Intrapartum Zidovudine Infusion Alone Failed to Reduce Both Maternal HIV-1 Viral Load and HIV-1 Infection in Infant†

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Abstract

A pilot clinical trial to assess the efficacy of intrapartum zidovudine (ZDV) infusion alone in the reduction of maternal viral load and its potential role in preventing vertical transmission of HIV-1. Twenty six, asymptomatic antiretroviral naïve HIV-1 infected pregnant women who had no prior antenatal care and were in labor were enrolled. Each patient received ZDV infusion at the rate of 2 mg/kg within the first hour. ZDV was then continuously infused at 1 mg/kg/h until delivery. Maternal plasma HIV-1 RNA prior to the commencement of ZDV infusion and within an hour after delivery were measured. HIV-1 transmission was documented by nested polymerase chain reaction in infants at six months of age. Median maternal plasma HIV-1 RNA prior to the ZDV infusion and after delivery was 29,401 and 32,555 copies/ml respectively, ($p>0.05$). The estimated HIV-1 transmission rate was 19.2 per cent (95% CI = 4-34). This result suggested that in asymptomatic HIV-1 infected pregnant women who were antiretroviral naïve and had no prior antenatal care, intrapartum ZDV infusion alone failed to reduce maternal HIV-1 viremia and the transmission rate of HIV-1.

Key word : Intrapartum, Zidovudine, HIV-1 Infection, Infant

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It has been estimated that at least 850,000 adults are currently infected with HIV in Thailand and heterosexual contact is the most common route of transmission[1]. The prevalence of HIV-1 infection in Thai pregnant women was approximately 2.3 per cent[2]. The rates of vertical transmission rate have been reported from 14-48 per cent in different cohorts worldwide[3]. The studies conducted in Bangkok have shown that the risk of HIV-1 vertical transmission is 24-33.3 per cent[4-6], whereas, studies in the north of Thailand revealed the transmission rates as high as 42-45 per cent[4,7]. The differences in the transmission rate may be partly related to a higher proportion of breast feeding among women in the northern cohorts. It has been estimated that approximately 10,000 Thai infants are born to HIV-1 infected mothers annually[8]. The AIDS Clinical Trial Group 076 (ACTG 076) study demonstrated that antepartum and intrapartum zidovudine administration to HIV-1 infected pregnant women together with a 6-week zidovudine administration to newborns, can reduce vertical transmission rate from 25 per cent to 8 per cent[9]. More recently, a study has shown that a short regimen of twice-daily oral zidovudine, in the absence of breast feeding, can reduce the risk of mother-to-child HIV-1 transmission by half[10]. This regimen can prevent HIV-1 vertical transmission during late pregnancy and labor in the less-developed countries where the ACTG 076 regimen cannot be implement. Zidovudine therapy has been shown to be effective in reducing perinatal HIV transmission regardless of maternal viral load[11]. However, approximately 5-9 per cent pregnant women who delivered at King Chulalongkorn Memorial Hospital had never received antenatal care[12]. Therefore, studies of the most appropriate intervention to prevent HIV-1 vertical transmission in such a population are important. We initiated a pilot study to investigate whether intrapartum infusion of zidovudine in HIV-1 infected women who have not received antepartum antiretroviral therapy could reduce maternal viremia and vertical transmission rate.

MATERIAL AND METHOD

This was a multicenter, open label study carried out in three tertiary government hospitals in Bangkok, Thailand. The enrollment was from July 19,1995 to October 6,1995. Twenty-six asymptomatic HIV-1 infected pregnant women who had no prior antenatal care and were in labor were enrolled. The major eligible criteria included: 1) Documented HIV-1 infection 2) No prior antiretroviral treatment 3) Hemoglobin level higher than 8 g per cent, and 4) Being able to bring the child for follow-up for at least 6 months after delivery. After counselling and obtaining a written informed consent, zidovudine infusion was given at the rate of 2 mg/kg during the first hour, followed by 1 mg/kg/h until delivery. Prior to infusion, maternal blood samples were collected for CD4+ T cell counts and plasma HIV-1 RNA measurements. Maternal blood samples were also collected within 1 hour after delivery for plasma HIV-1 RNA measurements. None of the infants were breastfed. Blood samples were collected from infants for HIV-1 proviral DNA testings at 6 months. Plasma HIV-1 RNA was measured by using Quantiplex® HIV RNA 1.0 assay (b DNA) (Chiron corporation, Emeryville, CA, USA) with detection limit of 10,000 copies/ml. The samples that were undetectable for HIV-RNA were then re-analysed by using Amplicor HIV Monitor® test (Roche Diagnostic System, Inc., Branchburg, NJ, USA) with the limit of detection of 500 copies/ml. Nested polymerase chain reaction (PCR) for the detection of HIV-1 proviral DNA (env and pol genes) was performed as previously described[13].

