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ROLE OF ANTIRETROVIRAL THERAPY IN HIV POSITIVE PREGNANT WOMEN

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ABSTRACT

Mother to child transmission of HIV can be prevented to a large extent by antiretroviral therapy. Zidovudine and Nevirapine are two drugs which are time tested and safe for mother and infant. Objective-To study the role of oral Zidovudine versus oral Niverapine in HIV positive pregnant women. Methods-A prospective clinical study enrolled 100 eligible consenting HIV positive pregnant women into two groups. One group received oral zidovudine 300mg bid from 34 wks gestation till term. They received 600mg oral zidovudine 1hr before cesarean section. The second group who came at term received single dose of oral niverapine 200mg at the onset of labor pains. They were destined for vaginal delivery unless there were obstetric indications for cesarean section. The newborns in both groups received antiretroviral syrup. Breast feeding was withheld in both groups. The infants were tested for HIV by DNA-PCR at 3mths of age. Results-At the end of 3mths of age all infants were tested negative for HIV by DNA-PCR .Two infants were tested equivocal. Conclusion-There was no significant difference between the Zidovudine and Nevirapine group in transmission of HIV till 3mths of age. Single dose Nevirapine during labor is a cost effective choice in developing countries.

INTRODUCTION

Spectacular advances have been made in the field of mother to child transmission (MTCT) of HIV since its initial description.[1] AIDS has already doubled the infant mortality in countries worst affected and is growing problem in India and South East Asia. HIV-I, the aetiological agent of AIDS can be vertically transmitted during pregnancy, childbirth or breast feeding. MTCT is by far the largest source of HIV infection in children < 15 year of age.[2] In industrialized countries the risk of an infant acquiring HIV infection from an infected mother ranges from 15-25%, which in developing countries is 25-45%.[2] The efficiency of MTCT in India is 48%. HIV transmission can occur during antepartum– 0-50%, Intrapartum – 50-80%, Postpartum – 7-22% period.[2]

Maternal factors like primary infection, advanced disease, STD increases the risk of transmission to the fetus. Factors like abruption, chorioamnionitis, mode of delivery, duration of labour, duration of rupture of membranes increases the risk of transmission.[3]

Polymerase chain reaction (PCR) if positive within 48hrs of birth it suggests antepartum

transmission. If negative within 48hrs but positive within 90-100days it suggests intrapartum transmission.If postive after 90days it suggests late transmission.[3]

Current WHO guidelines recommend combination short course antiretroviral therapy to HIV positive pregnant women unless they are severely immunocompromised at which point they should receive HAART.[4] Zidovudine is a nucleoside analog reverse transcriptase inhibitor safely used to prevent mother to child transmission.[4] Zidovudine has shown to reduce risk to as little as 8% when given in a three part regimen,postconception,delivery six weeks post delivery. Consistent and proactive precautionary measures such as rigorous use of antiretroviral therapy, cesarean section, heavy duty rubber gloves avoidance of mouth contact& breast feeding will further reduce MTCT to 1-2%. Nevirapine is a non nucleoside reverse transcriptase inhibitor used as a single dose in reducing MTCT to almost 50% compared with short course of zidovudine prophylaxis.WHO has endorsed the use of single dose of nevirapine prophylaxis in developing countries as a cost effective measure to reduce MTCT.[3,4]

Objective-To study the role of oral zidovudine versus oral Nevirapine in reducing MTCT in HIV positive pregnant women.

PATIENTS AND METHODS

This study was a prospective clinical study carried out in 100 HIV positive pregnant women in Private hospitals of Davangere Karnataka,India. The duration of the study was from November 2008 to December 2010.

Inclusion Criteria:

- All HIV positive pregnant women.

