

DOI: <https://dx.doi.org/10.18203/2320-1770.ijrcog20204793>

Original Research Article

Effect of triple drug antiretroviral therapy on CD4+ count in pregnant women with HIV and prevention of parent to child transmission

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Received: 04 August 2020

Revised: 12 September 2020

Accepted: 03 October 2020

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ABSTRACT

Background: India has moved from single drug Antiretroviral Therapy (ART) in 2002 to triple drug ART in 2013 to prevent parent to child transmission of HIV. The aim of the study was to know the effects of triple drug ART on maternal CD4+ count and prevention of HIV transmission to baby along with its adherence, side effects and pregnancy outcome.

Methods: A prospective study was done in Safdarjung Hospital, New Delhi on 40 HIV positive pregnant women who received single dose combination of triple drug ART. CD4+ count, LFT and KFT were done before beginning of ART and repeated after 6 months of ART. The infants received nevirapine prophylaxis and HIV status was determined by DBS PCR at 6 weeks.

Results: The median CD4+ count was 317 and 397 pre and post ART for 6 months respectively (p value < 0.001). Low birth weight (LBW) was seen in 43.59% which was statistically significant but confounded as 76.4% of these babies were preterm. 23.08% of babies had an APGAR of < 7 at 1 minute, out of which 77.7% were preterm. Nine out of 39 infants (one had abortion) needed NICU admission. Only one baby (2.56%) was HIV positive who died at 4 months of age due to pneumonia. There was no defaulter and no statistically significant changes in LFT and KFT after 6 months of ART.

Conclusions: Triple drug ART offers greater convenience improves fetomaternal outcome and minimize the risk of HIV transmission from mother to child.

Keywords: HIV, ART, Triple drug, CD4+ count

INTRODUCTION

Human immunodeficiency virus (HIV) is a retrovirus which attacks the T Helper cells (CD4 cells) and decreases immunity leading to opportunistic infections. HIV is known to affect pregnancy outcomes in many ways. There is higher incidence of spontaneous abortion, preterm labor, premature rupture of membranes (PROM), abruptio placenta, intrauterine growth retardation

(IUGR), stillbirth, low birth weight baby, neonatal sepsis, and a risk of transmission of HIV to child and neonatal deaths. HIV can be transmitted from HIV positive mother to offspring antenatally, intrapartum and postpartum through breastfeeding. Without antiretroviral preventive interventions, the risk of perinatal HIV transmission has varied between 15 to 45 percent, depending on maternal risk factors and breastfeeding practices.¹ The most consistent risk factors for

transmission has been maternal plasma and breast milk viral load followed by maternal immunologic status and clinical stage, as suggested by observational studies and clinical trials in non-breastfed and breastfed populations. Analyses of viral load levels in the original trial of zidovudine to prevent mother to child transmission (MTCT), as well as studies from Thailand, West Africa, Uganda, and Kenya, all demonstrate a direct positive correlation between maternal plasma viral load and risk of transmission to the infant.²⁻⁶

In India, antiretroviral (ARV) prophylaxis was started in year 2002 which had provision of giving single dose nevirapine (SdNVP).⁷ This regime which was continued till 2012, reduced perinatal transmission to 10% however it was unacceptable with aim of global target of elimination of new HIV in children by 2015.⁸ In September 2012, India transitioned from single dose Nevirapine prophylaxis to multi drug ARV prophylaxis. It was based on CD4 count and WHO clinical staging of disease. Regime was to start ARV from 14 weeks of gestation and to continue till 1 week after cessation of breastfeeding.⁷

Currently since December 2013, India has started triple drug (Tenofovir 300 mg + Lamuvidine 300 mg + Efavirenz 600, called TLE as first line treatment) antiretroviral therapy (ART) for all pregnant patients as soon as diagnosed irrespective of gestational age, CD4 count or WHO clinical stage of disease which has to be continued lifelong.^{9,10} Syrup Nevirapine at dose of 2 mg/kg is being given to all newborns for 6 weeks and duration is increased to 12 weeks if women did not receive ART for at least 24 weeks before delivery.⁷ Infants are being followed up at 6 weeks, 6 months and 18 months of age. At 6 weeks of age DNA PCR using dried blood spot (DBS) is used for diagnosis. At age >6 months, antibody test (rapid test) is done first, if positive then DBS is done. If DBS is positive whole blood sample (WBS) is done after which pediatric ART is started. Confirmation of diagnosis is done using 3 rapid antibody tests (even if first two tests were negative) at 18 months of age.¹⁰

The recommendation for initiation of a regimen as early in pregnancy as possible is supported by results from observational studies that suggest that earlier initiation of ART is associated with lower rates of transmission.^{11,12}

There are many operational and clinical challenges about current approach that need to be addressed including sustainability, ARV adherence and retention in care; concern about drug resistance with long term use when initiated in early HIV disease; safety, tolerance to drugs, feto-maternal outcome of increased ART exposure during pregnancy etc.

