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Randomized non-inferiority trial of two maternal single-dose nevirapine sparing regimens to prevent perinatal HIV in Thailand (PHPT-5)

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Abstract

Objectives—Perinatal single-dose nevirapine (sdNVP) selects for resistance mutations. The objective of this trial was to compare two maternal sdNVP-sparing regimens with standard zidovudine (ZDV)/sdNVP prophylaxis.

Design—PHPT-5 was a randomized, partially double-blind placebo-controlled, non-inferiority trial in Thailand (NCT00409591). Subjects were women with CD4 ≥ 250 cells/mm³ and their infants.

Methods—All women received ZDV from 28 weeks' gestation and their newborn infants for one week. Women were also randomized to receive A) NVP-NVP (reference): maternal intrapartum sdNVP with a 7-day "tail" of ZDV+lamivudine, plus infant NVP (one dose immediately, another 48 hours later); B) Infant-only NVP: maternal placebos for sdNVP and the "tail", plus infant NVP; C) LPV/r: maternal LPV/r starting at 28 weeks. Infants were formula-fed. HIV-diagnosis was determined by DNA-PCR.

Results—435 women were randomized between January 2009 and September 2010. Accrual was terminated prematurely following a change in Thai guidelines recommending antiretroviral combination therapy for all pregnant women. Data on 405 mothers and 407 live-born children were analyzed. Baseline characteristics were similar between arms. Intent-to-treat transmission rates were 3.8% (95% CI: 1.2–8.6) in NVP-NVP, 1.6% (0.2–5.6) in infant-only NVP and 1.4% (0.4–5.1) in LPV/r arms. As-treated rates were 2.2% (0.5–6.4), 3.2% (0.9–7.9) and 1.5% (0.2–5.2), respectively. Factors independently associated with transmission were prophylaxis duration <8 weeks (aOR 15.5; 3.6–66.1) and viral load at baseline ≥ 4 log₁₀ copies/mL (aOR 10.9; 1.3–91.5). Regimens appeared safe.

Conclusions—Transmission rates in all arms were low but non-inferiority was not proven. Antiretroviral prophylaxis for ≥ 8 weeks before delivery is necessary to minimize transmission risk.

Keywords

HIV; Prevention of Mother-to-child transmission; Antiretroviral Therapy; Clinical trial; Thailand

INTRODUCTION

Thai national 2007 [1] and WHO 2006 guidelines for prevention of mother-to-child transmission of HIV (PMTCT) in non-breastfeeding women [2] recommended until their 2010 revision [3] that women not requiring antiretroviral treatment for their own health—CD4 count ≥ 250 cells/mm³—receive zidovudine (ZDV) from 28 weeks' gestation (or as soon thereafter as possible) plus single-dose nevirapine (sdNVP) at onset of labor, and the newborn sdNVP at 48 to 72 hours of life, plus one week of ZDV. This regimen was simple, safe and efficacious, reducing HIV mother-child transmission (MTCT) to approximately 2% [4]. However, if women or infected infants exposed to nevirapine for PMTCT initiated non-nucleotide-reverse-transcriptase (NNRTI)-based antiretroviral therapy for their own health, virologic efficacy was decreased, possibly due to HIV resistance mutations [5–7]. These mutations could be partially prevented by administering a 2- or 3-drug "tail" to the mother

started immediately after sdNVP and lasting 1–4 weeks postpartum [8–10]. Moreover, a trial in Botswana had showed that sdNVP, given only to the child at birth, resulted in an intrapartum transmission rate not significantly higher than sdNVP provided to both mother and child [11]. In light of these results, plus emerging information that the protease inhibitor (PI) ritonavir-boosted lopinavir (LPV/r) by itself could lower viral load (VL) over a 2–3 month period to a similar extent as LPV/r plus ZDV-plus-lamivudine [12], we designed a 3-arm non-inferiority trial to compare the Thai standard of the time (ZDV from 28 weeks' gestation with sdNVP to mother and child) with two NVP-sparing regimens: ZDV starting at 28 weeks plus infant-only peripartum NVP; and ZDV plus LPV/r from 28 weeks, with no NVP. Lamivudine (3TC) was not added to LPV/r in order to avoid additional drug resistance and potential hepatotoxicity after 3TC interruption in a country where chronic hepatitis B infection is endemic [13, 14].

Following the 2010 revision of the WHO PMTCT guidelines [3], the Thai Ministry of Public Health modified its guidelines on October 1st 2010 to recommend ZDV + 3TC +LPV/r in all pregnant women regardless of their immunological status, starting after the end of the first trimester of pregnancy [15]. Enrollment in our protocol was stopped and, upon recommendation by the Data Safety Monitoring Board (DSMB), the study was unblinded and preliminary results communicated to the co-investigators. We report here the efficacy and safety results of the trial.

