Prevention of Human Immunodeficiency Virus (HIV) Transmission from Mother to Child—A Cohort Study in Singapore

C Y Chong,*FAMS, M Med, MRCP, W Y M Ng,*FAMS, MBBS, M Med, Y S Leo,**FAMS, M Med, MRCP, S Y Se-Thoe,***B Sc (Hons), M Phil, A E Ling,+FAMS, MBBS, FRCPA, K P Chan,++MBBS, DipBact

Abstract

***Introduction**: The landmark Paediatric AIDS Clinical Trials Group (PACTG) trial 076 showed in 1994 that antiretroviral therapy (ART) was effective in reducing maternal-child transmission of human immunodeficiency virus (HIV). This trial included antenatal oral zidovudine (ZDV), intrapartum intravenous ZDV, 6 weeks of oral ZDV to the babies and no breastfeeding. **Materials and Methods**: This study is an on-going, prospective, open-label trial conducted from 1995 in which we enrolled HIV-infected pregnant women using the above strategy. Since 1997, the antenatal component of the regimen was modified to include lamivudine with ZDV. All babies had serial HIV polymerase chain reaction (PCR) and antibody tests including enzyme-linked immunosorbent assay (EIA), particle agglutination (PA) and Western blot (WB) at day 1, 1 week, 1,2,3,6,12 and 18 months. **Results**: A total of 16 out of 19 eligible women were recruited from 1995 to 1999. The median age was 26 years (range 22 to 38 years), 38% were Singaporeans, median CD4 was 421 cells/mL (range 18 to 713 cells/mL) and median baseline gestational age was 23.5 weeks (range 8 to 32 weeks). None of the 16 children was infected as evidenced by 2 negative HIV PCRs including 1 done >4 months old with a follow-up of 6 months to 2 years. There was a statistically significant difference between the 3 HIV antibody tests at 12 months of age (**P** = 0.003), there being more negative results with WB as compared to PA (**P** = 0.02). However, the difference between the 3 tests at 18 months was not statistically significant. No long-term side effects in these children were seen. **Conclusion**: Although the number of patients in this study is small, the absolute prevention of transmission (95% confidence intervals 0%-17%) in this cohort supports the recommendation of antenatal HIV screening and treatment of those infected.*

***Ann Acad Med Singapore* 2001; 30:387-92**

Keywords: HIV, HIV PCR, Perinatal transmission

Introduction

Since the onset of the acquired immunodeficiency syndrome (AIDS) epidemic in the mid-1980s, the number of HIV-infected cases has risen sharply throughout the world. Globally, 5.8 million new HIV infections have been diagnosed in 1998 with 1.2 million being diagnosed in Southeast Asia. In Singapore, by 31 December 1999, 1136 patients were reported with HIV infection, of whom 481 were asymptomatic carriers, 272 AIDS cases and 383 deaths.[1] Seventy-two per cent were infected through heterosexual transmission, 14% (n = 157) homosexual transmission, 10% (n = 114) bisexual transmission, 2% (n = 23) intravenous drug use, 1% (n = 12) perinatal transmission (due to missed opportunities during antenatal follow-up), 0.4% (n = 5) organ transplant and 0.26% (n = 3) blood transfusion. Males outnumber females 7:1. The majority of the persons infected were in the 20 to 39 years age group (65%, n = 740) followed by the 40 to 59 years age group (26%, n = 299). The majority of the males (65%) were single, whereas 69% of the females were married.

Prior to 1994, the options available for HIV-infected

* *Consultant*
Department of Paediatric Medicine
KK Women's and Children's Hospital
** *Clinical Director*
Communicable Disease Centre
Tan Tock Seng Hospital
*** *Scientific Officer*
\+ *Director, HIV Reference Laboratory, Immunology Section*
\+\+ *Consultant*
Department of Pathology
Singapore General Hospital
Address for Reprints: Dr Chong Chia Yin, Department of Paediatric Medicine, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
E-mail: cychong@kkh.com.sg

pregnant women were limited to termination of pregnancy or avoidance of breastfeeding upon the diagnosis of HIV infection. The Paediatric AIDS Clinical Trials Group (PACTG) 076 demonstrated that through the use of antenatal, intrapartum and postnatal zidovudine (ZDV), the HIV transmission from mother to infant was significantly reduced by 67%.[2] Women have also increasingly opted to using these interventions to prevent perinatal transmission to their offspring.[3] The clinical benefit of combination therapy for HIV became evident from 1995 to 1996.[4,5] In Singapore, pregnant women are encouraged to undergo HIV testing during pregnancy. Those screened HIV-positive are referred to the Communicable Disease Centre (CDC), Tan Tock Seng Hospital for further treatment. The obstetric care of the pregnant woman is continued in her original hospital or transferred to KK Women's and Children's Hospital. Since 1995, HIV-infected pregnant mothers in Singapore were managed according to the PACTG 076 protocol with modification from 1997 onwards, of including lamivudine (3TC) antenatally to the mothers.

