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OBSTETRICS

Reduction of Mother-to-Child Transmission of HIV with Short-Course Zidovudine in Lampang Center Hospital

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ABSTRACT

Objective To study the efficacy of short-course oral zidovudine in reducing the risk of mother-to-child human immunodeficiency virus (HIV) transmission.

Materials and methods A prospective study which enrolled all consenting, eligible HIV-infected pregnant women attending antenatal care clinic. The zidovudine regimen included antepartum oral ZDV 300 mg twice daily initiated from 34-36 weeks' gestation, followed by oral ZDV 300 mg every 3 hours, at onset of labor until delivery. The newborns were given oral administration of ZDV syrup 2 mg/kg every 6 hours for one week. Mothers were asked not to breastfeed and provided with infant formula.

Setting Lampang Center Hospital.

Subjects 167 asymptomatic HIV infected pregnant women and their 168 infants.

Main outcome measures Perinatal HIV infection was defined by: 1) at least one positive plasma HIV RNA, or 2) two positive HIV DNA PCR at different time, or 3) positive anti-HIV at 18 months old or more.

Results From July, 1997 through July, 2000, 167 enrolled HIV-infected pregnant women gave birth to 168 live-born babies. Of 158 babies with known HIV-infection status, 10 babies were identified as HIV-infected. The transmission rate was 6.3 % (95% CI 3.1-11.3). The median of treatment profiles were 36 days of antepartum administration, and 3 doses of intrapartum therapy. The subjects were well tolerated to the drug, and no withdrawal due to adverse drug effect.

Conclusion This short-course regimen can satisfyingly reduce the vertical transmission rate, and be an optional preventive intervention in poor resource countries, with reasonable cost than long-course regimen.

Key words: HIV, perinatal transmission, zidovudine

Human immunodeficiency virus (HIV) type 1 may be transmitted from mother to infant. The timing of perinatal transmission also remains unclear. Lapointe and co-workers[1] reported on a child delivered by cesarean section at 28 weeks' gestation who was immediately separated from its mother. Subsequently, several series of abortuses were surveyed. HIV genome was identified using polymerase chain reaction (PCR) as early as the 12th week of pregnancy by Courgnaud and associates.[2] Soeiro and colleagues[3] studied human abortus tissue and suggested that up to 30% of HIV transmissions may occur by the second trimester of pregnancy. However, the possibility of contamination from maternal sources was difficult to exclude definitively in any study of aborted fetal tissues.

Although perinatal HIV transmission is now accepted as the most common route of infection of neonates, the rate and determinants of that transmission remain uncertain. Worldwide, about 15-45% of infants born to infected women have been reported to become HIV infected.[4,5] The reported transmission rates have shown wide geographic variation. In Thailand, HIV infection among women attending antenatal care services steadily increased from 0.8% in 1991 to 2.3% in 1995.[6] The increasing infection among women who desire pregnancy predicts an increasing number of HIV-infected infants in the future. The vertical transmission rate is 18.9% in non-prophylactic group.[7]

Zidovudine (ZDV) treatment of women during pregnancy and intrapartum, and infants during the early postnatal period has been shown to significantly reduce rate of perinatal HIV transmission. A clinical trial in the USA and France [AIDS Clinical Trials Group(ACTG) 076] showed that, in the absence of breastfeeding, ZDV given orally five times daily to HIV-infected pregnant women starting at 14-34 weeks' gestation, intravenously during labor, and orally to babies for 6 weeks, lowered the risk for perinatal HIV-transmission by two-thirds.[8]

Recent research has highlighted several promising interventions to reduce perinatal infection. Unfortunately, many of these interventions are unaffordable for or inaccessible to women in developing countries. Limiting factors are the cost of the intervention, the cost of availability of diagnostic tests on which some interventions depend, and women's access to health services. Cost reductive alternatives are needed.[9,10]

The Ministry of Public Health of Thailand is becoming more aware and concern of appropriate prevention of vertical transmission, and adapted protocol of ACTG 076 was developed, in variety of the regimens. The objective is to modify the preventive intervention, decreasing cost associated with ZDV, and expect to allow greater implementation of protocol in regions with limited health care resource. Dr. Vallop Thaineua, General Inspector Region 10, Ministry of Public Health at that time, saw that the upper part of Northern Thailand had highest prevalence of HIV infection in pregnant women, we could not wait for the trial results of shortened ZDV regimens. A short-course ZDV regimen of Region 10 was developed to examine the efficacy in prevention of perinatal HIV transmission. This observational study was conducted in all provincial and district hospitals of Region 10.

