Intensification of antiretroviral treatment with raltegravir for pregnant women living with HIV at high risk of vertical transmission

Thanyawee Puthanakit[1,2]*, Nattawan Thepnarong[1,2], Surasith Chaithongwongwatthana[2,3], Suvaporn Anugulruengkitt[1,2], Orawan Anunsittichai[2], Tuangtip Theerawit[2], Sasiwimol Ubolyam[4], Chitsanu Pancharoen[1,2] and Praphan Phanuphak[5]

[1] Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[2] Center of Excellence in Pediatric Infectious Diseases and Vaccines, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[3] Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[4] HIV-NAT Research Laboratory, Thai Red Cross AIDS Research Center, Bangkok, Thailand
[5] The Thai Red Cross AIDS Research Center, Bangkok, Thailand

Abstract

Objectives: The rate of vertical HIV transmission for women at high risk of HIV transmission stands at approximately 7.6%. In the present study we describe infant infection rates in women who had received raltegravir (RAL) intensification during pregnancy to a standard three-drug antiretroviral (ART) regimen in Thailand.

Methods: This prospective cohort study enrolled HIV-1-positive pregnant women at high risk of vertical transmission, as defined by (1) ART initiation at a gestational age (GA) ≥32 weeks or (2) HIV-1 RNA >1000 copies/mL at GA of 32–38 weeks while on ART. Women received a standard three-drug ART regimen with RAL intensification (400 mg twice daily) until delivery and continued on a three-drug ART regimen after delivery. Plasma HIV-1 RNA testing was performed before intensification and at delivery. Infant HIV-1 status was determined using DNA PCR at birth, and at 1, 2 and 4 months of life.

Results: Between February 2016 and November 2017, 154 pregnant women on ART were enrolled into the study with a median CD4 cell count and plasma HIV-1 RNA level of 382 cells/mm^3 and 4.0 $\log_{10}$ copies/mL, respectively. The three-drug combination consisted of either a lopinavir/ritonavir- (53%) or efavirenz-based (43%) regimen. Median GA at time of RAL initiation was 34 weeks (interquartile range [IQR] 33–36) and median duration was 21 days (IQR 8–34). The proportion of women who had a plasma HIV-1 RNA <50 and <1000 copies/mL at delivery was 45% and 76%, respectively. There were six infants with HIV infection, three in utero and three peripartum. Overall vertical transmission rate was 3.9% (95% confidence interval [CI] 1.4–8.2).

Conclusion: The majority of high-risk pregnant women living with HIV-1 who had received RAL intensification achieved viral suppression at delivery with a relatively low rate of vertical transmission. This intensification strategy represents an option for prevention in HIV-positive women at high risk of vertical transmission.

Keywords: raltegravir, HIV vertical transmission, prevention of mother-to-child transmission (PMTCT), high-risk HIV-positive pregnant women, late-presenting HIV

Introduction

The World Health Organization (WHO) has set targets to eliminate HIV vertical transmission by 2020 [1] using the following criteria: vertical transmission rate less than or equal to 50 per 100,000 live births and less than 2% in non-breastfeeding populations for at least a year [2]. Thailand was the first country in Asia to receive WHO validation for the elimination of vertical transmission by meeting these targets, with a rate of 1.9% in 2015 [3]. The Thai Ministry of Public Health has set goals to bring this rate below 1% [3,4].

The risk for mother-to-child transmission (MTCT) depends mostly on gestational age (GA) at the time of antiretroviral therapy (ART) initiation and HIV-1 viral load (VL) level before delivery. Earlier ART initiation and HIV suppression at the time of delivery are associated with a reduction of vertical transmission risk [5,6]. A study from the UK and Ireland has found that vertical transmission rates in pregnant women with levels of HIV-1 VL near delivery >10,000 and 1000–9999 copies/mL were 9.2% and 3.0%, respectively, in contrast to <0.1% if VL was <50 copies/mL [7]. Data from the Spectrum AIDS Impact model 2016 has estimated the probability of vertical transmission among pregnant women who had received ART for less than 4 weeks before delivery at 7.6% [8]. Women living with HIV-1 with a high VL who present in the late third trimester of pregnancy are unlikely to achieve an undetectable VL (<50 HIV-1 copies/mL) by the time of delivery when using standard three-drug non-nucleoside reverse transcriptase inhibitor (NNRTI)- or protease inhibitor (PI)-based ART.

