

History of the prevention of mother-to-child transmission of HIV in Thailand

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Abstract

Strategies for the prevention of mother-to-child transmission (PMTCT) of HIV have undergone considerable evolution based on scientific evidence, both at global and local levels. Because of the rapid expansion of the HIV epidemic among the heterosexual population, and the relatively advanced mother and child health infrastructure, Thailand has been the site of international study for more efficacious and cost-effective PMTCT regimens since mid-1990. The example of the Thai Red Cross Society in providing standard PMTCT care through public donations under the patronage of Her Royal Highness Princess Soamsawali is an example that non-governmental organisations in other countries can follow to accelerate access to standard PMTCT care. However, there are still many challenges before vertical transmission of HIV is completely eradicated.

Keywords: prevention of mother-to-child transmission, PMTCT, Thailand

Introduction

Thailand experienced its first HIV cases in 1985 [1]. Initially, the epidemic was among homosexuals and bisexuals, but later spread to people who inject drugs (PWID) and the heterosexual population [2]. In 1988, the first-known birth of a child to an HIV-infected woman occurred in Chulalongkorn University Hospital in Bangkok. The birth could not take place in the delivery room as a result of the hysteria among healthcare personnel. The delivery occurred instead on the AIDS ward and had to be performed by the Chairman of the Obstetrics and Gynaecology Department.

The HIV epidemic among pregnant women began in 1990. This followed the increase in the epidemic among men who became HIV-infected by female sex workers [2]. The height of the HIV epidemic among pregnant Thai women occurred around 1995, with a prevalence of 2%. With approximately one million deliveries a year during that period, 20,000 HIV-infected pregnant women were expected to be HIV positive. However, with the effective control of HIV infection through education, a condom campaign and universal access to antiretroviral therapy (ART), HIV prevalence among pregnant women in Thailand in 2014 was only 0.6% (Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand).

Following the report of zidovudine use in the ACTG 076 study [3], the first available antiretroviral agent for reducing mother-to-child HIV transmission in 1994, many research and service delivery activities have been undertaken in Thailand in order to find an effective and affordable ART regimen to prevent mother-to-child transmission (PMTCT) of HIV. This retrospective review documents the efforts in Thailand over the last two decades ahead of the decision to implement the WHO Option B+ for the Thai national PMTCT programme. This will hopefully encourage other countries with limited resources to move towards ending HIV vertical transmission as planned by UNICEF/WHO/UNAIDS [4].

Evolution of PMTCT in Thailand

According to the ACTG 076 regimen, zidovudine, or azidothymidine, was given to HIV-infected pregnant women starting from 14 weeks of gestation until delivery, together with peripartum zidovudine infusion. Newborns were given 6 weeks of zidovudine together with formula feeding. The treatment

regimen reduced the risk of HIV transmission by approximately two-thirds [3]. Following this ground-breaking report, as well as subsequent confirmatory studies [5], ZDV has been administered as standard of care for PMTCT in the Western world since 1994. However, its use in resource-limited settings has been constrained by its cost. As a consequence, a trial of placebo-controlled trial of a short course (4 weeks) of zidovudine in only the mothers was launched in Thailand in 1995 [6]. The ethics of this study were heavily criticised because of the placebo arm and the lack of a standard zidovudine arm as control [7].

In order to find an alternative option, rather than to be enrolled in the Thai-US CDC placebo-controlled short-course zidovudine trial, a public fund was created to provide a free standard zidovudine PMTCT regimen to HIV-infected pregnant women in Thailand. Her Royal Highness Princess Soamsawali gave one million Baht (equivalent to US\$50,000 then) to the Thai Red Cross Society (TRCS) in mid-1996 to start the Princess Soamsawali PMTCT Fund (Figure 1). The general public could also give to this fund and the donations were tax deductible. Any hospital throughout Thailand can request the PMTCT medications for their patients from TRCS and the medication is delivered to the hospital by express mail. The hospital was required to report back on treatment outcome in terms of HIV transmission and side effects [8].

