# COST-UTILITY ANALYSIS OF DRUG TREATMENTS IN PATIENTS WITH HBeAg POSITIVE CHRONIC HEPATITIS B (CHB)

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COST-UTILITY ANALYSIS OF DRUG TREATMENTS IN PATIENTS WITH HBeAg POSITIVE CHRONIC HEPATITIS B (CHB)

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ABSTRACT

The objectives of this study were to estimate the cost-utility of each drug treatment compared with palliative care in patients with HBeAg positive chronic hepatitis B (CHB) and to estimate the governmental budget impact when included in the National List of Essential Drugs (NLED) using an economic evaluation model. Cost-utility analysis was used to compare the medications in the treatments of HBeAg positive CHB patients. A Markov model was used to estimate the relevant costs and health outcomes during a lifetime horizon based on a societal perspective. Direct medical costs, direct non-medical costs and indirect costs were included, and health outcomes were life years (LY) and quality adjusted life years (QALYs). The results were presented as the incremental cost effectiveness ratio (ICER) in Thai baht (THB) per LY or QALY gained. One-way sensitivity and probabilistic sensitivity analyses were applied to investigate the effect of model variable uncertainties.

The results of this study suggested that providing generic lamivudine plus adding tenofovir when drug resistance occurred (ICER = -14,000 THB/QALY gained), generic lamivudine plus adding tenofovir based on the road map guideline (ICER = -8,000 THB/QALY gained) and tenofovir monotherapy (ICER = -5,000 THB/QALY gained) were dominant and cost-saving options compared to palliative care. Providing generic lamivudine plus adding tenofovir when drug resistance occurs could save healthcare costs of approximately 70,000 THB per patient, since the cost of serious complications could be avoided in the future. Moreover, CHB treatment could also prolong patients' overall survival by about 18 years. The governmental budget impact demonstrated that providing HBeAg positive CHB patients with generic lamivudine plus tenofovir when drug resistance occurs, or providing tenofovir monotherapy, could reduce the overall budget from the fifth or seventh fiscal year onwards, respectively. However, in the long run the budget costs for lamivudine and tenofovir would decrease, whereas that for palliative care would increase.

KEY WORDS: HEALTH TECHNOLOGY ASSESSMENT / ECONOMIC EVALUATION / CHRONIC HEPATITIS B / HEALTH ECONOMIC/ DRUG TREATMENT

115 pages

การประเมินต้นทุนอรรถประโยชน์ของการรักษาโรคไวรัสตับอักเสบบีชนิดเรื้อรังชนิดอีแอนติเจนบวก
COST-UTILITY ANALYSIS OF DRUG TREATMENTS IN PATIENTS WITH HBeAg POSITIVE CHRONIC HEPATITIS B (CHB)

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บทคัดย่อ

วัตถุประสงค์ของการศึกษานี้ เพื่อประเมินต้นทุนอรรถประโยชน์เปรียบเทียบระหว่างทางเลือกต่างๆ ในการรักษาด้วยยากับการรักษาแบบประคับประคองในผู้ป่วยโรคไวรัสตับอักเสบบีชนิดเรื้อรังที่มีอีแอนติเจนเป็นบวกและประเมินผลกระทบทางด้านงบประมาณ หากมีการบรรจุทางเลือกที่มีความคุ้มค่ามากที่สุดลงในชุดสิทธิประโยชน์ของหลักประกันสุขภาพถ้วนหน้าโดยใช้แบบจำลองทางเศรษฐศาสตร์ การวิเคราะห์ด้วยวิธีต้นทุนอรรถประโยชน์ถูกนำมาใช้เปรียบเทียบยาในการรักษาผู้ป่วยโรคไวรัสตับอักเสบบีชนิดเรื้อรังที่มีอีแอนติเจนเป็นบวก แบบจำลองมาร์คอฟถูกนำมาใช้ในการวิเคราะห์ต้นทุนและผลลัพธ์ของการรักษาที่เกิดขึ้นตลอดชีวิตใช้มุมมองของสังคมและมุมมองของรัฐบาลต้นทุนที่ศึกษาเป็นต้นทุนทางตรงทางการแพทย์ ต้นทุนทางตรงที่ไม่เกี่ยวกับทางการแพทย์และต้นทุนทางอ้อม ผลลัพธ์ทางสุขภาพคือปีชีวิตและปีสุขภาวะของผู้ป่วย ผลการศึกษานำเสนอในอัตราส่วนต้นทุนประสิทธิผลส่วนเพิ่ม การประเมินผลกระทบของความไม่แน่นอนของตัวแปรที่ใช้ในแบบจำลองโดยวิธีการวิเคราะห์ความไวแบบทีละตัวแปรและแบบความน่าจะเป็น

ผลการศึกษาเสนอแนะว่า การรักษาด้วยยา lamivudine เป็นทางเลือกแรกและใช้ tenofovir สำหรับผู้ป่วยที่มีเชื้อไวรัสดื้อยา (อัตราส่วนต้นทุนประสิทธิผล = -14,000 บาท/ปีสุขภาวะที่เพิ่มขึ้น) หรือใช้ตามแนวทางการรักษาแบบ road map (อัตราส่วนต้นทุนประสิทธิผล= -8,000 บาท/ปีสุขภาวะที่เพิ่มขึ้น) และการรักษาด้วย tenofovir (อัตราส่วนต้นทุนประสิทธิผล = -5,000 บาท/ปีสุขภาวะที่เพิ่มขึ้น) เป็นทางเลือกแรกสามารถประหยัดค่าใช้จ่ายได้เมื่อเทียบกับการรักษาแบบประคับประคอง นอกจากนี้ การรักษาด้วยยา lamivudine เป็นทางเลือกแรกและใช้ tenofovir สำหรับผู้ป่วยที่มีเชื้อไวรัสดื้อยาจะประหยัดต้นทุนประมาณ 70,000 บาทต่อผู้ป่วยหนึ่งรายจากการประหยัดค่ารักษาภาวะแทรกซ้อนในอนาคต นอกจากนี้ยังทำให้ผู้ป่วยมีอายุยืนยาวขึ้นประมาณ 18 ปี ซึ่งผลกระทบด้านงบประมาณของรัฐบาลของการใช้ยา lamividine และ tenofovir จะสามารถลดค่าใช้จ่ายโดยรวมได้ตั้งแต่ปีที่ 5 และปีที่ 7 ตามลำดับ อย่างไรก็ตามในระยะยาวงบประมาณสำหรับการรักษาด้วยยา lamividine และ tenofovir จะลดลง ในขณะที่งบประมาณสำหรับการรักษาแบบประคับประคองจะเพิ่มสูงขึ้น

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# LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| ADV | = | Adefovir |
| ALT | = | Alanine aminotransferase |
| Anti-HBe | = | Anti-hepatitis Be antibody |
| Anti-HBs | = | Anti-hepatitis Bs antibody |
| AST | = | Aspatate aminotransferase |
| CBA | = | Cost-benefit analysis |
| CBC | = | Complete blood count |
| CEA | = | Cost-effectiveness analysis |
| CHB | = | Chronic hepatitis B |
| CHC | = | Chronic hepatitis C |
| CI | = | Credible interval |
| CMA | = | Cost-minimization analysis |
| CPI | = | Consumer price index |
| CSMBS | = | Civil Servant Medical Benefit Scheme |
| CUA | = | Cost-utility analysis |
| ETV | = | Entecavir |
| FDA | = | Food and Drug Administration |
| GDP | = | Gross Domestic Product |
| HAI | = | Histological activity index |
| HBeAg | = | Hepatitis B e antigen |
| HBsAg | = | Hepatitis B surface antigen |
| HBV | = | Hepatitis B virus |
| HBV DNA | = | Hepatitis B virus deoxyribonucleic acid |
| HCC | = | Hepatocellular carcinoma |

# LIST OF ABBREVIATIONS (cont.)

| | | |
|---|---|---|
| HCV Ab | = | Hepatitis C virus antibody |
| HIV Ab | = | HIV antibody |
| HRQOL | = | Health-related quality of life |
| ICER | = | Incremental cost- effectiveness ratio |
| LMV | = | Lamivudine |
| NHSO | = | National Health Security Office |
| NLED | = | National List of Essential Drugs |
| NMB | = | Net monetary benefit |
| PEG | = | Pegylated interferon |
| PPP | = | Purchasing power parity |
| PSA | = | Probabilistic sensitivity analysis |
| PT | = | Prothrombin time |
| PTT | = | Partial thromboplastin |
| QALY | = | Quality adjusted life years |
| QoL | = | Quality of life |
| RCT | = | Randomized controlled trials |
| SA | = | Sensitivity analysis |
| SE | = | Standard error |
| SG | = | Standard gamble |
| SSS | = | Social Security Scheme |
| THB | = | Thai Baht |
| TNV | = | Tenofovir |
| TSH | = | Thyroid stimulating hormone |
| TTO | = | Time trade-off |
| TVD | = | Telbivudine |
| UC | = | Universal Coverage Scheme |
| WTP | = | Willingness to pay |

# CHAPTER I
# INTRODUCTION

Hepatitis B is an infectious disease of the liver caused by hepatitis B virus (HBV). It is transmitted through blood to blood contact, sexual contact, or mother to child. Hepatitis B is one of the world's most common and serious infectious diseases. An estimated 350 million people or more than one third of the world's population have been infected with the HBV (1). About 5% of the populations are chronic carriers of HBV, and nearly 25% of all carriers develop serious liver diseases such as chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) causing more than one million deaths every year (1). Chronic liver diseases and HCC associated with HBV infections are one of the most important public health problems in high-prevalence regions (2-3). These diseases can cause an increase in economic burden and decrease in quality of life of patients (2-3). The annual costs per person of compensated cirrhosis decompensated cirrhosis, and HCC are 251,000, 155,000, 172,000 THB, respectively (4).

The prevalence of HBV varies markedly among different regions of the world(5). Especially most Southeast Asian countries including Thailand have been classified as a high prevalence area of HBV. In the past, an estimated 4-5 million people are infected with HBV with the prevalence rate higher than 8% in Thailand (1). Since 1992, the Ministry of Public Health has implemented the nationwide hepatitis B vaccine immunization program for all newborns and provided hepatitis B immune globulin (HBIG) for babies born to carrier mothers (6). Consequently, the prevalence of HBV in Thailand was decreased to 4% (7).

Current HBV infection can be detected by the presence of hepatitis B surface antigen (HBsAg) in the serum. Infected individuals develop an acute infection, which may or may not result in symptoms. In most individuals, infection will resolve and HBsAg disappears from the serum, but the viruses persist in some patients who become chronically infected with hepatitis B. More than 95% of those infected with

HBV during adulthood make a full recovery and acquire immunity from future infection, while less than 5% of infected adults and more than 90% of infected neonates will develop chronic hepatitis B (CHB).

The diagnosis of CHB is based on the presence of HBsAg for 6 months or more after acute infection. Individuals chronically infected with HBV are at increased risk of developing cirrhosis leading to hepatic decompensation and HCC (8-9). Hepatitis B e antigen (HBeAg) is an indicator of viral replication. Active infection can be described as HBeAg positive or negative. HBeAg positive and HBeAg negative are different in terms of the response to treatment and rates of progression. HBeAg negative, the mutant strains of HBV that do not produce e antigen, is associated with a fluctuating course and a poor prognosis. About 31% of patients with HBsAg positive CHB are HBeAg positive CHB (10-11).

Drug treatments for CHB can reduce viral replication to the lowest possible level and maintain it through the long term. The goal of therapy for CHB is to improve quality of life and survival by preventing disease progression to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death. This goal can be achieved if HBV replication can be suppressed in a sustained manner. The accompanying reduction in histological activity of chronic hepatitis can decrease the risk of cirrhosis and HCC in non-cirrhotic patients as well as probably in cirrhotic patients but to a lesser extent (12). Currently six CHB medications including both oral (i.e., lamivudine, adefovir, entecavir and telbivudine) and intravenous (i.e., conventional interferon and pegylated interferon) dosage forms have been licensed by the Thai Food and Drug Administration (FDA). In addition, tenofovir has been approved by Thai FDA for the treatment of HIV, but not for CHB treatment yet. However, tenofovir 300 mg daily has been currently prescribed to CHB patients in clinical practice, since tenofovir has demonstrated high antiviral efficacy and low drug resistance rate for the treatment of CHB (13-14).

At present, only lamivudine has been included in the National List of Essential Drugs (NLED), but not other medications for patients with CHB. The results from economic evaluation in this study could be used as the information for policy decision making in Thailand.

## Conceptual framework

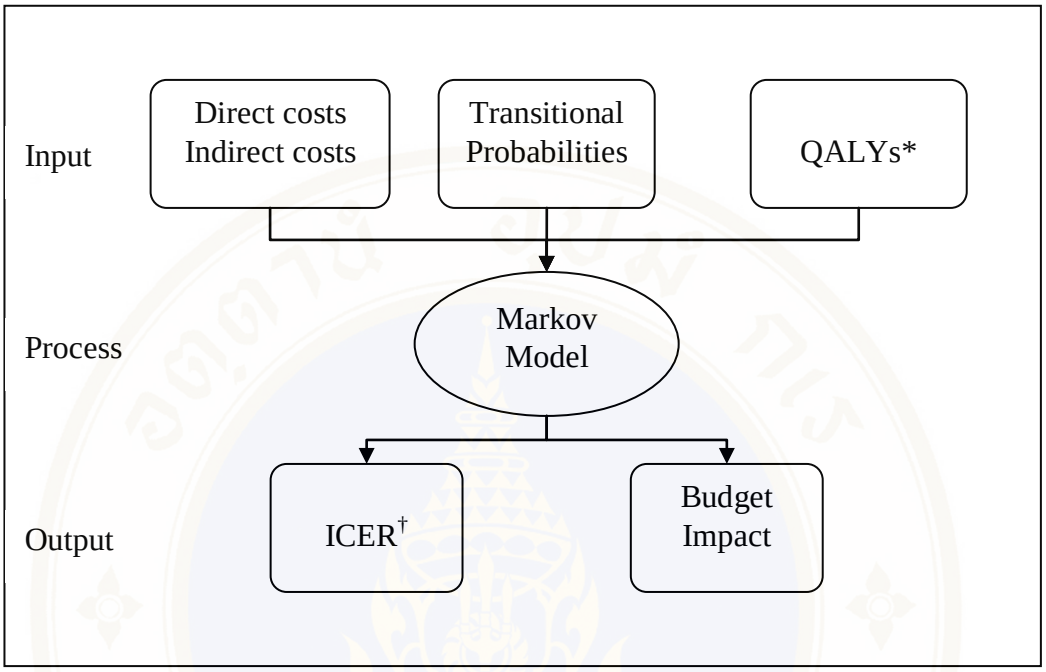



**Figure 1.1: The conceptual framework of the cost-utility and budget impact analysis**

*****QALYs=quality adjusted life years

† ICER=Incremental cost-effectiveness ratio

## Objectives

### General objectives

The objectives of this study were to compare the cost-utility of each drug treatment with palliative care in patients with HBeAg positive CHB and to estimate the governmental budget impact of the most cost-effective treatment when included in the NLED.

### Specific objectives

1. To estimate the costs and utility between drug treatments in patients with HBeAg positive CHB and palliative care.

2. To calculate the incremental cost-effectiveness ratio (ICER) for each compared intervention.

3. To estimate the governmental budget impact.

## Expected outcomes and Benefits

Currently only lamivudine has been included in the National List of Essential Drugs (NLED), but not other medications for patients with CHB. As a result, most CHB patients especially those under the Universal Coverage (UC) which covers a population of 45 million in Thailand still cannot have an access to other CHB medications (15). In fiscal year 2009, the National Health Security Office (NHSO) requested economic evaluation information to consider whether which drugs for HBeAg positive chronic hepatitis B patients should be included in the benefit package of UC scheme. Nevertheless, at present there has been no such data yet. The results from economic evaluation in this study could be used as the information for policy decision making in Thailand.

## Definition of terms

**Acute hepatitis B**

Acute hepatitis B is defined as abrupt manifestations of hepatic injury that occur within 6 months of exposure to HBV and resolve within 6 months after onset.

**Alanine aminotransferase (ALT)**

Alanine aminotransferase (ALT) is an enzyme that indicates liver inflammation.

**Antigen**

Antigen is any substance that the body regards as foreign or potentially dangerous and against which it produces an antibody.

**Anti-HBe**

Anti-HBe is the antibodies to the HBeAg antigen.

**Biochemical responses**

Biochemical responses are defined as changes in serum ALT levels by a decrease into the normal range

**Cirrhosis**

A condition in which the liver responds to injury or death of some of its cells by producing interlacing strands of fibrous tissue which are nodules or regenerating cells.

**Compensated cirrhosis**

Compensated cirrhosis means that the liver is still able to cope with or compensate for the damage and carry out most (sometimes all) of its functions**.**

**Cross-resistance**

Cross-resistance refers to the situation in which a decreased susceptibility to more than one antiviral drug and is conferred by the same amino acid substitution or a combination of amino acid substitutions. There are major clinical implications for the choice of drug to adapt antiviral therapy in case of resistance.

**Decompensated cirrhosis**

Decompensated cirrhosis is the final stage of the hepatitis B cycle that relates to liver damage. The liver at this stage will be covered with nodules and shrunken in size.

**HBeAg**

The non-structural viral protein exported from infected cells in non-viral proteins while hepatitis B is actively replicating.

**HBeAg-positive chronic hepatitis B**

HBeAg and HBV DNA are present in serum and anti- HBe is undetectable.

**HBeAg-negative chronic hepatitis B**

Infection by an HBV variant that prevents or down-regulates secretion of HBeAg in serum where it becomes undetectable, anti-HBe is detectable, and HBV DNA is present in serum.

**HBeAg seroconversion**

HBeAg seroconversion can be defined as HBeAg loss, undetectable level of serum Hepatitis B viral DNA and appearance of antibodies against HBeAg**.**

**High prevalence areas**

High HBV endemic areas have prevalence of chronic infection greater than 8%.

**Histological response**

Histological response is defined based upon scoring system for the grade and stage of chronic hepatitis and defined as a two point decrease in the histological activity index (HAI) which ranges from 0 to 18 with no worsening of fibrosis between pre-treatment and end-of-treatment liver biopsies. A more appropriate histological endpoint would be resolution of the chronic hepatitis with minimal or mild HAI scores (< 3 points).

**Incremental cost-effectiveness ratio (ICER)**

The alternatives are compared on the basis of the increments in costs and effectiveness**,** calculated by incremental cost divided by incremental effectiveness.

**Intermediate prevalence areas**

Intermediate HBV endemic areas have prevalence of chronic infection 1-8%.

**Low prevalence areas**

Low HBV endemic areas have prevalence of chronic infection less than 1%.

**Virological response**

Virological response based upon testing for level of HBV DNA in serum are the most appropriate criteria of assessing beneficial outcome of antiviral treatment which defined as the lack of detectable HBV DNA in serum and loss of HBeAg or seroconversion to anti-HBe.

# CHAPTER II
# LITERATURE REVIEW

The literature review is divided into five parts as follows

1. Description of chronic hepatitis B (CHB)
2. Clinical effectiveness of CHB medications
3. Health economic evaluation methods in healthcare
4. Cost-effectiveness model in health economic evaluation
5. Economic evaluation of CHB medications

## Part I Description of chronic hepatitis B (CHB)

### 1.1 Pathophysiology of CHB

Hepatitis B is an infectious disease of the liver due to infection by hepatitis B virus (HBV). HBV is the common virus known as deoxyribonucleic acid or DNA virus which belongs to the Hepadnaviridae family. HBV may help forming antigens which can stimulate the body's immune system to produce the antibodies which can neutralize or even destroy the virus. In fact, the immune reaction but not the virus seems to cause the liver inflammation. The outcome of HBV infection largely depends on the host-virus interaction, mediated by the adaptive immune response. The virus specific T cell response is one of the important factors in the pathogenesis of HBV infection (5). It is transmitted through blood to blood contact, sexual contact, or mother with hepatitis B who may pass HBV on to her infant. The person groups who have a higher risk of becoming infected with HBV are as follows (16).

1) People in an HBV infected person’s household

2) People who have sex with a person infected by HBV especially homosexual and multiple sexual partners

3) Health care workers

4) Hemophiliac and hemodialysis patients

5) Prisoners and prison workers

6) Persons who have ever injected drugs

7) Persons requiring immunosuppressive therapy

Current infection can be detected by the presence of hepatitis B surface antigen (HBsAg) in the serum. Infection with HBV can result in an acute or chronic disease. Infected individuals develop an acute infection, which may or may not result in symptoms. The most common symptoms of acute hepatitis B are loss of appetite, nausea, generally feeling poorly, and pain or tenderness in the right upper part of the abdomen. Generally the symptoms of acute hepatitis B do not persist longer than two or three months. In most individuals, infection will resolve and HBsAg disappears from the serum. However, the viruses still persist in some patients who become chronically infected with hepatitis B. The risk of becoming chronically infected varies according to age. More than 95% of those infected during adulthood make a full recovery and acquire immunity from future infection, while less than 5% of infected adults and more than 90% of infected neonates will develop CHB, if infected with HBV.

The diagnosis of CHB is based on the presence of HBsAg for 6 months or more after acute infection. Individuals chronically infected with HBV are at increased risk of developing cirrhosis leading to hepatic decompensation and hepatocellular carcinoma (HCC) (8-9). Hepatitis B e antigen (HBeAg) is an indicator of viral replication. Active infection can be described as HBeAg positive or negative. HBeAg positive and HBeAg negative are different in terms of the response to treatment and rates of progression. HBeAg negative, the mutant strains of HBV that do not produce e antigen, is associated with a fluctuating course and a poor prognosis. It is required to be established whether the individual is in the HBeAg positive or HBeAg negative phase of the infection. The tests for markers of HBV replication which are HBeAg, serum HBV DNA, anti-HBe and serum alanine aminotransferase (ALT) should be considered for determining the treatment.

### 1.2 Natural history of chronic hepatitis B

The natural history of CHB can be divided into five phases as follows (5, 12, 17-18).