METHODS

Trial design

PHPT-5 (NCT00409591) was a multicenter, phase 3, randomized, partially double-blind and placebo-controlled trial for women not eligible to initiate HAART during pregnancy for their own health, that is, with CD4 cell counts $\geq 250/\text{mm}^3$. All women received 300 mg of ZDV twice daily starting at 28 weeks' gestation or as soon as possible thereafter and 300 mg orally every 3 hours during labor, and all infants received 2 mg of ZDV per kilogram every six hours for one week after birth (6 weeks if their mothers had received ZDV for <4 weeks). The three randomized arms were:

- A. NVP-NVP arm (reference [4]): maternal intrapartum sdNVP 200 mg tablet (Boehringer-Ingelheim, Germany) plus a 7-day “tail” of ZDV 300 mg plus 3TC 150 mg twice daily starting immediately after delivery, and infant NVP (6 mg orally immediately after birth and again 48–72 hours after birth; for newborns weighing <2500 g, the dose was reduced to 2 mg/kg).
- B. Infant-only NVP arm: maternal placebos for sdNVP and the “tail,” and infant NVP as in arm A.
- C. LPV/r arm: maternal LPV/r 400/100 mg twice daily (Aluvia, Abbott Park, Illinois, USA) from 28-weeks' gestation or as soon as possible thereafter until delivery.

Participants

Eligible subjects were confirmed HIV-infected pregnant women participating in the Thai national PMTCT program who intended delivery and postnatal care at one of 43 study sites.

Women were enrolled if they had provided written informed consent, were >18 years of age, antiretroviral treatment-naïve (except for PMTCT of HIV), 28–36 weeks' gestational age, with CD4 count ≥ 250 cells/mm³, and had the following laboratory values within 14 days of enrollment: hemoglobin ≥ 8.5 g/dL, absolute neutrophils ≥ 750 cells/mm³, platelets $\geq 50,000$ cells/mm³, serum alanine aminotransferase $< 5\times$ the upper limit of normal, and serum creatinine $< 1.5\times$ the upper limit of normal. On June 4, 2010, following Thai adult treatment recommendations [15], the CD4 exclusion criteria for women were raised from < 250 to < 350 cells/mm³. Other exclusion criteria were WHO class III/IV HIV-associated disease, life-threatening fetal anomalies, active tuberculosis or contraindications to the study drugs.

Randomization and blinding

Randomization was performed centrally by fax, balancing treatment assignments in a ratio of 1:1:1. Participants were randomly assigned in blocks of six, stratified by site, gestational age (below or ≥ 32 weeks) and until June 4, 2010 by CD4 count (below or ≥ 350 cells/mm³). Randomization lists were encrypted in a database before study initiation. Maternal sdNVP and ZDV+3TC tail in Arms A and B were double blinded. Replacement NVP or matching PL doses as well as tail treatments were accessible in a blinded fashion at any participating hospital with the use of a code.

Follow-up

Women had an obstetrical examination and hematologic and biochemical testing every month until delivery. After delivery, they were seen at 7–10 days, 1 and 6 months for physical examination and laboratory tests. VL (Abbott m2000 RealTime© HIV-1 assay) and CD4 cell count were measured at baseline and delivery. C-section was planned upon decision of the obstetrical team, following the national guidelines [1]. Also by Thai guidelines, women were advised not to breastfeed, and formula milk was provided to mothers who, in the judgment of the medical team, would have difficulty purchasing it [1].

Infants were examined at birth, 7–10 days, one, two, four and six months. At each visit, the child's interval history was recorded and a physical examination performed. Blood was obtained for HIV diagnosis at birth (within 24 hours), 7–10 days, one, two, four and six months, hematology at birth, 7–10 days and 1 month, and chemistry at birth and 7–10 days.

Primary endpoint

Real-time DNA polymerase chain reaction (PCR) assay was performed on peripheral blood spotted onto filter papers, dried, and stored at -20°C [16]. The primary endpoint was infant HIV infection: two positive PCR tests in blood obtained on two separate occasions. Infants were considered uninfected if PCR results were negative twice after one month of age. For HIV-infected infants, transmission was labeled “in utero” if the sample obtained within 3 days of birth was positive and “intrapartum” when it was negative [17]. Twins and triplets were considered as a single entity, infected if at least one was HIV-infected.

Safety and adherence

Adverse event grading was based on the Division of AIDS, NIAID Table [18]. Serious adverse events (SAEs) were reported to the Ministry of Public Health, and to

GlaxoSmithKline and Boehringer Ingelheim if possibly related to study drugs. Study drug adherence was assessed at each visit by counting pills. Maternal NVP/placebo intake was directly observed. At each visit, mothers were interviewed about adherence to formula feeding.

Sample size

The study was designed to test for non-inferiority between the experimental and reference arms i.e. 95% confidence that the transmission rate difference does not exceed a predefined delta of 1.5%, considered as relevant from a clinical and public health perspective in Thailand. Based on our previous PHPT-2 study, we estimated the transmission rate in the reference group at 1.1% [4]. Using a 1-sided approach, a sample size of 664 evaluable patients per arm would ensure 80% power to rule out a difference greater than the predefined delta (PASS Package, Kaysville, Utah, USA). Assuming 5% unevaluable, 699 patients per arm were required.

Statistical Methods

Characteristics were compared among treatment groups using chi-square and Kruskal–Wallis tests. Non-inferiority was tested by intent-to-treat and as-treated analyses using the exact confidence intervals of the difference in transmission rates. Univariate and multivariate analyses including baseline, pregnancy and delivery characteristics were performed to identify factors associated with transmission using logistic regression.

