RESPONSE TO NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NNRTI)-BASED ANTIRETROVIRAL REGIMENS IN POSTPARTUM WOMEN WHO EXPOSED TO ZIDOVUDINE (AZT) AND SINGLE-DOSE NEVIRAPINE (SD-NVP) OR HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY (HAART) DURING PREGNANCY FROM MTCT-PLUS PROGRAMS, THAILAND

THIDARAT JUPIMAI

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RESPONSE TO NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NNRTI)-BASED ANTIRETROVIRAL REGIMENS IN POSTPARTUM WOMEN WHO EXPOSED TO ZIDOVUDINE (AZT) AND SINGLE-DOSE NEVIRAPINE (SD-NVP) OR HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY (HAART) DURING PREGNANCY FROM MTCT-PLUS PROGRAMS, THAILAND

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ABSTRACT

Objective & Method: This is a retrospective observational cohort study aimed at comparing the treatment efficacy of NNRTI-based regimens between HIV-1 infected women exposed to either AZT and sdNVP, or HAART during pregnancy for the prevention of mother-to-child transmission of HIV (PMTCT), and subsequently starting NNRTI-based HAART according to WHO guidelines with more than 12 months follow-up in the MTCT-Plus Program, Thailand. Samples were collected at four time-points; 4-8 weeks after delivery, at HAART initiation, 6 months after HAART initiation, and 12 months after HAART initiation. The samples were tested for HIV RNA and genotypic resistance if HIV RNA was>1,000 copies/mL.

Results: 52 postpartum women with available HIV RNA results at 12 months of HAART were enrolled; 27 received AZT and sdNVP (sdNVPgr), and 25 received NNRTI-based HAART (HAARTgr) for PMTCT. Median CD4 counts at HAART initiation were 181(148-209) and 185 (146-215) cells/mm^3 in sdNVPgr and HAARTgr, respectively. Patients in the HAARTgr initiated HAART earlier after delivery than patients in the sdNVPgr: median (IQR) 14.3(8.8-19.9) vs 31.13(23.83 -40.93) months, respectively (*$p<0.001$)*. After 12 months of HAART, all patients in the sdNVPgr were virologically suppressed. Twenty-one patients (84%) in the HAARTgr were virologically suppressed. There were 3 virologic failures, in which at least three of the following mutations were identified at the time of failure: M184V, K103N, T69N, Y181I, T215Y, K65R, Y115F, Y181C, and G190A. None of the 3 cases had mutations detected at 4-8 weeks after delivery or at HAART initiation.

Conclusion: The efficacy of NNRTI-based HAART at 12 months was good in postpartum women exposed to sdNVP or HAART for PMTCT. NNRTI mutations after sdNVP were found, while no mutation was found in HAARTgr using standard genotypic resistance assay. Ultrasensitive assays may help to detect minor resistance mutations when initiating HAART in postpartum women with previous exposure to PMTCT regimens.

KEY WORDS: NEVIRAPINE RESISTANCE/SINGLE-DOSE NEVIRAPINE/ POSTPARTUM WOMEN/ NNRTI-BASED REGIMENS

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ผลการรักษาด้วยยาต้านไวรัสสูตรที่ประกอบด้วยนอนนิวคลิโอไซรีเวอร์สทรานสคริปเตสอินฮิบิเตอร์ในหญิงหลังคลอดที่เคยได้รับยาต้านไวรัสซีโดวูดีนร่วมกับเนวิราปีนครั้งเดียวขณะคลอด หรือได้รับยาต้านไวรัสสูตร 3 ตัวขณะตั้งครรภ์ ในโครงการ "คืนชีวิตให้พ่อแม่เพื่อลูกน้อยที่ปลอดเอดส์ (MTCT-Plus) ประเทศไทย

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บทคัดย่อ

การศึกษาย้อนหลังในหญิงติดเชื้อเอชไอวีหลังคลอดที่เคยได้ยาต้านไวรัสเพื่อป้องกันการติดเชื้อเอชไอวีจากแม่สู่ลูกที่ได้ยาซีโดวูดีน (AZT) ร่วมกับยาเนวิราปีนครั้งเดียว (sdNVP) ขณะคลอดหรือได้ยาต้านไวรัสสูตร 3 ตัวที่มียากลุ่มนอนนิวคลิโอไซรีเวอร์สทรานสคริปเตสอินฮิบิเตอร์ร่วมด้วย (NNRTI-based HAART) ขณะตั้งครรภ์และได้รับการรักษาด้วยยาต้านไวรัสสูตร NNRTI-based HAART ตามเกณฑ์การรักษาขององค์การอนามัยโลกมานานกว่า 12 เดือน เพื่อเปรียบเทียบประสิทธิผลในการรักษาด้วยยาต้านไวรัสสูตร NNRTI-based HAART ในหญิงทั้งสองกลุ่ม โดยส่งตรวจตัวอย่างเลือดที่เก็บไว้ ณ เวลา 4-8 สัปดาห์หลังคลอด วันเริ่มยาเดือนที่ 6 และ 12 หลังเริ่มยาต้านไวรัสเพื่อตรวจหาเชื้อไวรัสและตรวจเชื้อดื้อยาในกรณีที่มีไวรัสในเลือด >1,000 copies/mL

หญิงหลังคลอด 52 คนเข้าเกณฑ์การศึกษาเคยได้ยา AZT และ sdNVP ขณะคลอด (กลุ่ม sdNVP) 27 คนและได้ยาต้านไวรัสสูตร NNRTI-based HAART ขณะตั้งครรภ์ (กลุ่ม HAART) 25 คน ค่าเฉลี่ย CD4 วันเริ่มยา (IQR) เป็น 181 (148-209) และ 185 (146-215) cells/mm^3 ในกลุ่ม sdNVP และกลุ่ม HAART ตามลำดับ กลุ่ม HAART เริ่มยาต้านไวรัสหลังคลอดเร็วกว่ากลุ่ม sdNVP อย่างมีนัยสำคัญทางสถิติ ค่าเฉลี่ยระยะเวลาหลังคลอดถึงวันเริ่มยาต้านไวรัส (IQR) เป็น 14(9-20) และ 31(24-41) เดือน ตามลำดับ ($p<0.0001$) กลุ่ม sdNVP ทุกคนและกลุ่ม HAART 21 คน (84%) มีปริมาณเชื้อไวรัสในเลือด <50 copies/mL ที่เดือน 12 หลังเริ่มยาต้านไวรัส 3 คนในกลุ่ม HAART พบการรักษาล้มเหลวและพบการกลายพันธุ์ของยีนที่สัมพันธ์กับการดื้อต่อยากลุ่ม NNRTI อย่างน้อย 3 ตำแหน่งดังนี้ M184V, K103N, T69N, Y181I, T215Y, K65R, Y115F, Y181C, และ G190A ทั้ง 3 คนไม่พบการกลายพันธุ์ของยีนที่ 4-8 สัปดาห์หลังคลอด และวันเริ่มยาต้านไวรัส

การรักษาด้วยยาต้านไวรัสสูตร NNRTI-based HAART ในหญิงหลังคลอดทั้งที่เคยได้ยา AZT และ sdNVP ขณะคลอด หรือเคยได้ยาต้านสูตร NNRTI-based HAART ขณะตั้งครรภ์ ณ เวลา 12 เดือนมีประสิทธิผลดี พบการกลายพันธุ์ของยีนที่สัมพันธ์กับการดื้อต่อยากลุ่ม NNRTI หลังคลอดในกลุ่มที่ได้ sdNVP ขณะคลอดในขณะที่ตรวจไม่พบในกลุ่มที่ได้ยาต้านไวรัสสูตร NNRTI-based HAART ขณะตั้งครรภ์ด้วยวิธี standard genotypic resistance assay การตรวจเชื้อดื้อยาด้วยวิธี Ultrasensitive assays ก่อนเริ่มยาต้านไวรัสในหญิงหลังคลอดที่เคยได้ยาเพื่อป้องกันการติดเชื้อจากแม่สู่ลูกจะช่วยให้สามารถตรวจพบการกลายพันธุ์ของยีนตำแหน่งที่สัมพันธ์กับการดื้อยาได้มากขึ้น

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LIST OF ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
AZT	Zidovudine
BID	Twice a day
CRF	Case Record Form
d4T	Stavudine
ddI	Didanosine
DSMB	Data and Safety Monitoring Board
EC	Ethics Committees
EFV	Efavirenz
FTC	Emtricitabine
GCP	Good Clinical Practice
GPO	Government Pharmaceutical Organization, Thailand
GPO-virs®	Combination of d4T/3TC/NVP
GPO-virz®	Combination of AZT/3TC/NVP
HAART	Highly Active Antiretroviral Therapy
HIV	Human immunodeficiency virus
ICAP	The International Center for AIDS Care and Treatment Program
IRB	Institute Review Board
LPV/r	Lopinavir/Retonavir
NHSO	The national health security office
NNRTI	Non-nucleoside reverse-transcriptase inhibitors
NRTI	Nucleoside reverse-transcriptase inhibitors
NVP	Nevirapine

LIST OF ABBREVIATIONS (cont.)

PCR	Polymerase chain reaction
PI	Protease Inhibitor
PMTCT	Preventing mother-to-child transmission of HIV-1
QA	Quality assurance
QC	Quality control
SAE	Serious Adverse Events
sdNVP	Single-dose of nevirapine
TID	Three times a day
TDF	Tenofovir
TRCARC	Thai Red Cross AIDS Research Centre
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

CHAPTER I
INTRODUCTION

1.1 Rational and Background

The use of maternal antepartum zidovudine (AZT) plus a single dose of intrapartum nevirapine (sdNVP) to prevent mother-to-child transmission (PMTCT) of human immunodeficiency virus type 1 (HIV-1) in HIV-1 infected pregnant women has long been recommended for resource limited settings, including Thailand prior to 2010(1-3). Good relative efficacy (4-7) in reducing perinatal transmission rate of HIV-1 was demonstrated with the use of this PMTCT regimen. However, there was a high rate of nevirapine (NVP) resistance mutations in postpartum women and infants after exposure to sdNVP; 19-75% in women and 33-87% of infants had mutations detected by standard genotyping techniques (8-11). When this group of patients needs to initiate antiretroviral therapy (ART) for their own health, It may a cause suboptimal response to subsequent nonnucleoside reverse-transcriptase inhibitor (NNRTI)-based highly active antiretroviral therapy (HAART) regimens, and may reduce long term efficacy of HAART

NNRTI, including NVP and efavirenz (EFV) are recommended to use in first line combination antiretroviral regimens in HIV-1 infected adults in resource limited settings, including Thailand (1). Generic, fixed dosed combinations of stavudine (d4T)/lamivudine(3TC)/NVP which is called GPO-virs®(12) and AZT/3TC/NVP which is call GPO-virz® (13) are manufactured by the Government Pharmaceutical Organization, Thailand (GPO). Thai patients can access HAART for free under the national health security office program (NHSO), and use of fixed dosed combination drugs also helps to maintain adherence to treatment.

Use of HAART during pregnancy for PMTCT could reduce perinatal HIV-1 transmission rate to less than 2% (14-16) and is currently one of the PMTCT options recommended by the World Health Organization (WHO) in 2010 for pregnant women

who do not require treatment for their own health(3). Use of HAART for PMTCT can reduce the chance of the development of NVP resistance in women after delivery (17) and therefore, compared to the use of AZT and sdNVP, can potentially better preserve NNRTI-based HAART as a treatment option for women after delivery.

We studied the efficacy of NNRTI-based HAART regimens among women, exposed to AZT and sdNVP or NNRTI-based HAART for PMTCT, who initiated NNRTI-based HAART for their own health after delivery.

1.2 Objective

1.2.1 Primary objective

To compare treatment efficacy of NNRTI-based HAART regimens at 12 months between postpartum women who received AZT and sdNVP or NNRTI-based HAART during pregnancy for PMTCT.

1.2.2 Secondary objective

1.2.1.1 To determine the rate of NVP resistance mutations 4-8 weeks after delivery in postpartum women who either received AZT and sdNVP or HAART during pregnancy for PMTCT

1.2.2.2 To compare treatment efficacy of NNRTI-based HAART regimens at 6 months between postpartum women who received AZT and sdNVP or HAART during pregnancy for PMTCT

1.3 Hypotheses

After 12 months of NNRTI-based HAART initiation, the postpartum women who received NNRTI-based HAART during pregnancy for PMTCT will have a higher rate virologic suppression compared to women who received AZT and sdNVP for PMTCT

CHAPTER II
LITERATURE REVIEW

2.1 Global HIV epidemic

The estimated number of persons living with HIV worldwide in December 2008 was 33.4 million [31.1 million–35.8 million], it was more than 20% higher than the number in 2000, and the prevalence was roughly threefold higher than in 1990. There are 31.3 million [29.2 million–33.7 million] HIV infected adults, 15.7 million are women [14.2 million–17.2 million], and 2.1 million [1.2 million–2.9 million] are children under 15 years. There was estimated to be 2.7 million [2.4 million–3.0 million] new infections in 2008 and 430,000 [240,000–610,000] of new infection are children under 15 years. There is estimated that 2 million [1.7 million–2.4 million] deaths due to AIDS-related illnesses occurred worldwide in 2008. The estimated number of new HIV infections was approximately 30% lower than at the epidemic's peak 12 years earlier as compare to the latest epidemiological data indicate that globally the spread of HIV appears to have peaked in 1996, when 3.5 million [3.2 million–3.8 million] new HIV infections occurred. (18) .

2.2 HIV epidemic in Thailand

The estimated number of people living with HIV in Thailand, end 2009 was 530,000. There are 520,000 HIV infected adults (age 15+), 210,000 are women. The estimated adults (age 15-49) HIV prevalence is 1.3%, and 28,000 people died from AIDS. The majority of Thailand's HIV infections occur through heterosexual sex and HIV prevalence among pregnant women, which reached a peak of 3.4% in 1992, had fallen to under 1% by 2009. (19)

2.3 Highly active antiretroviral therapy

Treatment with highly active antiretroviral therapy (HAART) is safe and effective. It reduces both the mortality and the morbidity associated with HIV infection (20). Thai national guidelines for antiretroviral therapy in HIV-1 infected adults and adolescents 2010 (1) recommend to start HAART at CD4+ T cell count <350 cells/mm3. HAART regimens containing AZT or tenoforvir (TDF) plus 3TC and NVP or EFV are recommended as preferred first-line regimens for treatment-naïve Thai patients. The use of d4T will be gradually phased out at the national program level. Both EFV and NVP is safe and effective, but EFV can potentially cause birth defects in infants exposed in utero during the first trimester of pregnancy, and therefore should not be used in women who might become pregnant and cost expensive than NVP.

2.4 Adherence to HAART regimens

Successful long-term treatment of HIV/AIDS is requires at least 95% adherence to HAART to achieve virologic suppression and prevent emergence of HIV drug-resistance that can cause treatment failure. Causes of poor adherence can be pill burden, side effects resulting in poor tolerability, patient lifestyle factors, and patient-provider relationships. To achieve adequate adherence, patients and health care providers must collaborate in the selection of a lifestyle-tailored regimen, characterized by convenient dosing, low pill burden, and tolerable side effects. (21, 22)

2.5 Use of antiretroviral drugs for the prevention of mother to child transmission of HIV

The use of maternal antepartum AZT plus sdNVP has long been recommended for resource limited settings, including Thailand prior to 2010(1-3). Good relative efficacy (4-7) in reducing perinatal HIV-1 transmission rate was demonstrated with the use of this PMTCT regimen. In resource rich settings, the use of

HAART during pregnancy for PMTCT was shown to reduce perinatal HIV-1 transmission rate to less than 2%(15, 16). The 2010 WHO guidelines has recently recommended AZT plus sdNVP or HAART as equally efficacious options of PMTCT for pregnant women who do not require treatment for their own health(3) based on the results of the Kesho Bora study(23).

The Kesho Bora study randomized 824 pregnant women with CD4 counts of 200-500 cells/mm^3 in Burkina Faso, Kenya, and South Africa to start lopinavir/ritonavir (LPV/r)-based HAART or AZT and sdNVP from 28-36 weeks of gestation. The cumulative rates of HIV transmission at birth were 1.8% (95% confidence interval, 95%CI, 0.9-3.7%) in the HAART group and 2.5% (95%CI 1.3-4.6%) in the AZT and sdNVP group, which were not significantly different. The incidence of laboratory and clinical serious adverse events in both mothers and their babies was similar between groups.

2.6 Development of nevirapine resistance after PMTCT exposure

A Meta analysis using MEDLINE and PASCAL databases between year 1997 - 2006 showed the prevalence of NVP resistance by population-based sequencing in HIV-1 infected woman exposed to sdNVP ± other antiretroviral drugs during pregnancy for PMTCT to be 35.7% (95%CI; 23.0-50.6) in 10 clinical research settings, and 4.5% (95%CI; 2.1-9.4) in 3 clinical research settings that gave an antiretroviral tail after delivery (11). Using allele-specific polymerase chain reaction assay which is a more sensitive assay to detect minor population of NVP resistant virus, 75% of women exposed to sd-NVP without tail developed NVP resistance after delivery compared to 18% of women exposed to NVP-based HAART without tail (p=0.007) in Kenya(17).