Exclusion Criteria:

Pregnant women diagnosed to have renal or liver disease. Patient selection was done based on HIV-ELISA and rapid tests. Pretest and posttest counseling was done. Detailed history and thorough clinical examination to was done to categorize them into:

a. Acute HIV infection
b. Asymptomatic latent infection
c. Persistent generalized lymphadenopathy
d. AIDS related complex

Routine antenatal investigations along with CD_4, CD_8 counts, baseline urea, creatinine AST, ALT levels were done. HIV ELISA test was done for both partners with two separate commercially available kits (accepted by NACO). A total of 3 rapid tests and one ELISA test was done. If ELISA was positive and any two rapid tests were positive, then the patient was considered positive for HIV.The recruited pregnant women were divided into two study groups based on their period of gestation

Study Group 1 Zidovudine (ZDV)

All HIV positive pregnant women received oral ZDV 300mg twice daily from 34 weeks of gestation and they were followed every 2 weeks till term. They were destined for elective cesarean section at 37 completed weeks. This group received 600mg oral ZDV 1 hour before elective cesarean section. Newborns received antiretroviral syrup for 6 weeks. Breast feeding was withheld.

Study group 2 (Nevirapine group)

This group included those pregnant women who came To hospitals for the 1st time at or near term. They were administered a single dose of oral nevirapine 200mg at the onset of labour pains. They were destined for vaginal delivery unless presence of other obstetric indications. Newborns received a single dose of antiretroviral syrup within 48-72 hours of birth. Breast feeding was withheld. Routine postnatal check-up at 6 weeks with evaluation by a physician trained in HIV therapy. Immunisation as per schedule. Pneumocystitispneumonia (PCP) prophylaxis.

DNA-Polymerase chain reaction (PCR) in the infant at 3 months of age.

RESULTS AND ANALYSIS

Table – 1: Comparison of age distribution of the two study groups (n=50)

Age group (years)	Study group 1(n=50)	Stud group 2 (n=50)
18 – 23	8 (16%)	10 (20%)
24 – 29	32 (64%)	33 (66%)
30 – 35	10 (20%)	7 (14%)

p = 0.68NS

Table – 1 shows that most of the pregnant women around 24-29 years i.e. 64% in group 1 and 66% in group 2 and this was comparable in both the groups.

Table-2: Parity distribution of the enrolled pregnant women in the two groups (n=50)

Parity	Study group 1 (n=50)	Study group 2 (n=50)
Primi	34 (68%)	31 (62%)
Multi	16 (32%)	19 (38%)

p = 0.67NS

Table – 2 shows the parity distribution in both the groups suggesting that most of them were primigravidae i.e. 68% in group 1 and 62% in group 2; it was comparable in both the groups.

Table-3: Duration of pregnancy when the women were first diagnosed to be HIV positive (n=50)

Trimester	Study group 1 (n=50)	Study group 2 (n=50)
I	3 (6%)	0
II	37 (74%)	5 (10%)
III	10 (20%)	45 (90%)

Table – 3 shows the time of diagnosis of seropositivity for HIV. In study group 1 74% were in the 2nd trimester and study group 2 90% were near term. None of the pregnant women were diagnosed positive before pregnancy.

Table-4: CDC Classification of signs and symptoms (n=50)

Signs and symptoms	Study group 1 (n=50)	Study group 2 (n=50)
I	8 (16%)	3 (6%)
II	34 (78%)	45 (90%)
III	8 (16%)	2 (4%)
IV	0	0

Table – 5 shows the distribution of signs and symptoms of the pregnant women in the two groups classified into four different stages (n=50).

I = Acute HIV syndrome
II = Asymptomatic latent infection
III = Persistent generalized lymphadenopathy
IV = AIDS related complex.

In group 1, 78% were in the asymptomatic phase as compared to 90% in group 2 which were comparable.

Table-5: HIV status of the partner women (n=50)

Husband's status	Study group 1 (n=50)	Study group 2(n=50)
Positive	32 (64%)	24 (48%)
Negative	8 (16%)	5(10%)
Unknown	10 (20%)	21 (42%)

Table – 5 shows that there were 16% in group 1 and 10% in group 2 whose husbands were diagnosed negative. In both the groups most of them belong to asymptomatic stage which is comparable in both the groups.

Table-6: Comparison of CD_4 counts of the pregnant women in the two groups (n=50)

CD_4 counts (cells/μL)	Study group 1 (n=50)	Study group 2 (n=50)
≤ 200	0	0
200-499	8	6
≥ 500	42	44

Table – 6 shows the distribution of CD_4 counts in both the groups. None of the pregnant women had CD_4 counts ≤ 200.