Ethics

The ethics committees of the Thai Ministry of Public Health, the Faculty of Associated Medical Sciences of Chiang Mai University, the Harvard School of Public Health and local hospitals approved the protocol. All study sites complied with research regulations of the United States Department of Health and Human Services.

RESULTS

Between January 9, 2009 and September 30, 2010, 1,210 HIV-infected pregnant women were screened for eligibility and 435 randomly assigned to study treatment. Enrollment, loss to follow-up, pregnancy outcomes, and available end points for each treatment group are summarized in Figure 1. Among the 435 women randomized, one was lost to follow-up and 6 withdrew before delivery. A total of 428 women delivered in the study including 4 who had stillbirths. 430 children were born alive, including 425 single, 4 twin, and 1 triple births. Because they delivered after the study was unblinded, 23 women and their infants were not included in the final analysis. This analysis is restricted to data from enrollment until 6 months after birth/delivery.

Characteristics of the women, deliveries, and infants

Characteristics of the women and newborns are presented in Table 1. At baseline, the median (Interquartile Range (IQR)) age was 27 (23–32) years, gestational age 28.6 (28.1–30.4) weeks, median CD4 453 (363 – 577) cells/mm³ and VL 4.0 (3.4–4.4) log₁₀ copies/mL. Almost all women were in WHO stage 1, and 4.9% and 3.2% of women were infected with

hepatitis B and C virus, respectively, with no difference between arms. Twenty-one women had been exposed to ART previously for PMTCT, 7 in each arm.

At delivery, median gestational age was 38.7 (37.8–39.7, 13.3% $\leq$ 37 weeks) with no difference between arms. The median duration of ZDV therapy was 10.1 (8.6–11.1) weeks. Thirty-one percent of deliveries were by cesarean section—47% of these before onset of labor. The median CD4 was 552 (414–689) cells/mm³, and the median VL at delivery was significantly lower in the LPV/r arm (1.6 log₁₀ copies) than in the 2 other arms (3.6 log₁₀ copies) ($p < 0.001$). The median infant birth weight was 3.0 kg (2.7–3.3), with no difference between arms (Table 1).

Study drug administration and adherence

There was no difference in timing of study drug administration between the NVP-NVP and infant-only NVP arms (Table 1). Adherence to study visits was above 99% in women and 100% in infants. Based on the pill count of drug returned, adherence was above 90% in 96.8% of the women for ZDV (similar in the 3 arms), and in 95.2% of them for LPV/r. Four percent (17/405) of women did not receive the intrapartum ZDV and 3% (8/263) did not receive the ZDV+3TC/placebo tail (no difference between study arms). Adherence to postnatal ZDV prophylaxis as assessed by the pediatrician was excellent in 98% of the infants. Only 6 infants (1.2%) received ZDV for less than 6 days, while 5.4% received it for more than one month because their mothers had received less than four weeks of ZDV prophylaxis (no difference between arms). Eight women did not receive their study drug before labor, 5 in the NVP-NVP arm and 3 in the infant-only NVP arm. All infants received their 1st NVP dose and only 1 did not receive the 2nd dose.

Efficacy analysis

End points were available for 402 (98.8%) of the 407 live-born infants included in the analysis. A total of 9 HIV transmissions occurred with no significant difference between groups (Table 2). Five transmissions were considered to have occurred *in-utero* and 4 *intra-partum*. The as-randomized transmission rate among those in the NVP-NVP group was 3.8% (95% CI, 1.2–8.6), 1.6% (0.2–5.6) in the infant-only NVP group and 1.4% (0.4–5.1) in the LPV/r group. The difference in transmission rate between infant-only NVP and the reference arm (NVP-NVP) was –2.2% (–5.5% to +1.1%) and that between LPV/r and the reference arm was –2.3% (–5.5% to +0.8%). The upper limit of the confidence interval of the difference in rates between infant-only NVP and NVP-NVP as well as LPV/r and NVP-NVP fell within the pre-defined non-inferiority limit of 1.5%.

As-treated transmission rates were as follows: 2.2% (0.5–6.3), 3.2% (0.9–8.0), and 1.5% (0.2–5.2), respectively (Table 2). The transmission rate difference between infant-only NVP and the reference arm (NVP-NVP) was 1.0% (–2.3% to +4.3%) and that between LPV/r and the reference arm was –0.7% (–3.4% to +2.0%). In both comparisons the upper limit of the confidence interval of the difference in rates exceeded the predefined non-inferiority threshold of 1.5%.

Among the 9 transmitting mothers, maternal VL at entry ranged from 3.1 to 5.7 log₁₀ copies/mL, CD4 count from 261 to 628 cells/mm³, ZDV prophylaxis duration from 27 to 77

days (6 <4 weeks), 4 women delivered prematurely, and only one delivered by C-section (but after onset of labor).