Raltegravir (RAL), an HIV-1 integrase inhibitor, is used in pregnancy [9,10] as it rapidly reduces HIV-1 VL by 2 $\log_{10}$ copies/mL within 2 weeks of treatment initiation [11-15] and it crosses the placenta, and has, therefore, a potential impact as a pre-exposure prophylaxis agent to prevent vertical transmission [14,16,17], as reported among late-presenting pregnant women in several countries such as Austria [15], Brazil [14] and France [11]. Pregnant women who were treated with RAL had an overall vertical HIV-1 transmission rate of 0.7%. However, the rate was higher at 1.3% among a subgroup of women who had received it during the third trimester of pregnancy [10].

The Thai elimination of mother-to-child transmission of HIV programme has investigated factors associated with vertical transmission among infants infected with HIV-1 who were born between 2014 and 2016. The major factors associated with transmission were: being late to antenatal care; incidental HIV-1 infection during pregnancy; and poor ART adherence [18]. As a result, we have set up a prospective pilot study in collaboration with the Thai Red Cross AIDS Research Center to assess the impact

*Corresponding author: Thanyawee Puthanakit, Division of Infectious Diseases, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Rama IV Road, Bangkok 10330, Thailand
Email: thanyawee.patchula.ac.th

of the addition of RAL to standard three-drug ART regimens on vertical transmission rates in HIV-1 positive pregnant women who were late-presenters or had high HIV-1 viral loads near delivery.

Methods

This prospective cohort study with RAL intensification in pregnant women at high risk for MTCT was initiated by the Thai Red Cross AIDS Research Centre, under the Patronage of Her Royal Highness Princess Soamsawali. A three-drug ART regimen is recommended during pregnancy in the Thai 2016 PMTCT guidelines using efavirenz, tenofovir disoproxil fumarate (TDF) plus either lamivudine (3TC) or emtricitabine (FTC). Alternative regimens include lopinavir/ritonavir (LPV/r) with either TDF or zidovudine (ZDV) plus 3TC. These guidelines also recommend an elective Caesarean section for high-risk pregnant women with an HIV-1 RNA level >1000 copies/mL at 34–38 weeks' GA or for those who have received a standard three-drug ART regimen for <12 weeks [19]. However, the mode of delivery in Thailand is dependent on physician discretion and hospital capacity.

The study inclusion criteria were: pregnant women with HIV infection who were initiated on ART at a GA ≥32 week or who had an HIV-1 RNA >1000 copies/mL at 32–38-weeks' GA despite being on ART. Pregnant women with HIV-1 infection from all areas of Thailand were given access to this programme. Their ART regimen was dispensed by their local hospital pharmacy, and RAL couriered from the Thai Red Cross AIDS Research Center to antenatal care clinics. Women provided written consent for participation in the study, which was approved by the Faculty of Medicine, Chulalongkorn University Institutional Review Board, Bangkok, Thailand.

Antiretroviral regimens during pregnancy and postpartum

Twice-daily oral RAL 400 mg was added to a standard three-drug ART regimen for pregnant women up until delivery. Raltegravir was stopped after delivery while the three-drug ART regimen was continued postpartum. The Thai 2016 PMTCT guidelines recommend a 6-week course of triple therapy with oral ZDV 4 mg/Kg and 3TC 2 mg/Kg every 12 hours, plus nevirapine (NVP) 4 mg/Kg once daily as a post-exposure prophylaxis regimen for infants born to mothers at high risk of vertical HIV-1 transmission. Infant formula is provided to HIV-exposed infants up to 18 months of age. Breast feeding is not recommended.

