Health and Economic Impact of Treatment-based Strategies on Chronic Hepatitis B in Ontario

by

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Author’s Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Background/Aim: The lives of about 257 million people in the world are being affected by chronic hepatitis B (CHB), and this contagious disease is gradually pushing them closer to the edge of death caused by cirrhosis and hepatocellular carcinoma. Ontario is closely connected to the rest of the world; more than 40% of the annual population growth over the past decade has come from immigrants. Addressing hepatitis B and achieving the World Health Organization (WHO)'s hepatitis elimination goals are vital. Tenofovir alafenamide (TAF) has been approved for treating CHB due to a proposed better safety profile in comparison to current therapies. However, its cost-effectiveness remains unknown. The aim of this thesis was to assess the health and economic impact of TAF and other treatments of CHB in Ontario.

Methods: Two types of health policy models were employed to compare strategies involving entecavir (ETV), tenofovir disoproxil fumarate (TDF), and TAF. 1) A state-transition model (STM) based on the natural history of CHB and the published literature was developed to evaluate the cost-effectiveness of the treatment strategies for hepatitis B envelope antigen (HBeAg)-positive and HBeAg-negative CHB patients from an Ontario Ministry of Health perspective. It adopted a lifetime time horizon, and outcomes measured were predicted number of liver-related disease and deaths, costs (2018 Canadian dollars), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). 2) An agent-based model (ABM) that accommodates differential selectivity, behavior, and network properties was developed to predict the impact of the treatment-as-prevention options on the incidence and prevalence of hepatitis B virus (HBV)-related health outcomes in Ontario over the next decade. We simulated the entire Ontario population, stratified by age, gender, residential address, and immigration status. Parameters were estimated from literature-derived estimates regarding Ontario demographics, epidemiology, and sexual behavior. Historical Ontario HBV data were used for calibration.

Results: 1) The STM found that TAF-containing strategies are unlikely to be a rational choice for treating CHB infections. For HBeAg-positive patients, TAF followed by ETV generated an additional 0.16 QALYs/person at an additional cost of $14,836.18 with an ICER of $94,142.71/QALY compared with TDF followed by ETV. Only 28.7% of the iterations showed that it is the optimal strategy with $50,000 willingness-to-pay threshold. For HBeAg-negative patients, ETV followed by TAF would prevent an additional 13 liver-related deaths per 1,000 CHB patients treated compared with TDF followed by ETV. It generated an additional 0.13 QALYs/person at an additional cost of $59,776.53

with an ICER of $461,162.21/QALY compared with TDF followed by ETV. 2) We calibrated the ABM-simulated number of reported acute hepatitis B (AHB) infections with the historical reported cases in Ontario. After extensive calibration and validation processes, our model showed a good match with the real-world observations. The ABM predicted that the actual prevalence of CHB in Ontario would decrease by 11.5% from 2017 to 2030 if all CHB patients eligible and ready for treatment begin to receive TDF followed by ETV or TAF followed by ETV after 2016. The reported incidence of AHB and the actual incidence of liver-related death are expected to fall by 48.9% and rise by 12.3% from 2017 to 2030, respectively. TAF followed by ETV was not found to be significantly different from TDF followed by ETV in reducing the prevalence and incidence of HBV-related health outcomes.

Conclusions: TAF is not cost-effective at its current cost. A 33.4% reduction in price would be required to make it cost-effective for HBeAg-positive patients with a $50,000 willingness-to-pay threshold. The percentages of decline in new CHB cases and liver-related deaths from 2017 to 2030 would be 37.8% and 77.3% lower than the percentages that the WHO is targeting, respectively. Ontario is unable to achieve the WHO's goals of eliminating new CHB cases and CHB deaths simply by relying on current treatment-as-prevention strategies.

Acknowledgments

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List of Abbreviations

AASLD – American Association for the Study of Liver Diseases

ABM – agent-based model

AHB – acute hepatitis B

ALT – alanine aminotransferase

BSC – best supportive care

CC – compensated cirrhosis

CHB – chronic hepatitis B

DC – decompensated cirrhosis

EASL – European Association for the Study of the Liver

EQ-5D – EuroQol-5 Dimension

ETV – entecavir

ETV→BSC – entecavir followed by best supportive care

ETV→TAF→BSC – entecavir followed by tenofovir alafenamide and followed by best supportive care

ETV→TDF→BSC – entecavir followed by tenofovir disoproxil fumarate and followed by best supportive care

FSA – forward sortation area

GOF – goodness of fit

HBeAg – hepatitis B envelope antigen

HBsAg – hepatitis B surface antigen

HBV – hepatitis B virus

HCC – hepatocellular carcinoma

HUI3 – Health Utility Index Mark 3

ICER – incremental cost-effectiveness ratio

IT – immune tolerance

LAM – lamivudine

NACI – National Advisory Committee on Immunization

PSA – probabilistic sensitivity analysis

QALY – quality-adjusted life year

SAE – serious adverse event

STM – state-transition model

TAF – tenofovir alafenamide

TAF→BSC – tenofovir alafenamide followed by best supportive care

TAF→ETV→BSC – tenofovir alafenamide followed by entecavir and followed by best supportive care

TDF – tenofovir disoproxil fumarate

TDF→BSC – tenofovir disoproxil fumarate followed by best supportive care

TDF→ETV→BSC – tenofovir disoproxil fumarate followed by entecavir and followed by best supportive care

WHO – World Health Organization

Chapter 1
Introduction

Chronic hepatitis B (CHB) is a viral infection that affects the liver, causing approximately 887,000 deaths worldwide in 2015.[1] It is a silent disease; most people are not aware of it when they are infected. As CHB can progress into cirrhosis or hepatocellular carcinoma (HCC) from long-term infection,[2] most people infected and diagnosed with it must be on lifelong treatment.[1]

1.1 Hepatitis B Virus Transmission Mode and Prevalence

Hepatitis B virus (HBV) can be transmitted through the blood, saliva, and other body fluids from an infected person.[1] Although effective hepatitis B vaccines have been available since 1982, new HBV infections are still common.[2] It has been estimated that the lives of 257 million people in the world are being affected by CHB,[1] and approximately 111,800 people with HBV are living in Canada.[3] The HBV infection rate in Canada is less than 1% of the Canadian population;[3] however, the prevalence of hepatitis B should not be ignored. More than one-fifth of the Canadian population was born abroad,[4] and most of the immigrants over the past decade came from regions with high-prevalence of hepatitis B, such as Asia and Africa.[1,4]

1.2 Natural History of Hepatitis B

People infected with HBV will initially develop acute hepatitis B (AHB).[2] The persistence of hepatitis B surface antigen (HBsAg) in the serum for at least six months is a major indicator of chronic infection.[1] The majority of patients with chronic infection are infected at birth or in early childhood.[5] However, a small proportion of patients develop chronic infection from AHB acquired during adulthood.[2]

CHB infection stages can be generally classified into four phases: the immune tolerant phase, immune clearance phase, inactive carrier phase, and reactivation phase.[2,5-7] Patients in the immune tolerant phase have high HBV viral load, normal alanine aminotransferase (ALT) levels, and minimal liver damage.[2,6,7] When the tolerogenic effect is lost during the first phase, patients enter the immune clearance phase.[2] Their immune system realizes that HBV is foreign, and the resulting immune response causes liver inflammation.[7] Hence, both elevated HBV viral load and ALT levels are the major features of this phase.[2] Hepatitis B envelope antigen (HBeAg) seroconversion may occur in patients with HBeAg-positive CHB.[7] The disease then enters the inactive carrier phase.[2,7] HBV viral load drops to an undetectable level, and ALT levels become normal, indicating mild or no liver injury.[2] Even if CHB

patients enter the inactive carrier phase, HBeAg reversion is still possible and might happen multiple times in the future.[6,7] They can also enter the reactivation phase and develop HBeAg-negative CHB,[5] which has a higher incidence of cirrhosis.[2] A very small minority of patients may develop HBsAg loss and completely recover from this chronic disease.[5]

About 2% to 10% of patients with CHB develop cirrhosis every year.[8] Subsequently, they may further deteriorate to decompensated cirrhosis (DC) or HCC at an annual rate of 5% to 10%.[8] The annual chance of death for patients with DC or HCC is 20% to 50%.[8]

1.3 Hepatitis B Virus Screening and Vaccination Policy

HBV screening for pregnant women, immigrants from high-prevalence regions of HBV, and other high-risk groups, such as those who have percutaneous or mucosal exposure to HBV, was suggested by the National Advisory Committee on Immunization (NACI);[9] however, only screening of pregnant women was implemented in Canada.[10] People in the immigration process are not required to receive HBsAg testing.[11] NACI also recommended HBV vaccination for all infants, children under the age of 18, and people at increased risk of HBV infection such as those who have unprotected sexual contacts with new partners.[9] Infants born to a mother with hepatitis B should be vaccinated within 12 hours of birth.[9] Since 1994, Ontario has initiated a routine HBV vaccination program for seventh-grade students,[9] and the completion rate has been very high (78% to 97%).[10]

1.4 Treatment of Chronic Hepatitis B

The primary goals of treating CHB are to achieve sustained suppression of HBV replication and liver disease remission and to prevent serious outcomes such as cirrhosis and HCC.[6] The treatment of HBeAg-positive CHB ends when HBeAg seroconversion occurs, but the endpoint of treating HBeAg-negative CHB is unknown.[6] Effective drugs with a high barrier to resistance, such as entecavir (ETV) and tenofovir disoproxil fumarate (TDF), have been developed. The resistance rate of ETV in treatment-naïve patients is below 1%,[12] and it may be effective for HBeAg-positive CHB patients with resistance to lamivudine (LAM).[8] While resistance to TDF has not yet been observed,[13-15] its long-term use may have a negative impact on the bones and kidneys.[14] Both TDF and ETV have lost their patents, allowing the availability of more affordable generic versions.[16]

ETV and TDF were recommended by the American Association for the Study of Liver Diseases (AASLD), the World Health Organization (WHO), and a number of guidelines and analyses as the most potent and cost-effective drugs to suppress HBV.[1,17-24] However, the approval of a novel prodrug

of TDF, tenofovir alafenamide (TAF), by the U.S. Food and Drug Administration for the treatment of CHB in November 2016 may impact these recommendations. Two randomized controlled trials were recently published comparing the efficacy of TAF and TDF, where TAF was found to be able to deliver the active metabolite to target cells more efficiently than TDF at a much lower dose, thereby reducing bone and renal toxic effects caused by systemic exposure.[14,15] Similar to TDF, its barrier to resistance is presumably very high.[14,15,25] However, its comparative cost-effectiveness with other treatments remains unknown.

At present, TDF and ETV are funded by the Ontario Drug Benefit Program.[16] Although TAF has been identified as a preferred therapy for patients with CHB in the guidelines released by the AASLD and the European Association for the Study of the Liver (EASL) due to clinical benefits,[17,26] it has not been listed as a reimbursed drug in Ontario.[16] The WHO's global hepatitis strategy calls for a 90% reduction in new CHB cases, a 65% reduction in CHB deaths, and an 80% treatment rate on eligible CHB patients worldwide by 2030,[27] and the Canadian government is committed to achieving these goals.[28] How TAF is going to affect the relative cost-effectiveness of each treatment option, and whether it is able to help us achieve the goals set by the WHO, need to be examined.

1.5 Health Policy Models

Health policy models are mathematical simulation tools that provide a platform to combine evidence of effectiveness, safety, and cost and provide support in analyzing the potential impact of health strategies for a given amount of expenditure. They are being increasingly relied on by healthcare providers and governments to make rational decisions about adopting healthcare programs and reimbursing new drugs. The benefit of treating some diseases such as CHB may only be observed after a long period of time. As such, health policy modeling is the only practical option for estimating the long-term impact of CHB treatment strategies. The two kinds of models that are suitable to simulate the potential impact of strategies on the development of CHB are the state-transition model (STM) and the agent-based model (ABM),[29,30] which are described below.

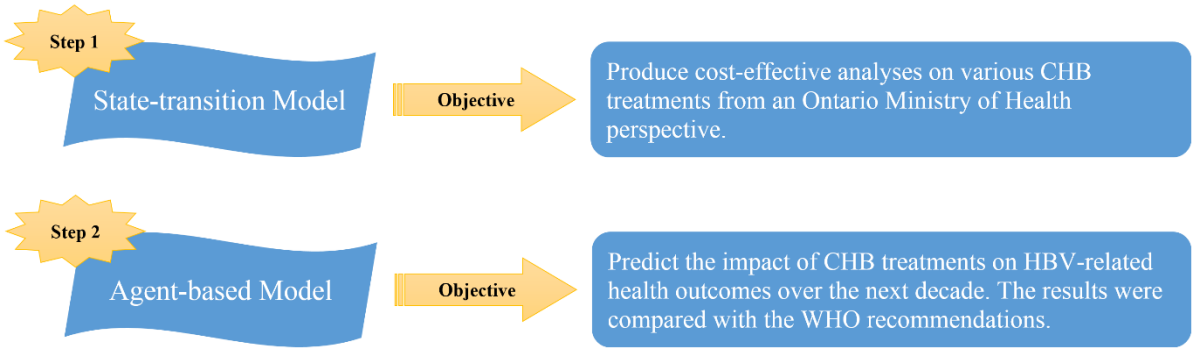
1.6 Knowledge Gaps and Objectives

Two knowledge gaps were identified. 1) Since the new drug, TAF, was approved for the treatment of CHB, there has not been any cost-effectiveness analysis in the literature involving it. 2) The prevalence of HBV is quite high in some regions such as Asia, and multiple antiviral therapies for treating CHB have been available in Canada before the year 2000;[1,18] however, there is no suitable infectious disease

model for hepatitis B that can be used to properly assess the impact of treatment as prevention until now.

The aim of this thesis was to assess the health and economic impact of TAF and other treatments of CHB in Ontario. Specifically, 1) an STM was employed to evaluate the cost-effectiveness of the available CHB treatment options from a provincial Ministry of Health perspective; and 2) an ABM was employed to predict the impact of the treatment-as-prevention options on the incidence and prevalence of HBV-related health outcomes in Ontario over the next decade (Figure 1.1). Two independent studies were conducted based on these two models, respectively. The STM and its results are explained in the following chapter, the ABM and its outcomes are explained in Chapter 3, and the last chapter is the overall conclusion of this thesis.

Figure 1.1 Objectives of the Models



CHB, chronic hepatitis B; HBV, hepatitis B virus; WHO, World Health Organization.

Chapter 2
State-transition Model

STMs are widely used in health-economic assessments.[29] The natural history of the disease is always considered to be the focus of building an STM. By conceptualizing complex medical problems into several mutually exclusive health states and simulating the transitions of a cohort or individuals among these states over a given number of cycles, parameters for decision making, such as life expectancy and overall costs, can be easily estimated. The advantage of STMs is that they are relatively easy to build and inspect if the number of health states is not large.[29] Its main disadvantage is that it is difficult to associate transition probabilities with the past experience of the simulated individuals, which limits its clinical applications.[29] An STM is suitable if the decision problem can be broken down into states, the target population is a closed cohort, and the interactions between individuals are less important.[29]

2.1 Review of Previous Cost-effectiveness Analyses

Numerous studies around the world have assessed the cost-effectiveness of available treatments on CHB infections, and a large proportion of them concluded that either TDF or ETV is the optimal strategy.[19-24] Three of these studies were conducted in Canada between 2011 and 2015.[19-21] One of them was done by Jing He et al..[19] They constructed an STM to project the lifetime health outcomes and costs associated with LAM, telbivudine, ETV, and TDF. In their model, patients who achieved viral suppression had lower disease progression rates than the others. They also allowed patients to switch to rescue therapies recommended by the Canadian and AASLD guidelines when viral resistance occurred,[17,31] and assumed that the resistance rate of the rescue therapies is zero. However, their model oversimplified the natural history of CHB. Their target patient population was limited to an HBeAg-positive cohort, and all HBeAg-negative health states were excluded from their model. The chance of HBeAg reactivation was included in the probability of HBeAg reversion, which means that HBeAg-negative CHB was assumed to be identical to HBeAg-positive CHB including the ability to become inactivated. Furthermore, the treatment strategies in their model were not applied to the state of compensated cirrhosis (CC), and HBeAg seroconversion cannot occur in CHB patients with cirrhosis. As a result, they found that TDF dominated all the other strategies evaluated.

Another study done by Helen Dakin et al. was based on a sophisticated STM.[20] They considered three cohorts: treatment-naïve non-cirrhotic CHB patients, treatment-naïve cirrhotic CHB patients, and LAM-resistant CHB patients with or without CC. HBeAg-positive and HBeAg-negative patients were

not evaluated separately; both of them were included in each cohort with a certain percentage. TDF, adefovir, ETV, LAM, and their most commonly used combinations (up to three treatments in sequence) were compared. Switching treatment occurred when viral suppression failed to be achieved in certain cases after one year or when drug resistance developed. Unlike the model developed by He et al.,[19] Dakin et al. not only considered HBeAg-negative health states but also divided severe liver disease states (such as DC and liver transplant) into two health states based on the HBeAg status. Treatments were applied to the CC states as well as the CHB states. However, they also considered some parameters that may not be significant, such as the relative risk of HBeAg seroconversion in patients treated for one year versus treated for more than one year. As a result, they found that TDF followed by LAM is the most cost-effective strategy for CHB patients with or without cirrhosis if the willingness-to-pay threshold was assumed to be $50,000/QALY. For all of the cohorts considered, strategies with TDF as the first treatment of the sequence were more effective than the other strategies. However, sensitivity analyses identified that the conclusions may be altered due to changes in 12 parameters including the time horizon, HBeAg seroconversion rates, disease progression rates, and discount rate.

An STM constructed by the Ontario Drug Policy Research Network had many similarities to the model developed by Dakin et al..[20,21] The major difference was that the DC state, liver transplant state, and post-liver transplant state were no longer separated based on HBeAg status. They considered four cohorts; the target population was divided according to their HBeAg status and the presence or absence of cirrhosis. TDF, ETV, LAM, and their sequential combinations were compared, and switching treatment was allowed when drug resistance or non-response to treatment occurred. Only two treatments were allowed in each strategy. In contrast to the previous two analyses,[19,20] this study found that TDF as the first-line therapy would only be optimal for HBeAg-positive CHB patients with cirrhosis. Initiating treatment with LAM would be relatively cost-effective for HBeAg-positive CHB patients without cirrhosis, and none of the treatment strategies considered was cost-effective for HBeAg-negative CHB patients regardless of cirrhosis status.

The values of the parameters used in the articles described above no longer represent their present values; the cost of TDF and ETV nowadays is almost one-third of the prices used in their models because of the availability of the generic versions.[16,19-21] Although these studies have produced valuable research methods and conclusions, their results may no longer reflect the current situation. Furthermore, none of them considered TAF as a treatment strategy for CHB infection.

2.2 Methods

To address these knowledge gaps, we developed an STM to evaluate the health and economic impact of TAF in the context of currently reimbursed CHB treatments.

2.2.1 Type of Economic Evaluation

The analysis is a cost-utility analysis conducted from an Ontario Ministry of Health perspective. The cost-effectiveness of the strategies was assessed using the predicted number of liver-related diseases and deaths, costs (2018 Canadian dollars), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs).

2.2.2 Cohorts

Two treatment-naïve cohorts were analyzed separately taking into account their different disease progression patterns: one consisted of HBeAg-positive non-cirrhotic CHB patients, while the other included HBeAg-negative non-cirrhotic CHB patients. Consistent with the published randomized controlled trials on TAF,[14,15] the average ages of the HBeAg-positive and HBeAg-negative cohorts at the beginning of treatment in the base case analysis were 38 and 45 years, respectively. In the sensitivity analyses, the effect of raising and reducing the starting age of treatment was determined.

2.2.3 Strategies

Three antiviral therapies recommended by the AASLD guidelines were considered: ETV (0.5mg tablet once daily), TDF (300mg tablet once daily), and TAF (25mg tablet once daily).[17] If a drug is unable to suppress the virus, or if the patients developed resistance to the drug during treatment, the patients will be treated with an alternative therapy. To simplify the complexity, we limited each patient to a maximum number of two types of antiviral treatments.[21] We also assumed that each case of drug resistance required an additional visit to a specialist physician. Drug resistance status was assumed to have no effect on the utilities in the base case analysis, and best supportive care (BSC) was defined as careful monitoring without antiviral treatment.[20] As recommended by the AASLD, seven treatment strategies were compared:[17]

1) TAF followed by BSC (TAF→BSC);
2) TDF followed by BSC (TDF→BSC);
3) ETV followed by BSC (ETV→BSC);

4) TAF followed by ETV and followed by BSC (TAF→ETV→BSC);

5) TDF followed by ETV and followed by BSC (TDF→ETV→BSC);

6) ETV followed by TAF and followed by BSC (ETV→TAF→BSC); and

7) ETV followed by TDF and followed by BSC (ETV→TDF→BSC).

2.2.4 Model Structure and Implementation

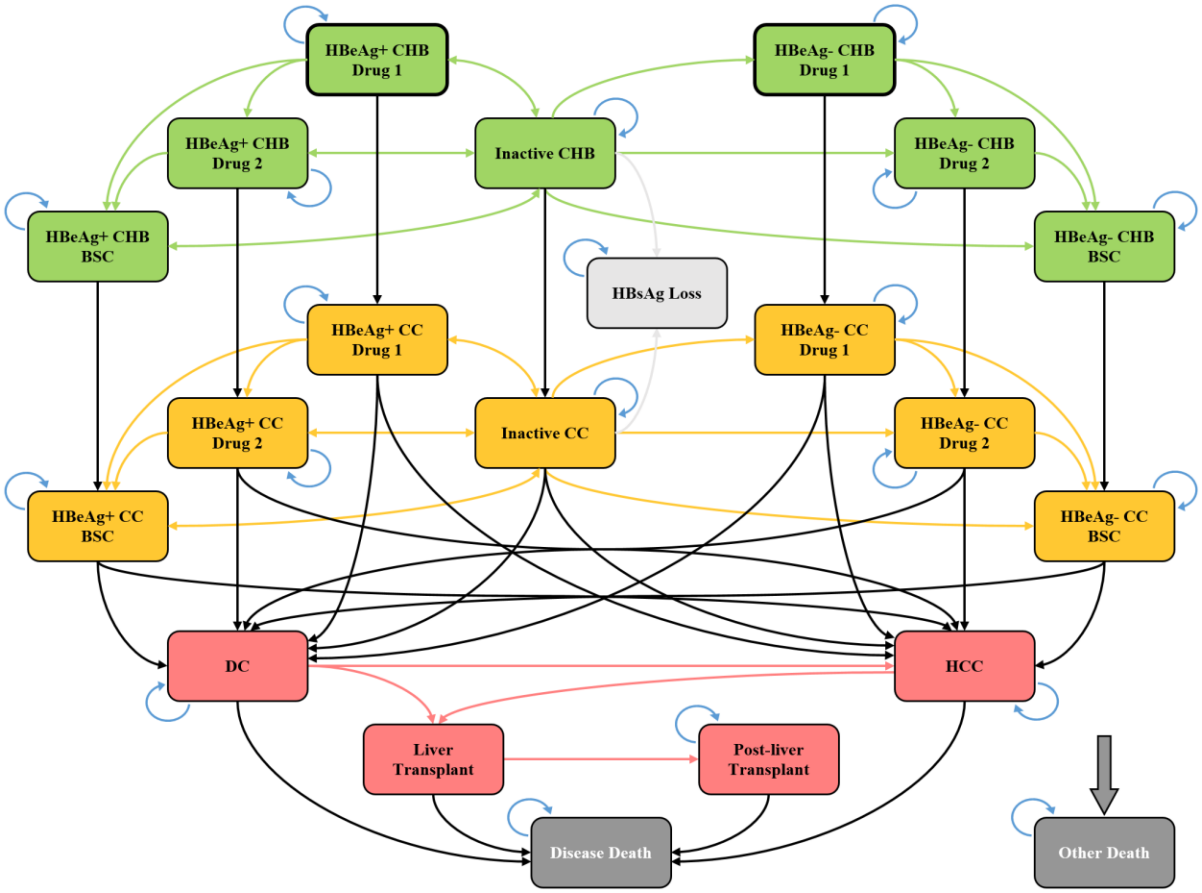
According to the natural history of CHB, multiple states of disease progression and a long-term time horizon need to be considered in the model. In order to achieve recurrence and complex transitions between the states, an STM was constructed using TreeAge Pro Suite 2019 software (TreeAge Software, Inc., Williamstown, MA, USA).[29] Thirty-three mutually exclusive health states were incorporated into the model, including one HBsAg loss state, thirteen non-cirrhotic CHB states, thirteen CC states, four severe liver disease states, and two death states. A simplified version of the model is shown in Figure 2.1. All patients in a non-death state had a certain probability to die due to reasons not associated with HBV.[32]

The length of each cycle was defined to be one year, and the disease status of each patient was simulated based on annual parameters. Patients can move to another health state or remain in their current state within each cycle depending on the annual state-transition probabilities. The costs and utilities of the patients at each time point were recorded for further calculations. The time horizon of the model was lifetime, which means that simulations end when all patients within the model have died. Cost and effectiveness values were discounted at an annual rate of 1.5% in the base case analysis.[33]

For the HBeAg-positive cohort, the model assumed that treatment is only applied to members with CHB or CC according to the AASLD guidelines.[17] When HBeAg reversion or hepatitis B reactivation occurs in patients in the inactive carrier phase, the model assumed that they will continue to be treated with the drug they used prior to entering that phase. For the HBeAg-negative cohort, we assumed that treatment is only applied to members with HBeAg-negative CHB or HBeAg-negative CC.[17] A treatment was terminated when HBeAg seroconversion is achieved, drug resistance is developed, or it is no longer able to suppress the virus.

