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Research Article

Perinatal transmission of HIV in women receiving anti-retroviral therapy/prophylaxis with zidovudine, lamivudine and nevirapine

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Abstract: This study was conducted to see the perinatal transmission among HIV infected women receiving anti-retroviral prophylaxis and therapy. This prospective study was conducted among women who were found to be HIV positive during antenatal screening. These women then received either anti-retroviral prophylaxis (ARV) or anti-retroviral therapy (ART) according to WHO classification and CD4 count.Group-1 women receivedARV from 28 weeks of gestation with Zidovudine + Lamivudine + Nevirapine, followed by Zidovudine+ Lamivudine for 7 days postpartum. The neonate received a single dose Nevirapine syrup followed by Zidovudinefor 6 weeks. Group-2 women received ART with Zidovudine , Lamivudine and Nevirapine antenatally and thereafter. Perinatal HIV transmission was seen by DNA PCR in the babies done at 6 weeks and 6 month of age.The perinatal transmission rate was 15% in Group 1and 10% in Group 2and this difference was not significant (p=1). In Group1, the transmission rate was lower in women delivered by elective CS as compared to those delivering vaginally but the difference was not significant. In Group 2, no such trend was seen which indicated that the mode of delivery did not affect the outcome. Analysis of this small group shows a trend (statistically not significant) in reduced perinatal transmission among women on ART (due to their HIV disease state) as compared to women receiving WHO 2006 abbreviated regimen of ARV.
Keywords: perinatal transmission, antiretroviral therapy, antiretroviral treatment.

INTRODUCTION

With an antenatal HIV prevalence of 0.7%, nearly 1, 89000 HIV positive women deliver each year and if vertical transmission rate of 30% then about 56,700 HIV infected infants are born every year [1]. Mother to child transmission (MTCT) can occur during pregnancy, labour (5-10%), delivery (10-15%), and breastfeeding (5-20%). MTCT may be reduced by 1.anti-retroviral drugs (ARVs) prophylaxis during pregnancy, labour, and to the neonate.2.delivery by scheduled caesarean section (CS)before labour onsetor ruptured membranes and avoiding breast feeding [2].AIDS Control Organization (NACO)India selected the single-dose Nevirapine (sdNVP) regimen from the WHO recommended abbreviated regimens of ARV prophylaxis to be used in resource-limited countries [3]. This is provided free at all Integrated Counseling and Testing Centres (ICTCs).In 2006, the WHO recommended a more effective abbreviated ARV prophylaxis regimen [4].Scheduled delivery by CS is recommended in those women with HIV RNA levels >1,000 copies/ml or unknown levels whether or not receiving ARVs [5].However, NACO recommends CS for obstetric indications only in view of the morbidity and expense of a CS and limited availability of safe blood transfusion [3].The WHO recommends exclusive breast feeding unless replacement feeding is affordable, feasible, acceptable, sustainable and safe (AFASS) [6].In our hospital, pregnant women were assessed for their HIV disease status clinically and by CD4 count. If eligible for anti-retroviral therapy (ART) they are provided with the triple drug regimen (zidovudine or AZT) + lamivudine or 3TC + NVP).If ineligible they are given either sdNVP prophylaxis or offered an alternate ARV prophylaxis regimen to reduce MTCT [2]. We followed all HIV positive pregnant women who delivered from June 2010 to December 2011 in order to observe maternal and neonatal outcome, including perinatal transmission rate.

