

Original Article

Thai national guidelines for the prevention of mother-to-child transmission of human immunodeficiency virus 2017

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Background: Thailand has made progress in reducing perinatal HIV transmission rates to levels that meet the World Health Organization targets for so-called “elimination” (<2%) of mother-to-child transmission (MTCT).

Objectives: To highlight the Thailand National Guidelines on HIV/AIDS Treatment Prevention Working Group issued a new version of its National Prevention of MTCT guidelines in March 2017 aimed to reduce MTCT rate to <1% by 2020.

Discussion of guidelines: The guidelines include recommending initiation of antepartum antiretroviral therapy (ART) containing tenofovir disoproxil fumarate (TDF) plus lamivudine (3TC)/emtricitabine (FTC) plus efavirenz regardless of CD4 cell count as soon as HIV is diagnosed for ART naïve HIV-infected pregnant women. An alternative regimen is TDF or zidovudine (AZT) plus 3TC/FTC plus lopinavir/ritonavir (LPV/r) for HIV-infected pregnant women suspected resistant to non-nucleoside reverse transcriptase inhibitors. Treatment should be started immediately irrespective of gestational age and continued after delivery for life. Raltegravir is recommended in addition to the ART regimen for HIV-infected pregnant women who present late (gestational age (GA) ≥32 weeks) or those who have a viral load (VL) >1000 copies/mL at GA ≥32 weeks. HIV-infected pregnant women who conceive while receiving ART should continue their treatment regimen during pregnancy. HIV-infected pregnant women who present in labor and are not receiving ART should receive single-dose nevirapine immediately along with oral AZT, and continue ART for life. Infants born to HIV-infected mothers are categorized as high or standard risk for MTCT. High MTCT risk is defined as an infant whose mother has a viral load (VL) > 50 copies/mL at GA > 36 weeks or has received ART <12 weeks before delivery, or has poor ART adherence. These infants should be started on AZT plus 3TC plus NVP for 6 weeks after delivery. Infants with standard MTCT risk should receive AZT for 4 weeks. Formula feeding exclusively is recommended for all HIV-exposed infants.

Keywords: Guidelines, HIV, mother-to-child transmission, Thailand

Introduction

Thailand is the first country in Asia to meet World Health Organization (WHO) targets for mother-to-child human immunodeficiency virus (HIV) transmission (MTCT) rate of <2% [1] and validate

so-called “elimination” of mother-to-child transmission of HIV in June 2016 [2]. This is especially remarkable given how grave the epidemic was among pregnant women in the mid-1990s: the prevalence of HIV among pregnant women was >2%, the mother-to-child

transmission rate was 24%, and >1,000 infants were born with HIV each year [2]. The Thailand Ministry of Public Health (MOPH) began implementing a national program for prevention of mother-to-child transmission of HIV (PMTCT) for all pregnant women using a short course of zidovudine (AZT) during 2000–2004 [3] and AZT plus single dose nevirapine (SD-NVP) (WHO Option A) during 2004–2010. During 2010–2014, Thailand's national PMTCT program included routine HIV counseling and testing for all pregnant women and their partners (HIV testing and counseling for couples) in antenatal care (ANC) settings, antiretroviral therapy (ART) for all HIV-infected pregnant women regardless of CD4 count starting from gestational age (GA) 14 weeks through delivery and continued based on CD4 count (WHO Option B) [4]. During 2014–2016, the guidelines recommended initiation antepartum ART including tenofovir disoproxil fumarate (TDF) plus lamivudine (3TC) or emtricitabine (FTC) plus efavirenz (EFV) regardless of CD4 cell count or clinical staging as soon as HIV is diagnosed for antiretroviral treatment (ART) naïve HIV-infected pregnant women and to continue for life regardless of CD4 count [5]. The overall MTCT rate in Thailand decreased from 4.6% in 2008 [6] (WHO Option A) to 2.3% in 2013 [7] (WHO Option B), and further to 1.9% in 2015 (WHO Option B+) [2]. The Thai national AIDS strategy 2016–2030 aims to reduce MTCT rate to <1% in 2020, with no perinatal HIV infection by 2030. The Thai national PMTCT working group identified potential causes of MTCT in Thailand during 2015–2016. The top 3 causes of MTCT in Thailand were late presentation (presentation \geq 32 weeks of GA) or no ANC, poor antiretroviral adherence or suspected viral resistance, and incident infection (e.g. women who seroconvert during late pregnancy or postpartum because of HIV serodiscordant partners) [8].

This article describes the Thai national PMTCT guidelines 2017 [9] aiming to increase dissemination, and facilitate access by health care providers in Thailand and internationally. This article provides recommendations for the practice of PMTCT management specific to a Thai context and to serve as a guidance to further reduce the MTCT rate to <1%. The guidelines are intended to apply to women living in Thailand who are at high risk of HIV infection, women of reproductive age who are living with HIV, HIV-infected pregnant women, their partners and babies.

Methods

The national PMTCT guidelines were developed through collaboration between Thailand's Department of Disease Control (DDC), Department of Health (DOH), Department of Medical Sciences (DMSc), Ministry of Public Health (MOPH), university hospitals, the Thai AIDS Society, and Thailand MOPH—U.S. Centers of Disease Control and Prevention (CDC). Relevant published literature in PubMed, international PMTCT guidelines [10–13], and the most recent relevant clinical studies conducted in Thailand and internationally were reviewed. The recommendations are based on available antiretroviral agents and laboratory support through the National AIDS Program and special projects in Thailand [9]. Several meetings were held by the Thai national PMTCT guideline working group during 2015–2016 to review and revise the guidelines. The Thai National HIV/AIDS Treatment and Prevention Guidelines Committee and People Living with HIV (PLHIV) network also provided comments on the draft recommendations in the meetings during the guideline development process. Changes to the guidelines were made based on comments from the Thai National HIV/AIDS Treatment and Prevention Guidelines Committee and PLHIV network's opinions. More detail about procedures for the guidelines development and the Thai National PMTCT Guideline Working Group Committee can be found at the *Thailand National Guidelines on HIV/AIDS Treatment and Prevention 2017* [9]. The Thai National HIV treatment and prevention guidelines development process was funded by DDC, Thailand MOPH.

