# Cost-Effectiveness of Tenofovir Alafenamide (TAF) compared to Entecavir (ETV) and Tenofovir Disoproxil Fumarate (TDF) for Treatment of Hepatitis B e Antigen-Positive Chronic Hepatitis B in China


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# Abstract

**Background:** Chronic hepatitis B (CHB) and related liver diseases are one of the main causes of death in China. Antiviral treatment for CHB can prevent disease progression and reduce the mortality. Tenofovir alafenamide (TAF) is a new drug approved for treating CHB in China. Compared with other drugs, TAF has better efficacy and safety profile, but also higher price.

**Objective:** The aim of this study is to evaluate the cost-effectiveness of TAF and other antiviral treatment strategies for Hepatitis B e Antigen (HBeAg) positive CHB patients.

**Method:** A state-transition Markov model was constructed to simulate the lifetime costs and effectiveness of eight treatment strategies involving entecavir (ETV), tenofovir disoproxil fumarate (TDF) and TAF from a Chinese healthcare perspective. The state-transition parameters were obtained from previous economic studies. Drug efficacy, cost and utility data were obtained from studies based on a Chinese cohort. The study measured 10-year cumulative incidence of liver complication, lifetime costs, quality-adjusted life years (QALYs), incremental cost-effectiveness ratios (ICERs). One-way deterministic and probabilistic sensitivity analyses were adopted to explore the uncertainties in the model. A scenario analysis was used to explore the impact of using branded drugs or generic drugs.

**Result:** In the base-case analysis, TAF followed by ETV therapy generated the highest ICERs of 62,907 USD/QALY, and TDF followed by ETV therapy generated the lowest ICERs of 14,197 USD/QALY. The results were sensitive to the virologic response rate and HBeAg seroconversion rate of drugs. In the probabilistic analysis, at a Chinese willingness-to-pay (WTP) threshold of 30,426 USD/QALY, TAF followed by ETV therapy had 12.30% chance to be the optimal treatment strategy, and TDF followed by ETV therapy had the highest probability of 36.60% to be the optimal treatment strategy.

**Conclusion:** TAF-basing therapies are not cost-effective at its current price. TDF followed by ETV therapy is the optimal treatment strategy for HBeAg-positive CHB patients in China. The response-guided therapies are more cost-effective than their monotherapies.

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# List of abbreviations

| | |
|---|---|
| CHB | Chronic hepatitis B |
| HBV | Hepatitis B virus |
| TAF | Tenofovir alafenamide |
| TDF | Tenofovir disoproxil fumarate |
| ETV | Entecavir |
| LAM | Lamivudine |
| TBV | Telbivudine |
| ADV | Adefovir |
| QALY | Quality-adjusted life year |
| ICER | Incremental cost-effectiveness ratio |
| WTP | Willingness-to-pay |
| WHO | World Health Organization |
| AASLD | American Association for the Study of Liver Diseases |
| EASL | European Association for the Study of the Liver |
| NAs | Nucleoside/Nucleotide analogues |
| IFN | Interferon |
| HBsAg | Hepatitis B surface antigen |
| Anti-HBsAg | Antibody against HBsAg |
| HBeAg | Hepatitis B e antigen |
| Anti-HBeAg | Antibody against HBeAg |

| | |
|---|---|
| HBcAg | Hepatitis B core antigen |
| Anti-HBcAg | Antibodies against the HBcAg |
| PCR | Real-time Polymerase Chain Reaction |
| ALT | Alanine transaminase |
| SAEs | Serious adverse events |
| NBMI | National Basic Medical Insurance |
| UEBMI | Urban Employee Basic Medical Insurance |
| URRBMI | Urban and Rural Resident Basic Medical Insurance |
| USD | US dollar |
| CNY | Chinese Yuan |
| CEA | Cost-effectiveness analysis |
| CBA | Cost-benefit analysis |
| CUA | Cost-utility analysis |
| HRQoL | Health-related quality of life |
| HUI | Health Utilities Index |
| SF-6D | Short Form 6D |
| DSA | Deterministic sensitivity analysis |
| PAS | Probabilistic sensitivity analysis |
| CDF | Cumulative Distribution Function |
| NMB | Net monetary benefit |
| CEAC | Cost-Effectiveness Acceptability Curve |
| CEAF | Cost-effectiveness acceptability frontier |

| | |
|---|---|
| CC | Compensated cirrhosis |
| DC | Decompensated cirrhosis |
| HCC | Hepatocellular carcinoma |
| LT | Liver transplantation |
| PLT | Post-liver transplantation |
| VRP | Virologic response |
| VRT | Virologic resistance |
| SEC | HBeAg seroconversion |
| CLN | HBsAg clearance |
| DT | Death |
| RR | Relative risk |
| HP | COBAS TaqMan HBV Test for use with the High Pure System |
| CAP/CTM | COBAS AmpliPrep/COBAS TaqMan HBV Test, v2.0 CAP/CTM |
| GDP | Gross domestic product |
| Abs dominated | Absolutely dominated |
| Ext dominated | Extendedly dominated |

# Chapter 1 Introduction

## 1.1 Introduction

Chronic hepatitis B (CHB) is caused by the Hepatitis B virus (HBV) infection and has become a global health problem. Global Hepatitis Report from World Health Organization (WHO) indicates that there are more than 257 million CHB patients worldwide. China has the highest hepatitis burden in the world with nearly 70 million people having chronic HBV infection, which is one-third of the global infected population (WHO, 2017). It also means approximately 1 in 20 people are living with chronic HBV infection in China. However, because there are no obvious symptoms in the early stage, and in consideration of side effects and the high financial burden, a large part of CHB patients choose not to get treatment. The rates of diagnosis and treatment are only 19% and 11%, respectively in China (Razavi-Shearer et al., 2018). Left untreated, CHB may lead to severe liver disease such as cirrhosis and hepatocellular carcinoma (HCC). Mortality due to viral hepatitis increased by 22% during the period from 2000 to 2015, and more than half of the deaths were caused by HBV (WHO, 2017). HBV-related liver diseases not only reduce the longevity and quality of life, but also increase the economic burden of the healthcare system. Assuming the annual treatment rates for CHB, cirrhosis and HCC are 5%, 95% and 95%, respectively, the Chinese government has to spend estimated 12 to 17 billion USD per year to provide treatments for HBV-related liver diseases (Chinese Center for Disease Control and Prevention, 2015).

Because of the threat from hepatitis B, WHO approved a global strategy to eliminate hepatitis B by 2030, with the target of reducing the incidence by 90% and the mortality by 65% (WHO, 2016). China also made a National Viral Hepatitis Control Plan (2017-2020), including measures of expanding vaccination coverage, introducing high-efficiency drugs, reducing medical cost and improving treatment effect by optimizing treatment strategy. Currently, the weighted prevalence of HBsAg in China has decreased to 0.32% among children younger than 5 years, which means the target of 30% reduction in incidence has been achieved[①](National

① The target of 90% reduction in incidence is equivalent to a 0.1% prevalence of HBsAg among children.

Health Commission, 2015). The mortality rate of HBV-related liver diseases was 16.42 per 100,000 people in 2016, which was still at a relatively high level, and mortality rate of HBV-related liver cancer even increased from 12.88 per 100,000 people in 1990 to 16.42 per 100,000 people in 2016 (Liu et al., 2019). One of the main reasons for the challenge of reducing mortality is the low treatment rate. To eliminate hepatitis B disease, expanding the treatment coverage and enhancing efficacy is necessary. Reducing the drug price and introducing highly effective and low toxic drugs contribute to the reduction of mortality.

The virus load is an important risk factor for disease progression in CHB patients. Patients with higher virus load face with higher risk of progressing to cirrhosis and HCC in Asia (Marugán & Garzón, 2009). However, currently, there is no treatment that can eradicate HBV infections, so suppressing viral replication and keeping the virus load at the lowest level is the realistic therapy to control HBV infection (Zhang et al, 2015). Nucleoside/Nucleotide analogues (NAs) and interferon (IFN) are two types of drugs approved in China for the treatment of CHB. Both NAs and IFN can suppress the HBV replication but IFN has greater side effects and also higher price, thus NAs are used more frequently for CHB treatment (Santantonio & Fasano, 2014). NAs includes lamivudine (LAM), telbivudine (TBV), adefovir (ADV), entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). The first three are high-resistance NAs and the last three are low-resistance NAs. Currently, the low-resistance NAs are recommended by Chinese Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2019) to be the first-line monotherapies, when resistance occur, response-guided therapies are used to optimize the treatment outcomes. The American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) also have the same recommendation.

ETV is the first low-resistance NAs approved for the CHB treatment in China. Compared with the high-resistance NAs, ETV has lower resistance rate and less side effects, thus it becomes the most widely used drug. In 2013, TDF was approved in China and the greatest benefit of TDF is the almost zero resistance rate (Liu et al., 2017). In 2019, TAF formally entered the Chinese market. Compared with TDF, TAF has less impact in kidney (Agarwal et al., 2018).

Moreover, both branded and generic drugs are available in China but the prices vary a lot. The price of branded ETV is nearly triple that of generic ETV. Because of the emergence of new drugs and government regulation, in recent years, the prices of NAs have declined a lot. Prices of branded TDF and TAF were cut by more than 50% and price of generic ETV even reduced by over 90%.

## 1.2 Objective of the Thesis

The main aim of this study is to evaluate of the cost-effectiveness of TAF and other low-resistance NAs drugs (ETV and TDF) for Chinese HBeAg positive CHB patients. The study will include a Markov model to simulate the progression of CHB with different treatment strategies. The results can help decision makers to formulate reasonable and practical policies to initiate the treatment of CHB, and achieve the targets for reducing the HBV infection incidence and mortality related to the severe liver diseases.

## 1.3 Research Question

This study is the first cost-effectiveness analysis of NAs including TAF for HBeAg positive CHB patients from the Chinese healthcare perspective. The main question the study aims to answer is: Whether the new drug TAF is cost-effective for HBeAg positive CHB patients under the Chinese WTP threshold? If not, which is the most cost-effective treatment strategy currently in China? In addition, this study also answers the following sub-questions: (1) For each low-resistance NA, is its response-guided therapy more cost-effective when compared with its monotherapy; (2) Which is the most cost-effective treatment strategy when only branded drugs (or generic drugs) are adopted for all patients; (3) Which is the most cost-effective treatment strategy when patients choose to continue the antiviral treatments to reduce the probability of CHB recurrence even they meet the conditions of drug withdrawal.

## 1.4 Structure of the Thesis

Chapter 2 introduces the background of this study, including the natural history of chronic HBV infection, HBV-related liver diseases, treatments for CHB, epidemiology and Chinese healthcare system. In addition, the previous cost-effectiveness studies about CHB are also introduced in this study. Chapter 3 presents the theoretical framework, including the theories about economic evaluation and sensitivity analysis. Chapter 4 presents the methods and materials applied in this study, including the design of the model, model structure and model inputs. Chapter 5 presents the results of the cost-effectiveness analysis, including the cost and outcome for each treatment strategy in the base-case analysis, and the sensitivity analysis for the uncertainty of the model. Moreover, the sub-question (2) and (3) are answered in the scenario analysis. Chapter 6 presents the discussion of this study, including the value, strengths and the limitations of the study. Chapter 8 presents the main conclusion based on the study and give a suggestion about the choice for the treatment for HBeAg-positive CBH patients in China.

# Chapter 2 Background

## 2.1 Epidemiology

CHB is a global health problem, 2 billion people globally have ever been infected with HBV among which 257 million are infected with chronic HBV (WHO, 2017). China has the highest hepatitis burden in the world, the HBsAg prevalence of the general population in China is 5% to 6%, and 70 million people have chronic HBV infection (Liu et al., 2019). Due to popularization of the HBV vaccine, during 1992 to 2014, the HBsAg prevalence declined from 10.1% to 2.6% among people aged 1-29 years and declined from 10.5% to 0.8% among children <15 years of age (Cui et al., 2017).

A study from Zhang et al (2019) analyzed the incidence of HBV in China from 2004-2016. The study indicated that the HBV incidence increased from 67.96/100,000 in 2004 to 88.82/100,000 in 2009 and then deceased to 68.74/100,000 in 2016. Moreover, group aged 1-9 years had the lowest incidence, and group aged 25-29 years had the highest incidence. Indeed, the HBV vaccine was integrated into the National Expanded Program on Immunization (EPI) in 1992. Most of the individuals in 25-29 age group (born in 1975-1988) were not vaccinated when they were born and infected via mother-to-child transmission (Zhang et al., 2019).

HBV transmits mainly via blood, mother-to-child transmission and sexual contact. With the popularization of HBV vaccine and Hepatitis B immune globulin, the successful rate of mother-to-child block is 90% for newborns with HBeAg positive mothers and 98% with HBeAg negative mothers (Sokal et al., 2013).

## 2.2 Natural History of Chronic HBV Infection

HBV is an enveloped DNA virus which consists of an outer lipid envelope and a nucleocapsid core, the nucleocapsid encloses the viral DNA (Churin, Roderfeld & Roeb, 2015). CHB is a chronic necro-inflammatory disease of the liver caused by persistent infection with HBV (Chisari, 2000). According to HBV and liver disease markers, the natural history of chronic

HBV infection can be divided into four phases, namely HBeAg positive chronic infection phase, HBeAg positive chronic hepatitis phase, HBeAg negative chronic infection phase, and HBeAg negative chronic hepatitis phase (EASL, 2017). Table 1 shows the natural history and the assessment of chronic HBV infection.

**Table 1** The natural history of chronic HBV infection

| **Markers** | **Phase** | | | |
|---|---|---|---|---|
| | **HBeAg positive chronic infection** | **HBeAg positive chronic hepatitis** | **HBeAg negative chronic infection** | **HBeAg negative chronic hepatitis** |
| HBsAg | + (> $1\times10^4$ IU/ml) | + | + (< $1\times10^3$ IU/ml) | + |
| Anti-HBsAg | − | − | − | − |
| HBeAg | + | + | − | − |
| Anti- HBeAg | − | − | + | + |
| HBV DNA | > $2\times10^7$ IU/ml | > $2\times10^4$ IU/ml | < $2\times10^3$ IU/ml | ≥ $2\times10^3$ IU/ml |
| ALT | Normal* | Elevated | Normal | Elevated |
| Liver disease | None/minimal | Moderate/severe | None/minimal | Moderate/severe |

*The upper limit of normal (ULN) of ALT is 40 IU/L

*HBsAg* hepatitis B surface antigen, *anti-HBsAg* antibody against HBsAg, *HBeAg* hepatitis B e antigen, *anti-HBeAg* antibody against HBeAg, *HBV DNA* hepatitis B virus DNA, *ALT* Alanine transaminase

HBV markers include serological markers and virologic markers. Main serological markers contain hepatitis B surface antigen (HBsAg), antibody against HBsAg (anti-HBsAg), hepatitis B e antigen (HBeAg) and antibody against HBeAg (anti-HBeAg) (Yuen et al., 2018). Those markers can be tested by the serological tests which can identify the type of antibodies and antigens in the blood (Krajden, McNabb & Petric, 2005).