Materials and methods

The study proposal was approved by the National Ethical Committee and Institutional Review Board. All known HIV-positive pregnant women attending antenatal care clinic at Lampang Center Hospital whom were diagnosed during a voluntary test for HIV antibody, and agreed to participate the study between July, 1997 to July, 2000, were voluntarily enrolled in this study, after counselling process for decision making. The subjects were tested with the third generation HIV-1 classic enzyme immunoassay (EIA). Positive sera were re-tested with a different third generation HIV-1 EIA, or gel particle agglutination, according to second strategy of the WHO-UNAIDS guidelines for HIV testing.[11] The eligible inclusion criterias were asymptomatic HIV infection, gestational age during 34-36 weeks, intending not to breastfeed, willingness to provide

voluntary informed consent, hemoglobin ≥ 8 g/dL, neutrophils ≥ 1,000/mm^3, and platelets ≥ 100,000/mm^3. The exclusion criterias were ZDV treatment before this pregnancy, allergy to ZDV, and unwillingness to participate the entire study.

The ZDV treatment consisted of antepartum oral ZDV 300 mg twice daily initiated from 34-36 weeks' gestation, and continued throughout the remainder of pregnancy. The subjects were suggested to have regular follow up every 1-2 weeks. Compliance with treatment was assessed by counting pills. The women were evaluated for drug adverse events and the clinical symptomatic HIV infections in every visit.

At the onset of labor, the women were suggested to take oral ZDV 300 mg immediately and refered themselves to the hospital. Intrapartum oral ZDV (300 mg every 3 hours) were administered until delivery. The women who were performed the elective cesarean section were prescribed ZDV 300 mg for three doses, 12, 9 and 6 hours before surgery. Breast feeding was not recommended to all the parturients. The infants were given oral administration of ZDV (syrup 2 mg/kg every 6 hours for one week), beginning within 4 hours after birth.

The infants were evaluated at birth by pediatricians and at 2, 4, 6, 9, 12 and 18 months follow-up visits. The peripheral blood specimens were tested for hemoglobin at birth and at 2 months of age, and for plasma HIV RNA or HIV DNA PCR at 2 and 4 months old. HIV RNA was identified in the first 75 infants at Research Institute of Health Science, Chiangmai University, and HIV DNA PCR was tested in the last 83 infants at Center of Medical Science, Chiangmai. One infant was diagnosed by anti-HIV when it was 18 months old because it lost to follow up and came later after one year old. The infants were diagnosed to be HIV infected by: 1) at least one positive plasma HIV RNA; or 2) two positive HIV DNA PCR at different time; or 3) positive anti-HIV at 18 months old or more. Each pair of twins was single transmission outcome. We used more than one method to diagnose HIV infection status because there was limitation of laboratory support and some infants might lost to follow up at earlier time and came later at older age. If there were discordance among PCR result, anti-HIV and clinical findings of infants we used anti-HIV for final diagnosis.

Results

During three-years period of intervention, there were 7,543 cases of pregnant women attending pre-test HIV counselling and testing, and 218 cases (2.9%) were HIV positive. 171 of 218 (78.4%) were willing to participate the study, however, there were 167/218 (76.6%) asymptomatic HIV- infected women and 168 infants were enrolled to the study. The distribution of study population and their eligibility were shown in Table 1.

Table 1. Distribution of study population and their eligibility

	Number (%)
Pregnant women	
Pre-test HIV counselling and testing	7,543
HIV seropositive	218/7,543 (2.9)
Lost to follow-up or did not want to continue on pregnancy	39/218 (17.9)
Gestational age more than 36 weeks	8/218 (3.7)
Voluntary participation	171/218 (78.4)
Delivered before 34 weeks' gestation	4/171 (2.3)
Received zidovudine	167/218 (76.6)

	Number (%)
Infants	
Life birth	168
Twins*	1
Early neonatal death **	2
Testing for HIV *	158/167 (94.6)
HIV infected	10/158 (6.3)
Non-testing for HIV	9/167 (5.4)
Early neonatal death with no PCR	1
Voluntary withdrawal	3
Lost to follow-up	5

