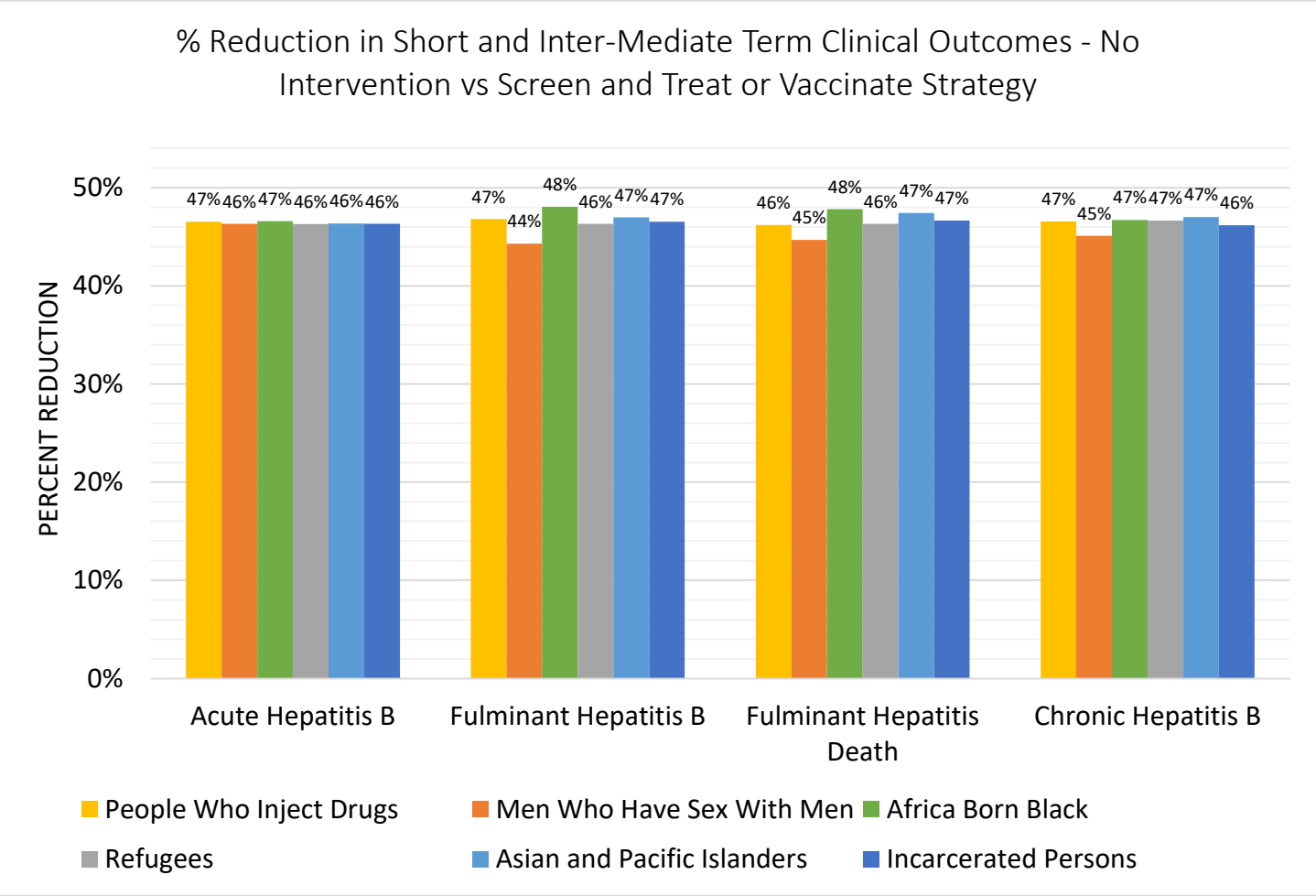

Figure S10: Short-term and intermediate clinical outcomes for each population in scenario analysis