Common types of serious adverse events (SAEs) of TAF, TDF, and ETV include urine erythrocytes, occult blood, ALT flares, and myalgia.[14,15,34] We assumed that SAEs only occur within the first

Figure 2.1 State-transition Model of Chronic Hepatitis B Progression



BSC, best supportive care; CC, compensated cirrhosis; CHB, chronic hepatitis B; DC, decompensated cirrhosis; HBeAg-, hepatitis B envelope antigen-negative; HBeAg+, hepatitis B envelope antigen-positive; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma.

year of taking a drug, and patients require two additional physician visits whenever an SAE occurs. Patients with SAEs were assumed to be closely monitored without discontinuing the current drug and switching to another.[17] Furthermore, the negative impact of SAEs on health utilities were also considered by the model.

2.2.5 Model Probabilities

All probabilities and ratios regarding health outcomes were obtained from the published literature and a recent systematic review and network meta-analysis as shown in Table 2.1.[12-15,25,32,35-58] If a treatment failed to achieve viral suppression, we assumed that this is equivalent to no virologic response.

Otherwise, the treatment is considered effective, and patients have less chance of developing CC, DC, and HCC while being treated.[55-57]

2.2.6 Costs

The annual cost of the HBsAg loss state was assumed to be the same as that of the average healthcare cost for an uninfected individual.[59] Additional annual costs regarding the health states were direct medical costs collected from the published literature (Table 2.1).[60] The brand price of TAF was obtained from the Canadian Agency for Drugs and Technologies in Health Common Drug Review,[61] and the costs of the other drugs were the generic prices obtained from the Ontario Drug Benefit Formulary.[16] These costs exclude professional fees and mark-ups on the drug costs that are charged by dispensing pharmacies. Additionally, these costs are considered the actual acquisition costs of the treatment, as the Ontario legislation prohibits cost rebates provided by a manufacturer pertaining to the cost by the operator of a pharmacy. Furthermore, the consultation fee for gastroenterologists was obtained from Ontario Ministry of Health and Long-Term Care Schedule of Benefits (Physician Services Under the Health Insurance Act).[62] All costs were inflated to 2018 prices using the Canadian Consumer Price Index.[63]

2.2.7 Utilities

The utilities of the health states were obtained from a study of more than four hundred CHB patients with or without treatment (Table 2.1).[64] Health Utility Index Mark 3 (HUI3) scores were the default values adopted in the models, with 1 representing perfect health and 0 representing death. EuroQol-5 Dimension (EQ-5D) scores were only considered in the sensitivity analyses. We assumed that all non-cirrhotic CHB states besides inactive CHB state have the same utility score, and all CC states have the same utility score. The utility of liver transplant in the first year was assumed to be the same as that of liver transplant after the first year. We also assumed that patients in the inactive CHB state and HBsAg loss state have the same utilities as the general Canadian adult population.

2.2.8 Sensitivity Analyses

One-way sensitivity analyses were conducted on the majority of parameters used by the model, and the ranges of most parameters analyzed were their credible intervals obtained from their sources (Table 2.1). 100,000 iterations of Monte Carlo simulation were conducted for each probabilistic sensitivity analysis (PSA) to determine the overall impact of parameter uncertainty on the results.

Table 2.1 Model Inputs for the State-transition Model

State-transition Probabilities						
Parameter	Baseline	Low	High	Distribution	SD[†]	Source
HBeAg+ CHB (without treatment) to Inactive CHB	0.0213	0.0079	0.0551	Beta	0.0173	14, 35
HBeAg+ CHB (without treatment) to HBeAg+ CC	0.044	0.022	0.088	Beta	0.0224	37, 38, 48, 49
Inactive CHB to HBsAg Loss	0.008	0.0005	0.02	Beta	0.0061	36-38
Inactive CHB to HBeAg+ CHB	0.0048	0.004	0.018	Beta	0.0067	36-38, 52
Inactive CHB to HBeAg- CHB	0.0254	0.02	0.05	Beta	0.0126	38, 52, 53
Inactive CHB to Inactive CC	0.001	0.001	0.002	Beta	0.0005	37, 38, 52
HBeAg- CHB (without treatment) to HBeAg- CC	0.029	0.015	0.058	Beta	0.0148	38, 50-52
HBeAg+ CC (without treatment) to Inactive CC	0.1	0.07	0.13	Beta	0.0153	Assume same as Non-cirrhotic CHB
HBeAg+ CC (without treatment) to DC	0.073	0.035	0.1	Beta	0.0194	38, 44-46
HBeAg+ CC (without treatment) to HCC	0.034	0.01	0.12	Beta	0.0439	38, 42-44
Inactive CC to HBsAg Loss	0.008	0.0005	0.02	Beta	0.0061	36-38
Inactive CC to HBeAg+ CC	0.0048	0.008	0.018	Beta	0.0067	36-38
Inactive CC to HBeAg- CC	0.0254	0.02	0.05	Beta	0.0126	38, 52, 53
Inactive CC to DC	0.008	0.004	0.016	Beta	0.0041	37, 38, 47
Inactive CC to HCC	0.022	0.011	0.044	Beta	0.0112	37, 38, 47
HBeAg- CC (without treatment) to DC	0.073	0.035	0.1	Beta	0.0194	38, 44-46
HBeAg- CC (without treatment) to HCC	0.037	0.01	0.12	Beta	0.0423	38, 41-44
DC to HCC	0.06	0.01	0.113	Beta	0.0270	38-41
DC to Liver Transplant	0.05	0	0.4	Beta	0.1786	38-40
DC to Disease Death	0.173	0.058	0.221	Beta	0.0587	38-40
HCC to Liver Transplant	0.15	0.05	0.4	Beta	0.1276	38-40
HCC to Disease Death	0.351	0.181	0.451	Beta	0.0867	38-40

Table 2.1 Continued

State-transition Probabilities						
Parameter	Baseline	Low	High	Distribution	SD[†]	Source
Liver Transplant to Disease Death	0.142	0.124	0.159	Beta	0.0092	54
Post-liver Transplant to Disease Death	0.034	0.024	0.043	Beta	0.0051	54
Relative Risk of CC for CHB Patients with Treatment vs No Treatment	0.308	0.231	0.385	Gamma	0.0393	55
Relative Risk of DC for CC Patients with Treatment vs No Treatment	0.5209	0.391	0.651	Gamma	0.0664	55
Relative Risk of HCC for CC Patients with Treatment vs No Treatment	0.3857	0.2892[‡]	0.4821[§]	Gamma	0.0492	56, 57
Treatment-related Probabilities						
Parameter	Baseline	Low	High	Distribution	SD[†]	Source
ETV - HBeAg Seroconversion	0.0561	0.0245	0.1172	Beta	0.0311	14, 35
ETV - Viral Suppression (HBeAg+ patients)	0.4788	0.2513	0.7247	Beta	0.1255	14, 35
ETV - Viral Suppression (HBeAg- patients)	0.7596	0.0194	0.9968	Beta	0.3776	15, 35
ETV - Resistance	0.0020	0.0015[‡]	0.0025[§]	Beta	0.0003	12
ETV - SAE	0.048	0.025	0.082	Beta	0.0173	35, 58
TDF - HBeAg Seroconversion	0.0809	0.0434	0.1422	Beta	0.0313	14, 35
TDF - Viral Suppression (HBeAg+ patients)	0.6675	0.4703	0.8230	Beta	0.1006	14, 35
TDF - Viral Suppression (HBeAg- patients)	0.9298	0.8570	0.9683	Beta	0.0372	15, 35
TDF - Resistance	0	0	0			13-15
TDF - SAE	0.071	0.031	0.139	Beta	0.0347	35, 58
TAF - HBeAg Seroconversion	0.1027	0.0770[‡]	0.1283[§]	Beta	0.0131	14
TAF - Viral Suppression (HBeAg+ patients)	0.6386	0.4789[‡]	0.7982[§]	Beta	0.0814	14
TAF - Viral Suppression (HBeAg- patients)	0.9404	0.7053[‡]	1.0000[§]	Beta	0.1199	15
TAF - Resistance	0	0	0			14, 15, 25
TAF - SAE	0.064	0.022	0.145	Beta	0.0413	35, 58

Table 2.1 Continued

Costs						
Parameter	Baseline	Low	High	Distribution	SD†	Source
Average Healthcare for an Uninfected Individual	$6,428.39	$4,821.29‡	$8,035.49§	Gamma	819.9479	59
Additional Cost of Non-cirrhotic CHB	$1,164.86	$1,029.83	$1,347.64	Gamma	93.2536	60
Additional Cost of CC	$2,550.70	$1,722.74	$4,759.02	Gamma	1,126.6986	60
Additional Cost of DC	$15,315.08	$11,333.54	$22,353.37	Gamma	3,590.9603	60
Additional Cost of HCC	$18,209.51	$14,469.40	$23,443.21	Gamma	2,670.2548	60
Additional Cost of Liver Transplant	$135,126.83	$128,664.16	$145,721.09	Gamma	5,405.2304	60
Additional Cost of Transplant Care after the First Year	$52,162.40	$45,616.53	$62,863.04	Gamma	5,459.5123	60
Unit Price of ETV (0.5mg tablet)	$5.50	$4.13‡	$6.88§	Gamma	0.7015	16
Unit Price of TDF (300mg tablet)	$4.89	$3.67‡	$6.11§	Gamma	0.6235	16
Unit Price of TAF (25mg tablet)	$19.55	$14.67‡	$24.44§	Gamma	2.4941	61
Consultant Visit	$165.43	$124.07‡	$206.79§	Gamma	21.1011	62
Utilities						
Parameter	Baseline	Low	High	Distribution	SD†	Source
Canadian Population Norm (HUI3)	0.93	0.85	1.00	Beta	0.0408	64
Canadian Population Norm (EQ-5D)	0.92	0.91	0.94	Beta	0.0102	Assume same as Non-cirrhotic CHB
Non-cirrhotic CHB (HUI3)	0.87	0.85	0.88	Beta	0.0102	64
Non-cirrhotic CHB (EQ-5D)	0.92	0.91	0.94	Beta	0.0102	64
CC (HUI3)	0.81	0.75	0.86	Beta	0.0306	64
CC (EQ-5D)	0.88	0.85	0.92	Beta	0.0204	64
DC (HUI3)	0.49	0.22	0.75	Beta	0.1378	64
DC (EQ-5D)	0.73	0.39	1.00	Beta	0.1735	64
HCC (HUI3)	0.85	0.76	0.95	Beta	0.0510	64

Table 2.1 Continued

Utilities						
Parameter	Baseline	Low	High	Distribution	SD†	Source
HCC (EQ-5D)	0.81	0.67	0.94	Beta	0.0714	64
Post-liver Transplant (HUI3)	0.72	0.60	0.83	Beta	0.0612	64
Post-liver Transplant (EQ-5D)	0.84	0.77	0.91	Beta	0.0357	64
Drug Resistance (disutility)	0.00	0.00	0.10			Assumption
SAE (disutility)	0.05	0.0375‡	0.0625§	Beta	0.0064	Assumption
Other Parameters						
Parameter	Baseline	Low	High	Distribution	SD†	Source
Discount Rate	0.015	0	0.05			33
Treatment Starting Age (HBeAg+ patients)	38	29‡	48§	Gamma	5.1020	14
Treatment Starting Age (HBeAg- patients)	45	34‡	56§	Gamma	5.6122	15

†Estimated based on its low and high values; ‡75% of its baseline value; §125% of its baseline value.

CC, compensated cirrhosis; CHB, chronic hepatitis B; DC, decompensated cirrhosis; EQ-5D, EuroQol-5 Dimension; ETV, entecavir; HBeAg, hepatitis B envelope antigen; HBeAg-, hepatitis B envelope antigen-negative; HBeAg+, hepatitis B envelope antigen-positive; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HUI3, Health Utility Index Mark 3; SAE, serious adverse event; SD, standard deviations; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

2.3 Results

2.3.1 Validation

An article published in 2012 reported that the lifetime risk of HCC in HBV carriers is about 15% to 40%.[65] For validation purposes, 1,000,000 trials of microsimulation were carried out on our model and estimated that approximately 22.9% of those initiated with HBeAg-positive non-cirrhotic CHB had developed HCC in their life (assuming they had the same chance to receive any of the seven treatment strategies considered in our study), which is compatible with the values stated in that article. Furthermore, the estimated percentage of disease death caused by HCC was around 41.2%, which closely matched with the percentage (46%) indicated from a study based on European data.[66]

2.3.2 Base Case

For the HBeAg-positive cohort, 1,000,000 trials of microsimulation were carried out using the base case parameters and found that TAF→ETV→BSC would prevent an additional 6 cases of HCC, 8 cases of DC, and 11 cases of liver-related death (including 4 deaths caused by HCC and 5 deaths caused by DC) per 1,000 CHB patients treated compared with TDF→ETV→BSC (Table A.1). It generated an additional 0.16 QALYs/person at an additional cost of $14,836.18 with an ICER of $94,142.71/QALY compared with TDF→ETV→BSC (Table 2.2). TAF→ETV→BSC was the most effective treatment strategy in terms of QALYs, likely due to the high HBeAg seroconversion rate of TAF. However, all strategies involving TAF were much more expensive than the others since the price of TAF is roughly four times the price of the other drugs considered. On the other hand, ETV→TDF→BSC was almost equally effective as TDF→ETV→BSC in terms of QALYs, but cost an additional $226.66 compared with TDF→ETV→BSC. ETV→TDF→BSC, ETV→BSC, TAF→BSC, and ETV→TAF→BSC were absolutely dominated since they were more expensive and less effective than some of the others. Therefore, TDF→ETV→BSC and TAF→ETV→BSC are likely to be the most cost-effective treatment strategies for HBeAg-positive CHB patients at a willingness-to-pay threshold of $50,000/QALY and $100,000/QALY, respectively.

For the HBeAg-negative cohort, TDF→ETV→BSC would prevent an additional 17 cases of HCC, 22 cases of DC, and 32 cases of liver-related death (including 14 deaths caused by HCC and 14 deaths caused by DC) per 1,000 CHB patients treated compared with TDF→BSC (Table A.1). It generated an additional 0.45 QALYs/person at an additional cost of $3,866.98 with an ICER of $8,616.22/QALY

Table 2.2 Base Case Cost-effectiveness Results

HBeAg-positive Cohort					
Strategy	Costs	ΔCosts	QALYs	ΔQALYs	ICER ($/QALY)
TDF→BSC	$274,743.42		22.8618		
TDF→ETV→BSC	$276,409.87	$1,666.46	23.5859	0.7241	2,301.27
TAF→ETV→BSC	$291,246.05	$14,836.18	23.7435	0.1576	94,142.71
Absolutely Dominated Strategies (all referencing TDF→BSC)					
ETV→BSC	$275,065.00	$321.58	22.0516	-0.8102	-396.92
ETV→TDF→BSC	$276,636.53	$1,893.11	23.5842	0.7224	2,620.63
TAF→BSC	$289,595.47	$14,852.05	23.0378	0.1760	84,384.47
ETV→TAF→BSC	$293,914.91	$19,171.49	23.7328	0.8711	22,009.56
HBeAg-negative Cohort					
Strategy	Costs	ΔCosts	QALYs	ΔQALYs	ICER ($/QALY)
ETV→BSC	$252,171.57		20.6444		
TDF→BSC	$259,274.75	$7,103.18	21.7453	1.1009	6,452.03
TDF→ETV→BSC	$263,141.73	$3,866.98	22.1941	0.4488	8,616.22
ETV→TAF→BSC	$322,918.26	$59,776.53	22.3238	0.1296	461,162.21
TAF→ETV→BSC	$326,730.09	$3,811.83	22.3243	0.0005	7,876,809.40
Absolutely Dominated Strategies (all referencing ETV→BSC)					
ETV→TDF→BSC	$263,272.76	$11,101.19	22.1938	1.5494	7,164.99
TAF→BSC	$323,109.82	$70,938.25	21.9112	1.2668	56,000.07

BSC, best supportive care; ETV, entecavir; HBeAg, hepatitis B envelope antigen; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

compared with TDF→BSC (Table 2.2). Multitherapy strategies were more effective than monotherapy strategies (strategies without considering any subsequent therapy) since they can suppress the virus and maintain ALT levels for a longer period of time. Similar to the HBeAg-positive cohort, ETV→TDF→BSC almost generated the same amount of QALYs as TDF→ETV→BSC did at an additional cost. Strategies involving TAF were much more expensive than the others. ETV→TAF→BSC is therefore not a rational choice as its ICER compared with TDF→ETV→BSC ($461,162.21/QALY) was far beyond the $100,000/QALY threshold. If we assume the willingness-to-pay threshold to be either $50,000/QALY or $100,000/QALY, TDF→ETV→BSC is likely to be the most cost-effective treatment for HBeAg-negative CHB patients.

2.3.3 One-way Sensitivity Analyses

For the HBeAg-positive cohort, the ten parameters that influence the ICER of TAF→ETV→BSC compared with TDF→ETV→BSC the most are shown in the tornado diagram (Figure A.1 (a)). The results of the base case analysis (at a willingness-to-pay threshold of $50,000/QALY) were generally reliable with the exception of the HBeAg seroconversion rates and viral suppression rates of the treatments. Since these rates determine the efficacy of a drug, changing any of them based on the 95% confidence intervals calculated from the published literature may alter the conclusions of this study.[14,15,35] If the HBeAg seroconversion rate of TAF is raised to 12.8%, TAF→ETV→BSC would likely to be the most cost-effective treatment strategy. Furthermore, changes in many parameters, including the discount rate and the price of TAF, may result in the most cost-effective treatment (at a willingness-to-pay threshold of $100,000/QALY) being replaced from TAF→ETV→BSC to either TDF→ETV→BSC or ETV→TDF→BSC. On the other hand, the conclusion that TDF→ETV→BSC is more cost-effective than TDF→BSC is unlikely to be altered by changes in any of the parameters used by the model if we assume the willingness-to-pay threshold to be either $50,000/QALY or $100,000/QALY (Figure A.1 (b)).

In the base case analysis, ETV→TDF→BSC almost produced the same amount of QALYs per person as TDF→ETV→BSC, but at an additional cost. The ICER of each of these two strategies compared with the other can be highly influenced by varying any of the parameters shown in Figure A.1 (c). In another sense, this figure may indicate that these two strategies are indistinguishable from each other. Since the differences between these two strategies are so small, changes in parameters are likely to cause a reversal of their relationship, and eventually, one of them will be absolutely dominated by the other.

For the HBeAg-negative cohort, the ten parameters that influence the ICER of ETV→TAF→BSC compared with TDF→ETV→BSC the most are shown in Figure A.1 (d). The results of the base case analysis (at a willingness-to-pay threshold of $100,000/QALY) were only sensitive to the viral suppression rates of the treatments. If the viral suppression rate of TDF for HBeAg-negative patients is reduced to 85.7%, ETV→TAF→BSC would likely to be the most cost-effective treatment. On the other hand, the conclusion that TDF→BSC is more cost-effective than ETV→BSC is only sensitive to the viral suppression rate of ETV (Figure A.1 (e)). In addition, switching all the health state utilities from HUI3 scores to EQ-5D scores did not significantly affect the ICERs.

2.3.4 Probabilistic Sensitivity Analyses

The cost-effectiveness of each strategy across a range of willingness-to-pay thresholds is shown in Figure 2.2. For the HBeAg-positive cohort, TDF→ETV→BSC had a 52.9% chance of being the optimal treatment strategy at a willingness-to-pay threshold of $50,000/QALY. The chances of TAF→ETV→BSC, ETV→TDF→BSC, and ETV→TAF→BSC were 28.7%, 14.1%, and 4.3%, respectively. The chances of the remaining three strategies were negligible. At a willingness-to-pay threshold of $100,000/QALY, the chances of TDF→ETV→BSC and ETV→TDF→BSC to be the optimal strategy shrunk to 42.8% and 9.4%, respectively. The chances of TAF→ETV→BSC and ETV→TAF→BSC rose to 39.6% and 8.1%, respectively. As a result, TDF→ETV→BSC has the highest chance of being the most cost-effective treatment for HBeAg-positive CHB infections even if randomness is allowed for most of the parameters used in the model. However, TAF→ETV→BSC still has a great potential to replace TDF→ETV→BSC and become the most cost-effective strategy.

