PHARMACOECONOMIC EVALUATION OF EFAVIRENZ-BASED ANTIRETROVIRAL THERAPY COMPARED WITH NEVIRAPINE-BASED THERAPY AMONG THAI HIV/AIDS PATIENTS

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การประเมินผลด้านเภสัชเศรษฐศาสตร์ของการใช้ยาต้านไวรัสที่มีเอฟฟาวิเรนซเป็นองค์ประกอบเปรียบเทียบกับยาต้านไวรัสที่มีเนวิราปีนเป็นองค์ประกอบสำหรับผู้ติดเชื้อและผู้ป่วยเอดส์ในประเทศไทย

นางอุษาวดี มาลีวงศ์

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อุษาวดี มาลีวงศ์: การประเมินผลเภสัชเศรษฐศาสตร์การใช้ยาต้านไวรัสที่มียาเอฟฟาวิเรนซเป็นองค์ประกอบเปรียบเทียบกับยาต้านไวรัสที่มียาเนวิราปีนเป็นองค์ประกอบสำหรับผู้ติดเชื้อและผู้ป่วยเอดส์ในประเทศไทย (PHARMACOECONOMIC EVALUATION/ ANTIRETROVIRAL DRUG/ NVP-BASED REGIMENS / EFV-BASED REGIMENS/ HIV/AIDS PATIENTS). อ.ที่ปรึกษาหลัก: รศ.ดร.วิทยา กุลสมบูรณ์, อ.ที่ปรึกษาร่วม: นายแพทย์ธนรักษ์ ผลิพัฒน์, 131 หน้า

ในประเทศไทย ยาต้านไวรัสที่มีเนวิราปีนเป็นองค์ประกอบ หรือชื่อทางการค้าว่า "จีพีโอเวอร์" เป็นยาที่รัฐกำหนดให้ใช้ในการเริ่มต้นการรักษาผู้ติดเชื้อและผู้ป่วยเอดส์ อย่างไรก็ตามผลข้างเคียงที่รุนแรงจากการใช้ยาดังกล่าว เช่น การเกิดภาวะเป็นพิษต่อตับ การเกิด SJS และ TEN ก็เป็นสิ่งที่บุคลากรทางการแพทย์คำนึงถึง วัตถุประสงค์ของการศึกษานี้คือ การประเมินความคุ้มค่าของการเริ่มต้นการรักษาผู้ติดเชื้อและผู้ป่วยเอดส์ในประเทศไทย ระหว่างยาต้านไวรัสที่มียาเอฟฟาวิเรนซเป็นองค์ประกอบเปรียบเทียบกับยาต้านไวรัสที่มีเนวิราปีนเป็นประกอบ ในการศึกษาครั้งนี้ ได้ประยุกต์ใช้แบบจำลอง Markov และมีการวิเคราะห์ความไม่แน่นอนแบบ Probabilistic sensitivity กับผู้ติดเชื้อและผู้ป่วยเอดส์ อายุระหว่าง 15 ถึง 65 ปี เพื่อเปรียบเทียบส่วนเพิ่มของต้นทุนและอรรถประโยชน์ที่ได้จากการเริ่มต้นการรักษาด้วยยาต้านไวรัสที่มียาเอฟฟาวิเรนซเป็นองค์ประกอบกับยาต้านไวรัสที่มีเนวิราปีนเป็นประกอบ ตัวแปรที่ใช้ในแบบจำลองได้ข้อมูลจากโรงพยาบาลศูนย์ 4 แห่ง มีเพียงค่าอัตราการตายของผู้ที่เริ่มต้นการรักษาด้วยยาต้านไวรัสที่มีเอฟฟาวิเรนซเป็นองค์ประกอบเท่านั้นที่มาจากการศึกษาอื่น การศึกษานี้ได้วิเคราะห์ความไม่แน่นอนของตัวแปรและนำเสนอผลการศึกษาในรูปแบบของ Cost-effectiveness (CE) planes และ Cost-effectiveness acceptability (AC) curves ผลการศึกษาสรุปว่า การเริ่มต้นการรักษาด้วยยาต้านไวรัสที่มีเนวิราปีนเป็นประกอบเพิ่มความเสี่ยงที่จะเกิดผลข้างเคียงที่รุนแรง เช่น ภาวะตับอักเสบ ภาวะเป็นพิษต่อตับ SJS และ TEN โดยมีอัตราอุบัติการณ์ที่ 11.3, 5.2, 3.5 และ 0.9 ต่อ 1000 ประชากร-ปี ตามลำดับ จากมุมมองของการให้บริการของภาครัฐ ค่าใช้จ่ายในการรักษาตลอดชีวิตของผู้ป่วยที่เริ่มต้นการรักษาด้วยยาต้านไวรัสที่มีเอฟฟาวิเรนซเป็นองค์ประกอบจะน้อยกว่าการเริ่มต้นการรักษาด้วยยาต้านไวรัสที่มีเนวิราปีนเป็นองค์ประกอบในทุกกลุ่มอายุ ยกเว้นผู้ป่วยที่เริ่มต้นการรักษาเมื่ออายุ 20 ปี การเริ่มต้นการรักษาด้วยยาต้านไวรัสที่มีเนวิราปีนเป็นองค์ประกอบจะทำให้อายุขัย (Life-year) ของผู้ป่วยในกลุ่มอายุ 30 ถึง 60 ปี เพิ่มขึ้น มากกว่ากลุ่มที่เริ่มต้นการรักษาด้วยยาต้านไวรัสที่มีเอฟฟาวิเรนซเป็นองค์ประกอบเพียงเล็กน้อย แต่ให้ปีสุขภาวะของภาระโรคที่กลับคืนมา (DALY averted) น้อยกว่าในทุกกลุ่มอายุ ผลการศึกษาจาก AC curves ของต้นทุน-อายุขัยที่เพิ่มขึ้น (cost/ LY gained) พบว่า ในผู้ป่วยที่มีอายุเมื่อเริ่มต้นการรักษาอยู่ในช่วง 20 ปี การเริ่มต้นการรักษาด้วยยาต้านไวรัสที่มีเนวิราปีนเป็นองค์ประกอบมีต้นทุน-ประสิทธิผลดีกว่า อย่างไรก็ตามการเริ่มต้นการรักษาด้วยยาต้านไวรัสที่มีเอฟฟาวิเรนซเป็นองค์ประกอบจะมีต้นทุน-ประสิทธิผลดีกว่า เมื่อผู้บริหารเต็มใจที่จะจ่ายมากกว่า 3 ล้านบาทต่อ 1 ปีอายุขัยที่เพิ่มขึ้น ในขณะที่กลุ่มที่ผู้ป่วยที่มีอายุเริ่มต้นการรักษาในช่วง 30 ถึง 60 ปี การเริ่มต้นการรักษาด้วยยาต้านไวรัสที่มีเอฟฟาวิเรนซเป็นประกอบมีต้นทุน-ประสิทธิผลดีกว่า ในการวิเคราะห์ต้นทุน-ปีสุขภาวะของภาระโรคที่กลับคืนมา (cost/ DALY averted) พบว่า การเริ่มต้นการรักษาด้วยยาต้านไวรัสที่มีเอฟฟาวิเรนซเป็นประกอบมีต้นทุน-ประสิทธิผลดีกว่าในทุกกลุ่มอายุ ยกเว้นในกลุ่มอายุ 20 ปีที่จะมีความคุ้มค่าเมื่อผู้บริหารเต็มใจที่จะจ่ายมากกว่า 1 ล้านบาทต่อ 1 ปีสุขภาวะของภาระโรคที่กลับคืนมา หากกำหนดให้ประเทศไทยมีค่าสูงสุดที่ยอมจ่ายสำหรับคุณภาพชีวิตเท่ากับ 2.7 แสนบาท ต่อ 1 ปีสุขภาวะของภาระโรคที่กลับคืนมา จะพบว่า การเริ่มต้นการรักษาด้วยยาต้านไวรัสที่มีเอฟฟาวิเรนซเป็นองค์ประกอบมีต้นทุน-ประสิทธิผลดีกว่าในทุกกลุ่มอายุ ยกเว้นในกลุ่มอายุ 20 ปีเช่นเดียวกัน จากผลการศึกษาดังกล่าวสรุปได้ว่า การเริ่มต้นการรักษาด้วยยาต้านไวรัสที่มีเอฟฟาวิเรนซเป็นประกอบมีต้นทุน-ประสิทธิผลดีกว่าในทุกกลุ่มอายุ ยกเว้นในกลุ่มอายุ 20 ปี ทั้งในส่วนของต้นทุน-อายุขัยที่เพิ่มขึ้น และต้นทุน-ปีสุขภาวะของภาระโรคที่กลับคืนมา ในปัจจุบันมีการใช้สิทธิ (Compulsory Licensing) กับยาเอฟฟาวิเรนซ โดยกระทรวงสาธารณสุข ทำให้ราคายาลดลง การเริ่มต้นการรักษาด้วยยาต้านไวรัสที่มีเอฟฟาวิเรนซเป็นองค์ประกอบจึงยิ่งมีต้นทุน-ประสิทธิผลดีกว่า เมื่อเปรียบเทียบกับการเริ่มต้นการรักษาด้วยยาต้านไวรัสที่มีเนวิราปีนเป็นองค์ประกอบ จากเหตุผลดังกล่าว จึงควรพิจารณาให้ยาต้านไวรัสที่มีเอฟฟาวิเรนซเป็นองค์ประกอบเป็นยาเริ่มต้นในการรักษาผู้ติดเชื้อและผู้ป่วยเอดส์ในประเทศไทย

สาขาวิชาเภสัชศาสตร์สังคมและบริหาร ลายมือชื่อนิสิต.....

ปีการศึกษา 2549 ลายมือชื่ออาจารย์ที่ปรึกษาหลัก.....

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KEY WORD: PHARMACOECONOMIC EVALUATION/ ANTIRETROVIRAL DRUG/ NVP-BASED REGIMENS / EFV-BASED REGIMENS/ HIV/AIDS PATIENTS

USAWADEE MALEEWNG: **PHARMACOECONOMIC EVALUATION OF EFAVIRENZ-BASED ANTIRETROVIRAL THERAPY COMPARED WITH NEVIRAPINE-BASED THERAPY AMONG THAI HIV/AIDS PATIENTS.** THESIS ADVISOR: VITHAYA KULSOMBOON, P.HD. THESIS COADVISOR : THANARAK PLIPAT, M.D., 131 pp.

NVP-based or GPO-VIR has been recommended for the first line therapy for Thai HIV/AIDS patients. Negative consequences from serious adverse drug reactions such as Hepatotoxicity, Steven Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) raised concern among health care providers. The aim of this study was to evaluate cost-effectiveness of the treatment starting with EFV-based therapy as compared with NVP-based therapy in Thai HIV/AIDS patients. A probabilistic Markov model applied to HIV/AIDS patients aged 15 to 65 years was developed to compare the marginal cost and marginal benefit of starting with EFV-based regimens and NVP-based regimens. Input parameters were extracted from cohort study of the four regional hospitals under this study. Only relative risk of death of the two medications from published article was used in the survival rate calculation. The study explored the effects of uncertainty around input parameters, presented as cost-effectiveness plane and cost-effectiveness acceptability (AC) curves. The results indicated that starting with NVP-based increase the risk of having serious adverse events such as hepatitis, cirrhosis, SJS, and TEN (11.3, 5.2, 3.5, 0.9 per 1,000 person-year, respectively), compared with EFV-based regimens. Using a health care provider perspective, the lifetime treatment cost of patients who started with EFV-based was less costly than NVP-based regimens in all age groups except for those who were 20 years. Starting with NVP-based had slightly higher LY gain than EFV-based in aged-group of 30 to 60 years, but had less DALY averted than EFV-based regimens. The findings from AC curves revealed that in patients 20 years, starting with NVP-based was the preferable choice at no extra budget available, however, starting with EFV-based was preferred when the WTP was above 3,000,000 Baht/LY gained. In each group of patient aged 30, 40, 50, and 60 years, the initial therapy using EFV-based was the preferable choice. In terms of cost-utility (baht per DALY averted), starting with EFV-based regimens was the preferable choice in all age groups except those who were 20 years. In this group, starting with EFV-based was preferable when the WTP was above 1,000,000 Baht/LY gained. Given a maximum acceptable willingness to pay threshold of 270,000 Baht/DALY starting with EFV-based was cost effective in all aged group except those who were 20 years. It can be concluded that EFV-based was a preferable choice in terms of cost per DALY averted as well as cost per LY gained, except in patients with 20 years. Presently, due to the decrease of the cost of EFV resulting from the compulsory licensing by the Ministry of Public Health, starting with EFV-based is more cost-effective than NVP-based. It is recommended that EFV-based should be used as the first line regimen for Thai HIV/AIDS patients.

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CHAPTER I

INTRODUCTION

1.1 Rationale

HIV/AIDS has become one of the leading causes of death in Thailand. There were 41,443 deaths among patients 15-44 year olds in 2002. In the year 2004, from a total population of 61 million in Thailand, it was estimated that 1,074,155 persons were infected with HIV since the beginning of the epidemic. Of these, 501,600 had died and 572,500 were currently living with HIV and AIDS. It was estimated that 55,000 HIV/AIDS patients would develop serious AIDS illnesses and approximately the same number would die from AIDS complications. It was also estimated that 19,500 new infections would occur during this year compared to 143,000 new infections in 1990 [(1)].

The use of combination antiretroviral therapy (ART) had led to decreased morbidity and mortality among patients with advanced HIV infection and AIDS [(2)]. Several ARV regimens were available in high-income countries such as the United States. Health authorities in these countries recommended treatment of all individuals with moderately advanced to advanced HIV infection using regimens of 3 or more antiretroviral drugs (highly active antiretroviral therapy or HAART)[(3)]. Despite achievement in ART extension in developed countries, treatment coverage increased slowly in developing countries, while the demand was overwhelming. By the end of 2005 only 15% of the patients who need ARV in developing countries had accessed to ARV therapy [(4)]. The high prices of the drugs and resource scarcity were the two factors contributing to such limited development in treatment scaling up. A few middle-income developing countries, notably Brazil and Thailand have introduced HAART successfully within nationally funded programs but still with limited regimens. To enhance the accessibility and affordability of ARV in developing countries WHO issued guidelines for ARV therapy in resource-limited settings. WHO recommended a three-drug first line treatment regimen using Stavudine (d4T), or Zidovudine (AZT), Lamivudine (3TC) and either Nevirapine (NVP) or Efavirenz (EFV) as the first line drugs [(5)].

In 2004, the Thai government introduced HAART through the National AIDS Policy for People Living with HIV/AIDS (NAPHA) Program for 50,000 targeted HIV/AIDS

patients [6]. Six standard ARV regimens were approved to use in this programs including NVP-based which was used as the first drug used, while EFV-based and Protease Inhibitor (PI) – based were set as alternative regimens. The consideration for standard regimens was related to the cost of drug itself. The success of the Thai Government Pharmaceutical Organization (GPO) to produce a cheaper drug combination of NVP-based named GPO-VIR, the combination of Stavudine (d4T), Lamivudine (3TC) and Nevirapine (NVP), was the major reason to establish this regimen to be first line. Its cheaper cost could cut down the monthly expense for one patient's ARV treatment from 13,000-14,000 baht to 1,200 baht.

During fiscal year (FY) 2004, 50,752 patients started ARV treatment through NAPHA and 13% dropped out. So the total number receiving ARV therapy was 44,089 patients. In addition, there were about 3,000 cases enrolled into this program each month. Assuring the same accrual rate, by the end of 2010 the number of HIV/AIDS cases receiving ARV therapy will increase to more than 200,000. In 2004, 85% of the ARV regimens in NAPHA were GPO-VIR, the remaining of 15% were other regimens because of the occurrence of adverse drug reactions from GPO-VIR. At this rate, within 5 years the number of these cases who can not use GPO-VIR will increase to 20,000-30,000 cases. In 2004, the budget for this program was about 720 million baht for GPO-VIR and 144 million baht for EFV-based regimens. Within five years from 2004, the budget will increase to 2,500 million baht for GPO-VIR and 720-1,100 million for EFV-based regimens.

Although the cost of the NVP-based ARV regimen appeared to be cheaper than the EFV-based regimen, the inferior of efficacy and safety of NVP as compared with EFV should be considered. The evidence from many trials revealed that NVP could cause serious and life-threatening adverse events such as cutaneous hypersensitivity reactions, including Steven Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and severe hepatic toxicity. These adverse events became an emerging cause of mortality in HIV-infected patients [7-15]. These serious adverse events did not only affect the patients' quality of life and successful of treatment, but also increased the budget of the program. Therefore, substitution with less toxic alternative should be warranted. In this regard, EFV was needed to be considered. EFV was recommended as a substitute for NVP in the ARV regimen. It had less toxicity and superior in efficacy, but was spared for the substitution of NVP when the patients had severe adverse event because of its higher cost.

Scarcity of health care budgets would lead health care decision makers to display not only safety and efficacy but also cost-effectiveness data when they decided to employ new health care technologies. Pharmacoeconomics evaluation (PE) has been an important tool to evaluate the efficiency of specific interventions in health care. PE can provide data regarding which interventions or pharmaceutical products are the most cost-effective. In the considerations of cost-effectiveness of antiretroviral therapy many trials indicated that HAART therapy is cost-effective in rich countries, compared not only to other HIV interventions but also to interventions for a variety of diseases and conditions. In Thailand, NVP-based or GPO-VIR was recommended for the first line therapy even though there was no evidence on its cost-effectiveness compared with other regimens such as EFV-based regimens. The purpose of this study was to use the decision model to quantify the incremental cost of EFV-based treatment compared with NVP-based treatment based on the drug utilization data from Thai HIV/AIDS patients.

1.2 Objectives

1.2.1 General objectives

To evaluate the cost and effectiveness of EFV-based therapy as compared with NVP-based therapy in Thai HIV/AIDS patients.

1.2.2 Specific objectives

1. To quantify the incidence of serious and life-threatening adverse events and the total cost of treatment among HIV/AIDS patients who received EFV-based and those who received NVP-based antiretroviral therapy.
2. To measure the disability-adjusted life year (DALY) in order to compare the difference of outcome between EFV-based and NVP-based antiretroviral therapy.
3. To measure the incremental cost-effectiveness ratio (ICER) of EFV-based compared with NVP-based antiretroviral therapy.
4. To conduct sensitivity analysis and determine the cut point of EFV cost for decision making.

1.3 Scope of the study

1. The data in this study were secondary data collected from medical records of HIV/AIDS patients from four regional hospitals.
2. The target in this study were HIV/AIDS patients who had their age of 15 years old or more, were naïve to triple combination antiretroviral therapy, had baseline CD4 cell count less than 250cells/mm3, and received a NVP-based or EFV-based regimen before January, 2004.
3. The effects of ARV treatment such as the adverse drugs events, AIDS related complications were collected during the follow up period.
4. Total cost of treatment of HIV/AIDS patients including the cost of ARV regimens and the treatment cost of adverse events and AIDS related complications were collected based on the cost from four regional hospitals under this study.
5. The Markov model in this study was constructed based on the patient-level data from four regional hospitals.

1.4 The expected outcome

The pharmacoeconomics evaluation would demonstrate the evidence of cost and consequence of providing EFV-based antiretroviral therapy compared with NVP-based therapy that could provide the policy options for decision makers to include the more cost-effectiveness regimens into benefit package for Thai HIV/AIDS patients.

CHAPTER II

LITERATURE REVIEWS

This Chapter provided the situation of antiretroviral treatments for HIV/AIDS patients in other countries, the situation of AIDS epidemics and the treatment in Thailand, the comparison of safety and efficacy between NVP-based and EFV-based regimens, the summary measures in population health, the economic evaluation and the implementation to health care setting, and the pharmacoeconomics studies of antiretroviral therapy.

2.1 Antiretroviral Treatment for HIV/AIDS patients Worldwide

An estimated 36 million people worldwide were infected with HIV [16]. In the mid-1990s, the HIV/AIDS community was informed about a scientific breakthrough which was the development of highly active antiretroviral therapy (HAART), a treatment "cocktail" of antiretroviral drugs. Since the emerging of HAART, the disease has been transformed into a disease with chronic condition. In wealthy countries, there had been dramatic success in the fight against HIV/AIDS that had been largely achieved through the use of antiretroviral therapy. Those with access to this treatment had highly gained from survival and quality of life. Despite this success, antiretroviral therapy remained largely inaccessible in the world's poorest countries, where interventions have focused almost exclusively on prevention. With soaring death rates from HIV/AIDS in low-income countries, both the prevention of viral transmission and the treatment of those already infected became global public health priorities.

2.1.1 HIV Treatment in High-Income Countries

Partially effective treatment for HIV-infected individuals was first introduced in 1986. Zidovudine (AZT), the first antiretroviral drug used for treating HIV infection, was shown to reduce both death and the opportunistic infections in individuals with advanced HIV infections [17]. For the next several years, incremental advances were made with the discovery of other antiretroviral drugs, including didanosine (ddI), lamivudine (3TC), and stavudine (d4T) among others. However, the benefits of single drug treatments were relatively short-lived; treatment failures often occurred within

months to a few years and usually were associated with the emergence of resistant strains of the virus. A breakthrough occurred when it was shown that combining 2 or 3 antiretroviral drugs in "cocktail" regimens could delay the emergence of drug resistance and lead to a more profound and prolonged benefit than single drugs. New classes of drugs, the protease inhibitors and nonnucleoside reverse transcriptase inhibitors, allowed for more potent 3-drug antiretroviral regimens. These regimens, known as HAART, had resulted in the reduction of HIV levels in the blood, often to undetectable levels, and had markedly improved immune function in HIV-infected individuals. Coincident with the introduction of these therapies, AIDS death rates during the past 6 years have plummeted in the United States and other wealthy countries.

Current US government recommendations suggested treatment of all individuals with moderately advanced to advanced HIV infection using HAART regimens of 3 or more antiretroviral drugs [3]. Recommendations in other high-income countries were similar. Finally, in wealthy countries recent cost-effectiveness studies indicated that HAART represented a highly cost-effective medical intervention, comparable in quality-adjusted years of life to treatment of hypertension.

2.1.2 HIV Treatment in Low-Income Countries

The success and continuing improvement in the prevention and treatment of AIDS in high-income countries was in contrast to what has been seen in low-income countries. Despite achievement in ART extension in developed countries, treatment coverage increased slowly in most parts of the developing world, where the demand was overwhelming. By the end of 2005 only 15% of the patients in need in developing countries had accessed to therapy [4]. A few middle-income developing countries, including Brazil and Thailand have introduced HAART successfully within nationally funded programs; however, these countries have approximately 10 times the per capita income of the poorest countries and lower HIV prevalence [16]. The obstructions to AIDS treatment in poor countries fell into several categories. First, poor countries lacked the adequate medical infrastructure to provide AIDS treatment safely and effectively. Second, difficulties with adherence to complicated medication regimens would promote and spread drug resistance. Third, antiretroviral drugs are expensive. Poor countries could not pay for themselves even for wealthy countries to get free for them.

However, the extension of proven effective medical care to the millions of people suffering from HIV infection in the developing countries is an urgent priority. A

number of HAART regimens are available in wealthy countries. The ideal regimens should be potent and well tolerated; should have low drug toxicity; should be simple for the patient to take; and should not be easy to develop drug resistance. There has been no proven data that one particular regimen is best for initiating therapy, therefore, several treatment regimens should be available for use in poor countries.

2.2 HIV/AIDS patients and treatment in Thailand

2.2.1 The situation of AIDS epidemics in Thailand

In the year 2004, from a total population of 61 million in Thailand, it was estimated that 1,074,155 persons were infected with HIV since the beginning of the epidemic. Among these, 501,600 had died and 572,500 were currently living with HIV and AIDS. Of these, it was estimated that 55,000 would develop serious AIDS illnesses and approximately the same number would die of AIDS complications. It was also estimated that 19,500 new infections would occur during the year 2004 compared to 143,000 new infections in 1990 [(1)].

2.2.2 Demand and number of patients needing antiretroviral treatment in Thailand

Highly active antiretroviral therapy (HAART) has clearly demonstrated its effect to improve HIV-related clinical outcomes, including the decrease of opportunistic infection and the increase of life span [(2)]. A great number of people living with HIV/AIDS created a huge demand for antiretroviral treatment. As compared with others countries Thailand has achieved some level of coverage through national policies. However the accessibility of ARV treatment was still low. WHO statistics showed that by the end of 2004, some 96,000 patients of 670,000 HIV sufferers were in need of ARV treatment, but at the beginning of 2004, only 23,000 people are on ARV treatment [(4)]. After the successful of providing generic drug GPO-VIR, the fix dose combination of Nevirapine (NVP), Lamivudine (3TC) and Stavudine (d4T). Thai government increased number of patients receiving triple combination antiretroviral treatment to be more than 50,000 cases at the end of fiscal year 2004.

2.2.3 Treatment and Care program for HIV/AIDS patients in Thailand

During 1982-1987, the government health education program on HIV was limited to commercial sex workers. In 1988, a widespread HIV/AIDS program was implemented to prevent and control HIV transmission. In 1991, AIDS prevention and control became a national priority at the highest level [18]. Thai government took several important steps that have since been credited with helping to slow the epidemic. First, the AIDS control program was moved from the Ministry of Public Health to the Office of the Prime Minister, increasing its political influence, and the budget was increased almost 20-fold to $44 million in 1993. Second, a massive public information campaign on AIDS was launched to society. Anti-AIDS messages aired every hour on the country's 488 state-owned radio and television stations, and every school was required to teach AIDS education classes. Third, the '100 percent condom program' was initiated. Condoms were distributed free to sex workers and their clients were required to use them. From 1992 to 1996, the National AIDS program received dramatic increases in funding, with the government providing more than $80 million annually. The national response to the disease evolved over time, and initial efforts focused on prevention.

In 1992, a limited, public-sector ART program was implemented, offering AZT monotherapy to people living with HIV/AIDS (PLWHA) in low-income groups [19]. However, this program was terminated in 1996 due to the quality of care and cost. The Health Ministry reallocated its ART budget to the Clinical Research Network and was reformulated into the Access to Care Initiative, to provide HAART on a service basis in 2000.

A dramatic policy shift took place in late-2001 as the newly elected government announced to provide free treatment to all clinically eligible people living with HIV/AIDS through Universal Health Coverage (UC) plan. In addition, the Thai Government Pharmaceutical Organization (GPO) could produce a combination of three drugs in highly active antiretroviral treatment, including Nevirapine, Lamivudine and Stavudine called “GPO-VIR”. Cheap generic versions of ARV were available in Thailand and cut down the monthly expense for one patient's ARV treatment from previously 13,000-14,000 baht (309.52-333.33 US dollars) to 1,200 baht (18 dollars). The annual cost was only 14,400 baht which was lower than the annual cost for eight other chronic diseases in the 30 baht health care program. For this reason, the Thai government established

the Access to Care Program (ATC) to provide ARV treatment for HIV/AIDS patients to cover 3,000 cases at the beginning and increase to 13,000 cases in 2004. Due to the reduction of the cost of ARV drug, the extension of the number of patients was made possible by the government annual budget of 250 million baht.

In 2004, the Thai government established National Access to Antiretroviral Program for people living HIV/AIDS called “NAPHA Program” [6].The goal of this policy included enhancing the accessibility of triple combination of antiretroviral treatment for PWA in Thailand. However, the benefits of NAPHA program did not cover the cost of adverse drug reaction and changing regimen due to drug resistance.

Six standard ARV regimens were set based on the cost of treatment and the availability of antiretroviral drug in Thailand. NVP-based was set to be first line regimen. The alternatives were EFV-based and PI-based in case of severe side effect or NNRTI resistance occurred. All cases that were enrolled into this program have to start with GPO-VIR, so it’s not covered the patients who have experienced to use other regimens. Six standard regimens were shown in Table 2.1.

Table 2.1: Standard regimens for antiretroviral drug in NAPHA program

First line regimen	d4T+3TC+NVP (GPO-VIR)
Alternative regimens	1) d4T+3TC+EFV
	2) AZT+3TC+NVP
	3) AZT+3TC+EFV
	4) d4T+3TC+IDV/RTV
	5) AZT+3TC+IDV/RTV

2.2.4 The monthly cost of antiretroviral treatment

Most of the antiretroviral drugs were available in Thailand and most of them were still on patent status, particularly in Protease Inhibitor group, so their cost was relatively high as compared to generic drugs. GPO-VIR was the first fix dose combination of triple antiretroviral drugs that could produce in Thailand. The cheaper cost of GPO-VIR, only 1,200-1,320 baht per month made HIV patients affordable for drugs. However, the use of GPO-VIR was limited because of the severe adverse reaction from NVP including skin hypersensitivity reaction or severe hepatotoxicity. In cases of changing to other regimens such as EFV-based regimens, the monthly cost of

antiretroviral drug was increased to 2 times as compared with GPO-VIR (see appendices III).

2.2.5 Antiretroviral regimen in NAPHA program

By the end of FY 2004, the number of cumulative cases receiving combination ARV treatment in the NAPHA program was 50,752 cases. With a dropout rate of 13% or 6,663 cases, the number of cases receiving ARV was 44,089 cases. In addition, there were about 3,000 cases enrolled into this program each month, so by the end of 2010 the number of HIV/AIDS cases receiving ARV will increase to more than 200,000 cases.

Eighty-five percent of the ARV regimens in NAPHA were GPO-VIR. The remaining 15% were other regimens, particularly EFV-based due to the occurrence of adverse drug reaction of GPO-VIR. Until now, there were about 4,000 cases of HIV/AIDS patients that faced toxicity of GPO-VIR and had to switch to other regimens. So, within 5 years from 2005, the number of cases needing other regimens are projected to increase to 20,000- 30,000. Based on this data, the expenditure to the Thai government was about 720 million baht for GPO-VIR and 144 million baht for EFV-based regimens. Within 5 years the budget is projected to be 2,500 million baht for GPO-VIR and 720-1,100 million or for EFV-based regimens.

In summary, the availability of GPO-VIR in Thailand has made it the first line regimen. However, the use of GPO-VIR was limited because of the severe and life-threatening adverse reaction from NVP including skin hypersensitivity reaction or severe hepatotoxicity. EFV was a suitable alternative to NVP in the ARV regimen, and it had less severe adverse events and a superior efficacy profile. However, since it was relatively more expensive, EFV was spared for the substitution of NVP when the patients had severe adverse event. However, public health policy makers should consider not only the cost of drug itself, but also the efficacy, safety, and cost-effectiveness data in the process of developing treatment strategies. The analysis of incremental cost and incremental effect of EFV compared with NVP would be important in antiretroviral treatment in the Thai setting that might benefit to health care service with budget constrain.

