ADVERSE EFFECTS OF ANTIRETROVIRAL DRUGS DURING PREGNANCY: A FIVE-YEAR REVIEW AT CHONBURI HOSPITAL, THAILAND

DARIN AREECHOKCHAI

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Darin Areechokchai
.....
Miss Darin Areechokchai
Candidate

.....
Asst. Prof. Wirach Maek-a-nantawat,
Dip. Thai Board of Allergy and Clinical Immunology
Major-Advisor

C. Bowon
.....
Asst. Prof. Chureeratana Bowonwatanuwong,
Dip. Thai Board of Internal Medicine
Co-Advisor

.....
Prof. Punnee Pitisuttithum, M.B., B.S.,
Dip. Thai Board of Internal Medicine
Co-Advisor

Benjaluck Phonrat
.....
Assoc. Prof. Benjaluck Phonrat,
M.Sc.
Co-Advisor

.....
Prof.M.R. Jisnuson Svati,
Ph.D.
Dean
Faculty of Graduate Studies

Udomsak Silacharoon
.....
Asst. Prof. Udomsak Silacharoon,
Dip. Thai Board of Internal Medicine
Chair
Master of Clinical Tropical Medicine
Faculty of Tropical Medicine

Thematic paper
Entitled

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for the degree of Master of Clinical Tropical Medicine
on
March 15, 2007

Darin Areechokchai
.....
Miss Darin Areechokchai
Candidate

.....
Mr. Somsit Tansuphasawaditkul,
Dip. Thai Board of Internal Medicine
Member

.....
Asst. Prof. Wichai Techasathit,
Dip. Thai Board of Preventive Medicine (Clinical)
Chair

.....
Prof. Punnee Pitisuttithum,
Dip. Thai Board of Internal Medicine
Member

.....
Asst. Prof. Wirach Maek-a-nantawat,
Dip. Thai Board of Allergy and Clinical Immunology
Member

.....
Assoc. Prof. Benjaluck Phonrat,
M Sc. (Trop. Med.)
Member

.....
Asst. Prof. Chureeratana Bowonwatanuwong,
Dip. Thai Board of Internal Medicine
Member

.....
Prof. M.R. Jisnuson Svati,
Ph.D.
Dean
Faculty of Graduate Studies
Mahidol University

.....
Assoc. Prof. Pratap Singhasivanon,
M.B.B.S., D.T.M.&H. (Bangkok),
M.P.M., Dr.P.H. (Epidemiology)
Dean
Faculty of Tropical Medicine
Mahidol University

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Darin Areechokchai

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DARIN AREECHOKCHAI 4938552 TMCT/M
M.C.T.M.
THEMATIC PAPER ADVISORS: WIRACH MAEK-A-NANTAWAT, M.D., F.R.C.P.(T), D.T.M.&H., M.SC., DIPLOMA BOARD OF ALLERGY AND CLINICAL IMMUNOLOGY, CHUREERATANA BOWONWATANATUWONG, B.SC., M.D., PUNNEE PITISUTTHITHUM M.B.,B.S., F.R.C.P.(T), D.T.M.&H. BENJALUCK PHONRAT, M.SC.

ABSTRACT

This retrospective descriptive study was conducted to assess the adverse effects of antiretroviral drugs and pregnancy outcomes among HIV-infected pregnant women receiving antiretroviral drugs for either combined antiretroviral therapy or prevention of mother-to-child transmission. The study cohort comprised 246 HIV-infected pregnant women who attended the antenatal care (ANC) clinic or delivered in Chonburi Hospital in 2002-2006. Their medical records were reviewed and/or they were interviewed in November 2006-January 2007.

Results: The median age of the pregnant women was 27 years; most were laborers and had lowincome levels. HIV-seroconversion was first detected among most of the pregnant women during ANC. 16.3% received combined antiretroviral therapy (ART) during ANC, 66.7% initiated prevention of mother-to-child transmission (PMTCT) regimens during ANC, and, 17.1% initiated PMTCT during labor. Overall, 24 adverse events from 21 HIV-infected pregnant women (8.5%, 95% confidence interval: 5.4-12.8%) were documented. There was an association between combined ART regimen and incidence of adverse events, including anemia, vomiting, and dyslipidemia. Thirteen (6.4%) pregnant women developed anemia after 4 weeks of zidovudine; 3 pregnant women developed dyslipidemia. The incidence of preterm delivery was 10.7%. Initiation of PMTCT in labor was associated with preterm delivery. The incidence of low Apgar score was 3.6%, which were associated with initiation of antiretroviral drug therapy in labor. No birth defect was suspected as being an adverse event related to antiretroviral drug therapy.

Recommendations: Close monitoring of adverse events in the mother, and during the development of the fetus is necessary for pregnant women receiving combined ART. For pregnant women receiving zidovudine for PMTCT, routine complete blood count should be performed as early as 5 weeks after taking zidovudine. The risk of low Apgar scores is higher for infants of HIV-infected pregnant women without PMTCT during ANC. Pregnant women should therefore be encouraged to access ANC.

KEY WORDS: ADVERSE EVENT/OUTCOME/ANTIRETROVIRAL/ PREGNANCY/THAILAND
89 P.

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LIST OF ABBREVIATIONS

Abbreviation or symbol	Term
AIDS	Acquired immune deficiency syndrome
ALT (SGPT)	Alanine aminotransferase
ANC	Antenatal care
ART	Antiretroviral therapy
AST (SGOT)	Aspatate aminotransferase
AZT	Zidovudine
CBC	Complete blood count
CD4	Cluster differentiation 4; marker for T helper cells
Cu.mm.	Cubic millimeter
D4T	Stavudine
DNA	Deoxyribonucleic acid
Eo	Eosinophil
GPO-vir	Trade name for a fixed combination of antiretroviral drugs: stavudine, lamivudine and nevirapine
g/L	Gram per liter
HAART	Highly active antiretroviral therapy
Hb	Hemoglobin
Hct	Hematocrit
HIV	Human immunodeficiency virus
LMP	Last menstrual period
Lym	Lymphocyte
mg	Milligram
mg/dl	Milligram per deciliter
ml	milliter
mmol/l	millimol per liter
Neu	Neutrophil

LIST OF ABBREVIATIONS (Cont.)

NNRTI	Non-nucleside reverse transcriptase inhibitor
NRTI	Nucleside reverse transcriptase inhibitor
NVP	Nevirapine
PI	Protease inhibitor
Plt	Platelet
PMTCT	Prevention of mother-to-child transmission
PPE	Pruritic papular eruption
RNA	Ribonucleic acid
Wbc	White blood cell
ZDV	Zidovudine
3TC	Lamivudine

CHAPTER I

INTRODUCTION

Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) are global major public health problems. Thailand has been affected from HIV/AIDS epidemic since the first AIDS case was reported in 1984 (Boonterm et al., 2005). For the next few years, gay men, sex workers, injecting drug users and tourists were more commonly affected than other groups. By the end of 2005, the estimated number of people living with HIV is 580,000 and estimated AIDS deaths is 21,000 (Joint United Nations Programme on HIV/AIDS, 2006). The main mode of transmission is via the heterosexual route accounting 80% of HIV infected people (United States Agency International Development, 2005).

The rising level of infection among sex workers in 1990's led to subsequent waves of the epidemic among the male clients of sex workers, their wives and partners, and their children. HIV prevalence among pregnant women reached a peak of 2.35% in 1995 and made around 1,200 children infected during pregnancy, at birth, or through breastfeeding in 1997. Between 1996 and 1997, a randomized controlled trial was carried out to study the provision of short-course zidovudine (AZT) to prevent mother-to-child transmission of HIV in Bangkok. This study showed that AZT reduced transmission of HIV from mother to child from 18.9% to 9.4% (Shaffer et al., 1999). Following this, a number of pilot programs were initiated in Thailand. The successful results of the pilot studies led clinicians in most provinces to demand government support for short-course AZT to prevent mother-to-child transmission. By 1999, AZT was being used in most hospitals in Thailand and the number of children infected via mother-to-child transmission was halved to 600 (World Health Organization, 2006).

Even with the use of AZT, however, mother-to-child transmission rates remain at or above 6 percent. When a clinical trial demonstrated the efficacy of a single dose of

nevirapine during labor plus a single dose to the newborn, the efficacy of perinatal nevirapine therapy added to zidovudine therapy had been studied in Thailand between 2001 and 2003. This study demonstrated the high efficacy of adding a single dose of nevirapine in the mother, with or without a dose in the infant, to oral zidovudine prophylaxis for the reduction of perinatal transmission of HIV. The observed reduction by 80% led to the early interruption of enrollment in the placebo–placebo group. On the basis of these findings and for additional logistic reasons, the ministry of public health in Thailand has recommended administration of nevirapine to both mother and infant (Lallement et al., 2004).

Additionally, in 2000, HAART (Highly Active Antiretroviral Therapy, effective HIV treatment that involves the combination of three or more antiretroviral drugs) was introduced to Thailand to dramatically improve the health and extend the lives of people living with HIV/AIDS. The initial regimens of 2 nucleoside reverse transcriptase inhibitors (NRTIs) + 1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) or 2 NRTIs + 2 protease inhibitors (PIs) are recommended.

In 2002, Thai government announced its plan to produce a low-priced combination-therapy antiretroviral drug called GPO-VIR, which has two doses (GPO-Vir S30 and S40). The pill of GPO-Vir30 is a 3-in-1 drug containing stavudine 30 mg, lamivudine 150 mg, and nevirapine 200 mg. According to the national plan for the prevention and alleviation of HIV/AIDS in Thailand, which runs between 2002 and the end of 2006, the government makes an official commitment to ensuring adequate treatment for all people living with HIV, and sets targets to improve treatment access for at least 80% of the people living with HIV and other affected individuals. In the recent years the number of people accessing this treatment has increased dramatically, significantly reducing the number of people dying from AIDS. The distribution of antiretroviral drugs has coincided with a dramatic drop in the number of officially reported AIDS-deaths – from 5,020 in 2004 to 1,640 in 2005 (Joint United Nations Programme on HIV/AIDS, 2006).

Increasing of these routine uses of antiretroviral therapy (ART) has led to a dramatic and sustained decrease in mortality and morbidity in HIV infections as well

as in the risk of mother-to-child transmission. In this scenario, it is not surprising that fertile HIV-infected women may decide to become pregnant expecting an offspring free of HIV infection and no more complications during pregnancy than in non-HIV-infected women. HIV infected pregnant women are currently recommended to receive similar HAART regimens as non-pregnant ones, except for considerations of potential adverse effects of such therapy on the fetus (Anna et al., 2006).

Despite the positive impact on HIV-related morbidity and mortality, the duration of exposure to antiretroviral therapy has been associated with complications. Almost 80% of pregnant women experienced one or more typical adverse effects of the drugs, such as anemia, nausea/vomiting, aminotransferase elevation, or hyperglycemia. Additionally, data are conflicting as to whether receipt of combination antiretroviral therapy during pregnancy is associated with adverse pregnancy outcomes such as preterm delivery (Perinatal HIV Guidelines Working Group, 2006).

In Thailand, data on adverse effects of antiretroviral therapy in pregnant women and pregnancy outcomes are limited due to less systematical recorded information regarding toxicity. To know the potential adverse effects of antiretroviral therapy specifically in pregnant women and fetus is very important for considering the antiretroviral regimens because various effective regimens are now widely prescribed for HIV-infected pregnant women. This retrospective and prospective study is a review of the adverse effects of antiretroviral therapy in HIV-infected pregnant women including the pregnancy outcomes.

CHAPTER II

REVIEW OF THE LITERATURE

2.1 Pregnancy and human immunodeficiency virus infection (El Beitune et al., 2004, Linda et al., 2001)

Impact of pregnancy on T lymphocyte populations

Given that T-cell lymphocytes are highly informative of immune function-decrease in HIV infection, several investigations have specifically examined relative alterations in CD4+ cell counts among HIV-infected and HIV-negative women. The first, published by Burns et al involved 192 HIV-infected and 148 HIV negative women being followed-up in New York. There were decreases in CD4+ cell count levels among HIV-infected women (Burns et al., 1996). Data from the European Collaborative Study and the Swiss HIV Pregnancy Cohort, however, did not find similar decreases, but rather found stable CD4+ percentages throughout pregnancy and up to 6 months after delivery (The European Collaborative Study and the Swiss HIV Pregnancy Cohort, 1997). Likewise, a study by Tuomala et al examined changes in lymphocyte subsets during and 1 year after pregnancy among HIV-infected women. This study concluded that both CD4+ CD8+ percentages remained stable during pregnancy and that postpartum changes that may be observed are most likely a return to pre-pregnancy baseline levels (Tuomala et al., 1997).

In summary, there appears to be some decrease in CD4+ cells during the period of pregnancy, and the rebound time to return to normal appears to be somewhat extended for HIV-infected women. Clearly, these observations are critical in that although they are not directly measuring the outcomes of primary interest, these markers have been shown to be of direct relevance to HIV disease progression.

Impact of HIV Infection on Pregnancy-Related Complications

An early study by Minkoff showed that HIV-infected women were more likely than their HIV-negative counterparts to have sexually transmitted diseases and medical complications associated with their pregnancies (Minkoff et al., 1990). A study by Temmerma followed up 315 HIV-infected and 311 HIV-negative women in Kenya. HIV infection was associated with low-birth-weight and prematurity, and HIV-infected women had higher rates of postpartum endometritis. HIV infection was not, however, associated with small-for-gestational age infants (Temmerman et al., 1995).

2.2 Antiretroviral Therapy (Perinatal HIV Guidelines Working Group., 2006)

Considerations regarding the use of antiretroviral drugs by HIV-1 Infected pregnant women and their infants

Combination antiretroviral therapy is the recommended standard treatment for HIV-1 infected adults who are not pregnant. Pregnancy should not preclude the use of optimal therapeutic regimens. However, recommendations regarding the choice of antiretroviral drugs for treatment of infected pregnant women are subject to unique considerations including possible changes in dosing requirements resulting from physiologic changes associated with pregnancy, potential effects of antiretroviral drugs on the pregnant woman, and the effects of the antiretroviral drug on the fetus and newborn.

Table 1: Antiretroviral drug use in pregnant HIV-infected women: pharmacokinetic and toxicity data in human pregnancy and recommendations for use in pregnancy.

ntiretroviral drugs	Pharmacokinetics in pregnancy	Concerns in pregnancy	Rational for Recommended Use in Drug Pregnancy
NRTIs/NtRTI		Potential maternal and infant mitochondrial toxicity.	Combination regimens, usually including two NRTIs with either an NNRTI or one or more PIs.
Recommended agents			
Zidovudine	significantly altered in pregnancy; no change in dose indicated	FDA category C. No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant.	Preferred NRTI for use in combination antiretroviral regimens in pregnancy; should be included in regimen unless significant toxicity or stavudine use.
Lamivudine	not significantly altered in pregnancy; no change in dose indicated.	FDA category C. No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant.	Lamivudine plus zidovudine is the recommended dual NRTI backbone for pregnant women.

Table 1: Antiretroviral drug use in pregnant HIV-infected women: pharmacokinetic and toxicity data in human pregnancy and recommendations for use in pregnancy. (Continue)

Antiretroviral drugs	Pharmacokinetics in pregnancy	Concerns in pregnancy	Rational for Recommended Use in Drug Pregnancy
Alternate agents			
Didanosine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated	FDA category B. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine	Alternate NRTI for dual nucleoside backbone of combination regimens. Didanosine should be used with stavudine only if no other alternatives are available.
Recommended agents			
Stavudine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated	FDA category C. Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated	Stavudine should be used with didanosine only if no other alternatives are available. Do not use with zidovudine due to potential for antagonism.
Abacavir	Phase I/II study in progress.	FDA category C. Hypersensitivity reactions occur in ~58% of non-pregnant persons. Patient should be educated symptoms of hypersensitivity reaction.	Alternate NRTI for dual nucleoside backbone of combination regimens. See footnote regarding use in triple NRTI regimen.

Table 1: Antiretroviral drug use in pregnant HIV-infected women: pharmacokinetic and toxicity data in human pregnancy and recommendations for use in pregnancy (Continue)

Antiretroviral drugs	Pharmacokinetics in pregnancy	Concerns in pregnancy	Rational for Recommended Use in Drug Pregnancy
NNRTIs			
Recommended agents			
Nevirapine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated	FDA category C. No evidence of human teratogenicity. Increased risk of fatal liver toxicity among women with CD4+ counts > 250/mm3 when first initiating therapy; unclear if pregnancy increases risk.	Nevirapine should be initiated in pregnant women with CD4+ counts > 250 cells/mm3 only if benefit clearly outweighs risk. in women with high CD4+ counts. Women who enter pregnancy on nevirapine regimens and are tolerating them well may continue therapy, regardless of CD4+ count.
Not recommended			
Efavirenz	No studies in human pregnancy.	FDA category D. There are three case reports of neural tube defects in humans after first trimester exposure; relative risk unclear.	Women of childbearing potential must be counseled regarding risks and avoidance of pregnancy. Alternative regimens should be strongly considered in women of child bearing potential.

Table 1: Antiretroviral drug use in pregnant HIV-infected women: pharmacokinetic and toxicity data in human pregnancy and recommendations for use in pregnancy (Continue)

Antiretroviral drugs	Pharmacokinetics in pregnancy	Concerns in pregnancy	Rational for Recommended Use in Drug Pregnancy
Protease inhibitors		Hyperglycemia, new onset or exacerbation of diabetes mellitus. Unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs.	
Recommended agents			
Nelfinavir	Adequate drug levels are achieved in No evidence of human teratogenicity pregnant women with nelfinavir. Well-tolerated.	FDA category B. No evidence of human teratogenicity. Well-tolerated.	Preferred PI for combination regimens in pregnant women, particularly if HAART is being given solely for perinatal prophylaxis.
Alternate agents			
Indinavir	Two studies including 18 women receiving indinavir 800 mg three times daily showed markedly lower levels during pregnancy compared to postpartum, although suppression of HIV RNA was seen.	FDA category C. Theoretical concern re: increased indirect bilirubin levels in the neonate, but minimal placental passage. Use of unboosted indinavir during pregnancy is not recommended.	Alternate PI to consider if unable to use nelfinavir or saquinavir-SGC/ritonavir, but would need to give indinavir as ritonavir-boosted regimen.

Nevirapine and hepatic/rash toxicity

Increases in hepatic transaminase levels (ALT and AST) associated with rash or systemic symptoms may be observed during the first 18 weeks of treatment with nevirapine. Signs and symptoms of systemic toxicity may be non-specific, and include fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal hepatic transaminases. Severe or life threatening rash occurs in approximately 2% of patients receiving nevirapine. Women initiating nevirapine with $CD4^{+}$ counts > 250 cells/mm^{3}, including pregnant women receiving antiretroviral drugs solely for prevention of transmission, have an increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity, which can be severe, life-threatening, and in some cases fatal. Hepatic toxicity has not been seen in women receiving single dose nevirapine during labor for prevention of perinatal transmission of HIV-1.