TDF→ETV→BSC also showed a clear advantage in the treatment of HBeAg-negative patients (Figure 2.2 (b)). It had a 66.5% chance of being the optimal treatment strategy at a willingness-to-pay threshold of $50,000/QALY. The chance of ETV→TDF→BSC was 28.8%, and the chances of the

Figure 2.2 Probabilistic Sensitivity Analysis: Cost-effectiveness Acceptability Curve

(a) HBeAg-positive Cohort

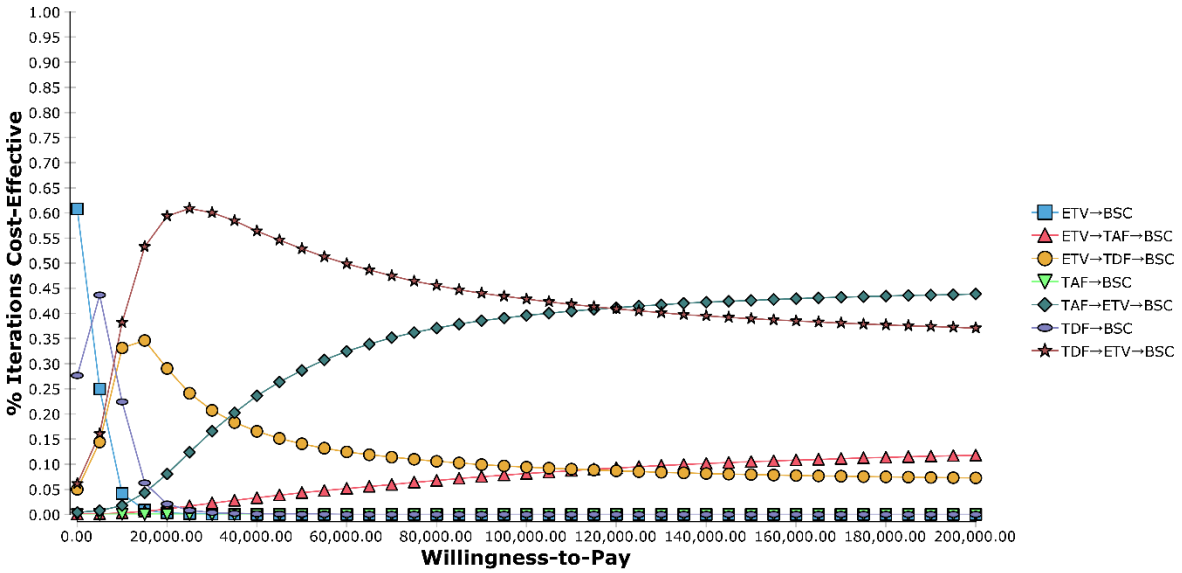
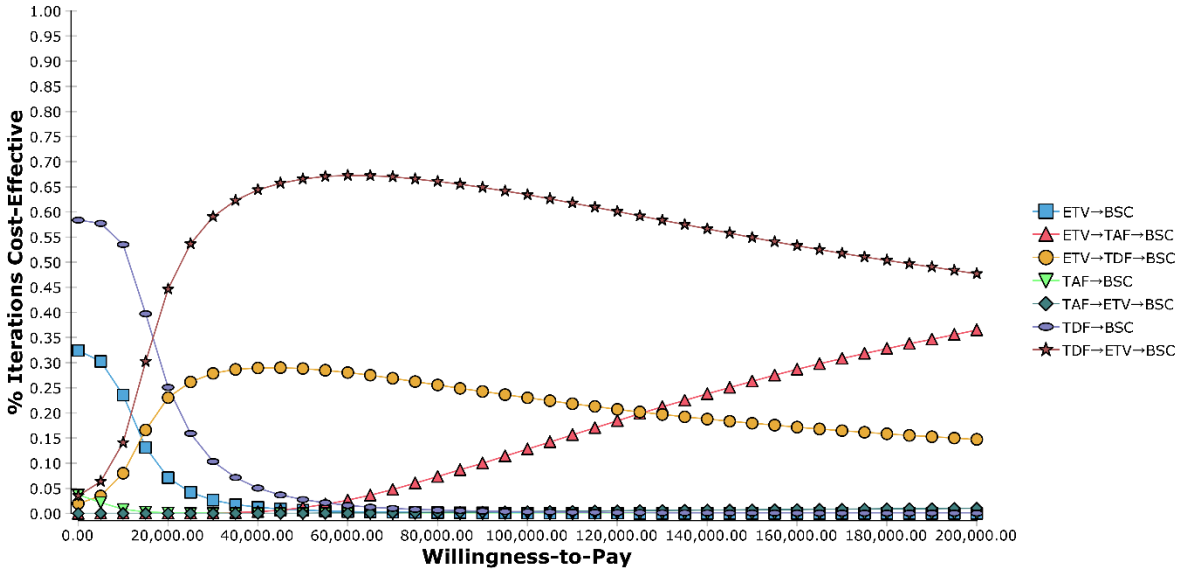


Figure 2.2 Continued

(b) HBeAg-negative Cohort



BSC, best supportive care; ETV, entecavir; HBeAg, hepatitis B envelope antigen; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

remaining five strategies were negligible. At a willingness-to-pay threshold of $100,000/QALY, the chances of TDF→ETV→BSC and ETV→TDF→BSC becoming the optimal strategy decreased to 63.4% and 23.0%, respectively. The chance of ETV→TAF→BSC increased to 12.8%. Therefore, TDF→ETV→BSC has the highest chance of being the most cost-effective treatment for HBeAg-negative CHB infections. However, the superiority of TDF→ETV→BSC compared with ETV→TAF→BSC may be weakened as the willingness-to-pay threshold reaches $200,000/QALY.

2.4 Discussion

We employed an STM to compare treatment strategies for CHB including ETV, TDF, and TAF, based on data from the available literature. The willingness-to-pay thresholds used by Canadian cost-effectiveness studies ranged from $50,000/QALY to $100,000/QALY.[19-21,38,67,68] At willingness-to-pay thresholds of $50,000/QALY to $100,000/QALY, TDF→ETV→BSC is relatively likely to be the most cost-effective treatment option for both HBeAg-positive and HBeAg-negative CHB patients, with ETV→TDF→BSC a potential alternative. At current prices, TAF-containing strategies were not found

to be cost-effective with $50,000 willingness-to-pay threshold. The results of the sensitivity analyses indicate that the model is robust, and uncertainty of model parameters is unlikely to alter the conclusions.

Our analysis was built upon the first STM that includes treatment strategies involving TAF and incorporated efficacy outcomes of the treatments from the latest systematic review and network meta-analysis.[35] In addition, our study also developed the first STM that takes into account the impact of treatment-related SAEs on the costs and utilities. Although some cost-effectiveness analyses regarding CHB had considered treatment-related adverse events,[24,69] the occurrence of adverse events was only treated as a sign of discontinuing treatment, without assessing its impact on costs and utilities as our analysis does. However, our study also has limitations. Long-term follow-up data regarding TAF is limited. Due to the nature of state-transition modeling, the model is unable to capture the impact of successful treatment on preventing viral transmission. The posted treatment price used by the model may also not be the same as the actual prices that public payers obtain through negotiations.

Although strategies involving TAF are unlikely to be a rational choice for treating patients with CHB at this time, decision-makers may also be interested in the possibility of a TAF-containing strategy to be the most cost-effective strategy compared with the cheapest strategy considered in our study alone. To figure this out, an analysis was performed in a similar manner to the PSA, and the results showed that the chance of TAF→ETV→BSC becoming the optimal treatment for the HBeAg-positive cohort increased from 72.4% to 83.5% when the willingness-to-pay threshold ranged from $50,000/QALY to $100,000/QALY (Figure A.2 (a)). In addition, a threshold analysis was conducted and found that TAF→ETV→BSC will likely be the most cost-effective treatment option (at a willingness-to-pay threshold of $50,000/QALY) for HBeAg-positive and HBeAg-negative CHB patients if the drug price of TAF is reduced by more than 33.4% and 68.3%, respectively (Table A.2).

This study assessed the predicted number of liver-related diseases and deaths, costs, QALYs, and ICERs of treatment strategies involving TAF as well as the other drugs for patients with HBeAg-positive CHB or HBeAg-negative CHB, which would accelerate the decision-making process and provide a reference for future research. The WHO's global hepatitis strategy calls for a 65% reduction in CHB deaths and a treatment rate of 80% in eligible CHB patients worldwide by 2030.[27] Our analysis may help decision-makers to develop the corresponding policies to reach these goals.

Chapter 3
Agent-based Model

Although STM is the traditional way to assess the cost-effectiveness of a strategy, it cannot be used to simulate the prevalence and incidence of hepatitis B, which is a contagious disease, in a region. In contrast to STM which focuses on disease state transitions with each individual in isolation, ABM revolves around human activities. Instead of conceptualizing complex problems into several mutually exclusive states, ABMs describe things happening in the real world in a more natural way.[30]

Agents simulated within an ABM can be identified by their characteristics such as age, sex, sexual identity, and immigrant status.[30] They can recognize their situation and act on the basis of their characteristics.[30] The interaction between agents is another key feature of this type of modeling.[30] A complex contact network can be assigned to individuals indicating to whom they can transmit the disease and from whom they can be infected, which plays an important role in simulating the spread of a disease. A healthy individual may be infected at a point in time due to his or her characteristics and behavior. By adopting ABMs, the prevalence of CHB within a community over time can be predicted. However, none of the existing analyses regarding the HBV epidemic until now were built upon ABMs.[19-24,38,69-72]

3.1 Methods

To address these knowledge gaps, we developed an ABM to predict the impact of the treatment-as-prevention strategies on HBV-related health outcomes,[30] such as the prevalence of CHB, in Ontario over the next decade. A simulation conducted by the model began with the construction of a virtual society based on the real demographic data from Ontario. Then, the model randomly assigned contacts between agents and established a sexual network. As the simulated population grew with the addition of newborns and immigrants, HBV was also simulated to be transmitted from infected agents to healthy agents through the sexual network. We calibrated the ABM-simulated number of reported AHB infections with the historical reported cases in Ontario. After extensive calibration and validation processes, our model was ready to be used for predicting future HBV-related health outcomes.

3.1.1 Strategies

Two treatment-as-prevention strategies were considered. The first strategy is TDF→ETV→BSC, the most cost-effective treatment for CHB infection found by the STM described in Chapter 2. The second one is TAF→ETV→BSC, which is the most clinically effective treatment strategy found in Chapter 2.

The time horizon of each simulation performed by the ABM was 25 years (2006 to 2030) to predict how closely the long-term health outcomes resulting from the two treatment-as-prevention strategies can match the goals set by the WHO,[27] with first 11 years (2006 to 2016) primarily for calibration and validation. Although TDF and ETV have been available in Canada since 2004 and 2006, respectively,[18] TAF was not approved for use in Canada until June 20, 2017. Therefore, we assumed that HBV-infected agents who are eligible for treatment had the same chance of receiving TDF→BSC, ETV→BSC, TDF→ETV→BSC, or ETV→TDF→BSC before 2017. The probability of receiving treatment for patients who know they are infected was assumed to rise from 0% to 40.7% from the beginning of 2006 to the end of 2016,[73] and this probability was assumed to remain unchanged from 2017 onwards.

The last 14 years (2017 to 2030) of a simulation were primarily for prediction. After 2017, all HBV-infected agents who are eligible for treatment were only likely to receive the same treatment strategy (one of the two treatment-as-prevention strategies considered). In order to highlight the impact of the treatment strategies applied during the prediction period (2017 to 2030) and to make a better comparison, we cleared the treatment history for all agents before the start of the prediction period.

3.1.2 Model Structure

In order to achieve the spread of disease due to human interactions and to predict the extent to which the long-term health outcomes of CHB treatment strategies match the WHO's goals,[27] an ABM was employed to simulate population dynamics and HBV transmission in Ontario from 2006 to 2030.[30] The model consisted of agents, contact networks among the agents, HBV vaccination, treatment of CHB, and the natural history of HBV based on the STM described in Chapter 2. Unlike the cohorts considered by the STM, the population targeted by the ABM was all people living in Ontario, including both HBV-infected patients and healthy people.

3.1.2.1 Characteristics of the Simulated Agents

A large number of individuals was simulated to represent the 12.2 million population of Ontario in 2006.[74] In order to alleviate the computational intensity, the scaling ratio between the simulated agents and the target population was set to 1:10. We probabilistically assigned characteristics, such as age,

gender, residential address, immigrant status, place of birth, and health status, to the simulated population based on the 2006 census of Canada and the published literature (Figure 3.1).[3,4,73,74] For the sake of simplicity, we assumed that everyone in this virtual society is heterosexual. The residential address of the agents was recorded as the forward sortation areas (FSAs) in which they live, and Ontario consisted of 509 FSAs in 2006.[74]

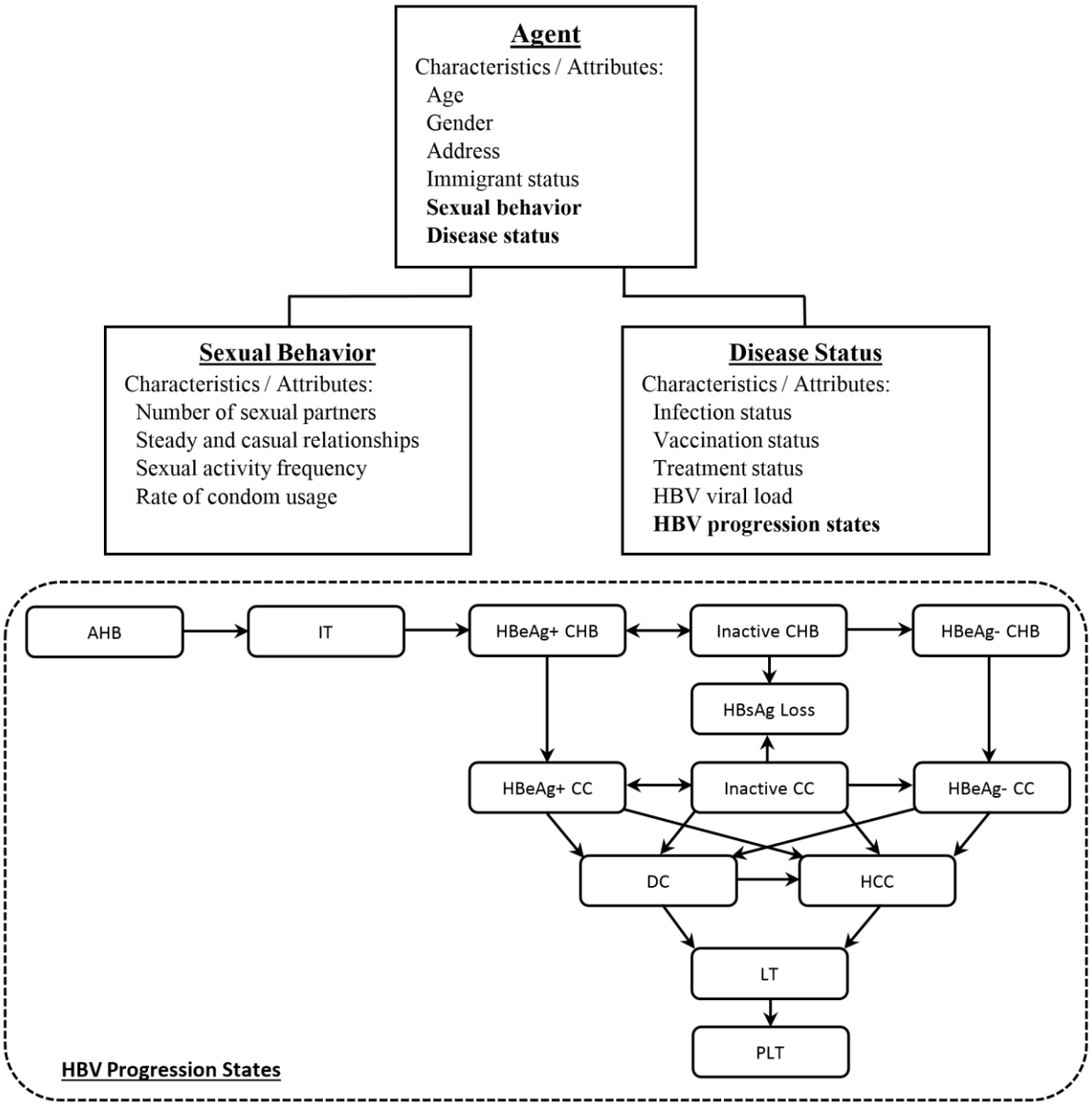
The health status of an agent was subdivided into vaccination status, infection status, age at infection, HBV viral load, awareness of being infected, and the disease progression state (which can be immune tolerance (IT), AHB, or any health states considered in the STM described in Chapter 2) he or she is currently in (Figure 3.1). Infants and young children have a much higher chance of developing CHB from AHB compared with adults, and adults in the AHB state are more likely to develop symptoms than infants and young children.[10] Patients who have developed AHB symptoms were assumed to automatically become aware that they are infected with HBV. Agents also followed the natural laws of aging and death. Everyone in the simulated population had a certain probability of death due to reasons unrelated to HBV, and this probability was based on the life tables provided by Statistics Canada.[32] We assumed that chronically infected agents will not leave the IT state until they reach the age of 12.[2,7]

Not everyone infected with HBV knows that they are infected. According to a recently published modeling study, only 58% of HBV-infected patients in Canada were diagnosed.[73] In the ABM, patients who know they are infected were eligible for treatment, and antiviral treatments were only applied to patients in the CHB or CC states according to the AASLD guidelines.[17] On the other hand, approximately 29% of the total population of Canada has immunity induced by hepatitis B vaccination.[3] As the age range narrows to 14 to 19, this ratio can be raised to 72.6% based on data provided by the Canadian Health Measures Survey.[3] Since Ontario has introduced a routine HBV vaccination program for seventh-grade students,[9] we assumed that 87.5% of the agents will be vaccinated at the age of 12.[10] We also assumed that a certain percentage of agents who do not know whether they are infected will voluntarily screen for HBV and a certain percentage of unvaccinated healthy agents will voluntarily receive hepatitis B vaccination every year.[75] How these two percentages were estimated is explained in Section 3.1.5.

3.1.2.2 Immigrants and Newborns

Immigration demographic data were obtained from Statistics Canada.[4,76] Individuals classified as immigrants included those who are, or who have ever been, landed immigrants or permanent residents.[4] Immigrants consisted of 24.0% of the total Ontario population in early 2006,[4] and we assumed that all

Figure 3.1 Agent-related Section of the Agent-based Model



AHB, acute hepatitis B; CC, compensated cirrhosis; CHB, chronic hepatitis B; DC, decompensated cirrhosis; HBeAg-, hepatitis B envelope antigen-negative; HBeAg+, hepatitis B envelope antigen-positive; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IT, immune tolerance; LT, liver transplant; PLT, post-liver transplant.

immigrants were born outside of Canada. Since HBV-related data, such as the prevalence of HBV, in many countries around the world are unknown or unavailable, the birthplace of all agents simulated was categorized into 19 regions:[4,73]

1) Canada;
2) North America, excluding Canada;
3) Central America;
4) Caribbean and Bermuda;
5) South America;
6) Western Europe;
7) Eastern Europe;
8) Northern Europe;
9) Southern Europe;
10) Western Africa;
11) Eastern Africa;
12) Northern Africa;
13) Central Africa;
14) Southern Africa;
15) West Central Asia and the Middle East;
16) Eastern Asia;
17) Southeast Asia;
18) Southern Asia; and
19) Oceania.

We assumed that people from the same region, regardless of the country in which they were born, have similar probabilities of being infected and diagnosed with HBV. Due to the lack of data, the probabilities of being infected and diagnosed with HBV in Southern Africa were assumed to be the same as the world averages.[73]

Newborns and immigrants were added to the virtual community every week based on real Canadian data.[76,77] Immigrants were assumed to be more inclined to migrate to more populated regions. The annual number of newborns and immigrants was assumed to remain unchanged from 2017 onwards.

The probability that a Canadian-born agent was infected before 2006 was assumed to be 0.4%.[3] The probability of a foreign-born agent being infected before 2006 or before immigrating to Canada was considered to be correlated with his or her birthplace. In order to match the overall HBV prevalence in Ontario in 2016 with the prevalence of HBV in Canada (0.6%) stated in a recently published article,[73] we calculated and assumed that immigrants are relatively economically self-sufficient and well educated so that they are 60% less likely to be infected with HBV before immigrating to Canada than the overall population of their home country, based on previous immigration data.[4,73] We also assumed

that the chance of immigrants receiving HBV vaccination before immigrating to Canada follows the same pattern as the vaccination rate of those born in Canada.[3]

3.1.2.3 Contact Networks

In the ABM, agents behaved and interacted with each other based on their characteristics. Age-appropriate agents formed a sexual network, which was assumed to be a scale-free network.[78,79] The probability that a randomly selected agent in the network has k sexual partners at the same time can be determined by

$$P(k) = \begin{cases} ck^{-\gamma} & ,if\ k > 0 \\ p_0 & ,if\ k = 0 \end{cases}$$

where c $(c \geq 0)$ is a normalizing constant,[78,79] γ $(\gamma > 1)$ is a constant that controls the shape of the distribution,[79] and p_0 $(0 \leq p_0 \leq 1)$ is a constant as defined by the formula.[78] The maximum number of partners an agent can manage was assumed to be 200,[78] and the model did not allow agents who are younger than 15 or older than 79 to make a sexual partner or to acquire or transmit HBV through sexual contacts.[4,32] We assumed that everyone has an expected number of partners that he or she can manage, and that number has been determined at the time he or she was born. Sexual relationships can be either casual or steady with a certain probability.[4,78] Steady relationships were assumed to be similar to marriage or living common-law. Only one steady relationship was allowed per agent.[78]

The model probabilistically pairs up random male and female agents every week if the total number of relationships in the sexual network does not exceed the expected maximum number. The probability of forming a sexual relationship between a female (denoted as F) and a male (denoted as M) is defined as

$$P(F,M) = \begin{cases} \left(P_{look}(F) * P_{look}(M) * P_{form}(age_M - age_F)\right)^{\beta\left(1-\frac{ENP_F+ENP_M-2}{2*MNP}\right)} & ,if\ dist_{F,M} \leq dist_{opt} \\ \frac{1}{100}\left(P_{look}(F) * P_{look}(M) * P_{form}(age_M - age_F)\right)^{\beta\left(1-\frac{ENP_F+ENP_M-2}{2*MNP}\right)} & ,otherwise \end{cases}$$

where P_{look} is the willingness of an agent to find a sexual partner,[79] P_{form} is the possibility of forming a relationship between two agents with a given age difference, β $(0 < \beta \leq 1)$ is a constant that controls the shape of the distribution, MNP $(MNP = 200)$ denotes the maximum number of partners that an agent can manage,[78] ENP $(ENP \in \{1,2,\dots,MNP\})$ represents the expected number of partners that an agent can manage, $dist_{F,M}$ is the distance between the residential address of the two agents, and $dist_{opt}$ denotes the maximum optimum distance for sexual relationships.[79] For agents with a steady partner,

the willingness to find additional partners was assumed to be lower than those without any steady partners. In determining ages of partners, a study found that for those married in England and Wales in 2001, the average age of the husband was 2.6 years older than his wife.[80] We assumed that the age difference between couples in Ontario is similar to that in England and Wales. As a result, sexual relationships between men and women in the model were more likely to be formed if their willingness to find a sexual partner is high, they have similar ages, they live close to each other, or the total number of partners they can manage is high.

The spread of HBV in the sexual network may occur when an infected agent had sexual contact with an uninfected agent, and the probability of disease transmission per sexual intercourse (P_{trans}) depends on the sex of the participants,[81] the health and treatment status of the infected agent, and whether condoms were used during the sexual activity. The probability of A (a healthy agent who has a steady relationship with an HBV-infected agent, S, and casual relationships with HBV-infected agents, $C_1, C_2, \dots, C_m$) being infected with HBV over a period of time can be calculated by

$$P(A) = 1 - \left(1 - P_{trans}(S, A)\right)^{N_S} * \prod_{i=1}^{m} \left(1 - P_{trans}(C_i, A)\right)^{N_{C_i}}$$

where N is the number of sexual activities conducted by the agent, A, and a given agent during the period. The more partners a person has, the less often he or she has sex with each partner. We assumed that the total number of sexual activities of an agent over a period of time follows a Poisson distribution, and the number of sexual activities assigned by an agent to his or her steady partner and casual partners may be very different. The ratio of the number of sexual activities assigned by an agent, A, to a casual partner, C, to the number assigned to a steady partner, S, was assumed to be

$$\frac{N_C}{N_S} = k^{-\alpha}$$

where k ($k \in \{2,3, \dots ,200\}$) is the total number of partners the agent, A, has and α ($\alpha \geq 0$) is a constant that controls the shape of the distribution. Agents who are newly infected with HBV started with AHB. Once their disease turned chronic, they will follow the path of disease progression defined by the STM described in Chapter 2.