The TRCS PMTCT regimen has been updated continuously as new scientific evidence emerges. For example, it was shortened to an 8-week antenatal period in 1998 when our initial results showed



Figure 1. Her Royal Highness Princess Soamsawali holds a baby born to an HIV-positive mother who was enrolled into the Princess Soamsawali PMTCT programme

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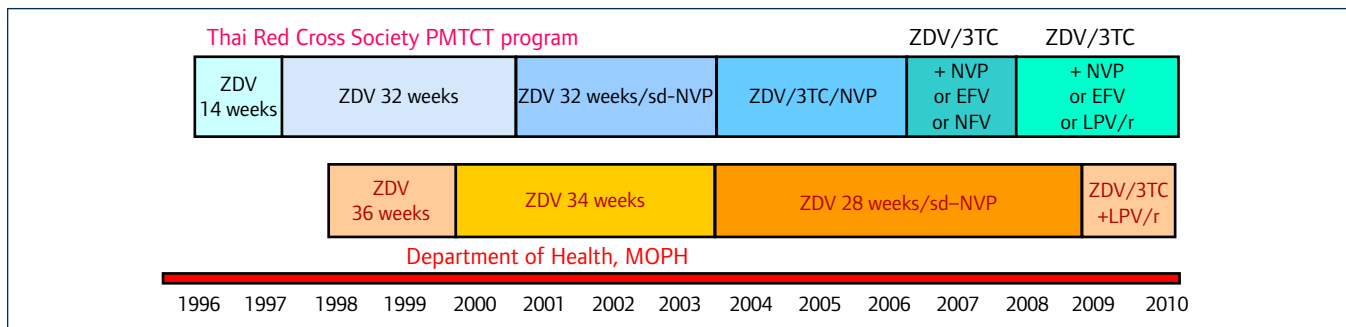


Figure 2. Evolution of PMTCT regimens in Thailand comparing the Thai Red Cross Society regimens and the Ministry of Public Health regimens starting and ending at various time periods from 1996 to 2010. ZDV: zidovudine; sd-NVP: single-dose nevirapine; 3TC: lamivudine; EFV: efavirenz; NFV: nelfinavir; LPV/r: lopinavir/ritonavir

equal efficacy to the original 24-week treatment period [8]. When the results of single-dose nevirapine from the HIVNET 012 came out [9], a single dose of nevirapine was added to the TRCS zidovudine regimen in 2000. The TRCS PMTCT regimen was changed again to a triple-drug regimen in 2004, starting at 14 weeks of gestation (Figure 2) [10]. These triple-drug regimens contained zidovudine and lamivudine with one of nevirapine, efavirenz or lopinavir/ritonavir. These TRCS regimens were always followed by 6 weeks of zidovudine to the newborns, together with formula feeding. The TRCS PMTCT donation programme also provided free formula to newborns until 12 months of age.

When the results of the ‘short-course zidovudine’ trial were published in 1999, it showed a 50% efficacy, reducing the rate of HIV transmission from 18.9% in the placebo group to 9.4% in the zidovudine arm [6]. It was therefore not effective enough to be implemented nationwide. At the same time, other groups such as the US Centers for Disease Control and the French agency were pursuing other more potent regimens such as a 12-week course of zidovudine plus a single-dose of nevirapine, or zidovudine plus lamivudine plus a single-dose of nevirapine [11], as well as measures to cover the tail of residual nevirapine when PMTCT was discontinued after delivery [11,12]. None of these clinical studies led to any agreed national regimen until 2010 when zidovudine/lamivudine with ritonavir-boosted lopinavir was selected by the Thai Ministry of Public Health (MOPH).

