Prevention of HIV Transmission from Mother-to-Child in Srinagarind Hospital

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Abstract

From January 1996 to December 1999, HIV infected pregnant women and their newborns were studied. Informed consent was obtained and HIV-tests were performed after counselling. ZDV for perinatal prophylaxis starting on week 14 to week 36 of gestation and continued throughout pregnancy was given following an ACTG 076 regimen except that during labour, intravenous ZDV was replaced by oral ZDV 300 mgs, given every 3-hours as a loading dose and ZDV syrup 2 mgs/kg every 6 hours for 7 days orally for the newborns. Newborn HIV-Ab and PCR were done at 6 weeks and 6 months after birth. Eighty-four HIV infected pregnant women were enrolled in the study, eighty-three of whom were delivered. The overall transmission rate was 5.2 per cent, with 3/58 children confirmed infected with HIV by at least two positive PCR test results.

Key word : HIV, Perinatal Transmission, ZDV (Zidovudine)

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Perinatal HIV transmission appears to vary among populations. In the absense of preventive measures, the risk of a baby acquiring the virus from an infected mother ranges from 15 per cent to 25 per cent in industrialized countries, and 25 per cent to 35 per cent in developing countries[1,2]. The difference is due largely to feeding practices : breast feeding is more common and usually practiced for

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a longer period in developing countries than in the industrialized world. Unprotected sex between men and women accounted for most of the new HIV infections estimated among adults. In addition, high fertility combined with poor access to information and services for the prevention of mother-to-child transmission resulted in some infected children being born to mothers with HIV.

It is not clear when vertical transmission occurs, and it seems that HIV may pass from mother-to-child during pregnancy (*in utero*), birth (intrapartum) and even after birth (through breastfeeding). Immunologic, virologic, obstetric and other maternal factors influence transmission, but their relative contributions are difficult to assess[3-6]. However, there is now indirect evidence suggesting that the risk of viral transmission may be greatest in late pregnancy or during delivery. This has, therefore, become the focus of attention as a possible period when intervention to reduce transmission risk may have the most benefit.

In 1989, the AIDS Clinical Trial Group protocol 076 (ACTG 076) was designed to assess the efficacy of ZDV in preventing the transmission of HIV from mothers to children. In order to provide maximum efficacy by covering all of the time periods when transmission might occur, women started taking oral ZDV between 14 to 34 weeks gestation and continued throughout pregnancy to prevent *in utero* transmission. ZDV IV infusion was administered during labor to prevent intrapartum transmission and oral ZDV was given to the newborn for 6 weeks to ensure the presence of the drug in the infant in case any infected maternal cells had passed into the infant's circulation during uterine contractions. All infants were bottle-fed, eliminating the risk of infection through breastmilk. In the ZDV group, 8.3 per cent of the infants were infected compared with 25.5 per cent of those in the placebo group[7]. All subsequent studies have confirmed the remarkable efficacy of pre-, peri- and postpartum ZDV prophylaxis for the prevention of mother-to-child transmission. Additional trials[8,9] have been conducted to determine if the antiretroviral treatments could be simplified and shortened while retaining substantial efficacy, thus improving feasibility, safety and patient compliance to treatment, while reducing treatment cost, side effects and the risk of drug resistance at individual as well as population levels. Moreover, much progress has been made in the early diagnosis of infection in exposed infants (born to HIV seropositive mothers). Polymerase chain reaction (PCR) technique and viral culture are the most sensitive tests and are able to diagnose 50 per cent of infants at birth and nearly 100 per cent by the age of 6 months[10,11].