The duration of the sexual relationships was simulated by an exponential distribution. A steady relationship usually lasts longer than a causal relationship.[79,82] Once a sexual relationship between a male and a female reached its predetermined time limit, the relationship ends. In addition, individuals

in the ABM had limited knowledge of themselves and the people around them. No one had the ability to investigate and exploit the underlying trends (such as the prevalence of HBV) that exist in the virtual society.

3.1.3 Implementation and Additional Assumptions

By combining multi-agent systems and complex networks, the ABM was developed using C++ programming language and object-oriented programming concepts.[83] In order to improve runtime efficiency of the main computer program containing the model, a number of model inputs were pre-computed outside the main program and converted to a program-readable format using the Visual Basic for Applications programming language. The time horizon of the model was 25 years (2006 to 2030). Each year was divided into 52 cycles, and the length of each cycle was defined as one week.

Based on immigration data obtained from the 2016 Canadian Census,[4] we assumed that Canada has three immigration periods (before 2006, 2006 to 2010, and 2011 to 2016), each with a unique structure of immigrant birthplace. Changes in immigration period led to variations in the prevalence and diagnostic rate of HBV in the 18 immigrant-sourced regions.[4,73] We assumed that the structure of immigrant birthplace will remain unchanged after 2016.

One of the difficulties affecting the feasibility of the program design is that it does not allow the establishment date of the relationship between two healthy agents to be determined. Thus, when a relationship should be broken is unknown to the program. The problem was solved by the memoryless property of the exponential distribution. Since the duration of the sexual relationships was assumed to follow an exponential distribution, the probability that a relationship ends in a cycle given that the relationship has lasted for an unknown period of time, t, can be expressed as

$$P(X < t + s \mid X > t) = 1 - P(X > t + s \mid X > t) = 1 - P(X > s) = P(X < s)$$

where X is the duration of a relationship, X follows an exponential distribution, and s is the length of a cycle. Thus, the program does not need to care about how long a relationship has been formed during simulations.

We assumed that 58.9% of the uninfected individuals between the ages of 15 and 79 have a steady partner in the model. This number was calculated by averaging the proportions of Ontarians (15 to 79 years old) who were married or living common-law in 2006, 2011 and 2016.[4] We also assumed that whether an agent has a steady partner is uncorrelated with his or her HBV infection status.

3.1.4 Input Data

The parameters adopted by the ABM regarding the natural history of CHB and CHB treatments were identical to those used in the STM and were collected from the same sources stated in Chapter 2. The parameters regarding AHB were obtained from the Public Health Agency of Canada (Table 3.1).[10] Population-related parameters, including demographic characteristics, annual number of immigrants and newborns, and fertility rates were obtained from Statistics Canada.[4,74,76,77,84,85] HBV screening and vaccination rates, prevalence and diagnostic rates of HBV in various countries, and treatment rates for patients diagnosed with HBV were collected from the Public Health Agency of Canada and the published literature.[3,9,10,73]

3.1.5 Calibration

Since certain parameters, especially those related to sexual networks and sexual behavior, are unavailable and unlikely to be accurately determined in the real world, we used a calibration process to estimate their values. The goal of this process was to match the reported number of AHB in Ontario from 2006 to 2014 produced by the ABM with the incidence of AHB reported in the real world.[86,87] The goodness of fit (GOF) of the model outputs to the calibration targets was assessed by the log-likelihood of the real-world observations. The calibration process was implemented primarily using O'Neill's version of the Nelder-Mead algorithm since it can fulfill the goal by conducting a relatively small number of simulations.[88,89] At the beginning of the process, a small set of value sets was selected from the uncertain parameter space based on a randomly generated set of uncertain parameter values. The calibrated range for each uncertain parameter was determined based on assumptions or articles related to the parameter.[75,79,81] At each iteration, the value set (within the set of uncertain parameter value sets) that produces the lowest GOF was replaced by a better set of values according to the algorithm. The calibration process ends when the values of GOF generated by the set of uncertain parameter value sets reach a steady equilibrium. This process was repeated several times to maximize the GOF that can be produced and avoid local minimal solutions. The final estimates of the uncertain parameters were the set of values that can produce an HBV epidemic that closely matched the observed data in Ontario to ensure that the model is the best representation of reality that can be achieved.

Table 3.1 Additional Model Inputs for the Agent-based Model

AHB-related Probabilities				
Parameter	Baseline	Low	High	Source
Probability of Developing AHB Symptoms (infants)	0.05	0.0375†	0.0625‡	10
Probability of Developing AHB Symptoms (children aged 1 to 5 years)	0.1	0.075†	0.125‡	10
Probability of Developing AHB Symptoms (adolescents and adults)	0.6	0.5	0.7	10
Probability of AHB to HBeAg+ CHB (infants)	0.9	0.675†	1‡	10
Probability of AHB to HBeAg+ CHB (children aged 1 to 5 years)	0.375	0.25	0.5	10
Probability of AHB to HBeAg+ CHB (adolescents)	0.075	0.05	0.1	10
Probability of AHB to HBeAg+ CHB (adults)	0.03	0.01	0.05	10
HBV Screening and Vaccination Related Probabilities				
Parameter	Baseline	Low	High	Source
Probability of Being Vaccinated at Age 12 Due to a School-based Vaccination Program	0.875	0.78	0.97	9, 10
Probability of Being Protected by Vaccines (people aged 12 to 13)	0.875	0.78	0.97	Assume same as the school-based vaccination program
Probability of Being Protected by Vaccines (people aged 14 to 19)	0.726	0.5445†	0.9075‡	3
Probability of Being Protected by Vaccines (people aged 20 to 24)	0.666	0.4995†	0.8325‡	3
Probability of Being Protected by Vaccines (people aged 25 to 29)	0.520	0.3900†	0.6500‡	3
Probability of Being Protected by Vaccines (people aged 30 to 34)	0.295	0.2213†	0.3688‡	3
Probability of Being Protected by Vaccines (people aged 35 to 39)	0.243	0.1823†	0.3038‡	3
Probability of Being Protected by Vaccines (people aged 40 to 49)	0.165	0.1238†	0.2063‡	3
Probability of Being Protected by Vaccines (people aged 50 to 59)	0.155	0.1163†	0.1938‡	3
Probability of Being Protected by Vaccines (people aged 60 to 69)	0.131	0.0983†	0.1638‡	3
Probability of Being Protected by Vaccines (people aged 70 to 79)	0.065	0.0488†	0.0813‡	3
Annual Probability of Voluntary Screening	0.0136	0	0.02	75, Calibration
Annual Probability of Voluntary Vaccination	0.0185	0	0.02	75, Calibration

Table 3.1 Continued

Other Parameters				
Parameter	Baseline	Low	High	Source
Number of Cycles per Year	52			Assumption
Initial Population Size	12,160,282			74
Population Scaling Ratio	0.1			Assumption
Relative Risk of Being HBV Infected for Immigrants vs General Population	0.4	0.3†	0.5‡	3, 4, 73
Minimum Age Allowed in the Sexual Network	15			4
Maximum Age Allowed in the Sexual Network	79			4, 32
Maximum Number of Sexual Partners Allowed per Person	200			78
Proportion of People in the Sexual Network Having a Steady Relationship	0.5888	0.4416†	0.7360‡	4
Mean Age Difference (male age minus female age) for a Couple	2.6			80
Standard Deviation of a Couple's Age Difference (male age minus female age)	6.3			80
Shape of the Distribution of Pairing Success Rate (beta)	0.4	0.3†	0.5‡	Assumption
Probability of HBV Transmission per Unprotected Sexual Intercourse (female to male)	0.0004	0.0003	0.0009	81, Calibration
Probability of HBV Transmission per Unprotected Sexual Intercourse (male to female)	0.0003	0.00018	0.0015	81, Calibration
Relative Risk of HBV Transmission for Infected People with Viral Suppression vs No Viral Suppression	0.1797	0.06	0.18	Calibration

†75% of its baseline value; ‡125% of its baseline value.

AHB, acute hepatitis B; CHB, chronic hepatitis B; HBeAg+, hepatitis B envelope antigen-positive; HBV, hepatitis B virus.

3.1.6 Validation

First, we validated the section of the ABM representing the natural history of hepatitis B. Two simulations on 1,000,000 individuals with the same characteristics as the two cohorts considered by the previously developed STM were performed, respectively. The lifetime health outcomes of the simulated population were compared with the results generated by the STM. Second, we determined how accurately the ABM (incorporating Ontario demographic data and calibrated uncertain parameter values) can estimate the reported incidence of AHB in Ontario in 2015 and 2016 and the population of Ontario from the end of 2006 to the end of 2018 compared with the real-world observations.[86,87,90] To eliminate the impact of randomness on the model outcomes, the results were the average of the results produced by 1,000 simulations using 1,000 randomly generated random number generator seeds.

3.1.7 Outcomes

The ABM predicted the actual prevalence of CHB, the reported incidence of AHB, and the actual incidence of CHB, DC, HCC, and liver-related death in Ontario from 2017 to 2030 for each of the treatment-as-prevention strategies considered. We performed 1,000 simulations for each strategy using the same set of random number generator seeds used to validate the model. The final results were the average of the results produced by the random number generator seeds.

3.1.8 Sensitivity Analyses

As recommended in a modeling guideline,[91] PSA, a type of sensitivity analysis that causes a large number of parameter changes, may be inappropriate for ABMs. The correlation between the parameters used by an ABM needs to be maintained to ensure that the model is a reasonable fit to the observed data,[91] which is difficult for PSA. Instead, we separately determined the impact of the following changes in the parameter regions on the prediction results based on our key assumptions:

1) increasing and decreasing the number of newborns by 25% after 2016;
2) increasing and decreasing the number of immigrants by 25% after 2016;
3) increasing and decreasing the HBV vaccination rate in immigrants aged 14 to 79 by 25% after 2016;
4) increasing and decreasing the HBV prevalence rates in immigrant-sourced regions after 2016 based on the credible intervals estimated from a published article and the 2016 Canadian Census;[4,73]

5) increasing and decreasing the HBV diagnostic rate in immigrants by 25% after 2016;

6) increasing and decreasing the treatment rate in HBV-infected patients who are eligible for treatment by 25% after 2016; and

7) increasing and decreasing the efficacy of TAF, TDF, and ETV after 2016 based on the credible intervals stated in Table 2.1.

All sensitivity analyses were conducted in a similar manner to the method described in Section 3.1.7.

3.2 Results

3.2.1 Validation

The lifetime health outcomes of HBeAg-positive and HBeAg-negative CHB patients treated with the corresponding treatment strategies estimated by the ABM and the STM described in Chapter 2 are shown in Table 3.2. All predictions generated by the two models closely match each other, including the lifetime probability of DC for patients initiated with HBeAg-positive non-cirrhotic CHB being 32.9% and 31.8% (assuming they had the same chance to receive any of the seven treatment strategies considered in Chapter 2) in the ABM and STM, respectively, and the lifetime probability of liver-related death being 41.8% and 41.6% in the ABM and STM, respectively. This indicates that the section of the ABM representing the natural history of hepatitis B is consistent with that of the STM.

3.2.2 Calibration

The optimal values of the 17 uncertain parameters found during the calibration process are shown in Table 3.3. The reported number of AHB cases from 2006 to 2016 observed in the real world and the one simulated by the ABM using this set of parameter values are shown in Figure 3.2.[86,87] The two trends are very similar to each other. Although the calibration process only attempted to estimate the uncertain parameter values that can produce a set of values that match the reported incidence of AHB in Ontario from 2006 to 2014 observed in the real world, the model-generated AHB incidence from 2015 to 2016 is also very close to the observed data. The GOF between the two curves was 3.41, and the maximum GOF that can be achieved is 4.93.

Table 3.2 Health Outcomes of 1,000 Patients Initiated with Non-cirrhotic Chronic Hepatitis B

(a) HBeAg-positive Cohort

Strategy	Model	DC (Number Prevented If Using TDF→ETV→BSC)		HCC (Number Prevented If Using TDF→ETV→BSC)		Liver-related Death (Number Prevented If Using TDF→ETV→BSC)		Liver-related Death Caused by DC (Number Prevented If Using TDF→ETV→BSC)		Liver-related Death Caused by HCC (Number Prevented If Using TDF→ETV→BSC)	
BSC	STM	391	(84)	281	(60)	520	(120)	244	(56)	212	(47)
	ABM	396	(78)	287	(56)	512	(110)	231	(49)	195	(39)
TAF→BSC	STM	323	(16)	231	(10)	423	(23)	200	(12)	173	(8)
	ABM	334	(16)	243	(12)	426	(24)	192	(10)	164	(8)
TDF→BSC	STM	332	(25)	237	(16)	434	(34)	205	(17)	178	(13)
	ABM	341	(23)	249	(18)	436	(34)	197	(15)	168	(12)
ETV→BSC	STM	363	(56)	260	(39)	478	(78)	225	(37)	196	(31)
	ABM	371	(53)	268	(37)	474	(72)	214	(32)	182	(26)
TAF→ETV→BSC	STM	299	(-8)	215	(-6)	389	(-11)	183	(-5)	161	(-4)
	ABM	312	(-6)	227	(-4)	394	(-8)	178	(-4)	153	(-3)
TDF→ETV→BSC	STM	307		221		400		188		165	
	ABM	318		231		402		182		156	
ETV→TAF→BSC	STM	298	(-9)	215	(-6)	389	(-11)	183	(-5)	161	(-4)
	ABM	310	(-8)	226	(-5)	393	(-9)	177	(-5)	153	(-3)
ETV→TDF→BSC	STM	306	(-1)	220	(-1)	399	(-1)	188	(0)	164	(-1)
	ABM	318	(0)	231	(0)	402	(0)	182	(0)	155	(-1)

Table 3.2 Continued

(b) HBeAg-negative Cohort

Strategy	Model	DC (Number Prevented If Using TDF→ETV→BSC)		HCC (Number Prevented If Using TDF→ETV→BSC)		Liver-related Death (Number Prevented If Using TDF→ETV→BSC)		Liver-related Death Caused by DC (Number Prevented If Using TDF→ETV→BSC)		Liver-related Death Caused by HCC (Number Prevented If Using TDF→ETV→BSC)	
BSC	STM	352	(98)	246	(76)	441	(144)	212	(66)	182	(60)
	ABM	366	(98)	257	(77)	443	(140)	206	(61)	172	(54)
TAF→BSC	STM	265	(11)	178	(8)	314	(17)	154	(8)	129	(7)
	ABM	279	(11)	189	(9)	320	(17)	152	(7)	124	(6)
TDF→BSC	STM	276	(22)	187	(17)	329	(32)	160	(14)	136	(14)
	ABM	289	(21)	198	(18)	334	(31)	158	(13)	130	(12)
ETV→BSC	STM	329	(75)	229	(59)	406	(109)	196	(50)	169	(47)
	ABM	344	(76)	239	(59)	408	(105)	191	(46)	158	(40)
TAF→ETV→BSC	STM	244	(-10)	162	(-8)	284	(-13)	140	(-6)	117	(-5)
	ABM	257	(-11)	173	(-7)	291	(-12)	139	(-6)	113	(-5)
TDF→ETV→BSC	STM	254		170		297		146		122	
	ABM	268		180		303		145		118	
ETV→TAF→BSC	STM	244	(-10)	162	(-8)	284	(-13)	140	(-6)	117	(-5)
	ABM	258	(-10)	172	(-8)	290	(-13)	139	(-6)	113	(-5)
ETV→TDF→BSC	STM	254	(0)	170	(0)	297	(0)	146	(0)	122	(0)
	ABM	267	(-1)	181	(1)	303	(0)	144	(-1)	118	(0)

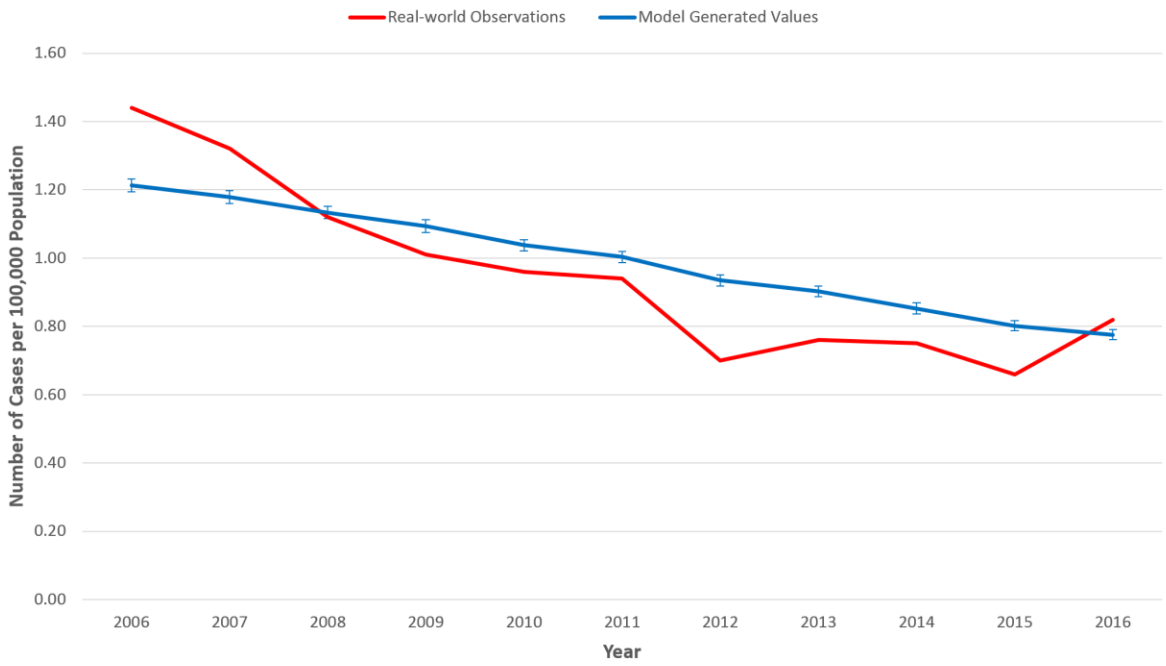
ABM, agent-based model; BSC, best supportive care; DC, decompensated cirrhosis; ETV, entecavir; HBeAg, hepatitis B envelope antigen; HCC, hepatocellular carcinoma; STM, state-transition model; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 3.3 Calibrated Parameters

Parameter	Calibrated Range	Optimal Value
Probability of a Female Having No Sexual Partner	0.075–0.125	0.1028
Probability of a Male Having No Sexual Partner	0.075–0.125	0.0784
Sexual Network Scale Free Gamma (female)	1.8–4.2	4.1700
Sexual Network Scale Free Gamma (male)	1.8–4.2	3.3511
Relative Risk of Looking for Sexual Partners for People with a Steady Partner vs No Steady Partner	0.15–0.45	0.2586
Maximum Optimum Distance for Sexual Relationships (km)	50–200	147.1690
Mean Steady Relationship Duration (year)	8–24	9.2863
Mean Casual Relationship Duration (year)	0.5–1.5	0.9782
Mean Number of Sexual Contacts per Person per Year	80–300	91.9641
Shape of the Distribution of Assigning Sexual Contacts (alpha)	0.5–2	1.8645
Probability of HBV Transmission per Unprotected Sexual Intercourse (female to male)	0.0003–0.0009	0.0004
Probability of HBV Transmission per Unprotected Sexual Intercourse (male to female)	0.00018–0.0015	0.0003
Relative Risk of HBV Transmission for Infected People with Viral Suppression vs No Viral Suppression	0.06–0.18	0.1797
Condom Use Rate for Steady Relationships	0.2–0.6	0.5256
Condom Use Rate for Casual Relationships	0.525–0.875	0.8478
Annual Probability of Voluntary Screening	0–0.02	0.0136
Annual Probability of Voluntary Vaccination	0–0.02	0.0185

HBV, hepatitis B virus.

Figure 3.2 Reported Incidence of Acute Hepatitis B



Although the model took into account the actual population of Ontario in 2006 and the actual annual number of newborns and immigrants,[74,76,77] the annual number of deaths simulated by the model mainly depended on the age and health status of the agents. This means that the simulated population size cannot be guaranteed to be the same as the actual population size of Ontario after 2006. However, the population of Ontario from the end of 2006 to the end of 2018 estimated by the model closely matched with the observed data,[90] as shown in Figure 3.3. As a result, the model incorporating the parameter values found through the calibration process is credible.

The calibration process found that the probability of a randomly selected male and a randomly selected female having no sexual partner in the model was 7.8% and 10.3%, respectively (Figure 3.4). The sexual network scale free gammas for males and females were found to be 3.4 and 4.2, respectively. This implies that 80.5% of the males and 83.7% of the females in the model had only one partner, and 11.7% of the males and 6.0% of the females had more than one partner.

