ADVERSE EVENTS OF ANTIRETROVIRAL PROPHYLAXIS REGIMEN FOR ELIMINATION AND PREVENTION OF MOTHER-TO-CHILD TRANSMISSION AMONG HIV-EXPOSED INFANTS

Miss Suvaporn Anugulruengkitt

A Dissertation Submitted in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy in Clinical Sciences
Common Course
FACULTY OF MEDICINE
Chulalongkorn University
Academic Year 2018

ผลข้างเคียงของยาต้านไวรัสที่ใช้เพื่อป้องกันการติดเชื้อสำหรับทารกที่คลอดจากมารดาติดเชื้อเอชไอวี

น.ส.สุวพร อนุกูลเรืองกิตติ์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
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Dissertation Title	ADVERSE EVENTS OF ANTIRETROVIRAL PROPHYLAXIS REGIMEN FOR ELIMINATION AND PREVENTION OF MOTHER-TO-CHILD TRANSMISSION AMONG HIV-EXPOSED INFANTS
By	Miss Suvaporn Anugulruengkitt
Field of Study	Clinical Sciences
Thesis Advisor	Associate Professor Thanyawee Puthanakit

Accepted by the FACULTY OF MEDICINE, Chulalongkorn University in Partial Fulfillment of the Requirement for the Doctor of Philosophy

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5874860730 : DOCTOR OF PHILOSOPHY
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Suvaporn Anugulruengkitt : ADVERSE EVENTS OF ANTIRETROVIRAL PROPHYLAXIS REGIMEN FOR ELIMINATION AND PREVENTION OF MOTHER-TO-CHILD TRANSMISSION AMONG HIV-EXPOSED INFANTS. ADVISOR: Assoc. Prof. Thanyawee Puthanakit

Background: Triple-drug antiretroviral prophylaxis of zidovudine (ZDV)/lamivudine (3TC)/nevirapine (NVP) for high risk HIV-exposed neonates is recommended within the Thai national program. However, there are limited data about the safety and drug concentration achieved with this regimen initiated at birth.

Objectives: This study aims to evaluate the safety of this triple drug neonatal prophylaxis regimen and to describe nevirapine concentration levels during the first 4 weeks of life.

Methods: A prospective cohort of HIV-exposed infants was conducted at 5 clinical sites in Thailand. We enrolled 100 high-risk HIV-exposed neonates (maternal HIV RNA >50 copies/mL prior to delivery or received antiretroviral therapy (ART) <12 weeks) who received ZDV/ 3TC twice daily, plus NVP (4 mg/kg/dose) once daily, from birth for 6 weeks, and 100 standard-risk HIV-exposed neonates who received a 4-week regimen of ZDV. Blood tests to assess hematologic and liver toxicities were performed at birth, 1, 2 and 4 months of life. Sparse plasma NVP concentrations were collected at day 1, 2, 7, 14, and 28 and assayed by a validated liquid chromatography-mass spectrometry assay.

Results: From October 2015 to November 2017, 200 infants were enrolled. Median (IQR) gestational age and birth weight were 38 (37-39) weeks and 2,873 (2,590-3,184) g, respectively. Common maternal ART regimens were TDF/3TC or emtricitabine (58%), ZDV/3TC (32%) in combination with efavirenz (50%), ritonavir boosted protease inhibitor (31%). There was no significant difference of adverse events between triple prophylaxis and ZDV alone; percentage of anemia 69.8% vs 66.3%, p=0.46. Median (IQR) hemoglobin level among infants who received triple prophylaxis were 9.9 (9.0-11.4) g/dL, 10.1 (9.3-11.0), and 11.7 (11.0-12.3) at aged 1, 2 and 4 months, respectively, which did not significantly differ between groups. Rate of HIV transmission among definite HIV-exposed high risk infants was 1.7% (95% CI 0.3%-8.9%). NVP concentrations were available from 48 infants (135 samples); median predicted NVP Ctrough were 1.34 mg/L, 2.24, 2.78, 2.20, and 0.81 on days 1, 2, 7, 14, and 28 of life, respectively. All infants maintained NVP concentrations above the proposed prophylactic target

Department: Common Course Student's Signature .....
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Suvaporn Anugulruengkitt

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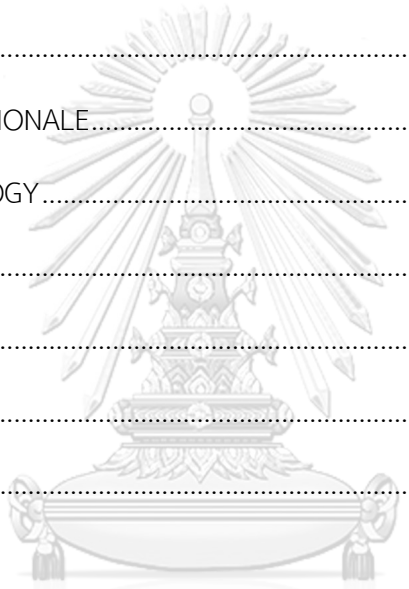

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BACKGROUND AND RATIONALE

Prevention of mother-to-child transmission (PMTCT) of HIV

HIV can be transmitted from an HIV-positive mother to child during pregnancy, intrapartum and postpartum from breastfeeding(1). Therefore, the concept of PMTCT comprises care and treatment for pregnant women, and providing prevention to their infant(2, 3). High coverage of antenatal care is essential to test HIV status in pregnant women and for appropriate treatment. HIV-pregnant women should receive the effective antiretroviral therapy (ART) regardless of CD4 count to reduce HIV viral load in the mother to decrease the risk of transmission to child(4). Neonates born to HIV-infected mother should receive replacement feeding and neonatal antiretroviral prophylaxis(2). Antiretroviral prophylaxis regimen should be efficacious to prevent HIV transmission with the lowest risk from antiretroviral exposure.

PMTCT program in Thailand

Thailand has been very effective at implementing strategies to prevent mother to child transmission of HIV and was the first country in Asia to receive validation from World Health Organization (WHO) for the elimination of vertical transmission with a rate of 1.9% in 2015(2). The program has successfully implemented a nationwide PMTCT programs starting from zidovudine (ZDV) monotherapy for HIV-infected pregnant women in 2000 and move towards triple antiretroviral therapy in all pregnant women regardless of CD4 count in 2010(3). The current HIV prevalence in pregnant Thai women is 0.6%. Estimated number of HIV-exposed live birth was 5,000 per year and approximately 100 newly infected infants per year(5). With a goal to reduce HIV mother to child transmission rates to below 1%, the

current Thai national guideline is focus on intensive intervention among high risk pregnant women. About 25% of HIV-infected pregnant women still have high plasma HIV RNA before delivery mostly due to start antiretroviral therapy (ART) in late pregnancy(6).

The summary of Thai perinatal HIV transmission intervention is shown in Figure 1. The combination of first-line antiretroviral regimen consisting of; tenofovir disoproxil fumarate (TDF) or ZDV, plus lamivudine (3TC) and efavirenz (EFV) are offered to all pregnant women and 4-week of ZDV to exposed neonates. The high risk pregnancy is defined as mothers whose no or short antenatal care, or incident HIV infection during pregnancy, or poor ART adherence, or receiving ART less than 12 weeks prior to delivery, or mother who has detectable viral load (VL) near delivery. These neonates are recommended to receive 6 weeks of ZDV/3TC/nevirapine (NVP)(5).

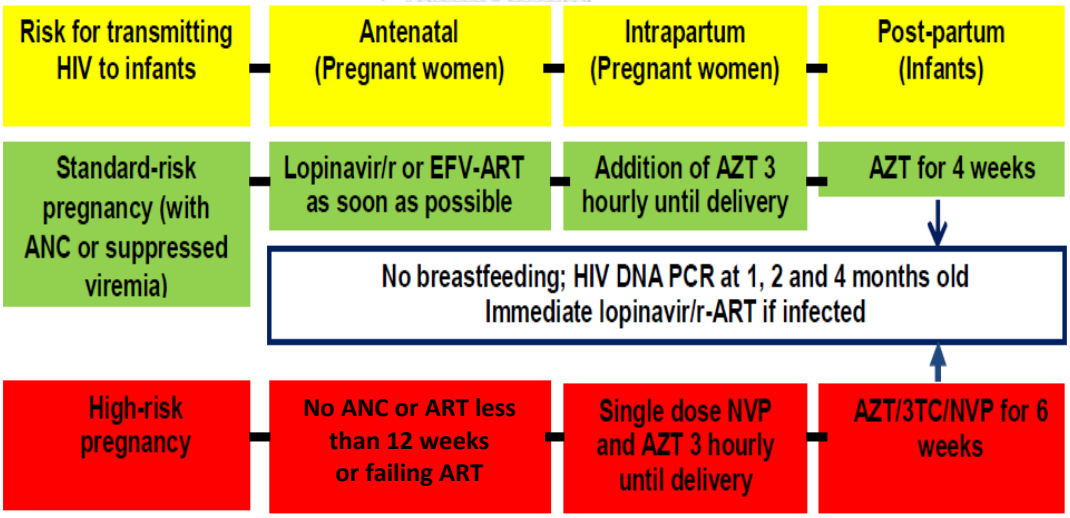


Figure 1. Summary of Thai perinatal HIV transmission intervention guideline 2016 which stratify by risk of HIV transmission

Effects of in utero maternal antiretroviral drugs exposure in neonates

ZDV rapidly crosses the placenta, achieving cord-to-maternal-blood ratios of about 0.80(7). In utero ZDV exposure leads to lower hemoglobin in neonates at birth but without significant clinical impact(8). About EFV, the average EFV cord blood/maternal blood concentration was 0.49(9). No data currently are available about the safety and pharmacokinetic of EFV in neonates. For protease inhibitors, lopinavir crosses the placenta poorly with cord blood/maternal concentration at delivery was only 0.2(10) but hepatotoxicity at birth was reported in 12% of neonates with mild elevated AST (11).

Recently, raltegravir use is increasing as an intensification regimen in late antenatal care pregnant women. The cord blood/maternal plasma concentration ratio of raltegravir was 1.03(12). No infant adverse events were reported to be related to in utero raltegravir exposure(13),(14) except a report from a retrospective study in 31 pregnant women showed mild elevation of transaminases in 35% of neonates(15).