* One set of twins was considered as single delivery in efficacy

** One case had positive plasma HIV RNA

The obstetric characteristics of pregnant women and infants were shown in Table 2. 158 subjects had regular follow up and complete therapy, and 159 infants had complete follow-up and were evaluated. The median age of the subjects was 24.5 years (range of 15-43 years). About 95(60.1%) were primiparous women, and the first antenatal visits were 46(29.1%) , 88(55.7%), and 24 (15.2%) at the first, second, and third trimester respectively. The medical and obstetric complications included syphilis (2 cases), vaginal condyloma accuminata (1 case), overt anemia (6 cases), hemoglobin H disease (2 cases), pregnancy induced hypertension (2 cases), post-term pregnancy (7 cases), previous cesarean section (5 cases), full blown AIDS development in the last month of pregnancy (2 cases) and puerperal infection (1 case). Besides, one subject had the history of amphetamine addiction. The median hemoglobin at the first antenatal visit was 11.0 g/dL, range of 4.7-14.1 g/dL, and 78 cases (49.4%) had hemoglobin less than 11.0 g/dL. Cesarean section were performed among 30 cases (19.0%), and 7 were elective cases. The choices of postpartum contraceptive methods were reported; tubal sterilization 68.2%, Norplants 7.6%, injectable contraception 17.2%, combined pills 3.6%, and unknown 3.4% respectively.

For infants, 77 (48.4%) were male and 82 (51.6%) were female. The median birth weight was 2,850 g, and range of 1,500 - 3,850 g. Nearly one-sixth (15.7%) were less than 2,500 g body weight.

Table 2. Obstetric characteristics of 158 pregnant women and 159 infants

	Number (range)	
Pregnant Women		
Median age (year)	24.5	(15-43)
Median hemoglobin at the first ANC visit (g/dL)	11.0	(4.7-14.1)
Median gestational age (week)	39	(35-43)
Median duration of labor (hour)	10.8	(1.3-59.5)
Median duration of ruptured membrane (hour)	0.9	(0-33.5)

	Number
Types of delivery	
Vaginal delivery	128 (81.0%)
Spontaneous delivery	118 (74.7%)
Vacuum or Forceps extraction	10 (6.3%)
Cesarean section	30 (19.0%)
Indicated	23 (14.6%)
Elective	7 (4.4%)
Infants	
Weight 1,500 - 1,999 g	4 (2.5%)
Weight 2,000 - 2,499 g	21 (13.2%)
Weight 2,500 - 2,999 g	74 (46.5%)
Weight 3,000 g or more	60 (37.7%)
Median birth weight (g)	2,850 (range 1,500-3,850)

Of 168 infants, One infant was dead at the first day of life, because of meconium aspiration, and HIV testing was omitted. The another one was dead at the third day of life, according to severe congenital anomalies, and had positive HIV RNA. Voluntary withdrawals were reported in 3 cases, among these, 2 cases were negative HIV DNA PCR at 2-months visit. Loss of follow-ups were noted in 5 cases. Of 158 infants with known HIV-infection status, 10 infants (6.3%) were HIV infected. One set of twins was born and had concordant uninfected outcomes. One healthy infant had 2 positive HIV DNA PCR at early visits and was diagnosed as non-infected because the anti-HIV was negative at 9 and 18 months of age. Two pregnant women developed full blown AIDS in the last month of gestation, and one infant was infected. Among 30 cases of cesarean section, 2 infants were HIV infected and one of these two infants was early neonatal death because of severe congenital anomalies and had positive HIV RNA. No HIV infection was detected in the elective cesarean section and vaginal operative cases.

Table 3 demonstrated the ZDV use and compliance. 136 women (86.1%) started the drug at 34 weeks' gestation. The median of antepartum drug administration was 36 days, range of 5-64 days. The median number of intrapartum drug use was 3 doses, range of 0-17. Of women whose labor began at home, 72.8% took a home labor dose and came to the hospital. Before ZDV administration, the median hemoglogin was 11.3 g/dL, range of 7.9-14.6 g/dL, and 63 cases (39.9%) had hemoglobin less than 11.0 g/dL. At onset of labor, the median hemoglogin was 11.1 g/dL, range of 8.1-14.2 g/dL, and 45.5% had hemoglobin less than 11.0 g/dL (based on 101 cases). Nausea and vomiting were found in 30 women (19.0%), however, the pregnant women were well tolerated without any serious adverse events. Only 4 infants had partial drug administration. At birth, the median hemoglobin was 16.5 g/dL, range of 10.1 - 23.3g/dL. At 2 months of age, the median hemoglobin was 9.2 g/dL, range of 6.9-12.7 g/dL(based on 74 infants).