METHODOLOGY

This prospective study was conducted in the Department of Obstetrics and Gynecology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh. Women visiting the Antenatal Clinic were counseled and screened for HIV infection by ELISA tests at the ICTC. Of these, the HIV positive women who delivered in PGIMER from June2010 to December 2011 were recruited for study. Depending on the clinical assessment of HIV disease and CD4 count, they were offered either ARV prophylaxis (Group-1) or ART (Group-2). The criteria for ARV prophylaxis wasCD4 >350 cells/mm^3 and WHO clinical Stage 1 or 2. ART was given to women with CD4<350 cells/mm^3or if they were in WHO clinical Stage 3 or 4.Group-1women received ARV prophylaxis according to WHO 2006 regimen which included tablet AZT 300mg twice a day from 28 weeks period of gestation (POG) and a combination of AZT 600mg+3TC 150mg + NVP 200mgat onset of labour or 3 hours prior to CS.A seven-day 'tail' of AZT 300mg + 3TC150 mg twice a day was continued for 1 week postpartum to the mother. Group-2, women put on triple drug regimen throughout pregnancy and continued lifelong (tablet AZT 300mg BD + 3TC 150 mg BD+ NVP 200 BD .Those with CD4 counts <200 cells/mm^3were given prophylaxis against opportunistic infections (Pneumocystis carinipneumonia) with 160mg trimethoprim and 800mg sulfamethoxazole once daily. All neonates received a single dose ofsyrup NVP (2mg/kg) within 72 hours of birth plus syrup AZT 4 mg/kg 12 hourly for 6 weeks. They were followed regularly in the antenatal clinic. At 32-34 weeks POG, the risks and benefits of vaginal delivery versus elective CS (to reduce perinatal HIV transmission) and exclusive breastfeeding versus exclusive replacement feeding was explained so that these women could make an informed choice regarding these options. All women received a course of broad spectrum antibiotics during labour and delivery for one week. Delivery details, neonatal outcome and complications during the postpartum period were noted. The mother and baby were followed for 6 months. The neonates received routine immunization, PCP prophylaxis with co-trimoxazole (from 6 weeks to 18 months) and were tested for HIV by DNA PCR at 4-6 weeks of age. The blood sample was taken by heel-prick and dried blood spot prepared. These samples were processed at the NACO laboratory in New-Delhi. If DNA PCR was negative, it was repeated at 4-6 months of age. If DNA PCR was positive then repeated immediately for confirmation of positive status. All HIV positive babies were registered at the Pediatric ART centre and treated with ART. HIV negative babies were advised to undergo HIV ELISA at 18 months as a confirmatory test.

RESULTS

Among 5355 antenatal screened women 66 were found to be HIV positive. Thirty-five women who delivered in PGIMER were recruited for study after obtaining a written consent In addition, 15 women reported directly in labour and were found to be HIV positive. Thus, a total of 81/5355 women were HIV positive, making the antenatal HIV sero-prevalence rate to be 1.5%. Of these, 35 women were included in this study as they had been supervised antenatally and delivered in this hospital. ARV was given to 21 women (Group 1) and ART to 14 women (Group 2) figure 1.The mean age of women in Group 1 was 27.05 years which was similar to the Group2 (26.86) yrs. Overall, 65.7% women were between the age group of 26-30 years. There were a total of 10/34 (29.4%) serodiscordant couples in the present study (one husband did not get tested for HIV), and each group had a similar proportion of serodiscordant couples. In Group 1, among the 6 serodiscordant couples, 4 women had been re-married after the death of the first husband due to AIDS. Hence, they had probably acquired HIV infection from their first husband. In the remaining 2, the cause of acquisition of HIV infection could not be ascertained. In Group 2, two women probably acquired HIV by heterosexual transmission from the previous husband. In remaining 2, there was history of prior surgical and occupational exposure. Thus, 30/34(88.2%) women had acquired HIV infection by heterosexual route in the two groups. Majority of women were housewives and majority of men were laborers by occupation in the both group "Table 1".

In Group 1, 15/21(71.4%) women had their baseline CD4 count between 351-500 cells/mm^3 and 6/21 (28.6%) had a baseline CD4 count of>500cells/mm^3. In Group 2, 11/14 (78.5%) women had a baseline CD4 count of ≤350 cells/mm^3. Three women of Group 2 had a CD4 count of >350 cells/mm^3 at their first visit during pregnancy. Of these 3, two women had already been receiving ART for the last 3 years prior to conception which was continued during the pregnancy. The mean haemoglobin of women in Group 1 was 10.4±1.02gm/dl which was similar to the mean haemoglobin of women in Group 2 (9.98±1.11gm/dl). The mean total leucocyte count and mean platelet count, liver function tests, renal function tests and other routine investigations were also normal in all women except for one woman in Group 2 who was found to be VDRL positive and received three doses of benzathine penicillin at weekly interval as treatment for the same "Table 2".In Group 2,one woman had spontaneous abortion at 16 weeks POG and one had an intrauterine fetal death at 33 weeks POG. Thus, MTCT could be seen in 12/14 women in Group 2. A total of 23/33 (69.6%) opted for an elective CS as the mode of delivery and 10/33 (30.4%) chose to deliver vaginally; of these, two required emergency CS for fetal distress and the duration of rupture of membranes (DROM) was <2 hrs in these two women. In Group 1, fourteen women delivered by elective CS, one by emergency CS and six women delivered vaginally. The mean duration of labour(DOL) was 8.29hrs and DROM