Neonatal antiretroviral prophylaxis regimens for high risk HIV-exposed neonates

Generally, current guidelines recommend combination of antiretroviral neonatal prophylaxis regimens for high risk HIV-exposed neonates in many countries(16-19). WHO recommendation is pending for more data. However, there are differences in antiretroviral dosage and duration of NVP prophylaxis(16-19). The 2016 WHO guidelines recommend dual prophylaxis with ZDV twice daily and nevirapine (NVP) once daily for the first 6 weeks of life(18). The US Department of Health and Human Services (DHHS) guidelines recommend 6 weeks of ZDV plus 3-dose of NVP (weight-band dosing) during the first week of life(17). British HIV Association (BHIVA) guidelines recommend 4 weeks of ZDV and lamivudine (3TC) plus NVP 2 mg/kg once daily during the first week then 4 mg/kg once daily during second week of life(16). In Thailand, a combination of 6-week ZDV/3TC/NVP (4 mg/kg once daily) is recommended as a prophylaxis regimen for these high risk infants aiming for

adequate plasma level of NVP and simplification for nationwide implementation(19). Theoretically, this regimen should provide good efficacy but may also pose more risk of adverse events.

Adverse events of antiretroviral prophylaxis among HIV-exposed neonates

There is a trend of higher rate of adverse events among HIV-exposed neonates who received combination regimen. Anemia occurred more frequently in infants who received three-drug prophylaxis compared to infants who received ZDV alone (63% vs. 39%, p = 0.04) but all anemia in the three-drug prophylaxis group were grade 1 or 2(20). In HPTN 040 study, risk of neutropenia among infants receiving zidovudine/lamivudine/nelfinavir regimen was 27.5% which was significantly higher than infants who received ZDV alone (16.4%) or ZDV plus 3 doses NVP (14.9%)(21). Another concern was hepatotoxicity from NVP. Rates of hepatotoxicity were low (3 from 273, 1.1%) among HIV-exposed infants who received long-course NVP regimens (more than 14 days of NVP)(22). As well as the other study in infant received single dose or 3-dose of NVP during first week of life found that the risk of hepatotoxicity were uncommon, occurring in 2.5%, and did not differ significantly among the group of ZDV monotherapy(21).

Nevirapine concentrations in neonates

NVP is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used worldwide as part of combination antiretroviral prophylaxis and therapy in neonates and infants(23). NVP is rapidly absorbed and transfer across placenta, therefore it is a good drug for PMTCT(24). The proposed plasma target trough NVP concentration for prophylaxis is 0.1 mg/L which is approximately 10 times the *in vitro* IC_{50} of NVP(25, 26). In early studies, a single maternal intrapartum dose of NVP plus a single 2-mg/kg oral dose to the infants at 48–72 hours after birth maintained infants serum concentrations above this threshold throughout the first 7 days

of life(27). Another study in neonates who received 3 doses of NVP during the first week of life, the NVP concentration levels remained more than 0.1 mg/L through the tenth day of life, and then drop below 0.1 mg/L in more than half of neonates by day 14(26). Therefore, the plasma level of NVP is expected to vary during the first 4 weeks of life. Nowadays, multiple dose combination antiretroviral prophylaxis are preferred for infants at high risk of HIV acquisition but there are differences in the recommended dosage and duration of NVP prophylaxis within these recommended regimens for non-breastfed infants(16-19). For HIV treatment, NVP is usually initiated with a lower 'lead-in' dose due to auto-induction of its own metabolism during the first 2 to 4 weeks of treatment(28) but it remains unclear if this is also required for prophylaxis which may need lower dose compare to treatment. Thai national guideline recommends NVP dosing 4 mg/kg once daily without lead-in dose aim to simplify usage of NVP in public health. However, pharmacokinetic data of this dosing regimen is limited. The NVP pharmacokinetic study in neonate is needed to correlate the level with toxicity, especially in the first two weeks with no lead-in dosing. Furthermore, maternal ART such as EFV can transfer across placenta to their infants(9). The metabolism of EFV is predominantly by the cytochrome P450 2B6 (CYP2B6) isoenzyme(29) and as NVP is also metabolized by this enzyme(30) it is possible that EFV passed from the mother could affect NVP concentrations in the neonate.

Objectives

The primary objective of this study is to compare the incidence of adverse events (AE) of 6-week ZDV/3TC/NVP versus 4-week ZDV prophylaxis regimen among non-breastfed HIV-exposed neonates. The secondary objectives are to determine HIV transmission rate and to describe NVP concentrations during the first 4 weeks of life among HIV-exposed high risk neonates who received ZDV/3TC/NVP. Figure 2 showed conceptual

framework of this study. Summary of study procedures and assessment is shown in Figure 3.

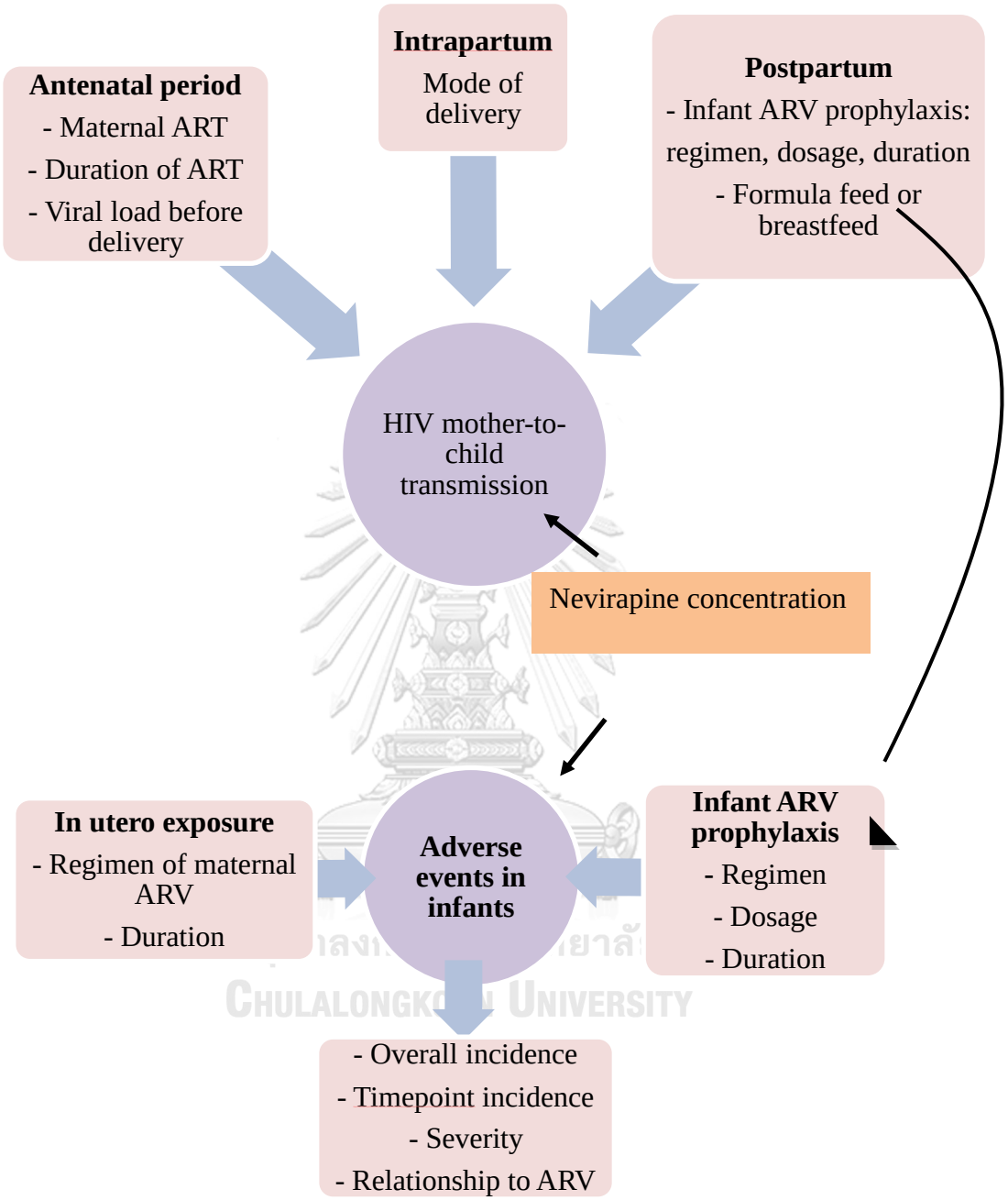


Figure 2. Conceptual framework of the study

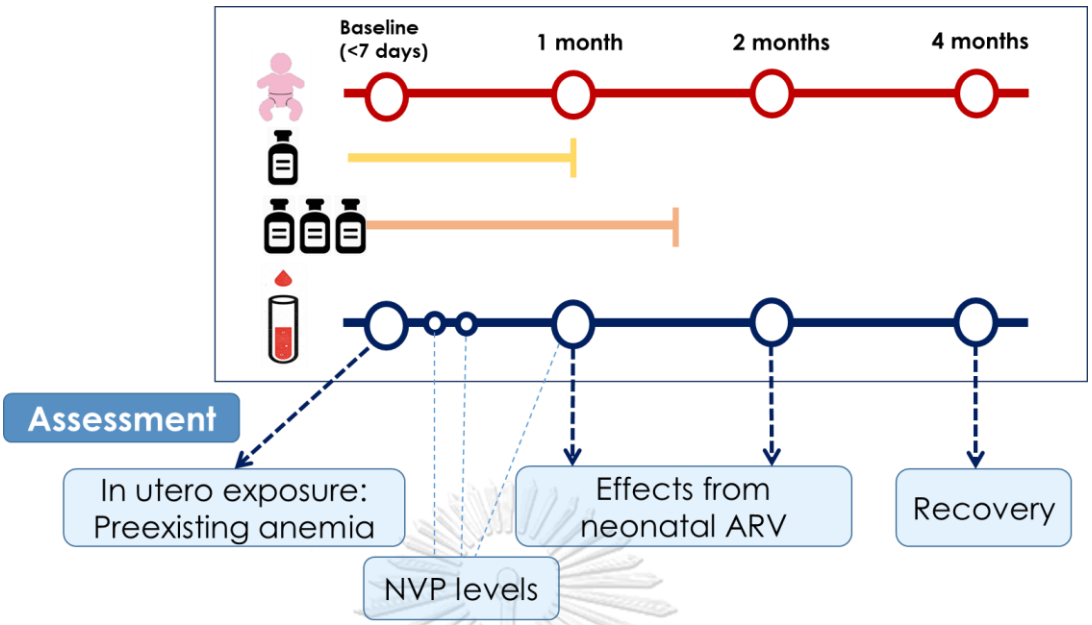


Figure 3. Study procedures and assessment

RESEARCH METHODOLOGY

Study design

This is a prospective, multi-site, observational study among 100 non-breastfed high risk HIV-exposed neonates who receive 6-week ZDV/3TC/NVP prophylaxis. One hundred neonates with standard risk of HIV transmission, who received 4-weeks ZDV prophylaxis, were enrolled as a comparison group for adverse events.