Methodology

This is an on-going, prospective, open-label trial including HIV-infected pregnant mothers and their newborn infants. The Ministry of Health encourages all pregnant women to undergo HIV screening. Those screened HIV positive by antibody tests are referred to the CDC, TTSH, which is the national referral centre for HIV disease, for further management. HIV-infected pregnant women were started on antenatal oral ZDV and since 1997, on a combination of ZDV and 3TC. At the CDC, pregnant women were followed up monthly with full blood counts; CD4 cell counts being done periodically. At labour, the mothers were given intravenous ZDV 2 mg/kg loading over 1 hour followed by 1 mg/kg/hour until delivery. Babies born to HIV-infected mothers were given oral ZDV 2 mg/kg 6 hourly (except for 1 premature baby who was given the intravenous form) for 6 weeks. Mothers were strictly told not to breastfeed but to use infant formulas. The HIV laboratory tests were offered to the mothers and their newborn infants for early detection of HIV transmission. The laboratory monitoring for babies comprised blood specimens for HIV nucleic acid detection by polymerase chain reaction (PCR) and HIV antibody detection by enzyme-linked immunosorbent assay (EIA), Western blot (WB) and particle agglutination (PA) tests. The blood samplings for the baby were done on day 1 of life, 1 week, 1, 2, 3, 6, 12 and 18 months of age. The Friedman test for statistical significance was done when comparing the 3 different HIV antibody assays. This study reports on patients enrolled from 1995 till 1999.

HIV Serology Tests

Plasma samples were tested for HIV antibodies using the Abbott HIV-1/HIV-2 third generation plus EIA test (Germany), Serodia HIV-1/HIV-2 PA (Fujirebio, Japan) and Genelabs Diagnostic Immunoblot 2.2 (Singapore). The manufacturers' recommendations were strictly adhered to for all testing procedures. The Abbott EIA test is a sandwich-based method and detects both antibodies to HIV-1 and HIV-2. In the Serodia PA test, HIV-1 and HIV-2 antigens are coated onto separate gelatin beads which agglutinate in the presence of the respective antibodies to HIV-1 or HIV-2.[6] Synthetic peptides of HIV-2 envelope protein and HIV-1 viral lysate form the basic ingredients in the Genelabs Diagnostic Immunoblot assay, in which anti-HIV IgG bound to the blotted antigens is detected *via* a colourimetric reaction.

Detection of HIV-1 Proviral DNA

Two PCR assays were used for the detection of HIV-1 proviral DNA: the Amplicor HIV-1 test kit (Roche Molecular System), which amplified the HIV-1 *gag* gene, and an in-house nested PCR test targeted at the HIV-1 *pol* gene.[7,8] Amplified products were analysed by the Captagene-GCN4 enzyme-linked assay (AMRAD Corporation, Melbourne, Australia).

HIV Viral Load

The Amplicor HIV-1 Monitor Test (Roche Molecular System) was used for quantification of HIV-1 viral load. It detects HIV-1 RNA that is present in EDTA-treated plasma sample through amplification of the viral *gag* gene. The test is divided into 5 major processes: Extraction of viral RNA from plasma sample, reverse transcription of the viral RNA to generate complementary DNA (cDNA), PCR amplification of the target cDNA, hybridisation of the amplified DNA to probes and detection of the probe-bound amplified DNA by colourimetric determination. The result is expressed as copies per mL of plasma.