Figure 3.3 Population of Ontario

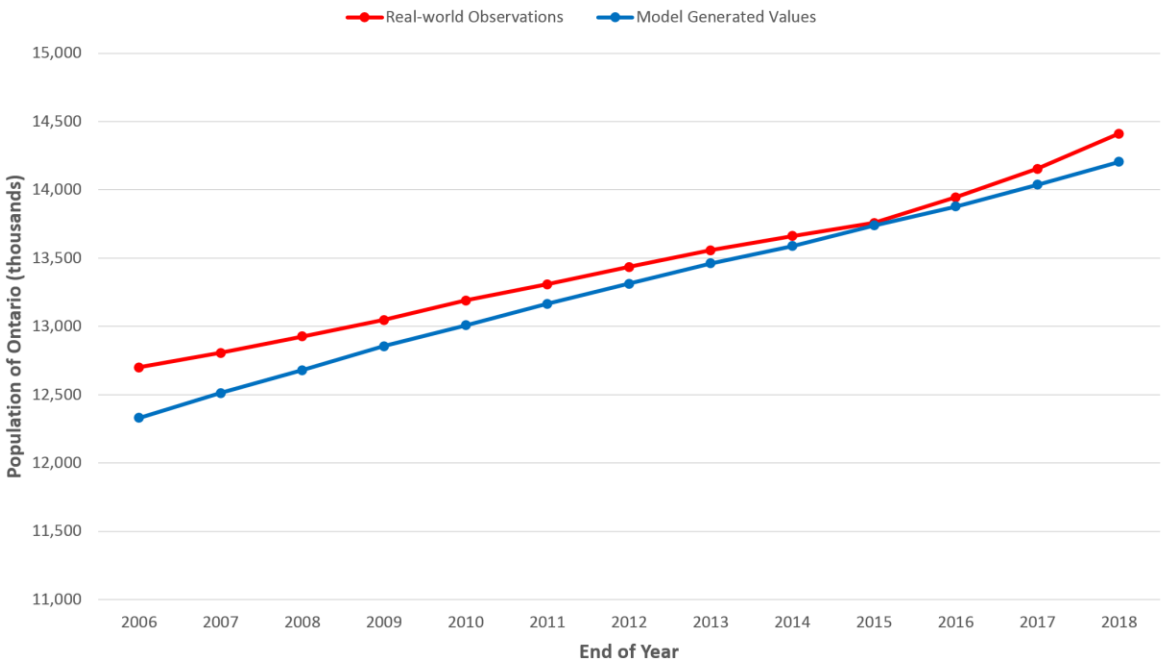
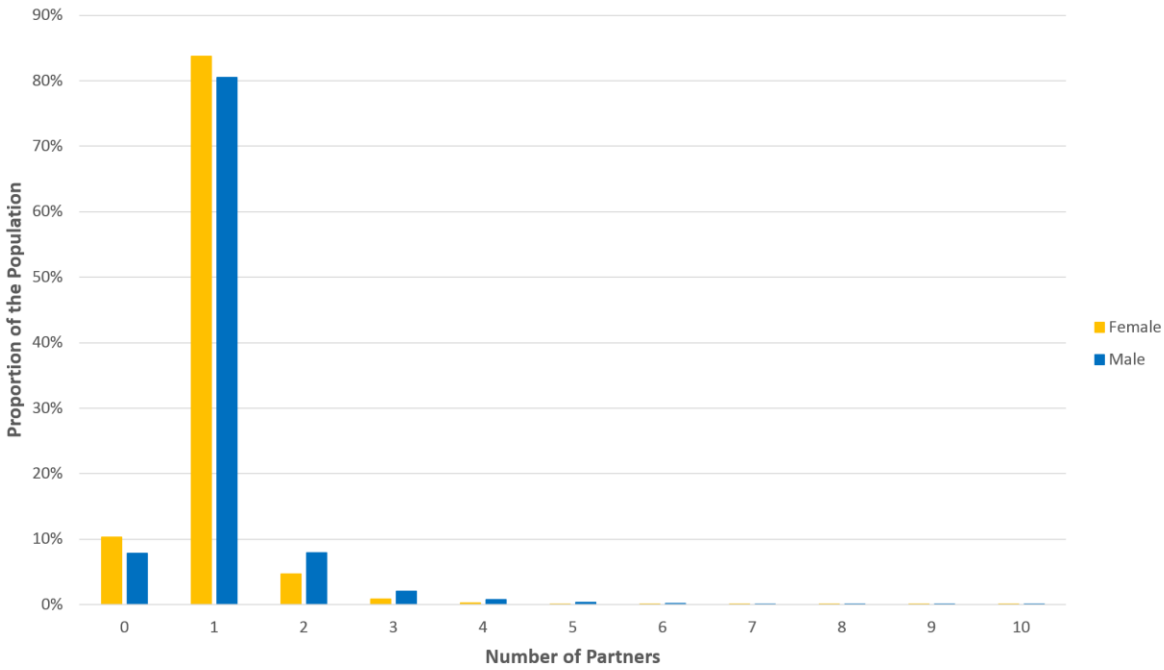


Figure 3.4 Proportion of the Simulated Population Having a given Number of Sexual Partners

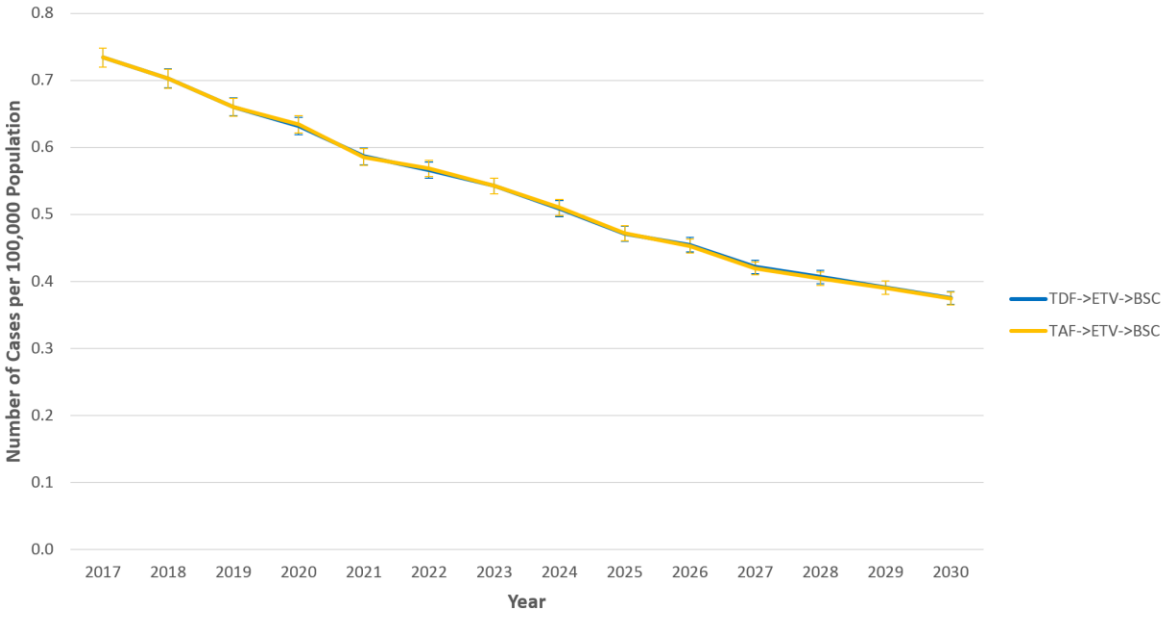


3.2.3 Prediction

Based on the calibrated ABM as described in Section 3.2.2, we projected the outcomes as mentioned in Section 3.1.7. The reported incidence of AHB and the actual incidence of CHB in Ontario from 2017 to 2030 predicted by the model are shown in Figure 3.5 and Figure 3.6. However, these incidence rates resulting from TDF→ETV→BSC and TAF→ETV→BSC were not significantly different from each other. For both of the strategies, the incidence of AHB and CHB decreased by roughly 48.9% and 52.2% from 2017 to 2030, respectively.

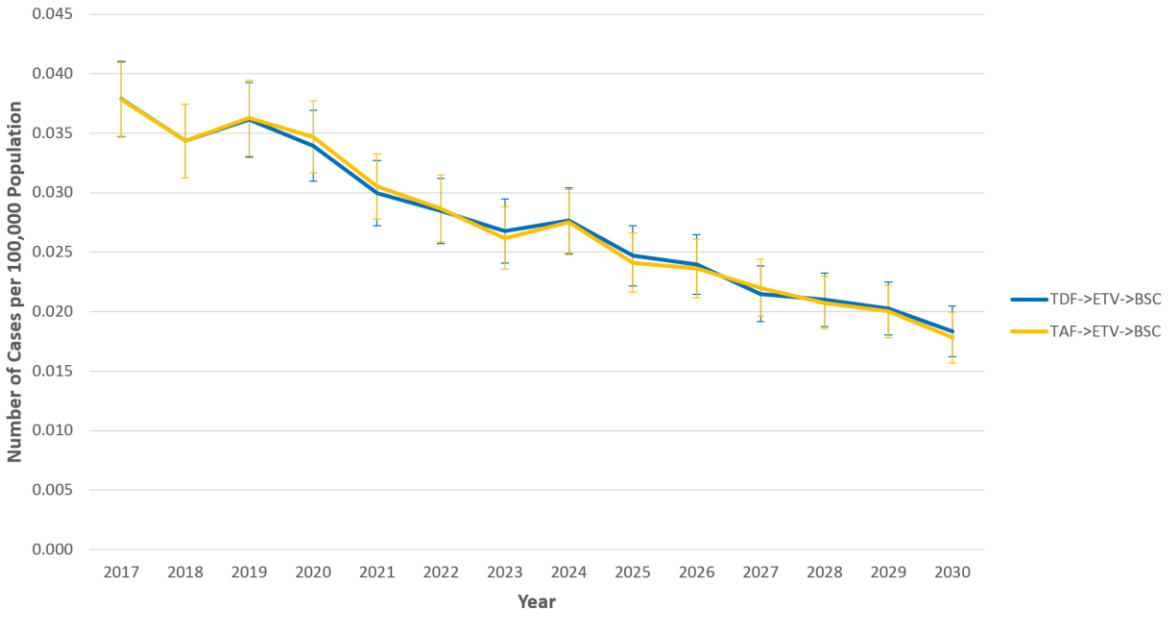
The ABM predicted that the actual prevalence of CHB in Ontario resulting from either TDF→ETV→BSC or TAF→ETV→BSC would decrease by 11.5% from 2017 to 2030, reaching 0.50% (Figure 3.7). Throughout the predicted years, the prevalence of CHB declined almost linearly, dropping by 5 per 100,000 population every year. Similar to the reported incidence of AHB, the two curves shown in Figure 3.7 almost overlapped each other, indicating that receiving TDF→ETV→BSC or TAF→ETV→BSC does not show a significant difference in the prevalence of CHB.

Figure 3.5 Reported Incidence of Acute Hepatitis B



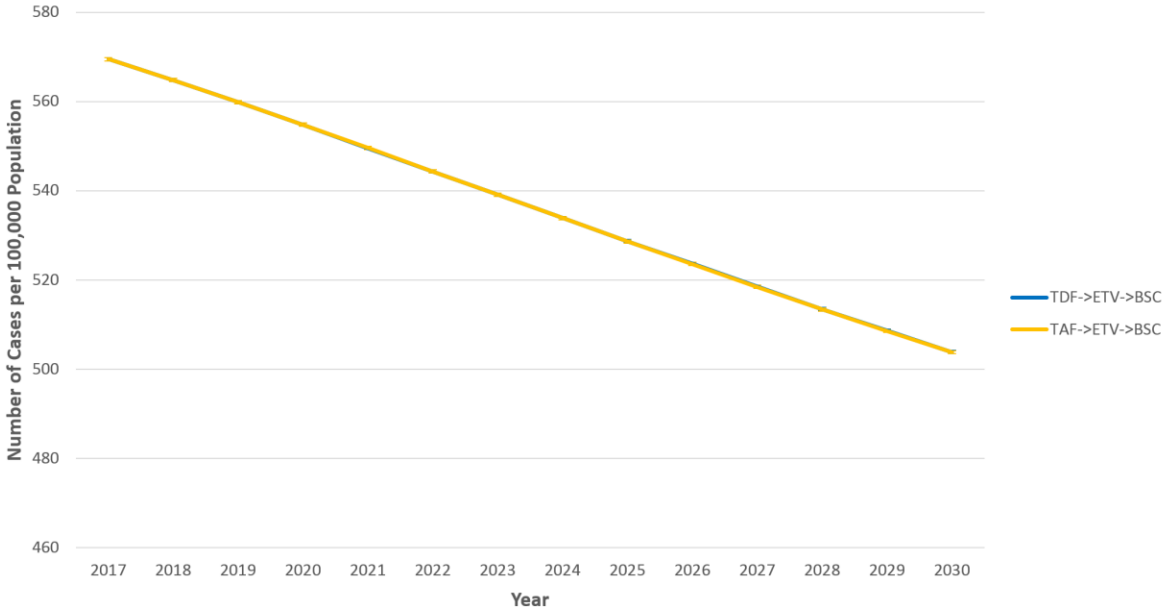
BSC, best supportive care; ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Figure 3.6 Actual Incidence of Chronic Hepatitis B



BSC, best supportive care; ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

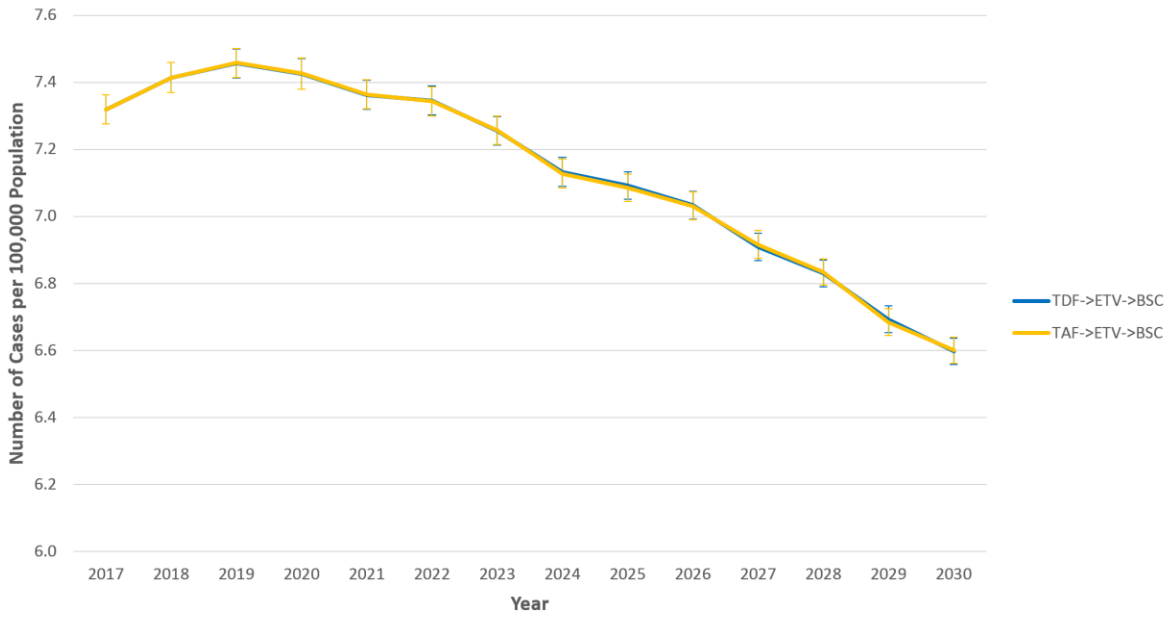
Figure 3.7 Actual Prevalence of Chronic Hepatitis B



BSC, best supportive care; ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

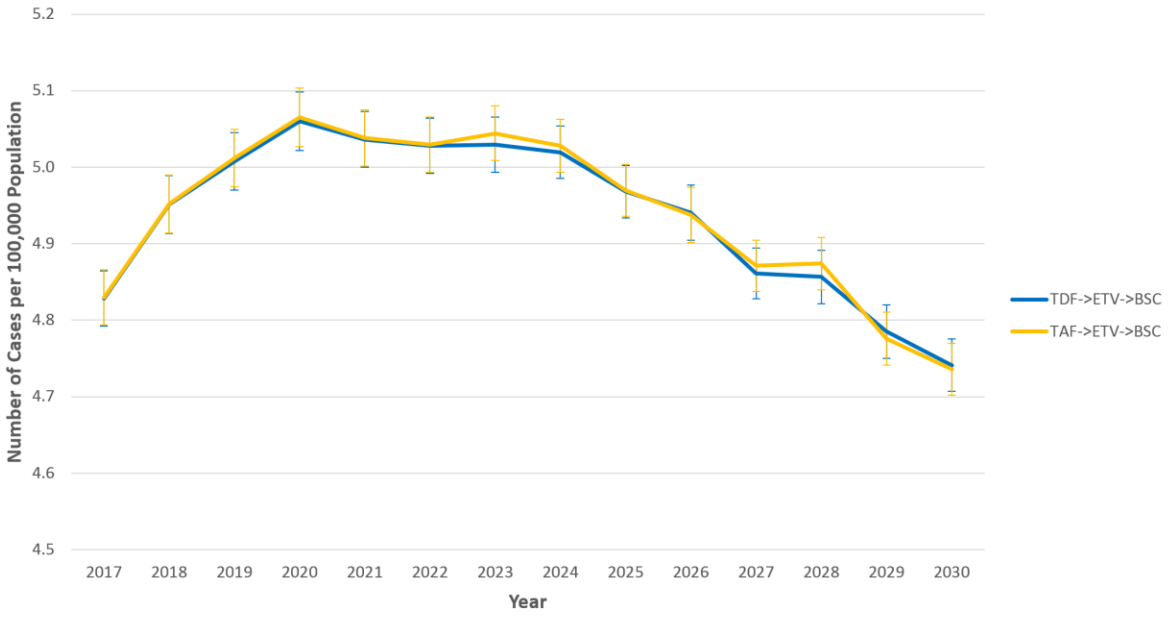
Receiving any of the two treatment-as-prevention strategies considered in this study did not show clear differences in the actual incidence of DC, HCC, and liver-related death either (Figure 3.8, Figure 3.9, and Figure 3.10). The model predicted that the incidence of DC in Ontario resulting from TDF→ETV→BSC and TAF→ETV→BSC decreased by 9.9% and 9.8% from 2017 to 2030, respectively. For both of the strategies, the incidence of HCC increased from 2017 to 2020 and then began to decline. In 2030, the incidence rates resulting from TDF→ETV→BSC and TAF→ETV→BSC decreased by 1.8% and 1.9% compared with those in 2017, respectively. The incidence of liver-related death was generally increasing throughout the predicted years but had tended to decline after 2024. Overall, the incidence of liver-related death resulting from the two strategies increased by roughly 12.3% on average from 2017 to 2030.

Figure 3.8 Actual Incidence of Decompensated Cirrhosis



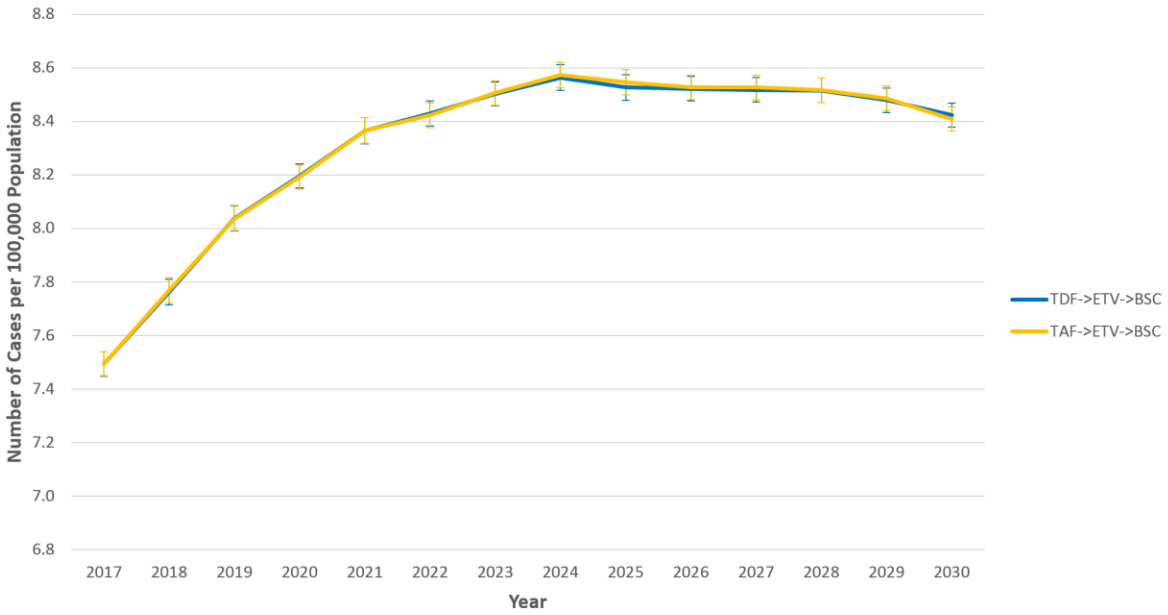
BSC, best supportive care; ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Figure 3.9 Actual Incidence of Hepatocellular Carcinoma



BSC, best supportive care; ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Figure 3.10 Actual Incidence of Liver-related Death



BSC, best supportive care; ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

3.2.4 Sensitivity Analyses

By incorporating the ABM with the optimal set of parameter values found through the calibration process, the effect of parameter changes mentioned in Section 3.1.8 on HBV-related health outcomes was projected. Immigrants may come from regions where the prevalence of HBV is higher than that in Canada. By increasing the number of immigrants after 2016 by 25%, the percentage of decline in the actual prevalence of CHB resulting from either TDF→ETV→BSC or TAF→ETV→BSC from 2017 to 2030 decreased to 7.0% compared with the prediction results (11.5%) described in the previous section (Figure 3.11 (a)). By decreasing the number of immigrants after 2016 by 25%, the percentage of decline in actual CHB prevalence from 2017 to 2030 increased to 16.4%. On the other hand, the increase and decrease in the number of immigrants after 2016 led to a drop in the reported incidence of AHB from 2017 to 2030 by about 46.1% and 53.1%, respectively (Figure 3.11 (b)). Since the impact of interventions on liver-related death takes a long time to be observed, changes in the number of immigrants have no clear effect on the actual incidence of liver-related death as shown in Figure 3.11 (c). Although the incidence rates from 2017 to 2026 resulting from increasing the number of immigrants were generally lower than that from decreasing the number of immigrants, this may be due to a dilution effect brought on by the growth of the total population. Contrary to decreasing the number of immigrants, increasing the total number of immigrants implies an increase in the number of HBV-

Figure 3.11 Impact of Changes in the Number of Immigrants on HBV-related Health Outcomes

(a) Actual Prevalence of Chronic Hepatitis B

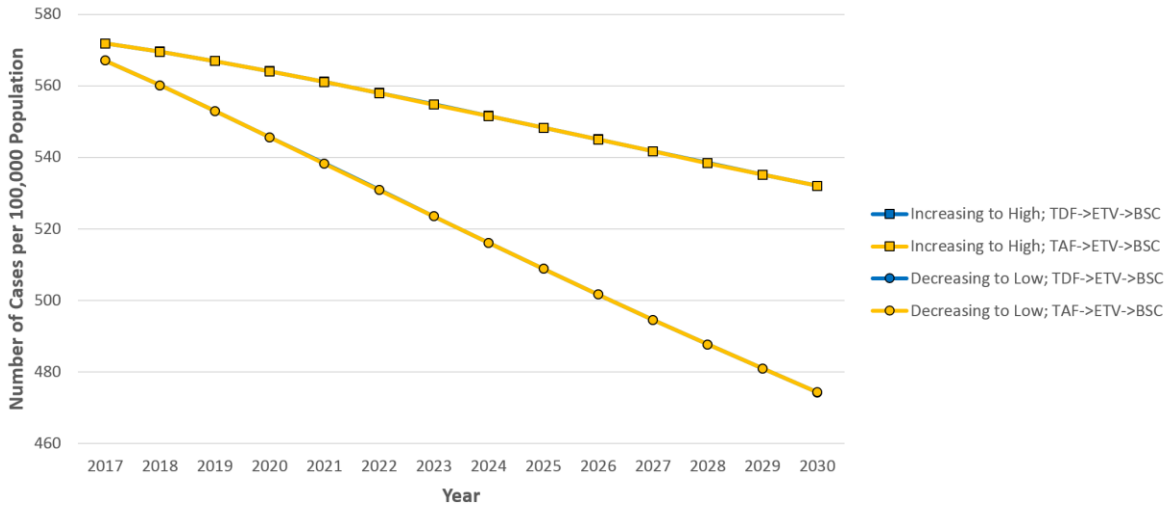
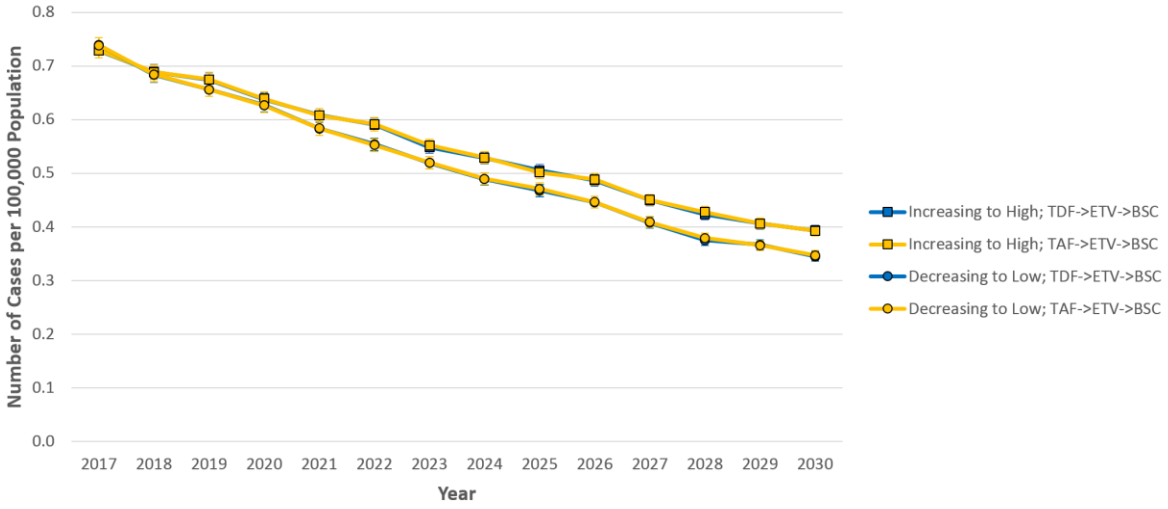
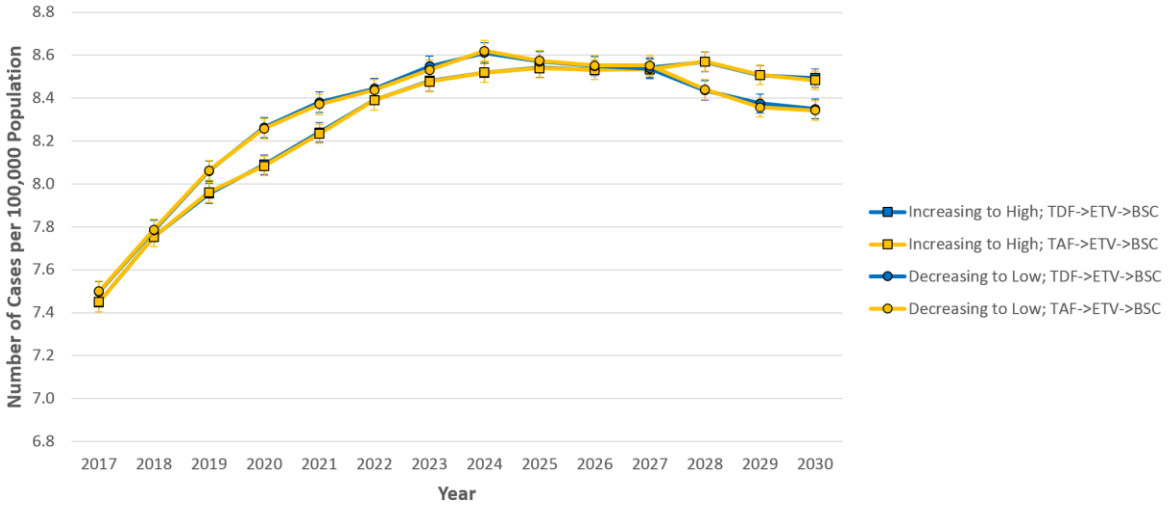


Figure 3.11 Continued

(b) Reported Incidence of Acute Hepatitis B



(c) Actual Incidence of Liver-related Death



BSC, best supportive care; ETV, entecavir; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

infected immigrants, which may be the reason why it did not result in a significant downtrend in the incidence of liver-related death as the year approached 2030.