HBsAg is the main component of the HBV surface, and it is the first serological marker appears after an individual is infected by HBV (Song, 2016). The presence of HBsAg in the serum indicates the patient is infected by HBV. For the acute HBV infection, the HBsAg can be cleaned by the immune system within two to six months, often accompanying with the occurrence of anti-HBsAg (Shiffman, 2010).The development of antibodies against HBsAg is known as HBsAg seroconversion (National Institute for Health Care Excellence, 2013). However, if HBsAg lasts for more than six months, it can be a chronic HBV infection (Song, 2016). The production of anti-HBsAg indicates the patient has the protective immunity against

HBV. The anti-HBsAg can be detected in patients who have been successfully vaccinated or recovered from HBV infection (Yuen et al., 2018).

HBeAg it appears in the blood shortly after HBsAg and indicates an active viral replication which means the patient is contagious (Kao, 2008). If the patient has an immune response to the HBV, HBeAg level will decrease accompanying with the production of anti-HBeAg which indicates the virus is inactive and the patient is less contagious (Sharma, Saini & Chwla, 2005). The development of antibodies against the HBeAg with undetectable or low HBV DNA levels is known as HBeAg seroconversion (National Institute for Health Care Excellence, 2013). The anti-HBeAg can present due to treatment, or spontaneously without treatment (Pungpapong, Kim & Poterucha, 2007). Because of the active viral replication, patients with positive HBeAg have higher risks of progressing to HBV-related liver diseases.

In addition, there is another antigen called hepatitis B core antigen (HBcAg), same with HBeAg, it also indicates replication of the virus (Liaw & Zoulim, 2016). Because HBcAg does not circulate in the blood, it cannot be detected by serological tests (Kao, 2008). There are two versions of antibodies against the HBcAg (anti-HBcAg). IgM anti-HBcAg indicates a recent HBV infection, and IgG anti-HBcAg indicates prior HBV infection (Kumar, Gupta & Jaiprakash, 2007).

HBV DNA is the virologic marker, and the quantification can be tested by real-time Polymerase Chain Reaction (PCR) assay which can make millions copies of a section of DNA and amplify the small segments of DNA to an enough amount for analysis (Garibyan & Avashia, 2013). The presence of HBV DNA in serum is a reliable marker of active HBV replication and the levels of HBV DNA in serum can be used to determine the status of chronic HBV infection (Pawlotsky, 2003). Patients with chronic HBV infection have HBV DNA levels below 2,000 IU/ml can be regarded as an inactive HBV carrier (Brunetto et al., 2010). Moreover, HBV DNA is an important factor that affect the disease progression. Patients with low HBV DAN level has the decreasing risk of progressing to advance live disease (Liaw, 2006).

Liver disease can be diagnosed by biochemical parameters and fibrosis markers. Alanine transaminase (ALT) is one of the biochemical parameters for liver disease (Hyder, Hasan & Mohieldein, 2013). ALT is an enzyme normally found inside liver cells, when the liver is damaged or inflamed, ALT can be released into the blood (Liu et al., 2014). Therefore, the elevated ALT levels in serum indicates a liver problem. Fibrosis is a marker of chronic liver diseases, which results from excessive accumulation of extracellular matrix (Liu et al., 2012).

Patients in the "HBeAg positive chronic infection" phase are also known as "chronic HBV carriers", and they have positive HBsAg with high level quantities, positive HBeAg and very high level of HBV DNA. ALT level is persistently within the normal range and there is minimal or no liver necroinflammation or fibrosis (EASL, 2017). Most are young patients in this phase and the patients can stay in this phase for a long time (e.g. From infancy to young adulthood), and the rate of spontaneous HBeAg seroconversion is very low in this phase (EASL, 2017). Because no obvious damage in the liver, treatments are not recommended in this phase but monitoring is still necessary (Chinese Society of Infectious Diseases & Chinese Society of Hepatology, 2019).

Patients in the "HBeAg positive chronic hepatitis" phase have positive HBsAg, positive HBeAg and high level of HBV DNA. ALT level elevates and there is moderate or severe liver necroinflammation or fibrosis. It may occur after several years of the first phase and patients who are infected in adulthood can always rapidly reach this phase (EASL, 2017). Because the liver is damaged, patients can begin treatment in this phase. Part of the patients can arrive HBeAg seroconversion spontaneously or by treatment and enter the HBeAg-negative infection phase.

Patients in the "HBeAg negative chronic infection" phase are also known as "inactive HBsAg carrier", and they have positive HBsAg with low level quantities, positive anti-HBsAg and undetectable or low HBV DNA levels. The ALT level is normal and only minimal or no necroinflammation and fibrosis (EASL, 2017). HBsAg clearance may occur spontaneously in this phase and patients have low risk of progression to severe liver diseases (Dusheiko, Wang & Carey, 2016).

Patients in the “HBeAg negative chronic hepatitis” phase have positive HBsAg, negative HBeAg, detectable anti-HBeAg and high levels of HBV DNA (but often lower than in HBeAg-positive patients), in addition, the ALT level is fluctuating or persistently elevates and there exists liver necroinflammation or fibrosis (EASL, 2017). The rates of spontaneous HBsAg clearance is low in this phase ((EASL, 2017).

The phases of chronic HBV infection are not necessarily sequential. Patients in the “HBeAg negative chronic infection” phase can enter the “HBeAg negative chronic hepatitis” phase or return back to the “HBeAg positive chronic hepatitis” phase (Wiegand et al., 2019).

## 2.3 HBV-related Liver Disease

CHB patients always face risks of progressing to severe liver diseases, cirrhosis and HCC. Cirrhosis is caused by long-term damage to the liver, and the damage leads to scarring, known as fibrosis, and the scar tissues replace the health liver tissue, then the liver become harder and gradually loss the normal function (Schuppan & Afdhal, 2008). There are two stages of cirrhosis, compensated cirrhosis and decompensated cirrhosis (Zipprich et al., 2012).

Patients with compensated cirrhosis often do not have symptoms related to the cirrhosis and maintain the main functions of the liver (Thornton, 2015). However, when the patients progress to decompensated cirrhosis, the liver can no longer function properly, and they often have symptomatic complications related to cirrhosis, including jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome or variceal hemorrhage (Harrison, 2015). Patients with decompensated cirrhosis are usually candidates for a liver transplant.

HCC is the most common primary liver malignancy, and patients with CHB and cirrhosis are high-risk cohort for developing to HCC (EASL, 2018). Treatments for HCC depends on many factors, such as such as disease stage, tumor size, individual’s age and general health and other elements. Therapies for HCC comprise surgical resection, liver transplantation and various locoregional treatments (Raza & Sood, 2014).

## 2.4 Treatment for CHB

Currently, there is no treatment can eradicate HBV infections; thus, the goal of the existing treatments is to improve survival and quality of life by maximally suppressing HBV replication, reducing hepatic necroinflammation and hepatic fibrosis, delaying and decreasing progression of cirrhosis, HCC and other complications (Mak et al., 2019). CHB patients who have HBV DNA level higher than 2,000 IU/ml, ALT level higher than ULN and/or at least moderate liver necroinflammation or fibrosis, should get the treatments (Chinese Society of Infectious Diseases & Chinese Society of Hepatology, 2019).

There are two therapies for CHB patients, NAs and IFN. Compared with IFN injections, oral NAs are more convenient and have smaller side effects (Santantonio & Fasano, 2014). Thus, NAs are more recommended for the general patients. However, the NAs have longer treatment courses and possibility for drugs resistance caused by adaptive mutations within the HBV genome, and the resistance can reduce the susceptibility of a virus to the inhibitory effects of a drug (Zoulim, 2011). Thus, low-resistance NAs are more recommended.

Currently, there are five NAs have been approved to treat CHB in China, including LAM, TBV, ADV, ETV, TDF and TAF. The first three are high-resistance NAs and the last three are low-resistance NAs. ETV, TDF and TAF are recommended by Chinese Guidelines for the prevention and treatment of chronic hepatitis B (2019) to be the first-line drugs for the high barrier to resistance.

Functional cure is regarded as the optimal treatment endpoint, characterized by the sustained off-therapy HBsAg loss, undetectable HBV DNA and normal ALT(Gish et al., 2015). Patients achieve functional cure have very low risk of relapse of CHB or progressing to HCC, however, functional cure is only rarely achieved (Xiaoqi & Zhang, 2018). Then, a treatment-induction partial immune control is regarded as satisfactory treatment endpoint, characterized by HBeAg loss and seroconversion to anti-HBeAg, undetectable HBV DNA and normal ALT (Kao & Chen, 2018). Many guidelines indicate that patients can terminate the treatment if they achieve

the partial immune control because the risk of progressing to advanced liver disease is lower in this phase.

The basic aim of the antiviral therapy is to obtain virologic response which is defined as the serum HBV DNA level is sufficiently low to be undetectable by a PCR assay (EASL, 2017). Drug resistance also occur during the therapy and can be defined as the detection of mutations in the HBV genome during NAs therapy and decreased susceptibility to drug (EASL, 2017). The cumulative drug-resistance incidence rate of 5-year ETV therapy was 1.2% for NA treatment-naïve patients with CHB and no resistance to TDF and TAF have been detected (Cai et al., 2019). If patients are resistant to the initial drugs, they can switch to another drug without cross-resistance (EASL, 2017). If the patients achieve virologic response, the risk of processing to cirrhosis and HCC is lower than patients with no treatment and drug resistance (Papatheodoridis et al., 2015).

The overall safety of NAs is satisfactory, but there are still infrequent serious adverse events (SAEs) in clinical application, such as renal insufficiency and low-phosphorous osteopathy with ADV or TDF therapy and lactic acidosis with LAM or ETV therapy (Kayaaslan & Guner, 2017). Follow-up is very important during antiviral therapy in order to monitor clinical efficacy, drug resistance, adverse events. During the treatment, HBV serological markers, HBV DNA level and biochemical parameters should be monitored every three to six months, and after treatment discontinuation, patients should be monitored monthly within the first three months, then every three months for at least one year and every six months after one year (Chinese Society of Infectious Diseases & Chinese Society of Hepatology, 2019).

## 2.5 CHB in Chinese Health Care System

There are two types of National Basic Medical Insurance (NBMI). Urban Employee Basic Medical Insurance (UEBMI) is for workers in urban areas, Urban and Rural Resident Basic Medical Insurance (URRBMI) is for individuals not covered by UEBMI (Meng et al., 2015). UEBMI is mandatory and financed by premiums paid by both employers and employees, while URRBMI is voluntary and financed by premiums and government finance (Meng et al., 2015).

In 2018, NBMI coverage reached 95% of the population (National Healthcare Security Administration, 2019).

The two types of basic medical insurance covers outpatient and inpatient expenses and also expenses of drugs in the national drug catalog for basic medical insurance, work-related injury insurance, and maternity insurance, but deductibles, co-payment, and reimbursement cap are different. Different areas in China have different details of basic medical insurance, generally, individuals with UEBMI can be reimbursed by 70% to 90% of the medical expenses, and individuals with URRBMI can be reimbursed by 50% to 70% of the medical expenses (National Healthcare Security Administration, 2019).

In order to reduce the burden of patients, all drugs for CHB treatment have been included in the national drug catalog and the drug costs can be reimbursed. Moreover, the prices of those drugs have decreased a lot due to drug price negotiation. The price of branded ETV (Baraclude) was dropped by 40%, and prices of branded TDF (Viread) and TAF (Vemlidy) were reduced by 33% and 54% respectively. In addition, generic drugs are also approved in China. Compared with the branded drugs, the prices of the generic drugs are much lower. Currently, 30% of those CHB patients choose branded drugs and 70% choose generic drugs. The price cuts resulting from reimbursement and negotiations can reduce the out-of-pocket amounts paid by patients and improve the willingness of treatment. In China, the prices of branded and generic drug are both under government regulation. The prices of the drugs are decided by the public tender system.

## 2.6 Review of Cost-effectiveness Studies

In recent years, the cost-effectiveness of NAs in treating CHB patients was shown in some studies. Toy, Hutton and So (2015) analyzed the cost-effectiveness of antiviral drugs, including NAs (LAM, ADV, ETV and TDF) and INF for CHB patients in China, and indicated that ETV monotherapy was likely to be the most cost-effective therapy with the drug prices at that time. Zhang et al. (2015) and Lai et al. (2016) reached the same conclusion. Zhang et al (2015) compared LAM, ADV, TBV and ETV and came to the result that ETV was the preferred

therapy at a willingness-to-pay (WTP) threshold of 18,924 USD per quality-adjusted life year (QALY) ( three times of per capita GDP of China in 2013) for HBeAg positive patients in China. The 10-year cumulative mortality of patients using ETV were decreased by 41% when compared with the high-resistance drug LAM.

Lai et al. (2016) evaluated the cost-effectiveness of monotherapies and rescue or add-on therapies of NAs (LAM, ADV, TBV, ETV and TDF) for Chinese HBeAg positive patients, and also pointed out that both ETV and TDF are cost-effective compared with no treatment strategy. However, though TDF had the best efficacy among those drugs, the incremental cost-effectiveness ratio (ICER) of TDF was far beyond the WTP threshold when compared with ETV. Thus, ETV was still the most cost-effective therapy. In addition, according to the sensitivity analysis, TDF monotherapy was the preferred therapy when its price dropped below to 1,820 USD per year.

A study from Dusheiko et al. (2017) compared TAF with TDF and ETV respectively from the third-party US payer perspective, and indicated that TAF dominated TDF with higher QALYs but lower costs. When compared with ETV, the ICERs of TAF was below the threshold. Consequently, TAF is the most cost-effective therapy in the US. In Canada, Tian et al. (2019) compared treatment strategies involving ETV, TDF and TAF and suggested that TAF was not cost-effective unless the drug piece wound drop by 33.4%. Different countries have different treatment costs and WTP threshold, thus they have different conclusions. Still, both of the two studies indicated that TAF could prevent additional cases of cirrhosis, HCC, liver transplantation and liver-related death compared to TDF and ETV.

# Chapter 3 Theoretical Framework

## 3.1 Economic Evaluation

Economic evaluation can be defined as the comparative analysis of interventions in terms of both their costs and outcomes (Drummond et al., 2015). It includes two main areas, first it deals with both costs and outcomes of interventions; second, choices can be made in allocation of resources (Cunningham, 2000). Since the healthcare resources are limited, economic evaluation is used to support decision of healthcare systems about which healthcare interventions to fund, particularly for the decision about reimbursement of new drugs (Briggs, Sculpher & Claxton, 2006).

### 3.1.1 Types of Economic Evaluation

There are three main types of economic evaluation: cost-effectiveness analysis (CEA), cost-benefit analysis (CBA) and cost-utility analysis (CUA) (Drummond et al., 2015). The three techniques have similar measurement for costs, that is costs are expressed in monetary unit, however, outcomes are expressed in different terms.

#### 3.1.1.1 Cost-effectiveness analysis

CEA expresses outcomes in natural units such as life-years gained, numbers of incidence avoided and numbers of disease detected. Thus, CEA is often applicable when comparing interventions with common effect but differ in magnitude (Drummond et al., 2015). Because of the specific expression of outcome in CEA, it is difficult to compare with interventions from other programs with different outcome units (Drummond et al., 2015). For policy-makers who have to compare the benefits of new interventions with the loss of any existing programs, CEA is not applicable. A more general technique which is applicable to all interventions is needed.

