Original Report

Effect of Immediate Neonatal Zidovudine on Prevention of Vertical Transmission of Human Immunodeficiency Virus Type 1

Sayomporn Sirinavin, MD;[*†] Winit Phaupradit, MD;[‡] Surasak Taneepanichskul, MD;[‡] Kalayanee Atamasirikul, MSc (Clinical Pathology);[§] Priyasuda Hetrakul, MD;[*†] Ammarin Thakkinstian, MSc (Biostatistics);[†] and Panyu Panburana, MD[‡]

ABSTRACT

Objectives: To describe the effects of various short zidovudine (ZDV) prophylactic regimens on vertical transmission of human immunodeficiency virus type 1 (HIV-I) infection, especially the effect of immediate neonatal ZDV prophylaxis.

Materials and Methods: The study included children of HIV-1-infected mothers who were born at a teaching hospital in Bangkok. The ZDV prophylaxis regimens varied by time periods that included: (1) no ZDV (1991–1996); (2) antenatal oral ZDV, 250 mg given twice a day starting at 34 to 36 weeks' gestation and continued until labor (1995–1998); (3) antenatal oral ZDV plus immediate neonatal oral ZDV, 6 mg/0.6 mL/dose started within the first 2 hours after birth and continued at 6-hour intervals for 4 to 6 weeks (1997–1998); and (4) intrapartum intravenous ZDV given in addition to regimen 3 (1998–1999). Neonatal ZDV was administered within 2 hours after birth in 95% of the neonates.

Results: In a cohort of 136 children born at least 9 months before the analysis date, the HIV-1 vertical infection rates were: (1) no ZDV, 11 of 48 (22.9%, 95% confidence interval [CI] = 12.0–37.3); (2) late antenatal ZDV, 10 of 47 (21.3%, 95% CI = 10.7–35.7); (3) late antenatal ZDV plus immediate neonatal ZDV, 0 of 28 (0%, 95% CI = 0–12.3); (4) late antenatal, intrapartum intravenous ZDV, plus immediate neonatal ZDV, 0 of 13 (0%, 95% CI = 0–24.7). An estimated 0% (95% CI = 0–8.6) of the infants who received immediate neonatal ZDV with or without intrapartum ZDV were infected, as compared with 22.1% (95% CI = 14.2–31.8) of those who received no ZDV or only late antenatal ZDV ($P < 0.001$).

Conclusion: The results of this study suggests high protective effect of immediate administration of neonatal ZDV. Perinatal components of antiretroviral prophylaxis provided the best results for protecting against vertical HIV-1 transmission.

Key Words: *AIDS, HIV, neonates, pregnancy, prophylaxis, vertical transmission, zidovudine*

Int J Infect Dis 2000; 4:148–152.

Zidovudine (ZDV) therapy has proved effective in reducing human immunodeficiency virus type 1 (HIV-1) transmission from infected pregnant women to their infants in randomized double-blind placebo-controlled trials in both non-breastfeeding and breastfeeding infants.[1-4] The Pediatric AIDS Clinical Trials Group protocol 076 showed that an intensive regimen of ZDV prophylaxis starting at 14 to 34 weeks' gestation, given intravenously during labor and delivery, and orally to the neonates for the first 6 weeks of life reduced the risk of vertical HIV transmission by two-thirds.[1] A shorter oral ZDV regimen beginning at 36 weeks of gestation, given orally during labor, without a neonatal component also reduced the risk of transmission by approximately 50%.[2]

Limited observational data suggest that the use of abbreviated ZDV regimens beginning intrapartum or in the first 48 hours of life had some protective effects.[5,6] Some evidence also suggests that giving the drug sooner after HIV exposure would be better.[7-9] This report describes the effect of immediate neonatal ZDV prophylaxis as well as failure of a regimen consisting of only late antenatal ZDV given twice daily to prevent vertical HIV-1 infection in non-breastfed neonates.