Results

Since 1995**,** 16 out of 19 eligible women were recruited for the study. Patients were excluded if there was no consent or if they were lost to follow-up. The maternal demographic data, CD4 cell count and gestational age at the start of HIV treatment are summarised in Table I. There were 6 (38%) Singaporean mothers, 7 (44%) Thai, 1 (6%) each of Indonesian, Cambodian and Malaysian origin. The median age of the mothers was 26 years (range 22 to 38) and the median CD4 cell count was 421 cells/mL (range 18 to 713 cells/mL). The duration of HIV medications which the pregnant women took before delivery was: <12 weeks (minimum 2 weeks), 7 patients (44%); 13 to 27 weeks, 8 patients (50%); 28 to 36 weeks, 1 patient (6 %). The median gestation at the start of anti-HIV treatment was 23.5 weeks (range 8 to 32 weeks) and the median duration of anti-HIV

TABLE I: MATERNAL DEMOGRAPHIC DATA AND DELIVERY PROFILE

Characteristic	No. of women (%)
Age (y)	
21-25	7 (44)
26-30	8 (50)
36-40	1 (6)
Year of HIV diagnosis	
1995	3 (19)
1996	4 (25)
1997	4 (25)
1998	4 (25)
1999	1 (6)
Nationality	
Singaporean	6 (38)
Thai	7 (44)
Malaysian	1 (6)
Indonesian	1 (6)
Cambodian	1 (6)
CD4 count at HIV diagnosis (cells/mL)	
<200	3 (19)
201-500	7 (44)
501-800	6 (38)
Hospital of delivery of baby	
KK Women's & Children's Hospital	10 (63)
Singapore General Hospital	3 (19)
Private hospitals	2 (12)
Tan Tock Seng Hospital	1 (6)
Mode of delivery	
Normal vaginal delivery	12 (75)
Elective caesarean section	2 (12)
Emergency caesarean section	2 (12)
Gestation at start of HIV treatment (weeks)	
<12	1 (6)
13-27	9 (56)
28-36	6 (38)
Birth weights of babies (g)	
< 2500 (840 g)	1 (6)
2500-3000	7 (44)
>3000	8 (50)
Duration of follow-up of babies (months)	
6	4 (25)
12	4 (25)
18	7 (44)
24	1 (6)

therapy was 14 weeks (range 2 to 24 weeks). During antenatal follow-up, 7 mothers (44%) were given ZDV alone, while 9 mothers (56%) were given a combination of ZDV and 3TC. Baseline HIV viral loads were available in 7 HIV-infected pregnant women and the median viral load was 41,118 copies/mL (range 312 to 349,083 copies/mL).

The sites of delivery were: 63% (10) at KK Women's and Children's Hospital, 19% (3) at Singapore General Hospital, 6% (1) at Tan Tock Seng Hospital (TTSH) and 12% (2) in private hospitals. The only patient who delivered at TTSH had an unexpected premature birth while she was being treated for *Pneumocystis carinii* pneumonia (PCP) in the intensive care unit. The mode of delivery was normal vaginal delivery in 12 patients (75%) and, elective caesarean section and emergency caesarean section in 2 patients each (12% each). The reasons for the emergency caesarean section were cephalopelvic disproportion in 1 patient (on monotherapy with ZDV) and premature rupture of membranes (PROM) in the other patient (on ZDV and 3TC). Complications during delivery included: PROM in 3 patients (19%), premature delivery in 1 patient (6%) at 29 weeks' gestation and poor progress from cephalopelvic disproportion in 1 patient (6%). The birth weights of the babies were 840 g in 1 patient (6%), 2500 to 3000 g in 7 patients (44%) and >3000 g in 8 patients (50%). The median birth weight was 3060 g (range 840 to 3655). All the babies have had negative HIV PCR to date with a follow-up of 6 to 24 months; mean of 13.9 months. All 16 babies were confirmed to be not infected with HIV based on the criteria of 2 negative HIV PCRs including one done after 4 months of age. Using the Friedman test, analysis of HIV antibody test results showed that there was a statistically significant difference between the 3 HIV antibody tests at 12 months of age (P = 0.003), there being more negative WB as compared to PA (P = 0.02). However, the comparison between EIA with PA and WB was not significant (P = 0.149 and 0.183). The difference between the 3 tests at 18 months was not statistically significant (Table II).