The aim of the study was to know feto-maternal outcome in HIV+ pregnant women on triple drug ART (TLE) mainly by observing changes in CD4+ count of the

mother and the rate of parent to child transmission as well as adherence to drugs and its side effects.

METHODS

This was a prospective study conducted in Vardhaman Mahavir Medical College and Safdarjung Hospital, New Delhi from October 2017 to March 2019.

Women who were attending the ANC OPD were offered participation in the study if they were HIV positive irrespective of period of gestation, CD4+ count and WHO clinical staging of disease. Women with known case of renal disease, hepatic disease and neuropsychiatric disturbances were excluded from the study. All women enrolled in the study received verbal as well as written study information through a patient information sheet. Informed consent was taken for themselves as well as their infants. A total of 42 women who were willing to participate and follow-up were finally enrolled in the study, out of these 2 were lost to follow up in very early stage of study, so outcome was analyzed in 40 women.

Patient's information was recorded according to a study tailored structured proforma. A thorough general physical examination and complete obstetric examination was performed in each visit. Apart from routine ANC investigation (Hemogram, blood group, VDRL, HBsAg, TSH, OGTT, Urine routine, USG) CD4+ count, LFT and KFT was also done before beginning of ART. Women were started on triple drug ART (Tenofovir 300mg + Lamivudine 300mg+ Efavirenz 600mg as a combination single tablet once daily) without waiting for reports (as per NACO protocols). The women were followed on each antenatal visit and enquired about adherence to drugs and any side effects/adverse effects of drugs. Pregnancy outcome, mode of delivery and details of infant including birth weight, APGAR score, neonatal intensive care unit (NICU) admission, incidence of birth asphyxia, jaundice and sepsis were noted. These infants received syrup Nevirapine for a duration of minimum 6 weeks. Infants were then followed up at 6 weeks of age for DNA PCR of dried blood sample (DBS). Repeat CD4+ count along with LFT and KFT was done after 6 months of initiation of ART.

Statistical analysis

Data collected at every visit was entered in Microsoft Excel spreadsheet. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean±standard deviation and median. Paired t-test was used for comparison of CD4+ count across time. Qualitative variables were correlated using Chi-Square test/Fisher's Exact test. A p-value of <0.05 was considered statistically significant. The data analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

Feto-maternal outcome was studied in 40 women. The mean age in our study was 25.35 ± 3.53 years with 14 (35%) of the study participants were illiterate and a majority 37 (92.5%) were housewives. Majority of women (45%) belonged to class 3 of socioeconomic status according to modified Kuppaswamy scale.¹³ Amongst these subjects, the rate of sero-discordancy was 37.5% with 15 out of 40 husbands were HIV negative. 24 husbands were positive while one could not be traced as couple was divorced.

Table 1: CD4+ count.

Range	Baseline CD4+ count		CD4+ count after 6 months of ART	
	(Total no of women-40)		(Total no of women-40)	
	Frequency	Percentage	Frequency	Percentage
<200	8	20	3	7.5
201-350	13	32.5	14	35
351-500	9	22.5	10	25
>500	10	25	13	32.5

The baseline CD4+ count in our study population ranged from 42 to 980 with 368.95 being the mean and 317 being the median while after six months of ART it improved with 434.48 as mean and 397 being median. The increase in CD4+ count was found to be statistically significant with p value of 0.001. After 6 months of ART, CD4+ count less than 200 was only in 7.5 percent of women compared to 20 percent before treatment.

Pregnancy outcome

Out of 40 women, 13 had preterm deliveries including 2 preterm LSCS (32.5%) while 26 had term deliveries including 5 term LSCS (65%) and 1 patient had abortion (2.50%). All 40 patients enrolled in our study had institutional delivery. Caesarean section was performed for obstetric indication only and not as a measure to decrease transmission from parent to child. Amongst 39 live born babies, 17 were less than 2.5 kg hence labeled as low birth weight (LBW) constituting 43.59% of all babies. Amongst these babies, 13 were preterm and 4 were term. Only 4 out of 26 term babies (15.38%) were low birth weight. Incidence of low birth weight in HIV+ pregnant women came out to be statistically significant (p value <0.0001) but it was confounded by the fact that majority of these low birth weight babies were preterm also (13 out of 17).

