ผลต่อการเข้าถึงยาของนโยบายบังคับใช้สิทธิเหนือสิทธิบัตรยาในประเทศไทย

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EFFECT OF THE COMPULSORY LICENSE ON THE PUBLIC PROVISION OF THE ANNOUNCED MEDICINE IN THAILAND

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A Thesis Submitted in Partial Fulfillment of the Requirements
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การวิจัยครั้งนี้มีวัตถุประสงค์เพื่อประเมินผลของการบังคับใช้สิทธิเหนือสิทธิบัตรยาต่อการเข้าถึงยาที่มีการบังคับใช้สิทธิบัตรยาได้แก่ Clopidogrel, Efavirenz และ Lopinavir/ritonavir ในโรงพยาบาล 3 แห่ง การศึกษาวิจัยนี้เป็นการศึกษาข้อมูลย้อนหลัง (Retrospective) โดยใช้ข้อมูลจากฐานข้อมูลอิเลกทรอนิคส์ของโรงพยาบาลมหาวิทยาลัย 1 แห่ง , โรงพยาบาลศูนย์ 1 แห่ง และโรงพยาบาลทั่วไป 1 แห่ง ระหว่างปี 2550 ถึง ปี2552 และนำมาวิเคราะห์แบบจำลองเพื่อทดสอบระดับนัยสำคัญของตัวแปรหุ่นของการมียา Generic ที่มีการบังคับใช้สิทธิบัตรในโรงพยาบาลแต่ละแห่งที่ส่งผลต่อจำนวนผู้ป่วยที่ได้รับยาที่มีการบังคับใช้สิทธิบัตรทั้ง 3 ชนิด นอกจากนี้ยังได้ทำการสัมภาษณ์บุคลากรทางการแพทย์ถึงปัจจัยที่มีผลต่อการเข้าถึงยาหลังจากการประกาศใช้นโยบายบังคับใช้สิทธิเหนื่อสิทธิบัตรยา จากผลการศึกษาพบว่าหลังจากการมียา Generic ที่มีการบังคับใช้สิทธิบัตรในโรงพยาบาลแต่ละแห่ง จำนวนผู้ป่วยที่ได้รับยา Clopidogrel เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ เช่นเดียวกับจำนวนผู้ป่วยที่ได้รับยาLopinavir/ritonaivir แต่จำนวนผู้ป่วยที่ได้รับยา Efavirenz กลับมีจำนวนลดลงอย่างมีนัยสำคัญทางสถิติ ถึงแม้การบังคับใช้สิทธิเหนือสิทธิบัตรยาจะสามารถเพิ่มการเข้าถึงยาได้แต่พบว่าสามารถเพิ่มการเข้าถึงยาได้เพียงบางกลุ่มเท่านั้น นอกจากนี้ยังพบว่าปัญหาการเข้าถึงยาไม่ได้เป็นปัญหาหลักในสถานพยาบาลขนาดใหญ่หรือในกลุ่มผู้ป่วยที่ใช้วิธีการจ่ายเงินแบบตามรายการแก่ผู้ให้บริการ ปัจจัยทางด้านคุณภาพของยา Generic ที่นำมาใช้เป็นปัจจัยที่ผู้ให้สัมภาษณ์คำนึงถึงมากที่สุด ความเชื่อมั่นของแพทย์ผู้สั่งจ่ายยาต่อยา Genericที่นำมาใช้เป็นปัจจัยสำคัญที่จะส่งผลต่อการเพิ่มการเข้าถึงยาหลังจากการประกาศใช้นโยบายบังคับใช้สิทธิเหนือสิทธิบัตรยา

ลายมือชื่อนิสิต.....สุธีรา เตชคุณวุฒิ.....

สาขาวิชา เศรษฐศาสตร์สาธารณสุข ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก.....

ปีการศึกษา 2552 ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์ร่วม .....

5185757029 : MAJOR HEALTH ECONOMICS

KEYWORDS : COMPULSORY LICENSING / ACCESS TO MEDICINE

SUTHIRA TAYCHAKHOONAVUDH: EFFECT OF THE COMPULSORY LICENSE ON THE PUBLIC PROVISION OF THE ANNOUNCED MEDICINE IN THAILAND. THESIS ADVISOR: ASSOC.PROF. PAITOON KRAIPORNSAK, Ph.D. THESIS CO-ADVISOR: ASSOC.PROF. SAUWAKON RATANAWIJITRASIN, 69 pp.

The aim of this study was to have a first field evaluation of the effect of compulsory licensing policy implementation on the access to the announced medicine. This study was a descriptive retrospective study using electronic pharmaceutical prescription data from 3 hospitals in 3 levels of health care settings from the period of 2007 to 2009. Explanatory model was employed to analyze the effect of the compulsory licensing policy implementation on number of patients receiving medicine. In-depth interview was also conducted to explore dimensions of access to medicine that have an effect on the implementation of compulsory licensing policy. Following the implementation of compulsory licensing policy, the number of patients receiving Clopidogrel and Lopinavir/ritonavir has significantly increased by 55.68% and 26.78%. While the number of patients receiving Efavirenz has significantly decreased by 25.86%. This result may be directly related to the policy and indicates that this method is successful in increasing the access to only some particular category of drugs. Type of hospital and health care scheme also has an impact on the access to medicine. Access to medicine may not be an issue in higher level of hospital or employed fee-for-service as its payment method to the health care providers. Quality of compulsory licensed medicine is the factor most interviewee are concerning of. Physician's perceptions toward the quality of the medicine then have an impact on the access to these medicines.

Field of Study : Health Economics

Academic Year : 2009

Student's Signature .....

Advisor's Signature .....

Co-Advisor's Signature .....

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CHAPTER I

INTRODUCTION

1.1 Problems and Its Significance:

Compulsory Licensing, an action that complies with the flexibilities of the Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS) allows the government to authorize itself or third parties the right to use the patents without authorization from the patent holder for the reason of the public policy. Compulsory licensing is a crucial issue in health sensitive patent law. The grant of compulsory license may increase the accessibility and affordability of life saving drugs. The action may also help in bringing such drugs to the group of low income patients especially in the third world countries.

Access to essential medicine is one of the major public health problems. Approximately thirty percent of the world's population, over 1.7 billion people, has inadequate access or no access at all to essential medicines (WHO, 2004). Several countries, for example USA, Canada, India, Zimbabwe, Malaysia, Zambia and Indonesia (Sripen et al, 2008), have used compulsory licensing as a tool to relieve the problem of medicine inaccessibility. However, compulsory licensing is still a controversial issue in balancing between the human rights in access to essential medicine and promoting the innovation by giving incentives to inventors.

A study of Thai Working Group on HIV/AIDS Projection (2001) has showed that cumulative number of HIV infected patients in 2007 was an estimated 1,109,000 comprised of 508,300 patients that required continuing care and treatment. Even the number of new HIV cases is decreasing in recent years; HIV patients need the patented second-line treatment medicine.

Non-Communicable disease for example, myocardial ischemia and cerebro-vascular accident is also one of the major public health problems. The diseases have been one of the leading causes of death in the country for many years. Besides, according to the

Ministry of Public Health (2007), almost 300,000 patients are now living with the diseases. However, only 30,000 patients accessed to the medicine treated due to the price of the medicine

After several negotiations (Compulsory Licensing Information Center, 2008) with the pharmaceutical company in order to reduce the price of the patented medicine, finally in late 2006 and early 2007, Thai Government announced its intention to introduce the government use of patents for 3 pharmaceutical products, including 2 antiretrovirals (ARVs): efavirenz and lopinavir/ritonavir combination and drug for heart disease: clopidogrel. According to the Ministry of Public Health (MOPH), the implementation of this policy aims at ensuring access to affordable medicines in the public sector. The action complied with the flexibilities of the TRIPs Agreement and the Thai patent Act.

After the compulsory licensing policy has been put into action, opposition comes from multi-national pharmaceutical companies who hold the patents of the medicine, governments of industrialized countries, and international pharmaceutical industry associations. On the other hand, the government use of patent was commended by international agencies and non-governmental organizations (NGOs).

Subsequently in 2008, the government has further use of patents of 4 more of pharmaceutical products which are an anticancer drug, Erlotinib (Tarceva®), Letrozole, Imatinib and Docetaxel. Thai government by Ministry of Public Health has a policy to continue issuing compulsory licensing in other essential medicines that considered as a public health problem.

1.2 Research Questions

1.2.1 Primary research question:

1. Does the implementation of the compulsory licensing policy significantly increase the level of access to the announced medicine?

1.2.2 Secondary research question:

1. How does the effect on the accessibility differ in each health care scheme; universal coverage, social security and civil servant benefit scheme?
2. How does the effect on the accessibility differ in different type of hospital?
3. How do other aspects of access to medicine; physical availability, and acceptability have an effect on the implementation of the compulsory licensing on the access to medicine?

1.3 Research Objectives

1.3.1 General Objective:

To have a first field evaluation of the effect of compulsory licensing policy implementation on the access to the announced medicine comparing them to prior level of access at 3 hospitals, Thailand

1.3.2 Specific Objectives:

1. To evaluate the effect of compulsory licensing policy implementation on the access to the announced medicine, by comparing before and after the implementation of the policy in terms of number of patients receiving the announced medicine and number of announced medicine being prescribed.
2. To determine the effect of the health care scheme on the accessibility before and after the implementation of compulsory licensing policy.
3. To determine the effect of the type of hospital on the accessibility before and after the implementation of compulsory licensing policy.
4. To examine dimensions of access to medicine; physical availability, acceptability, and quality of product and services, that would have an impact on the

effect of the compulsory licensing policy implementation on the access to the announced medicine.

1.4 Scope of the study:

This study was conducted in 3 hospitals in Thailand as a first field evaluation. Each is from different type of hospital; university hospital, regional hospital and provincial hospital. Study sites were selected as case studies since the announced medicine is mostly used in the higher level of the health care settings.

Medicine selected for the analysis were Clopidogrel, Combination of Lopinavir and rinotanir, and Efavirenz since these medicines has been announced the use of its patents by government since 2006. Medicines announced compulsory licensing afterwards were not included in the analysis.

The analysis took place from 2007 to 2009 in order to evaluate the effect of the compulsory licensing on the access to medicine comparing before and after the compulsory licensed medicine were available in the hospital in late 2007. The time period allows the policy to have a full effect on the access to these medicines.

1.5 Hypotheses:

Access to Clopidogrel, Combination of Lopinavir and rinotanir, and Efavirenz has increased and improved in both quantitative and qualitative measurement in this study.

1.6 Usefulness of the study:

The results of the study would demonstrate whether the implementation of the compulsory licensing policy is effective or not in terms of its objective achievement. If it is, the key decision makers could further use the policy as a tool to relieve the problem of the low accessibility of medicine. However, it must be further investigate other impact of the policy to see its cost and benefit.

In the case of ineffective policy results, the decision maker can in this case, examine whether the ineffective implementation occurs from theoretical failure or implementation failure in order to come across with other alternative policy or implementation process.

CHAPTER II

LITERATURE REVIEW

2.1 TRIPs Agreement and the Doha Declaration

2.1.1 TRIPs Agreement

Multiple causes underlie the global crisis of medicine accessibility including the unaffordable price of patented pharmaceutical product. The increase in the pharmaceutical product's price is to some extent result from The 1994 Agreement on Trade-Related Aspects of Property Rights (TRIPs Agreement). TRIPs Agreement states that all signatories are obliged to grant patents to pharmaceutical products which create monopolies for the use and sale of product (TRIPs Agreement, 1994). As a result, the price of pharmaceutical product has tended to increase to meet the multinationals firm owning the patents of the medicine that has an objective to maximize firm's profit.

There are few articles in the original TRIPS Agreement that is related to the pharmaceutical industry. First, the article 7 in the Agreement states that

"The protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations."

This indicates that protection of intellectual property rights should be for the purpose of promoting innovation "in a manner conductive to social and economic welfare, and to a balance of rights and obligations" Two important implications of these intellectual property rights has take some role in our public health system. On the positive side, this rights aims to promote medicine discovery and innovation through two mechanisms: the provision of incentives to inventors, and the disclosure of information to facilitate technology transfer. On

the contrary, as mentioned the market exclusivity granted to patent holders and associated high prices of patented products are among the key barriers to pharmaceuticals and therefore, the health of the population.

The adoption of a patent system in these countries has harmed poorer people who cannot afford to buy medicine. Nevertheless, the TRIPs Agreement itself contains some provisions in the Article 8 of the Agreement to allow countries to eliminate the negative consequences of granting patents in the controversial issue of suspending intellectual property rights for the purpose of public health and socio-economic need as stated below;

“Members may, in formulating or amending their laws and regulations, adopt measures necessary to protect public health and nutrition, and to promote the public interest in sectors of vital importance to their socio-economic and technological development, provided that such measures are consistent with the provisions of this Agreement.”

Moreover, the TRIPs Agreement also addresses the compulsory licensing. According to Article 30 and Article 31 that Members may provide limited exceptions to the exclusive rights conferred by a patent without the authorization of the right holder.

“Where the law of a Member allows for other use of the subject matter of a patent without the authorization of the right holder, including use by the government or third parties authorized by the government, the following provisions shall be respected:”

However, as stated that the other use in the Agreement may meet with some requirements for example in Article 31(b) which states that compulsory licensing may not be issues unless the proposed user has made unsuccessful reasonable efforts to obtain authorization from the rights holder on reasonable commercial terms. Member states can bypass the reasonable efforts requirement in case of a national emergency, extreme urgency, or for public non-commercial use.