Services for pregnant women and partners at the first ANC visit

At the first ANC visit, pregnant women should be assessed for a general physical examination (weight, height, blood pressure, oral health, and gestational exam), obstetrical risks, tetanus immunization history, tuberculosis (TB) symptoms, TB exposure, and consulted on their health and HIV testing history. The guidelines recommend that healthcare facilities providing ANC services should integrate couples HIV testing and counseling at the ANC clinic through the postpartum period to allow male partners of pregnant women to participate in caring for the mothers and infants, to identify discordant couples, and to prevent future HIV transmission [14, 15]. Pregnant women should be screened for anti-HIV

and syphilis at their first ANC visit and at GA 28–32 weeks. Other screening tests for pregnant women at first ANC visit include hematocrit/complete blood count, HBsAg, blood group, rhesus factor, thalassemia, and ultrasound according to indications. Pregnant women who inject drugs (PWID) or have a drug-injecting partner should be screened for anti-HCV. Partners of pregnant women should be screened for anti-HIV antibodies, syphilis (particularly partners of syphilis-infected women and partners with unprotected sexual risk behavior), and thalassemia screening (in case the woman is a thalassemia carrier).

HIV-infected pregnant women should be informed about the benefits of taking antiretroviral drugs (ARVs) to their own health, to prevent MTCT, and to prevent HIV transmission to HIV-uninfected sexual partners, the side effects of ARVs, and the importance of good drug adherence. HIV-infected pregnant women should be assessed for HIV/AIDS symptoms, history of prior ART including use of single dose nevirapine (SD-NVP) and results of prior ARV drug resistance testing, CD4 count, VL at GA 34–36 weeks, and other baseline laboratory findings (urinalysis, serum alanine aminotransferase (ALT), serum creatinine, hepatitis serology) according to adult HIV treatment and prevention guidelines [9]. All HIV-infected pregnant women should be screened for sexually transmitted infections (STI) regardless of signs and symptoms because pregnancy increases overall risk of STI and having an STI during pregnancy can affect the pregnancy outcome and unborn infant's health [16].

The guidelines recommend all pregnant women infected with HIV start ART as soon as possible after ART counseling regardless of CD4 count or clinical staging [13, 17].

Antepartum ARVs (Table 1)

Scenario 1: HIV-infected pregnant women who have not received ART before pregnancy

ART-naïve HIV-infected pregnant women should start TDF plus 3TC or FTC plus EFV as soon as possible regardless of CD4 count [12, 13]. Studies have shown rapidly increasing prevalence of primary HIV drug resistance among HIV naïve patients in Thailand during the period from 2007 to 2014 from 3% [18] to 8% [19], an alternative regimen, TDF or AZT plus 3TC or FTC plus lopinavir/ritonavir (LPV/r) is recommended for the HIV-infected pregnant women suspected to have non-nucleoside reverse-transcriptase inhibitor (NNRTI) resistance

with either of the following (a) has an HIV-infected sexual partner who has received ART and her partner has a history of NNRTI resistance or suspected resistance, or (b) was exposed to SD-NVP in a previous pregnancy or received NNRTI-based ART in the past, but stopped the treatment before pregnancy or has a history of NNRTI resistance. HIV genotypic resistance (RT gene) should be performed before ART initiation in settings where genotypic resistance testing is feasible. If there is no drug resistance, LPV/r-based ART regimen can be changed to NNRTI-based ART regimen postpartum. If the women cannot tolerate an ART regimen, guidance for switching ARV agents appears in **Table 2**.

The guidelines 2016 recommended adding raltegravir (400 mg) every 12 h as a 4th agent in addition to the basic ART regimen in HIV-infected pregnant women who present late at an ANC (≥ 32 weeks GA). Case series have shown rapid viral decay with the use of raltegravir initiated late in pregnancy to achieve viral suppression, thus theoretically reduce the risk of MTCT [10, 11, 20–24]. Raltegravir can be discontinued immediately after delivery. Although there was one case report of marked elevation of maternal liver transaminases following initiation of raltegravir [25], many studies have shown that raltegravir is well tolerated with no serious adverse events in pregnant women [10].

Scenario 2: HIV-infected pregnant women who conceived while receiving ART

HIV-infected pregnant women who conceive while already receiving ART should continue the same ART regimen if it provides virological suppression. If not, ART adherence should be assessed, an HIV specialist consulted, and a change in the ART regimen should be considered. For those who have a VL > 1000 copies/mL at ≥ 32 weeks GA, raltegravir (400 mg) every 12 h should be added to the ongoing ART regimen. For the woman who presents for care in the first trimester of her pregnancy, is taking EFV and has a suppressed VL, EFV can be continued. This is because the risk of neural tube defects associated with EFV occurs before 5–6 weeks GA, before most pregnancies are recognized [26]. However, pregnant women receiving EFV should be informed of possible adverse effects. In settings where a fetal ultrasound is feasible, assessment for a neural tube defect at 18–20 weeks GA should be considered.