Risk factors for transmission

Univariate and multivariate analyses of factors associated with HIV transmission are provided in Table 3. By univariate analysis, the gestational age at start of ZDV, and baseline VL and CD4 count were significantly associated with transmission, as well as premature delivery and duration of antiretroviral prophylaxis <8 weeks. In the multivariate analysis, factors remaining independently associated with transmission were VL 4 log₁₀ copies/ml at baseline (aOR 10.9; 95% CI 1.3–91.5) and duration of antiretroviral prophylaxis <8 weeks (aOR 15.5; 3.6–66.1).

Maternal and infant safety

Table 4 provides the maternal and infant safety events for each arm. Fifty-four women (13.1%) experienced 64 SAEs during pregnancy. The rate was significantly higher in the LPV/r arm compared to the 2 other arms combined (21.4% vs. 12.4%, $p=0.024$). Overall SAEs were related to pregnancy (47%), delivery complications (14%), or infections (19%); only 3% were related to HIV. During pregnancy, women in the LPV/r arm had more frequent hypercholesterolemia and hypertriglyceridemia than in the other 2 arms combined ($p<0.01$). No severe rashes were observed and only mild rashes occurred in 2 mothers 10 days postpartum (Table 4A).

The rates of adverse pregnancy outcomes (Table 4B) including stillbirth, preterm, very preterm delivery, low and very low birth weight and small for gestational age (defined as <10th percentile of the Thai norms [19]) did not differ between the LPV/r arm and the 2 other arms combined.

One hundred SAEs were reported among 75 infants (18.4%) until 6 months of age (Table 4C), with no differences between arms. Most events were related to infections, 11% possibly related to ART (mostly anemia and neutropenia), and 13% to HIV. There was one neonatal death from congenital heart malformation at 1 day of life in the infant-only NVP group. In the LPV/r group, one death occurred at 30 days, following surgery for congenital intestinal obstruction.

DISCUSSION

This 3-arm randomized clinical trial compared, in a formula-fed population, two NVP-sparing maternal regimens with the regimen that was recommended by WHO at the time of the trial, 3rd-trimester ZDV plus sdNVP [2]. The trial was stopped early because of a change in the Thai guidelines for PMTCT prophylaxis, and consequently full accrual was not achieved. Thus, although the observed transmission rates in the three arms were low and similar, both in the intention-to-treat and in the as-treated analyses, the trial could not demonstrate the non-inferiority of the experimental arms compared to the reference. Nevertheless, several important conclusions can be drawn.

In multivariate analysis, two critical risk factors for transmission were identified: antiretroviral treatment of less than 8 weeks during pregnancy, and high baseline maternal HIV viral load. Late commencement of maternal antiretroviral prophylaxis poses its risk through two separate mechanisms: first, transplacental HIV transmission before antiretrovirals have reached the fetus to provide pre-exposure prophylaxis and before maternal VL has been reduced, and, second, residual circulating maternal virus at delivery, the time of highest risk of transmission. The first of these two mechanisms applies to all prophylactic regimens but particularly to those containing drugs that readily cross the placenta, such as ZDV. The second pertains particularly to regimens containing drugs such as LPV/r that lower maternal VL but may not readily cross the placental barrier. Two studies of LPV/r in women during pregnancy have shown that VL consistently drops below 400 copies/ml and usually below 50 copies/mL 8–10 weeks after starting LPV/r alone [20], or as part of a HAART regimen [21]. Similarly in a sub-study of this trial [22], all women achieved viral load below 400 copies/mL after 8 weeks of ZDV plus LPV/r therapy.

The risk posed by high VL at delivery could probably be minimized by antiretroviral intensification in the peripartum period. Two- or three-drug infant post-exposure prophylaxis appears to be effective even when mothers present at delivery and have received no prophylaxis [23]. Data from this study suggest that 8 weeks is the interval below which women and their infants may need perinatal intensification, such as sdNVP and, in their infants, four weeks of combination antiretrovirals, as recommended in national and international guidelines [9, 15]. The benefit of postnatal antiretroviral intensification should be evaluated in this high risk situation.

VL at entry was significantly associated with overall transmission whereas VL at delivery was not. We believe the latter finding was a consequence of the fact that LPV/r which probably prevents intrapartum transmission primarily through reduction in viral load [24–26] was administered in only one arm. In the other two arms ZDV was the only drug administered during pregnancy, along with sdNVP to mother and/or infant at delivery. ZDV in this setting blocks transmission primarily by transplacental pre/post exposure prophylaxis in the fetus (and has little effect on VL)[27–30], and sdNVP, which also readily crosses the placenta, very likely also functions primarily by this mechanism [31, 32].

The fact that two transmissions in the NVP-NVP group occurred in women who had not received their assigned NVP treatment confirms that ideal prophylaxis should not have to depend on delivering a critical drug (sdNVP) in a setting where it may not be readily available, and in this sense a regimen such as LPV/r with one or two nucleotide-reverse-transcriptase inhibiting (NRTI) drugs taken during pregnancy is more accident-proof.