was 62.85 minutes. In Group 2, nine women delivered by elective CS, one by emergency CS and two delivered vaginally. The mean DOL was 5 hrs and DROM was 2hours and 24 minutes. Of the 33 babies who delivered (21 in Group 1 and 12 in Group 2), 30 were available for neonatal testing (20/21 in Group 1 and 10/12 in Group 2) and 3 did not come for follow-up and could not be contacted due to wrong addresses. A total of 4 babies were HIV positive, 3 in Group 1 and one in Group 2. In Group 1, of the 3 HIV positive babies, one was born vaginally and the median duration of DROM was 30 minutes. This was similar to the median DROM of 50 minutes among the 5/6 HIV negative babies born vaginally (p=0.351).The difference in the DOL was also not significant (p=0.632).

In Group 2, such difference was not noted with DROM and DOL because both babies were HIV negative after vaginal delivery. The mean POG at delivery was similar in the two groups was 38 wks. All the women in Group 1 received AZT 600+3TC150+sdNVP 200 mg 3 hours before CS or at onset of labour and in Group 2 continued their prescribed ART regimen. All women received broad-spectrum antibiotics in the intrapartum, postpartum period. All infants received cotrimoxazole prophylaxis started from 4–6 weeks of age until HIV infection could be excluded till 18 month of age"Table3"

A total of 4/30 (3 in Group 1 and 1 in Group 2) babies were found to be HIV positive on DNA PCR test and 26/30 (86.6%) were HIV negative, making the overall perinatal transmission rate of 13.3% . In Group 1, 3/20 (15%) and in Group 2, 1/10 (10%) babies were HIV positive. There was no statistically significant difference in the perinatal transmission rate of the two groups (p=1.0). Similar proportion of women had delivered by elective CS in the two groups (Group 1, 13/20 or 65% and Group 2, 7/10 or 70%; P=1).Overall, 20 women delivered by elective CS and 8 delivered vaginally. Among the elective CS, 2/20 (10%) and among the vaginal deliveries, 1/8 (12.5%) babies were HIV positive. This difference was statistically not significant (p =1.0)."Table 4"

DISCUSSION

The HIV sero-prevalence rate in pregnancy (1.5%) in the present study was higher than the prevalence rate of the several Indian states (1%) among pregnant women attending antenatal clinics as reported by the UNAIDS epidemiology fact sheet 2004 [1]. The mean age was similar to the mean age of 351 Argentinean HIV infected pregnant women reported by Adrina et al[7](27±5.8 years). In our study 94.2%) of the women were homemaker whereas only 62.2% Ethiopian women were homemakers as reported by Zinash et al [8]. Majority of women in the present study had possibly acquired HIV infection via the heterosexual route (85.7%) which is similar to the rate reported by Adrinas et al [7] among Argentinean women (80.8%).HIV discordance was found to be present in 10/35 (28.5%) couples in the present study and possibly acquired HIV infection from their first husband, A study of 152 heterosexual couples from Thailand reported 59% to be HIV seroconcordant, 28% to be serodiscordant with female members being HIV positive and 13% to be serodiscordant with male members being HIV positive reported by Lil et al [9], which is similar to the present study. However, this high serodiscordancy rate does not negate the fact that heterosexual transmission is the chief mode of HIV acquisition in India. The median CD4 count in present study was 470cells/mm^3 in Group 1 and 298cells/mm^3 in Group 2. The CD4 count did not affect the outcome in present study (Table2) whereas Leroy et al reported the effect of CD4 count in MTCT seen at 24 months in a breastfeeding population [10]. Transmission risk was lower in women with CD4 350-499/mm3 then among women with CD4 <350/mm^3. Garcia-Tejedor et al reported that CD4 count <500/ml increased the HIV transmission three times when the mother did not take any retroviral treatment [11]. However, no differences were observed if mother were receiving HAART. Scientific data from developed countries states that an elective CS performed prior to labour onset or ruptured membranes reduces MTCT. Cooper et al reported that elective CS reduced the MTCT from 8.4% (in vaginal delivery) to 1.6% with any drug use [12]. Similarly, in the present study, in Group 1 (ARV), elective CS reduced the MTCT from 16.7% to 7.7%, though this trend was statistically not significant (Table 4). In Group 2, no significant difference was noted between the outcomes in elective CS versus vaginal delivery. This result is in agreement with data from the European surveillance study by Townsend et al [13] who showed that there was no statistically significant difference in the perinatal transmission rate of HIV among women undergoing an elective CS or a planned vaginal delivery among the group of women on combination antiretroviral therapy or prophylaxis. In India; NACO guidelines mention that the risk of elective CS to reduce MTCT should be assessed carefully in the context of factors such as the risk of post-operative complications, safety of the blood supply and cost. In India, normal vaginal delivery is recommended unless the women has obstetric reason (like fetal-distress, obstructed labour, etc) .The policy in PGIMER is to follow NACO guidelines. Among the women who delivered vaginally, the mean duration of membrane rupture was about 1 hour, maximum being 3 hours and the mean duration of labour was 8 hours and maximum was 12 hours. As per the Green Top Guideline 2010 recommendations, an ARM is deferred till the second stage of labour in these women [14]. The ARV protocol offered in PGIMER has been followed since 2006 when the WHO reported this to be efficacious among the abbreviated regimens suggested for developing countries with MTCT rate of 4% or less reported by Halima et al [15]. The WHO recommended that countries adopt more effective antiretroviral regimens to increase the effectiveness of

