

## **Preventing Parent to Child Transmission of HIV: The Thai Experience**

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### **Introduction**

Worldwide, there are 40 million people living with HIV and 20 million have died of AIDS. One percent of person's ages 15 to 49 years has HIV. Women are becoming infected in growing numbers and surpassing men in many developing countries. In Thailand, 570,000 people are living with HIV, of these about 300,000 are women.<sup>1</sup> Despite standard recommendation in different regions to prevent perinatal human immunodeficiency virus (HIV) -1 transmission have been set for several years, approximately 630,000 children worldwide are perinatally infected with HIV each year, most of whom are born in developing countries.<sup>2</sup> In 2003, a total of 12.1 million of sub-saharan African were orphaned by AIDS.<sup>1</sup>

Although the majority of HIV-infected children live in Africa, the annual prevalence of HIV in Asian children is increasing rapidly.<sup>2</sup> In Thailand, the epidemic started in injection drug users and female commercial sex workers (CSW) and quickly spread to the clients of female CSWs and from them to wives, girlfriends, and children.<sup>3,4</sup>

HIV disease progresses more rapidly in children when compared to adults. By one year of age, 30% develop AIDS and by 5 years, at least half have AIDS.<sup>5-7</sup> Providing antiretroviral therapy to children is difficult in

developing countries because of limitations in availability, affordability and appropriate formulation. Children and families living with HIV face discrimination in their community and at school. It is important to put all effort into preventing perinatal transmission of HIV-1 infection.

### **Prevention of perinatal HIV-1 transmission**

Significant progress has been made in the past decade on preventing parent to child transmission of HIV. We now know that antiretroviral agents (ARV) prophylaxis, avoidance of breastfeeding and cesarean section in women with high HIV RNA can reduce transmission.<sup>8-11</sup> In Thailand, child mortality from infectious diseases is low, so the discontinuation of breastfeeding does not have an impact on infant disease-related mortality.<sup>7</sup>

In 1994, the results of the Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076 opened the door to a major preventive effect.<sup>12</sup> In this clinical trial, oral zidovudine (ZDV) was administered to HIV-infected pregnant women, beginning at any time between 14 and 34 weeks' gestation and continuing until labor when intravenous ZDV was used instead. Infants received ZDV syrup for 6 weeks and were formula fed. HIV transmission rate decreased from 22.6% in the placebo group to 7.6% in the ZDV group. This intervention was quickly adopted as a standard of care in most developed countries in conjunction with avoidance of breastfeeding. Due to the high cost and complexity, it is not possible to implement the original protocol as such in most developing countries.<sup>13, 14</sup>

A study from Uganda (HIVNET 012) studied the safety and efficacy in reducing perinatal HIV-1 transmission of administration of single dose

nevirapine (NVP) given orally to HIV-infected women during labor and another dose to the breast-fed infants within 72 hr after birth. This was compared with oral ZDV given at the onset of labor and then to the infants for 7 days after birth.<sup>15</sup> A reduction by 40% in transmission in the NVP compared to the ZDV group was seen. At 18 months of age, 16% of the infants in the NVP group compared to 26% in the ZDV group were infected.<sup>16</sup> This was a breakthrough strategy which is simple and can be implemented in resource-poor settings that practice breastfeeding.

In the SAINT study, half of the women were given the HIVNET 012 regimen except for an additional dose of NVP during the first few days after delivery and the other half had maternal ZDV/lamivudine (3TC) and infant ZDV. The transmission did not differ. At 2 months, 12% of infants in the NVP arm were infected and 9% of those in the ZDV/3TC arm had HIV.<sup>17</sup> In the PETRA study, three ZDV/3TC regimens were used compared to placebo, although there was an initial benefit especially when both the mothers and infants received ZDV/3TC, the preventative effect diminished considerably because of breastfeeding.<sup>18</sup>

The PACTG 316 study found no further transmission reduction when NVP single dose was given to women treated with HAART and to their infants.<sup>19</sup>

### **Prevention of perinatal HIV-1 transmission in Thailand**

From the early stages of the HIV epidemics in Thailand, breastfeeding in women infected with HIV was discouraged. The Thai government provides free formula for all HIV-exposed infants for at least 1 year. Therefore, no

breastfeeding was practiced in any of the studies or programs conducted in Thailand.