Several clinical trials of HIV PMTCT have tested maternal and infant regimens similar or close to those in our study. The study by Shapiro and colleagues compared maternal-plus-infant NVP at delivery with infant-only-NVP [11] in a regimen where mothers received ZDV monotherapy from 34 weeks' gestation. Infant infection rates at one month were not different between the maternal-plus-infant NVP and the infant-only NVP arms. Intrapartum infections were also not significantly different. The Kesho Bora study compared ZDV-plus-sdNVP prophylaxis with LPV/r-based HAART for prevention of MTCT in a mostly

breastfed population –78% were ever breast-fed— [33]. Infant HIV infection rates at 6 weeks of age were not significantly different. The PRIMEVA randomized trial in France compared LPV/r alone with a ZDV+3TC+LPV/r regimen starting at 26 weeks' gestation [20]. The rate of virological suppression <200 copies/ml 8 weeks after starting was the primary endpoint, and was not significantly different in the two groups. The only transmission was observed in the ZDV+3TC+LPV/r group. Finally, the large PROMISE trial (P1077, NCT01253538) compared two LPV/r-based regimens (one in addition to ZDV-plus-3TC, one in addition to tenofovir-plus-emtricitabine) vs. a ZDV-plus-sdNVP regimen almost identical to our reference arm. Infant infection rates were 1.8% in the ZDV-plus-sdNVP group, 0.5% in the ZDV+3TC+LPV/r group, and 0.6% in the tenofovir-plus-emtricitabine-plus-LPV/r group ($p<0.008$), showing the superiority of a LPV/r-plus-2 NRTIs regimen compared to ZDV-plus-sdNVP [34]. These rates were lower than those observed in our “as-treated” analysis, perhaps because women in our study initiated ART at 28 weeks (or later) gestation, while in PROMISE, median gestational age at enrollment was 26 weeks.

In this study, all interventions appeared safe with low rate of adverse pregnancy outcomes in all arms, but significantly more maternal SAEs in the LPV/r arm. The difference was related to a higher rate of pregnancy disorders in the LPV/r arm. The association between the use of PI during pregnancy with the risk of preterm, low birth or stillbirth is debated [34, 35]. The higher incidence of hypercholesterolemia and hypertriglyceridemia observed in women receiving the LPV/r arm compared to the other 2 arms can be attributed to the well-known dyslipidemic effect of LPV/r [36]. However, these cholesterol or triglyceride elevations were not associated with any acute clinical events. The MONARK study [12] had demonstrated that LPV/r mono-therapy had similar efficacy to ZDV+3TC+LPV/r in reducing VL after 24 weeks. Therefore, although ZDV+3TC+LPV/r would have been a more standard regimen, we chose to use ZDV+LPV/r to prevent the risk of hepatotoxicity after treatment interruption or additional resistance related to 3TC.

The major limitation in this study was its early closure following the change in Thai National PMTCT guidelines [14], which prevented definitive conclusions about comparative efficacy of the arms. The rise in the CD4 exclusion criteria for women from <250 to <350 cells/mm³ necessitated by new Thai adult treatment recommendations [1] had no impact on the results because randomization was stratified according to the CD4 level, less or above 350 cells/mm³.

In summary, this randomized three-arm trial of antiviral regimens to prevent MTCT of HIV was stopped early because of changes in national treatment guidelines and failed to show the equivalence of the regimens, but it also demonstrated several important points. First, rates of transmission in all three study arms were low. Second, women who received prophylaxis for less than 8 weeks were significantly more likely to transmit HIV, and it appears likely that, when mothers receive a shorter treatment during pregnancy, intensification in the *peripartum* period would be useful in further reducing transmission.