#### 3.1.1.2 Cost-utility analysis

CUA is a variant of CEA and often referred to as such, the only difference is that the outcomes of CUA are expressed in QALYs. Since health is a function of length of life and quality of life, QALYs is adopted to combine the two attributes into a single index and becomes a generic health outcome measure for various interventions (Prieto & Sacristán, 2003). With the generic measure, health outcomes of interventions from different programs can be compared. Health-related quality of life (HRQoL) is multidimensional concept which reflects physical, mental, emotional, functional and social well-being, depending on the health states (Yin et al., 2016). HRQoL is represented by quality weights which are based on the utilities (i.e. preferences) for health states (Drummond et al., 2015). The quality weights can be shown on a scale where 0 represents death and 1 represents perfect health. QALYs can be calculated using equation (1):

$$QALYs = Years\ of\ life\ \times HRQoL \tag{1}$$

The utility can be measured with various methods, including direct methods and indirect methods. Visual analogue scale, standard gamble and time trade-off are the three main direct method, and the Health Utilities Index (HUI), EQ-5D from the EuroQoL Group, and Short Form 6D (SF-6D) are the three widely used indirect methods (Drummond et al., 2015).

In some cases, disutility is also considered. Disutility represents the decrement in utility caused by a particular symptom or disease, and it can be calculated by subtracting utility values for a health state where particular symptom or disease occurs from a health state without any particular symptom or disease (York Health Economics Consortium, 2016).

#### 3.1.1.3 Cost-benefit analysis

CBA expresses outcomes in monetary units. As mentioned above, CEA and CUA are methods to find the best allocation of an existing budget but they cannot tell whether it is worth to expand the budget (Drummond et al., 2015). CBA is such a method to solve the problem. Moreover, since the effects and costs are both in monetary units, interventions in healthcare programs can be compared with interventions in other public programs. The monetary valuations of benefits (or outcomes) depend on the WTP surveys (York Health Economics

Consortium, 2016). The results of CBA can be shown by the net benefit, which is the difference between the benefit and cost of each intervention. An intervention is acceptable when the net benefit is larger than zero. However, CBA is not commonly used in healthcare programs because it is difficult to assess health outcome in monetary values (Drummond et al., 2015).

### 3.1.2 Perspective of Economic evaluation

Perspective is essential for economic evaluation as it determines the range of the costs and the outcomes included in the analyses. The three main perspective are healthcare payer perspective, healthcare sector perspective and society perspective (Garrison Jr et al., 2018).

The healthcare sector perspective includes the medical costs for managing the disease covered by third-party payers and paid for out-of-pocket by patients, but costs for obtaining healthcare (e.g. transportation and time off work) and other types of consumption associated with increased longevity (e.g. nutrition expense) are excluded (Garrison et al., 2018; York Health Economics Consortium, 2016).

Compared with the healthcare sector perspective, the healthcare payer perspective is much narrower, only the medical costs for managing the disease are included. Patients out-of-pocket costs are not included because they are not covered by the payers (Drummond et al., 2015; Garrison et al., 2018). Society perspective is even broader, it not only contains costs in health care sector but also costs for non-health-related impact in other sectors (e.g. criminal justice) and other non-medical cost for patients and relatives (e.g. productivity loss) (Drummond et al., 2005; Garrison et al., 2018).

### 3.1.3 The Process of Economic Evaluation

The process of economic evaluation starts with defining the research question and choosing an appropriate perspective. Second, target population and interventions have to be determined according to the research question. Third, an evaluation model has to be designed for the subsequent analysis. Forth, the outcomes and costs of all interventions are need to be identified and valued. In addition, an appropriate time horizon is need to be determined, and the costs and

outcomes with different time profiles should be discounted by a discount rate. Thereafter, the results of economic evaluation can be obtained.

The primary result of an economic evaluation is ICER, which indicates the additional cost per extra unit effect (e.g. QALY) gained by one intervention compared with another one (Bang & Zhao, 2012). ICER can be calculated by equation (2), where C is the cost, E is the effect, A is the intervention and B is the conventional healthcare.

$$ICER = \frac{Incrementel\ costs\ of\ an\ intervention}{Incrementel\ effect\ of\ an\ intervention} = \frac{\Delta C}{\Delta E} = \frac{C_A - C_B}{E_A - E_B} \quad (2)$$

The ICER can be used as a decision rule in resource allocation when compare with a WTP threshold. If the ICER of an intervention is less than the threshold, it can be considered as a cost-effective intervention.

When there are multiple mutually exclusive interventions available, each intervention is compared to the intervention with the next-lowest cost. If an intervention is less costly but has better effect than the comparator intervention, we can say the latter is absolutely dominated by the former (York Health Economics Consortium, 2016). An absolutely dominated intervention should be excluded irrespective of the WTP threshold.

Thereafter, ICERs can be calculated based on comparisons of moving from a lower cost to the next more costly and effective intervention and if the latter has a lower ICER than the former, we can say the former is extendedly dominated by the latter (Drummond et al., 2015). An extendedly dominated alternative should be ruled out and the comparison is repeated until all extendedly dominated alternatives are excluded.

After all dominated interventions are ruled out, ICERs of the remaining interventions are calculated by the comparisons of moving to increasingly costly and increasingly effective interventions. Intervention with the lowest ICER below the WTP threshold can be regarded as the most cost-effectiveness intervention.

## 3.2 Models of Economic Evaluation

Economic evaluation for decision-making is usually based on multiple sources. A decision-analytic model can bring all of the sources together to analyze a specific problem (Drummond et al., 2015, Yang et al., 2019). Moreover, a decision-analytic model provides a framework to define the mathematical relationship between entities (e.g. health states) and simulate the disease progress, and the costs and outcomes need for economic evaluation can be calculated by the mathematical relationship (Drummond et al., 2015).

There are various types of decision-analytic models; the decision tree model and the Markov model are the two most widely used models. The decision tree model is more suitable for "once-only" disease or event, and the Markov model is more suitable for long-term disease (e.g. chronic disease) because it can reflects the progression of the disease (Drummond et al., 2015, Sonnenberg & Beck, 1993).

In the Markov model, there is an important assumption which is called "memoryless" (Briggs, Sculpher & Claxton, 2006). It means the future states only depend on the current state, once patients enter a state, all patients are considered homogenous regardless of the past evens (Briggs, Sculpher & Claxton, 2006). The Markov model is based on a series of mutually exclusive states which represent possible prognoses. A patient can transit between those states in the Markov model at discrete time periods, "cycles" (Drummond et al., 2015). The length of the cycle is decided according to the progression of disease and the efficacy of interventions. The patient can either progress to a new state with a transition probability or remain in the same state. The proportion of patients in a certain state in a given cycle is multiplied with a transition probability to obtain the proportion of patients moving to another health state in the next cycle.

## 3.3 Validation of Economic Evaluation

Validation of the results is very important in economic evaluation because it can be taken as an indicator of the incredibility and reliability of model (Langley, 2017). Validation includes face validity, internal validity, cross validity, external validity, and predictive validity (Eddy et al.,

2012). Face validity is a more subjective assessment from experts about the model, data and results (Eddy et al., 2012).Internal validation checks the intrinsic consistency of the model, namely the logic relationship between the parameters and the outputs of the model (Haute autorité de santé, 2012). Cross validity can be implemented by comparing the results with other models analyzing the same problem (Eddy et al., 2012). External validation checks the reasonability of the results of the model, and it can be implemented by comparing the outputs with reliable empirical data (Haute autorité de santé, 2012). Predictive validity can be implemented by comparing the forecasted outcomes with the actual ones (Eddy et al., 2012).

## 3.4 Sensitivity Analysis

The ICERs are calculated using the deterministic estimators, however parameters used in the model are surrounded by uncertainty, which can cause a risk of making wrong (Briggs, Sculpher & Claxton, 2006). Hence, sensitivity analysis is used to explore the impact of uncertainty on the model results and make contribution to decision making (Drummond et al., 2015). Deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) are the two forms often used in economic evaluation.

### 3.4.1 Deterministic Sensitivity Analysis

DSA is a method to assess the isolated effect of one parameter or a set of parameters on the model result. In one-way deterministic sensitivity analysis only one parameter varies at one time and others are fixed, whilst in multiway sensitivity analysis more than one parameter vary simultaneously (York Health Economics Consortium, 2016). Scenario analysis is one of the solutions to present multiway analyses. Scenario analysis is used to explore economic evaluation results under alternative situations, each of which can affect the value of the parameters (Briggs & Gray, 1999). DSA can help to indicate how sensitive the results might be to change in a specific parameter or a set of paramters and to identify the importance of the parameters. However, it cannot reflect the combined effect of the uncertainty from all parameters, so one-way deterministic sensitivity analysis is not enough to represent uncertainty (Drummond et al., 2015).

### 3.4.2 Probabilistic Sensitivity Analysis

Because DSA have some limitations, PSA is recommended to capture the parameter uncertainty. PSA addresses this uncertainty of parameters simultaneously by assigning distribution to each parameter (Hatswell et al., 2018). Compared with DSA, the single point estimates are replaced by distributions of mean values, which make PSA to be more explicit (Drummond et al., 2015). The choice of distribution for each parameter is based on the characteristics of the parameters.

The probabilities are constrained in the range of zero and one, and the sum of the probabilities of mutually exclusive events must be one. Therefore, the beta distribution is chosen for binomial probability parameters because it has a constrained interval zero to one, which is appropriate for describing the characteristics of binomial probability parameters. Beta distribution have two positive parameters, α and β, which define the shape of the distribution. The parameter α can be defined as the number of the successful evens and β can be defined as the number of failed evens. When parameters α and β are unknown, mean and standard deviation can be used to calculate the parameter values by equation (3), where $\bar{\mu}$ is mean value and s is standard deviation.

$$\alpha + \beta = \frac{\bar{\mu}(1-\bar{\mu})}{s^2} - 1 \qquad \alpha = \bar{\mu}(\alpha + \beta) \tag{3}$$

When there are more than two transition options, instead of the beta distribution, the Dirichlet distributions is the first candidate for representing uncertainty in the multinomial probability (Krishnamoorthy, 2016). Dirichlet distributions is the multivariate generalization of the beta distribution (Ng, Tian & Tang, 2011).

The utilities are the weights for adjusting the life years, and the interval for the utility is from zero to one. Therefore, the beta distribution is also adopted to represent the uncertainty in the utility parameters.

The relative risk is a ratio of two probabilities (the probability of an event in the exposed group versus the probability of an event in the unexposed group), and the confidence interval of the

RR is calculated on the log scale (Tenny & Hoffman, 2019). Thus, lognormal distribution is appropriate for the relative risk parameters. The shape of the distribution can be defined by the mean and standard deviation.

The costs are always non-negative and can be calculated by the counts of the resource used in a fixed interval of time multiplied by the unit costs of the resource (Briggs, Sculpher & Claxton, 2006). Therefore, the gamma distribution is applied for the cost parameters because it is constrained on the interval zero to positive infinity, which is consistent with the characteristics of the cost parameters. The gamma distribution is parameterized by shape parameter α and scale parameter β. α and β can be calculated by mean and standard deviation with equation (4), where $\bar{\mu}$ is the mean value and $s$ is the standard deviation.

$$\alpha = \frac{\bar{\mu}^2}{s^2} \qquad \beta = \frac{s^2}{\bar{\mu}} \tag{4}$$

The parameters of distribution can be used to define the Cumulative Distribution Function (CDF), which is the probability that a variable has a value less than or equal to a given value (Forbes et al., 2011). However, when the variable value is unknown, the inverse function of the CDF is used to derive the variable value by given the integrated probability ((Briggs, Sculpher & Claxton, 2006) .

Monte Carlo simulation is used to perform PSA by generating random values of the parameters with defined distributions. The outputs of PSA are used to estimate the ICERs and the net monetary benefit (NMB) of interventions. NMB can be calculated by equation (5), where λ is the threshold, E is the effect of an intervention and C is the cost of an intervention.

$$NMB = \lambda \times E - C \tag{5}$$

The results of PSA can be shown by Cost-Effectiveness Acceptability Curve (CEAC) and cost-effectiveness acceptability frontier (CEAF). The CEAC is plotted for each intervention and indicates the probability that an intervention is cost-effective at different values of WTP threshold (Barton, Briggs & Fenwick, 2008). CEAF indicates the probability of the optimal

intervention at different values of WTP threshold (Barton, Briggs & Fenwick, 2008). CEAC and CEAF are used to represent the uncertainty in estimates of cost-effectiveness and can be produced by NMB.

Decision rules of NMB are evolved from the rule of the ICER. An intervention can be regarded as cost-effective if the NMB is more than zero (Briggs, Sculpher & Claxton, 2006). Monte Carlo simulation runs 1000 iterations and each iteration can produce a group of NMBs for all interventions with a given WTP threshold. For each iteration, the most cost-effective intervention with the highest NMB can be picked out from the group. Then the proportion of time that each intervention to be the optimal can be calculated. Repeat the process with a new threshold. CEACs can be derived by plotting the proportions of each intervention at different WTP thresholds. Interventions with the maximum NMB at each WTP threshold are picked out, and CEAF are obtained by plotting the proportion of those interventions ((Barton, Briggs & Fenwick, 2008).

## 3.5 Expected Value of Perfect Information

Because of the uncertainties, a correct decision based on the current information may become wrong once the current uncertainties are resolved (Briggs, Sculpher & Claxton, 2006). If so, the wrong decision will cause resource and cost forgone. CEAF shows the optimal option at different WTP thresholds, but does not indicates the consequence of making a wrong decision. The costs of uncertainty can be interpreted as the expected value of perfect information (EVPI), which is the difference in the monetary value of health gained between when the decision is made based on the current information and the decision is made on the perfect information (Briggs, Sculpher & Claxton, 2006). EVPI represents the maximum amount that one is willing to pay for reducing the uncertainty.

EVPI can be performed from the PSA results directly. It can be calculated by the expected NMB with perfect information minus the maximum NMB with current information in each iteration. The equation (6) shows the calculation, where j is the alternative invention, and $\theta$ is the uncertainty surrounding the decision.

$$EVPI = E_\theta max_j NB(j,\theta) - max_j E_\theta NB(j,\theta) \quad (6)$$

When EVPI for an individual patient is generated, it is also possible to get EVPI for the population which can be calculated by multiplying the total population of patients who are benefit from additional information over the expected lifetime of the intervention. The equation (7) shows the calculation, where I is the estimate of incidence, t is the effective lifetime of technology, r is the discount rate.

$$EVPI\ for\ the\ population = EVPI\ \times \frac{\sum_{t=1,2,\cdots,T} I_t}{(1+r)^t} \quad (7)$$

If EVPI is less than the cost of gathering supplemental information, further research for getting more information to reduce the uncertainty is worthwhile, otherwise, further research is not worthwhile.

# Chapter 4 Methods and Materials

## 4.1 Model Overview

### 4.1.1 Perspective

The treatment of CHB has been covered by the national basic healthcare system, therefore the analysis was conducted from the perspective of Chinese healthcare. With this perspective, health outcome reported by the patient and the direct medical cost associated with treating CHB and related liver disease were considered in this study.

### 4.1.2 Population

First, the age at treatment start in the model was set to 34 years. A study from Zhang et al (2019) analyzed the incidence of HBV in China from 2004-2016 and indicated the highest incidence was in the group aged 25-29 years (30-34 years in 2020).

Second, according to the natural history of CHB, the hypothetical patients have detectable HBsAg for at least 6 months and they are HBeAg positive (with HBV DNA $> 2 \times 10^4$ UI/ml). Meanwhile, the ALT level of the hypothetical patients is higher than the upper limit of normal range and at most.