Article31(b); “such use may only be permitted if, prior to such use, the proposed user has made efforts to obtain authorization from the right holder on reasonable commercial terms and conditions and that such efforts have not been successful within a reasonable period of time. This requirement may be waived by a Member in the case of national emergency or other circumstances of extreme urgency or in cases of public non-commercial use. In situations of national emergency or other circumstances of extreme urgency, the right holder shall, nevertheless, be notified as soon as reasonably practicable. In the case of public non-commercial use, where the government or contractor, without making a patent search, knows or has demonstrable grounds to know that a valid patent is or will be used by or for the government, the right holder shall be informed promptly;”

2.1.2 The Doha Declaration

In 2001, After the TRIPs Agreement, the WTO Ministerial Conference officially initiated the Doha Declaration on the TRIPS Agreement and Public Health. This has affirmed the rights of the member’s nations to issue compulsory licensing as mentioned in the Paragraph 5(b) of the Declaration (World Trade Organization, 2001) states that, Each Member has the right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted. As well as in the Paragraph 5(c) of the Declaration states, Each Member has the right to determine what constitutes a national emergency or other circumstances of extremely urgency, it being understood that public health crises, including those relating to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency or other circumstances of extreme urgency.

However, the Doha Declaration fell short of its objective to "promote access to medicines for all. TRIPS Agreement required that the majority of manufacture and sales resulting from compulsory licensing must be limited within the domestic market. Thus, many countries need to issue the compulsory licensing did not have the means or capacity to manufacture drugs. As a result, the Declaration also instructed in the Paragraph 6 that the

TRIPS Council to find a mechanism to make the effective use of the compulsory licensing before the end of 2002.

Paragraph 6 of the Doha Declaration;" We recognize that WTO Members with insufficient or no manufacturing capacities in the pharmaceutical sector could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement. We instruct the Council for TRIPS to find an expeditious solution to this problem and to report to the General Council before the end of 2002."

Though, it was not until August 2003 that the authority could reach an agreement to remove the limitations temporarily on exports of drugs under a compulsory license to countries that could not manufacture drug themselves. Soon after, this limitation was removed permanently by amending the TRIPs agreement during the 2005 WTO ministerial conference in Hong Kong or known as Hong Kong Declaration (World Trade organization, 2005).

2.2 Compulsory Licensing and its effect

Compulsory Licensing is a potentially powerful tool that countries can use to alleviate the access to essential medicine problem. Similar to other policy, it has its own benefits and detriments. Compulsory licenses can obviously remove patent barrier to an essential medicine, potentially saving lives of patients and improving the public health of dozens of nations. However, in order to increasing the access, it requires not only issuing compulsory licensing but also how to manage it properly. Otherwise, compulsory licensing would benefit only a small part of its intended recipients and facing unwanted side-effects of compulsory licensing. Compulsory licenses may cause temporary or permanent losses in foreign direct investment as patent-owning firms or nations seek a more business-friendly legal climate. Study of Robert (2008) found that a compulsory license can trigger the loss of significant foreign direct investment.

2.3 Thailand and the compulsory licensing policy

Thailand has put a lot of effort to provide wide range of health care service and medical treatment to Thai people for decades. This has included the beginning and continual development of health care delivery systems, disease control and health promotion programmes, and the most important, the universal coverage health care plan for all Thai people. Medicines, one pf the most important intervention in treatment and prevention of several diseases, like in other countries, Thailand has enforced many strategies to manage the pharmaceutical policy properly. The need for ensuring access to essential drug is also one of the most concerning issue as it is stated in one of the element of the National Drug Policy.

2.3.1 Access to medicine situation before compulsory licensing

Cumulative number of HIV infected patients in 2007 was an estimated 1,109,000 comprised of 508,300 patients that required continuing care and treatment (Thai Working Group on HIV/AIDS Projections, 2001). HIV is one of the major public health problems which cause deaths and economic burden to the country. In 2001, Thailand has implemented the 30 baht scheme to fill the coverage gap in the country's public health insurance system. At the beginning, the ARV-based medications and renal replacement therapy, including hemodialysis and peritoneal dialysis, were excluded from the benefit package owing to their unaffordable costs when being provided to all patients in need. However, in October 2003, the benefit scheme has been revised. The policy to provide free access to ARV medications to all needy people was adopted under the National Access to Antiretroviral Program for people living with HIV/AIDS (NAPHA). With the increasing number of patients under the program, the need for cheaper medicines especially the ARVs obviously increased since then. The NAPHA program, managing as a vertical program, later on officially included in Universal Coverage benefit packages since October 1, 2006. (Laichareonsup, 2007)

Non-Communicable disease for example, myocardial ischemia and cerebro-vascular accident is also one of the major public health problems. The diseases have been one of the leading causes of death in the country for many years. Besides, Documents from the Ministry of Public Health (2007), almost 300,000 patients are now living with the diseases. However, only 30,000 patients accessed to the medicine treated due to the price of the medicine.

2.3.2 Price Negotiation before Compulsory licensing policy was put into action in 2006-2007

According to the Compulsory licensing information center established consequently after the issue of compulsory licensing in Thailand, Ministry of Public health has negotiated with the Pharmaceutical companies which are the patent's owner several times before the Compulsory Licensing Policy was put into action to reduce the price of the medicines. For instance, on 16 November 2004, the Ministry sent an official letter to HIV medicine producers to ask for discounts (Compulsory Licensing Information Center, 2008). Face-to-Face Negotiations between the Ministry and the Pharmaceutical companies of ARV prices were arranged on 10 August and 28 December 2005 (Compulsory Licensing Information Center, 2008). From the first negotiation, MSD, the patent's owner of Stocrin® (efavirenz 600 mg) refused to reduce the medicine's price. On the other hand, the price of Kaletra® (LPV/r) was reduced by 32% (17,547.84 Baht per bottle to 11,877.00 Baht per bottle) through the negotiation with Abbott Laboratories. The second negotiation resulted in the reduction of Kaletra® (LPV/r)'s price again by 25% (from 11,877.00 Baht per bottle to 8,907.75 Baht per bottle). Abbott Laboratories also offered a free amount of Kaletra®(LPV/r) which made the net price per bottle fall to 5,938.50 baht and the price of Stocrin® (efavirenz 600 mg) was also reduced by 18.7% in November 2006 (from 1,723.00 Baht 1,401.00 Baht). However, according to the MOPH (quote in Sripen et al, 2008), the Ministry did not accept the proposals of the price reduction, it was claimed that the drugs remained much more expensive than their generic versions and also the budget implications of the programme were considered too high.

2.3.3 The implementation of Compulsory Licensing Policy

As stated by the Thai Patent Act (1979), Section 51 that any government ministries, bureaus and departments might exert the use of patents in order to carry out public services, or to prevent a severe shortage of food, medicines, or other consumption items. However, in such cases, the government had to pay a royalty to the patent holder and notify the company without delay. The action of the Ministry of Public Health in issuing the government use of the medicine patents conformed to the provision of the Act.

On 29 November 2006, the Director General of the Disease Control Department announced the introduction of government use of Efavirenz (Stocrin®) patent as the first ever public use of medicine patents in Thai history (Ministry of Public Health, 2006). The Government Pharmaceutical Organization (GPO) was assigned to be the implementer of this policy. The government use of Efavirenz patent will be continued until 31 December 2011. The medicine will be used only for the patient under the universal coverage scheme, social security scheme and the civil servant benefit scheme and the total number of patients using the medicine will not exceed 200,000 patients per year. The government will pay a royalty fee to the patent holder by 0.5% of the sales revenue of the generic version of Efavirenz by the GPO.

After the announcement of the first government use of medicine patent, the selection process for other medicines to the scheme continued. However, it was not until early January 2007 that Ministry decided to adopt the government use for second-line ARV combination of Lopinavir and Ritonavir (LPV/r or Kaletra®) and an anti-platelet drug, clopidogrel (Plavix®). The notifications on the enforcement of the flexibility for these two products were publicized on 24 and 25 January 2007, respectively (Ministry of Public Health, 2007) The Government Pharmaceutical Organization (GPO) was also assigned to be the implementer of these policies.

The government use of Lopinavir and Ritonavir patent will be continued until 31 January 2012. The medicine will be used only for the patients under the universal coverage scheme, social security scheme and the civil servant benefit scheme and the total number of patients using the medicine will not exceed 50,000 patients per year. For clopidrogrel, the government use of patent will be continued until the patent of the original clopigrogrel, Plavix® is finished or the need for the use of the medicine is reduced. The medicine will be used only for the patient under the universal coverage scheme, social security scheme and the civil servant benefit scheme and with the unlimited number of patients using the medicine. All the licenses offered the royalty fee of 0.5% of the total sale value to the patent holders.

A year after, on 4th January 2008, the Ministry has announced 4 more medicines that will be issued compulsory licensed. The government use of medicine patent includes an anticancer, Erlotinib (Tarceva®) (Ministry of Public Health, 2008), Letrozole (Ministry of Public Health, 2008), Imatinib (Ministry of Public Health, 2008), and Docetaxel (Ministry of Public Health, 2008). The government uses of medicine patent of the last three drugs will include in any brand that these medicine is a part in the active ingredients. The government use of patent of these medicines will be continued until the patent of the original drug is finished or the need for the use of the medicine is reduced. The medicine will be also used only for the patient under the universal coverage scheme, social security scheme and the civil servant benefit scheme and with the unlimited number of patients using the medicine. Royalty fee offered to the patent holders is 3%, 3%, 5% and 3% of the total sale revenue of Erlotinib, Letrozole, Imatinib and Docetaxel by the GPO respectively.

2.3.4 The importation and distribution of the compulsory licensed medicines

After the announcement of the government use of medicine patent, GPO the implementer of the compulsory licensing policy has imported and distributed the medicine to different health care settings. The importation of the medicine that was issued

compulsory licensing at the beginning has begun to import into the country since January 2007 (Sripen et al, 2008).

Table 1.1 Importation of ARVs and Clopidogrel under the government use scheme. As of June 2008

Medicine(producer)	Date	Quantity	Price
EFZ 600mg tablets (Ranbaxy)	Jan-May 2007	66,000 * 30 tablets	684 baht/30 tablets
	Sep-Dec 2007	100,000 * 30 tablets	571 baht/30 tablets
	Mar-Jun 2008	100,000 * 30 tablets	547 baht/30 tablets
EFZ 200mg tablets (Ranbaxy)	Jan-Mar 2008	10,000 * 90 tablets	670 baht/90 tablets
LPV/r tablets (Matrix)	Jan-Mar 2008	8,000 * 120 tablets	2,457baht/120 tablets
Clopidogrel tablets (Cadila)	Apr 08	2 million tablets	159 baht/100 tablets

Source: Sripen et al, 2008

2.4 The use and indication of medicine under compulsory licensing

2.4.1 Efavirenz

Efavirenz, also known as EFV, is a type of medicine called a non-nucleoside reverse transcriptase inhibitor (NNRTI) used to treat HIV. NNRTIs block reverse transcriptase, a protein that HIV needs to make more copies of itself.

According to the Clinical Practice Guideline developed by the Thai AIDS Society in 2008, Efavirenz can be used to substitute Nevirapine (NVP) which is the first line regimen in the case that patient develops a severe rash or hepatotoxicity from Nevirapine.(Somnuek et al, 2008)

2.4.2 Lopinavir and ritonavir combination

Lopinavir/ritonavir, also known as Kaletra, is a type of medicine called a protease inhibitor (PI) used to treat HIV. PIs act by blocking protease, a protein that HIV needs to make more copies of itself.

Lopinavir/ritonavir is a combined medicine used to substitute the second-line treatment of HIV; Efavirenz in the case that patient develops severe side effects from Efavirenz. (Somnuek et al, 2008)

2.4.3 Clopidogrel

Clopidogrel is an inhibitor of platelet aggregation. A variety of drugs that inhibit platelet function have been shown to decrease morbid events in people with established cardiovascular atherosclerotic disease as evidenced by stroke or transient ischemic attacks, myocardial infarction, unstable angina or the need for vascular bypass or angioplasty.

Clopidogrel bisulfate is indicated for the reduction of atherothrombotic events as follows; Recent MI, Recent Stroke or Established Peripheral Arterial Disease, Acute Coronary Syndrome. It has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia. (Compulsory Licensing Information Center, 2008)

2.5 Access to medicine

Despite its widespread use, 'access to medicines' is rarely operationally defined and measured (Penchansky and Thomas, 1981, Walkowiak et al, 2004). Penchansky and Thomas have defined access to care as “The degree of ‘fit’ between the patient and the health care system”. They also specified a set of more specific areas of fit between the

patients and the health care system or dimensions of access to care as 5 dimensions; affordability, availability, accessibility, accommodation, and acceptability.

Availability is defined as the relationship of the volume and type of existing services (and resources) to the clients' volume and types of needs. Accessibility is the relationship between the location of supply and the location of clients. Accommodation reflects the extent to which the provider's operation is organized in supplying the resources in ways that meet the constraints and preferences of the client. Affordability is determined by the relationship of prices of services and providers' insurances or deposit requirements to the clients' income, ability to pay, and existing health insurance. And finally, acceptability captures the extent to client's attitude about personal and practice characteristics of providers to the actual characteristics of existing providers and vice versa.

The concept of access to care developed by Penchansky and Thomas has been further used by the Management Sciences for Health (MSH) and World Health Organization in the consultative meeting of the recognized experts in order to develop the definition and dimension of the access to medicine (Management Science for Health and World Health Organization, 2000). The dimensions of access to medicine was finally developed which comprises of 4 dimensions and 1 crosscutting characteristics as follows;

- Physical availability – the relationship between the type and quantity of product and service needed and what is available;
- Affordability – the relationship between the products and services and the user's ability to pay for them;
- Geographic accessibility – the relationship between the location of the product or service and the location of the eventual user of the product or service;
- Acceptability –can be understood as patient satisfaction and is the congruity between the user's and the providers' attitudes and expectations about the products and services and the actual characteristics;

- Quality of products and services – an essential component that cuts across all the dimensions.