2.3 The comparison of Efficacy and Safety of Efavirenz-based regimens compared with Nevirapine-based regimens

In terms of efficacy, many trials revealed that the EFV-based regimens dominated in success rate both virological success and immunological success with shorter time and lower in discontinuation rates compared with the NVP-based regimens [7-15], especially in antiretroviral naïve patients. Matthews and others conducted the study in ARV naïve patients. The findings revealed that the percentage of patients achieving VL<500 copies/ml was 92% in the EFV-arm and 83% in the NVP-arm (p<.001). Similarly to the conclusion made by Keiser P and others. The findings showed that NVP had fewer patients with VL<400 copies/ml as compared with EFV (45% & 51%, p<.001) and had a shorter time to treatment failure (307 days VS 589 days, p<.001). The results from EuroSIDA study, a large clinical-based retrospective study in 64 clinics in Europe showed that at 12 months the virologic failure rate was 48% in EFV and 65% in NVP (p<.001). These results were similar to 2NN study, which showed the superiority of EFV in the number of treatment failure as compared with NVP, although there was not significantly difference (37.8% in EFV & 43.7% in NVP).

In addition, the NVP-based regimens seemed to be dominated by EFV-based regimens in terms of safety. NVP use was the leading cause for serious and life-threatening toxicity such as cutaneous hypersensitivity reaction including Steven Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), and also serious hepatotoxicity that became the major factor of drug discontinuation and death in treated HIV/AIDS patients. The findings made by Roberto M and others revealed that Liver toxicity was significant more in NVP than in EFV compared with baseline, while EFV use related to CNS disturbance. The findings of study made by W. Phillip Law and others showed the high relative incidence between severe hepatotoxicity and NVP use (the incidence of severe hepatotoxicity in NVP used was 18.6 /100 Person-Y (95%CI=10.6-29.8/100), while the incidence of severe hepatotoxicity in EFV used was 2.4 /100 Person-Y (95%CI=0.3-7.8/100)).

Table 2.2 Efficacy and Safety of Antiretroviral drug

Study	Objectives	Method	Subjects	Subject in each regimen	Outcomes	Results
Sabin , M., et al. (2001) Britain(7)	To compare the efficacy of 1st line HARRT in ARV naïve patients	An observational database from 2 hospitals	888 patients (6 months follow-up)	484 (PIs-based) 237 (NVP-based) 167 (EFV-based)	- The initial response VL<500 copies/ml - composite failure endpoint	-The percentage of patients with VL <500 copies/ml: -92% on EFV -83% on NVP -79% for all PIs (p<.001) -The composite failure endpoint : -127 (26.2%) in PIs arm - 52 (21.9%) in NVP arm - 19 (11.4%) in EFV arm
Philips, AN., et al. EuroSIDA team (2001) Europe (8)	To compare the efficacy of NVP-based VS EFV-based	A clinic-based, retrospective study in 64 clinics	1,932 patients	1,202 (NVP-base) 730 (EFV-base)	- Virologic failure (2 consecutive plasma HIV-RNA level greater than 500 copies/ml)	- At 12 months, virologic failure rate: -48% for EFV arm -65% for NVP arm - In virologic progression, the adjusted Relative Hazard for EFV VS NVP = 0.57(0.47-0.69); p<.001 - In clinical progression, the adjusted relative Hazard for EFV VS NVP = 0.49 (0.33-0.74); p<.001

Study	Objectives	Method	Subjects	Subject in each regimen	Outcomes	Results
Fellay, J., et al. Swiss HIV Cohort Study (2001) Switzerland (9)	To compare the prevalence of ADR between ARV drug regimens.	Cross-sectional study at the Swiss Cohort Study	- 1,160 patients		- Clinical and laboratory adverse events	- 47% (545 of 1,160) of patients presented with clinical adverse event. - 27% (194 of 712) with laboratory adverse events attributed to ARV treatment. - Among these 9% and 16% were graded as serious and severe toxicity. - NVP used related to enhancing of Serum transaminase conc OR=2.2(1.1-4.2), - EFV related to mood OR=1.5(1.0-2.2) and Sleep disorder OR=2.1(1.4-3.2) - 3TC used related to Lipodystrophy OR=1.8(1.4-2.4) - d4T used related to Lipodystrophy OR=1.6(1.2-2.2)

Study	Objectives	Method	Subjects	Subject in each regimen	Outcomes	Results
Keiser P., et al. (2002) USA (10)	To compare the efficacy of NVP-based VS EFV-based	A cohort analysis of 3 observational databases	1,078 ARV-naïve patients	523 (NVP-based) 555 (EFV-based)	- time to treatment failure - change in plasma HIV-RNA from baseline	- NVP patients had a shorter time to treatment failure compared with EFV (307 days & 589 days; p<.001) - NVP had fewer patients with plasma HIV-RNA<400 copies/ml (45% VS 51%; p<.001) - improved relative hazard with EFV compared to NVP (odds ratio=0.50; p<.001)
Law, W., P., et al. (2003) Thailand (11)	To examine rates and predictors of severe hepato-toxicity with ARV therapy	Prospective observational in RCT of ARV therapy at HIV-NAT	692 patients	342 (2 NRTI) 215 (with NNRTI combination) 135 (with PI combination)	- severe hepato-toxic events based on ALT level	- Incidence of severe hepatotoxicity in NVP used was 18.6 /100 Person-Y (95%CI=10.6-29.8/100). - Incidence of severe hepatotoxicity in EFV used was 2.4 /100 Person-Y (95%CI=0.3-7.8/100). -Incidence of severe hepatotoxicity in NPV used with HBV was 57.4 /100 Person-Y, while with HCV was 72.2 /100 Person-Y. - Predictors of severe hepatotoxicity were HBV or HCV co-infection, and NNRTI-based therapy.

Study	Objectives	Method	Subjects	Subject in each regimen	Outcomes	Results
Munsakool, W., Rodaree, P., and Munsakool, N. (2003) Thailand (12)	- To determine the effectiveness and SE of GPO-VIR therapy	Analytical longitudinal study	87 patients with 3 months follow-up	87 (GPO-VIR used)	-Change in CD4 count from baseline - ADR events	- CD4 count increased 99.25 cell / mm3 and mean body weight increased 2.89 kg. -Severe side effects were occurred in 13 cases (14.9%). The most common SE was rash (13.79%) and 1 case developed SJS.
Manosuthi W, Sungkanuparph S, Vibhagool, A, et al. (2004) Thailand (13)	To compare virologic and immunological response to NVP-based and EFV-based	A retrospective observational cohort study	53 ARV-naïve patients with advance HIV infection	24 (NVP-based) 29 (EFV-based)	- the time to virologic success - the immunologic response	- The patients with NVP-based had 25% (HR=0.75, 95% CI: 0.37, 1.51) lower chance of virologic success than EFV-based. - The median success times: -4 months in NVP -3 months in EFV. - The median times of CD4> 100 cell/ml: -5.6 months in NVP -4.4 months in EFV

Study	Objectives	Method	Subjects	Subject in each regimen	Outcomes	Results
Van Leth, F., Phanuphak, P., Ruxrungtham, K,, et al. Multi-center International study (14)	To compare the efficacy and safety of NVP-based VS EFV-based	A multi-center, open-label, randomized trial	1,216 ARV-naïve patients	-182 (NVP 400mg (1*1) +3TC+d4T) -322 (NVP 200mg (1*2) +3TC+d4T) -337 (EFV 600mg (1*1) +3TC+d4T) -175 (EFV 800mg and NVP 400 mg (1*1) +3TC+d4T)	-The proportion of patients with treatment failure - The efficacy of each regimen.	- The treatment failure occurred -96 (43.6%) of NVP once daily -169 (43.7%) of NVP twice daily - 151 (37.8%) of EFV -111 (53.1%) of NVP plus EFV - - The difference between NVP and EFV was 5.9%. - NVP plus EFV was associated with the highest frequency of clinical adverse events, and NVP once daily with significantly more hepatobiliary laboratory toxicities than EFV. - Of 25 observed deaths, two were attributed to NVP. - There were no significant difference among 4 groups in the proportion with plasma HIV-1 RNA <50 copies/ml at week 48 (p=0.193) and the increasing in CD4 (p=.800).

Study	Objectives	Method	Subjects	Subject in each regimen	Outcomes	Results
Manfredi, R., Calza, L., Chiodo, F. (2004) USA (15)	To compare the efficacy and tolerability of NVP and EFV-based regimen	An open-label, observational, prospective 18 months survey	-154 ARV naïve pts -288 experience pts -103 with salvage regimen	258 (NVP-based) 287 (EFV-based)	-Virologic and immunologic response - Tolerability response	-Among sub-groups only ARV naïve patients experienced greater EFV activity at 3-12 months associated with a significantly higher rate of complete viral suppression, while immunologic results proved significant only after 6-9 months. - In 1st month the discontinuation rates proved similar (4.2 and 4.3% for EFV and NVP). -Liver toxicity had a more significant increase in NVP than in EFV compared with baseline, while EFV use related to CNS disturbance.

2.4 Summary measures of population health

"Summary measures of population health" which is the measurement of population health, can be obtained by combining data on mortality and non-fatal health outcomes into a single number [20].Measurement of population health can be classified into two classes: *health expectancies* (e-g- disability-free life expectancy, disability adjusted life expectancy) and *health gaps* (disability-adjusted life years, healthy life years). Both classes of the summary measure used time (lived in health states or lost through premature death) as an appropriate common metric for measuring the impact of mortality and non-fatal health outcomes.

Health expectancies are population indicators that estimate the average time (in years) that a person could expect to live in a defined state of health. Examples include disability-free life expectancy (DFLE), active life expectancy and disability-adjusted life expectancy. These extend the concept of life expectancy to refer to expectations of various states of health.

Health gaps measure the difference between actual population health and some specified norm or goal. The principle characteristic defining a health gap measure is the population norm (age) chosen to define the period before which death or disability is considered premature. Since the consequence of this study concern about health lost due to a disease, only health gap measurement was used in the cost-effectiveness analysis.

2.4.1 Health gap measurement

The disability-adjusted life years (DALY) has been the most widely-used measure for health gap measurement. It measures the difference between a current situation and an ideal situation where everyone lives up to the age of the standard life expectancy, and in perfect health. DALY combines both time lost due to premature mortality and non-fatal conditions [21].This measure was used in The Global Burden of Disease and Injury (GBD), a joint study between the World Bank, the World Health Organization (WHO) and Harvard School of Public Health, which began in 1988 with the objective to quantify the burden of disease and injury of human populations and define the world's main health challenges.

DALY for a disease or health condition are calculated as the sum of the years of life lost due to premature mortality (YLL) in the population and the equivalent 'healthy' years lost due to disability (YLD) for incident cases of the health condition:

DALY = YLL + YLD

where:

YLL = years of life lost due to premature mortality.

YLD = years lived with disability.

The YLL metric corresponds to the number of deaths multiplied the standard life expectancy at the age which death occurs. The basic formula for calculating the YLL for a given cause, age or sex, is:

$$YLL = N \times L$$

where:

N = Number of death

L = Standard life expectancy at age of death (in years)

To estimate YLD on the population basis, the number of disability cases is multiplied by the average duration of the disease and the weight factor that reflect the severity of the disease on a scale from 0 (perfect health) to 1 (death). The basic formula for one disabling event is:

$$YLD = I \times DW \times L$$

where:

I = number of incident cases

DW = disability weight

L = average duration of disability (years)

2.4.2 Discounting and age weighting of disability adjusted-life year calculation

Discounting health with time reflects the social preference of a healthy year now, rather than in the future. To do this, the value of a year of life is generally decreased annually by a fixed percentage. The GBD applied a 3% time discount rate to year of life lost in the future to estimate the net present value of years of life lost.

$$YLL = \frac{N}{r}(1-e^{-rL})$$

where:

N = number of deaths.

L = standard life expectancy at age of death (years).

r = discount rate (e.g. 3% corresponds to discount rate of 0.03).

Similarly, the formula for YLD is:

$$YLD = \frac{I \times DW \times L\,(1-e^{-rL})}{r}$$

where:

N = number of incident cases.

DW = disability weight.

L = average duration of disability (years)

r = discount rate (e.g. 3% corresponds to discount rate of 0.03).

If both age-weighting and discounting are applied, and the years between the event and the life expectancy are summed, the initially simple formulas for YLL and YLD become more complicated (formula for a single death).

$$YLL = KCe^{(ra)} / (\beta+r)^2 \left[e^{-(\beta+r)(L+a)}[-(\beta+r)(L+a)-1] - e^{-(\beta+r)a}[-(\beta+r)a-1]\right]$$

where:

a = age of death (years).

r = discount rate (e.g. 3% corresponds to discount rate of 0.03).

= age weighting constant (e.g. =0.04).

K = age-weighting modulation constant (e.g. K=1).

C = adjustment constant for age-weights (e.g.C=0.1658).

L = standard life expectancy at age of death (years)

Similarly, by replacing the standard life expectancy in the YLL formula by the duration of disease and by multiplying by the disability weight, the YLD formula becomes the following (for a single disabling event):

$$YLD = I\,DW\,Ce^{(ra)} / (\beta+r)^2 \left[e^{-(\beta+r)(L+a)}[-(\beta+r)(L+a)-1] - e^{-(\beta+r)a}[-(\beta+r)a-1]\right]$$

where:

a = age of death (years).

r = discount rate (e.g. 3% corresponds to discount rate of 0.03).

C, , K = constants

L = duration of disability (years).

DW = disability weight.

In summary, antiretroviral therapy is widely used among Thai HIV/AIDS patients. The high cost of treatment will affect the overall budget of Thai health care. Furthermore, the negative effects of the treatments needed to be considered. Disability adjusted-life year (DALY) that measure the amount of health lost seems to be the useful tools to present the different outcome between two antiretroviral regimens.

2.5 The Economic evaluation and the implementation to health care setting

2.5.1 Welfare and non-welfare economics [22]

Theoretically, the decision of health care resource allocation should be based on economic evaluation, which may stem from welfare economics or non-welfare economics.

Welfare approaches:

Welfare economic is an area of economics. It incorporates the principles that individuals are the best judge of their own willing and that, if one person can be better off while another is not worse off, there is welfare improvement. However, only few policies can benefit some individuals without affecting others. To determine the resource allocation using welfare economics, the cost-benefit analysis (CBA) could be used. Cost-benefit analysis uses individuals' willingness to pay to assess the benefit of an intervention. Even though CBA has a strong support from traditional economic theory, it is sometimes not practical in health care for various reasons. The limitations of welfare economics using cost-benefit approach are

1) It creates incentive for patients to overstate the cost and understate the benefits of the alternatives.

2) It based on willingness to pay which include income parameter into the economic evaluation. This may skew allocation of health care resources toward the wealthy.

3) People are not satisfied with valuing length and quality of life in monetary terms.

4) The goals, such as equality of outcome, equality of opportunity, political feasibility, and national security, other than efficiency are not considered in CBA analysis.

Non-welfare approaches:

Alternatives to welfare economic move away from reliance on individual welfare to pursue societal objectives. They are referred to as non-welfarist approaches or decision maker approaches and extra-welfarism. These approaches all subscribe to the same healthcare objective to maximize the health outcome from the available resources based on societal perspective. Non-welfare approach emphasizes health as primary outcome for economic evaluation. When the focus is on health instead of utility, the question about the equity among those people who need special health, e.g. the handicapped, is solved. Even though they are not productive, they are still alive an entitled to minimize their health problems. The extra-welfarism also counts on non-health implications related to health, e.g. age. It therefore corrected the equity consideration in the non-health aspect as well. Practically, cost-effectiveness analysis (CEA) is used to determine the resource allocation

and cost-utility analysis (CUA) such as quality adjusted life year (QALY) is the outcome to be measured. QALY has been widely accepted and the economic evaluation using non-welfare approaches has been improved in dealing with uncertainty.

Though the welfare economic, in theoretical view point, should be suitable, its difficulties let to emphasize more on other alternative, non-welfare approach. Therefore, economic evaluation in this study was focus on non-welfare economic approach.

2.5.2 Defining economic evaluation

Economic evaluation in health care can be defined as the comparison of alternative options in terms of their costs and consequences [23]. Alternative options refer to the range of ways in which health care resources can be used to increase population health; for example, pharmaceutical and surgical interventions, screening and health promotion programs. Health care costs refer to the value of tangible resources available to the health care system; for example, clinical and other staff, capital equipment and buildings, and consumable such as drugs. Non-health service resources are also used to produce health care, such as the time of patients and their families. Consequences represent all the effect of health care programs other than those the resources. These generally focus on changes in individuals' health, which can be positive or negative.

Economic evaluation is increasingly used to inform the decisions of various health care systems about which health care interventions to need to be funded from available resources. This is particularly true for the decisions about the coverage or reimbursement of new pharmaceuticals. The first jurisdictions to use economic evaluation in this way were the public health systems in Australia and Ontario, Canada [24]. In the UK, the National Institute for Health and Clinical Excellence (NICE) has a wider preview in terms of health technologies, and uses economic evaluation to inform decisions about medical devices, diagnostic technologies and surgical procedures, as well as pharmaceuticals [25]. The increasing use of economic evaluation for decision makers has placed very clear requirement for researchers in terms of analytic methods. These include the need to incorporate all appropriate evidences into the analysis, to compare new technologies with the full range of relevant alternative options, and to reflect the uncertainty of evidence in the conclusion of the analysis.

2.5.3 Methods of economic evaluation

Drummondand and others [26] and Donaldson [27] discussed a number of methods of economic evaluation currently in use: cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-benefit analysis (CBA) and cost-utility analysis (CUA). These are terms which should be understood as they are likely to be seen more frequently in the literature.

1. Cost-minimization analysis

This form of analysis is used when the outcomes of two procedures being compared are identical and it is important that the outcomes of the alternative programs are proven to be the same if the method is used. The aim is usually to find the lowest cost program and the unit of measurement is cost per intervention.

2. Cost-effectiveness analysis

Cost-effectiveness was the most widely used method of economic analysis until the 1980s. This method is used when the programs may have differential success in outcome, as well as differential costs, but the outcome must be common to both programs (e.g. life years gained; blood pressure reduction). The disadvantage of the cost-effectiveness approach is that it cannot be used to assess a single program or to compare interventions which have several different clinical effects. This disadvantage leads to the development of cost-utility analysis (CUA). There are a number of similarities between CEA and CUA and the two terms are sometimes used synonymously.

3. Cost-benefit analysis

If the outcome of two health programs differs, then a common denominator must be established to allow comparisons of outcome. One way of doing this is in monetary terms and cost-benefit analysis aims to measure the costs and the consequences in terms of pounds, dollars etc. CBA differs from cost-effectiveness and cost-utility analyses in that costs and benefits of healthcare are expressed in the same units.

4. Cost-utility analysis

Utility refers to the value or worth of a particular health state or an improvement in that health state. Utility values lie between 0 and 1, where 0 is equivalent to death and 1 is equivalent to perfect health. CUA should be the method of choice when quality of life is an important outcome. It is also the ideal method when interventions affect both morbidity and mortality or when treatments have a wide range of different outcomes and a common unit is

required. Utility values may be estimated using values quoted in the literature or they may be measured directly using a number of techniques such as the Standard Gamble or the Time Trade-Off [28]. In CUA only final data (e.g. lives saved; days of illness avoided) can be used. Intermediate data, such as cases found, cannot be used as they cannot be converted into QALY gained.

2.5.4 Cost-effectiveness analysis (CEA) in health care

In the context of health care, CEA would typically be characterized as a tool to maximize the benefit on a health care budget. There are many examples in the CEA literature which use measures of health specific to the disease or intervention under consideration. Example of such measure is the percentage reduction in blood cholesterol (coronary heart disease). However, given the need in most health care systems to make resource allocation decisions across a whole range of disease areas, CEA has increasingly been based on a single measure of health. The quality-adjusted life-year (QALY) and disability adjusted life-year (DALY) are the most frequently used measure for this purpose.

2.5.5 The role of decision analysis and decision modeling in economic evaluation

Decision analysis represents a set of analytic tools that are quite distinct from CBA and CEA but can be seen as complementary to both analyses. In health care, it is an established framework to inform decision making under conditions of uncertainty. Decision analysis has been defined as a systematic approach to decision making under uncertainty. In the context of economic evaluation, a decision analytic model uses mathematical relationships to define a series of possible consequences that would flow from a set of alternative options being evaluated. Based on the input into the model, the likelihood of each consequence is expressed in terms of probabilities, and each consequence has a cost and an outcome. It is thus possible to calculate the expected cost and expected outcome of each option under evaluation.

A key purpose of decision modeling is to allow for the variability and uncertainty associated with all decisions. The way a decision model is structured will reflect the fact that the consequences of options are variable. For example, identical patients will response differently to a given intervention and it might be characterized in terms of dichotomous events such as ‘response’ and ‘non response’ to treatment. The likelihood of a response will be expressed as a probability, which is a parameter to the model. However, the estimation

of this parameter is uncertain and this should also be allowed using sensitivity analysis in the model.

Decision analysis has had a controversial role in economic evaluation in health care [29]. However, the growing use of economic evaluation to inform specific decision problems facing health care decision makers has seen an increased the important for decision modeling as a vehicle for evaluation. The strongest evidence for this is probably the 2004 methods guidelines from the National Institute for Clinical Excellence in the UK (NICE). Two most common forms of cohort model used in decision analysis for economic evaluation are the decision tree and Markov model.

The decision tree is probably the simplest form of decision model. The key features of a decision tree approach are

- A square decision node: indicate a decision point between alternative options.

- A circular chance node shows a point where two or more alternative events for a patient are possible.

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

- Probabilities show the likelihood of a particular event occurring at a chance node.

The Markov model is a commonly used approach in decision analysis to handle the added complexity of modeling option with a multiplicity of possible consequences. The added flexibility of Markov model related to the fact that it is structured around mutually exclusive disease states, representing the possible consequences of the options under evaluation. Instead of 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 states over a series of discrete time periods (cycle). Costs and effects are incorporated into these models as a mean value per state per cycle, and expected value are calculated by adding the costs and outcomes across the states and weighting according to the time the patients is expected to be in each state.

2.5.5 Data collection method in economic evaluation

To obtain the CE value of a therapeutic alternative for formulary decision making, one should consider what CE data sources will be used. CE published literature is widely used. In-house data from local health systems are the important source to conduct trial based CE studies that will reflect outcome from real life practice. Using epidemiologic data and outcome information from previous studies is a prerequisite to perform projection CE

modeling. Choosing specific CE data sources and suitable methods to obtain CE information will increase the role of CE in formulary decision making.

Currently, there is no objective way to assess the overall validity of estimates derived from pharmacoeconomic trials. Cook and others [30] proposed an evidence-ranking system that considered the design of a trial in determining the strength of recommendation that should be made from a particular trial (Table 2.4). This suggests that prospective randomized trials provide the highest quality evidence, whereas information derived from case studies may not be as useful in informing decision making.

Table 2.3 Level of evidence for therapy

Level	Type of trial	Grade
I	Randomized trials with low error	A
II	Randomized trials with high error	B
III	Non randomized concurrent cohort study	C
IV	Non randomized historical cohort study	C
V	Case series	C

However, this existing evidence ranking is likely to be of little use in pharmacoeconomic research. Evidence-ranking systems developed recently are more comprehensive [31], yet they are still insufficient for pharmacoeconomic purpose (Table 2.5). Additional work needs to be directed at developing evidence rankings that are applicable to pharmacoeconomic studies. The NHS Center for review and Dissemination has purposed a hierarchy of evidence that may provide a framework for pharmacoeconomic research. Table 2.5 showed that additional categories are appropriate for these ranking systems.

Table 2.4 Hierarchy of evidence

Experimental	
I	Well-designed randomized control trials
	Other types of trials
II-Ia	Well-designed controlled trial with pseudo-randomization
II-Ib	Well-designed controlled trials with no randomization
Observational studies	
II-2a	Well-designed cohort (prospective study) with concurrent controls
II-2b	Well-designed cohort (prospective study) with historical controls
II-2c	Well-designed cohort (retrospective study) with concurrent controls
II-3	Well-designed epidemiological case control (retrospective) study
	Large differences from comparisons between times and/or places with and without intervention (in some circumstances these may be equivalent to level II or I)
Expert opinion	
IV	Opinions of respected authorities based on clinical experience; descriptive studies and reports of expert committees

Source: NHS for Review and Dissemination (1996) cited in Christopher J. Evans and Bruce Crawford. Data collection methods in prospective economic evaluations: How accurate are the results. *Value in Health* 2000; 3: 277-286[31].

In summary, much evidence indicated that CE data are useful and has its increasing roles in formulary decision making. In health care, decision analysis is an established framework to inform decision making under conditions of uncertainty. In the context of economic evaluation, a decision analytic model uses mathematical relationships to define a series of possible consequences that would flow from a set of alternative options being evaluated. In addition, the Markov model is commonly used in decision analysis to handle the added complexity of modeling option with a multiplicity of possible consequences. The added flexibility of Markov model related to the fact that it is structured around mutually exclusive disease states, representing the possible consequences of the options under evaluation. Markov model seems to be an appropriate tool to compare the cost effectiveness between two alternatives treatments for HIV/AID patients. To obtain the decision model, it is necessary to consider choosing appropriate CE data sources. The choices to obtain CE information depend on the availability of published literature, the accessibility of databases, the readiness of human resources, the timeliness of CE results, and the magnitude of formulary decisions. Health care decision makers will choose an appropriate strategy that can minimize those limitations to achieve the CE results in order to allocate health care resources efficiently.

Only one trial comparing between safety and efficacy of EFV and NVP were conducted in Thailand. Using CE data from the literature reviews to perform CE modeling would have several limitations including variety in efficacy, safety, and cost data. The observational data from medical records in multi-center health care institutions seemed to be more appropriate to provide the information about ARV use for Thai HIV/AIDS patients and its complications in real setting and could be the input parameters in the Probabilistic Markov Model.

2.6 The cost-effectiveness study of antiretroviral treatments

The comparison of cost-effectiveness between triple combination therapy and no antiretroviral treatment in the Swiss Cohort Study [32] revealed that on the basis of projected survival in each scenario, ICER was 33,000 CHF or US$ 22,110 (base case), 14,000 CHF or US$ 9,380 (optimistic), and 45,000 CHF or US$ 30,150 (pessimistic) per year of life gained (100 CHF= US$67). The findings from Markov model made by Trueman and others [33] predicted that triple Nucleoside Analog therapy extended life expectancy by an additional 1.2 years compared with dual therapy. The ICER was estimated to be between 10,072-16,168 pounds per QALY gained. Similarly, the result of The AIDS Clinical Trial Group (ATCG 320) [34] pointed out that life expectancy adjusted for QOL increase from 1.53 to 2.91years. The ICER as compared with no therapy was $23,000 per QALY.

Miners and others [35] compared the cost-effectiveness between triple combination and dual combination antiretroviral treatment. The findings showed that the projected life expectancy for individuals treated with dual therapy and HAART were 11.6 years and 14.5 years, respectively. Assuming a 2 year additional treatment effect of HAART produced incremental cost-effectiveness ratios of £ 14,602 / life-year saved and £ 17,698 / QALY gained.

One study of the cost of GPO-VIR treatment in Thailand [36] revealed that treatment cost before receiving GPO-VIR was 4,346 baht per patient per year (PPPY) while the treatment cost after receiving GPO-VIR was 22,682 baht PPPY including 18,369 baht PPPY for ARV cost. The hospitalization cost reduced from 1,978 baht PPPY to 815 PPPY after receiving GPO-VIR. The reduction of hospitalization cost due to the decrease of severe opportunistic infection admitted. However, the treatment cost of ADR cost from GPO-VIR was a high proportion of hospitalization cost (48.4%). In addition, one study of annual cost of antiretroviral treatment in Thailand setting revealed that the estimated long term annual cost for ARV treatment full coverage ranged 4,000-11,000 million baht per year [37].

Based on several PE studies, HAART therapy was cost-effective in rich countries, compared not only to other HIV interventions but also to interventions for a variety of diseases and conditions. Because HAART helped people alive and generally in good health, each year of effective treatment for those with advanced HIV disease (those who would otherwise die) generally leads to an additional year of life saved. In fact, the cost-effectiveness of AIDS treatment roughly corresponds to its actual cost. Moreover, it does not incorporate the savings that HAART will permit in regard to hospital stays and treatment for opportunistic infections, as has been the experience in the United States, other wealthy countries, and middle-tier developing countries such as Brazil. Nor does this cost estimate include HAART epidemiological benefits, which have been shown to reduce overall disease incidence both by reducing the HIV viral load and transmissibility of HIV-positive individuals and by improving the efficacy of prevention programs.

Table 2.5 Pharmacoeconomic Evaluations studies in Anti-retroviral treatment

Study	Objectives	Design	Setting	Perspective	Interventions	Results
Sendi, P.P., et al. (1999) Switzerland Swiss cohort study (32)	To investigate the impact of HARRT funding policy on the society and health care system.	Markov Model based on Swiss HIV Cohort Study and a base-case scenario, a pessimistic and an optimistic scenario was developed.	Swiss Cohort Study	-Societal perspective - Health care provider perspective	- HARRT - No antiretroviral therapy (NART)	- On the basis of projected survival in each scenario, ICER was 33000 CHF (base case), 14000 CHF (optimistic), and 45000 CHF (pessimistic) per year of life gained (100 CHF= US$67). - When changes in productivity were included (societal perspective), cost-savings occurred in the base-case and optimistic scenarios. The ICER was 11000 CHF per year of life-gained in the pessimistic scenario.
Trueman, P., et al. (2000) UK (33)	To determine the ICER of triple combination nucleoside analogue (NA) compared with dual therapy.	Markov Model was developed and clinical data was derived from published clinical trials and large observation cohort.	UK HIV population	Third-party payer perspective	- Triple NA combination - Dual NA combination	- The model predicted that triple NA therapy extended life expectancy by an additional 1.2 years compared with dual therapy. - The ICER was estimated to be between 10,072-16,168 pounds per QALY gained.

Study	Objectives	Design	Setting	Perspective	Interventions	Results
Hammer, M., S., et al. (2001) USA (ATCG 320) (34)	To estimate the clinical benefits and cost-effectiveness of 3 drugs ARV regimen.	A mathematical simulation model of HIV was developed. Clinical data were derived from the ACTG 320 study	The AIDS Clinical Trial Group (ATCG 320)	Societal perspective	-HARRT - No antiretroviral therapy (NART)	- For patients similar to ATCG 320 life expectancy adjusted for QOL increase from 1.53 to 2.91 years. - The ICER as compared with no therapy was $23,000 per QALY - Base on the additional data from other major studies (Johns Hopkins, INCAS trial and Dupont 006 trial) the ICER for 3 drugs therapy ranged from $13,000 to $23,000.
Miners, A.H., et al. (2001) British (35)	To compare the cost-effectiveness of HARRT and 2 NRTI in HIV infected pts.	Different data source on the clinical effects and costs of treatments were combined using a Markov Model	English HIV treatment centers	UK public finance	- 243 pts received HARRT (2 NRTI +1PI or 1 NNRTI) - 172 pts received 2 NRTI	- The projected life expectancy for individuals treated with dual therapy and HARRT were 11.6 years and 14.5 years, respectively. - The cost of treatment and effects increased by 35% and 20%, respectively. - Assuming a 2 year additional treatment effect of HARRT produced incremental cost-effectiveness ratios of £ 14602 / life-year saved and £ 17698 / QALY saved.