Third, in order to make the analysis more pertinent to CHB patients, the hypothetical patients are not jointly infected by hepatitis A, C and D, also do not have co-infection with HIV. Moreover, the hypothetical patients do not have evidence of cirrhosis or HCC and also have no experience with liver transplantation. In addition, the hypothetical patients are treatment-naïve, which means the patients have less than 12 weeks of treatment with any nucleoside or nucleotide analogue.

### 4.1.3 Intervention

ETV, TDF and TAF are the three low-resistant drugs recommended by the Chinese Guidelines as first-line drugs for treating CHB, and only these drugs were considered in this study. In order

to monitor clinical efficacy, patient compliance, drug resistance and adverse events, regular follow-up is required during the antiviral therapy.

According to the Chinese Guidelines, patients can maintain the initial monotherapy treatment when they have virologic response. However, when virologic resistance arises, they should switch to a potent drug. Patients who are resistant to ETV can switch to TDF or TAF.

SAEs can affect the quality of life, and patients with SAEs should discontinue the current drug or switch to a new drug. According to the Chinese Guidelines, patients with SAEs by using ETV can switch to TDF or TAF, patients with SAEs by using TDF or TAF can switch to ETV.

The Chinese Guidelines recommends that HBeAg-positive CHB patients who undergo seroconversion after a finite period of treatment with ETV, TDF and TAF can discontinue the therapy after an additional three years of consolidation therapy. In base-case analyses, I adopted the recommendation. However, in practice, physicians are very cautious about the decision of drug withdrawal because it may cause the relapse and deterioration in CHB patients. Reijnders et al (2010) also suggests a long-term continuation of NAs treatment is necessary, irrespective of the occurrence of HBeAg seroconversion. Following the practical experience and the findings, an infinite therapy is discussed in a scenario analysis.

From the above, HBeAg-positive CHB patients can receive the following eight treatment strategies shown in Table 2.

**Table 2** Treatment strategies for HBeAg-positive CHB patients

| No | Treatment strategy | Description |
|---|---|---|
| 1 | ETV | ETV monotherapy |
| 2 | TDF | TDF monotherapy |
| 3 | TAF | TAF monotherapy |
| 4 | ETV→TDF | ETV switch to TDF because of drug resistance or SAEs |
| 5 | ETV→TAF | ETV switch to TAF because of drug resistance or SAEs |
| 6 | TDF→ETV | TDF switch to ETV because of drug resistance or SAEs |
| 7 | TDF→TAF | TDF switch to TAF because of drug resistance or SAEs |
| 8 | TAF→ETV | TAF switch to ETV because of drug resistance or SAEs |

*ETV* entecavir, *TDF* tenofovir disoproxil fumarate, *TAF* tenofovir alafenamide, *SEAs* serious adverse evens

### 4.1.4 Time Horizon

CHB is a chronic disease, and there is no thoroughly cure method currently. CHB patients always need a long-term treatment, some even need lifelong treatment. A short-term horizon is not enough to correctly measure the life-time consequences of the interventions. Therefore, lifetime horizon was assumed for the analysis. The lifetime horizon was set to 99 years old (65 cycles) because 99% of the patients died by that time.

### 4.1.5 Discount Rate

The costs and utilities were considered more than one year in this study, thus the costs and utilities in the future was discounted to the present values by a discounting rate using equation (8), where PV is the present value, FV is the future value, and r is the discounting rate.

$$PV = \frac{FV}{(1+r)^n} \tag{8}$$

The China Guideline for Pharmacoeconomic Evaluations (2011) considered the range for the discount rate to be 0% to 8%, and recommended to use the same discount rate for outcomes. Xie & Lie (2019) used least squares regression to estimate the pharmacoeconomic discount rate in China and recommended a discount rate of 5.2%. In addition, numerous CEA studies took 5% as an appropriate discount rate. Thus, in this study, 5% discount rate was used both for cost and utility.

### 4.1.6 Half-cycle Correction

In a Markov Model, all transitions are assumed to take place at the start or end of the cycle, but in reality, the transitions can occur at any point during the cycle. It may lead to overestimation or underestimation of the accumulated cost and outcome in the model. Thus, half-cycle correction was applied in the model using equation (9) to make the results more accurate, where A is total cost or total utility, and C is the cost or utility in one cycle.

$$A = \frac{1}{2} \times C_1 + C_2 + \cdots + C_{64} + \frac{1}{2} \times C_{65} \tag{9}$$

### 4.1.7 Cost-Effectiveness Analysis

CUA was adopted in this study to analyze the cost-effectiveness of different treatment strategies. lifetime QALYs, 10-year cumulative incidence of liver complications and costs were used as outcome measures. The eight treatment strategies were ranked from smallest to larges according to the cost value. When a treatment strategy had higher cost and higher QALYs compared with the treatment strategy with the next-lowest cost, ICER was performed. In contract, the ICER was not calculated if the treatment strategy had higher cost but lower QALYs. Moreover, because this study is based on the Chinese healthcare perspective, only direct medical costs were considered. Indirect costs and intangible costs were not included. Branded and generic drugs were distributed in proportion according to the actual conditions of the market in base-case analyses. Pure branded drugs and pure generic drugs situations were considered in scenario analysis to see whether the choice of drugs can affect the consequence.

## 4.2 Model Structure

CHB is a long-time chronic disease, so a Markov model was used in this study to assess the cost and effectiveness of NAs therapies for the HBeAg-positive CHB patients in China. Figure 1 shows the model structure. The Markov model was adapted from Zhang et al (2015) and Tian et al (2019). The Markov model contains 12 mutually exclusive health states: (1) Chronic hepatitis B (CHB); (2) HBeAg seroconversion (SEC); (3) HBsAg clearance (CLN); (4) Virologic response (VRP); (5) Virologic resistance (VRT); (6) serious adverse event (SAE); (7) Compensated cirrhosis (CC); (8) Decompensated cirrhosis (DC); (9) hepatocellular carcinoma (HCC); (10) Liver transplantation (LT); (11) Post liver transplantation (PLT); (12) Death. The length of the cycle in the model was set to one year, and the transitions between those mutually exclusive health states are presented by arrows in Figure 1. All states can lead to death, including all-cause death and disease-relative death. The liver disease-related death was considered in states of CHB, compensated cirrhosis (CC), decompensated cirrhosis (DC), HCC, liver transplant (LT) and post liver transplant (PLT), for other health states, only all-cause death was considered.

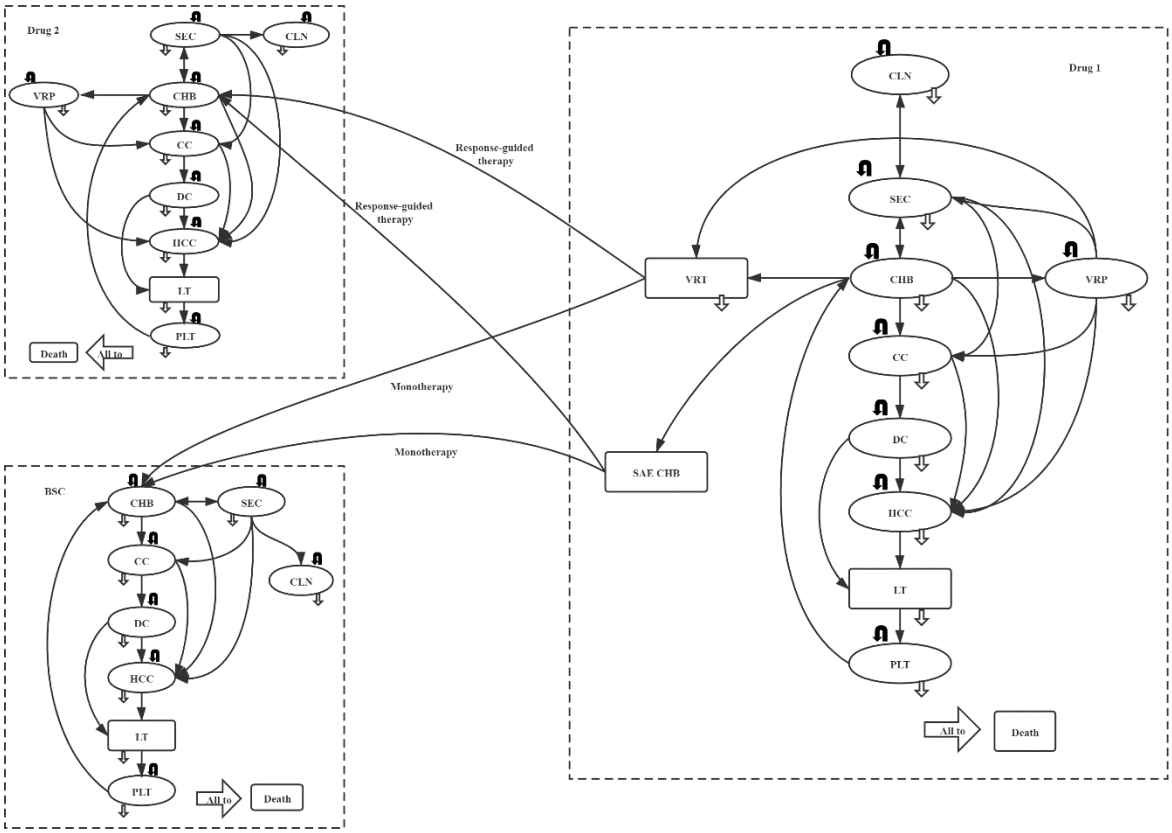


**Figure 1** Markov model of chronic hepatitis B. Ovals represent the health states, the rectangles represent events, the thin arrows represent the disease progression, the thick black arrows represent staying in the states and the white thick arrows represent progressing to death. *CHB* chronic hepatitis B, *CC* compensated cirrhosis, *DC* decompensated cirrhosis, *HCC* hepatocellular carcinoma, *LT* liver transplantation, *PLT* post-liver transplantation, *VRP* virologic response, *SEC* HBeAg seroconversion, *CLN* HBsAg clearance, *BSC* best supportive care, *SAE* serious adverse event

The patient enters the model in CHB state with the initial drug (drug 1) and can progress to HBeAg seroconversion (SEC), virologic response (VRP), compensated cirrhosis (CC) or HCC. If the patient develops serious adverse events (SAE) or virologic resistance (VRT), the initial drug will be discontinued. Then, the patient with monotherapy could either continue without treatment or switch to another drug (drug 2). For patient stays without treatment, I assume that he receives best supportive care (BSC), which is defined as monitoring without drug treatment. After switching to BSC or drug 2, the patient has the same progression with patient treated by the initial drug. In order to simplify the analyses, I assume that the patient can have a maximum number of two types of drugs, and that the patient will not develop serious adverse events (SAE) or virologic resistance (VRT) after switching to drug 2.

In virologic response (VRP) state, the drugs are effective and the virus is suppressed, though the patient still faces with the risk of progressing to compensated cirrhosis (CC) and HCC, but the risk is much lower. HBeAg seroconversion (SEC) can also occur in the virologic response (VRP) state. Moreover, because the HBV can mutate, though the patient achieves virologic response (VRP), virologic resistance (VRT) still can occur.

In HBeAg seroconversion (SEC) state, anti-HBeAg occurs, which means the viral replication is under control and the patient becomes inactive HBV carrier. The patient can discontinue the treatment after an additional three years of consolidation therapy. However, because the virus cannot be eliminated, the patient in HBeAg seroconversion state (SEC) still faces with the risk of CHB relapse. But the risk of progressing to compensated cirrhosis (CC) or HCC from HBeAg seroconversion state (SEC) is quite low. HBsAg clearance (CLN) occurs after HBeAg seroconversion (SEC), and it is the endpoint of the antiviral treatment, which means functional cure is acquired in this state. Patient who acquires HBsAg clearance (CLN) are assumed to have no risk of progressing to HBV-related disease.

Patients in compensated cirrhosis (CC) state can progress to decompensated cirrhosis (DC) and HCC, and patients in decompensated cirrhosis (DC) state can progress to HCC. A liver transplant (LT) is assumed to be the only treatment for decompensated cirrhosis (DC) and HCC in this study. After liver transplant (LT), patients can keep stable state (PLT) but still face with risk of recurrence of CHB.

## 4.3 Model Inputs

Model inputs were derived from the literatures, systematic reviews, clinical trials, healthcare database and China Statistics. The search strategy comprised of the following keywords: “chronic hepatitis B”, “HBeAg positive”, “cost-effectiveness”, “Markov”, “randomized controlled trial”, “efficacy” and combined with “nucleoside/nucleotide analogues”, “ETV”, “TDF”, “TAF”, “economic burden”, “quality of life”. The titles and abstracts of the articles were scanned to evaluate their relevance. Studies containing transition probabilities, costs and utilities were appraised whether apply to Chinses setting.

### 4.3.1 Transition Probability

#### 4.3.1.1 Health States Transition probability

The health states transition probabilities were derived from the published literatures which included cost-utility analyses about HBeAg positive CHB. The all-cause mortality of CHB patients was based on the Chinese life table from WHO multiply by the relative risk of mortality in HBV infected (HBsAg positive) patients from the REVEAL-HBV Study (Iloeje et al., 2007). It is the baseline mortality for all health states in this model. An additional disease-related mortality was applied to patients with CHB, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplant and post-liver transplant. The total mortality is the sum of the baseline mortality and the disease-related mortality. Table 3 shows the annual health states transition probabilities used in this study. The Chinese life table is shown in Table 4.