Of the 16 babies on follow-up, 1 had neutropenia and thrombocytopenia (absolute neutrophils 876 cells/mm^3, platelets 57 x 10^9/L) but no anaemia resulting from ZDV therapy. The mother was actually known to be HIV-infected even before this pregnancy but had defaulted follow-up. She presented at 27 weeks' gestation with PCP and a CD4 count of 18 cells/mL. This baby was born premature at 29 weeks with a birth weight of 840 g and had birth asphyxia (Apgar score 2 at 1 minute, 5 at 5 minutes). This baby also had hyaline membrane disease grade IV, patent ductus arteriosus which was closed with indomethacin and hypothyroidism on replacement L-thyroxine. The baby's intravenous ZDV was adjusted from 1.5 mg/kg 8 hourly to 12 hourly because of the haematologic complications; nonetheless, she completed 6 weeks of intravenous ZDV. There were no other haematologic side effects in the rest of the babies.

Discussion

This study of 16 mother-child pairs showed 100% efficacy (95% confidence interval 0%-17%) in the prevention of HIV perinatal transmission. Antenatal screening of HIV is essential for early therapeutic intervention. Several risk factors for increased risk of HIV perinatal transmission have been identified including: premature birth <37 weeks' gestation, prolonged rupture of membranes >4 hours, advanced clinical HIV disease, direct exposure of the fetus

TABLE II: RESULTS OF HIV ANTIBODY SEROREVERSION IN CHILDREN

Age	Antibody test	Reactive	Non-Reactive	HIV PCR	Positive	Negative
6 months	EIA	16	0	HIV-*gag*	0	16
(n = 16)	PA	16	0	HIV-*pol*	0	16
	WB	16	0			
12 months*	EIA	6	5	HIV-*gag*	0	11
(n = 11)	PA	10	1	HIV-*pol*	0	11
	WB†	2	9			
18 months**	EIA	1	6	HIV-*gag*	0	7
(n = 7)	PA	1	6	HIV-*pol*	0	7
	WB	0	7			

* There was a statistically significant difference in reactivity between the 3 HIV antibody methods at 12 months of age (P = 0.003). Post-hoc analysis showed that Western blot (WB) showed significantly more negative results as compared to PA (P = 0.02). Comparison between enzyme-linked immunsorbent assay (EIA) with particle agglutination (PA) and WB was not significant (P = 0.149 and 0.183)

** There was no statistically significant difference in the 3 HIV antibody tests at 18 months of age.

† Western blot results: "Reactive" represents WB positive, "Non-reactive" represents WB negative or indeterminate. All babies were WB positive from day 1 of life; they later became WB indeterminate or negative.

to maternal blood during delivery, chorioamnionitis and maternal viremia.[9-14] In addition, maternal viral load also correlates with HIV vertical transmission.[15,16] Although higher rates of transmission have been associated with higher plasma viral loads, there is no threshold value of viral load which can distinguish transmitters from non-transmitters.[17] Therefore, it is important to reduce the maternal viral load as far as possible and this can be achieved with the use of combination antiretroviral therapy (ART).[18] The rate of transmission can be reduced substantially from 25% to 8%[2] with ZDV alone and with elective caesarean section, a further reduction to 2 %.[19] In a breastfeeding cohort, the cumulative risk of HIV transmission was approximately 40%.[17] Twenty per cent of transmission occurred close to or at the time of delivery, 15% from breastfeeding and 5% *in utero* transmission.[20] The follow- up report of the PACTG 076 cohort suggested that ART was effective in reducing HIV transmission even if started intrapartum or postpartum compared to placebo.[21] The rates of HIV transmission were 6% if ZDV was started anytime antenatally, compared to 10% if started intrapartum, 9% if started in the neonate within 48 hours of delivery, and 18% if started in the neonate after 72 hours of delivery.[21] In our study, perinatal HIV transmission was prevented in 1 patient treated briefly for 2 weeks before delivery followed by postnatal treatment to the baby.