Laboratory methods

HIV-1 RNA levels were measured at the time of RAL initiation and at delivery using either plasma or dried blood spot (DBS) samples. Plasma HIV-1 RNA was performed using the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test (Roche Molecular system, NJ, USA) or the Abbott RealTime HIV-1 assay (Abbott Molecular Inc, IL, USA) with a limit of detection of 20 and 40 copies/mL, respectively. HIV-1 RNA testing using DBS specimens was performed using Abbott m2000rt (Abbott Molecular Inc, IL, USA) at the HIV-NAT Research Laboratory, Bangkok, Thailand. The assay has been validated and reports comparable HIV-1 RNA levels to those in plasma with a detection cut-off of 839 copies/mL. In this study, when the DBS HIV-1 RNA was reported as <839 copies/mL, it was categorised into the same group as plasma HIV-1 RNA 50–999 copies/mL and, if reported as undetectable, into the same group as plasma HIV-1 RNA <50 copies/mL.

The infant HIV-1 status was determined by DNA PCR at birth (0–7 days after birth) and at 1, 2 and 4 months of life [19]. HIV-1 infection in utero was defined by a positive HIV-1 DNA PCR result at birth. Infants were diagnosed as *HIV-1 infected* if they had two positive HIV-1 DNA PCR test results. *Uninfected* infants were defined as having at least two negative HIV-1 DNA PCR test results, with at least one performed at ≥4 months of age. *Probably uninfected* infants were defined as having at least two negative DNA PCR test results, with at least one negative at 2 months of age. *Possibly uninfected* infants were defined by a negative DNA PCR test result at birth and at 1 month. *Presumably uninfected* infants by the in utero route were defined by a negative DNA PCR test result at birth.

Statistical analysis

Data were analysed using the Stata version 13 programme. HIV-1 perinatal transmission rates are reported as percentages with 95% confidence intervals (CI). Regardless of the number of babies from one pregnancy, infants were counted individually. The proportion of pregnant women with HIV-1 RNA levels <50 and <1000 copies/mL at delivery is reported as a percentage. The viral decay rate was calculated by comparing HIV-1 RNA levels in $\log_{10}$ copies/mL at the time of RAL initiation and at delivery.

Results

Demographic data

Between February 2016 and November 2017, 154 HIV-positive high-risk pregnant women were prospectively enrolled to receive RAL intensification. Of these, 113 (73%) were late-presenting pregnant and untreated women, and 41 (27%) were on ART with a high HIV-1 VL. The three-drug ARV regimen was optimised by adding RAL for those in the group who were on ART with high VL. Women originated from various regions in Thailand, e.g. 39% from Bangkok and Central Thailand, 18% from the Northeast, 17% from the South, 16% from the East and 10% from the North. Their clinical characteristics are presented in Table 1. Median age was 23 (IQR 19–29) years, median CD4 cell count 382 cells/mm^3 (IQR 171–545) and median GA at the time of RAL initiation was 34

Table 1. Characteristics of pregnant women who received raltegravir intensification treatment (*n*=154)

Characteristics	Results
Age (years), median (IQR)	23 (19–29)
GA at time of receiving raltegravir (weeks), median (IQR)	34 (33–36)
Indication to receive raltegravir intensification	
Receiving ART with HIV-1 VL >1000 copies/mL (%)	41 (27)
Initiating ART at GA ≥32 weeks (%)	113 (73)
CD4 cell count (cells/mm^3), median (IQR), *n*=128	382 (171–545)
HIV-1 RNA at time of raltegravir initiation ($\log_{10}$ copies/mL), mean (SD), (*n*=133)	4.0 (0.8)
Antiretroviral drug regimens given with RAL, *n* (%)	
• TDF-3TC-EFV or TDF-FTC-EFV	66 (43)
• TDF-3TC-LPV/r	51 (33)
• ZDV-3TC-LPV/r	28 (18)
• Other regimens	9 (6)

GA: gestational age; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; TDF: tenofovir disoproxil fumarate; ZDV: zidovudine; 3TC: lamivudine

Table 2. Maternal HIV-1 viraemia at the time of raltegravir intensification and at delivery

HIV-1 RNA (copies/mL)	Total pregnant women		Receiving ART but had VL >1000 HIV-1 copies/mL at GA 32–38 weeks		Initiating ART at GA ≥32 weeks	
	Pre RAL (total number=133)	At delivery (total number=148)	Pre RAL (total number=39)	At delivery (total number=42)	Pre RAL (total number=94)	At delivery (total number=106)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
<50	0	67 (45)	–	12 (29)	0	55 (52)
50–1000	11 (8)	46 (31)	–	13 (31)	11 (12)	33 (31)
>1000–10,000	55 (41)	21 (14)	18 (46)	10 (24)	37 (39)	11 (10)
>10,000–100000	53 (40)	10 (7)	14 (36)	4 (10)	39 (42)	6 (6)
>100,000	14 (11)	4 (3)	7 (18)	3 (7)	7 (7)	1 (1)