From Table 3 the relative risk of mortality in HBV infected patients is 1.7, and from Table 4 the all-cause mortality of in the age group 30 to 34 years from the Chinese life table is 0.0010, resulting in a baseline mortality for HBV infected patients 30 to 34 equal to 0.0017 (1.7×0.0010). Moreover, from Table 4 the disease-related mortality of CHB is 0.0060, resulting in a mortality for CHB is 0.0077 (0.0060+0.0017). The rate was converted to probability using equation (10), where p is the probability, r is the rate and t is the period.

$$p = 1 - e^{-rt} \tag{10}$$

**Table 3** Base-case annual health states transition probabilites

| Parameters | Base-case value (SD*) | Range† | Distribution | Source |
|---|---|---|---|---|
| CHB | | | | |
| to CC | 0.0200 (0.0020) | 0.0180 - 0.0220 | Beta | [81] |
| to HCC | 0.0100 (0.0010) | 0.0090 - 0.0110 | Beta | [81] |
| to disease-related DT | 0.0060 (0.0006) | 0.0054 - 0.0066 | Beta | [79] |
| VRP | | | | |
| to CC | 0.0040 (0.0004) | 0.0036 - 0.0044 | Beta | [92] |
| to HCC | 0.0020 (0.0002) | 0.0018 - 0.0022 | Beta | [92] |
| to SEC | 0.0530 (0.0053) | 0.0477 - 0.0583 | Beta | [5] |

| Parameters | Base-case value (SD*) | Range† | Distribution | Source |
|---|---|---|---|---|
| SEC | | | | |
| to CHB | 0.0048 (0.0005) | 0.0043 - 0.0053 | Beta | [78] |
| to CC | 0.0100 (0.0010) | 0.0090 - 0.0110 | Beta | [79] |
| to HCC | 0.0020 (0.0002) | 0.0018 - 0.0022 | Beta | [79] |
| to CLN | 0.0080 (0.0008) | 0.0072 - 0.0088 | Beta | [78] |
| CC | | | | |
| to DC (without treatment) | 0.0730 (0.0073) | 0.0657 - 0.0803 | Beta | [79] [81] |
| to HCC (without treatment) | 0.0340 (0.0034) | 0.0306 - 0.0374 | Beta | [79] [81] |
| to disease-related DT | 0.0490 (0.0049) | 0.0441 - 0.0539 | Beta | [81] |
| RR CC to DC (with treatment) | 0.5209 (0.0664) | 0.4688 - 0.5730 | Log-normal | [79] |
| RR CC to HCC (with treatment) | 0.3857 (0.0492) | 0.3471 - 0.4243 | Log-normal | [79] |
| DC | | | | |
| to HCC | 0.0910 (0.0091) | 0.0819 - 0.1001 | Beta | [92] |
| to LT | 0.0500 (0.0005) | 0.0045 - 0.0055 | Beta | [92] |
| to disease-related DT | 0.1040 (0.0104) | 0.0936 - 0.1144 | Beta | [92] |
| HCC | | | | |
| to LT | 0.0500 (0.0050) | 0.0450 - 0.0550 | Beta | [92] |
| to disease-related DT | 0.5200 (0.0520) | 0.4680 - 0.5720 | Beta | [92] |
| LT | | | | |
| to disease-related DT | 0.1200 (0.0120) | 0.1080 - 0.1320 | Beta | [92] |
| PLT to CHB relapse | 0.0480 (0.0048) | 0.0432 - 0.0528 | Beta | [44] |
| PLT to disease-related DT | 0.0810 (0.0081) | 0.0729 - 0.0891 | Beta | [44] |
| RR of mortality in HBV infected patients | 1.7000 (0.1020) | 1.5300 - 1.8700 | Log-normal | [36] |

* Standard deviation is 10% of the mean base-case value

† Lower limit value is 90% of the base-case value, upper limit value is 110% of the base-case value

*CHB* chronic hepatitis B, *CC* compensated cirrhosis, *DC* decompensated cirrhosis, *HCC* hepatocellular carcinoma, *LT* liver transplantation, *PLT* post-liver transplantation, *VRP* virologic response, *SEC* HBeAg seroconversion, *CLN* HBsAg clearance, *DT* death, *RR* relative risk

For probabilistic analysis, Dirichlet distribution is the appropriate choice in situation where there are more than two transition options for each state. However, transition probabilities used in this model were derived from various sources, and the assumption for Dirichlet distribution

that patients come from the same population cannot be reached. Thus, in this study, the beta distribution was applied for all health states transition probabilities.

**Table 4** Age-specific all-cause mortality from Chinese life table

| Age | mortality (‰) | Age | mortality (‰) |
|---|---|---|---|
| 30-34 | 1.00 | 60-64 | 12.05 |
| 35-39 | 1.00 | 65-69 | 21.59 |
| 40-44 | 1.51 | 70-75 | 38.66 |
| 45-49 | 2.00 | 75-79 | 65.76 |
| 50-54 | 3.51 | 80-84 | 101.73 |
| 55-59 | 6.02 | 85+ | 190.24 |

source: https://www.who.int/gho/countries/chn/en/

#### 4.3.1.2 Treatment-related Transition Probability

Different NAs drugs have different efficacies, which are represented by the treatment-related transition probabilities of HBeAg seroconversion, virologic response and virologic resistance. In addition, HBeAg seroconversion can also occur spontaneously, but the probability is relatively low. Spontaneous HBeAg seroconversion probability was obtained from Zhu, Hussain & Lok (2002), and the beta distributions was assigned to it.

The treatment-related transition probabilities of TAF and TDF were obtained from a global randomized controlled trial 110, which were conducted on 873 (315 were Chinese) HBeAg-positive CHB patients to compare the safety and efficacy of TAF and TDF (Study TAF/TDF) (Chan et al., 2016). The approval of the branded TAF (Vemlidy) in China were supported by the results of this trial (Gilead Sciences, 2018). The treatment-related transition probabilities of TAF and TDF used in this study were derived from the Chinese subgroup in trial 110 (Chan et al., 2018). The treatment-related transition probabilities of ETV were derived from a randomized controlled trial supported by National Science and Technology Major Project which comparing the safety and efficacy of ETV and TDF for Chinese HBeAg-positive CHB patients (Study ETV/TDF) (Cai et al., 2019). Dirichlet distribution was assigned to the treatment-related transition probability, and the successful events in the trail was taken as alpha.

Because the two studies used different assays for measuring HBV DNA level. Study TAF/TDF applied COBAS TaqMan HBV Test for use with the High Pure System (HP), and the lower limit of quantitation is 29 IU/mL. But Study ETV/TDF applied COBAS AmpliPrep/COBAS TaqMan HBV Test, v2.0 (CAP/CTM), and the lower limit of quantitation is 20 IU/mL. In this study, HBV DNA level was assumed to be measured by HP with the 29 IU/mL lower limit of quantitation. Thus, the outcomes from Study ETV/TDF were adjusted to be consistent with the assumption. The adjustment process is shown in Appendix 1.

SAEs of NAs were also considered in this study, the probabilities of SAEs of TDF and TAF were obtained from Study TAF/TDF, and the probability of SAEs of ETV was obtained from Tian et al. (2019). The probability of SAEs were assigned with the beta distribution. Table 5 shows the annual treatment-related transition probabilities of ETV, TDF and TAF.

**Table 5** Annual treatment-related transition probabilities

| Parameters | Base-case value | Range* | Distribution | Source |
|---|---|---|---|---|
| Spontaneous | | | | |
| VRP | N/A | N/A | N/A | |
| VRT | N/A | N/A | N/A | |
| SEC | 0.0615 | 0.0554 - 0.0677 | Beta (4,61) | [15] |
| ETV | | | | |
| VRP | 0.6266 | 0.5639 - 0.6892 | Dirichlet (99,59) | [8] |
| VRT | 0.0063 | 0.0057 - 0.0070 | Dirichlet (1, 157) | [8] |
| SEC | 0.0949 | 0.0854 - 0.1044 | Dirichlet (15,143) | [8] |
| SAE | 0.0480 | 0.0432 - 0.0528 | Beta (12, 250) | [78] |
| TDF | | | | |
| VRP | 0.7037 | 0.6333 - 0.7741 | Dirichlet (76, 32) | [9] [10] |
| VRT† | 0 | 0 | N/A | |
| SEC | 0.0741 | 0.0667 - 0.0815 | Dirichlet (8, 100) | [9] [10] |
| SAE | 0.0643 | 0.0579 - 0.0707 | Beta (9, 131) | [10] |
| TAF | | | | |
| VRP | 0.6908 | 0.6217 - 0.7599 | Dirichlet (143, 64) | [9] [10] |
| VRT† | 0 | 0 | N/A | |
| SEC | 0.1111 | 0.1000 - 0.1222 | Dirichlet (23, 184) | [9] [10] |
| SAE | 0.0491 | 0.0442 - 0.0540 | Beta (14, 271) | [10] |

* Lower limit value is 90% of the base-case value, upper limit value is 110% of the base-case value

† No virologic resistance to TDF and TAF is detected currently.

*VRP* virologic response, *VRT* virologic resistance, *SEC* HBeAg seroconversion, *SAE* serious adverse events, *ETV* entecavir, *TDF* tenofovir disoproxil fumarate, *TAF* tenofovir alafenamide

### 4.3.2 Costs

This study is based on Chinese healthcare perspective, only direct medical costs were considered. The direct medical costs contain physician visit, examination and laboratory test, hospital stay, medication expense, treatment expense, nursing expense, monitoring and follow-up and management of disease complication related to adverse events. All early costs were inflated to 2019 price using China consumer price index, and then converted from Chinese Yuan (CNY) to US Dollar (USD) using the average exchange rate in 2019. Appendix 2 shows the consumer price index and average exchange rate.

#### 4.3.2.1 Drug costs

Both branded drugs and generic drugs are available in China, but generic drugs are more widely used. In order to conform to the actual situation, weighted average drug prices were adopted in the base-case analyses. The market shares of the branded and generic drugs were taken as the weights. For TAF, there is no generic drugs in China currently, so branded drugs are adopted for all patients. Because the prices of the drugs are decided by public tender system, the winning bid was taken as the drug price. Prices of branded and generic drugs were obtained from Yaozhi Medical databases. Table 6 shows the annual drug costs related to CHB.

**Table 6** Annual drug costs (USD, year 2019 value) related to CHB

| Parameters | Base-case value (SD*) | Range† | Distribution |
|---|---|---|---|
| Market share of generic drug | 0.70 (0.07) | 0.63 - 0.77 | Beta |
| Generic drug cost | | | |
| TAF | N/A | N/A | N/A |
| TDF | 467 (93) | 421 - 514 | Gamma |
| ETV | 379 (76) | 341 - 417 | Gamma |
| Branded drug cost | | | |
| TAF | 939 (188) | 845 - 1,033 | Gamma |
| TDF | 573 (115) | 516 - 631 | Gamma |
| ETV | 989 (198) | 890 - 1,088 | Gamma |

* Standard deviation of drug price is 20% (market share is 10%) of the mean base-case value

† Lower limit value is 90% of the base-case value, upper limit value is 110% of the base-case value

All drug costs expressed in USD per patients/year according to 2019 price

*ETV* entecavir, *TDF* tenofovir disoproxil fumarate, *TAF* tenofovir alafenamide

Source: https://data.yaozh.com/yaopinzhongbiao

#### 4.3.2.2 Health States costs

A nationwide survey of HBV-related economics burden was implemented in China between 1 March 2010 and 30 June 2010. The survey was performed in 27 hospitals from 12 cities with different economic development levels, and 4,726 patients were enrolled in the survey. Patients participated in the survey had face-to-face interviews to finish the questionnaire, and their medical records, hospital fees and length of stays were made available. The survey examined the direct, indirect and intangible costs of HBV-related disease within one year (Ma et al., 2017).

Health states costs (exclude HBsAg clearance and post-liver transplant) used in this study were based on this national survey. The annual cost for patients in HBsAg clearance state was assumed to be the same with the average annual direct medical cost for a normal individual which was derived from National Health Commission . All CHB states (HBeAg seroconversion state, virologic response, virologic resistance, SAEs and CHB) were assumed to have the same annual costs. Data on costs for treatment and care of post-liver transplant was limited, so the opinions of clinical experts were also considered. The costs of each health states are shown in Table 7. Detailed costs were presented in Appendix 3 and Appendix 4.

**Table 7** Annual health states costs (USD, year 2019 value) related to CHB

| Parameters | Base-case value (SD*) | Range† | Distribution | Source |
|---|---|---|---|---|
| CHB | 2,569 (514) | 2,312 - 2,826 | Gamma | [52] |
| CLN | 1,476 (295) | 1,329 - 1,624 | Gamma | [57] |
| SEC | 2,569 (513) | 2,312 - 2,826 | Gamma | Assumed equal to CHB |
| VRP | 2,569 (513) | 2,312 - 2,826 | Gamma | Assumed equal to CHB |
| VRT | 2,569 (513) | 2,312 - 2,826 | Gamma | Assumed equal to CHB |
| SAE | 2,569 (513) | 2,312 - 2,826 | Gamma | Assumed equal to CHB |
| CC | 4,560 (911) | 4,104 - 5,016 | Gamma | [52] |
| DC | 6,002 (1,200) | 5,401 - 6,602 | Gamma | [52] |
| HCC | 8,153 (1,631) | 7,337 - 8,968 | Gamma | [52] |
| LT | 42,498 (8,500) | 38,248- 46,747 | Gamma | [52] |
| Post LT | 8,584 (1,717) | 7,725 - 9,442 | Gamma | expert panel |

* standard deviation of health state costs is 20% of the mean base-case value

† Lower limit value is 90% of the base-case value, upper limit value is 110% of the base-case value

*CHB* chronic hepatitis B, *CLN* HBsAg clearance, *SEC* HBeAg seroconversion, *VRP* virologic response, *VRT* virologic resistance, *SAE* serious adverse events, *CC* compensated cirrhosis, *DC* decompensated cirrhosis, *HCC* hepatocellular carcinoma, *LT* liver transplantation, *PLT* post-liver transplantation

### 4.3.3 Utilities

Levy et al (2008) study used an interviewer-administered survey to collect utilities from respondents of six countries, which contained 200 Chinses respondents. Utilities for health states were measured with the standard gamble technique. Utilities from Levy et al (2008) study also be used in many previous studies. Thus, utilities from the Chinese subgroup in Levy et al (2008) were used in this study. Utility of virologic response was assumed equal to utility of CHB, and utilities of HBeAg seroconversion and HBsAg clearance were assumed equal to utility of normal health state without CHB. Furthermore, I assumed SAEs had negative impact on health utilities (disutility), but resistance had no negative impact (Tian et al., 2020). Health-state utilities related to CHB are presented in Table 8.

**Table 8** Health states utilities related to CHB

| Parameters | Base-case value (SD*) | Range | Distribution | Source |
|---|---|---|---|---|
| CHB | 0.52 (0.052) | 0.50 - 0.54 | Beta | [45] |
| CLN | 0.71 (0.071) | 0.70 - 0.73 | Beta | [45] |
| SEC | 0.71 (0.071) | 0.70 - 0.73 | Beta | [45] |
| VRP | 0.52 (0.052) | 0.50 - 0.54 | Beta | Assumed equal to CHB |
| CC | 0.57 (0.057) | 0.55 - 0.59 | Beta | [45] |
| DC | 0.26 (0.026) | 0.24 - 0.27 | Beta | [45] |
| HCC | 0.31 (0.031) | 0.29 - 0.33 | Beta | [45] |
| LT | 0.41 (0.041) | 0.39 - 0.43 | Beta | [45] |
| PLT | 0.55 (0.055) | 0.53 - 0.57 | Beta | [45] |
| SAE (disutility) | 0.05 (0.005) | 0.05 - 0.06 | Beta | Assumption |
| VRT (disutility) | 0 | 0 | N/A | Assumption |

*Standard deviation estimated on 10% of the baseline value

*CHB* chronic hepatitis B, *CLN* HBsAg clearance, *SEC* HBeAg seroconversion, *VRP* virologic response, *CC* compensated cirrhosis, *DC* decompensated cirrhosis, *HCC* hepatocellular carcinoma, *LT* liver transplantation, *PLT* post-liver transplantation, *SAE* serious adverse events, *VRT* virologic resistance

### 4.3.4 WTP Threshold

According to the recommendation of WHO, an intervention is cost-effective if the ICER is less than 3 times of gross domestic product (GDP) per capita (Bertram et al., 2016). The GDP per capita of China in 2019 was 10,142 USD, thus, the WTP threshold was set to be 30,426 USD/QALY in this study.

# Chapter 5 Results

The deterministic analysis, one-way deterministic sensitivity analysis, probabilistic sensitivity analysis, scenario analysis and EVPI were implemented in this study and the results were shown below.

## 5.1 Base-case Cost-Effectiveness Analysis

The model calculated the lifetime costs for per patient, QALYs gained, incremental costs, incremental QALYs and ICERs for the eight treatment strategies. The results for each treatment strategy are shown in Table 9. Among the eight treatment strategies, TAF→ETV therapy has the highest lifetime costs (51,932 USD) and also gains the highest QALYs (9.24 QALYs). Among the monotherapy subgroup, TAF monotherapy has the highest lifetime costs (51,268 USD) and also the highest QALYs (9.19 QALYs). In addition, TDF monotherapy has the lowest lifetime costs (47,341 USD) and ETV monotherapy has the lowest QALYs (9.10 USD/QALYs). Moreover, for each drug, its response-guided therapy always has the higher QALYs and also the higher costs compared with its monotherapy.