Recent short-course ART trials for preventing perinatal transmission have included ZDV monotherapy from 36 weeks' gestation, intrapartum ART with or without any postnatal medication to their children,[22-24] short courses of combination of ZDV and 3TC[25-27] or stavudine and didanosine.[28] However, these short course protocols have had an efficacy rate of 37% to 50% as compared to the 67% efficacy of the PACTG 076 protocol. The best efficacy rates (50%) of these short-course studies were seen in a Thai study in which the mothers were given ZDV from 36 weeks' gestation until labour; no post-natal treatment was given to this non-breastfed cohort.[22] To date, no long-term side effects have been associated with *in utero* exposure to ZDV in most studies.[29-31] However, there has been a recent French report of possible mitochondral toxicity occurring in 0.45% (8 out of 1754 infants) of children exposed to antenatal and post-natal ZDV alone or together with 3TC.[32] To date, this finding has not been substantiated in the US trials after examination of 353 deaths in more than 20,000 HIV-exposed children with and without retroviral drug exposure.[33] Other studies have shown no short-term side-effects and minimal perinatal transmission using combination therapy including protease inhibitors.[34-36] Another drug of interest in the prevention of perinatal HIV transmission is nevirapine. A simple regimen of a single dose to the mother during labour and within 72 hours of delivery to the newborn has been shown to be effective in reducing the rate of HIV transmission by 50%.[37] However, its long-term side effects are unknown. In the local context, nevirapine may serve as a good drug in situations where the maternal viral load remains high despite combination of ZDV and lamivudine or for women who present late. In this study, none of the children with a mean follow-up period of 13.9 months had any long-term clinical sequelae from ART. One child had vesico-ureteric reflux and urinary tract infection which was unrelated to his anti-HIV medications. The benefits of ART in preventing HIV transmission in our local setting outweigh the potential risk of mitochondral toxicity as noted in the French study.

Routine practice of elective caesarean section in preventing HIV perinatal transmission is debatable. Most studies on caesarean section were done before the era of highly active antiretroviral therapy (HAART) and were not randomised.[38,39] The only randomised European trial

comparing normal vaginal delivery to elective caesarean section showed that there was a reduced transmission with elective caesarean section; however, the benefit was not statistically significant if the pregnant women were already on ART.[40] A renowned editorial review recently commented that in order to reduce the rate of transmission hypothetically from 4 % to 0.8%, one would have to do 29 elective caesarean section in order to prevent a single case of HIV infection in the child.[41] The benefit of elective caesarean section may be offset by a 3 to 6 times increased risk of postoperative complications as compared to normal delivery, especially in patients with low CD4 counts and in developing countries where postoperative care may be inadequate.[42,43] In our study, 75% of the mothers had normal vaginal delivery including 2 with premature rupture of membranes (duration of PROM: 12.5 and 37 hours). The 2 patients who had elective caesarean section at private hospitals had fairly good CD4 cell counts (CD4: 401 cells/mL, no viral load done and CD4: 292 cells/mL, viral load: 5618). In our local context**,** the role of elective caesarean section is probably limited to the cases where the pregnant women have high HIV viral load despite combination therapy and/or if the pregnant women refused to take ART medications. All pregnant women are counselled at the CDC and are given the option of an elective caesarean section in consultation with their obstetrician.

A total of 135 HIV-infected women were diagnosed by the end of 1999; of these, 80% were detected in the last 5 years.[1]These figures serve as a reminder to medical practitioners not to be complacent about standard infection control precautions and to cultivate routine recommendation of HIV screening for all pregnant women. In a recent questionnaire survey on attitudes of obstetricians at a local hospital, it was found that only 44% of obstetricians offered the HIV test to their patients; even fewer would provide pre-test (17%) or post-test (19.5%) counselling.[44] This study has proven that the vertical transmission of HIV from mother to child can be prevented through ART (95% confidence interval 0%-17%). The authors strongly recommend routine offering of antenatal HIV screening together with counselling services to all pregnant women. ART can then be offered to those who are HIV-infected, thereby reducing the rate of transmission from mother to child.

Acknowledgements

This research project was funded by the Serology Section, Department of Pathology, Singapore General Hospital.