2.7 Treatment response after PMTCT exposure in women after delivery

Data from Thailand, Botswana (24) and South Africa has shown that there was no difference in treatment response between women who initiate HAART after 6 months exposed to sdNVP and women who were not exposed to sdNVP. These 2 studies found that women who initiated HAART within 6 months after exposure to sdNVP had poor responses to treatment compared to those who were not exposed to sdNVP. The researcher concluded that sdNVP remains one of the choices for PMTCT in resource limited settings.

The OCTANE study in 7 African countries, however, revealed that women with prior exposure to sdNVP had poorer response to NVP-based HAART than to LPV/r-based HAART as their initial HAART regimen after delivery. This study randomized postpartum women with at least 6 months after sdNVP exposure or without sdNVP exposure to receive NVP-based HAART or LPV/r-based HAART when CD4 count came below 200 cells/mm^3More women with sdNVP exposure had virologic failure or death in the NVP group than the LPV/r group (26% vs. 8%, p=0.001). The group difference decreased as the interval between sdNVP exposure and the start of HAART after delivery increased. Virologic failure or death was similar among women without prior exposure to sdNVP, 14% in the NVP group and 14% in the LPV/r group. (25)

There have been no studies comparing treatment response after delivery between women exposed to sdNVP or HAART for PMTCT. The MTCT-Plus Cohort in Thailand (Thai Red Cross AIDS Research Centre database) are following up postpartum women who were exposed to HAART or AZT plus sdNVP or AZT monotherapy for PMTCT during pregnancy and stopped these drugs after delivery due to high CD4 count. Therefore, we would like to study the differences in treatment response to NNRTI based- HAART regimens between postpartum women exposed to HAART or AZT plus sdNVP during pregnancy for PMTCT using this database.

CHAPTER III
MATERIAL AND METHODS

3.1 Study designed

This is a retrospective observational cohort study using the database from MTCT-Plus Program at the Thai Red Cross AIDS Research Centre.

3.2 Study population

This retrospective observation cohort includes women who enrolled in the MTCT-Plus Program at the Thai Red Cross AIDS Research Centre, Thailand between 1st February 2003 and 31st December 2007

3.2.1 Study inclusion criteria

3.2.1.1 Age > 18 years old

3.2.1.2 HIV-infected women who were exposed to AZT and sdNVP or HAART (AZT/3TC/NVP or EFV) during pregnancy for PMTCT

3.2.1.3 Started NNRTI-based HAART (NVP or EFV-based) for $\geq$ 12 months

3.2.2 Study exclusion criteria

3.2.2.1 Not on HAART or on HAART < 12 months

3.2.2.2 On HAART without NNRTI

3.3 Sample size calculation

From the MTCT-plus cohort database at The Thai Red Cross AIDS Research Centre, 644 women have been enrolled into program during February 1,

2003 to December 31, 2007. Approximately 127 patients met inclusion criteria in this study, 29 patients received HAART (AZT+3TC+NVP or EFV) during pregnancy for PMTCT and stopped HAART after delivery and 98 patient exposed to sdNVP in labour for PMTCT (Ratio of HAART group versus. sdNVP group is 1:3)

Sample size calculation in this study is to ensure that the numbers of patients who meet inclusion criteria in this study have enough power (at least 80% power) to test of difference between the two independent groups.

The primary efficacy parameter will be the proportion of subjects with virologic response, i.e. plasma HIV RNA is undetectable (HIV RNA level below the assay limit of detection; e.g., 50 copies/mL). A previous study by Anekthananon et al(12) reported on patients who were started on a simplified fixed-dose combination of stavudine, lamivudine and nevirapine (GPO-VIRS®;Thai Government Pharmaceutical Organization, Bangkok, Thailand) for 24 weeks. The proportion of patient with plasma HIV RNA < 50 copies/mL at 6 months after on GPO-VIRS® was 89.2% (On Treatment Analysis). Another study by Jourdain et al(26) reported treatment responses to NNRTI-based HAART regimen by measurement HIV RNA levels (virologic response rates) in women who were exposed to sdNVP for PMTCT. The proportion of patient with plasma HIV RNA < 50 copies/mL at 6 months after HAART was 49 % (On Treatment Analysis)

Formulas: Test of difference in 2 independent proportions (p1, p2)

p1, p2 = Proportion of … in group 1 and 2

$p = (p1+p2)/2$

$$n/\text{group} = \left(\frac{Z_{\alpha/2}\sqrt{2pq} + Z_{\beta}\sqrt{p_1q_1 + p_2q_2}}{p_1 - p_2} \right)^2$$

The sample size calculation using STATA software, version 10.0 by configuration parameter as following;

Assigned p1 = proportion of women who received HAART during pregnancy = 0.89

p2 = proportion of women who received sdNVP in labour = 0.49

Estimated sample size for two-sample comparison of proportions

Test Ho: p1 = p2, where p1 is the proportion in population 1 and p2 is the proportion in population 2

Assumptions: alpha = 0.0500 (two-sided)

power = 0.9500

p1 = 0.8900

p2 = 0.4900

n2/n1 = 3.00

Estimated required sample sizes:

n1 = 24

n2 = 72

n2/n1 = 1.00

Estimated required sample sizes:

n1 = 25

n2 = 25

Therefore, 24 patients in HAART group and 72 patients in sdNVP group would give 95% power to detect differences in the virologic response rate between these two groups of women at a 2 sided significance level of 5% and at least 25 patients in each group would give 80% power to detect differences between the 2 groups.

3.4 Study location and duration

Data collection was performed at MTCT – Plus Initiative Program, Thailand, during September 2008 – March 2010

3.5 MTCT-Plus Initiative Program

The MTCT-Plus Initiative is a multi-country, comprehensive HIV care and treatment program for pregnant and postpartum women and their families built on existing PMTCT services. It provides pregnant and postpartum women with holistic,

family – centered HIV care including HAART to the women, her partner, and her children (27). The MTCT-Plus Initiative program started enrollment pregnant women in Thailand from February 1, 2003 and this program has been supported by The International Center for AIDS Care and Treatment Program (ICAP), Columbia University Mailman School of Public Health, USA and The Thai Red Cross AIDS Research Centre.

Since the MTCT-Plus Initiative program started enrollment in Thailand in February 2003, the patients were enrolled and follow up at these 5 hospitals:

1. Chulalongkorn Hospital, Bangkok
2. Queen Savang Vatthana Memorial Hospital, Chonburi Province
3. Thammasat University Hospital, Bangkok
4. Police General Hospital, Bangkok
5. Queen Sirikit Hospital, Bangkok

Numbers of cumulative patients in the MTCT-Plus Initiative program during February 2003 – December 2007 are 644 women, 220 men (partners of women) 146 children (child) and 22 staff employees(28).

3.5.1 Criteria for initiating ART Treatment in adults

The criteria for initiating ART treatment for adults patient in MTCT-Plus Initiative program in Thailand is following WHO guidelines (29). From 2003 – December 2004, patients should start ART if they meet the following criteria;

- WHO stage 4
- CD4+ T cell count $\leq$ 200 cells/mm^3
- WHO stage 2 or stage 3 and CD4+ T cell count $\leq$ 350 cells/mm^3

Thereafter, in year 2005, WHO changed criteria to start ART treatment in adults according to the following criteria;

- WHO stage 4
- CD4+ T cell count < 200 cells/mm^3
- WHO stage 3 and CD4+ T cell count < 350 cells/ mm^3

3.5.2 Criteria to started ART in pregnant women for preventing mother-to-child transmission of HIV (PMTCT)

Pregnant women who received PMTCT prior to the enrollment into MTCT-Plus initiative program or who were enrolled into the MTCT-Plus initiative program between February 2003 – March 2004 and did not meet the criteria to start ART according to WHO guidelines (30, 31) received ART for PMTCT following standard guideline as below;

- Mothers received AZT 300mg BID from 32 week gestation till delivery and received AZT 300mg every 3 hours plus NVP 200mg 1 tablet during labour
- Infant received AZT syrup for 6 weeks after delivery plus NVP syrup 6 mg within 72 hours after delivery.

Pregnant women who were enrolled to the MTCT-Plus initiative program since April 2004 received HAART (AZT+3TC+NVP or EFV) from 28 week of gestations for PMTCT. Postpartum women who received HAART during pregnancy for PMTCT but not meet the criteria to start HAART according to WHO guideline stopped HAART after delivery. NVP or EFV was stopped immediately after delivery while AZT+3TC was continued for 7 days to reduce the development of NVP resistance.

3.5.3 Initial HAART regimens

In selecting a first-line antiretroviral treatment regimen, considerations included effectiveness, tolerability, cost, and ART sequencing, including the implications for subsequent regimens. The patients who met the criteria to start ART according to WHO guidelines received a first – line ART regimen from the following list. These are recommended initial regimens by WHO guidelines.

- AZT + 3TC + NVP
- d4T + 3TC + NVP
- AZT + 3TC + EFV
- d4T + 3TC + EFV

The used of fixed-dosed combination ART was preferred to minimize pill counts, facilitate adherence, and decrease the development of antiretroviral resistance.

3.5.4 Follow up visit and treatment monitoring

At baseline visit when ART was initiated, patients received an assessment where the following data was collected:

- Socio-demographic variables
- Medical history and treatment
- History of prior ART use for PMTCT
- History of prior ART use other than PMTCT
- Nutritional status
- Adherence
- History of prior ART intolerance or drug allergy
- Use of other medication or herbal
- Physical examination
- Blood collection for laboratory testing

The patients who started HAART in MTCT-plus initiative program were followed up at the MTCT-Plus clinic at baseline, week 2, 4, 6, 8 and every 2 months until 1 year, and every 3 months thereafter while they were participating in the MTCT-Plus initiative program.

3.5.5 Adherence Assessment

Adherence to care and treatment assessments were performed every follow up visit by asking “Did the patient miss any dose in the last 7 days or 30 days?” and “Did the patient have delayed dose more than 30 minutes in the last 30 days?” The study nurse called patients at weeks 1, 3, 5, 7 and month 3 and 5 to follow up ART adherence and ART toxicity. If patient reported any problem with taking ART, a home visit was provided.

3.5.6 Laboratory assessment

3.5.6.1 Performed CD4 testing at baseline visit and every 6 months after HAART was initiated.

3.5.6.2 Collected plasma to be stored for HIV RNA and genotypic resistance testing if HIV RNA> 1000 copies/ml. Samples for storage were

collected at 4-8 week after delivery, every 6 months before and after HAART was initiated. Samples were stored at –70°C in the laboratory of the Thai Red Cross AIDS research Centre.

3.5.6.3 A safety evaluation (hematology, blood chemistry, fasting glucose, lipid profile, liver function test and pancreatic enzymes) were performed at follow up visit according to the physician decision.

3.6 Study procedure

The study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University on October 9, 2008 and Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University on April 3, 2009. The approved Informed Consent Form by both IRBs was given to the patients by study nurses of MTCT – Plus initiative program when patient came to clinic visit in normal schedule of MTCT – Plus initiative. After the patients have signed and dated on written consent formed, the copies of signed and dated of written consent formed have been given to the patients.

Plasma storage samples of enrolled patients at time point 4-8 week after delivery, before HAART initiation after delivery, at 6 months after on HAART and 12 months after on HAART were send to performed plasma HIV RNA level at laboratory of the Thai Red Cross AIDS Research Centre for RNA measurement. If any sample had HIV RNA > 1,000 copies/mL, that sample was sent for genotypic resistance testing at Vaccine and Cellular Immunology Laboratory, Faculty of Medicine, Chulalongkorn University. The remaining blood sample storages belong to MTCT-Plus initiative program.

3.7 Measurements of plasma HIV-1 RNA

Plasma HIV RNA levels were assayed with the use of the Abbott RealTi*m*e HIV-1 assay on the *m*2000 system (Lower limit of detection, 40 copies/mL) (32)

3.8 HIV-1 genotypic drug resistance testing

HIV-1 genotypic drug resistance testing was performed using in-house method®(33, 34). HIV RNA was extracted from 500 µl of plasma by guanidinium isothiocyanate and isopropanol precipitation technique. HIV reverse transcriptase (RT) and protease (Pr) genes were reverse transcribed with RT-2955 primer (5'gct tta cct taa tcc ctg cat aat 3'). For first round of RT and Pr gene amplification, PI-1685 (5' GGA ATT TTC CTC AGA GCA GAC CAG 3') and RT-2955 were used to amplify approximately 1270 basepair (bp) PCR product (PCR conditions are : 94 ºC 2 min, 94 ºC 30 sec, 56 ºC 30 sec, 72 ºC 1 min for 35 cycles, 72 ºC 7 min and then 4 ºC). For the second round PCR, RT gene was amplified with primers RT-2143 (5' CTG TAC CAG TAA CAT TAA AGC CAG G 3') and RT-2923 (5'GCC CAA TTT AGT TTT CCC ACT AAT 3') and Pr gene was amplified with primers PI-1780 (5' –CGA AGC AGG AGC AGA AAG ACA AGG -3') and PI-2172 (5' CCA TTC CTG GCT TTA ATG TTA CTG GTA C 3') with the same PCR condition as in the first round. The 780 bp and 392 bp PCR products (codon 20-260 of RT and 1-99 of protease) were purified using QIAquick® PCR purification kit (Qiagen, Valencia, CA, USA). Amplicons were sequenced with BigDye terminators using an ABI 3130XL capillary sequencer (Applied Biosystems Inc., Foster City, CA, USA). The sequences were aligned and translated to deduced amino acids by Sequence Navigator Software provided with the company. The sequences were analyzed as compared to the CM240 reference sequence.

3.9 Data collection and monitoring

The data were transferred from the patient recorded of MTCT-Plus initiative program to a Case Record Form (CRF) designed for this study. Data were collected for 4 time points at 4-8 week postpartum, baseline (initiation of ART after delivery), 6 months after ART initiation and after 12 months on ART

Data on checking eligibility criteria, demographic, medical history and treatment, history of prior used ART including for PMTCT, number of pregnancy, number of live births, CD4+ T cell count at time within 4-8 week after delivery,

plasma storages at the time 4-8 week after delivery were collected in a screening form. Data collection at 6months and 12months of initiated ART are as same as baseline visit including adherence self report.

The Laboratory of Thai Red Cross AIDS Research Centre which performed HIV RNA testing and The Vaccine and Cellular Immunology Laboratory, Faculty of Medicine, Chulalongkorn University which performed genotypic resistance testing for the study are both qualified laboratories. Internal and external QA/QC were performed annually.

3.10 Ethical considerations

3.10.1 Institutional Review Board/Ethics Committee Review and Informed Consent

The MTCT-Plus program at the Thai Red Cross AIDS research centre, Thailand has been approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University prior the program started and all subjects have signed informed consent form to participate in the program.

This protocol, the informed consent document and any subsequent modifications must be reviewed and approved by the IRB and/or EC responsible for oversight of the study; Faculty of Medicine, Chulalongkorn University and Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (This was required for the thesis of Mahidol University's students). Written informed consent must be obtained from the subject. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject.

3.10.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without

written permission of the subject, except as necessary for monitoring by research team members, the IRB/EC, and sponsor.

3.10.3 Regulatory Authorities

At the Thai Red Cross AIDS Research Centre sites in Thailand, the protocol will be carried out under the provisions of Good Clinical Practice Guidelines (GCP) and regulated by the Thai FDA. In addition to the GCP Guidelines the trial will be regulated and conducted as per the Ethical Review Committee of the Faculty of Medicine, Chulaongkorn University, Thailand. This trial will be conducted in full concordance with the principles of the Declaration of Helsinki, October 2000 and the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, May 1997.

3.10.4 Subject withdrawal/Premature termination

Individual subjects could be withdrawal/premature termination any time without any reasons. This will not cause any effect to their treatment in MTCT-Plus program.

3.11 Study endpoint

3.11.1 Primary endpoint

Proportion of women who have virologic suppression after taking an NNRTI-based HAART regimen for 12 months.

3.11.2 Secondary endpoint

3.11.2.1 Rate of NNRTI resistance mutations detection at 4-8 weeks postpartum

3.11.2.2 Proportion of women who have virologic suppression at 6 months after taking an NNRTI based HAART regimen

3.11.3 Definition of study endpoints

3.11.3.1 Virologic suppression can be defined as one time reduction in HIV RNA level below the assay limit of detection (e.g.50 copies/mL). One hundred percent adherence is defined as patients who reported no missed doses and no dose delays of HAART in the 30 days preceding each follow up visit.

3.11.3.2 NNRTI resistance mutation includes K103N/S, V106A/M, Y181C/I/V, Y188L/C/H, and G190A/ S/E

3.11.4 NRTI and NNRTI resistance mutations (35)

The NRTI resistance mutations include;

M184V is the most commonly occurring NRTI resistance mutation.

In vitro, it causes high-level resistance to 3TC and FTC, low-level resistance to ddI and ABC and increased susceptibility to AZT, d4T, and TDF.

TAMs: Thymidine analog mutations (TAMs) are selected by the thymidine analogs AZT and d4T. TAMs decrease susceptibility to AZT and d4T and to a lesser extent to ABC, ddI, and TDF.

TAMs accumulate in two distinct but overlapping patterns:

- type I pattern: M41L, L210W, and T215Y;

Type I TAM cause higher levels of phenotypic and clinical resistance to the thymidine analogs and cross-resistance to ABC, ddI, and TDF than do the type II TAM.