Study participants

200 perinatally HIV-exposed infants including 100 infants who received ZDV/3TC/NVP prophylaxis and 100 infants who received ZDV prophylaxis regimen.

Inclusion criteria

- Neonates born to HIV positive pregnant women
- Age less than 7 days at enrollment
- Gestational age >34 weeks
- Birth weight >1500 grams
- Caregiver gives informed consent

Exclusion criteria

- Infants with life-threatening conditions
- Breastfed infants

Study recruitment

Neonates who born from HIV-positive mothers were stratified to two risk groups according to the Thai National guidelines. Definition of high risk of HIV transmission includes duration of antepartum maternal ART less than 12 weeks before delivery, or mother has poor compliance

with ART during pregnancy, or detectable maternal HIV VL near delivery. High risk HIV-exposed neonates received ZDV 4 mg/kg twice daily plus 3TC 2 mg twice daily and NVP 4 mg/kg once daily for 6 weeks. In contrast, neonates without those factors in high risk definition were stratified as low risk group and received ZDV 4 mg/kg twice daily for 4 weeks.

Study procedure (Table 1)

Participants were enrolled by availability sampling. According to the primary objective, each neonate was observed for clinical adverse events and checked for laboratory abnormalities consisting of complete blood count; including hemoglobin (g/dL) and neutrophil ($x10^6$/L), AST and ALT at birth, age 1, 2 and 4 months. Laboratory abnormalities are graded with the use of the Division of AIDS Toxicity Tables for Grading Severity of Pediatric Adverse Experiences(31) with grades 1, 2, 3, and 4 defining mild, moderate, severe, and life-threatening events (Table 2). All laboratory assays were performed by laboratories that are quality-assured.

Table 1. Study procedures

Procedures	Enrollment (≤7 days)	Day 28 (+/- 7 days)	2 month (+/- 7 days)	4 month (+/- 7 days)
Inform consent	x			
Medical history, Physical examination	x	x	x	x
Complete blood count	x	x	x	x
AST, ALT	x	x	x	x
HIV DNA PCR	(x) [1]	x	(x) [1]	(x) [1]

Table 1. Study procedures (continued)

Nevirapine concentration[2]	Day 1	Day 2	Day 5 (+/- 2 days)	Day 14 (+/- 7 days)	Day 28 (+/- 7 days)
Group 1 (n=25)	x[3]	x[4]		x	
Group 2 (n=25)		x[4]	x		x

[1]According to Thai National Guideline, HIV DNA PCR will be done routinely at 1 month, 2-4 month in low risk group. If infant is in high risk group and receive 6-weeks of ZDV/3TC/NVP additional HIV DNA PCR will be done at birth and 4 months of age.

[2] A substudy of nevirapine concentration were conducted in a subgroup of 50 neonates who received ZDV/3TC/NVP regimen. Infants were categorized to group 1 or 2 by purposive sampling.

[3] Within 1-6 hours after the first dose NVP.

[4] Within 1-6 hours after the second dose of NVP.

Table 2. Division of AIDS table for grading adverse events; November 2014[22]

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life threatening
Hemoglobin (g/dL)				
Visit 1 (age ≤7 days)	13.0-14.0	10.0-<13.0	9.0-<10.0	<9.0
Visit 2 (age 1 month)	9.5-11.0	8.0-<9.5	6.7-8.0	<6.7
Visit 3, 4 (age 2, 4 months)	9.5-10.4	8.5-<9.5	6.5-<8.5	<6.5
Absolute neutrophil count (/µL)				
Visit 1	1250-1500	1000-1249	750-999	<750
Visit 2, 3, 4	800-1000	600-799	400-599	<400
AST (U/L)				
Visit 1	187.5-375	376-750	751-1500	>1500
Visit 2, 3, 4	100-200	201-400	401-800	>800
ALT (U/L)				
All visit	56-112	113-225	226-450	>450

ULN; upper limit of normal

For the secondary objective to determine rate of HIV transmission, HIV DNA PCR were done routinely according to national guideline; low risk HIV-exposed infants at age 1 and 2-4 months, high risk HIV-exposed infants at birth, 1, 2 and 4 months. Definition of HIV status in infants(17) were defined as following; 1) Infants were categorized as not infected if they had 2 negative HIV DNA PCR tests with one obtained at age ≥1 month and one at age ≥4 months, 2) Infants were categorized as infected if HIV DNA PCR were positive on at least 2 separate occasions, 3) In utero transmission defined as positive HIV DNA PCR within 7 days of life 4) Peripartum transmission defined as first positive HIV DNA PCR after 7 days of life.

For another secondary objective, NVP concentration assays were conducted in a subgroup of 50 neonates. Each infant had 3 sparse plasma collections during the first, second and fourth week of life. Blood samples were collected at maximum 3 time points as shown in Table 1. Regarding quantification of infant NVP plasma concentrations, infant blood samples were centrifuged and plasma frozen at -20°C or below until analysis. Plasma drug concentrations were measured at the PHPT-AMS laboratory at Chiang Mai University. NVP was quantified using a reversed-phase liquid chromatography-triple quadrupole mass spectrometry (LC-MS/MS) method(32). This method was internally validated over the concentration range of 0.05-20 mg/L. The average accuracy was 95%-100% and precision (interassay and intra-assay) was <10% of the coefficient of variation (CV). The laboratory participates in two international external quality control programs for quantification of antiretroviral drugs: (1) the HIV/AIDS Clinical Pharmacology Quality Assurance program from the University at Buffalo, NY, which performs standardized inter-laboratory testing twice a year(33) and (2) ASQUALAB Quality Control program, France (http://www.asqualab.com/). Population means and variances of NVP pharmacokinetic parameters were estimated using a non-linear mixed effects regression model. The software program NONMEM (Version VII, ICON Development Solutions, MD, USA), with a Fortran

Compiler was used to fit NVP concentration-time data using the first-order conditional estimation method (FOCE) with interaction.

Study sites

This study was conducted at 5 participating sites;

1. Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, and HIV-NAT, the Thai Red Cross AIDS Research Centre

2. Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

3. Department of Pediatrics, Faculty of Medicine, Queen Sirikit National Institute of Child Health, , Bangkok, Thailand

4. Department of Pediatrics, Khon Kaen Hospital, Khon Kaen, Thailand

5. Chiang Rai Hospital, Chiang Rai, Thailand

Research study management across 5 sites

Chulalongkorn University serves as a coordinating center which is responsible for overall data management, monitoring, and communication among all sites. Site initiation and protocol training were conducted before study initiation included training in study procedures and training in data collection. Annually group meeting was held to report preliminary data and discussion. The research activities were monitored and overseen. Monitoring in data quality by general report of data quality and completeness, edit queries, and data cleaning were done. Annually group meeting was held to report preliminary data and discussion.

Sample size calculation

Power calculations for the primary objective were based on a test of two independent proportions for a single group of subjects. Prior data indicated that the proportion of anemia occurred among ZDV monotherapy was 0.55(8). If the anemia for case subjects is 0.75, we need 98 case subjects and 98 control subjects to be able to reject the null hypothesis.

For testing two independent proportions (two-tailed test)

Proportion in group1 (p_1) = 0.55(8), Proportion in group2 (p_2) = 0.75

Alpha (α) = 0.05, Beta (β) = 0.20, ratio (r) = 1.00

$$n_1 = \left[\frac{z_{1-\frac{\alpha}{2}} \sqrt{\bar{p}\bar{q}\left(1+\frac{1}{r}\right)} + z_{1-\beta} \sqrt{p_1 q_1 + \frac{p_2 q_2}{r}}}{\Delta} \right]^2$$

$$r = \frac{n_2}{n_1}, q_1 = 1 - p_1, q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + p_2 r}{1+r}, \bar{q} = 1 - \bar{p}$$

Under these assumptions, a sample size of 100 subjects give 80% power to detect a change in discordant proportions of 20% from baseline values at a two sided significance level of 5%.

Statistical Analysis

Data analysis for primary objective

Baseline characteristics were reported and compared by non-parametric statistics for continuous variables, and by parametric statistics for categorical variables. To study the effect of prophylaxis regimen on percentage of anemia over time, we evaluated rates of anemia by at aged 1 and 2 months. Because laboratory results at birth may affect by in utero ZDV exposure and result at 4 months of age reflect resolved of adverse events after discontinuation

of prophylaxis. The prevalence of laboratory adverse events for each infant that occurred between at age 1 and 2 months was compared between groups using Chi-square test or Fisher's exact test as appropriate. Maximal grading AE in each infant were counted and compared. Comparisons of categorical data between 6-week triple drug and 4-week zidovudine exposed infants were performed using Chi-square tests. Continuous data of levels of hemoglobin, neutrophil count, AST and ALT between groups were compared at aged 1, 2, 4 months by unpaired t-test. Factors associated with change overtime of hemoglobin in infants were analyzed using generalized estimating equations to adjust for baseline differences clustering effects. Infant who confirmed to be HIV positive and switch to treatment regimen was excluded from the subsequent analysis. Statistical significance was considered if *p*-value less than 0.05. Statistical analysis was performed using SPSS version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

Data analysis for secondary objectives

The HIV transmission rate was reported as percentage and 95% confidence interval calculated by binomial distribution. Statistical significance was considered if *p*-value less than 0.05. For the NVP levels, estimate NVP population pharmacokinetic parameters were performed by nonlinear mixed-effects regression models (NONMEM). Individual predicted NVP Ctrough (C_{24}) were compared to the proposed target for HIV prophylaxis of >0.1 mg/L.(26, 27)

Ethical consideration

The study protocol was submitted to the Institutional Review Boards of the 5 participating sites for ethical approval. The participants' mothers were informed and signed for their consent before enrollment. Ethical considerations are as following;

Respect of person: The investigator described the study procedure and provided inform consent. The participants' mothers decided by their own selves whether to join the study or not, without any effect on their medical management. The investigator had kept confidential the patients' information.