REFERENCES

1. HIV infection and AIDS in Singapore, 1999. Epidemiological News Bulletin 2000; 26:68-69.
2. Connor E M, Sperlin R S, Belber R, Kiselev P, Scott G, O'Sullivan M J, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS clinical Trial group Protocol 076 Study Group. N Engl J Med 1994; 331:1173-80.
3. Lyall E G, Stainsby C, Taylor G P, Ait Khaled M, Bingham S, Evans J A, et al. Review of uptake of interventions to reduce mother to child transmission of HIV by women aware of their HIV status. BMJ 1998; 316:268-70.
4. Kuritzkes D R, Quinn J B, Benoit S L, Shugarts D L, Griffin A, Bakatiari M, et al. Drug resistance and virologic response in NUCA 3001, a randomized trial of lamivudine (3TC) versus zidovudine(ZDV)versus ZDV plus 3TC in previously untreated patients. AIDS 1996; 10:975-81.
5. Katlama C, Ingrand D, Loveday C, Clumeck N, Mallolas J, Staszewski S, et al. Safety and efficacy of lamivudine-zidovudine combination therapy in antiretroviral-naïve patients. A randomized controlled comparison with zidovudine monotherapy. Lamivudine European HIV working group. JAMA 1996; 276:118-25.
6. Sng E H, Tan B B, Chik H L. Comparative evaluation of PA test for antibody to HIV. Genitourin Med 1988; 64:266-9.
7. Albert J, Fenyo E M. Simple, sensitive, and specific detection of human immunodeficiency virus type 1 in clinical specimens by polymerase chain reaction with nested primers. J Clin Microbiol 1990; 28:1560-4.
8. Kemp D J, Churchill M J, Smith D B, Biggs B A, Foote S J, Peterson M G, et al. Simplified colorimetric analysis of polymerase chain reactions: detection of HIV sequences in AIDS patients. Gene 1990; 94:223-38.
9. Mofenson L M, Lambert J S, Steihm E R, Bethel J, Meyer W A, Whitehouse J. Risk factors for perinatal transmission of HIV type 1 in women treated with zidovudine. N Engl J Med 1999; 341:385-93.
10. Kuhn L, Stein Z A. Mother-to-infant HIV transmission: Timing, risk factors and prevention. Pediatr Perinat Epidemiol 1995; 9:1-29.
11. John G C, Kreiss J. Mother-to-child transmission of human immunodeficiency virus type 1. Epidemiol Rev 1996; 18:149-57.
12. Lambert J S. Pediatric HIV infection. Curr Opin Pediatr 1996; 8:606-14.
13. Bryson Y J. Perinatal HIV transmission: Recent advances and therapeutic interventions. AIDS 1996; 10 (Supp l3):533-42.
14. Simonds R J, Steketee R, Nesheim S, Matheson P, Palumbo P, Alger L, et al. Impact of zidovudine use on risk and risk factors for peinatal transmission of HIV. Perinatal AIDS Collaborative Transmission studies. AIDS 1998; 12:301-8.
15. Garcia P M, Leslie M P H, Kalish L A, Pitt J, Minkoff H, Quinn T C, 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.
16. O Shea S, Newell M L, Dunn D T, Garcia Rodriguez M C, Bates I, Mullen J, et al. Maternal viral load, CD4 cell count and vertical transmission of HIV-1. J Med Virol 1998; 54:113-7.
17. Cao Y, Krogstad P, Korber B T, Kroup R A, Muldoon M, Macken C, et al. Maternal HIV-1 viral load and vertical transmission of infection: The Ariel Project for prevention of HIV transmission from mother to infant. Nat Med 1997; 3:549-52.
18. CDC guidelines for the use of anti-retroviral agents in HIV-infected adults and adolescents. MMWR Morb Mortal Wkly Rep 1998; 47 (RR-5):39-82.
19. The International Perinatal HIV group: The mode of delivery and the risk of vertical transmission of human immunodeficency virus type 1. N Engl J Med 1999; 340:977-87.
20. Stringer J S A, Vermund S H. Prevention of mother-to-child transmission of HIV-1. Curr Opin Obstet Gynecol 1999; 11:427-34.
21. Wade N A, Birkhead G S, Warren B L, Charbonneau T T, French T,

Wang L, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. N Engl J Med 1998; 339:1409-14.