Protease inhibitor therapy and hyperglycemia

Hyperglycemia, new-onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis have been reported with receipt of protease inhibitor antiretroviral drugs by HIV-1 infected patients. In addition, pregnancy is itself a risk factor for hyperglycemia; it is unknown if the use of protease inhibitors will increase the risk for pregnancy-associated hyperglycemia.

Combination antiretroviral therapy and pregnancy outcome

Data are conflicting as to whether receipt of combination antiretroviral therapy during pregnancy is associated with adverse pregnancy outcomes such as preterm delivery. A retrospective Swiss report evaluated the pregnancy outcome of 37 HIV-1 infected pregnant women treated with combination therapy. Almost 80% of women experienced one or more typical adverse effects of the drugs, such as anemia, nausea/vomiting, aminotransferase elevation, or hyperglycemia. A possible association of combination antiretroviral therapy with preterm births was noted. However, the contribution of maternal HIV-1 disease stage and other covariates that might be associated with a risk for prematurity was not assessed. A cohort study investigated the effects of combination retroviral therapy adjusting for CD4 count and intravenous

drug use; they found increased odds of preterm delivery for infants exposed to combination therapy compared with no treatment. Additionally, women receiving combination therapy that had been initiated before their pregnancy were twice as likely to deliver prematurely as those starting therapy during the third trimester.

In contrast, several other reports demonstrating elevated preterm birth rates among untreated women with HIV-1 infection. Additionally, in a large meta-analysis of seven clinical studies that included 2,123 HIV-1-infected pregnant women who delivered infants during 1990–1998 and had received antenatal antiretroviral therapy and 1,143 women who did not receive antenatal antiretroviral therapy, use of multiple antiretroviral drugs as compared with no treatment or treatment with one drug was not associated with increased rates of preterm labor, low birth weight, low Apgar scores, or stillbirth.

Table2: WHO guidelines for PMTCT drug regimens in resource-limited settings (World Health Organization, 2006)

	Pregnancy	**Labour**	**After birth: mother**	**After birth: infant**
Recommended	AZT after 28 weeks	single dose nevirapine; AZT+3TC	AZT+3TC for seven days	single dose nevirapine; AZT for seven days
Alternative (higher risk of drug resistance)	AZT after 28 weeks	single dose nevirapine	-	single dose nevirapine; AZT for seven days
Minimum (less effective)	-	single dose nevirapine; AZT+3TC	AZT+3TC for seven days	single dose nevirapine
Minimum (less effective; higher risk of drug resistance)	-	single dose nevirapine	-	single dose nevirapine

Table3: Thailand studies on PMTCT: Transmission rates at 6 months for non-breast feeding population (UNAIDS, 2005)

Study	Mother's treatment			Infant's treatment		Transmission rate (%)
	AZT at 28 weeks	AZT at 36 weeks	NVP single intrapartum	NVP infant	Other infant	
Thai	No	Yes	No	No	Yes (AZT)	10.5
PHPT-1	Yes	No	No	No	Yes (AZT)	5.6
Thai	Yes	No	No	No	Yes (AZT)	6.3
PHPT-2	Yes	No	Yes	No	No	2.8
	Yes	No	Yes	Yes	No	1.9

CHAPTER III
SPECIFIC OBJECTIVES

Primary objectives

1. To assess the adverse effects of antiretroviral drugs in HIV-infected pregnant women including;
    a. Combined antiretroviral therapy
    b. Regimens for prevention of mother-to-child transmission (PMTCT)
2. To evaluate the pregnancy outcomes of HIV-infected pregnant women receiving antiretroviral therapy.

Secondary objectives

1. To describe background characteristics of the pregnant women receiving antiretroviral drugs during pregnancy.

CHAPTER IV
MATERIALS AND METHODS

4.1 Study design

A retrospective descriptive study among 246 HIV-infected pregnant women in Chonburi hospital was conducted. Ethical clearance had been obtained from the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University and from the Ethics Committee of the Chonburi hospital.

4.2 Study area

Chonburi province is located in the Eastern Thailand. The province capital is Muang Chonburi, the area is 4.363 km^2. The study was carried out in Chonburi hospital, the regional hospital of the provinces in the Eastern Thailand. The hospital is situated about 60 km from the tourist town of Pattaya and around 80 km southeast of Bangkok.

The HIV clinic in Chonburi hospital is approximately taking care 2,500 HIV-infected persons included HIV-infected pregnant women who are referred from ANC clinic. Every pregnant woman who attends ANC clinic in Chonburi hospital will be received voluntary HIV counseling and testing. The hospital's system to take care HIV-infected pregnant women is shown in figure 1.

The pregnant women who are previously known HIV-infected persons and have already been taken care by HIV clinic will be continuously taken care in parallel with antenatal care. The combined ART regimens will be immediately reconsidered when the known HIV-infected persons become pregnant.

The pregnant women who have no ANC and present to the hospital when they are in labour will be tested for anti-HIV by the rapid test. The HIV seropositive pregnant women will be given intrapartum AZT every 3 hours and/or single dose NVP until delivery.

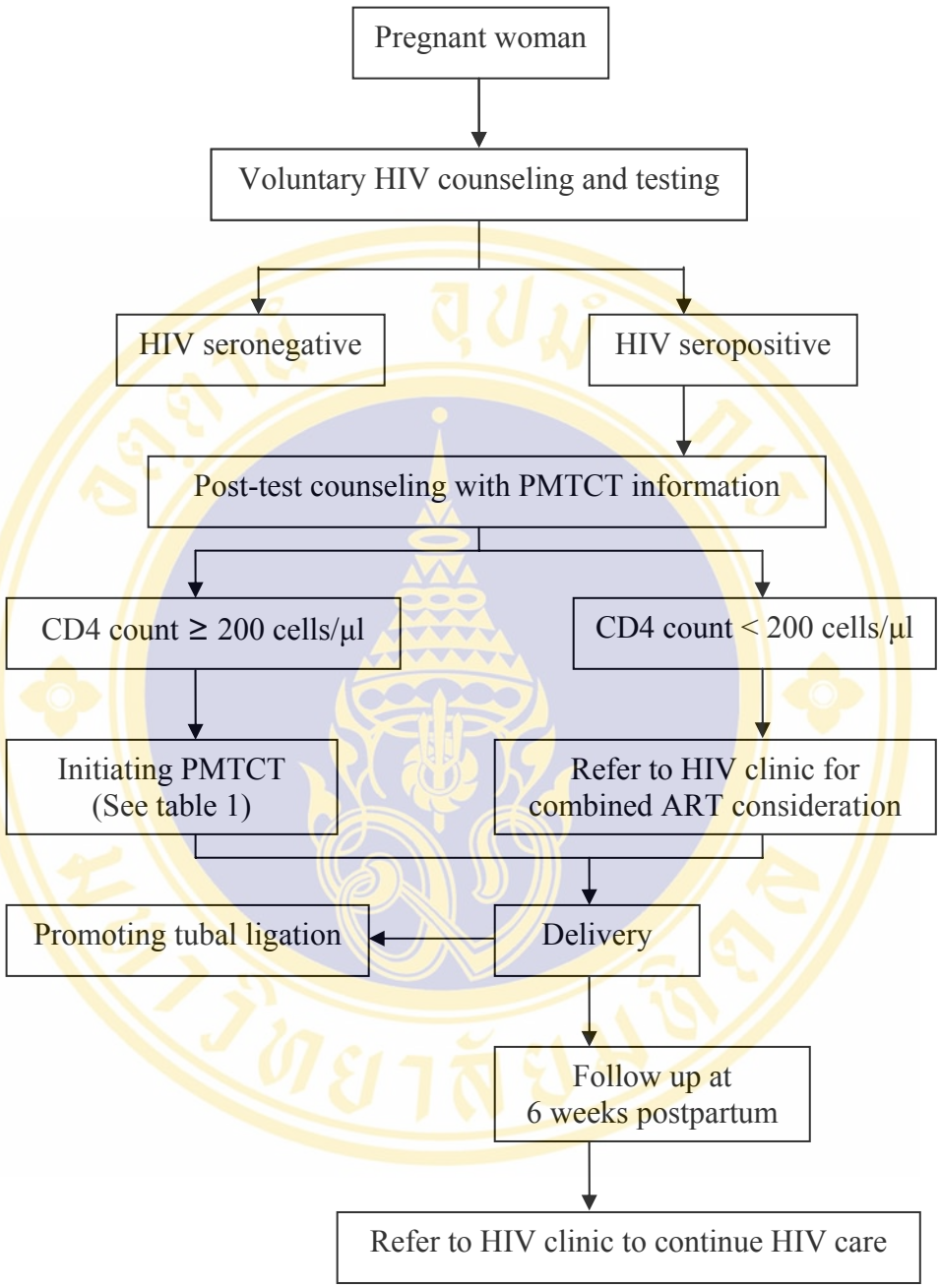


Figure 1: Guideline for management of HIV-infected pregnant women, Chonburi hospital 2002 - 2006.

The PMTCT regimens in Chonburi hospital are various by year according to the national program for management of HIV infection and the research implemented in the hospital. Table 4 summarizes the PMTCT regimens in Chonburi hospital by year, 2002 – 2006.

Table 4: PMTCT regimens in Chonburi hospital, 2002 – 2006.

PMTCT regimens	During ANC	Intrapartum	Postpartum
2002			
National program	AZT at 31 weeks	None	None
PHPT2	AZT at 28 weeks	Single dose NVP	
2003			
National program	AZT at 31 weeks	Single dose NVP	None
2004			
National program	AZT at 28 weeks	Single dose NVP	None
2005			
National program	AZT at 28 weeks	Single dose NVP	None
PHPT4 (DDI tailed end)	AZT at 28 weeks	Single dose NVP	AZT+DDI 3 weeks
3TC tailed end	AZT at 28 weeks	Single dose NVP	AZT+3TC 2-4 weeks
2006			
National program	AZT at 28 weeks	Single dose NVP	None
PHPT4 (DDI tailed end)	AZT at 28 weeks	Single dose NVP	AZT+DDI 3 weeks
3TC tailed end	AZT at 28 weeks	Single dose NVP	AZT+3TC 2-4 weeks
PATCG 1032	AZT at 28 weeks	Single dose NVP	A: AZT+DDI 4 weeks B: AZT+DDI+LPV 7 days

The infant born to HIV-infected pregnant women will be fed infant formula milk instead of breast feeding. The antiretroviral drugs given to infants are following:

- AZT syrup 2 mg/kg/dose in every 6 hours for 1 week plus
- Single dose NVP 2mg/kg with in 72 hours after birth

The infants' HIV status will be determined with two different ELISA at 12 months old and confirmed seropositive at 18 months old.

4.3 Study population

Inclusion criteria were HIV-infected pregnant women who had attended antenatal care clinic and/or deliver, and/or terminate pregnancy in the Chonburi Hospital from 1 January 2002 to 31 December 2006 and met the following criteria;

1) Confirmed HIV infection by at least two reactive results with two different HIV antibody testing
2) Received any antiretroviral drug for either combine antiretroviral therapy or prevention of mother-to-child transmission aimed to decrease mortality and morbidity in HIV infection and/or decrease in the risk of mother-to-child transmission

An exclusion criterion was any HIV-infected pregnant women who did not willing to join the study.

4.4 Sample size

In order to assess the adverse events of antiretroviral therapy in HIV-infected pregnant women, the sample size was calculated using Epi info 2002.

Base on the total population of HIV-infected pregnant women attending antenatal care clinic at Chonburi hospital over five years is approximately 350 and a randomized, double-blind trial in Thai pregnant women that revealed the rates of adverse events were 216 (15%) reports from a total of 1,411 enrolled pregnant women (Lallemant et al., 2004). Therefore, total population 350, 15% adverse events is assumed to be an estimate proportion of HIV-infected pregnant women who develop adverse events, with 10% acceptable error then sample size calculated by Epi info 2002 is equal to 302.

The sample size was at least 302 HIV-infected pregnant women receiving antiretroviral therapy.

4.5 Sampling

In fact, the total number of pregnant women registered in ANC clinic and/or labour room in Chonburi hospital during 2002 – 2006 was 325 women. Of those, only 270 pregnant women had medical records available. Twenty-four of 270 women were not received antiretroviral drugs during pregnancy. Therefore, a total of 246 pregnant women received antiretroviral drugs were included without sampling.

4.6 Outcome of the study

The interesting outcome including;

1) Adverse effects of antiretroviral drugs
   - Hypersensitivity reactions: skin rash
   - Gastrointestinal symptoms e.g. nausea, vomiting, or diarrhea
   - Anemia
   - Neutropenia
   - Hyperlipidemia
   - Hepatotoxicities including elevated liver enzymes, fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure
   - Hyperglycemia / gestational diabetes
2) outcomes of pregnancy
   - Abortion
   - Death fetus in utero
   - Still birth
   - Birth weight
   - Apgar score
   - Preterm delivery
   - Pre-eclampsia
   - Birth defects
   - Perinatal HIV infection
3) Outcomes of HIV infection
   - Opportunistic infection development
   - Asymptomatic
   - AIDS

The outcomes are defined as following;

Table 5: The cut-off point and grading of adverse events (AIDS Clinical Trial Groups, 2005)

Adverse events	Grading of toxicities			
	Grade I	**Grade II**	**Grade III**	**Grade IV**
Anemia(Hb g/dl)	8.0 – 9.4	7.0 – 7.9	6.5 – 6.9	< 6.5
Neutropenia (absolute neutrophil count /L)	1-1.5 x 10^9	0.75-0.99 x 10^9	0.5-.0749 x 10^9	< 0.5 x 10^9
Hepatotixicity (ALT)	1.25–2.5 x upper normal limit	> 2.5-5 x upper normal limit	5-10 x upper normal limit	> 10 x upper normal limit
Hypertriglyceridemia (mmol/l)	3-4.51	4.52-8.48	8.49-13.56	>13.56
Hypercholesterolemia (Cholesterol mmol/l)	> 1-1.3 x upper normal limit	> 1.3-1.6 x upper normal limit	> 1.6-2.0 x upper normal limit	> 2.0 x upper normal limit
Skin rash	Erythema pruritus	Diffuse maculopapular rash or dry desquamation	Vesiculation or moist desquamation or ulceration	Exfoliative dermatitis or mucous membrane involvement or erythema multiforme or suspected Stevens Johnson syndrome or necrosis

Gestational diabetes

By 100 gram oral glucose tolerance test, a woman has gestational diabetes when she is pregnant and has any two of the following: a fasting plasma glucose of more than 105 mg/dl, a 1-hour glucose level of more than 190 mg/dl, a 2-hour glucose level of more than 165 mg/dl, or a 3-hour glucose level of more than 145 mg/dl.

Abortion

Expulsion from the uterus of an embryo or fetus prior to the stage of viability (< 20 weeks of gestation or fetal weighs < 500 grams)

Premature delivery

Giving lived-birth after the stage of viability but less than 37 weeks of gestation

Low birth weight

Birth weight less than 2,500 grams

Low Apgar score

Apgar score less than 7

Still birth

A child or fetus dead at birth

Death fetus in utero

Death of fetus before delivery, death having occured on or after 20 weeks gestation

Pre-eclampsia

A condition that pregnant woman get three specific symptoms : water retention, high blood pressure (systolic BP≥140 or diastolic BP≥90 mmHg recorded on ≥ 2 occasions at least 6 hours apart) and protein in the urine (urinary protein greater than 300 mg/24 hour urine collection or at least 1+ in random urine dipstick).

Birth defect

Any defect present in a baby at birth.

4.7 Data collection

Data collection was based on the availability of medical records (OPD card, admitted chart and antenatal care record), of all HIV-infected pregnant women who had attended antenatal care clinic, delivered, or terminated pregnancy in Chonburi hospital and received antiretroviral therapy either combine antiretroviral therapy or antiretroviral drugs for prevention of mother-to-child transmission. The standard questionnaires/case record forms were developed and filled in by reviewing the medical record forms, and interviewing the pregnant women during the data collection period to gather the data as following;

- Demographic data; age, occupation, smoking, alcohol, other drugs, underlying disease Incomes
- History of HIV infection; first HIV diagnosis, CD4+ counts, clinical category at the first diagnosis, opportunistic infections, antiretroviral drugs and previous adverse effects
- ANC history; LMP, gravid, parietal, history of previous pregnancy, gestational age of each visit, routine antenatal physical examination, and laboratories, ultrasound and gestational assessment, supplementary drugs, pregnancy complications, clinical category at the first ANC visit and delivery or pregnancy termination, opportunistic infection, antiretroviral drugs
- Other laboratory data; Syphilis, hepatitis profile, hematologic finding, liver function, kidney function, urine analysis and other specific tests related to HIV infection and antiretroviral therapy
- Adverse effects of antiretroviral drugs and the outcome of pregnancy (see outcome of the study)

4.8 Data analysis

All data collected by reviewing medical records will be entered and analyzed by using statistical software Epi Info 2002 revision 2.

Demographic, clinical manifestations and laboratory results will be summarized. The qualitative data will be expressed as frequency and percentage or proportion. The quantitative data, which are normally distributed, will be expressed as mean and standard deviation (SD) and then analyzed by parametric tests. The quantitative data, which are non-normally distributed, will be expressed as median and minimum-maximum and then analyzed by non-parametric method.

Univariated analyses with Fisher exact test were used to find out the association between maternal characteristics or antiretroviral regimens and the interesting outcome. The variables that gave significant association from the univariated analyses were analyzed by multivariate analyses to control confounding factors. A p-value of less than 0.05 was considered to be statistically significant based on univariated analysis.

4.9 Ethical consideration

The Ethical Committee of the Faculty of Tropical Medicine, Mahidol University and the Ethical Committee of Chonburi Hospital approved the research protocol. The investigator did confidentially review all related information from the medical records in a private room under the institute authority. The subject identity extracted information will be mentioned only serial number and name initials for the archive clinical record forms.

CHAPTER V
RESULTS

This retrospective – prospective descriptive study had been carried out to assess the adverse effects of antiretroviral drugs among HIV-infected pregnant women who received antiretroviral drugs for either combined antiretroviral therapy or prevention of mother-to-child transmission. The study had also been to evaluate the pregnancy outcomes of those HIV-infected pregnant women.

By 2002 - 2006, a total of 325 HIV-infected pregnant women had been registered in the ANC clinic and/or in the labour room of the Chonburi hospital, Chonburi province, Thailand. Two hundred and seventy of them were reviewed their medical records; 24 (8.9%) had not received antiretroviral drugs and 246 (91.1%) received antiretroviral drugs during pregnancy. Therefore, the study was conducted among 246 HIV-infected pregnant women who received antiretroviral drugs and had attended antenatal care clinic, delivered, or terminated pregnancy in the hospital.