Table 2: Comparison of both CD4+ count.

	Sample size	Mean± SD	Median	Range	Inter quartile range	P-value
CD4+ count baseline	40	368.95±218.62	317	42-980	209-491.5	0.001
CD4+ count after 6 months	40	434.48±225.74	397	102-1100	277.5-543	

Table 3: Pregnancy outcome and mode of delivery.

Pregnancy outcome (no-40)		Frequency	Percentage
	Abortion		1
Pre-term delivery		13	32.50%
Term delivery		26	65.00%
Mode of delivery (no-40)	Caesarean Section	7 (5 Term and 2 preterm)	17.5%
	Hysterotomy	1	2.5%
	Term vaginal delivery	21	52.5%
	Preterm vaginal delivery	11	27.5%

APGAR score is taken at 1 and 5 minutes after birth. In our study 9 out of 39 (23.06%) had an APGAR score of <7 at 1 minute after birth, out of this 7 were preterm

babies. However all 39 infants had an APGAR score of >7 at five minutes. These points towards excellent neonatal resuscitation at our institute (Table 4).

Table 4: Birth weight and APGAR score.

Neonatal Outcome		Pre term	Term	Total	P value
Birth weight	>2.5 kg	0	22	22	<.0001
	<2.5 kg	13	4	17	
APGAR Score at 1 minute	<7	7	2	9	0.003
	>7	6	24	30	

Nine infants out of 39 infants (23.08%) were admitted to Neonatal ICU (NICU). Out of these 5 admissions were because of prematurity with low birth weight, 3 were because of respiratory distress and one were due to hyperthermia with sepsis. A total of 16 out of 39 women constituting 41.03% of the study population chose top feeding over breast feeding to decrease the transmission

to baby. 38 out of 39 infants (97.44%) were DBS PCR negative at six weeks while one infant tested positive. This one infant died at four months of age due to pneumonia.

Table 5: Neonatal outcome.

Neonatal outcome	Frequency	Percentage
NICU Admission	Yes 9	23.07%
	No 30	76.92%
Jaundice within 24 hrs after birth	Yes 13	33.33%
	No 26	66.66%
Hyperthermia within 24 hrs after birth	Yes 6	15.38%
	No 33	84.61%
Birth asphyxia	Yes 1	2.56%
	No 38	97.43%
HIV status of baby at 6 weeks after birth	Positive 1	2.56%
	Negative 38	97.43%
Infant feeding	Breast feeding 23	58.97%
	Top feeding 16	41.02%

Table 6: KFT and LFT.

Name of investigations	Blood value	Before start of ART (no-40)	After 6 months of ART (no-40)	P value
Total Bilirubin	<0.8	38 (95.0%)	40 (100%)	0.494
	>0.8	2 (5%)	0	
SGOT	<80	33 (82.5%)	39 (97.5%)	0.057
	>80	7 (17.5%)	1 (2.5%)	
SGPT	<80	34 (85%)	39 (97.5%)	0.108
	>80	6 (15%)	1 (2.5%)	
Blood urea	<40	36 (90%)	40 (100%)	0.115
	>40	4 (10%)	0	
Creatinine	<1	39 (97.5%)	39 (97.5%)	1
	>1	1 (2.5%)	1 (2.5%)	

Side effects and adherence to drugs

A total 22.5% women complained of nausea and vomiting but this subsided as pregnancy progressed. This proves that it was due to pregnancy and not due to drugs. All 40 women were adhered to ART and there was no defaulter. No baby had any gross congenital anomaly.

17.5% and 15% of women had deranged SGOT & SGPT respectively at the start of therapy but it was associated with itching. These women were followed with more frequent LFT, it was decreasing trend and after 6 months of ART only one woman (2.5%) had deranged value. This shows that it was pregnancy related complication and not due to drugs. There were no statistically significant changes in LFT and KFT after 6 months of ART.