22. Shaffer N, Chuachoowong R, Mock P A, Bhadrakom C, Siriwasin W, Young N L, et al. Short-course zidovudine for perinatal transmission in Bangkok, Thailand: A randomised controlled trial. Lancet 1999; 353: 773-80.
23. Wiktor S Z, Ekpini E, Karon J M, Nkengasong J, Maurice C, Severin S T, et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Côte d'Ivoire: a randomised trial. Lancet 1999; 353:781-5.
24. Dabis F, Msellati P, Meda N, Welffeng-Ekra C, You B, Manigart O, et al. 6-month efficacy, tolerance and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Côte d'Ivoire and Burkina Faso: a double-blind placebo controlled multicentre trial. Lancet 1990; 353:786-92.
25. A positive response to perinatal HIV [editorial]. Lancet 1999; 353:511.
26. Saba J, on behalf of the PETRA Trial study team. Interim analysis of early efficacy of 3 short course ZDV/3TC combination regimens to prevent mother-to- child transmission of HIV-1: the PETRAS trial. Program and abstracts of 6th Conference on Retroviruses and Opportunistic Infection; 1999 Jan 31-Feb 4; Chicago, USA. Abstract S7.
27. Silverman N S, Watts D H, Hitti J, Money D M, Livingston E, Axelrod J, et al. Initial multicenter experience with double nucleoside therapy for human immunodeficiency virus infection during pregnancy. Infect Dis Obstet Gynecol 1998; 6:237-43.
28. Gray G, McIntyre J, Jikov B, et al. Preliminary efficacy, safety, tolerability and pharmacokinetics of short-course regimens of nucleoside analogues for prevention of mother-to-child transmission of HIV. Program and abstracts of XIII International AIDS conference; 2000 Jul 9-14; Durban, S. Africa. Abstract TuOrB 355.
29. Sperling R S, Shapiro D E, McSherry G D, Britto P, Cunnigham B E, Culnane M, et al. Safety of maternal-infant zidovudine regimen utilized in pediatric AIDS clinical trial group 076 study. AIDS 1998; 12:1805-13.
30. Culnane M, Fowler M G, Lee S S, McSherry G, Brady M, O'Donnell K, et al. Lack of long-term effects of in-utero exposure to zidovudine among uninfected children born to HIV-infected women. JAMA 1999; 281: 151-7.
31. McSherry G D, Shapiro D E, Coombs R W, McGrath N, Frenkel L M, Britto P, et al. The effects of zidovudine in the subset of infants infected with human immunodeficiency virus type-1. J Pediatr 1999; 134:717-24.
32. Blanche S, Tardieu M, Rustin P, Slama A, Barret B, Firtion G, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. Lancet 1999; 354:1084-9.
33. Smith M E, US Nucleoside safety review of HIV-exposed children in IS studies. Program and abstracts of 2nd Conference on Global Strategies for prevention of HIV transmission from mothers to infants; 1999 Sept; Montreal, Canada. Abstract 096.
34. O'Sullivan M J, Scott G, Yasin S, Mitchell C, Scott W, Duthely M. Protease inhibitors: Is preterm delivery a risk? Am J Obstet Gynecol 1999; 180:S105. Abstract 353.
35. Stek A, Kramer F, Fassett M, Khoury M. The safety and efficacy of protease inhibitor therapy for HIV infection during pregnancy. Am J Obstet Gynecol 1999: 180: S6, Abstract 14.
36. Morris A, Zorilla C, Vajaranant M, Dobles A, Cu-uvin S, Joneg T, et al. A review of protease inhibitor use in 89 pregnancies. Abstracts of the 6th Conference on Retroviruses and Opportunistic infections; 1999 Jan 31-Feb 4; Chicago, Ill. Abstract 686.
37. Guay L A, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet 1999; 354:795-802.
38. Mandelbrot L, Le Chenadec J, Berrebi A, Bongain A, Benifla J L, Delfraissy J F, et al. Perinatal HIV-1 transmission: Interaction between ZDV prophylaxis and mode of delivery in French perinatal cohort. JAMA 1998; 280:55-60.
39. Dunn D T, Newell M-L, Mayaux M J, Kind C, Hutto C, Goedert J J, et al. Mode of delivery and vertical transmission of HIV-1: a review of prospective studies. J Acquir Immune Defic Syndr Hum Retrovirol 1994; 7:1064-6.
40. The European mode of delivery collaboration. Elective caesarean section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomized clinical trial. Lancet 1999; 53:1035-9.
41. Stringer J S A, Rouse D J, Goldenberg R L. Prophylactic caesarean delivery for the prevention of perinatal human immunodeficiency virus transmission: The case for restraint. JAMA 1999; 281:1946-9.
42. Semprini A E, Castagna C, Ravizza M, Fiore S, Savasi V, Muggiasca M L, et al. The incidence of complications after caesarean section in 156 HIV-positive women. AIDS 1995; 9:913-7.
43. Grubert T A, Reindell D, Kastner R, Lutz-Friedrich R, Belohradsky B H, Dathe O. Complications after caesarean section in HIV-infected women not taking antiretroviral treatment. Lancet 1999; 354:1612-3.
44. Tan T Y T, Teo K P, Tan K H. Antenatal HIV screening—Knowledge, attitudes and practices of obstetricians in KKH. Singapore Med J 1999; 40:733-7.