- type II pattern: D67N, K70R, T215F, and K219Q/E.

The presence of all three type I TAM markedly reduces the clinical response to ABC, ddI, and TDF.

Non-TAMs: The most common mutations in patients developing virologic failure while receiving a non thymidine analog containing NRTI backbone include M184V alone or M184V + K65R or L74V.

K65R causes intermediate resistance to TDF, ABC, ddI, 3TC, and FTC, low-level resistance to d4T, and increased susceptibility to AZT.

Mutations M184V plus K65R have been reported primarily in patients receiving the NRTI backbone TDF/3TC and less commonly ABC/3TC or TDF/ FTC.

L74V causes intermediate resistance to ddI and ABC, and a slight increase in susceptibility to AZT and TDF.

M184V plus L74V occurs primarily in persons receiving ABC/3TC or ddI/3TC/FTC backbones.

Multi-NRTI: Amino acid insertions at codon 69 generally occur in the presence of multiple TAM, and in this setting are associated with intermediate resistance to 3TC and FTC and high-level resistance to each of the remaining NRTI.

Q151M is a 2-bp mutation (CAG --> ATG) that is usually accompanied by two or more of the following mutations: A62V, V75I, F77L, and F116Y.

The Q151M complex causes high-level resistance to AZT, d4T, ddI, and ABC, and intermediate resistance to TDF, 3TC, and FTC.

The NNRTI resistance mutations include;

Primary NNRTI mutations

Each of the primary NNRTI resistance mutations - K103N/S, V106A/M, Y181C/I/V, Y188L/C/H, and G190A/ S/E - cause high-level resistance to NVP and variable resistance to EFV, ranging from about 2-fold for V106A and Y181C, 6-fold for G190A, 20-fold for K103N, and more than 50-fold for Y188L and G190S.

Secondary NNRTI mutations

L100I, K101P, P225H, F227L, M230L, and K238T are secondary mutations that usually occur in combination with one of the primary NNRTI resistance mutations.

L100I and K101P, which occur in combination with K103N, further decrease NVP and EFV susceptibility from 20-fold with K103N alone to more than 100-fold.

Minor NNRTI mutations

A98G, K101E, V108I, and V179D/E are common NNRTI resistance mutations that reduce susceptibility to NVP and EFV about 2-fold to 5-fold.

The PI resistance mutations include (36)

Primary mutation; D30N, V32I, L33F, M46I/L, I47A, G48V, I50L/V, I54M/L, L76V, V82A/F/L/T/S. I84V, N88S AND L90M

Secondary mutation; L10I, L10F, K20R, K20M, M36I, M46I, M46L, I54V, A71V, A71T, G73S, V77I, M93L

3.11.5 Evaluation of other variables that may be associated with treatment responses

- Duration of treatment for PMTCT during pregnancy
- Time to initiate NNRTI base HAART after delivery
- Changes in treatment regimen during PMTCT and during on HAART
- Age at initiation of PMTCT and age at initiation of HAART
- Number of pregnancies

3.12 Data analysis

The data analysis is for group comparisons on study end point in postpartum women divided into two groups according to characteristics of PMTCT therapy that was received; sdNVP or HAART

3.12.1 Statistical analysis

The statistical analyses were done using STATA Software, version 10.0. Student t-test or nonparametric Mann-Whitney U tests were used for comparison of quantitative variables and Chi-Square test or Fisher exact test was used for comparison of qualitative variables as appropriate. Exact logistic regression models were use for

predictors of virologic failure in patients**.** Variable covariate with $p<0.15$ in univariate analysis were adjusted for in multivariate model.

All patients had primary endpoint data available at 12 months and were included in the analysis. For the secondary endpoint, some patients had missing data at six months. For analysis of this endpoint we first included only patients who had test results available (available data) and then in sensitivity analysis imputed the 6 month value for missing outcome variable, replacing it with the 12 month value.

CHAPTER IV
RESULTS

4.1 Baseline characteristics

There were 644 women enrolled in the MTCT-Plus initiative program, Thailand during February 1, 2003 to December 31, 2007; 119 postpartum women were on HAART for at least 12 months (data updated till July 31, 2009); 29 patients received AZT 300mg every 12 hours during pregnancy from 32 weeks gestation through delivery, 57 patients received AZT 300mg every 12 hours from 32 weeks of gestation though delivery and received NVP 200mg 1 tablet (sdNVP) during labour and 33 patients received AZT/3TC/NVP or EFV regimen for PMTCT from 28 week of gestations.

In our study, 52 patients met inclusion criteria and had stored blood samples available at 12 months after initiation of NNRTI-based HAART. 27 patients were enrolled into group 1: sdNVP group who received AZT during pregnancy and sdNVP in labour for PMTCT and 25 patients were enrolled into group 2: HAART group who received AZT/3TC/NVP or EFV regimen during pregnancy for PMTCT (Figure 4.1).

Baseline characteristics (Table 4.1) were reported for 2 time points, one is at the time of PMTCT and another one is at the time of HAART initiation. Median ages at PMTCT (interquartile range, IQR) were 27.43 (24.89 – 29.86) and 29.84 (26.09 – 31.48) years in sdNVP and HAART groups, respectively. 20 of 23 patients had HIV subtype AE, 1 patient had HIV subtype B, and 2 had unknown HIV subtype (Table 4.3).

Most patients had CDC classification A at PMTCT; 23 (85.19%) and 23 (92.0%) in sdNVP and HAART group, respectively. Median CD4+ T cell count (IQR) at PMTCT; 346 (233 – 561) and 280 (241.5 – 331.5) cells/mm^3 in sdNVP and

HAART group, respectively. Patients in HAART group received longer PMTCT during pregnancy than patients in sdNVP group: Median days of PMTCT during pregnancy (IQR) were 66 (58-79) and 52 (41-70) days, respectively *(p=0.0488)*. There were 4 patients in HAART group and none in sdNVP group who changed ART during pregnancy.

Patients in the HAART group initiated ART after delivery earlier than patients in the sdNVP group. Median months (IQR) 14.3 (8.8-19.9) versus 31.13 (23.83 – 40.93) months, respectively (*p<0.001)*. Median CD4+ T cell count at HAART initiation were 181 (148 – 209) and 185 (146-215) cells/mm^3, and median log_{10} viral load (IQR) were 4.9 (4.10 – 5.18) and 4.9 (4.6-5.08) in sdNVP group and HAART group, respectively. Only 2 patents (3.85%); one in sdNVP group and one in HAART group had CDC classification C at HAART initiation, other patients were A (46.15%) and B (50%), most of patients in both groups started HAART with AZT/3TC/NVP (76.92%) which was not statistically different.

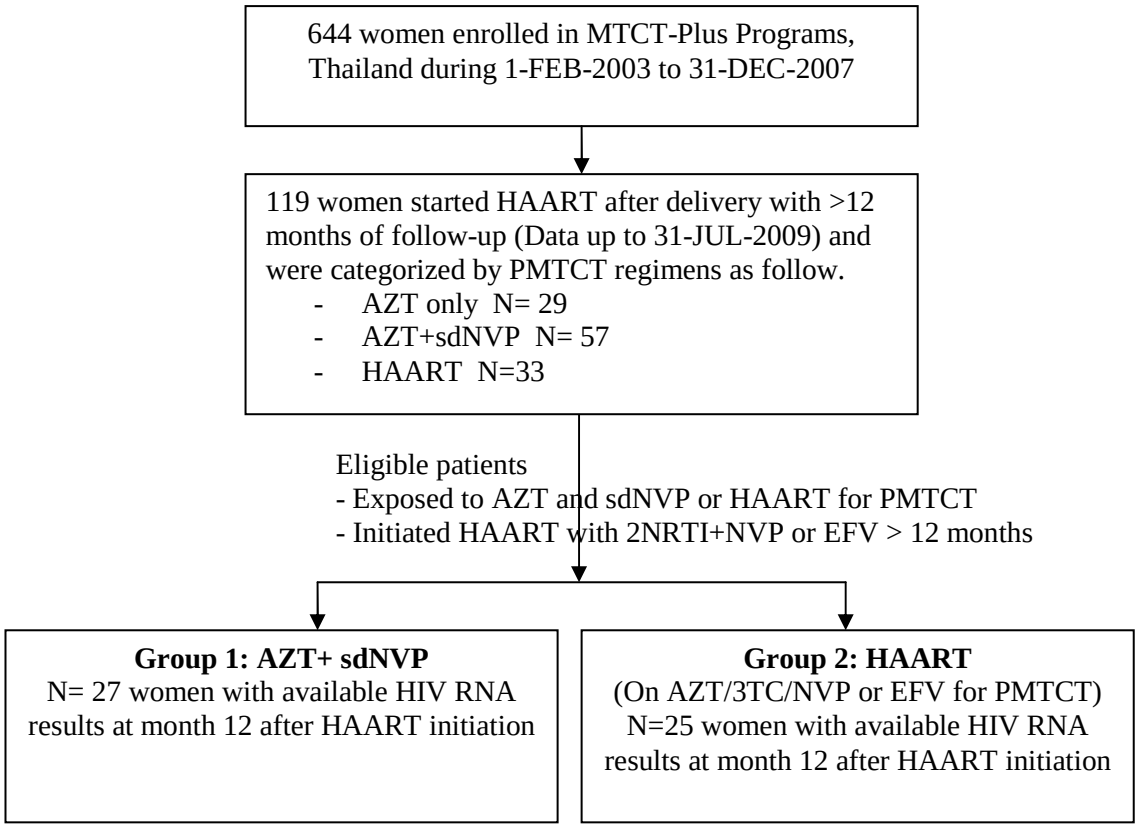

Figure 4.1 Study Profile. HAART, highly active antiretroviral therapy; PMTCT, prevention of mother-to-child transmission of HIV-1; AZT, zidovudine; sdNVP, single-dose nevirapine; NRTI, nucleoside analog reverse transcriptase inhibitors; EFV, efavirenz; 3TC, lamivudine.

Table 4.1 Demographic characteristics of HIV-1 infected women initiating treatment with NNRTI-based HAART regimen after delivery, according to previous exposure to PMTCT regimens, MTCT-Plus Initiative Programs, Thailand, 1-FEB-2003 to 31-DEC-2007

Characteristic	**sdNVP (n = 27)**	**HAART (n = 25)**	***p-value***	**Overall (n = 52)**
At PMTCT				
Median age at PMTCT, years (IQR)	27.43 (24.89-29.86)	29.8411 (26.09-31.48)	*0.1308*	28.34 (25.05-30.75)
Median days since first HIV positive diagnosis (IQR)	85(18-140)	89(17-117)	*0.7625*	87(17.5-133)
CDC classification, n (%)			*0.670*	
A	23 (85.19)	23 (92.0)		46 (88.46)
B	4 (14.81)	2 (8.0)		6 (11.54)
C	0 (0)	0(0)		0(0)
Number of pregnancies, n (%)			*0.930*	
1	10 (37.04)	9 (36)		19 (36.54)
2	14 (51.85)	12(48)		26 (50)
≥3	3 (11.11)	4 (16)		7 (13.46)
Median number of days of ART during pregnancy (IQR)	52(41-70)	66 (58-79)	*0.0488*	59 (44.5-74.5)
Median CD4+ T cell count (IQR) cells/mm3	N=3 346 (233-561)	N=24 280 (241.5-331.5)	*0.5370*	N=27 283 (241-346)
Number of women changing ART regimen during pregnancy, n(%)	0 (0)	4 (16)	*0.047*	4 (7.96)

Table 4.1 Demographic characteristics (Continue.)

Characteristic	sdNVP (n = 27)	HAART (n = 25)	*p-value*	Overall (n = 52)
At HAART initiation				
Median months after delivery when initiating HAART (IQR)	31.13 (23.83 -40.93)	14.3 (8.8-19.9)	*>0.0001*	23.08 (13.37-33.55)
CDC classification, n (%)			*0.891*	
A	13 (48.15)	11 (44)		24 (46.15)
B	13 (48.15)	13 (52)		26 (50)
C	1 (3.7)	1 (4)		2 (3.85)
Median CD4+ T cell count (IQR) cells/mm^3	181 (148-209)	185 (146-215)	*0.7416*	184 (147-213)
Median Log_{10} viral load at HAART initiation (IQR)	N=8 4.9(4.10-5.18)	N=14 4.9(4.6-5.08)	*0.7848*	N=22 4.9 (4.48-5.08)
ART Regimen n (%)			*0.448*	
1. AZT/3TC/EFV	0 (0)	2 (8)		2 (3.85)
2. AZT/3TC/NVP	23(85.19)	17 (68)		40 (76.92)
3. d4T/3TC/EFV	0 (0)	1 (4)		1(1.92)
4. d4T/3TC/NVP	3 (11.11)	3 (12)		6 (11.54)
5. TDF/FTC/NVP	1 (3.7)	2 (8)		3 (5.77)

Note: Used Mann-Withiney U Test for comparison of continuous variables and Fisher Exact Test for categorical variables.

4.2 Treatments efficacy of NNRTI-based regimens

100% of patients in sdNVP group and 80% of patients in HAART group had virologic suppression (*p=0.109* by available data and *p=0.020* by sensitivity analysis) at month 6 after on taking an NNRTI–based HAART regimen. All patients in sdNVP group and 21(84%) in HAART group had virologic suppression *(p=0.047)* at months 12 after HAART**.** Median CD4+ T cell count changes (IQR) at 6 months and 12 months were 107 (57-201) and 156(126-275) cells/mm^3 in sdNVP group and 136(91-171) and 168(136-213) in HAART group respectively. non-significant difference between the 2 group.

9 (33.33%) patients in sdNVP group and 3(12.00%) in HAART group had changes to ART regimen in the first 12 months *(p=0.045*).Most of patients had changes ART regimen due to not tolerate to the side effect of ARV; 6 of 12 patients had changes NVP to EFV due to side effects which including ALT elevated, develop hepatitis, rash and Steven's Johnson syndrome, 2 patients had changes d4T to AZT due to lipodystrophy, 1 patient had changes AZT to d4T due to nausea and 1 patients had changes AZT to ddI due to hyperpigmentation. There were 2 patients has changes NNRT to PI due to treatment failure and develop NNRTI drug resistance

All patents reported as good adherence (>98%). Twenty (74%) patients in the sdNVP group and 21(84%) patients in the HAART group reported 100% of adherence at month 12 after HAART initiation(Table 4.2). One of the 3 patients in the HAART group who had virologic failure had an HIV RNA > 30,000 copies/mL without mutation at month 6 while reporting 100% adherence.

Table 4. 2 Virologic efficacy of NNRTI-based HAART regimens at months 6 and 12 after initiation

Characteristic	**sdNVP (n = 27)**	**HAART (n = 25)**	***p-value***	**Overall (n = 52)**
At Month 6 after initiating NNRTI-based HAART				
Number of patient who have VL suppression, n (%) (available data)*	N=17 17(100)	N=20 16(80)	*0.109*	N=37 33(89.19)
Number of patient who have VL suppression, n (%) (sensitivity analysis)**	27(100)	20(80)	*0.020*	47(90.38)
Median CD4+ T cell count changes (IQR), cells/mm^3	107(57-201)	136(91-171)	*0.7141*	123(84-79)
Number of patients who reported 100% adherence ***, n(%)	22 (81.48)	23 (92)	*0.422*	45(86.54)
At Month 12 after initiating NNRTI-based HAART				
Number of patient who have VL suppression, n (%)	27(100)	21(84)	*0.047*	48(92.31)
Median CD4+ T cell count changes (IQR), cells/mm^3	156 (126-275)	168 (136-213)	*0.8907*	163 (116-262)
Number of patient changed or stopped ARV drugs after initiation, n(%)	9(33.33)	3(12.00)	*0.101*	12(23.08)
Number of patients who reported 100% adherence, n(%)	20(74.07)	21(84)	*0.503*	41(78.85)

Note: Used Mann-Withiney U Test for comparison of continuous variables and Fisher Exact Test for categorical variables.

* only patients with a 6 month result available were included in the analysis

** Sensitivity analysis, if 6 month HIV-RNA results were missing they were replaced with the 12 months results in the analysis model.

*** Patients reported no missed dose and no delayed dose of HAART within 30 days prior to the follow up visits

4.3 Resistance mutations

Twenty of 23 (87%) patients were HIV-1vsubtype AE, one patient was HIV-1 subtype B and 2 patients were unknown. Five patients in sdNVP group with stored blood samples available at base line when HAART was initiated which who had detectable viral load; K103N which is related to NVP resistance was identified in one patient. The other 4 patients had no mutations.

