Evolution of Interventions to Prevent Mother-To-Child Transmission of HIV: Perspective from Thailand

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In 2009, the Joint United Nations Programme on HIV/AIDS (UNAIDS) called for the virtual elimination of mother-to-child transmission of HIV by 2015.[1] This is a realistic aim and can be achieved with significantly increased action to implement proven strategies to prevent HIV transmission to the women and to the babies. An estimated 370,000 children worldwide were newly infected with HIV in 2009,[1] which translates into 1,013 children who became newly infected globally each day. Most of these infections could be prevented by various steps of interventions to prevent mother-to-child transmission of HIV (PMTCT) such as antiretroviral drugs for the pregnant women and the newborn babies, selective mode of delivery, and formula feeding or antiretroviral therapy during the nursing period in settings where formula feeding is not feasible. In 2009, 82% of 972,000 Thai pregnant women had HIV testing.[1] HIV prevalence among Thai pregnant women was estimated to be 0.7% and the resulting 5,500 pregnant women received drugs for PMTCT (approximately 95.0% coverage) in the same year.[1,2]

In Thailand, the national PMTCT program was first launched in 2000 and the program has long been commended at the international level for its advancement and success as compared to other developing countries.[2,3] The program consisted of an opt-out HIV voluntary counseling and testing for all pregnant women, the provision of antiretroviral drugs free of charge to pregnant woman and their newborn babies, and the provision of free formula feeding to the babies up to one year of age.[4] However, as HIV-related health infrastructures in Thailand have dramatically improved during the past 10 years in response to the global and national efforts to increase access to HIV care and treatment,[5] there has come the need to revise the PMTCT practices in Thailand aiming for the elimination of new HIV infection in babies while also preserving antiretroviral treatment options for women after delivery and HIV-infected babies. Although faced with several challenges, in October 2010, Thailand announced its revised national PMTCT policy to provide three-drug antiretroviral regimens to all HIV-infected pregnant women regardless of their CD4 count.[4] This paper will review the history of PMTCT interventions in Thailand along with the challenges faced and lessons learnt throughout its evolution in the country. Future perspectives on the direction of the PMTCT program in Thailand in the next decade are also discussed.

Timing and risk factors of mother-to-child transmission of HIV

HIV can be transmitted from the mother to her baby throughout the antenatal period, intrapartum period, and postpartum period through breastfeeding. With no intervention to prevent mother-to-child transmission, the HIV transmission rate is estimated to be approximately 25% in a non-breastfeeding population and can be as high as 40% in a breastfeeding population.[6] Timing with the highest risk of HIV transmission includes the last trimester of pregnancy and during delivery.[6] Risk factors for HIV transmission include low maternal CD4 count, vaginal delivery, prolonged rupture of membrane prior to delivery, preterm delivery, low birth weight, and most importantly high maternal plasma HIV-RNA.[7,8] Breastfeeding is a route of transmission at the rate of 10-20%,[9] with the highest rate during the first 5 months of life.[10]

Interventions to prevent mother-to-child transmission of HIV

Since HIV transmission can occur at all time points starting from the beginning of pregnancy to the period after delivery, interventions to prevent mother-to-child transmission of HIV can therefore be provided at all these

time points. These interventions can be categorized into interventions given during the antenatal period, intrapartum period and postpartum period.

Antepartum PMTCT interventions

To maximally and rapidly reduce maternal plasma HIV-RNA, the most important risk factor for HIV transmission, antiretroviral drug(s) must be provided to pregnant women at an early gestational age. Use of combination antiretroviral drug(s) can increase the maternal CD4 count and improve overall maternal health and most importantly reduce the risk of HIV transmission to the babies compared to none or mono-drug treatment.[11,12]

Intrapartum PMTCT interventions

Pregnant women in labor can be provided with a high-dose antiretroviral drug, usually zidovudine (AZT) 300 mg every 3 hours, in order to prepare an adequate drug level in the babies prior to delivery. Intrapartum antiretroviral drug(s) given to pregnant women work as a pre-exposure prophylaxis treatment for babies, prior to their exposure to maternal blood and secretions during delivery. In addition, selecting elective caesarean section as mode of delivery can also help reduce transmission risk[13,14] especially when HIV-infected pregnant women receive suboptimal antepartum antiretroviral treatment or still have high maternal plasma HIV-RNA prior to delivery.