In 1996, the Thai Red Cross Society (TRCS), with the support of Princess Soamsawali and the Ministry of Public Health (MOPH) of Thailand, initiated a donation campaign called “Save a Child’s Life from AIDS”. The key objectives were to prevent perinatal HIV-1 transmission by procuring ZDV for HIV-infected pregnant women through public donation, and to test the feasibility and acceptability of ZDV therapy. This program used a modified PACTG 076 regimen with a lower daily dose of ZDV during pregnancy and oral instead of intravenous ZDV during labor resulting in a transmission rate of 6% which is much less than 20% in women who did not receive ZDV reported by others.<sup>14</sup> Later on, it was found that transmission was not different whether women started ZDV before or after 30 weeks’ gestation.<sup>13</sup> In late 1999, TRCS recommended that antepartum administration of ZDV for HIV-infected pregnant women in this program should begin at 32 weeks’ gestation (> 6-8 weeks before delivery) and continue until labor.

In 1997, the Bangkok Collaborative Perinatal HIV Transmission Study group, known as “The Bangkok Study”, conducted a placebo-controlled short course ZDV prophylaxis for perinatal HIV transmission. Oral ZDV was administered to HIV-infected pregnant women, beginning at 36 weeks of gestation and continued during delivery. No ZDV was given to the infants. A 50% reduction in transmission was seen with an infection rate of 9% in the treated group compared to 19% in the placebo group.<sup>14</sup> This study raised much debate regarding the ethics of placebo-controlled trial in developing countries when an effective treatment is known.<sup>16, 20, 21</sup>

In the same year, Lallemand M et al studied the transmission rate when different lengths of maternal and infant ZDV were used and found that a longer maternal treatment by starting at 28 weeks gestation was crucial in reducing transmission while the length of infant treatment was not as important.<sup>22</sup>

In 1999, a group of Thai investigators explored the use of 3TC in combination with ZDV in a single arm non-randomized study.<sup>23</sup> Women were given ZDV/3TC from 34 weeks gestation until delivery and the infants received 4 weeks of ZDV monotherapy. The transmission rate was 2.8%.

In 2000, after the HIVNET 012 result was known, TRCS incorporated NVP single dose into its TRCS regimen in attempt to further reduce transmission. Of the first 116 infants born at King Chulalongkorn Memorial Hospital in which the TRCS regimen was used, no one contracted HIV infection.<sup>24</sup> The benefits of single dose NVP in addition to ZDV in reducing perinatal HIV transmission was confirmed by Lallemand M et al.<sup>25</sup> When a single dose of NVP was given to both mothers and infants in addition to ZDV, transmission rate was 2.2% compared to 7.2% in the ZDV alone arm.

With the emerging data of resistance from single dose NVP, the TRCS decided to modify the donation program once more to give only HAART (ZDV/3TC/NVP) to all women (Table 1). Women with a more advanced HIV disease start HAART sooner and continue it after delivery. Women with a milder disease or CD4 higher than 200 cells/mm<sup>3</sup> can stop HAART after delivery. NVP is stopped 7 days before the nucleoside analogs in order to prevent resistance.

## **Thailand National Prevention Program**

In 1997, the MOPH of Thailand decided to conduct an operational research using short-course ZDV as part of a comprehensive perinatal HIV prevention program in public health hospitals which was later scaled up to a nationwide program.<sup>26, 27</sup> Between October 2000 and July 2001, 93% of about 300,000 women who gave birth agreed to HIV testing and 3,958 was found to be HIV positive (1.2%). Seventy percent of women received ZDV and over 80% of infants received ZDV and infant formula.<sup>26</sup> All pregnant women are counseled and offered voluntary HIV blood testing. All HIV-infected pregnant women are offered ZDV treatment from 34 weeks of gestation until delivery, and ZDV is given to infants, the length depends upon the maternal ZDV treatment time (Table 2). Cesarean section is recommended in women with HIV RNA more than 1,000 copies/ml. HIV antibody testing in infants is performed at the age of 12 and 18 months. Because of the markedly lower transmission rate achieved by adding a single dose of NVP to ZDV demonstrated by Lallemand M et al, the MOPH of Thailand decided in 2003 to include this component in its new guidelines (Table 2).

## **MTCT plus programs in Thailand**

The goal of MTCT plus is to provide the whole family with medical and psychological care and support in order to improve their quality of life, inter-family relationship and contribution to society. The program offers opportunistic infection screening, HAART, monitoring and HIV diagnosis for all family members. A team of obstetricians, internists, pediatricians, nurses, counselors,

educators and nutritionists works together to provide comprehensive care to the families.

In October 2002, the MOPH of Thailand started a pilot MTCT plus program in four provinces enrolling 350 pregnant women per year with funding from the Global Fund for AIDS, Tuberculosis and Malaria. There is plan to scale up this program to all provincial and regional hospitals. In the same year, the TRCS also started its MTCT plus program funded partly by Columbia University and has so far enrolled 600 mothers, fathers and infants.