(1) Immune tolerant phase

Immune tolerant phase is characterized by HBeAg positivity, anti-HBe negativity, high levels of serum HBV DNA (>$10^7$ IU/ml), normal levels of ALT, mild or no liver necroinflammation and no or slow progression of fibrosis. These patients are believed to have immune tolerance to HBV and very low spontaneous rate of HBeAg loss. The CHB patients in this phase are safe and need no treatment but their disease phase must be followed.

(2) Immune reactive phase

Immune reactive phase is characterized by HBeAg positivity, a lower level serum HBV DNA (>$10^4$ IU/ml), increased or fluctuating levels of ALT, moderate or severe liver necroinflammation and more rapid progression of fibrosis compared to the previous phase. It may last for several weeks to several years. In addition, the rate of spontaneous HBeAg loss is increased. This phase may occur after several years of immune tolerance. The immunity cannot control the infection of CHB, therefore the patients in this phase should be treated.

(3) Inactive HBV carrier phase

Inactive HBV carrier phase may follow seroconversion from HBeAg to anti-HBe antibodies. It is characterized by very low or undetectable serum HBV DNA levels (<$10^3$ IU/ml) and normal ALT. As a result of immunological control of the infection, this state confers a favorable long-term outcome with a very low risk of cirrhosis or HCC in the majority of patients. HBsAg loss and seroconversion to anti-HBs antibodies may occur spontaneously in 1–3% of cases per year, usually after several years with persistently undetectable HBV DNA.

(4) HBeAg negative CHB

These patients are HBeAg negative and harbor HBV variants with nucleotide substitutions in the precore and/or the basal core promoter regions where are unable to express HBeAg. HBeAg negative is associated with a fluctuating

course and a poor prognosis. It is characterized by absence of HBeAg, presence of anti-HBe, detectable serum HBV DNA, elevated ALT and chronic inflammation.

(5) HBsAg-negative phase

After HBsAg loss, HBV DNA is not detectable in the serum while anti-HBe antibodies with or without anti-HBs are detectable. HBsAg loss is associated with improvement of the outcome with reduced risk of cirrhosis, decompensation and HCC. Immunosuppression may lead to reactivation in these patients.

CHB usually causes microinflammatory changes that evoke a fibrotic response in the liver. Many infected individuals will develop cirrhosis and are at risk for the development of HCC (19). From the study on the risk of cirrhosis, HCC, decompensation and liver-related mortality in patients with chronic HBV infection in Asian countries, it was found that the corresponding 5-year cumulative incidences of cirrhosis were 8% and 13% for HBeAg positive CHB and HBeAg negative CHB patients, respectively. The 5-year cumulative incidence of hepatic decompensation in patients with early stage of cirrhosis was 15%. The corresponding 5-year HCC cumulative incidences were 1%, 3%, and 17% for inactive carriers, CHB without cirrhosis and with compensated cirrhosis, respectively. Based on liver related mortality rates according to clinical status and geographic area, 5-year liver related death rate among inactive carriers was 14%. Moreover, when hepatic decompensation occurs, mortality rate increases remarkably ranging from 70 to 85% at 5-year follow up (18).

### 1.3 Epidemiology of CHB

Hepatitis B is one of the world's most common and serious infectious diseases. HBV is a widespread virus with a global distribution. An estimated 350 million people or more than one third of the world's population have been infected with the HBV (1). About 5% of the populations are chronic carriers of HBV, and nearly 25% of all carriers develop serious liver diseases such as chronic hepatitis, cirrhosis, and hepatocellular carcinoma. HBV infection causes more than one million deaths every year (1).

A study of the distribution of the various forms of chronic hepatitis B in different parts of world is presented in Figure 2.1 (20) and Table 2.1 (21). The study indicated that in many Southeast Asian countries such as Thailand, Malaysia, Indonesia, Vietnam, Laos and Myanmar, a high frequency of HBsAg population has been found (20). The HBsAg carrier rate varies from 0.1 to 20% in different populations around the world. The incidence of HBsAg carrier state in populations is related most importantly to the incidence and age of primary infection (22).

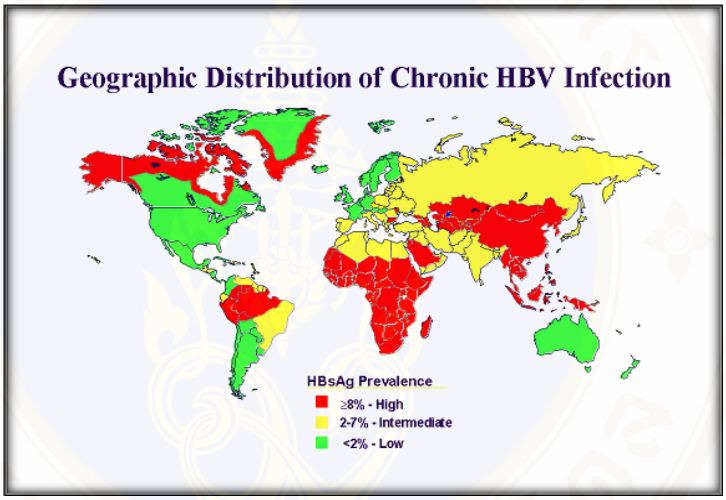



**Figure 2.1 HBsAg prevalence in different regions of the world**

**Table 2.1: Prevalence of hepatitis B in various areas**

| Area | % of CHB population | | | |
|---|---|---|---|---|
| | **HBsAg** | **Anti-HBs** | **Neonatal** | **Childhood** |
| **Low prevalence areas:** Northern, Western, and Central Europe, North America, Australia | 0.2-0.5 | 4-6 | Rare | Infrequent |
| **Intermediate prevalence areas:** Eastern Europe, The Mediterranean, Russia and the Russian Federation, Southwest Asia, Central and South America | 2-7 | 20-55 | Frequent | Frequent |
| **High prevalence areas:** Parts of China, Southeast Asia, Tropical Africa | 8-20 | 70-95 | Very frequent | Very frequent |

In low prevalence areas of the world, the highest incidence of the disease has been seen in teenagers and young adults. Despite the low incidence of disease has been occurred in the general population, the people who contact with blood to blood or sexual contact have a high rate of HBV infection. In high prevalence areas, different epidemiological patterns have been found. In these regions, most infections occur in infants and children as a result of maternal-neonatal transmission or close childhood contact, although percutaneous exposure with contaminated needles or following unsafe injections is always possible in these countries (23). The chronic liver disease and HCC associated with HBV infections are one of the most important public health problems in high-prevalence regions. In Thailand, the prevalence of hepatitis B virus in the general population is higher than 8%. The prevalence rate of HBsAg positive is 8-10% for males and 6-8% for females. However, the Ministry of Public Health has

implemented the nationwide hepatitis B vaccination program for all newborns and provided hepatitis B immune globulin (HBIG) for babies who born to carrier mothers since 1992 (6). As a result, the prevalence of HBV in Thailand was decreased to 4% (7). About 31% of patients with HBsAg positive CHB are HBeAg positive CHB (10-11).

### 1.4 The treatment of HBeAg positive chronic hepatitis B

1.4.1 Pretherapeutic assessment of liver disease

The assessment of relationship between HBV infection and liver disease and their severity should be performed. The clinical practice guidelines for diagnosis and management of HBeAg positive CHB of Thailand Consensus Recommendations for Management of Chronic Hepatitis B 2009 by Liver Society Thailand defined the patients who needed the treatment as follows (24-25).

1) Patients who have detectable serum HBsAg for at least 6 months

2) Patients who have evidence of active HBV viral replication which is detectable level of serum hepatitis B viral DNA more than or equal 20,000 IU/ml

3) Patients who have serum ALT level at 1.5-10 times the upper limit of the normal range for at least 3 months (except in patients with cirrhosis or impending decompensation should be treated if they have normal ALT)

4) Patients who have evidence of CHB on liver biopsy

5) Patients who receive the test for HCV Ab and HIV Ab before the treatment

6) Patients who has no underlying disease causing hepatitis B

Patients with viral replication but persistently normal or minimally elevated ALT levels or inactive CHB infection should not be treated. They need an adequate follow-up and HCC surveillance every 3-6 months.

1.4.2 Goal of CHB therapy

The aims of treatment of CHB are to reduce HBV DNA level as low as possible for eliminating infectivity to prevent transmission and spread of HBV

and to increase the possibility of HBeAg loss leading to histologic improvement. Therefore, the goal of treatment is to stop or slow the progression of liver disease to prevent compensated cirrhosis, decompensated cirrhosis and HCC.

1.4.3 Endpoint of CHB therapy

The course of CHB is typically silent and associated with few signs or symptoms of disease for many years. The development of clinical outcomes does not usually occur for years to decades after diagnosis. Thus, clinical efficacy of CHB treatment can be assessed by using short-term intermediate histologic improvement, biochemical responses and virologic responses. The endpoint of treatments for HBeAg positive CHB using markers of HBV replication in serum and liver are HBeAg seroconverion (i.e., HBeAg loss and gain of anti-HBe), the sustained inhibition of viral replication (i.e., low level of HBV DNA) and normalization of serum ALT level (26).

1.4.4 Drug treatments for CHB

Currently, six medications licensed by the Thai FDA and available for the treatment of CHB are 1) conventional interferon alpha 5-10 MU three times/week, 2) pegylated interferon alpha 2a or 2b 180 mcg weekly, 3) lamivudine 100-150 mg daily, 4) adefovir dipivoxil 10 mg daily, 5) entecavir 0.5 mg daily, and 6) telbivudine 600 mg daily. In addition, tenofovir has been approved by Thai FDA for the treatment of HIV, but not for CHB treatment yet. However, tenofovir 300 mg daily has been currently prescribed to CHB patients in clinical practice, since tenofovir has demonstrated high antiviral efficacy and low drug resistance rate for the treatment of CHB (13-14). These medications can be classified in to two major classes which are immune modulators as well as nucleoside and nucleotide analogues (27-28).

1. Immune modulators

Immune modulators (e.g., conventional interferon alpha and pegylated interferon alpha (PEG) 2a or 2b) are the drugs which help improving human immune system to against the virus entry into hepatocytes and activate viral ribonuclease in order to inhibit HBV replication. The advantages are finite treatment course and no drug resistance but the disadvantages are frequent subcutaneous injection, frequent adverse events, contraindicated in advanced cirrhosis and high costs.

2. Nucleoside and nucleotide analogues

Nucleoside and nucleotide analogues (e.g., lamivudine, adefovir, entecavir, telbivudine and tenofovir) are the drugs which directly inhibit reverse transcriptase and thereby impair viral replication. Each treatment may be used as the first line monotherapy. However, there are differences in term of the potency, resistance rate and price among these nucleoside and nucleotide analogues. It has been reported that adefovir is less efficacious and engenders higher rates of resistance (12, 28-29). Lamivudine is an inexpensive drug but frequently has drug resistance (12, 28-29). Telbivudine is a potent inhibitor of HBV but produces a low genetic barrier to resistance (12, 28-29). Entecavir is a potent antiviral agent showing potent viral suppression and has high barrier to resistance but expensive (12, 28-29). Tenofovir has demonstrated high antiviral efficacy in the treatment of CHB and has the low rate of resistance (13-14). Therefore, the ideal drug would be the nucleoside or nucleotide with potent viral suppression and high genetic barrier to resistance in order to achieve sustained viral suppression.

1.4.5 Management of antiviral drug resistance

Antiviral drug resistance reflects the reduced susceptibility of a virus to the inhibitory effect of a drug and results from a process of adaptive mutation in the HBV polymerase gene. Resistance is defined as the selection of variants bearing amino acid substitutions conferring reduced susceptibility to drugs that result in treatment failure. The pattern of development of HBV resistant mutants is varied by chemical class of nucleoside analogues which can be categorized as 1) L-nucleosides such as lamivudine and telbivudine, 2) acyclic phosphonates such as adefovir and tenofovir and 3) cyclopentenes such as entecavir (30). In case of resistance, an appropriate rescue therapy which is adding-on the second drug without cross resistance is the most efficient strategy (12). Thus, the management of antiviral drug resistance is as follows.

1) Lamivudine resistance

Tenofovir should be added or if tenofovir is not yet available, adefovir should be added.

2) Adefovir resistance

It is recommended to switch to tenofovir if available and add the second drug without cross resistance or add lamivudine, entecavir or telbivudine.

3) Telbivudine resistance

Tenofovir should be added or if tenofovir is not yet available, adefovir should be added.

4) Entecavir resistance

Tenofovir should be added.

Recent studies have shown that detectable HBV DNA at the 6th month of therapy was associated with a much higher resistance rate. Thus, if HBV DNA level is more than 60 IU/ml at the 6th month of therapy, non cross-resistance drugs should be added (31-35). Moreover, European Association for the Study of the Liver (EASL) guideline recommended that for the management of lamivudine or telbivudine resistance with a partial virologic response at week 24, the treatment should be changed to a more potent drug (i.e., entecavir or tenofovir) or added a more potent drug without cross resistance. Furthermore, for entecavir, tenofovir or adefovir resistance with a partial virologic response at week 48, the second drug based on the guidelines should be added.

1.4.6 Treatment monitoring and discontinuation

During the treatment, ALT level should be monitored at least every 3 months and HBeAg and HBV DNA level should be monitored at least every 6 months. Patients receiving interferon or PEG therapy should be monitored every 2 weeks during the first and second months and then adverse effects should be monitored and test of complete blood count (CBC) and test of thyroid function should be performed every 4-6 weeks. For patients receiving adefovir therapy, renal function should also be monitored. After the end of therapy and HBeAg seroconversion occurred, ALT level, HBeAg and HBV DNA level should be monitored the same as during therapy for relapse detection. Furthermore, loss of HBsAg and seroconversion to anti-HBs is clearly the most desired endpoint and can be considered as a complete response. The patients with HBeAg positive can discontinue the treatment when seroconversion occurred at least 6 months of additional treatment after HBeAg seroconversion.

## Part II Clinical effectiveness of CHB medications

Clinical efficacy of CHB treatment can be assessed by histologic improvement, biochemical responses and virologic responses. HBeAg seroconversion is one of the virological responses which can be defined as 1) HBeAg loss, 2) undetectable level of serum Hepatitis B viral DNA and 3) appearance of antibodies against HBeAg. Therefore, HBeAg seroconversion is an indicator for discontinuing CHB treatment. To assess clinical efficacy in terms of HBeAg seroconversion among treatment options for HBeAg positive CHB, the literatures on clinical effectiveness of available treatments which are specifically recommended for HBeAg positive CHB patients were reviewed. A systematic review of randomized controlled trials of treatments for patients with HBeAg-positive CHB was performed through the Pubmed and Cochrane databases using the key words as follows.

(efficac* OR effectiv* OR “relative risk” OR
“meta analysis” OR “RR”)
AND
(“RCT” OR randomi* OR “clinical trial*”)
AND
(entecavir OR peginterferon* OR pegintron* OR “PEG” OR
pegylated OR lamivudine OR telbivudine OR adefovir OR tenofovir)
AND
("hepatitis B" OR “chronic hepatitis B” OR “HBV”)
AND
(“HBeAg” OR “HBsAg” OR seroconvers* OR seroclearanc*)

Inclusion criteria

1. The RCT or meta-analysis studies comparing interventions which are 1) lamivudine 2) adefovir 3) entecavir 4) telbivudine 5) tenofovir 6) PEG and 7) palliative care or no treatment

2. The studies on the patients aged at least 18 years with HBeAg positive CHB who required the treatment based on the following criteria.

- Patients who had detectable serum HBsAg for at least 6 months
- Patients who had serum ALT level 1.5 -10 times the upper limit of the normal range for at least 3 months

- Patients who had evidence of chronic hepatitis on liver biopsy
- Patients who had detectable level of serum Hepatitis B viral DNA

3. The studies measuring outcome as HBeAg seroconversion rate
4. The studies with treatment duration for one year
5. Publication date during 1995-2010
6. Only English language studies

Exclusion criteria

1. The studies without recommended dose for CHB
2. The studies of patients with advanced liver diseases such as decompensated cirrhosis and HCC.

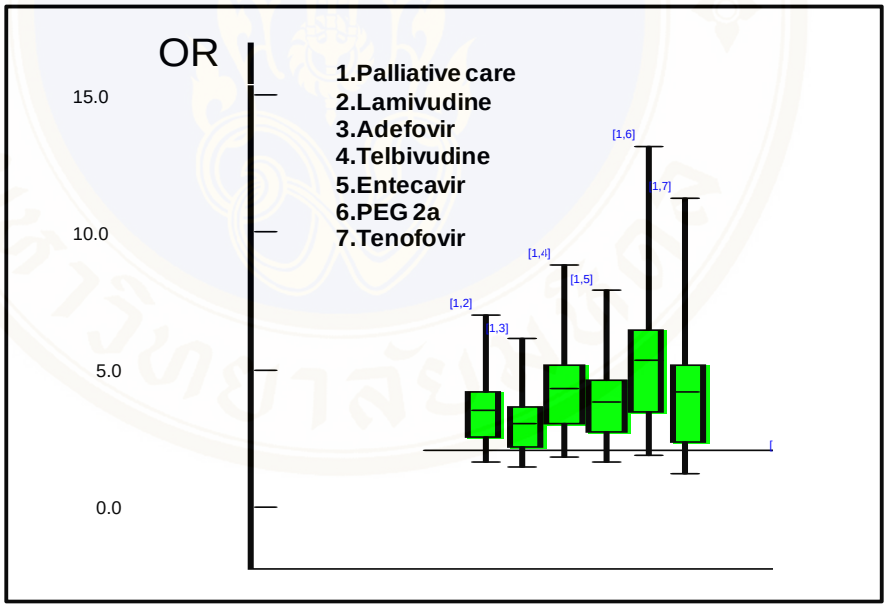
Bayesian approach and WinBUGS14 (Medical Research Council and Imperial College of Science, Technology and Medicine, United Kingdom) software program were used to perform meta-analysis. Mixed treatment or indirect comparison meta-analysis was applied. Odds ratio and its 95% credible interval were used as the summary efficacy of the medication. Heterogeneity test was applied for testing the variation of study outcomes between studies.

Based on systematic reviews, 294 abstracts were reviewed and 14 relevant RCTs were included in the analysis (36-49). None of 14 RCTs included all seven treatment options. Fourteen articles were evaluated by Jadad score's criteria. Thirteen articles had Jadad score equal or greater than 3 (36-38, 40-49). There were two studies comparing lamivudine with placebo (40-41), five studies comparing lamivudine with entecavir (38-39, 42-44), two studies comparing lamivudine with telbivudine (45, 47) and one study comparing lamivudine with PEG 2a (37). There were four studies comparing adefovir with placebo (1 study) (36), entecavir (1 study) (48), telbivudine (1 study) (46) or tenofovir (1 study) (49). Table 2.2 and Figure 2.2 present the odds ratio of HBeAg seroconversion rate and its 95% credible interval (CI) of all treatments compared with palliative care. There are statistical significance differences in odds ratio of HBeAg seroconversion rate between each treatment and palliative care.

**Table 2.2: Odds ratio of HBeAg seroconversion rate of all treatments compared with palliative care**

| Treatment | Odds ratio (95% CI) |
|---|---|
| PEG 2a | 5.36 (2.17-10.46) |
| Telbivudine | 4.29 (2.05-7.68) |
| Tenofovir | 4.17 (1.41-9.23) |
| Entecavir | 3.85 (1.90-6.72) |
| Lamivudine | 3.52 (1.81-6.09) |
| Adefovir | 3.03 (1.57-5.31) |

**Figure 2.2: Box plot for the odds ratio of HBeAg seroconversion rate of all treatments compared with palliative care**




Patients with HBeAg positive CHB receiving lamivudine, adefovir, entecavir, telbivudine, tenofovir or PEG 2a are about three to five times more likely to have HBeAg seroconversion rate compared to those without treatment. However, the RCT studies of PEG 2b were not included because their dose and treatment duration were different from the studies of other treatments. Although patients with HBeAg seroconversion can stop the treatment, their CHB disease progression may have been the same as those without HBeAg seroconversion and still receiving the treatment.

Not only HBeAg seroconverion but also histologic improvement as well as virologic and biochemical responses should be considered when assessing clinical efficacy.

Until now, there has been no study related to quality of life CHB patients who receive antiviral treatment yet. Nevertheless, based on the quality of life studies in Chinese chronic hepatitis C (CHC) outpatients receiving antiviral (i.e., interferon alpha plus ribavirin), it was indicated that CHC patients had lower health-related quality of life (HRQOL) than those without CHC (50). Moreover, antiviral treatment reduced HRQOL of CHC patients at the early phase of treatment, mainly in non-sustained virological responders. The HRQOL may return to pretreatment values at the end of treatment and significantly improve at the $6^{th}$ month after stopping the treatment in sustained virological responders (50).

## Part III Health economic evaluation methods in healthcare

Economic evaluation is defined as a comparative analysis of alternatives in terms of both their costs and outcomes. The cost component is always measured in monetary unit, while the outcome component can be measured in various ways. Based on different outcome measurements, the full economic evaluation is divided into four types of analysis. There are cost-benefit analysis (CBA), cost-minimization analysis (CMA), cost-utility Analysis (CUA), and cost-effectiveness analysis (CEA) (51)

**1. Cost-Benefit Analysis (CBA)** compares costs and consequences of two or more alternatives that have different outcomes. Costs and outcomes are measured in monetary unit. The benefit from a program and all the costs of providing a program are identified and converted into equivalent dollars in the year in which they occur. The objective of cost-benefit analysis is to find the alternative with the most favorable cost- to-benefit ratio. The limitation of cost-benefit analysis is valuation of outcome in monetary units. Many outcomes such as years of life saved or quality of life, are difficult to value in monetary terms.

**2. Cost-Minimization Analysis (CMA)** compares costs of two or more alternatives that have equivalent outcomes. The outcomes of the alternatives are assumed to be equal, only costs of each alternative have been estimated. Cost-

minimization analysis shows only cost savings of one program or treatment over another.