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Appendix

Study sites, Co-Investigators and number of participants enrolled

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Prachanukroh Hospital, Dr. Jullapong Achalapong, Dr. Kanchana Preedisripipat, Dr. Rawiwan Hansudewechakul (15); Prapokklao Hospital, Dr. Prapap Yuthavisuthi, Dr. Chaiwat Ngampiyaskul (14); Nakornping Hospital, Dr. Aram Limtrakul, Dr. Suparat Kanjanavanit (14); Health Promotion Center Region 10, Dr. Suraphan Sangsawang, Dr. Kanokwan Jittayanun (13); Khon Kaen Hospital, Dr. Thitiporn Siriwachirachai, Dr. Trakarn Saelim, Dr. Sirijitt Wasanawatna (11); Maharaj Nakhon Si Thammarat Hospital, Dr. Sukit Mahattanan, Dr. Somsri Kotchawet (11); Phayao Provincial Hospital, Dr. Jittapol Hemvuttiaphan, Dr. Pornchai Techakunakorn (10); Vachira Phuket Hospital, Dr. Sompong Wannun, Dr. Somnuk Chirayus, Dr. Weerasak Lawtongkum (10); Songkhla Hospital, Dr. Supha-arth Phon-in, Dr. Wannee Limpitkul (10); Mae Chan Hospital, Dr. Surachai Piyaworawong, Dr. Sudanee Buranabanasatean (8); Chonburi Hospital, Dr. Nantasak Chotivanich, Dr. Suchat Hongsiwong (8); Pathumthani Hospital, Dr. Boonrak Wiriyachoke, Dr. Kallaya Srinavarat (8); Phaholpolpayuhasaena Hospital, Dr. Yupa Srivarasat, Dr. Pornsawan Attaviniytrakarn (7); Chiang Kham Hospital, Dr. Chaiwat Putiyanun, Dr. Vanichaya Wanchaitanawong (6); Phan Hospital, Mr. Sookchai Theansavetrakul, Dr. Sivaporn Jungpichanvanich (6); Lampang Hospital, Dr. Prateung Liampongsabuddhi, Dr. Sukanya Pituksiripan, Dr. Kultida Pongdetudom (6); Fang Hospital, Dr. Jantana Jungpipun, Dr. Areerat Limpastan (6); Panasnikom Hospital, Dr. Manoch Chakorngowit, Dr. Wisith Pholsawat (6); Regional Health Promotion Centre 6, Khon Kaen, Dr. Kraisorn Vivatpatanakul, Dr. Narong Winiyakul, Dr. Sansanee Hanpinitak (5); Mahasarakham Hospital, Dr. Sakchai Tonmat, Dr. Pairoaj Sitsirat, Dr. Sathaporn Na-Rajsima (5); Trat Hospital, Dr. Sompong Kittipibul, Dr. Suleng Laomanotham (5); Bhuddasothorn Hospital, Dr. Annop Kanjanasing, Dr. Ratchanee Kwanchaipanich (4); Pranangkla Hospital, Dr. Surachai Pipatnakulchai, Dr. Paiboon Lucksanapisitkul (4); Chomthong Hospital, Dr. Arunsri Iamthongin, Dr. Apichai Phiyarom (4), Wiangpapao Hospital, Dr. Toranong Pilalai (4); Nong Khai Hospital, Dr. Nusra Puarattana.aronkorn, Dr. Sathit Potchalongsin (3); Kalasin Hospital, Dr. Bunpode Suwannachai, Dr. Sakulrat Srirojana (3); Lamphun Hospital, Dr. Wanmanee Matanasarawut, Dr. Pornpun Wannarit (2); Mae Sai Hospital, Dr. Rattakarn Paramee, Dr. Sirisak Nanta (2); Health Promotion Hospital Regional Center I, Dr. Somsak Wachirachaikan, Dr. Surat Sirinontakan (2); Queen Sirikit Hospital, Dr. Pradchaya Kerdkrung, Capt. Temsiri Hinjiranandana (2); Buddhachinaraj Hospital, Dr. Kanchanpan Sukonpan, Dr. Narong Lertpienthum (2); Chiang Saen Hospital, Dr. Ittipol Chaitha (2); Sanpatong Hospital, Dr. Prayoon Khamja, Dr. Noppadon Akarathum (0)

Figure 1. Participants flow chart

*Among the 775 women who were not enrolled: 26 moved to another town or were lost to follow-up, 13 delivered before pre-enrollment evaluations, 22 terminated their pregnancy, 369 started highly active antiretroviral therapy, 272 did not meet the inclusion criteria, 66 had other reasons and 7 women, already screened, were not randomized following the termination of the study after the changes in the national guidelines.

Table 1

Characteristics of women at enrollment, delivery and neonates

Maternal Characteristics at enrollment		NVP-NVP (N=138)	Infant-only NVP (N=129)	LPV/r (N=145)	All (N=412)
Median Age (Interquartile range)(IQR) (years)		27 (23.0–32.0)	28 (23.0–33.0)	27 (23.0–32.0)	27 (23.0–32.0)
Median gestational age at enrollment (IQR) (weeks)		28.7 (28.3–31.0)	28.6 (28.1–30.4)	28.4 (28.1–30.4)	28.6 (28.1–30.4)
Median CD4 count (IQR) (cells/mm ³)		456 (366–577)	452 (360–568)	451 (363–583)	453 (363–577)
Median Viral load (IQR) (log ₁₀ copies/mL)		4.0 (3.5–4.6)	3.9 (3.4–4.3)	4.1 (3.4–4.5)	4.0 (3.4–4.4)
WHO classification stage 2 (%)		2.9	1.6	2.1	2.2
Median gestational age at start of ZDV (IQR) (weeks)		28.4 (28.0–29.0)	28.3 (28.0–28.9)	28.3 (28.0–29.0)	28.3 (28.0–28.9)
Median Hemoglobin level (IQR) (g/dL)		11.2 (10.4–11.8)	11.0 (10.4–11.6)	11.1 (10.5–11.7)	11.1 (10.4–11.7)
Hepatitis B surface antigenemia (%)		4.4	5.4	4.8	4.9
Hepatitis C antibodies (%)		4.4	2.3	2.8	3.2
Exposure to PMTCT during a previous pregnancy (%)		4.9	5.0	4.6	4.8

