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

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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/mm³ and 4.0 log₁₀ 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 vertical HIV 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 log₁₀ 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 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.
The study inclusion criteria were: pregnant women with HIV-1 infection, physician discretion and hospital capacity. However, the mode of delivery in Thailand is dependent on the facility. The assay has been validated and the HIV-NAT Research Laboratory, Bangkok, Thailand. The assay was dispensed by their local hospital laboratory, 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.

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-1 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 analyzed 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 log10 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/mm³ (IQR 171–545) and median GA at the time of RAL initiation was 34 (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.

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/mm³), median (IQR), n=128 | 382 (171–545) |
| HIV-1 RNA at time of raltegravir initiation (log₁₀ 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 |
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, 10,000–100,000 copies/mL, and >100,000 copies/mL were 53 (40%), 14 (11%), and 11 (8%), respectively.

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.

### Table 2. Maternal HIV-1 viremia 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) |
| >10,000–100,000 | 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 (22 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 |

**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 with a resource-limited setting achieved a plasma HIV-1 RNA <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 log10 copies/mL decrease during a median 21 days of RAL intensification. This level of viral decay is smaller than previously reported (1.1 log10 copies/mL per week), and may be explained by the lower participant baseline HIV-1 RNA level in our study (4.0 log10 copies/mL compared to 5.4 log10 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 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 at birth: positive at day 28 and negative at days 60, 74: positive at birth: negative at days 28, 86: positive.

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, GpP | 21, GpP | 37 GpP | 16 GpP | 41 GpP | 20 years GpP |
| 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/mm3)               | 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 | positive | positive | at birth: negative at days 69, 83: positive | at birth: negative at day 28, 86: positive | at birth: negative at days 28, 86: positive |
| Remarks                                  | 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) |         |
health programme. The current Thai national guidelines 2016 have recommended RAL intensification for pregnant women at high viral load 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.

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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/strategies/2016-2021/ghs-strategy/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/2016/9789241505888/en/ (accessed January 2018).
3. Lolekha R, Boonsuk S, Plapit T et al. Elimination of mother-to-child transmission of HIV – Thailand. MMWR Morb Mortal Wkly Rep 2016, 65: 562–566.
4. Phanuphak P, 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 Chevalier P, Richaud P 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. Townend CL, Byrne L, Cortina-Bogas 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, Cuaronello A et al. Improving estimates of children living with HIV from the Spectrum AIDS Impact Model. AIDS 2017; 31 Suppl 1: S3–S22.
9. Antiretroviral Pregnancy Registry. Antiretroviral pregnancy registry interim report for 1 January 1989 through 31 July 2017. Wilmington, NC. Available at: www.apregs.org/InterimReport.aspx (accessed January 2018).
10. Maliaikkal 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. Bascouiran 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. Norgrega I, Travassos AG, Hagushara 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, Touzeu V, Get M et al. Raltegravir in pregnancy: a case series presentation. Int J STD AIDS 2011, 22: 358–360.
16. Hegazi A, McKowen D, Doehrlit 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. Torp-Pedersen C, Laleka R, Pavapatmongkhon 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 WEFD 1394.
19. Lolekha R, Chokephaibukit K, Phanuphak P et al. Thailand national guidelines for the prevention of mother-to-child transmission. Asian Biomed 2017; 11: 140–145.
20. de Ruiter A, Taylor GP, Clayden P et al. British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (interim review). HIV Med 2014, 15 Suppl 4: 1–77.
21. Westling K, Pettersson K, Kalanda 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, Giro 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, Rulk ML et al. Raltegravir pharmacokinetics in neonates following maternal dosing. J Acquir Immune Defic Syndr 2014; 67: 310–315.
24. Naiwatanaul T, Voramongkol N, Pursumvan 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. Ghose J, Syha 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. MOPEC0399.
26. Sibude J, Warsawski 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 MOAB004.
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. Zach R, Jacobson D, Mayoni 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 MOAX002L8.
29. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant women 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).

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