In Thailand, HIV infection among women attending antenatal care services steadily increased from 0.8 per cent in 1991 to 2.3 per cent in 1995 [12]. The increasing infection among women who desire pregnancy predicts an increasing number of HIV-infected infants in the future. The efficacy of ZDV prophylaxis treatments of varing duration has been evaluated in several organizations. The Thai Red Cross Society is becoming more aware and concerned about appropiate prevention of vertical transmission, and the adapted protocol of ACTG 076 was developed to decrease the cost associated with ZDV, and expected to allow greater implementation of protocol in regions with limited health care resource. The Bangkok Collaborative Perinatal HIV Tranmission Study Group was a randomized placebo-controlled trial where women were treated with ZDV from 36 weeks gestational age. This prospective study aimed to look at the vertical transmission rate (VTR) of HIV in asymptomatic HIV infected pregnant women who had been given ZDV during pregnancy, delivery and after birth to their babies for the prevention of HIV transmission from mother to child in Srinagarind Hospital.

MATERIAL AND METHOD

Between January 1996 and December 1999, all known HIV-positive pregnant women attending the antenatal clinic at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University were enrolled in the study. Informed consent was obtained and HIV-testing were performed after counselling. The inclusion criteria were asymptomatic HIV infection, gestational age during 14-36 weeks, and hemoglobin $\geq$ 11 g/dl. The exclusion criteria were ZDV treatment before this pregnancy or allergy to ZDV.

ZDV for the prevention of HIV vertical transmission starting on week 14 to 36 of gestation and continued throughout pregnancy was given following an ACTG 076 regimen except that during labour, intravenous ZDV was replaced by oral ZDV 300 mgs given every 3-hours as a loading dose and ZDV syrup 2 mg/kg every 6 hours for 7 days orally for the newborns.

The subjects were advised to have regular follow-up every two weeks. Antenatal vitamins in-

cluding iron supplement were given and the CBC, platelet count, urine analysis, VDRL, HBsAg were performed on first admission to the study and repeated at 32 weeks of gestational age. All of them were evaluated for drug adverse events and the clinical symptoms of HIV infections at every visit.

Physical examination of the newborn was performed by neonatologists and the peripheral blood specimens were tested for HIV by PCR technique at 6 weeks and 6 months after birth and for HIV-Ab by Enzyme immunoassay (EIA) at 6 weeks, 6 months and 18 months. The infants were concluded to be HIV infected by at least two positive PCR.

RESULTS

Eighty-four HIV infected pregnant women were enrolled in the study, eighty-three of whom were delivered. Fifty-seven per cent of the sample group were under the age of 25, sixty-five per cent were primigravida, nearly all of them (99%) were infected through heterosexual transmission. Thirty-four per cent of them received ZDV before 20 weeks of gestational age and thirty per cent received after 32 weeks. Eighty seven per cent gave birth at term, 88 per cent of babies were delivered vaginally (Table 1). The overall transmission rate was 5.2, with 3/58 infants confirmed infected with HIV by at least two positive PCR test results. (Table 2, 3). Sex, gestational age at birth and body weights of the HIV seropositive children are shown in Table 4.

DISCUSSION

Zidovudine (ZDV) treatment of women during pregnancy, intrapartum and infants during the early postnatal period has been shown to significantly reduce the rate of perinatal HIV transmission. The ACTG 076 which included 3 to 5 months of antepartum oral ZDV (100 mg 5 times a day) and continued throughout the remainder of pregnancy. Intrapartum intravenous ZDV (loading dose 2 mg/kg) was started at onset of labor followed by continuous infusion (1 mg/kg/h) until delivery. The infants were given oral administration of ZDV (syrup 2 mg/kg every 6 hours for six weeks), beginning 8 to 12 hours after birth. The proportions of infection at 18 months, as estimated by the Kaplan-Meier method were 8.3 per cent in the ZDV group and 25.5 per cent in the placebo group, a 67.5 per cent relative reduction in the risk of transmission. The vertical transmission rate of the Thai Red Cross society regimen was 5.8 per cent and of the Bangkok Col-

Table 1. Mother enrollment characteristics.