Beneficence: Participation in this project had some benefit to the patients from monitoring side effect of antiretroviral drugs and involved very low risk to the participants from blood drawing. This project would not adversely affect the patients' health or disease outcome.

Justice: Fair procedures in the selection of participants were performed with no preference in selection of subjects. The investigator offered research to all pregnant women during study period without favor or undesirable persons.

RESULTS

From October 2015 to November 2017, 218 HIV-exposed infants were screened, 200 HIV-exposed infants were enrolled, including 100 infants who received ZDV/3TC/NVP prophylaxis and 100 infants who received ZDV prophylaxis regimen (Table 3).

Table 3. Number of screening and enrollment by study site

	Screening	Enrollment	ZDV/3TC/NVP prophylaxis	ZDV prophylaxis	NVP substudy
King Chulalongkorn Memorial Hospital	84	75	44	31	18
Siriraj Hospital	3	3	0	3	0
Queen Sirikit National Institute of Child Health	42	34	21	13	11
Chiangrai Prachanukroh Hospital	54	54	23	31	11
Khon Kaen Hospital	35	34	12	22	10
Total	218	200	100	100	50

Baseline characteristics are shown in Table 4. Median (IQR) gestational age and birth weight were 38 (37-39) weeks and 2,873 (2,590-3,184) g, respectively. In high risk group, mothers were younger (median age 23 vs 32 years, p <0.001) and the median infant birth weight was lower (2,822 vs 2,950 g, p=0.06). Common maternal ART regimens were tenofovir (TDF) /3TC or emtricitabine (FTC) (58%), ZDV/3TC (32%) in combination with EFV (50%), ritonavir-boosted protease inhibitor (31%). The reason to determine as high risk of

transmission were as following; 48 detectable maternal viral load of which 21 had VL >1000 copies/mL (c/mL), 20 no viral load results near delivery, 14 receiving ART less than 12 weeks, 10 no antenatal care, 5 poor adherence, 2 incident case, and 1 physician decision due to infant's birth injury. The reasons to determine as low risk of transmission in ZDV-received infants consisted of 96 undetectable viral load near delivery, 3 no VL results but received ART before pregnancy with good adherence and 1 with detectable maternal VL of 1,143 copies/mL at GA 32 weeks but infant received ZDV alone due to physician preferences. Among infants received ZDV/3TC/NVP, 75% were birth weight (BW) ≥2500 g with mean (SD) NVP dosage 13 (2.2) mg, whereas low birth weight infants (BW <2500 g) received NVP with mean (SD) 9 (1.4) mg.

Table 4. Characteristics of HIV-exposed infants and mothers

	Total (N=200)	6-week ZDV/3TC/NVP prophylaxis (n = 100)	4-week ZDV prophylaxis (n = 100)	*p*-value
Mothers				
Median (IQR) of gestational age at delivery, weeks (IQR)	38 (37-39)	38 (37-39)	38 (38-39)	0.26[+]
Median (IQR) of maternal age, years	26 (21-34)	23 (20-29)	32 (24-35)	<0.001[+]
Premature (<37 weeks), n (%)	27 (14)	18 (18)	9 (9)	0.06
Mode of delivery, cesarean section (%)	99 (50)	46 (46)	53 (53)	0.32
Maternal antiretroviral therapy regimen, n (%)				
No ART	16 (8)	16 (16)	0	<0.001
NRTI-backbone				0.47
ZDV plus xTC	63 (32)	28 (28)	35 (35)	
TDF plus xTC	116 (58)	55 (55)	61 (61)	
Others: d4T, ddI plus xTC	5 (3)	1 (1)	4 (4)	
NNRTI-based				0.008
EFV	99 (50)	49 (49)	50 (50)	
NVP	20 (10)	2 (2)	18 (18)	
PI-based	62 (31)	31 (31)	31 (31)	
Raltegravir-based	3 (2)	2 (2)	1 (1)	
Raltegravir intensification	17 (9)	17 (17)	0 (0)	<0.001
Maternal VL <50 c/mL before delivery (%)	97 (66%) (n = 147)	1 (2%) (n = 50)	96 (99%) (n = 97)	<0.001

Table 4. Characteristics of HIV-exposed infants and mothers (continued)

	Total (N=200)	6-week ZDV/3TC/NVP prophylaxis (n = 100)	4-week ZDV prophylaxis (n = 100)	*p*-value
Mothers				
Timing start maternal ART, n (%)				<0.001
Prior to current pregnancy	56 (28)	10 (10)	46 (46)	
During current pregnancy	128 (64)	74 (74)	54 (54)	
At delivery (no ANC)	10 (5)	10 (10)	0	
No ART (incidence case)	6 (3)	6 (6)	0	
Infants				
Sex, male (%)	109 (55)	57 (57)	52 (52)	0.48
Birth weight <2500 grams, n (%)	37 (19)	23 (23)	14 (14)	0.10
Median (IQR) birth weight (grams)	2,873 (2,590-3,184)	2,822 (2,531-3,152)	2,941 (2,669-3,222)	0.19+
Median (IQR) length (cm.)	50.0 (48.0-52.0)	48.8 (41.0-56.0)	50.0 (39.0-58.0)	0.05+
Median (IQR) of head circumference, cm.	33.0 (32.0-34.0)	32.5 (31.7-33.9)	33.0 (32.0-34.0)	0.02+

3TC: Lamivudine; ART: Antiretroviral therapy; d4T: Stavudine; ddI: Didanosine; NVP: Nevirapine; TDF: Tenofovir; VL: Viral loads; xTC: Lamivudine or emtricitabine; ZDV: Zidovudine.

p-value calculated by Chi-square test except + by unpaired t-test

During follow-up period, 188 infants (94%), 93 infants of ZDV/3TC/NVP group and 95 of ZDV group, had follow-up until complete study as shown in Table 5 with 97% had blood tests as defined in the protocol (Table 6).

Table 5. Number of subjects at each visit by group

	Total	ZDV/3TC/NVP prophylaxis	ZDV prophylaxis
Enrollment	200	100	100
Age 1 month	196	98	98
Age 2 months	189	93	96
Age 4 months	188	93	95

Table 6. Number of laboratory tests deviated from protocol (not included patients who loss to follow-up)

	ZDV/3TC/NVP prophylaxis	ZDV prophylaxis
Enrollment	2 CBC, 2 AST, 5 ALT	2 CBC, 4 AST, 2 ALT
Age 1 month	1 AST, 1 ALT	1 Hb, 2 ANC, 1 AST, 1 ALT
Age 2 months	1 AST, 1 ALT	-
Age 4 months	-	-

3TC: Lamivudine; NVP: Nevirapine; ZDV: Zidovudine; CBC: complete blood count; Hb: hemoglobin; WBC: absolute neutrophil counts; AST: aspartate transaminase; ALT: alanine aminotransferase

One infant who received ZDV/3TC/NVP was excluded from analysis at 2 months due to diagnosis of HIV infection and switch prophylaxis to treatment regimen. A total of 378 laboratory abnormalities occurred in 4-month follow-up period; 191 events were reported in 90 ZDV/3TC/NVP patients compared to 187 events in 85 ZDV prophylaxis patients (Table 7).

Table 7. All grade laboratory abnormalities overall and by group

Adverse event (AE) rates[+]; Number of events/tests (%), number of subjects[++]	ZDV/3TC/NVP	ZDV	p-value*
All grade anemia	156/380 (41.1%), 86 infants	149/386 (38.6%), 84 infants	0.72
Grade 3-4 anemia	14/380 (3.7%), 9 infants	13/386 (3.4%), 10 infants	0.82
All grade neutropenia	19/380 (5.0%), 17 infants	24/385 (6.2%), 17 infants	0.47
Grade 3-4 neutropenia	6/380 (1.6%), 5 infants	4/385 (1.0%), 3 infants	0.46
Elevated AST	3/380 (0.8%), 2 infants	2/386 (0.5%), 2 infants	0.61
Elevated ALT	13/378 (3.4%), 7 infants	12/383 (3.1%), 4 infants	0.82
Total AE	191	187	

3TC: Lamivudine; NVP: Nevirapine; ZDV: Zidovudine; AST: aspartate transaminase; ALT: alanine aminotransferase

[+]According to DAIDS Grading toxicity table 2014

**p*-value calculated by Chi-Square test

[++]Number of subjects counted by maximal grading AE in each infant

Hematologic adverse events

Overall, there was no significant difference of hematotoxicity between ZDV/3TC/NVP prophylaxis and ZDV alone; all grade anemia (41.1% vs 38.6%, p=0.72), all grade neutropenia (5.0% vs 6.2%, p=0.47) (Table 7). Rates of all grade anemia and neutropenia at age 1 and 2 months between ZDV/3TC/NVP prophylaxis and ZDV alone were also not significantly different (69.8% vs 66.3%, p=0.46 and 7.8% vs 7.8%, p=1.00, respectively) (Table 8). The percentages and severity of anemia and neutropenia at each visit compared between groups are shown in Figure 4.