Study	Objectives	Design	Setting	Perspective	Interventions	Results
Loongban, S. (2003) Thailand (36)	To determine weather the reduction of OI treatment cost among patients by GPO-VIR offsets their increased cost.	Retrospective observational study in secondary data for 1 year.	Saraburi Province, Thailand	Societal perspective	-Patients with GPO-VIR therapy -Patients with no ARV therapy	- The treatment cost before receiving GPO-VIR was 4,346.2 baht per patient per year (PPPY). - The treatment cost after receiving GPO-VIR was 22,682.1 baht PPPY including 18,369.2 baht PPPY for GPO-VIR cost and 4,313.0 baht PPPY for treatment cost. - Treatment cost of ADR cost from GPO-VIR was as high proportion of hospitalization cost (48.4%).
Kulsomboon, V., et al. (2003) Thailand (37)	To obtain the cost-benefit data of triple ARV therapy of HIV patients in Thailand.	Cost-benefit analysis model was employed using treatment cost and outcome data from Bamrasnaradoon Hospital, Thailand.	Bamrasnaradoon Hospital, Nonthaburi, Thailand.	Societal perspective	-Patients with ARV therapy -Patients with no ARV therapy	- The average annual cost treatment cost in ARV group was 87,168 baht (2,075 US$) and the cost in no-ARV was 11,115 baht (264 US$) - The result indicated that cost-benefit ratio of GPO-VIR was 2.68-2.94 which was the most efficient option and the estimated long term annual cost for ARV treatment full coverage ranged 4,000-11,000 million baht per year.

CHAPTER III

RESEARCH METHODOLOGY

This chapter provided the description of the methodology including the population and subjects, data collection, decision model developing, and data analysis. This research was a retrospective cohort study, comparing the difference in cost of treatment and disability adjusted life year (DALY) among HIV/AIDS patients receiving EFV-based therapy compared to NVP-based therapy. The data of ARV utilizations and its effects including out-patient visit and hospitalization due to adverse event and AIDS-related complications were collected from patient profiles and medical records from 4 multi-center health care institutions. Their costs of treatments were collected from the same resources. The costs of treatment included cost of antiretroviral drugs, cost of out-patient visit and hospitalization due to adverse event of antiretroviral drugs and AIDS-related complications and other medical service. The consequences of treatment were focused on the incidence of serious and life-threatening toxicity and AIDS related complications during antiretroviral therapy and disability adjusted life year (DALY). Cost-effectiveness evaluation was employed using Health care provider perspective. Probabilistic Markov Model was conducted based on observation data to predict the cost-effectiveness results comparing between two alternative regimens.

3.1 Study Populations

3.1.1 Population Characteristics

The populations of the study were the HIV/AIDS patients who received NVP-based or EFV-based therapy through 12 Control Disease Center (CDC) regions covering 868 hospitals in Thailand since FY 2004. The provinces that were separated based on CDC region were described below. (See table 3.1)

Table 3.1 Information of 12 Control Disease Center (CDC) regions.

No	Region	CDC Region	Province
1	Central/Eastern	1	Samutprakan, Nonthaburi, PathumThani, Ayudhaya, Angthong
2	Central/Eastern	2	Saraburi, Lopburi, Singburi, Chai Nat, Suphanburi, Nakorn Nayok
3	Central/Eastern	3	Chonburi, Rayong, Chantaburi, Trad, Cha Cherng Chao, Prajeenburi, Srakaew
4	Central/Eastern	4	Rajburi, Karnchanaburi, Prajuabkirikan, Pethburi, Nakorn Pratom, Samutsongkram, Samutsakorn
5	North-East	5	Burirum, Nakornratchasima, Chaiyaphum, Surin,Mahasarakham
6	North-East	6	Nongkai, Udornthani, Sakolnakorn, Nongbualamphu, Kalasin, Khon Kaen, Loei
7	North-East	7	Amnajcharern, Mukdaharn, Srisaket, Roi-et, Nakorn Phanom, Yasothorn, Ubonratchatani
8	North	8	Nakornsawan, Uthaithani, Kamphangpeth, Tak, Sukothai
9	North	9	Utharadij, Phrae, Nan, Pitsanulok, Pichit, Petchaboon, Phayao
10	North	10	Chaingmai, Chaingrai, Lumpang, Lumpoon, Maehngsorn
11	South	11	Chumporn, Ranong, Krabi, Phan-nga, Nakornsrithammaraj, Surajthani, Phuket
12	South	12	Songkhla, Yala, Patalung, Trang, Satool, Pattani, Narathiwas

3.1.2 Sampling Method

3.1.2.1 Selected CDC regions

Thailand was divided into 12 CDC regions. These CDC regions were grouped into four geographic regions (see table 3.1). One CDC regions were selected to be the representative in each geographic region. The selected CDC regions must have at least

one province which is implemented intensive monitoring ADR program. So, CDC regions 3, 7, 10, and 11 were selected. (See table 3.2)

3.1.2.2 Selected hospitals

One regional hospital in each CDC regions was selected to represent each geographic region. The selected regional hospitals are described below. (See table 3.2)

Table 3.2 Selected provinces in 4 regions

Region	CDC region	Hospitals
Central/Eastern	3	Chonburi hospital
North-east	7	Supprasttiprasong hospital
North	10	Lampang hospital
South	11	Had-Yai hospital

3.1.2.3 Selected subjects

Inclusion criteria for HIV/AIDS patients in this study were:

(1) Having their age of 15 years old or more

(2) Being naïve to triple combination antiretroviral therapy

(3) Having CD4 cell count < 250 cells/µl

(4) Receiving a NVP-based or EFV-based regimen before January, 2004.

Medical record of each eligible patient was reviewed since receiving ART until the end of the study, in January, 2006. So each case has follow-up period at least 2 years taking ARV regimen.

3.2 Sample size calculation

Sample size of each arm was calculated by using the formula for calculating a sample for proportions [38]

$$No = \frac{Z^2 p q}{e^2}$$

No = the sample size

Z^2 = the abscissa of the normal curve that cuts off an area at the tails (1-equals the desired CI, 95%CI)

e = the desired level of precision

p = the estimated proportion of an attribute that is presented in the population

q = 1-p

The results from many trials revealed that the occurrence of adverse events due to NVP-based therapy range between 15-30% [3] and EFV-based therapy range between 2-8% [3].

$$\text{No. in NVP-arm} = \frac{(1.96)^2 (0.30) (0.70)}{(0.05)^2} = 323 \text{ cases}$$

$$\text{No. in EFV-arm} = \frac{(1.96)^2 (0.08) (0.92)}{(0.05)^2} = 113 \text{ cases}$$

3.3 Data sources and data collection

The data into this study were secondary data that available in the patient profiles, and medical records from selected hospitals. Data collection was separated into two parts including the consequences of the treatment and the total cost of treatment that were described below:

3.3.1 The consequences of the treatment were

- Adverse drug events and
- AIDS related complications

Out-patient visits and Hospitalization due to adverse events and AIDS related complications were collected since the initial of ARV therapy to January, 2006.

3.3.2 Total cost of treatment were

- Cost of ARV drugs (NVP-based or EFV-based regimens)
- Cost of out-patient visit due to adverse drug reaction and AIDS-related complications
- Cost of hospitalization due to adverse drug reaction and AIDS-related complications
- Cost of Laboratory and monitoring
- Cost of Medical service

3.4 Developing the decision model

An economic Markov model was created to estimate long term effects from the treatment on HIV disease progression. This study developed a decision-analytic model using a target population of HIV/AIDS patients aged 15-65 years. The data was obtained from the retrospective cohort study of 4 regional hospitals. Treatment of either NVP-based regimens or EFV-based regimens was modeled for the remaining lifetime of the prevalence cohort. A cycle length of 1-year for the full health states and months for the sub-states were used for the analysis. The model also included the difference in the rate of complications between the two treatment modalities to be sub-states in the model.

The stages of developing a decision model [39]

1. Specify the decision problem
2. Defining the boundaries of the model
3. Structuring a decision model
4. Identifying and synthesizing evidence
5. Dealing with uncertainty and heterogeneity

A probabilistic sensitivity analysis using second-order Monte Carlo simulation was carried out. All input parameters were assigned a probability distribution to reflect the feasible range of value that each input parameter could attain. This process was repeated 1000 alterations to provide a range of possible values given the specified probability distributions.

3.5 Data Analysis

3.5.1 Measurement of the incidence of serious and life-threatening toxicity and serious AIDS related complications (person-time) [40]

$$\text{Incidence Density} = \frac{\text{Severe ADR events and AIDS related complications}}{\text{Total person-time of observation}}$$

3.5.2 The cost-effectiveness analysis

1) The incremental cost effectiveness ratio (ICER) [41]

ICER is the measurement to compare each program with the next less expensive option to determine the additional investment required for increase benefit.

The ICER is defined as $\rho = \Delta C / \Delta E$ where:

ΔC means incremental cost that will be calculated by the total cost of EFV-based treatment minus the total cost of NVP-based treatment

ΔE means the difference in consequence that will be calculated by the difference between Disability-adjusted life years (DALY) averted in starting with EFV-based therapy and NVP-based regimens.

$$\text{ICER} = \frac{\Delta C}{\Delta E} = \frac{\text{Total Cost of EFV-based} - \text{Total Cost of NVP based}}{\text{Net change in DALY averted}}$$

If a treatment program results in higher effectiveness but less cost, it is called a “dominate” program whose ICER is negative, meaning cost saving. If a treatment program emerges as being more costly but less effective, then the more costly treatment is considered to be a “dominated”.

3.5.3 Analyzing and presenting simulation output from probabilistic model

The results of large number of Monte Carlo simulation are presented in terms of cost-effectiveness (CE) plane and cost-effectiveness acceptability (AC) curves.

1) Cost-effectiveness (CE) plane

Cost-effectiveness (CE) plane is often employed to show how decisions can be related to both costs and effects [42]. The CE plane is presented in figure 3. The horizontal axis divides the plane according to incremental cost (positive above, negative below) and the vertical axis divides the plane according to incremental effects (positive to the right, negative to the left). This divides the incremental cost-effectiveness plane into four quadrants through the origin [43].

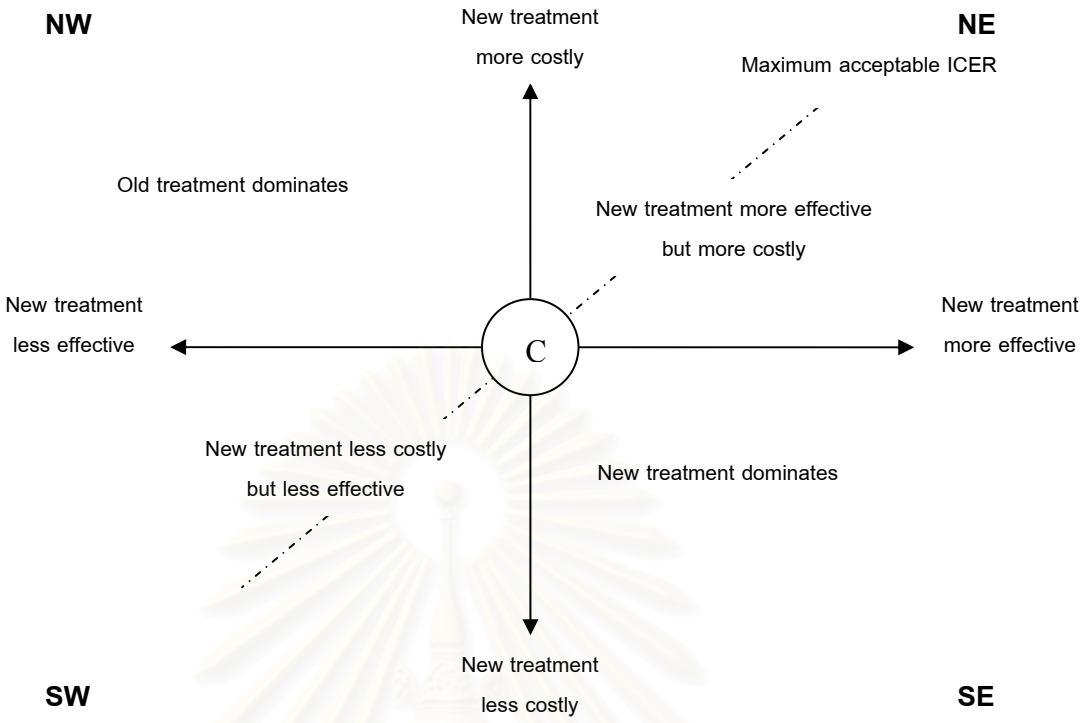


Figure3.1 The cost-effectiveness plane: comparing a new treatment to a currently provided control treatment (the origin).

Each quadrant has a different implication for the decision. If the ICER fell in the southeast quadrant, with negative costs and positive effects, then ICER are always considered cost-effective. If the ICER fell in the northwest quadrant, with positive costs and negative effects, then ICER are never considered cost-effective. If the ICER fell in the northeast quadrant, with positive costs and positive effects, or southwest quadrant, with negative costs and negative effects, trade-offs between costs and effects would need to be considered. These quadrants represent the situation where new treatment may be cost-effective compared to old treatment, depending upon the maximum amount that the decision-maker is willing to pay for health effects (maximum acceptable ceiling ratio). The new intervention is deemed cost-effective if the ICER falls below this threshold and not cost-effective if falls upper this threshold.

2) Cost-effectiveness acceptability curves

Cost-effectiveness acceptability curve was proposed by van Hout and others [44] and was based on the bivariate distribution of the cost and effect difference on the CE plane. CE acceptability curves were originally introduced to represent the uncertainty concerning the cost-effectiveness of the health care intervention in the context of

decisions of two interventions as an alternative to confidence intervals around ICERs. This curve gives an estimate of the proportion of the sampling distribution of costs and effects that lie below the price line in the CE plane, the price being the maximum willingness to pay for a gain effect unit. The computation of CE acceptability curves can also be based on the net benefit approach [45] as proposed by Briggs and Fenn [43]. Denote the average cost difference between the new and old treatment by $\mu\Delta C = \mu C_1 - \mu C_0$ and the average effect difference by $\mu\Delta E = \mu E_1 - \mu E_0$. From this, the ICER is defined as:

$$ICER = \frac{\mu\Delta C}{\mu\Delta E},$$

Assuming $\mu\Delta E \neq 0$, when $\mu\Delta E > 0$ and $\mu\Delta C > 0$ ($\mu\Delta E < 0$ and $\mu\Delta C < 0$) the ICER represents the additional average cost of producing one more unit of health effects achieved by the new or old treatment. When $\mu\Delta E > 0$ and $\mu\Delta C \leq 0$ ($\mu\Delta E < 0$ and $\mu\Delta C \geq 0$) the ICER reflects that new or old treatment dominates.

To maximize health gain subject of a scarce resources, then, the new treatment should replace the existing treatment if ICER < λ, where λ is the maximum price society is willing to pay for one more unit of health effects. As shown by Stinnett and Mullahy [4] and Tambour et al. [6] the decision rule ICER < λ can be expressed as $\lambda\mu\Delta E - \mu\Delta C > 0$. The left hand side of this expression is the monetary value of the change in health effects less the change in costs, defines a monetary net benefit (NB) measure

$$NB(\lambda) = \lambda\mu\Delta E - \mu\Delta C$$

Based on the net benefit, the decision rule is that the new treatment should replace the old treatment if NB (λ) >0. The net benefit is positive for all ICERs lying to the right (or below) of the price line in the CE plane and negative for all ICERs to the left (or above) of the price line.

CHAPTER IV

RESULTS

The results of the study consisted of the population and demographic data, the antiretroviral utilization, Incidence of serious adverse events and major opportunistic infections during ARV treatment, structuring the Markov model, and the Probabilistic Markov Model results. The details of the results were in the following.

4.1 Population and demographic data

There were 408 patients who started with NVP-based regimens, 118 patients (28.9%) from Supprasittiprasong Hospital, 105 patients (25.7%) from Chonburi Hospital, 100 patients (24.5%) from Lampang Hospital, and 85 patients (20.8%) from Had-Yai Hospital.

Of the total 116 patients who started with EFV-based regimens, 81 patients (69.8%) were from Chonburi Hospital, 32 patients (27.6%) were from Lampang Hospital and 3 patients (2.6%) were from Had Yai Hospital (Table 4.1)

Table 4.1 Number of HIV/AIDS Patients in this study

Hospital Name	HIV/AIDS patients who started with NVP-based regimen		HIV/AIDS patients who started with EFV-based regimen	
	Number of patients	Percent	Number of patients	Percent
Supprasittiprasong	118	28.9	None	-
Chonburi	105	25.7	81	69.8
Lampang	100	24.5	32	27.6
Had Yai	85	20.8	3	2.6
Total	408	100.0	116	100.0

The characteristics of HIV/AIDS patients were shown in Table 4.2. Of all the 408 patients who started with NVP-based regimens, 51.2 % were males. Among different age groups, 75.2% was 30 to 44 years old, 14.0% was 45 to 59 years old, and 10.0% was 15 to 29 years old. Of these, 38.7% was in the Universal Coverage Scheme, 33.3% was in out-of-pocket, 27.1% was in the Social security Scheme (SSS), and 6.9%

was in the Civil Servants' Medical Benefits Scheme (CSMBS). Most of the patients (42.4%) started NVP-based regimens when they had CD4 count less than 50 cell / mm^3, 21.3% started when CD4 count were 50 to 100 cell/mm^3, and 15.9% started when CD4 count were 101 to 150 cell/mm^3.

Of all the 116 patients who started with EFV-based regimens, 55.2 % were males. Among different age groups, 66.4% was 30 to 44 years old, 23.3% was 45 to 59 years old, and 7.8% was 15 to 29 years old. The majority of patients who started with EFV-based regimen were in the Civil Servants' Medical Benefits Scheme (CSMBS), 31% were in out-of-pocket, 17.2% were in the Universal Coverage Scheme (UC), and 15.5% were in the Social security Scheme (SSS). Most of the patients (43.1%) started EFV-based therapy when they have CD4 count less than 50 cell / mm^3, 19.0% started when CD4 count were 50 to 100 cell/mm^3, and 18.1% started when CD4 count were 101 to 150 cell/mm^3.

This finding showed the significantly difference between those who started with NVP-based regimens and EFV-based regimens in age and the benefits scheme of the patients (p-value <0.05).

Table 4.2 Baseline characteristics of patients who started with NVP-based and EFV-based regimens

Characteristics	Patients who started with NVP-based regimens		Patients who started with EFV-based regimens		P-value
	No.	Percent	No.	Percent	
Gender					0.519
Male	209	51.2	64	55.2	
Female	199	48.8	52	44.8	
Age range (years)					0.034*
15-29 years old	41	10.0	9	7.8	
30-44 years old	307	75.2	77	66.4	
45-59 years old	57	14.0	27	23.3	
60-69 years old	3	0.7	3	2.6	
Benefit Right					0.000*
Out of pocket	136	33.3	36	31.0	
SSS	86	21.1	18	15.5	
CSMBS	28	6.9	42	36.2	
UC	158	38.7	20	17.2	
Baseline CD4 count					0.564
0 – 49 cell/mm^3	173	42.4	50	43.1	
50 – 100 cell/mm^3	87	21.3	22	19.0	
101 – 150 cell/mm^3	65	15.9	21	18.1	
151 – 200 cell/mm^3	54	13.2	10	8.6	
201 – 250 cell/mm^3	29	7.1	13	11.2	
Total	408	100.0	116	100.0	

4.2 Antiretroviral utilization

The data of antiretroviral utilization were collected since the initial of treatment. The switching of ARV regimens due to adverse events and AIDS related complications was collected during the data collection period. Of the total 408 patients who started with NVP-based regimens, 59.6% continued previous regimens until the end of data collection period. While, 30.1% of the patients received 2 ARV regimens, 8.1% of patients received 3 ARV regimens, and 2.2% received 4 ARV regimens until the end of data collection period. Of the 116 patients who started with EFV-based regimens, 69.0% continued previous regimens until the end of data collection, while 27.6% received 2 ARV regimens, and 3.4% received 3 ARV regimens. (Table 4.3)

Table 4.3 Number of ARV regimens during the data collection period

No. of regimen	HIV/AIDS patients who started with NVP-based regimens		HIV/AIDS patients who started with EFV-based regimens	
	Number	Percent	Number	Percent
1 regimen	243	59.6	80	69.0
2 regimens	123	30.1	32	27.6
3 regimens	33	8.1	4	3.4
4 regimens	9	2.2	None	-
Total	408	100.0	116	100.0

4.2.1 Duration of treatment, types of ARV regimens, and treatment status in HIV/AIDS patients who started with NVP-based regimens

4.2.1.1 Duration of treatment

The time frame of data collection started from the initial of treatment to the end of data collection period in Jan, 2006. Half of patients (52%) received ARV for 2 to 3 years. About 34.8% received ARV for 3 to 4 years. The average duration of receiving ARV in this group was 2.83 $\pm$ 0.86 years.

4.2.1.2 Types of ARV regimens

The results in Table 4.4, 4.6, 4.8, and 4.10 described the types of ARV regimens which were used as first, second, third, and forth regimens in HIV/AIDS patients who started with NVP-based regimens. The results in Table 4.5, 4.7, and 4.9 showed the causes of shifting to other regimens.

Table 4.4 the ARV regimens which were used as the first line regimens in patients who started with NVP-based regimens.

Type of ARV regimens	Number	Percent
Nevirapine + Lamivudine + Stavudine	402	98.5
Nevirapine + Lamivudine + Zidovudine	2	0.5
Nevirapine + Lamivudine + Dadinozine	2	0.5
Nevirapine + Dadinozine + Zidovudine	2	0.5
Total	408	100.0

Of all the 408 patients who started with NVP-based regimens, 40.4 % had to switch to the second regimens. The causes of switching to the second regimens were presented in Table 4.5. Adverse drug events were the main reasons for changing the antiretroviral regimens (89.7%). Eleven cases (6.7%) developed Tuberculosis and switched to EFV-based regimens. Five cases (3%) developed drug resistance and switched to Protease Inhibitor-based regimens.

Table 4.5 Causes of switching to the second ARV regimens.

Causes of switching regimens		Number	Percent
Adverse events	Lipodystrophy	57	34.5
	Erythrema multiforme	19	11.5
	Drug induce hepatitis	18	10.9
	Exfoliative dermatitis	16	9.7
	Maculopapular rash	10	6.1
	Lactic acidosis	8	4.8
	Hepatotoxicity	6	3.6
	Peripheral Neuropathy	5	3.0
	Steven Johnsons syndrome (SJS)	4	2.4
	Severe Nausea and Vomiting	3	1.8
	Toxic Epidermal necrolysis (TEN)	1	0.6
	Liver function elevation	1	0.6
Disease related complications	Tuberculosis	11	6.7
	Pyelonephritis	1	0.6
Other	Drug Resistance	5	3.0
Total		165	100.0

About 165 patients who started with NVP-based regimens had to switch to the second regimens, 40.6% changed within NVP-based group, 55.8 % switched to EFV-based regimens, and 3.8 % switched to PI-based regimens. (Table 4.6)

Table 4.6 the ARV regimens which were used as the second regimens in the patients who started with NVP-based regimens.

Group of ARV	Type of ARV regimens	Number	Percent
NVP-based regimens	Nevirapine + Lamivudine + Zidovudine	57	34.5
	Nevirapine + Lamivudine + Dadinozine	10	6.1
EFV-based regimens	Efavirenz + Lamivudine + Stavudine	76	46.1
	Efavirenz + Lamivudine + Zidovudine	12	7.3
	Efavirenz + Lamivudine + Dadinozine	2	1.2
	Efavirenz + Indinavir + Ritronavir	2	1.2
PI-based regimens	Indinavir + Ritronavir + Lamivudine + Stavudine	2	1.2
	Indinavir + Ritronavir + Lamivudine	2	1.2
	Indinavir + Ritronavir + Lamivudine + Zidovudine	1	0.6
	Kaletra + Saquinavir + Lamivudine	1	0.6
	Total	165	100.0

Of those who received second regimens, 25.5 % still faced with adverse events and AIDS related complications and had to switch to the third regimens. The causes of switching to the third regimens were presented in Table 4.7. Of those who had to switch to the third regimens, 66.7% had adverse events. Nine cases (21.4%) developed drug resistance and switched to PI-based regimens. Only four cases (8.8%) recovered from Tuberculosis after treatment and received GPO-VIR again.

Table 4.7 Causes of switching to the third ARV regimens

Causes of switching regimens		Number	Percent
Group	Detail		
Adverse event	Lipodystrophy	19	45.2
	Lactic acidosis	2	4.8
	Peripheral Neuropathy	2	4.8
	Hot flush and itching	2	4.8
	Anemia	1	2.4
	Severe diarrhea	1	2.4
	Severe Nausea and Vomiting	1	2.4
Disease related complications	Rhodococosis	1	2.4
Other	Drug Resistance	9	21.4
	Tuberculosis cured	4	8.8
Total		42	100.0

Of the 42 patients who used the third regimens, 34.3% changed the regimens within NVP-based group, 40.5 % switched to EFV-based regimens, and 25.2 % switched to PI-based regimens. The details of each regimen were described in table 4.8

Table 4.8 the ARV regimens which were used as the third regimens in patients who started with NVP-based regimens.

Group of ARV	Type of ARV regimens	Number	Percent
NVP-based regimens	Nevirapine + Lamivudine + Dadinozine	7	16.7
	Nevirapine + Lamivudine + Stavudine	4	9.5
	Nevirapine + Lamivudine + Zidovudine	3	7.1
EFV-based regimens	Efavirenz + Lamivudine + Zidovudine	8	19.0
	Efavirenz + Lamivudine + Dadinozine	7	16.7
	Efavirenz + Lamivudine + Stavudine	1	2.4
	Efavirenz + Indinavir + Ritronavir	1	2.4
PI-based regimens	Indinavir + Ritronavir + Nelfinavir	2	4.8
	Indinavir + Ritronavir + Lamivudine	2	4.8
	Indinavir + Ritronavir + Dadinozine + Zidovudine	2	4.8
	Indinavir + Ritronavir + Lamivudine + Zidovudine	1	2.4
	Indinavir + Ritronavir + Dadinozine + Stavudine	1	2.4
	Indinavir + Ritronavir + Lamivudine + Saquinavir	1	2.4
	Indinavir + Ritronavir + Lamivudine + Stavudine	1	2.4
	Kaletra + Saquinavir + Lamivudine	1	2.4
	Total	42	100.0

Of the 42 patients who used the third regimens, 7 cases (77.8%) faced with adverse events and had to switch to the Forth regimens (Table 4.9). Two cases (2.2%) developed drug resistance and switched to PI-based regimens. The details of forth regimens for nine cases were described in table 4.10.

Table 4.9 Causes of switching to the forth ARV regimens

Causes of switching regimens		Number	Percent
Adverse event	Complicated diarrhea	2	22.2
	Hepatotoxicity	1	11.1
	Lipodystrophy	1	11.1
	Lactic acidosis	1	11.1
	Hyperlipidemia	1	11.1
	Severe Nausea and Vomiting	1	11.1
Other	Drug Resistance	2	22.2
Total		9	100.0

Table 4.10 the ARV regimens which were used as the forth regimens in patients who started with NVP-based regimens.

Group of ARV	Type of ARV regimens	Number	Percent
Nevirapine-based	Nevirapine + Lamivudine + Zidovudine	1	11.1
EFV-based	Efavirenz + Lamivudine + Dadinozine	4	44.4
Protease Inhibitor Based	Indinavir + Ritronavir + Emtricitabine	1	11.1
	Indinavir + Ritronavir + Lamivudine + Zidovudine + Saquinavir	2	22.2
	Indinavir + Ritronavir + Atazanavir	1	11.1
	Total	9	100.0

4.2.1.3 Treatment status at the end of data collection

Until the end of data collection in Jan, 2006, 94.4% of HIV/AIDS patients continued their treatments. Twenty-three cases (5.6%) died from AIDS related complications (Table 4.11). The causes of death were presented in table 4.12.

Table 4.11 the status of patients who started with NVP-based regimens.

Treatment status	Number	Percent
Continuing on the ARV regimens	385	94.4
Death	23	5.6
Total	408	100.0

Table 4.12 Causes of death of patients who started with NVP-based regimens.

Causes of death	Number	Percent
Cryptococus Meningitis	4	17.4
Toxoplasmosis	2	8.7
Acute respiratory failure	2	8.7
Tuberculosis	2	8.7
Cirrhosis	1	4.3
MAC	1	4.3
Not specified	11	47.8
Total	23	100.0

4.2.2 Duration of treatment, types of ARV regimens, and treatment status in HIV/AIDS patients who started with EFV-based regimens.

4.2.2.1 Duration of treatment

The time frame of data collection started from the initial of treatment to the end of data collection period in Jan, 2006. Most of patients (41.4%) received antiretroviral therapy for 4 to 5 years. About 30.2% received antiretroviral therapy for 2 to 3 years. The average duration of receiving ARV in this group was 3.77 $\pm$ 1.06 years.

4.2.2.2 Types of ARV regimens

The results in Table 4.13, 4.15, and 4.17 described types of ARV regimens which were used as first, second, third, and forth regimens in HIV/AIDS patients who started with EFV-based regimens. The results in Table 4.14 and 4.16 showed the causes of switching to other regimens.

Table 4.13 the ARV regimens which were used as the first line treatment in patients who started with EFV-based regimens.

Type of ARV regimens	Number	Percent
Efavirenz + Lamivudine + Stavudine	71	61.2
Efavirenz + Lamivudine + Zidovudine	24	20.7
Efavirenz + Stavudine + Dadinozine	10	8.6
Efavirenz + Lamivudine + Dadinozine	7	6.0
Efavirenz + Dadinozine + Zidovudine	4	3.4
Total	116	100.0

Of the 116 patients who started with EFV-based regimens, 41.0 % had to switch to the second regimens. The causes of switching to the second regimens were shown in Table 4.14. Most of the patients (91.7%) had adverse events. Three cases (8.3%) developed drug resistance and switched to PI-based regimens.

