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Prevention of Mother to Child Transmission of HIV-1 Using Antiretroviral Drug - Zidovudine

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OBJECTIVE - To determine the reduction of mother to child transmission (MTCT) rate of HIV infection after antiretroviral prophylaxis and the efficacy and acceptance of Zidovudine (ZDV) as drug intervention in HIV infected pregnant women to reduce MTCT of HIV. **MATERIAL AND METHODS -** One hundred and sixtythree pregnant women detected HIV - seropositive at Voluntary Counselling and Testing services at our prenatal clinic were included in the study. They were then tested for their immune status by CD4/CD8 cell counts and viral load test between 28 and 34 weeks of gestation. Protocol included offering Tablet ZDV 300mg twice a day free of cost through donation by a non-government organisation, from the 34th week to the onset of labor and Tablet ZDV 300 mg, 3 hourly during labor till the birth of the baby. Cesarean section was done for obstetric indications only. Seropositive women were given 1% betadine vaginal douching during labor and deliberate rupture of membranes was avoided. New-born baby's blood was tested by RT-PCR test at birth and at 2 and 6 months of age. Women were given a informed choice for breast-feeding options. Outcome measures were number of babies infected with HIV as determined by RT-PCR test, effect of maternal drug prophylaxis on perinatal transmission rate and morbidity and mortality of HIV - infected and non-infected infants. **RESULTS -** One woman opted for termination of pregnancy and 60 were lost to follow up before delivery; 47/104 (49.04%) women took ZDV prenatally and 55 during labor. In all, 9/71 (12.6%) babies tested at birth were RT-PCR positive. Ten babies died during follow up. **CONCLUSION -** There is need for emphasis on behavioral change among young women and men through provision of voluntary counseling and testing services.

Key words : perinatal transmission of HIV, mother to child transmission, antiretroviral prophylaxis

Condensation

The perinatal transmission rate of HIV-1 in Mumbai among ZDV - naive women was reduced to 11.2% using Thai protocol of ZDV during pregnancy and labor.

Introduction

Transmission of HIV infection from mother to child is a major concern for developed as well as developing countries[1]. India has just emerged with a major epidemic of HIV[2]. Sero-prevalence of HIV infection in pregnant women has increased from 0.8% in 1992 to 4.2% in 1998 in Mumbai, India[3]. The prevalence has stabilized to 3.5% in pregnant women in last 4 years as shown by NACO sentinel surveillance study. HIV-infected children are known to fall sick repeatedly and this will take away a major share of public health resources. Thus, there is an urgent need for behavioral intervention through voluntary counseling and testing services for effective control of HIV epidemic. Several studies using anti-retroviral drugs are reported to have reduced the rate of perinatal transmission[4]. Zidovudine (ZDV), a nucleoside reverse transcriptase inhibitor is said to be a potent drug known to reduce perinatal transmission without much side effects in pregnant women[5]. Mother's immune status as derived by CD4/CD8 lymphocyte cell counts and by viral load correlates directly with vertical transmission rate[6]. Intrapartum measures like vaginal douche with antiseptic lotion and policy of avoiding premature rupture of membranes also are reported to reduce the perinatal transmission[7,8].

Transmission of HIV infection is shown to be higher during labor in various studies done earlier[9,10]. Exposure to high viral load in vaginal secretions during natural birth is reported to be the crucial event for transmission through baby's oral and nasal mucosa[11]. Also, gush of blood associated with shearing and separation of placenta consequent to uterine contractions before cutting of umbilical cord may be associated with high rate of trans-placental transfer of the infection[6].

Breast-feeding is also known to transmit HIV infection especially in early months of feeding[12]. Benefits of breast feeding which are traditionally accepted in the Indian society were lost by the concept of not to breast feed the

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baby. Mumbai is an epicentre of HIV infection in India. The mother to child transmission of HIV in Mumbai without drug intervention during pregnancy and labor is reported to be 36%[13]. There is no reliable data on drug intervention for prevention of mother to child transmission of HIV from Indian settings, using RT-PCR technology on the baby's blood to know immediate transmission of HIV to the newborn. We underlook this study to evaluate ZDV prophylaxis for perinatal transmission.

Material and Methods

Two thousand nine hundred nineteen women attending antenatal clinic between April 1999 and February 2000 were exposed to information on HIV/STD and reproductive health using flip charts, video films, group talks and behavioral intervention. HIV test was offered and those who voluntarily opted for it were provided with pre-test counseling. Informed written consent was obtained in local understandable language for blood test for HIV. Those who declined consent were also provided regular antenatal care. From those who consented, 3-5 ml blood was collected in plain sterile test tubes and was tested by Microwell ELIZA (Biochem Immunosystems, Canada) and spot (Organics, Israel) for HIV-1/2. All women were given post-test counseling and those found to be HIV sero-positive were given Tab ZDV 300 mg twice a day for prophylaxis from 34 weeks till the onset of labor (Thailand regimen). They were instructed to come every week for follow up and collect next week's stock of drugs. Immune status was assessed at 30 to 34 weeks of gestation by CD4/CD8 count (Capsellia, Sanofi, France) and also by viral load test (Amplicor, Roche, USA). Frequent hemoglobin monitoring was planned for anemia in women taking ZDV.