Statistical analysis was done with SPSS package. Baseline characteristics were calculated by descriptive statistic. The comparison of maternal factors and treatment of infected infants and non-infected infants was performed using Mann-Whitney U test.

RESULTS

Twenty-six asymptomatic pregnant women were enrolled in the study. The baseline characteristics of this cohort are summarised in Table 1. Median maternal age and gestational age were 24 years (range 21-33 years) and 40 weeks (range 38-42 weeks), respectively. Median CD4+ T cell count and plasma HIV-1-RNA before zidovudine infusion were 597 (range 235-1,102) cells/mm^3 and 29,401 (range 2,282-60,345) copies/ml, respectively. The modes of delivery were as follows : spontaneous vaginal delivery 20 cases, forceps extraction 1 case, vacuum extraction 1 case and, cesarean section 4

Table 1. Baseline characteristics of HIV-1 infected mothers.

Parameters	Median (range)
Maternal age (years) n= 26	24 (21-33)
Gestational age (weeks)	40 (38-42)
Weight (kgs)	62 (52-87)
Hematocrit (%)	35.5 (32-39)
WBC (cells/mm^3)	9,850 (4,300-19,200)
CD4+ T cells (cells/ mm^3)	597 (235-1,102)
Plasma HIV-1 RNA (prior to ZDV infusion, copies/ml)	29,401 (2,282-60,345)

Table 2. Maternal factors and infant outcomes.

Maternal factors	Infected group (n = 5) Median (range)	Non-infected group (n = 21) Median (range)	P*
CD4+ T cells count (cells/mm^3)	648 (494-792)	590 (235-1,102)	NS
Maternal plasma HIV-RNA (copies/ml)			
Before ZDV infusion	37,320 (11,020-60,345)	24,300 (2,282-60,000)	NS
After ZDV infusion	25,940 (18,770-38,330)	25,600 (2,370-70,772)	NS
Duration of labor before ZDV infusion (h)	2.8 (1.4-16.2)	4.6 (1.2-7.8)	NS
ZDV infusion time (h)	4.0 (1.3-5.1)	4.5 (0.7-13.6)	NS
Mode of delivery			NS
• Spontaneous vaginal	3	17	
• Forceps extraction	0	1	
• Vacuum extraction	1	0	
• Cesarean section	1	3	

* Mann-Whitney U Test

cases. There were 26 newborn infants ; 12 were males and 14 were females with a median birth weight of 3,050 (range 2,150-4,000) grams.

Median maternal plasma HIV-1 RNA levels prior to initiating zidovudine infusion were 29,401 (range 2,282-60,345) copies/ml, and the values within an hour after delivery were 32,555 (range 2,370-70,772). There was no significant change in maternal plasma viral load.

HIV-DNA PCR results at 6 months of age were positive for 5 infants. This gave a transmission rate of 19.2 per cent (95% CI = 4-34). Comparison of maternal factors and mode of delivery between the infected infants and the non-infected infants namely maternal CD4+ T cell count, plasma RNA, the time course of zidovudine infusion, duration of labor before zidovudine infusion and, zidovudine infusion time are shown in Table 2.

DISCUSSION

The results of ACTG 076 study showed that the administration of zidovudine to a selected group of women during the second and third trimester of pregnancy, during labour and to their newborn infants can reduce perinatal transmission by approximately two-thirds[9]. However, the complexity and cost of this approach make this intervention, particularly among developing countries unfeasible and impossible. Recently, several studies, including those by Collaborative Perinatal HIV Transmission Study Group and the DITRAME Study Group have shown that a short course of zidovudine can reduce the risk for mother-to-child HIV-1 transmission by half in non-breast fed infants and, by approximately 38 per cent in breast-fed babies, respectively[10,14,15]. More interestingly, a recent study has found that intrapartum and neonatal single-dose nevirapine lowered the risk of HIV-1 transmission during the first 14-16 weeks of life by nearly 50 per cent in a breast-fed population[16]. This simple and inexpensive regimen could decrease mother-to-child transmission in less-developed countries[17]. However, these results were reported after our pilot study had been performed.

Maternal viral load is one of the important factors involved in HIV mother-to-child transmission[10,15,18]. Our pilot study demonstrated that intrapartum zidovudine infusion alone failed to reduce maternal HIV-1 load in antiretroviral-naive mothers. Failure to reduce the HIV-RNA levels in the present study may be due to the short infusion time of zidovudine to overcome the maternal viremia. Median infusion time of our study was 4.5 hours, whereas, the estimated half-life of free virion was about 6 hours[19].