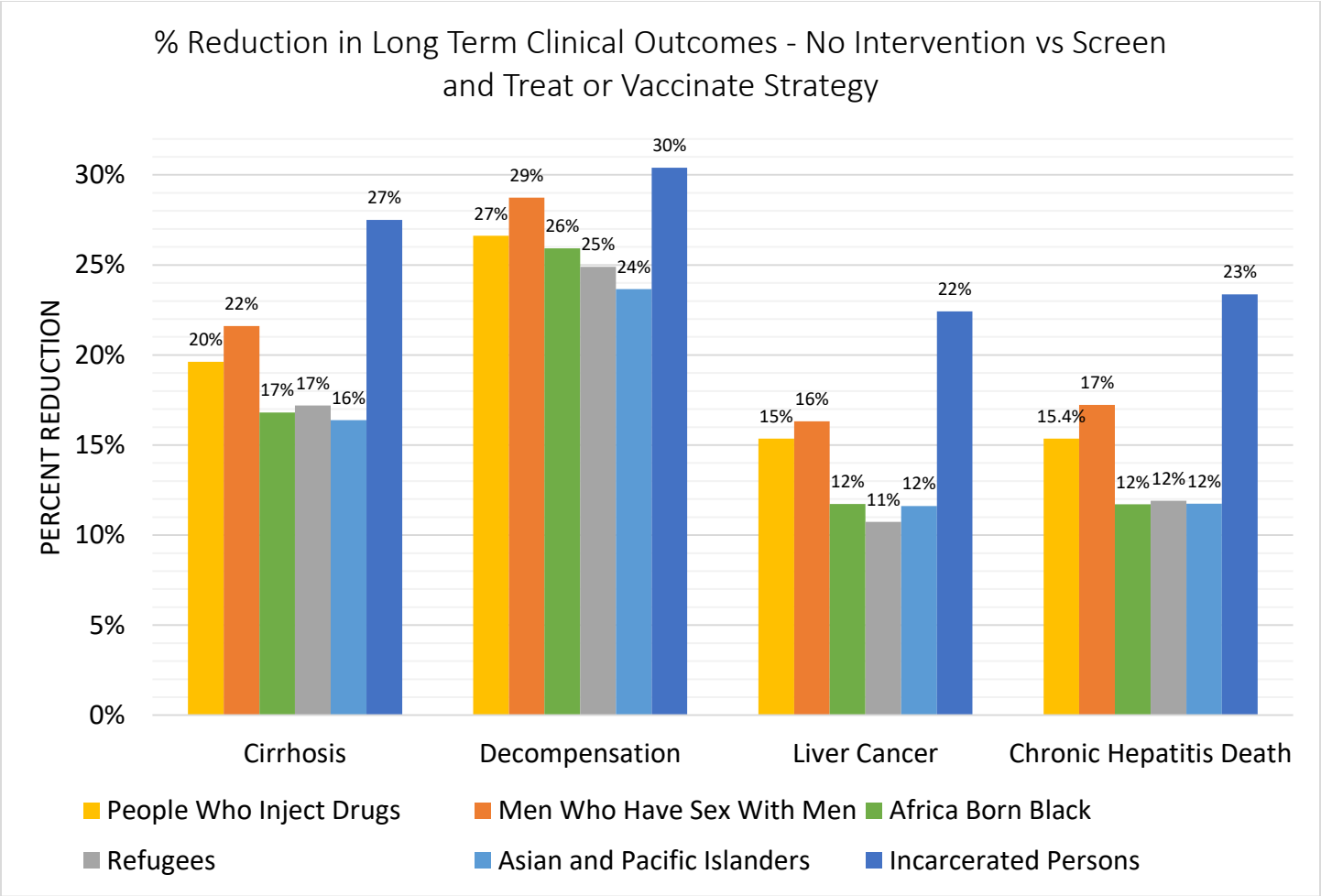

Figure S11: Long-term clinical outcomes for each population in scenario analysis

VI. Additional One-Way Analyses

This section presents additional one-way analyses. More in depth versions of tornado diagrams are shown. A table on the impact of hepatitis B population-specific prevalence and incidence rate on is shown in a table.

1. Tornado Analyses:

The main paper presents the top sex variables impacting the incremental cost-effectiveness ration (ICER). These analyses provide more details (for the top 20 inputs) about the uncertainty around the inputs and their impact on the model outputs.

Six tornado diagrams are shown, one for each population modeled.