Intrapartum intervention in the form of Tab ZDV 300 mg 3 hourly, betadine 1% vaginal douche once during labor and avoidance of premature rupture of membrane was adopted. As a policy, cesarean section was done for obstetric indication only. Baby's cord blood was collected at birth in EDTA vacuutainer observing all aseptic precautions and was tested for qualitative RT-PCR using primer 431/462 base-pairs[13].

HIV sero-positive women were counseled regarding breast-feeding options. Informed choice for breast-feeding was left to the couple. Babies of HIV sero-positive mothers and equal number of babies born to HIV sero-negative mothers were followed-up for one year. Baby's blood was retested by qualitative RT-PCR at 2 and 6 months of infancy. Defaulting mothers were paid home visits by a counselor to know the health status of the babies.

Data were analysed for co-factors of perinatal transmission and included immune status of mother, her viral load, role of interventions adopted and possible effects of breast-feeding using Epi-Info 5.0.

Results

Of 2919 women, 2725 (93.3%) who consented and were screened for HIV infections and 163 (5.9%, CI 0.95; 2.8, 4.9) women were found to be HIV-1/2 sero-positive by the two tests. Fiftyeight women were lost to follow-up before delivery. One woman opted for termination of pregnancy. Of the remaining 104 women who delivered with us, 47 women took ZDV as offered to them in antenatal period but dosages were modified due to irregular follow up for various reasons and 55 women took ZDV during labor. Of the 104 women who delivered at the recruited hospital, six required cesarean section for various obstetric indications. 9/71 (12.6%) babies were tested positive by qualitative RT-PCR up to 3 month's of age. Blood of 33 babies could not be tested as the blood clotted, hemolysed or was insufficient and some women had hidden their HIV serostatus at the time delivery and never came for follow up after delivery to give second sample for testing.

Mode of Delivery

98/104 women delivered vaginally and 9 of the babies were RT-PCR positive at birth. Of six women who underwent cesarean delivery, none had her baby HIV sero-positive at birth. Three of our 13 preterm born babies were HIV sero-positive at birth (Table - I).

Prenatal and Intrapartum drug Prophylaix

Despite free supply of ZDV, only 47/104 women took ZDV. Women coming with labor pains were also offered tablet ZDV 300 mg 3 hourly till they delivered. Duration of antenatal drug prophylaxis for more than 28 days showed reduced rate of transmission than that in those who took it for less than 28 days (Table II). Of the 31 women reporting to hospital in early labor and taking three or more dosages of intrapartum prophylasis, two had transmitted the infection to their children (2/31-6.45%) as against 2/24 (8.3%) who had taken two or less dosages (Table III). Combined prenatal and intrapartum drug prophylaxis was shown to have good potential benefit (Table IV).

Among the women having preterm delivery, most have not taken ZDV as the policy was to start ZDV by 34 weeks of pregnancy as per Thai regimen. Those who took ZDV had taken it for less than 7 days, practically amounting to no prophylaxis. Hence drug dose and outcome was not studied in preterm delivery. In future, we may submit meta-analysis of our various studies.

But in women, who had not taken ZDV, the transmission was higher in preterm than in term babies. None of our women have taken ZDV for more than 35 days. Thai regimen shows that ZDV prophylaxis for 28 days provides significant protection in resource limited countries.

Presence or absence of vaginal infection did not show significant difference in transmission rate (Table V). Vaginal douching with antiseptic lotion did not reduce it substantially either. But presence of wart in three women suggested associated HPV viral infection and one of them had transmitted the infection to her child.

In the study, 89/104 had ruptured the membranes at the time of delivery or less than 4 hours earlier and 9/89 transmitted the infection to the new born. None of the children born to mothers with ROM for more than 4 hours transmitted the infection. This difference in perinatal tansmission was not significant probably due to the small numbers involved.