ART: antiretroviral therapy; GA: gestational age; RAL: raltegravir; VL: viral load

Table 3. HIV status of infants of women who received raltegravir intensification treatment during late pregnancy

Infant HIV status (total number=155)	*n* (%)	95% CI
HIV infection (two positive HIV-1 DNA PCR tests)	6 (3.9)	1.4–8.2
Definitely uninfected (≥2 negative HIV-1 DNA PCR up to 4 months of age)	82 (52.9)	44.7–61
Probably uninfected (1 negative HIV-1-DNA PCR up to 2 months of age)	47 (30.3)	23.2–38.2
Possibly uninfected (one negative HIV-1-DNA PCR up to 1 month of age)	14 (9.0)	5.0–14.7
Presumably uninfected by the in utero route (one negative HIV-1-DNA PCR at birth)	6 (3.9)	1.4–8.2

(IQR 33–36) weeks with a median interval between their enrolment date and RAL initiation of 2 days (IQR 0–4). Median duration of RAL therapy was 21 days (IQR 8–34 days), with 41% of women receiving <2 weeks; 25% 2–4 weeks; 22% 4–6 weeks and 11% 6–9 weeks of treatment.

HIV-1 RNA in pregnant women

Baseline HIV-1 RNA level measurements at the time of RAL initiation are described in Table 2 using plasma (70%) and DBS sample (30%) testing with 92% of women at >1000 copies/mL, and 51% >10,000 copies/mL. HIV-1 RNA testing at the time of delivery showed that 67 (45%) and 113 (76%) of pregnant women had achieved a low HIV-1 RNA at levels <50 copies/mL and <1000 copies/mL, respectively. HIV-1 RNA testing was performed using plasma (76%) and DBS samples (24%). The HIV-1 RNA results at levels <50 copies/mL were tested using 50 plasma and 17 DBS samples. The HIV-1 RNA test results at 50–1000 copies/mL were performed using 39 plasma and seven DBS samples.

Of 154 pregnant women, 127 had paired sample of HIV-1 RNA at the time of RAL initiation and at delivery. The median HIV-1 RNA decrease was 1.64 $\log_{10}$ copies/mL with a median duration of RAL intensification of 21 days (IQR 8–34).

HIV-1 vertical transmission rates

There were 155 infants born, including two sets of twins, and one fetal death in utero. Seventy-five (48%) were delivered by Caesarean section and 80 (52%) by vaginal delivery. The median GA at birth was 39 weeks (IQR 38–39). Of the births, 11% were preterm deliveries (GA <37 weeks) and 19% of infants were born with a low birth weight (<2500 g). All infants were formula-fed.

In total, there were six HIV-positive infants (two positive HIV-DNA PCR), giving a 3.9% (95% CI 1.4–8.3) vertical transmission rate as shown in Table 3. There were three in utero and three peripartum HIV infections. Clinical characteristics of the HIV-1 infected children are shown in Table 4. Three infants acquired HIV in utero, the mothers having initiated ART, or received raltegravir intensification at 34–35 weeks' GA, possibly after transmission had occurred. For the three infants who were infected peripartum, one of the mothers (Case 6) reported not taking ART as documented by lack of VL decrease. In another case (Case 4), the infant had received only ZDV as neonatal prophylaxis, which was not appropriate in this case.

The transmission rate, stratified by mode of delivery and indication for RAL use, is presented in Table 5. In addition, six infants were presumably HIV-1 uninfected in utero with negative HIV-1 DNA PCR test results at birth before being lost to follow-up. Maternal HIV-1 RNA at time of delivery was <200 copies/mL in five cases and 4338 copies/mL in the remaining one.