PATIENTS AND METHODS

Participants

The study was carried out at Ramathibodi Hospital, a teaching hospital in Bangkok, which serves a mixed population of lower and middle socioeconomic class people.

*Division of Infectious Diseases, Department of Pediatrics; †Division of Clinical Epidemiology, Office of the Dean; ‡Department of Obstetrics and Gynaecology; §Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Address correspondence to Dr. Sayomporn Sirinavin, Division of Infectious Diseases, Department of Pediatrics, Ramathibodi Hospital, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand. E-mail: rassr@mahidol.ac.th.

The annual delivery rate is approximately 8000 of which 99% registered at 6 to 14 weeks of gestation. Routine voluntary antenatal anti-HIV screening tests with counseling have been practiced since 1990. The tests were performed at first registration for antenatal care during the first trimester and were repeated at week 32 of pregnancy.

The study included all pregnant women who had tested anti-HIV positive, decided to continue pregnancy, and had deliveries at Ramathibodi Hospital between November 1991 and February 1999. All deliveries by HIV-infected mothers were assisted by obstetricians or residents training in obstetrics and gynecology. The first infant delivered by an HIV-infected mother at this hospital was born in November 1991.

Prophylaxis Regimens and Follow-up

Since January 1995, HIV-infected women have been given information about ZDV prophylaxis. Regimens have changed as information about and affordability of the drugs has improved. Zidovudine prophylaxis practices included:

Group 1. No ZDV (1991-1996)
Group 2. Antenatal oral ZDV 250 mg (Retrovir™, Glaxo, Wellcome Operations, Greenfort, UK) given orally twice daily starting at 34 to 36 weeks and continued until labor without intrapartum ZDV (1995-1998)
Group 3. In addition to the regimen used in group 2, neonatal ZDV syrup (Retrovir, Glaxo) 6 mg/0.6 mL/dose given orally every 6 hours starting as soon as possible after birth and continued for 4 to 6 weeks (1997-1998)
Group 4. In addition to the regimen used in group 3, intrapartum injectable ZDV (Retrovir, Glaxo) 2 mg/kg of body weight, given intravenously for 1 hour, followed by 1 mg/kg per hour until delivery (1998-1999).

There were two pairs of alternate periods of practice between group 2 and group 3 during April 1995 to December 1998. Oral ZDV syrup had been given to neonates during January to August 1997, and was not given during September 1997 to January 1998, because the donated ZDV syrup had been consumed and because some preliminary information suggested that the neonatal component might be unimportant when antenatal prophylaxis was given. It was started again in January 1998, when it had been noted that, by stopping the drug, the transmission rate seemed to increase.

All women were counseled not to breastfeed and lactation inhibition hormone was given. Compliance to the oral ZDV regimen by pregnant women was observed by pill counts at each weekly visit. Administration of oral ZDV syrup to neonates as soon as possible after birth was recommended practice at this hospital. The infants stayed in the hospital during the first 3 days of life, during which oral ZDV was given by nurses every 6 hours after the first dose. A bottle of 100 mL ZDV syrup was given to the mothers on discharge from the hospital. The mothers were trained by pediatricians or nurses about administration of ZDV syrup to the infants, and medication practice was checked at the 1-month visit. Medical and social care for the families were provided.

Laboratory Methods

Anti-HIV tests were performed at the immunology laboratory of this hospital, using commercially available tests (AxSYM HIV-1/HIV-2, Abbott Laboratories, Chicago, Illinois; and SERODIA-HIV, Fujirebio Inc., Tokyo, Japan), following the manufacturers' instructions. Pregnant women were confirmed to be positive to anti-HIV antibody with the Western blot technique.

Outcome Assessment

All infants were followed prospectively at the pediatric infectious disease clinic. They were evaluated at 1 month and regularly after that according to the well-child care schedule. Blood tests for anti-HIV were performed at 6, 9, 12, and 15 or 18 months of age.