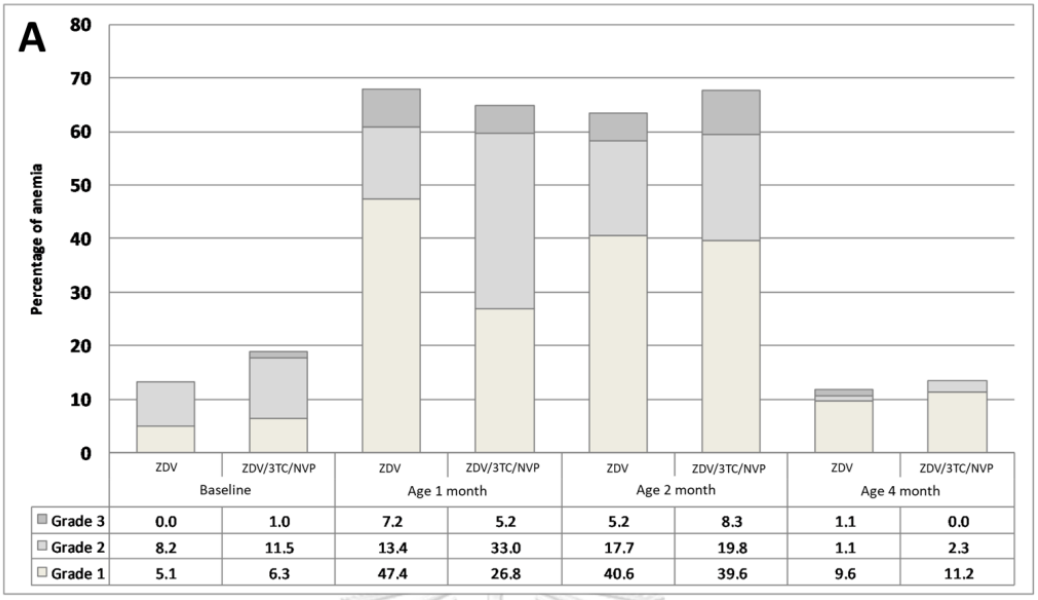
Table 8. Adverse event rates and severity at age 1 and 2 months, by group

Adverse event (AE) rates[+]; Number of events (%)	ZDV/3TC/NVP (n=192[++])	ZDV (n=193[+++])	p-value*	Relative risk (95% CI)
All grade anemia	134 (69.8%)	128 (66.3%)	0.46	1.06 (0.93-1.21)
Grade 3-4 anemia	13 (6.8%)	13 (6.7%)	0.97	1.01 (0.48-2.11)
All grade neutropenia	15 (7.8%)	15 (7.8%)	1.00	1.00 (0.50-1.99)
Grade 3-4 neutropenia	3 (1.6%)	1 (0.5%)	0.29	1.01 (0.48 -2.11)
Elevated AST	2 (1.1%)	2 (1.0%)	0.92	1.02 (0.14-7.14)
Elevated ALT	8 (4.2%)	4 (2.1%)	0.24	2.03 (0.62-6.63)

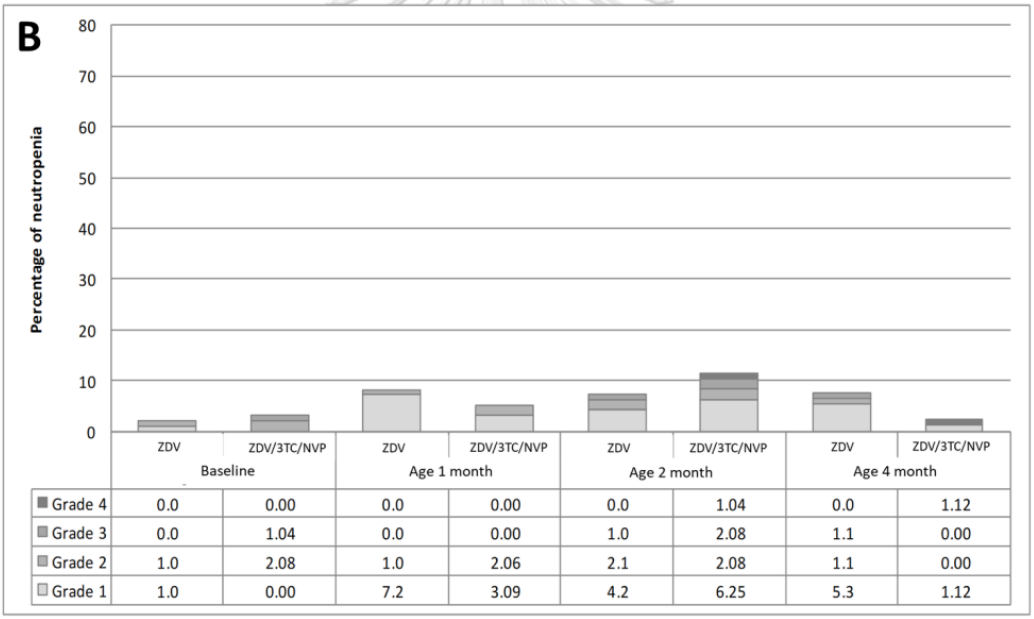
3TC: Lamivudine; NVP: Nevirapine; ZDV: Zidovudine; AST: aspartate transaminase; ALT: alanine aminotransferase

[+]According to DAIDS Grading toxicity table 2014,*p-value calculated by Chi-Square test

[++]Except AST, ALT; n=190, [+++]Except neutrophil counts; n=192



	Baseline		Age 1 month		Age 2 month		Age 4 month	
	ZDV	ZDV/3TC/NVP	ZDV	ZDV/3TC/NVP	ZDV	ZDV/3TC/NVP	ZDV	ZDV/3TC/NVP
Grade 3	0.0	1.0	7.2	5.2	5.2	8.3	1.1	0.0
Grade 2	8.2	11.5	13.4	33.0	17.7	19.8	1.1	2.3
Grade 1	5.1	6.3	47.4	26.8	40.6	39.6	9.6	11.2



	Baseline		Age 1 month		Age 2 month		Age 4 month	
	ZDV	ZDV/3TC/NVP	ZDV	ZDV/3TC/NVP	ZDV	ZDV/3TC/NVP	ZDV	ZDV/3TC/NVP
Grade 4	0.0	0.00	0.0	0.00	0.0	1.04	0.0	1.12
Grade 3	0.0	1.04	0.0	0.00	1.0	2.08	1.1	0.00
Grade 2	1.0	2.08	1.0	2.06	2.1	2.08	1.1	0.00
Grade 1	1.0	0.00	7.2	3.09	4.2	6.25	5.3	1.12

Figure 4. Frequency and severity of neutropenia compare between 2 groups.

A: Percentage of anemia by age, B: Percentage of neutropenia by age.

Laboratory abnormalities are graded with the use of the Division of AIDS Toxicity Tables for Grading Severity of Pediatric Adverse Experiences[31]. ZDV: zidovudine; 3TC: lamivudine; NVP: nevirapine.

Rates of anemia were increasing at aged 1 and 2 months in both groups with no significant different between groups. Grade 2 anemia significantly occurred more frequently in infants received ZDV/3TC/NVP prophylaxis (28.1% vs 15.0%, p=0.008) (Figure 5). However, by 4 months of age, all infants with severe anemia and/or neutropenia (grade 3-4) had either normalized or improved to grade 1.

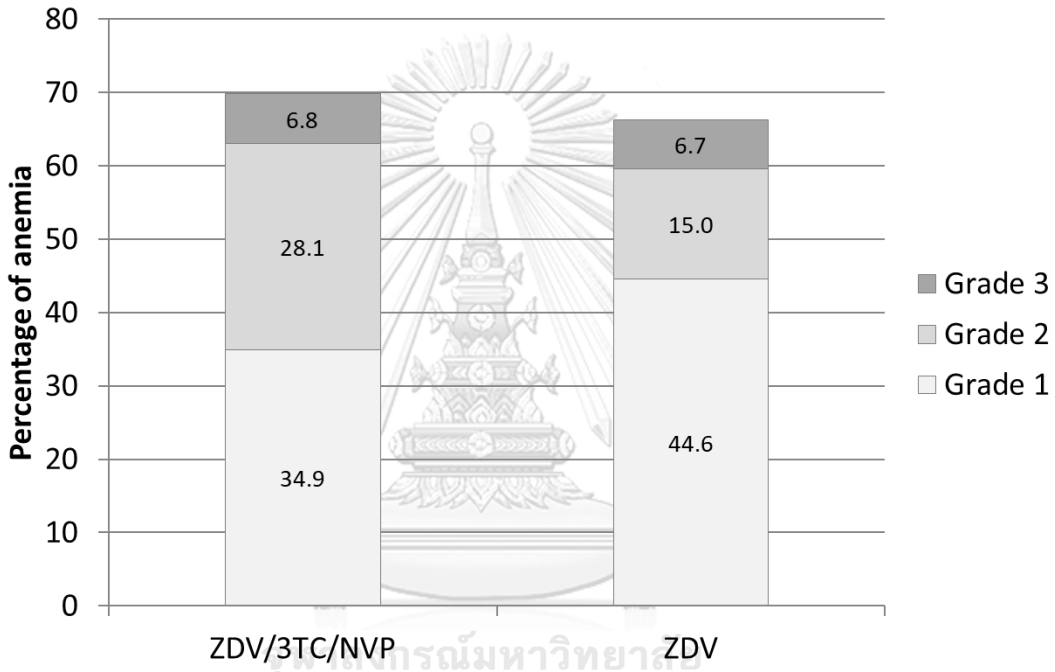


Figure 5. Rates of anemia and severity at aged 1 and 2 months compare between 2 groups. Laboratory abnormalities are graded with the use of the Division of AIDS Toxicity Tables for Grading Severity of Pediatric Adverse Experiences[31]. ZDV: zidovudine; 3TC: lamivudine; NVP: nevirapine.

Comparing hemoglobin and neutrophil level between triple and ZDV prophylaxis at aged 1, 2 and 4 months showed that there was no significant difference between groups (Figure 6). Median (IQR) hemoglobin level among infants who received triple prophylaxis were 9.9 (9.0-11.4) g/dL, 10.1 (9.3-11.0), and 11.7 (11.0-12.3) at aged 1, 2 and 4 months,

respectively. At age 1 and 2 months, median hemoglobin level was lower than the cut-off for anemia for age in both groups.