**Table 9** Base-case cost-effectiveness results of treatmet strategies for HBeAg positive CHB patients

| Treatment strategy | Costs (USD) | Δcosts (USD) | QALYs | ΔQALYs | ICERs (USD/QALY) | NMB (USD) |
|---|---|---|---|---|---|---|
| TDF | 47,341 | N/A | 9.13 | N/A | N/A | 230,303 |
| ETV | 47,752 | 411 | 9.10 | -0.03 | Abs dominated | 229,000 |
| TDF→ETV | 48,084 | 743 | 9.18 | 0.05 | 14,197 | 231,152 |
| TDF→TAF | 48,523 | 439 | 9.18 | 0.00 | Ext dominated | 230,801 |
| ETV→TDF | 48,821 | 737 | 9.19 | 0.01 | 50,718 | 230,858 |
| ETV→TAF | 49,556 | 735 | 9.20 | 0.01 | Ext dominated | 230,320 |
| TAF | 51,268 | 1,712 | 9.19 | -0.01 | Abs dominated | 228,227 |
| TAF→ETV | 51,932 | 3,111 | 9.24 | 0.05 | 62,907 | 229,251 |

*ETV* entecavir, *TDF* tenofovir disoproxil fumarate, *TAF* tenofovir alafenamide, *QALYs* quality-adjusted life-years, *ICER* incremental cost-effectiveness ratio, *NMB* net monetary benefit, *Abs dominated* absolutely dominated, *Ext dominated* extendedly dominated

In addition, as Table 10 shows, the 10-year cumulative incidences of compensated cirrhosis, decompensated cirrhosis, HCC and mortality for TAF monotherapy are 7.34%, 1.16%, 3.65%

and 7.53%. TAF monotherapy can prevent an additional one cases of compensated cirrhosis and one cases of HCC per 1,000 CHB patients when compared with TDF monotherapy, and prevent an additional three cases of compensated cirrhosis, one cases of HCC and five cases of death per 1,000 CHB patients when compared with ETV monotherapy. Moreover, the 10-year cumulative incidences and mortality for TAF→ETV therapy are 6.87%, 1.11%, 3.37% and 7.15% respectively. TAF→ETV therapy can prevent an additional three cases of compensated cirrhosis, one case of decompensated cirrhosis, two cases of HCC and one cases of death per 1,000 CHB patients when compared with TAF monotherapy.

**Table 10** Modelled clinical outcome of treatment strategies

| Treatment strategy | 10-year cumulative incidence of liver complications | | | |
|---|---|---|---|---|
| | CC | DC | HCC | DT |
| TDF | 7.36% | 1.18% | 3.76% | 7.43% |
| ETV | 7.66% | 1.23% | 3.89% | 7.92% |
| TDF→ETV | 6.72% | 1.11% | 3.38% | 7.18% |
| TDF→TAF | 6.71% | 1.10% | 3.37% | 7.16% |
| ETV→TDF | 6.96% | 1.15% | 3.48% | 7.39% |
| ETV→TAF | 6.97% | 1.15% | 3.48% | 7.39% |
| TAF | 7.34% | 1.16% | 3.65% | 7.53% |
| TAF→ETV | 6.87% | 1.11% | 3.37% | 7.15% |

*ETV* entecavir, *TDF* tenofovir disoproxil fumarate, *TAF* tenofovir alafenamide, *CC* compensated cirrhosis, *DC* decompensated cirrhosis, *HCC* hepatocellular carcinoma

The higher QALYs and the lower incidences of liver complications for TAF-basing therapy (TAF monotherapy and TAF→ETV therapy) are likely due to the better viral suppression and HBeAg seroconversion effects of TAF. However, the costs of TAF-basing therapies are always higher than the others. This is because no generic TAF has been approved in China and the branded TAF is expensive than generic TDF and ETV.

Moreover, as seen in Figure 2, TAF monotherapy, ETV monotherapy, ETV→TAF therapy and TDF→TAF therapy are under the cost-effectiveness frontier. ETV monotherapy and TAF monotherapy are absolutely dominated, since they are more expensive but less effective. TDF →TAF therapy is extendedly dominated by ETV→TDF therapy and ETV→TAF therapy is extendedly dominated by TAF→ETV therapy. TDF monotherapy, TDF→ETV therapy,

ETV→TDF therapy and TAF→ETV therapy lie on the cost-effectiveness frontier line and are not dominated by other strategies.

The lifetime costs for the TDF→ETV therapy are 48,084 USD, and gains 9.18 QALYs. The ICERs of TDF→ETV therapy is 14,197 USD/QALY which is below the WTP threshold of 30,426 USD/QALY. The ICERs of ETV→TDF therapy and TAF→ETV therapy are 50,718 USD/QALY and 62,907 USD/QALY respectively, which are beyond the WTP threshold. Among the eight treatment strategies, TDF→ETV therapy has the highest NMB of 231,152 USD. Based on the results of the deterministic analysis, TAF-basing therapies are not cost-effective, and TDF→ETV therapy is likely to be the most cost-effective treatment strategy for HBeAg positive CHB patients in China at the WTP thresholds of 30,426 USD/QALY.

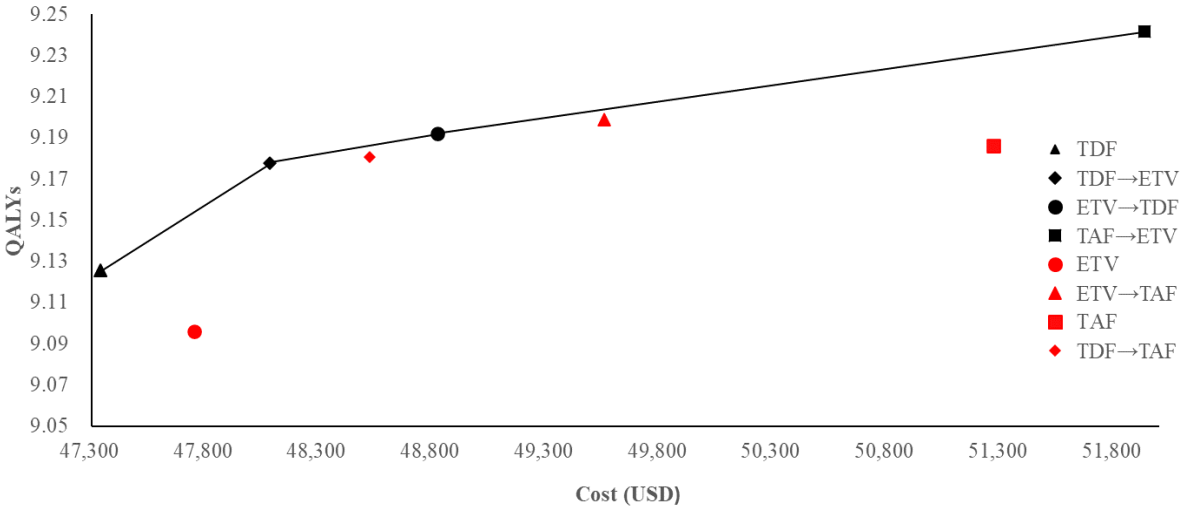


**Figure 2** Cost effectiveness of different treatment strategies for HBeAg positive CHB patients. The *x-axis* reoresrnts the lifetime costs (USD) and the *y-axis* represents the lifetime quality-adjusted life-years (QALYs). *Straight line* represents the cost-effectiveness frontier. *ETV* entecavir, *TDF* tenofovir disoproxil fumarate, *TAF* tenofovir alafenamide

## 5.2 One-Way Deterministic Sensitivity Analysis

A one-way deterministic sensitivity analysis for TDF→ETV therapy was conducted by varying each parameter over the range of values given in Section 4.3, and then to see whether there was a substantial impact on the result. The ten most important parameters are shown in tornado diagram in Figure 3.

The utility in virologic response state is the most influential parameter, and the other parameters have little impact. Higher utility in virologic response state yields higher NMB. In addition, none of these parameters changes the conclusion that TDF→ETV therapy is the most cost-effective treatment strategy, except for HBeAg seroconversion and virologic response rates of TDF and ETV. Because these rates represent the efficacy of drug, changing the rates may alter the conclusion. If HBeAg seroconversion rate of ETV is raised to 0.0997 and above or virologic response rate is raised to 0.6798 and above, ETV→TDF therapy would like to be the most cost-effective treatment strategy. On the contrary, if HBeAg seroconversion rate of ETV is decreased to 0.0689 and below or virologic response rate is decreased to 0.6519 and below, ETV→TDF therapy would like to be the most cost-effective treatment strategy.

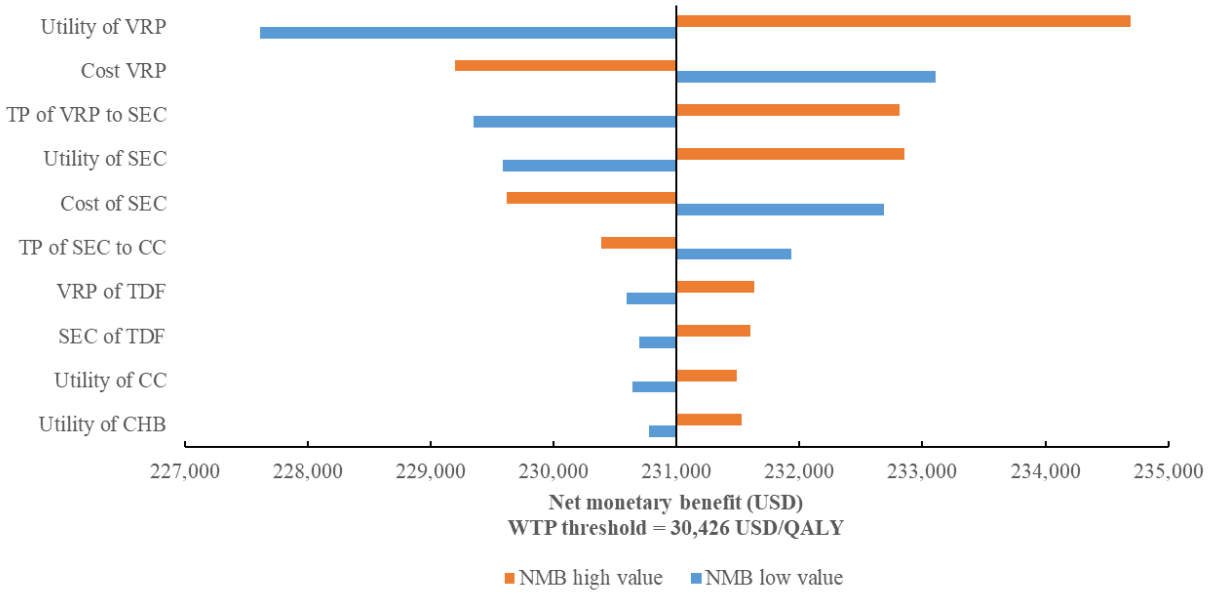


**Figure 3** Tornado diagram of the ten most important parameters influence TDF→ETV therapy. *VRP* virologic response, *SEC* HBeAg seroconversion, *CC* compensate cirrhosis, *CHB* chronic hepatitis B, *TP* transition probability

## 5.3 Scenario Analysis

In order to analyze the impact of drug types, the market share of generic drugs was switched to 0 and 1 respectively, and the results are shown in Table 11 and Table 12. When the branded drugs are adopted by all patients, TDF→TAF therapy becomes the optimal treatment strategy. This is because the price of branded TAF is lower than branded ETV. In the monotherapy

subgroup, TDF monotherapy is still the most cost-effective treatment strategy at the WTP threshold of 30,426 USD/QALY. However, when the generic drugs are adopted by all patients, ETV→TDF therapy becomes the optimal treatment strategy. In the monotherapy subgroup, ETV monotherapy also becomes the most cost-effective treatment strategy at the WTP threshold of 30,426 USD/QALY. This is because the price of generic ETV is much lower than other drugs. Moreover, in both scenarios, the response-guided therapy of each drug is always better than its monotherapy. TAF-basing therapy is not cost-effective.

**Table 11** Base-case cost-effectiveness results of treatmet strategies using branded drugs

| Treatment strategy | Costs (USD) | Δcosts (USD) | QALYs | ΔQALYs | ICERs (USD/QALY) | NMB |
|---|---|---|---|---|---|---|
| TDF | 48,076 | | 9.13 | | | 229,567 |
| TDF→TAF | 49,258 | 1,182 | 9.18 | 0.06 | 21,408 | 230,065 |
| TDF→ETV | 49,273 | 15 | 9.18 | -0.003 | Abs dominated | 229,964 |
| TAF | 51,268 | 2,010 | 9.19 | 0.01 | Ext dominated | 228,227 |
| ETV | 51,764 | 496 | 9.10 | -0.09 | Abs dominated | 224,988 |
| TAF→ETV | 52,276 | 3,018 | 9.24 | 0.06 | 49,366.68 | 228,907 |
| ETV→TDF | 52,944 | 668 | 9.19 | -0.05 | Abs dominated | 226,735 |
| ETV→TAF | 53,568 | 1,292 | 9.20 | -0.04 | Abs dominated | 226,309 |

*ETV* entecavir, *TDF* tenofovir disoproxil fumarate, *TAF* tenofovir alafenamide, *QALYs* quality-adjusted life-years, *ICER* incremental cost-effectiveness ratio, *NMB* net monetary benefit, *Abs dominated* absolutely dominated, *Ext dominated* extendedly dominated

**Table 12** Base-case cost-effectiveness results of treatmet strategies using generic drugs

| Treatment strategy | Costs (USD) | Δcosts (USD) | QALYs | ΔQALYs | ICERs (USD/QALY) | NMB |
|---|---|---|---|---|---|---|
| ETV | 46,033 | | 9.10 | | | 230,719 |
| TDF | 47,026 | 993 | 9.13 | 0.03 | Ext dominated | 230,618 |
| ETV→TDF | 47,054 | 1,021 | 9.19 | 0.10 | 10,619 | 232,624 |
| TDF→ETV | 47,575 | 520 | 9.18 | -0.01 | Abs dominated | 231,662 |
| ETV→TAF | 47,837 | 783 | 9.20 | 0.01 | Ext dominated | 232,040 |
| TDF→TAF | 48,208 | 371 | 9.18 | -0.02 | Abs dominated | 231,116 |
| TAF | 51,268 | 3,431 | 9.19 | -0.01 | Abs dominated | 228,227 |
| TAF→ETV | 51,785 | 4,731 | 9.24 | 0.05 | 95,652 | 229,398 |

*ETV* entecavir, *TDF* tenofovir disoproxil fumarate, *TAF* tenofovir alafenamide, *QALYs* quality-adjusted life-years, *ICER* incremental cost-effectiveness ratio, *NMB* net monetary benefit, *Abs dominated* absolutely dominated, *Ext dominated* extendedly dominated

In order to analyze the impact of the treatment duration, an infinite therapy was assumed for the CHB patient, irrespective of the occurrence of HBeAg seroconversion. Patients continue the treatment have lower risk of CHB relapse (Reijnders et al., 2010). The transition probabilities from HBeAg seroconversion to CHB, CC and HCC with infinite treatment therapy were assumed to be 50% less than that with finite treatment therapy. The results are shown in Table 13. It indicates that regardless whether the treatment is finite or infinite, TDF →ETV therapy is always the most cost-effectiveness treatment strategy. Moreover, in the monotherapy subgroup, TDF monotherapy is still the most cost-effective treatment strategy at the WTP threshold of 30,426 USD/QALY. the response-guided therapy of each drug is always better than its monotherapy. TAF-basing therapy is not cost-effective.