From the dimensions of accessibility, Thailand's current health care system also has an effect on the accessibility of the medicine. Thailand has been implemented the 30 baht scheme to fill the coverage gap in the country's public health insurance system since 2002. The implementation result in the universal coverage of the health insurance of Thai population which comprise of 3 main health care schemes; civil servant medical benefit scheme that covers government officers and their families, social security scheme that covers workers and universal coverage scheme that covers the rest of the population. Different health care schemes employ different payment mechanism to the health care providers. Capitation payment mechanism is used in the universal coverage scheme and social security scheme, while civil servant medical benefit scheme use fee-for-service as its payment method. Payment mechanism itself reflects the scheme's affordability; one dimension that would effect access to medicine. Studies have shown that different payment methods have different impact on the accessibility of the health care. (Zuckerman et al, 2002), (Hsiao, 2000), (Stearns SC, 1992)

The access to medicine is not only affected by the health care scheme in the health care system. Type of hospitals are another factor that has an impact on the access to medicine. According to Thailand Health Profile (2004), Type of hospitals or level of health care settings in Thailand can be divided into 5 levels as follows;

1. Self-Care at Family Level

2. Primary Health Care Level: The primary health care services include those organized by the community in providing services related to health promotion, disease prevention, curative care and rehabilitative care. The medical and health technologies applied at this level are generally not so high. Service providers are the people themselves; village health volunteers (VHVs) or other non-governmental volunteers.

3. Primary Care Level. Primary care is provided by health personnel and general practitioners (GPs).

4. Secondary Care Level. Medical and health care at this level is managed by medical and health personnel with intermediate level of specialization. General and specialized medical facilities include the following:

1) Community hospitals. A community hospital is located in a district or minor-district with 10 to 150 inpatient beds, covering a population of 10,000 or more, and staffed by doctors and other health professionals.

2) General or regional hospitals and other large public hospitals. A general hospital in this category is located in a provincial city or a large district town, equipped with 200 to 500 beds, while a regional hospital located in a provincial city has over 500 beds and medical specialists in all fields.

3) Private hospitals. Most private hospitals are operated as a business entity with both full-time and part-time staff, and clients are required to pay for services.

5. Tertiary Care. Medical and health services at this level are provided by medical specialists and health professionals. Tertiary care facilities include:

1) General hospitals

2) Regional hospitals

3) University hospitals and large public hospitals belonging to other ministries or local administrative organizations.

4) Large private hospitals have medical specialists in all specialties.

The differences of each type pf hospitals that the patients have accessed also have an impact on the access to medicine. Number of specialties and physicians in each level of health care settings that will prescribe the medicine reflects the physical availability dimension of the access to medicine.

2.6 National medicinal drug policies evaluation

Increasingly, educational, administrative and policy interventions are being carried out to improve the quality of medication use and/or contain costs. Such interventions can be implemented at the institutional, regional or national level (Wagner et al, 2002,).

A time series is a sequence of values of a particular measure taken at regularly spaced intervals over time. Time series analysis consisted of several techniques for modeling autocorrelation in temporally sequenced data and is well suited to address secular trends and evaluate interventions (Wagner et al, 2002).Statistical manipulation is used to decompose dependent variables into its autocorrelated and residual (unexpected) components. Statistical test then hinges on whether the residual components exhibit patterns consistent with the hypothesis. The residual components support the hypothesis that an intervention affected the dependent variable if they were above 95% CI at the times specified a priori as those in which the intervention should have an effect. (Ong et al, 2003)

Outcome measurement for time series studies of the health policy evaluation can include medication use, utilization of other health services or clinical measures. Research note of Wagner emphasized that Outcomes can be expressed as averages, proportions or rates. Examples of drug use-related measures are the average number of drugs prescribed per patient, average antibiotic prescription cost, percent of enrollees receiving a particular drug or percent of patients treated according to guidelines. Examples of other service utilization would be average length of hospital stay or monthly rate of admission to nursing homes, whereas clinical measures might include average diastolic blood pressure in a group of patients, or percentage diabetic patients achieving adequate glucose control. (Wagner et al, 2002). Several health policy evaluation researches have been conducted by using time series modeling method employing different techniques and different outcome measurement. For example, impact of limited Fluoroquinolone reimbursement policy on antimicrobial prescription claims has been assessed using time series descriptive plots of number of beneficiaries receiving antimicrobials and the number, duration, and cost of prescriptions of antimicrobials (MacCara et al, 2001). Another research of (Ong 2003) make use of time series analysis in evaluating the effect of increase copayments on the prescription of Psychiatric medicine. The techniques used in this study was Box-Jenkins autoregressive, integrated, moving average time series modeling method by using defined daily doses (DDD) per 1000 inhabitants as an outcome measurement. Health outcome has

also been used an outcome measurement of the health policy intervention as it is believed that the health policy intervention would have the final outcome on the patients' health. Study of cardiovascular outcome after a change in prescription policy for clopidogrel was conducted using interrupted time series analysis (Cynthia et al, 2008).

CHAPTER III

METHODOLOGY

3.1 Study Design and Methodology

This is a descriptive retrospective study aims at evaluating the change of access of the announced medicine in three public hospitals. Each hospital is from different level of health care settings; one university hospital, one regional hospital and one general hospital. Access to the announced medicine in this study employed dimensions of the access to medicine developed by MSH and WHO as follows;

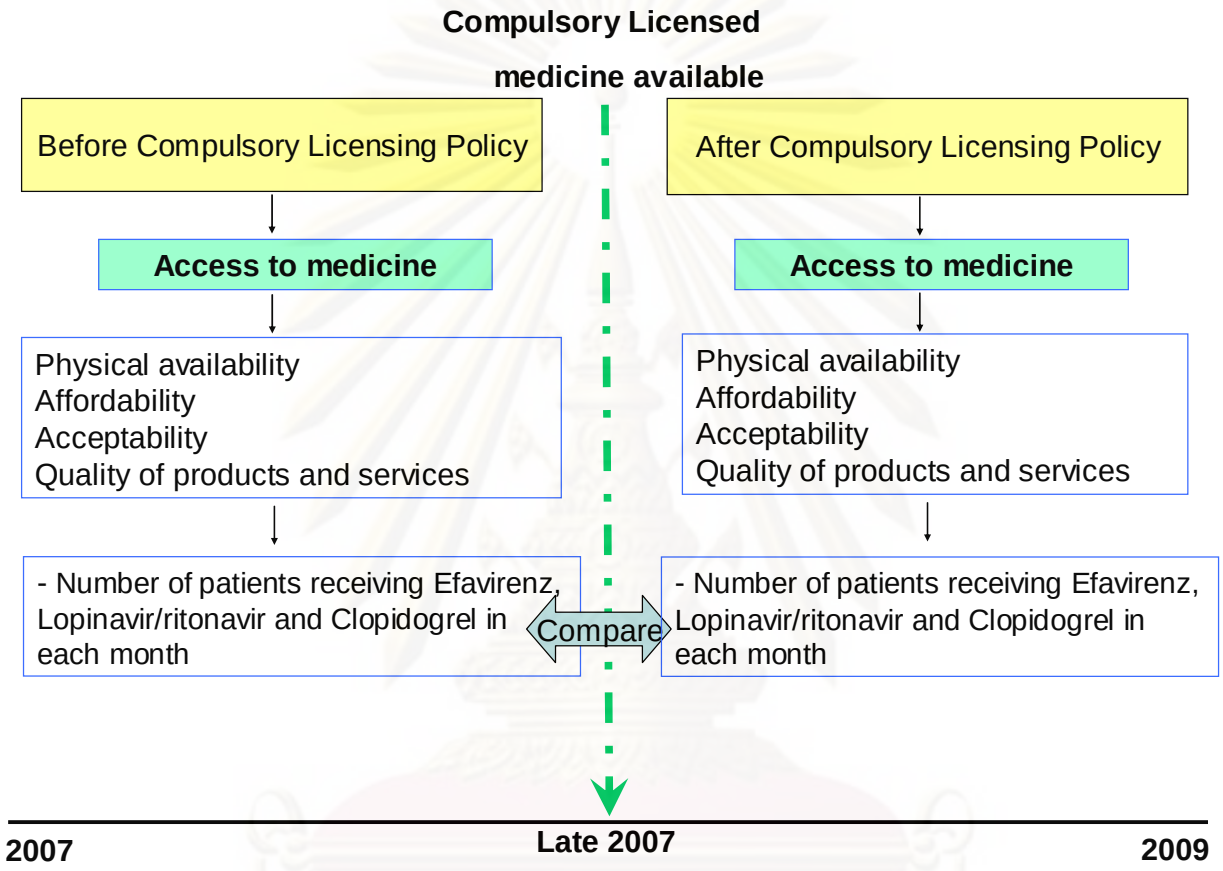
- Physical availability
- Affordability
- Geographical accessibility
- Acceptability
- Quality of products and services

However, in this study Geographical accessibility in this study was not taken into the analysis since the medicine under compulsory licensed are managed under Government Pharmaceutical Organization (GPO) system. The system has been distributing medicine all over the country for many years.

Even the government has issued compulsory licensed on these three medicines (Clopidogrel Efavirenz, lopinavir/ritonavir) since 2006; number of hospitals which compulsory licensed medicines are available in the hospital is still limited. Hospitals were selected based on the availability of these three compulsory licensed medicines in their hospital drug list for some period of time to allow the policy to have a full effect on the access to medicine.

3.2 Conceptual Framework

Figure 3.1 Conceptual Framework: Hypothesized changes after compulsory licensing



3.3 Data Source and collection

Data collections in this study were divided into 2 parts;

1. Secondary data which is electronic medical and pharmaceutical prescription database from 3 hospitals in 3 levels of health care settings; university hospital, regional hospital and general hospital were extracted for the analysis. Hospitals' characteristics are described below in Table3.1. Data include patients' demographic characteristics, patients' health benefits, and medicine being prescribed. Information from these databases was

linked together with the use of encrypted identifiers for patients. Number of patients receiving each compulsory licensed medicine in each week between 2007 and 2009 were extracted to evaluate the change on the access to medicine after compulsory licensing. All Patients received at least one time of these 3 medicines (Clopidogrel, Efavirenz and Lopinavir/ritonavir) either both original medicine or compulsory licensed medicine were included in the analysis.

Table 3.1 Hospitals' characteristics

Hospital	Region	Number of beds	Average Outpatient department Visits
University Hospital	Central	1200 beds	2000 visits
Regional Hospital	East	500 beds	1400 visits
General Hospital	East	360 beds	700 visits

2. In-depth Interviews using open-ended questions with hospital staff from hospital where compulsory licensed medicines were available and literature review will be conducted to gather information and opinion on the dimensions of access to medicine *(Physical availability, Acceptability and Quality of products and services).* These dimensions would reflect its effect on the access to medicine after compulsory licensing has been putted into action.

Key informants included Physician from 2 specialties; Cardiologist as a main user of Clopidogrel and Infectious as a main user of Efavirenz and Lopinavir/ritonavir. Since there are no cardiologist and infectious in the hospital, physicians who are a main user of Clopidogrel and Antiretroviral medicine are medicine specialist. In order to have a clear understanding on the compulsory licensed medicine procurement process, pharmacist who has a direct involvement in antiretroviral medicine and who is responsible in drug procurement process were also included in the interview.

Table 3.2 Details of interviewee in each hospital

Hospital	Number of Physicians	Details	Number of Pharmacists	Details
University Hospital	1	1 infectious	1	1 Pharmacist who responsible in drug procurement process
Regional Hospital	2	1 infectious 1 cardiologist	2	1 Pharmacist with direct involvement in ARV program 1 Pharmacist who responsible in drug procurement process
General Hospital	2	2 Physicians with medicine specialty	2	1 Pharmacist with direct involvement in ARV program 1 Pharmacist who responsible in drug procurement process
Total	5		5	

Questions for each interviewee were different based on interviewee's roles and responsibilities. The questions were focused on the following topics;

Physical availability

- Type of medicine available in the hospital(compulsory licensed or original medicine or both)
- Event of medicine out of stock
- Process of procuring the medicine under CL

Acceptability

- Provider's acceptability and satisfaction of the medicine under CL

Quality of products

- Quality of drug products under CL

3.4 Data Analysis

Number of patients receiving each announced medicine (EFZ, LPV/r, Clopidogrel) in each week were extracted from the database. The effect of the compulsory licensing on the access to medicine or in this case number of patients receiving each announced medicine was analyzed using explanatory model.

The dependent variables or the number of patients receiving each announced medicine (original and generic) were decomposed using the explanatory model. The analysis will be divided into 3 equations (3 dependent variables; Y_t) as follows;

Clopidogrel…….equation (1)

Lopinavir and ritonavir combination……equation (2)

Efavirenz……equation (3)

Time period in this analysis was divided into 2 parts, before compulsory licensed medicine were available in the hospital, after compulsory licensed medicine were available in the hospital. Dummy variables were used to determine each period in the equation.

Another two dummy variables were added to equation (2) and equation (3) to identify the effect of 3 types of hospital; university hospital, regional hospital and general hospital. For equation (1), Since Clopidogrel was not available in most university hospital including hospital selected in the analysis; only one dummy variable was added to identify the effect of 2 types of hospital; regional hospital and general hospital.

Subgroup analyses of each sets of health care scheme of each medicine were done to compare the effect of the health care scheme on the access to each medicine after compulsory licensing.