Age (yrs)	No	%
15-20	7	8.33
21-25	41	48.81
26-30	27	32.14
31-35	6	7.14
36-40	3	3.57
>40	-	-
Total	84	100

Number of previous live births	No	%
0	55	65.48
1	29	34.52
Total	84	100

Risk factors	No	%
Heterosexual	83	98.81
IVDU or partner IVDU	-	-
Blood transfusion	1	1.19
Total	84	100

ZDV started (weeks)	No	%
14-16	10	11.90
17-21	19	22.62
22-26	15	17.86
27-31	15	17.86
32-36	25	29.76
Total	84	100

GA.At birth (weeks)	No	%
<34	-	-
34-36	2	2.41
>37	72	86.75
Unknown	9	10.84
Total	83	100

Route of delivery	No	%
Vaginal delivery	73	88.05
Caesarean section	1	1.21
Unknown	9	10.84
Total	83	100

Table 2. Demographics of the newborns.

Live born children	No	%
Yes	74	89.16
No	-	-
Unknown	9	10.84
Total	83	100

Sex	No	%
Male	37	44.58
Female	37	44.58
Unknown	9	10.84
Total	83	100

Birth weight (grams)	No	%
<2,500	6	7.23
2,500-2,999	23	27.71
3,000-3,499	41	49.41
3,500-3,999	3	3.61
<4,000	1	1.20
Unknown	9	10.84
Total	83	100

laborative Perinatal HIV Transmission Study Group regimen was 9.4 per cent[13]. In the present study, we aimed to look at the VTR of HIV in asymtomatic HIV infected pregnant women who had been given ZDV during pregnancy, delivery and after birth to their babies. The women had received antenatal care between January 1996 and December 1999. At that time it has already proved that ZDV given to the mothers for the prevention of HIV transmission from mother-to-child was worked, so a comparison group could not be ethically justified. The authors made the assumption as others have done in previous studies that, in both developed and developing countries, in the absense of preventive measures, the risk of a baby acquiring the virus from an infected mother ranges from 15 per cent to 25 per cent. All the mothers in the present study were advised not to breastfeed. Most pregnant women known to be HIV positive in the period under study were not denied intervention as it would have been unethical. The overall transmission rate was 5.2 per cent, HIV infection was defined by 2 positive PCR obtained from peripheral blood specimens taken at 6 and 24 weeks postpartum. The proportion of loss of follow-up was 10 per cent, the main reason was that they had moved to other places.

Given the belief that perhaps two-thirds of transmission occurs around delivery, Caesarean section, by limiting exposure of the baby to contaminated maternal fluids, intuitively seems to offer some protection. Analysis based on the European Collaboration Study suggested a 50 per cent reduction in transmission with Caesarean section relative to vaginal delivery[14]. However, other studies have not confirmed this result. In particular, the large French

Table 3. Follow-up of children and transmission outcome (based on PCR testing).

	No	PCR+ve	HIV-Ab-ve	HIV-Ab+ve
6 weeks	66	3	-	66
6 months	58	3	5	53
18 months	38	-	35	3

Table 4. HIV seropositive children.

No	Sex	GA at birth (week)	Birth weight (kg)	GA received ZDV
1	Male	39	3,150	32
2	Female	38	3,040	21
3	Female	40	3,100	21

perinatal study showed no effect of mode of delivery[15]. Meta-analysis of 12 studies has shown an odds ratio of 0.80 for transmission with Caesarean section[16]. The 95 per cent confidence interval (CI) extended to unity, and the authors concluded that the results of their analysis did not justify the routine use of Caesarean section delivery for HIV infected women, a conclusion reiterated by Peckham and Gibb[17]. More recently, a further US study did not confirm an independent effect of Caesarean section[18]. HIV positive mothers are at an increased risk of complications when delivered by Caesarean section, particularly those with a CD_4 count less than 200 x 10^6/L[19]. Thus, the evidence that elective Caesarean section reduces the risk of vertical transmission is inconclusive, and this issue should be resolved by the international mode of delivery trial currently in progress.

