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Zidovudine use to Reduce Perinatal HIV Transmission in Southern Thailand : A Preliminary Report

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ABSTRACT

Objective Variety of zidovudine (ZDV) treatment for prevention of perinatal HIV transmission is now performing in developing countries. A decision model was used to examine the efficacy and cost reduction. The AIDS Clinical Trial Group (ACTG) 076 regimen was particularly adapted to use oral ZDV instead of intravenous ZDV intrapartum, to evaluate efficacy and cost reduction of zidovudine in reducing the perinatal transmission.

Design A prospective study which includes antepartum oral ZDV (500 mg daily) initiates between 14 and 34 weeks gestation, followed by oral ZDV (300 mg every 3 hours) at onset of labor until delivery. The newborns are given oral administration of ZDV (syrup 2 mg/kg every 6 hours for six weeks).

Setting Hat Yai Regional Hospital.

Subjects Sixty asymptomatic HIV infected pregnant women and their 61 infants.

Main outcome measures Perinatal HIV infection was defined by at least two positive nested polymerase chain reaction (PCR) obtained from peripheral blood specimens of the infants taken at 1, 4 and 6 months consequently.

Results Four out of 51 infants (7.8%) with complete follow-up were seropositive.

Conclusion The reduction rate of perinatal HIV transmission in this study is similar with ACTG 076 regimen, whereas intrapartum oral ZDV of the original and local brand can reduce cost to two-third and one-tenth, respectively.

Key words : HIV, perinatal transmission, zidovudine

Human immunodeficiency virus (HIV) type 1 may be transmitted from mother to infant during antepartum, intrapartum, and postpartum period. Immunologic, virologic, obstetric and other maternal factors influence transmission, but their relative contributions are difficult to assess.[1-7] About 15-45% of infants borne to infected women have been reported to become HIV infected.[8,9]

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.[10] The AIDS Clinical Trial Group Protocol (ACTG 076) which included 3 to 5 months of antepartum oral ZDV (100 mg 5 times a day) initiated between 14 and 34 weeks' gestation 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/hr) 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.

HIV infection was defined by 1 positive viral culture obtained from peripheral blood specimens taken at birth, 12, 24 and 78 weeks postpartum. Preliminary results showed HIV infection (at least 1 positive culture) in 7.2% (13 of 180) in the treatment group and 21.7% (40 of 184) in the untreated control group. The proportions of infection at 18 months, as estimated by the Kaplan-Meier method, were 8.3% in the ZDV group and 25.5% in the placebo group, a 67.5% relative reduction in the risk of transmission.[10]

In Thailand, HIV infection among women attending antenatal care services steadily increased from 0.8% in 1991 to 2.3% in 1995.[11] The increasing infection among women who desire pregnancy predicts an increasing number of HIV-infected infants in the future. 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.[12,13] The Thai Red Cross Society is becoming more aware and concern of appropriate prevention of vertical transmission, and adapted protocol of ACTG 076 was developed. Intrapartum oral ZDV instead of intravenous ZDV is modified to decrease the cost associated with ZDV, and expected to allow greater implementation of protocol in regions with limited health care resource. This study examined the relationship between effectiveness and cost reduction of ZDV for prevention of perinatal HIV transmission.

Materials and Methods

All known HIV-positive pregnant women attending antenatal care clinic at Hat Yai Regional Hospital whom were diagnosed during a voluntary test for HIV antibody, and agreed to participate the study between August 23, 1996 to December 12, 1997, were voluntarily enrolled in this study. The subjects were tested with the third generation HIV-1 classic EIA (Enzyme immunoassay). Positive sera were retested with a different third generation HIV-1 EIA, or Gel particle agglutination, according to second strategy of the WHO-UNAIDS guidelines for HIV testing.[14] The eligible inclusion criteria were asymptomatic HIV infection, gestational age during 14-34 weeks, and hemoglobin ≥ 10 g/dL. The exclusion criteria were ZDV treatment before this pregnancy, or allergy to ZDV. Each woman insisted to continue gestation after perinatal risk counselling.