The following linear regression model was specified to estimate the numbers of patients receiving each announced medicine before compulsory licensed medicine available in the hospital and the changes in numbers of patients receiving each announced medicine following the compulsory licensed medicine available in each hospital. The effect of the type pf hospital on the number of patients receiving each announced medicine was shown in the coefficient of the dummy variable added in the model.

$$Log(nu\_pts_{)} = \beta_0 + \beta_1 log(t) + \beta_2 D_{implement} + \beta_3 D_{hosplevel} + e_t$$

.....equation (1)

Where;

nu_pts = number of patients receiving Clopidogrel in each week

t = time is a continuous variable indicating time in weeks at time t from the start of the observation period

In order to estimate the effect of the time period before and after compulsory licensed medicine were available in the hospital; a Dummy variable was added defined as follows:

$D_{implement}$ = { 1 if before compulsory licensed medicine were available in the hospital; 0 otherwise

In order to estimate the effect of the type of hospital (regional hospital and general hospital) on the number of patients receiving Clopidogrel, another Dummy variable was added defined as follows:

$D_{hosplevel}$ = { 1 if regional hospital; 0 otherwise

$$Log(nu\_pts) = \beta_0 + \beta_1 log(t) + \beta_2 D_{implement} + \beta_3 D_{hosplevel1} + \beta_4 D_{hosplevel2} + e_t$$

.....equation (2)

Where;

nu_pts = number of patients receiving Efavirenz in each week

t = time is a continuous variable indicating time in weeks at time t from the start of the observation period

In order to estimate the effect of the time period before and after compulsory licensed medicine were available in the hospital; a Dummy variable was added defined as follows:

$D_{implement}$ = 1 if before compulsory licensed medicine were available in the hospital

0 otherwise

In order to estimate the effect of the type of the hospital on the number of patients receiving Efavirenz, another 2 Dummy variables were added defined as follows:

$D_{hosplevel1}$ = 1 if university hospital

0 otherwise

$D_{hosplevel2}$ = 1 if regional hospital

0 otherwise

$$Log(nu\_pts) = \beta_0 + \beta_1 log(t) + \beta_2 D_{implement} + \beta_3 D_{hosplevel1} + \beta_4 D_{hosplevel2} + e_t$$

.....equation (3)

Where;

nu_pts = number of patients receiving Lopinavir/ritonavir in each week

t = time is a continuous variable indicating time in weeks at time t from the start of the observation period

In order to estimate the effect of the time period before and after compulsory licensed medicine were available in the hospital; a Dummy variable was added defined as follows:

$D_{implement}$ = { 1 if before compulsory licensed medicine were available in the hospital; 0 otherwise

In order to estimate the effect of the type of the hospital on the number of patients receiving Lopinavir/ritonavir, another 2 Dummy variables were added defined as follows:

$D_{hosplevel1}$ = { 1 if university hospital; 0 otherwise

$D_{hosplevel2}$ = { 1 if regional hospital; 0 otherwise

In the first equation, β_0 estimates the baseline level of the outcome, number of patients receiving Clopidogrel, at time zero; β_1 estimates the percentage change in the number of patients receiving Clopidogrel that occurred with each week before the intervention (i.e. the baseline trend); β_2 estimates the percentage change in the number of patients receiving Clopidogrel immediately after the compulsory licensed Clopidogrel was available in the hospital compared with the trend before compulsory licensing; β_3 estimates the effect of the regional hospital on the number of patients receiving each announced medicine

In this second and third equation, β_0 will estimate the baseline level of the outcome, number of patients receiving Efavirenz or Lopinavir/ritonavir, at time zero; β_1 estimates the

percentage change in the number of patients receiving Efavirenz or Lopinavir/ritonavir that occurred with each week before the intervention (i.e. the baseline trend); β_2 estimates the percentage change in the number of patients receiving Efavirenz or Lopinavir/ritonavir immediately after the compulsory licensed Efavirenz or Lopinavir/ritonavir were available in the hospital compared with the trend before compulsory licensing; β_3 estimates the effect of the university hospital on the number of patients receiving each announced medicine and β_4 estimates the effect of the regional hospital on the number of patients receiving each announced medicine

Data collected from the in-depth interview and literature review were used to assess the dimension of accessibility (Physical availability, Acceptability and Quality of products and services) that would have an effect on the access to medicine after compulsory licensing.

CHAPTER IV

RESULTS AND DISCUSSIONS

4.1 Findings: Availability of original and compulsory licensed medicine in each hospital

Availability of original and compulsory licensed medicine before and after the compulsory licensing policy implementation were shown in Table 4.1. Prior to compulsory licensing announcement, availability of the original and compulsory licensed medicines was different among hospital and type of medicine.

Compulsory licensed clopidogrel was still not available in the selected university hospital during the period of this study. From the interview, the unavailability of the compulsory licensed clopidogrel is owing to the hospital policy toward the compulsory licensed medicine. On the contrary, after the Compulsory licensed clopidogrel was available in regional hospital, the original version of clopidogrel has been withdrawn from the hospital drug list which is similar to general hospital. It must also be noted that the availability of the original clopidogrel or Plavix® prior compulsory licensed medicine in this hospital was only for some certain cases requested by the physician. The medicine is not officially available in the hospital medicine list.

Efavirenz and Lopinavir/ritonavir both original and compulsory licensed were available in the university and general hospital prior and after the implementation of compulsory licensing policy. However, in the regional hospital, original Efavirenz and Lopinavir/ritonavir were available before the implementation of CL policy and only compulsory licensed medicine are available once the policy has been implemented. In the case of general hospital, the original lopinavir/ritonavir was presented only one month before the compulsory licensed medicine was made available.

According to interviewees in the hospitals, Efavirenz and Lopinavir/ritonavir are categorized as antiretroviral medicine or ARV which is differently managed from other type of medicine. Antiretroviral medicine is vertically managed by National AIDS program

(NAPHA) for Universal Coverage patients and social security office (SSO) program for social security patients. Medicines used under this program are separately procured by National Health Security Office (NHSO) and Social Security Office (SSO). Thus, which medicine and what type; original or compulsory licensed copies medicine depends on NHSO and SSO. Physicians or hospital staffs must key-in patients' laboratory test to request for each patient's ARV regimen and must reenter the patients' data if there is a regimen change. These medicines are then distributed through Government Pharmaceutical Organization (GPO)'s distribution network or known as Vendor Management Inventory (VMI). The program allows hospitals to order or adjust the amount of ARV medicine they require via an internet program. Once orders are placed the GPO sends the medicine directly to hospital.

The time when each compulsory licensed medicine was presented in each hospital is varied as shown in Table 4.2. Each hospital has there own process in selecting medicine in to their hospital medicine list. Thus, which type of medicine, original or compulsory licensed medicine, and when it is available in each hospital were different. However, this does not apply to the antiretroviral medicine used under the National Aids Program (NAP) and SSS program as mentioned above. Medicines used in these programs whether compulsory licensed or original product were separately selected, procured and distributed through the centralized National Health Security Office (NHSO) and Social Security Office. According to the interviewee in the hospital, the difference of the available date of compulsory licensed Efavirenz and Lopinavir/ritonavir between each hospital can be explained by the leftover stock of the original medicine for each type of patients left in each hospital. As for the regional hospital, original version of Efavirenz and Lopinavir/ritonavir were at the beginning, replaced by compulsory licensed medicine only in NAP and SSS patients. Later on, this regional hospital has decided to fully replace the original medicines with the compulsory licensed product by adding the compulsory licensed medicine into the hospital drug list. All patients not only NAPHA and SSS patients are now prescribed with compulsory licensed product. This is different to university and general hospital, some

patients which paid by their own money or under the Civil Servant Medical Benefit Scheme still can access to original product.

Efavirenz, Lopinavir/rotinavir and Clopidogrel were announced the government use of its patents on 29 November 2006, 24 January 2007 and 25 January 2007 respectively (Ministry of Public Health, 2006), (Ministry of Public Health, 2007). From the Ministry of Public Health documents, the first importation of 600 mg Efavirenz was in January 2007, one month after the announcing of the government use of its patent. However, the compulsory licensed medicine of 200 mg Efavirenz, Lopinavir/ritonavir and Clopidogrel were not imported to the country until January 2008, March 2008 and April 2008 correspondingly (Sripen et al, 2008). The distribution process after the medicine has been imported was taken 1-9 months before the medicine were truly available for the patients.

Table 4.1 Availability of the CL medicine in each hospital before and after the CL policy has been implemented

Medicine	Type of Medicine	University Hospital		Regional Hospital		General Hospital	
		Before CL	After CL	Before CL	After CL	Before CL	After CL
Efavirenz 200 mg	Original	Yes	Yes	Yes	N/A	N/A	N/A
	CL	N/A	Yes	N/A	Yes	N/A	N/A
Efavirenz 600 mg	Original	Yes	Yes	Yes	N/A	Yes	N/A
	CL	N/A	Yes	N/A	Yes	N/A	Yes
Lopinavir/ritonavir	Original	Yes	Yes	Yes	N/A	Yes	N/A
	CL	N/A	Yes	N/A	Yes	N/A	Yes
Clopidogrel	Original	Yes	Yes	Yes	N/A	Yes	N/A
	CL	N/A	N/A	N/A	Yes	N/A	Yes

* available only for some certain case but not in the hospital drug list

** available 1 month before CL

*** available until 18 June 2008 After that only CL efavirenz is available in the hospital

**** Lopinavir/ritonavir original : one capsule contain 133.3 mg of Lpv and 33.3 mg of ritonavir

***** Lopinavir/ritonavir CL : one tablet contain 200 mg of Lpv and 50 mg of ritonavir

Table 4.2 Time when each medicine are available in each hospital

	University Hospital	Regional Hospital	General Hospital
Efavirenz 200 mg	13 January 2009 NAPHA	30 May 2008 NAPHA	N/A
		6 October 2008 SSS	
Efavirenz 600 mg	14 September 2007 NAPHA	June 2007 NAPHA	June 2007 NAPHA
		12 July 2007 SSS	
		18 June 2008 for all patients	
Lopinavir/ritonavir	8 May 2008 NAPHA	25 April 2008 NAPHA	28 August 2008 NAPHA
	18 September 2008 SSS	26 August 2008 SSS	
		27 October 2008 for all patients	
Clopidogrel	N/A	31 October 2008	17 October 2008

4.2 Findings: Effect of the compulsory licensing policy on the access to Efavirenz, Lopinavir/ritonair and Clopidogrel

4.2.1 Effect of the compulsory licensing policy on the access to Efavirenz, Lopinavir/ritonavir and Clopidogrel in each hospital.

Access to Clopidogrel, Efavirenz and Lopinavir/ritonavir and prior and after the compulsory licensing policy were compared using time series data to analyze the relationship between the number of patients receiving each announced medicine (dependent variables) and time trend, the effect of the compulsory licensing policy, and the type of hospital (independent variables). Data were divided by type of medicine; Efavirenz, Lopinavir/ritonavir and Clopidogrel; into three datasets. The variable names, description, mean, and standard error of Efavirenz, Lopinavir/ritonavir and Clopidogrel dataset was shown in Table 4.3, 4.4 and 4.5 respectively.

Table 4.3 Descriptive Statistics of the variables in Efavirenz Dataset N=392

variable	description	mean	se
ln nu_pts	Natural log of number of patients receiving Efavirenz	3.14496	1.360977
ln t	Natural log of time (week)	3.952184	0.891334
dimple	Dummy variable for the implementation of CL policy (0=before CL; 1=thereafter)	0.815934	0.388071
hosplevel1	Dummy variable for Hosplevel1 (1=unviersity hospital, 0=else)	0.357143	0.479817
hosplevel2	Dummy variable for Hosplevel2 (1=regional hospital, 0=else)	0.35989	0.480629

Table 4.4 Descriptive Statistics of the variables in Lopinavir/ritonavir Dataset N=313

variable	description	mean	se
ln nu_pts	Natural log of number of patients receiving lopinavir/ritonavir	1.870028	0.963023
ln t	Natural log of time (week)	3.793607	0.893945
dimple	Dummy variable for the implementation of CL policy (0=before CL; 1=thereafter)	0.650655	0.477808
hosplevel1	Dummy variable for Hosplevel1 (1=unviersity hospital, 0=else)	0.449782	0.498561
hosplevel2	Dummy variable for Hosplevel2 (1=regional hospital, 0=else)	0.423581	0.495208

Table 4.5 Descriptive Statistics of the variables in Clopidogrel Dataset N=266

variable	description	mean	se
ln nu_pts	Natural log of number of patients receiving clopidogrel	2.534131	1.112195
ln t	Natural log of time (week)	3.915648	0.938455
dimple	Dummy variable for the implementation of CL policy (0=before CL; 1=thereafter)	0.293233	0.456103
hosplevel	Dummy variable for Hosplevel (0=general hospital, 1=regional hospital)	0.50000	0.500943

Natural log of number of patients receiving each medicine was a dependent variable in all datasets. The intercept represent the baseline level of number of patients receiving each medicine at time zero in general hospital. Natural log of time, dummy variables for the implementation of compulsory licensing policy and dummy variables for the type of hospital are independent variables. The implementation of compulsory licensing policy in each hospital and in each group of patients is different. This analysis specified the first week compulsory licensed medicine was available in each hospital as a cutting point between two periods of time. Thus, before the compulsory licensed medicine was made available in each hospital, the dummy variable for the implementation of compulsory licensing policy is equal to 0 and thereafter the dummy variable is equal to 1.

Since the compulsory licensed clopidogrel is not available in the selected university hospital, the analysis of clopidogrel is comprised of two hospital's datasets which is regional hospital and general hospital. As a result, only one dummy variable for the type of hospital was in the Clopidogrel dataset.

The summary of the results from the estimated model of Efavirenz, Lopinavir/ritonavir, and Clopidogrel are shown in Table 4.6. The results from the estimated model were also attached in Appendices. The adjusted R square of the Efavirenz, Lopinavir/ritonavir, and Clopidogrel regression are 0.56, 0.64 and 0.88 with an F statistic of 103.98, 101.38 and 327.82 and a probability-value of F statistics <0.0001 respectively indicating that the model explains a large part of the variation of number of patients receiving each medicine.