How to read the tornado diagrams: the blue bars indicate the lower ICER for the value listed first in the range; orange bars indicate an increase for the 2nd value in the range. These ranges are the uncertainty around the input and the length of the bars reflects the impact on the ICER of the uncertainty.

a. Asian and Pacific Islanders

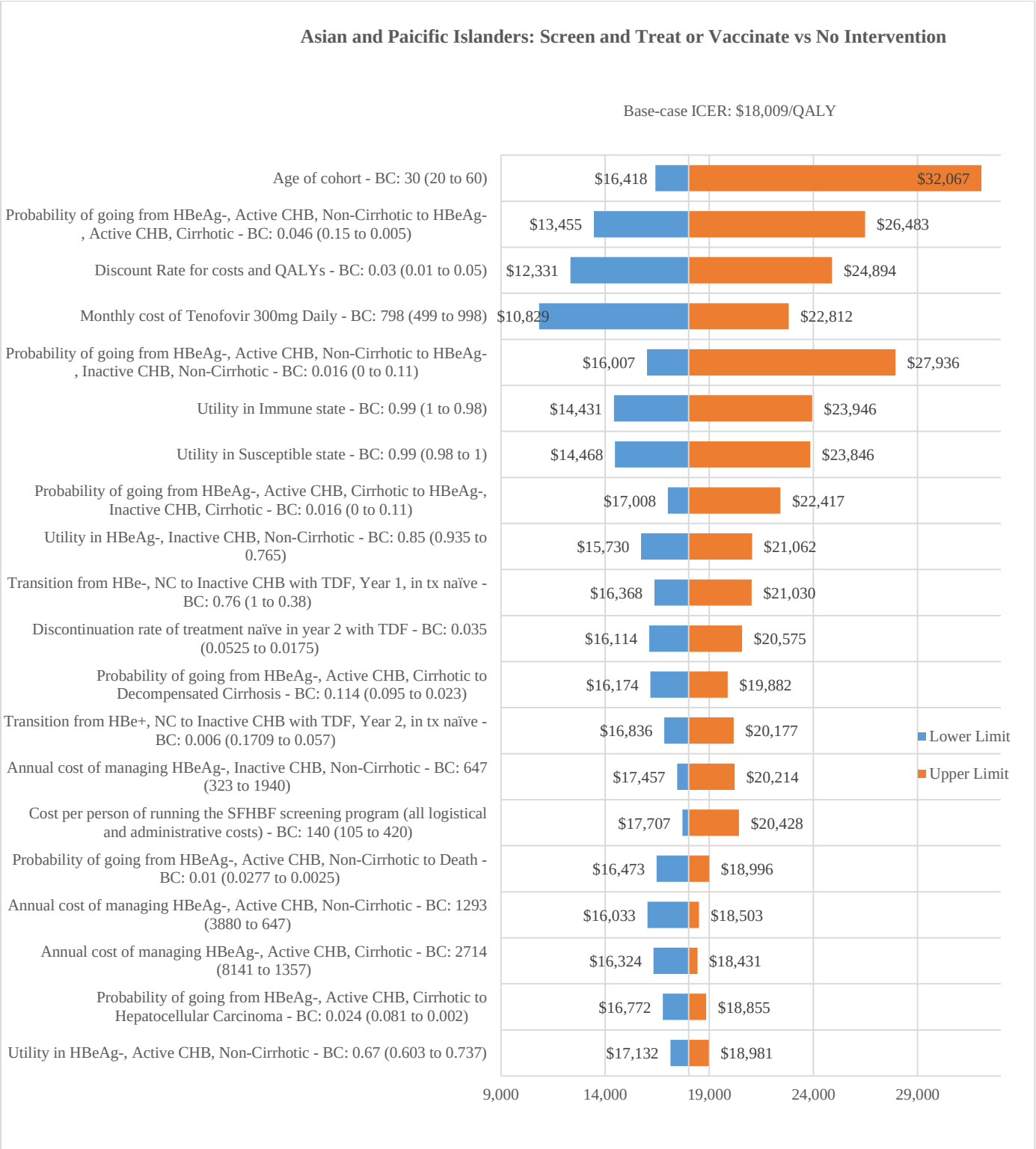

Figure S12: Sensitivity analysis for the inclusive strategy compared to no intervention for Asian and Pacific Islanders