There were 18 patients in HAART group with stored blood sample available at 4-8 weeks after delivery, baseline of HAART initiation, month 6 and month 12, which were detectable viral load. Three patients among this group had virologic failure; First patient had L33F which causes PI resistance detected at 4-8 weeks after delivery and at HAART initiation, this patient had M184V and K103N which causes NRTI and NNRTI resistance detected at month 12 after on NNRTI-based HAART regimen. Second patient had T215Y, T69N, M184V and Y181I which causes NRTI and NNRTI resistance detected at both month 6 and month 12 after on NNRTI-based HAART regimen and the third patient had K65R, Y115F, M184V, Y181C and G190A which causes to NRTI and NNRTI resistance detected at months 6 after on NNRTI-based HAART. None of the 3 cases had NRTI or NNRTI mutations detected at 4-8 weeks after delivery or at HAART initiation. The other 15 patients had no NRTI, NNRTI of PI resistance mutation detected at 4-8 weeks after delivery or at HAART initiation (Table 4.3)

Table 4.3 Genotypic resistance results by standard assay at 4-8 week after delivery, base line of NNRTI-based HAART initiation and after on HAART for 6 and 12 months

Pt.	Time to initiated HAART after delivery (months)	HIV Subtype	NRTI , NNRTI and PI Resistance mutation(s)				First line regimen	Virologic failure (yes/no)	Drug related to viral mutation
			4-8 weeks postpartum	Baseline HAART	Months 6	Months 12			
sdNVP Group									
1	83	AE	NAv	No mutation	NA	NA	AZT/3TC/NVP	No	-
2	52	AE	NAv	K103N	NA	NA	AZT/3TC/NVP	No	NVP
3	27	AE	NAv	No mutation	NA	NA	AZT/3TC/NVP	No	-
4	38	AE	NAv	No mutation	NA	NA	AZT/3TC/NVP	No	-
5	6	AE	NAv	No mutation	NA	NA	AZT/3TC/NVP	No	-
HAART Group									
6	22	UNK	No mutation	NAv	NA	NA	AZT/3TC/NVP	No	-
7	13	AE	NAv	No mutation	NA	NA	AZT/3TC/NVP	No	-
8	18	AE	No mutation	NAv	NA	NA	AZT/3TC/NVP	No	-
9	23	AE	NAv	No mutation	NA	NA	AZT/3TC/EFV	No	-
10	10	AE	L33F	L33F	No mutation	M184V, K103N,	AZT/3TC/NVP	Yes	3TC, NVP
11	21	AE	No mutation	No mutation	NA	NA	AZT/3TC/EFV	No	-
12	24	AE	No mutation	NAv	NA	NA	TDF/FTC/NVP	No	-
13	15	AE	No mutation	No mutation	NA	NA	AZT/3TC/NVP	No	-

Table4.3 Genotypic resistance results by standard assay (Continue)

Pt.	Time to initiated HAART after delivery (months)	HIV Subtype	NRTI , NNRTI and PI Resistance mutation(s)				First line regimen	Virologic failure (yes/no)	Drug related to viral mutation
			4-8 weeks postpartum	Baseline HAART	Months 6	Months 12			
					HAART Group				
14	19	AE	NAv	No mutation	NA	NA	D4T/3TC/NVP	No	-
15	2	AE	No mutation	No mutation	T69N, M184V, Y181I	T215Y, M184V, Y181I	AZT/3TC/NVP	Yes	3TC, NVP
16	20	AE	No mutation	No mutation	NA	NA	AZT/3TC/NVP	No	-
17	8	UNK	No mutation	NAv	NA	NA	AZT/3TC/NVP	No	-
*18	43	AE	NAv	No mutation	NA	NA	AZT/3TC/NVP	No	-
19	15	AE	No mutation	No mutation	NA	NA	AZT/3TC/EFV	No	-
20	14	AE	No mutation	NAv	NA	NA	D4T/3TC/NVP	No	-
21	12	B	NAv	No mutation	NA	NA	AZT/3TC/NVP	No	-
**22	33	AE	No mutation	NAv	K65R, Y115F, M184V, Y181C, G190A	NAv	TDF/FTC/NVP	Yes	TDF, FTC, NVP
***23	15	AE	No mutation	NAv	NA	NA	AZT/3TC/NVP	No	-

Note: Resistance testing were done with at lease 1 available of storage samples from four time points which had HIVRNA> 1000 copies/mL (NAv = sample is not available, NA = not applicable due to VL suppression at this time point)
*Patients no.18 has changed NVP to EFV at one week after initiated ART due to Hepatitis (AE)
**Patient no 22, drug resistance was detectable at week 36 and patient has changed ART to AZT/3TC/LPV/RTV at week 36
***Patient no 23 has changed AZT to DDI at week 24 due to hyper pigmentation (AE)

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4.4 Risk factors associated with detectable viral load after on NNRTI-based HAART regimen

In univariate analysis those in the HAART group were more likely to experience virologic failure after 12 months of HAART (OR;4.44,95%confidence interval [CI]; 0.46 to +INF, *p=0.09*).

Patients who start HAART within 1 year after delivery had a higher chance of virologic failure compares to patients who start HAART after 1 year delivery [OR; 9.58; 95%CI; 0.45 t0 618.78, *p=0.091*)] and Patients who took ART during pregnancy ≥74 days had a higher chance of virologic failure [OR; 5.90 ; 95%CI; 0.28 to 373.33, *p=0.17*]. Patients who changes or stopped ART while on PMTCT had a higher chance of virologic failure [OR;7.08; 95%CI; 0.10 to 179.01, *p=0.21*]

PMTCT group and timing of HAART after delivery both met inclusion criteria for multivariate modeling. In these multivariate models, although both factors showed an increased odds of virological failure, neither reached statistical significance and the significance level was reduced compared to that seen in univariate analysis. The odds ratio for virological failure in those taking HAART for PMTCT was 2.41 (95% CI;0.199 to +INF) compared to those who used sdNVP; and the odds ratio for virological failure for those initiating HAART within one year of delivery was 4.93(95% CI;0.22 to 333.77) compared to those imitating HAART after one year. Because of small numbers of subjects who experienced virological failure it was not possible to use logistic regression to quantitate the level of risk. For this reason, we used exact logistic regression to help to describe the risk and calculate confidence intervals around this risk. (Table 4.4)

Table 4.4 Exact logistic regression models of predictors of virologic failure

Characteristic	Univariate analysis		Multivariate analysis	
	OR (95% CI)	***P-value***	**AOR (95% CI)**	***P-value***
Patient group HAART vs sdNVP (Ref)	4.44 (0.46 to +INF)	*0.1041*	2.41 (0.199 to +INF)	*0.5037*
Duration if ART during pregnancy ≥74 days vs <74 days (Ref)	5.90 (0.28 to 373.33)	*0.1729*	-	
Changed or stopped ART while on PMTCT (Yes vs NO)	7.08 (0.10 to 179.01)	*0.2174*	-	
Initiated HAART within 1 year after delivery (Yes vs No)	9.58 (0.45 to 618.78)	*0.0910*	4.93 (0.22 to 333.77)	*0.4626*
CD4+ T cell count at HAART initiation <200 vs ≥200 (Ref)	0.23 (0.004 to 4.69)	*0.2462*	-	
VL log10 at HAART initiation ≥5logs vs <5logs (Ref.)	4.02 (0.18 to 274.65)	*0.5273*	-	

Note; OR , Odd Ratio; CI, confidence interval; AOR, adjusted odds ratio.

Table 4.5 Summary of patient characteristics by virologic failure

Characteristics	Fail (n = 3)	Not fail (n = 49)
At PMTCT		
Median age, years (IQR)	29.84 (25.98-32.46)	28.31 (24.98-30.72)
ARM; N (%)		
sdNVP group	0 (0)	27 (55.10)
HAART group	3 (100)	22 (44.90)
CDC classification n (%)	3 (100)	43 (87.76)
A	0 (0)	6 (12.24)
B	0 (0)	0 (0)
C		
Median number of days of ART during pregnancy (IQR)	79 (39-99)	59 (45-73)
Median CD4+ T cell count (IQR), cells/mm3	N=3 328 (239 -335)	N=24 280 (241.5-352)
Number of women changing ART regimen during pregnancy, n(%)	1(33.33)	3(6.12)
At HAART initiation		
Median months after deliver when initiating HAART (IQR)	9.83 (1.76-32.9)	23.1(14.1-34.2)
CDC classification n (%) at HAART	0 (0)	24 (48.98)
A	3 (100)	23 (46.94)
B	0 (0)	2 (4.08)
C		
Median CD4+ T cell count (IQR), cells/mm3	202 (105-215)	183(148-212)
Median Log10 viral load at HAART initiation (IQR)	N=3 5.08 (4.97 -5.87)	N=19 4.82 (4.46-5.03)
At Month 12 after initiating NNRTI-based HAART		
Median CD4+ T cell count change (IQR), cells/mm3	136(0-268)	164(120-256)
Number of patient changed or stopped ARV drugs after initiation, n(%)	1(33.33)	11(22.45)
Number of patients who reported 100% adherence, n(%)	3(100)	38(77.55)

CHAPTER V
DISCUSSION

The results of this study were discussed on the following issues;

5.1 NNRTI resistance after delivery and at HAART initiation

5.2 Virologic failure at first year of NNRTI – base HAART regimen

5.1 NNRTI resistance after delivery and at HAART initiation

Our study found low rate of NNRTI mutation after delivery and at baseline before HAART initiation; 1 of 5 (20%) patients in the sdNVP group and 0 of 18 (0%) patients in the HAART group had K103N. Previous studies showed NNRTI resistance mutation in 45% of women exposed to AZT/sdNVP at 1 month postpartum using standard assay(4) and in 75% at 3 months postpartum using allele specific PCR(17). Using allele specific PCR, 18% of women exposed to HAART also had NNRTI resistance mutation at 3 months after delivery.

These following factors may explain the low rate of NNRTI mutation found in our women.

1) Longer duration of AZT (8wk) or HAART (10-12wk) during pregnancy in our study compare to the other studies (6wk) (4, 17): This might allow for lower HIV RNA level at the time of exposure to sdNVP or at the time of HAART discontinuation. Women in the HAART group also received AZT+3TC tail after discontinuation of NNRTI and therefore might have reduced chance to have NNRTI resistance mutation developed.

2) HIV-1 subtype AE: Data from Siriraj Hospital, Thailand showed lower frequency of NVP mutations among mothers infected with HIV-1 subtype AE, compared with mothers infected with HIV-1 subtype B (16% vs 38%) who received AZT from 34 weeks of gestation and sdNVP plus oral AZT during labor (37), and African studies in Uganda and Malawi showed higher rate of NVP resistance mutation

at 6-8 week after exposure to sdNVP among women with subtypes C or D than subtype A; 69.2% in HIV-1 subtype C, 36.1% in HIV-1 subtype D and 19.4% in HIV-1 subtype A (38).

3) Use of standard genotypic resistance assay: Use of ultrasensitive assays may help to detect minor variant resistance mutations (39, 40).

No NNRTI mutation was found in our HAART group women. However, discontinuation of NNRTI-based HAART, within or outside the PMTCT setting, can cause NNRTI mutation although at a much lower rate than when sdNVP was discontinued (41-43). Therefore, using PI-based HAART (LPV/r) for pregnant women with high CD4+ T cell count who will discontinue HAART after delivery would be preferred.

5.2 Virologic failure at first year of NNRTI – base HAART regimen

In our study; all of the patient who were exposure to AZT and sdNVP (sdNVP group) for PMTCT had virologics suppression while 21of 25 (84%) patients who received HAART during pregnancy for PMTCT had virologics suppression at months 12 after initiated NNRTI-based HAART regimen (HAART group) *(p=0.47).* This finding is contrast with the hypothesis.

Three patients in HAART group had virologics failures, in which at least three of the following mutations were identified at the time of failure: M184V, K103N, T69N, Y181I, T215Y, K65R, Y115F, Y181C, and G190A. None of the 3 cases had mutations detected at 4-8 weeks after delivery or at HAART initiation.

The rate of virologic failure after NNRTI-based HAART initiation in HAART group is similar to in general adults naïve patients who were initiated NNRTI-based HAART regimen (20% vs 19.09% at 6 months) (12) and there was low rate of virologic failure in women exposure to AZT and sdNVP compared to the study in Botswana which reported 41.9 % virologic failure among women exposure to sdNVP and initiated NNRTI-based HAART regimen within 6 month after delivery (24), and the NNRTI Response Study in Zambia, Kenya and Thailand also report 41%, 37% and 24% rate of treatment failure among women exposure to sdNVP and

initiated NNRTI-based HAART regimen within 6 month, between 7-12 months and >12 months after delivery, respectively. The study suggested women requiring ART within 12 months of NVP exposure should not be treat with NNRTI-based ART regimen as a first line (44) Low rates of virologic failure in our study may cause of long duration after delivery before HAART initiation; 31.13(23.83 – 40.93) months (IQR) as compared to other study (24, 45, 46).

Those 3 women in HAART group who had virologic failure reported 100% of adherence, however the adherence assessment in our study is only self report of missed dosed or delay dosed with 30 day prior to study visit, no pill count. It may over report of treatment compliance as one of the 3 patients in the HAART group who had virologic failure had an HIV RNA > 30,000 copies/mL without mutation at month 6 while reporting 100% adherence.

PMTCT regimen and duration after delivery before HAART initiation were not found to be significant risk factors for virologic failure among women with prior PMTCT exposure in our study by multivariate analysis.

The limitations of our study were 1) subjected number was small; 2) time difference between the two PMTCT regimens. This is cause of missing data in sdNVP group than HAART group. The MTCT-Plus Program, Thailand have been enrolled patients sine February 2003 until 31 December 2007; there were almost 6 years long term follow up upon December 2009 while this study performed data collection. The PMTCT regimen had changes at least 3 times since program start according to WHO and National guideline as mention in CHAPTER III. The patients who were enrolled in to this study; sdNVP group received PMTCT during May 2000 – Mar 2004 and patient in HAART group received PMTCT during April 2004 – September 2006. The data on CD4+ T cell count at PMTCT in patient sdNVP group were missing; only 3 patients has available results (233, 346, 561 cells/mm^3) while 24 patients in HAART group has CD4+ T cell count at PMTCT; median (IQR) 280 (241-331.5) cells/mm^3

MTCT-Plus program had studied to answer the question “Is stopping AZT/sdNVP safer than stopping HAART in women after delivery that do not required therapy for their own health?” The results of this study shown stopped HAART is not results in higher rate of death or clinical progression compare to stop AZT/NVP for 15 months follow up. Patient who have CD4+ T cell count < 350 cells/mm^3 was risk for

HAART needs shortly after delivery when treatment response may be suboptimal thus HAART should be initiate during pregnancy and continue postpartum for this women, (47).

In our study, the median CD4+ T cell count of patients in HAART group prior to PMTCT initiation is lower than 350 cells/mm^3 and tended to lower than those in the sdNVP group; therefore may explain the shorter duration between delivery time and HAART initiation time in the HAART group. At the start of HAART after delivery, median CD4+ T cell count of patient in AZT/sdNVP group and HAART group were similar in this study (370 versus 390 cells/mm^3, *p=0.727*).

CHAPTER VI
CONCLUSION AND RECOMMENDATION

In our study, the efficacy of NNRTI-based HAART at 12 months was good in postpartum women exposed to either sdNVP or HAART for PMTCT.

NNRTI resistance mutations after sdNVP exposure were found, while no mutation was found in HAART group, using standard genotypic resistance assay. Use ultrasensitive assays may help to detect minor resistance mutations when initiating HAART in postpartum women with previous exposure to PMTCT regimens.

PMTCT regimen and duration after delivery before HAART initiation were not found to be significant risk factors for virologic failure among women with prior PMTCT exposure in our study by multivariate analysis. However, in setting where infrastructure for advanced PMTCT regimen could be made available, we propose the use of PI-based HAART for pregnant women with high CD4+ T cell count who will discontinue HAART after delivery to avoid unnecessary development of NNRTI mutation and to initiate HAART early, and continue after delivery for those with CD4+ T cell count <350 cells/mm^3 to avoid unnecessary treatment interruption and the need to re-start HAART early after delivery.

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APPENDICES

APPENDIX A

CASE RECORD FORM

sd-NVP vs HAART	**Screening visit**	PID I_I_I_I_I_I_I_I_I Initials: I_I_I *First Last*

Date of visit: I__I__I I__I__I I__I__I
dd mm yy

Written informed consent is obtained	1☐ Yes 0☐ No	Date: I__I__I I__I__I I__I__I *dd mm yy*

Eligibility Criteria

Inclusion Criteria (all the answer must be 'Yes')

		Yes	**No**
1.	Age > 18 years old	1☐	0☐
2.	Exposed to AZT and sd-NVP or HAART during pregnancy	1☐	0☐
3.	Started NNRTI-based HAART for ≥ 12 months	1☐	0☐
4.	Written informed consent	1☐	0☐

Exclusion Criteria (all the answer must be 'No')

		Yes	**No**
1.	Not on HAART or on HAART < 12 months	1☐	0☐
2.	On HAART without NNRTI	1☐	0☐

Screening outcome

The patient is:

☐ Eligible and **Treatment during pregnancy is**

1☐ Arm1: sd-NVP
2☐ Arm2: HAART

☐ Not eligible.