Table – 7: Complications of pregnancy observed in the two groups

Complications	Study group 1	Study Group 2
PIH	4	1
Rh –ve	5	2
Fibroid	2	-
Previous	5	-
Anaemia	6	6
PROM	2	2

Table - 7 shows the comparison of complication between the two study groups. In study group 1, there were 4 patients of PIH, 5 of Rh –ve pregnancy, 2 cases of fibroid diagnosed intraoperative and 5 previous cesarean section. In the study group 2, there was one patient with PIH, 6 with anaemia who received blood transfusion for the same and 2 patients had PROM.

Table-8: HIV status of the infant at 3 months of age done by DNA PCR (n=50)

HIV status in infants	Study group 1 (n=50)	Study group 2(n=50)
Positive	0	0
Negative	48	49

Table 8 shows the final analysis of 100 infants 48 in group 1 and 49 in group 2 at the end of 3 months by DNA PCR (single test)

None of the infants were tested positive at the end of 3 months.2 infants tested equivocal

Table-9: Comparison of mode of delivery (MOD) between the two groups (n=50)

MOD	Study group 1 (n=50)	Study group 2(n=50)	
Vaginal	2 (4%)	40 (71.43%)	P=0.0003
LSCS	48 (96%)	10 (28.57%)	

Cesarean section	Study group 1 (n=48)	Study group 2 (n=10)	
Elective	40 (68.42%)	0 (16.67%)	P=0.01
Emergency	8 (121.05%)	10 (83.33%)	

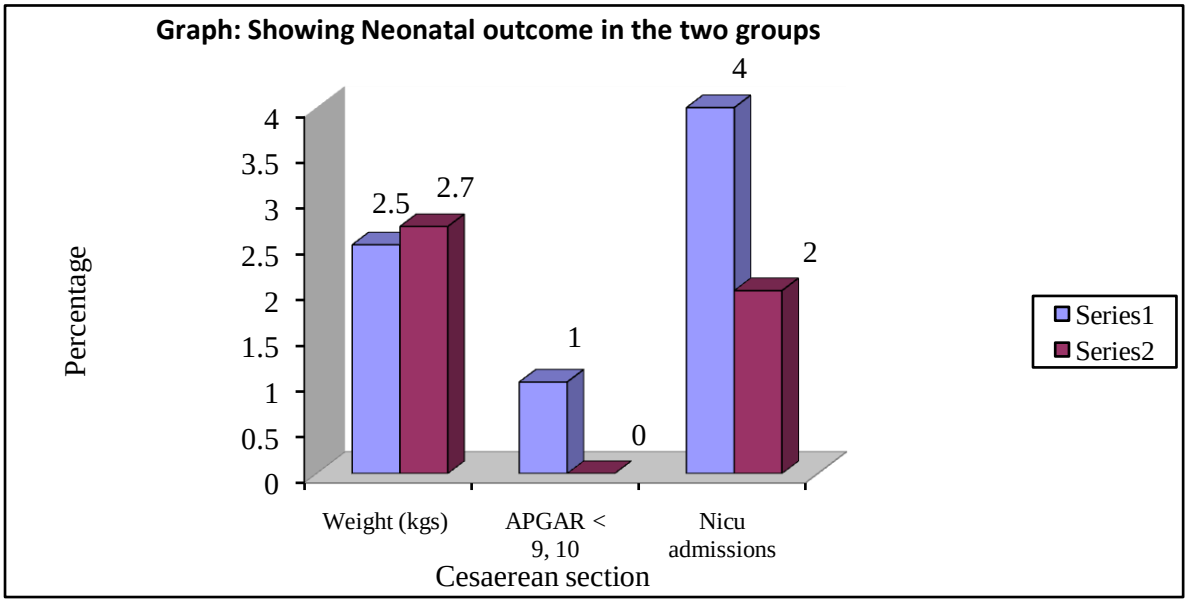
Table – 9 shows distribution of pregnant women depending on the route of delivery. All the pregnant women who received zidovudine prophylaxis ended up in cesaerean section except one multigravida who delivered normally.

All the pregnant women in the nevirapine group delivered vaginally except six who ended up cesaerean section for other obstetric indications.

Neonatal outcome in the two groups

Details of new born At birth	Study group 1	Study group 2
Weight (kgs) (median)	2.5 (1.3-3.7)	2.7 (2.3-3.2)
APGAR < 9, 10	1	-
NICU admissions	4	2
IUGR	1	-
Lymphadenopathy (at 3 months of age)	1	-

Graph –shows us the details of outcome of the newborns at birth and at 3 months of age.