If Caesarean section is to be carried out, it should be performed using a technique aimed at minimising contact of the fetus with maternal blood. Such a "bloodless" technique was described by Towers et al[20] and can be achieved by using a vicryl stapling device (made by Autosuture, Norwalk, Connecticut, USA) for the lower segment incision; by keeping membranes intact as long as possible, and by washing the baby carefully on the table. Rapid clamping of the umbilical cord is necessary to avoid maternal-fetal transfusion during separation of the placenta. The same kind of attention should apply to babies delivered vaginally. In the present study only 1 out of 73 was delivered by Caesarean section because of breech presentation in primigravida.

The authors strongly advised the women not to breastfeed and all of the newborns received formula feeding. Breastfeeding appears to double the risk of transmission of HIV compared with a baby who is not breastfed. In some developing countries, where formula feeding carries a significant risk of mortality, the balance of risk is more difficult. Assessment of risk must be particularised for different countries, social groups, women and babies. Nevertheless, where there is a high infant mortality associated with malnutrition and infectious disease, WHO/UNICEF supports breastfeeding by the baby's own mother, regardless of her HIV status[21].

SUMMARY

Worldwide, obsteticians can help to ensure good accessible care for women with HIV and encourage condom distribution and use. The fact that much vertical transmission may be prevented has focused increasing attention on the availability of HIV testing at antenatal clinics. There are now clear advantages for the fetus when the woman's HIV intection is known. Nevertheless, HIV is seen as a test with particular implications which is separate from other routine tests, the need for careful counselling and informed consent has been emphasised. The results of the ACTG O76 trial, the information on breastfeeding, the more effective treatment, the possibility of reducing sexual transmission and the low prevalence of HIV all seem in favour of standardising (the availability) of HIV testing services in antenatal clinics. Moreover, we have much to contribute in the prevention of vertical transmission of HIV and by participating in a different antiviral regimen. In summary, we conclude that prophylactic ZDV seems to be effective and feasible in preventing HIV vertical transmission in our setting. However, a better outcome could be expected if HIV serostatus was known for all childbearing women planning to become pregnant or, at least, for all pregnant women in the first trimester.

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การป้องกันการติดเชื้อเอ็ชไอวีจากมารดาสู่ทารกในโรงพยาบาลศรีนครินทร์

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เป็นการศึกษาการป้องกันการติดเชื้อเอ็ชไอวีจากมารดาสู่ทารกในครรภ์ โดยการให้ยาต้านไวรัสชนิดเดียว (Zidovudine) ในขณะตั้งครรภ์ ตั้งแต่อายุครรภ์ 14–36 สัปดาห์เป็นต้นไป จนกระทั่งคลอด และให้ยาชนิดเดียวกันรับประทานระหว่างคลอด หลังคลอดให้ทารกรับประทานนาน 7 วัน พร้อมทั้งให้นมผสมทดแทนนมมารดา จากการตรวจเลือดเพื่อติดตามภาวะการติดเชื้อในทารกด้วยวิธี PCR หลังคลอด 6 สัปดาห์ และ 6 เดือน และตรวจหาเอ็ชไอวีแอนติบอดีย์จนกระทั่งอายุ 18 เดือน พบว่า มีสตรีตั้งครรภ์ที่ได้รับยาคลอดแล้วทั้งหมด 83 คน สามารถตรวจ PCR ในเด็กได้ถึง 6 เดือน จำนวน 58 คน พบทารกติดเชื้อ 3 คน คิดเป็นร้อยละ 5.2 หากเปรียบเทียบอัตราการติดเชื้อเอ็ชไอวีจากมารดาสู่ทารกโดยไม่ได้รับการป้องกันใด ๆ ของประเทศไทย ซึ่งพบได้ร้อยละ 20–25 แล้ว แสดงว่าในการศึกษานี้สามารถลดการติดเชื้อเอ็ชไอวีจากมารดาสู่ทารกในครรภ์ได้สูงถึงร้อยละ 80

คำสำคัญ : เอ็ชไอวี, การติดเชื้อจากมารดาสู่ทารก, ไซโดวูดีน

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