The ZDV treatment consisted of antepartum oral ZDV (200 mg in the morning and 300 mg in the evening) initiated between 14-34 weeks gestation, and continued throughout the remainder of pregnancy. The subjects were suggested to

have regular follow-up every two weeks, and the hemoglobin investigation was performed every eight weeks ; including iron supplement. 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. 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 six weeks), beginning within 12 hours after birth.

The infants were evaluated at birth by neonatologists and the peripheral blood specimens were tested for HIV by nested polymerase chain reaction (PCR) technique using HIV-1 pol primer at 1, 4 and 6 months consequently. The infants were concluded to be HIV infected by at least two positive PCR.

Results

During sixteen-month period of intervention, 77 eligible asymptomatic HIV infected women were enrolled to the study. Sixty subjects had regular follow up and completed the therapy, and 51 infants had complete follow-up and evaluation. The mean age of the subjects was 24.08 years, (range 17-34 years). Nearly two-third (63.3%), 38 of 60, were in the age group of 15-25 years old, and (65.0%), 39 of 60) had primary school education. About one-third (36.6%), 22 of 60 were housewives, followed by one-fourth (25.0%), 15 of 60, were blue-collar workers, and (18.3%), 11 of 60 were farmers, (11.6%), 7 of 60 were small businesspersons, and (8.3%), 5 of 60 were unspecified. Most of them (73.3%), 44 of 60 had family incomes between 1,000 to 10,000 Baht per month, and average income was 7,648.3 Baht per month.

No one recognized that they got HIV infection, and most of the husbands (88.3%, 53 of 60), refused to have voluntary test. Whereas 2 of 7 (28.5%) of the husbands had negative results of HIV antibody test. Half (51.6%), 31 of 60, were primigravida. One of them (1.6%) had adverse drug event such as nausea and vomiting, but she could tolerate well to the drug. The information and details of antenatal care and delivery are showed in Table 1.

Nearly two-third (61.7%), 37 of 60, were prescribed ZDV at the gestational age of 21-30 weeks, and most of them (76.7%), 46 of 60, delivered at term (38-40 weeks) ; average 38.5 weeks. Nearly two-third (65.0%), 39 of 60, had duration between rupture of membrane to delivery shorter than 1 hour.

Two-third (40 of 61) were male and one-third (21 of 61) were female infants. Among these, one of the women had delivered twins, and both were male. One-third of the women (20 of 60) had voluntary postpartum tubal terilization. Fifty-one infants had complete follow-up, 7.8% (4 of 51) had at least two PCR positive. (See Table 2) Ten of 61 infants (16.4%) were lost follow up.

Discussion

The mechanism by which zidovudine reduced the risk of maternal-infant HIV infection is not established. Maternal zidovudine may have reduced the viral load and diminished the viral exposure of the fetus in utero, of the infant at delivery, or both. Therapeutic concentrations of zidovudine in the fetus and the newborn may have prevented HIV infection.[10]

The significant reduction in vertical HIV transmission demonstrated in ACTG 076 regimen

Table 1. Information and details of antenatal care and delivery.

	number (N = 60)	percent
Gestational age when started ZDV treatment (weeks)		
14-20	14	23.3
21-30	37	61.7
30-34	9	15.0
Number of antenatal visit		
1-5	10	16.7
6-10	30	50.0
11-15	18	30.0
> 15	2	3.3
Gestational age at delivery (weeks)		
35-37	11	18.3
38-40	46	76.7
41-44	3	5.0
Duration between repture of membrane to delivery (hours)		
< 1		
1-4	39	65.0
> 4	10	16.7
	11	18.3
Mode of delivery		
Spontaneous vaginal delivery	47	78.3
Vacuum extraction	4	6.7
Forceps extraction	1	1.7
Cesarean section	8	13.3

Table 2. Descriptions of four cases of HIV-positive pregnant women with HIV infected infants