Table 4.14 Causes of switching to the second ARV regimens

Causes of switching regimens		Number	Percent
Group	Detail		
Adverse events	Lipodystrophy	22	61.1
	Peripheral Neuropathy	4	11.1
	Hyperlipidemia	3	8.3
	Dizziness	2	5.6
	Severe diarrhea	1	2.8
	Maculopapular rash	1	2.8
Other	Drug Resistance	3	8.3
Total		36	100.0

Among 36 patients who used second regimens, 83.4% changed the regimens within EFV-based group, 11.2 % switched to PI-based regimens, and 2 cases (5.6%) switched to GPO-VIR. The details of each regimen were described in table 4.15

Table 4.15 the ARV regimens which were used as the second regimens in patients who started with EFV-based regimens.

Group of ARV	Type of ARV regimens	Number	Percent
NVP-based	Nevirapine + Lamivudine + Stavudine	2	5.6
EFV-based regimens	Efavirenz + Lamivudine + Zidovudine	19	52.8
	Efavirenz + Lamivudine + Dadinozine	9	25.0
	Efavirenz + Lamivudine + Stavudine	1	2.8
	Efavirenz + Stavudine + Dadinozine	1	2.8
PI-based regimens	Indinavir + Ritronavir + Nelfinavir	1	2.8
	Indinavir + Ritronavir + Atazanavir	1	2.8
	Indinavir + Ritronavir + Saquinavir	1	2.8
	Indinavir + Ritronavir + Zidovudine+ Lamivudine	1	2.8
	Total	36	100.0

Among 36 patients who used second regimens, 4 cases (11.1%) faced with adverse events and switched to the third regimens. Three cases (75.0%) switched to the third regimens due to lipodystrophy. One case (25.0%) developed drug resistance and switched to PI-based regimen (Table 4.16). The details of the third regimens were described in table 4.17.

Table 4.16 Causes of switching to the third regimens

Causes of switching regimens		Number	Percent
Adverse events	Lipodystrophy	3	75.0
Other	Drug Resistance	1	25.0
Total		4	100.0

Table 4.17 the ARV regimens which were used as the third regimens in patients who started with EFV-based regimens.

Group of ARV	Type of ARV regimens	Number	Percent
EFV-based	Efavirenz + Lamivudine + Dadinozine	3	75.0
Protease Inhibitor Based	Lopinavir /Ritronavir + Zidovudine	1	25.0
	Total	4	100.0

4.2.2.3 Treatment status at the end of data collection

Until the end of data collection in Jan, 2006, all patients continued their ARV treatments.

4.3 Incidence of serious adverse events and major opportunistic infections during ARV treatment

4.3.1 The incidence of serious and long term adverse events of HIV/AIDS patients who started with NVP-based regimens

Based on the 1,154 person-year time exposed of HIV/AIDS patients who started with NVP-based regimens, the incidence of serious and long term adverse events of HIV/AIDS patients who started with NVP-based regimens were calculated and presented in table 4.18.

Table 4.18 the incidence of serious and long term adverse events of HIV/AIDS patients who started with NVP-based regimens

Adverse events	events	Incidence rate (/1000 person-year)	Time to develop Median [IQR]*
High TG/Cholesterol	19	16.5	850d[635,1030]
Lactic acidosis	16	13.9	470d[362,760]
Exfoliative Dermatitis	15	12.9	16d[13,30]
Acute Hepatitis	13	11.3	60d[25,500]
Cirrhosis	6	5.2	425d[292,835]
SJS	4	3.5	13d[11,65]
TEN	1	0.9	28d

* Inter quartile range

4.3.2 The incidence of major opportunistic infections (OIs) of HIV/AIDS patients who started with NVP-based regimens

Based on the 1,154 person-year time exposed of HIV/AIDS patients who started with NVP-based regimens, the incidence of major opportunistic infections (OIs) of HIV/AIDS patients who started with NVP-based regimens were calculated and presented in table 4.19.

Table 4.19 the incidence of major opportunistic infections of HIV/AIDS patients who started with NVP-based regimens

Major OIs	events	Incidence rate (/1000 person-year)	Time to develop Median [IQR]
TB	17	14.7	270d[120,500]
PCP	14	12.1	120d[52,225]
Crypto Meningitis	11	9.5	60d[30,180]
CMVR	10	8.7	60d[30,165]
Penicillosis	8	6.9	90d[37,172]
MAC	6	5.2	180d[52,673]
Toxoplasmosis	6	5.2	225d[52,324]
Nocardiosis	2	1.7	287d[120,365]

4.3.3 Incidence of serious and long term adverse events of HIV/AIDS patients who started with EFV-based regimens

Based on the 438 person-year time exposed of HIV/AIDS patients who started with EFV-based regimens, the incidence of serious and long term adverse events of HIV/AIDS patients who started with EFV-based regimens were calculated and presented in table 4.20.

Table 4.20 the incidence of serious and long term adverse events of HIV/AIDS patients who started with EFV-based regimens

Adverse events	events	Incidence rate (/1000 person-year)	Time to develop Median [IQR]
High TG/Cholesterol	15	34.2	850d[665,1030]
Diabetes (DM)	1	2.3	605d

4.3.4 Incidence of major opportunistic infections (OIs) of HIV/AIDS patients who started with EFV-based regimens

Based on the 438 person-year time exposed of HIV/AIDS patients who started with EFV-based regimens, the incidence of major opportunistic infections (OIs) of HIV/AIDS patients who started with EFV-based regimens were calculated and presented in table 4.21.

Table 4.21 the incidence of major opportunistic infections of HIV/AIDS patients who started with EFV-based regimens

Major OIs	events	Incidence rate (/1000 person-year)	Time to develop Median [IQR]
CMVR	1	2.3	160d
TB	1	2.3	120d

4.4 Probabilistic Markov Model

4.4.1 Structuring the model

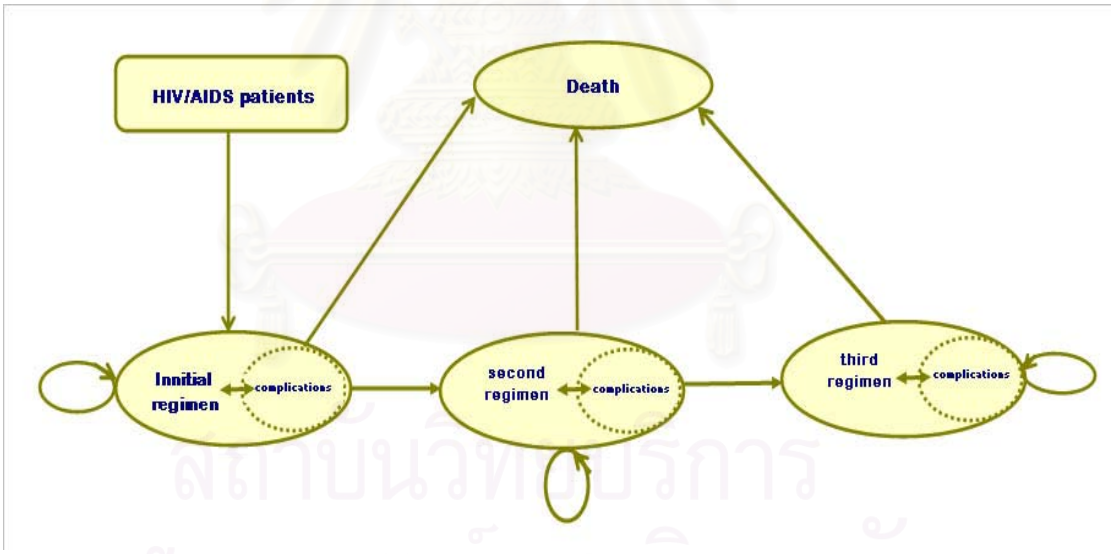
An economic model was created to estimate long term effects from the treatment of HIV disease progression. The main principle of the model was that to be effective. Antiretroviral regimens must not only reduce viral load, but also be tolerated by patients who are willing to adhere to it over time. The model evaluated the effect of initial choice of triple therapy on the progression of an HIV positive population through 4 states, starting with the naïve to treatment state (1^{st} regimens), switching to the 2^{nd} regimens, switching to the 3^{rd} regimens, and death (figure. 4.1).

This study developed a decision-analytic model using a target population of HIV/AIDS patients aged 15-65 years. The Markov model structure shown in figure 4.1 illustrated the mutually exclusive health states that a patient commencing treatment on either NVP-based or EFV-based might go through. Health states were denoted by the solid oval-lines. The model also included sub-states (dotted oval lines) to reflect the difference in the rate of complications between the two treatment modalities. An arrow indicated that movement from one state to another is possible. The likelihood of movement between each state (“transition probability”) was determined by using data from the retrospective cohort study in the multi-centre 4 regional hospitals. Treatment of either NVP-based or EFV-based was modeled for the remaining lifetime of the prevalence cohort. A cycle length of 1-year for the full health states and months for the sub-states were used for the analysis.

The model was used to quantify the costs and effects of two long-term alternative treatments for HIV/AIDS patient in each age group and each CD4 at baseline. In the model, patients might start either with NVP-based or with EFV-based and remained on the same treatment until the next cycles. Moving to other health states (second and third regimens) was dependent on the developing of complications during treatment such as developing of moderate or severe adverse drug reactions, opportunistic infections, or drug resistances. Moving to the final state (death) might or might not be related with the occurrence of complications. Patients could die from non HIV/AIDS causes, such as cardiovascular disease. In each case, it was assumed that the event would only happen at the end of each cycle.

The simulations were conducted to model cost and events over a 99-year period to cover the maximum total period over which the whole cohort would reasonably be expected to survive.

Figure 4.1 Schematic diagram of the Markov Model



States of the model were represented by the ovals, transitions between states represented by the arrows.

To comply with the guideline for conducting heath economic, all costs and outcomes were discounted at a rate of 3.5 % [46].

Outcome measures

Probability of moving to next health states

The probability of moving to the next health states (from first regimen to second regimen, third regimen and death) were estimated using the survival analysis of a hypothetical cohort of patients from the retrospective cohort study of HIV/AIDS patients in 4 regional hospitals. To adjust the survival rate, CD4 at baseline, age of patients and ordering of ARV regimen were used as covariates of disease progressions.

The data from the retrospective cohort study of HIV/AIDS patients in 4 regional hospitals consisted of 408 records of patients who started with NVP-based regimens and 116 records of patient who started with EFV-based regimens. Due to the follow up period of 3 years, no one died in the group of the patients who started with EFV-based regimens. The existing data were not applicable to calculate the survival rate of the patients started with EFV-based regimens. From a Cochrane review [47], the finding from a randomize control trial (2NN study) [14] revealed that NVP-based had a higher death rate compared with EFV-based (RR [95%CI] =1.33 [0.50, 3.53]). Therefore, it was assumed in this analysis that the HIV/AIDS patients who started with NVP-based regimens had 1.33 times (SE 0.49) higher death rate in the first health state compared with HIV/AIDS patients who started with EFV-based regimens.

Using the statistical software package STATA (Stata Corp, College Station, TX), this study initially applied a non-parametric Kaplan-Meier approach to fit Kaplan-Meier curves and plotted graphs of log against log(time) which were generally linear, indicated that a Weibull survival model would adequately fit the data. The study consequently used the “streg” module of STATA to perform maximum likelihood estimation for parametric regression of the Weibull survival models.

For the Weibull distribution, for example, the survival function, which describes the probability of survival as a function of age [39] is

$$S(t) = \exp[-H(t)]$$

and

$$H(t) = \lambda t^{\gamma}$$

Where H(t) is the cumulative hazard; λ (lambda) is the scale parameter; t is time in days; and γ (gamma) is the shape parameter that describes the instantaneous the hazard rate h(t), which increases with age if γ >1. The λ depends on the covariate, age, according to the formula

$$\lambda = \exp[(\text{age\_coefficient} \times \text{age}) + \text{cons}]$$

The transitional probability of dying during the cycle, *tp(c)*, is therefore estimated from the following formula (where c is the number of cycle):

$tp(c) = 1-\exp[H(t-c)-H(t)]$

Disability-adjusted survival

This study adjusted outcomes for disability adjusted-life year (DALY) by using the disability weight (DW) from Global Burden of Diseases (GBD) [48], Dutch Study [49] (see appendix I), and expert opinion. For co-morbidities such as AIDS patients who developed tuberculosis, the multiplicative adjustment method was applied to assess the disability weight [50].

The concept of multiplicative adjustment method was described below:

It was assume that the increase in disability due to co-morbidity disability was proportional. Total disability for an individual having more diseases could be written as:

$w(1,2)=1-(1-w1)(1-w2)$

Where: $w(d) = 1-\prod_{d}(1-wd)$

$w(1,2)$ disability weight of an individual with disease 1 and 2

$w(d)$ disability weight of an individual with d diseases

Costs

Using health care provider perspective, the cost of treatment in this study was direct health care cost. The costs of treatment in this study included the cost of ARV drugs, the cost of laboratory testing, the cost of medical service, the cost of hospital service and the cost of treatment the complications such as adverse events and opportunistic infections in out-patient and in-patient visits. The costs of treatment were derived based on the cost data from the retrospective cohort of HIV/AIDS patients in 4 regional hospitals. The cost of adverse events and opportunistic infections treatment were the average cost of treatment from four regional hospitals. Only cost of ARV regimens were adjusted by the reference cost of ARV drugs from Bureau of AIDS, Tuberculosis and Sexually Transmitted Infection, MOPH and GPO [51,52] (see appendix II) to minimize the variation of cost of ARV drug in this study. All costs were reported in 2004 Thai Baht for each health state and were discounted at the rate of 3.5%.

Uncertainty analysis

A probabilistic sensitivity analysis with second-order Monte Carlo technique was carried out in Microsoft Office Excel 2003. All input parameters were assigned a probability distribution to reflect the feasible range of value that each input parameter

could attain. The beta-distribution was the choice of distribution for probability parameters which were bounded by zero and one. The gamma distribution which ensured positive value was modeled for all rate and unit cost parameters. Normality on the log-odds scale with covariance matrix and Cholesky decomposition were applied for survival parameters [53]. The simulation chosen one value from each distribution simultaneously and calculated cost and effectiveness pairs. This process was repeated 1000 alterations to provide a range of possible values given the specified probability distributions. The incremental cost and incremental effect were represented visually by using the cost-effectiveness plane and cost-effectiveness acceptability curves. The details of means and standard error (SE) of input parameters were shown in Table 4.22.

Table 4.22 Means and standard error (SE) of input parameters

Parameter description	Distribution	Mean	SE
Weibull survival			
Weibull survival in NVP group. Outcome:death			
Constant value for baseline hazard	Lognormal	-5.0534	1.1441
CD4 baseline coefficient for baseline hazard	Lognormal	-0.0190	0.0061
regimen coefficient for baseline hazard	Lognormal	-1.2305	0.5623
ln (γ)	Lognormal	-0.3856	0.2024
Weibull survival in NVP group. Outcome:Switching from Reg1 to Reg2			
Constant value for baseline hazard	Lognormal	- 6.1716	0.5250
CD4 baseline coefficient for baseline hazard	Lognormal	0.0031	0.0011
age coefficient for baseline hazard	Lognormal	0.0282	0.0106
ln (γ)	Lognormal	- 0.4930	0.0715
Weibull survival in NVP group. Outcome :Switching from Reg2 to Reg3			
Constant value for baseline hazard	Lognormal	- 10.2941	1.2661
age coefficient for baseline hazard	Lognormal	0.0602	0.0192
ln (γ)	Lognormal	0.0127	0.1378
Weibull survival in EFV group. Outcome:Switching from Reg1 to Reg2			
Constant value for baseline hazard	Lognormal	- 7.1410	1.2231
CD4 baseline coefficient for baseline hazard	Lognormal	0.0005	0.0022
age coefficient for baseline hazard	Lognormal	- 0.0021	0.0198
ln (γ)	Lognormal	- 0.1448	0.1524

Note: All input parameter were obtained from 4 regional hospital

Table 4.22 Means and standard error (SE) of input parameters (cont.)

Parameter description	Distribution	Mean	SE
Weibull survival in EFV group. Outcome: Switching from Reg2 to Reg3			
Constant value for baseline hazard	Lognormal	-6.8363	3.0088
age coefficient for baseline hazard	Lognormal	0.0108	0.0560
ln (γ)	Lognormal	-0.4629	0.4716
Transitional Probability			
Relative risk of NVP compared to EFV: Outcome death			
Relative risk of EFV-based compared with NVP based **	Gamma	1.3300	0.4990
Annual rate of having complications			
Probability of Meningitis events in 1st regimen in NVP-based	Beta	0.0196	0.0069
Probability of TB events in 1st regimen in NVP-based	Beta	0.0417	0.0099
Probability of MAC events in 1st regimen in NVP-based	Beta	0.0098	0.0049
Probability of Toxoplasmosis events in 1st regimen in NVP-based	Beta	0.0172	0.0064
Probability of CMVR events in 1st regimen in NVP-based	Beta	0.0245	0.0076
Probability of PCP events in 1st regimen in NVP-based	Beta	0.0294	0.0084
Probability of skin 2 events in 1st regimen in NVP-based	Beta	0.1299	0.0166
Probability of SJS events in 1st regimen in NVP-based	Beta	0.0123	0.0054
Probability of Hepatitis events in 1st regimen in NVP-based	Beta	0.0245	0.0076
Probability of Hepatotoxic events in 1st regimen in NVP-based	Beta	0.0221	0.0073
Probability of HighTG events in 1st regimen in NVP-based	Beta	0.0294	0.0084
Probability of Hepatotoxic events in 2nd regimen in NVP-based	Beta	0.0025	0.0024
Probability of HighTG events in 2nd regimen in NVP-based	Beta	0.0123	0.0054

** Note: Data of RR of death came from Cochrane Systematic Review (47)

Table 4.22 Means and standard error (SE) of input parameters (cont.)

Parameter description	Distribution	Mean	SE
Probability of HighTG events in 3rd regimen in NVP-based	Beta	0.0025	0.0024
Probability of TB events in 1st regimen in EFV-based	Beta	0.0085	0.0085
Probability of CMVR events in 1st regimen in EFV-based	Beta	0.0085	0.0085
Probability of skin 2 events in 1st regimen in EFV-based	Beta	0.0085	0.0085
Probability of HighTG events in 1st regimen in EFV-based	Beta	0.1624	0.0340
Resource cost parameter			
Direct medical care costs i.e. direct costs of treatment			
Monthly Cost of drug 1st regimen in NVP-based	Gamma	1750.0000	519.2210
Monthly Cost of drug 2nd regimen in NVP-based	Gamma	2657.0000	732.8054
Monthly Cost of drug 3rd regimen in NVP-based	Gamma	9552.0000	7000.4490
Monthly Cost of drug 1st regimen in EFV-based	Gamma	3067.0000	537.3730
Monthly Cost of drug 2nd regimen in EFV-based	Gamma	4223.0000	2280.8220
Monthly Cost of drug 3rd regimen in EFV-based	Gamma	9552.0000	7000.4490
Average cost of Meningitis treatment	Gamma	14184.1250	2199.5206
Average cost of MAC treatment	Gamma	20048.5000	2213.2468
Average cost of Tuberculosis treatment	Gamma	9266.1538	1162.5913
Average cost of CMV rhinitis treatment	Gamma	25064.0000	4213.4115
Average cost of Toxoplasmosis treatment	Gamma	5167.7143	2134.7126
Average cost of PCP treatment	Gamma	6506.7273	1245.3200
Average cost of ADR treatment(skin grade 2)	Gamma	437.7925	184.1442
Average cost of ADR treatment(SJS)	Gamma	3420.0000	346.1545
Average cost of ADR treatment(Hepatitis)	Gamma	1797.4000	194.2507

Table 4.22 Means and standard error (SE) of input parameters (cont.)

Parameter description	Distribution	Mean	SE
Average cost of ADR treatment (Hepatotoxicity)	Gamma	6159.3750	2402.0790
Average cost of ADR treatment (HighTG)	Gamma	3650.0000	1245.5200
Utility parameter			
Disability weight for AIDS without complications		0.5600*	
Disability weight for AIDS with meningitis & toxoplasmosis		0.9617**	
Disability weight for AIDS with TB		0.6898**	
Disability weight for AIDS with MAC and PCP		0.8064**	
Disability weight for AIDS with CMVR		0.7492**	
Disability weight for AIDS with grade 2 skin reaction		0.6150**	
Disability weight for AIDS with SJS&TEN		0.7593**	
Disability weight for AIDS with Hepatitis		0.6524**	
Disability weight for AIDS with Hepactotoxic & cirrhosis		0.7092**	
Disability weight for AIDS with HighTG		0.6150**	

Note:

* DW of AIDS came from GBD [48] and Dutch study [49]

** DW of AIDS with co-morbidities using multiplicative adjustment method [50]

4.4.2 Probabilistic Markov Model results

The results were presented in terms of the lifetime costs, health outcomes (life-year (LY) gained and disability-adjusted life year (DALY) averted) and incremental cost-effectiveness ratio (ICER) compared between starting with NVP-based and EFV-based regimens. Two types of sub-group analysis were conducted including age-group analysis (by controlling baseline CD4 count at 200cell/mm3) and baseline CD4 -group analysis (by controlling age at baseline treatment at 35 years-old).

4.4.2.1. The lifetime cost

a) The lifetime cost classified by age-group

Using health care provider perspective, the lifetime cost of treatment of the patients who started with EFV-based offered more costly in patient age group 20 years old(Table 4.23). In contrast, in the older patients (30 to 60 years-old), providing EFV-based regimens as initial treatment were cheaper than NVP-based regimens.

Table 4.23 Lifetime cost of starting with NVP-based and EFV-based regimens classified by age-group (control baseline CD4 count at 200cell/mm3)

Age (year)	NVP-based regimens (1)	EFV-based regimens (2)	Cost difference (Baht) (2-1)
20	1,577,343	1,764,171	186,828
30	1,757,242	1,591,355	(165,887)
40	1,803,500	1,437,897	(365,603)
50	1,733,432	1,181,098	(552,334)
60	1,459,949	921,157	(538,792)

Cost in baht 2004 price level

b) The lifetime cost classified by CD4 at baseline-group

The lifetime cost of treatment with providing EFV-based as the first-line regimens was cheaper in all groups of the patients classified by baseline CD4 count (Table 4.24). The difference of lifetime costs between starting with EFV-based regimens and NVP-based regimens was increased depending on the higher value of baseline CD4 count.

Table 4.24 Lifetime cost of starting with NVP-based and EFV-based regimens classified by baseline CD4 group (control age at initial of treatment at 35 years-old)

Baseline CD4 count (cell/mm3)	NVP-based regimens (1)	EFV-based regimens (2)	Cost difference (Baht) (2-1)
50	1,373,620	1,330,031	(43,589)
100	1,558,370	1,415,996	(142,374)
150	1,715,064	1,506,485	(208,579)
200	1,820,083	1,519,453	(300,630)
250	1,863,897	1,553,925	(309,972)

Cost in baht 2004 price level

4.4.2.2 The life-year (LY) gained

a) The life-year (LY) gained classified by age-group

Compared with providing NVP-based as the first-line regimen, starting with EFV-based offered more LY gained in patient age 20 years. While in the patient age group 30 to 60 years, starting with NVP-based regimens offered more LY gained than EFV-based regimens (Table 4.25). In These groups of patients, the difference of LY gained between starting with EFV-based regimens and NVP-based regimens was increased depending on the age of patient at baseline treatment.

Table 4.25 LY gained of starting with NVP-based and EFV-based regimens classified by age group (control baseline CD4 count at 200cell/mm3)

Age (year)	NVP-based regimens (1)	EFV-based regimens (2)	LY gained difference (2-1)
20	21.865	21.897	0.032
30	20.279	20.275	(0.004)
40	18.277	18.248	(0.029)
50	15.653	15.617	(0.036)
60	12.601	12.554	(0.047)

b) The life-year (LY) gained classified by baseline CD4-group

The patients starting with EFV-based offered more LY gained among the patients who initiated the regimen at low CD4 count baseline i.e. 50 to 100cell/mm3. The patients starting with EFV-based regimens at higher baseline CD4 count offered slightly less LY gained compared to NVP-based regimens (Table 4.26).

Table 4.26 LY gained of starting with NVP-based and EFV-based regimens classified by baseline CD4 group (control age at initial of treatment at 35 years-old)

Baseline CD4 count (cell/mm3)	NVP-based regimens (1)	EFV-based regimens (2)	LY gained difference (2-1)
50	16.413	16.604	0.191
100	18.154	18.160	0.006
150	19.028	19.027	(0.001)
200	19.354	19.328	(0.026)
250	19.489	19.467	(0.022)

4.4.2.3 Disability-adjusted life year (DALY) averted

a) Disability-adjusted life year (DALY) averted classified by age-group

Compared with providing NVP-based as the first-line regimen, introducing EFV-based regimens offered more DALY averted in all age groups (Table 4.27). The DALY averted was decreased depending on the increase of the age of patients.

Table 4.27 DALY averted of starting with NVP-based and EFV-based regimens classified by age group (control baseline CD4 count at 200cell/mm3)

Age (year)	NVP-based regimens (1)	EFV-based regimens (2)	DALY averted difference (2-1)
20	5.316	5.469	0.192
30	5.138	5.277	0.139
40	4.869	4.995	0.126
50	4.425	4.537	0.112
60	3.801	3.893	0.092

b) Disability-adjusted life year (DALY) averted classified by baseline CD4 count

Compared with providing NVP-based as the first-line regimen, introducing EFV-based regimen offered more DALY averted in all CD4 baseline levels (Table 4.28). The DALY averted was increased depending on the increase of the age of patients.

Table 4.28 DALY averted of starting with NVP-based and EFV-based regimens classified by baseline CD4 group (control age at initial of treatment at 35 years-old)

Baseline CD4 count (cell/mm3)	NVP-based regimens (1)	EFV-based regimens (2)	DALY averted difference (2-1)
50	4.358	4.527	0.169
100	4.754	4.888	0.134
150	4.947	5.086	0.139
200	5.023	5.154	0.131
250	5.053	5.186	0.133

4.4.2.4 Incremental cost-effectiveness ratio (ICER)

a) Incremental cost-effectiveness ratio (ICER) classified by age-group

In terms of baht per LY gained, in patient age group 20 years old, providing the EFV-based regimens as first line treatment offered more costly and more LY gained, then the incremental cost was to 5,538,375 baht per LY gained. In contrast, in patient age 30 to 60 years, providing the EFV-based regimen as first line treatment offered less costly and less LY gained. The Incremental cost of starting with EFV-based regimens ranged from 11,463,659 baht per LY gained in age group 60 years old to 41,471,750 baht per LY gained in age group 30 years old (Table 4.29).

In terms of baht per DALY averted, in patient age group 20 years old, providing the EFV-based regimens as first line treatment offered more costly and more DALY averted, then the incremental cost was to 973,063 baht per DALY averted. In contrast, in patient age 30 to 60 years, providing the EFV-based regimens as first line treatment dominated NVP-based regimens (offered less costly and more DALY averted).

Table 4.29 Incremental cost-effectiveness ratio (ICER) of starting with EFV-based regimens compared with NVP-based regimens classified by age group (control baseline CD4 count at 200cell/mm3)

Age (year)	Incremental cost-effectiveness ratio (ICER)	
	Baht per LY gained	Baht per DALY averted
20	5,538,375	973,063
30	41,471,750	Dominate (1,193,432)
40	12,607,000	Dominate (2,901,611)
50	15,342,611	Dominate (4,931,554)
60	11,463,659	Dominate (5,856,435)

b) Incremental cost-effectiveness ratio (ICER) classified by baseline CD4 group

In terms of baht per LY gained, in patients with 50 to 100cell/mm3 of CD4 at baseline, providing the EFV-based regimens as first line treatment dominated NVP-based regimens. In contrast, in patients with 15o to 250cell/mm3 of CD4 at baseline, providing the EFV-based regimen as first line treatment offered less costly and less LY gained (Table 4.30).

In terms of baht per DALY averted, providing the EFV-based regimen as first line treatment dominated NVP-based in all baseline CD4 groups.

Table 4.30 Incremental cost-effectiveness ratio (ICER) of starting EFV-based regimens compared with NVP-based regimens classified by baseline CD4 group (control age at baseline treatment at 35 years)

Baseline CD4 count (cell/mm3)	Incremental cost-effectiveness ratio (ICER)	
	Baht per LY saved	Baht per DALY averted
50	Dominate (228,215)	Dominate (227,026)
100	Dominate (23,729,000)	Dominate (1,024,273)
150	208,579,000	Dominate (1,655,389)
200	11,562,692	Dominate (2,684,196)
250	14,089,636	Dominate (3,369,261)

4.2.2.5 Uncertainty analysis

The interactions between the uncertainty parameters were assessed by sampling 1,000 times with the parameters' probability density functions using Monte Carlo simulation. In uncertainty analysis, the results of cost-effectiveness in terms of incremental cost per incremental LY gained and cost-utility in terms of incremental cost per incremental DALY averted were presented by cost-effectiveness planes and cost-effective acceptability curves.

4.2.2.5.1 Uncertainty of cost per life-year gained in sub-group analysis

a) Uncertainty of cost per life-year gained classified by age-group

Figure 4.2 (a-e) showed 1000 iterations of simulations that were presented in terms of the incremental cost and LY gained for starting with EFV-based regimens compared with NVP-based regimens classified by age-group when X-axis represented incremental LY gained and Y-axis represented incremental cost.

Figure 4.2 Cost effectiveness plane of LY gained of EFV-based regimens compared with NVP-based regimens classified by age groups.

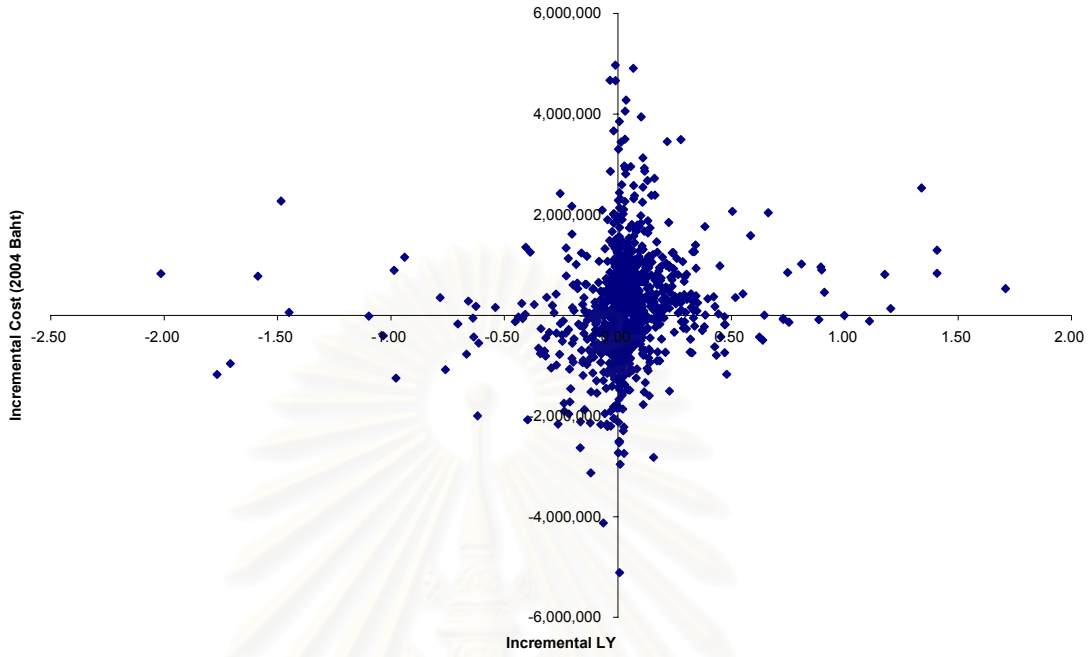


Figure 4.2 (a) CE plane of LY gained of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with 20 years old at baseline treatment

Figure 4.2(a) presented incremental costs and LY gained of EFV-based regimens in the patient age 20 years by controlling the baseline CD4 count at 200cell/mm3. The results from 1,000 iterations of simulations showed substantial variations in cost but small variations in LY gained, resulting in ellipse-shape alongside Y-axis. More than half (68%) of data simulated fell into the east quadrant, which indicated that starting with EFV-based regimens yielded more LY gained than NVP-based regimens. Forty-two percent of the data simulated fell into the northeast quadrant, representing more LY gained and more costly. Whether or not the EFV-based regimens was cost-effective compared with NVP-based regimens, it depended on how much the decision makers are willing to pay for one unit of LY gained. Approximately 26 % of the data simulated fell into the southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens.