b. Africa Born Black Population

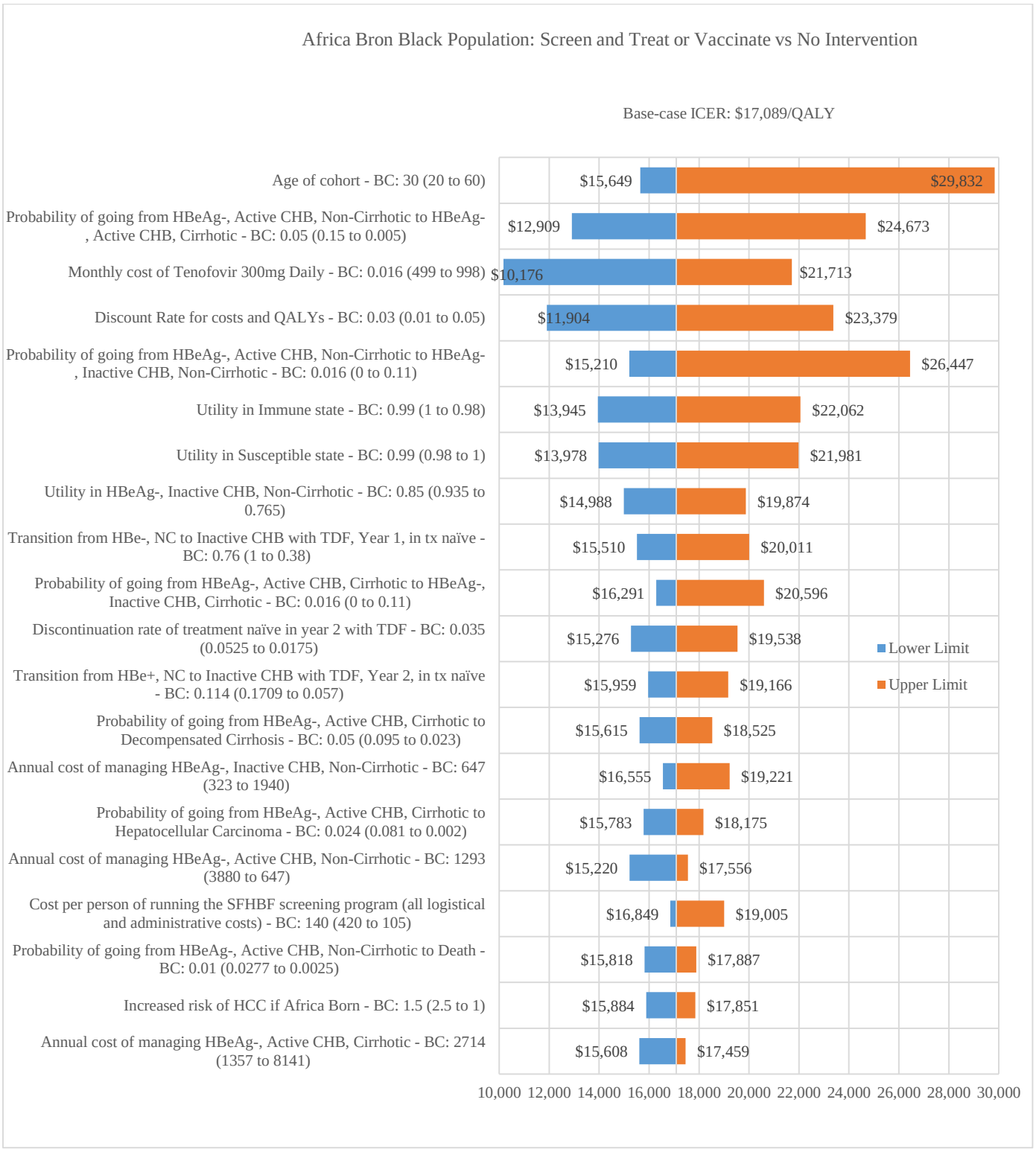

Figure S13: Sensitivity analysis for the inclusive strategy compared to no intervention for Africa Born Black Population