Serious adverse events in infants

There were two infants with congenital anomalies, one with trisomy 21 and the other with gastroschisis. Two deaths occurred: one in utero and one in the neonatal period. In the case of the in utero death, the mother was diagnosed with HIV-1 infection 3 years before the pregnancy and initiated on a TDF/3TC/LPV/r/RAL regimen at a GA of 33 weeks. Thirteen days later she presented to hospital with reduced fetal movements and was referred to a tertiary care centre within 24 hours. The fetus was vaginally delivered as an in utero fetal death with a body weight of 1835 g. The second infant death occurred at home at 7 days of life from an unknown cause. The mother was a migrant with a CD4 cell count of 548 cells/mm^3 and a plasma HIV-1 RNA level, at the time of RAL initiation, of 4325 copies/mL and 192 copies/mL at the time of delivery. She had received ZDV, 3TC and LPV/r with RAL intensification for 21 days. This infant was born at GA 39 weeks, birth weight was 2990 g with no perinatal complications and a negative HIV-1 DNA PCR at birth.

Discussion

The rate of HIV vertical transmission in this study among high-risk HIV-1-positive pregnant women for MTCT with late presentation or persistent viraemia who had received RAL intensification to their three-drug ART regimen was 3.9%, which is lower than the estimation from the 2016 Spectrum AIDS Impact model of 7.6%. Importantly, we have shown that the majority of these women within a resource-limited setting achieved a plasma HIV-1 RNA

Table 4. Clinical information about the six HIV-1 infected infants

Clinical information	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Maternal age (years) and history	20, G_1P_0 Diagnosed 3 years prior	21, G_1P_0 Seroconverted during pregnancy	37 G_3P_2 Diagnosed at first trimester but denied ART	16 G_1P_0 Seroconverted during pregnancy	41 G_4P_3 Seroconverted during pregnancy	20 years G_1P_0 ART interrupted during GA 30–36 weeks
ART regimen	TDF/3TC/EFV at 20 weeks	TDF/3TC/EFV at 35 weeks	ZDV/3TC/LPV/r at 35 weeks	TDF/3TC/LPV/r at 33 weeks	TDF/3TC/LPV/r at 36 weeks	TDF/3TC/EFV at 36 weeks
CD4 cell count (cells/mm^3)	302	281	–	596	–	–
GA at RAL initiation (weeks)	34	34	35	34	36	36
HIV-1 RNA at RAL initiation (copies/mL)	5833	1145	2159	1514	15,127	107,651
RAL duration (days)	14	23	29	29	18	8
HIV-1 RNA at delivery (copies/mL)	1848	Undetectable	Undetectable	<40	486	140,284
Mode of delivery	Elective Caesarean section	Vaginal delivery	Vaginal delivery	Elective Caesarean section	Elective Caesarean section	Vaginal delivery
Birth weight (g)	2690	2720	2940	2690	2690	3000
Neonatal PEP	ZDV/3TC/NVP	ZDV/3TC/NVP	ZDV/3TC/NVP	ZDV	ZDV/3TC/NVP	ZDV/3TC/NVP
HIV-1 DNA PCR	**at birth: positive** at day 24: positive	**at birth: positive** at day 21: positive	**at birth: positive** at day 30: positive	at birth: negative at days 69, 83: **positive**	at birth, day 28: negative at days 60, 74: **positive**	at birth: negative at days 28, 86: **positive**

ART: antiretroviral therapy; EFV: efavirenz; G: gravidity; LPV/r: lopinavir/ritonavir; NVP: nevirapine; P: parity; PEP: post exposure prophylaxis; RAL: raltegravir; TDF: tenofovir disoproxil fumarate; ZDV: zidovudine; 3TC: lamivudine.

Table 5. HIV-1 vertical transmission rate for those children with two positive HIV-DNA PCR test results stratified by mode of delivery

	Total *n*/number of total deliveries (%)	Vaginal delivery *n*/number of total deliveries (%)	Caesarean section *n*/number of total deliveries (%)	Remarks
Receiving ART but VL >1000 copies/mL at GA 32–38 weeks	1/42 (2.4)	0/21 (0)	1/21 (4.7)	One in utero infection
Initiating ART at GA ≥32 weeks	5/113 (4.4)	3/59 (5.1)	2/54 (3.7)	Two in utero, three peripartum infections
Total transmission rate	6/155 (3.9)	3/80 (3.9)	3/75 (4.0)	

ART: antiretroviral therapy; GA: gestational age; VL: viral load

<1000 copies/mL at the time of delivery and that half of the infants were born by vaginal delivery. Therefore, we suggest that a RAL-based intensification strategy might be an option to achieve a reduction of HIV-1 vertical transmission among pregnant women at high risk in this type of setting where an elective Caesarean section is not routinely available.