Table 4.6 Results from estimated model of Efavirenz, Lopinavir/ritonavir and Clopidogrel

Medicine	No. of patients receiving medicine at time zero in general hospital	Natural rate of no.of patients receiving medicine when time change by 1%	Effect of the implementation of CL policy on no. of patients receiving medicine	Estimated No. of patients effected by CL (No.of patients/week)	No. of patients receiving medicine in university hospital comparing to general hospital	No. of patients receiving medicine in general hospital comparing to general hospital
Efavirenz	1.60 patients	22.12% increase	25.86% decrease	12.71 patients/week decrease	256.88%	302.76%
Lopinavir/ritonavir	0.14 patients	47.82% increase	26.78% increase	0.71 patients/week increase	228.90%	187.81%
Clopidogrel	*1.14 patients*	36.00 % increase	55.68% increase	7.31 patients/week increase	N/A	144.38%

Table 4.7 Actual number of patients receiving each medicine comparing before and after Compulsory Licensing

Medicine	Actual No. of patients receiving medicine(average/week)		Actual No. of patients receiving medicine in general hospital (average/week)		Actual No. of patients receiving medicine in regional hospital(average/week)		Actual No. of patients receiving medicine in university hospita(average/week)	
	Before CL	After CL	Before CL	After CL	Before CL	After CL	Before CL	After CL
Efavirenz	34.72	38.71	1.23	3.5	62.62	67.61	38.92	45.72
Lopinavir/ritonavir	3.24	10.05	0.03	1.09	3.49	12.88	7.49	13.77
Clopidogrel	13.01	29.97	4.92	18.76	20.77	42.4	N/A	N/A

At time zero in general hospital, natural log of 0.4746, -1.9432 and 0.1347 or approximately 1.60 patients, 0.14 patients and 1.14 patients are recieiving Efavirenz, Lopinavir/ritonavir and Clopidogrel respectively. It has shown that number of patients receiving each medicine was increasing while there was a change in time (natural log of T or Ln(T)). From the estimation, 47.82%, 22.12% and 36.00% of number of patients receiving Clopidogrel, Lopinavir/ritonavir, and Efavirenz were siginificantly ($p < 0.00001$) increased when the time change by 1%.

The estimation has showed that after the implementation of compulsory licensing policy, number of patients receiving Clopidogrel has been increased by 55.68% ($p<0.00001$) and number of patients receiving Lopinavir/ritonavir has been increased by 26.78% ($p=0.0401$) respectively. In contrast, the number of patients receiving Efavirenz has been decreased by 25.86% ($p=0.0180$) after compulsory licensing policy has been implemented.

Type of hospital has show a large effect on the number of patients receiving each medicine. Numbers of patients receiving Clopidogrel and Lopinavir/ritonavir are higher in regional hospital comparing to general hospital by 144.38% and 187.81% respectively. Similarly, number of patients receiving Lopinavir/ritonavir is 228.90% higher in university hospital than general hospital. The effect of hospital type has shown the same result in number of patients receiving Efavirenz which is 302.76% higher in regional hospital comparing to general hospital. However, it has produced a different result in university hospital. Number of patients receiving Efavirenz is only 256.88% higher than general hospital which is less than regional hospital.

Table 4.7 shows the actual number of patients receiving each medicine in 3 selected hospitals. Number of patients receiving each medicine has increased after compulsory licensing. The increase in number of patients receiving Clopidogrel and Lopinavir/ritonavir was a result from its increasing natural rate of patients receiving the medicine and also compulsory licensing. However, from the estimation the increase in number of patient receiving Efavirenz was only from the increase in natural rate of patient receiving each medicine though not the effect from compulsory licensing.

4.2.2 Effect of the compulsory licensing policy on the access to Efavirenz, Lopinavir/ritonavir and Clopidogrel in each health care scheme.

In order to evaluate the effect of compulsory licensing policy on the access the Efavirenz, Lopinavir/ritonavir and Clopidogrel in each health care scheme, the dataset were then divided into 3 groups of patients by patient's health care scheme; Civil Servant Benefit Scheme, Social Security Scheme and Universal Coverage Scheme. Each dataset was also analyzed using the same explanatory model to examine the relationship between the number of patients receiving each announced medicine (dependent variables) and time trend, the effect of the compulsory licensing policy, and the type of hospital (independent variables).

Table 4.8 summarizes the results from the estimated model of Efavirenz, Lopinavir/ritonavir and Clopidogrel in Civil Servant Beneficiaries patients, Social Security Beneficiaries patients and Universal Coverage Beneficiaries patients. In this analysis, it must also be noted that the NAPHA patients were included in the Universal Coverage Group since they are together manage by the National Health Security Office (NHSO). The baseline levels of the number of patients receiving Efavirenz of each group are shown in the constant term (c). At time zero in general hospital, natural log of -.1520, -0.2353 and 0.3177 or approximately 0.86 Civil Servant Beneficiaries patients, 0.79 Social Security Beneficiaries patients and 1.14 Universal Coverage Beneficiaries patients are receiving Efavirenz each week. It has shown that number of patients receiving Efavirenz was increasing while there was a change in time (natural log of T or Ln(T)) in every group of patients. From the estimation, 18.28% and 18.16% of number of Social Security Beneficiaries patients and Universal Coverage Beneficiaries patients receiving Efavirenz were siginificantly (p=0.0004, 0.0028 respectively) increased when the time change by 1%. While there was an increase in number of Civil Servant Beneficiaries patients receiving Efavirenz by 3.44% when the time change by 1%, the increase is not statistically significance (p=0.56).

Table 4.8 Results from estimated model of Efavirenz, Lopinavir/ritonavir and Clopidogrel in each subgroup of health care scheme

Medicine	No. of patients receiving medicine at time zero in general hospital			Natural rate of no.of patients receiving medicine when time change by 1%			Effect of the implementation of CL policy on no. of patients receiving medicine		
	CSMBS patients	SSS patients	UC patients	CSMBS patients	SSS patients	UC patients	CSMBS patients	SSS patients	UC patients
Efavirenz	*0.86 patients*	*0.79 patients*	*1.14 patients*	*3.44% increase*	18.28% increase	18.16% increase	*1.91% increase*	24.01% decrease	*13.77% decrease*
Lopinavir/ritonavir	0.26 patients	0.47 patients	0.14 patients	31.10% increase	20.45% increase	45.44% increase	*0.46% increase*	*10.33% increase*	*24.39% increase*
Clopidogrel	1.68 patients	*0.71 patients*	0.23 patients	20.12% increase	*13.99% increase*	52.07% increase	*11.17% increase*	32.53% increase	96.21% increase

The implementation of Compulsory Licensing policy has differently effect the access to Efavirenz in each group of patients. Only 1.91% insignificance increased in Civil Servant Beneficiaries patients after CL implementation. While there was 24.01% significantly decrease ($p<0.05$) in number of Social Security Beneficiaries patients receiving Efavirenz and 13.77% decrease in number of Universal Coverage Beneficiaries Beneficiaries patients receiving Efavirenz after the implementation of Compulsory Licensing Policy.

Similar to Efavirenz model, the analysis of the NAPHA patients was included in the Universal Coverage Group. At time zero in general hospital; natural log of -1.3578, -0.7550 and -1.9519 or approximately 0.26 Civil Servant Beneficiaries patients, 0.47 Social Security Beneficiaries patients and 0.14 Universal Coverage Beneficiaries patients are receiving Lopinavir/ritonavir each week as shown in the coefficient of the constact term (c). Number of patients receiving Lopinavir/ritonavir was increasing while there was a change in time (natural log of T or Ln(T)) in every group of patients. From the estimation, 31.00%, 20.45% and 45.44% of number of Civil Servant Beneficiaries patients, Social Security Beneficiaries patients and Universal Coverage Beneficiaries patients receiving Lopinavir/ritonavir were siginificantly ($p =0.0012$, 0.0245, 0.0000 respectively) increased when the time change by 1%.

The implementation of Compulsory Licensing policy has increased the access to Lopinavir/ritonavir in every group of patients. After the Compulsory Licensed medicine was available in the hospital, it was observed that there was 24.39%, 10.33% and 0.46% increase in number of Universal Coverage Beneficiaries patients, Social Security Beneficiaries patients and Civil Servant Beneficiaries patients respectively.

For Clopidogrel, since the medicine was not available in the selected university hospital, the model only included the data from two hospitals; regional hospital and general hospital. From the estimation, at time zero in general hospital; natural log of 0.5199, -0.3455 and -1.4507 or approximately 1.68 Civil Servant Beneficiaries patients, 0.71 Social Security Beneficiaries patients and 0.23 Universal Coverage Beneficiaries patients are receiving Clopidogrel each week. From the model, there was an 20.12%(p

<0.00001), 13.99%(p=0.0539) and 52.07% (p <0.00001) significantly increase in number of Civil Servant Beneficiaries patients, Social Security Beneficiaries patients and Universal Coverage Beneficiaries patients receiving Clopidogrel when the time changed by 1%.

Access to Clopidogrel in every group of patients has increased after the Compulsory Licensed medicine was available in the hospital. It was observed that there was 96.21%(p<0.00001), 32.53%(p=0.0260) and 11.17%(p=0.3353) increase in number of Universal Coverage Beneficiaries patients, Social Security Beneficiaries patients and Civil Servant Beneficiaries patients respectively.

4.3 Findings: Effect of dimensions of Access to Medicine on the access to Efavirenz, Lopinavir/ritonavir and Clopidogrel in the selected hospital after Compulsory Licensing policy implementation

Access to the announced medicine in this study employed dimensions of the access to medicine developed by MSH and WHO (Management Science for Health and World Health Organization, 2000). Effect of dimension of Access to Medicine on the access to compulsory licensed medicine was studied by interviewing hospital staffs in the selected hospital using open-ended questions to explore the dimensions of access. The interview in each dimension was summarized as follows (The results from each interviewee are summarized in Appendix);

4.3.1 Physical Availability

Compulsory licensed antiretroviral medicines selected in this study which is Efavirenz and Lopinavir/ritonavir was available in all of the three selected hospital. However, Clopidogrel, was available only in regional hospital and general hospital.

According to the interviewee from the university hospital, a pharmacist who responsible in procuring the medicine, in order to procure the medicine there were several major factors to considered; quality of medicine, price of medicine, the guarantee of availability of the medicine. Even the price of the compulsory licensed medicine is cheaper than original medicine, the quality of medicine is still doubtful by

the physicians especially cardiologists in the hospital. Clopidogrel is prescribed in patients undergoing percutaneous coronary intervention (PCI) with stenting after acute myocardial infarction in order to reduce stent thrombosis and to reduce the rate of death from cardiovascular causes, myocardial infarction, or stroke (Smith SC Jr et al, 2005). Cardiologist in this hospital has some concern on the quality of the compulsory licensed Clopidogrel for example, its bioequivalence, clinical equivalence, toxicity and most of all patients' outcome comparing to patients prescribed with original Clopidogrel. Another concerning factor is the guarantee of availability of compulsory licensed medicine. There were some incidences of Clopidogrel out-of-stock in some hospital heard. Thus, supply shortage was another uncertain factor. Medicine procured to the hospital should not be switched from brand to brand continually since it will effect the patients' compliance and also the treatment outcome especially in the critical patients undergoing PCI. For the antiretroviral medicine, hospital has no ability to choose which brand of medicine; original or compulsory licensed to use with the patients under the Access to Care program and Social Security program. Thus, in this university hospital the compulsory licensed medicine is available for the patients under these programs. As for other patients, the use of original or compulsory licensed medicine depends on patients' ability to pay, patient's benefit scheme and physician's choices.

The problem of compulsory licensed medicine out-of-stock had also been faced by another interviewee, pharmacist who responsible in procuring medicine in general hospital. Compulsory licensed clopidogrel is out-of-stock after the hospital has switched from original product to compulsory licensed version. During that, the hospital has temporarily switched back to Plavix®, the original version of clopidogrel. This also happened in compulsory licensed Lopinavir/ritonavir used under Access to Care program.

4.3.2 Affordability

All interviewees from every hospital agree that the price of compulsory licensed medicine is more affordable comparing to original medicine. However, some of them for example, pharmacist from university hospital has suggested that price may not be the

most important issue in procuring the medicine if the medicine cannot proved to be equally effective to the original medicine. This has also be confirmed by a medicine specialist in general hospital that compulsory licensed medicine needed further clinical studied on their effectiveness to ensure the quality of these medicines.

4.3.3 Acceptability

Opinions on this dimension of access can be classified as follows;

1. Physical appearance: Most interviewees are satisfied with the physical appearance including the packaging of the compulsory licensed medicine. However, there is some suggestion from pharmacist in the general hospital that the packaging of the compulsory licensed medicine like other Government Pharmaceutical Organization (GPO)'s product has similar packaging. As a result, the probability of the medication error during the prescribing process can occurred.

Another aspect on physical appearance of the compulsory licensed medicine is its dosage and dosage form. Compulsory licensed Lopinavir/ritonavir is a 200mg lopinavir and 50 mg ritonavir tablet which is a different dosage form from its original soft gel capsule 133.33 lopinavir and 33.33 ritonavir. According to an infectious specialist in the university hospital, the tablet form of lopinavir/ritonavir is easier to use than the original soft gel lopinavir/ritonavir since it does not need to be kept in the refrigerator which is required in soft gel dosage form. The interviewee also commented that the dosage of the compulsory licensed medicine (200 mg of lopinavir and 50 mg of ritonavir) is more convenient for patient since number of tablet per meal is less.