c. Incarcerated Persons

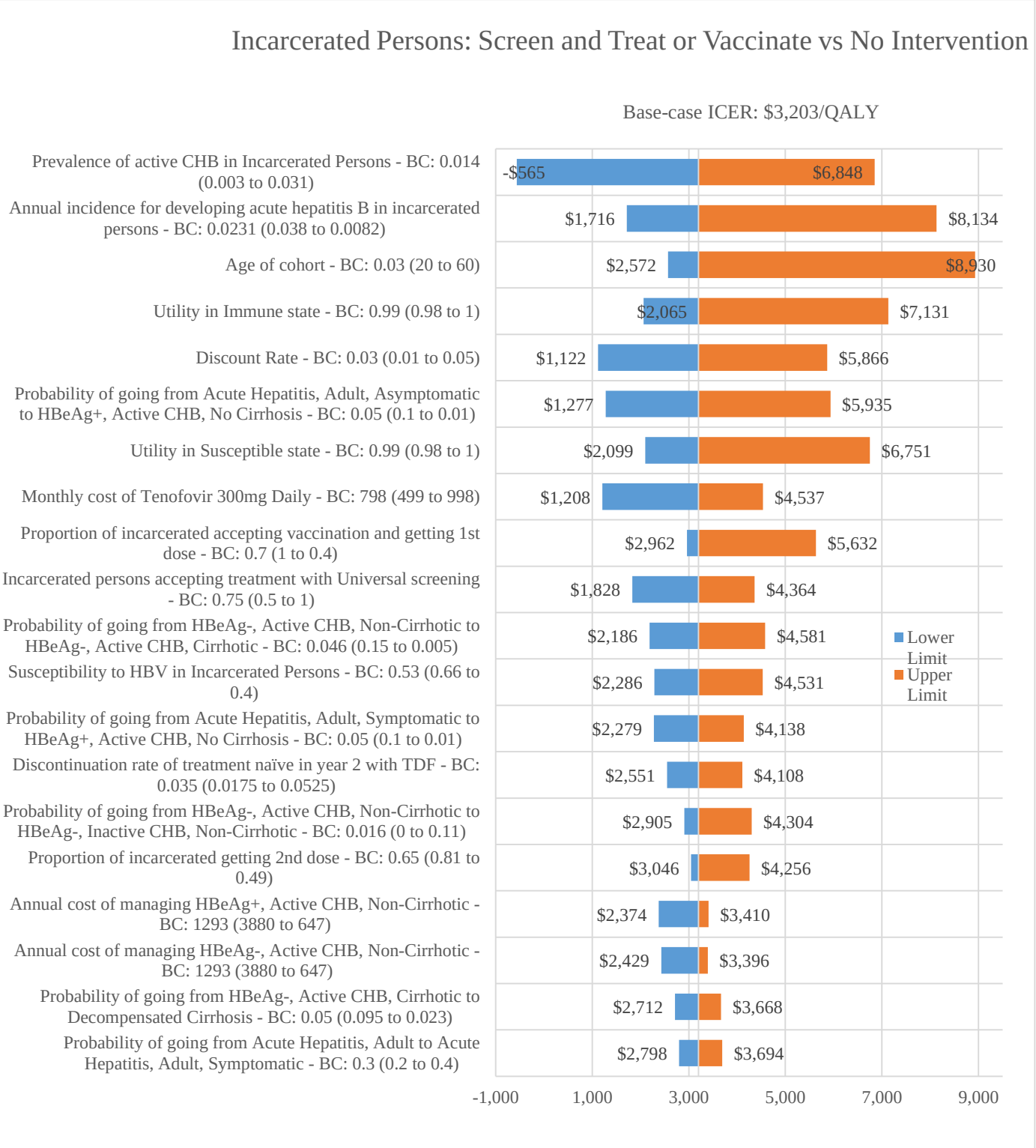

Figure S14: Sensitivity analysis for the inclusive strategy compared to no intervention for Incarcerated Individuals