**Table 13** Base-case cost-effectiveness results of infinit treatmet strategies

| Treatment strategy | Costs (USD) | Δcosts (USD) | QALYs | ΔQALYs | ICERs (USD/QALY) | NMB |
|---|---|---|---|---|---|---|
| TDF | 49,016 | | 9.15 | | | 229,235 |
| ETV | 49,694 | 678 | 9.12 | -0.03 | Abs dominated | 227,695 |
| TDF→ETV | 49,940 | 924 | 9.20 | 0.05 | 18,112 | 229,864 |
| TDF→TAF | 50,496 | 556 | 9.20 | 0.00 | Ext dominated | 229,394 |
| ETV→TDF | 50,973 | 1,034 | 9.21 | 0.01 | 69,202 | 229,284 |
| ETV→TAF | 51,924 | 950 | 9.22 | 0.01 | Ext dominated | 228,532 |
| TAF | 54,942 | 3,018 | 9.21 | -0.01 | Abs dominated | 225,195 |
| TAF→ETV | 55,742 | 4,768 | 9.26 | 0.05 | 94,686 | 226,048 |

*ETV* entecavir, *TDF* tenofovir disoproxil fumarate, *TAF* tenofovir alafenamide, *QALYs* quality-adjusted life-years, *ICER* incremental cost-effectiveness ratio, *NMB* net monetary benefit, *Abs dominated* absolutely dominated, *Ext dominated* extendedly dominated

## 5.4 Probabilistic Sensitivity Analysis

The uncertainty of the cost-effectiveness results across a range of WTP thresholds are presented on the CEAC in Figure 4 and CEAF in Figure 5. The CEAC shows that TDF→ETV therapy has 36.00% probability to be the most cost-effectiveness treatment strategy at the WTP threshold of 30,426 USD/QALY. The probabilities of ETV→TDF therapy, TAF→ETV therapy, TDF monotherapy and ETV monotherapy are 32.60%, 11.70%, 9.70% and 6.90% respectively. The probabilities of TAF monotherapy, ETV→TAF strategy and TDF→TAF strategy are

negligibly low. Therefore, TDF→ETV therapy has the highest probability to be the most cost-effectiveness treatment strategy for HBeAg positive patients in China. However, when the WTP threshold increases to 62,000 USD/QALY, TAF→ETV therapy becomes the most cost-effectiveness treatment strategy. The CEAF also indicates the same consequence.

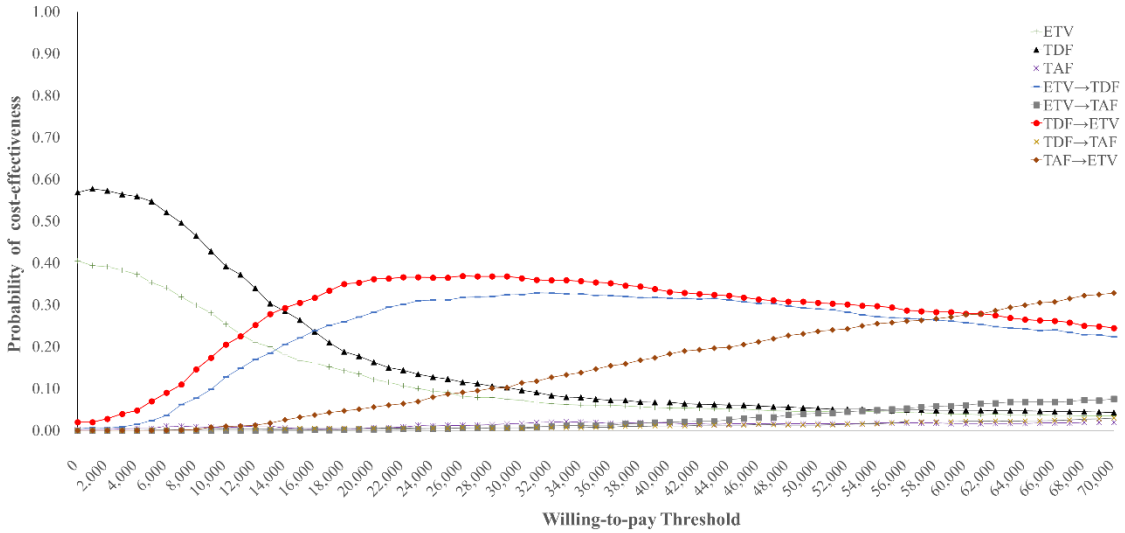


**Figure 4** Cost-effectiveness acceptability curves of different treatment strategies**.** The y-axis represents the probability the strategy is cost-effectiveness. The x-axis represents the WTP threshold. *ETV* entecavir, *TDF* tenofovir disoproxil fumarate, *TAF* tenofovir alafenamide

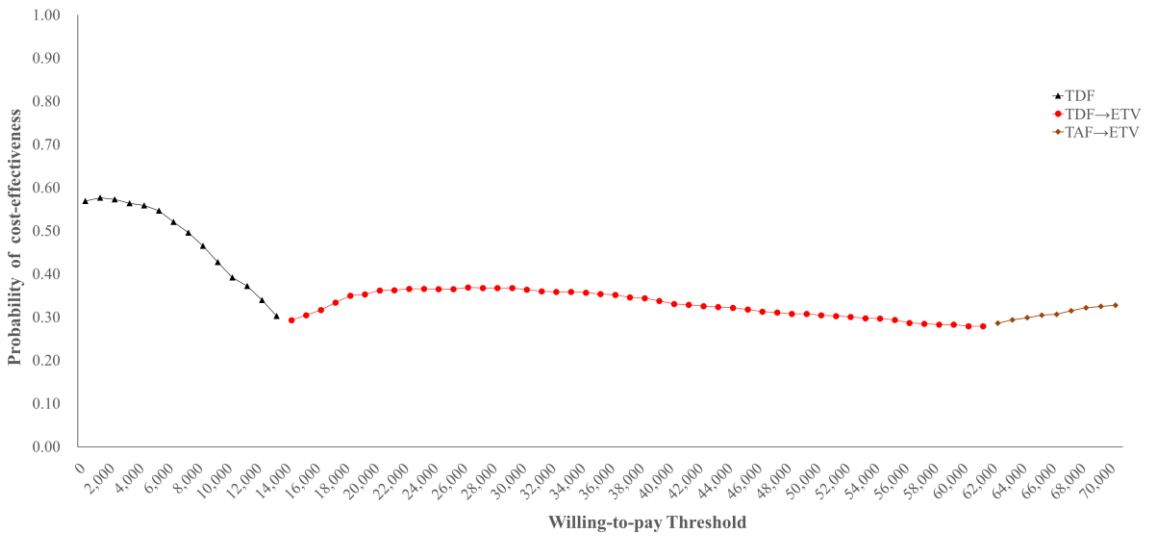


**Figure 5** Cost-effectiveness acceptability frontier for HBeAg positive CHB patients**.** The y-axis represents the probability the strategy is cost-effectiveness. The x-axis represents the WTP threshold. *ETV* entecavir, *TDF* tenofovir disoproxil fumarate, *TAF* tenofovir alafenamide

Scatter plots were applied to compare TDF→ETV therapy with TDF monotherapy, ETV→TDF therapy and TAF→ETV therapy because they dominated other treatment strategies. Results are shown in Figure 6.

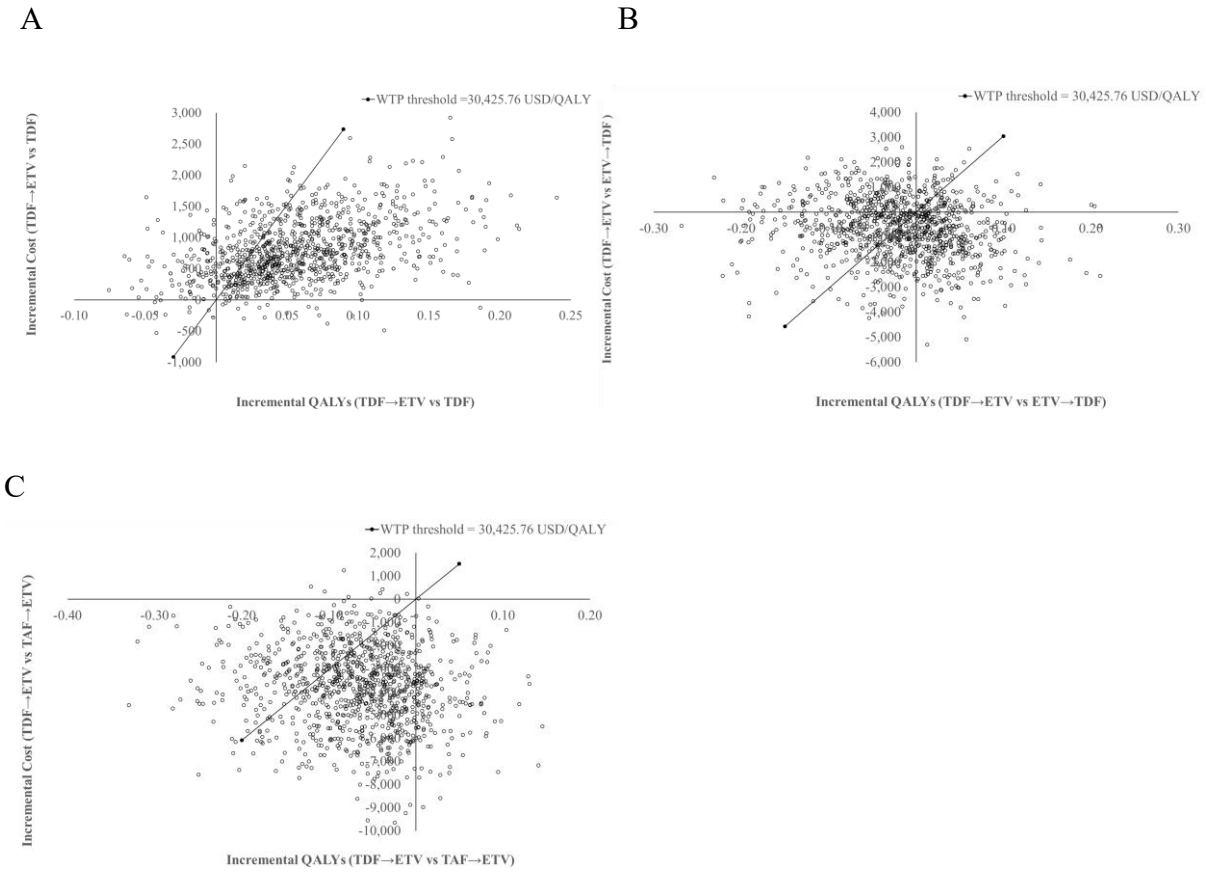


**Figure 6** Probabilistic results of incremental cost-effectiveness comparison between treatment strategies. TDF→ETV therapy with TDF monotherapy (A), TDF→ETV therapy with ETV→TDF therapy (B), TDF→ETV therapy with TAF→ETV therapy (C), The y-axis represents the incremental costs. The y-axis represents the incremental quality-adjusted life years (QALYs). Dots below the straight line reflect the simulations where ICERs with TDF→ETV strategy or TAF monotherapy are less than the Chinese WTP threshold.

In the cost-effectiveness plane A, most of the ICERs land in the north-east quadrant, illustrating that TDF→ETV strategy is more costly and also gains more QALYs compared with TDF monotherapy. TDF→ETV therapy dominates TDF monotherapy in 77.70% simulations. In the cost-effectiveness plane B, ICERs scatter in the four quadrants, TDF→ETV strategy dominates ETV→TDF therapy in 52.5% simulations. In the cost-effectiveness plane C, most of the ICERs land in the south-west quadrant, illustrating that TDF→ETV strategy is less costly and also

gains less QALYs compared with TAF→ETV therapy. TDF→ETV therapy dominates TAF→ETV strategy in 74.10% simulations.

## 5.5 The Expected Value of Perfect Information

The EVPI curve in Figure 7 shows The EVPI value steadily increases to infinity from the WTP threshold value of 0 to 70,000 USD/QALY. When the WTP threshold is 30,426 USD/QALY, the EVPI is 1,295 USD. As the CEAF curve shows when the WTP threshold increases from 0 to 15,000 USD/QALY, the probability of the optimal treatment strategy decreases from 60% to 30%, which means the probability of acquiring an opportunity loss (or making a wrong decision) increases, so the EVPI curve increases. Then the probability of the optimal treatment strategy stands around 30%, which means the probability of acquiring an opportunity loss does not change greatly. But the magnitude of the opportunity loss augments as the WTP threshold increases. Thus, the EVPI keeps increasing from the WTP threshold of 0 to 15,000 USD/QALY. As a result, the EVPI is consistent with the CEAF.

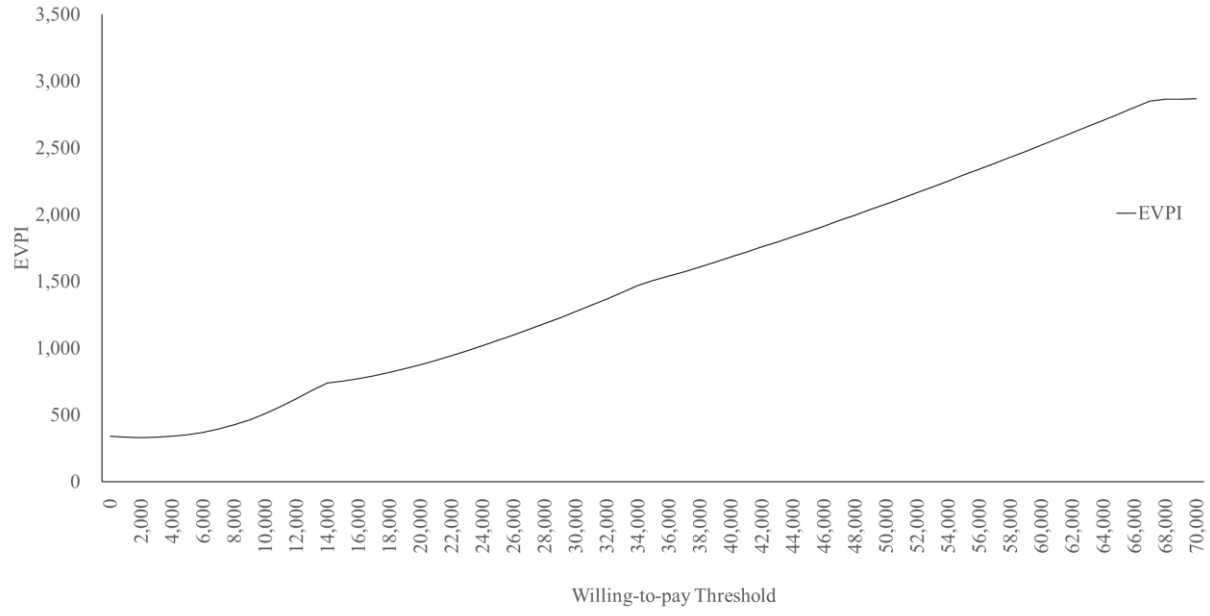


**Figure 7** The expected value of perfect information of the comparison of treatment strategies

The EVPI for population is shown in Figure 8. The lifetime of NAs was assumed to be 10 years in this study. Currently, there are 5% of the population in China are HBsAg positive, and 20%

of those are HBeAg positive (Liu et al., 2019). According to the National Bureau of Statistics, there are estimated 28 million 34-year old people, so the effective population over 10-lifetime of NAs is 2,270,190 people. When the WTP threshold is 30,426 USD/QALY, the EVPI for population is 2,938,811,550 USD. It means further research would be potentially cost-effective if the cost for the further research is less than 2,938,811,5450 USD.