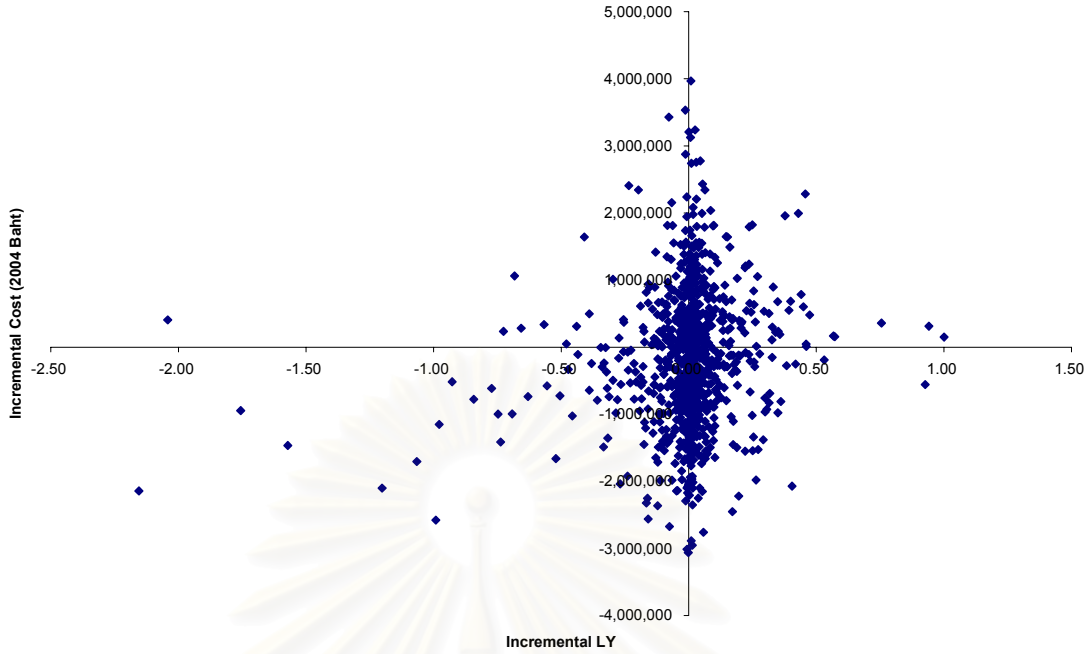


Figure 4.2 (b) CE plane of LY gained of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with 30 years old at baseline treatment

Figure 4.2(b) presented incremental costs and LY gained of EFV-based regimens in the patient age 30 years by controlling the baseline CD4 count at 200cell/mm3. The results from 1,000 iterations of simulations showed substantial variations in cost but small variations in LY gained, resulting in ellipse-shape alongside Y-axis. More than half (58%) of the data simulated fell into the east quadrant, which indicated that starting with EFV-based regimens yielded more LY gained than NVP-based regimens. Approximately 32 % of the data simulated fell into the southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens. Twenty-six percent of the data simulated fell into the northeast quadrant (more LY gained and more costly) and the southwest quadrant (less LY gained and less costly). Whether or not the EFV-based regimens was cost-effective compared with NVP-based regimens, it depended on how much the decision makers are willing to pay for one unit of LY gained.

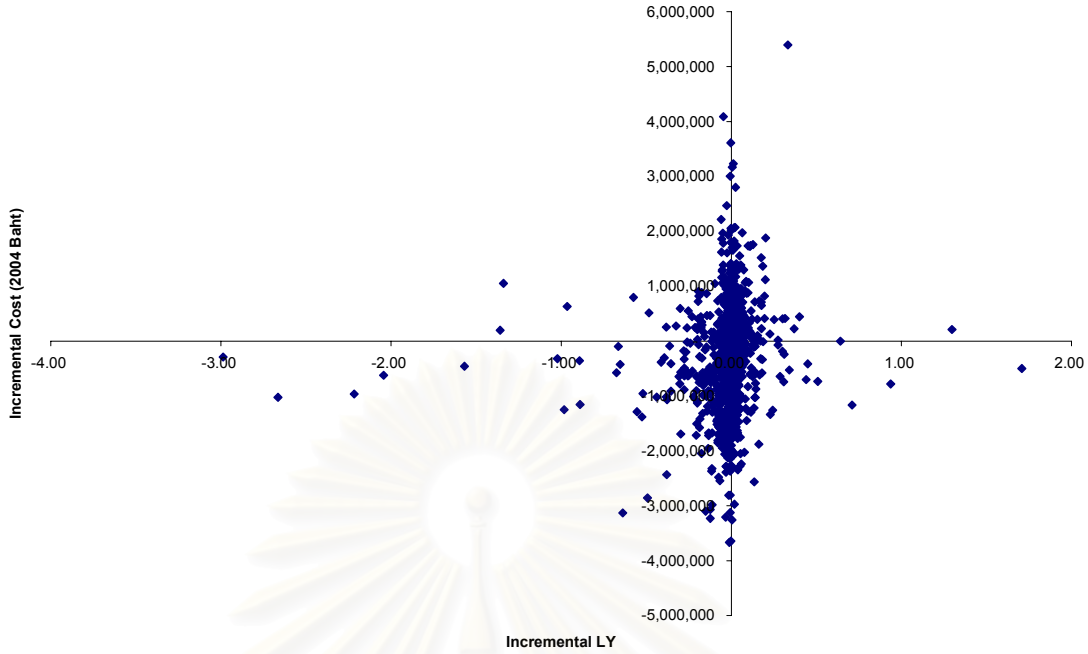


Figure 4.2 (c) CE plane of LY gained of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with 40 years old at baseline treatment

Figure 4.2(c) presented incremental costs and LY gained of EFV-based regimens in the patient age 40 years by controlling the baseline CD4 count at 200cell/mm3. The results from 1,000 iterations of simulations showed substantial variations in cost but small variations in LY gained, resulting in ellipse-shape alongside Y-axis. More than half (67%) of the data simulated fell into south quadrant, which indicated that starting with EFV-based regimens was cheaper than NVP-based regimens. Approximately 38 % of the data simulated fell into southwest quadrant. Approximately 29 % of the data simulated fell into southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens.

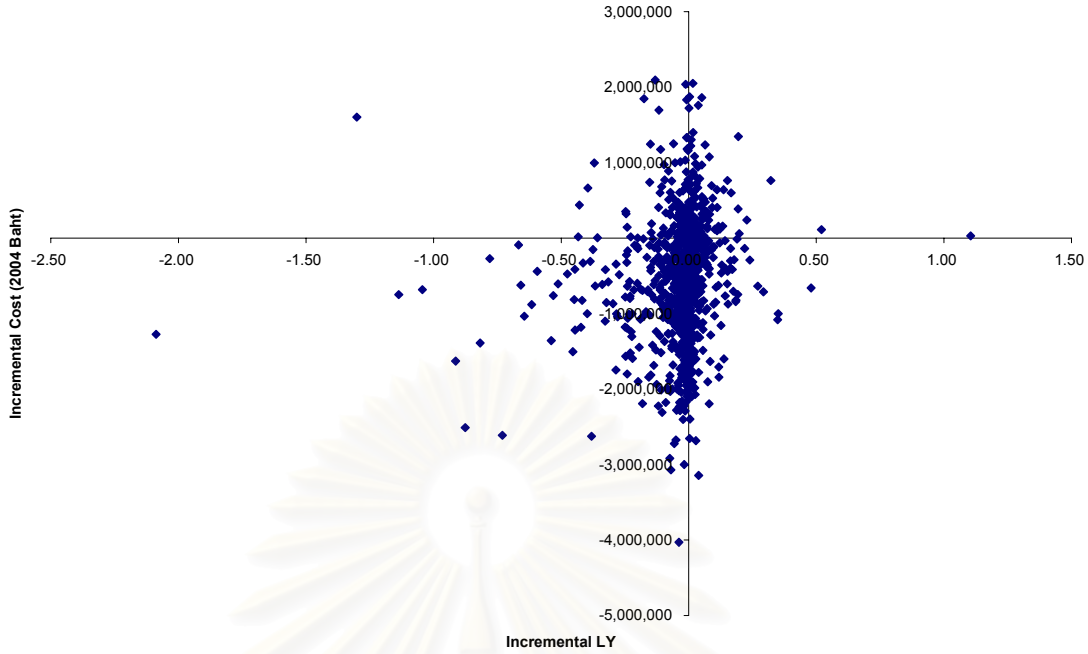


Figure 4.2 (d) CE plane of LY gained of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with 50 years old at baseline treatment

Figure 4.2(d) presented incremental costs and LY gained of EFV-based regimens in the patient age 50 years by controlling the baseline CD4 count at 200cell/mm3. The results from 1,000 iterations of simulations showed substantial variations in cost but small variations in LY gained, resulting in ellipse-shape alongside Y-axis. Most of the data simulated fell into south quadrant, which indicated that starting with EFV-based regimens was cheaper than NVP-based regimens. Fifty-one percent of the data simulated fell into southwest quadrant. Approximately 27 % of the data simulated fell into southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens.

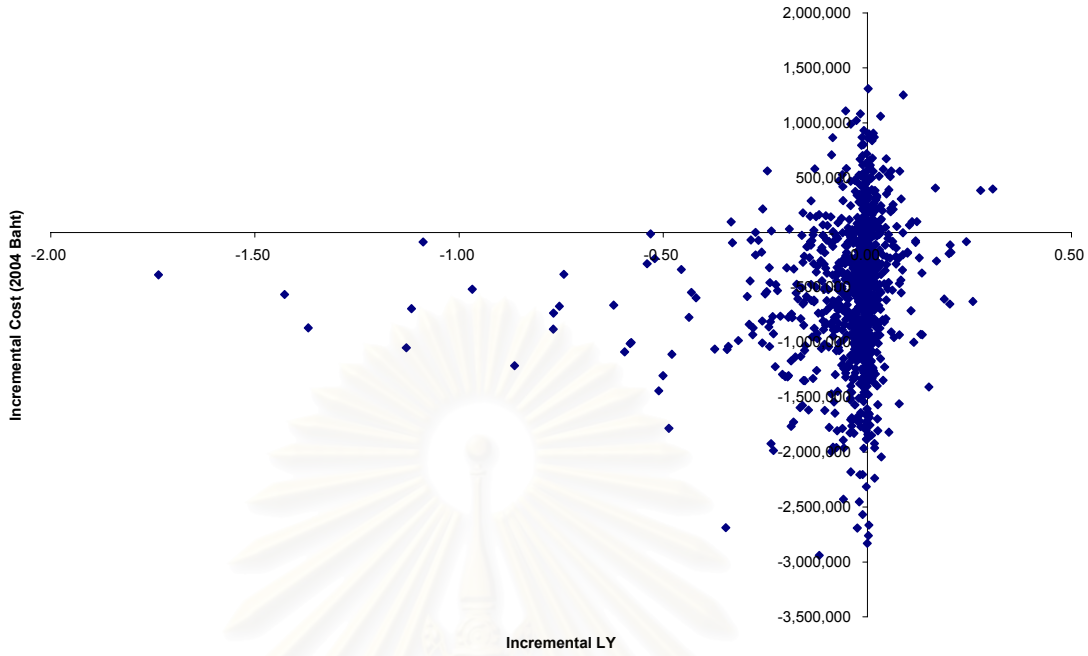


Figure 4.2 (e) CE plane of LY gained of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with 60 years old at baseline treatment

Figure 4.2(e) presented incremental costs and LY gained of EFV-based regimens in the patient age 60 years by controlling the baseline CD4 count at 200cell/mm3. The results from 1,000 iterations of simulations showed substantial variations in cost but small variations in LY gained, resulting in ellipse-shape alongside Y-axis. Most of the data simulated fell into the south quadrant which indicated that starting with EFV-based regimens was cheaper than NVP-based regimens. Fifty-nine percent of the data simulated fell into southwest quadrant. Approximately 24 % of the data simulated fell into southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens.

In conclusions, the differences of cost per life-year gained of the patients who had CD4 200cell/mm3 at baseline compared between those who started with EFV-based regimens and NVP-based regimens were significantly depended on the patients' age. For example, young patients (e.g. 20 to 30 years-old) who started with EFV-based regimens yielded more LY gained with more or less costly compared with those started with NVP-based regimens. In contrast, old patients (e.g. 40 to 60 years-old) who started with EFV-based regimens had less costly and less LY gained compared with NVP-based regimens. These findings pointed out that the age of HIV/AIDS patients at

baseline treatment was a major factor that significantly affected to the treatment cost as well as LY gained. However, the probabilistic sensitivity analysis indicated uncertainty around estimated costs and outcomes in the model as they could be seen in figure 4.2(a-e).

Figure 4.3 Cost effectiveness acceptability curve of LY gained of EFV-based regimens compared with NVP-based regimens classified by age-group.

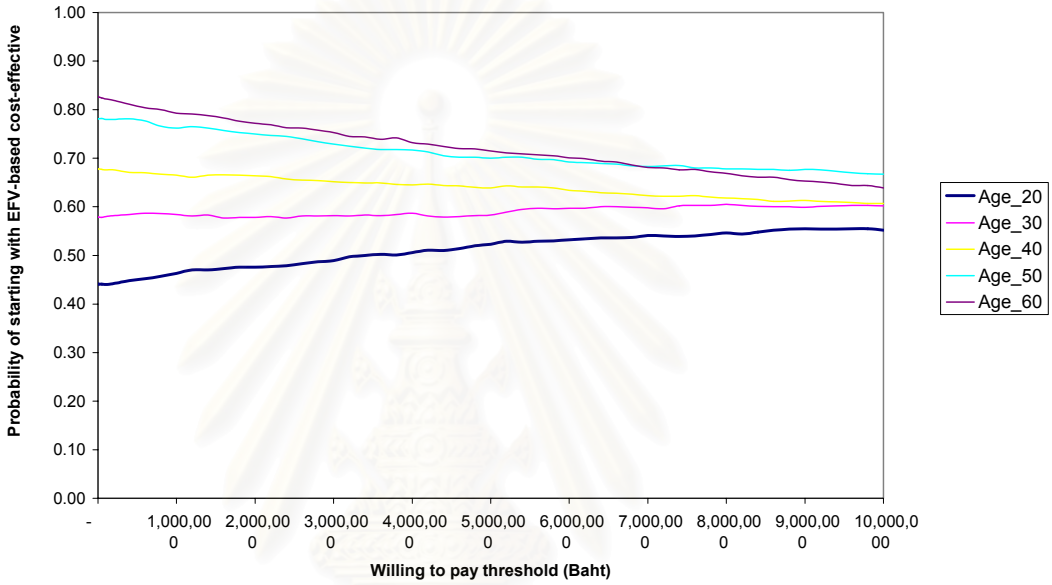


Figure 4.3 presented the cost effectiveness acceptability curve of LY gained in the patients who started with EFV-based regimens compared with NVP-based regimens classified by age-group. To determine which treatment regimens were cost-effective, the age of patients and WTP threshold had to be taken into consideration.

In the patients age 20 years, at zero willingness to pay (WTP) threshold or no extra budget available, it was more likely that starting with NVP-based was a preferable choice by which considering the probability 0.57. However, the higher WTP threshold, the lower likelihood that NVP-based regimen was still cost-effective. Starting with EFV-based regimens in this age group was preferable when the WTP was above 3,000,000 Baht/LY gained.

In the patients age 30 years, at zero willingness to pay (WTP) or not extra budget available, it was more likely that starting with EFV-based was a preferable

choice by which considering the probability 0.57 and asymptotes to this increasing of WTP.

In contrast, in the older patients (age 40 to 60 years), at zero willingness to pay (WTP), it was more likely that starting with EFV-based was a preferable choice by which considering the probability 0.68, 0.78, and 0.82. However, the higher WTP threshold the lower likelihood that EFV-based regimen was still cost-effective.

These explanations were based on the results from CE planes. In younger patients, starting with EFV-based regimens seemed to be more costly and gained more life-year compared to NVP-based regimens. Increasing of the willingness to pay thresholds (WTP) for a unit of life-year (LY) gained raised the probability of EFV-based regimens to be more cost effective. On the other hand, starting with EFV-based regimens in older group seemed to less costly and less life-year gained. Increasing the willingness to pay thresholds (WTP) for a unit of life-year (LY) gained decreased the probability of EFV-based regimen to be more cost effective. However, the declines of curves in these age groups were not much enough to support the preferable option to use NVP-based regimens. The probability of EFV-based to be cost-effective was still higher than 0.5.

b) Uncertainty of cost per life-year gained classified by CD4 at baseline groups

Figure 4.4(a-e) showed 1000 iterations of simulation that were presented in terms of the incremental cost and LY gained of starting with EFV-based regimens compared with NVP-based regimens classified by CD4 at baseline group when X-axis represented incremental LY gained and Y-axis represented incremental cost.

Figure 4.4 Cost effectiveness plane of LY gained of EFV-based regimens compared with NVP-based regimens classified by CD4 at baseline groups

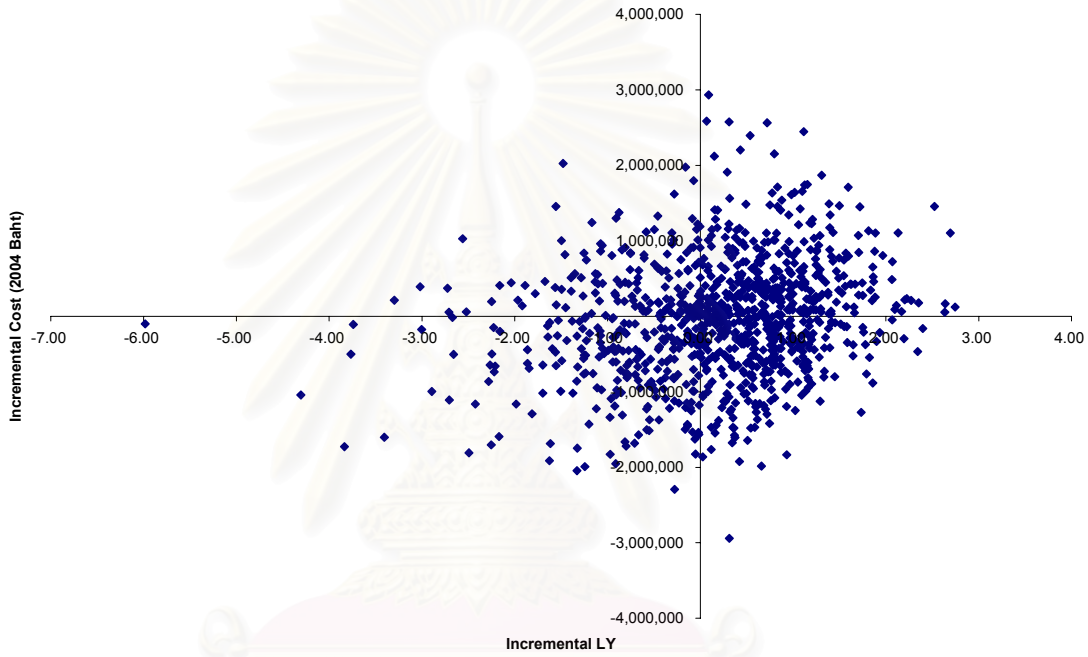


Figure 4.4 (a) CE plane of LY gained of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with CD4 baseline at 50cell/mm3

Figure 4.4(a) presented incremental costs and LY gained of EFV-based regimens in the patient with baseline CD4 at 50cell/mm3 by controlling the age at initial of treatment at 35 years old. Most of the data simulated fell into the east quadrant, which indicated that starting with EFV-based regimens yielded more LY gained compared with NVP-based regimens. Approximately 35% of the data simulated fell into northeast quadrant. A same proportion of the data simulated fell into the northeast, the southeast, and the southwest quadrant. Approximately 29 % of the data simulated fell into southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens.

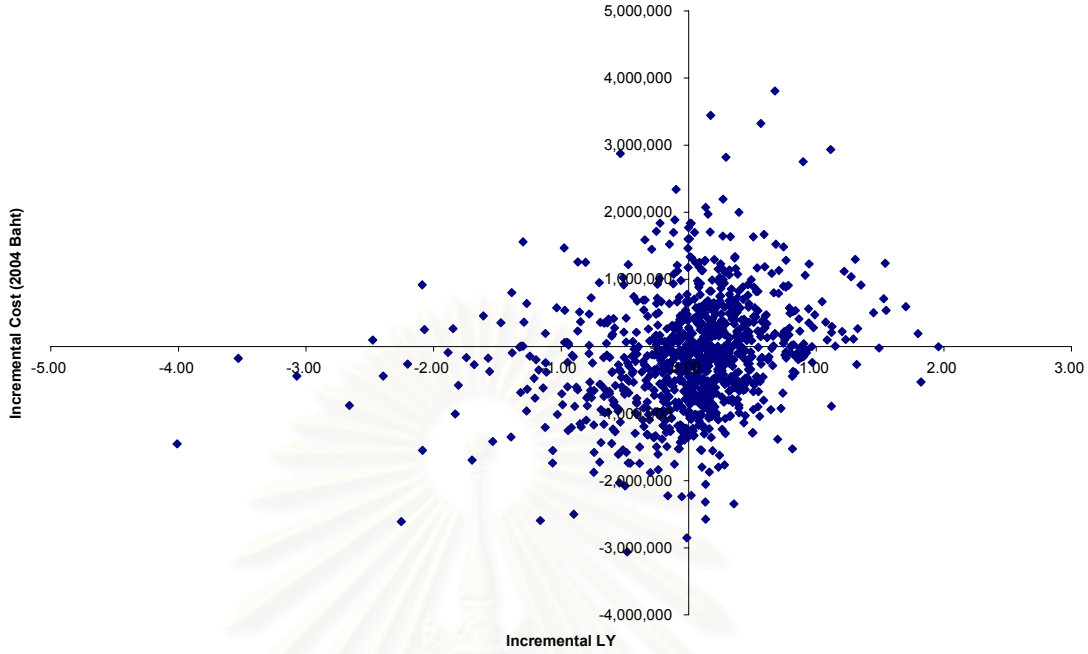


Figure 4.4 (b) CE plane of LY gained of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with CD4 baseline at 100cell/mm3

Figure 4.4(b) presented incremental costs and LY gained of EFV-based regimens in the patient with baseline CD4 at 100cell/mm3. Most of the data simulated fell into the south quadrant, which indicated that starting with EFV-based was cheaper than NVP-based regimens. Approximately 31 % of the data simulated fell into southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens. Approximately 29 % and 27 % of the data simulated fell into the southwest and the northeast quadrant.

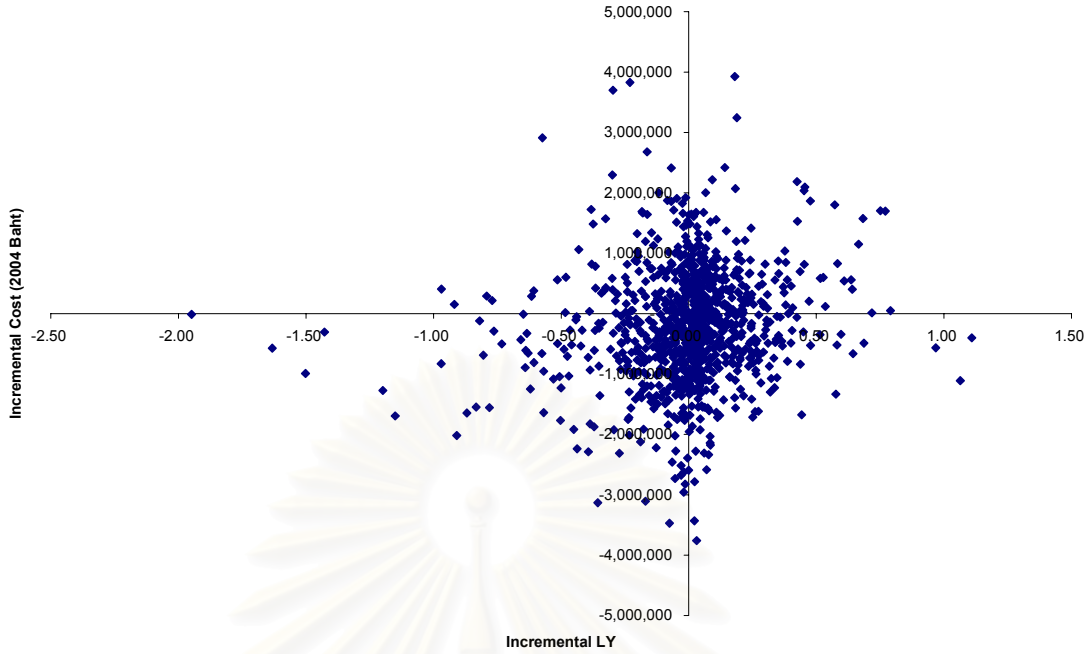


Figure 4.4 (c) CE plane of LY gained of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with CD4 baseline at 150cell/mm3

Figure 4.4(c) presented incremental costs and LY gained of EFV-based regimens in the patient with baseline CD4 at 150cell/mm3. Most of the data simulated fell into the south quadrant, which indicated that starting with EFV-based was cheaper than NVP-based regimens. Approximately 32 % of the data simulated fell into the southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens. Approximately 28 % of the data simulated fell into the southwest quadrant.

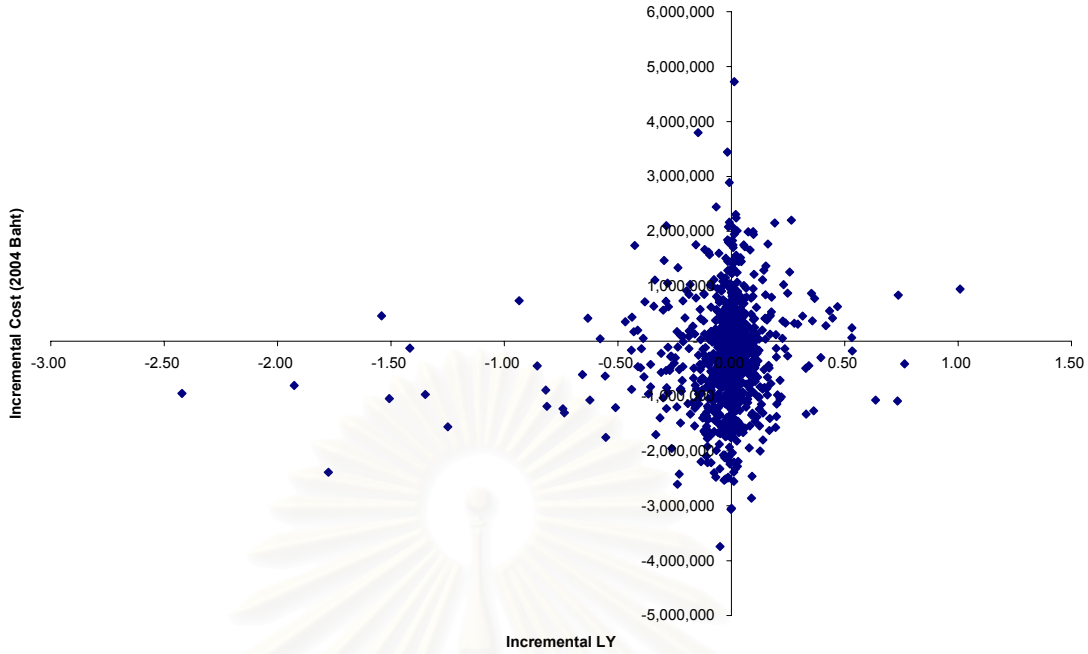


Figure 4.4 (d) CE plane of LY gained of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with CD4 baseline at 200cell/mm3

Figure 4.4(d) presented incremental costs and LY gained of EFV-based regimens in the patient with baseline CD4 at 200cell/mm3. Most of the data simulated results showed substantial variations in cost but small variations in LY gained, resulting in ellipse-shape alongside Y-axis. Most of data simulated fell into the south quadrant, which indicated that starting with EFV-based was cheaper than NVP-based regimens. Approximately 35 % of the data simulated fell into the southwest quadrant. Approximately 29 % of the data simulated fell into the southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens.