Table 3. ZDV use and compliance

Number = 158	Number (%)
Gestational age when started the drug	
34 weeks	136 (86.1)
35 weeks	13 (8.2)
36 weeks	9 (5.7)
Median of antepartum drug use (day)	36 (range 5-64)
< 14 days	4 (2.5)
14-27 days	34 (21.5)
28-41 days	65 (41.1)
42 days or more	55 (34.8)
Compliance*	
Full compliance	152 (96.2)
Partial non-compliance	2 (1.3)
Non-compliance	4 (2.5)
Median of intrapartum dose	3 (range 0-17)
0-1 dose	40 (25.3)
2-3 doses	54 (34.2)
4 doses or more	64 (40.5)

* Full compliance: shortage not more than 2 inconsequent doses, partial non-compliance: shortage 3-5 inconsequent doses or 2 consequent doses, non-compliance: shortage more than 5 inconsequent doses or more than 2 consequent doses.

Discussion

Our study shows that, in the absence of breastfeeding, a short-course of oral ZDV can reduce the rate of perinatal HIV-transmission to 6.3%. Whereas in 1996-1997, our hospital had only non-breastfeeding policy in HIV-infected mothers, the transmission rate was as high as 21.7%.[12] Our findings yield the comparable rate of perinatal HIV-transmission with the original ACTG 076 regimen[8] (6.3% versus 8.3%).

The average duration of ZDV use in the ACTG 076 regimen was 11 weeks,[8] compared with 5.1 weeks in this study. The expense of short-course regimen is relatively lower and possibly more compliance. In addition, about 95% of transmission during pregnancy occurs in the last two months of gestation.[13] The late third trimester regimen is appropriate for developing countries , not only in term of efficacy but also effectiveness , including suitable for delayed antenatal attending. The recent study in Thailand also has showed that, in the absence of breastfeeding, a short-course ZDV given in late pregnancy (at 36 weeks' gestation) and labor lowered the risk for perinatal HIV-transmission from 18.9% to 9.4% (50.1% reduction).[7] The oral ZDV is convenient, available, acceptable and cheaper than injectable one. While the pharmacokinetic study between oral and injectable ZDV reveals no significant difference of concentration in the umbilical cord blood.[14]

We also used ZDV in the newborn because , in the absence of breastfeeding , about two - thirds of perinatal HIV transmission occurs during labor[13] and the study of Wade NA, et al[15] found that there was reduction of perinatal HIV transmission even with the use of abbreviated regimen that was begun in the first 48 hours after birth. We gave ZDV for one week in the newborn which is cheaper

and less complex than the 6 weeks' duration of the ACTG 076 regimen, and we do not know how long the treatment in the infant will give the best result and safe. The recent four-armed study of ZDV regimens[16] has showed that the long-long (started in the mother at 28 weeks' gestation with 6 weeks of treatment in the infant) , long-short (started at 28 weeks' gestation with 3 days of treatment in the infant), and short-long regimen (started at 35 weeks' gestation with 6 weeks of treatment in the infant) had equivalent efficacy (transmission rates were 6.5%, 4.7% and 8.6% respectively). These were significantly etter than the short-short regimen (started at 35 weeks' gestation with 3 days of treatment in the infant) which had transmission rate of 10.5%. The optimal duration of treatment both in pregnant women and newborns is still inconclusive, however, the antepartum treatment at 34-36 weeks' gestation and newborn of one week duration as this study shows the comparable efficacy.

Our findings show that this short-course regimen can be an optional preventive intervention in developing countries or countries with high prevalence of HIV infection in pregnant women. However, even this shortened regimen requires a health policy, an organised health infrastructure, access to prenatal care, testing and counselling for HIV infection, and provision of ZDV. The non-breastfeeding approach is also recommended avoiding the postpartum transmission.[17] When implemented nationwide in Thailand, this regimen could prevent many vertical transmissions. The advantage of the preventive program is secondary cost saving, as well as the health care system cost for HIV infected infants.

Since 2000, the Ministry of Public Health has endorsed and promoted the nationwide program of mother-to-child HIV prevention , a short-course of ZDV in both pregnant women and newborns. ZDV should be given to all eligible HIV infected pregnant women and begins as soon as possible at 34 weeks' gestation. The adjusted treatment of the newborn is recommended depend on antepartum ZDV administration. If the drug adherence during antepartum has maintained at least 4 weeks, the newborn only receives one week of ZDV. When antepartum maintainance is less than 4 weeks, then the newborn extensively receives 6 weeks of ZDV.

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