DISCUSSION

The response to therapy as well as progression of disease was followed by CD4+ count. The baseline CD4+ count in our study ranged from 42-980 with 368.95±218.62 being the mean and 317 being median. In our study 80% of women had CD4+ count >200 at the start of treatment. Similarly 89% and 84.6% of women had CD4+ count more than 200 in studies conducted by Dadhwal et al and Gautam et al respectively.^{14,15}

CD4+ count after taking 6 months of ART in our study population improved in range from 102-1100 with 434.48±227.54 as mean and 397 being median. The increase in CD4+ count after taking 6 months of ART was found to be statistically significant in our study with a p value of 0.001. These statistics support the fact that triple drug ART comes with a favourable fetomaternal outcome. Improvement in CD4+ count is associated with improvement in quality of life as well, along with decreased morbidity and mortality with decreased risk of opportunistic infections.

These women were followed till delivery to see foetal outcome. Out of 40 women enrolled in our study, 13 women had preterm deliveries (32.5%), 26 had term deliveries (65%) and one patient had an abortion (2.50%). This was similar to studies done by Dinh and Gibango where preterm deliveries was 32.1% and 35% respectively whereas study done by Yadav et al it was much higher with 52%.¹⁶⁻¹⁸

In our study 32 (80%) women had vaginal deliveries while 7 (17.5%) babies were born by emergency caesarean section. Caesarean section was performed for obstetric indication only and not as a measure to decrease parent to child transmission. This was almost similar to observations made by Gautam et al where 70.75% were vaginal deliveries and 29.25% pregnancies were terminated by caesarean section.¹⁵ In our study birth weight ranged from 1.38-3.5 kg with 2.48±0.62 kg being the mean weight. This was comparable to mean birth weight of 2593±499 grams in study population enrolled by Dadhwal et al.¹⁴

A total 17 out of 39 babies were low birth weight (<2.5 kg), out of these 13 were preterm while 4 babies were term. In our study incidence of low birth weight came out to be significant with a p value of <0.001 but this result was confounded by the fact that 13 out of 17 low birth

weight infants were preterm. In this study 9 (23.08%) of babies had an APGAR score of <7 at one minute after birth. Out of these babies 7 were preterm and 2 were term babies. APGAR score <7 was a statistically significant value in our study with a p value of 0.003 but the fact that majority of these babies were preterm could be the reason for a low APGAR score at 1 minute. Compared to APGAR score at 1 minute, APGAR score at 5 minutes improved in all the babies. This favorable improvement could be due to excellent neonatal resuscitation provided by care givers at tertiary care centre. Out of 39 infants in our study, 9 (23.08%) needed admission to NICU which was a higher number as compared to 8.5% reported by Dadhwal et al.¹⁴

All women were explained the risks and benefits associated with infant feeding practices; 58.97% chose breastfeeding whereas 41.03% opted for top feeding of their babies. Study done by Dinh et al in 2013-14 also shown that majority of women, 70% chose exclusive breastfeeding.¹⁶ On the contrary, Dadhwal et al and Radhika et al had 83.9% and 63.9% of their subjects chose top-feeding.^{14,19} The decision of breastfeeding versus top-feeding differed depending upon study period because breastfeeding is now being promoted under WHO B+ regimen treatment for HIV.

The rate of parent to child transmission in our study was 2.56% with only 1 baby out of 39 tested positive at 6 weeks by DNA PCR. This was comparable to 3.3% observed by Dadhwal et al and 3.4% by Radhika et al.^{14,19} Only 1.92% babies were positive in study done by Gautam et al while as low as 0.7% were positive in study by Girma et al.^{15,20} Out of 39 infants in our study, no neonatal mortality was reported. Only 1 infant (2.5%) died at 4 months of age due to pneumonia; this was the only infant who tested positive at 6 weeks. Similarly only 0.92% infants died in post natal period in Girma et al study group while Gautam et al reported a neonatal mortality of 14.28% and Radhika et al reported a neonatal mortality of 8.37%.^{15,19,20} Excellent result in neonatal mortality in our study could be due to quality care provided by a multi-disciplinary approach and good neonatal ICU facilities at our institute which decreased neonatal morbidity and mortality.

CONCLUSION

Our study has shown that triple drug ART helps to minimize the risk of HIV transmission from mother to child. Single dose combination of triple drugs (Tenofovir 300mg + Lamivudine 300mg+ Efavirenz 600mg) offers greater convenience, allows adherence, significantly increases CD4 count and hence improves fetomaternal outcome.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Dwivedi A, Gupta R, Agarwal KC, Rani KU. Effect of triple drug antiretroviral therapy on CD4+ count in pregnant women with HIV and prevention of parent to child transmission. *Int J Reprod Contracept Obstet Gynecol* 2020;9:4462-7.