2. Quality of products and services: Acceptability on this aspect of compulsory licensed medicine is varied. Some physicians and pharmacists are quite confident with the quality of compulsory licensed medicine. Most stated that the medicine is imported by Government Pharmaceutical Organization (GPO). Thus, the quality of medicine at least is guaranteed by the government. On the other side, some physicians especially specialists for example, cardiologist, infectious in secondary and tertiary hospital mostly claimed that there is no clinical trial to assure that compulsory licensed medicine is

clinically equal to its original product. These physicians are not confidence in prescribing compulsory licensed medicine especially in critical patients such as patients undergoing PCI with stent which prescribed with Clopidogrel or HIV patients who is resistant to other drug and required second line regimen as lopinavir/ritonavir. However, these physicians mostly agreed that in non-critical patients for example, the use of clopidogrel in coronary artery disease prophylaxis in patients who cannot use aspirin may be suitable. Nonetheless, all interviewees affirmed that the use of compulsory licensed medicine should be monitored or undergoing the clinical trial to assure the quality of these medicines.

4.3.4 Quality of Products and Services

Quality of products and services is an essential component of access and cutting across all dimensions (Management Science for Health and World Health Organization, 2000). Quality of compulsory licensed medicine has been an aspect which has been mentioned by the interviewees in all other dimensions of access to medicine; physical availability, affordability and acceptability. Most interviewees suggested that the quality of compulsory licensed medicine could not be evaluated accurately by the interviewee since number of patients receiving compulsory licensed medicine in each hospital is still limited. Up till now, serious side effects in patients receiving compulsory licensed medicine have not been reported in the studied hospital. However, the most concerning issues of the interviewees were treatment outcome of patient receiving these medicine comparing to the original medicine which as mentioned could not accurately evaluated by most interviewees.

Besides, all interviewees have agreed that the quality of medicine has an influence on selecting which medicine to procure and also their perceptions on the medicine which will eventually affect their prescribing patterns.

4.4 Discussions

According to the Ministry of Public Health, Compulsory licensing policy has been implemented in order to alleviate the access to medicine problems. In this study, it was showed that a change from prior-compulsory licensing policy to after-compulsory licensing policy was associated with a substantial increase in number of patients receiving Clopidogrel and Lopinavir/ritonavir. However, this effect has not been shown in the number of patients receiving Efavirenz. This result may be directly related to the policy and indicates that this method is successful in increasing the access to only some particular category of drugs.

According to the Clinical Practice Guideline developed by the Thai AIDS Society in 2008 (Somnuek et al, 2008), Efavirenz can be used to substitute Nevirapine (NVP) which is the first line regimen in the case that patient develops a severe rash or hepatotoxicity from Nevirapine. While Lopinavir/ritonavir is a combined medicine used to substitute the second-line treatment of HIV; Efavirenz in the case that patient develops severe side effects from Efavirenz. The increase in number of patients receiving Lopinavir/ritonavir and the decrease in number of patients receiving Efavirenz may also associated with this clinical practice guideline. From the clinical practice guideline, these two medicine themselves are substitutes products. The decrease in lopinavir/ritonavir's price would also cause the demand for Efavirenz to fall also. From the issue above, it has confirmed that compulsory licensed may not be an effective tool in increasing access to some medicine especially when the compulsory licensed medicines are substitute products. Another effect the policy makers should be concerned of is the HIV drug resistance. The compulsory licensing policy may increase the access to second line HIV medicine in some patients who truly need it. On the other hand, it may also increase the use in some patients who has not yet required these second line medicines which as a results increase the possibility of HIV drug resistance.

Type of hospital should also be considered as one of the major factor which has an impact on the access to medicine. Access to some medicine may not be an issue in some type of hospital comparing to other type of hospital for example, number of

patients receiving Lopinavir/ritonavir is very low in general hospital comparing to university hospital. On the contrary, number of patients receiving some medicine may be higher in lower level of hospital as observed in higher number of patients receiving Efavirenz in regional hospital comparing to university hospital. This is owing to number of patients in each hospital and also patients' characteristic, complication of patient's disease and prevalence of disease in each hospital. Efavirenz, the second-line treatment of HIV is used more widely in regional hospital than university hospital where patients' disease are more complicated and required newer generation of medicine. These findings suggest that in order to maximize the number of compulsory licensing policy's intended recipients; type of hospital where access to the medicine is a problem should be targeted to provide the information on what and when compulsory licensed medicine are available, the process to obtain these medicines and also how to prescribe this medicine appropriately.

When comparing between each health care scheme in each type of medicine, the implementation of compulsory licensing policy has differently change the access to medicine. In civil servant benefit scheme patient group, compulsory licensing policy has not increased access to medicine in all three selected medicine. This has confirmed that access to medicine may not be a problem in this group of patients which employed fee-for-service as its payment method to the health care providers. In the social security service patient, the significantly increase in access to medicine is observed only in patients receiving Clopidogrel. While in the patients receiving Efavirenz, the number of patient receiving the medicine was significantly decrease, the number of patients receiving Lopinavir/ritonavir was not significantly increase similar to the increase in the analysis of all patients. This may be due to the limited number of patients receiving Lopinavir/ritonavir included in this study. The pattern shows in the social security patients group is shown in the universal coverage group also.

It should also be noted that even the number of patients receiving Clopidogrel may increase significantly; university hospital where compulsory licensed Clopidogrel is not available has not been included in the analysis. These findings suggest that even the policy itself works successfully in increasing access; the magnitude of the increase

may be only a small fraction of its intended effect since medicines are still unavailable in some hospital. This has also confirmed that even compulsory licensed medicine is now affordable, the quality of these medicines are still the most concerning factors. Access cannot be fully increased if the health care providers are not confidence in the compulsory licensed medicine. It is therefore crucial that clinical trial comparing the effectiveness of original and compulsory licensed medicine should be done or at least the use of compulsory licensed medicine should be monitored in order to assure the quality and effectiveness of these medicines. Otherwise, the acceptability of the physician who prescribed the medicine would have an effect on the implementation of the policy in increasing access.

Demand for health care was determined by both patient and physician factors. Physicians in the health care market act as a patients' agent to make their decision on what medicine would be used. Therefore, effect of compulsory licensing on access to medicine does not reflect the change real demand of the medicine by the patient. On the contrary, it reflects the acceptability of the compulsory licensed medicine by the physician.

After the announcement of the compulsory licensing policy in late 2006, it took more than 1 and a half year before the medicine is actually available in the hospital. After that, hospital is still not confidence whether the medicine will be continually available. These policy management topics should also be taken into account by the policy makers since it will affect the acceptability of the physician and pharmacists in the hospital.

Lastly, the quality of medicine and/or patient's clinical outcome has not been included in this explanatory model. It was assumed that the quality of original and compulsory licensed medicine is equal and would produce the same outcome. The increase in access then might not related to the increase in patients' treatment outcome or quality of life.

CHAPTER V

CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusion

The introduction of a compulsory licensing policy was to increase access to medicine which was a major public health issues found in most countries. After the implementation of the policy in Thailand in late 2006, the policy has not been evaluated whether the implementation has significantly alleviated the access to medicine issue.

This study has shown that the implementation of compulsory licensing policy was associated with the significantly increase in overall number of patients receiving Clopidogrel and Lopinavir/ritonavir. However, the number of patients receiving Efavirenz has been decreased. Accordingly, the overall access to antiviral drug has been increased. Efavirenz and Lopinavir/ritonavir are both antiretroviral medicine, it is observed in this study that the change in number of patients receiving each medicine after the implementation of compulsory licensing policy was in the different trend. Lopinavir/ritonavir is a combined medicine used to substitute the second-line treatment of HIV; Efavirenz in the case that patient develops severe side effects from Efavirenz. (Somnuek et al, 2008). Both medicines are in this case are substitute products and thus, the decline in Lopinavir/ritonavir price results in the decrease in Efavirenz's demand.

Level of hospital also has an impact on the access to medicine. Number of patients receiving medicine is higher in university hospital, regional hospital and general hospital respectively. However, this doesn't apply to every category of medicine. It was found in this study that number of patients receiving Efavirenz in regional hospital is higher comparing to university hospital. This is owing to patients' characteristic, complication of patient's disease and prevalence of disease. Efavirenz, the second-line treatment of HIV is used more widely in regional hospital than university hospital where patients' disease are more complicated and required newer generation of medicine.

Health care scheme is also an important factor as different payment method effect the access to health care. This study has confirmed that access to medicine may

not be an issue in the group of patients which employed fee-for-service as its payment method to the health care providers such as civil servant benefit scheme. The compulsory licensing policy has not increased access to medicine in all three selected medicine in this group of patients. While in the social security service and universal coverage patients which employed capitation payment method, the significantly increase in access to medicine is observed only in patients receiving Clopidogrel. While in the patients receiving antiretroviral medicine, the number of patient receiving the medicine was not increased. This due to the vertical management of the antiretroviral medicine which health care providers were provided with the needed medicine with no cost. Thus, payment method in this case does not affect the access to medicine.

While exploring dimensions of access through interviewing health care providers, the most important dimension nearly all interviewees concerned of is the quality of the compulsory licensed medicine. Quality of compulsory licensed medicine was concerned until the selected university hospital was not including the medicine into their hospital medicine list. Thus even the medicine is affordable; the acceptability of the physician especially on its quality is a fundamental aspect that will allow the physical availability of the medicine for the patient.

5.2 Recommendations

1. To increase access to medicine, government should not consider only announcing the compulsory licensing policy but also the management of policy to be effectively implemented. Time period took from announcing the policy until the medicine was truly available in the hospital, event of medicine out of stock or information provided on what and when the compulsory licensed medicine is truly available is the problem faced in the management process of the compulsory licensing policy which government should also consider.

2. Level of hospital has also contributed a large effect on the access to medicine. Thus, in order to target the intended recipients, government should

focus on providing information of compulsory licensed medicine to the hospital where access to medicine is an issue.

3. Different health care schemes show different level of access to medicine. Thus, in order to increasing access to medicine, compulsory licensing may not be the only means. Payment mechanism of the scheme for example has also shown that it has a large impact on the access to not only medicine but the health care service.

4. Quality of compulsory licensed medicine is the factor most health care providers are concerning of. Physician's perception toward the quality of the medicine then influence the prescription pattern and therefore, have an impact on the access to these medicine. Thus, government should also focus on assuring the quality of the compulsory licensed medicine for example, providing clinical data or conducting clinical trial proving compulsory licensed medicine is clinically equivalent to the original one.

5.3 Limitation of the study and suggestion for further study

1. Some limitations in this study should be noted. Since quality of medicine and/or patient's clinical outcome has not been included in this explanatory model. It was assumed that the quality of original and compulsory licensed medicine is equal and would produce the same outcome. Study (Soumerai et al, 1991) found that health system components are interrelated and it is possible that the policy implementation affected other areas. The study of effectiveness of compulsory licensed medicine should also be done in order to assure the quality of these medicines.

2. Given that the study is the first field evaluation, number of hospital in this study is limited. Further study on the effect of compulsory licensing policy on the access to these medicines in more hospitals should also be done.

3. Lopinavir/ritonavir is an advanced antiretroviral medicine which is not widely used especially in general hospital. Number of patients receiving

Lopinavir/ritonavir may be too small particularly in the subgroup analysis in each health care scheme.

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Appendix

TableA.1 Results of estimated model of number of patients receiving Efavirenz

Variable	Coefficient	Std. Error	t-Statistic	p-value
C	0.4746	0.1353	3.5086	0.0005
ln(T)	0.2212	0.0468	4.7315	0.0000
DIMPLE	-0.2586	0.1089	-2.3756	0.0180
HOSPLEVEL1	2.5688	0.0638	40.2818	0.0000
HOSPLEVEL2	3.0276	0.0625	48.4559	0.0000

Adjusted R-squared = 0.88

F Statistic = 327.82 Prob(F-statistic) < 0.00001

TableA.2 Results of estimated model of number of patients receiving Lopinavir/ritonavir

Variable	Coefficient	Std. Error	t-Statistic	p-value
C	-1.943275	0.254257	-7.642954	0.0000
ln(T)	0.478159	0.070123	6.81887	0.0000
DIMPLE	0.267824	0.12973	2.064472	0.0401
HOSPLEVEL1	2.289027	0.126525	18.09153	0.0000
HOSPLEVEL2	1.878114	0.126417	14.85655	0.0000

Adjusted R-squared = 0.64

F Statistic = 101.38 Prob(F-statistic) < 0.00001

TableA.3 Results of estimated model of number of patients receiving Clopidogrel

Variable	Coefficient	Std. Error	t-Statistic	p-value
C	0.1347	0.2523	0.5338	0.5940
ln(T)	0.3600	0.0642	5.6064	0.0000
DIMPLE	0.5568	0.1221	4.5613	0.0000
HOSPLEVEL	1.4438	0.0953	15.1529	0.0000

Adjusted R-squared = 0.56

F Statistic = 103.98 Prob(F-statistic) < 0.00001

TableA.4 Results of estimated model of number of patients receiving Efavirenz in Civil Servant Benefit Scheme patients

Variable	Coefficient	Std. Error	t-Statistic	p-value
C	-0.1520	0.2502	-0.6076	0.5440
ln(T)	0.0344	0.0602	0.5718	0.5679
DIMPLE	0.0191	0.1202	0.1593	0.8735
HOSPLEVEL1	2.8292	0.1856	15.2407	0.0000
HOSPLEVEL2	1.2384	0.1917	6.4612	0.0000

Adjusted R-squared = 0.68

F Statistic = 139.73 Prob(F-statistic) < 0.00001

TableA.5 Results of estimated model of number of patients receiving Efavirenz in Universal Coverage patients

Variable	Coefficient	Std. Error	t-Statistic	p-value
C	0.3177	0.1813	1.7522	0.0806
ln(T)	0.1816	0.0604	3.0061	0.0028
DIMPLE	-0.1377	0.1342	-1.0264	0.3054
HOSPLEVEL1	1.3264	0.0799	16.6001	0.0000
HOSPLEVEL2	2.7422	0.0797	34.4148	0.0000