Table 1. Recommendations for the use of antiretroviral drugs in HIV-infected pregnant women and HIV-exposed infants for HIV treatment and for prevention of mother-to-child transmission of HIV

Antepartum period	Intrapartum period	Postpartum period	Newborn (formula feeding + ARVs)
Scenario 1: never received antiretroviral treatment (<i>Initiate ART as soon as possible regardless of gestational age or CD4 count</i>)			
	Continue the antepartum regimen plus AZT [†] 300 mg every 3 h until delivery or a single dose AZT 600 mg at the onset of labor.	Continue ART after delivery for all women ^{§§} .	Categorized infants by MTCT risk. <i>Infants with standard MTCT risk^{††}:</i> initiate AZT (syrup) 4 mg/kg/dose every 12 h, initiate within 1 h after delivery, and continue for 4 weeks. For infants born at <30 weeks of gestation, the dosage of AZT syrup is 2 mg/kg/dose every 12 h for 4 weeks [67]. For infants born at 30–35 weeks of gestation, the dosage of AZT syrup is 2 mg/kg/dose every 12 h for 2 weeks then 3 mg/kg/dose every 12 h for 2 weeks [67]. <i>Infants with high MTCT risk^{††}:</i> initiate AZT (syrup) 4 mg/kg/dose every 12 h + 3TC (syrup) 2 mg/kg/dose every 12 h + NVP (syrup) 4 mg/kg/dose every 24 h for 6 weeks.
First-line recommended regimen[†]			
TDF/FTC/EFV (300/200/600 mg) one tablet once daily or TDF (300 mg) + 3TC (300 mg) + EFV (600 mg) once daily			
Alternative regimen[§]			
(AZT + 3TC) 1 tablet + LPV/r (200/50) 2 tablets every 12 h; or			
TDF/FTC (300/200 mg) or TDF (300 mg) + 3TC (300 mg) once daily + LPV/r (200/50) 2 tablets every 12 h			
Scenario 2: ever received ART			
Continue the regimen that suppressed VL <50 copies/mL. Modify the regimen as needed for complete viral suppression. EFV can be continued during pregnancy even in the first trimester.	Continue the regimen plus AZT ^{††} 300 mg every 3 h until after delivery or a single dose of AZT 600 mg at the onset of labor.	Continue the same regimen according to the National Adult HIV Treatment and Prevention Guidelines.	See infant recommendations above.

Table 1. (Continued) Recommendations for the use of antiretroviral drugs in HIV-infected pregnant women and HIV-exposed infants for HIV treatment and for prevention of mother-to-child transmission of HIV

Antepartum period	Intrapartum period	Postpartum period	Newborn (formula feeding + ARVs)
Scenario 3: presenting in labor and had not received ART during pregnancy			
Delivery is expected within 2 h	A single dose of AZT 600 mg	Initiate ART according to the National Adult HIV Treatment and Prevention Guidelines.	See recommendation of ARV regimen for infants with high MTCT risk above.
Delivery is expected after 2 h	AZT 300 mg every 3 h until delivery or a single dose of AZT 600 mg + a single dose of NVP 200 mg at the onset of labor.		

Abbreviations: 3TC, lamivudine; ART, antiretroviral treatment; AZT, zidovudine; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; MTCT, mother-to-child HIV transmission; NVP, nevirapine; TDF, tenofovir disoproxil fumarate

†If CD4 <200 cells/μL, give TMP-SMX, 2 tablets every 24 h.

‡(1) Adding raltegravir (400 mg) every 12 h as a 4th agent in addition to basic ART regimen in HIV-infected pregnant women who present late at ANC (≥32 weeks GA) and never receive ART or (2) women who receive ART >12 weeks, but VL >1,000 copies/mL at GA ≥32 weeks. Raltegravir can be discontinued after delivery.

§LPV/r-ART should be used in pregnant women suspected to have NNRTI resistance, e.g. history of partners on ART and suspected to have drug resistance, or pregnant women who previously received AZT+SD-NVP, or received ART in the past but stopped the treatment before pregnancy, or has a history of NNRTI resistance.

¶Consider omitting oral AZT during intrapartum period if HIV VL <50 copies/mL near time of delivery and good ART adherence. Intravenous AZT is not recommended and not available in Thailand.

††Standard MTCT risk: defined as an infant whose mother had documentation of low VL (<50 copies/mL) at ≥36 weeks GA. If the maternal VL from >36 weeks is not available, an infant can still be considered standard risk if mother received HAART for at least 12 weeks before delivery with history of good adherence.

‡‡High MTCT risk: defined as an infant whose mother had VL >50 copies/mL at ≥36 weeks GA. If the maternal VL from >36 weeks is not available, an infant can still be considered high risk if (1) the mother received ART for <12 weeks before delivery, or (2) the mother has a report of poor ART adherence in the past 12 weeks.

§§If the women discontinue ART, do the following: (1) if the women received LPV/r-based ART before delivery, discontinue all drugs simultaneously postpartum; (2) if the women received TDF + 3TC + EFV before delivery, stop EFV but continue TDF/FTC or TDF + 3TC for 14 days postpartum

Table 2. Suggested antiretroviral drugs substitution for specific drug intolerance in adults

Drug that cannot be tolerated	Recommended substitution
AZT, e.g. severe anemia	TDF (300 mg, every 24 h)
TDF, e.g. effects on kidney or allergy to drug	AZT (200–300 mg, every 12 h)
LPV/r, e.g. nausea and diarrhea	EFV (600 mg, every 24 h)
EFV, e.g. severe dizziness	LPV/r (200/50), 2 tablets every 12 h
LPV/r and EFV	NVP (if CD4 count before ART initiation <250 cells/ μ L). The use of NVP in pregnant women with CD4 count >250 cells/ μ L is not recommended because of a higher risk of hepatitis.
LPV,EFV,NVP	Boosted atazanavir (ATV/r, 300/100, once daily)
EFV, LPV/r, NVP, and ATV/r	Refer to an HIV specialist. In the meantime, pregnant women should at least receive AZT monotherapy. If only AZT is given during antenatal care and delivery, a single dose NVP must be given in addition to AZT during onset of labor.