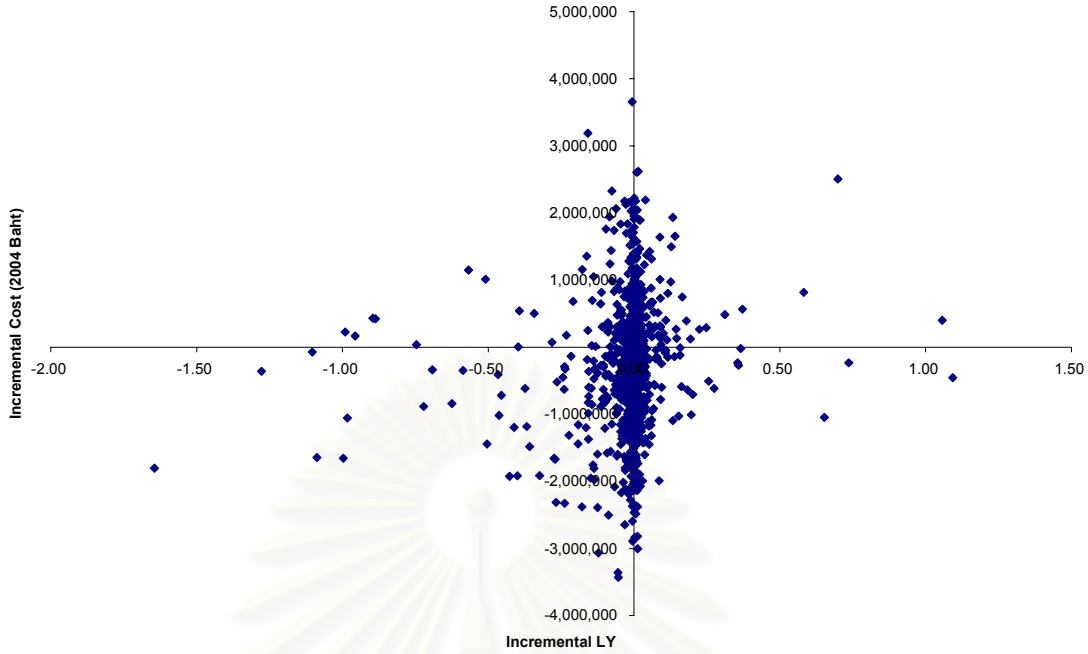


Figure 4.4 (e) CE plane of LY gained of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with CD4 baseline at 250cell/mm3

Figure 4.4(e) presented incremental costs and LY gained of EFV-based regimens in the patient with baseline CD4 at 250cell/mm3. Most of the data simulated showed substantial variations in cost but small variations in LY gained, resulting in ellipse-shape alongside Y-axis. Most of the data simulated fell into the south quadrant, which indicated that starting with EFV-based regimens was cheaper than NVP-based regimens. Approximately 38 % of the data simulated fell into the southwest quadrant. Approximately 27 % of the data simulated fell into southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens.

In conclusions, the difference of cost per life-year gained for patients who are 35 years old at baseline treatment compared between those who started with EFV-based regimen and NVP-based regimen was dependent on the patients' baseline CD4 count. From these figures, baseline CD4 had influence on cost and outcome in terms of LY gained. With the low level of baseline CD4 (e.g. 50 to 150 cell/mm3), the patients who started with EFV-based regimens yielded more LY gained than NVP-based regimens. With the high level of baseline CD4 (e.g. 200 to 250 cell/mm3), the patients who started with EFV-based regimens yielded less LY gained than NVP-based regimens. With low level of baseline CD4 (e.g. 50cell/mm3), starting with EFV-based regimens was more

expensive than NVP-based regimens. While, with the middle to high level of baseline CD4 (e.g. 100 to 250 cell/mm3) starting with EFV-based regimens yielded less costly than NVP-based regimens. However, the probabilistic sensitivity analysis indicated uncertainty around estimated costs and outcomes in the model as they could be seen in figure 4.4(a-e).

Figure 4.5 Cost effectiveness acceptability curve of LY gained of EFV-based regimens compared with NVP-based regimens classified by CD4 at baseline group.

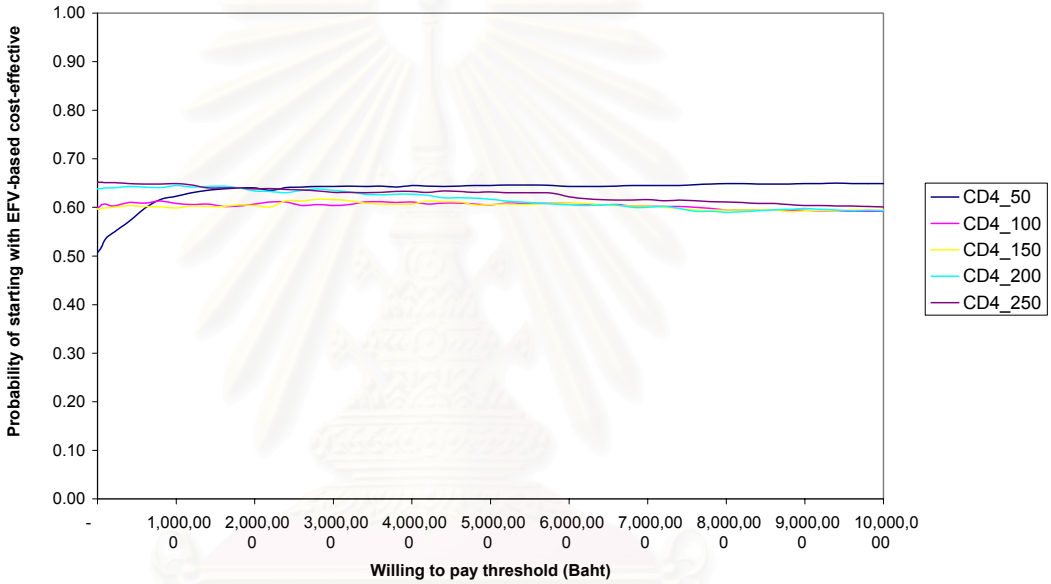


Figure 4.5 presented the cost effectiveness acceptability curve of LY gained of the patients who started with EFV-based regimens compared with NVP-based regimens classified by baseline CD4 group.

This figure showed that in the patients who are 35 years old at baseline treatment, starting with EFV-based regimens was cost-effective in all baselines CD4 count, resulting in more than 0.5 of probability.

4.2.2.5.2 Uncertainty of cost per Disability-adjusted life year (DALY) averted in sub-group analysis

a) Uncertainty of cost per DALY averted classified by age-group

Figure 4.6(a-e) showed 1000 iterations of simulation that were presented in terms of the incremental cost and DALY averted of starting with EFV-based regimens compared with NVP-based regimens classified by age-group when X-axis represented incremental DALY averted and Y-axis represented incremental cost.

Figure 4.6 Cost effectiveness plane of DALY averted of EFV-based regimens compared with NVP-based regimens classified by age group

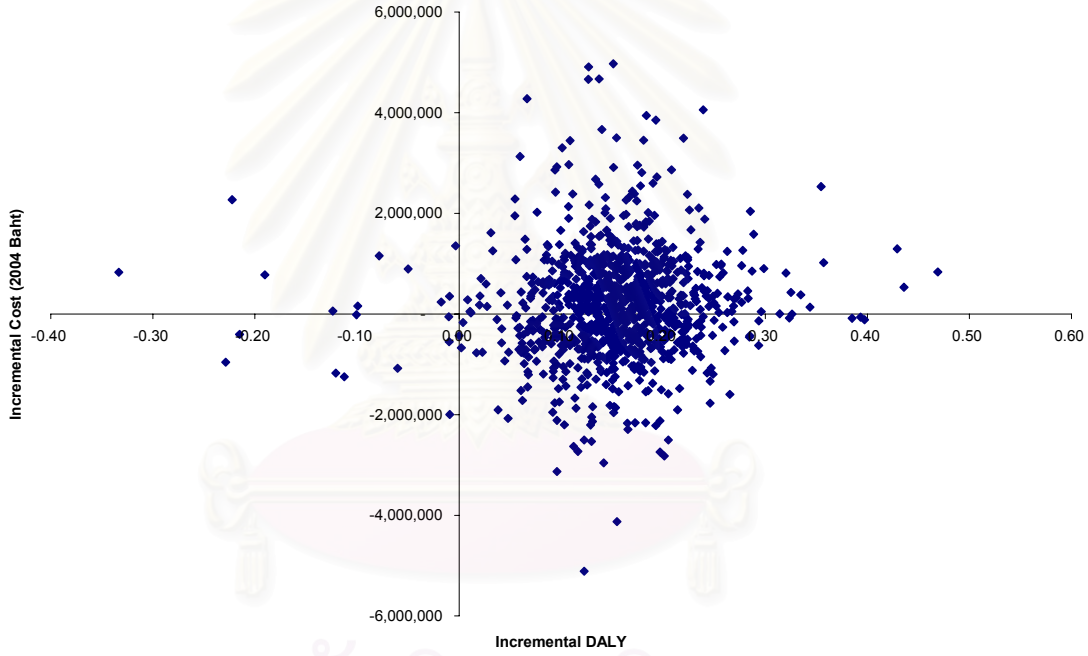


Figure 4.6 (a) CE plane of DALY averted of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with 20 years old at baseline treatment

Figure 4.6(a) presented incremental costs and DALY averted of EFV-based regimens in the patient age-group 20 years-old by controlling the baseline CD4 count at 200cell/mm3. Ninety-seven percent of the data simulated fell into east quadrant, which indicated that starting with EFV-based yielded more DALY averted than NVP-based regimens. The majority of the data simulated, approximately 54% fell into the northeast quadrant, which indicated more DALY averted and more costly. Approximately 43% of

the data simulated fell into the southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based.

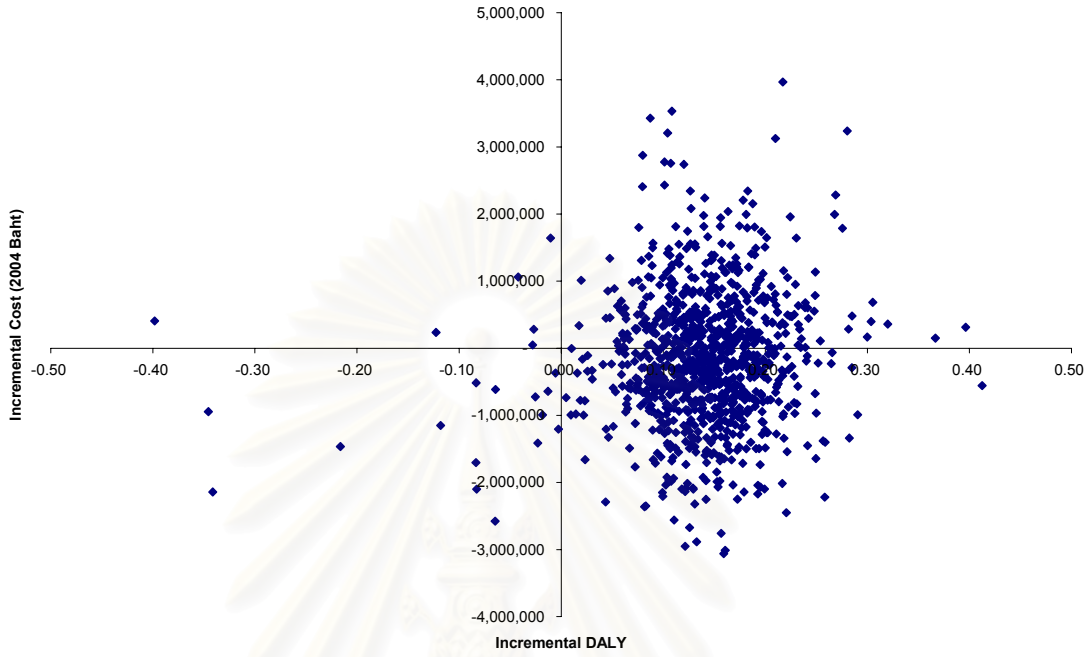


Figure 4.6 (b) CE plane of DALY averted of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with 30 years old at baseline treatment

Figure 4.6(b) presented incremental costs and DALY averted of EFV-based regimens in the patient age-group 30 years-old by controlling the baseline CD4 count at 200cell/mm3. Ninety-seven percent of the data simulated fell into east quadrant, which indicated that starting with EFV-based yielded more DALY averted than NVP-based regimens. The majority of the data simulated about 56% fell into the southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens. Approximately 42% of the data simulated fell into northeast quadrant, which indicated that starting with EFV-based regimens yielded more DALY averted and more costly.

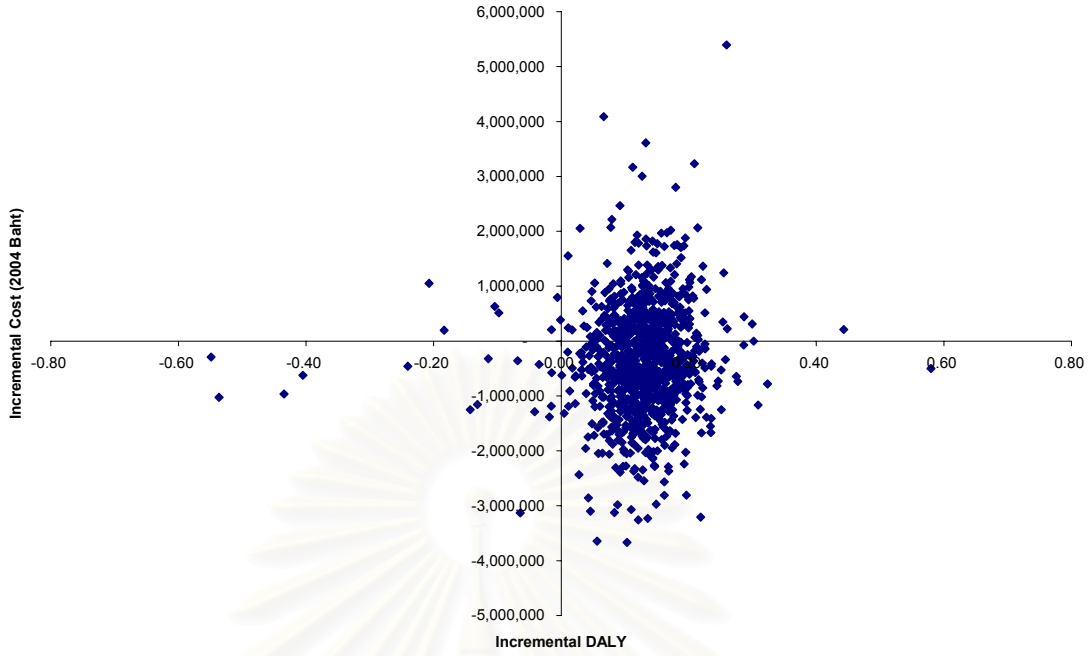


Figure 4.6 (c) CE plane of DALY averted of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with 40 years old at baseline treatment

Figure 4.6(c) presented incremental costs and DALY averted of EFV-based regimens in the patient age-group 40 years-old. Most of the data simulated fell into the east quadrant, which indicated that starting with EFV-based regimens yielded more DALY averted than NVP-based regimens. Approximately 66% of the data simulated fell into the southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens. Approximately 32% of the data simulated fell into the northeast quadrant.

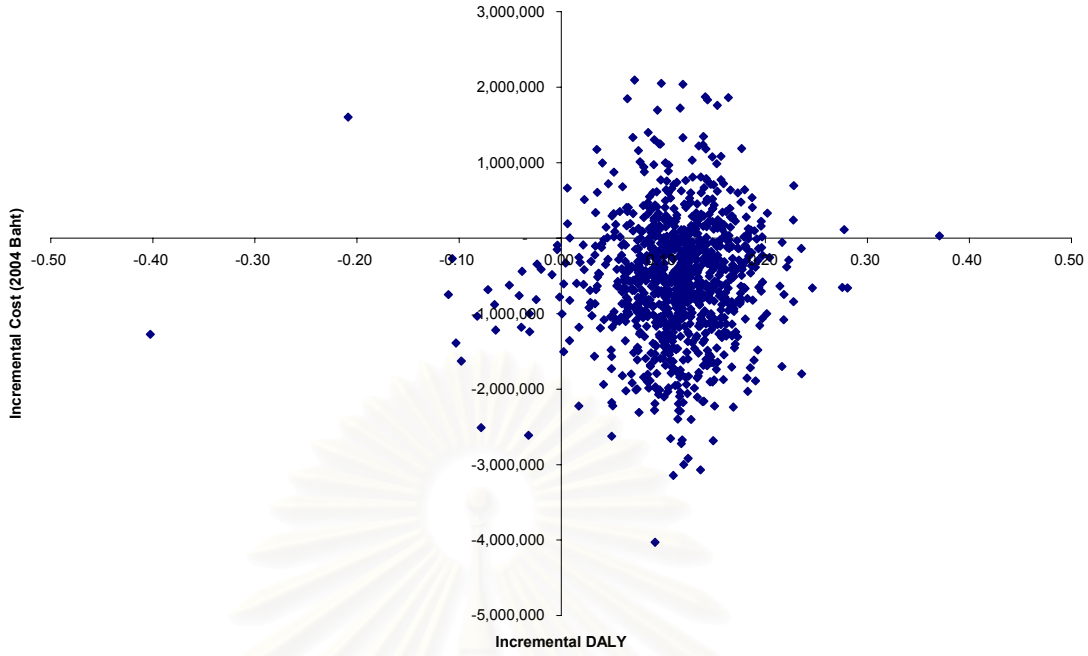


Figure 4.6 (d) CE plane of DALY averted of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with 50 years old at baseline treatment

Figure 4.6(d) presented incremental costs and DALY averted of EFV-based regimens in the patient age-group 50 years-old. Most of the data simulated fell into the east quadrant which indicated that starting with EFV-based regimens had more DALY averted than NVP-based regimens. The majority of the data simulated (approximately 76%) fell into the southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens. Approximately 22% of the data simulated fell into the northeast quadrant.

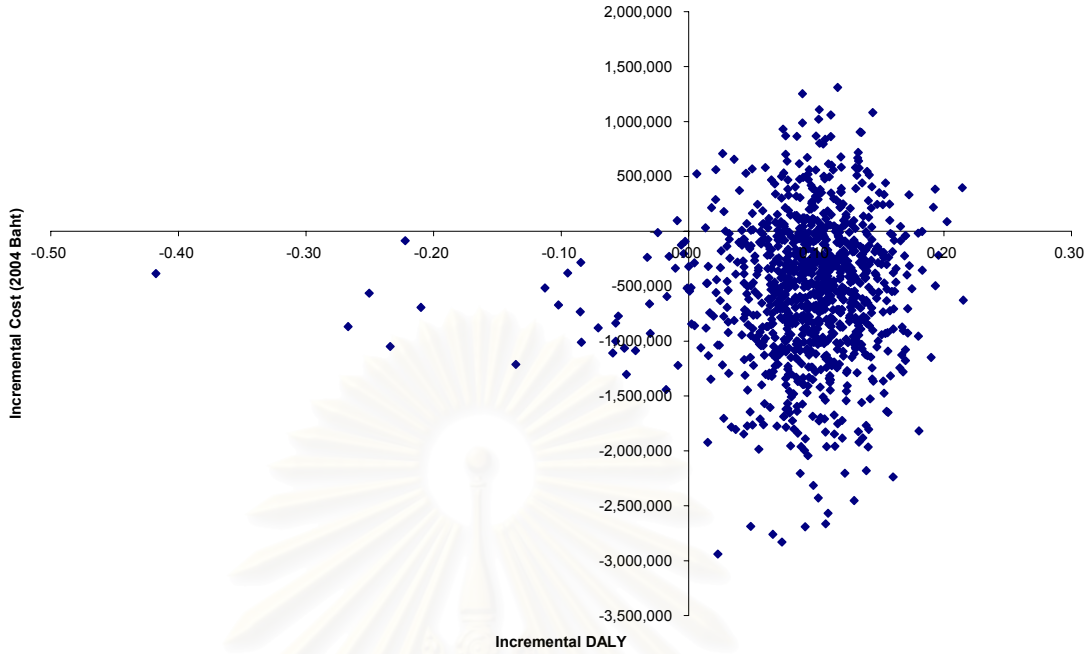


Figure 4.6 (e) CE plane of DALY averted of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with 60 years old at baseline treatment

Figure 4.6(e) presented incremental costs and DALY averted of EFV-based regimens in the patient age-group 60 years-old. Most of the data simulated fell into the south quadrant, which indicated that starting with EFV-based regimens was cheaper than NVP-based regimens. Approximately 60% of the data simulated fell into southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens. About 17% of the data simulated fell into the northeast quadrant.

In conclusions, the incremental cost per DALY averted for patients who had CD4 200cell/mm3 at baseline compared between those who started with EFV-based regimens and NVP-based regimens were similar in all aged groups. Majority of the data simulated fell into the east quadrant, which indicated that starting with EFV-based regimens yielded more DALY averted than NVP-based regimens. However, the difference of cost of treatment between starting with EFV-based regimens and NVP-based regimens was dependent on age. In younger age group (e.g. 20 years old), introducing EFV-based as first line regimens was expensive than NVP-based regimens. In contrast, in the middle to old aged groups (e.g.30 to 60 years old), introducing EFV-based as first line regimen was cheaper than NVP-based regimens.

Figure 4.7 Cost effectiveness acceptability curve of disability-adjusted life-year (DALY) averted of EFV-based regimens compared with NVP-based regimens classified by age groups.

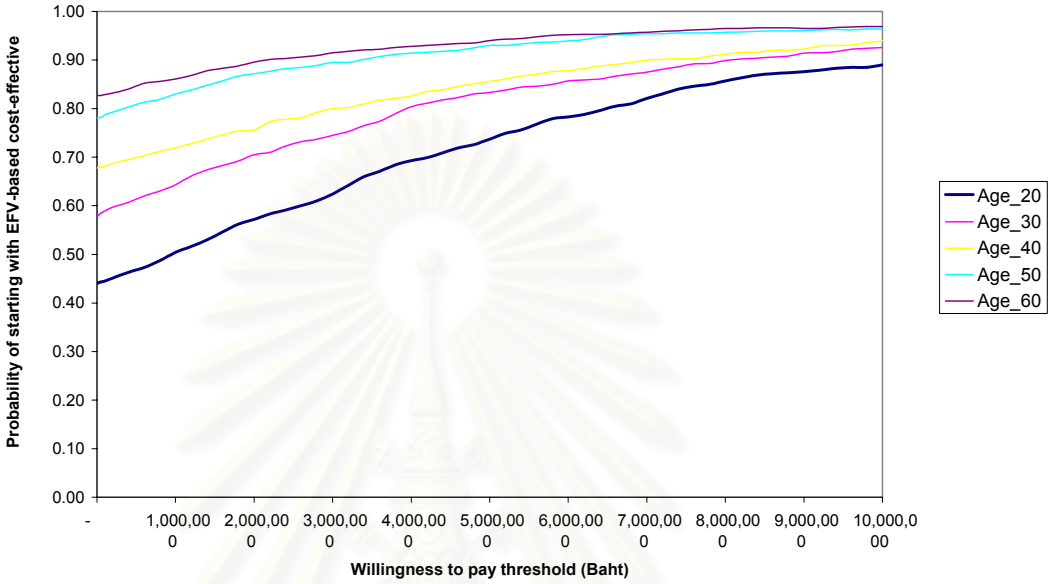


Figure 4.7 presented the cost effectiveness acceptability curve of DALY averted of starting with EFV-based regimens compared with NVP-based regimens classified by age-group.

By controlling baseline CD4 at 200cell/mm3, those who were 20 years old at baseline treatment, at zero willingness to pay (WTP) or not extra budget available it was more likely that starting with NVP-based regimens was a preferable choice by which considering the probability 0.55. However, the higher WTP threshold, the lower likelihood that NVP-based regimen was still cost effective. Starting with EFV-based in this age group was preferable when the WTP was above 1,000,000 Baht/LY gained.

At the same level of baseline CD4, for the middle and old age-group (e.g. 30 to 60 years-old), at zero willingness to pay (WTP) or not extra budget available, it was more likely that starting with EFV-based regimens was a preferable choice by which considering the probability more than 0.5. The probability of EFV-based being cost effective was increased depending on the increase of WTP threshold.

Although, there was not accepted threshold for adopting health technologies in Thailand, this study applied the threshold that was recommended by the commission on Macroeconomics and Health, which suggested the use of three times of gross domestic

product (GDP) per capita as the threshold for consideration in developing countries [54]. This would indicate a willingness to pay threshold in Thailand of 270,000 Baht per disability-adjusted life year (DALY) averted based on 2004 Thai GDP and population.

Given a maximum acceptable willingness to pay of 270,000 Baht/DALY, starting with EFV-based was cost effective in all aged group except who were 20 years old at baseline treatment that NVP-based regimens was preferable choice.

b) Uncertainty of cost per DALY averted classified by CD4 at baseline group

Figure 4.8(a-e) showed 1000 iterations of simulation that were presented in terms of the incremental cost and DALY averted of starting with EFV-based regimens compared with NVP-based regimens classified by CD4 at baseline groups when X-axis represented incremental DALY averted and Y-axis represented incremental cost.

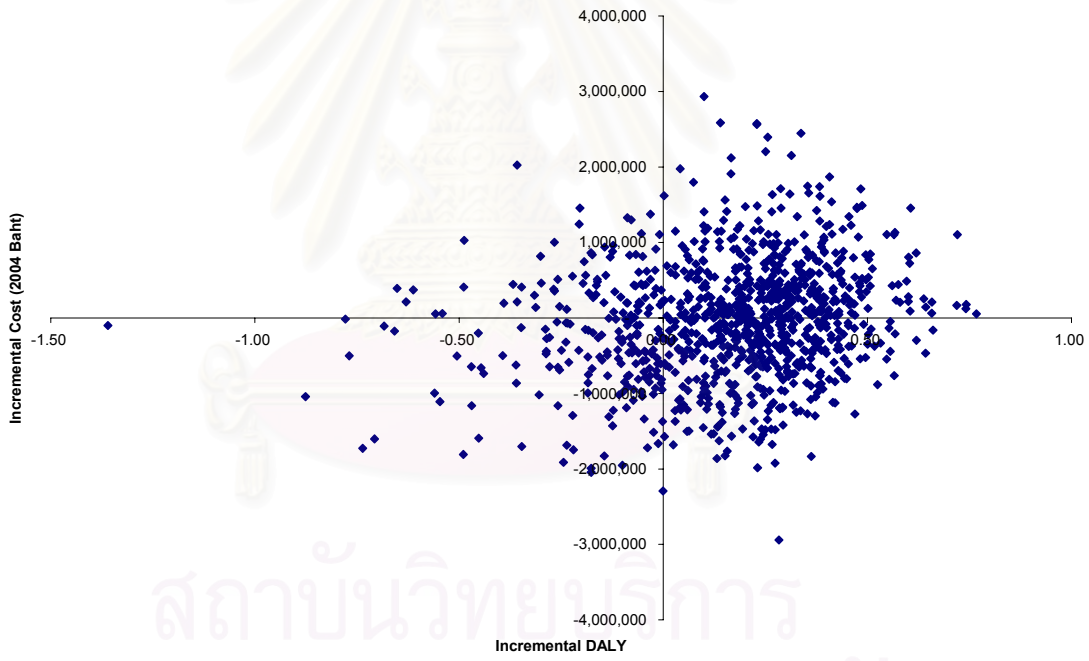


Figure 4.8 (a) CE plane of DALY averted of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with CD4 baseline at 50cell/mm3

Figure 4.8(a) presented incremental costs and DALY averted of EFV-based regimens in the patient with baseline CD4 at 50cell/mm3 by controlling the age at initial of treatment at 35 years old. Most of the data simulated fell into the east quadrant, which indicated that starting with EFV-based regimens yielded more DALY averted than NVP-based regimens. Approximately 41% of the data simulated fell into the northeast quadrant, which indicated that starting with EFV-based regimens yielded more DALY

averted and more costly. Whether or not the EFV-based regimens was cost-effective compared with NVP-based regimens, it depended on how much the decision makers are willing to pay for one unit of DALY averted. Approximately 37% of the data simulated fell into the southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens.

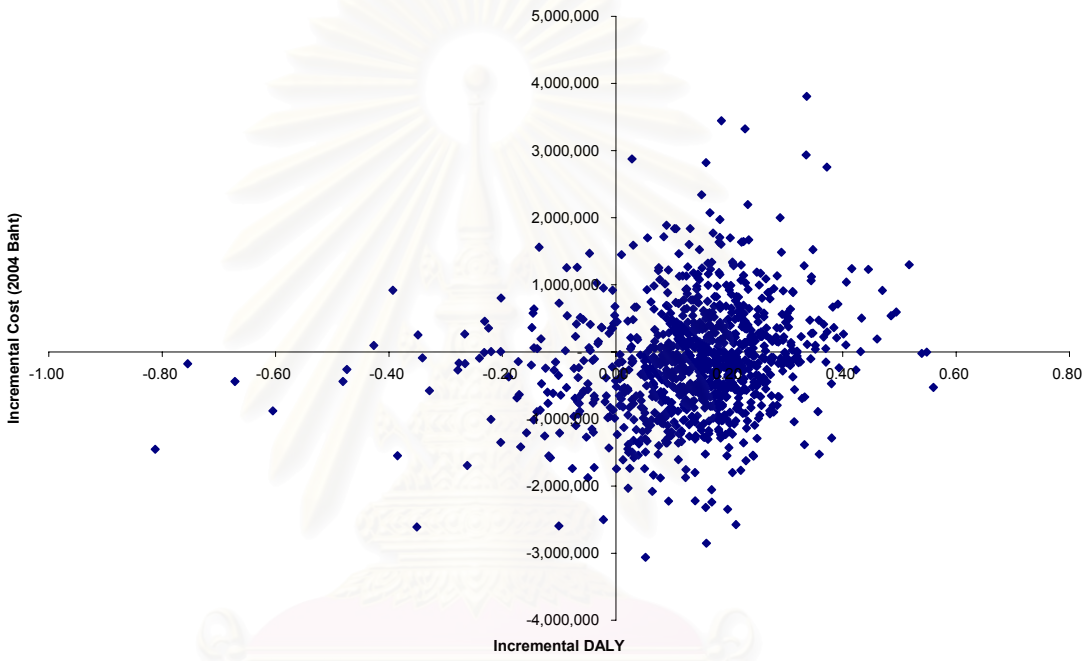


Figure 4.8 (b) CE plane of DALY averted of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with CD4 baseline at 100cell/mm3

Figure 4.8(b) presented incremental costs and DALY averted of EFV-based regimens in the patient with baseline CD4 at 100cell/mm3. Most of the data simulated fell into the east quadrant, which indicated that starting with EFV-based yielded more DALY averted than NVP-based regimens. Approximately 52% of the data simulated fell into the southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens. Approximately 36% of the data simulated fell into the northeast quadrant.