- Both in group1 and group 2 the median body weighs of the infants were comparable. However the group 1 had two low birth weight and, one IUGR babies.
- In group 1 only one baby had an APGAR < 9 because of fetal distress.
- In group 1 there were four NICU admissions.
- At 3 months of age one baby had lymphadenopathy.

DISCUSSION

In this study we chose the shorter ZDV therapy like in the study done by Shaffer et al. however, we continued antiretroviral therapy in the infant unlike the Bangkok trial.

since we know that most of the transmission occurs close to the time of delivery, short course of ZDV therapy was most effective in lowering intrapartum transmission with minimal adverse effects, good compliance and low cost.

Comparing the study of Connor et al i.e. PACTG076 trial, with study done by Shaffer et al the decrease in transmission was 68% v/s 50% i.e. slightly a better reduction in transmission by Connor et al may be because the babies were also treated and the longer duration of treatment[7,8].

A study done by Guay et al in Uganda compared short course ZDV along with single dose intrapartum nevirapine[5]. This study shows that HIV free survival was significantly longer than with short course ZDV therapy over a similar period of time.

In our study we gave the patients the benefit of treatment like a short course Bangkok trial done by Shaffer et al to all the HIV positive pregnant women who came during early antenatal period and those who came in labour were given dose intrapartum therapy[11,12]. Hence in the ZDV therapy the pregnant women got multiple doses unlike the nevirapine group. Moreover the babies of the nevirapine group also received a single dose. The study had no HIV positive infants at 3 months of age suggesting that both the drugs have proven equal efficacy.

One of the reasons contributing to this fact may be that in both the study groups the pregnant women were in the asymptomatic phase and in studies done by Connor et al, Shaffer et al and mainly Guay et al the pregnant women were not in asymptomatic phase and had lower CD_4 counts unlike in this study[8]. All the women irrespective of the drug they received opted not to breast feed unlike the above mentioned study. Early findings from ongoing European Cohort studies by Andiman W, Boncheen D et al supported by meta-analysis of data on individual patients from the prospective Cohort studies suggest that the risk of vertical transmission was significantly lower among HIV-infected women who underwent cesarean section before onset of labour and rupture of membranes[3 6]. However this study did not seem show any relationship between the mode of delivery and the risk of transmission.

It is because of elective cesarean section or emergency cesarean section done before the onset of active labour or is it because the group of pregnant women were mainly in the asymptomatic phase with CD4 counts > 200 cells/μL, is evidently difficult to explain.

However, more so the role of elective cesarean section in reducing transmission of HIV is controversial.

May be the main limitation in our study was that viral load in the form of RNA copies could not be done because of financial reasons and more so because of nonavailability of the facility.

Since the ACOG guidelines clearly stresses on the importance of RNA copies which may or may not correlate with CD_4 counts, RNA copies becomes a

must for deciding the mode of delivery[9]. Discussing the neonatal outcome in the ZDV group the newborns were of comparatively lesser birth weight.

The data published in the PACTG076 proved the efficacy of ZDV to an extent that they had to discontinue the placebo even in the study because of its safety profile[10]. Despite the importance of this break through concern still persisted about women of low CD4 counts (or advanced disease) which was excluded, in the PACTG076 trial. Although long time consequences of ZDV when used during pregnancy to reduce perinatal transmission are still not fully known and concerns including potential mutagenic and carcinogenic effects, possible teratogenicity and possible effects on neurodevelopment and reproductive system persist[9].

Does ZDV prophylaxis contribute to LBW (low birth weight) is not known because there are no studies reporting it. However, among the two newborns with LBW, one had underlying PIH in the mother and the other had IUGR before ZDV therapy. Study done by Selwyn et al Johnstone et al found no significant difference in frequency of preterm or LBW.[11]

CONCLUSION

The group of pregnant women in this study were mainly in the asymptomatic stage.

- Considering the neonatal outcome there was no significant difference between the zidovudine and nevirapine group. In this study mode of delivery did not seem to effect the transmission risk.
- Both the drugs were well tolerated and no serious adverse effects were seen among neonates. Single dose nevirapine may be a cost-effective choice.

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