The study results are divided into 7 parts: 1. HIV seroprevalence among pregnant women; 2. Maternal characteristics; 3. Maternal past medical history; 4. Maternal previous HIV status and experience in antiretroviral drugs; 5. Antenatal care, HIV status and antiretroviral regimens during pregnancy; 6. Maternal adverse events of antiretroviral drugs during pregnancy; 7. Pregnancy outcomes

5.1 HIV seroprevalence among pregnant women

The number of pregnant women attending labour room in Chonburi hospital was approximately twice of the number of pregnant women attending ANC clinic each year during 2002 – 2006. The HIV seroprevalence of pregnant women attending ANC clinic was always higher than of those attending labour room. During ANC, the HIV seroprevalence was highest in 2002 (2.4%) and lowest in 2004 – 2005 (1.8%) as well as the seroprevalence during labour which was highest in 2002 (1.6%) and lowest in 2004 (1.1%). However, the trend of seroprevalences of pregnant women both attending ANC and labour room had not been declined. The seroprevalences of pregnant women attending ANC clinic during 2002 – 2006 were 2.4%, 2.2%, 1.8%, 2.0% and 2.0% whereas the seroprevalences of pregnant women attending labour room were 1.6%, 1.6%, 1.1%, 1.2%, 1.3% and 1.3% by year. (Table 6)

Table 6: HIV seroprevalence of pregnant women attending ANC clinic compared to pregnant women attending labour room.

Year	ANC clinic		Labour room	
	Total	**HIV positive (%)**	**Total**	**HIV positive (%)**
2002	2232	54 (2.4)	4351	69 (1.6)
2003	2308	51 (2.2)	4720	74 (1.6)
2004	2470	44 (1.8)	4939	52 (1.1)
2005	2492	45 (1.8)	5003	58 (1.2)
2006	2352	47 (2.0)	5100	67 (1.3)
Total	11854	241 (2.0)	24113	320 (1.3)

5.2 Maternal characteristics

Maternal characteristics of 246 HIV-infected pregnant women are described in table 7. They were 16 – 41 years old, with the median age of 27 years. The majority of age group was 20 – 29 years, 61.8%, followed by 30 – 39 years, 29.3%. HIV-infected teenage pregnancies at 2002, 2003, 2004, 2005 and 2006 were 10.6%, 8.0%, 3.4%, 11.5%, and 7.7%, respectively by year, which were lower than the percentage of teenage pregnancy in general population in Chonburi hospital, 12.6%, 12.4%, 14.3%, 14.5%, and 14.1%, respectively by year. The trend of HIV-infected teenage pregnancy has not been increasing as teenage pregnancy in general population.

Most of the pregnant women had registered residency in Muang district, Chonburi, 59.3%. The top five other district residencies in Chonburi province were Bang lamoong, Sri racha, Panasnikom, Banbeung and Panthong. The other residency provinces mostly were Chacheungsao and some provinces in the north-eastern Thailand. Regarding occupation, 73.6% were labourer, 14.6% were housewives, 5.3% merchants or having their own businesses, 3.3% students, 0.8% farmers, 0.4% Government officers, and 2.0% of them were unemployed. Only 51 pregnant women had the data of their incomes ranged from “no income” to “17,000 baht per month”. There were 33.3% pregnant women reported a monthly income “6,001 – 10,000 baht”, and 5.9% earned more than 10,000 baht per month however the majority reported their monthly incomes as “no income” (29.4%) and “3,001 – 6,000 baht” (27.5%).

The majority of pregnant women still was coupled (90.1%), 7.4% were separated and 1.2% were widowed. There was a pregnant woman (0.6%) who reported unspecified spouse because of having multiple sex partners. For the total number of spouse(s) that pregnant women have ever had, 117 (72.2%) were having the first spouse, 39 (24.1%) the second spouse, 5 (3.1%) the third spouse, and 1 (0.6%) the fourth spouse. Among those who were coupled, 47 (54.0%) of their current spouses were also HIV seropositive whereas 40 (46.0%) of them were discordant.

According to 40 discords, 4 (10.0%) of them reported being coupled with the first spouse, 34 (85.0%) with the second spouse, and 2 (5%) with the third spouse.

Table 7: Maternal characteristics of HIV-infected pregnant women.

General characteristics	No. of pregnant women	Percent
Age (years) (n=246)		
Less than 20	20	8.1
20 - 29	152	61.8
30 – 39	72	29.3
40 – 49	2	0.8
Median age (IQR) = 27 (23 – 30)		
Age range = 16 – 41		
Registered residency (n=246)		
Chonburi		
: Muang Chonburi	146	59.3
: Other districts	56	22.8
Other provinces	44	17.9
Occupation (n=246)		
Labourer	181	73.6
Housewife	36	14.6
Merchant	13	5.3
Student	8	3.3
Farmer	2	0.8
Government officer	1	0.4
Unemployed	5	2.0
Average monthly income (n=51)		
No income	15	29.4
≤ 3,000 baht	2	3.9
3,001 – 6,000 baht	14	27.5
6,001 – 10,000 baht	17	33.3
≥ 10,001 baht	3	5.9

Table 7: Maternal characteristics of HIV-infected pregnant women. (Continue)

General characteristics	No. of pregnant women	Percent
Marital Status (n=163)		
Couple	148	90.1
Separate	12	7.4
Widow	2	1.2
Unspecified (multiple partners)	1	0.6
Number of spouse(s) that ever had (n=162)		
1	117	72.2
2	39	24.1
3	5	3.1
4	1	0.6
HIV status of current spouse (n=87)		
Seropositive	47	54.0
Seronegative	40	46.0

5.3 Past medical history

Figure 2 shows the percentage of interesting medical history of 246 HIV-infected pregnant women receiving antiretroviral drugs. Overall, 31 (12.6%) pregnant women reported past medical history. Drug allergy carried the highest percentage of interesting medical history, 4.1%, which were 4 pregnant women with history of nevirapine allergy (1 was Steven Johnson's syndrome) prior to this pregnancy, 4 penicillin allergy, 1 sulfadiazine allergy, and 1 tetracycline and norfloxacin allergy. Other allergy, smoking, and other underlying diseases contributed the same percentage, 2.8%. The other allergy history included 5 asthma, 1 allergic rhinitis and 1 seafood allergy. The other diseases were 2 heart diseases, 1 diabetes mellitus, 1 thyrotoxicosis, 1 hepatitis B carrier, 1 hypertension and 1 systemic lupus erythematosus. Drug addict pregnant women included an amphetamine addiction and 2 heroin addictions simultaneously treated with methadone.

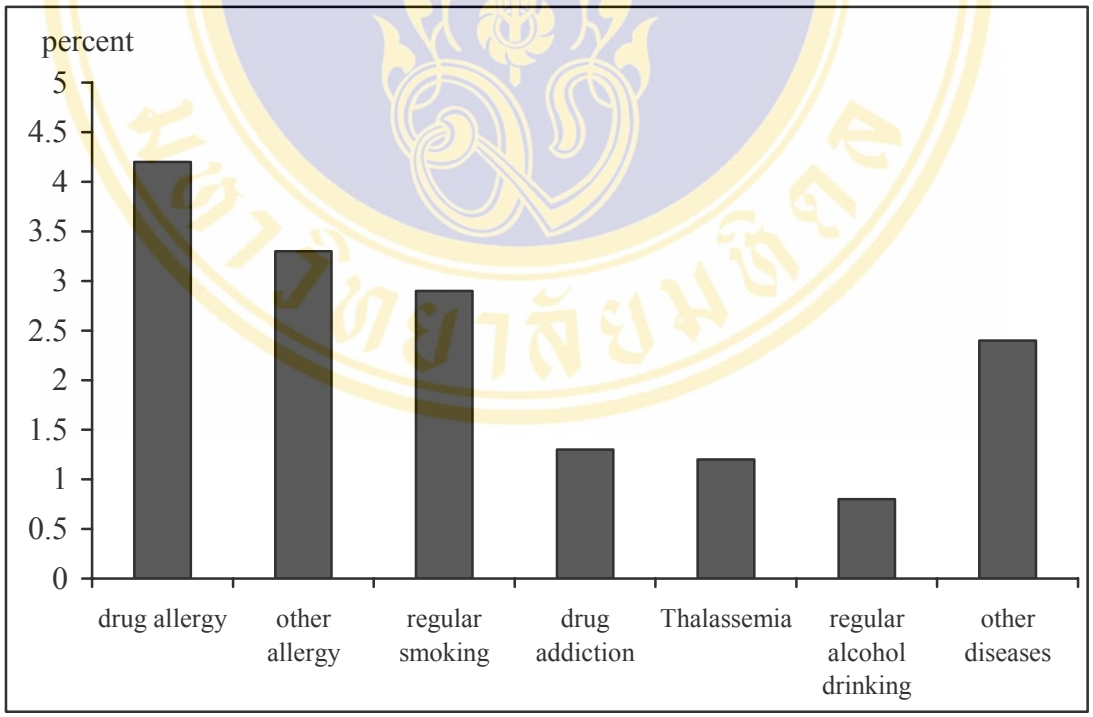


Figure 2: Percentage of interesting medical history among HIV-infected pregnant receiving antiretroviral drugs. (n=246)

5.4 Maternal HIV history and experience in antiretroviral drugs

5.4.1 HIV-seropositive detection

Figure 3 shows the percentage of the first detection of HIV-seropositive among 246 HIV-infected pregnant women receiving antiretroviral drugs. The majority of them, 180 (73.2%), were firstly detected HIV-seropositive when they were attending ANC clinic, 37 (15%) were firstly detected prior to this pregnancy, and 29 (11.8%) during labour.

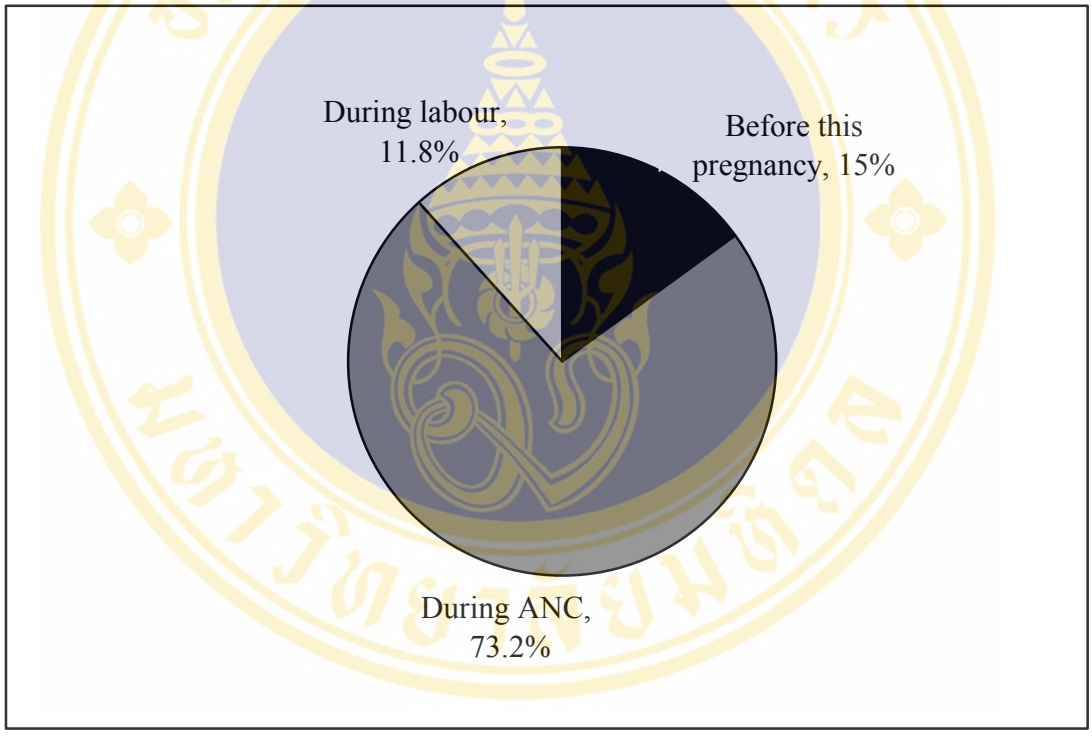


Figure 3: Percentage of the first detection of HIV-seropositive among HIV-infected pregnant women receiving ART. (n=246)

Comparing the percentage of the timing of HIV-seropositive detection by year, there was no significant increase or decrease trend of the timing of first HIV detection. In 2002 – 2006, HIV-seropositive had been detected during ANC, 78.7%, 78.0%, 72.4%, 65.4%, and 73.6% respectively. HIV-seropositive detected before pregnancy were 14.9%, 10.0%, 17.2%, 23.1%, and 15% whereas HIV-seropositive detected in labour were 6.4%, 12.0%, 10.3%, 11.5%, and 11.4% respectively.

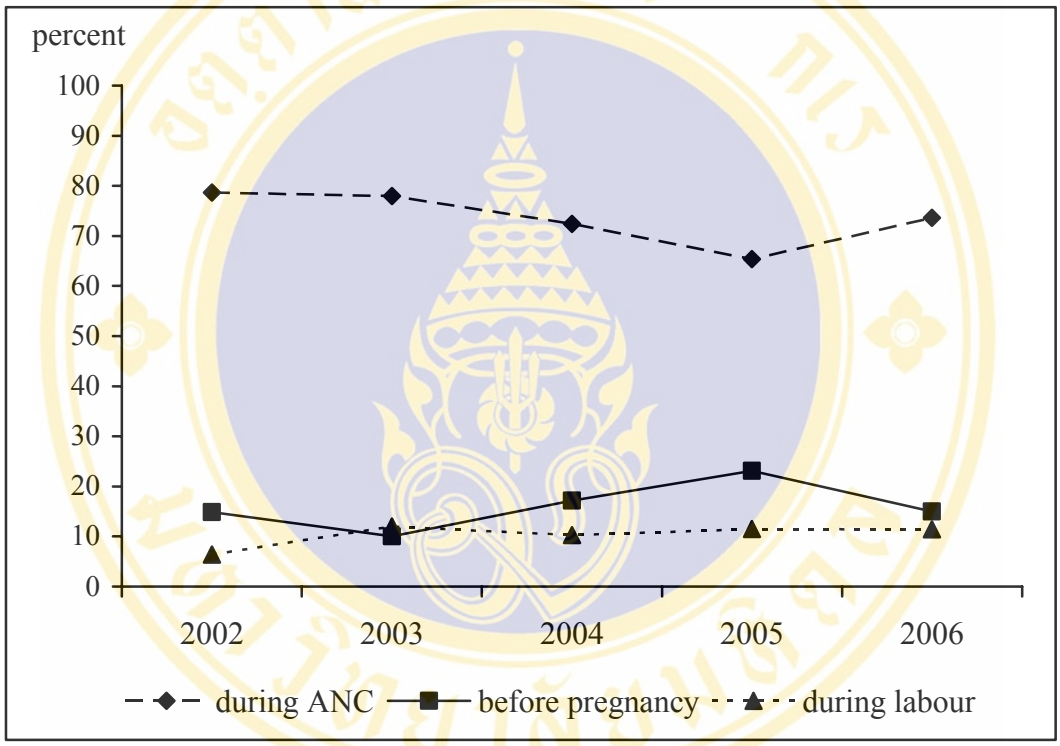


Figure 4: Trend of timing of first HIV-seropositive detection among HIV-infected pregnant women receiving antiretroviral drugs. (n=47, 50, 58, 52, 39 respectively)

According to the residency of HIV-infected pregnant women receiving antiretroviral drugs, 62.2% of the pregnant women who were firstly detected HIV-seropositive during ANC were Muang Chonburi residents and 54.1% of whom detected HIV-seropositive before this pregnancy were Muang Chonburi residents. Only 48.3% of the pregnant women who were detected HIV-seropositive in labour were Muang Chonburi residents where as 27.6% were the resident of other districts in Chonburi province, and 24.1% were other provincial residents. (Figure 5)

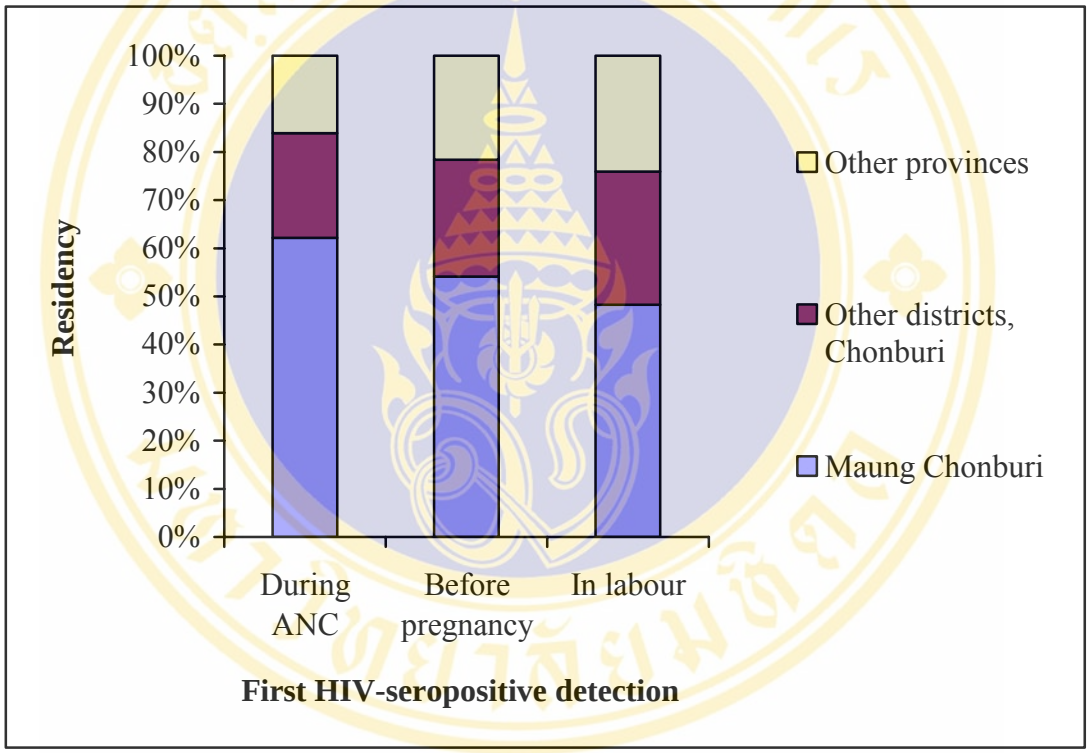


Figure 5: Percentage of residency of HIV-infected pregnant women receiving antiretroviral drugs by the timing of first HIV-seropositive detection.

5.4.2 Experience in antiretroviral drugs

There were 37 pregnant women who were firstly detected HIV-seroconversion prior to this pregnancy, 19 (51.4%) of them had been experienced to antiretroviral drugs; 17 combined ART, one dual (DDI + D4T) regimen, and one zidovudine plus single dose nevirapine for PMTCT in the previous gravid. The other 18 (48.6%) pregnant women had never been experienced.