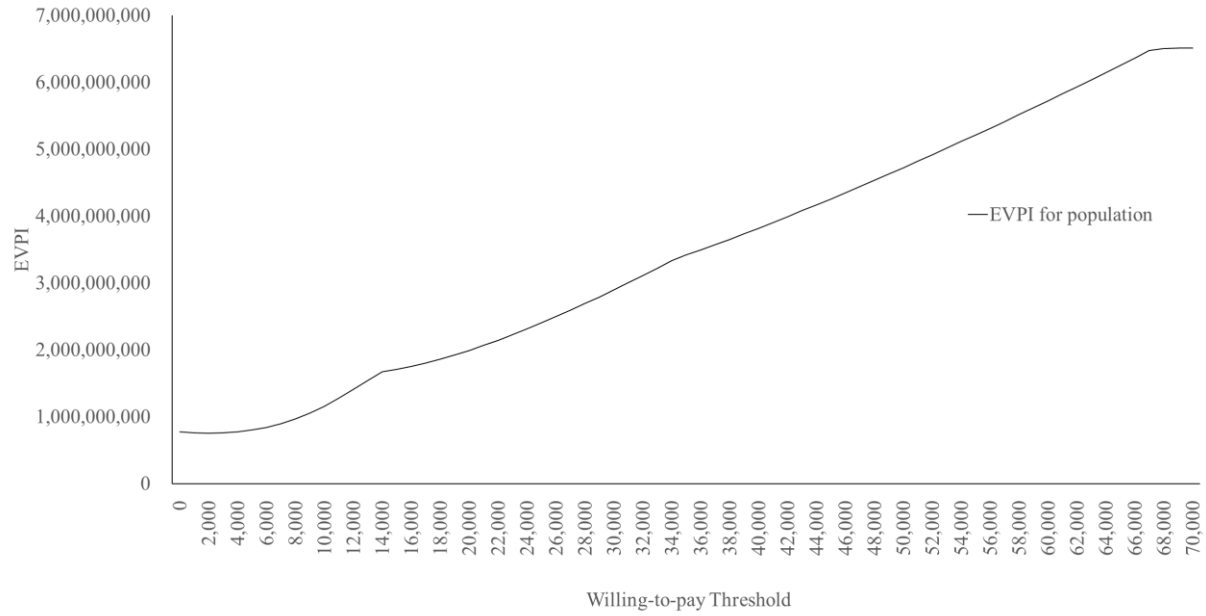


**Figure 8** The expected value of perfect information for population of the comparison of treatment strategies

# Chapter 6 Discussion

The study evaluated the cost-effectiveness of eight treatment strategies for HBeAg positive CHB patients in China. It is the first cost-effectiveness analysis of NAs including TAF for HBeAg positive CHB patients from the Chinese healthcare perspective. The study can help decision makers by providing the economic and health outcomes evidence with regard to treatments of CHB in China. The results of the cost-effectiveness analysis yielded three main findings.

First, TAF-basing strategies are more effective with higher QALYs, but are also more costly than other strategies. Thus, TAF-basing strategies are not cost-effective at the current prices. TDF→ETV therapy is likely to be the most cost-effective treatment strategy at the WTP threshold of 30,426 USD/QALY for HBeAg positive CHB patients in China. When only monotherapies were considered, ETV monotherapy is dominated by TDF monotherapy, and the ICER of TAF monotherapy is beyond the WTP threshold, thus TDF is the most cost-effective treatment strategy. In addition, because of the optimized resistance and SAEs rates, the response-guided therapy is always more effective compared with its monotherapy.

In a conclusion, TDF has price advantage when compared with TAF, and has efficacy advantage when compared with ETV. TDF is the optimal choice among the three low-resistance NAs drugs for HBeAg-positive CHB patients in China. This conclusion is consistent with the trend that though ETV is still the main drugs used for CHB treatment, the proportion of TDF is increasing rapidly in recent years (Feng et al., 2019).

The sensitivity analysis indicates that there existed high uncertainty in the efficacy data, which could alter the conclusion. The CEAC also indicates that TDF→ETV therapy is the optimal treatment strategy with the highest probability of 36.00%. However, ETV→TDF therapy also has 32.60% probability to be the best option at the WTP threshold of 30,426 USD/QALY. The uncertainty in the efficacy data might be due to the short-term follow-up of the clinical trials. Moreover, when the WTP threshold is increased to 62,000 USD/QALY, TAF→ETV is likely to be the optimal treatment strategy. When the WTP threshold dropped to 14,000 USD/QALY

or below, TDF monotherapy is optimal choice. Moreover, the EVPI also suggests that further information would be useful to reduce the decision uncertainty if the expected cost of further research is less than 1,295 USD per individual.

Second, the choice of branded drug or generic drug may affect the conclusion but TAF-basing therapies are not cost-effective under branded drug price or generic drug price. TDF→TAF therapy becomes the optimal treatment strategy under the branded drug price. However, under the generic drug price, ETV→TDF became the optimal one. This is because branded ETV is expensive than branded TAF and TDF, the annual costs of branded ETV is 989 which is nearly 1.7 times of the annual costs of branded TDF. Still, the generic ETV is cheaper than generic TDF, the annual costs of generic ETV is 379 which is 80% of the annual costs of generic TDF. The price differences under the three drug types lead to the different conclusion.

Third, according to the scenario analysis, when the patient continues the treatment even after HBeAg seroconversion occur, TAF-basing therapies are still not cost-effective and TDF→ETV therapy remains the most cost-effective option for HBeAg positive CHB patients. It means the treatment duration might not affect the conclusion. The infinite therapy yields higher QALYs and also higher costs when compare with its finite therapy, and the ICERs are far beyond the WTP threshold. Thus, infinite therapy is not cost-effective.

Results in this study were compared with other studies to check validity of the model. The previews studies of cost-effectiveness of NAs for Chinese CHB patients from Zhang et al (2015), Toy, Hutton and So (2015) and Lai et al (2016) indicated that ETV monotherapy was the best choice when compared with other NAs therapy or INF. However, this study concludes that TDF→ETV therapy is the most cost-effective treatment strategy. The different conclusions are mainly due to the changes in variety of drugs and drug costs.

Zhang et al (2015) only included ETV and other high-resistance NAs, thus outcomes of TDF and TAF cannot be reflected. Toy, Hutton and So (2015) and Lai et al (2016) included ETV, TDF and other high-resistance. Toy, Hutton and So (2015) used the drug price in 2014 and Lai et al (2016) used the drug price in 2015. At that time, the price of branded TDF was 1.6 times

of the branded ETV and even 2.2 times of the generic ETV, but the efficacy of ETV was not too much lower than TDF, so, there was no doubt that ETV was more preferred. However, after the generic TDF was approved, and the prices of NAs drugs decreased, the price gap between TDF and ETV became smaller. In this study, the annual costs of generic TDF is only 1.2 times of the generic ETV, and the annual branded TDF was even lower than ETV. Thus, the TDF took the place of ETV became the optimal choice for Chinese CHB patients.

Some similar cost-effectiveness analysis about NAs have been conducted in other countries. A study from Canada also indicated that TDF→ETV therapy was likely to be the most cost-effective strategy for HBeAg positive CHB patients (Tian et al., 2020). But a study from the US had a different result and it indicated that TAF was the most cost-effective strategy. It is reasonable that different countries have different results, because the parameters (such as costs, utilities and WTP threshold) are different, especially the costs and the WTP threshold. Countries with high WTP for an additional QALY may prefer TAF to be the first choice for CHB treatment.

This study is the first cost-effectiveness analysis of NAs for Chinese CHB patients, which included TAF treatment strategy. Moreover, the impact of the treatment-related SAEs on the utility were also considered in this study. In addition, the latest costs for NAs were used in this study to reflect the present values, and the branded and generic drugs were both taken into account in this study. However, there are several limitations.

First, though the treatment-related transition probabilities used in this study were based on the Chinese population, the health state transition probabilities were obtained from literature using cohorts from different countries, and it may not accurately reflect the situation in China. Second, the treatment-related transition probabilities were based on the information for one year. This many have overestimated the efficacy of the drugs or underestimated the resistance in the subsequent years. The long-term results gathered over 2-5 years follow-up may be closer to real practice. Moreover, HBV DNA was assumed to be tested by HP, and the lower limit of quantitation is 29 IU/mL. Different test methods have different lower limit which may affect the efficacy data. If a test with the lower limit of quantitation is less than 29 IU/mL (e.g. 20

IU/mL) is used for analysis, the virologic response rates may become higher. In addition, the initial treatment-related transition probabilities of ETV was based on CAP/CTM with the lower limit of quantitation of 20 IU/mL. The adjusted treatment-related transition probabilities of ETV used in this study may have deviation from the real data.

Third, the hypothetical patients were assumed not have coinfection with HIV. Actually, the prevalence of HIV-HBV co-infection is nearly 10% in China (Singh et al., 2017). Patients who are co-infected with HIV and HBV face an increased risk for liver-related morbidity and mortality. Moreover, the hypothetical patients were assumed not have evidence of cirrhosis, HCC and also have no experience with liver transplantation. In practice, many patients start the antiviral treatment when they have symptoms of cirrhosis or HCC. In this case, the transition probability between health states may be different. A study from Xie et al. (2018) indicates that the annual transition probability from compensated cirrhosis to HCC after resection in HBV-related HCC patients is 15%. It is much higher than the transition probability for CHB patients without experience of resection used in this study. The different probability may affact the results.

Fourth, in order to simplify the analysis, patients who switched to the second drug were assumed to have no resistance or SAEs. This assumption may underestimate the resistance or SAEs rate of the drugs. Fifth, the health state costs used in this study were obtained from a study in 2010 and inflated all cost to 2019 price, but the inflated costs may not same as the actual costs. Sixth, the model only considered the low-resistance drugs, which may not reflect the actual situation in China. Though the low-resistance drugs are the first-line drugs recommended by the guideline, the high-resistance drugs and INF are still prescribed in some areas because of the lower costs (Feng et al., 2019). The annual costs for branded ADV are 553 USD and the annual costs for generic ADV are even lower, only about 200 USD. Moreover, the WTP threshold was set to be three time of the GDP in 2019, but this threshold may not be suitable for all areas in China, because the economic development is unbalanced. Areas with a relatively high economic level may have a higher WTP threshold, and low economic level may have a lower WTP threshold.

Furthermore, this study only focused on the HBeAg positive CHB patients, but there are still lots of HBeAg negative CHB patients also need treatment, thus additional research could be focused on the cost-effectiveness of NAs for HBeAg negative CHB patients. Moreover, compared with TDF, TAF is safer and has less kidney injury (Chan et al., 2016). It is recommended to investigate cost-effectiveness of CHB patient sub-groups with kidney disease.

# Chapter 7 Conclusion

In conclusion, the results from the study shows TAF-basing therapies are not the optimal choices. Though TAF has higher benefits, this does not outweigh the differences in costs. Thus, TDF→ETV therapy appears to be the most cost-effective antiviral treatment strategy for HBeAg positive CHB patients in China with the current drug price. This conclusion is corresponding with the recommendation of the guideline. However, currently, ETV is the mainly used low-resistance drug for CHB patients in China. According to the result of the study, the government may consider improving the procurement volume of TDF instead of ETV. The better efficacy of TDF can contribute to reduce the incidence of cirrhosis, HCC and mortality caused by HBV infection and reach the goal of eliminating hepatitis B by 2030.

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# Appendix

**Appendix 1** The transition probability adjustment process of ETV

| Outcomes | TDF | | | ETV | |
|---|---|---|---|---|---|
| | (20 IU/mL) N=157 A | (29 IU/mL) N=108 B | C= A/B | (20 IU/mL) N=158 D | (29 IU/mL) N=158 E =D/C |
| VRP | 0.8065 | 0.7037 | 1.15 | 0.7190 | **0.6266** |
| VRT | 0 | 0 | | | **0.0063*** |
| SEC | 0.1226 | 0.0741 | 1.65 | 0.1569 | **0.0949** |

*The annual resistant probability was calculated from the five-year accumulated resistance rate

*VRP* virologic response, *VRT* virologic resistance, *SEC* HBeAg seroconversion, *TDF* tenofovir disoproxil fumarate, *TAF* tenofovir alafenamide

**Appendix 2** Consumer price index and average exchange rate in China

| Year | Consumer price index (last year = 100) | Year | Consumer price index (last year = 100) |
|---|---|---|---|
| 2010 | 103.3 | 2015 | 101.4 |
| 2011 | 105.4 | 2016 | 102.0 |
| 2012 | 102.6 | 2017 | 101.6 |
| 2013 | 102.6 | 2018 | 102.1 |
| 2014 | 102.0 | 2019 | 102.9 |
| Average exchange rate in 2019 | | USD/CNY = 6.99 | |

**Appendix 3** Detailed annual health states costs (USD, year 2019 value) related to CHB

| Health states | Outpatient frequency | Inpatient frequency | Inpatient length of stay | Outpatient costs | Inpatient cost | Total cost |
|---|---|---|---|---|---|---|
| CHB | 3.12 | 1.24 | 30.6 | 145 | 2,424 | 2,569 |
| CC | 4.65 | 1.70 | 33.2 | 518 | 4,042 | 4,560 |
| DC | 4.52 | 1.87 | 27.1 | 480 | 5,521 | 6,002 |
| HCC | 4.16 | 1.87 | 22.9 | 735 | 7,418 | 8,153 |
| LT | 7.33 | 3.25 | 46.4 | 5,487 | 37,011 | 42,498 |
| CLN | 2.57 | / | 9.3 | 104 | 1,373 | 1,476 |

*CHB* chronic hepatitis B, *CC* compensated cirrhosis, *DC* decompensated cirrhosis, *HCC* hepatocellular carcinoma, *LT* liver transplantation, *CLN* HBsAg clearance

**Appendix 4** Detailed annual inpatient cost costs (USD, year 2019 value) related to CHB

| Health states | Bedding | Nursing | Drug | examination and laboratory test | Treatment | Other | Total |
|---|---|---|---|---|---|---|---|
| CHB | 166 | 60 | 1,484 | 439 | 175 | 99 | 2,424 |
| CC | 223 | 87 | 2,555 | 648 | 278 | 251 | 4,042 |
| DC | 244 | 104 | 3,498 | 834 | 464 | 376 | 5,521 |
| HCC | 244 | 100 | 4,458 | 1,021 | 1,022 | 574 | 7,418 |
| LT | 960 | 384 | 14,540 | 5,510 | 3,208 | 12,409 | 37,010 |