☐ Eligible but will not be randomized due to other the reason

Please specify: _____

1. Demographic Data

Date of Birth: I__I__I I__I__I I__I__I
dd mm yy

2. Documentation of HIV Infection

Date of positive HIV-1 test: I__I__I I__I__I I__I__I
dd mm yy

Current clinical CDC HIV Classification 1☐ A 2☐ B 3☐ C

3. Antiretroviral Therapy History Before HAART (including during pregnancy)

Code	ARV name	Start Date	Stop Date (tick if ongoing)	If stop ART, Indicate Reason
I__I__I__I		___/____/____ dd mm yy	____/____/____ 1☐ dd mm yy	
I__I__I__I		___/____/____ dd mm yy	____/____/____ 1☐ dd mm yy	
I__I__I__I		___/____/____ dd mm yy	____/____/____ 1☐ dd mm yy	
I__I__I__I		___/____/____ dd mm yy	____/____/____ 1☐ dd mm yy	
I__I__I__I		___/____/____ dd mm yy	____/____/____ 1☐ dd mm yy	
I__I__I__I		___/____/____ dd mm yy	____/____/____ 1☐ dd mm yy	
I__I__I__I		___/____/____ dd mm yy	____/____/____ 1☐ dd mm yy	

4. Date of Delivery I__I__I I__I__I I__I__I
dd mm yy

Number of pregnancies I__I__I

Number of Children I__I__I

Is this child HIV-infected?
1☐ Yes
2☐ No
3☐ Other, specify______________________

5. CD4 count most recent date (within 4-8 week after delivery) 1☐ **Not done**

Date: I__I__II__I__II__I__I
dd mm yy

CD4 + cells: I__I__I % I__I__I__I__I__I /mm^3

6. Plasma storage at the time 4-8 week after delivery 1☐ **Not done**

Date of specimen collection: I__I__I I__I__I I__I__I
dd mm yy

6.1 HIV virology

1☐ **Not done**

HIV-RNA: > ☐ < ☐ = ☐ I__I__I__I__I__I__I__I copies/ml.

6.2 Genotyping assay

Date of specimen collection: I__I__II__I__II__I__I 1☐ **Not done**
dd mm yy

Date of Report: I__I__II__I__II__I__I
dd mm yy

NRTI mutation: ______________________

NNRTI mutation: ______________________

Other RT mutation: ______________________

sd-NVP vs HAART **Baseline visit**

PID I_I_I_I_I_I_I_I_I

Initials: I_I_I
First Last

Date of visit: I__I__I I__I__I I__I__I
dd mm yy

Treatment during pregnancy:
1☐ Arm1: sd-NVP
2☐ Arm2: HAART

History

1. HIV-Related Illnesses

Has the patient experienced any new or recurrent HIV-Related illnesses or any change in existing HIV-Related illnesses since delivery including today?

1☐ Yes 0☐ No

If **'Yes'**, please complete those events in the **HIV-Related Illnesses** section of this CRF.

2. Other Adverse Event

Has the patient experienced any new (serious) adverse event or any change in existing events since delivery including today?

1☐ Yes 0☐ No

If **'Yes'**, please complete those events in the **Adverse Event** section of this CRF.

3. Concomitant Medication

Has the patient taken any new medications or has the dosage of medication previously reported changed, since delivery including today?

1☐ Yes 0☐ No

If **'Yes'**, please complete those medication in the **Concomitant Medication** section of this CRF.

ARV

4. Trial Medication

Does the patient start HAART today?

1☐ Yes 0☐ No

If **'Yes'**, please complete those medication in the **Trial Medication Log** section of this CRF.

Physical Examination

5. Measurements and Evaluations **Not done**

Weight:	I__I__I__I.I__I kg.	☐
Height:	I__I__I__I.I__I cm.	☐

6. Vital signs **Not done**

Blood pressure:	I__I__I__I/I__I__I__I mm Hg	☐
Heart rate:	I__I__I__I bpm	☐
Respiratory rate:	I__I__I__I breaths per minute	☐
Body temperature:	I__I__I.I__I °C	☐

7. Physical Examination

Body part or system:			
	Ears, nose & throat	1☐normal	
		2☐abnormal	Specify_____
	Head & Neck	1☐normal	
		2☐abnormal	Specify_____
	Cardiovascular	1☐normal	
		2☐abnormal	Specify_____
	Lung	1☐normal	
		2☐abnormal	Specify_____
	Abdomen	1☐normal	
		2☐abnormal	Specify_____
	Lymph Nodes	1☐normal	
		2☐abnormal	Specify_____
	Skin	1☐normal	
		2☐abnormal	Specify_____
	Musculoskeletal	1☐normal	
		2☐abnormal	Specify_____
	Neurological	1☐normal	
		2☐abnormal	Specify_____
	Other	1☐normal	
		2☐abnormal	Specify_____

Laboratory

[If Lab-abnormalities are Grade 3 or 4, please complete in Adverse Event Form]

8. Baseline Visit lab (before HAART)

8.1 Hematology

Date of specimen collection: I__I__II__I__II__I__I (dd mm yy) ☐ **Not done**

		Not done			Not done
Hemoglobin:	I__I__I.I__I g/dl	☐	WBC:	I__I__I.I__I__I 10^3/µl	☐
Hematocrit:	I__I__I.I__I %	☐	Neutrophils:	I__I__I.I__I %	☐
Platelet:	I__I__I__I 10^3/µl	☐	Lymphocytes:	I__I__I.I__I %	☐
			Eosinophils:	I__I__I.I__I %	☐

8.2 Biochemistry

Date of specimen collection: I__I__II__I__II__I__I (dd mm yy) ☐ **Not done**

		Not done			Not done
Glucose:	I__I__I__I__I mg/dl	☐	Total bilirubin:	I__I__I.I__I__I mg/dl	☐
BUN:	I__I__I.I__I g/dl	☐	Direct bilirubin:	I__I__I.I__I__I mg/dl	☐
Creatinine:	I__I. I__I__I g/dl	☐	SGOT / AST:	I__I__I__I U/L	☐
Cholesterol:	I__I__I__I__I mg/dl	☐	SGPT / ALT:	I__I__I__I U/L	☐
Triglycerides:	I__I__I__I__I mg/dl	☐	Alkaline Phosphatase:	I__I__I__I U/L	☐
HDL-chol:	I__I__I__I mg/dl	☐	Amylase:	I__I__I U/L	☐
LDL-chol:	I__I__I__I mg/dl	☐	Sodium (Na):	I__I__I__I mmol/l	☐
			Potassium(K):	I__I. I__I__I mmol/l	☐

8.3 Immunology

Date of specimen collection: I__I__II__I__II__I__I (dd mm yy) ☐ **Not done**

		Not done			Not done
CD4 + cells	I__I__I %	☐	count:	I__I__I__I__I /mm^3	☐
CD8 + cells	I__I__I %	☐	count:	I__I__I__I__I /mm^3	☐

8.4 HIV virology

Date of specimen collection: I__I__II__I__II__I__I (dd mm yy) ☐ **Not done**

HIV-RNA: > ☐ < ☐ = ☐ I__I__I__I__I__I__I copies/ml.

8.5 Genotyping assay

Date of specimen collection: I__I__II__I__II__I__I (dd mm yy) ☐ **Not Done**

Date of Report: I__I__II__I__II__I__I (dd mm yy)

NRTI mutation: _____

NNRTI mutation: _____

Other RT mutation: _____

sd-NVP vs HAART **Month 6** PID I_I_I_I_I_I_I_I_I

Initials: I_I_I
First Last

Date of visit: I__I__I I__I__I I__I__I
dd mm yy

Treatment during pregnancy:
1☐ Arm1: sd-NVP
2☐ Arm2: HAART

History

1. HIV-Related Illnesses

Has the patient experienced any new or recurrent HIV-Related illnesses or any change in existing HIV-Related illnesses since the last visit including today?

1☐ Yes 0☐ No

If **'Yes'**, please complete those events in the **HIV-Related Illnesses** section of this CRF.

2. Other Adverse Event

Has the patient experienced any new (serious) adverse event or any change in existing events since the last visit including today?

1☐ Yes 0☐ No

If **'Yes'**, please complete those events in the **Adverse Event** section of this CRF.

3. Concomitant Medication

Has the patient taken any new medications or has the dosage of medication previously reported changed, since the last visit including today?

1☐ Yes 0☐ No

If **'Yes'**, please complete those medication in the **Concomitant Medication** section of this CRF.

ARV

4. Trial Medication

Has the patient's trial medication been changed since the last visit including today?

1☐ Yes 0☐ No

If **'Yes'**, please complete those medication in the **Trial Medication Log** section of this CRF.

5. Adherence self report

	Yes	No
1. Did the patient miss any dose in the last ☐ 7 days or ☐ 30 days?	1☐	2☐
If yes, How many time?	I__I__I__I times	
2. Did the patient have delayed dose more than 30 minutes in the last 30 days?	1☐	2☐
If yes, How many time?	I__I__I__I times	

Physical Examination

6. Measurements and Evaluations **Not done**

Weight:	I__I__I__I.I__I kg.	☐
Height:	I__I__I__I.I__I cm.	☐

7. Vital signs **Not done**

Blood pressure:	I__I__I__I/I__I__I__I mm Hg	☐
Heart rate:	I__I__I__I bpm	☐
Respiratory rate:	I__I__I__I breaths per minute	☐
Body temperature:	I__I__I.I__I °C	☐

8. Physical Examination

Body part or system:			
	Ears, nose & throat	1☐normal	
		2☐abnormal	Specify_____
	Head & Neck	1☐normal	
		2☐abnormal	Specify_____
	Cardiovascular	1☐normal	
		2☐abnormal	Specify_____
	Lung	1☐normal	
		2☐abnormal	Specify_____
	Abdomen	1☐normal	
		2☐abnormal	Specify_____
	Lymph Nodes	1☐normal	
		2☐abnormal	Specify_____
	Skin	1☐normal	
		2☐abnormal	Specify_____
	Musculoskeletal	1☐normal	
		2☐abnormal	Specify_____
	Neurological	1☐normal	
		2☐abnormal	Specify_____
	Other	1☐normal	
		2☐abnormal	Specify_____

Laboratory

[If Lab-abnormalities are Grade 3 or 4, please complete in Adverse Event Form]

9. Follow up Visit lab (month 6 after HAART)

9.1 Hematology

Date of specimen collection: I__I__II__I__II__I__I (dd mm yy) ☐ **Not done**

		Not Done			Not done
Hemoglobin:	I__I__I.I__I g/dl	☐	WBC:	I__I__I.I__I__I $10^3/\mu l$	☐
Hematocrit:	I__I__I.I__I %	☐	Neutrophils:	I__I__I.I__I %	☐
Platelet:	I__I__I__I $10^3/\mu l$	☐	Lymphocytes:	I__I__I.I__I %	☐
			Eosinophils:	I__I__I.I__I %	☐

9.2 Biochemistry

Date of specimen collection: I__I__II__I__II__I__I (dd mm yy) ☐ **Not done**

		Not Done			Not done
Glucose:	I__I__I__I__I mg/dl	☐	Total bilirubin:	I__I__I.I__I__I mg/dl	☐
BUN:	I__I__I.I__I g/dl	☐	Direct bilirubin:	I__I__I.I__I__I mg/dl	☐
Creatinine:	I__I. I__I__I g/dl	☐	SGOT / AST:	I__I__I__I U/L	☐
Cholesterol:	I__I__I__I__I mg/dl	☐	SGPT / ALT:	I__I__I__I U/L	☐
Triglycerides:	I__I__I__I__I mg/dl	☐	Alkaline Phosphatase:	I__I__I__I U/L	☐
HDL-chol:	I__I__I__I mg/dl	☐	Amylase:	I__I__I U/L	☐
LDL-chol:	I__I__I__I mg/dl	☐	Sodium (Na):	I__I__I__I mmol/l	☐
			Potassium(K):	I__I. I__I__I mmol/l	☐

9.3 Immunology

Date of specimen collection: I__I__II__I__II__I__I (dd mm yy) ☐ **Not done**

		Not Done			Not done
CD4 + cells	I__I__I %	☐	count:	I__I__I__I__I /mm^3	☐
CD8 + cells	I__I__I %	☐	count:	I__I__I__I__I /mm^3	☐

9.4 HIV virology

Date of specimen collection: I__I__II__I__II__I__I (dd mm yy) ☐ **Not done**

HIV-RNA: > ☐ < ☐ = ☐ I__I__I__I__I__I__I copies/ml.

9.5 Genotyping assay

Date of specimen collection: I__I__II__I__II__I__I (dd mm yy) ☐ **Not Done**

Date of Report: I__I__II__I__II__I__I (dd mm yy)

NRTI mutation: _____

NNRTI mutation: _____

Other RT mutation: _____

sd-NVP vs HAART **Month 12**

PID I_I_I_I_I_I_I_I_I

Initials: I_I_I
First Last

Date of visit: I__I__I I__I__I I__I__I
dd mm yy

Treatment during pregnancy:
1☐ Arm1: sd-NVP
2☐ Arm2: HAART

History

1. HIV-Related Illnesses

Has the patient experienced any new or recurrent HIV-Related illnesses or any change in existing HIV-Related illnesses since the last visit including today?

1☐ Yes 0☐ No

If **'Yes'**, please complete those events in the **HIV-Related Illnesses** section of this CRF.

2. Other Adverse Event

Has the patient experienced any new (serious) adverse event or any change in existing events since the last visit including today?

1☐ Yes 0☐ No

If **'Yes'**, please complete those events in the **Adverse Event** section of this CRF.

3. Concomitant Medication

Has the patient taken any new medications or has the dosage of medication previously reported changed, since the last visit including today?

1☐ Yes 0☐ No

If **'Yes'**, please complete those medication in the **Concomitant Medication** section of this CRF.

ARV

4. Trial Medication

Has the patient's trial medication been changed since the last visit including today?

1☐ Yes 0☐ No

If **'Yes'**, please complete those medication in the **Trial Medication Log** section of this CRF.

5. Adherence self report	**Yes**	**No**
2. Did the patient miss any dose in the last ☐ 7 days or ☐ 30 days?	1☐	2☐
If yes, How many time?	I__I__I__I times	
3. Did the patient have delayed dose more than 30 minutes in the last 30 days?	1☐	2☐
If yes, How many time?	I__I__I__I times	

Physical Examination

6. Measurements and Evaluations **Not done**

Weight:	I__I__I__I.I__I kg.	☐
Height:	I__I__I__I.I__I cm.	☐

7. Vital signs **Not done**

Blood pressure:	I__I__I__I/I__I__I__I mm Hg	☐
Heart rate:	I__I__I__I bpm	☐
Respiratory rate:	I__I__I__I breaths per minute	☐
Body temperature:	I__I__I.I__I °C	☐

8. Physical Examination

Body part or system:			
	Ears, nose & throat	1☐normal	
		2☐abnormal	Specify_____
	Head & Neck	1☐normal	
		2☐abnormal	Specify_____
	Cardiovascular	1☐normal	
		2☐abnormal	Specify_____
	Lung	1☐normal	
		2☐abnormal	Specify_____
	Abdomen	1☐normal	
		2☐abnormal	Specify_____
	Lymph Nodes	1☐normal	
		2☐abnormal	Specify_____
	Skin	1☐normal	
		2☐abnormal	Specify_____
	Musculoskeletal	1☐normal	
		2☐abnormal	Specify_____
	Neurological	1☐normal	
		2☐abnormal	Specify_____
	Other	1☐normal	
		2☐abnormal	Specify_____

Laboratory

[If Lab-abnormalities are Grade 3 or 4, please complete in Adverse Event Form]

9. Follow up Visit lab (month 12 after HAART)

9.1 Hematology

Date of specimen collection: I__I__II__I__II__I__I (dd mm yy) ☐ **Not done**

		Not Done			Not done
Hemoglobin:	I__I__I.I__I g/dl	☐	WBC:	I__I__I.I__I__I 10^3/µl	☐
Hematocrit:	I__I__I.I__I %	☐	Neutrophils:	I__I__I.I__I %	☐
Platelet:	I__I__I__I 10^3/µl	☐	Lymphocytes:	I__I__I.I__I %	☐
			Eosinophils:	I__I__I.I__I %	☐

9.2 Biochemistry

Date of specimen collection: I__I__II__I__II__I__I (dd mm yy) ☐ **Not done**

		Not Done			Not done
Glucose:	I__I__I__I__I mg/dl	☐	Total bilirubin:	I__I__I.I__I__I mg/dl	☐
BUN:	I__I__I.I__I g/dl	☐	Direct bilirubin:	I__I__I.I__I__I mg/dl	☐
Creatinine:	I__I. I__I__I g/dl	☐	SGOT / AST:	I__I__I__I U/L	☐
Cholesterol:	I__I__I__I__I mg/dl	☐	SGPT / ALT:	I__I__I__I U/L	☐
Triglycerides:	I__I__I__I__I mg/dl	☐	Alkaline Phosphatase:	I__I__I__I U/L	☐
HDL-chol:	I__I__I__I mg/dl	☐	Amylase:	I__I__I U/L	☐
LDL-chol:	I__I__I__I mg/dl	☐	Sodium (Na):	I__I__I__I mmol/l	☐
			Potassium(K):	I__I. I__I__I mmol/l	☐

9.3 Immunology

Date of specimen collection: I__I__II__I__II__I__I (dd mm yy) ☐ **Not done**

		Not Done			Not done
CD4 + cells	I__I__I %	☐	count:	I__I__I__I__I /mm^3	☐
CD8 + cells	I__I__I %	☐	count:	I__I__I__I__I /mm^3	☐

9.4 HIV virology

Date of specimen collection: I__I__II__I__II__I__I (dd mm yy) ☐ **Not done**

HIV-RNA: > ☐ < ☐ = ☐ I__I__I__I__I__I__I copies/ml.