The vertical transmission rate in this study was 19.2 per cent (95% CI = 4-34) and was not significantly different from the non-treated group [3]. The comparison analysis among the HIV transmitters *versus* the non-transmitters showed no significant differences in median maternal CD4+ T cell counts, viral load, duration of labor and duration of zidovudine infusion. Nevertheless, this pilot study consisted of a small sample size of 26 cases, therefore, the power to achieve statistical significance may be compromised and this should be taken into consideration.

In HIV-1 infected women who come to the labor suite without previous antiretroviral treatment, a principal approach similar to post-exposure chemoprophylaxis regimens should be instituted. Wade et al found that the vertical transmission rate was approximately 10.0 per cent and 9.3 per cent when zidovudine was begun in the intrapartum period and within 48 hours of life in infants, respectively[20]. Guay et al found that intrapartum and neonatal single-dose nevirapine lessens the risk of HIV-1 transmission during early life by nearly 50 per cent in a breastfed population[16]. Therefore, these stratagies should be implemented in this setting.

In conclusion, our results suggested that intrapartum zidovudine infusion alone failed to reduce both maternal viral load and vertical transmission in HIV-infected pregnant women. A recently reported study of a more practical, simple and cost-effective intervention, intrapartum and neonatal single-dose nevirapine, may be the most appropriate post-exposure prophylaxis for preventing HIV-1 vertical transmission in HIV-infected mothers who are in labor with no previous antiretroviral treatment. Further investigation of the most cost-effective means to further reduce the risk of vertical transmission is warranted.

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การให้ยาไซโดวูดีนหยดเข้าทางหลอดเลือดดำเพียงอย่างเดียวมีความล้มเหลวในการลดทั้งปริมาณไวรัสเอ็ชไอวีในเลือดมารดาและการติดเชื้อไปสู่ทารก†

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การศึกษานำร่องเพื่อประเมินประสิทธิผลของการให้ยาไซโดวูดีนเพียงอย่างเดียวหยดเข้าทางหลอดเลือดดำในการลดปริมาณไวรัสเอ็ชไอวีในเลือดมารดาและป้องกันการติดเชื้อไปสู่ทารกในสตรีตั้งครรภ์ที่เจ็บครรภ์คลอดจำนวน 26 คนที่ติดเชื้อเอ็ชไอวี ไม่มีอาการหรืออาการแสดงของโรคเอดส์ ไม่เคยได้รับยาต้านไวรัสเอดส์มาก่อน และไม่ได้ฝากครรภ์ แต่ละคนได้รับยาไซโดวูดีนหยดเข้าทางหลอดเลือดดำในอัตรา 2 มิลลิกรัมต่อน้ำหนักตัว 1 กิโลกรัมในหนึ่งชั่วโมงแรกและหยดต่อเนื่องในอัตรา 1 มิลลิกรัมต่อน้ำหนักตัว 1 กิโลกรัมต่อหนึ่งชั่วโมงจนกระทั่งคลอด เจาะเลือดสตรีนี้ก่อนให้ยาและภายในหนึ่งชั่วโมงหลังคลอดเพื่อตรวจวัดปริมาณไวรัส ติดตามทารกจนกระทั่งอายุ 6 เดือนเพื่อเจาะเลือดตรวจด้วยวิธีปฏิกิริยาลูกโซ่ว่าติดเชื้อไวรัสเอดส์หรือไม่ ค่ามัธยฐานของปริมาณไวรัสก่อนให้ยาและภายในหนึ่งชั่วโมงหลังคลอดมีค่า 29,401 และ 32,555 กอปปี้ต่อมิลลิลิตรตามลำดับซึ่งไม่แตกต่างกันทางสถิติ ($p>0.05$) อัตราการติดเชื้อเอ็ชไอวีในทารกร้อยละ 19.2% (ช่วงความเชื่อมั่นร้อยละ 95 เท่ากับ 4-34) ผลการศึกษานี้แสดงว่าการให้ยาไซโดวูดีนเพียงอย่างเดียวหยดเข้าทางหลอดเลือดดำในสตรีตั้งครรภ์ที่เจ็บครรภ์คลอดที่ติดเชื้อเอ็ชไอวี ไม่มีอาการหรืออาการแสดงของโรคเอดส์ ไม่เคยได้รับยาต้านไวรัสเอดส์มาก่อนนั้นไม่สามารถลดปริมาณไวรัสเอ็ชไอวีในเลือดมารดาและไม่สามารถลดอัตราการติดเชื้อในทารกได้

คำสำคัญ : ระยะเจ็บครรภ์คลอด, ยาไซโดวูดีน, การติดเชื้อเอ็ชไอวี, ทารก

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