d. Refugees

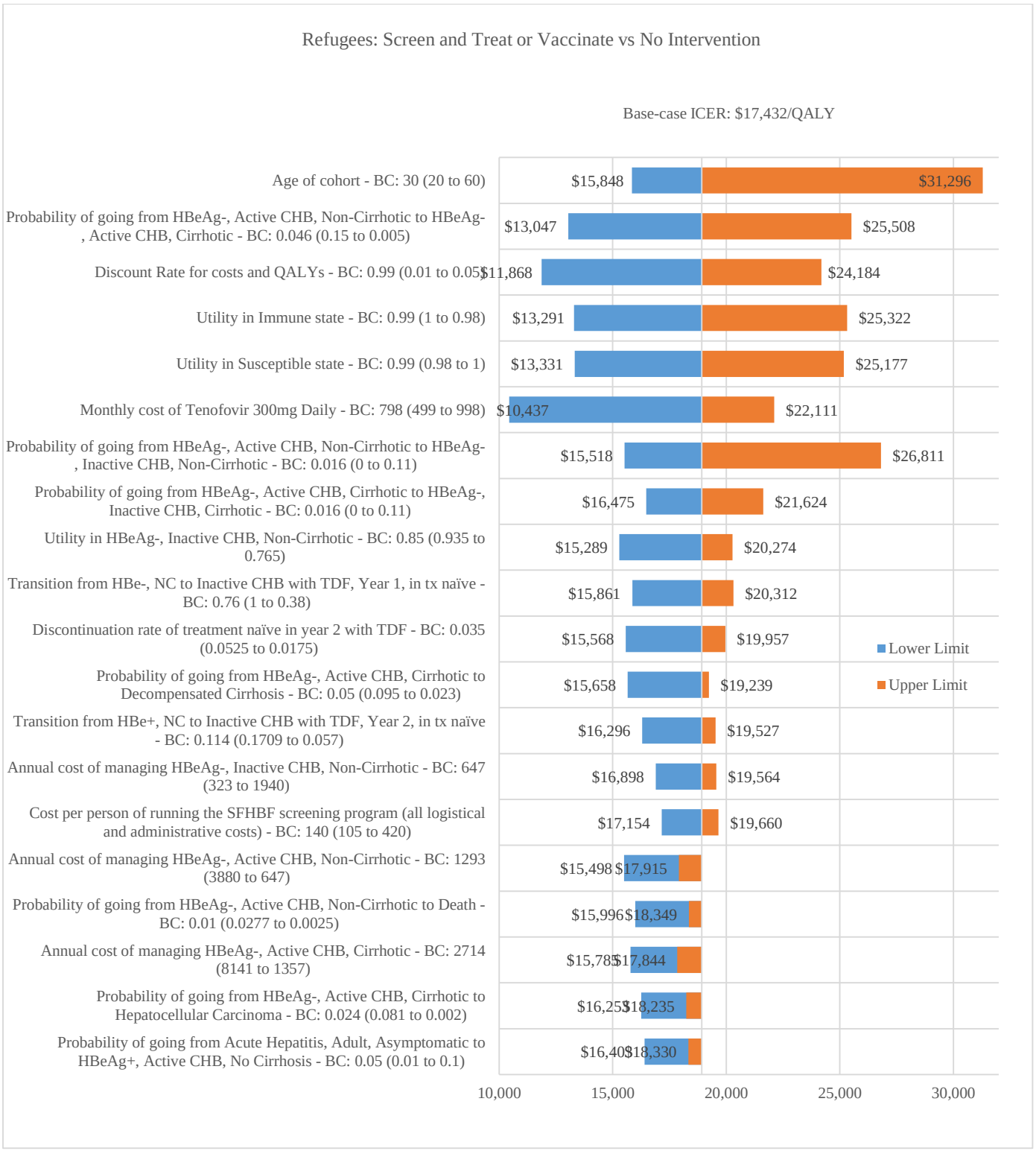

Figure S15: Sensitivity analysis for the inclusive strategy compared to no intervention for Refugees