Abbreviations: ART, antiretroviral treatment; AZT, zidovudine; ATV/r, atazanavir/ritonavir; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NVP, nevirapine; TDF, tenofovir disoproxil fumarate

Scenario 3: Management of HIV-infected pregnant women who present in labor and are not currently receiving ART

HIV-infected pregnant women who have not received antepartum ART are at high risk of transmitting HIV to their infants [27]. ARVs should be given to these women as soon as possible during labor to provide adequate drug levels in their newborn infants during delivery. In this setting, the guidelines recommend immediate SD-NVP together with oral AZT at the onset of labor. If delivery is expected within 2 h of presentation, SD-NVP should not be given, because there is not sufficient time for NVP to cross the placenta to the infants. Women should initiate ART immediately after delivery to provide protection against NVP “monotherapy” and resistance development, and continue ART for life [5, 12]. If labor exceeds 2 h and the setting allows, a cesarean section should be performed 4 h after giving ARVs to reduce the risk of HIV transmission.

Intrapartum ARVs

The antepartum ART regimen should be continued during the intrapartum period and after delivery. In addition, oral AZT should be given at the onset of labor regardless of the woman’s antepartum ART regimen or history of AZT resistance. Use of intrapartum AZT is to ensure adequate AZT levels in the infant to prevent acquisition of HIV during delivery

[28]. The virus transmitted in MTCT is likely to be a wild type, which is susceptible to AZT. Maternally administered AZT rapidly crosses the placenta to the fetus and penetrates well into the fetal central nervous system, the target organ for HIV infection. Intrapartum AZT may be omitted in pregnant women who have a VL <50 copies/mL at GA >36 weeks with good ART adherence [10, 11]. Intrapartum SD NVP in addition to AZT is given only to HIV-infected pregnant women who receive no antenatal ART or who received antepartum AZT monotherapy [4, 29]. SD-NVP can be omitted if delivery is expected within 2 h because adequate levels of NVP may not be achieved in the mother for placental transfer to the infant [30].

Postpartum ARVs for mothers

After delivery, ART should be immediately continued and lifelong ART is recommended for all HIV-infected women regardless of CD4 count levels (WHO Option B+) [31] (Table 1). All women should be referred to HIV specialists for HIV treatment.

Postpartum discontinuation of ART

Discontinuation of ART postpartum is not recommended. However, if a pregnant woman is unable to continue ART after delivery, CD4 count should be monitored every 6 months. The instructions for discontinuation of ART vary by regimen. For pregnant women who receive protease inhibitors

(PI) such as LPV/r during pregnancy, all drugs can be discontinued at the same time after delivery. For pregnant women who receive NNRTIs such as EFV or NVP during pregnancy, administering 2 NRTIs (AZT or TDF and 3TC or FTC) for 14 days is recommended after discontinuation of the NNRTI to reduce the development of NNRTI resistance [32–34].

ARV management for infants born to HIV-infected mothers

Infants born to HIV-infected mothers are categorized into 2 groups (standard risk and high risk) based on their risk for MTCT. The majority of pregnant women who receive and adhere to ART and who do not have baseline viral resistance are able to achieve an undetectable VL within 8–12 weeks after ART initiation [35, 36]. Studies in the United Kingdom and France reported that the MTCT rate can be as low as 0.09% if VL near the time of delivery was <50 copies/mL, compared with an MTCT rate of 1% with VL of 50–399 copies/mL and 2.6% with VL of 400–999 copies/mL [36, 37]. Women who initiate ART before conception or during the first and second trimester were more likely to have VL <50 copies/mL near the time of delivery than those who initiated ART during the third trimester [37].

Infant with standard MTCT risk: defined as an infant whose mother has documentation of low VL (≤ 50 copies/mL) near the time of delivery (34–36 weeks GA). If maternal VL from ≥ 36 weeks GA is not available, an infant should still be considered standard risk if the mother had received ART for at least 12 weeks before delivery with a history of good adherence. AZT syrup should be given to the infant as soon as possible after delivery and continued for 4 weeks. AZT dosage is adjusted depending on gestational age at delivery (Table 1).

Infant with high MTCT risk: defined as an infant whose mother has VL >50 copies/mL at 34–36 weeks GA. If the maternal VL from ≥ 36 weeks is not available, an infant can still be considered high risk if (1) the mother received ART for <12 weeks before delivery, or (2) the mother has a report of poor ART adherence in the past 12 weeks. High risk infants should be given AZT plus 3TC plus NVP in pediatric formulation [11, 38] as soon as possible after delivery, preferably within 6–12 h of delivery and continued

for 6 weeks (Table 1). Triple ART infant prophylaxis for 6 weeks appears to be safe with high NVP concentrations being rapidly achieved and maintained during the first 4 weeks of life [39].

For infants born to HIV-infected women who did not receive antenatal ART, ART prophylaxis should not be initiated in infants aged >48 h; this recommendation is based on data showing a significant decline in efficacy after that time. Infants at high risk for MTCT should receive close follow-up and early infant diagnosis according to the national pediatric HIV treatment and care guidelines [9].

Laboratory monitoring of HIV-infected pregnant women receiving ART

HIV-infected pregnant women require close clinical and laboratory monitoring. Potential clinical complications include NNRTI-induced hepatitis, LPV/r-associated metabolic side effects and a possible increase in the risk of glucose intolerance [40, 41]. Recommended laboratory monitoring is detailed in Table 3.

Prophylaxis against opportunistic infections among HIV-infected pregnant women

HIV-infected pregnant women should be screened for history of exposure to TB and TB symptoms. In pregnant women with CD4 counts <200 cells/ μ L, *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis with trimethoprim–sulfamethoxazole (TMP-SMX) should be given, even in the first trimester [42, 43]. TMP-SMX should be started at least 2 weeks after ART initiation to ensure that ART is well-tolerated. One tablet of folic acid should be given once daily in all pregnancies. Fluconazole is not recommended in pregnant women even among women with CD4 counts <100 cells/ μ L because safety data on the use of fluconazole during pregnancy are limited [44]. Use of fluconazole in pregnancy should be considered only if the benefits clearly outweigh risks [45].