The British HIV Association (BHIVA) guidelines for the management of HIV-1 infection in pregnant women recommend the use of a three- or four-drug regimen that includes RAL for women who present late after 28 weeks of pregnancy with an unknown VL or with a VL >100,000 copies/mL [20]. In the present study, addition of RAL as a fourth drug to the regimen during pregnancy provided a simple way for reverting to a standard three-drug regimen postpartum.

We have observed that a plasma HIV-1 RNA <1000 copies/mL was achieved by 76% of study participants by the time of delivery with a median 1.6 $\log_{10}$ copies/mL decrease during a median 21 days of RAL intensification. This level of viral decay is smaller than previously reported (1.1 $\log_{10}$ copies/mL per week), and may be explained by the lower participant baseline HIV-1 RNA level in our study (4.0 $\log_{10}$ copies/mL compared to 5.4 $\log_{10}$ copies/mL) and also a shorter RAL duration [21]. There is an initial rapid HIV-1 RNA decay phase during the first 14 days of RAL administration [22]. This has most likely contributed to the high proportion of participants achieving a plasma HIV-1 RNA <1000 copies/mL, despite the short time period of RAL intensification.

The vertical transmission rate of HIV-1 was higher in our study than in a review where it stood at 1.3% in a subgroup of 153 pregnant women who had received RAL during the third trimester of pregnancy [10]. This might be explained by the shorter intensification duration and higher rate of vaginal delivery in our participants. The reduction in vertical transmission rates associated with RAL intensification might be explained by the rapid VL reduction in pregnant women and transplacental drug transfer to provide post-exposure prophylaxis to the fetus. Indeed, a previous study had shown a median 1.48 cord blood/maternal plasma RAL concentration ratio [20], with concentration in neonates remaining above the IC95 for wild-type HIV-1 up to 36 hours post-delivery [23].

The present study was a pilot, operational research study that tested the feasibility of using nationwide RAL intensification in a population at high risk for vertical transmission in a resource-limited country. There are three important features of our programme: (1) communication via telephone, fax, email and mobile phone-based messaging from remote hospitals to the Thai Red Cross Center in Bangkok to confirm eligibility criteria; (2) logistical support for drug distribution to remote hospitals by couriers, with a median time from enrolment to RAL initiation of

2 days; and (3) the use of DBS specimens to quantify maternal HIV-1 RNA levels and HIV-1 DNA in infants. Therefore, we could ascertain HIV-1 viral load among the majority of pregnant women and also the HIV-1 infection status of all the infants in this cohort. This study leveraged on an established infrastructure for nationwide implementation of PMTCT and an early HIV-1 infant diagnostic programme [24]. The RAL intensification could, therefore, be implemented successfully in the nationwide health programme. The current Thai national guidelines 2016 have recommended RAL intensification for pregnant women at high risk and, if listed in the national essential drug list, RAL will be accessible at all hospitals throughout Thailand [19].

We are aware of the limitations in this study, which include a lack of randomisation within the control arm. However, we considered it unethical to randomly allocate women to a standard three-drug regimen versus RAL intensification when there is support in the literature and the BHIVA guidelines for this type of intensification intervention in late-presenting pregnant women. Also, we cannot provide data on systematic adverse event (AE) monitoring and reporting in these pregnant women and their offspring, for example hepatitis and hyperbilirubinemia; however, we believe we have captured serious AEs such as infant death and congenital anomalies. French authors have described an absence of increased risk of birth defects or severe AEs in infants after RAL use during pregnancy [25,26]. Detailed data on the mode of delivery were also incomplete in this study, with a lack of information on whether Caesarean sections were performed on an emergency or elective basis. Lastly, six infants who were presumed HIV-1 uninfected as they had a documented negative HIV-1-DNA PCR result at birth lacked a follow-up until 4 months of age. Their mothers had a low plasma HIV-1 RNA at birth and these infants had been prescribed a three-drug post-exposure ART regimen perinatally. We can also add that in this study, there may have been issues with adherence to ART as RAL is administered as a twice-daily regimen in pregnancy. Dolutegravir (DTG), a newer integrase inhibitor, is given once daily and therefore potentially offers superior dosing convenience. Pharmacokinetic data on its use in pregnant women have been published [27], as well as pilot data from Botswana where this drug is used as a first-line regimen in HIV-1 positive adults [28]. However, further data on the use of DTG in pregnancy are needed. Because of drug interactions, as is the case with efavirenz, and therefore a need to dose DTG at 50 mg twice daily when in combination, DTG might also be associated with decreased adherence to medication in some instances [29].