Delivery Characteristics (excluding women who delivered after study unblinding)		NVP-NVP (N=135)	Infant-only NVP (N=128)	LPV/r (N=142)	All (N=405)
Median length of gestation at delivery (IQR) (weeks)		38.7 (37.8–39.6)	38.9 (37.9–40.0)	38.5 (37.6–39.5)	38.7 (37.8–39.7)
Median duration of ZDV therapy (IQR) (weeks)		10.1 (8.4–11.1)	10.3 (9.1–11.4)	10.0 (8.6–11.1)	10.1 (8.6–11.1)
Median time from onset of labor to maternal study drug administration (hours)		3.0 (1.7–5.9)	2.9 (1.5–5.6)	-	3.0 (1.6–5.6)
Median time from maternal study drug administration to delivery (hours)		4.4 (1.9–8.4)	4.0 (1.6–7.8)	-	4.2 (1.7–8.1)
Median duration of membranes rupture (hours)		0.5 (0.1–2.0)	0.3 (0.1–2.2)	0.6 (0.1–3.5)	0.5 (0.1–2.7)
C-section delivery (%)		28.9	31.3	31.7	30.6
Among C-section, % before onset of labor and rupture of membranes		43.6	52.5	44.4	46.8
Median CD4 count (IQR) (cells/mm ³)		533 (400–728)	515 (401–681)	558 (434–679)	552 (414–689)
Median Viral load (IQR) (log ₁₀ copies/mL)		3.7 (3.0–4.2)	3.5 (3.1–4.0)	1.6 (1.3–2.0)	3.1 (1.9–3.8)

Characteristics of live-born infants		NVP-NVP (N=134)	Infant-only NVP (N=130)	LPV/r (N=143)	All (N=407)
Male sex (%)		49.3	53.1	46.2	49.4
Median Birth weight (IQR) (kg)		3.0 (2.7–3.3)	3.0 (2.8–3.3)	2.9 (2.6–3.2)	3.0 (2.7–3.3)

Table 2

Intent-to-treat and as-treated transmission rates

	NVP-NVP	Infant-only NVP	LVP/r
Intent-to treat	N=132	N=126^a	N=138^b
HIV infections (<i>in utero</i>)	5 (3)	2 (1)	2 (1)
Rates (95% CI)	3.8% (1.2% to 8.6%)	1.6% (0.2% to 5.6%)	1.4% (0.4% to 5.1%)
Delta (95% CI)		-2.2% (-5.5% to +1.1%)	-2.3% (-5.5% to +0.8%)
As treated^c	N=136	N=125	N=135
HIV infections (<i>in utero</i>)	3 (2)	4 (2)	2 (1)
Rates (95% CI)	2.2% (0.5% to 6.3%)	3.2% (0.9% to 8.0%)	1.5% (0.2% to 5.2%)
Delta (95% CI)		1.0% (-2.3% to +4.3%)	-0.7% (-3.4% to +2.0%)

^aExcluding 2 concordant triplets^bExcluding 4 concordant twins

^cProtocol deviations included 3 women randomized to the LPV/r group who received sdNVP as well as their infants –2 because of LPV/r toxicity and the other one because she delivered in a non-study hospital. These women were considered in the NVP-NVP group in the as-treated analysis; 5 women randomized to the NVP-NVP arm did not receive intrapartum sdNVP. Among them, the 4 women who delivered a liveborn infant were considered in the infant-only NVP group in the as-treated analysis; 5 women randomized to the Infant-only NVP arm received open label sdNVP intrapartum instead of the study treatment and were considered in the NVP-NVP group in the as treated analysis. There was one report of breast-feeding by the mother.

Table 3Maternal and infant characteristics^a associated with perinatal HIV transmission

	Odds Ratio (OR)	95% CI	P value	Adjusted OR	95% CI	P value
Maternal characteristics						
Gestational age at enrollment 30 weeks	3.2	0.9–12.3	0.085			
Length of gestation at start of ZDV (30 weeks)	8.1	2.1–31.0	0.002			
Hemoglobin level 10 g/dl	0.5	0.1–2.3	0.343			
Viral load 4 log ₁₀ copies/ml at baseline	8.0	1.0–64.2	0.053	10.9	1.3–91.5	0.027
CD4 count <450 cells/mm ³ at baseline	8.4	1.0–67.6	0.046			
Viral load * CD4 count interaction	0.99	0.99–1.00	0.185			
Delivery Characteristics						
Length of gestation at delivery <37 weeks	5.7	1.5–21.8	0.012			
Duration of maternal ARV treatment <8 weeks ^b	12.3	3.0–41.8	0.001	15.5	3.6–66.1	<0.001
Viral load at delivery 3 log ₁₀ copies/mL	1.8	0.5–7.4	0.399			
Characteristics of live-born infants						
Birth weight < 2500g	3.5	0.9–14.6	0.081			
Female sex	1.2	0.3–4.7	0.748			

^a Characteristics explored in the univariate and multivariate analysis were the following: gestational age at enrollment 30 weeks, length of gestational at start of ZDV 30 weeks, Hemoglobin level 10 g/dL, Viral load 4 log₁₀ copies/mL at baseline, CD4 count <450 cells/mm³ at baseline, cesarean section, premature rupture of membranes, premature delivery (gestational age less than 37 weeks), duration of ZDV prophylaxis <8 weeks, viral load at delivery 3 log₁₀ copies/mL at delivery, birth weight <2500 grams, sex, interaction of the viral load and CD4 cell count.

^b Different cutoffs for the duration of ART during pregnancy were examined: a 12-week cutoff could not be tested because no transmission was observed in women with 12 weeks ART. The 10-week cutoff was not associated with transmission. The 8 and 6-week cutoffs were both associated with transmission with multivariate models equally fit, while the 4-week cutoff was not. Because our sub-study [22] had shown that all women achieved viral load below 400 copies/mL after 8 weeks of LPV/r+ZDV therapy, the 8-week cutoff was chosen. Also, in terms of public health implications, it seemed more appropriate to use the more inclusive cutoff.