Delivery procedures

Vaginal delivery is recommended for HIV-infected women who have no obstetrical indications for cesarean delivery. Invasive procedures such as fetal scalp electrodes, forceps extraction, vacuum extraction, and artificial rupture of the membranes should be avoided unless there is a clear medical indication for the procedure. The risk of MTCT is

Table 3. Recommended laboratory monitoring for HIV-infected pregnant women receiving antiretroviral therapy (ART)

Monitoring	Baseline	Follow-up during pregnancy after ART initiation
Laboratory tests		
CD4 count	<ul style="list-style-type: none"> - Perform CD4 count as soon as possible after diagnosis of HIV infection. 	<ul style="list-style-type: none"> - Monitor CD4 count every 6 months.
HIV viral load (VL)	<ul style="list-style-type: none"> - Not needed[†]. 	<ul style="list-style-type: none"> - Monitor HIV VL at 34–36 weeks of gestation[‡] after at least 4 weeks of ART.
Complete blood count (CBC)	<ul style="list-style-type: none"> - Perform CBC in all cases before ART initiation. - If Hb <8 g/dL or Hct <24%, AZT should not be used. Use TDF instead. 	<ul style="list-style-type: none"> - Monitor CBC at 4–8 weeks after initiation of AZT. - If Hb <8 g/dL or Hct <24%, change AZT to TDF. However, intrapartum AZT every 3 h during labor should still be given.
Creatinine (Cr)	<ul style="list-style-type: none"> - Cr levels in all cases before ART initiation. 	<ul style="list-style-type: none"> - Monitor Cr at 3 and at 6 months after TDF initiation.
Alanine aminotransferase (ALT)	<ul style="list-style-type: none"> - If Cr clearance <60 mL/min, do not use TDF. - ALT levels in all cases before ART initiation. 	<ul style="list-style-type: none"> - If Cr clearance <60 mL/min while receiving TDF, switch to AZT. - Repeat ALT level measurements if clinically indicated and every 6 months.
Urine sugar	<ul style="list-style-type: none"> - If ALT >2.5 times the upper limit of normal (ULN), avoid NVP. - Monitor urine sugar in all cases before ART initiation. 	<ul style="list-style-type: none"> - If women receive NVP-based ART and ALT >2.5 times the ULN, change NVP to EFV or LPV/r. - Monitor urine sugar at every antenatal care visit. Monitor UA including urine protein every 6 months for women receiving TDF.
Glucose challenge test (GCT) 50 g [§]	<ul style="list-style-type: none"> - Perform GCT in women with intrapartum diabetic risks. - If blood sugar ≥140 mg/dL, perform 100 g OGTT or consult obstetrician. 	<ul style="list-style-type: none"> - If urine sugar is positive while receiving LPV/r, switch to EFV. - Monitor GCT in women who are receiving LPV/r at 24–28 weeks gestational age or at least 4 weeks after LPV/r initiation. If blood sugar ≥140 mg/dL, perform 100 g OGTT or consult obstetricians.

Abbreviations: ALT, alanine aminotransferase; ANC, antenatal care; AZT, zidovudine; CBC, complete blood count; d4T, stavudine; EFV, efavirenz; GCT, glucose challenge test; ART, antiretroviral therapy; Hb, hemoglobin; Hct, hematocrit; HIV VL, viral load; LPV/r, lopinavir/r; NVP, nevirapine; OGTT, oral glucose tolerance test; TDF, tenofovir disoproxil fumarate; UA, urinalysis; ULN, upper limit of normal.

[†]Baseline VL is not recommended in the Thai guidelines. The main reason behind is the budget limitation, and mostly, baseline VL does not change management.

[‡]Generally pregnant women with good ART adherence for >8–12 weeks should have HIV VL <1,000 copies/mL. HIV VL testing at 34–36 weeks GA is a benefit for those with poor adherence or with <4 weeks of ART or suspected drug resistance. If HIV VL is >1,000 copies/mL, consider performing elective caesarean section before the onset of labor. If HIV VL >50 copies/mL, give AZT/3TC/NVP to infants for 6 weeks to PMTCT.

[§]50 g glucose challenge test (GCT): measuring the plasma or serum glucose concentration 1 h after a 50 g oral glucose load.

^{||}100 g oral glucose tolerance test (OGTT): measuring the fasting plasma or serum glucose concentration at 1, 2, and 3 h after a 100 g oral glucose load. All women whose blood glucose concentration exceeds the glucose threshold value (fasting blood sugar ≥105 mg/dL, serum glucose at 1 h after oral glucose load ≥190 mg/dL, at 2 h ≥165 mg/dL, and at 3 h ≥145 mg/dL) should be referred to obstetricians for proper management.

increased with premature rupture of the membranes (PROM) >4 h before delivery [46]. In the case of PROM, labor should be induced to reduce time to delivery unless a mother is on ART with virologic suppression near time of delivery [47, 48]. If episiotomy is required, it should be performed immediately before delivery to reduce neonatal exposure to maternal blood and secretions.

Elective cesarean section before the onset of labor and before the rupture of membrane can reduce the risk of MTCT [49] especially in women with VL >1,000 copies/mL at ≥36 weeks GA. However, the risk of maternal complications with cesarean section is higher than with vaginal deliveries. In settings where cesarean section is feasible and safe, elective cesarean section should be considered in HIV-infected pregnant women at 38 weeks GA who are at high risk of MTCT such as women who did not receive antepartum ART or received ART for <4 weeks, had poor ART adherence, or had VL >1,000 copies/mL at ≥36 weeks GA. In addition, cesarean section should be considered for an obstetric indication if the expected infant weight is >3,500 g. Cesarean section should be considered as early as possible during the intrapartum period for cases with poor progression of labor, or if the delivery is likely to occur at >4 h after the membranes rupture. The benefits of emergency cesarean section for PMTCT are not clear. Additionally, emergency cesarean delivery may increase the risk of postpartum maternal morbidity [49].