9.5 Genotyping assay

Date of specimen collection: I__I__II__I__II__I__I (dd mm yy) ☐ **Not Done**

Date of Report: I__I__II__I__II__I__I (dd mm yy)

NRTI mutation: _____

NNRTI mutation: _____

Other RT mutation: _____

HIV-Related Illnesses Form | **sd-NVP vs HAART** | PID I_I_I_I_I_I_I_I_I

Page I__I of I__I | Initials: I_I_I (*First Last*)

Ref. NO	Code	Diagnosis	New or Relapse?	Date of diagnosis (dd/mm/year)	Was the diagnosis	Stop Date (dd/mm/year)	Was any Medication prescribed? Yes or No	Hospitalized? (Y/N)
	Use code # and Diagnosis from the HIV-related Illness list		1=New 2=Relapse		1 = Definitive 2 = Presumptive 3 = Possible	Tick if ongoing at end of study	If yes, complete "Concomitant Med. From" ***1=Yes 0=No***	
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		

sd-NVP vs HAART		PID I_I_I_I_I_I_I_I_I
Adverse Event Form	**Page I__I of I__I**	Initials: I_I_I *First Last*

Code	Toxicity Grading (Lab)
1	Mild
2	Moderate
3	Severe
4	Life-threatening
	Severity Evaluation (Clinical)
5	Mild
6	Moderate
7	Severe

Relationship to trial medication	
0	Not related
1	Unlikely
2	Possible
3	Probable
4	(Almost) certain

Please enter all complaints, events or abnormalities found upon examination as well as lab-abnormalities Grade 3 or 4 that CANNOT be classified as an HIV-related illness.

Ref. No	**CODE**	**Drug Generic Name**	**Indication**	**Dose**	**Units**	**Freq.** **(only code)**	**Route** **(only code)**	**Start Date** (dd/mm/year)	**Stop Date** (dd/mm/year) Tick if on going at the end of study
	I__I__I__I__I__I								☐
	I__I__I__I__I__I								☐
	I__I__I__I__I__I								☐
	I__I__I__I__I__I								☐
	I__I__I__I__I__I								☐
	I__I__I__I__I__I								☐
	I__I__I__I__I__I								☐
	I__I__I__I__I__I								☐
	I__I__I__I__I__I								☐
	I__I__I__I__I__I								☐

Concomitant Medication Form

sd-NVP vs HAART

Page I__I of I__I

PID I_I_I_I_I_I_I_I_I

Initials: I_I_I
First Last

Please report details of all drug used with the exception of study medication

Ref. No	CODE	Drug Generic Name	Indication	Dose	Units	Freq. (only code)	Route (only code)	Start Date (dd/mm/year)	Stop Date (dd/mm/year) Tick if on going at the end of study
	I__I__I__I__I__I								☐
	I__I__I__I__I__I								☐
	I__I__I__I__I__I								☐
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	I__I__I__I__I__I								☐
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Table show Route Code

Code	Route
1	PO = By mouth
2	IM = Intramuscular
3	IV = Intravenous
4	SC = Subcutaneous
5	TO = Topical
6	IH = InhALTion

Table show Frequency Code

Code	Description
1	OD
2	BID
3	TID
4	QID
5	Alternate day

Trial Medication Log

sd-NVP vs HAART

Page I__I of I__I

PID I_I_I_I_I_I_I_I_I

Initials: I_I_I
First Last

(Temporarily or permanently discontinuing the use of an antiretroviral medication should be documented as a dose modification to 0 mg.)

Ref NO#	**Code ARV**	**ARV Name**	**Start Date** (dd/mm/year)	**Dose** (in mg.)	**Freq.** (only code)	**Stop Date** (dd/mm/year) tick if ongoing at the end of study	**Reason for stop** (only code)	**Specify reason** (These codes need to specify 9, 10,11 and 14)
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		
	I__I__I__I					☐		

Table show Frequency code

Code	**Description**
1	OD
2	BID
3	TID
4	QID
5	Alternate day

Table show reason for stop Trial Medication Log

Code	**Description**	**Code**	**Description**
1	Disease progression (new CDC class event)	8	Dose change or stop according to protocol
2	Pregnancy	9	AE or SAE or HIV-illness, please specify
3	Worsening of other pre-existing disease	10	Patient's request, please specify
4	Lack of initial virologic response	11	Physician's decision, please specify
5	Consent withdrawn	12	Loss to follow up
6	Non-adherence	13	Death
7	Other protocol violation	14	Other, please specify

HIV-NAT

Important CDC classification for HIV and AIDS

CD4+T cell Categories	Clinical categories		
	A Asymptomatic, acute (primary) HIV or PGL	B Symptomatic, not A or C conditions	C AIDS indicator conditions
1: ≥ 500/mm^3	A1	B1	C1
2: 200-499/mm^3	A2	B2	C2
3: < 200/mm^3	A3	B3	C3

Category A : - Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Category B : See HIV Related illnesses, CDC-B events
Category C : See HIV Related illnesses, CDC-C events

HIV Related Illnesses			
CDC-B events			
B01	Bacillary angiomatosis	B07	Listeriosis
B02	Candidiasis oropharyngeal	B08	Oral hairy leukoplakia
B03	Candidiasis vulvovaginal (persistent, recurrent, or unresponsive to therapy)	B09	Pelvic inflammatory disease
		B10	Peripheral neuropathy
B04	Cervical dysplasia (moderate or severe) / Cervical carcinoma in situ	B11	Persistent fever (>1month duration)
		B12	Persistent diarrhoea (>1month duration)
B05	Herpes zoster (shingles), involving at least two distinct episodes or more than one dematome	B13	Pruritic papular eruptions
		B14	Others to be specified
B06	Idiopathic thrombocytopenia purpura		
CDC-C events			
C01	Candidiasis of bronchi, trachea, or lungs	C14	Lymphoma, Burkitt's (or equivalent term)
C02	Cervical cancer, invasive	C15	Lymphoma, immunoblastic (or equivalent term)
C03	Coccidioidomycosis, disseminated or extrapulmonary	C16	Lymphoma, primary, of the brain
		C17	M.avium complex or M.Kansasii, disseminated or extrapulmonary
C04	Cryptococcosis, extrapulmonary		
C05	Cryptosporidiosis, chronic intestinal (>1month duration)	C18	M.tuberculosis, any site (pulmonary or extrapulmonary)
C06	Cytomegalovirus disease (other than liver, spleen, or nodes)	C19	Mycobacterium, other or unidentified species, disseminated or extra pulmonary
C07	Cytomegalovirus retinitis (with loss of vision)	C20	Oesophageal candidiasis
C08	Herpes simplex : chronic ulcer(s) (>1month duration) ; or bronchitis, pneumonitis, or oesophagitis	C21	Pneumocystis carinii pneumonia
		C22	Pneumonia, recurrent (≥2distinct episodes)
		C23	Progressive multifocal leukoencephalopathy
C09	Histoplasmosis, disseminated or extrapulmonary	C24	Salmonella septicaemia, recurrent
C10	HIV-related encephalopathy	C25	Toxoplasmosis of the brain
C11	HIV-wasting syndrome		
C12	Isosporiasis, chronic intestinal (>1month duration)		
C13	Kaposi's sarcoma		
Other HIV-related events			
D01	Aspergillosis	D08	Syphilis-primary
D02	Isosporiasis	D09	Syphilis-secondary
D03	Leishmaniasis	D10	Syphilis-tertiary
D04	Microsporidiasis	D11	Syphilis-latent
D05	Nocardiasis	D12	Syphilis-neuro
D06	Penicillium marneffei, disseminated	D13	Other to be specified
D07	Rhodococcus equii		

HIV-NAT

Adverse Events Code

Laboratory	
L01	Anemia (decreased Hb)
L02	ALT(SGPT) elevated
L03	Alkaline phosphatase (ALP, ALK) elevated
L04	Amylase elevated
L05	AST(SGOT) elevated
L06	Cholesterol elevated
L07	CPK elevated
L08	Creatinine elevated
L09	Gamma GT elevated / GGT
L10	Hyperglycemia
L11	Hypoglycemia
L12	Hyperbilirubinaemia (total bilirubin)
L13	Lactate elevated
L14	LDH elevated
L15	Lipase elevated
L16	Neutropenia
L17	Partial thromboplastin time elevated
L18	Prothrombin time elevated
L19	Triglyceride elevated
L20	Thrombocytopenia
L21	Urinalysis abnormal , specify proteinuria, haematuria, leucocyturia
L97	Other clotting disorder, specify fibrinogen, fibrin split product
L98	Other haematological disorder, specify leucocytosis, leucopenia, methemoglobin, thrombocytosis
L99	Other biochemistry abnormalities specify, hypo or hyper anemia, blood urea nitrogen, calcemia, kalemia, magnesemia, natremia, phosphatemia

Cardiovascular	
T01	Arrhythmia
T02	High blood pressure
T99	Other cadiovascular events specify cardiac arrest, hypotention, (subdural) haematoma, haemoptysis, (cerebral) haemorrhage, heart failure, infective endocarditis, oedema, palpitations, percarditis, shock, Raynauds's syndrome (cold extremities), thrombosis, varicosis, vasculitis

Dermatological / skin	
X01	Alopecia
X02	Body hair increased
X03	Dry lips
X04	Dry skin
X05	Ingrown nails
X06	Itching, pruritus, excoriation, scratching
X07	HSV infection
X08	Rash, specify erythroderma, exfoliative dermatitis, reaction at site of administration, Steven's Johnson syndrome, toxic epidermal necrolysis
X99	Other skin events, specify flushing, primary neoplasm (BCC, Bowens, SCC)

Gastro-Intestinal	
G01	Abdominal bloating, distention
G02	Abdominal pain, epigastric pian
G03	Acute hepatitis (non B/C), specify
G04	Angular chelitis
G05	Anorexia
G06	Cholecystitis, cholelithiasis
G07	Chronic hepatitis (non B/C) specify
G08	Constipation
G09	Diarrhoea <1month
G10	Diarrhoea >1month (not HIV-related)
G11	Dry mouth
G12	Dysphagia, difficulty swallowing
G13	Enlarged liver (hepatomegaly)
G14	Enlarged spleen (splenomegaly)
G15	Flatulence, eructation
G16	Gingivitis
G17	Haemorrhoids
G18	Hepatitis B (chronic)
G19	Hepatitis C (chronic)
G20	Indigestion, oesophageal reflux, gastritis
G21	Infectious gastro-enteritis
G22	Jaundice, icterus
G23	Nausea
G24	Pancreatitis
G25	Peri-anal abnormalities, specify abscess, excoriation, fissure, irritation, ulceration
G26	Stomatitis
G27	Taste change, perversion, metalic taste
G28	Tooth ache, dental caries
G29	Ulcer in mouth
G30	Vomiting
G98	Other mouth, ENT events specify tooth abscess, parotitis / parotid enlargement
G99	Other GI events, specify appendictitis, ascites, bleeding (rectal, lower, upper GI), bowel obstruction, cholangitis (sclerosing), colitis, ulcers, (peptic, gastric, duodenal), pus, rectal discharge, salmonellosis, toxic megacolon

Ophthalmology	
E01	Conjuctivitis
E02	Visual disturbance, specify
E99	Other ophthalmological events, blepharitis, keratitis, retinal necrosis, or detachment, retinitis other than CMV, toxoplsmosis

Musculo-skeletal	
M01	Arthralgia
M02	Arthritis
M03	Back pain (not flank pain)
M04	Myalgia
M05	Muscle strength decreased
M99	Other musculo-skeletal events, specify bacterial infection (bone or joint), CNT tissue disorder (anterior uveitis), cramp, gout, muscular weakness or wasting, myopathy, spasms, tetany

HIV-NAT

Adverse Events Code

Neurological	
N01	Confusion
N02	Convulsions, fits, epilepsy
N03	Dizziness, giddiness, vertigo
N04	Drowsiness
N05	Encephalopathy (non HIV-related)
N06	Headache
N07	Insomnia
N08	Memory loss
N09	Mood change, specify dysphoria, aggression, mania
N10	Peripheral neuropathy
N11	Poor concentration
N12	Transient numbness/tingling (paraesthesia), not considered peripheral neuropathy
N99	Other neurological condition, specify Anal disturbances (sphincter, reduced tone, incontinence), ataxia (gait, limb), atrophy (cerebral, cortical), cerebellar signs, coma, deafness, hyper/hypo reflexia, impotence, increased/decrease tone, indeterminate intracerebral lesions, labyrinthitis, nerve palsy (7^{th} cranial nerve, pseudobulbar), nystagmus, papillitis, papilloedema, paresis, post herpetic neuralgia, radiculopathy, spastic diplegia, speech disturbances (delayed, dysarthria, dysphasia, slurred), tinnitus, tremor, trigeminal neuralgia, urinary disturbances (sphincter, retention, incontinence)

Haematological	
H01	Pancytopenia
H99	Other haematological events, specify bruising, haemarthrosis, haemorrhage or blood loss (not specified elsewhere), joint bleed, petechiae, polycythaemia, purpura

Systemic	
S01	Allergic reaction
S02	Bacteremia, sepsis
S03	Diabetes, abnormal glucose tolerance test
S04	Fatigue
S05	Fever of unknown origin (>12 hour)
S06	Flu-like illness, flu-syndrome
S07	Night sweats
S08	Weight loss > 10% in 6 months (not AISDS defining)
S09	Other systemic events, specify drug fever

Psycho-social	
P01	Anxiety
P02	Depression
P03	Drug abuse, specify alcohol, (non) IV drugs
P99	Other psycho-social events, specify reduced libido, suicide attempt

Urogenital	
U01	Abnormal menstruation, specify Amenorrhoea, oligomenorrhoea, menorrhagia
U02	Chlamydia
U03	Cystitis, UTI
U04	Dysuria
U05	Flank pain
U06	Genital and perinatal warts
U07	Gonorrhoea
U08	Haematuria (macroscopic)
U09	Nocturia
U10	Non-specific urethritis (NSU)
U11	Pregnancy
U12	Renal colic
U13	Renal fialure
U14	Syphilis
U15	Vaginal discharge unspecified
U99	Other UG events, specify pyelonephritis, polyuria

Respiratory	
R01	Asthma
R02	Breathlessness or dyspnoea-SOB
R03	Bronchitis
R04	Chest pain / discomfort
R05	Common cold
R06	Cough
R07	Ear ache / otitis media
R08	Epistaxis
R09	Non-infectious rhinitis
R10	Pneumonia
R11	Snusitis
R12	Tonsillitis, pharyngitis, sore throat
R13	Wheezing, acute bronchospasm
R14	Other respiratory events, specify bronchiolitis, chronic deafness, lung abscess, pleural effusion, pneumonitis, pneumothorax, (asymptomatic chronic lymphoid interstitial), pulmonay embolism, tuberculosis (prior to HIV infection)

Infective non HIV	
I99	Other non HIV infective events, specify Bacterial abscess or internal organ/body cavity, CMV of liver, disseminated toxoplasmosis, infestation (eg. scabies, pediculosis), malaria, microsporidiosis (not specified or <1 month of diarrhoea), septicaemia (not salmonella or pneumococcal), spleen/lymph nodes

Miscellaneous	
V01	Endocrine disorder, specify addison's disease
V02	Death
V03	Lipodystrophy
V04	Offspring with congenital abnormality
V05	Surgical operation, specify
V06	Trauma, sprain, fracture

Immune Recovery Syndrome (TB)	
Z99	IRS (Immune Recovery Syndrome) from TB, specify (lymph node etc.)