Between 1996 and 2015, 7786 patients from 94 hospitals throughout Thailand received PMTCT medications from TRCS funded through the Princess Soamsawali PMTCT Fund. Among 1832 pregnant women enrolled into the TRCS PMTCT programme who received a triple-drug regimen between 2004 and 2010, the transmission rate was found to be 1.1%. Around 85% of these women were treatment-naïve and their median CD4 cell count was 367 (252–516) cells/mm³. Median (IQR) gestational age at first antenatal care was 25 (18–29) weeks and duration of triple-drug regimens during pregnancy was 10.4 (7.3–13.4) weeks. Severe (grade III/IV) adverse events, including elevation of alanine aminotransferase and rash, were found in less than 1.5% and resolved after modification of the PMTCT regimens. PMTCT duration of <1 month (odds ratio 3.7, 95% CI 1.2–11.9, *P*=0.03) was a significant risk factor for transmission by multivariate analysis [13].

The government of Thailand started to give the triple-drug regimen to all HIV-infected pregnant women (Option B of WHO Guidelines) in 2010. This has resulted in a marked reduction in requests for PMTCT medications from TRCS since 2011. The project resources are now being used to provide PMTCT medications for illegal migrant women who are not eligible for the free ART provided by the Thai government.

The decision by the Thai government to implement the WHO Option B in 2010 was brave. It was partly influenced by the

demand as spearheaded by the TRCS and data from the Princess Soamsawali PMTCT Fund. In addition, the recommendations by WHO and UNICEF, under the leadership of Gottfried Hirnschall and Craig McClure, respectively, in recommending Option B and B+ in the WHO 2010 Treatment Guidelines was also important and enabled Thailand to make its own decision more quickly.

It is interesting to note that when the Thai MOPH made the decision to offer triple-drug therapy to pregnant women (WHO Option B), the only recommended regimen comprised zidovudine/lamivudine/ritonavir-boosted lopinavir in order to simplify the medication and prevent the need for tapering zidovudine and lamivudine when nevirapine or efavirenz was used. The proposal to implement the WHO Option B+ was heavily debated in 2013. Many obstetricians and paediatricians were concerned about the mothers’ adherence since they were still healthy and would be busy nursing the newborns. However, when the Adult Treatment Guidelines Committee decided to recommend initiation of ART at any CD4 cell count in the updated guidelines (2014), the PMTCT Guidelines Committee also adopted the WHO option B+ so that all pregnant women would continue triple-drug therapy after delivery in the same way as all other adults [14].

With the nationwide adoption of WHO Option B in 2010 and Option B+ in 2014, it is expected that the rate of vertical HIV transmission in Thailand will fall below 1%. The Thai MOPH is expecting to receive the UNAIDS/UNICEF certification of elimination of mother-to-child transmission of HIV (i.e. transmission rate less than 2% in non-breastfeeding populations) during 2016. Data from the end of 2015 showed that the vertical HIV transmission rate was 1.90%.

Despite of the Option B+ approach, there are several reasons for the high transmission rate. The first is late or no antenatal care. In 2014, median gestational age at first antenatal care among HIV-infected pregnant women was 19 weeks and 8% had no antenatal care (Department of Health, Ministry of Public Health, Thailand). There are certainly opportunities to improve earlier access to antenatal care for all pregnant women, which will enable the detection of HIV infection early enough to allow effective viral load suppression prior to delivery with the use of triple-drug regimens. Ideally, HIV RNA quantification should be carried out 2–4 weeks before the expected delivery date to identify pregnant women with unsuppressed HIV RNA close to delivery. This information would help in making the decisions for elective Caesarean section and intensification of PMTCT regimens. Thailand is currently piloting such an intensification with raltegravir for pregnant women who have received less than 12 weeks of treatment with a PMTCT regimen and for those who have viral loads over 1000 copies/mL at week 36 of gestation. Adding this rapid acting antiretroviral should accelerate viral suppression prior to the delivery. The efficacy of this intensified PMTCT regimen will be known by the end of 2017.