Among those 19 pregnant women who experienced to antiretroviral drugs, 16 of them has continued combine ART, 3 had stopped antiretroviral drugs including a pregnant women who was stopped PMTCT regimen after delivery. The last antiretroviral regimens that 16 pregnant women had been continuing until the first ANC visit were shown in figure 6. Eight (21.6%) HIV-infected pregnant women had taken 2NRTIs + NVP, 5 (13.5%) 2NRTIs + EFV, 3 (8.1%) 2NRTIs + IDV/RTV. Five pregnant women had taken 2NRTIs + EFV were stopped EFV and switched to others at 8, 11, 23, 25 weeks of gestational age. However, one was not stopped EFV because she presented to ANC clinic at 35 weeks of gestational age.

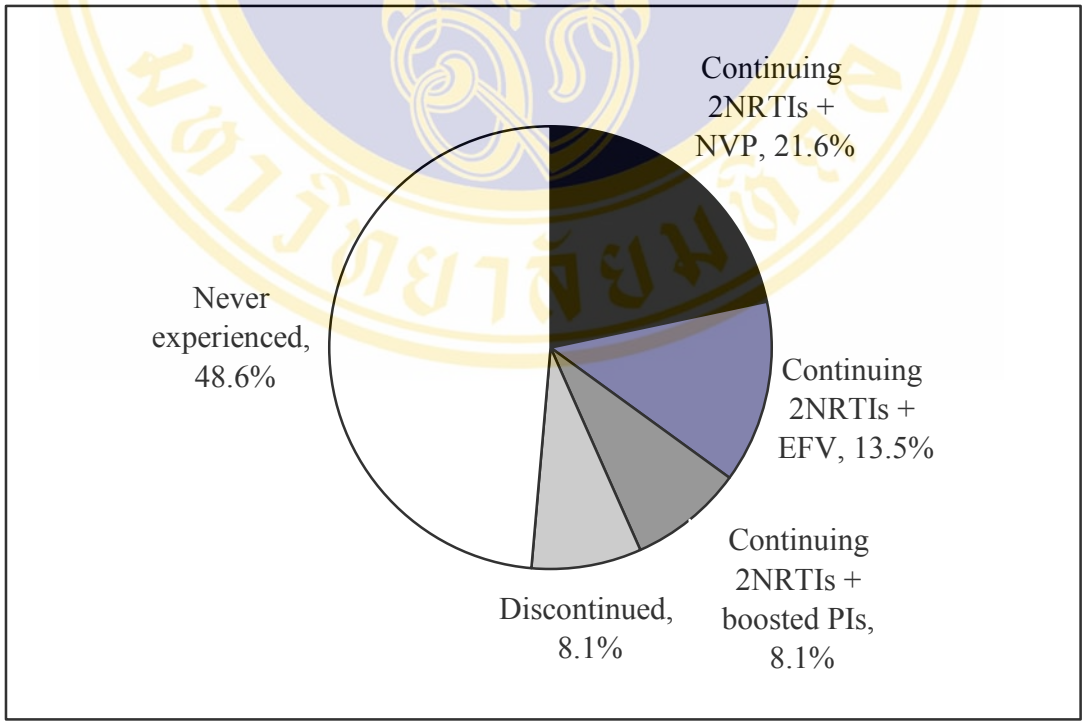


Figure 6: Percentage of the last antiretroviral regimens that known HIV-infected pregnant women had been continuing until the first ANC visit. (n=37)

5.4.3 HIV condition

The details of HIV conditions among those 37 pregnant women who were detected HIV-seropositive prior to this pregnancy were described in detail in table 8. The median (min – max) year of known HIV status prior to this pregnancy of the ART experienced pregnant women was 3 (1- 12) years whereas the median year of the ART naïve pregnant women was shorter, 2 (1 – 7) years.

Regarding baseline CD4 count at the first HIV detection, 4 (21.1%) of the ART experienced pregnant women had baseline CD4 count more than 200 cells/µl. One of them, with a high baseline CD4 count as 1000 cells/µl, received antiretroviral drugs for PMTCT and discontinued after delivery. Two of them, baseline CD4 count 265 and 420 cells/µl, had CD4 count less than 200 cells/µl after following up and started ART in 2000 and 2002 respectively without presentation of opportunistic disease. The other one, with baseline CD4 count 382 (10%) cells/µl, developed lymph node tuberculosis in 2002 and was treated GPOvir. Nearly all ART naive pregnant women had never been checked their CD4 count. Only 2 (11.1%) of them were checked and had baseline CD4 count more than 200 cells/µl. However, all of the ART naïve pregnant women were in clinical category A whereas 9 (47.4%) of the ART experienced pregnant women were in clinical category C with the opportunistic infections including tuberculosis, PCP, esophageal candidiasis, Cryptococcus meningitis, and Mycobacterium avium complex.

When the HIV-infected pregnant women presented in ANC clinic, those with the ART experienced had an increase median CD4 count to 282 (8; 120 – 825) cells/µl. Only 3 (15.8%) of them had CD4 count less than 200 cells/µl. The pregnant woman presenting in ANC clinic with the lowest CD4 count, 8 (1%) cells/µl, had been detected HIV infection and started combined ART since February 2003 with baseline CD4 count 13 (1%) cells/µl. She discontinued ART by herself after July 2004 and then came to ANC clinic in December 2005 without opportunistic disease. Of those ART naïve pregnant women, the median CD4 count during ANC dropped to 282 (158 – 810) cells/µl.

Table 8: HIV condition of 37 HIV-infected pregnant women who were firstly detected HIV-seropositive prior to this pregnancy.

HIV status	Total (%) (n=37)	ART experienced (%) (n=19)	ART naïve (%) (n=18)
Years of known HIV status prior to this pregnancy			
Within 1 year	14 (37.9)	7 (36.8)	7 (38.9)
>1 – 5 years	18 (48.6)	9 (47.4)	9 (50)
> 5 years	5 (13.5)	3 (15.8)	2 (11.1)
Median years (min – max)	2 (1 - 12)	3 (1 - 12)	2 (1 - 7)
Baseline CD4 count at first HIV detection (cells/µl)			
< 100	7 (18.9)	7 (36.8)	0 (0)
100 – 199	4 (10.8)	4 (21.1)	0 (0)
≥ 200	6 (16.2)	4 (21.1)	2 (11.1)
No data	20 (54.1)	4 (21.1)	16 (88.9)
Median CD4 (min – max)	150 (10 - 1000)	114 (10 – 1000)	384 (328 - 440)
Clinical category at the first HIV detection			
Category A	28 (75.7)	10 (52.6)	18 (100)
Category B	0 (0)	0 (0)	0 (0)
Category C	9 (24.3)	9 (47.4)	0 (0)
CD4 count during ANC (cells/µl)			
< 100	1 (2.7)	1 (5.3)	0 (0)
100 – 199	4 (10.8)	2 (10.5)	2 (11.1)
≥ 200	28 (75.7)	14 (73.7)	14 (72.8)
No data	4 (10.8)	2 (10.5)	2 (11.1)
Median CD4 (min – max)	282 (8; 120 – 825)	282 (8; 120 – 825)	282 (158 – 810)

The details of HIV conditions among 180 pregnant women who were detected HIV-seroconversion during ANC were described in detail in table 9. The median gestational age at the first detection of HIV-seroconversion was 19.5 weeks. The majority of them, 151 (83.9%), were firstly detected HIV-seroconversion before or at 28 weeks of gestation and 27 (15%) were firstly detected between 29 weeks to prior to delivery. The median CD4 count was 325.5 cells/µl. There were 24 (13.3%) of them having CD4 count less than 200 cells/µl. The pregnant woman who had the lowest CD4 count, 2 (0%) cells/µl, was in clinical category C. She was admitted to Chonburi hospital with perianal abscess and herpes labialis (Condyloma), and then was detected pregnancy with HIV-seropositive during admission. Regarding the clinical category, most of them, 177 (98.2%), were classified in category A.

Table 9: HIV condition of 180 HIV-infected pregnant women who were firstly detected HIV-seropositive during ANC.

HIV status	No. of pregnant women	Percent
Gestational age at first HIV detection		
≤ 28 weeks	151	83.9
29 weeks – prior to delivery	27	15.0
No data	2	1.1
Median GA (min – max) = 19.5 (6 – 39)		
CD4 count during ANC (cells/µl)		
< 50	3	1.7
50 – 99	1	0.6
100 – 199	20	11.0
≥ 200	104	57.8
No data	52	28.9
Median CD4 (min – max) = 325.5 (2 – 996)		
Clinical category at the first ANC visit		
Category A	177	98.2
Category B	2	1.2
Category C	1	0.6

Overall, the HIV condition during pregnancy of 246 pregnant women receiving antiretroviral drugs were categorised by CDC classification in table 10.

Table 10: CDC classification at the first ANC visit/in labour of 246 HIV-infected pregnant women receiving antiretroviral drugs.

CD4 category	Clinical category			
	A	B	C	Total
1 (≥ 500 cells/µl)	36	0	0	**36**
2 (200 – 499 cells/µl)	88	1	7	**96**
3 (< 200 cells/µl)	25	1	3	**29**
Unknown CD4 count	83	1	1	**85**
Total	**232**	**3**	**11**	**246**

5.5 Antenatal care and antiretroviral regimens during pregnancy

5.5.1 Antenatal care

According to the availability of ANC and delivery data of 246 HIV-infected pregnant women, 169 (68.7%) of them had both attended ANC clinic and delivered in Chonburi hospital, 70 (28.5%) had only delivered in Chonburi hospital, and 7 (2.8%) had only attended ANC clinic in Chonburi hospital but gone to deliver in other hospitals. (Figure 7)

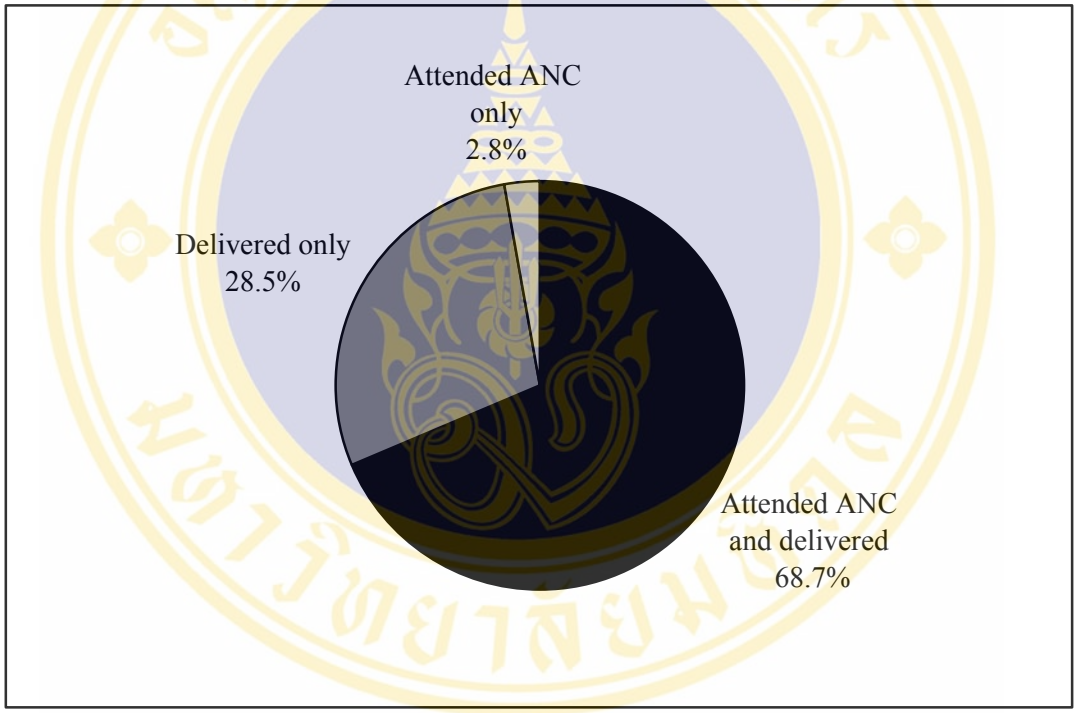


Figure 7: Percentage of the patterns of ANC and delivery in Chonburi hospital of 246 HIV-infected pregnant women.

Table 11 shows the general characteristics and ANC history of 246 HIV-infected pregnant women receiving antiretroviral drugs according to the pattern of ANC and delivery in Chonburi hospital. Most of the pregnant women, 115 (68%), who had attended and also delivered in Chonburi hospital were local residents in Muang Chonburi whereas most of the pregnant women who had either attended ANC, 6 (85.7%), or delivered, 40 (57.2%), in Chonburi hospital were registered in other residencies.

Regarding the number of gravid and parity, 100 (41.3%) of 246 pregnant women were the second gravid, 72 (29.8%) were the first gravid, and 70 (28.9%) were the third or more. Ninety-nine (40.9%) had one parity, 96 (39.7%) had none, and 47 (19.4%) had two or more. No difference of gravid and parity according to the pattern of ANC and delivery in Chonburi hospital.

Majority, 191 (72.6%), of 246 pregnant women had attended the Chonburi hospital only. There were 70 (28.5%) pregnant women who had never attended ANC clinic prior to delivery in Chonburi hospital. Of these, 23 pregnant women visited Chonburi hospital for delivery without ANC neither in Chonburi nor other places, and 47 pregnant women attended ANC clinic in other hospitals and were referred to Chonburi for delivery. Fifty-seven (23.8%) of pregnant women began to attend ANC early in the first trimester, 117 (49.0%) in the second trimester, and 42 (17.1%) in the third trimester whereas 23 (9.6%) had no ANC.

Only 14 (6.1%) pregnant women gave the history of previous pregnancy with HIV infection. Five (2.0%) pregnant women had reactive VDRL. Four of them were confirmed syphilis infection by positive TPHA; two were completely treated with Benzathine penicillin, the other two were not treated because of loss to follow up. Fifteen (6.1%) of pregnant women had positive HBsAg.

Table 11: General characteristics and ANC history of 246 HIV-infected pregnant women by the patterns of ANC and delivery in Chonburi hospital.

Pregnancy and ANC history	Total (%) (n=246)	Attended ANC and delivered (%) (n=169)	Attended ANC only (%) (n=7)	Delivered only (%) (n=70)
Residency				
Chonburi				
: Muang Chonburi	146 (59.3)	115 (68.0)	1 (14.3)	30 (42.9)
: Other districts	56 (22.8)	29 (17.2)	4 (57.1)	23 (32.9)
Other provinces	44 (17.9)	25 (14.8)	2 (28.6)	17 (24.3)
Average monthly income				
No income	15 (29.4)	10 (28.6)	1 (16.7)	4 (40.0)
≤ 3,000 baht	2 (3.9)	2 (5.7)	0 (0)	0 (0)
3,001 – 6,000 baht	14 (27.5)	10 (28.6)	2 (33.3)	2 (20.0)
6,001 – 10,000 baht	17 (33.3)	11 (31.4)	3 (50.0)	3 (30.0)
≥ 10,001 baht	3 (5.9)	2 (5.7)	0 (0)	1 (10.0)
Gravid				
1	72 (29.8)	45 (26.9)	1 (16.7)	26 (37.7)
2	100 (41.3)	69 (41.3)	4 (66.7)	27 (39.1)
3 or more	70 (28.9)	53 (31.7)	1 (16.7)	16 (23.2)
Parity				
0	96 (39.7)	64 (38.3)	2 (33.3)	30 (43.5)
1	99 (40.9)	68 (40.7)	3 (50.0)	28 (40.6)
2 or more	47 (19.4)	35 (21.0)	1 (16.7)	11 (15.9)

Table 11: General characteristics and ANC history of 246 HIV-infected pregnant women by the patterns of ANC and delivery in Chonburi hospital. (Continue)

Pregnancy and ANC history	**Total (%) (n=246)**	**Attended ANC and delivered (%) (n=169)**	**Attended ANC only (%) (n=7)**	**Delivered only (%) (70)**
No. of ANC/delivery places apart from Chonburi hospital				
0	191 (72.6)	164 (97.0)	4 (57.1)	23 (32.9)
1	54 (22.0)	5 (3.0)	3 (42.9)	46 (65.7)
2	1 (0.4)	0 (0)	0 (0)	1 (1.4)
Gestational age at first visit (trimester; weeks)				
1^{st} ; 1 – 13	57 (23.8)	44 (26.0)	2 (28.6)	11 (17.2)
2^{nd} ; 14 – 27	117 (49.0)	93 (55.0)	4 (57.1)	20 (31.3)
3^{rd} ; 28 – prior to delivery	42 (17.6)	31 (18.3)	1 (14.3)	10 (15.6)
In labour	23 (9.6)	0 (0)	0 (0)	23 (35.9)
Previous pregnancy with HIV infection				
Yes	14 (6.1)	13 (8.0)	0 (0)	1 (1.6)
No	216 (93.9)	150 (92.0)	4 (100.0)	62 (98.4)

5.5.2 Antiretroviral regimens during pregnancy

Table 12 describes the antiretroviral regimens that 246 HIV-infected pregnant women received during pregnancy and gestational age at starting antiretroviral drugs. Forty (16.3%) of 246 pregnant women received combined ART. Of those, 16 pregnant women had received combined ART since before pregnancy (5 treated with with 2NRTIs + EFV). They firstly attended ANC clinic and EFV were discontinued at 8, 11, 23, 25 weeks of gestational age, one was not stopped EFV because she presented to ANC clinic late at 35 weeks of gestational age. The other 24 pregnant women received combined ART because of 12 having low CD4 count, 2 having opportunistic infections, 4 attending ANC later than 28 weeks of gestation and 6 no indication for combined ART.

There were 164 (66.7%) of 246 pregnant women who received PMTCT regimens during ANC. Of those, 76 (46.3%) started PMTCT before or at 28 weeks of gestation, 88 (23.2%) started PMTCT after 31 weeks. Moreover, 3 pregnant women had poor adherence to AZT during ANC because of irregular ANC visit.

Forty-two pregnant women received PMTCT in labour only; 23 having no ANC, and 19 having irregular ANC visits.

Table 12: Gestational age of 246 HIV-infected pregnant women when starting antiretroviral drugs by antiretroviral regimens during pregnancy.

Antiretroviral regimens during pregnancy	**Number of pregnant women started antiretroviral drugs at different week of gestation**					
	Before ANC	**1 - 28**	**29 - 31**	**32 - before labour**	**In labour**	**Total**
Combined ART	16	18	3	4	0	40
PMTCT started in ANC	0	76	50	38	0	164
PMTCT started in labour	0	0	0	0	42	42
Total	**16**	**94**	**53**	**42**	**42**	**246**

Figure 8 shows the variety of antiretroviral regimens according to the timing of ART initiation among 40 HIV-infected pregnant women receiving combined ART during pregnancy. There were 16 pregnant women who have continued combined ART, 8 (50%) of them continued 2NRTIs + NVP, 6 (37.5%) continued 2NRTIs + IDV/RTV. There was a pregnant woman who had been treated with AZT, 3TC, EFV and continuing the regimen during pregnancy. She presented to ANC at 35 weeks of gestation and her ART regimen was not changed. Twenty-four pregnant women initiated combined ART during ANC, 16 (66.7%) of them initiated 2NRTIs + NVP, 7 (29.2%) initiated 2NRTIs + IDV/RTV.