Children were classified as uninfected if they had negative anti-HIV tests twice between the ages of 8 and 15 months or a negative anti-HIV test once at 15 to 18 months. Criteria for the diagnosis of HIV infection included persistence of HIV antibodies at or after 15 to 18 months of age.

Statistical Analyses

For continuous data, Student's t-test was used if the assumption of normal distribution was met; if not, Kruskal-Wallis test was applied. For qualitative data, chi-squared test was used, and Fisher's exact test was applied if the numbers of expected values were less than 5 in more than 20% of all cells. Exact confidence intervals (CI) were calculated for relative risk (RR) and proportions. Stata Statistical Software on a microcomputer was used for all calculations.[10]

RESULTS

Characteristics of Mothers and Infants

A total of 136 HIV-infected pregnant women delivered at Ramathibodi Hospital during the study period. All women had acquired HIV infection by sexual contacts, and none had a history of drug injection. Characteristics of mothers and infants in the study are presented in Table 1. Forty-eight mother-infant pairs did not receive any ZDV (group 1), 47 received late antenatal ZDV (group 2), 28 received neonatal ZDV syrup in addition

Table 1. Characteristics of Mothers and Infants in the Study

Characteristics	*Group 1 No ZDV n = 48*	*Group 2 Antenatal ZDV n = 47*	*Group 3 Antenatal & Neonatal ZDV n = 28*	*Group 4 Antenatal, Intrapartum & Neonatal ZDV n = 13*	*P-Value*
Mothers					
Median age (y) (range, y)	26 (16–36)	25 (20–36)	28 (17–37)	26 (19–36)	0.837*
Median weight at gestational week 36 (kg) (range, kg)	61 (51–71)	62 (44–83)	61 (48–93)	63 (47–71)	0.787*
Duration of antenatal ZDV therapy (d)					
14–28 (n) (%)	0	26 (55)	18 (64)	5 (38)	0.314†‡
29–42 (n) (%)	0	17 (36)	7 (25)	6 (46)	
43–56 (n) (%)	0	3 (6)	2 (7)	0 (0)	
> 56 (n) (%)	0	1 (2)	1 (4)	2 (15)	
Labor and delivery					
Median duration of labor (min) (range, min)	507 (57–1247)	712 (0–1684)	732 (0–1466)	851 (178–1324)	0.209*
Median time of membrane rupture to delivery (min) (range, min)	186 (6–1835)	217 (0–1564)	77 (0–1227)	355 (15–994)	0.117*
Type of delivery (n) (%)					
Vaginal delivery	48 (100)	40 (85)	22 (79)	9 (69)	0.001†§
Cesarean section					
After membrane rupture	0 (0)	6 (13)	4 (14)	4 (31)	
Before membrane rupture	0 (0)	1 (2)	2 (7)	0 (0)	
Infants					
Median gestational age (wk) (range, wk)	39 (34–41)	39 (37–42)	38 (37–42)	40 (38–40)	0.276*
Median birth weight (g) (range, g)	2945 (1580–3590)	3130 (2390–3750)	3070 (2520–4060)	3070 (2540–4410)	0.183*

ZDV = zidovudine. *Kruskal-Wallis test; †Fisher's exact test; ‡comparing group 2, 3, and 4; §P = 0.347 when comparing group 2, 3, and 4.

to late antenatal ZDV (group 3), and 13 received late antenatal, intrapartum, and immediate neonatal ZDV syrup (group 4). There were no statistically significant differences among study groups in the characteristics of the mothers. Duration of antenatal ZDV prophylaxis was comparable in groups 2, 3, and 4 (P = 0.314). There were more cases of delivery by cesarean section in group 2, 3, and 4 than in group 1 (P = 0.001), but the proportion of cases having cesarean section before amniotic membrane rupture was similar (P = 0.323), and there was no statistically significant difference in types of delivery among groups 2, 3, and 4 (P = 0.347). Postpartum duration when ZDV syrup was initiated in the neonates was less than 30 minutes in 56%, less than 1 hour in 70%, less than 2 hours in 95%, and less than 18 hours in all cases. All infants in groups 3 and 4 received oral neonatal ZDV for 4 to 6 weeks, and 90% for 6 weeks.