prevention of MTCT. The overall perinatal transmission rate of 13.3% (15% in Group 1 and 10% in Group 2) at 6 months of age in the present study is not low, considering the high rate of elective CS (70%) and replacement feeding (100%) among these women. In the ACTG 076 trial in USA, Connor et al [2] reported MTCT at 18 months to be 8.3% in women receiving AZT from 14 weeks, intrapartum intravenous AZT and AZT to infant only for 6 weeks. Shaffer et al [16]. Lallemant et al [17] reported MTCT as 4.1% in women who received AZT from 28 weeks, intrapartum AZT +single dose NVP and AZT +single dose NVP to the infant for 6 weeks. We could not find a reason for a higher rate of MTCT in the present study except that differences exist among different population groups. Direct comparison of MTCT rates among different trials is difficult due geographical difference. However, the trend towards a lower rate in Group 2 women who are rather at a higher risk of MTCT due to their advanced disease reflects the likely benefit of maternal ART combination regimens given over a longer duration antenatally over abbreviated regimens of AZT monotherapy with addition of single dose NVP at labour onset. This observation is mentioned by the WHO 2010 guidelines too. We did not find any relation of MTCT with mode of delivery. Though there was a trend towards reduced MTCT with elective CS in Group 1 (7.7% versus 16.7% with vaginal delivery), it was not statistically significant. No such trend was observed in Group 2. Use of combination ART has been reported to reduce the effect of other risk factors for vertical transmission like CD4 < 500/mm3, ruptured membranes > 6 hours, labour duration > 5 hours, low birth weight and vaginal delivery reported by Garcia et al [11] The benefit of elective CS has been evaluated among women using monotherapy AZT and a high viral load; whereas CDC now recommends vaginal delivery among women on HAART and viral load < 1000 copies/ml.

Thus, an analysis of this small group of HIV positive women points towards trends (statistically not significant) in reduced MTCT among women on combination ART (due to their HIV disease state) as compared to women receiving WHO 2006 abbreviated regimen of AZT from 28 weeks.