HIV-NAT

Concomitant Medication Code

1.Analgesics/ Antipyretics/ Antireumatic	
Analgesics, miscellaneous	
1001	Floctafenine
1002	Metamizole
1003	Paracetamol
1004	Tramadol
	Narcotic
1011	Other nacotic, specify Codeine, morphine, pethidine
Nonsteriodal anti inflammatory (NSAID)	
1021	Diclofenac
1022	Ibuprofen
1023	Indomethacin
1024	Mefenamic
1025	Naproxen
1026	Piroxicam
1027	Tenoxicam
1028	Other NSAID, specify
Salicylate	
1031	Acetylsalicylic acid
Analgesic, topical	
1041	Methylsalicylate
1042	Mucopolysaccharidepolysulfate
1043	Unknown topical analgesic, specify
1044	Other topical analgesic, specify
Analgesic, urinary	
1051	Phenazopyridine
	Antigout agents
1061	Allopurinol
1062	Colchicine
Muscle relaxant	
1071	Paracetamol+carisoprodol
1072	Paracetamol+orphenadrine
1073	Tolperisone
Selective cyclooxygenase-2 inhibitor	
1081	Celecoxib
1082	Rofecoxib
Unknown, other	
1091	Unknown analgesic
1092	Other analgesic, specify

2. Anti allergic (anaphylaxis) respiratory	
Antihistamines/ decongestants and combination	
2001	Acrivastine
2002	Brompheniramine maleate
2003	Cetirizine
2004	Chlorpheniramine
2005	Diphenhydramine
2006	Epinefrine
2007	Fexofenadine
2008	Hydroxizine
2009	Levocabastine
2010	Loratadine
2011	Mebhydrolin
2012	Pseudo-ephedrine
2013	Tripolidine+pseudoephedrine(Actifed)
2014	Unknown antihistamine
2015	Other antihistamine, specify
Antitasive/ mucolitic agents	
2021	Acetylcysteine
2022	Ambroxal
2023	Bromhexine
2024	Carbocysteine
2025	Codeine+glycerylguiacolate+phenylpropanol amine
2026	Codeine+promethazine
2027	Dextromethophan
Bronchodilators	
2031	Ipratropium+fenoterol
2032	Salbutamol
2033	Salmeterol
2034	Terbutaline sulphate
2035	Theophylline
2036	Unknown bronchodilator
2037	Other bronchodilator, specify procoterel
Nonsteriodal anti inflammatory	
2041	Ketotifen
2042	Pizotifen
2043	Sodium chromoglycate
Anti-inflammatory steroids and combinations	
2051	Beclomethasone
2052	Beclomethasone+salbutamal
2053	Budesonide
2054	Dexamethasone
2055	Fluticasone
2056	Prednisolone
Combibation cold-preparations	
2061	Paracetamol 500mg+chlorpheniramine 2mg+phenylpropanolamine 15mg (Tiffy)
2062	Paracetamol 300mg+chlorpheniramine 1mg+phenylpropanolamine 12.5mg (Decolgen)
Unknown, other	
2071	Unknown anti allergic
2072	Other anti allergic, specify (brompheniramine 12mg+phenyleprine 15mg+phenylpropanolamine 45mg), (brompheniramine 6mg+phenyleprine 7.5mg+phenylpropanolamine 17.5mg)

3. Anti malarial drug	
3001	Chloroquine
3002	Halofantrine
3003	Mefloquine
3004	Primaquine
3005	Quinine
3006	Other anti malarial drug

4. Anti convulsant	
Antiepileptic	
4001	Carbamzepine
4002	Phenobarbital
4003	Phenytoin
4004	Valproic acid
4005	Unknown anti convulsant, specify
4006	Other anti convulsant, specify

HIV-NAT

Concomitant Medication Code

5. Tranquilizer/ hypnotics	
Anti depressants	
5001	Amitriptyline
5002	Doxepin
5003	Unknown anti depressants
5004	Other anti depressant, specify
Benzodiazepine	
5011	Alprazolam
5012	Clorazepate
5013	Clobazam
5014	Diazepam
5015	Flunitrazepam
5016	Lorazepam
5017	Midazolam
5018	Temazepam
5019	Triazolam
5020	Other benzodiazepin, specify chlordiazepoxide
Anti psychotics	
5031	Chlorpromazine
5032	Haloperidol
5033	Other antipsychotic, specify Fluxotine, fluvoxamine, paroxtine, serraline

6. Anti helminthics	
6001	Albendazone
6002	Levamisole
6003	Mebendazole
6004	Niclosamine
6005	Thiabendasole
6006	Unknown anti helminthic
6007	Other anti helminthic, specify

7. Anti bacterials	
Beta lactam antibiotics	
7001	Amoxycillin
7002	Amoxycillin+clavulinate
7003	Ampicillin
7004	Cephalosporin, specify Cefalexin, cefaclor, cefazolin, flucloxacillin
7005	Cloxacillin, dicloxacillin, flucloxacillin
7006	Penicillin(benzathine, benzyl, procaine)
Macrolides	
7011	Azithrimycin
7012	Clarithromycin
7013	Clindamycin
7014	Erythromycin
7015	Midecamycin
7016	Roxithromycin
Aminoglycosides	
7021	Amikacin
7022	Gentamycin
	Quinolones
7031	Ciprofloxacin
7032	Diiodohydroxyquinoline+furazolidon
7033	Norfloxacin
7034	Ofloxacin
Tetracyclines	
7041	Doxycycline
7042	Tetracycline
Sulfonamides	
7051	Co-trimoxazole
7052	Dapsone
Nitroimidazoles	
7061	Metronidazole
7062	Tinidazole
Antimicrobials, topical	
7071	Bactracin+neomycin
7072	Mupirocin
7073	Silver sulfadiazine
7074	Other topical antimicrobacterial, specify
Other antimicrobials	
7081	Atovaquone
7082	Chloramphenicol
7083	Clindamycin
7084	Nitrofurantoin
7085	Spectinomycin
7086	Trimethoprim
Unknown other	
7091	Unknown antibacterials
7092	Other antibacterial, specify Diiodohydroxyquinoline+furazolidon

8. TB and leprosy drug	
8001	Clofazimine
8002	Ethambutol
8003	Isoniazid
8004	Pyrazinamide
8005	Rifampicin
8006	Streptomycin
8007	Other TB/leprosy drug, specify

9. Anti fungal drug	
9001	Amphotericin B
9002	Clotrimazole troches
9003	Fluconazole
9004	Flucytosine
9005	Griseofulvin
9006	Itraconazole
9007	Ketoconazole
9008	Miconazole
9009	Nytatin
9010	Nytatin+diiodohydroxyquin+benzalkonium
9011	Other anti fungal, specify

10. Other anti protozoals	
10001	Pentamidine inhalation
10002	Pentamidine parenteral
10003	Pyrimethamine
10004	Sulfadiazine
10005	Sulfadoxine-pyrimethamine
10006	Other anti protozoals, specify

11. Antiviral	
11001	Acyclovir
11002	Ganciclovir
11003	Unknown antiviral
11004	Other antiviral, specify Alpha-interferon, beta-interferon, gamma-interferon, cytarabine, foscarnet, ribavirin

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Concomitant Medication Code

12. Anti neoplastic	
12001	Other anti neoplastic, specify Adriamycin, bleomycin, cyclophosphamide, daunorubicin, doxorubicin, vinblastine, vincristine, vindesine

13. Gastrointestinal	
Anti emetic	
13001	Domoperidone
13002	Metoclopramide
13003	Promethazine
13004	Prochlorperazine
13005	Unknown anti emetic
13006	Other anti emetic, specify
Peptic ulcer/ gastro-oesophageal reflux	
13011	Aluminium hydroxide
13012	Cimetidine
13013	Colloidal bismuth
13014	Combined antacid
13015	Famotidine
13016	Lansoprazole
13017	Magnesium hydroxide
13018	Misoprostol
13019	Omeprazole
13020	Ranitidine
13021	Sucralfate
13022	Unknown peptic ulcer/GOR medication
13023	Other peptic ulcer/GOR medication, specify
Anti motility	
13031	Diphenoxylate
13032	Loperamide
13033	Unknown anti motility
13034	Other ant motility, specify
Laxatives	
13041	Bisacodyl
13042	Ispaghula husk
13043	Psylium
13044	Unknown laxatives
13045	Other laxatives, specify
Anti spasmodic	
13051	Hyoscine
13052	Hyocine+paracetamol
13053	Unknown anti spasmodic
13054	Other anti spasmodic, specify Dicyclomine, meberverine, drotaverine, clidinium+chlordiazepoxide, oxyphencyclimine
Unknown, other	
13061	Unknown GI
13062	Other GI, specify Local anti hemorrhoidals, cisapride, antiflatulants

14. Anti vertigo/ anti emetics	
14001	Betahistine
14002	Cinnarazine
14003	Dimenhydrinate
14004	Unknown anti vertigo
14005	Other anti vertigo/ anti emetics, specify

15. Recreational	
15001	Amphetamine
15002	Cocaine
15003	Crack cocaine
15004	Heroin
15005	Methadone
15006	Opium
15007	Other recreational drug, specify

16. Vitamins/ minerals/Nutritions	
Vitamins/ minerals	
16001	FBC
16002	Folic acid
16003	Folinic acid
16004	Multivitamin/ minerals
16005	Multivitamin/ mineral/ iron
16006	Vitamin A
16007	Vitamin B6
16008	Vitamin B12
16009	Vitamin B complex
16010	Vitamin C
16011	Vitamin E
16012	Unknown vitamin
16013	Other vitamin, specify
16021	Herbs/ Nutritions
16031	ORS
16032	IV-fluid
16041	Unknown vitamin/ mineral
16042	Other vitamins/ minerals, specify

17. Ear/ nose/ mouth/ throat/ eye	
Ear, nose, mouth, throat	
17001	Antazoline+tetrahydrozoline
17002	Lozenge
17003	Unknown ENT
17004	Other ENT, specify
Eye	
17011	Dexamethasone+framycetin+gramicidin
17012	Unknown eye
17013	Other eye, specify

18. Dermatological	
Topical steroids	
18001	Betamethasone
18002	Clobetasol
18003	Desoxymethasone
18004	Fluocinolone
18005	Hydrocortisone
18006	Mometasone
18007	Triamcinolone acetonide cream
Combination steroid and anti inflammatory/anti infective	
18011	Betamethasone+clioquinol
18012	Betamethasone+gentamicin+tolnaffate+ lodochlorhydroxyquin
18013	Betamethasone+neomycin
18014	Betamethasone+salicylic acid
18015	Isoconazole+difluocortolone
18016	Miconazole+hydrocortisone
18017	Triamcinolone+nystatin+neomycin
Anti acne	
18021	Benzoyl peroxide

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Concomitant Medication Code

18022	Tretinoin (vitamin A acid)
18023	Unknown anti acne
18024	Other anti avne, specify Calamine, lindane, salicylic acid+lactic acid

19. Vaccine/ antisera	
19001	Unknown vaccine
19002	Other vaccine, specify Tetanus toxiod, hepatitis A, hepatitis B Ig, rabies Ig

20. Transfusions	
20001	Whole blood
20002	Red cells
20003	Platelets
20004	Other transfusion, specify

21. Hormones/ contraceptives	
21001	Cyproterone+ethinylestradiol
21002	Depomedroxyprogesterone acetate
21003	Levonorgestrel
21004	Other oral contraceptives, specify

22. Metabolism	
Hypoglycemic agents	
22001	Insulin
22002	Oral hypoglycemic agents
Antihyperlipidemic agents	
22011	Atorvastatin
22012	Fenofibrate
22013	Gemfibrozil
22014	Other lipid lowering agents
22015	Thyroid/ antithyroid agents
Unknown, other	
22021	Unknown agents affecting metabolism
22022	Other agents affecting metabolism, specify

23. cardiovascular	
Anti-hypertension	
23001	Angiotensin converting enzyme inhibitor
23002	Beta-blockers
23003	Calcium channel blockers
23004	Diuretics
Unknown, other	
23011	Unknown cardiovascular agents
23012	Other cardiovascular agents, specify

8. TB and leprosy drug (NEW DRUG)	
8008	RIMSTAR

APPENDIX B
PATIENT INFORMATION SHEET AND INFORMED CONSENT FORM

เอกสารแจ้งข้อมูลสำหรับอาสาสมัครโครงการวิจัย

ชื่อโครงการวิจัย: ผลการรักษาด้วยยาต้านไวรัสสูตรที่ประกอบด้วยนอนนิวคลิโอไซด์รีเวอร์สทรานสคริปเตทอินฮิบิเตอร์ในหญิงหลังคลอดที่เคยได้รับยาต้านไวรัสซิโดวูดีนร่วมกับเนวิราปีนครั้งเดียวขณะคลอดหรือได้รับยาต้านไวรัสสูตรสามตัวขณะตั้งครรภ์ในโครงการคืนชีวิตให้พ่อแม่เพื่อลูกน้อยที่ปลอดเอดส์ ประเทศไทย

ผู้สนับสนุนการวิจัย: บัณฑิตวิทยาลัย คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล และ โครงการคืนชีวิตให้พ่อแม่เพื่อลูกน้อยที่ปลอดเอดส์ ประเทศไทย

ผู้ทำวิจัย: น.ส.ธิดารัตน์ จุพิมาย นักศึกษาปริญญาโท สาขาวิชาวิทยาการระบาด
ภาควิชาเวชศาสตร์ป้องกันและสังคม
คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล
ที่อยู่: HIV-NAT ศูนย์วิจัยโรคเอดส์ สภากาชาดไทย
104 ถนนราชดำริ ปทุมวัน กรุงเทพฯ 10330
โทรศัพท์: 0 2255 7334 ถึง 5 ต่อ 127
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อาจารย์ที่ปรึกษาหลัก:	ผศ.นพ.วิชัย เตชะสาธิต	ภาควิชาเวชศาสตร์ป้องกันและสังคม คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล 2 ถนนพรานนก แขวงศิริราช เขตบางกอกน้อย กรุงเทพฯ 10700 โทรศัพท์: 0 2419 7388 ต่อ 447
อาจารย์ที่ปรึกษาร่วม:	พญ.นิตยา ภานุภาค พึ่งพาพงศ์	ศูนย์วิจัยโรคเอดส์ สภากาชาดไทย 104 ถนน ราชดำริ ปทุมวัน กรุงเทพฯ 10330 โทรศัพท์: 0 2553 0996 ถึง 7
	ดร.สุณี ศิริวิชยกุล	ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ถนนพระราม 4 ปทุมวัน กรุงเทพฯ 10330 โทรศัพท์: 0 2256 4579
	ดร.สตีเฟน เคอร์	HIV-NAT ศูนย์วิจัยโรคเอดส์ สภากาชาดไทย 104 ถนน ราชดำริ ปทุมวัน กรุงเทพฯ 10330 โทรศัพท์: 0 2255 7334 ถึง 5 ต่อ 112

เรียน ผู้เข้าร่วมโครงการวิจัยทุกท่าน

เอกสารนี้เป็นเอกสารที่แสดงข้อมูลเพื่อใช้ประกอบการตัดสินใจของท่านในการเข้าร่วมการศึกษาวิจัย อย่างไรก็ตามก่อนที่ท่านตกลงเข้าร่วมการศึกษาดังกล่าว ขอให้ท่านอ่านเอกสารฉบับนี้อย่างละเอียด เพื่อให้ท่านได้ทราบถึงเหตุผลและรายละเอียดของการศึกษาวิจัยครั้งนี้ หากท่านมีข้อสงสัยใดๆ เพิ่มเติม กรุณาซักถามจากทีมงานของผู้ทำวิจัย หรือผู้ร่วมในโครงการวิจัยซึ่งจะเป็นผู้สามารถให้ความกระจ่างแก่ท่านได้

ท่านสามารถขอคำแนะนำในการเข้าร่วมโครงการวิจัยนี้จากครอบครัว เพื่อน หรือแพทย์ประจำตัวของท่านได้ ถ้าท่านตัดสินใจแล้วว่าจะเข้าร่วมโครงกการวิจัยนี้ ขอให้ท่านเซ็นชื่อยินยอมในเอกสารแสดงความยินยอมของโครงการวิจัยนี้

วัตถุประสงค์ของการศึกษา

วัตถุประสงค์หลักจากการศึกษาในครั้งนี้คือเพื่อประเมินผลการรักษาด้วยยาต้านไวรัสสูตรที่มี ยาต้านไวรัสเนวิราปีน หรืออีฟาไวเรนซ์ร่วมด้วย ในหญิงติดเชื้อเอชไอวีหลังคลอดที่เคยได้รับยาต้านไวรัสซิโดวูดีนร่วมกับเนวิราปีนครั้งเดียวขณะคลอดเพื่อป้องกันการติดเชื้อจากแม่สู่ลูก เปรียบเทียบกับหญิงที่ได้รับยาต้านไวรัสสูตร 3 ตัวขณะตั้งครรภ์ โดยมีจำนวนผู้เข้าร่วมโครงการวิจัยประมาณ 130 คน

<u>วิธีการที่เกี่ยวข้องกับการวิจัย</u>

หากท่านมีคุณสมบัติที่เหมาะสมและยินยอมเข้าร่วมในโครงการวิจัยนี้ ผู้วิจัยจะทำการส่งตัวอย่างเลือดของท่านที่เคยเก็บไว้ในโครงการคืนชีวิตให้พ่อแม่เพื่อลูกน้อยที่ปลอดเอดส์ ณ เวลาหลังคลอด ก่อนเริ่มยาต้านไวรัสสูตร 3 ตัวหลังคลอด เดือนที่ 6 และเดือนที่ 12 หลังเริ่มยาต้านไวรัสสูตร 3 ตัว เพื่อตรวจหาปริมาณเชื้อไวรัสเอชไอวีในเลือด หากพบว่าตัวอย่างเลือดใดๆ มีปริมาณเชื้อไวรัสเอชไอวีสูงมากกว่า 1,000 ต่อมิลลิลิตร จะส่งตัวอย่างเลือดนั้นๆ เพื่อตรวจเชื้อดื้อยาต้านไวรัสต่อไป

ผู้วิจัยจะทำการรวบรวมข้อมูลทางการแพทย์ และการมาตรวจตามนัดในโครงการคืนชีวิตให้พ่อแม่เพื่อลูกน้อยที่ปลอดเอดส์ที่มีอยู่แล้วของท่าน ในระหว่างการตั้งครรภ์ หลังคลอดจนกระทั่งครบปีแรกภายหลังที่ท่านรับประทานยาต้านไวรัสอย่างต่อเนื่อง ทั้งนี้ได้แก่ข้อมูลการรับประทานยาต้านไวรัส การเปลี่ยนสูตรยาต้านไวรัส ความสม่ำเสมอในการรับประทานยาต้านไวรัส อาการข้างเคียงที่เกิดจากการรับประทานยาต้านไวรัส อาการเจ็บป่วยต่างๆ ที่เกิดขึ้นกับท่านตลอดจนการรักษาอาการเจ็บป่วยนั้นๆ และการรับประทานยาอื่นๆ ที่ไม่ใช่ยาต้านไวรัส แล้วนำมาวิเคราะห์เพื่อประเมินผลการรักษา ณ เวลา 6 เดือน และ 1 ปี ภายหลังที่ท่านรับประทานยาต้านไวรัสสูตร 3 ตัวที่มียาต้านไวรัสเนวิราปีน หรืออีฟาไวเรนซ์ร่วมด้วย