Postpartum PMTCT interventions

Babies born to HIV-infected women are considered HIV-exposed babies. Antiretroviral drug(s) provided to the babies as soon as possible after delivery can act as post-exposure prophylaxis drug(s) for the babies, similar to the use of antiretroviral drug(s) for health care personnel exposed to occupational risk. Complete avoidance of breastfeeding also plays a major role in preventing unnecessary HIV transmission after delivery. In the settings where formula feeding is not feasible, exclusive breast feeding and antiretroviral therapy during the duration of nursing in the mothers and/or in the babies can reduce the risk of transmission.[15-17]

Thailand health system infrastructure for HIV and PMTCT

Thailand was ranked as a lower-middle income country based on its Gross National Income per capita.[1] However, the health care financial schemes of the country, cover almost all patients in need, with the social security scheme for employees, the civil servant medical benefit scheme for government employees, and the universal coverage scheme for the rest of the patients. Thailand began to pilot a national antiretroviral treatment (ART) program in 2000 as the Access to Care program and then expanded this program in 2004 into the National Access to Antiretrovirals for People Living with HIV/AIDS (NAPHA) program aiming for universal access to ART by Thai patients.[5] Access to ART has expanded rapidly during the past years and approximately 200,000 Thai patients (75% ART coverage) had started ART by 2009.[2] All public sector regional, provincial, and district hospitals and some private and university hospitals in Thailand are currently providing ART to eligible HIV-infected patients.[5]

Evolution of PMTCT interventions in Thailand

The initiation of the PMTCT program in Thailand was led by the Thai Red Cross AIDS Research Center (TRC-ARC) in 1996 supported by public donation under the patronage of Her Royal Highness Princess Soamsawali. The TRC-ARC PMTCT program has been shown to be effective and feasible for implementation.[18] The effort to procure free AZT for impoverished HIV-infected Thai pregnant women largely originated from local and international ethical concerns for several PMTCT trials, sponsored by a developed country, which used Thailand as one of their study sites. These trials aimed to study the natural history of perinatal HIV infection or to perform placebo-controlled trials of short-course AZT without fully informed participants of the availability of full-course AZT in Thailand if the women could pay the cost or without charge from the TRC-ARC.[19,20] It was not until the year 2000 that the Thailand Ministry of Public Health (MOPH) began implementing the national PMTCT program which consisted of an opt-out HIV voluntary counseling and testing for all pregnant women, the provision of short-course AZT to pregnant woman (started from 34 weeks of gestation) and their babies (1-4 weeks), and the provision of free formula feeding to the babies[4] after a pilot program which started in 1998 showed successful implementation in a large region of the country.[21] In 2004, based on the HIVNET 012 study which demonstrated great efficacy of single-dose nevirapine (sd-NVP) in reducing vertical transmission[22] and the efficacy of sd-NVP in addition to the standard AZT regimen[23], the Thai MOPH changed the PMTCT treatment to AZT at 28 weeks gestation plus the use of sd-NVP to pregnant women during labour and to the newborn babies. This change in the national PMTCT regimen was seen to be in line with the 2004 World Health Organization (WHO) PMTCT recommendations for resource-constrained countries.[24] Unfortunately, data were gradually accumulated worldwide on the development of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance in women after delivery and in infected babies from the use of sd-NVP for PMTCT, with poor clinical outcomes when NNRTI-based regimens were subsequently used for treatment in these patients.[25-30]

In 2006, following the expansion of ART access to all HIV-infected individuals in Thailand with CD4<200 cells/mm^3, the MOPH changed the PMTCT treatment regimen to use a highly active antiretroviral therapy (HAART), primarily AZT + lamivudine (3TC) + nevirapine (NVP), to pregnant women with CD4 count <200 cells/mm^3. For the women with CD4 more than 200 cells/mm^3, AZT mono-therapy plus sd-NVP was still recommended with the addition of 7-day AZT + 3TC tail therapy after delivery in women[4] to reduce the chance of NNRTI resistance development based on the results from the TOPS study.[31] Again, these changes followed the 2006 WHO PMTCT recommendations for resource-constrained countries.[32]