In conclusion, we have shown in an open-label, prospective observational cohort study that RAL intensification of a three-drug ART regimen in pregnancies at high risk for vertical transmission in a resource-limited setting such as Thailand is feasible, is associated with a VL <1000 copies/mL in the majority of women at the time of delivery, and might be effective in decreasing vertical transmission in the context of an established PMTCT programme. It may be regarded as an effective strategy to further reduce vertical transmission, and achieve an overall vertical transmission rate below 1% in the country.

Acknowledgements

The authors thank Dr Kulkanya Chokephaibukit, Dr Rangsima Lolekha and Dr Yos Teerawattananon for their advice on data analysis. They also thank the staff at the HIV-NAT Research Laboratory, Bangkok, Thailand for performing DBS HIV RNA testing. Lastly, they would like to acknowledge Dr Wipaporn Natalie Songtaweesin, for editing the manuscript and Miss Rachaneekorn Nadsasarn for manuscript preparation.

Funding

This study was supported by a grant from the Princess Soamsawali PMTCT Fund, the Ratchadapiseksompotch Fund (RA 59/032), Faculty of Medicine, Chulalongkorn University and the Thailand Research Fund (IRG 5780015), Department of Pediatrics, Faculty of Medicine, Chulalongkorn University.

Declaration of interests

The authors declare no conflicts of interest.