e. People Who Inject Drugs

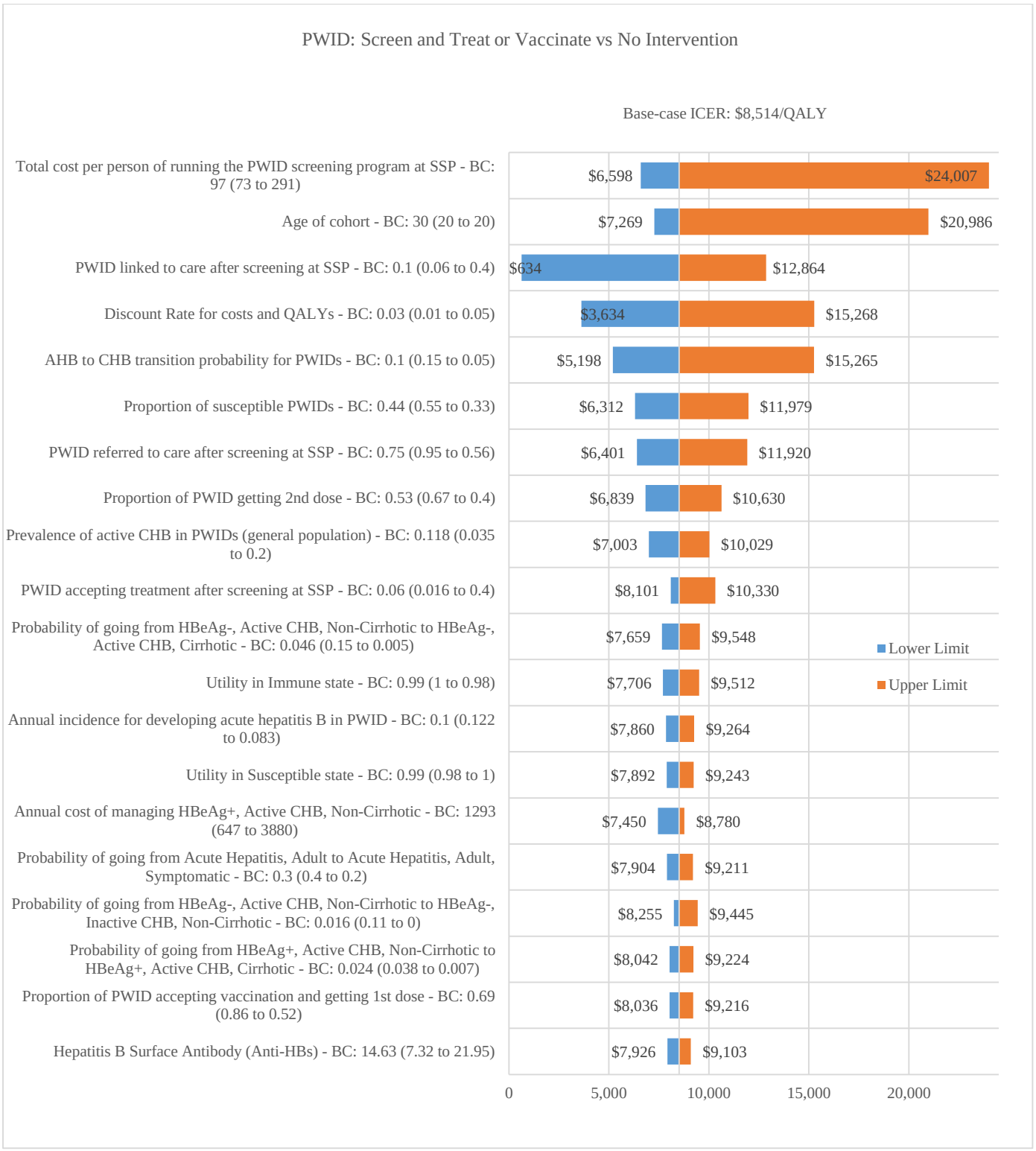

Figure S16: Sensitivity analysis for the inclusive strategy compared to no intervention for People Who Inject Drugs