The other regimen were; 1 AZT, 3TC, NFV which was initiated during ANC in a pregnant women who could afford NFV; and 1 SQV, IDV/RTV in a pregnant women who developed ABC resistance confirmed by genotype testing in 2004. During ANC, her viral load rose up to 4,900 copies and genotype testing confirmed HIV resistance so that her ART regimen was changed to a double boosted PIs (SQV, IDV/RTV) at 20 weeks of gestation.

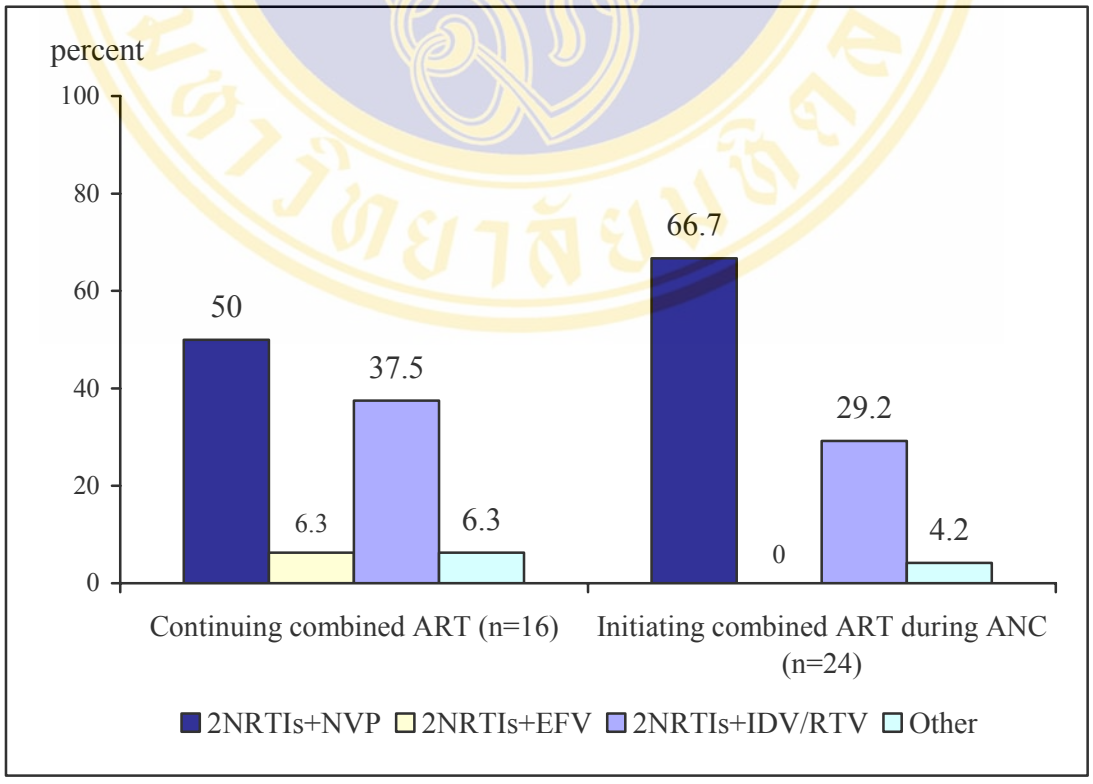


Figure 8: Percentage of combined ART according to the timing of ART initiation among 40 HIV-infected pregnant women receiving combined ART.

Figure 9 shows the percentage of the timing of PMTCT regimens according to the timing of PMTCT initiation among 206 HIV-infected pregnant women receiving PMTCT during pregnancy. There were 164 pregnant women initiated PMTCT regimens during ANC, 118 (72%) of them received AZT + single dose NVP, 36 (22%) received AZT + single dose NVP + tailed end which was AZT + 3TC or AZT + DDI expanded to mother after delivery until 2 – 4 weeks postpartum. Forty-two pregnant women initiated PMTCT in labour, 38 (90.5%) of them received AZT + single dose NVP, 2 (4.2%) received AZT alone in labour, and 2 (4.2%) received single dose NVP only.

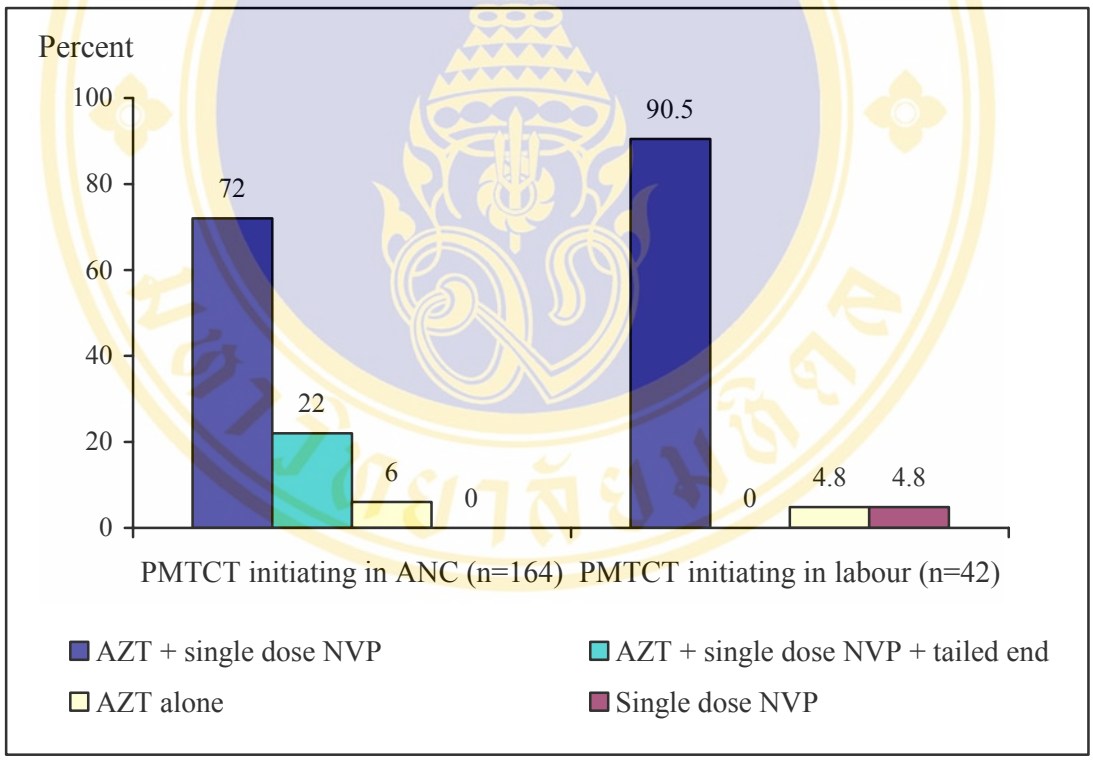


Figure 9: Percentage of the PMTCT regimens according to the timing of PMTCT initiation among 206 HIV-infected pregnant women receiving PMTCT.

5.6 Maternal adverse events of antiretroviral drugs during pregnancy

The analyses of maternal adverse events of antiretroviral drugs include 246 HIV-infected pregnant women receiving antiretroviral drugs during pregnancy, of whom 40 (16.3%) received combined ART, 164 (66.7%) started PMTCT during ANC, and 42 (17.1%) started PMTCT in labour.

Overall, 24 adverse events from 21 (8.5%, 95%CI: 5.4% – 12.8%) HIV-infected pregnant women were documented. The incidence of each adverse event was demonstrated in figure 10, 13 (5.3%) pregnant women developed anemia, 4 (1.6%) nausea and vomiting, 3 (1.2%) dyslipidemia, and 1 (0.4%) hepatotoxicity and rash.

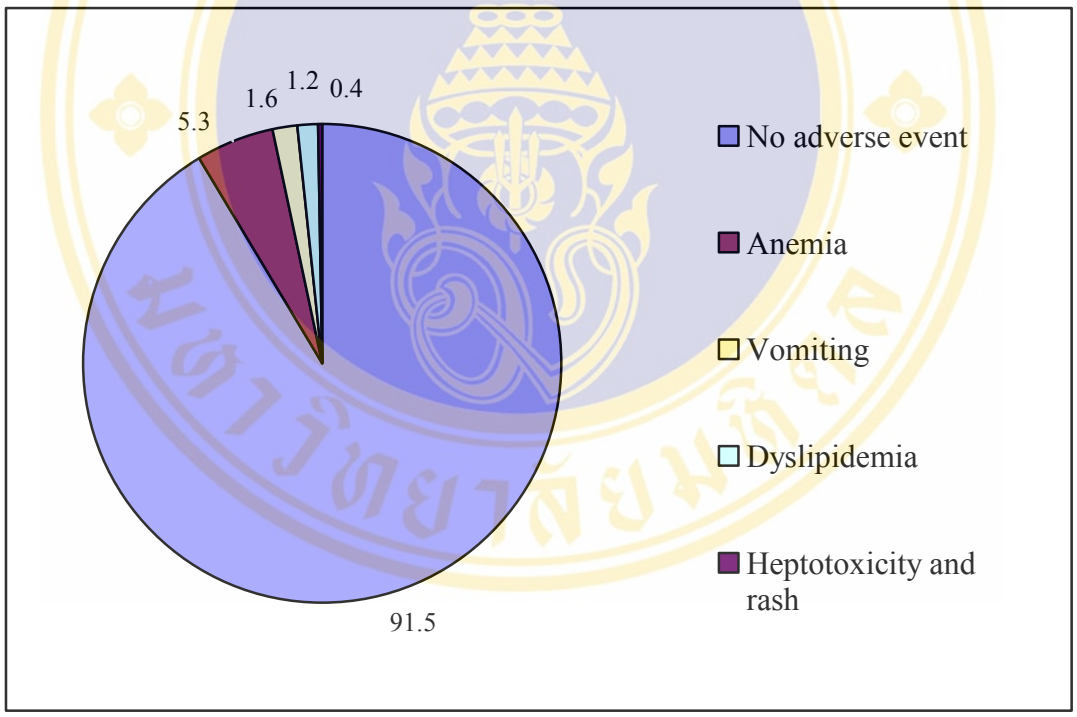


Figure 10: Percentage of adverse events among 246 HIV-infected pregnant women receiving antiretroviral drugs during pregnancy.

According to the antiretroviral regimens and timing of antiretroviral drugs initiation, none of the HIV-infected pregnant women initiating PMTCT in labour reported adverse event. The adverse events among pregnant women receiving combined ART and starting PMTCT during ANC were 32.5% and 4.9%, respectively. Table 13 compares the adverse events among 40 HIV-infected pregnant women receiving combined ART with 164 HIV-infected pregnant women starting PMTCT during ANC by univariated analysis. The combined ART had significant higher incidence of anemia, vomiting, and dyslipidemia than the PMTCT during ANC.

The median (min – max) duration of antiretroviral exposure among the pregnant women received combined ART was 13 (4 – 40) weeks whereas the pregnant women starting PMTCT during ANC's was 10 (less than 1 – 23) weeks.

Table 13: Univariated analysis of adverse events of 204 pregnant women receiving combined ART or starting PMTCT during ANC.

Adverse events	**Total (%) (n=204)**	**Antiretroviral regimens**		***P* value**
		Combined ART (%) (n=40)	**PMTCT during ANC (%) (n=164)**	
Anemia	13 (6.4)	6 (15.0)	7 (4.3)	0.02
Vomiting	4 (2.0)	3 (7.5)	1 (0.6)	0.02
Dyslipidemia	3 (1.5)	3 (7.5)	0 (0)	0.01
Hepatotoxicity and rash	1 (0.5)	1 (2.5)	0 (0)	0.20
Total	21 (10.4)	13 (32.5)	8 (4.9)	

According to the history of allergy to either drug or others including allergic rhinitis, asthma, and seafood, 17 pregnant women reported having history of allergy. Table 14 compares the adverse events among 241 HIV-infected pregnant women receiving antiretroviral drugs by the history of allergy. Totally, the incidence of adverse events among pregnant women who had history of allergy was 17.6% whereas the incidence among the pregnant women who had no allergy was 8.0%. However, no statistically significant difference of each adverse event between the two groups of pregnant women was detected.

Table 14: Univariated analysis of adverse events of 241 pregnant women receiving antiretroviral drugs according to the history of allergy.

Adverse events	**Total (%) (n=241)**	**History of allergy**		***P* value**
		Present (%) (n=17)	**Absent (%) (n=224)**	
Anemia	13 (5.4)	0 (0)	13 (5.8)	0.38
Vomiting	4 (1.7)	1 (5.9)	3 (1.3)	0.26
Dyslipidemia	3 (1.2)	1 (5.9)	2 (0.9)	0.20
Hepatotoxicity and rash	1 (0.4)	1 (5.9)	0 (0)	0.07
Total	21 (8.7)	3 (17.6)	18 (8.0)	

According to the CD4 count during pregnancy, table 15 compares the adverse events among 161 HIV-infected pregnant women receiving antiretroviral drugs by the CD4 count during ANC less than 200 vs. equal or more than 200 cells/µl. The incidence of anemia is significantly different between the pregnant women who had CD4 less than 200 cells/µl and who had the higher CD4 (17.2% vs. 5.3%; p value = 0.04). Therefore, when control low CD4 count (less than 200 cells/µl) by multivariate analysis, there was no significant association between combined ART and anemia; p value = 0.36.

Table 15: Univariated analysis of adverse events of 161 pregnant women receiving antiretroviral drugs according to CD4 count during ANC.

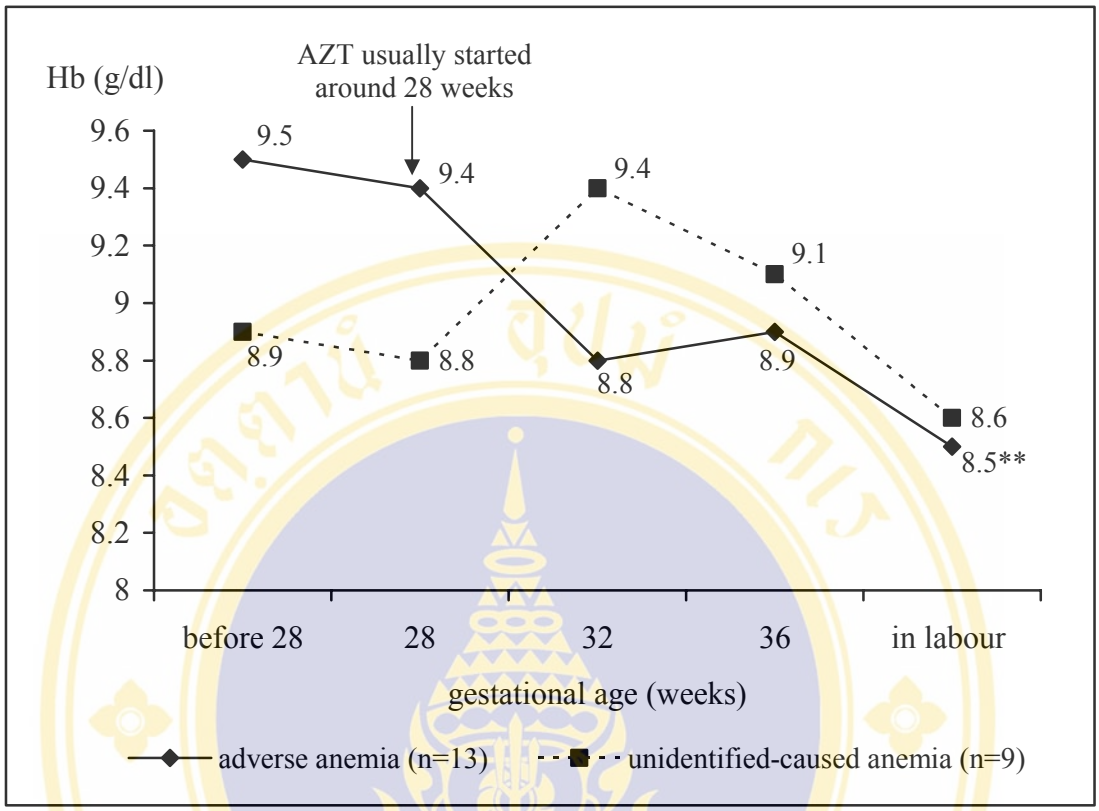
Adverse events	**Total (%) (n=161)**	**CD4 count (cells/µl)**		***P* value**
		Less than 200 (%) (n=29)	**Above or equal 200 (%) (n=132)**	
Anemia	12 (7.5)	5 (17.2)	7 (5.3)	0.04
Vomiting	4 (2.5)	1 (3.4)	3 (2.3)	0.55
Dyslipidemia	3 (1.9)	1 (3.4)	2 (1.5)	0.45
Hepatotoxicity and rash	1 (0.6)	1 (3.4)	0 (0)	0.18
Total	20(12.4)	8 (27.6)	12 (9.1)	

5.6.1 Anemia

Of those 246 pregnant women receiving antiretroviral drugs during pregnancy, a total of 22 (8.9%) developed anemia regarding the cut-off point of haemoglobin level less than or equal to 9.4 g/dl. When excluding 42 pregnant women receiving PMTCT only in labour because of short duration of exposure, the incidence of anemia was 22 (10.8%). Thirteen HIV-infected pregnant women receiving antiretroviral drugs during ANC developed anemia after four weeks of antiretroviral drugs. The other 9 HIV-infected pregnant women receiving antiretroviral drugs during ANC and developed anemia were considered as unidentified-caused anemia because they developed anemia prior to antiretroviral drugs. The median hemoglobin, hematocrit and MCV level of 13 pregnant women with adverse anemia due to antiretroviral drugs were compared to 9 pregnant women with unidentified-caused anemia. (Figure 11 - 13)

The median haemoglobin among 13 pregnant women with adverse anemia obviously dropped from 9.4 to 8.8 g/dl after starting AZT until delivery whereas the median haemoglobin among 9 pregnant women considered as unidentified caused anemia increased for a while before dropped again at the last four weeks of gestation.

The median hematocrit of pregnant women with adverse anemia also obviously dropped from 29.5 to 26% after starting AZT but the median hematocrit in labour was increased to 30.5%. The median hematocrit of pregnant women with unidentified caused anemia was slightly increased. Median MCV of pregnant women with adverse anemia was slightly increased from 81.5 to 86.7 fL whereas the median MCV of pregnant women with unidentified caused anemia was always lower and slightly decreased from 71.9 to 68.8 fL.