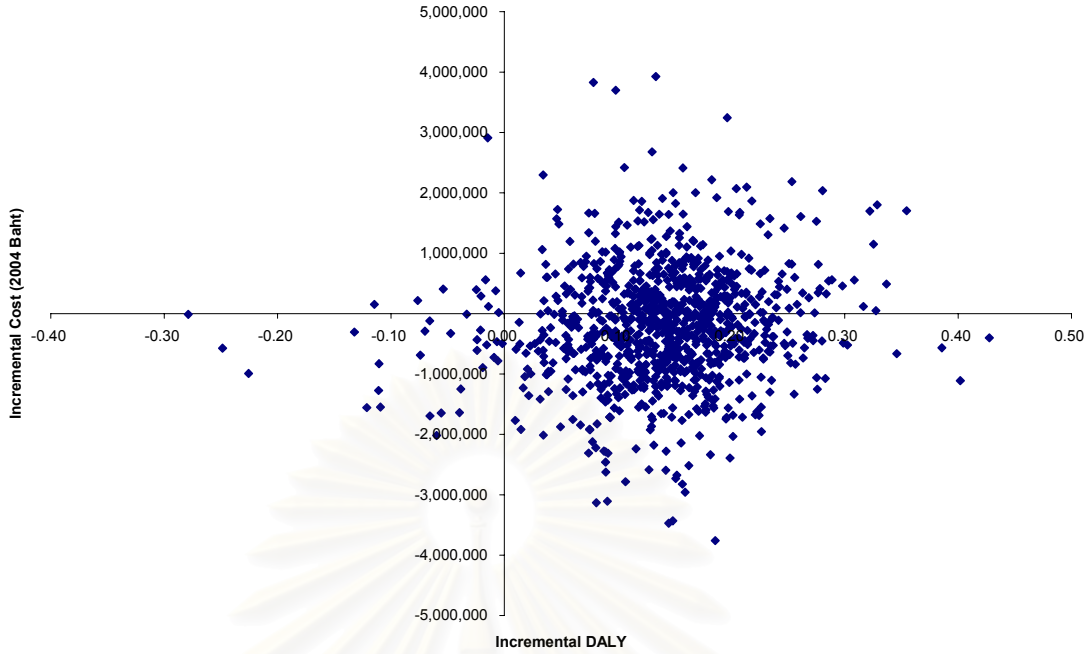


Figure 4.8 (c) CE plane of DALY averted of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with CD4 baseline at 150cell/mm3

Figure 4.8(c) presented incremental costs and DALY averted for EFV-based in the patient with baseline CD4 at 150cell/mm3. Almost of the data simulated fell into the east quadrant, which indicated that starting with EFV-based had more DALY averted than NVP-based regimens. Approximately 57% of the data simulated fell into the southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens. Approximately 39% of the data simulated fell into the northeast quadrant.

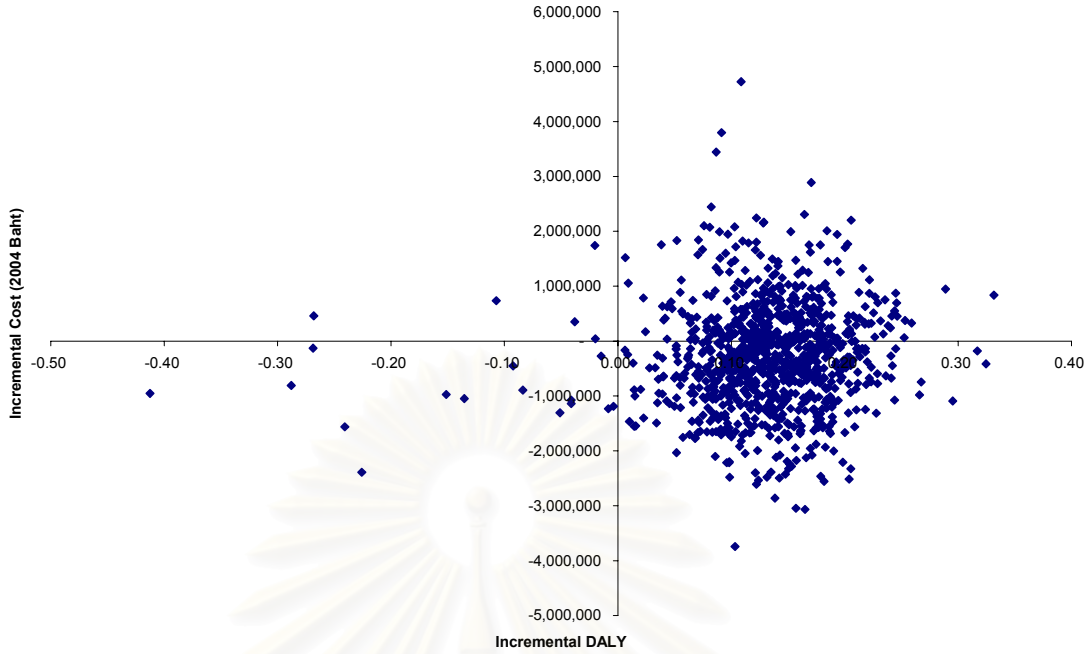


Figure 4.8 (d) CE plane of DALY averted of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with CD4 baseline at 200cell/mm3

Figure 4.8(d) presented incremental costs and DALY averted of EFV-based regimens in the patient with baseline CD4 at 200cell/mm3. Almost of the data simulated fell into the east quadrant, which indicated that starting with EFV-based regimens had more DALY averted than NVP-based regimens. Approximately 62% of the data simulated fell into the southeast quadrant, which indicated that starting with EFV-based dominated NVP-based regimens. Approximately 36% of the data simulated fell into the northeast quadrant.

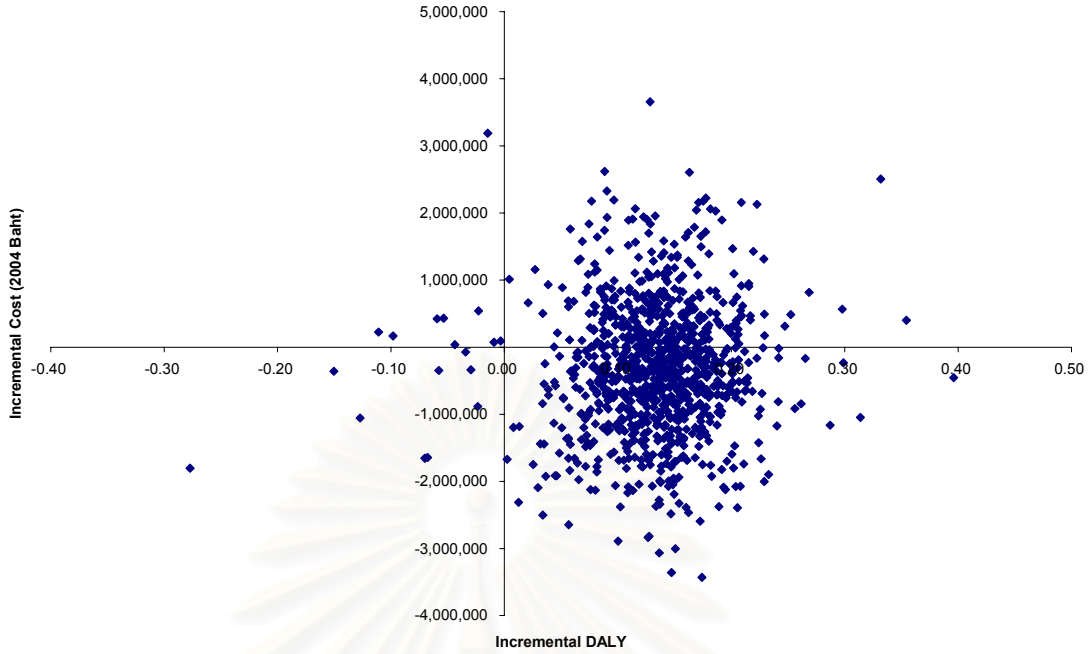


Figure 4.8 (e) CE plane of DALY averted of EFV-based regimens compared with NVP-based regimens in HIV/AIDS patients with CD4 baseline at 250cell/mm3

Figure 4.8(e) presented incremental costs and DALY averted of EFV-based regimens in the patient with baseline CD4 at 250cell/mm3. Almost of the data simulated fell into the east quadrant, which indicated that starting with EFV-based regimens had more DALY averted than NVP-based regimens. Approximately 64% of the data simulated fell into the southeast quadrant, which indicated that starting with EFV-based regimens dominated NVP-based regimens. Approximately 34% of the data simulated fell into the northeast quadrant.

In conclusions, the incremental cost per DALY averted for patients who had CD4 200cell/mm3 at baseline compared between those who started with EFV-based regimens and NVP-based regimens were similar in all baselines CD4. Majority of the data simulated fell into the east quadrant, which indicated that starting with EFV-based regimens yielded more DALY averted than NVP-based regimens. However, the difference of cost of treatment was dependent on baseline CD4 count. With low level of baseline CD4 (e.g. 50cell/mm3), introducing EFV-based as first line regimen had more costly than NVP-based. In contrast, with the higher level of baseline CD4 (e.g.100 to 250cell/mm3) introducing EFV-based as first line regimen had less costly than NVP-based regimens.

Figure 4.9 Cost effectiveness acceptability curve of disability-adjusted life year (DALY) averted of EFV-based regimens compared with NVP-based regimens classified by CD4 at baseline group.

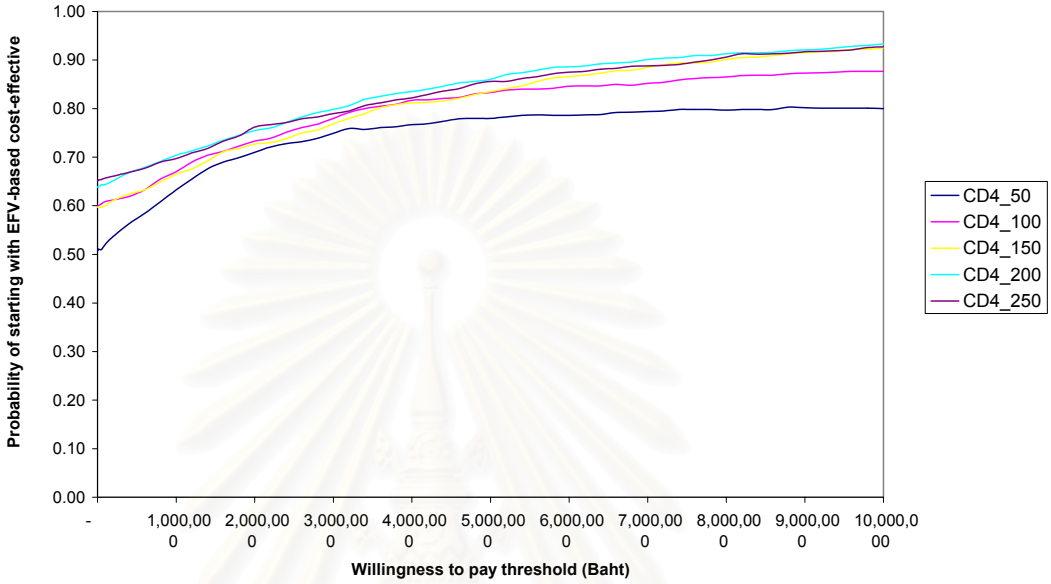


Figure 4.9 presented the cost effectiveness acceptability curve of DALY averted of EFV-based regimens compared with NVP-based regimens classified by baseline CD4 count.

By controlling 35 years of age at baseline treatment, the findings presented the same directions in all subgroups. At zero Baht of willingness to pay (WTP) or not extra budget available, it was more likely that starting with EFV-based regimens was a preferable choice in all sub groups by which considering the probability more than 0.5. The probability of EFV-based being cost effective was increased depending on the increase of WTP threshold. These findings pointed out that for the patients who were 35 years old at baseline treatment, starting with EFV-based regimens dominated NVP-based regimens in all baseline CD4 counts.

CHAPTER V

DISCUSSIONS

This chapter discussed about the study results, the methodology related issues, Compulsory Licensing (CL) of Efavirenz and economic evaluation, the limitations of conducting economic evaluation in Thailand, and the feasibility of using economic evaluation among decision-makings. The details of the discussions were in the following.

5.1 Discussions based on the study results

5.1.1 The incidence of serious adverse events and major opportunistic infections

The findings of the incidence of serious adverse events in the HIV/AIDS patients who started with NVP-based of this study were congruent with the conclusions made by Anekthananon and others [55] and Getahun and others [56]. The findings from these studies revealed that hepatotoxicity and skin rashes were the major adverse events caused by Nevirapine. Although, the results from the study of Ananworanich and others [57] revealed that there were no difference of the incidence of grade II and III skin reactions between those who used NVP-based and EFV-based regimens, no cases of serious skin reactions were found in the group of patients starting with EFV-based regimens in this study.

The higher incidence of major opportunistic infections such as Cryptococcus Meningitis, MAC, PCP, and also tuberculosis were found more in the group of HIV/AIDS patient who started with NVP-based regimens than EFV-based regimens. These complications might affect the quality of life of the patients as well as the effectiveness of treatment.

5.1.2 Cost-effectiveness and cost-utility results

To explore the impacts of age and CD4 baseline level on the treatment cost and effectiveness, two types of sub-group analysis were conducted including age-group analysis (by controlling baseline CD4 count at 200cell/mm3) and baseline CD4 count-group analysis (by controlling age at baseline treatment at 35 years-old).

5.1.2.1 Lifetime treatment cost

a) Sub-analysis of age-group

Using health care provider perspective, for those who started with EFV-based treatment the lifetime treatment cost decreased of depended on the increase of the age at baseline treatment. For those who started with NVP-based treatment, the lifetime treatment cost increased when the age at baseline treatment was between 20 to 40 years old. However, the lifetime treatment cost decreased when the age at baseline treatment was between 50 to 60 years old. Starting with EFV-based regimens offered less costly in all age group except for those who were 20 years old at baseline treatment.

Besides the cost of ARV drugs in each regimen, the survival rate and the switching rate are two factors that influence the lifetime treatment cost in those who started with NVP-based. In addition, the survival rate and the switching rate are associated with the age at baseline treatment. Initiation of the treatment at young age e.g. 20 to 40 years old, the switching rate acted as the major factor that made the lifetime cost of treatment increased. While, initiation of the treatment at the old age e.g. 50 to 60 years old, the survival rate acted as the major factor that make the lifetime cost of treatment decreased.

For those who started with EFV-based, only the survival rate was the major factor that affected to the decrease of lifetime treatment cost.

b) Sub-group analysis of CD4 baseline

Using health care provider perspective, the increase of the life-time treatment costs of EFV-based regimens and NVP-based regimens were dependent on the increase of baseline CD4 level. In addition, providing EFV-based regimens as the first-line regimen offered cheaper treatment cost than NVP-based in every level of CD4 baseline.

5.1.2.2 Life-year (LY) gained and Disability-adjusted life year (DALY) averted

a) Age-group analysis

The NVP-based first-line regimens had slightly higher LY gain than EFV-based regimens in all age groups except 20 years. Introducing EFV-based regimens as the first-line treatment offered more DALY averted in all age groups than NVP-based regimens. The decrease of life-year(LY) gained and disability adjusted life-year (DALY) averted was dependent on the increase of age at baseline treatment.

The changes of LY gained and DALY averted needs to be explored. Although, the NVP-based first-line regimens offered slightly higher LY gained compared to EFV-based regimens, the higher incidences of serious adverse events and major opportunistic infections in NVP-based group increased the disability, while they decreased the DALY averted of the patients. Therefore starting with EFV-based regimens offered more DALY averted than NVP-based regimens in all subgroups.

b) Sub-group analysis of CD4 baseline

The patients starting with EFV-based offered more life-year gained among the patients who initiated the regimen at low CD4 count baseline i.e. 50 to 100cell/mm3. The patients starting with EFV-based regimens at higher baseline CD4 count offered slightly less LY gained compared to NVP-based regimens. Starting with EFV-based offered more DALY averted in all CD4 baseline level compared to NVP-based regimens.

5.1.2.3 Cost-Effectiveness

a) Sub-analysis of age-group

Comparing between EFV-based and NVP-based, the incremental costs per life-year gained were dependent on age at baseline treatment. The findings showed that the EFV-based first line treatment offered more costly and more life-year gained in the group of patient aged 20 years old, but less costly and less life-year gained in the group of patients aged 30 to 60 years old.

In terms of baht per DALY averted, in patient age group 20 years old, providing the EFV-based regimen as first line treatment offered more costly and more DALY averted. EFV-based regimen dominated NVP-based regimen, or in other words EFV-based regimen offered less costly and gain more DALY averted then NVP-based regimen in the group of patients aged 30 to 60 years old.

b) Sub-group analysis of CD4 baseline

In patients with 50 to 100cell/mm3 CD4 at baseline, providing the EFV-based regimen as first line treatment dominated NVP-based (offered less costly and gained more life-year). In contrast, in patients with 150 to 250cell/mm3 CD4 at baseline, providing the EFV-based regimen as first line treatment offered less costly and less life-year gained. The Incremental cost of providing the EFV-based regimen as first line treatment ranged from 11,562,692 baht per life-year gained in patient with baseline CD4 count at 200 cell/mm3 to 208,579,000 baht per life-year gained in patient with baseline CD4 count at 150 cell/mm3

Nevertheless, in terms of cost per DALY averted, providing the EFV-based regimen as first line treatment dominated NVP-based in all CD4 baseline groups.

5.1.2.4 Uncertainty Analysis

a) Sub-analysis of age-group

(a) Uncertainty of cost per life-year gained

The findings from CE planes and AC curves in terms of cost per LY gained pointed out that the age of HIV/AIDS patients at baseline treatment was a major factor that significantly affected the treatment cost as well as life-year gained. In the young patients (e.g. 20 years old), at zero willingness to pay (WTP) threshold or no extra budget available, starting with NVP-based was the preferable choice. However, starting with EFV-based was preferred when the WTP was above 3,000,000 Baht/LY gained.

In middle- to old age-group (e.g. 30 to 60 years-old), at no extra budget available, starting with EFV-based was the preferable choice. However, the probability of preferable of starting with EFV-based decreased when the WTP threshold increased.

These explanations were based on the results from CE planes. In younger patients, starting with EFV-based regimens seemed to be more costly and gained more life-year compared to NVP-based regimens. Increasing of the willingness to pay thresholds (WTP) for a unit of life-year (LY) gained raised the probability of EFV-based regimens to be more cost effective. On the other hand, starting with EFV-based regimens in older group seemed to less costly and less life-year gained. Increasing the willingness to pay thresholds (WTP) for a unit of life-year (LY) gained decreased the probability of EFV-based regimen to be more cost effective. However, the declines of curves in these age groups were not much enough to support the preferable option to use NVP-based regimens. The probability of EFV-based to be cost-effective was still higher than 0.5.

(b) Uncertainty of cost per DALY averted

The findings from CE planes and AC curves in cost per DALY averted pointed out that those HIV/AIDS patients with 200cell/mm3 of CD4 baseline, starting with EFV-based regimens was the preferable choice in all age groups. In age group 20 years, starting with NVP-based was cost effective at no extra budget available but starting with EFV-based was preferable when the WTP was above 1,000,000 Baht/LY gained. Given a maximum acceptable willingness to pay threshold of 270,000 Baht/DALY which is about 3 times of the Thai GDP, starting with EFV-based was cost effective in all aged group except those who were 20 years old.

a) Sub-group analysis of CD4 baseline

(a) Uncertainty of cost per life-year gained

The findings from CE planes and AC curves regarding cost per LY gained showed that for the patients who were 35 years old starting with EFV-based at baseline treatment, this EFV-based option was more cost effective in all baselines CD4 count. The results showed that more than 50% of the probability indicated that starting with EFV-based was cost-effective.

(b) Uncertainty of cost per DALY averted

Similarly, for the cost utility AC curves (per DALY averted), starting with EFV-based was the preferable choice in every level of CD4 baselines. The increase of the probability of EFV-based to be cost effective occurred when there was higher WTP.

In conclusion, age of HIV/AIDS patients at baseline treatment was the major factor that significantly affected the treatment cost as well as effectiveness, including LY gained and DALY averted.

5.1.3 Accessibility of ARV treatment in real practice

The findings from this study revealed that more than half (64%) of HIV/AIDS patients in this study had baseline CD4 count less than 100 cell/mm3. Although the criterion for starting the treatment was a patient must have CD4 count less than 200 cell/mm3, in reality patients could not access the ARV treatment at this CD4 level. The findings from this study showed that the level of baseline CD4 to initiate the treatment had an impact on LY gained as well as DALY averted of the patients in positive direction. The problems of accessibility ARV treatment at CD4 level lower than 200cell/mm3 needed to be improved by the decision makers.

5.2 Methodology related issues

5.2.1 The Flexibility of Markov Modeling

In general, Markov structures usually were constructed based on the progression of illness. Intermediate health outcomes or clinical symptoms were used to define the health states. The HIV/AIDS Markov model was usually constructed based on the progression of CD4 count which was the surrogate outcome. However, the CD4 count may not reflects the change of outcome based on the adverse drug reaction and may not indicate the change of the cost based on the switching of regimens. In this study, the structure of Markov model was constructed based on the change of ARV therapy from our cohort data. The model was constructed based on the switching of ARV regimens through the four states including, starting with the naïve to treatment state (1^{st} regimens), switching to 2^{nd} regimens, switching to 3^{rd} regimens and death. This approach can capture the change of cost and outcome from each health state based on the switching of ARV regimen. The methodological advantage of Markov analysis, particularly, in capturing the value from the transitional state based on the health outcomes and costs reflects the flexibility of the model construction.

5.2.2 Data source in the model

Ideally, the economic evaluation should be based on unbiased estimates of the difference in clinical effectiveness between the two therapies. Data from systematic reviews and Clinical trials are likely to be the best sources. However, they have constraints in terms of the length of follow-up and the differences of consequences of the therapy among difference settings [58]. In addition, several factors may differ between the trial and actual practice such as compliance of the patients.

In Thailand, Only one trial, the 2NN study, compared safety and efficacy between EFV-based and NVP-based regimens. Using cost-effectiveness data from other settings to perform the economic evaluation may have several limitations including the variety in efficacy, safety, and cost data. In our study, the retrospective data of four regional hospitals were used in economic evaluation.

Although, the bias due to employing the observational data might occur, we minimized this bias by including the covariates such as age, baseline CD4, and other factors associated with survival and switching rate in Weibull survival models.

5.2.3 Input parameters

All input parameters were obtained from cohort study. However, there was limitation regarding the availability of data used in the model. Due to the period of 3 years follow-up, no one died in the group of the patients starting with EFV-based. Hence, the survival rate of this alternative might be bias. From a Cochrane systematic review [47], the finding from a randomize control trial (2NN study) [14] revealed that NVP-based had a higher death rate compared with EFV-based (RR [95%CI] =1.33 [0.50, 3.53]). Therefore, it was assumed in this analysis that the HIV/AIDS patients who started the ART with NVP-based had 1.33 times (SE 0.49) higher death rate in the period of using the first regimen compared with HIV/AIDS patients who started with EFV-based regimens.

Due to the lack of disability weight (DW) data of some serious adverse events such as SJS and TEN, and major opportunistic infections such as MAC, PCP, and also CMVR, the disability weight of these complications were justified. In our study, the expert opinion was used to identify the severity of these complications.

5.2.4 Sensitivity analysis

Probabilistic sensitivity analysis (PSA) was applied in this study in order to recognize the uncertainties from the selected parameters and observational data. The probabilistic sensitivity analysis (PSA) is increasingly demanded by health care regulators and reimbursement agencies when assessing the cost-effectiveness of technologies based on economics modeling [59]. This guidance requires that all estimates of input parameters in a model must be specified as full probability distribution, rather than point estimates, to represent the uncertainty surrounding their value [60]. The usual way to disseminate the uncertainty is the Monte Carlo method, whereby random values of the model input parameters are simulated and the model is run for each simulated parameter set. The resulting sample of the outputs characterizes the output uncertainty. To obtain accurate PSA we typically need 1000 or more rounds to run the model [61].

5.3 Compulsory Licensing (CL) of Efavirenz and Economic Evaluation

In November 2006, Thailand's Ministry of Public Health issued the compulsory licensing (CL) for Efavirenz [62]. The CL took effect immediately after the announcement and will last until December 31, 2011. It permits the Thai Government Pharmaceutical organization (GPO) to import generic version of Efavirenz from other countries or produce the drug itself, although Merck still has patent on Efavirenz in Thailand. The CL substantially reduced the cost of EFV. While the cost of patented Efavirenz is about 2,300 baht per month (1 bottle contained 30 tablets once daily), the cost of generic drug from India is only 700 baht per month. To analyze the impact on the cost reduction of EFV, threshold analysis was conducted using 700 baht per month of EFV instead of 2,300 baht into our probabilistic decision model. Sub-group analyses of age at baseline treatment and CD4 baseline were conducted. The findings from threshold analysis indicated that in case of the reduction of EFV cost, the probability of EFV-based was cost-effective in all age groups and all CD4 baseline levels (see figure 5.1 to 5.4). In terms of incremental cost per LY gained and also the incremental cost per DALY averted, starting with EFV-based regimens were the preferable choices in all age-group and all CD4 baseline levels.

Figure 5.1 Cost effectiveness acceptability curve of LY gained of EFV-based regimens compared with NVP-based regimens classified by age group.

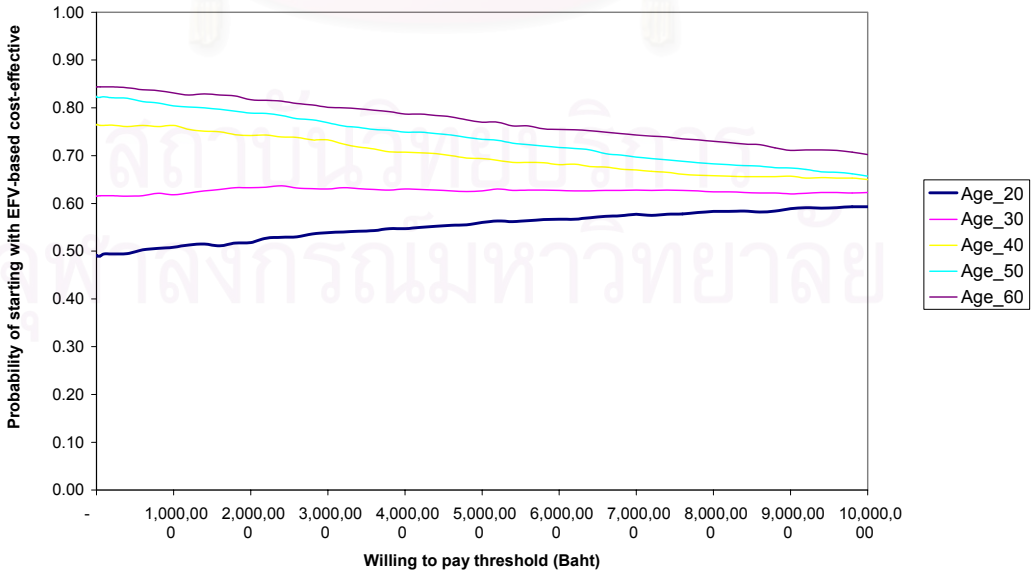


Figure 5.2 Cost effectiveness acceptability curve of LY gained of EFV-based regimens compared with NVP-based regimens classified by CD4 at baseline group.

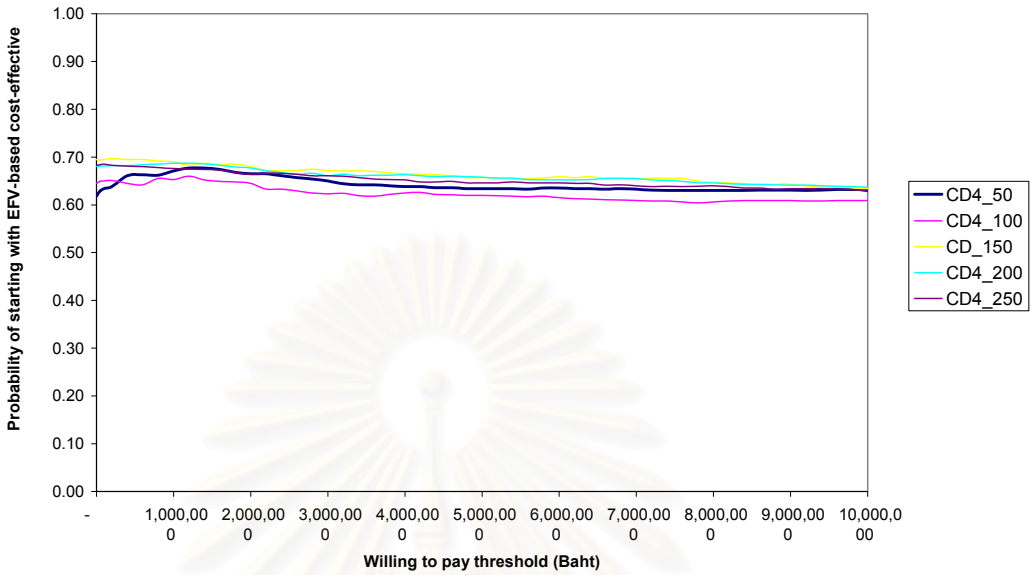


Figure 5.3 Cost effectiveness acceptability curve of DALY averted of EFV-based regimens compared with NVP-based regimens classified by age group.

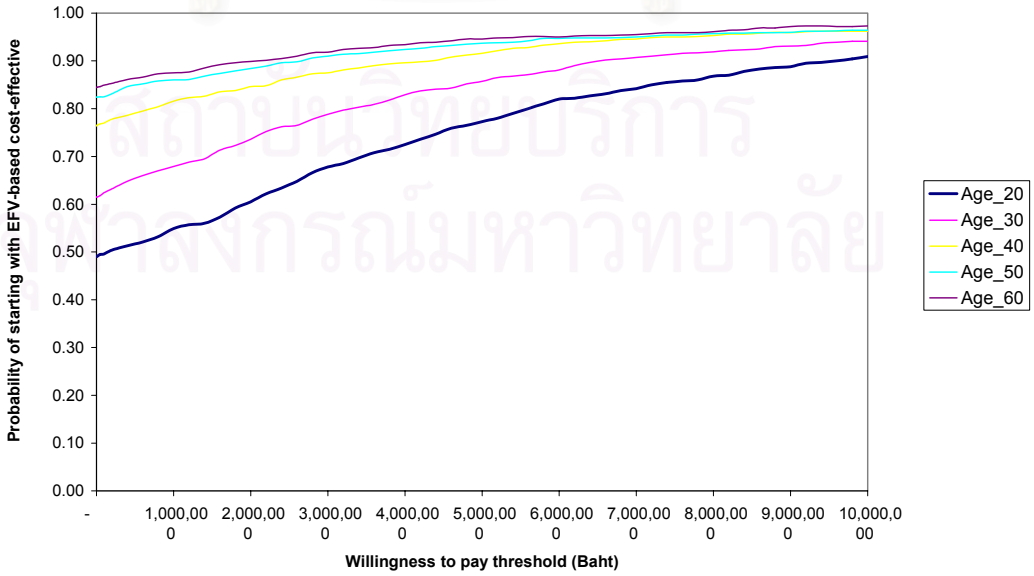
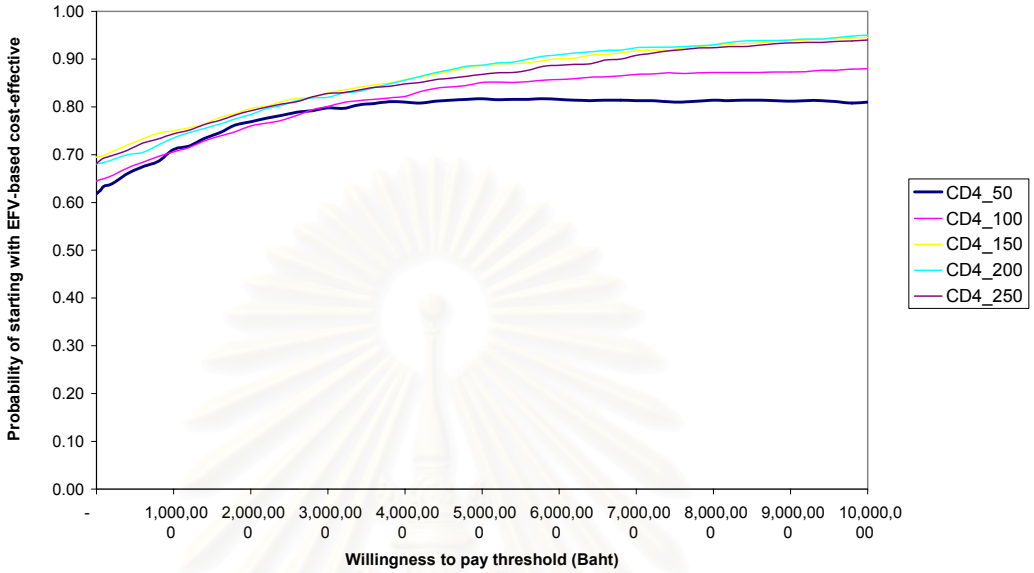


Figure 5.4 Cost effectiveness acceptability curve of DALY averted of EFV-based regimens compared with NVP-based regimens classified by CD4 at baseline group.