Adjusted R-squared = 0.77

F Statistic = 301.07 Prob(F-statistic) < 0.00001

TableA.6 Results of estimated model of number of patients receiving Efavirenz in Social Security patients

Variable	Coefficient	Std. Error	t-Statistic	p-value
C	-0.2353	0.1613	-1.4587	0.1457
ln(T)	0.1828	0.0510	3.5836	0.0004
DIMPLE	-0.2401	0.1129	-2.1255	0.0343
HOSPLEVEL1	1.0144	0.0753	13.4644	0.0000
HOSPLEVEL2	3.0530	0.0747	40.8887	0.0000

Adjusted R-squared = 0.87

F Statistic = 528.71 Prob(F-statistic) < 0.00001

TableA.7 Results of estimated model of number of patients receiving Lopinavir/ritonavir in Civil Servant Benefit Scheme patients

Variable	Coefficient	Std. Error	t-Statistic	p-value
C	-1.3578	0.3535	-3.8414	0.0002
LOG(T)	0.3100	0.0939	3.2995	0.0012
DIMPLE	0.0046	0.1481	0.0310	0.9753
HOSPLEVEL1	1.6958	0.1790	9.4760	0.0000
HOSPLEVEL2	0.2984	0.2008	1.4857	0.1396

Adjusted R-squared = 0.59

F Statistic = 51.89 Prob(F-statistic) < 0.00001

TableA.8 Results of estimated model of number of patients receiving Lopinavir/ritonavir in Universal Coverage patients

Variable	Coefficient	Std. Error	t-Statistic	p-value
C	-1.9519	0.3131	-6.2332	0.0000
LOG(T)	0.4544	0.0776	5.8522	0.0000
DIMPLE	0.2439	0.1319	1.8490	0.0661
HOSPLEVEL1	0.8972	0.1668	5.3789	0.0000
HOSPLEVEL2	1.7750	0.1706	10.4054	0.0000

Adjusted R-squared = 0.51

F Statistic = 49.67 Prob(F-statistic) < 0.00001

TableA.9 Results of estimated model of number of patients receiving Lopinavir/ritonavir in Social Security patients

Variable	Coefficient	Std. Error	t-Statistic	p-value
C	-0.7550	0.3795	-1.9895	0.0486
LOG(T)	0.2045	0.0899	2.2739	0.0245
DIMPLE	0.1033	0.1699	0.6080	0.5442
HOSPLEVEL1	0.4745	0.2237	2.1210	0.0357
HOSPLEVEL2	1.3479	0.2264	5.9528	0.0000

Adjusted R-squared = 0.41

F Statistic = 25.42 Prob(F-statistic) < 0.00001

TableA.10 Results of estimated model of number of patients receiving Clopidogrel in Civil Servant Benefit Scheme patients

Variable	Coefficient	Std. Error	t-Statistic	p-value
C	0.5199	0.2367	2.1967	0.0290
ln(T)	0.2012	0.0599	3.3577	0.0009
DIMPLE	0.1117	0.1157	0.9654	0.3353
HOSPLEVEL	1.1910	0.0908	13.1151	0.0000

Adjusted R-squared = 0.44

F Statistic = 60.52 Prob(F-statistic) < 0.00001

TableA.11 Results of estimated model of number of patients receiving Clopidogrel in Universal Coverage patients

Variable	Coefficient	Std. Error	t-Statistic	p-value
C	-1.4507	0.3146	-4.6105	0.0000
ln(T)	0.5207	0.0759	6.8590	0.0000
DIMPLE	0.9621	0.1150	8.3652	0.0000
HOSPLEVEL	1.2899	0.0971	13.2829	0.0000

Adjusted R-squared = 0.65

F Statistic = 117.39 Prob(F-statistic) < 0.00001

TableA.12 Results of estimated model of number of patients receiving Clopidogrel in Social Security patients

Variable	Coefficient	Std. Error	t-Statistic	p-value
C	-0.3455	0.3434	-1.0061	0.3169
ln(T)	0.1399	0.0717	1.9518	0.0539
DIMPLE	0.3253	0.1439	2.2605	0.0260
HOSPLEVEL	0.2526	0.2049	1.2330	0.2205

Adjusted R-squared = 0.15

F Statistic = 6.74 Prob(F-statistic) =0.00034

Figure A.1 Number of patients receiving Efavirenz in each week comparing before and after Compulsory licensed Efavirenz were available in the hospital

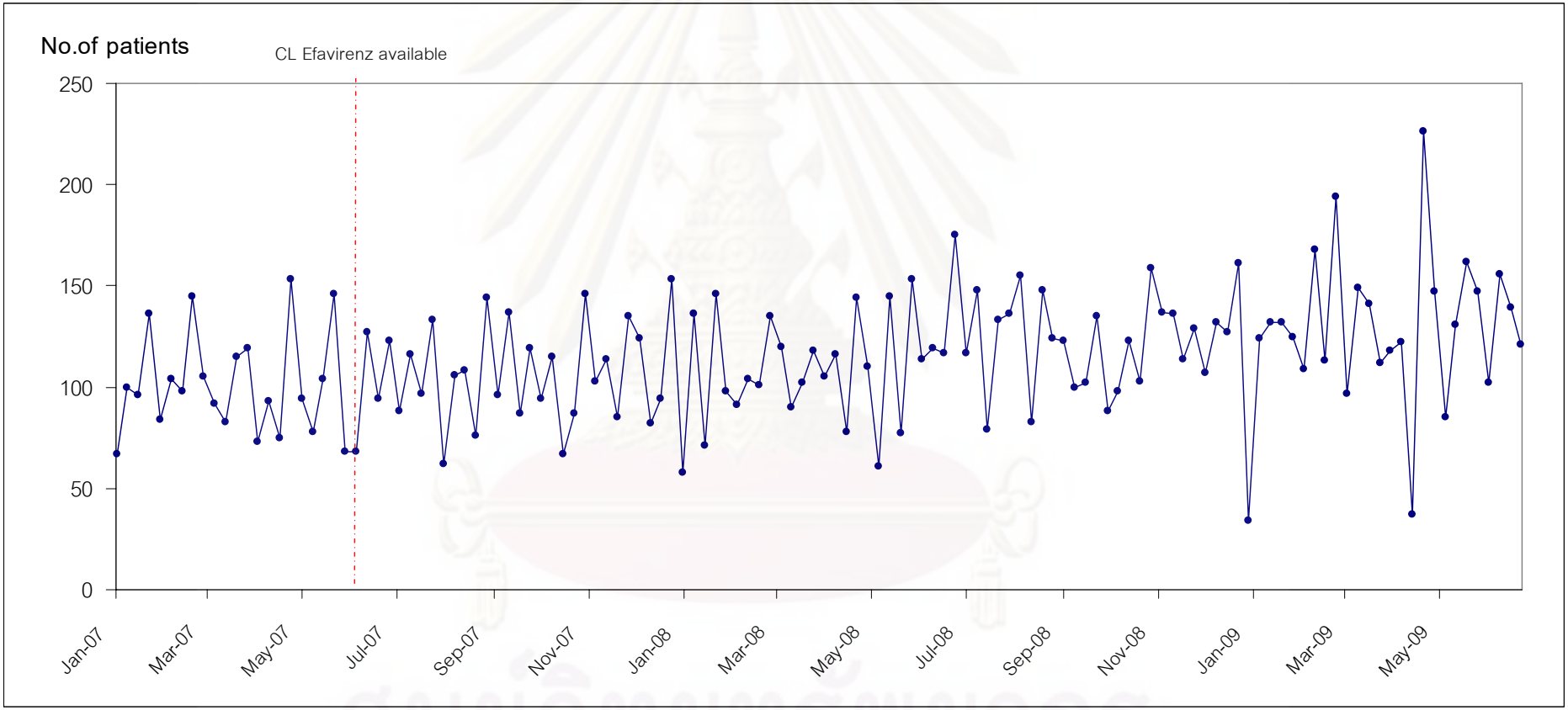


Figure A.2 Number of patients receiving Lopinavir/ritonaivir in each week comparing before and after Compulsory licensed Lopinavir/ritonaivir were available in the hospital

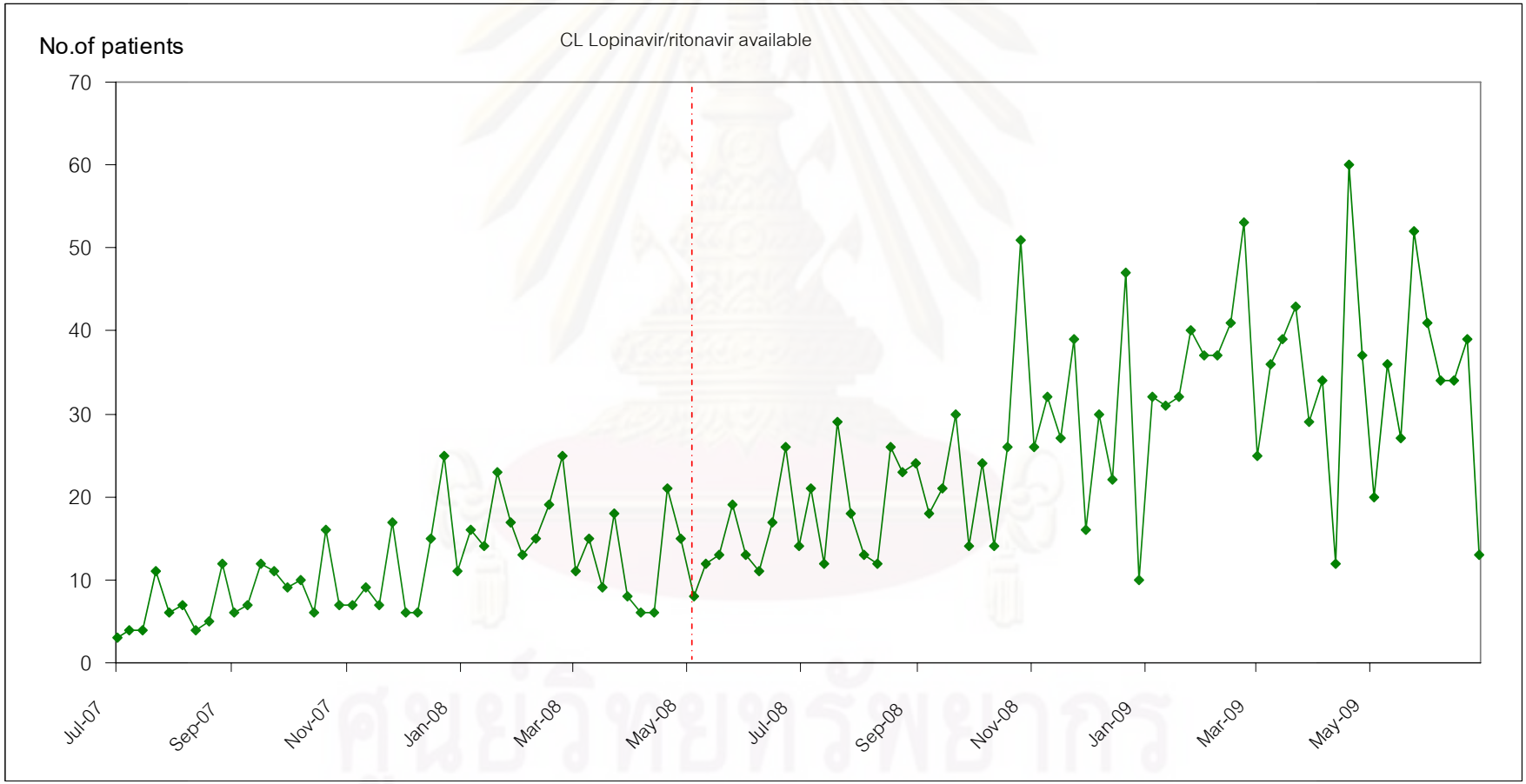
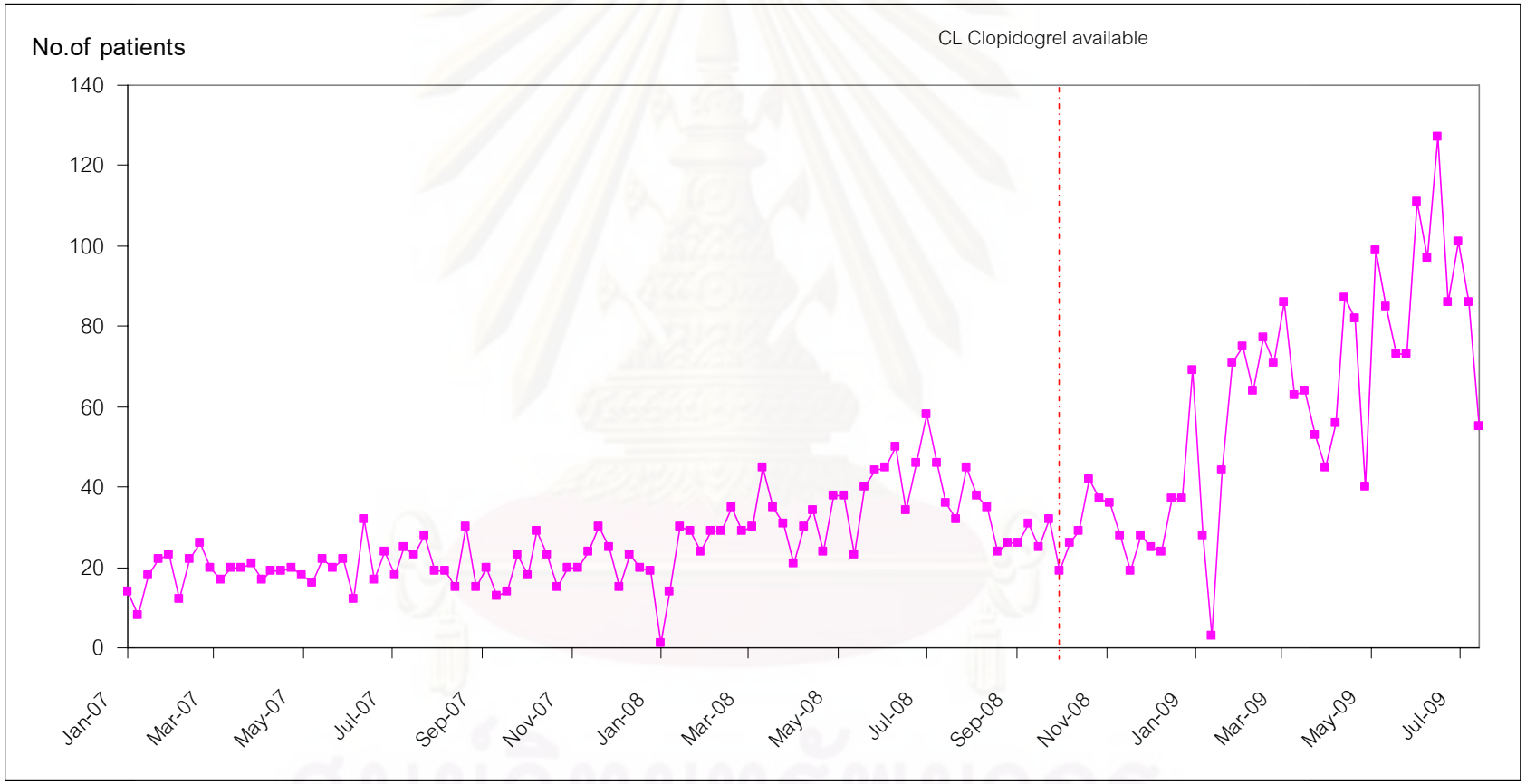