Similar to changes in the number of immigrants, increasing the HBV prevalence rates in immigrant-sourced regions after 2016 caused the percentage of decline in the actual prevalence of CHB and the reported incidence of AHB from 2017 to 2030 to fall to 7.0% and 46.2%, respectively (Figure B.1 (a) and Figure B.1 (b)). Decreasing the prevalence of HBV in immigrant-sourced regions after 2016 caused the percentage of decline in the prevalence of CHB and the incidence of AHB to rise to 15.8% and 52.0%, respectively. As changes in the HBV prevalence rates in immigrant-sourced regions only affect the proportion of HBV-infected people in immigrants without directly changing the size of the population, the increase and decrease in these rates after 2016 led to an increase in the actual incidence of liver-related death from 2017 to 2030 by about 14.5% and 9.5%, respectively (Figure B.1 (c)).

Since the ABM did not consider perinatal infections, all newborns were considered non-infected with HBV when they were added to the virtual society created by the model. By increasing the number of newborns after 2016 by 25%, the percentage of decline in the actual prevalence of CHB from 2017 to 2030 increased to 14.0%, regardless of the treatment-as-prevention strategies considered (Figure B.2 (a)). By decreasing the number of newborns after 2016 by 25%, the percentage of decline was reduced to 8.8%, while the reported incidence of AHB resulting from increasing the number of newborns was generally lower than that resulting from decreasing the number of newborns as shown in Figure B.2 (b). The increase and decrease in the number of newborns after 2016 also led to an increase in the actual incidence of liver-related death in Ontario from 2017 to 2030 by approximately 8.7% and 15.9%, respectively (Figure B.2 (c)).

Changes in the remaining four parameter regions described in Section 3.1.8 did not have a significant impact on the HBV-related health outcomes (Figure B.3, Figure B.4, Figure B.5, and Figure B.6). Excluding the HBV vaccination rate in immigrants, all of them are directly related to the treatment of CHB. In addition, all changes considered in the sensitivity analyses failed to significantly differentiate the effect of the two treatment-as-prevention strategies on the health outcomes.

3.3 Discussion

The ABM predicted an 11.5% decline in the actual prevalence of CHB in Ontario from 2017 to 2030 if all CHB patients eligible and ready for treatment begin to receive TDF→ETV→BSC or TAF→ETV→BSC after 2016. Although TAF is a novel prodrug of TDF approved for the treatment of CHB in recent years, TAF→ETV→BSC was not found to significantly differ from TDF→ETV→BSC in reducing the prevalence of CHB in this study. WHO's global hepatitis strategy calls for a 90%

reduction in new CHB cases, and a 65% reduction in CHB deaths worldwide by 2030.[27] Our model predicted that the reported incidence of AHB and the number of new CHB cases in Ontario would only drop by 48.9% and 52.2%, respectively. This is far below the target set by the WHO. Conversely, the actual number of liver-related death is expected to increase by approximately 12.3% from 2017 to 2030, regardless of the treatment-as-prevention strategies considered. HBV-related health outcomes were found to be sensitive to the number of immigrants and newborns, and the prevalence of HBV in the immigrant-sourced regions. Furthermore, the conclusion that TDF→ETV→BSC and TAF→ETV→BSC have no significant difference in reducing the prevalence and incidence of HBV-related health outcomes is unlikely to be altered due to changes in any of the seven parameter regions considered in the sensitivity analyses.

Our analysis was built upon the first ABM associated with hepatitis B transmission. This model adequately solved the limitation of STMs related to their inability to simulate the impact of strategies on the spread of HBV. The ABM we developed can provide evidence on whether long-term HBV elimination goals can be achieved by treatment-as-prevention strategies. However, our study also has limitations. The model cannot simulate the repartition of the FSAs in Ontario and the uneven development of the population size of the FSAs due to changes in the economic environment, which may differentiate the geographical structure of the contact networks from reality. To highlight the impact of the treatment-as-prevention strategies applied during the prediction period and to make a better comparison, we assumed that all CHB patients who are eligible and ready for treatment can begin to receive TAF in early 2017. However, TAF was not allowed to enter the Canadian market until the second half of 2017. We assumed that the vaccination rate of the immigrants before immigrating to Canada is similar to that of Canadian-born people at the corresponding age, which may not be consistent with the actual situation. Although HBV is known to be a virus that is commonly transmitted through maternal-child contact, sexual activities, and injection drug use, our model only considered sexual transmission among heterosexual partners, which may underestimate the incidence and prevalence of future HBV-related health outcomes. However, a published article indicates that perinatal or horizontal infection in early childhood occurs mainly in high-prevalence regions of hepatitis B such as Asia and Africa.[2] In low-prevalence regions such as Canada, sexual behaviors and injection drug use between adolescents and adults are the main routes of HBV transmission.[2] In addition, our program structure has provided a framework for adding perinatal, horizontal, and homosexual transmissions in the future.

Although BSC alone (which is equivalent to not receiving any antiviral treatment) is unreasonable to be considered as a strategy to deal with CHB as both TDF and ETV have been listed as reimbursed drugs in Ontario, decision-makers may also be interested in how much more effectively TDF→ETV→BSC can eliminate AHB incidence and CHB prevalence in Ontario until 2030 compared with having no antiviral treatment at all. To figure this out, an analysis was performed in a similar manner to Section 3.2.3, and the results showed that the reported incidence of AHB resulting from TDF→ETV→BSC was slightly lower than that of BSC in most of the years predicted (Figure B.7). Figure B.8 shows how the magnitude of actual CHB prevalence resulting from TDF→ETV→BSC is greater than that resulting from BSC. Overall, the prevalence rates resulting from TDF→ETV→BSC was lower than that resulting from BSC. However, the variation in the prevalence rates between having treatment and not having treatment was almost negligible, which is less than 0.2 per 100,000 population. Although TDF→ETV→BSC was found to be the most cost-effective strategy for treating CHB infections in Chapter 2, it was not found to have a significant difference in reducing the prevalence and incidence of HBV-related health outcomes compared with BSC alone. This may be due to the low HBV diagnostic rate (58%) and the low post-diagnosis treatment rate (40.7%) in Canada,[73] as well as the non-100% viral suppression rates of the drugs.[14,15,35]

By combining multi-agent systems and complex networks, we developed a complex network model that reflects the dynamics of HBV transmission, which enables forecasting of the epidemiology of HBV for policy-level decision making in Canada. The results suggest that current treatment-as-prevention strategies do not play a significant role in achieving the WHO's goals of eliminating new CHB cases and CHB deaths.[27] Some potential curable CHB treatments are currently in clinical trials.[92] As these treatments prepare to enter the market, the analysis can be run again. Further analysis can be conducted to assess whether the goals set by the WHO can be achieved through other interventions, such as combination strategies involving screening and vaccination.

Chapter 4
Conclusions

4.1 Summary of Results

The results generated by the STM described in Chapter 2 shows that TDF→ETV→BSC is relatively likely to be the most cost-effective treatment option for both HBeAg-positive and HBeAg-negative CHB patients, which is consistent with the AASLD guidelines.[17] ETV→TDF→BSC is also a good treatment strategy for HBeAg-positive patients. Strategies involving TAF are unlikely to be a rational choice for treating CHB infections as the price of TAF is more than four times that of TDF, but its efficacy is not comprehensively better than TDF. Public drug plans are therefore not recommended to reimburse TAF at the current price.

The ABM described in Chapter 3 predicted that the actual prevalence of CHB in Ontario would decrease by 11.5% from 2017 to 2030 if all CHB patients eligible and ready for treatment begin to receive TDF→ETV→BSC or TAF→ETV→BSC after 2016. The reported incidence of AHB and the actual incidence of CHB are expected to fall by 48.9% and 52.2% from 2017 to 2030, respectively. The actual incidence of liver-related death is expected to rise by 12.3% from 2017 to 2030, regardless of the treatment-as-prevention strategies considered. The model predicted that the percentages of decline in new CHB cases and liver-related deaths from 2017 to 2030 would be 37.8% and 77.3% lower than the percentages that the WHO is targeting, respectively.[27] Although TAF→ETV→BSC was found to be the most effective strategy for treating CHB infections in Chapter 2, it was not found to be significantly different from TDF→ETV→BSC in reducing the prevalence and incidence of HBV-related health outcomes in Chapter 3. Since receiving antiviral treatment did not show clear differences from no antiviral treatment, current treatment-as-prevention strategies do not play a significant role in achieving the WHO goals of eliminating new CHB cases and CHB deaths.

4.2 Thesis Contributions

The vast majority of analyses in the literature regarding HBV infection are unable to predict the prevalence of CHB at future time points,[19-24] and CHB-related analyses based on models other than STMs are limited. In order to fill this knowledge gap, this thesis accomplished the first analysis of hepatitis B that is built upon an ABM. Since HBV is highly contagious, finding and understanding strategies that can limit human-to-human transmission in a region is critical to reducing the global

prevalence of CHB. By combining multi-agent systems and complex networks, we developed the first AMB that can simulate HBV transmission between individuals through contact networks based on real demographic data from Ontario, which helps Canada move towards the goals set by the WHO.[27]

Most CHB patients must continue to be treated for the rest of their lives.[1] If they are not being treated effectively, they are likely to develop severe liver diseases such as HCC.[2] Although TAF has been identified as a preferred therapy for patients with CHB in the guidelines released by the AASLD and the EASL due to clinical benefits,[17,26] its cost-effectiveness compared with other HBV treatment options was previously unknown. This thesis produced the first cost-effectiveness analysis of hepatitis B that is built upon an STM that considers treatment strategies involving TAF and incorporated efficacy outcomes of the treatments from the latest systematic review and network meta-analysis.[35] We also developed the first STM that takes into account the impact of treatment-related SAEs on the costs and utilities. This would not only update people's perception of the existing CHB drugs but also provide policy-level support for achieving CHB-related goals.

4.3 Future Work

As long-term follow-up efficacy outcomes of TAF are unavailable, future studies should incorporate more sophisticated long-term data as it becomes available to find the optimal treatment strategy for CHB infections. The impact of differences in people's income levels and education levels on partner selection and disease progression can also be considered in the two models. Future research can further enhance the ABM developed in this thesis (by adding perinatal and horizontal infections, homosexual and bisexual networks, and HBV transmission associated with injection drug use) and optimize our analyses to find out which combinations of interventions (such as combination strategies involving screening and vaccination) can most likely achieve the goals of CHB elimination. Costs and utilities can also be incorporated into the ABM to assess the cost-effectiveness of HBV elimination strategies for real-world populations.

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Appendix A

Additional Results Generated by the State-transition Model

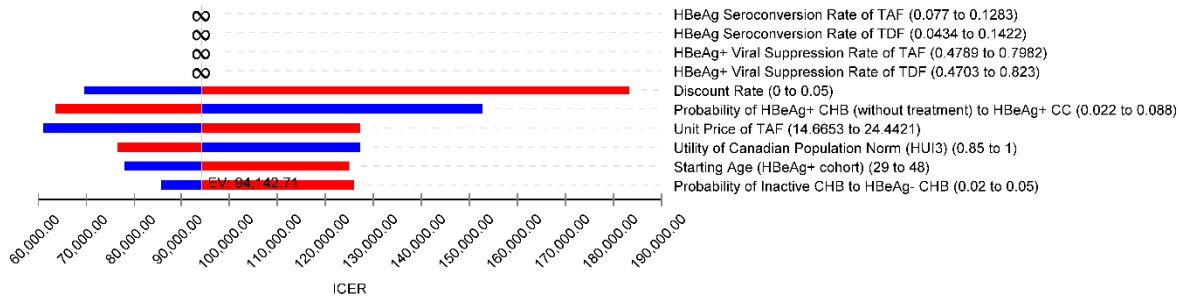
Table A.1 Health Outcomes of 1,000 Patients Initiated with Non-cirrhotic Chronic Hepatitis B

Strategy	DC (Number Prevented If Using TDF→ETV→BSC)		HCC (Number Prevented If Using TDF→ETV→BSC)		Liver-related Death (Number Prevented If Using TDF→ETV→BSC)		Liver-related Death Caused by DC (Number Prevented If Using TDF→ETV→BSC)		Liver-related Death Caused by HCC (Number Prevented If Using TDF→ETV→BSC)	
HBeAg-positive Cohort										
TAF→BSC	323	(16)	231	(10)	423	(23)	200	(12)	173	(8)
TDF→BSC	332	(25)	237	(16)	434	(34)	205	(17)	178	(13)
ETV→BSC	363	(56)	260	(39)	478	(78)	225	(37)	196	(31)
TAF→ETV→BSC	299	(-8)	215	(-6)	389	(-11)	183	(-5)	161	(-4)
TDF→ETV→BSC	307		221		400		188		165	
ETV→TAF→BSC	298	(-9)	215	(-6)	389	(-11)	183	(-5)	161	(-4)
ETV→TDF→BSC	306	(-1)	220	(-1)	399	(-1)	188	(0)	164	(-1)
HBeAg-negative Cohort										
TAF→BSC	265	(11)	178	(8)	314	(17)	154	(8)	129	(7)
TDF→BSC	276	(22)	187	(17)	329	(32)	160	(14)	136	(14)
ETV→BSC	329	(75)	229	(59)	406	(109)	196	(50)	169	(47)
TAF→ETV→BSC	244	(-10)	162	(-8)	284	(-13)	140	(-6)	117	(-5)
TDF→ETV→BSC	254		170		297		146		122	
ETV→TAF→BSC	244	(-10)	162	(-8)	284	(-13)	140	(-6)	117	(-5)
ETV→TDF→BSC	254	(0)	170	(0)	297	(0)	146	(0)	122	(0)

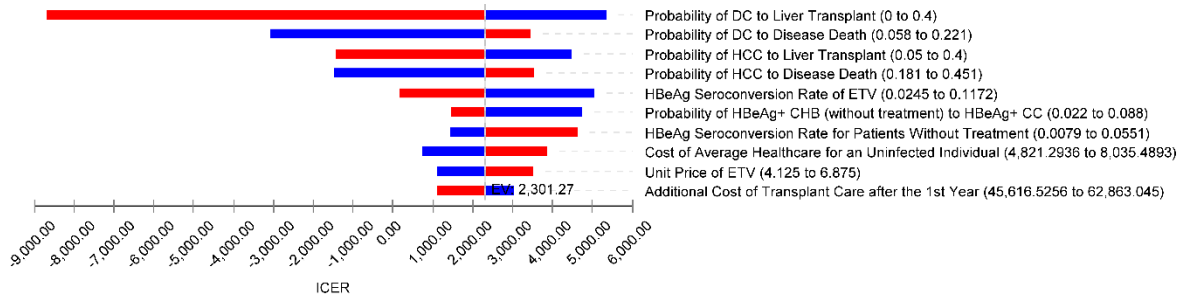
BSC, best supportive care; DC, decompensated cirrhosis; ETV, entecavir; HBeAg, hepatitis B envelope antigen; HCC, hepatocellular carcinoma; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Figure A.1 One-way Sensitivity Analyses: Tornado Diagrams

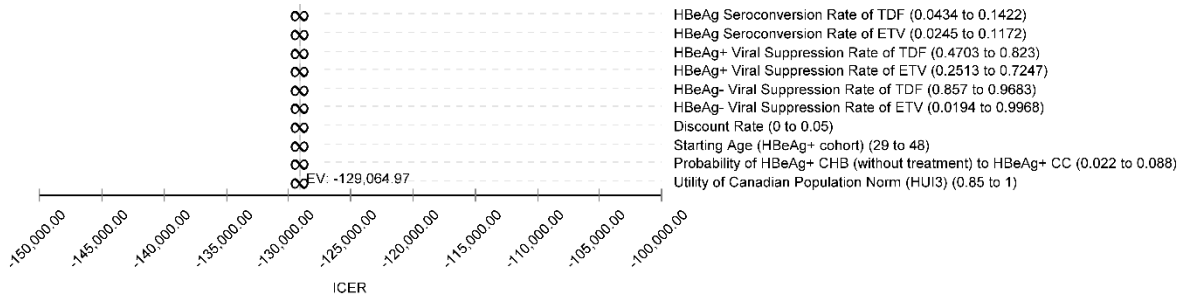
(a) HBeAg-positive Cohort: TAF→ETV→BSC vs TDF→ETV→BSC



(b) HBeAg-positive Cohort: TDF→ETV→BSC vs TDF→BSC



(c) HBeAg-positive Cohort: ETV→TDF→BSC vs TDF→ETV→BSC



(d) HBeAg-negative Cohort: ETV→TAF→BSC vs TDF→ETV→BSC

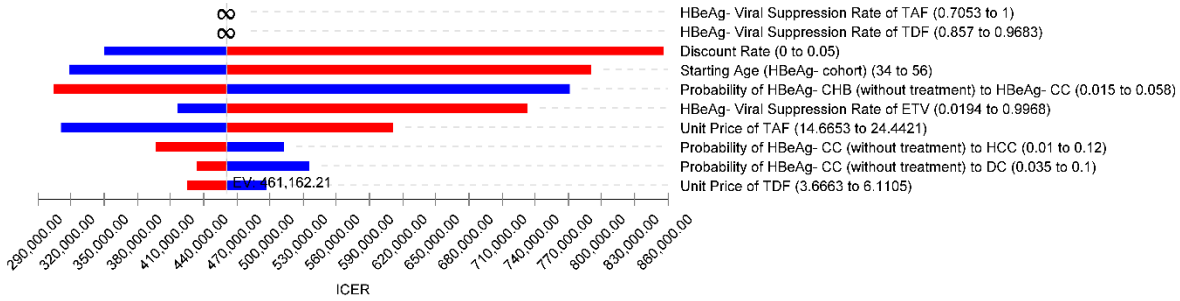
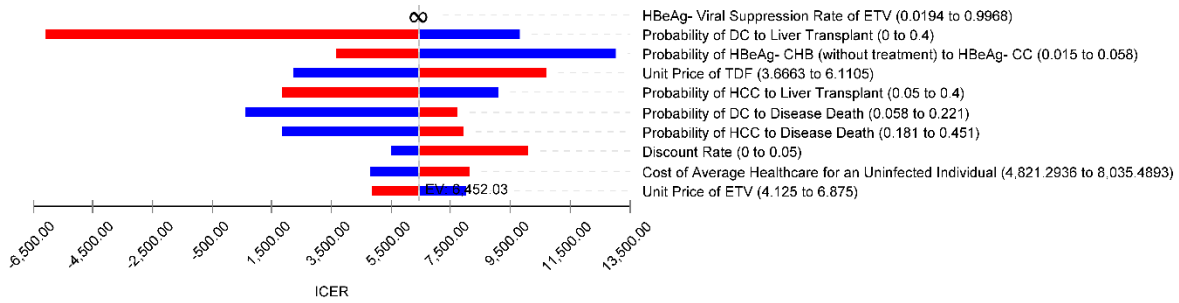


Figure A.1 Continued

(e) HBeAg-negative Cohort: TDF→BSC vs ETV→BSC

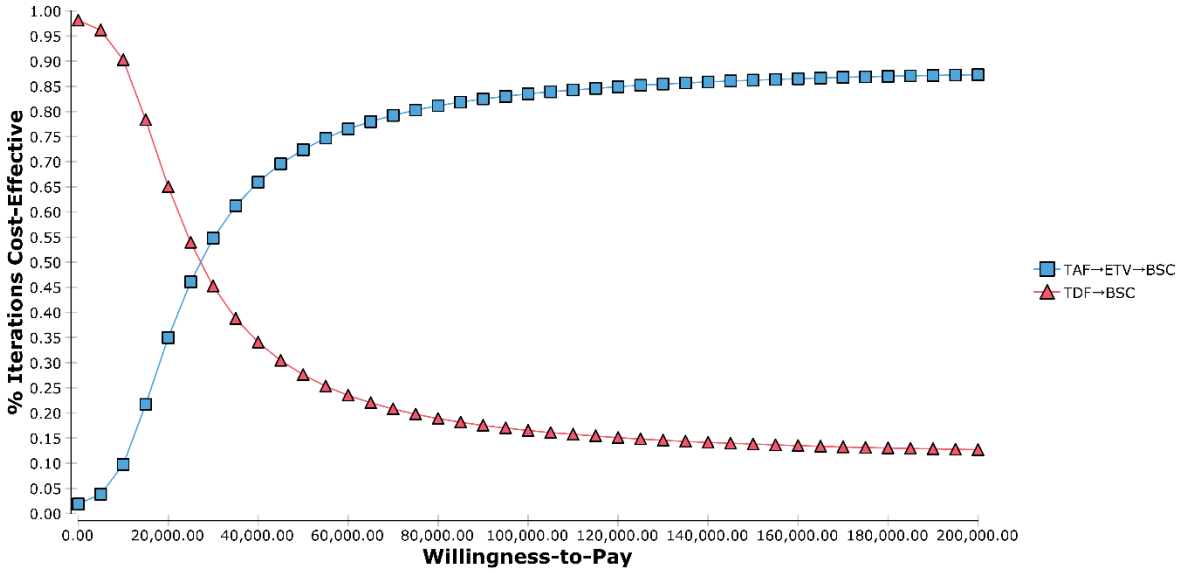


∞ indicates that changing the value of the parameter within the given range will certainly alter the conclusion. Red bars and blue bars represent the results of the high and low values of the parameters, respectively.