Table 4

Maternal and infant safety

4 A. Safety in women		NVP-NVP N=138	Infant-only NVP N=129	LPV/r N=145	All N=412	p-value ^d
Women experiencing at least one SAE						
Number (%)		12 (8.7)	17 (13.2)	25 (17.2)	54 (13.1)	0.092
Number of SAEs		15	18	31	63	0.024
HIV-related		-	1	1	2	
Pregnancy related		5	7	18	30	
Delivery related		5	2	2	9	
Possibly ART related		-	2	4	5	
Infections		2	6	4	12	
Others		3	-	2	5	
Number of women with toxicity at least one time at any visit during pregnancy (%)						
Anemia grade 2		8 (5.8)	4 (3.1)	2 (1.4)	14 (3.4)	0.152
Fasting glucose grade 2		7 (5.3)	2 (1.6)	7 (5.0)	16 (4.1)	0.595
Fasting cholesterol grade 3		10 (8.1)	17 (14.7)	29 (22.0)	56 (15.1)	0.009
Fasting triglycerides grade 2		4 (3.2)	4 (4.3)	25 (18.9)	33 (8.8)	<0.001
Total bilirubin grade 1		5 (3.6)	3 (2.3)	10 (6.9)	18 (4.4)	0.078
SGPT grade 2		4 (2.9)	1 (0.8)	7 (4.8)	12 (2.9)	0.123
Rashes at delivery		-	-	-	-	
Rashes at 7–10 days post-partum		1 (0.7)	1 (0.7)	-	2 (0.5)	0.544
4 B. Adverse pregnancy outcomes						
		NVP-NVP (N=135)	Infant-only NVP (N=128)	LPV/r (N=142)	All (N=405)	p-value ^d
Stillbirths ^b		1 (0.7%)	0 (0%)	3 (2.1%)	4 (1.0%)	0.126
Preterm delivery (<37 weeks)		17 (12.6%)	16 (12.5%)	21 (14.8%)	54 (13.3%)	0.542
Very preterm deliveries (<34 weeks)		2 (1.5%)	3 (2.3%)	3 (2.1%)	8 (2.0%)	1.000
Low birth weight (<2500g)		17 (12.7%)	18 (13.9%)	21 (14.7%)	56 (13.8%)	0.763
Very low birth weight (<2000g)		3 (2.2%)	5 (3.9%)	5 (3.5%)	13 (3.2%)	0.776

4 B. Adverse pregnancy outcomes

	<u>NVP-NVP (N=135)</u>	<u>Infant-only NVP (N=128)</u>	<u>LPV/r (N=142)</u>	<u>All (N=405)</u>	<u>p-value^d</u>
Small for gestational age (< 10 th percentile ^c)	6 (4.5%)	6 (4.6%)	10 (7.0%)	22 (5.4%)	0.359

4 C. Safety in children during the first 6 months

	<u>NVP-NVP N=134</u>	<u>Infant-only NVP N=130</u>	<u>LPV/r N=143</u>	<u>All N=407</u>	<u>p-value^d</u>
Children experiencing at least one SAE					
Number (%)	26 (19.4)	26 (20.0)	23 (16.1)	75 (18.4)	0.476
Number of SAEs	36	32	32	100	0.423
Infections	13	11	20	44	
Birth related	6	7	4	17	
HIV related	9	4	-	13	
Possibly related to ART (anemia/neutropenia)	2	6	3	11	
Congenital anomalies ^b	-	3	2	5	
Others	6	1	3	10	
Neonatal death ^c	-	1	0	1	
Number of children with toxicity grade at least one time at any visit during the first 6 months (%)					
Anemia grade 2 at 1 month	34 (25.4)	40 (30.8)	46 (32.2)	120 (29.5)	0.437
Anemia grade 2 at 6 month	6 (4.5)	5 (3.8)	4 (2.8)	15 (3.7)	0.759
SGPT grade 2 at 7–10 days	-	2 (1.5)	1 (0.7)	3 (0.7)	0.422
Rashes at 7–10 days	3 (2.2)	2 (1.5)	2 (1.4)	7 (1.7)	0.898

^dFisher exact test for the comparison of LPV/r versus (NVP-NVP+Infant-only NVP)^dFisher exact test for the comparison of LPV/r versus (NVP-NVP+Infant-only NVP)^b4 stillbirths: one in the NVP-NVP arm subsequent to a rupture of membranes > 48 hours, three in the LPV/r arm including one suspected to be related to domestic violence (history of blunt injuries by spouse and scalp hematoma and intracerebral hemorrhage at autopsy) and 2 from unknown reasons.^cDefined as <10th percentile of the Thai norms [19]^dFisher exact test for the comparison between the 3 arms^bCongenital anomalies: one umbilical polyp, one congenital intestinal obstruction, one agenesis of corpus callosum, one atrial septal defect and one heart malformation.

neonatal death from congenital heart malformation at 1 day of life in the infant-only NVP arm.

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