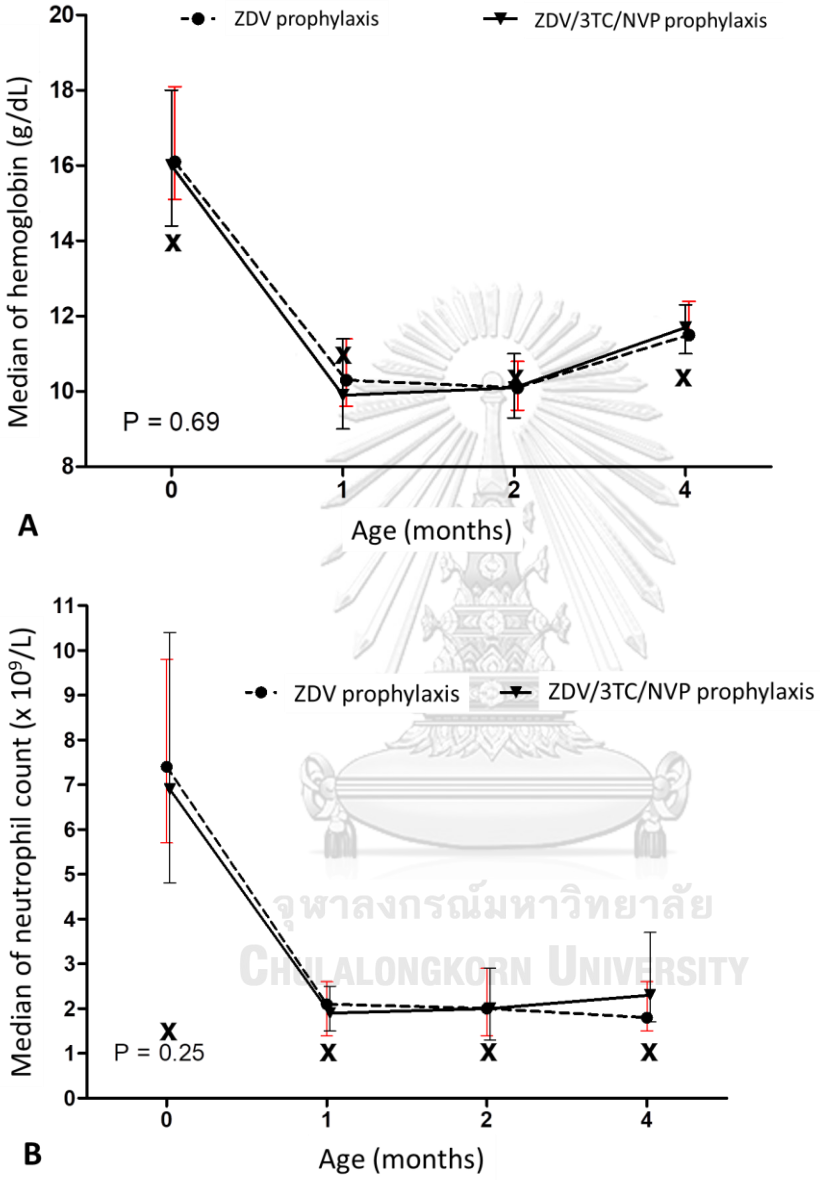


Figure 6. Hematological parameters compared between both groups; ZDV prophylaxis (dashed line) and ZDV/3TC/NVP prophylaxis (solid line).

A: Median of hemoglobin (g/dL) by age, B: Median of neutrophil counts (x 109/L) by age. X represents lower cut-off of hemoglobin and neutrophil counts by age. Whisker ends represents interquartile range. P-value calculated by unpaired t-test.

Comparing anemia rates at age 1 and 2 months by antepartum zidovudine exposure showed no significant difference between group (Table 9). Using generalized estimating equations to identify factors associated with change overtime of hemoglobin in infants found that no effect of factors, except birth weight, were seen on the hemoglobin level over the 4-month period.

Table 9. Antepartum zidovudine exposure and anemia rates at age 1 and 2 months by group

Antepartum ZDV exposure	Infant anemia at age 1 and 2 months	ZDV/3TC/NVP (n = 190 tests)	ZDV (n = 193 tests)	p-value*
No	No anemia	45 (24%)	49 (25%)	0.33
	Anemia	92 (48%)	78 (41%)	
Yes	No anemia	11 (6%)	16 (8%)	0.65
	Anemia	42 (22%)	50 (26%)	

3TC: Lamivudine; NVP: Nevirapine; ZDV: Zidovudine.

**p*-value calculated by Chi-Square test

Hepatotoxicity adverse events

Overall, there was no significant difference of hepatotoxicity between ZDV/3TC/NVP prophylaxis and ZDV alone; elevated AST (0.8% vs. 0.5%. p=0.61), and elevated ALT (3.4% vs. 3.1%, p=0.82) (Table 7). Rates of elevates AST and ALT at age 1 and 2 months between ZDV/3TC/NVP prophylaxis and ZDV alone were 1.1% vs 1.0%, p=0.92 and 4.2% vs 2.1%, p=0.24, respectively (Table 8). There were 13 infants with elevated transaminase of which maternal ART backbone of 9 LPV/r, 3 EFV and 1 no ART (Table 10). Therefore, there were 15% (9 from 62) infants with in utero LPV/r exposure and 3% (3 from

99) in utero EFV exposure developed elevated transaminase. However, only 2 from 13 infants had elevated transaminase at birth.

Table 10. Summary of infants with elevated transaminase

No.	**Sex**	**GA (weeks)**	**BW (grams)**	**Maternal ART**	**Infant prophylaxis**	**Elevated transaminase^{+}, U/L, (timing)**	**NVP Ctrough, mg/L (Day of test)**		
1	M	39	3450	AZT/ 3TC/ LPV/r	ZDV/3TC/ NVP	AST 218 (day 2)	2.440 (D2)	3.453 (D4)	not done
2	M	40	3005	AZT/ 3TC/ LPV/r	ZDV/3TC/ NVP	ALT 86 (month 2)	1.304 (D1)	2.280 (D2)	1.978 (D14)
3	M	38	2910	TDF/ 3TC/ LPV/r	ZDV/3TC/ NVP	ALT 74 (month 2)	2.423 (D2)	3.515 (D5)	1.016 (D28)
4	F	39	2710	TDF/ 3TC/ LPV/r	ZDV/3TC/ NVP	ALT 59 (month 1)	1.723 (D2)	2.606 (D7)	0.876 (D31)
5	M	40	2748	TDF/ 3TC/ EFV	ZDV/3TC/ NVP	ALT 102 (month 2)	2.361 (D2)	2.985 (D3)	0.553 (D28)
6	F	39	3320	AZT/ 3TC/ LPV/r	ZDV/3TC/ NVP	ALT 58 (month 1)	Not tested		
7	M	40	3180	TDF/ 3TC/ LPV/r	ZDV/3TC/ NVP	ALT 67 (month 2)	Not tested		
8	M	39	2716	TDF/3TC/EFV	ZDV/3TC/ NVP	ALT 57 (baseline)	Not tested		
9	M	40	3380	no ANC	ZDV/3TC/ NVP	AST 400, ALT 305 (grade 3, month 1)	Not tested		

Table 10. Summary of infants with elevated transaminase (continued)

No.	Sex	GA (weeks)	BW (grams)	Maternal ART	Infant prophylaxis	Elevated transaminase+, U/L, (timing)	NVP Ctrough, mg/L (Day of test)		
10	M	38	2800	AZT/ 3TC/ LPV/r	ZDV	ALT 119 (grade 2,month 4)		NA	
11	F	37	2330	AZT/ 3TC/ LPV/r	ZDV	AST 185 (month 2), ALT 67 (month 1) ALT 115 (grade 2, month 2)		NA	
12	M	39	2315	TDF/ 3TC/ LPV/r	ZDV	AST 119, ALT 90 (month 2)	NA	2.606 (D7)	0.876 (D31)
13	F	39	3050	TDF/ FTC/ EFV	ZDV	ALT 65 (month 2)	NA	2.985 (D3)	0.553 (D28)

+All were grade 1 except case number 9 and 11

ALT: alanine aminotransferase; AST: aspartate transaminase; ART: antiretroviral therapy; BW: birthweight; F: female; FTC: emtricitabine; GA: gestational age; LPV/r: ritonavir-boosted lopinavir; M: male; NA: not applicable; TDF: tenofovirdisoproxil fumarate; ZDV: zidovudine; 3TC: lamivudine.

Clinical adverse events

There was one neonate who had a generalized maculopapular rash at day of life 4. Three days later, he developed fever with watery diarrhea and was hospitalized with a final diagnosis of culture-negative early neonatal sepsis. NVP was discontinued due to suspected NVP hypersensitivity and the rash was resolved 2 days after. During hospitalization, laboratory evaluation showed normal *AST* 20 U/L, ALT 16 U/L, and eosinophil 70 /μL. The result of NVP C_{24} at day 1 and 2 were 1.13 and 1.91 mg/L, respectively. In high risk group, there were 9 cases with elevated liver function test. Only 1 case with elevated ALT grade 3 (ALT 305 U/L) at aged 1 month which possibly related to ART. His baseline AST and ALT

at birth were 89 and 14 U/L, respectively. At aged 1 month, AST increased to 400 U/L (grade 2) and ALT 305 U/L (grade 3). He had no fever, no vomiting, and no other symptoms. NVP was discontinued due to the possibility of NVP-related increased transaminase. Two days later, AST was 152 U/L (grade 1) and ALT was 216 U/L (grade 2). NVP concentration at 12 hours post-dose was 1.55 mg/L. Laboratory results at follow-up visit of age 2 months showed AST 102 U/L and ALT 70 U/L (grade 1), at age 4 months showed AST 36 U/L and ALT 27 U/L. Other non-specific clinical adverse events which not related to antiretroviral prophylaxis such as respiratory tract infection, were reported 18 events in triple prophylaxis and 14 events in ZDV prophylaxis (p = 0.19).

HIV transmission rate

Among 100 HIV-exposed high risk infants who received triple antiretroviral drugs prophylaxis, 6 infants were loss to follow-up; 4 had two negative HIV DNA PCR test but at age <4 months, and 2 infants had 1 negative HIV DNA PCR test results at birth before being lost to follow-up. Among 94 infants who had complete blood tests for HIV DNA PCR, 1 neonate whose maternal VL at GA 34 weeks was 5,833 c/mL, acquired in-utero HIV infection (positive HIV DNA PCR at birth). Therefore, rate of HIV transmission among HIV-exposed high risk infants who received triple antiretroviral drugs prophylaxis was 1.1% (95% CI: 0.2%-5.6%). Further calculation was performed by excluding infants with no definite data of high risk whom maternal VL not tested (n=20) or maternal ART duration less than 12 weeks (n=14) and showed rate of transmission 1.7% (95% CI: 0.3%-8.9%).