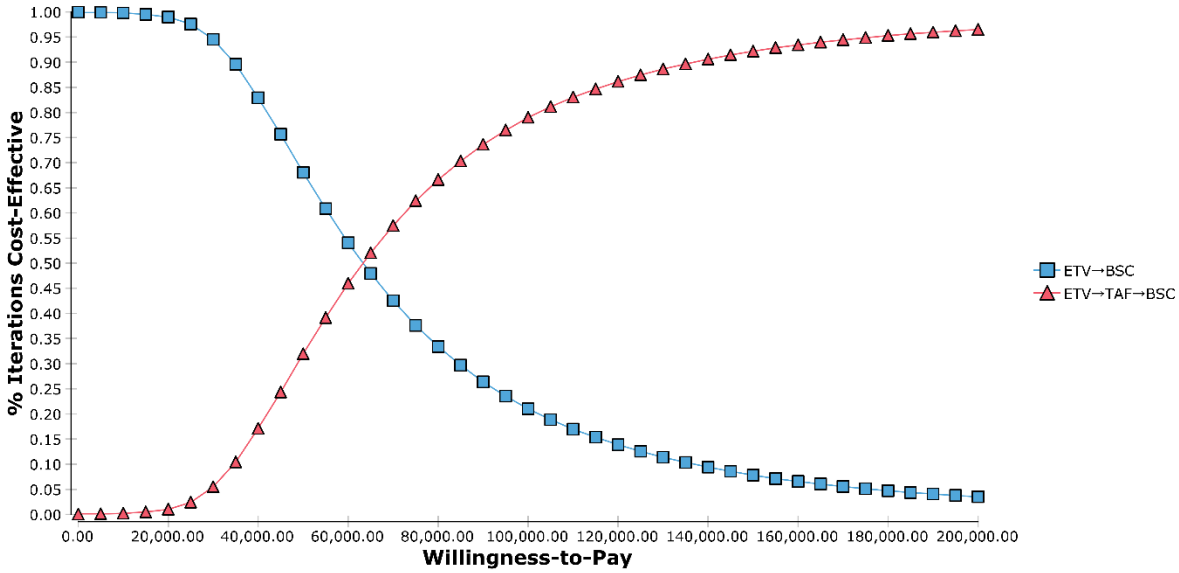
BSC, best supportive care; ETV, entecavir; CC, compensated cirrhosis; CHB, chronic hepatitis B; DC, decompensated cirrhosis; HBeAg, hepatitis B envelope antigen; HBeAg-, hepatitis B envelope antigen-negative; HBeAg+, hepatitis B envelope antigen-positive; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Figure A.2 Probabilistic Sensitivity Analyses: Cost-effectiveness Acceptability Curves

(a) HBeAg-positive Cohort



(b) HBeAg-negative Cohort



BSC, best supportive care; ETV, entecavir; HBeAg, hepatitis B envelope antigen; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table A.2 Threshold Analysis Cost-effectiveness Results

HBeAg-positive Cohort; Unit Price of TAF: $13.02					
Strategy	Costs	ΔCosts	QALYs	ΔQALYs	ICER ($/QALY)
TDF→BSC	$274,743.42		22.8618		
TDF→ETV→BSC	$276,409.87	$1,666.46	23.5859	0.7241	2,301.27
TAF→ETV→BSC	$284,289.50	$7,879.62	23.7435	0.1576	50,000.00
Absolutely Dominated Strategies (all referencing TDF→BSC)					
ETV→BSC	$275,065.00	$321.58	22.0516	-0.8102	-396.92
ETV→TDF→BSC	$276,636.53	$1,893.11	23.5842	0.7224	2,620.63
TAF→BSC	$282,638.92	$7,895.50	23.0378	0.1760	44,859.61
ETV→TAF→BSC	$285,933.06	$11,189.64	23.7328	0.8711	12,846.11
HBeAg-negative Cohort; Unit Price of TAF: $6.20					
Strategy	Costs	ΔCosts	QALYs	ΔQALYs	ICER ($/QALY)
ETV→BSC	$252,171.57		20.6444		
TDF→BSC	$259,274.75	$7,103.18	21.7453	1.1009	6,452.03
TDF→ETV→BSC	$263,141.73	$3,866.98	22.1941	0.4488	8,616.22
ETV→TAF→BSC	$269,622.80	$6,481.07	22.3238	0.1296	50,000.00
TAF→ETV→BSC	$269,809.35	$186.54	22.3243	0.0005	385,475.31
Absolutely Dominated Strategies (all referencing ETV→BSC)					
ETV→TDF→BSC	$263,272.76	$11,101.19	22.1938	1.5494	7,164.99
TAF→BSC	$266,189.07	$14,017.51	21.9112	1.2668	11,065.70
HBeAg-negative Cohort; Unit Price of TAF: $7.82					
Strategy	Costs	ΔCosts	QALYs	ΔQALYs	ICER ($/QALY)
ETV→BSC	$252,171.57		20.6444		
TDF→BSC	$259,274.75	$7,103.18	21.7453	1.1009	6,452.03
TDF→ETV→BSC	$263,141.73	$3,866.98	22.1941	0.4488	8,616.22
ETV→TAF→BSC	$276,103.88	$12,962.15	22.3238	0.1296	100,000.00
TAF→ETV→BSC	$276,731.28	$627.40	22.3243	0.0005	1,296,470.29
Absolutely Dominated Strategies (all referencing ETV→BSC)					
ETV→TDF→BSC	$263,272.76	$11,101.19	22.1938	1.5494	7,164.99
TAF→BSC	$273,111.01	$20,939.44	21.9112	1.2668	16,530.01

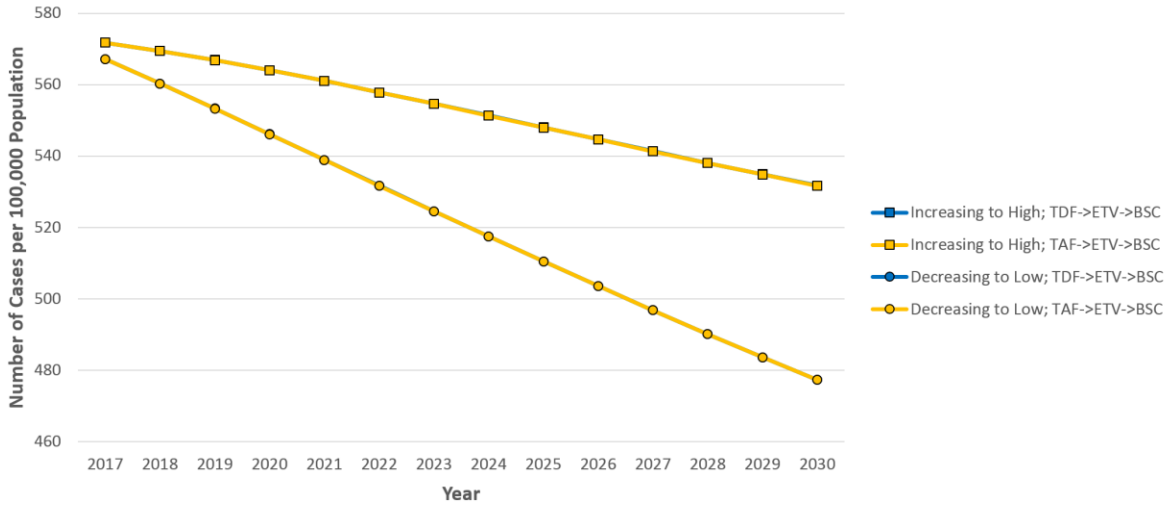
BSC, best supportive care; ETV, entecavir; HBeAg, hepatitis B envelope antigen; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Appendix B

Additional Results Generated by the Agent-based Model

Figure B.1 Impact of Changes in the HBV Prevalence Rates in Immigrant-sourced Regions on HBV-related Health Outcomes

(a) Actual Prevalence of Chronic Hepatitis B



(b) Reported Incidence of Acute Hepatitis B

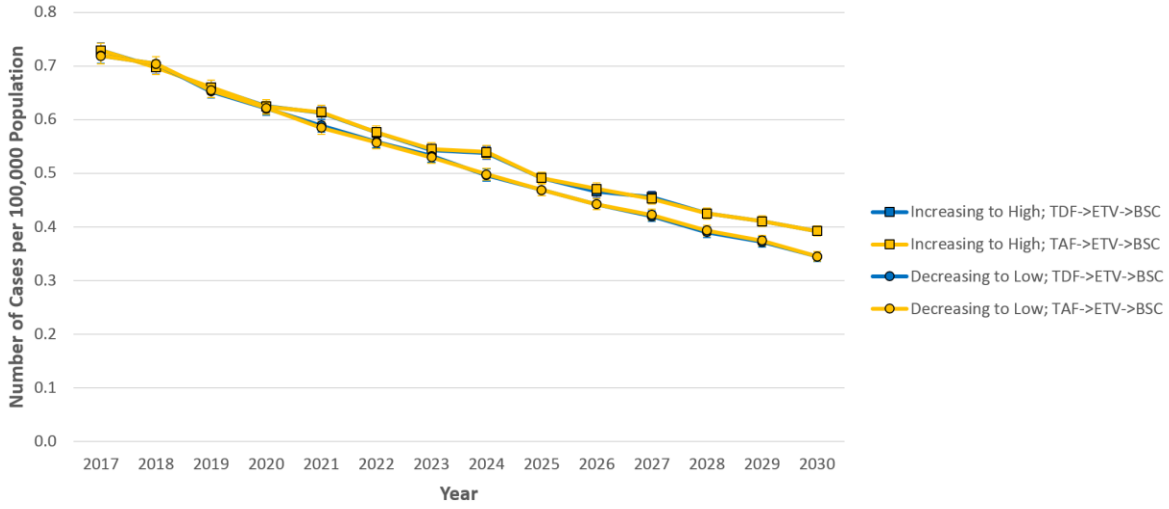
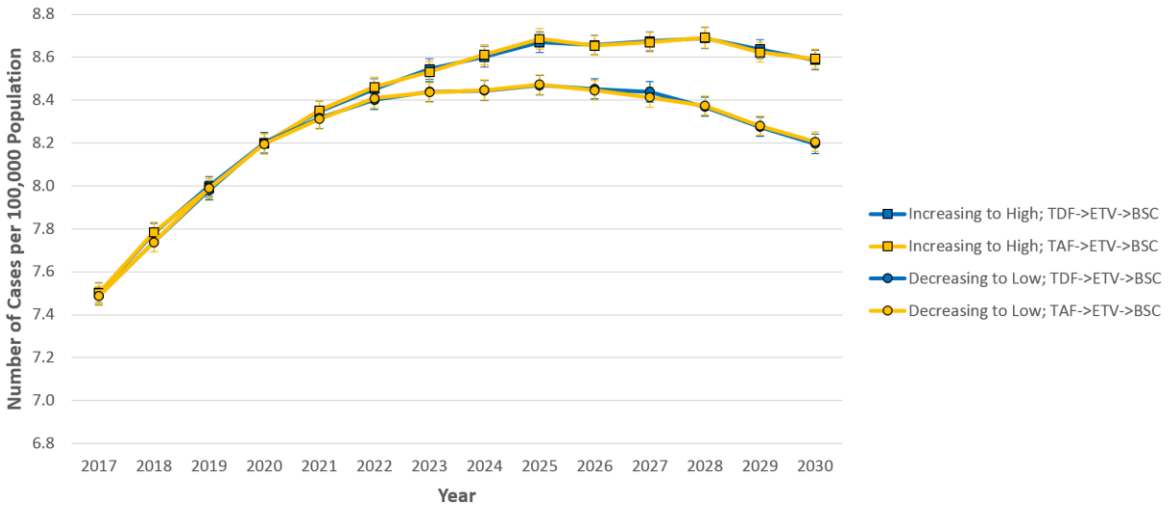


Figure B.1 Continued

(c) Actual Incidence of Liver-related Death



BSC, best supportive care; ETV, entecavir; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Figure B.2 Impact of Changes in the Number of Newborns on HBV-related Health Outcomes

(a) Actual Prevalence of Chronic Hepatitis B

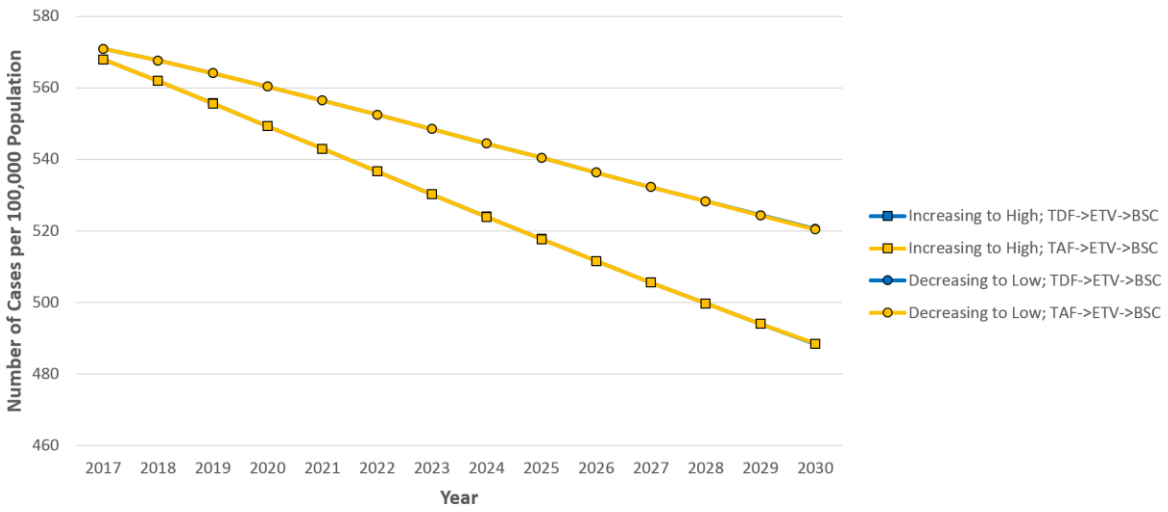
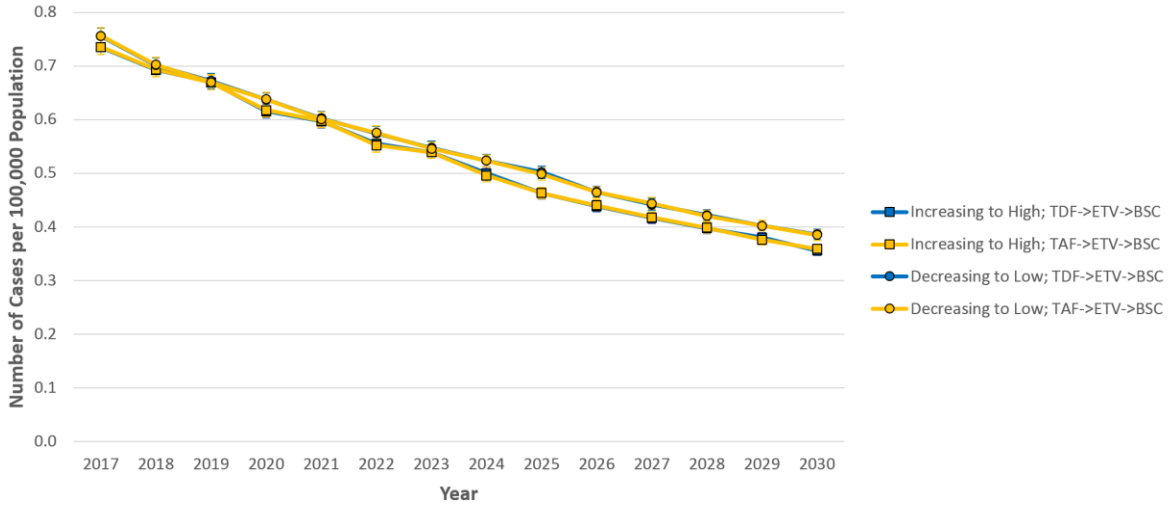
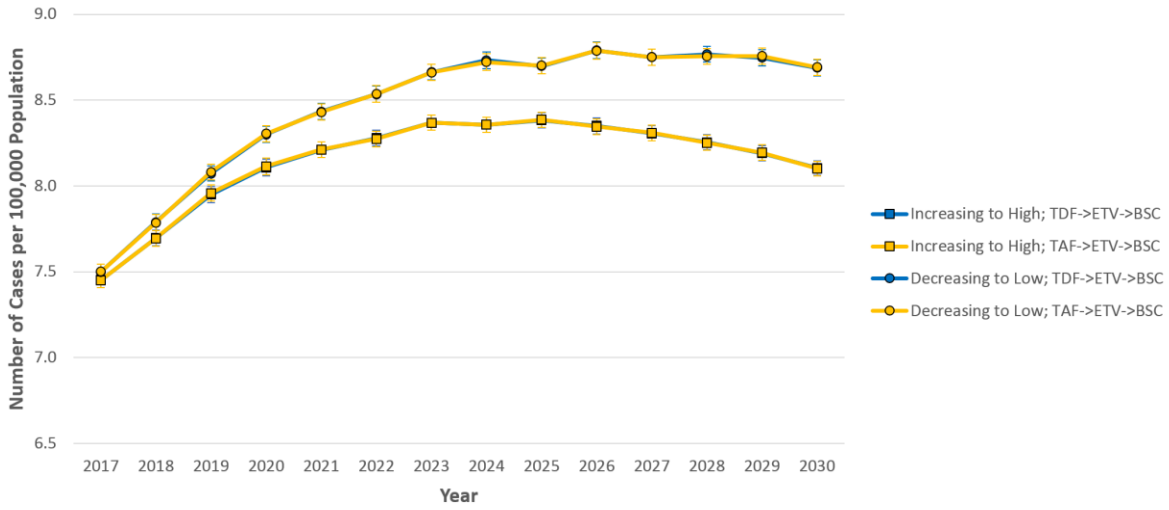


Figure B.2 Continued

(b) Reported Incidence of Acute Hepatitis B



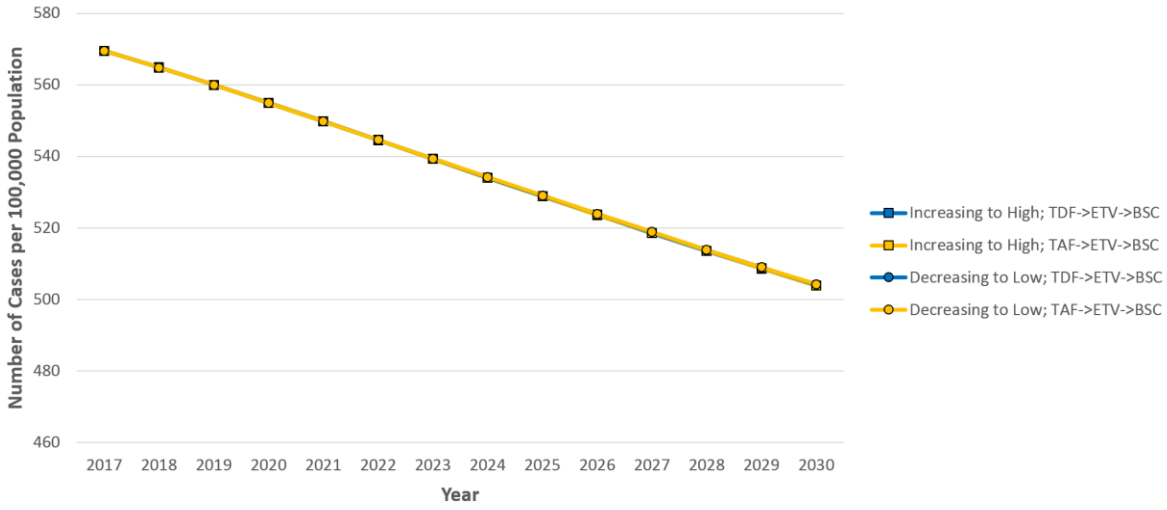
(c) Actual Incidence of Liver-related Death



BSC, best supportive care; ETV, entecavir; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Figure B.3 Impact of Changes in the HBV Vaccination Rate in Immigrants Aged 14 to 79 on HBV-related Health Outcomes

(a) Actual Prevalence of Chronic Hepatitis B



(b) Reported Incidence of Acute Hepatitis B

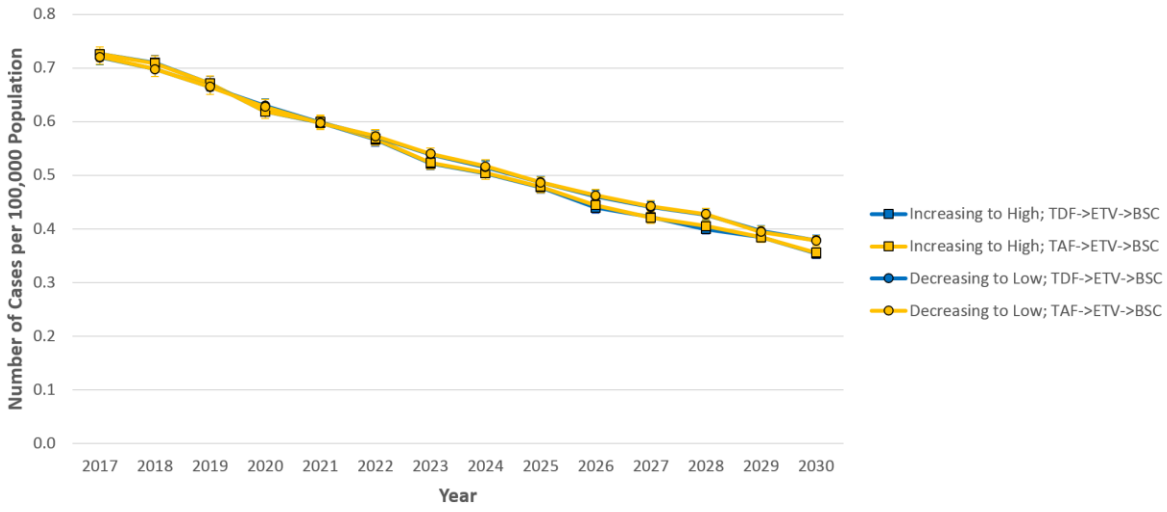
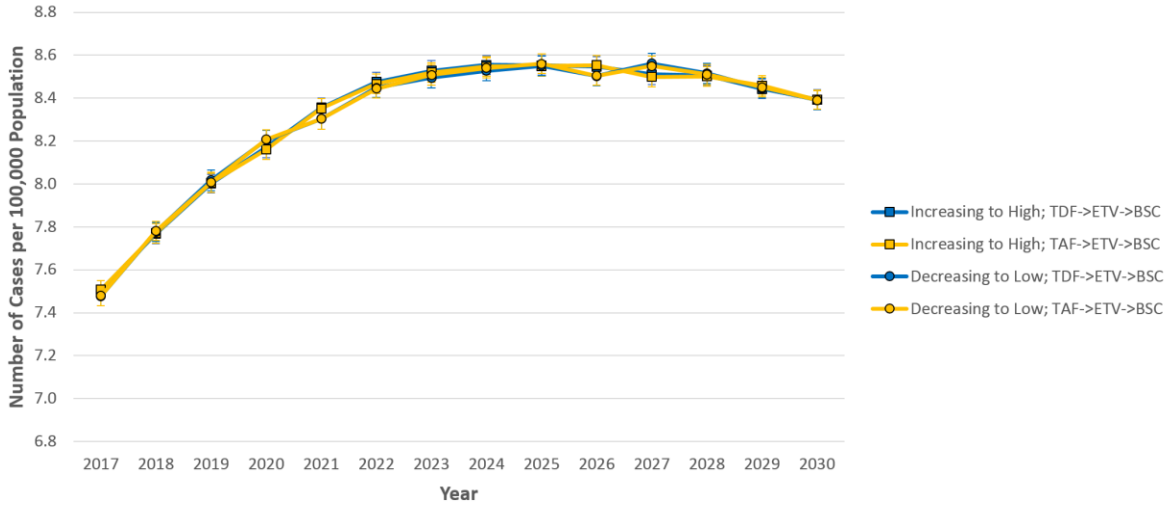