References

1. WHO. 2016. Global health sector strategy on HIV, 2016–2021. Geneva. Available at: www.who.int/hiv/strategy2016-2021/ghss-hiv/en/ (accessed January 2018).
2. WHO. 2016. Global guidance on criteria and processes for validation: elimination of mother-to-child transmission of HIV and syphilis. Geneva. Available at: www.who.int/reproductivehealth/publications/rtis/9789241505888/en/ (accessed January 2018).
3. Lolekha R, Boonsuk S, Plipat T *et al.* Elimination of mother-to-child transmission of HIV – Thailand. *MMWR Morb Mortal Wkly Rep* 2016; **65**: 562–566.
4. Phanuphak N, Phanuphak P. History of the prevention of mother-to-child transmission of HIV in Thailand. *J Virus Erad* 2016; **2**: 107–109.
5. Thea DM, Steketee RW, Pliner V *et al.* The effect of maternal viral load on the risk of perinatal transmission of HIV-1. New York City Perinatal HIV Transmission Collaborative Study Group. *AIDS* 1997; **11**: 437–444.
6. Tubiana R, Le Chenadec J, Rouzioux C *et al.* Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis* 2010; **50**: 585–596.
7. Townsend CL, Byrne L, Cortina-Borja M *et al.* Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000–2011. *AIDS* 2014; **28**: 1049–1057.
8. Mahy M, Penazzato M, Ciaranello A *et al.* Improving estimates of children living with HIV from the Spectrum AIDS Impact Model. *AIDS* 2017; **31 Suppl 1**: S13–S22.
9. Antivirial Pregnancy Registry. Antiretroviral pregnancy registry interim report for 1 January 1989 through 31 July 2017. Wilmington, NC. Available at: www.apregistry.com/InterimReport.aspx (accessed January 2018).
10. Maliakkal A, Walmsley S, Tseng A. Critical review: review of the efficacy, safety, and pharmacokinetics of raltegravir in pregnancy. *J Acquir Immune Defic Syndr* 2016; **72**: 153–161.
11. Boucoiran I, Tulloch K, Pick N *et al.* A case series of third-trimester raltegravir initiation: Impact on maternal HIV-1 viral load and obstetrical outcomes. *Can J Infect Dis Med Microbiol* 2015; **26**: 145–150.
12. Hegazi A, Hay P. HIV seroconversion in the third trimester of pregnancy: using raltegravir to prevent mother-to-child transmission. *Int J STD AIDS* 2013; **24**: 245–246.
13. Lennox JL, DeJesus E, Lazzarin A *et al.* Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet* 2009; **374**: 796–806.
14. Nobrega I, Travassos AG, Haguihara T *et al.* Short communication: use of raltegravir in late-presenting HIV-infected pregnant women. *AIDS Res Hum Retroviruses* 2013; **29**: 1451–1454.
15. Taylor N, Touzeau V, Geit M *et al.* Raltegravir in pregnancy: a case series presentation. *Int J STD AIDS* 2011; **22**: 358–360.
16. Hegazi A, Mc Keown D, Doerholt K *et al.* Raltegravir in the prevention of mother-to-child transmission of HIV-1: effective transplacental transfer and delayed plasma clearance observed in preterm neonates. *AIDS* 2012; **26**: 2421–2423.
17. McKeown DA, Rosenvinge M, Donaghy S *et al.* High neonatal concentrations of raltegravir following transplacental transfer in HIV-1 positive pregnant women. *AIDS* 2010; **24**: 2416–2418.
18. Tonpudsa C, Loleka R, Pavaputanondh P *et al.* Remaining causes of mother to child HIV transmission (MTCT) in Thailand: barriers to achieving an MTCT rate of <1%. *IAS 2017*. July 2017. Paris, France. Abstract WEPED 1394.
19. Lolekha R, Chokephaibulkit K, Phanuphak N *et al.* Thailand national guidelines for the prevention of mother-to-child transmission. *Asian Biomed* 2017; **11**: 145–159.
20. de Ruiter A, Taylor GP, Clayden P *et al.* British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). *HIV Med* 2014; **15 Suppl 4**: 1–77.
21. Westling K, Pettersson K, Kaldma A, Naver L. Rapid decline in HIV viral load when introducing raltegravir-containing antiretroviral treatment late in pregnancy. *AIDS Patient Care STDS* 2012; **26**: 714–717.
22. Andrade A, Rosenkranz SL, Cillo AR *et al.* Three distinct phases of HIV-1 RNA decay in treatment-naive patients receiving raltegravir-based antiretroviral therapy: ACTG A5248. *J Infect Dis* 2013; **208**: 884–891.
23. Clarke DF, Acosta EP, Rizk ML *et al.* Raltegravir pharmacokinetics in neonates following maternal dosing. *J Acquir Immune Defic Syndr* 2014; **67**: 310–315.
24. Naiwatanakul T, Voramongkol N, Punsuwan N *et al.* Uptake of early infant diagnosis in Thailand's national program for preventing mother-to-child HIV transmission and linkage to care, 2008-2011. *J Int AIDS Soc* 2016; **19**: 20511.
25. Ghosn J, Sylla B, Morand-Joubert L *et al.* 'Real life' use of raltegravir during pregnancy in France: the Coferal-IMEA048 retrospective study. *IAS 2017*. July 2017. Paris, France. MOPEC0599.

26. Sibiude J, Warszawski J, Blanche S *et al.* Evaluation of the risk of birth defects among children exposed to raltegravir in utero in the ANRS-French Perinatal Cohort EPF. *IAS 2017*. July 2017. Paris, France. Abstract MOAB0204.
27. Mulligan N, Brookie MB, Capparelli EV *et al.* Dolutegravir pharmacokinetics in HIV-infected pregnant and postpartum women. *Conference on Retroviruses and Opportunistic Infections*. February 2016. Boston, MA, USA. Abstract P438.
28. Zash R, Jacobson D, Mayondi G *et al.* Dolutegravir / tenofovir / emtricitabine (DTG/TDF/FTC) started in pregnancy is as safe as efavirenz / tenofovir / emtricitabine (EFV/TDF/FTC) in nationwide birth outcomes surveillance in Botswana. *IAS 2017*. July 2017. Paris, France. Abstract MOAX0202LB.
29. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant hiv-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. Available at: https://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/447/dolutegravir–tivicay–dtg- (accessed January 2018).