NVP concentrations

Fifty high risk infants were enrolled into the analysis of NVP concentrations during the first month of life. Two infants were excluded due to their mother receiving a NVP-contained ART which would impact infant NVP concentrations detectable at birth due to passage of NVP through the placenta.

Baseline characteristics of the 48 infants included in this analysis are shown in Table 11. Among these, 25 (52%) were male, and 12 (25%) preterm infants (GA 34-37 weeks). The median (range) gestational age (GA) was 38 (34-40) weeks, and birth weight was 2,803 (1,570-3,888) grams. Mean (SD) dosage of NVP at birth was 13 (2.1) mg in BW ≥2500 grams and 9 (2.0) mg in BW <2500 grams.

Table 11. Baseline demographic data of infants in nevirapine subgroup analysis and their mothers (n = 48)

Characteristics	
Infant	
Male, n (%)	25 (52)
Median (range) gestational age at birth, weeks	38 (34-40)
Median (range) birth weight, grams	2,803 (1,570-3,888)
Prematurity (GA 34-37 weeks), n (%)	12 (25)
Mother	
Median (range) age at delivery, year	21 (15-40)
Viral load tested, n (%)	28 (58%)
VL <50 copies/mL	2 (7%)
VL <1000 copies/mL	15 (54%)

Table 11. Baseline demographic data of infants in nevirapine subgroup analysis and their mothers (continued)

Characteristics	
Mothers	
Antiretroviral treatment, n (%)	5 (10)
No ART	43 (90)
Combination antiretroviral therapy	
Nucleoside analogue backbone	
TDF/3TC or TDF/FTC	27 (63)
ZDV/3TC	15 (35)
ZDV/TDF	1 (2)
NNRTI-based	
Efavirenz	24 (56)
Protease inhibitor-based	
Lopinavir/ritonavir	17 (40)
Raltegravir-based	2 (4)

3TC: Lamivudine; ART: Antiretroviral therapy; FTC: Emtricitabine; GA: Gestational age; TDF: Tenofovir; ZDV: Zidovudine

Regarding maternal ART, 4 women (8%) did not receive ART due to no antenatal care, 1 woman (2%) received ZDV monotherapy, and 43 women (90%) received combination ART. Common maternal ART back-bones were TDF/3TC or TDF/FTC (60%), ZDV/3TC (38%) in combination with EFV (54%), or with a ritonavir boosted HIV protease inhibitor (38%). All infants were not infected with HIV, based on negative HIV DNA polymerase chain reaction tested at birth, and 1, 2 and 4 months of life.

Among 48 infants, 135 plasma samples were included in the population pharmacokinetic analysis. Population estimates (interindividual variability) for NVP oral clearance (CL/F) and total volume of distribution (Vd/F) were 0.116 L/hr/3 kg (0.19) and 4.95

L/3 kg, respectively. Proportional residual variability was 0.45. All relative standard errors were <24% and <35% for structural and variability parameters, respectively. Maternal EFV-based ART was tested for inclusion in the model but was found not to influence infant NVP pharmacokinetic parameters. Median (IQR) predicted NVP C_{24} were 1.34 mg/L (1.13-1.84, n=24), 2.24 (2.00-2.59, n=48), 2.78 (2.61-3.12, n=23), 2.20 (1.86-2.44, n=22), and 0.81 (0.58-0.98, n=18) on days 1, 2, 7, 14, and 28 of life, respectively (Figure 7). All infants maintained NVP concentrations above the prophylactic target threshold of 0.1 mg/L during the first 4 weeks. There was one neonate whose birth weight was less than 2,000 grams with predicted NVP C_{24} concentrations at ages 2, 7, 28 days of 1.70, 3.12 and 1.20 mg/L, respectively. There were no statistical differences of predicted NVP C_{24} among term and preterm infants (p=0.963). Among this NVP subgroup analysis, 5 infants developed elevated transaminase grade 1 but none of them had clinical hepatitis. Predicted NVP C_{24} levels among these infants were shown in Figure 7.

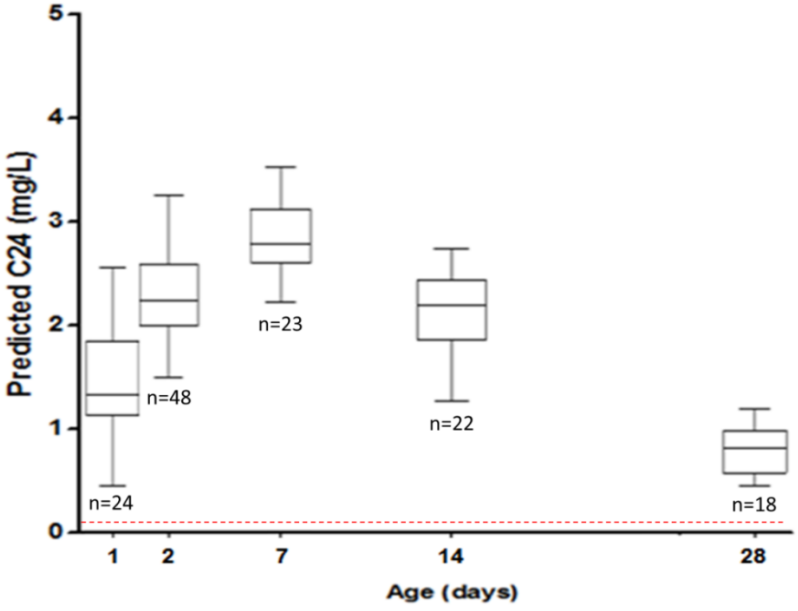


Figure 7. Box and whisker plot of predicted nevirapine trough concentrations (C24) (mg/L) over the first month by age.
Box ends represents 25th and 75th percentiles. Whisker ends represents 1st and 99th percentiles. Dashed line indicates NVP prophylactic target level 0.1 mg/L.

EFV concentrations

There were 20 (42%) infants whose mother received EFV-based ART during pregnancy. Infant 'washout' of EFV concentrations were assessed in the samples collected during the first month of life. Mean EFV concentrations were 1.29, 1.45 and 0.76 mg/L at age <24 hours, 24-48 hours and >2-7 days, respectively, and all sample collected after 7 days of life had undetectable (<0.1 mg/L) EFV levels.

DISCUSSION

There was an increasing usage of combination antiretroviral regimen for infant with high risk of HIV acquisition but remains controversial on regimen, dosage and duration(16-19). Our prospective observational study of 6-week ZDV/3TC/NVP prophylaxis, NVP dosing 4 mg/kg once daily without lead-in, for high risk for HIV acquisition in infants demonstrated that this regimen resulted in grade ≥2 anemia 34.9% compared to 21.7 % in ZDV regimen but all severe anemia resolved at age 4 months. The results support this simplified regimen to be implemented in public health settings in Thailand and elsewhere.

Early maternal antiretroviral treatment combined with infant prophylaxis, including during breastfeeding, is very effective at preventing mother to-child transmission of HIV(17). In 2016, approximately two-thirds of HIV-infected pregnant women received antiretroviral treatment to prevent transmission of HIV to their babies(34). This rapid scale up of PMTCT programs in countries with a high burden of HIV has led to almost a 50% decline in the number of new infections among children between 2010 and 2016(34). The Ministry of Public Health in Thailand has made PMTCT of HIV a high priority since the beginning of the epidemic. Today, there is a high coverage of PMTCT in Thailand with 95.6% of pregnant women accessing antiretroviral treatment(2). In 2016 it was announce that Thailand was the first country in Asia to eliminate mother to child transmission of HIV and syphilis, with a rate of 1.9% in 2015. However, pregnant women who present late for antenatal care (i.e. less than 4-12 weeks of ART) are at a higher risk of transmitting HIV to their infant(35). A 6-week triple combination antiretroviral prophylaxis regimen of ZDV/3TC/NVP was recently recommended in Thailand for neonates at high risk of HIV infection. Our study provided safety data of 6-week ZDV/3TC/NVP regimen and endorsed current regimen in Thailand.

Maternal antiretroviral treatment and infant antiretroviral prophylaxis has been shown to greatly prevent mother-to-child HIV transmission(21, 36). The 2016 WHO guidelines recommends that neonates with high risk of HIV acquisition from mothers should receive dual prophylaxis with ZDV twice daily and NVP once daily for the first 6 weeks of life, whether they are breastfed or formula fed(18). Also, WHO has developed weight-bands dosing guidelines to simplify infant NVP prophylactic dosing (18). Thai National guideline recommends 6-week of ZDV/3TC/NVP triple prophylaxis for high-risk neonates with NVP dosing 4 mg/kg initiated at birth.

Our study found that there was no significant difference in the overall severity of laboratory AE between groups. For infants receiving combination prophylaxis regimen, severe AE grade 3-4 occurred in 15% vs 13% ($p = 0.68$) of infants received triple prophylaxis and infants received ZDV alone, respectively. These findings are similar to recent study from US evaluated AE in infants who received at least two weeks of a three-drug combination of ZDV/3TC/NVP found that in three-drug antiretroviral prophylaxis compared to infants receiving ZDV alone; 11% vs. 17% ($p = 0.74$) developed an AE grade ≥3(20). In our study, all grade anemia occurred more frequently in infant received triple prophylaxis especially grade 2 anemia but no difference in severe anemia. The finding was also compatible with published study reported that receiving three-drug regimen of ZDV/3TC/NVP with varied duration of NVP from single dose or up to 2-4 weeks found anemia grade 1 occurred in 63% of infants but all of these were grade 1 or 2(20). The differences were the rate of all grade anemia in our study was higher; 39.8% occurred in 85% of infants, and the severity of anemia which grade 3 anemia were reported. However, grade 3 anemia had been resolved or improved by 4 months of age.

In terms of neutropenia, HPTN040 study(21) reported a significant higher rate of neutropenia among infants receiving ZDV/3TC/nelfinavir regimen (27.5%) more than infants

received ZDV plus 3 doses NVP (14.9%), or infants received ZDV alone (16.4%). In contrast, our study found that there was no significant differences of neutropenia among infants received triple prophylaxis and ZDV prophylaxis, comparable to other report in infants who received at least two weeks of a three-drug combination of ZDV/3TC/NVP found that the frequency of neutropenia was higher in this group (47% vs 39% in the ZDV alone group) but not significant different(20). Comparing the numbers and severity of neutropenia in infants received combination regimen, we found all grade and severe neutropenia occurred in 17% and 5% infants, respectively which were less than previous data(20) (47% and 12%) despite longer duration of NVP exposure in our study.