Figure B.3 Continued

(c) Actual Incidence of Liver-related Death



BSC, best supportive care; ETV, entecavir; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Figure B.4 Impact of Changes in the HBV Diagnostic Rate in Immigrants on HBV-related Health Outcomes

(a) Actual Prevalence of Chronic Hepatitis B

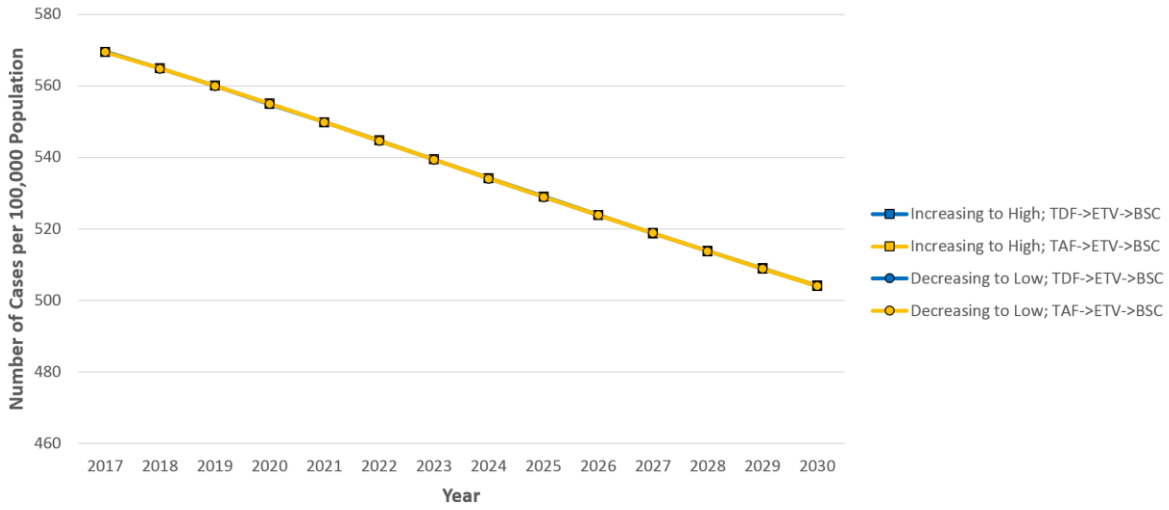
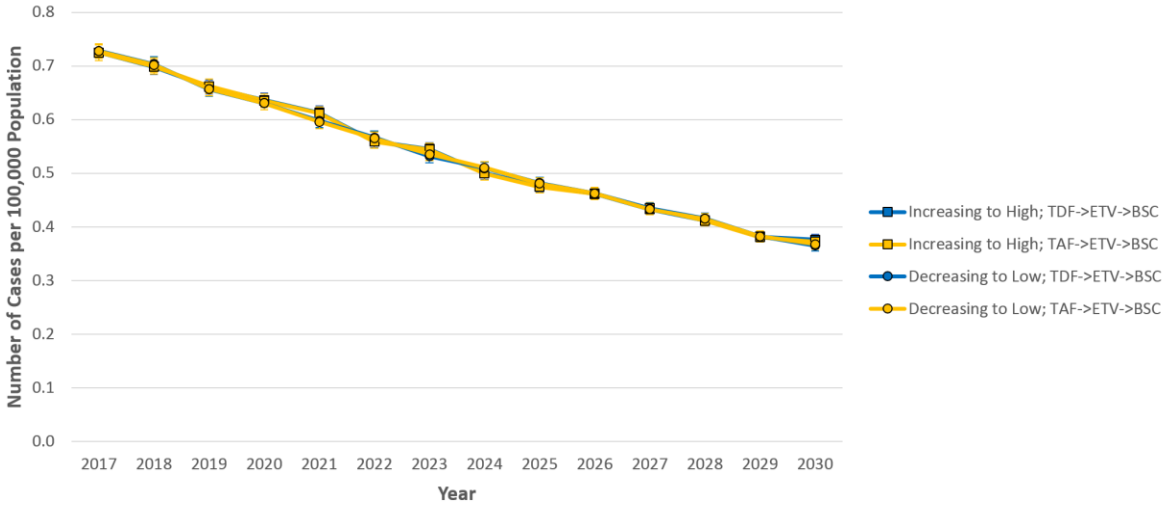
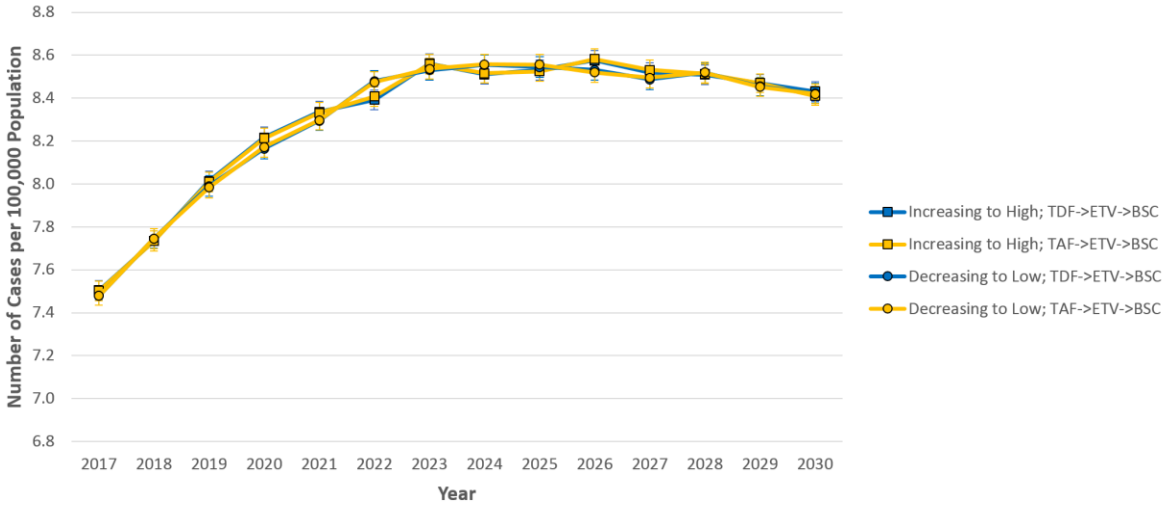


Figure B.4 Continued

(b) Reported Incidence of Acute Hepatitis B



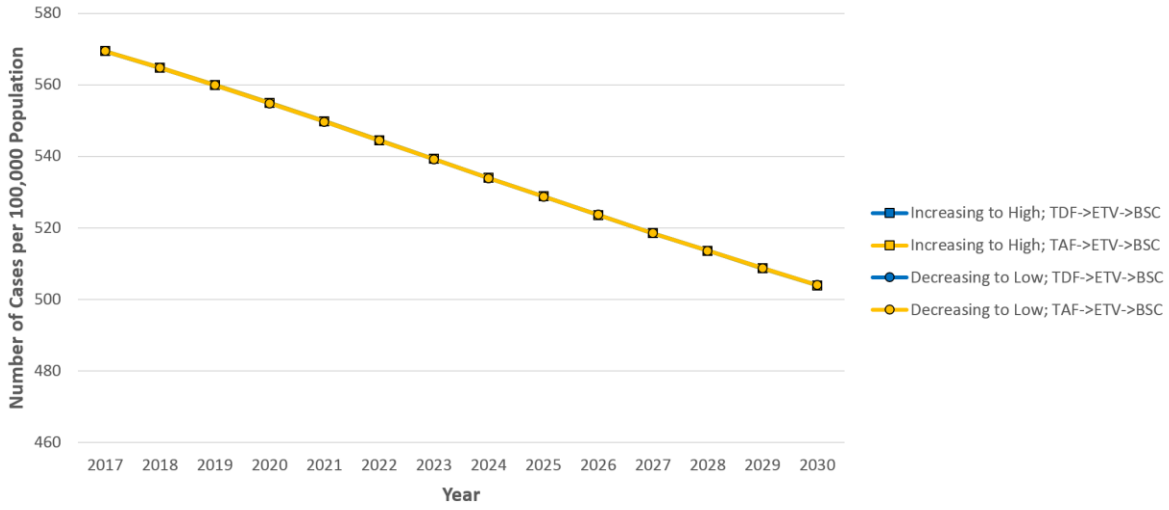
(c) Actual Incidence of Liver-related Death



BSC, best supportive care; ETV, entecavir; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Figure B.5 Impact of Changes in the Treatment Rate in HBV-infected Patients Who Are Eligible for Treatment on HBV-related Health Outcomes

(a) Actual Prevalence of Chronic Hepatitis B



(b) Reported Incidence of Acute Hepatitis B

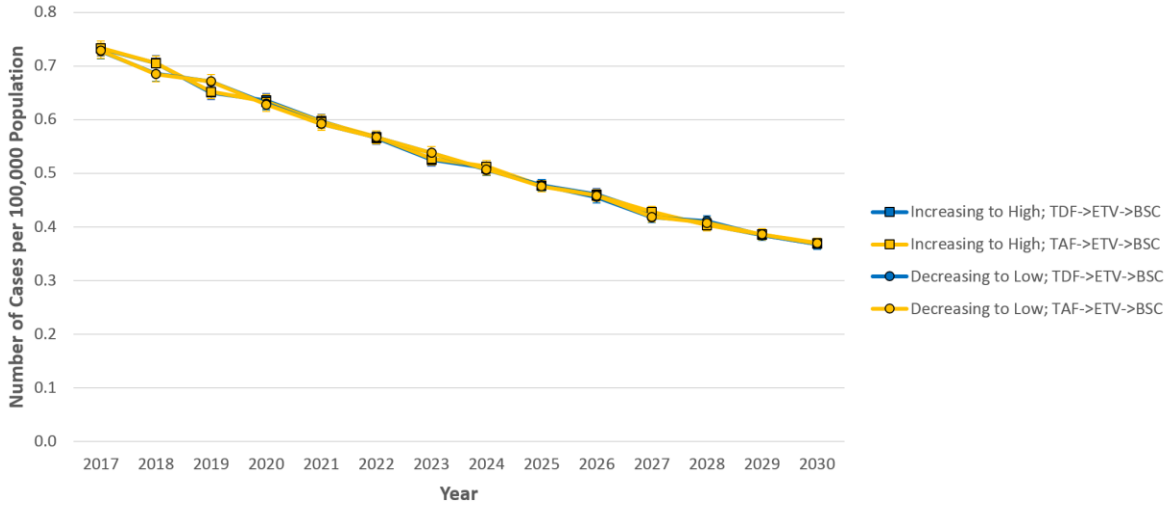
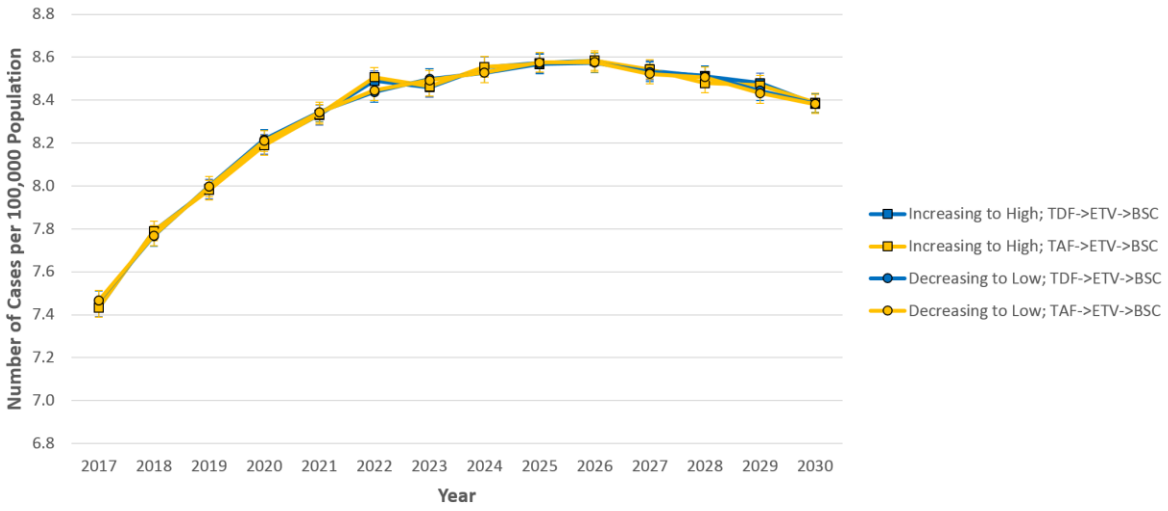


Figure B.5 Continued

(c) Actual Incidence of Liver-related Death



BSC, best supportive care; ETV, entecavir; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Figure B.6 Impact of Changes in the efficacy of the Treatments on HBV-related Health Outcomes

(a) Actual Prevalence of Chronic Hepatitis B

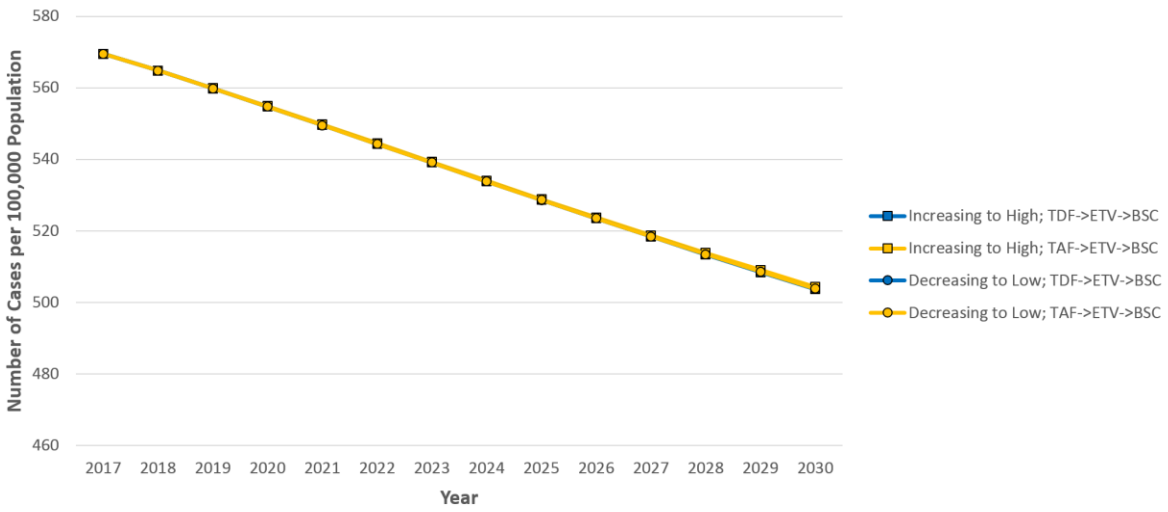
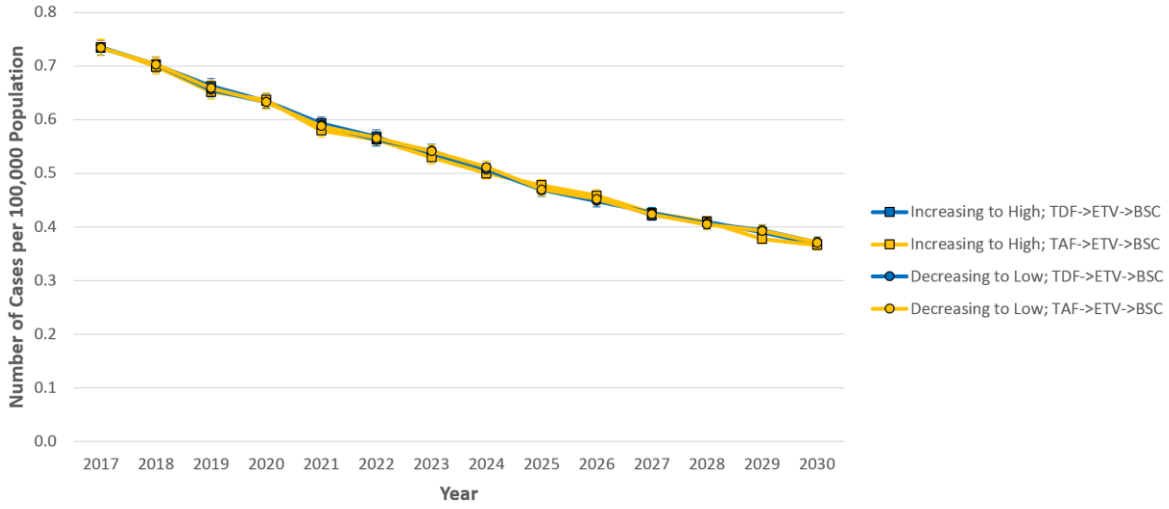
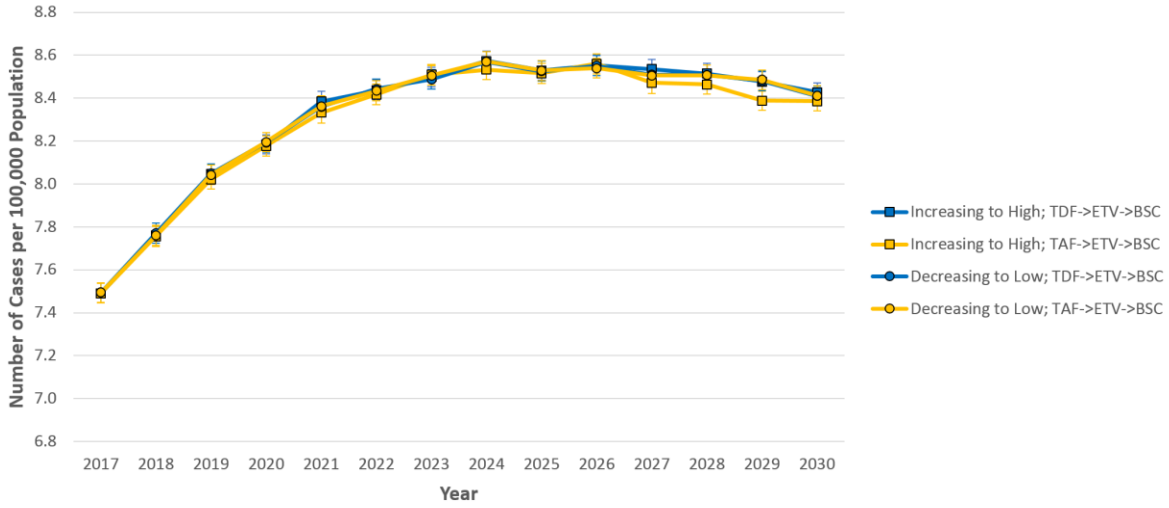


Figure B.6 Continued

(b) Reported Incidence of Acute Hepatitis B

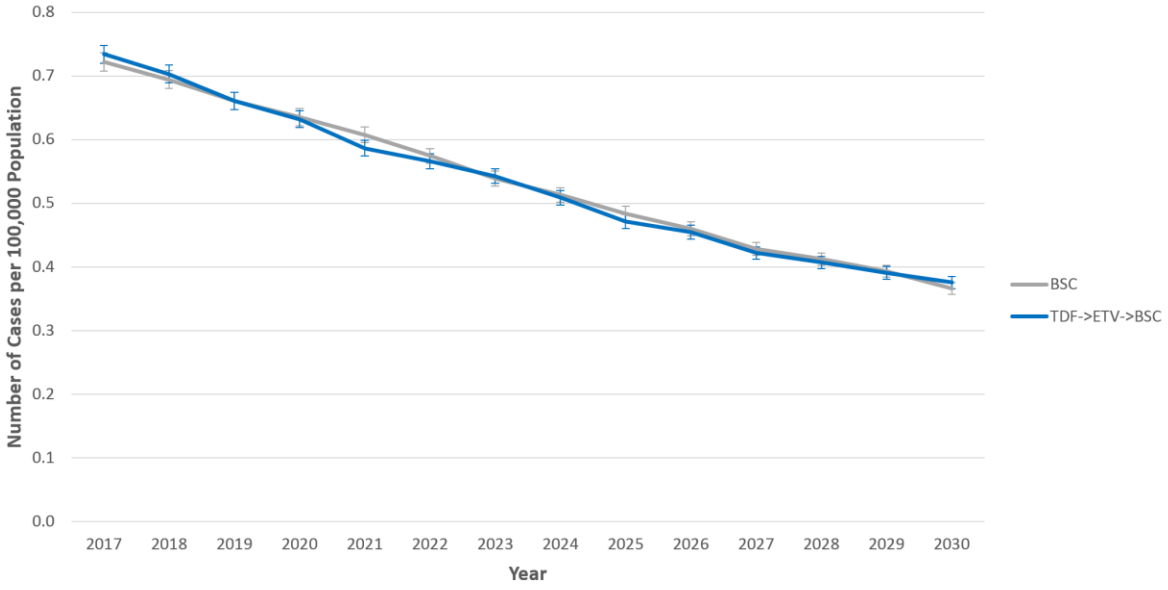


(c) Actual Incidence of Liver-related Death



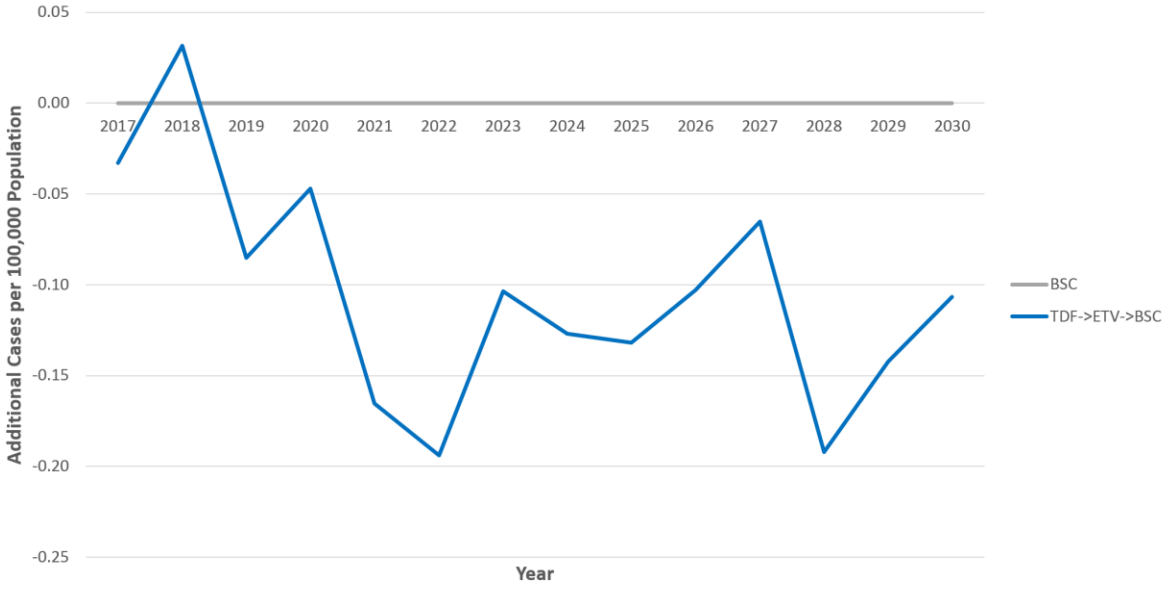
BSC, best supportive care; ETV, entecavir; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Figure B.7 Reported Incidence of Acute Hepatitis B



BSC, best supportive care; ETV, entecavir; TDF, tenofovir disoproxil fumarate.

Figure B.8 Additional Cases of Chronic Hepatitis B Compared with BSC



BSC, best supportive care; ETV, entecavir; TDF, tenofovir disoproxil fumarate.