The second reason for this rate of vertical HIV transmission is if a woman who tested HIV-negative at her first antenatal care visit later seroconverts during the pregnancy or the breastfeeding period. These new infections can originate from a partner who was already infected but had never been tested or who was also newly infected from other partners. In 2015, approximately 10% of newly diagnosed HIV-positive infants were born to women whose HIV-positive status was only diagnosed near delivery or during the breastfeeding period (Department of Health, Ministry of Public Health, Thailand). This problem can be partially solved by implementing a second HIV test during the third trimester and also encouraging partners to have an HIV test during antenatal care. However, although it is already recommended, in 2015 the partners of only 42% of pregnant women in Thailand were tested for HIV during antenatal care or after delivery (Department of Health, Ministry of Public Health, Thailand).

Another reason for transmission is difficulty in accessing antenatal care and PMTCT for non-Thai migrant workers in the country. This in part explains why vertical HIV transmission rates are still above 1% in Thailand. Health insurance is available through the Social Security Scheme for registered migrants and the Migrant Health Insurance Card for non-registered migrants in Thailand. Efforts are being made to strengthen these health insurance systems and to encourage enrolment of non-Thai migrant workers to ensure access to timely healthcare services, including PMTCT.

Discussion

Preventing or eliminating HIV transmission from mother to child is technically possible due to the availability of potent antiretrovirals that can reduce the HIV viral load in the mother down to levels that are not associated with transmission to the child (i.e. less than 1000 copies/mL). Lessons from the past have demonstrated that this cannot be accomplished by the administration of one or two ARV drugs such as zidovudine or zidovudine plus single-dose nevirapine, but requires a triple-drug PMTCT regimen.

The safety and affordability of triple-drug PMTCT regimens in pregnant women and newborns in resource-limited settings have been major concerns. As a consequence of cost concerns, there have been double-standards in PMTCT guidelines over the last two decades with gold standard triple-drug regimens recommended in resource-rich countries and less effective solutions in resource-poor countries. In addition, despite being able to afford triple-drug PMTCT, some middle-income countries were reluctant to recommend its use because it had not been recommended by WHO and UNICEF. Thankfully, since 2013 we now have WHO guidelines that only recommend triple-drug PMTCT regimens (Option B at least). This has made it easier for many countries to make appropriate national PMTCT recommendations.

The example of the TRCS initiative in setting up the country's standard for the most effective PMTCT regimens available, shows that large, local non-profit organisations such as the Red Cross/Red Crescent can mobilise resources for PMTCT care before governments make policy decisions. The availability of a PMTCT regimen provided by TRCS PMTCT programme combined with reductions in the price of antiretrovirals influenced the final MOPH decision in 2010 to use triple-drug regimens for PMTCT.

The Princess Soamsawali PMTCT Fund was nominated as one of the UNAIDS Best Practices in 2000 as a good example of public mobilisation for HIV funding. Charities that save lives of newborns are generally well supported in any society, particularly those with royal patronage. Additionally, donations can be encouraged by

making them more attractive for other financial reasons, for example tax deductions.

The experience from Thailand tells us that effective PMTCT drugs alone cannot completely prevent vertical transmission of HIV. PMTCT also requires an effective mother and child health infrastructure and a collaborative management programme. Innovative approaches are still needed to reinforce early access to PMTCT and to enhance PMTCT interventions for pregnant women and their newborns when HIV infection is discovered late in pregnancy, for example with intensified PMTCT regimens or potentially with broadly neutralising antibodies administered to newborns [15].

Conclusion

PMTCT has undergone considerable evolution based on scientific evidence, both at global and local levels. Because of the rapid expansion of the HIV epidemic among the heterosexual population, and the relatively advanced mother and child health infrastructure, Thailand had the privilege of being selected as a site of international study on more efficacious and cost-effective PMTCT regimens since mid-1990. The example of the Thai Red Cross Society in providing standard PMTCT care through public donations under the patronage of Her Royal Highness Princess Soamsawali is an example that non-governmental organisations in other countries can follow to accelerate access to standard PMTCT care. However, there are still many challenges before vertical transmission of HIV is completely eradicated.

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