Regarding the level of hemoglobin and neutrophil, the lower mean hemoglobin and absolute neutrophil counts were observed in combination regimen compared with ZDV alone received infants at age 1 month but was no longer observed at age 2 and 4 months. This finding was comparable to a retrospective study in Canada(37) even though the difference on combination prophylaxis consisted of 6-week ZDV/3TC and either NVP or nelfinavir. The median level of hemoglobin from both groups was less than cut-off of anemia for age at age 1 and 2 months, and tends to increase to normal range at 4 months of age. We imply that laboratory abnormality was resolved without harmful risk by 4 months of age.

In utero exposure may cause elevate transaminase in neonates. Our study reported elevated transaminase in 13 infants. Rate of elevated transaminase was 15% in infants with in utero LPV/r exposure which was comparable to published report of 12% (11). Contrastly, our study did not showed abnormal transaminase in 20 neonates who had in utero raltegravir exposure compared to 35% in previous study(15).

Nevirapine is a potent NNRTI favorable for use in preventing intrapartum transmission(38). The side effects of NVP are hepatotoxicity and hypersensitivity(28). In previous study on infected children who received NVP treatment dose with no lead-in found

that NVP rash was lower in younger age especially less than 2 years old(39), however, safety data of no lead-in strategies in neonates are limited. Our study reported events rates of 1.1% elevated AST and 4.2% elevated ALT in infants who received 6-week ZDV/3TC/NVP prophylaxis. Compare to published study(20) in infants receiving three-drug regimen including ZDV/3TC/NVP with varied duration of NVP from single dose or up to 2-4 weeks reported 3% of elevated AST grade 1 with no reported of elevated ALT. We hypothesize that longer NVP exposure may increase risk to develop elevated transaminase, however there was no clinical and statistically significant difference with ZDV prophylaxis. Another concern of NVP side effects was rash or hypersensitivity. The hypersensitivity reactions in infants consisted of rash and were accompanied by eosinophilia, with or without fever(40). In previous study, hypersensitivity reaction was reported of 1.9% in HIV-exposed infants who received ZDV/3TC plus 28 weeks NVP(40). Our study found only one infant who received combination regimen and developed rash without eosinophilia. These data support low prevalence of side effects from NVP in terms of both elevate transaminase and rash. Comparable with previous study in neonates who received NVP-based ART prophylaxis found that neonates are generally well-tolerated through the first 4 weeks of life(41).

Regarding risk of HIV transmission, the target rate of transmission for elimination MTCT among non-breastfed infants is less than 2%(1). In published study, rate of HIV mother to child transmission among non-breastfed infants who do not received antiretroviral drug is 5.7% in utero and 4.8% during intrapartum period despite 6-week of ZDV prophylaxis(21). Therefore, combination of antiretroviral drug is needed in these high risk groups. The NICHD-HPTN 040/P1043 clinical trial evaluated different 3 regimens in high risk infant and found that HIV transmission rates were highest in the zidovudine-alone group (4.8% at 3 months vs. 2.2% in the two-drug group and 2.4% in the three-drug group). Therefore both the dual- and triple- combination regimens reduced the risk of intrapartum transmission by approximately 50% compared with infant prophylaxis with ZDV alone(21).

Although published evidence of the combination prophylaxis effectiveness, it remains limited data on efficacy of 6-week ZDV/3TC/NVP for HIV transmission prevention. Published study(42) demonstrated that estimated probability of peripartum HIV transmission among pregnant women who received ART less than 4 weeks was 7.6%. Our study showed that neonatal antiretroviral prophylaxis can decrease peripartum HIV transmission with rate of HIV transmission among definite HIV-exposed high risk infants who received triple antiretroviral drugs prophylaxis was 1.7% (95% CI 0.3%-8.9%). The lower rate may explained by effect of triple prophylaxis in neonates and also the use of raltegravir intensification in pregnant women. However, wide range of 95% CI of rate of mother-to-child HIV transmission in our study was found due to the limited sample size.

In terms of definition of high-risk infants, this study defined based on maternal viral load and ART duration which was similar to other guidelines, but using threshold of viral load >50 copies/mL or maternal ART less than 12 weeks before delivery which different from WHO guidelines(43) that high risk are defined as infants born to women with HIV viral load >1000 copies/mL in the four weeks before delivery; or born to women who have received ART less than 4 weeks at the time of delivery. These made more cases included in terms of high risk group in our study and also in practices in Thailand, aims to eliminate mother-to-child transmission of HIV.

As previously stated, combination prophylaxis is more effective than single-drug prophylaxis for the prevention of intrapartum mother-to-child transmission in infants born to mothers who received no antepartum ART(21). However, it still remains unclear whether dosage and duration of NVP prophylaxis are preferable to prevent HIV transmission. The 2016 WHO guidelines**(18)** recommended dual prophylaxis with ZDV twice daily and NVP once daily for the first 6 weeks of life. In the context of a public health approach, since 2010 the WHO has recommended infant NVP prophylaxis dosing using weight-bands(44). For

infants ≥2,500 grams and whose mother was receiving ART it was recommended to administer 15 mg of NVP once daily for 6 weeks. This weight band dosing was based on achieving sustained exposure among infants of >0.1 mg/L with the least dose change. Pharmacokinetics data of NVP in neonates starting 2 mg/kg at birth then switching 4 mg/kg at 7 days are available(45) but data in neonates starting 4 mg/kg at birth are lacking.

Our study complied with the standard of care in Thailand and initiated NVP 4 mg/kg at birth. Mean of NVP dosing from our study was 13 mg in infants BW ≥2500 g and 9 mg in infants BW <2500 g, which is close to the WHO weight-band dosing (15 mg if BW≥2500 g and 10 mg if BW < 2500 g). Thus, our results are reassuring for the Thai and can also provide evidence to support the WHO weight band dosing for high risk infants in terms of achieving sustained NVP exposure >0.1 mg/L. However, the lower dose in our study may bias towards lower risk of side effects compared with WHO dosing regimens.

Also, NVP is initiated for HIV treatment using a lower lead-in dose for 2 weeks due to auto-induction of its own metabolism(28) and to lower the risk of adverse events but it is unclear if this lead-in period is also necessary when initiating NVP prophylaxis. In South Africa, a NVP prophylaxis dose of 2 mg/kg once daily for the first 2 weeks followed by 4 mg/kg once daily was evaluated in low birth weight infants. This dose strategy was shown to achieve target prophylactic concentrations in infants <2000 grams(25). Other study in Canada looking at neonates GA ≥32 weeks whose lead-in NVP was dosed at 150 mg/m2 daily for the first 2 weeks then twice daily for 14 days, this body surface area-based dosing was approximately 2 to 4 times compared to dosing in our study aimed to achieved therapeutic target trough 3-8 mg/L, found that NVP trough levels was normalization over the first 4 weeks of life. Interestingly, prematurity GA<34 weeks were significantly associated with higher drug exposure and lower empiric dosing is recommended(41). Contrast to our result that we could not identify significant differences of predicted NVP C_{24} among term and

preterm infants. This may explain by the small number of preterm in our study. In a separate study in Thailand, where infants received triple prophylaxis of ZDV/3TC/NVP for 2 weeks; NVP dosing 2 mg/kg for 7 days, then 4 mg/kg for 7 days (in the presence of maternal intrapartum single dose NVP) model simulations for a 3-kg infant at birth predicted that >99% of infants would attain NVP trough concentrations >0.1 mg/L after 2 days, although this would decrease to approximately 93% at 14 days of life(45). Our study demonstrates that initiating NVP 4 mg/kg at birth rapidly achieved prophylactic target concentrations during the first week of life. Interestingly, without a dose adjustment at 14 days, NVP concentrations dropped more than 50% between the second and fourth week of life. This decrease of NVP concentrations with time may be explained by maturation of liver enzymes in infants and also a decline of actual dose per weight. Nevertheless, despite this decline all infants maintained NVP concentrations above prophylactic target level through the first month of life. The pharmacokinetic data from this study support the weight-band dosing without adjustment in the first 4-6 weeks of life. For implementation, triple regimen with NVP dosing 4 mg/kg initiating at birth may apply in resource-limited settings to simplify the regimen with adequate level for prophylaxis.

EFV is commonly used as combination antiretroviral therapy in pregnant women in resource-limited settings. Maternal EFV can transfer to their infants across placenta with a reported cord blood/maternal concentration ratio of 0.49(9). To date, no data on EFV ‘washout’ in infants has been reported. In our study, EFV concentrations in infants were detectable in the first 48 hours, then dropped and were undetectable after the first week of life. Although, NVP and EFV are metabolized primarily by the same isoenzymes CYP2B6 isoenzymes, our study found that maternal EFV treatment did not affect infant NVP concentrations.

This is a large study with complete follow-up 94% retention on safety of combination prophylaxis regimen of 6-week ZDV/3TC/NVP includes pharmacokinetic data of NVP in high risk HIV exposed neonates. We also included infants received ZDV alone prophylaxis for comparison. In addition, the observational study made less missing laboratory data compared to a retrospective study. The limitation was the lack of liver function test at age 2 weeks which typical time for hepatotoxicity occurrence. This is because the study procedures aim not to disturb regular follow-up and wish not to add on number of phlebotomy. The limitation of NVP concentrations study was we did not include preterm GA <34 weeks and we have only one case with BW <2000 g who may require lead-in dosing due to potential for supratherapeutic levels(41). The data on how NVP 4 mg/kg/day affect NVP concentrations in these premature neonates are lacking and need for additional study.

In conclusion, 6-weeks of combination triple prophylaxis consisting of ZDV/3TC/NVP with administration of NVP 4 mg/kg once daily from birth in high-risk HIV-exposed neonates appears to be safe and provides adequate NVP concentrations above the prophylactic target level during the first month of life. These findings also support the weight-band dosing without lead-in period of NVP prophylaxis

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