Vertical HIV-1 Transmission

Human immunodeficiency virus type 1-infection status of all infants was diagnosed by anti-HIV tests. Of 136 infants of HIV-infected mothers, 132 were at least 15 months of age at the time of data analysis, and four infants who were 9 to 14 months old had had negative anti-HIV tests twice.

The estimated vertical HIV infection rates of different ZDV prophylaxis regimens are presented in Table 2. They were 11 of 48 (22.9%; 95% CI = 12.0–37.3) of the children in the non-ZDV group, and 10 of 47 (21.3%; 95% CI = 10.7–35.7) in the late antenatal ZDV group, which had no statistically significant difference (RR = 0.93; 95% CI = 0.43–1.98). Since the rates of vertical transmission and characteristics of mothers and infants are similar in the two groups, data were combined as an HIV transmission rate of 21 of 95 (22.1%; 95% CI = 14.2–31.8).

Addition of neonatal ZDV to the late antenatal ZDV regimen decreased the infection rate to 0 of 28 (0%; 95% CI = 0–12.3). In addition, no HIV transmission occurred in 13 infants who received intrapartum intravenous ZDV in addition to antenatal and neonatal ZDV. An estimated 0% (95% CI = 0–8.6) of the infants who received immediate neonatal ZDV with or without intrapartum ZDV were infected, as compared with 22.1% (95% CI = 14.2–31.8) of those receiving no ZDV or only late antenatal ZDV (P < 0.001).

Prophylaxis regimens were alternately practiced between late antenatal ZDV regimens without (group 2) or with (group 3) neonatal ZDV during April 1995 to December 1998. There were consistent findings that the two subgroups of group 2 (late antenatal ZDV) had similar transmission rates (5/26 and 5/21), and that none of infants in the two subgroups of group 3 (late antenatal plus neonatal ZDV) were HIV infected (0/12 and 0/16).

DISCUSSION

The study showed no protective effect against vertical HIV-1 transmission in a breastfeeding population of a

Table 2. Effects of Different Zidovudine (ZDV) Prophylactic Regimens on Vertical HIV Transmission Rates

Group	Study Periods	Prophylaxis Regimen	HIV Transmission Rates		Relative Risk (95% CI)*
			Number	Percentage (95% CI)	
1	Nov. '91–Mar. '96	No ZDV	11/48	22.9 (12.0–37.3)	1.00
2	Apr. '95–Jan. '98		10/47	21.3 (10.7–35.7)	0.93
	a. Apr. '95–Jan. '97	250 mg bid oral ZDV	5/26	19.2 (6.6–39.3)	(0.43–1.98)
	b. Sep. '97–Jan. '98	in late pregnancy	5/21	23.8 (8.2–47.2)	
3	Jan. '97–Dec. '98	250 mg bid ZDV	0/28	0.0 (0.0 –12.3)	0.00
	a. Jan. '97–Aug. '97	in late pregnancy,	0/12	0.0 (0.0–26.5)	(0.00–0.59)†
	b. Jan. '98–Dec. '98	and neonatal ZDV syrup	0/16	0.0 (0.0–20.6)	
4	Jan. '98–Feb. '99	250 mg bid oral ZDV in late pregnancy, intravenous ZDV during labor, and neonatal ZDV syrup	0/13	0.0 (0.0 –24.7)	0.00 (0.00–1.35)†
1 & 2	Nov. '91–Jan. '98	No ZDV or only antenatal ZDV	21/95	22.1 (14.2–31.8)	1.00
3 & 4	Jan. '97–Feb. '99	Any regimen consisting of immediate neonatal ZDV	0/41	0.0 (0.0–8.6)‡	0.00 (0.00–0.40)†