** N = 5 because of missing data of CBC of the pregnant women during labour.

Figure 11: The median hemoglobin level of pregnant women with adverse anemia compared to pregnant women with unidentified-caused anemia.

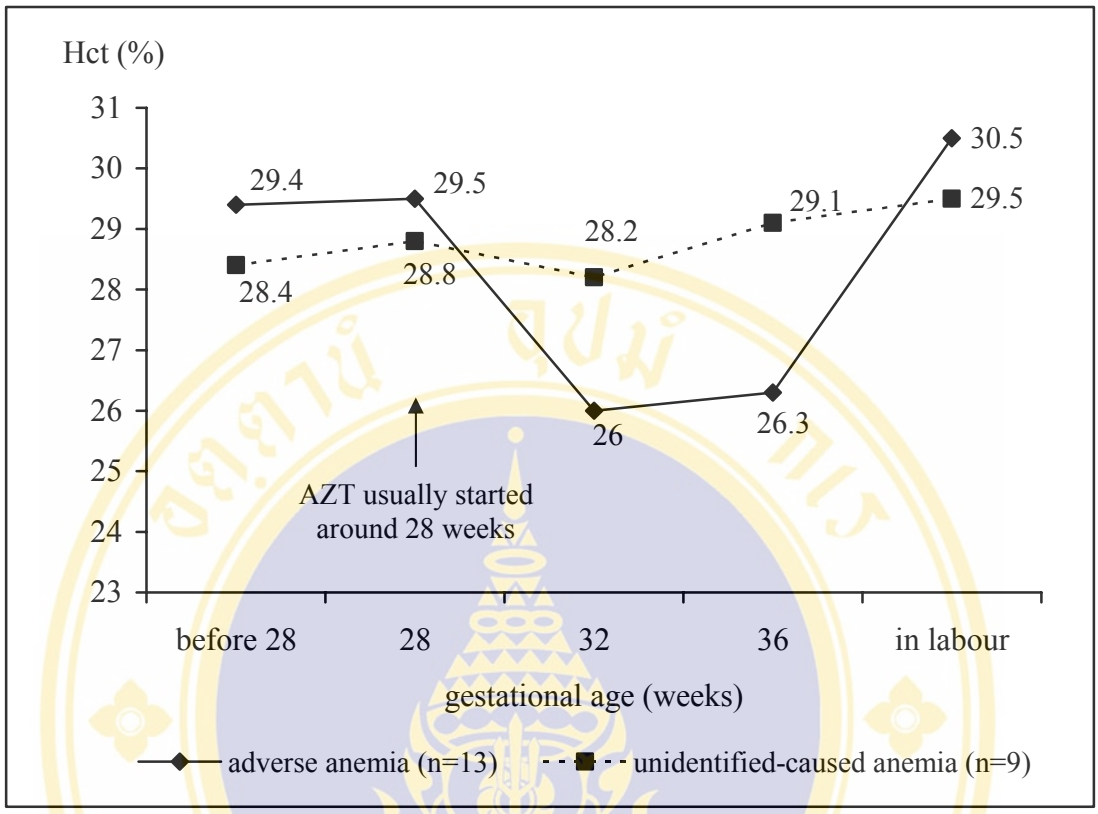


Figure 12: The median hematocrit level of pregnant women considered as adverse anemia due to antiretroviral drugs compared to pregnant women with other caused anemia.

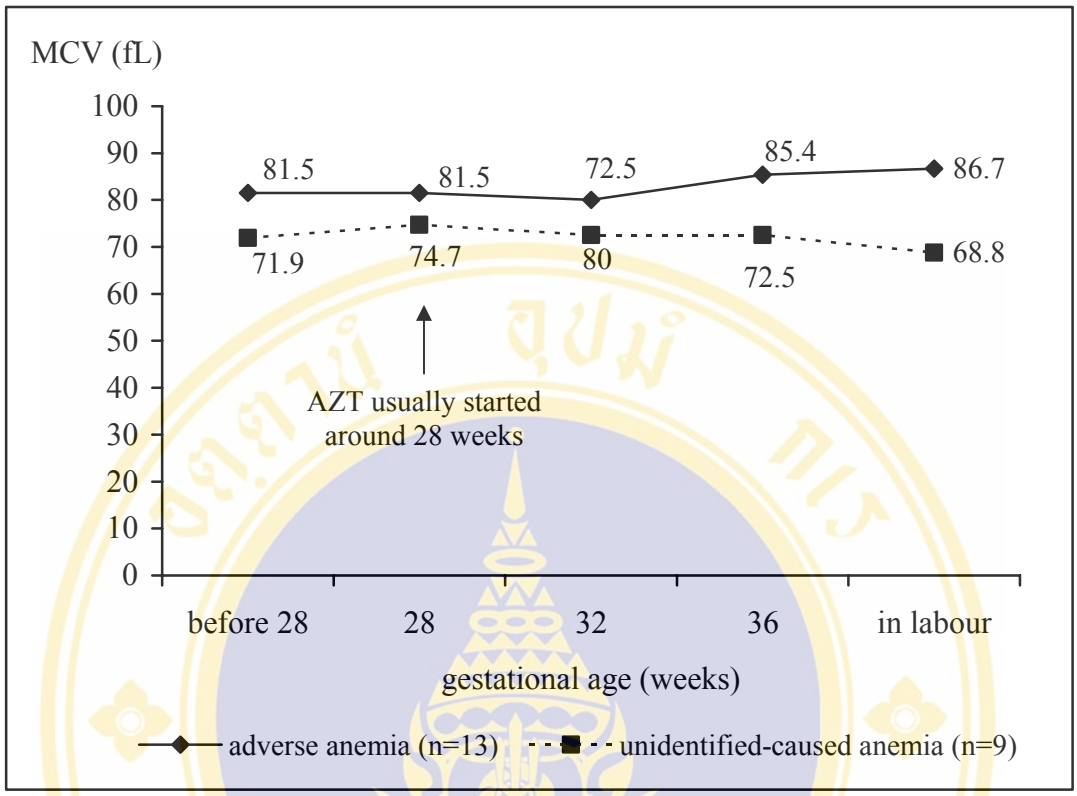


Figure 13: The median MCV level of pregnant women considered as adverse anemia due to antiretroviral drugs compared to pregnant women with other caused anemia.

Of those 13 pregnant women with adverse anemia due to antiretroviral drugs, 10 were classified as severity grade I, 2 were grade II, and 1 were grade IV (AIDS clinical trial groups, 2005). The median time (min – max) after taking AZT until developing anemia was 5 (4 – 9) weeks. A pregnant woman who developed grade IV anemia had been given AZT, 3TC and NVP since 22 weeks of gestation because her CD4 count was only 139 cells/µl and percentage of CD4 was only 8%. Her hematocrit and haemoglobin at starting ART was 33.2% and 10.8 g/dl. She was detected anemia at 31 weeks of gestation with hematocrit 12.5% and haemoglobin 4.3 g/dl. Her MCV also dropped from 93.6 to 80%. Therefore, she was given blood transfusion and her ART regimen was changed to D4T, 3TC and NVP. At delivery, her hematocrit was 11.1% and haemoglobin 3.8 g/dl. She was given packed red cell 4 units. After delivery, she continued taking D4T, 3TC and NVP. Her anemia improved at post partum 6 weeks with hematocrit of 37.8% and haemoglobin of 11.9 g/dl.

A pregnant woman with anemia also had leukopenia. She has been diagnosed HIV infection since 2003 with baseline CD4 count of 18 cells/µl and percentage of CD4 was 4%. She had ever been infected with tuberculosis and also Mycobacterium avium complex. Before pregnancy, she had been taking D4T, 3TC and EFV. She was detected pregnancy late at 25 weeks of gestation, however ART regimen was changed to AZT, 3TC and NVP abruptly. At 36 weeks of gestation, she developed anemia grade I with hematocrit 25.8% and haemoglobin 8.8 g/dl. The absolute neutrophil count was also low, 1,269 cells/cu.mm. One unit of packed red cell was given to her. AZT was changed to D4T again and D4T was continued until she delivered. At postpartum 6 weeks, her anemia was completely recovered with hematocrit 38.5% and haemoglobin 13.1 g/dl.

Regarding the anemia management, 3 pregnant women with anemia were given blood transfusion. Two pregnant women were reduced AZT dosage and two pregnant women were switched AZT to D4T. Table 16 describes the clinical course of 13 pregnant women with adverse anemia in detail. The combined ART had more severe anemia compared to the PMTCT during ANC (median Hb in labour were 6.3 g/dl VS 9.5 g/dl, respectively).

Table 16: Clinical course of 13 pregnant women with adverse anemia due to antiretroviral drugs.

Pregnant women No.	CD4 count at ANC	GA when starting AZT	Antiretroviral regimens	CBC before starting Antiretroviral regimens			CBC at 4-9 weeks after Antiretroviral regimens			management
				Hb	Hct	MCV	Hb	Hct	MCV	
1	2	32	AZT, 3TC, IDV/RTV	9.3	29.4	80.4	8.6	26	NA	
2	10	28	AZT, 3TC, NVP	9.4	28	72	7.0	21.5	NA	Reduce AZT, PRC 1 unit
3	139	22	AZT, 3TC, NVP	10.8	33.2	93.6	4.3	12.5	80	Switch AZT to D4T, PRC 5 units
4	161	28	AZT, 3TC, NVP	10.1	34	69.2	9.4	29.9	72	
5	189	28	AZT	10.1	29	87.9	8.4	24.9	108	
6	212	28	AZT, 3TC, NVP	9.4	26	64	8.8	25.1	86.4	
7	303	29	AZT	9.4	29	NA	8.2	25.5	82	
8	314	27	AZT	9.6	29.7	82.5	9.4	28	82	
9	353	28	AZT	11.1	31.3	87.9	9.0	26.5	92	
10	432	31	AZT	NA	32	87.5	8.9	26.9	NA	
11	498	26	AZT	NA	NA	NA	8.8	28.2	76.6	
12	520	31	AZT	8.5	26.6	62	7.8	24.3	60	Reduce AZT
13	NA	25	AZT, 3TC, NVP	NA	NA	NA	8.8	26	NA	Switch AZT to D4T, PRC 1 unit

5.6.2 Nausea and vomiting

Only 4 (1.6%) of 246 pregnant women were documented about nausea and vomiting complaint after taking antiretroviral drugs; 2 were suspected from AZT, 1 DDI and 1 EFV.

5.6.3 Dyslipidemia and gestational DM

Three pregnant women developed dyslipidemia during pregnancy. All of them were diagnosed HIV infection and received HAART before pregnancy. Two of them were changed the HAART regimens with EFV based to be AZT, 3TC, IDV/RTV at 8 and 12 weeks because of pregnancy. Dyslipidemia were detected after taking IDV/RTV for 25 and 13 weeks, respectively. The other was changed the HAART regimen from AZT, 3TC, NVP to be SQV, IDV/RTV at 25 weeks of gestation due to ARV resistance. She was diagnosed dyslipidemia after taking IDV/RTV for 13 weeks. Each of them developed hypertriglyceridemia grade I, hypercholesterolemia grade II, and both hypertriglyceridemia grade II and hypercholesterolemia. (Table 17)

The pregnant women with both hypertriglyceridemia and hypercholesterolemia also had gestational DM. She was treated with Lopid^{R}. The HAART regimen was changed to D4T, 3TC, EFV after delivery. At 7 weeks of postpartum, her fasting blood sugar, triglyceride, and cholesterol turned to be normal.

Table 17: Laboratory test abnormalities of three HIV-infected pregnant women who received HAART and developed dyslipidemia, Chonburi hospital, 2002 – 2006

Pregnant women	Age	GA starting IDV/RTV	GA detecting dyslipidemia	FBS mg/dl	Triglyceride (mmol/L)	Cholesterol (mmol/L)
I	41	8	33	87	241	295
II ∓	41	12	25	116	433	257
III	28	25	38	103	592	NA

∓ The pregnant woman had abnormal 100 gram OGTT, 260, 220, and 139 mg/dl at 1, 2, and 3 hour post taking glucose respectively. Triglyceride and cholesterol increased to 832 and 280 mmol/L at 37 weeks of gestation.

5.6.4 Hepatotoxicity and rash

A pregnant woman developed both hepatotoxicity and NVP rash. She had history of penicillin allergy and was diagnosed HIV infection when firstly attended ANC clinic in Chonburi hospital at 21 weeks of gestation. Her baseline CD4 count was 198 cells/µl so she started taking AZT, 3TC and NVP at 28 weeks of gestation. When she came to follow up at 32 weeks of gestation, she complained of erythematous papules on her body, without mucosal involvement. ALT was checked and found to be elevate from 8 U/L at 26 weeks of gestation to 57 U/L. Therefore NVP was stopped and changed to IDV and RTV because of rash and hepatotoxicity grade I. After delivery, ALT was decrease to 8 U/L.

5.5 Pregnancy outcomes

5.7.1 Delivery

Figure 14 shows the percentage of mode of delivery among 246 pregnant women receiving antiretroviral drugs during pregnancy. Majority of them, 177 (72.0%) had normal delivery, 49 (19.0%) were caesarean section, 7 (2.8%) vacuum extraction, and 2 (0.8%) forceps extraction.

Among 49 pregnant women who delivered by caesarean section, the caesarean indications included; 15 previous caesarean section, 9 cephalo-pelvic disproportion, 5 breech presentation, 9 having other indications, 4 elective caesarean section due to low CD4 count, and 7 elective caesarean section without specified indication.

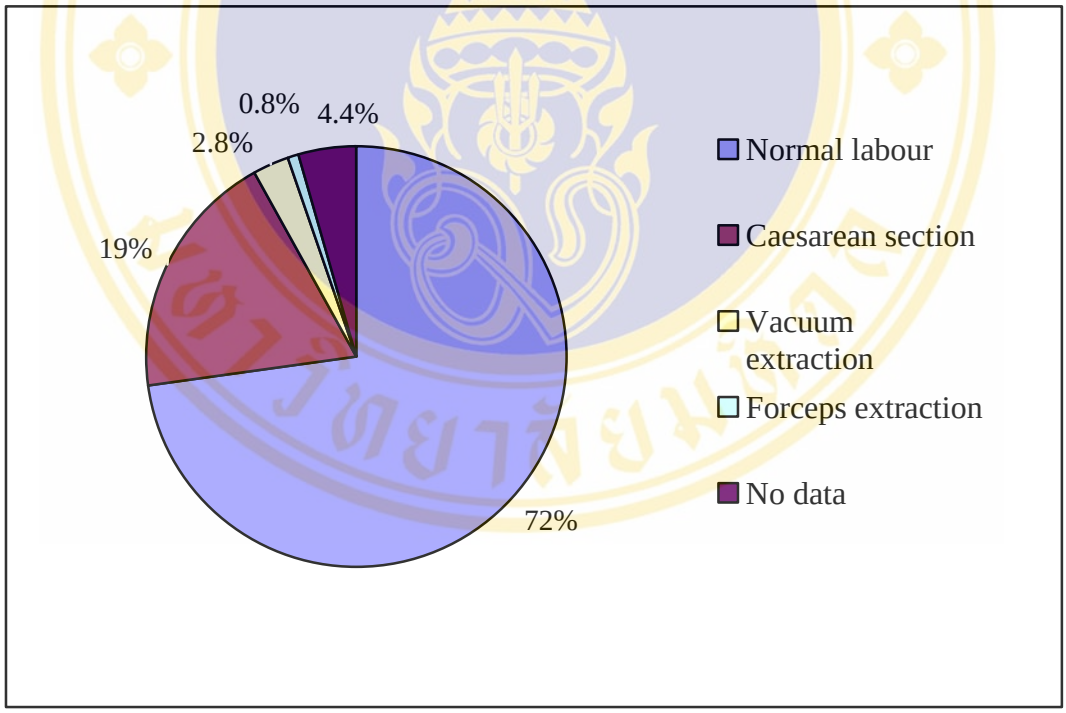


Figure 14: Percentage of mode of delivery among 246 pregnant women receiving antiretroviral drugs during pregnancy.

Table 18 describes the outcomes and the complications of delivery among pregnant women receiving antiretroviral drugs. Most of the pregnant women, 208 (88.9%), had term delivery, 25 (10.7%) preterm, and 1 had stillbirth. Most of the pregnant women, 209 (89.3%), also had no delivery complication, 17 (7.3%) had preterm labour pain, 4 (1.7%) premature rupture of membrane, and 4 (1.7%) pre-eclampsia.

The pregnant woman who delivered a stillbirth was 31 years old with the first gravid without underlying disease. She had been diagnosed HIV-infected pregnancy since eight weeks of gestation at Bangpakong hospital. VDRL and HBsAg were negative. Data of CD4 count was not documented. She had been taking AZT for PMTCT since 31 weeks of gestation without adverse event. At 36 weeks of gestation, she came to the ANC of the hospital by herself. She gave normal labour at 37 weeks of gestation but the neonate was stillbirth with hydrocephalus.

According to the antiviral regimens during pregnancy, the pregnant women who initiating PMTCT regimens during ANC had higher proportion of term delivery and lower proportion of preterm delivery compared to delivery outcome of the pregnant women received combined ART or initiated PMTCT in labour. The incidences of preterm labour pain, premature rupture of membrane, and pre-eclampsia were also lower among the pregnant women who initiating PMTCT regimens during ANC.

Table 18: Delivery outcome and delivery complication of 246 HIV-infected pregnant women according to the antiviral regimens during pregnancy.

Delivery	Total (n=234)	Combined ART (%) (n=31)	PMTCT started in ANC (%) (n=161)	PMTCT started in labour (%) (n=42)
Delivery outcome				
Term (≥ 37 weeks)	208 (88.9)	25 (80.6)	149 (92.5)	34 (81.0)
Preterm (21–36 weeks)	25 (10.7)	6 (19.4)	11 (6.8)	8 (19.0)
Stillbirth	1 (0.4)	0 (0)	1 (0.6)	0 (0)
Delivery complication				
No	209 (89.3)	24 (77.4)	149 (92.5)	36 (85.7)
PLP	17 (7.3)	5 (16.1)	6 (3.7)	6 (14.3)
PROM	4 (1.7)	1 (3.2)	3 (1.9)	0 (0)
Pre-eclampsia	4 (1.7)	1 (3.2)	3 (1.9)	0 (0)

Excluding the pregnant women who had no available delivery data, the incidences of preterm delivery, premature labour pain, premature rupture of membrane, and pre-eclampsia were compared according to antiretroviral regimens during pregnancy in table 19. The incidence of preterm delivery and preterm labour pain among the pregnant women initiated PMTCT during ANC were significantly lower than the incidences among the other two groups of pregnant women, *p* value = 0.02 and 0.01 respectively. However, when controlling the maternal conditions including elderly pregnancy, multigravida, low CD4 count, and anemia by multivariate analysis, only pregnant women initiated PMTCT in labour had significant association with preterm delivery, p value = 0.01.