**3. Cost-Utility Analysis (CUA)** is similar to cost-effectiveness analysis, except the outcomes are measured in terms of patient preference of quality of health care outcome. Cost-utility analysis is most useful in evaluating health programs that extend life but with serious side effects such as cancer chemotherapy or arthritis are not recommended.

**4. Cost-Effectiveness Analysis (CEA)** is the tool that is used to address the limitations of cost-benefit analysis by using physical or natural units as outcome measures. Cost-effectiveness analysis compares costs and consequences of alternatives that achieve the objective at the least cost. When treatment alternatives are not therapeutically equivalent, or when it is inappropriate to express benefits (outcome) in monetary units, cost-effectiveness analysis may provide a more appropriate evaluation technique. Cost-effectiveness analysis is one of the tools that is used to evaluate treatment alternatives. For drug therapy, these alternatives may be different drugs or comparison between drug treatment and non drug treatment. Cost-effectiveness analysis involves assessing the cost and consequences of pharmaceutical products and services, with non-equivalent therapeutic outcome. After the costs and effectiveness of the alternatives are obtained, two approaches have been used to compare them in CEA:

1) Cost-effectiveness ratio approach: the alternatives are compared on the basis of the average cost per unit of effectiveness (sometimes, average effectiveness per unit cost). Generally, the most cost-effective alternative has the lowest average cost per unit of effectiveness.

2) Incremental cost-effectiveness ratio (ICER) approach: the alternatives are compared on the basis of the increments in costs and effectiveness.

Normally, lower ICER is preferable because it implies less incremental cost for a unit of effectiveness. The ICER indicates the additional costs that an alternative has over another as compared to the additional effectiveness.

Incremental cost effectiveness ratio (ICER) is calculated by incremental cost divided by incremental effectiveness

$$ICER = (C_I - C_N)/(E_I - E_N)$$

Where,

$C_I$ = Intervention cost or current practice cost

$C_N$ = Null cost

$E_I$ = Intervention effectiveness or current effectiveness

$E_N$ = Null effectiveness

## Part IV Cost-effectiveness model in health economic evaluation

Cost-effectiveness model approach is widely used in health-care economic evaluations. It is a systematic way to help making a decision making under conditions of uncertainty. In the context of economic evaluation, the modeling technique uses mathematical relationships to define a series of possible consequences that would flow from a set of alternative options being evaluated. A key purpose of the modelling is to allow for the variability and uncertainty associated with all decisions (52). Two types of cost-effectiveness models commonly used in economic evaluation are decision tree and Markov models.

**Decision tree model**

The decision tree is probably the simplest form of decision model. The key features of a decision tree approach are as follows (52).

1. A square decision node, typically at the start of a tree, indicates a decision point between alternative options.

2. A circular chance node shows a point where two or more alternative events for a patient are possible. These are shown as branches coming out of the node. For an individual patient, which event they experience is uncertain.

3. Pathways are mutually exclusive sequences of events and are the routes through the tree.

4. Probabilities show the likelihood of a particular event occurring at a chance node (or the proportion of cohort of apparently homogeneous patients expected to experience the event). Moving left to right, the first probabilities

in the tree show the probability of event. Subsequent probabilities are conditional which means that the probability of an event given that an earlier event has or has not occurred. Multiplying probabilities along pathways estimates the pathway probability which is a joint probability. Expected costs and outcomes are based on the summation of the pathway values weighted by the pathway probabilities.

There are five steps in decision tree model which are (53)

*Step I Identifying the objectives and developing the model structure*

After the research question is developed, the research objectives are specifically defined at the beginning of modelling. The research question should clearly state the competing interventions, target population and outcome measures. The perspective of the study and the length of follow-up should also be specifically defined. The structure of the model is developed on the basis of an understanding of the nature of disease progression, required exactness of results and the user's perspective. However, with restricted availability of data, compromises need to be made when developing the model structure. As the model is a process of simulating disease progression, it is extremely important that the model structure be validated to meet the quality criteria.

*Step II Assigning probabilities*

The probabilities are assigned to the model after the model is validated. Sources of probabilities include medical literature (i.e., meta-analyses, clinical trials, or observational studies) and expert opinions. Some techniques have been used to obtain probabilities in mathematical models, including survival models and multivariate logistic regression analysis.

*Step III Assigning utilities and costs*

The final step of developing the model is to assign a value to the relevant health states. The assignment of health utilities and costs is performed separately. The health utility, ranging from 0 to 1, is multiplied with the natural unit of measure (e.g., life-years gained) to produce the quality-adjusted life year resulting from the investigated health-care intervention. Costs must also be assigned to each state of the model. Costs of different states usually vary, depending on the resource use and unit prices.

*Step IV Calculating health outcomes and costs and incremental analysis*

Both expected health outcomes and costs are calculated separately by a process referred to as 'folding back. Such folding back may be processed in a simple decision tree. The expected health outcomes of the chance node are the sum of the products of health utilities in each branch multiplied by the probabilities of that branch. The expected outcomes of the decision node are equal to the node with the highest branch. Incremental analyses need to be performed for health outcomes and costs, and incremental cost-effectiveness ratios (ICERs) should be calculated.

*Step V Sensitivity analysis*

The expected results from the model, referred to as base-case results, are usually obtained from average estimates of inputs (including probabilities, utilities, and costs). Sensitivity analysis is conducted to examine the robustness of results. If the result is sensitive to a variable, the magnitude of its effect on the results is investigated, and if necessary, revisions are made to estimates of the appropriateness of the model structure. In deterministic analysis, simple sensitivity analysis, extreme analysis and threshold analysis point estimates or range estimates are applied to assess the effect of variables on results. Probabilistic analysis (Monte Carlo simulation) incorporates the probability distribution of key variables to produce the distribution of expected results.

**Markov model**

The Markov model is a commonly used approach in decision analysis to handle the added complexity of modelling options with a multiplicity of possible consequences. The added flexibility of the Markov model relates to the fact that it is structured around mutually exclusive disease states, representing the possible consequences over time being modeled as a large number of possible pathways as in a decision tree, a more complex prognosis is reflected as a set of possible transitions between the disease state over a series of discrete time periods, called cycle. The length of these cycles depends on the disease and interventions being evaluated. Each state in the model has a cost and outcome such as a utility value associated with it. Costs and effects are typically incorporated into these models as a mean value per state per cycle, and expected values are calculated by adding the costs and outcomes across the state and weighting according to the time the patient is expected to be in

each state. The speed which patients move between the states in the model is determined by a set of transition probabilities.

## Part V Economic evaluation of CHB medications

The cost of treatment CHB and complication (compensated cirrhosis, decompensated cirrhosis and HCC) are very expensive (4), therefore economic evaluation studies are needed. To review economic evaluation studies on drug treatment options for patients with CHB, the studies comparing interventions currently available for the treatment of CHB patients (i.e., lamivudine, adefovir, entecavir, telbivudine, tenofovir, interferon, pegylated interferon) with palliative care or no treatment were included. A systematic review was conducted to identify full health economic evaluation studies (i.e., cost-effectiveness, cost-utility, cost-benefit analyses) comparing treatment options in patients with CHB and published between 2000 and January 2010. These studies were searched through the Pubmed and Cochrane databases using the key words as follows.

(cost effective* OR cost utilit* OR cost benefit OR
cost evaluation* OR economic evaluation*)
AND
(hepatitis B OR liver inflam*)
AND
(lamivudine OR zeffix OR epivir OR adefovir* OR viread OR entecavir* OR baraclude OR tenofovir* OR viread OR telbivudine OR sebivo OR interferon* OR intron* OR peginterferon* OR pegintron* OR pegasys OR PEG OR thymosin OR zadaxin)
NOT vaccin*NOT transplant* NOT malignan*

Exclusion criteria were the studies related to only cost or outcome analysis, vaccination, mutation analysis of drug resistance, or target populations (i.e., patients with HCC, cirrhosis, malignant, hepatitis C, or transplantation). The outcomes of this review focused on both the choices of method used and results of economic evaluation. The inclusion and exclusion criteria used for study selection are shown in Table 2.3.

**Table 2.3 Inclusion and exclusion criteria of Economic evaluation of CHB medications**

| Inclusion criteria | Exclusion criteria |
|---|---|
| Studies comparing both cost and outcome of the treatment for patients with CHB<br>Publication date during 2000-2010 | Studies related to only cost or outcome analysis<br>Studies related to vaccination<br>Studies related to mutation analysis of drug resistance<br>Studies with target populations (i.e., patients with HCC, cirrhosis, malignant, hepatitis C, or transplantation). |

For the data collection process, a data extraction sheet was developed based on the Centre for Reviews and Dissemination's data extraction template. The data extraction sheet for each study is available from the author on request. A summary of the considered data items can be found. The details extracted from each included study were as follows: (1) author, year, country, (2) disease and patient group, (3) objective, (4) intervention, (5) perspective, (6) source of data, (7) outcome, (8) method, (9) discounting rate, (10) sensitivity analysis, and (11) incremental cost-effectiveness result.

The methodological quality assessment of included economic evaluation studies and systematic review studies was assessed using Drummond's criteria (Table 2.4) (54) Study quality was assessed and data were extracted by one reviewer. Items were scored as positive, negative, or unclear.

**Table 2.4 Drummond's criteria for evaluating economic evaluation studies**

| Criteria |
|---|
| Was a well-defined question posed in an answerable form? |
| Was a comprehensive description of the competing alternatives given |
| Was there evidence that the programme's effectiveness had been established? |
| Were all the important and relevant outcomes and costs for each alternative identified? |
| Were outcomes and costs measured accurately in appropriate units |
| Were the outcomes and costs valued credibly? |
| Were outcomes and costs adjusted for different times at which they occurred |
| Was an incremental analysis of the outcomes and costs of alternatives performed? |
| Was a sensitivity analysis performed? |
| Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers? |
| Were the conclusions of the evaluation justified by the evidence presented? |
| Can the results be applied to the local population? |

*Note: All items have three possible responses which are yes (+), no (-), and cannot tell (N/A).

The primary literature search by electronic databases identified 72 citations. After screening of all titles and abstracts, only 32 articles were identified. Of all 32 full articles, 26 articles comparing both costs and outcomes of two or more drug treatments for patients with CHB were included (55-80). The result of systematic literature search is shown in Figure 2.3.

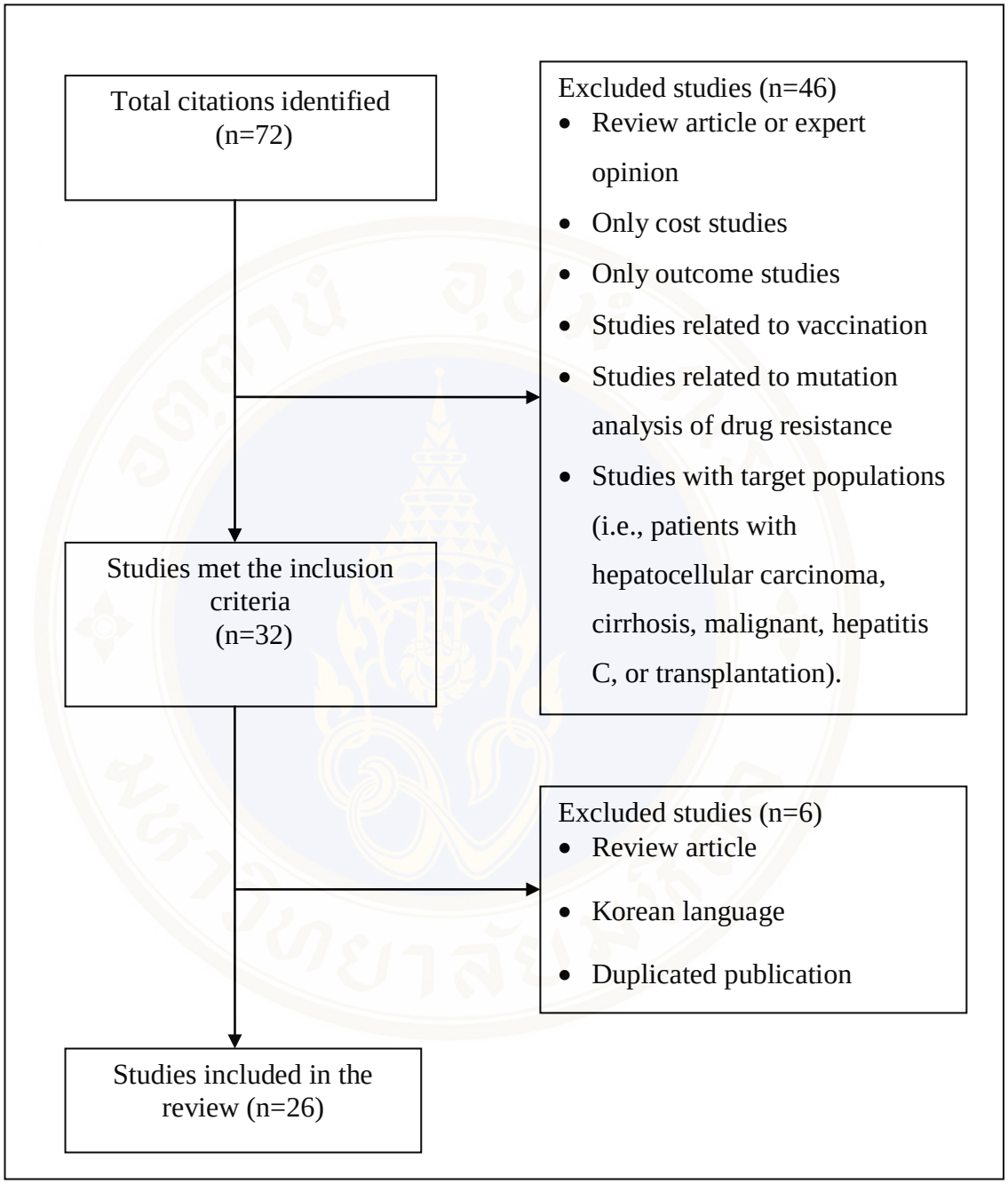



**Figure 2.3 Result of systematic literature search**

Most studies clearly described the objectives, competing alternatives and specified the cost and outcome measures. It could be seen that about 69% (18 out of 26) of all studies passed 9 out of 12 Drummond's criteria (See appendix A) (55-56, 58-73, 75, 79).

The results showed that seventy-two abstracts were reviewed and only 26 articles were included as shown in appendix B. Fifteen studies were conducted in Europe and America (56-60, 64-66, 69, 71-72, 75-78), whereas eleven studies were performed in Asia (55, 61-63, 67-68, 70, 73-74, 79-80). It was found that disease and patient groups in all studies were classified into four groups which are patients with HBeAg positive (6 articles) (60-61, 66, 69-70, 79), HBeAg negative (3 articles) (63-64, 71), both HBeAg positive and negative (7 articles) (55, 57-59, 62, 65, 67) and patients with unidentified HBeAg status (10 article) (56, 68, 72-78, 80). Regarding the perspective, most studies were analyzed based on the perspectives of health care system (13 articles) (57-59, 62, 65, 68-71, 73-74, 78, 80) or third party payer (10 articles) (55, 60-61, 63-64, 66, 72, 75, 77, 79), but only two studies performed based on patient's perspective (56, 67).

Direct medical costs such as cost of drugs, lab, admission, diagnosis and professional fees were included in all studies. Since there were two studies performing based on patient's perspective, they collected both direct and indirect cost (i.e., productivity loss) (56, 67). The outcomes were measured in terms of life years saved (LYs) and/or quality-adjusted life year gained (QALYs). Incremental cost effectiveness (ICER) was used to interpret the results of cost-effectiveness analysis. In term of time horizon, lifetime, ten years or one year were used in the models. Data were generally obtained from systematic review, published literature and clinical trials. Markov model (11 articles) was more frequently used (55-57, 60, 62-64, 66-67, 69-70) compared to decision tree model (5 articles) (58, 65, 71, 77, 79). Both Markov and decision tree models used in three articles (76, 78, 80) but the models were not presented in seven articles (59, 61, 68, 72-75). Discounting rate of 3% (8 articles) (58, 60-63, 71, 73, 79) and 5% (1 article) (67) were used for both cost and outcome. Only one article used 6% for discounting cost and 1.5% for outcome (56) but others articles did not present discounting rate. Probabilistic (7 articles) (56, 60-61, 64, 66, 73, 79) and one-way (4 articles) (58-59, 67, 75) sensitivity analyses were mainly applied to

test parameter uncertainties. Two articles were tested both one-way and probabilistic sensitivity analyses (63, 69).

All of ten studies (i.e., seven studies in America (57-60, 64, 66, 79), two studies in Asia (61, 80) and one study in Australia (65)) showed that entecavir was more cost-effective when compared with lamivudine. Two studies which are in America and Europe showed that adefovir was more cost-effective when compared with lamivudine (56, 71). One study showed that telbivudine was more cost-effective when compared with lamivudine (55). One study showed that tenofovir was more cost-effective when compared with entecavir, telvibudine, adefovir (57). Two studies showed that interferon was not cost-effective when compared with lamivudine (74, 77). One study showed that interferon was more cost-effective when compared with lamivudine and adefovir (72). Three studies (i.e., two studies in Asia, one study in Europe) showed that pegylated interferon was more cost-effective when compared with lamivudine (63, 68-69). One study showed that pegylated interferon was more cost-effective when compared with interferon (56). For combination treatment, two studies showed that lamivudine increased life expectancy and reduced the lifetime risk of cirrhosis and carcinoma when added with interferon (63, 76). Moreover, three studies showed that medications treatment of CHB with antiviral therapy for a long term treatment decreased the rate of disease progression and were highly cost-effective compared with a short-term treatment (62, 67, 70).

Based on the systematic review, it was found that studies' results were relatively varied due to the differences in time horizon and variables used in the models such as drug resistance rate, efficacy on viral suppression, resistance rate and price of the medications for CHB. In addition, most studies were supported by pharmaceutical industries. For example, five articles were supported by Bristol Myers Squibb and the result showed that entecavir was superior compared to other drugs (58, 61, 65, 79-80). One article was supported by Glaxo Wellcome and the result showed that lamivudine was more cost-effective than interferon and this study used only one year of time horizon which might cause a difference in efficacy for treatment CHB if the study used a longer time horizon (76). In addition, most studies did not consider drugs' side effects such as suppression of granulocytes, platelets, and lymphocytes which could lead to higher costs and worse outcomes.

Recently, lamivudine has been included in the National List of Essential Drugs (NLED) but not other medications for patients with CHB. The results in this study suggested that there has been no study related to cost-effectiveness analysis of the treatment in patients with CHB in Thailand yet. The cost-utility analysis of drug treatments among patients with CHB in Thailand would be required to investigate for future research as it would be useful information for making decision on whether which drug should be included in the NLED.

# CHAPTER III
# METHODOLOGY

The methodology of this study was consisted of 11 parts as follows.

1. Study design
2. Perspective
3. Study population
4. Intervention
5. Economic evaluation
6. Time horizon
7. Cost measurement
8. Health outcome
9. Discounting
10. Uncertainty analysis
11. Budget impact analysis

## 1. Study design

This study performed the cost-utility analysis based on economic model to compare drug treatments in patients with HBeAg positive CHB. A Markov model was used to estimate the relevant costs and health outcomes during lifetime horizon with one year cycle length**.** The study also estimated the governmental budget impact of the most cost-effective treatment when included in the benefit package of UC scheme during fiscal year 2010 to 2019.

## 2. Perspective

Cost-utility analysis was performed based on the societal perspective. Budget impact analysis was conducted based on the governmental perspective.

## 3. Study population

Study population was HBeAg positive CHB patients aged at least 30 years who required the treatment based on the following criteria.

- Patients who had detectable serum HBsAg for at least 6 months
- Patients who had serum ALT level one point 1.5 -10 times the upper limit of the normal range for at least 3 months
- Patients who had detectable level of serum hepatitis B viral DNA more than or equal 20,000 IU/ml
- And/or patients who had evidence of CHB on liver biopsy

## 4. Intervention

This study compared all available CHB medications for the treatment of HBeAg positive CHB in Thailand including both oral (i.e., original lamivudine, generic lamivudine, adefovir, entecavir, telbivudine and tenofovir) and intravenous dosage forms (i.e., pegylated interferon, PEG) with palliative care. In addition, based on the current clinical practice guidelines, the set of interventions was studied into two scenarios depended upon when the second drug was added for the management of CHB drug resistance as follows.

1) Adding the second drug when drug resistance occurred (22 interventions)

2) Adding a more potent drug without cross-resistance when the HBV DNA level more than 60 IU/ml at a partial response at week 24 based on the road map guideline which is recommended to apply for only low genetic barrier drugs (i.e., lamivudine and telbivudine) (6 interventions)

***Scenario 1: Adding another drug when drug resistance occurs***

1) Generic lamivudine (adding adefovir)
2) Generic lamivudine (adding tenofovir)
3) Original lamivudine (adding adefovir)
4) Original lamivudine (adding tenofovir)
5) Adefovir (adding generic lamivudine)

6) Adefovir (adding original lamivudine)

7) Telbivudine (adding adefovir)

8) Telbivudine (adding tenofovir)

9) Entecavir (adding adefovir)

10) Entecavir (adding tenofovir)

11) Tenofovir

12) PEG at the first year and generic lamivudine at the third year if treatment failed (adding adefovir)

13) PEG at the first year and generic lamivudine at the third year if treatment failed (adding tenofovir)

14) PEG at the first year and original lamivudine at the third year if treatment failed (adding adefovir)

15) PEG at the first year and original lamivudine at the third year if treatment failed (adding tenofovir)

16) PEG at the first year and adefovir at the third year if treatment failed (adding generic lamivudine)

17) PEG at the first year and adefovir at the third year if treatment failed (adding original lamivudine)

18) PEG at the first year and telbivudine at the third year if treatment failed (adding adefovir)

19) PEG at the first year and telbivudine at the third year if treatment failed (adding tenofovir)

20) PEG at the first year and entecavir at the third year if treatment failed (adding adefovir)

21) PEG at the first year and entecavir at the third year if treatment failed (adding tenofovir)

22) PEG at the first year and tenofovir at the third year if treatment failed

***Scenario 2: Adding a more potent drug without cross-resistance when the HBV DNA level more than 60 IU/ml***

23) Generic lamivudine (adding adefovir)

24) Generic lamivudine (adding tenofovir)

25) Original lamivudine (adding adefovir)
26) Original lamivudine (adding tenofovir)
27) Telbivudine (adding adefovir)
28) Telbivudine (adding tenofovir)

Thus, there were a total of 29 interventions (i.e., 22 interventions of Scenario 1 and 6 interventions of Scenario 2 compared with palliative care)

## 5. Economic evaluation

### 5.1 Model structure

Figure 4 illustrates a structure of Markov model that was used to estimate the relevant costs and health outcomes during lifetime horizon with one year cycle length. The study compared 28 mutually exclusive treatment options as stated above with palliative care.