*Group 1 served as the reference group in comparison with group 2, 3, and 4; and group 1 & 2 was the reference group in comparison with group 3 & 4. CI = confidence interval. †Exact confidence intervals of odds ratio; ‡$P < 0.001$ for comparison with the reference group 1 or group 1 & 2.

prophylactic regimen consisting of late antenatal ZDV given twice a day for 2 to 6 weeks without an intrapartum or neonatal component. There were more cases of delivery by cesarean section in the ZDV groups than the non-ZDV group, but cesarean section was performed after amniotic membrane rupture in almost all cases. There was no difference among the four groups in the proportion of cases having cesarean section performed before membrane rupture, which would affect the transmission rates.[11] This study also demonstrated that addition of immediate neonatal ZDV, given orally within 2 hours after birth for 4 to 6 weeks, resulted in a highly protective effect against vertical HIV transmission. Two pairs of alternate practices between antenatal ZDV regimen and a regimen consisting of antenatal ZDV plus immediate neonatal ZDV showed consistent findings.

Several reports have demonstrated that antenatal ZDV played a role in prevention of vertical HIV-1 infection.[2-6,12-14] Most participants received oral ZDV, 100 mg, five times daily during pregnancy with or without oral ZDV during labor, and without neonatal ZDV,[5-6,12-14] or received antenatal ZDV, 300 mg, twice daily and every 3 hours during labor.[2-4] None of the previous reports that demonstrated protective effects of antenatal regimens consisted of twice daily doses of ZDV without the drug given during labor and intrapartum, as is being reported from this study. Since the interval between doses was 12 hours, the duration between the last dose of ZDV and childbirth could be too long, which resulted in inadequate protective concentration during delivery and after birth, when HIV was inoculated and infected. Phaupradit and colleagues reported in 30 pregnant women from group 2 of this study that the duration between the last dose of ZDV and delivery was 16.5 ± 6.0 h and that umbilical cord serum concentration of ZDV did not achieve therapeutic level in all, but there was no information about the effect on viral loads.[15] Maternal HIV-1 viral load was reported as a risk factor for vertical transmission,[16-19] and antenatal ZDV treatment had an effect in lowering maternal viral concentration at delivery, which was partly responsible for decreasing risks of vertical infection.[2,17] The antenatal ZDV component in this study might have had some effect on decreasing maternal viral loads that was not enough to affect the risk for transmission but might have contributed to protection by enhancing the protective effect of the immediate neonatal component. Information about viral loads and immunologic status of the mothers was not available in this study, but none of them was severely ill during pregnancy or delivery.

This study also demonstrated a high protective effect against vertical HIV-1 transmission when the ineffective antenatal regimen was accompanied by immediate neonatal ZDV, which suggested a high impact of the neonatal component. Wade and co-workers reviewed data from the HIV polymerase chain reaction (PCR) testing service of the New York State Department of Health, and concluded that there were reductions in the rates of perinatal transmission of HIV-1 even with the use of abbreviated regimens that were begun intrapartum or in the first 48 hours of life.[5] The subcategorized data suggested that those who received ZDV within 12 hours after birth might have had a lower risk for HIV infection than those who received the drug at 12 to 24 hours (1/17 vs. 1/4).[8] Fiscus and colleagues, in an observational study, showed that three of seven neonates given oral ZDV within 48 hours after birth developed HIV-1 infection.[6] This represents a high transmission rate, although two of the three infants had in utero infection. The theory that antenatal and neonatal

regimens should not prevent in utero transmission is supported by a study by Shaffer et al.[2] Two studies in Bangkok reported that in utero HIV-1 transmission rates were approximately 5.5 and 6.7%.[2,16] Failure of prophylaxis due to in utero transmission did not occur in this study, which could be explained by the low incidence of in utero transmission in the Bangkok population and by the small sample size in the study.