In 2009, there were strong collaborative efforts by expert clinicians, researchers and non-governmental organization (NGO) leaders to advocate the strategy to maximally reduce or eliminate PMTCT in Thailand. A cost-effectiveness study was carried out in 2009 by the Department of Health (DOH), Thai AIDS Society (TAS), and Health Intervention and Technology Assessment Program (HITAP) to evaluate the strategy of HAART for all pregnant women in Thailand. The results of the study demonstrated that the three-drug antiretroviral regimens for PMTCT were cost-saving compared to AZT + sd-NVP under the Thai health care setting. A feasibility study to assess technical and practical barriers of introducing three-drug antiretroviral regimen for PMTCT, was conducted

during the same period in 46 public hospitals in 4 provinces of Thailand, which also revealed that replacing AZT + sd-NVP with the three-drug antiretroviral regimen for PMTCT was feasible in the field. These studies provided evidence-based recommendations to the Advisory Committee on AIDS in Mother and Child, Ministry of Public Health, which develops the national PMTCT guidelines, and the Subcommittee of HIV/AIDS System Development of the National Health Security Office (NHSO), which provides financial support to the national PMTCT program. In 2010, after almost 6 years of widespread AZT + sd-NVP use for PMTCT in Thailand amongst concerns about the development of NNRTI resistance raised locally and globally, the MOPH national PMTCT regimen was finally changed to include the three-drug antiretroviral regimen which consisted of AZT + 3TC + lopinavir/ritonavir (LPV/r) for all pregnant women.[4] This important decision was made around the same time that the WHO PMTCT recommendations for resource-constrained countries moved from recommending AZT + sd-NVP as the only option for PMTCT in women who are not yet eligible for ART to recommending either three-drug antiretroviral regimens or AZT + sd-NVP as equal options.[33]

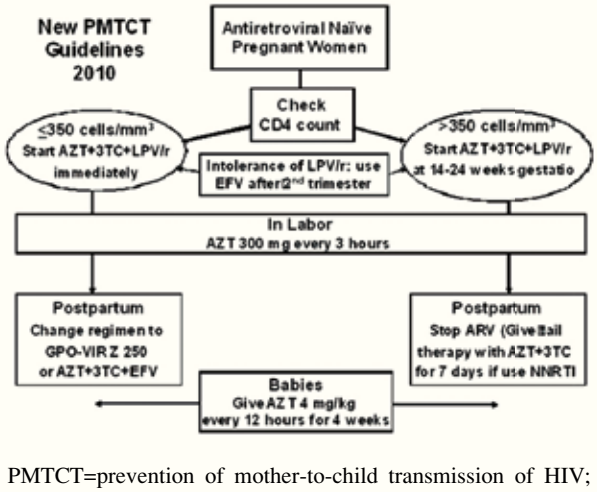
There are several factors to be considered when prescribing the three-drug antiretroviral regimens to pregnant women. The maternal CD4 count is the major reason behind the national PMTCT recommendation to use LPV/rtv in all pregnant women in Thailand. Women with a CD4 count higher than 250-350 cells/mm^3 may be at increased risk of developing NVP-related hepatotoxicity and fatal cases were reported.[34,35] The CD4 count turnaround time may be long in certain settings and this may unnecessarily delay the initiation of ARV in pregnant women. Therefore, a regimen containing LPV/rtv is the preferred option as it can be initiated without the need to wait for the CD4 count result. Another reason is the concern of NNRTI resistance development when discontinuing regimens containing NNRTI. With efavirenz (EFV) or NVP-based regimens, a one-week tail of AZT + 3TC is necessary to prevent, although not eliminate, the development of NNRTI resistance. Using AZT+3TC+ LPV/rtv as the single preferred regimen will ease the implementation at country levels. The new National PMTCT treatment guidelines are shown in Figures 1 and 2.

Safety of antiretroviral drugs in pregnancy

None of the antiretroviral drugs used in pregnancy is Food and Drug Administration (FDA) category A (adequate evidence of safety in human fetus). However, the registry in the United States and the United Kingdom revealed no effect of antiretroviral therapy and congenital abnormality or birth defect.[36,37] The pregnancy status reduces the exposure of protease inhibitors, but has no effect on the pharmacokinetics of nucleoside reverse transcriptase inhibitor (NRTI) and NNRTI. Drug toxicity may be more often prevalent in pregnant women compared to non-pregnant women, but mostly manageable.[38] A stavudine and didanosine combination induce lactic acidosis that could be serious in pregnancy.[39,40] EFV was reported to associate with neural tube defect in animals and humans, but with unknown frequency. It is therefore not recommended to use this drug in the first trimester. However, a study revealed 38 women who became pregnant while receiving EFV had no adverse outcomes,[41] suggesting that pregnancy can continue, but prenatal diagnosis of neural tube defect is warranted. AZT has been associated with transient anemia, but rarely severe. Finally, there are conflicting data on the use of protease inhibitors in pregnancy and premature delivery or low birth weight.[42-44] Long term safety follow-up of perinatal exposure to antiretroviral therapy in children is underway.