<u>ความเสี่ยงที่อาจได้รับ</u>

โครงการนี้ไม่มีการทำหัตถการใดๆ เพิ่มเติมกับอาสาสมัคร ทั้งนี้ผู้ทำวิจัยจะนำเอาข้อมูลของท่านที่มีอยู่แล้วในการเข้าร่วมโครงการคืนชีวิตให้พ่อแม่เพื่อลูกน้อยที่ปลอดเอดส์มาวิเคราะห์ และนำตัวอย่างเลือดที่เก็บไว้มาวิเคราะห์เพิ่มเติม จึงไม่มีความเสี่ยงใดๆ เกิดขึ้นกับท่านได้

<u>ประโยชน์ที่อาจได้รับ</u>

ในการเข้าร่วมโครงการนี้ท่านอาจจะไม่ได้รับประโยชน์โดยตรงจากการเข้าร่วมโครงการ แต่ผลการศึกษาทั้งหมดจะนำไปสู่การพัฒนานโยบายการให้ยาต้านไวรัสเพื่อป้องกันการติดเชื้อจากแม่สู่ลูกในระดับประเทศได้โดยมีเป้าหมายเพื่อประสิทธิผลที่ดีที่สุดในการลดการติดเชื้อในทารก พร้อมไปกับการป้องกันการเกิดเชื้อดื้อยาที่ไม่จำเป็นในหญิงหลังคลอดได้

ผลการตรวจหาปริมาณเชื้อไวรัสเอชไอวีในเลือด รวมถึงผลการตรวจเชื้อดื้อยาต้านไวรัส จากตัวอย่างเลือดของท่าน จะถูกส่งต่อไปยังแพทย์ผู้ทำการดูแลรักษาท่านอยู่ ซึ่งอาจจะมีประโยชน์ในการใช้ประกอบการวางแผนดูแลรักษาท่านต่อไป

ค่าใช้จ่ายสำหรับอาสาสมัครที่เข้าร่วมโครงการวิจัย

โครงการนี้ไม่มีค่าตอบแทนเป็นเงินให้แก่ผู้เข้าร่วมโครงการแต่อย่างใด

การเข้าร่วมและการสิ้นสุดการเข้าร่วมโครงการวิจัย

การเข้าร่วมโครงการวิจัยครั้งนี้เป็นไปโดยความสมัครใจ หากท่านไม่สมัครใจจะเข้าร่วมการศึกษาแล้ว ท่านสามารถถอนตัวได้ตลอดเวลา การขอถอนตัวออกจากโครงการวิจัยจะไม่มีผลต่อการดูแลรักษาโรคของท่านแต่อย่างใด

การปกป้องรักษาข้อมูลของอาสาสมัคร

ข้อมูลที่อาจนำไปสู่การเปิดเผยตัวของท่าน จะได้รับการปกปิดและจะไม่เปิดเผยแก่สาธารณชน ในกรณีที่ผลการวิจัยได้รับการตีพิมพ์ ชื่อและที่อยู่ของท่านจะต้องได้รับการปกปิดอยู่เสมอ โดยจะใช้เฉพาะรหัสประจำโครงการวิจัยของท่าน

จากการลงนามยินยอมของท่าน ผู้ทำวิจัย และผู้สนับสนุนการวิจัยมีสิทธิ์สามารถเข้าไปตรวจสอบบันทึกข้อมูลทางการแพทย์ของท่านได้ตลอดเวลาแม้สิ้นสุดโครงการวิจัยแล้วก็ตาม หาก

ท่านต้องการยกเลิกการให้สิทธิ์ดังกล่าว ท่านสามารถเขียนบันทึกขอยกเลิกการให้คำยินยอม โดยส่งไปที่

นางสาวธิดารัตน์ จุพิมาย
ศูนย์วิจัยโรคเอดส์ สภากาชาดไทย
เลขที่ 104 ถนน ราชดำริ ปทุมวัน กรุงเทพฯ 10330

หากท่านขอยกเลิกการให้คำยินยอมหลังจากที่ท่านได้เข้าร่วมโครงการวิจัยแล้ว ข้อมูลส่วนตัวของท่านจะไม่ถูกบันทึกเพิ่มเติม อย่างไรก็ตามข้อมูลอื่นๆ ของท่านอาจถูกนำมาใช้เพื่อประเมินผลการวิจัย

จากการลงนามของท่าน ผู้ทำการวิจัยสามารถบอกรายละเอียดของท่านที่เกี่ยวกับการเข้าร่วมโครงการวิจัยนี้แก่แพทย์ผู้รักษาท่านได้

สิทธิ์ของผู้เข้าร่วมในโครงการวิจัย

ในฐานะที่ท่านเป็นผู้เข้าร่วมในโครงการวิจัยท่านจะมีสิทธิ์ดังต่อไปนี้

1. ท่านจะได้รับทราบถึงลักษณะและวัตถุประสงค์ของโครงการวิจัยในครั้งนี้

2. ท่านจะได้รับการอธิบายเกี่ยวกับระเบียบวิธีการวิจัยทางการแพทย์ในการวิจัยครั้งนี้
3. ท่านจะได้รับการอธิบายถึงความเสี่ยงและความไม่สบายที่จะได้รับจากการวิจัย
4. ท่านจะได้รับการอธิบายถึงประโยชน์ที่ท่านอาจจะได้รับจากการวิจัย
5. ท่านจะมีโอกาสซักถามเกี่ยวกับงานวิจัยหรือขั้นตอนที่เกี่ยวข้องกับงานวิจัย
6. ท่านจะได้รับทราบว่าการยินยอมเข้าร่วมในโครงการวิจัยนี้ ท่านสามารถขอถอนตัวจากโครงการเมื่อไดก็ได้ โดยผู้เข้าร่วมโครงการวิจัยสามารถขอถอนตัวจากโครงการโดยไม่ได้รับผลเสียใดๆ ทั้งสิ้น
7. ท่านจะได้รับสำเนาเอกสารใบยินยอมที่มีทั้งลายเซ็นและวันที่
8. ท่านจะได้โอกาสในการตัดสินใจว่าจะเข้าร่วมในโครงการวิจัยหรือไม่ก็ได้ โดยปราศจากการใช้อิทธิพลบังคับข่มขู่ หรือการหลอกลวง

หากท่านมีข้อปัญหาทางจริยธรรมการวิจัย สามารถติดต่อได้ที่ คณะกรรมการจริยธรรมการวิจัย คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิยาลัย ตึกอานันทมหิดลชั้น 3 โรงพยาบาลจุฬาลงกรณ์ ถนนพระราม 4 ปทุมวัน กรุงเทพฯ 10330 โทร 022564455 ต่อ 14, 15 ในเวลาราชการ

ขอขอบคุณในการร่วมมือของท่านมา ณ ที่นี้

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Version dated: 23 กันยายน 2551

เอกสารแสดงความยินยอมเข้าร่วมในโครงการวิจัย

การวิจัยเรื่อง ผลการรักษาด้วยยาต้านไวรัสสูตรที่ประกอบด้วย นอนนิวคลิโอไซด์รีเวอร์สทรานสคริปเตทอินฮิบิเตอร์ในหญิงหลังคลอดที่เคยได้รับยาต้านไวรัสซิโดวูดีนร่วมกับเนวิราปีนครั้งเดียวขณะคลอดหรือได้รับยาต้านไวรัสสูตรสามตัวขณะตั้งครรภ์ ในโครงการคืนชีวิตให้พ่อแม่เพื่อลูกน้อยที่ปลอดเอดส์ ประเทศไทย

วันให้คำยินยอม วันที่.....เดือน.....พ.ศ.....

ข้าพเจ้า นาง/นางสาว.....ได้อ่านรายละเอียดจากเอกสารข้อมูลสำหรับผู้เข้าร่วมโครงการวิจัยที่แนบมาฉบับวันที่ 23 กันยายน 2551 และข้าพเจ้ายินยอมเข้าร่วมโครงการวิจัยโดยสมัครใจ

ข้าพเจ้าได้รับสำเนาเอกสารแสดงความยินยอมเข้าร่วมในโครงการวิจัยที่ข้าพเข้าได้ลงนาม และวันที่พร้อมด้วยเอกสารข้อมูลสำหรับผู้เข้าร่วมโครงการวิจัย ทั้งนี้ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยถึงวัตถุประสงค์ของการวิจัย ระยะเวลาของการทำวิจัย วิธีการวิจัย ความเสี่ยงที่อาจเกิดขึ้นจากการวิจัย รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัย ข้าพเจ้ามีเวลาและโอกาสเพียงพอในการซักถามข้อสงสัยจนมีความเข้าใจอย่างดีแล้ว โดยผู้วิจัยได้ตอบคำถามต่างๆ ด้วยความเต็มใจไม่ปิดบังซ่อนเร้นจนข้าพเจ้าพอใจ

ข้าพเจ้ามีสิทธิที่จะบอกเลิกเข้าร่วมในโครงการวิจัยเมื่อใดก็ได้ โดยไม่จำเป็นต้องแจ้งเหตุผล และการบอกเลิกการเข้าร่วมการวิจัยนี้ จะไม่มีผลต่อการรักษาโรค หรือสิทธิอื่นๆ ที่ข้าพเจ้าพึงได้รับต่อไป

ผู้วิจัยรับรองว่าจะเก็บข้อมูลส่วนตัวของข้าพเจ้าเป็นความลับ และจะเปิดเผยได้เฉพาะเมื่อได้รับการยินยอมจากข้าพเจ้าเท่านั้น บุคคลอื่นในนามของผู้สนับสนุนการวิจัย คณะกรรมการพิจารณาจริยธรรมการวิจัยหรือผู้ได้รับอำนาจมอบหมายสามารถเข้ามาตรวจและประมวลข้อมูลของผู้เข้าร่วมวิจัย ทั้งนี้จะต้องกระทำไปเพื่อวัตถุประสงค์เพื่อตรวจสอบความถูกต้องของข้อมูลเท่านั้น โดยการตกลงที่จะเข้าร่วมการศึกษานี้ข้าพเจ้าได้ให้คำยินยอมที่จะให้มีการตรวจสอบข้อมูลประวัติทางการแพทย์ ของผู้เข้าร่วมวิจัยได้

ผู้วิจัยรับรองว่าจะไม่มีการเก็บข้อมูลใดๆ ของผู้เข้าร่วมวิจัยเพิ่มเติม หลังจากข้าพเจ้าขอยกเลิกการเข้าร่วมโครงการวิจัยและต้องการให้ทำลายเอกสารและ/หรือ ตัวอย่างที่ใช้ตรวจสอบทั้งหมดที่สามารถสืบค้นถึงตัวข้าพเจ้าได้

ข้าพเจ้าเข้าใจว่าข้าพเจ้ามีสิทธิ์ที่จะตรวจสอบหรือแก้ไขข้อมูลส่วนตัวของข้าพเจ้าและสามารถเลิกการให้สิทธิในการใช้ข้อมูลส่วนตัวของข้าพเจ้าได้โดยต้องแจ้งให้ผู้วิจัยรับทราบ

ข้าพเจ้าได้ตระหนักดีว่าข้อมูลในการวิจัยรวมถึงข้อมูลทางการแพทย์ที่ไม่มีการเปิดเผยชื่อจะผ่านกระบวนการต่างๆ เช่นการเก็บข้อมูล การบันทึกข้อมูลในคอมพิวเตอร์ การตรวจสอบ การวิเคราะห์ และการรายงานเพื่อวัตถุประสงค์ทางวิทยาศาสตร์ รวมทั้งการใช้ข้อมูลทางการแพทย์ในอนาคตหรือการวิจัยทางด้านเภสัชภัณฑ์เท่านั้น

ข้าพเจ้ายินดีลงนามในเอกสารยินยอมนี้เพื่อเข้าร่วมการวิจัยด้วยความเต็มใจ

.....ลงนามผู้ยินยอม

(.....) ชื่อผู้ยินยอมตัวบรรจง

วันที่.....เดือน.....พ.ศ.....

ข้าพเจ้าได้อธิบายถึงวัตถุประสงค์ของการวิจัย วิธีการวิจัย ความเสี่ยงที่อาจเกิดขึ้นจากการวิจัย รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัยอย่างละเอียด ให้ผู้เข้าร่วมในโครงการวิจัยตามนามข้างต้นได้รับทราบและมีความเข้าใจดีแล้ว พร้อมลงนามในเอกสารแสดงความยินยอมด้วยความเต็มใจ

.....ลงนามผู้ทำวิจัย

(.....) ชื่อผู้ทำวิจัยตัวบรรจง

วันที่.....เดือน.....พ.ศ.....

.....ลงนามพยาน

(.....) ชื่อพยานตัวบรรจง

วันที่.....เดือน.....พ.ศ.....

APPENDIX C
INSTITUTE REVIEW BOARD
CERTIFICATE OFAPPROVAL

2 PRANNOK Rd. BANGKOKNOI
BANGKOK 10700

Tel. (662) 4196405-6
FAX (662) 4196405

MAHIDOL UNIVERSITY
Since 1888
Siriraj Institutional Review Board

Certificate of Approval

COA no.Si 165/2009

Protocol Title : Response to Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-based antiretroviral regimens in postpartum women who exposed to zidovudine (AZT) and single-dose nevirapine (sd-NVP) or Highly Active Anti-Retroviral Therapy (HAART) during pregnancy from MTCT-Plus programs, Thailand

Protocol number : 684/2551(EC1)

Principal Investigator/Affiliation : Miss Thidarat Jupimai / Department of Preventive and Social Medicine
Faculty of Medicine Siriraj Hospital, Mahidol University

Research site : Faculty of Medicine Siriraj Hospital

Approval includes :

1. SIRB Submission Form
2. Proposal Version 1.1 date 23 September 2008
3. Participant Information Sheet
4. Informed Consent Form
5. Case Record Form Version 1.1 date 28-Dec-2008

Approval date : April 3, 2009

Expired date : April 2, 2010

This is to certify that Siriraj Institutional Review Board is in full Compliance with International Guidelines For Human Research Protection such as the Declaration of Helsinki, the Belmont Report, CIOMS Guidelines and the International Conference on Harmonization in Good Clinical Practice (ICH-GCP).

Prof. Jariya Lertakyamanee, M.D.
Chairperson

April 10, 2009
date

(Clin. Prof. Teerawat Kulthanan, M.D.)
Dean of Faculty of Medicine Siriraj Hospital

April 21, 2009
date

หน่วยพิมพ์โรงพยาบาลศิริราช 2341 / 3,000 แผ่น / ก.ย 51 / Mat. 10023252

COA No. 743/2008
IRB No. 344/51

INSTITUTIONAL REVIEW BOARD
Faculty of Medicine, Chulalongkorn University
1873 Rama 4 Road, Patumwan, Bangkok 10330, Thailand, Tel 662-256-4455 ext 14, 15

Certificate of Approval

The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, is in full compliance with the International guidelines for human research protection as Declaration of Helsinki, The Belmont Report, CIOMS Guideline and International Conference on Harmonization in Good Clinical Practice (ICH-GCP)

Study Title : Response to Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-based antiretroviral regimens in postpartum women who exposed to zidovudine (AZT) and single-dose nevirapone (sd-NVP) or Highly Active Anti-Retroviral Therapy (HAART) duringPregnancy from MTCT-Plus programs, Thailand

Study Code : -

Study Center : Chulalongkorn University

Principal Investigator : Miss Thidarat Jupimai

Document Reviewed :

1. Research Proposal version 1.1 date 23 September 2008
2. Thai Information sheet for research volumteer version date 23 September 2008
3. Thai Informed Consent Form version date 23 September 2008
4. Case record form (CRF) version 1.0 date 1 June 2008
5. Investigator's curriculum Vitac

Signature: ..... **Signature:** .....
(Emeritus Professor Anek Aribarg, M.D.)
Chairman of
The Institutional Review Board

(Professor Areerat Suputtitada,M.D.)
Committee and Secretary of
The Institutional Review Board

Date of Approval : October 9, 2008

Approval Expire Date : October 9, 2009

Approval is granted subject to the following conditions: (see back of this Certificate)

BIOGRAPHY

NAME	Miss Thidarat Jupimai
DATE OF BIRTH	20 January 1979
PLACE OF BIRTH	Prachuap Khiri Khan, Thailand
INSITITUTIONS ATTENDED	Srinakharinwirot University, 1997-2001 : Bachelor of Science (2nd Hon.), Health Education Mahidol University, 2007-2010 : Master of Science (Epidemiology)
SCHOLARSHIPS	The Siriraj Graduate Scholarship, 2007 The Siriraj Graduate Thesis Scholarships, 2008
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