Women who will have a cesarean section should receive AZT 600 mg as a single dose at least 4 h before surgery. Women who did not receive prior ARV during pregnancy should also be given SD-NVP 200 mg at least 4 h before surgery. Routine prophylactic antibiotic (ampicillin or cefazolin) should also be given within 60 min before the surgery.

Interactions with commonly used obstetric medications and certain ARVs can occur. PIs are potent CYP3A4 enzyme inhibitors and may interact with drugs that use this metabolic pathway. Use of methyl ergometrine, an ergotamine, should be avoided among women receiving LPV/r or other PIs as it may cause severe vasoconstriction [50]. Conversely, EFV, a CYP3A4 enzyme inducer, may decrease methyl ergometrine levels resulting in inadequate vasoconstrictive effect [51]. Oxytocin should be used instead of methyl ergometrine for prevention and management of uterine atony in women receiving EFV.

Management in special situations

Pregnant women who are HIV seronegative, but whose partners are HIV-infected

These women should be evaluated for risks and symptoms associated with HIV infection, including sex without a condom during the previous 3 months and history of acute retroviral syndrome (i.e. fever, swollen glands, muscle and joint pain, sore, and rash), respectively. The HIV treatment history of the partners should also be assessed (**Figure 1**).

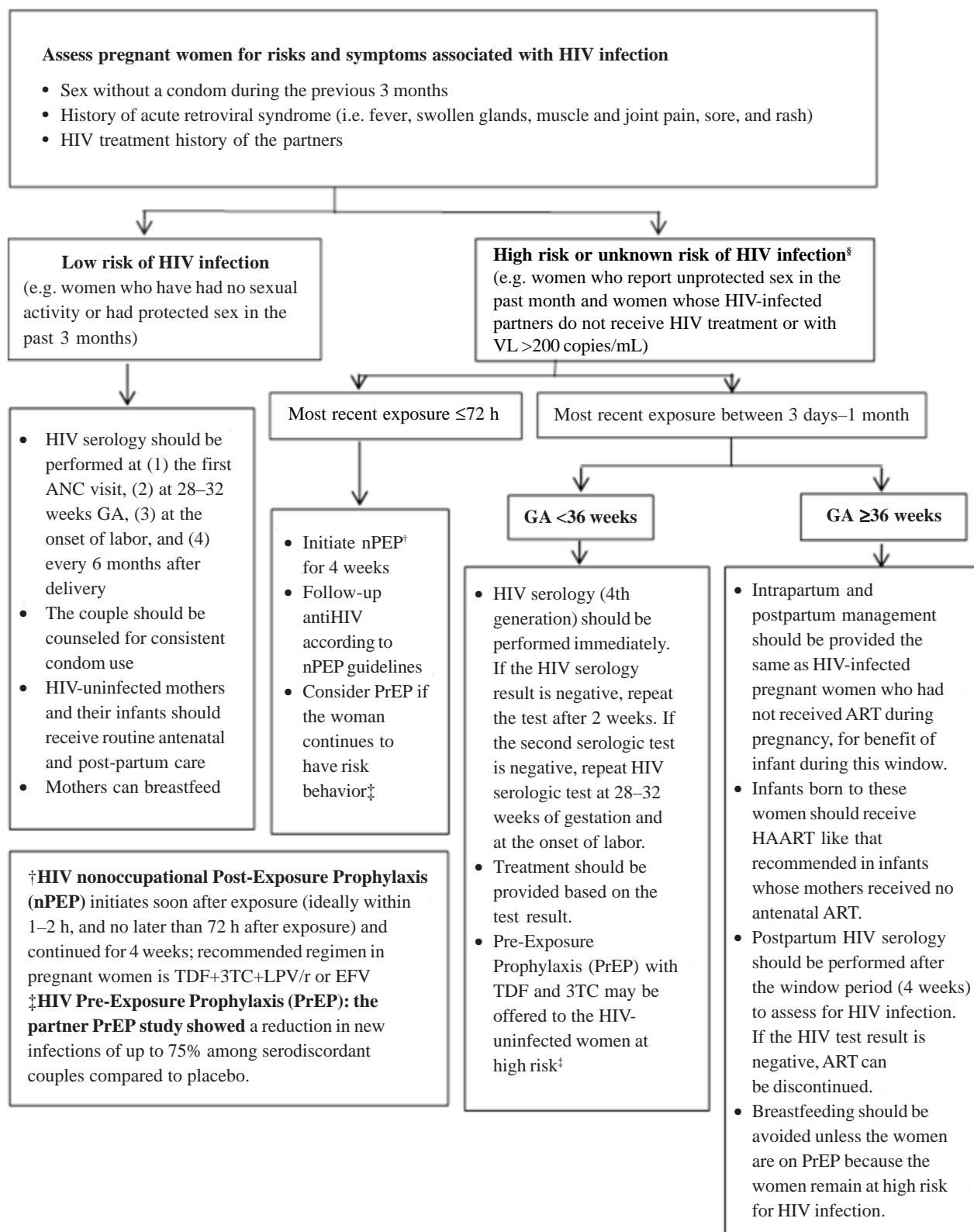
Women with a low risk of HIV infection such as women who have had no sexual activity, had protected sex in the past 3 months or women whose HIV-infected partners receive HIV treatment and VL <200 copies/mL [52] should have HIV serology tested at (1) the first ANC visit, (2) at 28–32 weeks GA, (3) at the onset of labor, and (4) every 6 months after delivery. The couple should be counseled for consistent condom use regardless of HIV status and treatment. HIV-uninfected mothers and their infants should receive routine antenatal and postpartum care. Mothers can breastfeed.

Women with a high risk or unclear risk of HIV infection including (1) women who report unprotected sex in the past month potentially putting them in the HIV diagnostic “window period”; (2) women whose HIV-infected partners do not receive HIV treatment; (3) women whose partners have VL >200 copies/mL, should be managed according to their most recent sexual risk exposure and gestational age as follows.