Discussion

This study determines HIV transmission from mother to child amongst ZDV-naïve population following ZDV drug prophylaxis in Mumbai. Reduction in MTCT by 2/3 due to ZDV drug prophylaxis is documented. Even offering the antiretroviral therapy (ART) free of cost was not acceptable to some due to disbelief in the diagnosis. Poor compliance was seen because of poor understanding of the disease and poor follow up. Short course of prophylaxis was due to late antenatal registration, denial of drug prophylaxis by spouse after initiating prophylaxis or onset of preterm labor. Lowered rate of perinatal transmission was demonstrated in women who had taken ZDV for more than 15 days and intrapartum 3 dosages. However duration of drug prophylaxis is not the only key factor in reduction of MTCT of HIV[13]. Maternal prenatal pre-therapy serum HIV-1 viral load higher than 50,000 RNA copies / ml and CD4 T-cell count lower than 350/cmm also pay important role in risk for transmission. Mode of delivery showed no correlation. Cesarean section performed for obstetric indication did not show any increase in post-operative infection rate. Since few cesarean sections were done, its protective benefit could not be documented. Douching of vagina with antimicrobial agent during labor did not reduce the perinatal transmission, which may be due to inadequate concentration of betadine or lack of proper technique. Rupture of membrane for less than 4 hours has shown to have no reduction in the rate of transmission, in fact all transmission were seen in this group only. However, prolonged rupture of amniotic membranes was thought to be associated with ascending bacterial (non-specific) infection and chorio-amnionitis before labor and the birth of the baby is presumed to accelerate the trans-placental transfer of HIV-infection.

Breast-feeding decision was left to the couple. Breast-feeding is traditionally accepted as the best choice. Psychological pressure of family members may compel women to breast-feed the child. Over all 45 women accepted the offer of free supply of formula milk to baby and top fed as advised. At the end of one month, 2/9 (22.2%) perinatally infected babies died due to prematurity as against 8/85 (9.41%) of noninfected full term babies of infected women. Rest of the non-infected babies born to HIV infected women were found to be healthy as against 94% of non-infected babies of non-infected mothers. This illness outcome correlated with poor socio-economic condition, poor maternal literacy and poor understanding of hygiene.

The co-factors of perinatal transmission were not analyzed, as all of them were not studied due to inadquate funding available. Base line evaluation of these factor were earlier studied by us[13].

The efficacy of the drug AZT (not A2D) lies in doses and duration of the therapy. In ACTG 076 regimen of New York, the drug was started from the 14th week of pregnancy orally 100mg fives times a day till the woman went into labor. During labor the same drug was given intravenously 2mg / kg as loading dose over one hour followed by maintenance drip of 1mg / kg till the birth of the child. The result was reduction of perinatal transmission from 25.5% in control group to 8% in study group[15].

Abrreviated ACTG 076 regimen was tried in US in 1996-97 as oral AZT 100mg five times a day from 34th week until labor. During labor AZT was given as in New York regimen mentioned above. Results showed 9% perinatal transmission. There was no control in this study[12].

During the course of our study, it was observed that initial fear and apathy of doctors, technicians and nurses was slowly replaced by gradual acceptance. This change of attitude is not self-sustainable in a traditionally hierarchical system and requires constant persuasion.

Women of reproductive age need intensive awareness campaigns and counseling for HIV infection. They need to be empowered for drugstherapy, breast-feeding and contraception. Antiretroviral drugs need to be made available free of cost in public hospitals. If possible, HIV testing should be made routine with counseling at marriage and on antenatal registration.

Table I : Mode of Delivery and MTCT

Mode of delivery	N = 104	MTCT as RT-PCR Positive	
Pre term vaginal delivery	13	3	23.07%
Full term vaginal delivery	85	6	7.05%
Preterm cesarean section	01	Nil	nil
Full term cesarean section	05	Nil	nil
Total	104	9	8.65%

Table II : Prenatal ZDV and MTCT with Antiretroviral Prophylaxis

Prenatal doses	N=104	MTCT as RT-PCR positive		Odds ratio (confidence interval)	
Nil	57	6	10.5%	**	
1-28 days	32	3	09.37%	0.88	(0.16 – 4.40)
More than 29 days	15	0	nil	0.61	(0.03 – 5.97)
Total	104	9	8.65%	**	

Table III : Intrapartum ZDV and MTCT

Intrapartum ZDV	N=104	MTCT as RT-PCR positive		Odds ratio (confidence interval)	
Nil	47	5	10.6%	**	
1-2 dosages	24	2	8.0%	0.73	(0.09 – 4.8)
3 or more dosages	31	2	6.45%	0.56	(0.07 – 3.61)

Table IV : Combined Effect of Antiretroviral Prophylaxis on MTCT

		Intrapartum ZDV / MTCT as RT-PCR	
Prenatal	N = 104	Nil or one dose	2 – 3 dosages
Nil	57	5/43 – 11.63%	1/14 – 7,14% (OR - 54; CI 0.14, 38.31)
1-28 days	32	1/12 – 8.33% (OR – 0.41; CI 0. 13,35.34)	1/20 – 5.0% (OR-2.44; CI 0.24, 59,09)
29 days – more	15	0/4 (OR – 0.02; CI 0.02, 11.59)	0/11 (OR – 1.28; CI 0. 12,32.3)

OR – odds ratio, CI – confidence interval

Table V : Vaginal Infection and MTCT

STD status	N = 89	MTCT as RT – PCR Positive	
No vaginal discharge	54	05	9.09%
Vaginal discharge	32	03	9.37%
Vaginal warts	03	01	33.3

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