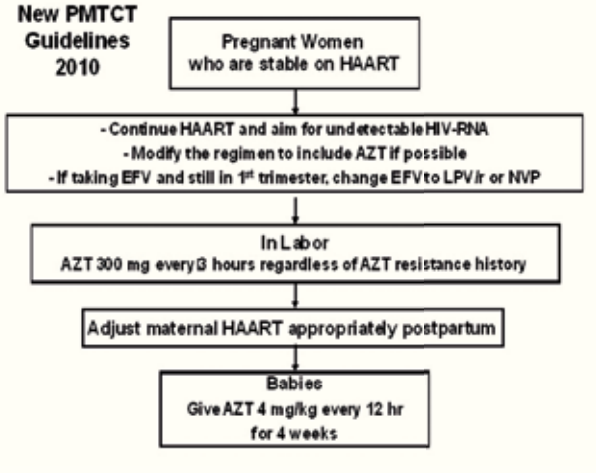
Challenges and lessons learnt from the evolution of PMTCT interventions in Thailand

The main challenge faced during these years of PMTCT program evolution included the strong influence that the WHO PMTCT recommendations had upon the revision of the MOPH national PMTCT guidelines. The national PMTCT program is operated under the DOH, MOPH, which oversees all maternal and child health issues



PMTCT=prevention of mother-to-child transmission of HIV; AZT=zidovudine; 3TC=lamivudine; LPV/r=lopinavir/ritonavir; EFV=efavirenz; GPO-VIR Z 250=AZT+3TC+nevirapine fixed-dose combination; NNRTI=non-nucleoside reverse transcriptase inhibitor

Fig 1. Antiretroviral regimens of the 2010 National PMTCT Program in women who have not received antiretroviral therapy



PMTCT=prevention of mother-to-child transmission of HIV; HAART=highly active antiretroviral therapy; AZT=zidovudine; EFV=efavirenz; LPV/r=lopinavir/ritonavir; NVP=nevirapine

Fig 2. Antiretroviral regimens of the National PMTCT Program in women who have been receiving antiretroviral therapy before pregnancy.

in Thailand while the national HIV care and treatment program is operated under the Department of Disease Control, MOPH. These separate operational systems also served as one of the challenges, for example, the health infrastructure developed during the countrys expansion of ART access might not be seen by the DOH as the readiness for the national PMTCT program to provide the three-drug antiretroviral regimen. Another challenge for the implementation of any new countrys guidelines has been how the MOPH could effectively make the stakeholders (i.e. obstetricians, neonatologists, pediatricians, internists, and other health care workers) in the whole country understand and follow the guidelines correctly.

Conclusion and future perspective

Currently, all HIV-infected pregnant women in Thailand receive triple-drug antiretroviral regimens to maximally reduce the transmission of HIV to their babies. This will not only reduce the countrys burden on the treatment of HIV-infected babies, but also on the treatment of women after delivery and infected babies who have developed NNRTI resistance from previous exposure to sd-NVP. The PMTCT knowledge is changing rapidly and every stakeholder in the country will need to learn how to implement the knowledge wisely. For Thailand, it can be foreseen that the number of HIV-infected children will decrease in the near future with increasing use of the three-drug antiretroviral regimen for PMTCT as data from the TRC-ARC program showed a transmission rate of as low as 1.0% after the use of the three-drug regimens.[45] However, data on pregnancy outcomes and long-term consequences of ARV exposure in the babies will need to be closely monitored.

More efforts are needed in order to promote early antenatal care (ANC) and increase the ANC rate among HIV-infected Thai pregnant women. Although the rate of antenatal care attendance in pregnant women in Thailand has been very high around 95%, it is lower to 87% in HIV-infected pregnant women and many of them presented in late pregnancy. Most of the infected babies will be from the mothers who did not receive optimal antenatal treatment. In addition, the follow-up rate of HIV-exposed babies for laboratory diagnosis of final HIV status will need to be improved. The proportion of HIV-infected women on ART who become pregnant will increase similar to other countries with rapid expansion of ART access in the past decade. Clinicians will need to be aware of the possibility that the next generation of HIV-infected pregnant women will be exposed to various antiretroviral drugs and will need to be familiar with how to monitor outcomes in mothers and in babies born to these women.

Efforts to prevent HIV infection among the general population are unequivocally important to reduce new HIV infection in mothers-to-be women. The promotion of HIV education, condom use and HIV counseling and testing are examples of such strategies. HIV testing of husbands during ANC, regardless of the womens HIV status, will also prevent HIV infection along the course of pregnancy and in future pregnancy.

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