	Case 1	Case 2	Case 3	Case 4
Gravida	1	1	1	2
Gestational age when started ZDV treatment (weeks)	26	27	26	23
Gestational age at delivery (weeks)	38	38	40	39
Duration between onset of labor to delivery (hour : minute)	3 : 14	8 : 40	12 : 05	13 : 07
Duration between rupture of membrane to delivery (hour)	0	27	9	5
Presentation	breech	vertex	vertex	vertex
Mode of delivery	cesarean section	spontaneous	spontaneous	cesarean section
Fetal weight (gm)	2,500	2,630	3,250	3,300

has resulted in the issuance of public health guidelines for offering voluntary HIV counselling and testing to all pregnant women. If a women is found to be infected, the risks and benefit of ZDV treatment are to be discussed and if appropriate, the ZDV treatment should be recommended. ZDV therapy was chosen and successfully taken by 60 of 77 (77.9%) of women who complete their pregnancy and medication. Many factors may affect acceptance of ZDV or other coming antiretroviral drugs. Team approach should be one of the approaches to ensure the continuation antenatal, intrapartum and neonatal ZDV therapy, including follow-up of the infants. Nevertheless the drop out rate of infant follow up is (16.4%) 10 of 61. That is a pitfall of the counselling and follow-up process.

Modified ACTG 076 regimen of ZDV in this study yielded the similar rate of perinatal HIV transmission with the original ACTG 076 regimen and had few side effects. The reduction rate of perinatal transmission is satisfactory and acceptable. However, it can not be comparable with the original ACTG 076 regimen due to lack of placebo, randomized control trial. It is also pros and cons in the study design, the former concept aims to double blind, randomized control which is more advantage in the statistical analysis, where the later idea is based on the original study and its result is high statistical significant.

In addition, the cost saving in the program was the secondary gain, as well as the health care systems cost for HIV infected infants. Many researchers chose to study the regimens that combined antepartum, intrapartum and neonatal therapy because the exact period of maternal-infant HIV transmission is uncertain. In Thailand, many on-going studies confine in simple and less costly regimens, e.g. the effect of ZDV in late pregnancy on HIV vertical transmission.[15] The coming conceptual tramework is whether short regimen among mothers or infants can comparable with long term therapy.

However, the vaginal cleansing intervention used intrapartum has only a marginal reduction in the HIV transmission rate and cannot recommended as an effective health approach to reduce perinatal HIV transmission.[16] Some evidence does point to intrapartum transmission but there are no empiric data to support a protective effect to cesarean section, and, in fact, there are reports of infected babies who had been delivered abdominally.[17]

The evaluation of the cost reduction can roughly be estimated. The average duration of labor time was 8.94 hours (approximate figure = 9), and average maternal body weight was 60.36 kilograms (approximate figure = 60). By crude estimation, the ACTG 076 protocol was modified to use oral instead of intravenous form intrapartum, regarding the oral ZDV and ZDV syrup were constant cost. Three doses of oral ZDV were used, which is equal to 3 X 300 = 900 mg (300 mg every 3 hours), whereas the one initial intravenous dose was 1 X 2 X 60 = 120 mg (2 mg/kg) plus eight maintenance doses 8 X 1 X 60 = 480 mg. The total intravenous dose was 600 mg (three vials) individually. According to the survey in March 1998, the intravenous ZDV (original brand only) will be 502 Baht per 250 mg vial or 3 X 502 = 1,506 Baht per case. The original brand, oral ZDV is 44.43 Baht (approximate figure = 45 Baht), and the cost per case will be 9 X 45 = 405 Baht. However, the local brand, oral ZDV is 15 Baht, and the cost per case will be 9 X 15 = 135 Baht. The cost reduction comparisons between the original and local brand are shown in Table 3.

The original brand oral ZDV could reduce cost from 1,506 Baht to 405 Baht per case, or

Table 3. Comparisons of the cost of oral and intravenous ZDV intrapartumly used.

Treatment	Original brand (Baht)		Local brand (Baht)		Difference (Baht)
	IV	Oral	IV	Oral	
Intravenous ZDV intrapartum (per case)	1,506	-	-	-	-
Modify to original brand oral ZDV (per case)	-	405	-	-	1,101
Modify to local brand oral ZDV (per case)	-	-	-	135	1,371
Intravenous ZDV intrapartum (60 cases)	90,360	-	-	-	-
Modify to original brand oral ZDV (60 cases)	-	24,300	-	-	66,060
Modify to local brand oral ZDV (60 cases)	-	-	-	8,100	82,260

from 90,360 Baht to 66,060 Baht in this study, decreased to one-third. For the local brand oral ZDV could diminish cost to 135 Baht per case, or to 8,100 Baht for the study, diminished to one-tenth.

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