f. Men Who Have Sex with Men

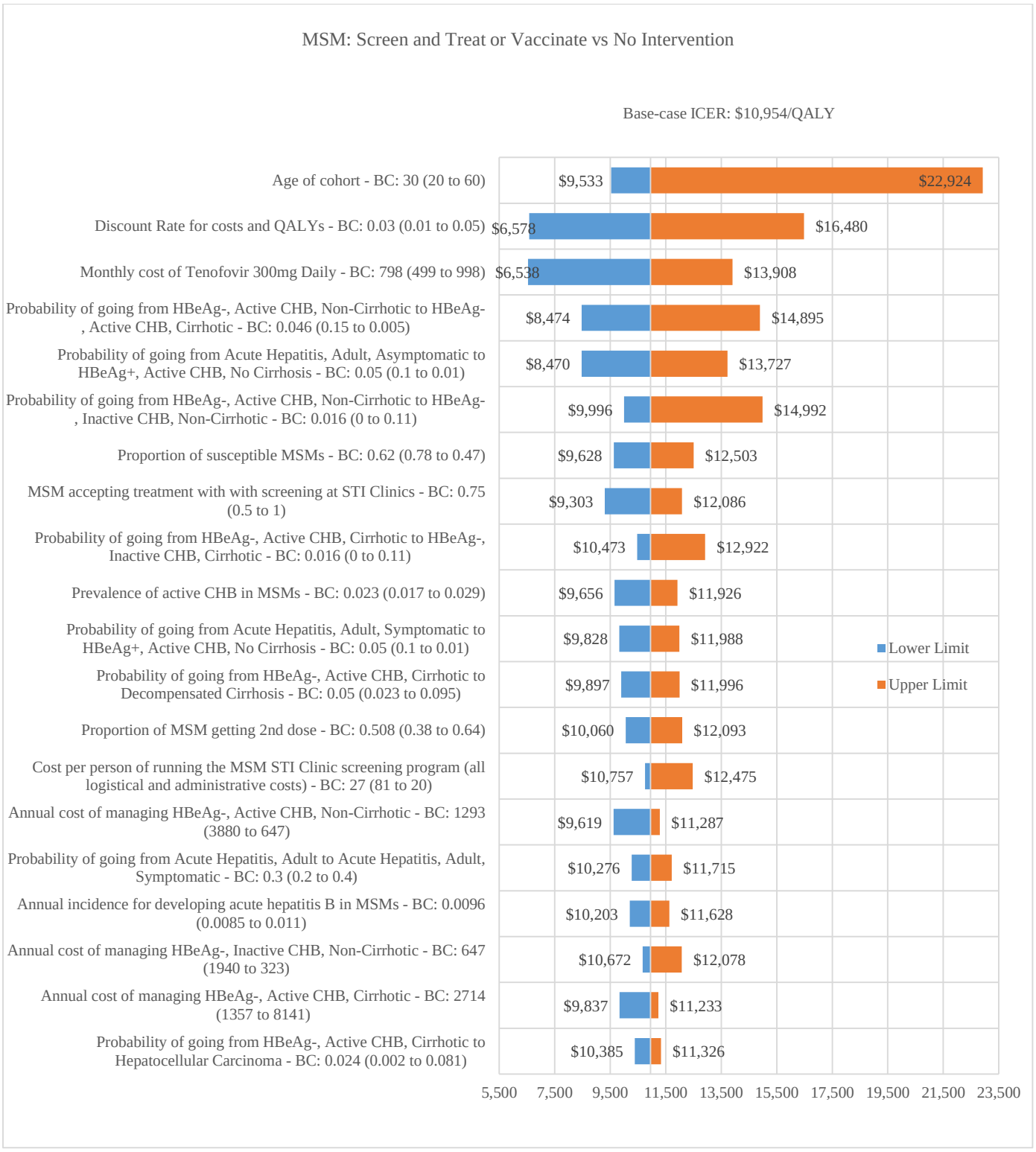

Figure S17: Sensitivity analysis for the inclusive strategy compared to no intervention for Men Who Sex with Men

2. Effect of uncertainty around population-specific prevalence and incidence rates on ICER

The table below shows the effect of uncertainty around population-specific prevalence and incidence on the cost-effectiveness of the inclusive strategy when compared to no intervention.

The difference in ICER ranges listed in the table below show the maximum effect of the uncertainty for range for each variable in a given population in cost-effectiveness ratios. A low difference in ICERs means that the ICERs between the lower and the upper range of uncertainty were small, thus unlikely to effect the cost-effectiveness of a given strategy. While a large difference in the ICER range shows a greater impact of the uncertainty around that input on the cost-effectiveness ratios. The ICERs for incarcerated population, people who inject drugs, and men who have sex with men were most sensitive to the uncertainty ranges. However, a finding of note in these analyses was that across all uncertainty ranges, the ICERs remained below USD 50,000/QALY (or highly cost-effective for the United States).

Table S39: Effect of prevalence and incidence on cost-effectiveness of the inclusive strategy, by population

	Prevalence of hepatitis B		Incidence rate of hepatitis B	
Population	Base-Case (Range)	Difference in ICER Range (USD/QALY)	Base-Case (Range)	Difference in ICER Range (USD/QALY)
Asian and Pacific Islanders	0.079 (0.059 to 0.099)	$240	0.0064 (0.0047 to 0.0081)	$951
Africa Born Blacks	0.097 (0.073 to 0.12)	$299	0.0064 (0.0047 to 0.0081)	$849
Incarcerated Persons	0.014 (0.003 to 0.031)	$7,413	0.0231 (0.0082 to 0.038)	$6,418
Refugees	0.063 (0.0474 to 0.079)	$498	0.0064 (0.0047 to 0.0081)	$1,164
People Who Inject Drugs	0.118 (0.035 to 0.2)	$3,026	0.10 (0.083 to 0.122)	$1,404
Men Who Have Sex with Men	0.023 (0.017 to 0.029)	$2,270	0.0096 (0.0085 to 0.011)	$1,425

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