For a pregnant woman who presents at the clinic ≤72 h after their most recent exposure, nonoccupational postexposure prophylaxis (nPEP) using TDF plus 3TC or FTC plus EFV or LPV/r should be considered. Available data from animal studies indicate that nPEP is most effective when initiated as soon as possible after HIV exposure; it is unlikely to be effective when initiated >72 h after exposure [46, 53].

For a pregnant woman who presents at the clinic >72 h after their most recent exposure:

-If the woman presents at <36 weeks GA, HIV serology (4th generation) should be performed immediately. If the HIV serology result is negative, the test should be repeated after 2 weeks. If the second serologic test is negative, an additional HIV serologic test at 28–32 weeks GA is recommended, and again at the onset of labor. Treatment should be provided based on the test result. Pre-exposure prophylaxis



[§]**Note:** HIV DNA or RNA (qualitative) can be considered for early HIV diagnosis in settings where the tests are feasible

Figure 1. Management of HIV-seronegative pregnant women whose partners are infected with HIV

(PrEP) with TDF plus 3TC or FTC may be offered to the HIV-uninfected women at high risk for HIV to reduce to the risk of sexual HIV transmission [54, 55].

-If the woman presents at ≥ 36 weeks GA or within 2 days after delivery, she should receive intrapartum and postpartum management in the same way as HIV-infected pregnant women who had not received ART during pregnancy (expert opinion). The infants born to these women should receive similar ART recommended for infants whose mothers received no antenatal ART. Postpartum HIV serology should be performed after the window period to assess for HIV infection. If the HIV test result is negative, ART can be discontinued; however, breastfeeding should be avoided unless the women are on PrEP because the women remain at high risk for HIV infection.

Pregnant women with indeterminate HIV serology

These women should be evaluated for risk of HIV infection and for signs or symptoms of acute retroviral syndrome. If the woman has an HIV-negative partner, HIV serologic testing should be done at (1) first ANC visit, (2) at 32–34 weeks of gestation, (3) at the onset of labor, and (4) every 6 months after delivery. Treatment and care of the mothers and infants are based on the HIV serologic test results. If the HIV serologic results are consistently negative, care is provided in the same way as for HIV-uninfected women and their infants.

Pregnant women with acute HIV infection

Acute HIV infection (AHI) is the period during the first 4–6 weeks after HIV acquisition. About 60%–90% of people with AHI may present with the clinical signs and symptoms of acute retroviral syndrome that appear 2 to 3 weeks after HIV infection [53]. Studies have shown that the risk of HIV transmission is higher during AHI because of high VL [56, 57]. Therefore, if AHI occurs during pregnancy, effective ART must be initiated as soon as possible to reduce the risk of MTCT.

Comprehensive care for HIV-infected women and their families during the postpartum period

Standard postpartum and general health care should be provided. Attention should be paid to specific

postpartum issues, e.g. puerperal infection, side effects from ARVs, provision of medication to inhibit lactation and prevent breast engorgement or mastitis, and postpartum check-up at 4–6 weeks after delivery, which should include cervical Pap smear. Postpartum, these women should be referred to HIV specialists for standard HIV treatment and care. In addition to medical care, the women and their families should be provided appropriate psychological and social support, including assessments for postpartum depression, and childrearing issues.

Caring for male partner

If the male partner is unaware of the woman's HIV positive status, the woman's readiness for HIV disclosure to the male partner should be assessed and promoted. Voluntary HIV counseling and testing should be offered to partners of HIV-infected women. HIV-infected male partners should be referred for HIV treatment and care. Male partners of HIV-infected women should receive positive health promotion services, including promotion of safer sex practices, general health care, and avoidance of substance abuse. For male partners not infected with HIV, the guidelines recommend practicing safe sex, promoting healthy relationship with positive partner, and HIV testing every 6 months.

Family planning for people living with HIV

All HIV-infected women of reproductive age should receive preconception counseling on reproductive health, sexual health, and family planning that covers contraceptive methods available to prevent unintended pregnancy. HIV-infected women who do not desire pregnancy should be offered effective contraceptive options (**Table 4**) and counseled on the importance of consistent condom use (dual protection).

HIV-infected women who wish to conceive should receive counseling on the risks and benefits of pregnancy. Counselors should provide a preconception assessment and recommend appropriate contraceptive methods to reduce MTCT risks. The couple should be counseled on reproductive options (**Table 5**) to prevent HIV transmission. Before conception, HIV-infected pregnant women should be receiving ART and have virologic suppression. Both partners should be screened and treated for STIs [10].

Table 4. Effective contraceptive options for HIV-infected women [17, 58]

Birth control options	Description
Sterilization	Male or female sterilization is the best option for those who do not want more children.
Intrauterine device (IUD)	HIV-infected women can safely use copper IUD (Cu-IUD) and levonorgestrel IUD (LNG-IUD) [59]. Women living with severe or advanced HIV clinical disease should generally not initiate use of the LNG-IUD until their illness has improved [60] because of increasing risk of pelvic inflammatory disease. If IUD has already been inserted, there is no need to remove it in women who are HIV-infected [60].
Hormonal implant	Contraceptive implant is recommended for HIV-infected women because of its effectiveness for a long period (3–5 years), safety, and convenience. There is no study on the effect of antiretroviral (ARV) drugs on hormonal levels in patients who receive a contraceptive implant; however, there have been reports of breakthrough pregnancy in HIV-infected women who receive ARV after >24 months of Implanon implant [61].
Contraceptive injection	In Thailand, depot medroxyprogesterone acetate (DMPA) 150 mg injection is available. This intramuscular contraceptive injection is effective, safe, and convenient. A study on the use of DMPA in HIV-infected women shows that there is no interaction between ARV and DMPA. A cohort study revealed no significant change in CD4 count or HIV VL level in patients who use non-nucleoside reverse transcriptase inhibitors (NNRTI) or protease inhibitors (PI), after receiving DMPA [62], and the duration of efficacy is not altered.
Oral contraceptives	Oral contraceptive pills commonly used in Thailand are a combined hormonal type consisting of ethinyl estradiol (EE) estrogen, a progestin such as levonorgestrel (LNG), norethindrone (NET), and norgestimate (NGM). The amounts of hormone content vary. Generally, standard oral contraceptives have EE 30–35 mg in each tablet. If EE is <30 mg, the hormone is considered to be an ultra-low dose; the preparation aims to reduce hormonal side effects. HIV-infected women who take oral contraceptive pills should be informed about potential interactions between ARV (efavirenz or ritonavir-boosted PIs) and contraceptive hormones that could lower contraceptive efficacy. It is recommended to use oral contraceptives pills with EE ≥30 mg in each tablet [63]. Condoms should always be used along with contraceptive pills.