Figure 3.1 shows the schematic diagram of the Markov model. The health states of patients receiving PEG or palliative care were consisted of six states as follows: 1) CHB with HBeAg positive 2) stable state 3) compensated cirrhosis 4) decompensated cirrhosis 5) hepatocellular carcinoma (HCC) and 6) death. However, for patients receiving antiviral treatments which were 1) original lamivudine 2) generic lamivudine 3) telbivudine 4) adefovir 5) entecavir and 6) tenofovir, in addition to six health states above, CHB with HBeAg positive with drug resistance state was added. The arrows represent the possible transitions from one state to another. All transitional probabilities were obtained from systematic reviews and meta-analysis.

Based on Figure 3.1, all patients who required the treatment based on the mentioned criteria above started at the CHB with HBeAg positive state. For the patients receiving antiviral drugs, if drug resistance was detected or level of serum HBV DNA more than 60 IU/ml, the patients would move to drug resistance state. The patients receiving palliative care or those successfully treated with PEG at the first year would move to stable state. If HBeAg positive CHB patients either with or without drug resistance had HBeAg secoconversion, they would move to stable state.

In addition, the patients in stable state could also reverse to CHB with HBeAg positive state.

HBeAg positive CHB patients either with or without drug resistance and those in stable state could move to compensated cirrhosis, decompensated cirrhosis and HCC states. Patients being in either compensated or decompensated cirrhosis state could reverse to primary state, except for those with HCC, they could move to death state only. Patients in all states could stay at the same state and could move to death state.

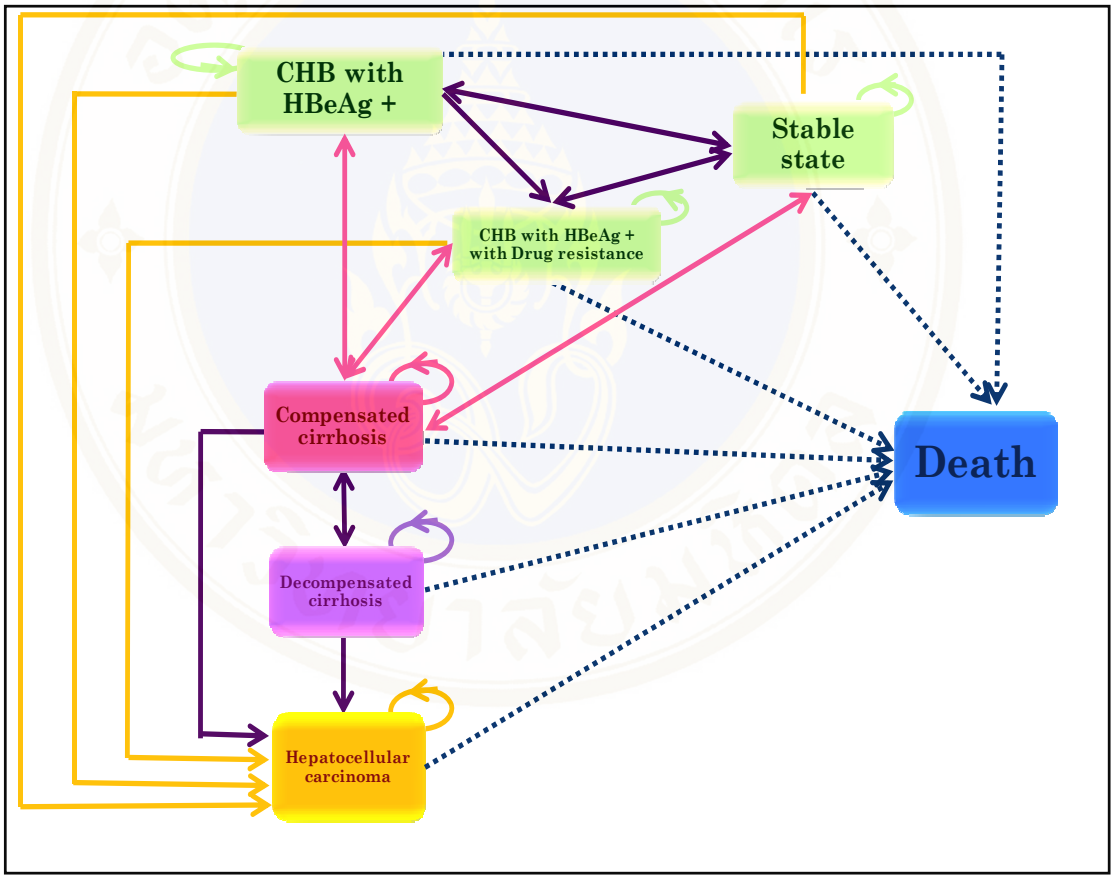



**Figure 3.1 Schematic diagram of the Markov model for CHB**

### 5.2 Model assumptions

Both scenarios have the same model assumptions which were

1. Oral antiviral treatment could be stopped when HBeAg seroconversion with undetectable HBV-DNA had been documented on two separate occasions at least 6 months apart.

2. The duration of treatment with PEG was one year, but if the treatment fails, oral antiviral treatment would be used.

3. For patients who developed drug resistance due to lamivudine, telbivudine or entecavir, adefovir or tenofovir would be added to the regimen.

4. For patients who developed drug resistance due to adefovir, lamivudine would be added to the regimen.

5. The patients who received tenofovir would not develop drug resistance.

6. Efficacy of generic lamivudine was the same as that of original lamivudine.

7. Each treatment had differences in seroconversion rate and resistance rate.

8. Patients with drug resistance had the same disease progression rate, and mortality rate as those without drug resistance.

**5.3 Transitional probabilities**

Transitional probabilities used in this study are as follows (Table 5).

1. The transition to drug resistance
2. The transition to HBeAg seroconversion
3. The transition to compensated cirrhosis
4. The transition to decompensated cirrhosis
5. The transition to HCC
6. The transition to death

The transitional probabilities of clinical efficacy in terms of HBeAg seroconversion of HBeAg-positive CHB treatment options were estimated from a systematic review and meta-analysis using a Bayesian random effect model analyzed by WinBUGS1.4 (Medical Research Council and Imperial College of Science, Technology and Medicine, United Kingdom). All other transitional probabilities were obtained from systematic reviews of the published articles in Thai and other countries (Table 5). In addition, mortality rates of Thai general population at each age were used in the analysis (81).

## 6. Time horizon

Costs and health outcomes were estimated over a 70-year period in order to cover the expected lifetime horizon.

## 7. Cost measurement

### 7.1 Direct medical costs

The relevant direct medical costs data in this study were cost of CHB medications, cost of other medications, cost of laboratory and diagnostic tests, cost of procedures, cost of outpatient visits and cost of hospitalizations (IPD admission) (Table 5). However, costs of the treatment for adverse drug events were not included in this study. The costs of antiviral drugs were estimated using reference prices published by Drug and Medical Supply Information Center (DMSIC), the Ministry of Public Health, Thailand (82). The costs of laboratory and diagnostic tests were estimated using reference prices published by the Comptroller General's Department, the Ministry of Finance, Thailand (83). The cost of complication states such as compensated cirrhosis, decompensated cirrhosis and HCC were obtained from the published study in Thailand (4).

### 7.2 Direct non-medical and indirect costs

According to the societal perspective, direct non-medical costs (i.e., cost of transportation, food and time loss due to receiving treatment) but not direct medical costs incurred outside hospital were included. Moreover, indirect costs including only morbidity costs were calculated from the productivity loss due to sick leave, while mortality costs were excluded.

All direct non-medical and indirect costs were obtained from a systematic review in Thailand. Cost of transportation and food were obtained from the Standard Cost List for Health Technology Assessment (84). Costs of time loss due to receiving treatment were calculated from the multiplication of the minimum wage rate and time loss due to physician visits per year. Cost of productivity loss of complication states such as compensated cirrhosis, decompensated cirrhosis and HCC were calculated from average length of stay per admission (days) and the number of hospital

admission (hospitalization) per year multiplied by the minimum wage rate of Bangkok population obtained from the Department of Labour Protection and Welfare (4, 85).

All costs were converted and reported value in year 2010 using the consumer price index (CPI) (86). For international comparison, costs were converted to international dollars using purchasing power parity (PPP) $ exchange rate at 1 PPP$(2009) = 17.8 Thai baht (87).

## 8. Health outcomes

The health outcomes were life years (LYs) gained and quality adjusted life years (QALYs) gained which is the multiplication of LYs gained and utility score. The utility or the quality of life scores of patients were retrieved from a systematic review from electronic databases (i.e., Pubmed and Cochrane databases). The key words used were as follows: (“Quality of Life” [Mesh] OR “QALYs” OR utility*) AND (hepatitis B OR “CHB” OR “chronic hepatitis B”). Inclusion criteria were the studies with quality of life presented in utility index (0=death and 1=full health) and measured by time trade-off (TTO), standard gamble (SG), or EQ-5D instruments. One eligible study reported that the mean utility index of CHB patients was 0.68 (95%CI=0.66-0.70). In addition, the mean utility indices of CHB patients with compensated cirrhosis, decompensated cirrhosis, and HCC were 0.69 (95%CI=0.66-0.71), 0.35 (95%CI=0.32-0.37) and 0.38 (95%CI=0.36-0.41), respectively (88) (Table 5). The health outcomes of each intervention were compared with palliative care.

## 9. Discounting

Due to time horizon more than one year, all future costs and future outcomes were discounted at the rate of 3% (89). Sensitivity analysis was performed at the discount rate of 0% and 6%.

## 10. Uncertainty analysis

One-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were conducted to examine the effect of uncertainty about parameters in the model. One-way sensitivity analysis is to simply vary each parameter to the highest and

lowest possible values in the model by given amount and examine the impact that the change has on model's results. The possible values are usually reasonable to vary the parameters according to the confidence intervals of the data. A tornado diagram was useful in demonstrating the impact that a fixed change in each parameter has on the main outcomes. In this study, only important parameters of the most cost-saving intervention were selected to perform one-way sensitivity analysis.

The second order Monte Carlo simulation was used to perform PSA by using Microsoft Office Excel 2010 (Microsoft Corp., Redmond, WA). According to the attainable range of each input parameter value, probability distributions were assigned to all parameters: (90) 1) beta-distribution, which is determined to the values in range zero to one, is the distribution of probability and utility parameters, 2) gamma-distribution, which is attributed to the positive values, is the costs parameters distribution, and 3) log-normal distribution is modeled for survival parameters as constant and coefficient for baseline hazard, and ancillary parameter (gamma) of death and failure events. Table 5 shows the distribution and range of each input parameter value. Using simulation by sampling from the distribution of each variable with 1,000 iterations, the analysis provides the feasible values series of total costs, health outcomes, and incremental cost–effectiveness ratio (ICER) in baht per LY and QALY gained. Consequently, all of them were averaged and expressed in the term of probabilistic value. The ICER is calculated by incremental cost divided by incremental effectiveness.

$$ICER = (C_M - C_P) / (E_M - E_P)$$

Where,

$C_M$ = CHB medication cost

$C_P$ = Palliative care cost

$E_M$ = CHB medication effectiveness

$E_P$ = Palliative care effectiveness

In addition a net monetary benefit (NMB) was calculated to determine the intervention giving the maximum expected NMB for each value of ceiling ratio (the

value of society would be willingness to pay (WTP) for intervention giving one QALY gained). In Thailand, the WTP per QALY gained thresholds for implementation health technology and intervention of policy decision makers (i.e., the Subcommittee for Development of the National List of Essential Drugs and the Subcommittee for Development of the Benefit Packages) are 100,000 baht and 300,000 baht per QALY gained or the one time and three times of the gross domestic product (GDP) per capita, respectively, based on 2008 Thai GDP per capita, current prices (National currency) was 134,036 baht (91). Eventually, the results of the PSA were presented as a cost-effectiveness acceptability curves.

## 11. Budget impact analysis

The Markov-based budget impact model was developed to evaluate direct medical cost for HBeAg positive chronic hepatitis B patients based on the governmental perspective over 10 fiscal years. The model calculated and compared only direct medical costs for palliative care with the most cost-effective option with the discount rate of 3%. The number of CHB patients who required the treatment derived from the incidence and the prevalence of HBeAg positive CHB patients who aged more than 30 years. Thai population aged more than 30 years in 2010 was 35.8 million. The incidence of CHB patients aged more than 30 years was 77,267 per year (obtained data from the Burden of Disease and Injury in Thailand project of International Health Policy Program;IHPP, Ministry of Public Health). The prevalence of hepatitis B virus in the general population (4%) and 31% of patients with HBsAg positive CHB are HBeAg positive CHB (10-11). The number of HBeAg positive CHB patients who would receive the treatments was assumed based on expert opinion indicating that only 1 out of 3 patients would require the treatment based on the above mentioned criteria. Thus, the incidence and prevalence of HBeAg positive CHB used in the Markov model was 8,500 and 147,973 per year, respectively.

**Table 3.1 Input parameters used in economic model**

| Parameter | Distribution | Mean | SE | Reference |
|---|---|---|---|---|
| **Yearly discount rate (%)** | | | | |
| Costs (range) | | 3(0-6) | | (92) |
| Outcomes (range) | | 3(0-6) | | (92) |
| **Transitional probability baseline parameters** | | | | |
| Probability of stable to chronic state | Beta | 0.143 | 0.0650 | (93) |
| Probability of chronic to stable state | Beta | 0.056 | 0.0180 | (36) |
| Probability of chronic to compensated in $1^{st}$-$10^{th}$ year | Beta | 0.054 | 0.0543 | (94) |
| Probability of chronic to compensated in $11^{th}$-$20^{th}$ year | Beta | 0.134 | 0.1338 | (94) |
| Probability of chronic to compensated in >$20^{th}$ year | Beta | 0.329 | 0.3292 | (94) |
| Probability of chronic to HCC in $1^{st}$-$5^{th}$ year | Beta | 0.000 | 0.0000 | (95) |
| Probability of chronic to HCC in $6t^{h}$-$10^{th}$ year | Beta | 0.006 | 0.0061 | (95) |
| Probability of chronic to HCC in >$10^{th}$ year | Beta | 0.008 | 0.0081 | (95) |
| Probability of chronic to death in $1^{st}$-$5^{th}$ year | Beta | 0.010 | 0.0102 | (95) |
| Probability of chronic to death in $6^{th}$-$10^{th}$ year | Beta | 0.014 | 0.0144 | (95) |

Chronic= CHB with HBeAg positive state; HCC= Hepatocellular carcinoma; SE= Standard error; LMV= Lamivudine; ADV= Adefovir; TVD= Telbivudine; ETV= Entecavir; TNV= Tenofovir; PEG= Pegylated interferon.

**Table 3.1 Input parameters used in economic model (cont.)**

| Parameter | Distribution | Mean | SE | Reference |
|---|---|---|---|---|
| Probability of chronic to death in >10$^{th}$ year | Beta | 0.025 | 0.0252 | (95) |
| Probability of compensated to decompensated in 1$^{st}$-3$^{th}$ year | Normal | 0.042 | 0.0003 | (96) |
| Probability of compensated to decompensated in 4$^{th}$-5$^{th}$ year | Normal | 0.094 | 0.0005 | (96) |
| Probability of compensated to decompensated in >5$^{th}$ year | Normal | 0.066 | 0.0003 | (96) |
| Probability of compensated to HCC in 1$^{st}$-3$^{th}$ year | Normal | 0.014 | 0.0002 | (96) |
| Probability of compensated to in HCC 4$^{th}$-5$^{th}$ year | Normal | 0.036 | 0.0003 | (96) |
| Probability of compensated to HCC in >5$^{th}$ year | Normal | 0.030 | 0.0002 | (96) |
| Probability of compensated to death in 1$^{st}$-3$^{th}$ year | Beta | 0.014 | 0.0135 | (96) |
| Probability of compensated to death in >3$^{th}$ year | Beta | 0.046 | 0.0461 | (96) |
| Probability of decompensated to HCC | Beta | 0.035 | 0.0354 | (97) |
| Probability of decompensated to death in 1$^{st}$ year | Normal | 0.260 | 0.0004 | (98) |
| Probability of decompensated to death in 2$^{nd}$ year | Normal | 0.390 | 0.0005 | (98) |
| Probability of decompensated to death in >2$^{nd}$ year | Normal | 0.240 | 0.0003 | (98) |
| Probability of HCC to death in 1$^{st}$ year | Beta | 0.848 | 0.0011 | (98) |

Chronic= CHB with HBeAg positive state; HCC= Hepatocellular carcinoma; SE= Standard error; LMV= Lamivudine; ADV= Adefovir; TVD= Telbivudine; ETV= Entecavir; TNV= Tenofovir; PEG= Pegylated interferon.

**Table 3.1 Input parameters used in economic model (cont.)**

| Parameter | Distribution | Mean | SE | Reference |
|---|---|---|---|---|
| Probability of HCC to death in >1st year | Beta | 0.920 | 0.0009 | (98) |
| **Transitional probability of treatment parameters** | | | | |
| Probability of chronic to compensated | Beta | 0.006 | 0.0023 | (99) |
| Probability of chronic to HCC | Beta | 0.009 | 0.0045 | (100) |
| Probability of chronic to death | Beta | 0.002 | 0.0023 | (100) |
| Probability of compensated to HCC | Beta | 0.015 | 0.0034 | (101) |
| Probability of compensated to death | Beta | 0.007 | 0.0070 | (100) |
| Probability of decompensated to HCC | Beta | 0.035 | 0.0127 | (102) |
| Probability of decompensated to death | Beta | 0.126 | 0.0291 | (103) |
| Probability of compensated to chronic | Beta | 0.478 | 0.0665 | (104) |
| Probability of HCC to death | Beta | 0.034 | 0.0227 | (105) |
| **Efficacy of treatment parameters** | | | | |
| Relative risk of seroconversion of LMV | Normal | 3.519 | 1.3707 | Meta-analysis |
| Relative risk of seroconversion of ADV | Normal | 3.028 | 1.3833 | Meta-analysis |

Chronic= CHB with HBeAg positive state; HCC= Hepatocellular carcinoma; SE= Standard error; LMV= Lamivudine; ADV= Adefovir; TVD= Telbivudine; ETV= Entecavir; TNV= Tenofovir; PEG= Pegylated interferon.

**Table 3.1 Input parameters used in economic model (cont.)**

| Parameter | Distribution | Mean | SE | Reference |
|---|---|---|---|---|
| Relative risk of seroconversion of TVD | Normal | 4.286 | 1.4054 | Meta-analysis |
| Relative risk of seroconversion of ETV | Normal | 3.846 | 1.3833 | Meta-analysis |
| Relative risk of seroconversion of PEG | Normal | 5.356 | 1.4987 | Meta-analysis |
| Relative risk of seroconversion of TNV | Normal | 4.167 | 1.6403 | Meta-analysis |
| Probability of delay seroconversion of PEG | Normal | 0.410 | 0.0489 | (37) |
| **Probability of resistance parameters** | | | | |
| Probability of LMV resistance | Beta | 0.214 | 0.0214 | (12) |
| Probability of ADV resistance | Beta | 0.066 | 0.0066 | (12) |
| Probability of TVD resistance | Beta | 0.089 | 0.0089 | (12) |
| Probability of ETV resistance | Beta | 0.002 | 0.0002 | (12) |
| Probability of TNV resistance | Beta | 0.000 | 0.0000 | (12) |
| **Yearly cost of drugs (direct medical cost)** | | | | |
| Cost of generic LMV | Gamma | 1,797 | 180 | (82) |
| Cost of original LMV | Gamma | 34,871 | 3,487 | (82) |

Chronic= CHB with HBeAg positive state; HCC= Hepatocellular carcinoma; SE= Standard error; LMV= Lamivudine; ADV= Adefovir; TVD= Telbivudine; ETV= Entecavir; TNV= Tenofovir; PEG= Pegylated interferon.

**Table 3.1 Input parameters used in economic model (cont.)**

| Parameter | Distribution | Mean | SE | Reference |
|---|---|---|---|---|
| Cost of ADV | Gamma | 70,298 | 7,030 | (82) |
| Cost of TVD | Gamma | 51,504 | 5,150 | (82) |
| Cost of ETV | Gamma | 85,745 | 8,575 | (82) |
| Cost of TNV | Gamma | 15,559 | 1,556 | (82) |
| Cost of PEG | Gamma | 527,379 | 52,738 | (82) |
| Cost of generic LMV+ADV | Gamma | 72,095 | 7,210 | (82) |
| Cost of original LMV+ADV | Gamma | 105,169 | 10,517 | (82) |
| Cost of TVD+ADV | Gamma | 121,802 | 12,180 | (82) |
| Cost of ETV+ADV | Gamma | 156,043 | 15,604 | (82) |
| Cost of generic LMV+TNV | Gamma | 17,356 | 1,736 | (82) |
| Cost of original LMV+TNV | Gamma | 50,430 | 5,043 | (82) |
| Cost of TVD+TNV | Gamma | 67,063 | 6,706 | (82) |
| **Yearly cost of treatment of complications (direct medical cost)** | | | | |
| Cost of treatment of Compensated cirrhosis | Gamma | 81,264 | 81,264 | (4) |
| Cost of treatment of Decompensated cirrhosis | Gamma | 125,127 | 125,127 | (4) |

Chronic= CHB with HBeAg positive state; HCC= Hepatocellular carcinoma; SE= Standard error; LMV= Lamivudine; ADV= Adefovir; TVD= Telbivudine; ETV= Entecavir; TNV= Tenofovir; PEG= Pegylated interferon.