The factors responsible for the high rate of effectiveness of this neonatal regimen could be the immediate administration of ZDV after birth and the regularity and reliability of administration. The immediateness of administration of neonatal ZDV may be more important in a situation in which the intrapartum component has not been administered than in cases in which it has been given. The limitation of this report is that information was derived from an observational study and the effect of the antenatal component, which was not effective by itself, could not be confidently excluded. A randomized controlled trial would provide stronger evidence.

ACKNOWLEDGMENTS

The authors thank pediatric and obstetric residents and nurses for their dedication; Professor Benja Petchclai, Department of Pathology, for laboratory support; and Ms. Yupa Saengtong, Division of Infectious Disease, Department of Pediatrics, for her devoted assistance.

REFERENCES

1. Connor EM, Sperling RS, Gelber R, et al. For the Pediatric AIDS Clinical Trial Group Protocol 076 Study Group. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994; 331:1173-1180.
2. Shaffer N, Chuachoowong R, Mock P, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Lancet 1999; 353:773-780.
3. Wilktor SZ, Ekpini E, Karon JM, et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomised trial. Lancet 1999; 353:781-785
4. Dabis F, Msellati P, Meda N, et al. For the DITRAME Study Group. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Cote d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. Lancet 1999; 353:786-792.
5. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. N Engl J Med 1998; 339:1409-1414.
6. Fiscus SA, Schoenbach VJ, Wilfert C. Correspondence. Short courses of zidovudine and perinatal transmission of HIV. N Engl J Med 1999; 340:1440-1441.
7. Shih CC, Kaneshima H, Rabin L, et al. Post-exposure prophylaxis with zidovudine suppresses human immunodeficiency virus type 1 infection in scid-hu mice in a time-dependent manner. J Infect Dis 1991; 163:625-627.
8. Wade NA, Birkhead GS, French PT. Correspondence. Short courses of zidovudine and perinatal transmission of HIV. N Engl J Med 1999; 340:1442-1443.
9. Case-control study of HIV seroconversion in health care workers after percutaneous exposure to HIV-infected blood: France, United Kingdom, and United States, January 1988-August 1994. MMWR Morb Mortal Wkly Rep 1995; 44:929-933.
10. StataCorp. Stata statistical software: release 5.0. College Station, Texas: Stata Corporation, 1997.
11. The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1. A meta-analysis of 15 prospective cohort studies. N Engl J Med 1999; 340:977-987.
12. Matheson PB, Abrams EJ, Thomas PA, et al. Efficacy of antenatal zidovudine in reducing perinatal transmission of human immunodeficiency virus type 1. J Infect Dis 1995; 172:353-358.
13. Fiscus SA, Adimora A, Schoenbach VJ, et al. Perinatal HIV and effect of zidovudine therapy on transmission in rural and urban counties. JAMA 1996; 275:1483-1488.
14. Simpson BJ, Shapiro ED, Andiman WA. Reduction of the risk of vertical transmission of HIV-1 associated with treatment of pregnant women with orally administered zidovudine alone. J Acquir Immune Defic Syndr Hum Retrovirol 1997; 14:145-152.
15. Phuapradit W, Sirinavin S, Taneepanichskul S, et al. Maternal and umbilical cord serum zidovudine levels in human immunodeficiency virus infection. Aust N Z J Obstet Gynaecol 1998; 38:288-292.
16. Mock PA, Shaffer N, Bhadrakom C, et al. For the Bangkok Collaborative Perinatal HIV Transmission Study Group. Maternal viral load and timing for mother-to-child HIV transmission, Bangkok, Thailand. AIDS 1999; 13:407-413.
17. Sperling RS, Shapiro DE, Coombs RW, et al. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. N Engl J Med 1996; 335:1621-1629.
18. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. N Engl J Med 1999; 341:394-402.
19. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. N Engl J Med 1999; 342:485-493.