Based on the findings from this study, the lower incidence of serious adverse events and major opportunistic infections yielded more DALY averted of EFV-based regimen compared to NVP-based regimen. This made EFV-based regimen more preferable than NVP-based regimen. Presently, due to the decrease of the cost of EFV from 2,300 baht to 700 baht per month, it is clear that the government policy decision should be made in favor of EFV-based to be the first line regimen for Thai HIV/AIDS patients.

5.4 The limitations of conducting economic evaluation in Thailand

In general, the limitations of conducting the economic evaluation included:

1) Lack of standard guidelines for conducting health economic evaluation

2) Availability of cost and outcome data

3) Lack of complete single source of information

In Thailand, well established economic evaluation guideline has not yet proposed to be used. Several studies reported the differences of methodology issues and the quality of economic evaluation [63]. However, at the current situation in Thailand, a group of academics and health economists is preparing to develop a national methodological guideline for conducting health economic evaluation. This guideline is

expected to ensure standards that enable the comparisons of value for money across health care interventions for inclusion into the health care benefit package [64].

Currently, there are limited numbers of clinical studies in Thailand. Most of the effectiveness results in Thailand were collected from observational study. These studies usually measure the intermediate outcome rather than the terminal outcome. In terms of cost data, few unit cost analyses were conducted. It is difficult to calculate the overall cost of treatment.

Lacking of complete single source of information usually found in Thai situation. To conduct an economic evaluation in Thailand, the researchers usually used multiple sources of information which would lead to the bias from inconsistency.

The lack of availability of cost and outcome data is a major problem for constructing an economic evaluation for ARV treatment in Thailand. Currently, only one trial, the 2NN study, comparing the safety and efficacy between EFV and NVP was conducted in Thailand. In addition, due to a period of short time follow-up, the terminal outcome or death could not be captured. Using cost and outcome data from other settings to perform the economic evaluation may have several limitations including the variation of efficacy, safety, and cost data. Based on the limitations mentioned above, therefore we collected the data from real practice. The data were collected from medical records from four regional hospitals which were used as the source of cost and outcome data in our study. The longer follow up time of 3 years in our study yield the advantages in outcome beyond short time clinical trials.

Although, we tried to solve the problem of limited data by conducting our own cohort study, there are two weaknesses in our study. First, the biases from cohort data need to be considered. To minimize these biases, the covariates including age, baseline CD4, and other factors that were associated with survival and switching rate were adjusted in Weibull survival models.

The second weakness is the variation of cost of treatment among the hospitals. To adjust the variation of cost in this study, the reference cost of ARV drugs from Bureau of AIDS, Tuberculosis and Sexually Transmitted Infection, MOPH and GPO [51, 52] were used.

5.5 Feasibility of using economic evaluation among decision-makings

At present, the concept of health economic evaluation is relatively clear and widely accepted in academic worldwide. In several countries, economic evaluation has

been formally adopted for health care decision-making [65, 66]. However, several barriers could affect the feasibility of the use of economic evaluation in health resource allocation. Particularly among Thai health policy decision-making, the findings from Teerawattananon revealed that several barriers could restrict the use of economic evaluation [63]. These factors included:

1) A lack of appropriate economic evaluation information for policy decision makers

2) Inadequate knowledge and understanding about economic evaluation among the potential users

3) A lack of support by stakeholders due to its limitation in capturing all relevant interests for making decisions to coverage health care technology in the benefit package.

In addition, there are other factors beyond economic evaluation results which influence resource allocation in health care [67]. These factors were the availability of health care resources, the availability of relevant information and expert advice, the equity considerations, the climate of opinions in society, the pressure of non-government groups and patient network, and also the policy of the government.

Although the finding from this study revealed that starting with EFV-based was a preferable choice for Thai HIV/AIDS patients, several obstacles in policy decision-making process in Thailand including the understanding of economic evaluation, the equity dimension, and the concern of decision maker on lifetime cost that need to be considered.

The understanding of economic evaluation result and its application is the major constraint that limits the use of CE result among policy decision makers.

In the context of the Universal coverage (UC) in Thailand, an explicit objective of the UC policy is to increase equity of coverage and to reduce catastrophic spending. The DALY maximization concept is not only the goal in health care resource allocation.

Although the life-year (LY) gained and the Disability-adjusted life-year (DALY) averted are the accepted outcomes to compare the two alternative choices. The lifetime cost of treatment is not widely accepted among health policy decision-makers. In this study, within a short period after initial treatment, starting with NVP-based had cost less than EFV-based, but NVP-based had more cost in lifetime treatment. The scarcity of budget will lead the policy makers to select the alternative treatment that yields less

cost within a short period. Therefore, the short-term cost may enhance the use of NVP-based as the preferable choice.

CHAPTER VI

CONCLUSIONS AND RECOMMENDATIONS

This chapter provided the conclusions, policy recommendation and recommendation for further of study. The details of the conclusions and recommendations were in the following.

CONCLUSIONS

1. The incidences of adverse events and major opportunistic infection

The findings from this study indicated that HIV/AIDS patients who started with NVP-based had higher incidence of adverse events compared to those who started with EFV-based regimens, particularly the serious and life-threatening adverse event such as Steven Johnson Syndrome (SJS), Toxic Epidermal Necrosis (TEN), hepatitis and cirrhosis. These serious adverse events were the factors that have impacts to the disability of the HIV/AIDS patients. They also increased the DALY lost for those patients as well as the cost of treatment. However, the incidences of long term adverse event such as the elevator of tri-glyceride (TG) and hyper cholesterol incidences increased in those who started with EFV-based compared to those who started with NVP-based regimens.

Furthermore, the incidence of major opportunistic infections of HIV/AIDS patients who started with NVP-based regimens was higher than those who started with EFV-based regimens. These major complications such as Cryptococcus Meningitis, Toxoplasmosis, MAC, PCP, and Tuberculosis could increase the DALY lost for those patients as well as the cost of treatment.

2. The uncertainty of cost-effectiveness and cost-utility results

2.1 Uncertainty of cost per life-year gained

For the patients who had CD4 level at 200cell/mm3, the findings of this study revealed that in the young patients (e.g. 20 years-old), at zero willingness to pay (WTP) threshold or no extra budget available, starting with NVP-based was the preferable choice. However, starting with EFV-based was preferred when the WTP was above 3,000,000 Baht/LY gained. While, in middle- to old age-group (e.g. 30 to 60 years-old), at no extra budget available, starting with EFV-based was the preferable choice.

However, the probability of preferable of starting with EFV-based decreased when the WTP threshold increased.

For the patients who were 35 years old, the findings revealed that EFV-based option was more cost-effective in all baselines CD4 counts. The results showed that more than 50% of the probability indicated that starting with EFV-based was cost-effective.

2.2 Uncertainty of cost per DALY averted

The findings from CE planes and AC curves in cost per DALY averted pointed out that those HIV/AIDS patients with 200cell/mm3 of CD4 baseline, starting with EFV-based regimens was the preferable choice in all age groups. In age group 20 years, starting with NVP-based was cost effective at no extra budget available but starting with EFV-based was preferable when the WTP was above 1,000,000 Baht/LY gained. Given a maximum acceptable willingness to pay threshold of 270,000 Baht/DALY which is about 3 times of the Thai GDP, starting with EFV-based is cost effective in all aged group except those who were 20 years old.

Starting with EFV-based was the preferable choice in every level of CD4 baselines. The increase of the probability of EFV-based to be cost effective occurred when there was higher WTP.

In conclusion, age of HIV/AIDS patients at baseline treatment was the major factor that significantly affected the treatment cost as well as effectiveness, including LY gained and DALY averted.

POLICY RECOMMENDATIONS

1. Improving the accessibility of ARV treatment at high level of CD4 baseline

Although the criterion for starting the treatment was that a patient must have CD4 count less than 200 cell/mm3, in reality patients could not access the ARV treatment at this CD4 level. The findings from this study showed that the level of baseline CD4 to initiate the treatment had an impact on life-year gained as well as DALY averted of the patients in positive direction. The problems of accessibility ARV treatment at CD4 level lower than 200cell/mm3 needs to be improved at the policy level by the decision makers.

2. Improving the use of economic evaluation in policy making

Although, the finding from economic evaluation revealed that starting with EFV-based is preferable choice, in reality, there are several limitations of using economic data in the process of policy decision-making. To maximize the utilization of economic evaluation results in the health care policy decision-making, Drummond [67] mentioned several strategies included:

1) maintaining methodological standards
2) producing economic evidence in a timely fashion
3) increasing the local validity of study results
4) increasing the decision-maker involvement in the study
5) improving the dissemination of study results
6) taking note of the availability of policy instruments
7) recognizing the conflicts and incentives surrounding the study

Focusing to Thai context, there are several more specific points that need to be concerned.

Developing the national methodological guideline for conducting health economic evaluation is an important strategy to improve the quality of information and enhance the acceptability of health policy decision makers.

The misunderstanding of the concept of economic evaluation and its' applications is another problems need to be solved. Teerawattananon [63] found that majority of the Thai policy makers misunderstood the concept and the application of economic evaluation. Consequently, it is necessary for decision makers to clearly understand about the method of economic evaluation. The understanding would lead the confidence in using the economic evaluation evidence.

In the context of the Universal coverage (UC) in Thailand, an explicit objective of the UC policy was to increase equity of coverage and to reduce catastrophic spending. The DALY maximization concept is not only the goal in health care resource allocation. Economic evaluation should be used with equity, necessity, social solidarity, and economic security criteria to enhance political and public acceptance of health care benefit package.

RECOMMENDATIONS FOR FURTHER STUDY

1. Most of the studies available in Thailand had a short period of follow up. Using the data would lead the under estimation of costs and effects of the interventions. To conduct an economic evaluation, the time horizon should be long enough to capture the full costs and effects of the interventions. Based on the WHO recommendation [68], CEA should evaluate all interventions over a period of 10 years at full implementation. The well established longitudinal study will increase the accuracy of the effects of the interventions.

2. The economic evaluation using health care provider perspective is widely used in health policy decision-making. Based on this perspective, only health care provider costs were used in the analysis. However, there are others costs such as costs paid by the patients that should not be neglected. The economic evaluation using the societal perspective should be conducted to cover all aspects of treatment costs.

3. The Disability-adjusted life year (DALY) is primarily a measure of disease burden (disability weights measure loss of functioning). Another cost-utility evaluation mostly used in economic evaluation is the quality-adjusted life year (QALY). The QALY emphasized on the quality of life of the patients in various health states. HIV/AIDS can increase the disability of the patients and decrease the quality of life of the patients. Therefore, the QALY economic evaluation of Thai HIV/AIDS patients should be conducted to support the DALY results.

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APPENDICES

APPENDIX I: Disability Weights for Diseases and Conditions (Except Cancers and Injuries)

Sequela	Average disability weight [a]	Range [b]	Source
Tuberculosis—cases	0.271	0.264-0.294	GBD 1990 [c] , varies with age
Syphilis			
Congenital syphilis	0.315		GBD 1990
Primary	0.015	0.014-0.015	GBD 1990 [c] , varies with age
Secondary	0.048	0.044-0.048	GBD 1990 [c] , varies with age
Tertiary—neurologic	0.283		GBD 1990
Chlamydia			
Cervicitis	0.049		GBD 1990
Neonatal pneumonia	0.280		GBD 1990
Ophthalmia neonatorum	0.180		GBD 1990
Pelvic inflammatory disease	0.327	0.194-0.382	GBD 1990 [c] : untreated 0.420, treated 0.169
Ectopic pregnancy	0.549		GBD 1990
Tubo-ovarian abscess	0.548		GBD 1990
Chronic pelvic pain	0.122		GBD 1990
Infertility	0.180		GBD 1990
Symptomatic urethritis	0.067		GBD 1990
Epididymitis	0.167		GBD 1990
Gonorrhea			
Cervicitis	0.049		GBD 1990
Corneal scar—blindness	0.600		GBD 1990
Ophthalmia neonatorum	0.180		GBD 1990
Pelvic inflammatory disease	0.169		GBD 1990
Ectopic pregnancy	0.549		GBD 1990
Tubo-ovarian abscess	0.548		GBD 1990
Chronic pelvic pain	0.122		GBD 1990
Infertility	0.180		GBD 1990
Symptomatic urethritis	0.067		GBD 1990
Epididymitis	0.167		GBD 1990
Corneal scar—low vision	0.233	0.233-0.245	GBD 1990 [c] , varies with age
Stricture	0.151		GBD 1990
HIV/AIDS			
HIV cases	0.135	0.123-0.136	GBD 1990 [c,] varies with age

Sequela	Average disability weight [a]	Range [b]	Source
AIDS cases	0.505		GBD 1990
Diarrheal diseases—episodes	0.105	0.086-0.119	GBD 1990 [c], varies with age
Pertussis			
Episodes	0.129	0.016-0.160	GBD 1990
Encephalopathy	0.450	0.402-0.484	GBD 1990 [c], varies with age and treatment
Poliomyelitis—cases—lameness	0.369		GBD 1990
Diphtheria			
Episodes	0.231		GBD 1990
Neurological complications	0.078		GBD 1990
Myocarditis	0.323		GBD 1990
Measles—episodes	0.152		GBD 1990
Tetanus—episodes	0.633	0.604-0.640	GBD 1990 [c], varies with age
Meningitis			
Streptococcus pneumoniae—episodes	0.615	0.613-0.616	GBD 1990 [c], varies with age
Haemophilus influenzae—episodes	0.616	0.613-0.616	GBD 1990 [c], varies with age
Neisseria meningitidis—episodes	0.615	0.613-0.616	GBD 1990 [c], varies with age
Meningococcaemia without meningitis—episodes	0.152		GBD 1990
Deafness	0.229	0.213-0.233	GBD 1990 [c], varies with age and treatment
Mental retardation	0.456	0.402-0.484	GBD 1990 [c], varies with age and treatment
Motor deficit	0.380	0.339-0.460	GBD 1990 [c], varies with age and treatment
Seizure disorder	0.097	0.046-0.142	GBD 1990 [c], varies with age and treatment
Hepatitis B—episodes	0.211	0.170-0.212	GBD 1990 [c], varies with age
Hepatitis C—episodes	0.211	0.170-0.212	GBD 1990 [c], varies with age
Malaria			
Episodes	0.191	0.172-0.211	GBD 1990 [c], varies with age and treatment
Neurological sequelae	0.471	0.443-0.471	GBD 1990 [c], varies with age and treatment

Sequela	Average disability weight [a]	Range [b]	Source
Anemia	0.012	0.012-0.013	GBD 1990 [c] , varies with age
Trypanosomiasis—episodes	0.350		GBD 1990
Chagas' disease			
Infection	0.000		GBD 1990
Cardiomyopathy without congestive heart failure	0.062		GBD 1990
Cardiomyopathy with congestive heart failure	0.270	0.186-0.308	GBD 1990 [c] : untreated 0.323, treated 0.171
Megaviscera	0.240		GBD 1990
Schistosomiasis—infection	0.006	0.005-0.006	GBD 1990 [c] , varies with age
Leishmaniasis			
Visceral	0.243		GBD 1990
Cutaneous	0.023		GBD 1990
Lymphatic filariasis			
Hydrocele > 15 cm	0.073	0.066-0.075	GBD 1990 [c] , varies with age
Bancroftian lymphedema	0.106	0.067-0.128	GBD 1990 [c] , varies with age
Brugian lymphedema	0.116	0.064-0.128	GBD 1990 [c] , varies with age
Onchocerciasis			
Blindness	0.600		GBD 1990
Itching	0.068		GBD 1990
Low vision	0.260		GBD 1990 [d]
Leprosy			
Cases	0.000		GBD 1990
Disabling leprosy	0.152		GBD 1990
Dengue—dengue hemorrhagic fever	0.210	0.195-0.211	GBD 1990 [c] , varies with age
Japanese encephalitis			
Episodes	0.616	0.613-0.616	GBD 1990 [c] , varies with age
Cognitive impairment	0.468	0.402-0.484	GBD 1990 [c] , varies with age and treatment
Neurological sequelae	0.380	0.339-0.460	GBD 1990 [c] , varies with age and treatment
Trachoma			
Blindness	0.600		GBD 1990
Low vision	0.278	0.227-0.282	GBD 1990 [d] : untreated 0.282, treated 0.227

Sequela	Average disability weight [a]	Range [b]	Source
Ascariasis			
High-intensity infection	0.000		GBD 1990
Contemporaneous cognitive deficit	0.006		GBD 1990
Cognitive impairment	0.463		GBD 1990
Intestinal obstruction	0.024		GBD 1990
Trichuriasis			
High-intensity infection	0.000		GBD 1990
Contemporaneous cognitive deficit	0.006		GBD 1990
Massive dysentery syndrome	0.116	0.114-0.138	GBD 1990 [c], varies with age
Cognitive impairment	0.024		GBD 1990
Hookworm disease (ancylostomiasis and necatoriasis)			
High-intensity infection	0.000		GBD 1990
Anemia	0.024		GBD 1990
Cognitive impairment	0.024		GBD 1990
Lower respiratory infections			
Episodes	0.279		GBD 1990
Chronic sequelae	0.099		GBD 1990
Upper respiratory infections			
Episodes	0.000		GBD 1990
Pharyngitis	0.070		GBD 1990
Otitis media			
Episodes	0.023		GBD 1990
Deafness	0.229	0.213-0.233	GBD 1990 [c], varies with age and treatment
Maternal hemorrhage			
Episodes	0.000		GBD 1990
Severe anemia	0.093	0.087-0.093	GBD 1990 [c], varies with age
Maternal sepsis			
Episodes	0.000		GBD 1990
Infertility	0.180		GBD 1990
Hypertensive disorders of pregnancy—episodes	0.000		GBD 1990
Obstructed labor			
Episodes	0.000		GBD 1990

Sequela	Average disability weight [a]	Range [b]	Source
Cesarean section for obstructed labor	0.349		GBD 1990
Stress incontinence	0.025		GBD 1990
Rectovaginal fistula	0.430		GBD 1990
Abortion			
Episodes	0.000		GBD 1990
Infertility	0.180		GBD 1990
Reproductive tract infection	0.067		GBD 1990
Other maternal conditions			
Stress incontinence	0.025		GBD 1990
Low birthweight—all sequelae	0.106		GBD 1990
Birth asphyxia and birth trauma— all sequelae	0.372	0.343-0.379	GBD 1990 [c] : untreated 0.381, treated 0.334
Protein-energy malnutrition			
Wasting	0.053		GBD 1990
Stunting	0.002		GBD 1990
Developmental disability	0.024		GBD 1990
Iodine deficiency			
Goiter grades 1 and 2	0.000		GBD 1990
Mild developmental disability	0.006		GBD 1990
Cretinoidism	0.255		GBD 1990
Cretinism	0.804		GBD 1990
Vitamin A deficiency			
Xerophthalmia	0.000		GBD 1990
Corneal scar	0.276	0.274-0.282	GBD 1990 [c] , varies with age
Iron-deficiency anemia			
Mild	0.000		GBD 1990
Moderate	0.011	0.011-0.012	GBD 1990 [c] , varies with age
Severe	0.090	0.087-0.093	GBD 1990 [c] , varies with age
Cognitive impairment	0.024		GBD 1990
Diabetes mellitus			
Cases	0.015	0.012-0.018	GBD 1990 [c] : untreated 0.012, treated 0.033
Diabetic foot	0.133	0.130-0.136	GBD 1990 [c] : untreated 0.137, treated 0.129

Sequela	Average disability weight [a]	Range [b]	Source
Neuropathy	0.072	0.066-0.076	GBD 1990 [c] : untreated 0.078, treated 0.064
Retinopathy—blindness	0.550	0.511-0.595	GBD 1990 [c] : untreated 0.600, treated 0.493
Amputation	0.102	0.086-0.151	GBD 1990 [c] : untreated 0.155, treated 0.068
Unipolar depressive disorders			
Mild episode	0.140		Netherlands study [e]
Moderate episode	0.350		Netherlands study [e]
Severe episode	0.760		Netherlands study [e]
Dysthymia	0.140		Netherlands study [e]
Bipolar affective disorder—cases	0.367	0.309-0.387	Untreated 0.400, treated 0.140
Schizophrenia—cases	0.528	0.406-0.572	GBD 1990 [c] , varies with age and treatment
Epilepsy—cases	0.113	0.052-0.142	GBD 1990 [c] , varies with age and treatment
Alcohol use disorders—cases	0.155		[d]
Alzheimer's disease and other dementias—cases	0.666	0.627-0.667	GBD 1990 [c] , varies with age
Parkinson's disease—cases	0.351	0.324-0.395	GBD 1990 [c] , varies with age and treatment
Multiple sclerosis—cases	0.411	0.410-0.437	GBD 1990 [c] , varies with age
Drug use disorders—cases	0.252		GBD 1990
Post-traumatic stress disorder—cases	0.105		GBD 1990
Obsessive-compulsive disorder—cases	0.127	0.122-0.129	GBD 1990 [c] : untreated 0.129, treated 0.080
Panic disorder—cases	0.165	0.153-0.171	GBD 1990 [c] : untreated 0.173, treated 0.091
Insomnia (primary)—cases	0.100		[f]
Migraine—cases	0.029	0.025-0.030	[f]
Mild mental retardation, lead-caused—cases	0.361		Netherlands study [e]
Glaucoma			
Low vision	0.247	0.227-0.282	GBD 1990 [d] : untreated 0.282, treated 0.227

Sequela	Average disability weight [a]	Range [b]	Source
Blindness	0.600		GBD 1990
Cataracts			
Low vision	0.271	0.234-0.280	GBD 1990 [d] : untreated 0.282, treated 0.227
Blindness	0.568	0.511-0.595	GBD 1990 [c] : untreated 0.600, treated 0.488
Vision disorders, age-related and other			
Low vision	0.263	0.227-0.282	GBD 1990 [d] : untreated 0.282, treated 0.227
Blindness	0.600		GBD 1990
Hearing loss, adult onset			
Mild	0.000		Assumed to have no disability for GBD
Moderate, treated	0.040		Assumed similar to mild hearing loss [f]
Moderate, untreated	0.120		Netherlands study [e]
Severe or profound, treated	0.120		Assumed similar to moderate loss [f]
Severe or profound, untreated	0.333		GBD 1990 deafness weight [c]
Rheumatic heart disease—cases	0.253	0.186-0.300	GBD 1990 [c] : untreated 0.323, treated 0.171
Hypertensive heart disease—cases	0.243	0.201-0.300	[f] : untreated 0.323, treated 0.171
Ischemic heart disease			
Acute myocardial infarction	0.437	0.405-0.477	GBD 1990 [c] : untreated 0.491, treated 0.395
Angina pectoris	0.137	0.108-0.207	GBD 1990 [c] : untreated 0.227, treated 0.095
Congestive heart failure	0.234	0.186-0.300	GBD 1990 [c] : untreated 0.323, treated 0.171
Cerebrovascular disease			
First-ever stroke cases	0.920		[f]
Long-term stroke survivors	0.270	0.228-0.295	[d] , varies with age and treatment
Inflammatory heart disease—all	0.252	0.201-0.300	GBD 1990 [c] : untreated 0.323,

Sequela	Average disability weight [a]	Range [b]	Source
sequelae			treated 0.171
Chronic obstructive pulmonary disease			
Mild and moderate symptomatic cases	0.170		Netherlands study [e]
Severe symptomatic cases	0.530		Netherlands study [e]
Asthma—cases	0.043	0.036-0.050	[f] : untreated 0.054, treated 0.043
Peptic ulcer disease			[f]
Cases with antibiotic treatment	0.003		GBD 1990
Cases not treated with antibiotic	0.115		GBD 1990
Cirrhosis of the liver—symptomatic cases	0.330		GBD 1990
Appendicitis—episodes	0.463		GBD 1990
Nephritis and nephrosis			
Acute glomerulonephritis	0.091	0.082-0.104	GBD 1990 [c] , varies with age and treatment
End-stage renal disease	0.098	0.087-0.107	GBD 1990 [c] , varies with age and treatment
Benign prostatic hypertrophy—symptomatic cases	0.038		GBD 1990
Skin diseases—cases	0.056		[f]
Rheumatoid arthritis—cases	0.199	0.185-0.221	GBD 1990 [c] : untreated 0.233, treated 0.174
Osteoarthritis			
Hip	0.126	0.118-0.147	GBD 1990 [c] : untreated 0.156, treated 0.108
Knee	0.129	0.118-0.147	GBD 1990 [c] : untreated 0.156, treated 0.108
Gout—cases	0.132	0.061-0.189	[f]
Low back pain			
Episode of limiting low back pain	0.061		[e]
Acute intervertebral disc disorder	0.061		[f]
Chronic intervertebral disc disorder	0.121	0.103-0.125	[f]
Abdominal wall defect—cases	0.850		GBD 1990
Anencephaly—cases	0.850		GBD 1990

Sequela	Average disability weight [a]	Range [b]	Source
Anorectal atresia—cases	0.850		GBD 1990
Cleft lip—cases	0.049	0.002-0.082	GBD 1990 [c] : untreated 0.016, treated 0.098
Cleft palate—cases	0.101	0.036-0.187	GBD 1990 [c] : untreated 0.015, treated 0.231
Esophageal atresia—cases	0.850		GBD 1990
Renal agenesis—cases	0.850		GBD 1990
Down syndrome—cases	0.593		GBD 1990
Congenital heart anomalies—cases	0.323		GBD 1990
Spina bifida—cases	0.593		GBD 1990
Dental caries—episodes	0.081		GBD 1990
Periodontal disease—cases	0.001		GBD 1990
Edentulism—cases	0.020	0.007-0.052	GBD 1990 [c] : untreated 0.062, treated 0.001

Source: Authors' compilation.

a. Global average disability weight.

b. Minimum and maximum disability weights if there is variation across age-sex-region categories. For disability weights based on the GBD 1990 study, further details of age-sex variation, treated and untreated weights, are given in annex tables 3 and 4 of Murray and Lopez 1996a.

c. Disability weights from GBD 1990 (Murray and Lopez 1996a).

d. Disability weights based on GBD 1990 (Murray and Lopez 1996a) with some revisions.

e. Disability weights drawn from Netherlands disability weights study (Stouthard and others 1997).

f. Provisional disability weights based on GBD 1990 or Netherlands weights for comparable health states.

APPENDIX II: Cost of Branded and Generic Antiretroviral Drug in Thailand, November, 2004

ARV drugs	Strength (mg) and daily dose	Cost per patient/ month			
		Branded drugs		Generic drugs	
		Baht	US$	Baht	US$
NRTI					
Abacavir (ABC)	300 x 2	10080	252.0	n.a.	n.a.
Dadinosine (ddI)	100 x 4	1033	25.8	50	1.3
Lamivudine (3TC)	150 x 2	6048	151.2	600	15.0
Stavudine (d4T)	30 x 2	4146	103.7	210	5.3
Stavudine (d4T)	40 x 2	4326	108.2	270	6.8
Zidovudine (AZT)	300 x 2	4644	116.1	1020	25.5
AZT+3TC	(300+150) x 2	8340	208.5	1500	37.5
NNRTI					
Efavirenz (EFV)	600 x 1	2319	58.0	n.a.	n.a.
Nevirapine (NVP)	200 x 2	1666	41.7	900	22.5
NtRTI					
Tenofovir (TDF)	300 x 1	n.a.	n.a.	n.a.	n.a.
PI					
Indinavir (IDV)	400 x 6	4860	121.5	n.a.	n.a.
Nelfinavir (NFV)	250 x 10	9344	233.6	n.a.	n.a.
Ritonavir (RTV)	100 x 2	2542	63.6	n.a.	n.a.
Saquinavir (SQV)	100 x 1	984	246.0	n.a.	n.a.
Indinavir + ritronavir (IDV/r)	400 x 4	3240	81.0	n.a.	n.a.

ARV drugs	Strength (mg) and daily dose	Cost per patient/ month			
		Branded drugs		Generic drugs	
		Baht	US$	Baht	US$
Lopinavir+ritronavir (LPV/r)	(133.3+33.3) x 6	12692	317.3	n.a.	n.a.
Saquinavir+ritronavir (SQV/r)	(1000+100) x 2	11964	299.1	n.a.	n.a.
First line (MOPH guidelines)					
3TC+d4T+NVP	(150+30+200) x 2	11860	296.5	1200	30.0
3TC+d4T+EFV	(150+40+200) x 2	12040	301.0	1320	33.0
d4T+3TC+EFV	(40+150) x 2+ 600 x 1	12513	312.8	2579	64.5
AZT+3TC+EFV	(300+150) x 2+ 600 x 1	10006	250.2	3819	95.5
AZT+3TC+NVP	(300+150+200) x 2	17684	442.1	2400	60.0
d4T+3TC+IDV/r	30/40+150+800/100	13434	335.9	3500	87.5
AZT+3TC+IDV/r	300+150+800/100	21032	525.8	4740	118.5
Second line (HIV-NAT)					
IDV+RTV+EFV	800+100+600	9721	243.0		
IDV+RTV+AZT+3TC	800+100+200/300+150	8902	222.6		
Second line (WHO guideline)					
ABC+ddI+LPV/r		22822	570.6		
ABC+ddI+SQV/r	(300+400+1000/100) x 2	22094	552.4		
TDF+ddI+LPV/r					
TDF+ddI+SQV/					

Source: Bureau of AIDS, Tuberculosis, and Sexually Transmitted Infection, MOPH 2004; Duncombe 2004; GPO 2004; MSF 2004. cited in

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