**Table 3.1 Input parameters used in economic model (cont.)**

| Parameter | Distribution | Mean | SE | Reference |
|---|---|---|---|---|
| Cost of treatment of HCC | Gamma | 153,021 | 153,021 | (4) |
| **Yearly cost of laboratory (direct medical cost)** | | | | |
| Cost of laboratory for screening (i.e., HBeAg, HBeAb) | Gamma | 650 | 650 | (83) |
| Cost of laboratory for pretreatment (i.e., AST, ALT, Serum albumin, Hepatic ultrasound, HBV DNA, HVC Ab, HIV Ab, PT, CBC, PTT) | Gamma | 3,350 | 3,350 | (83) |
| Cost of laboratory for monitor (i.e., ALT, HBV DNA, HBeAg) | Gamma | 4,200 | 4,200 | (83) |
| Cost of laboratory monitor for PEG (I.e., ALT, HBV DNA, HBeAg, CBC, TSH) | Gamma | 10,620 | 10,620 | (83) |
| Cost of laboratory monitor for ADV (i.e., Creatinin, BUN, ALT, HBV DNA, HBeAg) | Gamma | 4,560 | 4,560 | (83) |
| Cost of laboratory for posttreatment (i.e., ALT, HBeAg, Anti Hbe, HBV DNA) | Gamma | 4,900 | 4,900 | (83) |

Chronic= CHB with HBeAg positive state; HCC= Hepatocellular carcinoma; SE= Standard error; LMV= Lamivudine; ADV= Adefovir; TVD= Telbivudine; ETV= Entecavir; TNV= Tenofovir; PEG= Pegylated interferon.

**Table 3.1 Input parameters used in economic model (cont.)**

| Parameter | Distribution | Mean | SE | Reference |
|---|---|---|---|---|
| **Yearly cost of patient (direct non-medical cost)** | | | | |
| Cost of transportation | Gamma | 571.32 | 571.32 | (84) |
| Cost of food | Gamma | 210.44 | 210.44 | (84) |
| **Yearly cost of patient (indirect medical cost)** | | | | |
| Cost of time loss due to receiving treatment | Gamma | 824 | 824 | (85) |
| Cost of productivity loss of compensated cirrhosis | Gamma | 47.65 | 47.65 | (4, 85) |
| Cost of productivity loss of decompensated cirrhosis | Gamma | 626.55 | 626.55 | (4, 85) |
| Cost of productivity loss of HCC | Gamma | 1,701.42 | 1,701.42 | (4, 85) |
| **Utility parameters** | | | | |
| Utility weight for Chronic | Normal | 0.68 | 0.00005 | (88) |
| Utility weight for Compensated Cirrhosis | Normal | 0.69 | 0.00016 | (88) |
| Utility weight for Decompensated Cirrhosis | Normal | 0.35 | 0.00031 | (88) |
| Utility weight for HCC | Normal | 0.38 | 0.00026 | (88) |

Chronic= CHB with HBeAg positive state; HCC= Hepatocellular carcinoma; SE= Standard error; LMV= Lamivudine; ADV= Adefovir; TVD= Telbivudine; ETV= Entecavir; TNV= Tenofovir; PEG= Pegylated interferon.

# CHAPTER IV
# RESULTS

The results of this study were divided into three parts as follows:

1. Cost-utility analysis
2. Uncertainty analysis
3. Budget impact analysis

## Part one: Cost-utility analysis

The cost-utility analysis based on societal perspective estimated the life time cost and health outcomes which were quality adjusted life years (QALYs) and life years (LYs) of each treatment option for HBeAg positive CHB patients. Total costs, LYs and QALYs of all treatments compared with palliative care in patients with HBeAg positive CHB aged 30 year are shown in Table 4.1. The cost of generic lamivudine plus adding tenofovir when drug resistance occurred was the lowest (456,000 THB), followed by generic lamivudine plus adding tenofovir based on the road map guideline (490,000 THB) and tenofovir monotherapy (501,000 THB). All three interventions had lower cost than palliative care. The CHB patients receiving pegylated interferon (PEG) at the first year and adefovir at the third year if the treatment failed and then adding original lamivudine when drug resistance occurred due to adefovir had the highest cost (1,812,000 THB). In addition, patients receiving palliative care had less LYs (13.13) and QALYs (8.63) compared to those receiving CHB treatments (LYs=21, QALYs=13.7).

**Table 4.1 Total costs, LYs and QALYs of all interventions for HBeAg positive CHB patient aged at 30 years**

| Interventions | Total costs (THB) †* | LYs | QALYs |
|---|---|---|---|
| Generic LMV (+TNV) | 456,000 | 20.87 | 13.66 |
| Generic LMV (+TNV based on the road map guideline) | 490,000 | 20.87 | 13.66 |
| TNV | 501,000 | 20.89 | 13.67 |
| Palliative care | 527,000 | 13.13 | 8.63 |
| Original LMV (+TNV) | 937,000 | 20.87 | 13.66 |
| PEG at 1st yr. and original LMV at 3nd yr. if treatment failed (+ TNV) | 953,000 | 20.89 | 13.67 |
| Original LMV (+TNV by Road map) | 971,000 | 20.87 | 13.66 |
| Generic LMV (+ADV) | 982,000 | 20.87 | 13.66 |
| PEG at 1st yr. and TNV at 3nd yr. if treatment failed | 1,057,000 | 20.91 | 13.69 |
| TVD (+TNV) | 1,091,000 | 20.90 | 13.68 |
| Generic LMV (+ADV by Road map) | 1,134,000 | 20.87 | 13.66 |
| TVD (+TNV by Road map) | 1,134,000 | 20.87 | 13.66 |
| PEG at 1st yr. and original LMV at 3nd yr. if treatment failed (+ TNV) | 1,325,000 | 20.89 | 13.67 |
| ADV (+generic LMV) | 1,364,000 | 20.85 | 13.64 |
| PEG at 1st yr. and generic LMV at 3nd yr. if treatment failed (+ ADV) | 1,371,000 | 20.89 | 13.67 |
| TVD (+ADV) | 1,429,000 | 20.90 | 13.68 |

†Total costs are calculated in 2010 THB

* Costs are rounded up to nearest 1,000 THB

**Table 4.1 Total costs, LYs and QALYs of all interventions for HBeAg positive CHB patient aged at 30 years (cont.)**

| Interventions | Total costs (THB) †* | LYs | QALYs |
|---|---|---|---|
| PEG at 1st yr. and TVD at 3nd yr. if treatment failed (+ TNV) | 1,442,000 | 20.92 | 13.69 |
| Original LMV (+ADV) | 1,463,000 | 20.87 | 13.66 |
| ETV (+TNV) | 1,519,000 | 20.88 | 13.67 |
| ETV (+ADV) | 1,536,000 | 20.88 | 13.67 |
| ADV (+original LMV) | 1,564,000 | 20.85 | 13.64 |
| Original LMV (+ADV by Road map) | 1,616,000 | 20.87 | 13.66 |
| PEG at 1st yr. and ADV at 3nd yr. if treatment failed (+ generic LMV) | 1,648,000 | 20.88 | 13.66 |
| TVD (+ADV by Road map) | 1,657,000 | 20.90 | 13.68 |
| PEG at 1st yr. and TVD at 3nd yr. if treatment failed (+ADV) | 1,710,000 | 20.92 | 13.69 |
| PEG at 1st yr. and original LMV at 3nd yr. if treatment failed (+ADV) | 1,744,000 | 20.89 | 13.67 |
| PEG at 1st yr. and ETV at 3nd yr. if treatment failed (+TNV) | 1,771,000 | 20.90 | 13.68 |
| PEG at 1st yr. and ETV at 3nd yr. if treatment failed (+ADV) | 1,785,000 | 20.90 | 13.68 |
| PEG at 1st yr. and ADV at 3nd yr. if treatment failed (+ original LMV) | 1,812,000 | 20.88 | 13.66 |

†Total costs are calculated in 2010 THB

* Costs are rounded up to nearest 1,000 THB

Cost-utility analysis was performed to compare all medications in the treatment of HBeAg positive CHB patients. The results were presented as the incremental cost effectiveness ratio (ICER) in THB per LY gained (Table 4.2) and

QALY gained (Table 4.3) when compared with palliative care. According to the Thai Subcommittee for Development of the National List of Essential Drugs, the willingness to pay (WTP) threshold for a QALY gained for the adoption of health technologies and interventions is between one and three times the Thai GDP (i.e., approximately 100,000 to 300,000 THB) (106). In this study, providing generic lamivudine plus adding tenofovir when drug resistance occurred (ICER = -9,000 THB/LY gained or -14,000 THB/QALY gained), generic lamivudine plus adding tenofovir based on the road map guideline (ICER = -5,000 THB/LY gained or -8,000 THB/QALY gained) and tenofovir monotherapy (ICER = -3,000 THB/LY gained or -5,000 THB/QALY gained) were dominant and cost-saving options compared to palliative care (Table 4.2 and 4.3). Negative ICER values indicated that the interventions had higher effectiveness and lower costs when compared with palliative care.

**Table 4.2 Incremental cost, incremental LYG and incremental cost-effectiveness ratio of all interventions compared with palliative care among HBeAg positive CHB patient aged at 30 years**

| Intervention | Incremental cost (THB) | Incremental LYs | ICER per LY gained |
|---|---|---|---|
| Generic LMV (+TNV) | -72,000 | 7.74 | Dominant* |
| Generic LMV (+TNV by Road map) | -38,000 | 7.74 | Dominant* |
| TNV | -26,000 | 7.76 | Dominant* |
| Original LMV (+TNV) | 409,000 | 7.74 | 53,000 |
| PEG at 1st yr. and generic LMV at 3nd yr. if treatment failed (+ TNV) | 426,000 | 7.77 | 55,000 |
| Original LMV (+TNV by Road map) | 444,000 | 7.74 | 57,000 |
| Generic LMV (+ADV) | 454,000 | 7.74 | 59,000 |
| PEG at 1st yr. and TNV at 3nd yr. if treatment failed | 530,000 | 7.78 | 68,000 |
| TVD (+TNV) | 564,000 | 7.78 | 72,000 |
| Generic LMV (+ADV by Road map) | 606,000 | 7.74 | 78,000 |
| TVD (+TNV by Road map) | 606,000 | 7.74 | 78,000 |
| PEG at 1st yr. and original LMV at 3nd yr. if treatment failed (+ TNV) | 798,000 | 7.77 | 103,000 |
| ADV (+LMV_GPO) | 837,000 | 7.72 | 108,000 |
| PEG at 1st yr. and generic LMV at 3nd yr. if treatment failed (+ ADV) | 844,000 | 7.77 | 109,000 |
| TVD (+ADV) | 902,000 | 7.78 | 116,000 |

†ICERs are rounded up to nearest 1,000 THB

*Negative ICER due to higher effectiveness and lower costs of intervention compared with palliative care

**Table 4.2 Incremental cost, incremental LYG and incremental cost-effectiveness ratio of all interventions compared with palliative care among HBeAg positive CHB patient aged at 30 years (cont.)**

| Intervention | Incremental cost (THB) | Incremental LYs | ICER per LY gained |
|---|---|---|---|
| PEG at 1st yr. and TVD at 3nd yr. if treatment failed (+ TNV) | 915,000 | 7.79 | 117,000 |
| Original LMV (+ADV) | 936,000 | 7.74 | 121,000 |
| ETV (+TNV) | 991,000 | 7.75 | 128,000 |
| ETV (+ADV) | 1,009,000 | 7.75 | 130,000 |
| ADV (+original LMV) | 1,037,000 | 7.72 | 134,000 |
| Original LMV (+ADV by Road map) | 1,088,000 | 7.74 | 141,000 |
| PEG at 1st yr. and ADV at 3nd yr. if treatment failed (+ generic LMV) | 1,120,000 | 7.75 | 145,000 |
| TVD (+ADV by Road map) | 1,130,000 | 7.78 | 145,000 |
| PEG at 1st yr. and TVD at 3nd yr. if treatment failed (+ADV) | 1,182,000 | 7.79 | 152,000 |
| PEG at 1st yr. and original LMV at 3nd yr. if treatment failed (+ADV) | 1,216,000 | 7.77 | 157,000 |
| PEG at 1st yr. and ETV at 3nd yr. if treatment failed (+TNV) | 1,243,000 | 7.78 | 160,000 |
| PEG at 1st yr. and ETV at 3nd yr. if treatment failed (+ADV) | 1,257,000 | 7.78 | 162,000 |
| PEG at 1st yr. and ADV at 3nd yr. if treatment failed (+ original LMV) | 1,284,000 | 7.75 | 166,000 |

†ICERs are rounded up to nearest 1,000 THB

*Negative ICER due to higher effectiveness and lower costs of intervention compared with palliative care

**Table 4.3 Incremental cost, incremental QALYs and incremental cost-effectiveness ratio of all interventions compared with palliative care among HBeAg positive CHB patient aged at 30 years**

| Intervention | Incremental cost(THB) | Incremental QALYs | ICER per QALYgained |
|---|---|---|---|
| Generic LMV (+TNV) | -72,000 | 5.03 | Dominant* |
| Generic LMV (+TNV by Road map) | -38,000 | 5.03 | Dominant* |
| TNV | -26,000 | 5.04 | Dominant* |
| Original LMV (+TNV) | 409,000 | 5.03 | 81,000 |
| PEG at 1st yr. and generic LMV at 3nd yr. if treatment failed (+ TNV) | 426,000 | 5.05 | 84,000 |
| Original LMV (+TNV by Road map) | 444,000 | 5.03 | 88,000 |
| Generic LMV (+ADV) | 454,000 | 5.03 | 90,000 |
| PEG at 1st yr. and TNV at 3nd yr. if treatment failed | 530,000 | 5.06 | 105,000 |
| TVD (+TNV) | 564,000 | 5.05 | 112,000 |
| Generic LMV (+ADV by Road map) | 606,000 | 5.03 | 121,000 |
| TVD (+TNV by Road map) | 606,000 | 5.03 | 121,000 |
| PEG at 1st yr. and original LMV at 3nd yr. if treatment failed (+ TNV) | 798,000 | 5.05 | 158,000 |
| ADV (+LMV_GPO) | 837,000 | 5.01 | 167,000 |
| PEG at 1st yr. and generic LMV at 3nd yr. if treatment failed (+ ADV) | 844,000 | 5.05 | 167,000 |
| TVD (+ADV) | 902,000 | 5.05 | 178,000 |

†ICERs are rounded up to nearest 1,000 THB

*Negative ICER due to higher effectiveness and lower costs of intervention compared with palliative care

**Table 4.3 Incremental cost, incremental QALYs and incremental cost-effectiveness ratio of all interventions compared with palliative care among HBeAg positive CHB patient aged at 30 years (cont.)**

| Intervention | Incremental cost(THB) | Incremental QALYs | ICER per QALYgained |
|---|---|---|---|
| PEG at 1st yr. and TVD at 3nd yr. if treatment failed (+ TNV) | 915,000 | 5.06 | 181,000 |
| Original LMV (+ADV) | 936,000 | 5.03 | 186,000 |
| ETV (+TNV) | 991,000 | 5.04 | 197,000 |
| ETV (+ADV) | 1,009,000 | 5.04 | 200,000 |
| ADV (+original LMV) | 1,037,000 | 5.01 | 207,000 |
| Original LMV (+ADV by Road map) | 1,088,000 | 5.03 | 216,000 |
| PEG at 1st yr. and ADV at 3nd yr. if treatment failed (+ generic LMV) | 1,120,000 | 5.04 | 222,000 |
| TVD (+ADV by Road map) | 1,130,000 | 5.05 | 224,000 |
| PEG at 1st yr. and TVD at 3nd yr. if treatment failed (+ADV) | 1,182,000 | 5.06 | 233,000 |
| PEG at 1st yr. and original LMV at 3nd yr. if treatment failed (+ADV) | 1,216,000 | 5.05 | 241,000 |
| PEG at 1st yr. and ETV at 3nd yr. if treatment failed (+TNV) | 1,243,000 | 5.05 | 246,000 |
| PEG at 1st yr. and ETV at 3nd yr. if treatment failed (+ADV) | 1,257,000 | 5.05 | 249,000 |
| PEG at 1st yr. and ADV at 3nd yr. if treatment failed (+ original LMV) | 1,284,000 | 5.04 | 255,000 |

†ICERs are rounded up to nearest 1,000 THB

*Negative ICER due to higher effectiveness and lower costs of intervention compared with palliative care

In addition, the ICER results of all interventions among HBeAg positive CHB patient aged at 30 years are presented as the cost-effectiveness planes which Y-axes represents incremental cost and X-axes demonstrates incremental effectiveness (i.e., LYs and QALYs as shown in Figure 4.1and 4.2, respectively) when compared with palliative care. The ICERs of three interventions (i.e., generic lamivudine plus adding tenofovir when drug resistance occurred, generic lamivudine plus adding tenofovir based on the road map guideline and tenofovir monotherapy) were located on the lower right-hand quadrant of the plane in Figure 4.1 and 4.2 indicated that these three best interventions had higher effectiveness and lower costs or cost-saving compared to palliative care. Moreover, to consider the next best intervention subsequent to tenofovir monotherapy, providing PEG at the first year and generic lamivudine at the third year if the treatment failed and then adding tenofovir when drug resistance occurred yielded incremental LYs or QALYs of 0.01 higher compared to providing tenofovir only. However, this intervention might not cost-effective, because very high costs (i.e., 11 million or 170 million THB) would be needed to spend in order to gain only 0.01 LY or QALY compared to tenofovir monotherapy. The other remainder interventions might not cost-effective either due to similar above reason.

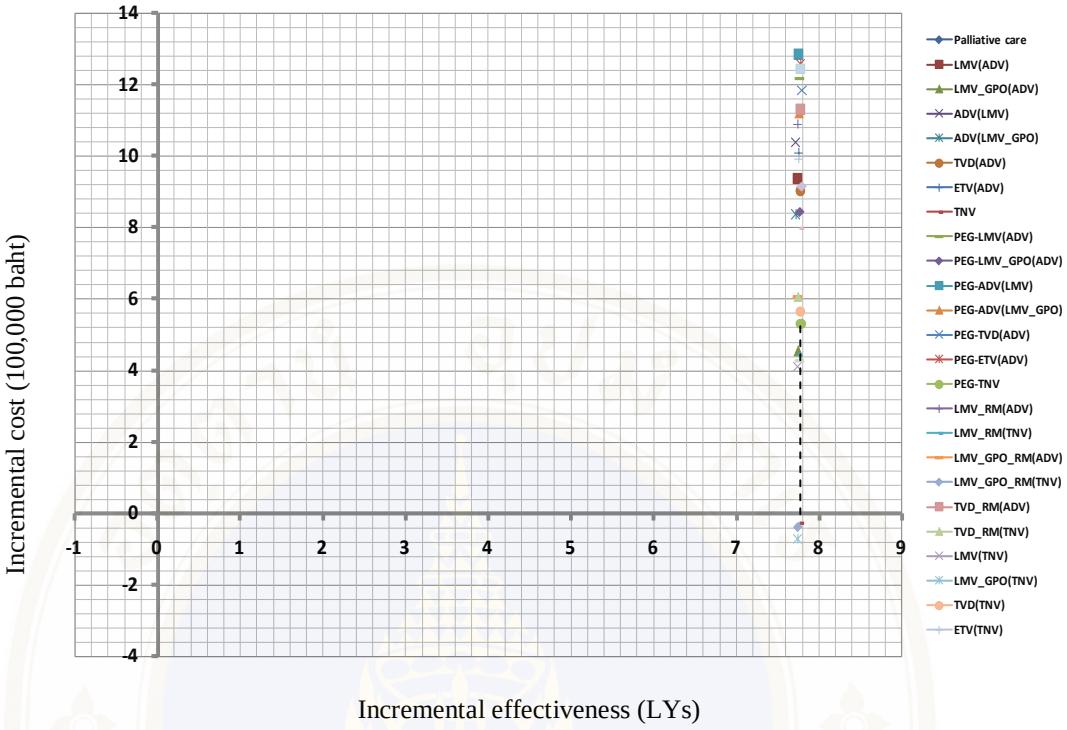



**Figure 4.1 Incremental cost-effectiveness ratios (ICERs/LYs) of all interventions compared with palliative care among HBeAg positive CHB patient aged at 30 years**

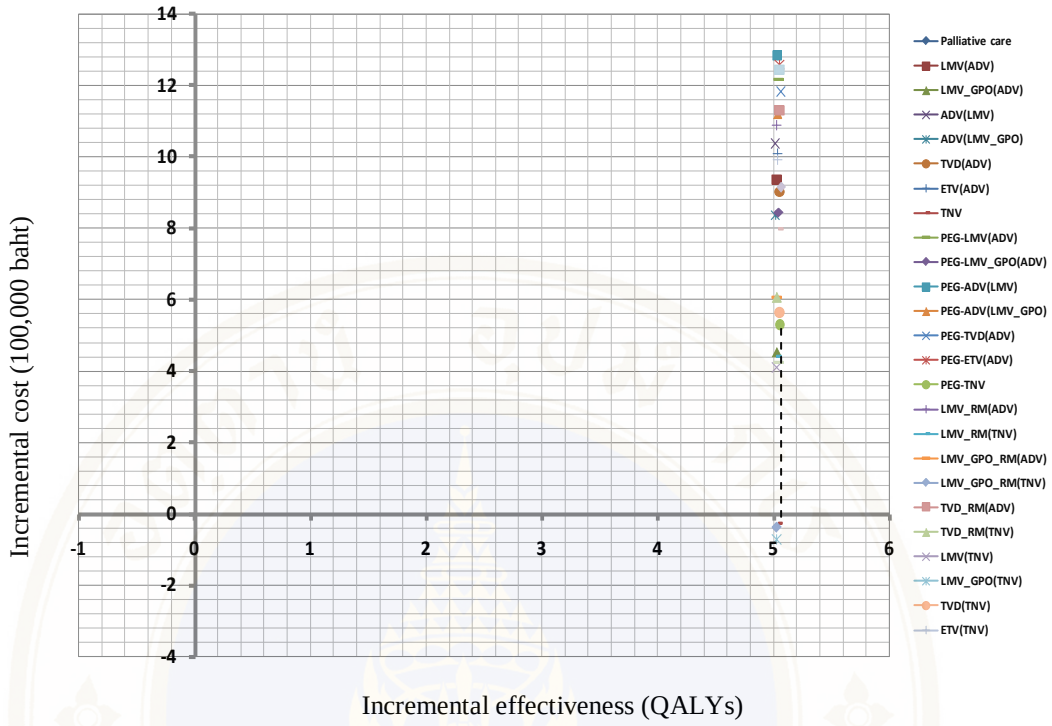



**Figure 4.2 Incremental cost-effectiveness ratios (ICERs/QALYs) of all interventions compared with palliative care among HBeAg positive CHB patient aged at 30 years.**

Moreover, Table 4.4 shows total costs, LYs and QALYs of four interventions (i.e., generic lamivudine plus adding tenofovir when drug resistance occurred, generic lamivudine plus adding tenofovir based on the road map guideline, lamivudine and palliative care) for HBeAg positive CHB patients at age 40, 50, 60 and 70 years. The results indicated that total costs, LYs and QALYs would be decreased when age of patients increased. For example, HBeAg positive CHB patients receiving generic lamivudine plus adding tenofovir when drug resistance occurred at age 40 (405,000 THB), 50 (343,000 THB), 60 (286,000 THB) or 70 (209,000 THB) years had the lowest cost, whereas those receiving palliative care at age 40 (496,000 THB), 50 (455,000 THB), 60 (384,000 THB) or 70 (291,000 THB) years had the highest cost. In addition, patients receiving each CHB treatment at age 40 (19 LYs, 13 QALYs), 50 (17 LYs, 11 QALYs), 60 (14 LYs, 9 QALYs) and 70 (11 LYs, 7 QALYs) years had almost equal total LYs and QALYs which were higher compared

to those receiving palliative care at age 40 (12.77 LYs, 8.40 QALYs), 50 (12.04 LYs, 7.94 QALYs), 60 (10.86 LYs, 7.19 QALYs) and 70 (8.94 LYs, 5.95 QALYs).