Figure A.3 Number of patients receiving Clopidogrel in each week comparing before and after Compulsory licensed Clopidogrel were available in the hospital



TableA.13 Results from the interview with the Physician in the hospital

			Interviewee 6	Interviewee 7	Interviewee 8	Interviewee 9	Interviewee 10
	Hospital		University hospital	Regional hospital	Regional hospital	General hospital	General hospital
	Position		Physician with infectious specialty	Physician with cardiologist specialty	Physician with infectious specialty	Physician with medicine specialty	Physician with medicine specialty
	Experience in CL medicine		Direct involvement in ARV medicine for more than 15 years	Experienced in cardiology department for 4 years	Direct involvement in ARV program for 1 year	Direct involvement in drug selection process for 2-3 years	Experienced in medicine department which responsible in cardiogy patient and infectiuos patients for more than 5 years
	Dimension of Access						
1	**Physical Availability**						
1.1	Availability of medicine	Efavirenz	Both original and CL medicine are available in the hospital. CL medicine used in the hospital is used in the NAPHA and SSS patients. Original medicine is still used in some group of patients, for exmaple CSMBS patients after the CL medicine was made available in the hospital.	Only CL Efavirenz is available after the implementation of CL. CL Efavirenz has fully replaced the used of Storcrin® in every group of patients	Only CL Efavirenz is available after the implementation of CL. CL Efavirenz has fully replaced the used of Storcrin® in every group of patients	Only CL Efavirenz is available after the implementation of CL. CL Efavirenz has fully replaced the used of Storcrin® in every group of patients	Only CL Efavirenz is available after the implementation of CL. CL Efavirenz has fully replaced the used of Storcrin® in every group of patients
		Lopinavir/ritonavir	Both original and CL medicine are also available in the hospital. CL medicine used in the hospital is used in the NAPHA and SSS patients as CL Efavirenz and Original medicine is still used in some group of patients after the CL medicine was made available in the hospital.	Only CL LPV/r is available after the implementation of CL. CL Lpv/r has also fully replaced the used of Kaletra® in every group of patients	Only CL LPV/r is available after the implementation of CL. CL Lpv/r has also fully replaced the used of Kaletra® in every group of patients	Only CL LPV/r is available after the implementation of CL. CL Lpv/r has also fully replaced the used of Kaletra® in every group of patients	Only CL LPV/r is available after the implementation of CL. CL Lpv/r has also fully replaced the used of Kaletra® in every group of patients
		Clopidogrel	Does not have direct experience on the use of Clopidogrel.	Only CL Clopidogrel is available after the implementation of CL. CL Clopidogrel has also fully replaced the used of Plavix® in every group of patients	Does not have direct experience on the use of Clopidogrel.	Only CL Clopidogrel is available after the implementation of CL. CL Clopidogrel has also fully replaced the used of Plavix® in every group of patients	Only CL Clopidogrel is available after the implementation of CL. CL Clopidogrel has also fully replaced the used of Plavix® in every group of patients

TableA.13(Continue) Results from the interview with the Physician in the hospital

		Interviewee 6	Interviewee 7	Interviewee 8	Interviewee 9	Interviewee 10
2	**Affordability**	Price of CL medicine is much more afforadable than the orignal product. However, price of the medicine is not the most important factor in procuring the medicine.	Price of CL medicine is cheaper than the orignal product. Though, price of the medicine is not the most important factor in procuring the medicine.	Price of CL medicine is much more afforadable than the orignal product.	Price of CL medicine is much more afforadable than the orignal product.	Price of CL medicine is much more afforadable than the orignal product.
3	**Acceptability**					
3.1	Physical appearance	Satisfied with the physical appearance of the CL medicine.Also, he has pointed out that the tablet form of lopinavir/ritonavir is easier to use than the original soft gel lopinavir/ritonavir since it does not need to be kept in the refrigerator which is required in soft gel dosage form. The interviewee also commented that the dosage of the compulsory licensed medicine (200 mg of lopinavir and 50 mg of ritonavir) is more convenient for patient since number of tablet per meal is less.	satisfied with the physical appearance of the CL medicine	satisfied with the physical appearance of the CL medicine	satisfied with the physical appearance of the CL medicine	satisfied with the physical appearance of the CL medicine
3.2	Quality of products and services	No clinical data supporting that CL medicine is clinical equivalence to the original medicine. Thus, he is not confidence in prescribing CL medicine to the critical patients for example, patients who develops drug resistance and required lopinavir/ritonavir. However, in the NAPHA and SSS patients, it is not his decision in selecting what brand of the medicine will be prescribed.	Since there are no clinical trial conducted to support that CL medicine is clinical equivalence to the original medicine. Thus, he is not confidence in prescribing CL medicine to his AMI patients. He suggested that the use of CL clopidogrel may be suitable in chronic patients, for example, the use of clopidogrel in coronary artery disease prophylaxis in patients who cannot use aspirin. However, the hospital has fully replaced the original medicine with the CL version.	Believe that CL medicine is similar to original medicine in terms of its efficacy. He believe that the medicine is imported by the GPO which is a reliable source.	Believe that CL medicine is similar to original medicine. However, government should further monitor the use of these medicine in the patients.	He believe that the use of CL clopidogrel may be suitable in chronic patients, for example, the use of clopidogrel in coronary artery disease prophylaxis in patients who cannot use aspirin. However, the use of CL clopidogrel in AMI patients should be further investigated using clinical trial. However, since the hospital is a general hospital, no AMI patients are treated in the hospital.
4	**Quality of products and services**	All agree that this could not be aacurately evaulated by the interviewee. They also agree that clinical trial and other qulaity assurance process should be done by the government. So they would feel more confidence in prescribing the medicine.				

TableA.14 Results from the interview with the Pharmacist in the hospital

			Interviewee 1	Interviewee 2	Interviewee 3	Interviewee 4	Interviewee 5
	Hospital		University hospital	Regional hospital	Regional hospital	General hospital	General hospital
	Position		Pharmacist	Pharmacist	Pharmacist	Pharmacist	Pharmacist
	Experience in CL medicine		Direct involvement in drug procurement process for more than 10 years	Direct involvement in drug procurement process for 2 years	Direct involvement in ARV program for 3 years	Direct involvement in drug procurement process for 5 years	Direct involvement in ARV program for 11/2 years
	Dimension of Access						
1	**Physical Availability**						
1.1	Availability of medicine	Efavirenz	Both original and CL medicine are available in the hospital. CL medicine used in the hospital is used in the NAPHA and SSS patients. Original medicine is still used in some group of patients, for exmaple CSMBS patients after the CL medicine was made available in the hospital.	Only CL Efavirenz is available after the implementation of CL. CL Efavirenz has fully replaced the used of Storcrin® in every group of patients	Only CL Efavirenz is available after the implementation of CL. CL Efavirenz has fully replaced the used of Storcrin® in every group of patients	Only CL Efavirenz is available after the implementation of CL. CL Efavirenz has fully replaced the used of Storcrin® in every group of patients	Only CL Efavirenz is available after the implementation of CL. CL Efavirenz has fully replaced the used of Storcrin® in every group of patients
		Lopinavir/ritonavir	Both original and CL medicine are also available in the hospital. CL medicine used in the hospital is used in the NAPHA and SSS patients as CL Efavirenz and Original medicine is still used in some group of patients after the CL medicine was made available in the hospital.	Only CL LPV/r is available after the implementation of CL. CL Lpv/r has also fully replaced the used of Kaletra® in every group of patients	Only CL LPV/r is available after the implementation of CL. CL Lpv/r has also fully replaced the used of Kaletra® in every group of patients	Only CL LPV/r is available after the implementation of CL. CL Lpv/r has also fully replaced the used of Kaletra® in every group of patients	Only CL LPV/r is available after the implementation of CL. CL Lpv/r has also fully replaced the used of Kaletra® in every group of patients
		Clopidogrel	Only original medicine, Plavix® is available in the hospital. CL clopidogrel is still not available. The interviewee has pointed out factors need to be considered in what medicine should be procured, quality of medicine, price of medicine, the guarantee of availability of the medicine. Even the price of the CL medicine is cheaper than original medicine, the quality of medicine is still doubtful by the physicians especially cardiologists in the hospital. Clopidogrel is prescribed in patients undergoing PCI with stenting after AMI. Thus, Cardiologist in this hospital has some concerns on the quality of the CL Clopidogrel for example, its clinical equivalence, toxicity and most of all patients' outcome comparing to patients prescribed with original medicine. Some incidences of Clopidogrel out-of-stock in other hospital was heard. Thus, supply shortage was another uncertain	Only CL Clopidogrel is available after the implementation of CL. CL Clopidogrel has also fully replaced the used of Plavix® in every group of patients	Does not have direct experience on prescribing of Clopidogrel.	Only CL Clopidogrel is available after the implementation of CL. CL Clopidogrel has also fully replaced the used of Plavix® in every group of patients	Does not have direct experience on prescribing of Clopidogrel.

TableA.14(Continue) Results from the interview with the Pharmacist in the hospital

			Interviewee 1	Interviewee 2	Interviewee 3	Interviewee 4	Interviewee 5
1.2	Process of procuring	Antiretroviral medicine	Through Government Pharmaceutical organization system, VMI. Physicians or hospital staffs must key-in patients' laboratory test to request for each patient's ARV regimen and must reenter the patients' data if there is a regimen change. These medicines are then distributed through Government Pharmaceutical Organization (GPO)'s distribution network or known as Vendor Management Inventory (VMI). The program allows hospitals to order or adjust the amount of ARV medicine they require via an internet program. Once orders are placed the GPO sends the medicine directly to hospital.				
		Clopidogrel	N/A	Through Government Pharmaceutical organization system, VMI.	Through Government Pharmaceutical organization system, VMI.	Through Government Pharmaceutical organization system, VMI.	Through Government Pharmaceutical organization system, VMI.
1.3	Events of medicine out of stock		N/A	N/A	N/A	CL clopidogrel is out-of-stock after the hospital has switched from original product to CL version. During that, the hospital has temporarily switched back to Plavix®. This also happened in CL Lopinavir/ritonavir used under Access to Care	N/A
2	**Affordability**		Price of CL medicine is much more afforadable than the orignal product. However, price of the medicine is not the most important factor in procuring the medicine.	Price of CL medicine is much more afforadable than the orignal product.	Price of CL medicine is much more afforadable than the orignal product.	Price of CL medicine is much more afforadable than the orignal product.	Price of CL medicine is much more afforadable than the orignal product.
3	**Acceptability**						
3.1	Physical appearance		satistied with the physical appearance of the CL medicine	satistied with the physical appearance of the CL medicine	satistied with the physical appearance of the CL medicine	The packaging of the CL medicine like other Government Pharmaceutical Organization (GPO)'s product has similar packaging. As a result, the probability of the medication error during the prescribing process can occurred	satistied with the physical appearance of the CL medicine
3.2	Quality of products and services		No clinical data supporting that CL medicine is clinical equivalence to the original medicine. Thus, still doubtful in the quality of the medicine.	Quite confidence in the CL medicine since it is imported by the GPO which at least guaranteed by the government.	Believe that CL medicine is similar to original medicine in terms of its efficacy.	Believe that CL medicine is similar to original medicine in terms of its efficacy.	Believe that CL medicine is similar to original medicine in terms of its efficacy.
4	**Quality of products and services**		This could not be evaluated accurately by the interviewee since number of patients receiving compulsory licensed medicine in each hospital is still limited. Clinical trial in patients receiving CL medicine should be done by the government.	could not be evaluated accurately by the interviewee since number of patients receiving compulsory licensed medicine in each hospital is still limited	No major differences between the use of original and CL medicine.	no serious side effects was found by the interviewee.	No major differences between the use of original and CL medicine.

Biography

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