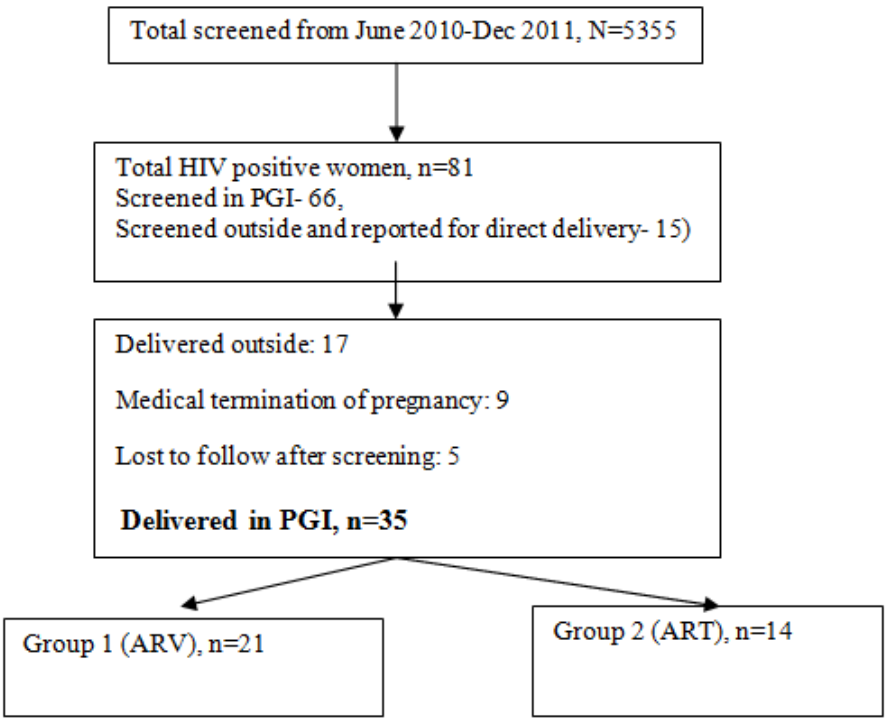

Fig-1: Flowchart depicting recruitment of HIV positive pregnant women in the present study.

Table-1: Demographic data of the HIV positive pregnant women

		Group1 (ARV) n=21 (%)	Group2 (ART) n=14 (%)
Mean Age (years)	Women	27.05	26.86
	Husband	31.3	30.07
Husband HIV status	Positive	14	10
	Negative	6	4
	Not known	1	0
Likely risk factor for HIV infection	Heterosexual route	18	12
	Not known	3	
	Obstetric intervention		1
	Occupational exposure		1
Occupation (women)	Housewife	20	13
	Working	1	1
Occupation(men)	Labourer	12	5
	Farmer	1	4
	Driver	2	0
	Shopkeeper	6	5

Table 2: Investigation of the HIV positive pregnant women

		Group:1(ARV) n=21(%)	Group:2(ART) n=14(%)
CD4count(cells/mm^3)	<250	0	4 (28.5)
	251-350	0	7 (50)
	351-500	15 (71.4)	2 (14.2)
	>500	6 (28.5)	1 (7.1)
	Median&(IQR)	470 (384-533)	298 (202-334)
Haemoglobin(gm/dl)	Mean±sd	10.4±1.02	9.98±1.11
Total leucocyte count (cells/mm^3)	mean±sd	6940±1251	7522±1524
Platelet count (lakh / mm^3)	mean±sd	2.07±0.5288	2.05±0.6186

Table-3: Delivery details of the HIV positive pregnant women

Mode of delivery		**Group:1(ARV) n=21**	**Group:2 (ART) n=12**
Elective CS		14	9
Vaginal delivery	**Emergency CS**	1	1
	Vaginal	6	2
Mean (DROM)		62.85 min±53.45	
Mean DOL		8.2hr±2.39	5hrs
Median DROM of women whose babies were HIV negative		50min (n=5)	1hr&24hrs
Median DROM of women whose babies were HIV positive		30min (n=1)	
Median DOL of women whose babies were HIV negative		8hrs (n=5)	5hrs
Median DOL of women whose babies were HIV positive		6hrs (n=1)	
Mean birth weight ±SD		2.729 kg±0.488	2.825±0.55
Period of gestation at delivery (weeks) Mean ±SD		38.4±0.785	38±0.66

Duration of rupture of membranes (DROM), duration of labour (DOL)

Table-4: Distribution of HIV DNA PCR results of the babies in the two groups

DNA PCR results of the babies	Group1(ARV) n=20 (%)		Group2(ART) n=10 (%)		P-value
Positive	3 (15%)		1(10%)		1
Negative	17 (85%)		9(90%)		1
	Elective CS	Vaginal delivery	Elective CS	Vaginal delivery	
Positive	1(7.7%)	1(16.7)	1(14.3)	0	1
Negative	12(92.3)	5(83.3)	6(85.7)	2(100)	1

CONCLUSION

Overall HIV Pregnant women transmit the infection to the baby and these are some intervention to reduce MTCT but in present study the transmission rate was more as compared to other studies may because of limited number of women in study .In spite of high transmission rate these regimens still help to reduce the HIV infection.To prove the efficacy of these regimen required more trial and large sample size. In ART Group the outcome was better despite of low CD4 count indicating that if we provide combination therapy for longer duration the result can be better.

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