**Table 4.4 Total costs, LYs and QALYs of four interventions for HBeAg positive CHB patients at age 40, 50, 60 and 70 years**

| Interventions | Age (Year) | Total costs (THB) †* | LYs | QALYs |
|---|---|---|---|---|
| Generic LMV (+TNV) | 40 | 405,000 | 19.16 | 12.55 |
| | 50 | 343,000 | 16.86 | 11.06 |
| | 60 | 286,000 | 13.95 | 9.15 |
| | 70 | 209,000 | 10.65 | 7.00 |
| Generic LMV (+TNV based on the road map guideline) | 40 | 439,000 | 19.16 | 12.55 |
| | 50 | 376,000 | 16.86 | 11.06 |
| | 60 | 318,000 | 13.95 | 9.15 |
| | 70 | 238,000 | 10.65 | 7.00 |
| TNV | 40 | 451,000 | 19.18 | 12.56 |
| | 50 | 387,000 | 16.88 | 11.07 |
| | 60 | 329,000 | 13.96 | 9.16 |
| | 70 | 248,000 | 10.66 | 7.00 |
| Palliative care | 40 | 496,000 | 12.77 | 8.40 |
| | 50 | 455,000 | 12.04 | 7.94 |
| | 60 | 384,000 | 10.86 | 7.19 |
| | 70 | 291,000 | 8.94 | 5.95 |

†Total costs are calculated in 2010 THB

* Costs are rounded up to nearest 1,000 THB

Incremental cost, incremental LYs, incremental QALYs and incremental cost-effectiveness ratio of three cost-saving interventions (i.e., generic lamivudine plus adding tenofovir when drug resistance occurred, generic lamivudine plus adding tenofovir based on the road map guideline, lamivudine compared with palliative care among HBeAg positive CHB patients aged 40, 50, 60 and 70 years were shown in Table 4.5 and Table 4.6. The results showed that providing generic lamivudine plus adding tenofovir when drug resistance occurred, generic lamivudine plus adding tenofovir based on the road map guideline or tenofovir monotherapy for HBeAg positive CHB patients at age between 40-70 years was still dominant and cost-saving option compared to palliative care.

**Table 4.5 Incremental cost, incremental LYs and incremental cost-effectiveness ratio of three cost-saving interventions compared with palliative care among HBeAg positive CHB patients at age 40, 50, 60 and 70 years**

| Interventions | Age (Year) | Incremental cost (THB) | Incremental LYs | ICER per LY gained |
|---|---|---|---|---|
| Generic LMV (+TNV) | 40 | -91,000 | 6.39 | -14,000 |
| | 50 | -112,000 | 4.82 | -23,000 |
| | 60 | -98,000 | 3.09 | -32,000 |
| | 70 | -82,000 | 1.72 | -48,00 |
| Generic LMV (+TNV based on the road map guideline) | 40 | -57,000 | 6.39 | -9,000 |
| | 50 | -79,000 | 4.82 | -16,000 |
| | 60 | -66,000 | 3.09 | -21,000 |
| | 70 | -52,000 | 1.72 | -30,000 |
| TNV | 40 | -45,000 | 6.41 | -7,000 |
| | 50 | -68,000 | 4.84 | -14,000 |
| | 60 | -55,000 | 3.10 | -18,000 |
| | 70 | -42,000 | 1.72 | -25,000 |

[†]Total costs are calculated in 2010 THB

* Costs are rounded up to nearest 1,000 THB

**Table 4.6 Incremental cost, incremental QALYs and incremental cost-effectiveness ratio of three cost-saving interventions among HBeAg positive CHB patients at age 40, 50, 60 and 70 years**

| Interventions | Age (Year) | Incremental cost (THB) | Incremental QALYs | ICER per QALYs gained |
|---|---|---|---|---|
| Generic LMV (+TNV) | 40 | -91,000 | 4.14 | -22,000 |
| | 50 | -112,000 | 3.12 | -36,000 |
| | 60 | -98,000 | 1.97 | -50,000 |
| | 70 | -82,000 | 1.05 | -78,000 |
| Generic LMV (+TNV based on the road map guideline) | 40 | -57,000 | 4.14 | -14,000 |
| | 50 | -79,000 | 3.12 | -25,000 |
| | 60 | -66,000 | 1.97 | -34,000 |
| | 70 | -52,000 | 1.05 | -49,000 |
| TNV | 40 | -45,000 | 4.15 | -11,000 |
| | 50 | -68,000 | 3.13 | -22,000 |
| | 60 | -55,000 | 1.97 | -28,000 |
| | 70 | -42,000 | 1.06 | -40,000 |

†Total costs are calculated in 2010 THB

* Costs are rounded up to nearest 1,000 THB

## Part two: Uncertainty analysis

### 1.1 One way sensitivity analysis

One-way sensitivity analysis was conducted to investigate the effect of model variable uncertainty and presented as tornado diagram as show in Figure 4.3. We selected only important parameters of the most cost-saving intervention (i.e., generic lamivudine plus adding tenofovir when drug resistance occurred). Discount

rate of 0% and 6% were used. The ranges of 95% confidence interval of transitional probabilities, utility scores and cost of generic and original lamivudine were applied. The minimum cost of tenofovir (i.e., 10 THB per tablet) was obtained from the estimated price by the director of the Government Pharmaceutical Organization (GPO) and the maximum cost of 235 THB per tablet was assumed to be equal to the price of entecavir because the prices of tenofovir and entecavir were similar in the US. Moreover, 95% confidence intervals of the cost for treatment of all complications (i.e., compensated cirrhosis, decompensated cirrhosis and HCC) were applied in the model.

It was found that when altering the value of each parameter, the ICER per QALY gained was the most sensitive to the changes in the cost of treatment of compensated cirrhosis, the price of tenofovir, the price of lamivudine, the cost of treatment of decompensated cirrhosis, the cost of treatment of HCC, the discount rate of 0% and 6% per annum for cost and outcome, the relative risk of seroconvertion of lamivudine and the probability of chronic state to death state. It was noted that the ICER was less sensitive to the changes in the utility score of HCC state, probability of compensated cirrhosis state to HCC state and the utility score of decompensated cirrhosis state.

As the one-way sensitivity results shown the cost of treatment of all complications (i.e., compensated cirrhosis, decompensated cirrhosis and HCC) would be the most affect to changing the ICER value. Moreover the direct medical costs of complication states were obtained from the published study of hepatitis C in Thailand (4). This study was multi-center observational study conducted at five major tertiary care hospitals in Thailand, so that the cost of treatment of all complications might be lower than from those conducted in CHB patients or in regional hospital. The ICER would be change from negative to positive, so it was not cost-saving. However, it would be still cost-effective intervention because the ICER in one-way sensitivity were lower than one times the Thai GDP per capita (106).

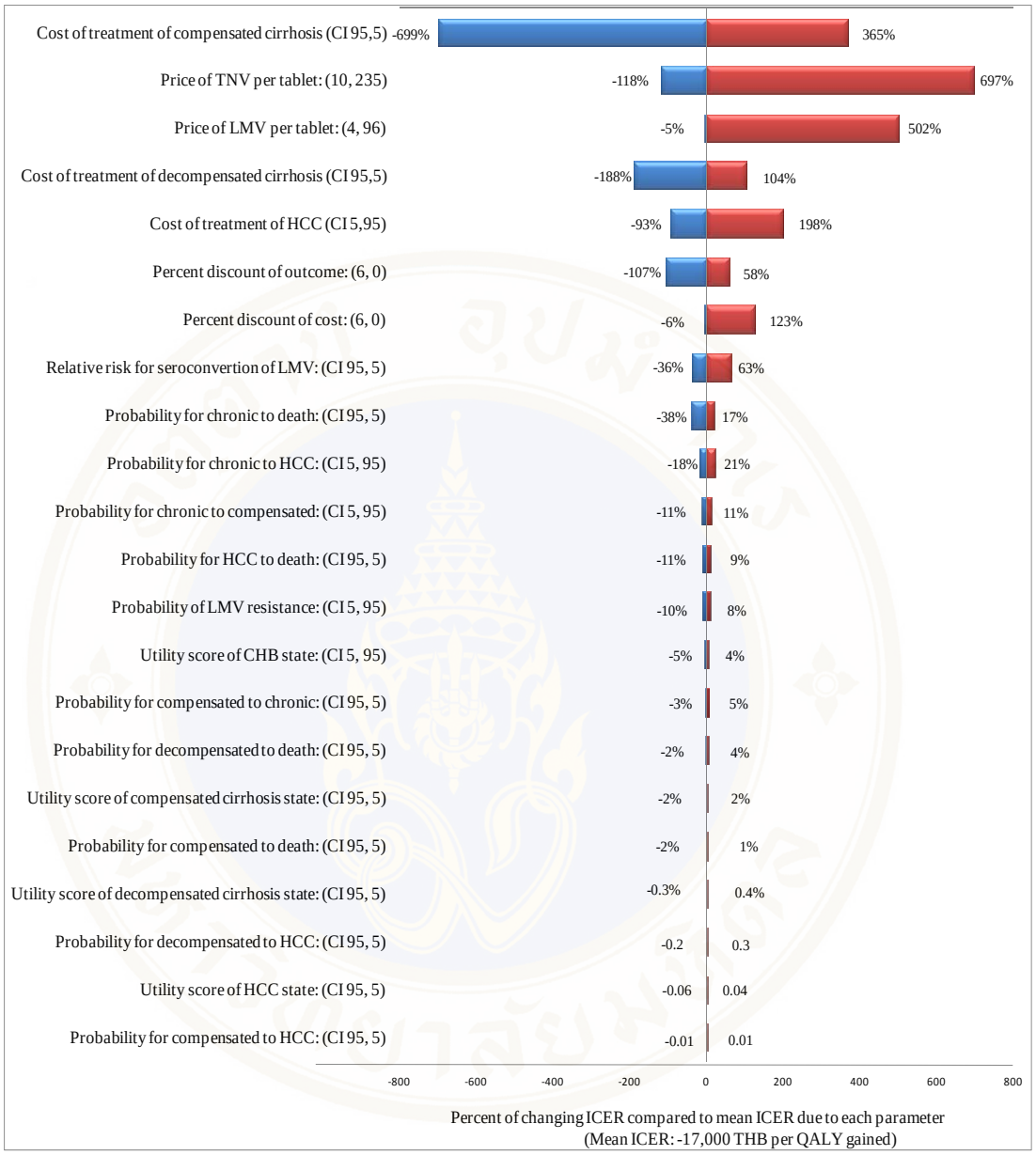



**Figure 4.3 Tornado diagram showing the sensitivity of the ICER to plausible ranges of individual parameters**

### 2.2 Probabilistic sensitivity analysis (PSA)

Base on societal perspective**,** PSA was carried out the impact of the uncertainty of input parameters of which distributions were defined and shown in Table 3.1. PSA were presented as a cost-effectiveness acceptability curves. According to the Thai Subcommittee for Development of the National List of Essential Drugs, the willingness to pay (WTP) threshold for a QALY gained for the adoption of health

technologies and interventions is between one and three times the Thai GDP (i.e., approximately 100,000 to 300,000 THB), shown by the vertical dashed lines in Figure 4.4.

Figure 4.4 illustrates the cost-effectiveness acceptability curve base on the PSA results among HBeAg positive CHB patients who received treatment intervention. When compared with all interventions, at a WTP threshold of 100,000 and 300,000 THB per QALY gained, the probabilities that providing generic lamivudine plus adding tenofovir when drug resistance occurred would be cost-effective was 78% and 75%, respectively. When the WTP threshold increased, the probabilities of providing tenofovir monotherapy being cost-effective would also be increased, while as the probabilities of providing generic lamivudine plus adding tenofovir when drug resistance occurred being cost-effective would be decreased.

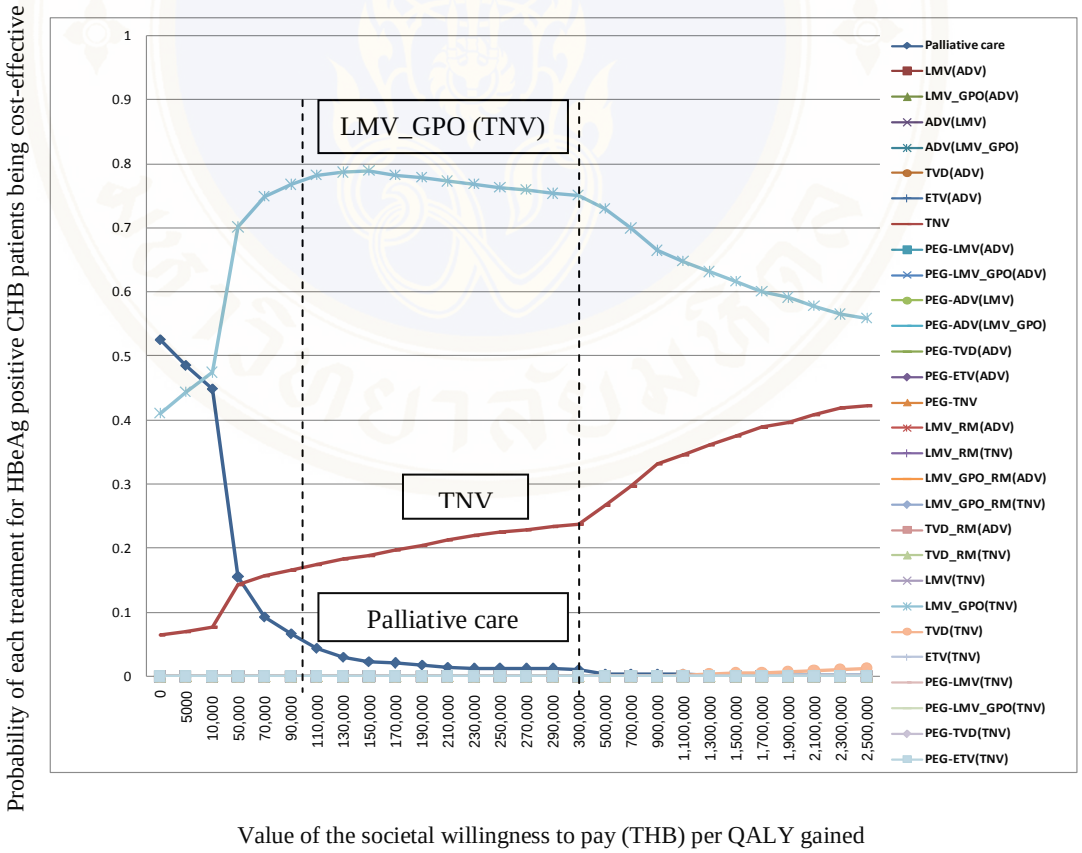



**Figure 4.4 Cost-effectiveness acceptability curve of treatment intervention for HBeAg positive CHB patients**

## Part three: Budget impact analysis

Based on the results of cost-utility analysis, providing generic lamivudine plus adding tenofovir when drug resistance occurred and tenofovir monotherapy were found to be cost-saving options. Therefore, the budget impact analysis was conducted to calculate how much impact on future expenditures when adopted these two interventions in the treatment of HBeAg positive CHB patients compared with palliative care based on the NHSO's perspective. The governmental budget impact of providing generic lamivudine plus adding tenofovir when drug resistance occurred and tenofovir compared with palliative care among HBeAg positive CHB patients aged more than 30 years during fiscal years 2010 to 2019 is presented in Table 4.7.

According to the results, the first year total budget required for providing generic lamivudine plus adding tenofovir when drug resistance occurred was 938 million THB and increased to 2,902 and 3,257 million THB at the fifth and tenth years, respectively. In addition, the total budget of providing tenofovir was 3,092 million THB at the first year and increased to 3,549 and 3,669 million THB at the fifth and tenth years, respectively. The total budget required for providing palliative care was 657 million THB at the first year and dramatically increased to 2,975 and 6,625 million THB at the fifth and tenth years, respectively.

When compared with palliative care, the incremental budget of providing generic lamivudine plus adding tenofovir when drug resistance occurred increased at the second year and steadily decreased. Finally the budget could be saved after the fifth year. In addition, the incremental budget of tenofovir monotherapy compared with palliative care gradually decreased and finally could be saved at the seventh year.

**Table 4.7 Estimated total budget impact (million THB) during fiscal years 2010 to 2019 of providing generic lamivudine plus adding tenofovir when drug resistance occurred and tenofovir compared with palliative care for HBeAg positive CHB patients**

| Fiscal year | Estimated total budget (million THB) | | | Incremental budget (million THB) | |
|---|---|---|---|---|---|
| | Generic LMV(+TNV) | TNV | Palliative care | Generic LMV(+TNV) | TNV |
| 2010 | 938 | 3,092 | 657 | 281 | 2,435 |
| 2011 | 1,741 | 3,183 | 1,305 | 436 | 1,878 |
| 2012 | 2,246 | 3,212 | 1,922 | 324 | 1,290 |
| 2013 | 2,610 | 3,380 | 2,480 | 130 | 900 |
| 2014 | 2,902 | 3,549 | 2,975 | -73 | 574 |
| 2015 | 3,140 | 3,720 | 3,380 | -240 | 340 |
| 2016 | 3,192 | 3,705 | 4,339 | -1,147 | -634 |
| 2017 | 3,223 | 3,694 | 5,019 | -1,796 | -1,325 |
| 2018 | 3,244 | 3,682 | 5,511 | -2,267 | -1,829 |
| 2019 | 3,257 | 3,669 | 6,625 | -3,369 | -2,957 |

At present, only lamivudine has been included in the NLED, but not tenofovir for patients with CHB. Thus, the information on the required budget when included tenofovir in the benefit package based on the NHSO's perspective would be useful. Table 4.8 demonstrates the estimated number of new cases and the budget of providing generic lamivudine plus adding tenofovir when drug resistance occurred for only new HBeAg positive CHB cases aged more than 30 years on the governmental budget during fiscal years 2010 to 2019. Of all new cases, some patients could stop the treatment because they had good response or had seroconversion occurred, while some patients required the treatment. The number of only new HBeAg positive CHB cases patients who need the treatment would increase from 8,500 people at the first year to nearly 60,000 people at the tenth year. The number of new HBeAg positive CHB cases who required tenofovir was used to calculate the the budget of tenofovir with the prices of 43 THB and 10 THB per tablet as shown at the fourth and the fifth

column, respectively (Table 4.8). However, we did not discount the total budget because the policymakers would like to know the exact budget when included tenofovir into the NLED.

At the first year, the budget of providing generic lamivudine plus adding tenofovir when drug resistance occurred including the cost of treatment, cost of monitoring and cost of lamivudine but not the cost of tenofovir was 51 million THB. When the price of tenofovir was 43 or 10 THB per tablet, the budget of tenofovir was 29 or 7 million THB at the second year, respectively. As the number of new cases increased, the budget of tenofovir would be increased in the next years.