Table 5. Conception method options for HIV-concordant and serodiscordant couples

Male	Female	Options of conception methods
HIV-negative	HIV-positive	<ol style="list-style-type: none"> 1. Self-insemination 2. Intrauterine insemination (IUI) 3. Sexual intercourse on the day of ovulation while the female partner has VL<50 copies/mL; several methods may be used to prevent transmission to the male partner such as pre- and postexposure antiretroviral prophylaxis and male circumcision.
HIV-positive	HIV-negative	<ol style="list-style-type: none"> 1. Assisted reproduction with the use of donor sperm 2. IUI 3. Sexual intercourse on the day of ovulation while the male partner has VL<50 copies/mL; pre- and postexposure antiretroviral prophylaxis may also be given to the female partner.
HIV-positive	HIV-positive	<ol style="list-style-type: none"> 1. IUI 2. Self-insemination while the male partner has VL <50 copies/mL 3. Sexual intercourse on the day of ovulation while both partners have VL <50 copies/mL

Caring for infants born to HIV-infected mothers

Universal precautions to prevent transmission of blood-borne infection are recommended when caring for the infants of HIV-infected mothers. Invasive procedures, such as gastric tube insertion, should be avoided to prevent mucosal trauma. Routine vitamin K administration and routine birth vaccinations for infants, including *Bacillus Calmette–Guérin* and hepatitis B virus vaccines, should be given. ARVs for infants should be provided as recommended in **Table 1**. Side effects of ARVs and HIV-related symptoms should be monitored in these infants. Infants who have signs and symptoms of anemia should be investigated with complete blood count to monitor hemoglobin and white blood cell levels. Exclusive replacement feeding with infant formula is recommended for all infants of HIV-infected mothers. Instruction on safe food preparation and nutrition should be provided. The parents should be counseled not to give prechewed food to the babies.

All infants born to HIV-infected mothers should receive TMP-SMX for prophylaxis of PCP beginning at 4–6 weeks old continuing until HIV-infection is excluded or until infants are aged >6 months and are without HIV clinical symptoms [64]. HIV-infected infants should be given TMP-SMX prophylaxis until they are one year old. TMP-SMX prophylaxis is based on an assessment of the age-specific CD4 count or percentage thresholds for prophylaxis according to the *Thailand National Guidelines on HIV/AIDS Treatment and Prevention 2017* [9].

Laboratory tests to determine the HIV status of the infants: all infants born to HIV-infected mothers should have a blood test for HIV DNA by polymerase chain reaction (PCR) when they are 1 and 2 months old. Infants at high risk of acquiring infection should receive another PCR test at birth [65] and at 4 months old (if their first PCR test was HIV negative). Data in Thailand has shown that all HIV infections diagnosed using HIV PCR at birth occurred among infants at high MTCT risk [66] and HIV-infected infants who were detected with HIV PCR at birth were more likely to initiate ART earlier than HIV-infected infants who have a positive HIV PCR test result at later visits [67]. Early ART initiation in HIV-infected infants was associated with better virological control after initial suppression [68], limited HIV reservoir size [69–72], and reduced early infant mortality rate [73]. If the HIV DNA PCR test result at one month is negative, all ARV prophylaxis drugs

can be discontinued simultaneously. If the infant has a positive DNA PCR test result, presumptive diagnosis of HIV infection, a DNA PCR test should be performed immediately to confirm the result and ART should be initiated immediately. Diagnosis of HIV infection can be made with at least 2 concordant HIV positive results. More detail of early infant diagnosis and pediatric HIV treatment and care can be found in the *Thailand National Guidelines on HIV/AIDS Treatment and Prevention 2017* [9].

In summary, Thai national PMTCT guidelines 2017 aim to reduce the MTCT rate to <1% by promoting HIV testing for couples, and counseling to identify HIV serodiscordant couples and provide guidance on how to manage HIV serodiscordant couples. In addition, identification of pregnant women with a high risk of MTCT is encouraged by increasing the uptake of VL monitoring before delivery and provide intensification of ART for mothers with high VL and late-presenters. The guidelines emphasize the importance of good ART adherence, lifelong ART, and retention to care by provision of psychosocial support and counseling for pregnant women and their family. Infants born to HIV-infected mothers are managed based on their risk for MTCT. Exclusive formula feeding is recommended for all HIV-exposed infants. To facilitate the rapid implementation of the guidelines, the Thai government organized a series of training on the new HIV treatment and prevention guidelines for health care professionals, including the PMTCT section, during March–April 2017. A PMTCT job-aids that simplify the PMTCT guidelines has been developed and will be distributed to all public ART sites in 2017. Uptake of the new PMTCT guidelines implementation and MTCT rate should be monitored through the national PMTCT monitoring system (<http://pmtct.anamai.moph.go.th/phims/>) and national AIDS program reports (<http://napdl.nhso.go.th/NAPPWebReport/>).

Competing interests

The authors declare that they have no competing interests.

Author contributions

All authors contributed to the conception and design. RL drafted the manuscript, and KC, NP, SC, SK, PC, and SB critically revised it. All authors approved the final submitted version and take full responsibility for all statements made in the manuscript.

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