Table 19: Univariated analysis of delivery complication of 234 HIV-infected pregnant women by antiretroviral regimens during pregnancy.

Delivery outcome and complication	Total (n=234)	Combined ART (%) (n=31)	PMTCT started in ANC (%) (n=161)	PMTCT started in labour (%) (n=42)	*P* value
Preterm (21-36 weeks)	25 (10.7)	6 (19.4)	11 (6.9)	8 (19.0)	0.02
PLP	17 (7.3)	5 (16.1)	6 (3.7)	6 (14.3)	0.01
PROM	4 (1.7)	1 (3.2)	3 (1.9)	0 (0)	0.56
Pre-eclampsia	4 (1.7)	1 (3.2)	3 (1.9)	0 (0)	0.56

Table 20 describes the infant characteristics of 246 HIV-infected pregnant women by antiretroviral regimens during pregnancy. Totally, the incidence of low birth weight was as high as 49 (20.0%); 39 low birth weight and 10 very low birth weight. The infants born to pregnant women initiated PMTCT in labour had the highest incidence of both low birth weight, 8 (19.0%), and very low birth weight, 5 (11.9%). The incidence of low Apgar score was 9 (3.6%); 5 low Apgar score and 4 very low Apgar score included one stillbirth (Agar score = 0). Low Apgar score was also highest among the infant born to pregnant women initiated PMTCT in labour, 5 (11.9%).

Table 20: Infant characteristics of 246 HIV-infected pregnant women by antiretroviral regimens during pregnancy.

Infant characteristics	Total (n=246)	Combined ART (%) (n=40)	PMTCT started in ANC (%) (n=164)	PMTCT started in labour (%) (n=42)
Birth weight (grams)				
VLBW; < 2000	10 (4.1)	2 (5.0)	3 (1.8)	5 (11.9)
LBW ; 2000 – 2499	39 (15.9)	6 (15.0)	25 (15.2)	8 (19.0)
≥ 2500	178 (72.4)	21 (52.5)	128 (78)	29 (69.1)
No data	19 (7.7)	11 (27.5)	8 (4.9)	0 (0)
Apgar score				
0 – 3	4 (1.6)	1 (2.5)	2 (1.2)	1 (2.4)
4 – 6	5 (2.0)	0 (0)	1 (0.6)	4 (9.5)
7 – 10	219 (89.0)	28 (70.0)	154 (93.9)	37 (88.1)
No data	18 (7.3)	11 (27.5)	7 (4.3)	0 (0)
Birth defect				
Yes	4 (1.6)	0 (0)	3 (1.8)	1 (2.4)
No	223 (90.7)	29 (72.5)	153 (93.3)	41 (97.6)
No data	19 (7.7)	11 (27.5)	8 (4.9)	0 (0)
Congenital infection				
Yes	2 (0.8)	0 (0)	0 (0)	2 (4.8)
No	224 (91.1)	29 (72.5)	155 (94.5)	40 (95.2)
No data	20 (8.1)	11 (27.5)	9 (5.5)	0 (0)
HIV status (n=51)				
Positive	8 (15.7)	0 (0)	7 (16.7)	1 (16.7)
Negative	43 (84.3)	3 (7.0)	35 (83.3)	5 (83.3)

Four (1.6%) of infants had congenital defect included the stillbirth infant with hydrocephalus. The other three were;

1. Sensorineural hearing loss infant was born to the pregnant woman initiated PMTCT during labour. The mother was 21 years old with the second gravid. She had no underlying disease and no ANC history. She was admitted in the Chonburi hospital at estimated 27 weeks of gestation with failure to inhibit preterm labour pain. Rapid test for anti-HIV was positive. VDRL and HBsAg were negative. She was performed caesarean section because of placenta previa. The infant was very low birth weight, 1,070 grams with Apgar score 6. He was admitted to NICU and developed congenital pneumonia, necrotizing enterocolitis and died. Sensoryneural hearing loss was detected during admission.
2. Gastroschisis infant was born to 23 years old mother initiated AZT for PMTCT at 28 weeks of gestation. The infant was term but low birth weight, 2,350 grams.
3. Polydactyl infant was born to the mother having low CD4 count, 197 cells/µl and initiated AZT for PMTCT at 31 weeks. The infant was delivered because of premature rupture of membrane. Birth weight was 1,930 grams and Apgar score 10.

Only 2 (0.8%) of infants had congenital infection, which was pneumonia. Only 51 infants could be found the result of perinatal HIV infection. The perinatal HIV infection rate was 15.7%. None of the infants born to pregnant women received combined ART had perinatal HIV infection.

Excluding the missing data, the incidence of low birth weight, low Apgar score were compared by the timing of antiretroviral drug initiation in mother, maternal CD4 count during ANC, and timing of the first ANC attending (Table 21 – 22). Only the incidence of low Apgar score was significantly lower among the pregnant women who firstly visited to ANC clinic before or at 28 weeks than the pregnant women who firstly visited to ANC clinic later. Low apgar score was also significantly lower among the pregnant women initiated antiretroviral drugs before or during ANC than the pregnant women initiated antiretroviral drugs in labour. However, when controlling elderly pregnancy and multigravida by multivariate analysis, only pregnant women initiated PMTCT in labour had significant association with low Apgar score, p value = 0.006.

Table 21: Incidence of low birth weight and low Apgar score by the antiviral regimens during pregnancy.

Infant	Total (%) (n=227)	Combined ART (%) (n=29)	PMTCT started in ANC (%) (n=156)	PMTCT started in labour (%) (n=42)	*P* value
LBW < 2,500 grams	49 (21.6)	8 (27.6)	28 (17.9)	13 (31.0)	0.13
Low Apgar score < 7	8 (3.5)	1 (3.4)	2 (1.3)	5 (11.9)	0.004

Table 22: Incidence of low birth weight and low Apgar score by the gestational age at first ANC visit.

Infant	Total	Gestational age at first ANC visit		P value
		Before or 28 weeks	After 28 weeks	
LBW < 2,500 grams	48 (21.8)	32 (19.2)	16 (30.2)	0.07
Low Apgar score ≤ 7	9 (4.1)	3 (1.8)	6 (11.3)	0.01

CHAPTER VI
DISCUSSION

After the increasing of the recommended treatment with combined ART and the success of the national PMTCT program in Thailand, the morbidity and mortality of HIV infections are dramatically decreased as well as the risk of mother-to-child transmission. Despite the positive impact on HIV-related morbidity and mortality, the duration of exposure to antiretroviral therapy has been associated with complications.

In the scenario of PMTCT, many studies reported a number of pregnant women experienced typical adverse effects of the antiretroviral drugs such as anemia, nausea and vomiting, aminotransferase elevation, or hyperglycemia. Additionally, data has been conflicting as to whether receipt of combination antiretroviral therapy during pregnancy is associated with adverse pregnancy outcomes such as preterm delivery.

This study focuses on the adverse events of antiretroviral therapy in HIV-infected pregnant women including the pregnancy outcomes. The maternal characteristics and antenatal care history were also reviewed as their association with the adverse events and particularly the pregnancy outcomes. The results are discussed below.

6.1 HIV seroprevalence among pregnant women

The number of pregnant women registered to the labour room in Chonburi hospital was approximately 2,000 – 2,500 more than those registered to ANC clinic. These data reflect to a large number of pregnant women who had 1) delivery complications and were referred to Chonburi as the regional hospital, 2) irregular antenatal care, or 3) no antenatal care. This number of pregnant women included some HIV-infected women that would affect to the coverage and effectiveness of the prevention of mother-to-child transmission.

The trend of HIV seroprevalence among the pregnant women attended ANC clinic in the hospital had not been declined during 2002 – 2006, 2.4%, 2.2%, 1.8%, 1.8%, and 2.0%. It was continuously higher than the national seroprevalence among the same population during the same period, 1.4%, 1.2%, 1.0%, 1.0%, and 0.87%

(Bureau of Epidemiology, Thai MoPH, 2006). The higher seroprevalence might be explained by that Chonburi is an industrial province and in the same time, it has a tourist area, Pattaya, a famous destination for foreign sex tourism. Therefore the province contains a lot of commercial sex workers and immigrant factory workers who are at the high risk of HIV transmission (Bureau of Epidemiology, Thai Ministry of Public Health, 2004)

6.2 Maternal characteristics

The maternal characteristics of described in 246 HIV-infected pregnant women receiving antiretroviral drugs during pregnancy showed The median age of 27 years old which was older than the HIV-infected pregnant women enrolled in the short-course AZT trial for perinatal HIV-1 transmission in Bangkok (Shaffer et al., 1999) and single dose perinatal NVP plus standard AZT to prevent mother-to-child transmission of HIV-1 in Thailand (Lallemant et al., 2004) respectively. Majority of age group was 20 – 29 years which are the working age group. The proportion of teenage pregnancy among HIV-infected pregnant women was 8.1% compared to 9.2% in the national HIV serosurveillance 2004 (Bureau of Epidemiology, Thai Ministry of Public Health, 2004). The proportion of teenage HIV-infected pregnancy in Chonburi hospital was also lower than the proportion of teenage pregnancy in general population.

. As high as 40.7% of the pregnant women were non-local residents of Muang Chonburi. They emigrated from other districts, neighbouring provinces, even from Northeast region for employment. Therefore, most of the pregnant women were the labourer, 73.6%, and had rather low level of income.

Even though 90.1% of them were coupled, 27.8% reported that they ever had previous spouse(s) and 46% were discordant with their current spouse. These data indicated the problem of HIV-infected persons having serial spouses and concealing their HIV status followed by transmitting HIV to their spouses and offspring.

6.3 Past medical history

Ten (4.1%) of the pregnant women reported history of drug allergy before this pregnancy including 4 pregnant women with NVP allergy and 6 (2.8%) reported other histories allergy. It was interesting to assess the maternal adverse event of antiretroviral drugs among them whether there is any association between history of allergy and the adverse events of antiretroviral drugs.

An amphetamine and two heroin addicted HIV-infected individuals became pregnant during their methadone course. Surprisingly, they were firstly detected HIV-seropositive in ANC clinic instead of detection in the methadone clinic even they had been high risk persons of HIV infection should be emphasized HIV prevention and control not only no sharing needles but also condom use.

6.4 Maternal HIV history and experience in antiretroviral drugs

Majority of the pregnant women, 73.2%, were firstly detected HIV-seropositive during ANC. 11.8% of pregnant women were detected HIV-seropositive in labour and lost their benefit of getting the effective PMTCT. However, the proportion of pregnant women detected HIV-seroconversion during ANC was higher, and the proportion of pregnant women detected HIV-seropositive in labour was lower than the population-based surveillance of reduction of mother-to-child HIV transmission in Thailand, 2001 – 2003 by Plipat and colleagues which revealed 66.7% of pregnant women detected HIV-seropositive during ANC and 14.8% detected HIV-seropositive in labour. (Plipat et al., 2007). The feasibility of Chonburi hospital to early detect HIV-seropositive is another goal to encourage the hospital to achieve in the future.

Regarding the trend of timing of HIV detection in Chonburi hospital, the treand of HIV detection before pregnancy showed a slightly increasing during 2003 - 2006. This would be the effects of better standard HIV care and treatment of combined ART in HIV-infected Thais and pregnant women under the HIV/AIDS care programs. However the trend of HIV detection in labour was quite stable. Therefore, it is important to promote the unknown HIV status pregnant women to have ANC and voluntary HIV counselling and testing. Particularly, the non-local residents of Muang Chonburi represented the high percentage of first HIV detection during delivery among HIV-infected pregnant women. It shows that this group of non-local residents

might not reach the antenatal care because of their migration and the problem of health insurance coverage.

There were 37 (15%) pregnant women firstly detected HIV-seroconversion before this pregnancy, 16 of them experienced and were continuing combined ART including 5 pregnant women who were taking EFV. They discontinued EFV at 8, 11, 23, 25 weeks of gestational age, and the other pregnant women came to ANC late at 35 weeks so EFV was not withdrawn. Even though no birth defect in the pregnant women taking EFV, since EFV has been classified as “FDA pregnancy category D” with the significant teratogenicity of central nervous system malformations in monkeys (Perinatal HIV Guidelines Working Group, 2006) and evidences of neural tube defects in infants born to mothers receiving EFV during the first trimester (Bristol-Meyer Squibb Company, 2004). All women receiving EFV must be informed this serious adverse effect and birth control, or at least, ANC attendance as early as possible when they become pregnant.

The HIV conditions among 37 pregnant women firstly detected HIV-seroconversion before this pregnancy showed the shorter period of known HIV status prior to this pregnancy in ART naive (median time 2 years) than the ART experienced pregnant women (median time 3 years). The other baseline HIV conditions ART naive pregnant women were also better than of those experienced; median baseline CD4 count at first HIV detection were 384 vs. 114 cells/µl, and the percentage of women in clinical category A were 100% vs. 52.6%. However, when presenting in the ANC clinic, the CD4 count of these two groups were comparable (median CD4 count of 282 cells/µl in both ART naive and ART experienced). The increasing CD4 count of the ART experienced indicated the efficacy of ART to improve the condition of HIV-infected persons as also mention in the study of Getahun and colleagues to the efficacy of GPO-vir in advanced HIV infection that revealed an increasing of median CD4 count of the subjects from 13 to 191 cells/µl at 48 weeks of GPO-vir (Getahun et al. 2006).

Of those 180 (73.2%) pregnant women who were firstly detected HIV-seroconversion during ANC, the median gestational age at HIV detection was 19.5 weeks, additionally, 83.9% of them were detected at less than or 28 weeks of gestation which was early to implement the national standard PMTCT regimen in mothers, AZT

started at 28 weeks plus single dose intrapartum NVP (Department of Health, Thai MoPH, 2003). The median CD4 count was 325.5 cells/µl and 98.2% were classified in the clinical category A.

6.5 Antenatal care and antiretroviral regimens during pregnancy

Majority of the pregnant women had both attended and delivered in Chonburi hospital, 68% of them were the local residents of Muang Chonburi whereas most of the pregnant women who had only attended ANC clinic or delivered in Chonburi hospital were the non-local residents. This might also be the effect of migration for employment. There was no different pattern of ANC and delivery among each gravid and parity. Twenty-three (9.3%) pregnant women had not visited any ANC clinic before delivery in Chonburi hospital. These 9.3% were exactly non-ANC pregnant women as almost equal as the percentage of non-ANC pregnant women in the study of Plipat and colleagues, 9.2% (Plipat et al., 2007).

Regarding the history of previous pregnancy with HIV infection, 13 out of 14 pregnant women who had previous pregnancy with HIV infection came to attend ANC clinic in this pregnancy. It indicated their concern about importance of antenatal care and PMTCT for HIV-infected pregnancy.

According to the antiretroviral regimens during pregnancy, 40 (16.3%) of 246 pregnant women received combined ART. Of those, 6 pregnant women had no indication to initiate combined ART. Most of them attended ANC clinic at private hospitals or clinics outside Chonburi hospital and one of them was a government employee. Concerning their affordability and the efficacy of combined ART that can reduce perinatal transmission rate to less than 2% (Lallement et al., 2000), combined ART were prescribed.

Despite only 23 (9.3%) pregnant women had no ANC, as high as 42 (17.1%) of 246 pregnant women initiated PMTCT just in labour. Nineteen pregnant women had attended ANC but had not received antiretroviral drugs because of inadequate or irregular ANC visits. All HIV-seroconversion pregnant women should be performed post HIV test counselling and emphasized about the importance of ANC and PMTCT. If they loss from ANC clinic and have poor adherence to PMTCT regimen, the seeking system must be activated to encourage them regularly attended ANC clinic as

same as the phone-call system in HIV clinic to remind the HIV-infected persons for regularly follow up.

Regarding the antiretroviral regimens during pregnancy, most of pregnant women received AZT for PMTCT or combined regimens. Therefore anemia and nausea/vomiting were expected to be common adverse events among the mothers. Particularly, 3.8% - 38% of pregnant women in general population will develop anemia during pregnancy depend on the nutritional status and trimester (CDC, United States, 1990). The pregnant women receiving AZT may develop more severe anemia than the non-pregnant persons receiving AZT and the pregnant women not receiving AZT. Fourteen pregnant women received combine ART with PIs, hyperglycemia and hyperlipidemia might occur in this group. Twenty-four pregnant women had received NVP since during ANC, NVP rash and the elevated aminotransferrase should be considered (Perinatal HIV Guidelines Working Group, 2006).

6.6 Maternal adverse events of antiretroviral drugs during pregnancy

Overall, 24 adverse events from 21 (8.5%, 95%CI: 5.4% - 12.8%) HIV-infected pregnant women were documented. The incidence was lower compared to 15% in the study of Lallement and colleagues (Lallement et al., 2004). The lower incidence of adverse events in this study might be explained by; 1) this study is retrospective study, the incidence of adverse events was depended on the medical records and the physicians' documentation to the medical records whereas the study of Lallement and colleagues was prospective clinical trial, 2) all of the pregnant women in the study of Lallement and colleagues received standard AZT regimen for PMTCT whereas 17.1% of the pregnant women in our study just initiated antiretroviral drug during labour. Therefore, when we excluded these number pregnant women, the incidence of adverse events was recalculated and equaled to 10.4% (95%CI: 6.5% - 15.3%).

According to the antiretroviral regimens, the incidence of adverse events of pregnant women receiving combined ART was higher than of the pregnant women starting PMTCT during ANC. The higher incidence of adverse events among pregnant women receiving combined ART might be explained by; 1) advance stage of HIV condition 2) more type and pill of drugs, 2) longer duration of antiretroviral drug exposure. Anemia, vomiting, and dyslipidemia were significantly different but not

hepatotoxicity and rash because too small number of the adverse events occurred in pregnant women received combined ART and none of pregnant women received PMTCT.

According to the history of allergy either to drug or others, there was no association between history of allergy and the adverse events. There was also no difference between CD4 count and vomiting, dyslipidemia, or hepatotoxicity.

Using the cut-off point of haemoglobin lower than 9.4 g/dl to define the adverse anemia due to AZT. Thirteen (6.4%) pregnant women receiving antiretroviral drugs during ANC developed anemia after four weeks of antiretroviral drugs. The anemia incidence in this study was similar to the study of Lallement and colleagues, 7% (Lallement et al., 2004) but much lower than in the study of Lorenzi and colleagues, 40.5% (Lorenzi et al., 1998). Anemia carried the significant difference between the pregnant women who had CD4 count less than and above 200 cells/µl. However, anemia can also be affected by the maternal HIV condition.