**Table 4.8 Budget of providing generic lamivudine plus adding tenofovir when drug resistance occurred for new HBeAg positive CHB cases during fiscal years 2010 to 2019**

| Fiscal year | Number of new HBeAg positive CHB cases who required the treatment (person) | Number of new cases who required TNV (person) | Budget including the cost of treatment, cost of monitoring and cost of lamivudine (million THB) | Budget of TNV with the price of 43 THB/tablet (millionTHB) | Budget of TNV with the price of 10 THB/tablet (millionTHB) |
|---|---|---|---|---|---|
| 2010 | 8,500 | - | 51 | - | - |
| 2011 | 15,281 | 1,819 | 117 | 29 | 7 |
| 2012 | 21,633 | 4,454 | 196 | 71 | 17 |
| 2013 | 27,668 | 7,544 | 290 | 120 | 30 |
| 2014 | 33,468 | 10,886 | 388 | 175 | 41 |
| 2015 | 39,090 | 14,361 | 500 | 230 | 50 |
| 2016 | 44,509 | 17,905 | 608 | 290 | 68 |
| 2017 | 49,761 | 21,480 | 716 | 348 | 82 |
| 2018 | 54,871 | 25,065 | 823 | 406 | 95 |
| 2019 | 59,857 | 28,648 | 929 | 465 | 109 |

Table 4.9 shows the estimated number of all cases and the budget of providing generic lamivudine plus adding tenofovir when drug resistance occurred for all HBeAg positive CHB cases aged more than 30 years on the governmental budget during fiscal years 2010 to 2019. At the first year, the budget including the cost of treatment, cost of monitoring and cost of lamivudine but not the cost of tenofovir was 938 million THB. At the second year, the budget of tenofovir was 521 or 122 million THB if the price of tenofovir was 43 or 10 THB per tablet, respectively.

**Table 4.9 Budget of providing generic lamivudine plus adding tenofovir when drug resistance occurred for all HBeAg positive CHB cases during fiscal years 2010 to 2019**

| Fiscal year | Number of all HBeAg positive CHB cases who required the treatment (person) | Number of new cases who required TNV (person) | Budget including the cost of treatment, cost of monitoring and cost of lamivudine (million THB) | Budget of TNV with the price of 43 THB/tablet (millionTHB) | Budget of TNV with the price of 10 THB/tablet (millionTHB) |
|---|---|---|---|---|---|
| 2010 | 156,473 | - | 938 | - | - |
| 2011 | 133,327 | 33,485 | 1,272 | 521 | 122 |
| 2012 | 132,210 | 50,323 | 1,574 | 809 | 190 |
| 2013 | 132,734 | 61,348 | 1,860 | 990 | 230 |
| 2014 | 134,438 | 69,057 | 2,145 | 1,121 | 263 |
| 2015 | 136,951 | 74,864 | 2,430 | 1,210 | 280 |
| 2016 | 138,855 | 79,594 | 2,515 | 1,296 | 304 |
| 2017 | 141,189 | 83,709 | 2,601 | 1,363 | 320 |
| 2018 | 143,822 | 87,474 | 2,684 | 1,425 | 334 |
| 2019 | 146,662 | 91,033 | 2,766 | 1,483 | 348 |

# CHAPTER V
# DISCUSSION

The discussion of this study was divided in to three parts as follows:

1. Cost-utility analysis
2. Budget impact analysis
3. Limitations of study

## Part I: Cost-utility analysis

The economic evaluation information to consider whether which drugs for HBeAg positive CHB patients should be included in the NLED was requested by the NHSO in fiscal year 2009. However, until now there has been no such data yet. Therefore, this study was the first to compare the cost-utility of all available treatments with palliative care in patients with HBeAg positive CHB based on societal perspective in Thai context as well as to estimate the governmental budget impact of the most cost-effective treatment when included in the NLED.

Based on the results of this study, it was suggested that providing generic lamivudine plus adding tenofovir when drug resistance occurred, generic lamivudine plus adding tenofovir based on the road map guideline and tenofovir monotherapy were dominant and cost-saving interventions compared to palliative care. Providing generic lamivudine plus adding tenofovir when drug resistance occurred could save healthcare cost of approximately 70,000 THB per patient, since the cost of serious complications could be avoided in the future. Moreover, CHB treatment could also prolong patients' overall survival about 18 years. It was found that generic lamivudine would be the most cost-saving treatment and it has already been included in the NLED. Thus, lamivudine should be considered to be the first drug for the treatment of HBeAg positive CHB patients who required the treatment base on the criteria. However, based on the systematic reviews, most studies indicated that entecavir (10

studies) (57-61, 64-66, 79-80), adefovir (2 studies) (56, 71), telbivudine (1 study) (55), and pegylated interferon (3 studies) (63, 68-69) were more cost-effective compared to lamivudine. The results of this study were not in accordance with other previous published studies, since we considered drug resistance due to lamivudine and its management to imitate the real current clinical practice and generic lamivudine which was very inexpensive in Thailand was also included as an intervention.

Although lamivudine can cause HBV DNA suppression in most HBeAg positive CHB patients, it is also associated with a high rate of drug resistance (12). Currently, there have been no other CHB treatments with low rate of drug resistance which is included in the NLED. In addition to lamivudine, our study indicated that tenofovir was also a cost-saving option to be used as either the first or second drug for the management of drug resistance due to lamivudine. Similarly, the study of Buti et al revealed that tenofovir was associated with lower costs and higher efficacy over entecavir, telbivudine and adefovir (57). At present tenofovir has not been approved by the Thai FDA for the treatment of CHB yet, even though tenofovir has demonstrated high antiviral efficacy and low drug resistance rate for patients with CHB (13-14).

Our study indicated that tenofovir was a cost-saving or cost-effective option to be used as either the first or second drug for the management of drug resistance due to lamivudine. Therefore, tenofovir should be included in the NLED. From the expert's opinion, if both lamivudine and tenofovir were in the NLED, using tenofovir as the first drug would be better given that tenofovir had very low resistance rate. It would be more convenient for clinicians to provide tenofovir as the first-line treatment in order to reduce the time and cost of drug resistance management compared with providing lamivudine. Even though the patients taking tenofovir had drug resistance, lamivudine could still be added. However, it should be noted that tenofovir has also been implicated in causing renal toxicity. Tenofovir can cause acute renal failure, Fanconi syndrome, proteinuria or tubular necrosis. These side effects are due to accumulation of the drug in proximal tubules (107). In addition, when considering to provide CHB treatment to HBeAg positive CHB patients aged older than 30 years (i.e., 40-70 years), three interventions (i.e., generic lamivudine plus adding tenofovir when drug resistance occurred, generic lamivudine plus adding

tenofovir based on the road map guideline and tenofovir monotherapy) were still dominant and cost-saving interventions compared with palliative care. Therefore, providing these three interventions in elderly HBeAg positive CHB patients would be still very beneficial.

Moreover, our study was the first to study the set of interventions into two scenarios depended upon when the second drug was added for the management of CHB drug resistance either adding the second drug when drug resistance occurred or adding a more potent drug without cross-resistance when the HBV DNA level more than 60 IU/ml at a partial response at week 24 based on the road map guideline which is recommended to apply for only low genetic barrier drugs (i.e., lamivudine and telbivudine). The results suggested that the total cost of HBeAg positive CHB treatment with the management of drug resistance based on the road map guideline was higher compared with adding the second drug when drug resistance occurred. Nevertheless, total LYs and QALYs obtained from both scenarios of the management of drug resistance were not different.

However, three major issues (i.e., the prices of tenofovir and lamivudine, resistance rate of tenofovir, and cost of all complications) are needed to be addressed. First, it was noted that the price of tenofovir in this study was obtained from the current market price of tenofovir in Thailand which was relatively inexpensive due to the discounted price (43 THB) proposed by the pharmaceutical company. At present, the price of tenofovir is about equal to that of entecavir in other countries. If the maximum expected price of tenofovir was assumed to be equal to the price of entecavir (235 THB per tablet), the ICER would be changed from dominant value to 100,000 THB per QALY gained when compared with palliative care. Similarly, if the price of lamivudine was changed to be the price of original lamivudine, the ICER would be changed to 81,000 THB per QALY gained. Based on the Thai Subcommittee for Development of the NLED, the willingness to pay (WTP) threshold for a QALY gained for the adoption of health technologies and interventions is between one and three times the Thai GDP (i.e. approximately 100,000 to 300,000 THB). Therefore, when changing the prices to possible maximum values, tenofovir monotherapy or lamividine was cost-effective in Thai context although it was not a cost-saving intervention (106).

Second, according to the current studies related to drug resistance, the resistance rate of tenofovir used in this study was 0% (12). If resistance rate of tenofovir was assumed based on the expert's opinion to be equal to that of entecavir, tenofovir was a cost-effective intervention in Thai context with the ICER of 5,000 THB per LY gained or 8,000 THB per QALY gained compared with palliative care. Third, direct medical costs of complication states in this study were obtained from the published study of hepatitis C, a multi-center observational study conducted at five major tertiary care hospitals in Thailand (4). The costs of all complications (i.e., compensated cirrhosis, decompensated cirrhosis and HCC) might be lower than those conducted in CHB patients or regional hospitals. Based on sensitivity analysis results, the costs of all complications had the most effect on the changes in the ICER values. However, those three interventions would be cost-effective because the ICER values were lower than one time the Thai GDP per capita (106).

## Part II: Budget impact analysis

The governmental budget impact demonstrated that provision of generic lamivudine and adding tenofovir when drug resistance occurred or tenofovir monotherapy for HBeAg positive CHB patients could reduce the overall budget from the fifth or seventh fiscal year onwards, respectively. However, in the long run, the budget of lamivudine and tenofovir decreased, whereas that of palliative care increased. Furthermore, the provision of generic lamivudine and adding tenofovir when drug resistance occurred or tenofovir could help the NHSO saving the budget compared with palliative care. It was noted that the prices of tenofovir used in this study were obtained from the current price proposed by the pharmaceutical company (43 THB) and the price estimated by the GPO director if tenofovir is produced and launched to the market, so that change in prices will be affected to the governmental budget impact.

## Part III: Limitations of study

This study had several limitations as follows:

1. Due to the lack of transitional probabilities data for CHB patients in Thailand, some transitional probabilities were obtained from systematic reviews of the published articles in other countries.

2. There has been utility data of CHB but not for all complication states (i.e., compensated cirrhosis, decompensated cirrhosis and HCC) in Thai CHB patients, so that the utility data of CHB patients with complications were obtained from multinational study (88).

3. Costs of the treatment for adverse drug events were not included in this study.

# CHAPTER VI
# CONCLUSIONS

The conclusions of this study were divided into two parts as follows:

1. Recommendations for policy decision making
2. Recommendations for the further study

## Part I: Recommendations for policy decision making

In 2009, the NHSO requested the study on economic evaluation of drug treatments for CHB patients for the development of health benefit package under universal health care coverage scheme process of International Health Policy Program (IHPP) and Health Intervention and Technology Assessment Program (HITAP)**.** Thus, the results of this study could be used to inform the Subcommittee of the Benefit package Design that lamivudine should be still included in the NLED and tenofovir should be included in the NLED for CHB patients.

Generic lamivudine already contained in the NLED was the most cost-effective. Thus, the access to the treatment for HBeAg positive CHB patients should be enhanced. Since CHB patients do not usually have symptoms, they do not know that they have CHB disease and require treatment. Thus, healthcare provides as well as policymakers under health insurance schemes should accelerate patients' awareness to get an access to CHB screening and treatment. However, lamivudine may cause drug resistance in CHB patients and at present there has been no treatment to manage drug resistance included to the NLED. In addition, this study showed that providing tenofovir monotherapy or adding tenofovir as the second drug for the treatment of HBeAg positive CHB patients with drug resistance was the cost-saving intervention. Therefore, tenofovir should be considered to be included in the NLED. Currently tenofovir has been registered for the treatment of HIV but not CHB treatment in

Thailand yet. Therefore, Thai FDA should consider ways to register tenofovir in the indication of CHB treatment for the benefit of the patients and the country.

Recently screening to diagnose CHB can be performed in community hospitals, while treatment and monitoring were usually done in teaching hospitals. There have been very few gastroenterologists can manage CHB complicated conditions and most of them are at university and regional hospitals. Therefore, the Ministry of Public Health (MOPH) should enhance the ability of general hospitals to increase the number of gastroenterologists who could treat and monitor CHB patients. Moreover, the MOPH should develop a good referral system of the community hospitals and encourage the development of national guidelines for the treatment of CHB disease.

Based on the results, the costs of CHB treatment were very expensive; however, these costs could be avoided by preventing the HBV infection. Hepatitis B vaccine is the best protection against hepatitis B virus. The meta-analysis study of Chen et al. showed that hepatitis B vaccine could prevent the HBV infection among health-care providers (108). Since 1992, the Ministry of Public Health has implemented the nationwide hepatitis B vaccine immunization program for all newborns and provided hepatitis B immune globulin (HBIG) for babies born to carrier mothers (6). Consequently, the prevalence of HBV in Thailand was dropped to 4% (6). Nevertheless, adult populations who were born before 1992 may still have a chance to be infected with HBV. Therefore, the MOPH should provide the interventions such as screening people who have no immunity to HBV and encouraging them to receive the HBV vaccination in order to reduce the spread of infection among adult populations.

## Part II: Recommendations for the further study

1. Utility parameter, one of the important parameters that were sensitive to the changes in ICER values should be derived from Thai data.

2. Since currently in Thailand there have been a very few gastroenterologists and laboratory facilities for CHB treatment and monitoring, the feasibility of CHB treatment and monitoring provision system should be further investigated.

3. As this study compared all treatments for HBeAg positive CHB patients, further study for HBeAg negative CHB patients should be conducted.

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# APPENDICES

# APPENDIX A

**Paper extraction according to Drummond checklists**

| Study | Chen W. (2009) | Jones J. (2009) |
|---|---|---|
| 1. Was a well-defined question posed in an answerable form? | + | + |
| 2. Was a comprehensive description of the competing alternatives given | + | + |
| 3. Was there evidence that the programme's effectiveness had been established? | + | + |
| 4. Were all the important and relevant outcomes and costs for each alternative identified? | + | + |
| 5. Were outcomes and costs measured accurately in appropriate unit | + | + |
| 6. Were the outcomes and costs valued credibly? | + | + |
| 7. Were outcomes and costs adjusted for different times at which they occurred | N/A | + |
| 8. Was an incremental analysis of the outcomes and costs of alternatives performed? | + | + |
| 9. Was a sensitivity analysis performed? | N/A | + |
| 10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers? | + | + |
| 11. Were the conclusions of the evaluation justified by the evidence presented? | + | + |
| 12. Can the results be applied to the local population? | - | + |

*Note: All items have three possible responses which are yes (+), no (-), and cannot tell (N/A).

**Paper extraction according to Drummond checklists (cont.)**

| Study | Buti M. (2009) | Costa Am. (2008) | Calcagno JI.(2008) | Spackman D. 2008 | You JH. (2008) |
|---|---|---|---|---|---|
| 1. Was a well-defined question posed in an answerable form? | + | + | + | + | + |
| 2. Was a comprehensive description of the competing alternatives given | + | + | + | + | + |
| 3. Was there evidence that the programme's effectiveness had been established? | + | + | + | + | + |
| 4. Were all the important and relevant outcomes and costs for each alternative identified? | + | + | + | + | + |
| 5. Were outcomes and costs measured accurately in appropriate unit | + | + | + | + | + |
| 6. Were the outcomes and costs valued credibly? | + | + | + | + | + |
| 7. Were outcomes and costs adjusted for different times at which they occurred | N/A | + | N/A | + | N/A |
| 8. Was an incremental analysis of the outcomes and costs of alternatives performed? | + | + | + | + | + |
| 9. Was a sensitivity analysis performed? | N/A | + | + | + | N/A |
| 10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers? | - | + | + | - | - |
| 11. Were the conclusions of the evaluation justified by the evidence presented? | + | + | + | + | + |
| 12. Can the results be applied to the local population? | - | + | - | - | - |

*Note: All items have three possible responses which are yes (+), no (-), and cannot tell (N/A).

**Paper extraction according to Drummond checklists (cont.)**

| Study | Yuan Y. (2008) | Lacey L. (2008) | Veenstra DL. (2008) | Veenstra DL. (2008) | Yuan Y. (2008) |
|---|---|---|---|---|---|
| 1. Was a well-defined question posed in an answerable form? | + | + | + | + | + |
| 2. Was a comprehensive description of the competing alternatives given | + | + | + | + | + |
| 3. Was there evidence that the programme's effectiveness had been established? | + | + | + | + | + |
| 4. Were all the important and relevant outcomes and costs for each alternative identified? | + | + | + | + | + |
| 5. Were outcomes and costs measured accurately in appropriate unit | + | + | + | + | + |
| 6. Were the outcomes and costs valued credibly? | + | + | + | + | + |
| 7. Were outcomes and costs adjusted for different times at which they occurred | + | + | + | N/A | + |
| 8. Was an incremental analysis of the outcomes and costs of alternatives performed? | + | + | + | + | + |
| 9. Was a sensitivity analysis performed? | + | N/A | + | + | + |
| 10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers? | + | + | + | + | + |
| 11. Were the conclusions of the evaluation justified by the evidence presented? | + | + | + | + | + |
| 12. Can the results be applied to the local population? | + | - | - | - | + |

*Note: All items have three possible responses which are yes (+), no (-), and cannot tell (N/A)

**Paper extraction according to Drummond checklists (cont.)**

| Study | Arnold E. (2008) | Veenstra DL. (2007) | Lacey LF. (2007) | Sun X. (2007) | Veenstra DL. (2007) |
|---|---|---|---|---|---|
| 1. Was a well-defined question posed in an answerable form? | + | + | + | + | + |
| 2. Was a comprehensive description of the competing alternatives given | + | + | + | + | + |
| 3. Was there evidence that the programme's effectiveness had been established? | + | + | + | + | + |
| 4. Were all the important and relevant outcomes and costs for each alternative identified? | + | + | + | + | + |
| 5. Were outcomes and costs measured accurately in appropriate unit | + | + | + | + | + |
| 6. Were the outcomes and costs valued credibly? | + | + | + | + | + |
| 7. Were outcomes and costs adjusted for different times at which they occurred | N/A | N/A | + | N/A | + |
| 8. Was an incremental analysis of the outcomes and costs of alternatives performed? | + | + | + | + | + |
| 9. Was a sensitivity analysis performed? | N/A | + | + | N/A | + |
| 10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers? | + | + | - | + | + |
| 11. Were the conclusions of the evaluation justified by the evidence presented? | + | + | + | + | + |
| 12. Can the results be applied to the local population? | + | + | + | + | + |

*Note: All items have three possible responses which are yes (+), no (-), and cannot tell (N/A)

**Paper extraction according to Drummond checklists (cont.)**

| Study | Larry L. (2007) | Buti M. (2006) | Kanwal F. (2005) | Pwu RF. (2002) |
|---|---|---|---|---|
| 1. Was a well-defined question posed in an answerable form? | + | + | + | + |
| 2. Was a comprehensive description of the competing alternatives given | + | + | + | + |
| 3. Was there evidence that the programme's effectiveness had been established? | + | + | + | + |
| 4. Were all the important and relevant outcomes and costs for each alternative identified? | + | + | + | + |
| 5. Were outcomes and costs measured accurately in appropriate unit | + | + | + | + |
| 6. Were the outcomes and costs valued credibly? | + | + | + | + |
| 7. Were outcomes and costs adjusted for different times at which they occurred | N/A | + | N/A | + |
| 8. Was an incremental analysis of the outcomes and costs of alternatives performed? | + | + | + | + |
| 9. Was a sensitivity analysis performed? | N/A | + | + | + |
| 10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers? | - | + | + | + |
| 11. Were the conclusions of the evaluation justified by the evidence presented? | + | + | + | + |
| 12. Can the results be applied to the local population? | + | + | + | - |

*Note: All items have three possible responses which are yes (+), no (-), and cannot tell (N/A)

**Paper extraction according to Drummond checklists (cont.)**

| Study | Aggarwal R. (2002) | Orlewska E. (2002) | Crowley S. (2002) | Brooks EA. (2001) | Crowley (2000) |
|---|---|---|---|---|---|
| 1. Was a well-defined question posed in an answerable form? | + | + | + | + | + |
| 2. Was a comprehensive description of the competing alternatives given | + | + | + | + | + |
| 3. Was there evidence that the programme's effectiveness had been established? | + | + | + | + | + |
| 4. Were all the important and relevant outcomes and costs for each alternative identified? | + | + | + | + | + |
| 5. Were outcomes and costs measured accurately in appropriate unit | + | + | + | + | + |
| 6. Were the outcomes and costs valued credibly? | + | + | + | + | + |
| 7. Were outcomes and costs adjusted for different times at which they occurred | - | N/A | N/A | N/A | N/A |
| 8. Was an incremental analysis of the outcomes and costs of alternatives performed? | - | + | - | - | + |
| 9. Was a sensitivity analysis performed? | + | + | N/A | N/A | N/A |
| 10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers? | - | - | - | - | - |
| 11. Were the conclusions of the evaluation justified by the evidence presented? | + | + | + | + | + |
| 12. Can the results be applied to the local population? | - | - | - | - | - |

*Note: All items have three possible responses which are yes (+), no (-), and cannot tell (N/A)

# APPENDIX B

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part characteristic of study**

| | Study | Disease and patient group | Objective | Intervention | Perspective | Source of data |
|---|---|---|---|---|---|---|
| 1 | Chen W. 2009 (China) | HBeAg+ /- CHB | To evaluate long-term cost effectiveness of TVD and LMV for the treatment of CHB | 1.TVD<br>2.LMV | Social health insurance | From 2 years GLOBE clnical trial Annual medical expenditure Literature |
| 2 | Jones J. 2009 (UK) | CHB (not progressed to cirrhosis) | To update and extend a 2006 report on the clinical effectiveness and cost-effectiveness of adefovir and PEG for the treatment of CHB | 1.ADV<br>2.PEG<br>3.LMV<br>4.IFN | NHS and personal social services | Systematic review (13 databases were searched including MEDLINE EMBASE and the Cochrane Library |
| 3 | Buti M. 2009 (Spain) | HBeAg+/- CHB | To estimate the cost-effectiveness of the oral antiviral treatments in patients with CHB | 1.LMV<br>2.ADV<br>3.TVD<br>4.ETV<br>5.TNV | Spanish National Health System | N/A |
| 4 | Costa Am. 2008 (Brazil) | HBeAg+/- CHB | To describe the standard treatment, the use of resources and direct cost for each stage of CHB in the SUS syetem,in 2005 | 1.LMV<br>2.ETV | Brazilian public health system | Published sources |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part characteristic of study (cont.)**

| | Study | Disease and patient group | Objective | Intervention | Perspective | Source of data |
|---|---|---|---|---|---|---|
| 5 | Calcagno J. 2008 (Argentina) | HBeAg+/-CHB | To evaluate the cost-effectiveness of ETV vs. LMV in Argentina | 1.LMV<br>2.ETV | Argentina's health system and social | RCT Observational studies Argentina vital statistics |
| 6 | Spackman D. 2008 (USA) | HBeAg+ CHB | To compare the cost effectiveness of ADV, ETV, LMV, PEG and TVD | 1.LMV<br>2.ADV<br>3.TVD<br>4.ETV<br>5.PEG | US payer | Literature |
| 7 | You JH. 2008 (Hong Kong) | CHB | To review published studies on the pharmacoeconomics of ETV for treatment of CHB | 1.ETV<br>2.LMVand/or ADV | N/A | Literature search on Medline and Embase over the period of 1998-2008 |
| 8 | Yuan Y. 2008 (China) | HBeAg+ CHB | To evaluate the cost-effectiveness of ETV treatment in China, based on projected clinical benefits from its superior viral suppression efficacy | 1.LMV<br>2.ETV | Chinese Social Security program | Published China specific data |
| 9 | Lacey L. 2008 (Taiwan) | HBeAg+/-CHB | Economic evaluation of short-duration treatments of CHB and longer duration antiviral treatment for up to 5 years | 1.short duration<br>2.long duration | Taiwan health-care system | N/A |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part characteristic of study (cont.)**

| | Study | Disease and patient group | Objective | Intervention | Perspective | Source of data |
|---|---|---|---|---|---|---|
| 10 | Veenstra DL. 2008 (Taiwan) | HBeAg-CHB | To evaluate the incremental cost-effectiveness of 48 weeks of PEG-2a compared to 48 weeks of LMV | 1.LMV<br>2.PEG-2a<br>3.PEG-2a combined with LMV | Taiwan Bureau of National Health Insurance | Published literature and a survey of clinical experts in Taiwan |
| 11 | Veenstra DL. 2008 | HBeAg- CHB | To examine the clinical and economic outcomes of potential treatment strategies and durations for HBeAg-negative CHB | 1.ETV<br>2.LMV<br>3.ADV | Payer | Literature |
| 12 | Yuan Y. 2008 | HBeAg+ CHB | To estimate the long-term health and economic impact of treating HBV with ETV vs. LMV in patients who are positive for HBeAg based on the efficacy and safety results of the Phase 3, double-blind, RCT, Benefits of ETV for Hepatitis B Liver Disease (BEHoLD) | 1.ETV<br>2.LMV | U.S. third-party payer | Published sources |
| 13 | Arnold E. 2008 (Australia) | HBeAg+/- CHB | To estimate the cost effectiveness of ETV versus LMV 100 in the treatment of CHB patients naïve to nucleos(t)ide therapy. | 1.ETV<br>2.LMV | Australian healthcare | N/A |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part characteristic of study (cont.)**

| | Study | Disease and patient group | Objective | Intervention | Perspective | Source of data |
|---|---|---|---|---|---|---|
| 14 | Veenstra DL. 2007 (USA) | HBeAg+ CHB | To evaluate the cost effectiveness of treatment of HBeAg+ CHB with ETV compared with LMV with ADV salvage | 1.ETV<br>2.LMV addition of ADV for patients who developed virologic breakthrough | US-payer | Publicly available data |
| 15 | Lacey LF. 2007 (Singapore) | HBeAg+/- CHB | The economic evaluation of short-duration treatments of CHB and longer duration antiviral treatment for up to 5 years | 1.short duration treatment<br>2.long duration treatment | Singapore healthcare system and CHB patient | Systematic literature review |
| 16 | Sun X. 2007 (China) | CHB | To systematically overview economic evidence of antiviral therapies for CHB | 1.LMV<br>2.ADV<br>3.IFN<br>4.PEG | Health care sector | Systematic review (6 databases and 8 major journals) |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part characteristic of study (cont.)**

| | Study | Disease and patient group | Objective | Intervention | Perspective | Source of data |
|---|---|---|---|---|---|---|
| 17 | Veenstra DL. 2007 (UK) | HBeAg+ CHB | To assessed the clinical outcomes and costs of 48 weeks of peginterferon alpha-2a vs. 4 years of lamivudine | 1.48 weeks of PEG 2.4 years of LMV use of ADV salvage treatment for LMV-resistant patients | UK National Health Service | Literature |
| 18 | Larry L. 2007 (China) | HBeAg+ CHB | To assess the economic evaluation of short- and long-term antiviral treatments of HBeAg-positive CHB | 1.short duration treatment 2.long duration treatment | Chinese health care system | N/A |
| 19 | Buti M. 2006 (Spain) | HBeAg- CHB | To estimate the cost-effectiveness over a 4-year duration of lamivudine and adefovir dipivoxil for patients with HBeAg-negative CHB | 1.LMV 2.ADV | Spanish Public Health System | Clinical trials |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part characteristic of study (cont.)**

| | Study | Disease and patient group | Objective | Intervention | Perspective | Source of data |
|---|---|---|---|---|---|---|
| 20 | Kanwal F. 2005 (USA) | CHB | To determine whether and under what circumstances the improved efficacy of ADV offsets its increased cost compared with LMV or IFN | 1.No HBV treatment<br>2. IFN<br>3.LMV<br>4.ADV<br>5.LMV with crossover toADV upon resistance ("ADV salvage" strategy) | Third-party payer | Systematic review of MEDLINE from 1970 to 2005 |
| 21 | Pwu RF. 2002 (Taiwan) | CHB (35 yr.) | To evaluate the cost effectiveness of IFN from a burden of disease perspective | 1.IFN<br>2.Standard care | N/A | Data collected in Taiwan |
| 22 | Aggarwal R. 2002 (India) | CHB (30 yrs.) | To evaluate the cost effectiveness of interferon-alpha for treatment CHB in India | 1.untreated with IFN<br>2.treated with IFN with evidence of viral replication and CHB, but not cirrhosis | N/A | Available literature |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part characteristic of study (cont.)**

| | Study | Disease and patient group | Objective | Intervention | Perspective | Source of data |
|---|---|---|---|---|---|---|
| 23 | Orlewska E. 2002 (Poland) | CHB | To estimate the cost-effectiveness of alternative therapeutic strategies for the management of CHB in Poland | 1.LMV (1st choice)[A] 2.IFN (2nd choice)[B] 3.only IFN[C] 4.no antiviral treatment[D] | Polish health-care (payer) | Clinical data from the literature and local data on health-care resource utilization and unit costs |
| 24 | Crowley S. | CHB | To estimates clinical outcomes and cost-effectiveness of LMV compared with other treatment scenarios for CHB | 1.LMV and IFN[A] 2.IFN only[B] 3.no treatment[C] | Australian health-care provider | 1.clinical trials 2.published studies a hepatologist's questionnaire 4.expert panel follow up |
| 25 | Brooks EA. 2001 (USA) | CHB | To determine whether LMV or IFN is the more successful treatment for CHB given budget | 1.LMV 2.IFN | Third-party payer | Clinical data were taken from RCT |
| 26 | Crowley SJ. 2000 (Australia) | CHB | To estimate the short term and long term cost effectiveness associated with the introduction of LMV for CHB | 1.LMV 2.IFN 3.no treatment | Healthcare perspective | Hypothetical cohorts of patients with CHB, representative of those likely to receive treatment in clinical practice in Australia |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part methodology of study**

| | Study | Cost | | Outcome | Method | Discounting | Sensitivity analysis (SA) |
|---|---|---|---|---|---|---|---|
| | | Direct | Indirect | | | | |
| 1 | Chen W. 2009 (China) | N/A | N/A | ICER (QALYs) | CEA (Markov model) | N/A | N/A |
| 2 | Jones J. 2009 (UK) | Direct med cost (laboratory tests diagnostic tests, outpatient visits and costs of the progressive liver disease health states) | N/A | ICER (QALYs) | CEA (Markov model) | 6%(costs), 1.5%(out comes) | Probabilistic SA, Deterministic SA |
| 3 | Buti M. 2009 (Spain) | N/A | N/A | ICER (LYs, QALYs) | CUA (Markov model) | N/A | N/A |
| 4 | Costa Am. 2008 (Brazil) | Direct med cost (admissions, diagnostic and therapeutic interventions, complementary exams,expenses with drugs and professional fees | N/A | cost per patient with undetectable viral load cost per LY gained, QALY gained | CUA (Decision tree model) | 3% | One way SA(cost) |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part methodology of study (cont.)**

| | Study | Cost | | Outcome | Method | Discounting | Sensitivity analysis (SA) |
|---|---|---|---|---|---|---|---|
| | | Direct | Indirect | | | | |
| 5 | Calcagno J. 2008 (Argentina) | Direct med cost drugs clinical events their complicatons | N/A | LYs, QALYs | CUA | N/A | One way SA |
| 6 | Spackman D. 2008 (USA) | N/A | N/A | QALYs | CUA (Markov model) | 3% | Probabilistic SA |
| 7 | You JH. 2008 (Hong Kong) | N/A | N/A | ICER | CUA (Decision tree, Markov model) | N/A | N/A |
| 8 | Yuan Y. 2008 (China) | Direct medical cost | N/A | QALYs | CUA | 3% | Probabilistic SA |
| 9 | Lacey L. 2008 (Taiwan) | N/A | N/A | ICER (QALYs) | CUA (Markov model) | 3% | N/A |
| 10 | Veenstra DL. 2008 (Taiwan) | Direct medical cost | N/A | ICER (LYs, QALYs) | CUA (Markov model) | 3% | One way SA, Probabilistic SA |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part methodology of study (cont.)**

| | Study | Cost | | Outcome | Method | Discounting | Sensitivity analysis (SA) |
|---|---|---|---|---|---|---|---|
| | | Direct | Indirect | | | | |
| 11 | Veenstra DL. 2008 | N/A | N/A | ICER (QALYs) | CUA (Markov model) | N/A | Probabilistic SA |
| 12 | Yuan Y. 2008 | Direct med cost | N/A | ICER (QALYs) | CUA (Decision tree model) | 3% | Probabilistic SA |
| 13 | Arnold E. 2008 (Australia) | Direct med cost | N/A | ICER (LYs, QALYs) | CUA (Decision tree model) | N/A | N/A |
| 14 | Veenstra DL. 2007 (USA) | N/A | N/A | QALYs | CUA (Markov model) | N/A | Probabilistic SA |
| 15 | Lacey LF. 2007 (Singapore) | Direct med cost (outpatient consultations, inpatient admissions, antiviral drug | Indirect cost (lost income and lost productivity) | ICER (LYs, QALYs) | CUA (Markov model) | 5% | One-way SA |
| 16 | Sun X. 2007 (China) | N/A | N/A | ICER (QALYs) | CUA | N/A | N/A |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part methodology of study (cont.)**

| | Study | Cost | | Outcome | Method | Discounting | Sensitivity analysis (SA) |
|---|---|---|---|---|---|---|---|
| | | Direct | Indirect | | | | |
| 17 | Veenstra DL. 2007 (UK) | N/A | N/A | ICER | CUA Markov model | 0.3(QALYs) | One-way SA, probabilistic SA |
| 18 | Larry L. 2007 (China) | N/A | N/A | ICER (QALYs) | CUA Markov model | N/A | N/A |
| 19 | Buti M. 2006 (Spain) | Direct med costs (cost of drug acquisition, visits, diagnostic or laboratory tests) | N/A | ICER | Decision analysis model | 3% | SA |
| 20 | Kanwal F. 2005 (USA) | N/A | N/A | ICER | CUA | N/A | SA |
| 21 | Pwu RF. 2002 (Taiwan) | N/A | N/A | ICER (QALYs) | CUA | 3% | Probabilistic SA (Monte Carlo simulation) |
| 22 | Aggarwal R. 2002 (India) | Direct med costs Indian prices of IFN usual costs of medical treatment in India based on expert opinion | N/A | QALYs | CUA | Undiscounted /discounted analyses | SA |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part methodology of study (cont.)**

| | Study | Cost | | Outcome | Method | Discounting | Sensitivity analysis (SA) |
|---|---|---|---|---|---|---|---|
| | | Direct | Indirect | | | | |
| 23 | Orlewska E. 2002 (Poland) | Direct med costs | N/A | ICER | CUA | N/A | One-way SA and extreme scenario analysis |
| 24 | Crowley S. | N/A | N/A | ICER | CEA (Decision tree, Markov model) | N/A | N/A |
| 25 | Brooks EA. 2001 (USA) | Direct med cost (drugs) | N/A | HBeAg seroconversion rates and rates of progression to cirrhosis | CEA (Decision tree model) | N/A | N/A |
| 26 | Crowley SJ. 2000 (Australia) | N/A | N/A | ICER (QALYs) | CEA (Decision tree, Markov model) | N/A | N/A |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part results of study**

| | Study | Result |
|---|---|---|
| 1 | Chen W. 2009 (China) | 1.The incremental cost for 1 additional QALY gained with TVD in treating HBeAg-positive and -negative CHB were 5403 yuan and 28239 yuan in Beijing , as well 4916 yuan and 29618 yuan in Guangzhou, 2.ICER with TVD vs. LMV were 1282 yuan and 31565 yuan for HBeAg-positive and -negative CHB |
| 2 | Jones J. 2009 (UK) | Both ADV and PEG are beneficial for patients with CHB in terms of suppressing viral load, reducing liver damage-associated biochemical activity, inducing HBeAg seroconversion, and reducing liver fibrosis and necro-inflammation. The effects of long-term treatment with ADV are generally durable, with relatively low rates of resistance. In most cases, cost-effectiveness estimates were within acceptable ranges |
| 3 | Buti M. 2009 (Spain) | TNV is associated with lower costs and higher efficacy over ETV, TVD and ADV in HBeAg-positive patients, and TVD and ETV in HBeAg-negative patients |
| 4 | Costa Am. 2008 (Brazil) | ETVin comparison with LMV, resulted in a lower cost per patient reaching undetectable viral load, a lower cost per LY saved and lower cost per QALY gained, in both HBeAg negative and HBeAg-positive patients, resulting in reduced costs for public health system ENT resulted in lower ICERs than LMV:R$-7,938 and R$-5,420 per percent of patients reaching an undetectable viral load,R$-2,626 and R$-1,424 per LY gained, and R$-2,930 and R$-1,590 per QALY gained,in HBeAg-positive and negative patients |
| 5 | Calcagno J. 2008 (Argentina) | ETV showed a higher reduction in viral load than LMV, that implied fewer disease complications HBeAg positive and negative patients treated with ETV had 0.49 and 0.57 LY gained and 0.44 and 0.51 QALY gained per patient in comparison with LMV |
| 6 | Spackman D. 2008 (USA) | ETV (18.70 QALYs) and PEG (18.64 QALYs) provided the largest treatment benefits overall, followed by TVD (18.55 QALYs) |
| 7 | You JH. 2008 (Hong Kong) | All four studies showed that ETV was cost-effective in the treatment of CHB with the incremental cost per QALY gained below the commonly accepted benchmark |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part results of study (cont.)**

| | Study | Result |
|---|---|---|
| 8 | Yuan Y. 2008 (China) | The percentage of patients achieving HBV DNA <300 copies/ml at week 48, ETV was superior to LMV (78.7% vs. 46.7%, respectively [P < 0.05]) Compared with LMV, using ETV cost an incremental 17,590 RMB per QALY gained (95% CI 6333-56,407) |
| 9 | Lacey L. 2008 (Taiwan) | Short-course therapies of up to 1-year treatment had limited impact on improving patient survival. Long-term viral suppression with LMV and ADV sequential rescue therapies (including add-on therapies) for up to 5 years were found to be highly cost-effective by international standards (estimated to be NT$580,000 per QALY for Taiwan) |
| 10 | Veenstra DL. 2008 (Taiwan) | The gain in QALYs for 48 weeks of peginterferon alfa-2a compared to 48 weeks of lamivudine was 0.45 at an additional cost of 157,000 NTD (4900 USD), resulting in an ICER of 347,000 NTD (10,900 USD) per QALY gained The gain in Life expectancy was 0.38 and an ICER 413,770 NTD per LY gained |
| 11 | Veenstra DL. 2008 | Increasing treatment duration improved QALYs and was generally cost-effective for all three drugs 5 on-1 off treatment strategy with ETV improves health outcomes in a cost-effective manner compared to alternative strategies |
| 12 | Yuan Y. 2008 | ETV was superior to LMV in the proportion of subjects who achieved undetectable HBV DNA at week 48 (69.1% vs. 39.8%, respectively) The incremental cost of using ETV was $3,230 per QALY gained (95% CI), $2,312-$4,528), with 99.3% of PSA-derived estimates below $5,000 per QALY |
| 13 | Arnold E. 2008 (Australia) | Compared with LMV, ETV generated an estimated incremental cost per LYG of Australian dollars ($A) 5046 and an estimated incremental cost per QALY of $A5952 in the HBeAg+ve CHB patient population, an estimated incremental cost per LYG of $A7063 and an estimated incremental cost per QALY of $A8003 in the HBeAg-ve CHB patient population, and an overall estimated incremental cost per LYG of $A5853 and an estimated incremental cost per QALY of $A6772 in the general CHB population |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part results of study (cont.)**

| | Study | Result |
|---|---|---|
| 14 | Veenstra DL. 2007 (USA) | The estimated 10-year cumulative incidence of cirrhosis for patients initiated on ETV was 2.3% lower than for those on LMV (20.5% vs. 22.8%). The discounted incremental cost per QALY gained was $US7600 in the base-case analysis, and the 95% central range from PSA was $US2500-$US19 100. Combination therapy for treatment-naive patients led to an increase in costs without improvement in patient outcomes compared with ETV monotherapy. |
| 15 | Lacey LF. 2007 (Singapore) | Treatment of CHB with antiviral therapy for 5 years substantially decreased the rate on disease progression Compared with 1-year treatment with LMV, sequential antiviral therapies for up to 5 years (i.e. LMV plus ADVon emergence of LMV resistance or ADV plus LMV on emergence of ADV resistance) are highly cost-effective by international standards |
| 16 | Sun X. 2007 (China) | In Australia and Poland, LMV-preferred strategies dominated IFN In the US, ADV salvage produced US$8446 per additional QALY compared with IFN In Spain, the cost of ADV was US$34,840 for additional virological response In Taiwan, the use of PEG-alpha produced US$11,711.4 per additional QALY, compared with LMV. In China, the ICER of combination therapy LMV ranged from US$2860 to US$22,160 per additional loss of HBeAg, and IFN-alpha vs. LMV ranged from US$2490 to US$8890 per additional loss of HBeAg |
| 17 | Veenstra DL. 2007 (UK) | PEG-2a 48 wks compared with long-term LMV, giving an ICER of pound 10,400 per QALYs. Treatment with PEG-2a although more expensive than LMV therapy, provides improvement in health outcomes below the current UK cost-effectiveness threshold |
| 18 | Larry L. 2007 (China) | In comparison with no antiviral treatment, LMV administered for 1-year is a highly cost-effective short-course treatment. Longer duration antiviral treatments, LMV plus ADV or ADV plus LMV as a rescue medication are both cost-effective strategies, resulting in a more sustained decrease in the rate of disease progression |
| 19 | Buti M. 2006 (Spain) | The average cost-effectiveness ratio (cost per responding patient at year 4) was €28,375 for LMV arm and €28,132 for the ADV arm The incremental cost-effectiveness ratio of ADV vs. LMV (cost per additional responding patient with ADV) was €27,872 Long-term treatment with ADV is a cost-effective strategy in patients with HBeAg-negative CHB |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part results of study (cont.)**

| | Study | Result |
|---|---|---|
| 20 | Kanwal F. 2005 (USA) | The "do nothing" strategy was least effective Compared with the "do nothing" strategy, using IFN cost an incremental 6337 dollars to gain 1 additional QALY Compared with IFN, the ADV salvage strategy cost an incremental 8446 dollars per QALY gained Both the LMV and ADV monotherapy strategies were more expensive yet less effective than the alternative strategies and were therefore dominated In sensitivity analysis, IFN was most cost-effective in health care systems with tight budgetary constraints and a high prevalence of HBeAg-negative patients |
| 21 | Pwu RF. 2002 (Taiwan) | Patient treated with IFN in Taiwan would have gain in life expectancy of 0.41 years (or 0.18 QALYs) ICER was 492.000 New Taiwan dollars (NT$; 14,200 US$ at 34.7 NT$/US$) per QALY |
| 22 | Aggarwal R. 2002 (India) | The QALY lived by the two cohorts were 23.69 and 22.75 years, respectively, representing a gain of 0.94 years for the IFN-treated group In developing countries with a low per capita Income, IFN therapy for chronic hepatitis B may not be cost-effective |
| 23 | Orlewska E. 2002 (Poland) | The best results in terms of seroconversion and nonprogression to cirrhosis were achieved for strategy A, costs were lowest for strategy D, and strategies B and C were dominated by strategy A The ICER comparing strategy A with strategy D was 57,855 Polish new zloty (PLN) per extra seroconversion and 79,550 PLN per cirrhosis case avoided |
| 24 | Crowley S. | One-year progression to cirrhosis was estimated at 5.1% with scenario A, compared to 12.2% and 12.7%, scenarios B and C, respectively. From the long-term analysis, LMV is expected to increase life expectancy by years and reduce the lifetime risk of compensated cirrhosis, decompensated cirrhosis and HCC by 6%, 12% and 12%, respectively |
| 25 | Brooks EA. 2001 (USA) | LMV is more cost-effective therapy than IFN-alpha for the treatment of CHB |

**Data extraction form of systematic review for cost-effectiveness analysis of CHB part results of study (cont.)**

| | Study | Result |
|---|---|---|
| 26 | Crowley SJ. 2000 (Australia) | In the short term, more patients sero-converted when LMV was available, with an incremental cost-additional seroconversion In the long term, the introduction of LMV increased life expectancy by 3.9 years (3.2 QALYs) compared with when IFN-alpha was the only treatment, or 4.6 years (3.8 QALYs) compared with no treatment |

# BIOGRAPHY

| | |
|---|---|
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