### **Resistance and treatment of mothers and infants after exposure to non-HAART regimens for perinatal prevention**

The concerns regarding the risk of resistance and its long-term consequence when non-HAART regimens are used in the prevention of perinatal HIV transmission has just been endorsed by the report by Jourdain G et al. Women in Thailand who participated in the Perinatal HIV Prevention Trial-2 study<sup>25</sup> were treated with NVP-based HAART when their CD4 fell below 250 cells/mm<sup>3</sup>.<sup>28</sup> It was found that women who were exposed to NVP had the lowest treatment response rate even when no mutations were detected on genotyping. At 6 months after starting HAART, only 38% and 52% of women exposed to NVP with and without NVP mutations respectively had HIV RNA below 50 copies/ml compared to 68% of those who were not exposed to NVP. This raised an important issue, as NVP-based therapy is the most available and affordable HAART regimen in Thailand and in other developing nations. The resistance to ZDV does occur, but to a lesser extent.<sup>29, 30</sup> Because the consequence of NVP resistance is great, a single mutation to NVP confers

resistance to both NVP and EFV, it is worrisome that mutations to NVP occur in 20 to 32% of women and infants exposed to single dose NVP.<sup>28, 31, 32</sup> The spread of NVP resistant virus is also an issue of concern. The Pediatric guidelines from the United States and World Health Organization have suggested that infants be treated with HAART according to the availability and affordability of the region.<sup>33-35</sup> There is not enough information to warrant avoidance of the exposed PMTCT drugs at this time.

Advocates for short course HAART have argued that to prevent resistance, a regimen with ability to suppress HIV RNA must be used. However, the benefit needs to be weighed against the toxicity relating to continuous treatment with NVP. A recent report showed that pregnant women especially those with high CD4 might be at more risk for liver toxicity. Four pregnant women out of 18 had fulminant hepatitis following 4-6 weeks of ZDV/3TC/NVP.<sup>36</sup> Using short course HAART may not be feasible in settings less developed than Thailand.

## **CONCLUSION**

Thailand's experience in implementing a national program to reduce the transmission of HIV from parent to child has encouraged other nations to start their own pilot programs. The biggest challenge is to expand coverage beyond the pilot projects to reach all HIV-infected pregnant women and their families. This requires leadership and planning to improve infrastructure, training, motivating, retaining the necessary health care staff, and improving distribution systems so that HIV test kits, medication, and infant formula are consistently available to those who need them. Thailand is now moving towards the next

step by scaling up the MTCT plus program to provide long-term comprehensive care to HIV-infected women and their families.

**Table 1. The Thai Red Cross Society Donation Program Guidelines for Perinatal HIV Prevention.**

Periods	Procedures
Antepartum	<ul style="list-style-type: none"> <li data-bbox="507 454 1378 562">□ If CD4 <math>\leq</math> 200 or CD4 <math>\leq</math> 350 and CDC B or C: ZDV/3TC/NVP from 14 weeks</li> <li data-bbox="507 595 1378 703">□ If CD4 &gt; 200 and CDC A: ZDV/3TC/NVP from 28 weeks or request MOPH regimen (See Table 2)</li> </ul>
Intrapartum	<ul style="list-style-type: none"> <li data-bbox="507 752 826 786">□ Continue 3TC/NVP</li> <li data-bbox="507 819 1102 853">□ Give ZDV 300 mg orally every 3 hours</li> </ul>
Postpartum	<ul style="list-style-type: none"> <li data-bbox="507 902 1378 1077">□ GPO-vir® (fixed dose combination of d4T/3TC/NVP) in mothers if antepartum CD4 <math>\leq</math> 200 or CD4 <math>\leq</math> 350 and CDC B or C</li> <li data-bbox="507 1122 1378 1296">□ Stop NVP immediately after delivery and continue ZDV/3TC for another 7 days if antepartum CD4 &gt; 200 and CDC A</li> <li data-bbox="507 1341 799 1375">□ No breastfeeding</li> </ul>

**Table 2. The Ministry of Public Health Guidelines for Perinatal HIV**

**Prevention.**

Periods	Procedures
Antepartum	<ul style="list-style-type: none"><li>❑ ZDV from 28 weeks (300 mg twice daily)</li></ul>
Intrapartum	<ul style="list-style-type: none"><li>❑ ZDV 300 mg orally every 3 hours during labor</li><li>❑ NVP 200 mg at onset of labor</li></ul>
Postpartum	<ul style="list-style-type: none"><li>❑ ZDV 2 mg/kg every 6 hours for 1 week if mothers received at least 4 weeks of antepartum ZDV or 6 weeks if mothers received less than 4 weeks of antepartum ZDV</li><li>❑ NVP 6 mg once before 72 hours of age (2 mg/kg if birth weigh is less than 2500 grams)</li><li>❑ No breastfeeding</li></ul>

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