The other 9 (4.4%) pregnant women receiving antiretroviral drugs during ANC developed unidentified-caused anemia. The median haemoglobin of pregnant women with unidentified caused anemia was low before 28 weeks of gestation and became better after 28 weeks and dropped again at the last four weeks of gestation which was the normal pattern of haemoglobin level in pregnant women that normally decrease at the early of pregnancy and increase until the third trimester (CDC, United States, 1990) whereas the median haemoglobin of pregnant women with adverse anemia was obviously dropped after starting AZT until delivery. The median hematocrit of these two groups of pregnant women showed the similar patterns except the rising of hematocrit at delivery among pregnant women with adverse anemia. This increasing might be explained by the intervention to anemia before delivery, 2 pregnant women were reduced AZT dosage, two were switched AZT to be D4T, and three of them were given blood transfusion.

Nausea and vomiting occurred in only 1.6% of the pregnant women. It was low incidence because of no documentation rather than being exact as it would.

Three pregnant women developed dyslipidemia which were presumed to be due to PIs. One of them also had abnormal 100 gram OGTT but did not need insulin to control her blood sugar. Even though two of them were elderly pregnancy, 41 years

old, and no baseline lipid profile, they developed dyslipidemia after taking PIs for 25 and 13 weeks which were possible to be adverse effect of PIs. (Perinatal HIV Guidelines Working Group, 2006)

6.7 Pregnancy outcomes

Majority of the pregnant women gave normal delivery. Among the pregnant women who delivered by caesarean section, 11 of them were performed elective caesarean section; 4 due to low CD4 count but the other 7 had no specified indications. However, the fact that caesarean section added to antiretroviral drugs in pregnant women can reduce perinatal transmission rate to less than 2% (Lallement et al., 2000) and tubal ligation can be done in the same operation, these would be the reason of elective caesarean section that some obstetricians offered to the HIV-infected pregnant women.

Regarding delivery outcome and complication, the incidence of preterm delivery was 10.7% similar to 11.9% – 12.3% in the study of Lallement and colleagues (Lallement et al., 2004). When compared preterm delivery according to the antiretroviral regimen during pregnancy, the pregnant women receiving combine ART had a significant higher incidence of preterm delivery than the pregnant women initiating PMTCT during pregnancy, 19.4% vs. 6.9%. This information supported by the study of Lorenzi and colleagues that identified the incidence of preterm delivery in the pregnant women receiving dual or combined ART as high as 27% (Lorenzi, 1998). The incidence of preterm delivery was also significantly higher among the pregnant women initiating PMTCT in labour than the pregnant women initiating PMTCT during pregnancy, 19.0% vs. 6.9%. This might be the effect of no antenatal care.

There was a still birth infant born to the mother initiating AZT at 31 weeks of gestation. The infant was also hydrocephalus which more likely to be the sequence of congenital infection rather than the adverse event of AZT. The incidence of pre-eclampsia was 1.7%, quite similar to the incidence of pre-eclampsia in general population, 2.8% (Suy et al., 2006). The incidence of pre-eclampsia among pregnant women receiving combined ART was 3.2% in contrast to 19.1% from the study of Suy and colleagues (Suy et al., 2006).

Regarding the infants, the incidence of low birth weight was as high as 20% compared to 7.9% - 9.3% in the study of Lallement and colleagues (Lallement et al., 2004) and 5.9% - 9.2% in the study of Shaffer and colleagues (Shaffer et al., 1999). The pregnant women initiating PMTCT in labour carried the high percentage of low birth weight. These no or inadequate ANC pregnant women might be the cause of high incidence of low birth weight in our study. However, no significant difference of low birth weight according to the timing of antiretroviral drug initiation, maternal CD4 count, or gestational age at first ANC visits.

The incidence of low Apgar score was 3.6%, it was significantly higher among the pregnant women initiated antiretroviral drug in labour and the pregnant women firstly visiting ANC clinic later than 28 weeks of gestation. These differences might also be the effect of no or inadequate ANC.

No birth defect suspected to be the adverse event of antiretroviral drugs. Five pregnant women who received EFV gave normal baby. An infant with sensorineural hearing loss born to no ANC pregnant women and the hearing loss should be the sequel of preterm infant.

Only 51 infants could be found the result of HIV infection. The perinatal HIV transmission rate was high as 8 (15.7%). Among them there were 4 of them admitted to the hospital because of pneumonia or diarrhea and were detected HIV seropositive. The sick children were more likely to come to the hospital and received HIV testing. Therefore, the perinatal HIV transmission rate would be higher than expected.

6.8 Limitations of the study

Our study had several limitations that must be taken into account when interpreting the findings:

1) This study mostly retrospective reviewed medical record. The completeness of data was depended on the physicians' documentation. The socioeconomic data were hardly to be found. The non-serious adverse events such as nausea, vomiting, and abdominal pain might not be documented and led to the low incidence.
2) This study had been carried out only in Chonburi hospital, Chonburi province which has a high HIV prevalence and non-ANC pregnant women. Therefore the result of the study may not represent the other areas in Thailand.
3) By duration of the study, 2002 – 2006, many HIV/AIDS policies have been used in Thailand e.g. PMTCT regimens, GPO-vir that influenced to the practice of HIV-infected pregnancy care and the outcomes of interest.
4) The ICD10 codes of HIV-related diagnoses were routinely not entered into the computer-based system. Therefore, we could not search for the diagnosis "HIV-infection with abortion" and "HIV-infection with ectopic pregnancy". Only the pregnant women who gave birth were recruited in this study.
5) As a high proportion of the non-local residents, a small number of children born to HIV infected pregnant women were followed up in Chonburi hospital and performed HIV testing at 12 and 18 months old.

CHAPTER VII
CONCLUSIONS

7.1 Conclusions

This retrospective – prospective descriptive study had been carried out to assess the adverse effects of antiretroviral drugs and the pregnancy outcome among 246 HIV-infected pregnant women who received antiretroviral drugs for either combined antiretroviral therapy or prevention of mother-to-child transmission.

The trend of HIV seroprevalence among the pregnant women attended ANC clinic in the hospital had not been declined during 2002 – 2006 and continuously higher than the national seroprevalence among the same population.

The mothers were at median age of 27 years old. Majority of them were the working age group. There was a high percentage of the pregnant women who were non-local residents of Muang Chonburi and immigrated for employment. Therefore, most of them were the labourer and had rather low level of income. The data of marital status, number of previous couple, and discord indicated the problem of HIV-infected persons having serial spouses and concealing their HIV status.

Majority of the pregnant women were firstly detected HIV-seroconversion during ANC. However, the trend of HIV detection in labour was stable. Therefore, it is important to promote all pregnant women to have ANC and voluntary HIV counselling and testing, particularly, the non-local residents of Muang Chonburi who represented the high percentage among the pregnant women who were firstly detected HIV-seroconversion in labour.

Five of 37 pregnant women were firstly detected HIV-seroconversion before pregnancy were continuing combined ART with EFV. However, there was no teratogenic effect of EFV.

Of those 180 pregnant women who were firstly detected HIV-seroconversion during ANC, most of them were detected at less than or 28 weeks of gestation which was proper to implement the national standard PMTCT regimen in mothers.

Majority of the pregnant women had both attended and delivered in Chonburi hospital and 9.3% had no ANC history. There were 16.3% of pregnant women received combined ART during ANC, 66.7% initiated PMTCT regimens during ANC, and, 17.1% initiated PMTCT in labour.

Overall, 24 adverse events from 21 (8.5%, 95%CI: 5.4% - 12.8%) HIV-infected pregnant women were documented. According to the antiretroviral regimens, there was an association between pregnant women receiving combined ART and the incidence of vomiting and dyslipidemia. Thirteen (6.4%) pregnant women developed anemia after four weeks of AZT. Nausea and vomiting occurred in only 1.6% pregnant women. Three pregnant women developed dyslipidemia, one of them also had abnormal 100 gram OGTT.

The incidence of preterm delivery was 10.2%. There was an association between the pregnant women initiating PMTCT in labour and the incidence of preterm delivery. The incidence of pre-eclampsia was similar to the incidence of pre-eclampsia in general population. The pregnant women initiating PMTCT in labour carried the high percentage of low birth weight. The incidence of low Apgar score was 3.6% and associated to the pregnant women initiated antiretroviral drug in labour and the pregnant women firstly visiting ANC clinic later than 28 weeks of gestation. No birth defect suspected to be the adverse event of antiretroviral drugs.

7.2 Recommendations

1) Regarding the high seroprevalence of pregnant women, and most of them were working age group and laborer, the HIV prevention and control program should be more emphasized particularly, to the laborers such as factory workers in Chonburi.
2) The HIV-infected persons having serial spouses and concealing their HIV status can transmit HIV to their spouses and offspring. The HIV counseling should also address the benefit of disclosure and condom use with their couple.
3) The non-local residents of Muang Chonburi pregnant women should be able to access ANC and voluntary HIV counselling and testing without health insurance problem.
4) All women receiving EFV must be informed the teratogenic effect of EFV and birth controls, or at least, attending ANC as early as possible when they become pregnant.
5) The HIV-infected pregnant women who loss from ANC clinic should be traced for regularly attended ANC clinic and have good adherence to PMTCT regimen.
6) It is necessary to have more close monitoring of adverse events in mother and also the development of fetus in the pregnant women receiving combined ART.
7) In the pregnant women receiving AZT for PMTCT, routine complete blood count should be performed as early as 4 weeks after taking AZT. The anemia should be rapidly corrected to prevent the intrauterine growth retardation of infant.
8) Low Apgar score of infant should be highly aware in the HIV-infected pregnant women who have no PMTCT during ANC.
9) HIV status of infant should be more determined.

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APPENDIX

Patient ID ……

CASE RECORD FORM

Record date __/__/____ (dd/mm/yyyy)

Demographic data

1. Coding patient
   Hospital number …… Admission number …….

2. Age …….. Years Birth date __/__/____

3. Province: [ ] 1) Muang [ ] 2) Other districts in Chonburi [ ] 3) Others …..…

4. Occupation: [ ] 1) Farmer [ ] 2) Teacher [ ] 3) Government employee
   [ ] 4) Labourer [ ] 5) Housewife [ ] 6) Student
   [ ] 7) Business / Merchant [ ] 8) Others ……..

5. Incomes (per month): ……..baht

6. Number of past spouses …...persons
   HIV-infected spouse [ ] 1) Yes no. ….. [ ] 2) No [ ] 3) not available

Past history / other underlying diseases

7. History	Code	Remarks
Smoking		
Alcohol		
Drug addiction		
Drug allergy		
Other allergies		
Liver diseases		
Anemia		
Hypertension		
Other diseases		

Code: 1 = present 2 = absent 9 = no record

Previous HIV status and ART (before this gravid)

8. First HIV detection :

8.1 first HIV detection [ ] 1) at ANC date__/__/__ [ ] 2) before ANC date__/__/__

8.2 CD4+ count ……..cell/µl …..… % 8.3 CD4/CD8 ……

9. Clinical category at first HIV detection:

[ ] A1	[ ] A2	[ ] A3
[ ] B1	[ ] B2	[ ] B3
[ ] C1	[ ] C2	[ ] C3

Note: Clinical Category

CD4+ category*	Category A	Category B	Category C
≥ 500	A1; asymptomatic	B1; symptomatic, not A/B	C1; AIDS indicator±
200-499	A2; PGL	B2; symptomatic, not A/B	C1; AIDS indicator±
< 200	A3; acute HIV infection	B3; symptomatic, not A/B	C1; AIDS indicator±

*cell/µl

± see appendix B

10. Previous ART:

Regimens	Drugs and dosages	date start	date off
[ ] 1) Single drug for treatment			
[ ] 2) Dual drugs for treatment			
[ ] 3) HAART			
[ ] 4) AZT for PMTCT			
[ ] 5) AZT+intrapartum NVP			
[ ] 6) others …….			

ANC history

11. Baseline information :

LMP __/__/____ Expected date of delivery __/__/____

Gravid …….. Parity ……..

Previous HIV-infected pregnancy [ ]1) Yes [ ] 2) No [ ] 3) no record

HBsAg [ ] 1) positive [ ] 2) negative [ ] 3) no record

VDRL [ ] 1) positive [ ] 2) negative [ ] 3) no record

CBC; Hb ……g/dl Hct …. % MCV……..% Plt count……/cu.mm.

(at GA….wk) Wbc ……..cell/cu.mm. Neu ….% Lym ….% Eo ….%

12. Previous pregnancy's complication :

[ ] 1) Yes, specify [ ] 2) No

12.1 …….

12.2 …….

13. ANC visits :

Routine ANC	Number of visit							
	1	2	3	4	5	6	7	8
date of visit								
gestational age by LMP (week)								
Physical examination								
body weight								
temperature (degree celcious)								
blood pressure (mmHg)								
edema								
Laboratory finding								
Hematocrit (%)								
urine protein								
urine sugar								

14. ANC 's complication:

[ ] 1) Yes, specify [ ] 2) No

ANC 's complications	Onset (week of gestational age)
14.1	
14.2	

HIV and ART during pregnancy

15. Clinical category at first ANC visit:

[ ] A1 [ ] A2 [ ] A3

[ ] B1 [ ] B2 [ ] B3

[ ] C1 [ ] C2 [ ] C3

16. ART during pregnancy :

Regimens	Drugs and dosages	date start	date off
[ ] 1) Single drug for treatment			
[ ] 2) Dual drugs for treatment			
[ ] 3) HAART			
[ ] 4) AZT for PMTCT			
[ ] 5) AZT+intrapartum NVP			
[ ] 6) others ……..			

17. Adverse effect of ART during pregnancy: [ ]1) yes, specify [ ] 2) No

Adverse effects	Code	Date of onset	Intervention/Rx and results
skin rash			
fever			
nausea/vomiting			
diarrhea			
anemia			
hepatotoxicity			
other1 ……			
other2 ……			

Code: 1 = present 2 = absent 9 = no record

18. Supplement drugs during pregnancy :

18.1 …….

18.2 …….

Pregnancy outcome

19. Clinical classification at delivery or terminate pregnancy:

[ ] A1 [ ] A2 [ ] A3

[ ] B1 [ ] B2 [ ] B3

[ ] C1 [ ] C2 [ ] C3

20. Pregnancy outcome	Onset of outcome	GA at onset	Note
[ ] 1) term delivery			
[ ] 2) preterm delivery			
[ ] 3) pre-eclamsia			
[ ] 4) abortion			
[ ] 5) death fetus in utero			
[ ] 6) still birth			
[ ] 7) others ……..			

21. Neonatal status :

21.1 Birth weight ……..grams 21.2 Apgar score …….

21.3 Birth defect [ ] 1) Yes …… [ ] 2) No [ ] 3) NA

21.4 Congenital infection [ ] 1) Yes …… [ ] 2) No [ ] 3) NA

21.5 HIV infection [ ] 1) Yes …… [ ] 2) No [ ] 3) NA

Opportunistic infection / diseases during this pregnancy

22. Opportunistic infection	Code	Date of onset	Rx. and results
PPE			
thrombocytopenia			
peripheral neuropathy			
chronic diarrhea			
pulmonary tuberculosis			
pneumonia			
others ……			

Code: 1 = present 2 = absent 9 = no record

Laboratory finding

Tests	Gestational age (month)				
	≤ 2	> 2-3	> 3-6	> 6-9	Delivery
CD4+ count (cell)					
CD4+ count (%)					
Viral load (copies/ml)					
Hb (g/dl)					
Hct (%)					
plt (per cu.mm.)					
wbc (per cu.mm.)					
% neutrophil					
% lymphocyte					
blood glucose (mg/dl)					
BUN (mg/dl)					
Cr (mg/dl)					
bilirubin (mg/dl)					
ALT (U/L)					
other1……					
other2……					

WHO clinical classification of established HIV infection

Table 1. WHO clinical classification of established HIV infection

HIV-ASSOCIATED SYMPTOMS	WHO CLINICAL STAGE
Asymptomatic	1
Mild symptoms	2
Advanced symptoms	3
Severe symptoms	4

Table 2. WHO-proposed immunological classification for established HIV infection

HIV-ASSOCIATED IMMUNODEFICIENCY	AGE-RELATED CD4 VALUES			
	<11.months (%CD4+)	12–35 months (%CD4+)	36–59 months (%CD4+)	>5 years (absolute number per.mm3.or %CD4+)
None or not significant	>35	>30	>25	>.500
Mild	30–35	25–30	20–25	350−499
Advanced	25–29	20–24	15−19	200−349
Severe	<25	<20	<15	<200 *or* <15%

WHO clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV infection

Clinical stage 1
Asymptomatic
Persistent generalized lymphadenopathy

Clinical stage 2
Unexplained moderate weight loss (<10% of presumed or measured body weight)
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infections

Clinical stage 3
Unexplained severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhoea for longer than one month
Unexplained persistent fever (above37.5 ^{o}C intermittent or constant for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis
Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained anemia (<8g/dl), neutropaenia (< 0.5 x 10^{9} per litre) and/or chronic thrombocytopaenia (< 0.5 x 10^{9} per litre)

Clinical stage 4
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genitaloranorectal of more than one month's duration or visceral at any site)
Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extra-pulmonary tuberculosis
Kaposi's sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extra-pulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis (extra-pulmonary histoplasmosis or coccidiomycosis)
Recurrent septicemia (including non-typhoidal *Salmonella*)
Lymphoma (cerebral or B-cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

FDA pregnancy categories

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown any risk to the fetus in the first three months of pregnancy, and there's no evidence of later risk either. Very few medications have been tested to this level.
B	There have been no adequate, well-controlled studies in women but studies using animals have not found any risk to the fetus, or animal studies have found risk that was not confirmed by adequate studies in pregnant women. Not many adequate studies have been performed in pregnant women, so the first situation (not enough information) usually applies if a medication is assigned to this category.
C	There have been no adequate, well-controlled studies in women, but studies using animals have shown a harmful effect on the fetus, or there haven't been any studies in either women or animals. Caution is advised, but the benefits of the medication may outweigh the potential risks.
D	There is clear evidence of risk to the human fetus, but the benefits may outweigh the risk for pregnant women who have a serious condition that cannot be treated effectively with a safer drug.
X	There is clear evidence that the medication causes abnormalities in the fetus. The risks outweigh any potential benefits for women who are (or may become) pregnant.

BIOGRAPHY

Name: Darin Areechokchai
Date and Place of Birth: October 9, 1976 Bangkok, Thailand
Sex: Female
Citizenship: Thai
Marital status: Single
Home address: 104 Vibhavadi 22
Chatuchak District, Bangkok 10900, Thailand
Home tel: (66) 2-513-8777
Office address: Bureau of Epidemiology, Department of Disease Control
Ministry of Public Health (MoPH)
Tivanon Road, Nonthaburi 11000, Thailand
Tel: (66) 2-590-1882; (66) 2-590-1876 **Fax:** (66) 2-591-8579
Mobile: (66) 1-498-7445
e-mail: rinfetp@gmail.com

Education / Certificates:

2000: Doctor of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

2005: Certificate of International Field Epidemiology Training Program (FETP), Bureau of Epidemiology, Ministry of Public Heath, Thailand

2006: Diploma in Tropical Medicine and Hygiene (DTM&H), Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand