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Original Article

Internal Medicine Section

Safety and Efficacy of Fixed Drug Combination Tenofovir, Lamivudine and Efavirenz to Prevent Transmission of HIV

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ABSTRACT

Introduction: Mother-to-child transmission of HIV can occur during pregnancy, labour, or breastfeeding. The first-line regimen for prophylaxis in HIV infected pregnant women is combination of Tenofovir, Lamivudine and Efavirenz (TLE).

Aim: To evaluate the safety and efficacy of the TLE regimen in the Prevention of Mother-To-Child Transmission (PMTCT) of HIV.

Materials and Methods: The present hospital-based, retrospective cohort study was conducted at ART centre, Prevention of Parent to Child Transmission (PPTCT) centre, and Department of Medicine, SP Medical College, Bikaner from July 2016 to June 2019. HIV positive gravidas, on triple-drug regimen TLE (Tenofovir 300 mg, Lamivudine 300 mg, Efavirenz 600 mg) before conception and, those detected HIV reactive antenatally during study period were included in this study and started on TLE regimen. After delivery, these newborns were given syrup Nevirapine as per the PPTCT guidelines. Infants were tested with Rapid test and PCR for HIV, at six weeks, six months, 12 months, and 18 months of life.

Results: Out of 87 pregnant women, enrolled and delivered at the study institute, 85 were live births and two were stillbirths. Out of 85 live-born babies, four have died during infancy and two were lost to follow-up despite repeated counselling. Five babies were referred to nearby Anti-Retroviral Therapy (ART) centers. So, the study followed 74 babies out of which one girl child was found to be positive for HIV-1 at 18 months of age (transmission rate of HIV was 1.35 and efficacy of TLE 98.65%). No major adverse effects of TLE were noted and all women continued TLE.

Conclusion: The use of a triple-drug regimen (TLE) declined the risk of transmission of HIV from mother-to-child at negligible level, without drug resistance and with safety and tolerability as compared to single drug.

Keywords: Anti-retroviral therapy, Prevention, Transmission

INTRODUCTION

According to WHO, approximately 37.9 million people were living with HIV and 1.7 million new infections and 7,70,000 people died from AIDS-related illnesses in 2018 [1]. According to the National AIDS control organisation (NACO) report, an estimated 2.14 million people were living with HIV in India, out of which around 42% were females and children (<15 years) accounted for 6.54%. In India, an estimated 87.58 thousand new HIV infections occurred in 2017, and children <15 accounted for 4.3%. An estimated 22,677 pregnant women needed ART to PMTCT of HIV in 2017 in India [2].

Parent-to-child transmission is responsible for around 5% of HIV infection. It is the second most common mode of transmission of HIV after sexual transmission. In the absence of any interventions, HIV transmission from mother-to-child can be 15-45%. Mother-to-child transmission of HIV can occur during pregnancy, labour, or breastfeeding. The prevalence of HIV in pregnant women was reported 0.5-3.3% in India. To reduce the burden of the disease by preventing the transmission from parent to child, in March 2014, the NACO started more efficacious multidrug ARV regimen in the national guidelines for the PMTCT of HIV program [3].

In the year 2015, WHO recommended antiretroviral therapy for all HIV positive pregnant women regardless of CD4 cell count and to continue ART lifelong. Infants born to HIV-infected mothers should also receive post-exposure antiretroviral prophylaxis [4]. The recommended first-line regimen for ARV prophylaxis in HIV infected pregnant women is Tenofovir 300 mg+Lamivudine 300 mg+Efavirenz 600 mg (TLE), similar to nonpregnant adults. TLE regimen is preferred because of fewer side-effects, once-daily dosing schedule, increased adherence, and reduced risk of resistance [3,4].

Early screening of antenatal mother, administration of ART and lifelong continuation, institutional delivery, follow-up and administration of ART to the infant and contraception are crucial for PMTCT of HIV [5]. This study was designed to assess the socio-demographic variables, pregnancy outcome, safety, and efficacy of the TLE regimen for PMTCT in seropositive mothers.

MATERIALS AND METHODS

The present hospital-based, retrospective cohort study was conducted at ART centre, PPTCT centre, and Department of Medicine, SP Medical College, Bikaner from July 2016-June 2019. It is a tertiary care centre in northwestern Rajasthan (India). The study protocol was approved by the Institutional Review Board {No: F.29. (Acad) SPMC/2019/4160} and informed consent was taken from each study subject for initiation of the drug regime.

All the HIV-1 reactive pregnant females who had been taking ART regimen TLE before conception and continued during the antenatal and postnatal period formed the study population. The data belonged to July 2016-June 2019 and the analysis was done in December 2019. As this was a retrospective study, so all the available patient records were considered.

Inclusion criteria: HIV-1 reactive pregnant females who had taken Fixed Drug Combination (FDC) of TLE before delivery and babies born to them who had received syrup nevirapine as per the PPTCT guidelines [3].

Exclusion criteria: Those HIV-1 positive pregnant females who had refused to give syrup nevirapine to their babies and who didn't give consent for testing the HIV status of their babies.

Study Procedure

Detailed proforma were filled from hospital records which included information regarding demographics, socioeconomic factors, obstetric history, history of a spouse, testing of spouse and previous children

for HIV, ART status of spouse, and WHO staging of HIV/AIDS [2,6]. Socioeconomic status was determined in this study by the modified BG Prasad scale 2018 [7]. Detailed investigations including complete blood count, plasma glucose, renal function, liver function, CD4 counts, HBsAg, HCV, etc., were done. Details about any minor (gastrointestinal) or major (haematological, pancreatitis, renal dysfunction, hepatotoxicity etc.,) adverse reactions to the TLE regimen were noted from hospital records. The mode of delivery and outcome of the baby was also noted.

Postexposure prophylaxis, in form of syrup nevirapine 2 mg/kg, was started within 6-12 hours of delivery and was continued for six weeks, if the mother was started on ART within 12 weeks of gestation; while it was continued up to 12 weeks if mother had started ART after 12 weeks of gestation. Mother was counselled and advised for the choice of alternative feed or breast-feed and contraceptive advice was given. After delivery, all infants were registered and serial screening was done for babies by PCR and rapid test for HIV at six weeks, six months, 12 months and 18 months of age. Samples in the form of Dried Blood Spots (DBS) and plasma were taken at the ICTC center of the institute.

STATISTICAL ANALYSIS

Quantitative and qualitative data were analysed at the end of the study period and the findings were used to evaluate the safety and efficacy of the TLE regimen for PMTCT in HIV reactive mothers and the possible contributory factors affecting HIV transmission to the baby.

RESULTS

A total of 87 seropositive gravidas were enrolled and delivered in the same institute. The mean age of the study subjects was 25.4±3.66 and ranged from 19 to 39 years. The majority of them were illiterate (66.67%), were of socioeconomic class IV and V (53.47%), were residing in a rural area (62.07%), and were housewives (39.08%). In terms of WHO staging of HIV out of 87 subjects, 32 were in stage I, 24 were in stage II, 18 were in stage III and 13 were in stage IV disease, respectively. All of the women with stage III and IV disease were already diagnosed preconceptionally were on ART. Out of 87, 7 women (8.04%) had coexisting Hepatitis B infection and none had co-existing Hepatitis C infection. Out of 87 women, 68 (78.16%) had CD4 count of ≤500/mL and 19 (21.84%) had CD4 count of >500/mL. Voluntary testing of the spouse was done for 69 patients out of whom 64 couples were seroconcordant and five couples were serodiscordant [Table/Fig-1].

In terms of parity, majority 36 (41.38%) were primipara. Total 33 (37.93%) women were preconceptionally diagnosed as HIV seropositive and already on the TLE regimen. Out of 87 women, 54 (62.07%) were diagnosed HIV reactive during the antenatal check as a part of the PPTCT program, out of which three (3.45%) started TLE regimen in first trimester, 26 (29.88%) in second trimester and 25 (28.73%) in third trimester. All women were compliant and took the TLE regimen regularly. No major adverse effects of drugs were noted except minor gastrointestinal side-effects and all women continued TLE regimen till last follow-up [Table/Fig-1].

Of the total 87 gravidas, 79 (90.81%) were delivered by vaginal delivery, and 8 (9.19%) by caesarean section due to obstetric indications. Out of these 87 deliveries, two were stillbirth and four babies died in the infantile period due to diarrhoea, acute respiratory illness, malnutrition, and unknown reason respectively. The mean birth weight of infants delivered was 2.61±0.45 kg. Out of 85 live births, 30 babies were low birth weight (<2.5 kg), 78 (91.76%) were breastfed and seven (8.13%) were top-fed. Two women lost to follow-up, even after repeated counseling and five babies were referred to nearby ART centers. So the study followed 74 infants for mean follow time of 18 months. In these 74 babies, 73 were negative for HIV and one girl child tested positive for HIV during follow-ups at 18 months of age (transmission rate was 1.35% and efficacy of TLE 98.65%) [Table/Fig-2].

Variables		Number	Percentage
Age (years)	Mean±SD; (range)	25.4±3.66; (19-39)	
Education	Illiterate	58	66.67
	Primary	17	19.54
	High school	9	10.34
	Graduate	3	3.45
Socioeconomic class	I	4	4.6
	II	10	11.49
	III	23	26.44
	IV	35	40.23
	V	15	17.24
Residential area	Rural	54	62.07
	Urban	33	37.93
Occupation	Housewife	34	39.08
	Labourer	33	37.93
	Private service	8	9.19
	Govt. service	12	13.8
WHO stage	I	32	36.79
	II	24	27.58
	III	18	20.69
	IV	13	14.94
Co-existing HBV infection		7	8.04
Co-existing HCV infection		0	0
CD4 count	<200/mL	7	8.04
	201-350/mL	32	36.79
	351-500/mL	29	33.33
	>500/mL	19	21.84
Spouse HIV status	Positive	64	73.56
	Negative	5	5.75
	Not known	18	20.69
Spouse ART status (n=64)	On ART	61	95.31
	Not on ART	3	4.69
Parity	G1	30	34.48
	G2	36	41.38
	G3	14	16.1
	>G3	7	8.04
Timing of HIV detection	Preconception	33	37.93
	Antenatal	54	62.07
Timing of start of ART	Preconception	32	36.79
	First trimester	3	3.45
	Second trimester	27	31.03
	Third trimester	25	28.73
	>32 weeks	0	0
Adverse effects of ART	Minor (gastrointestinal)	11	12.64
	Major (haematological, pancreatitis, renal dysfunction, hepatotoxicity etc.,)	0	0
Mode of delivery	Vaginal	79	90.81
	LSCS	8	9.19

[Table/Fig-1]: Maternal baseline characteristics (n=87).

Outcome		Number	Percentage (%)
Stillbirth		2	2.3
Live birth (n=85)	Infantile death	4	4.7
	Lost to follow-up	7	8.24
	On follow-up	74	87.06
Birth weight (n=85)	Mean±SD (Kg)	2.61±0.45	
	3-3.5 Kg	16	18.82
	2.5-3 Kg	37	43.53
	2-2.5 Kg	28	32.94
	1.5-2 Kg	2	2.35
Type of feeding (n=85)	Breast feeding	78	91.76
	Top feeding	7	8.14
HIV status of baby followed (n=74)	Positive	1	1.35
	Negative	73	98.65

[Table/Fig-2]: Outcome of babies (n=87).

DISCUSSION

The United Nations program on HIV/AIDS reported that 82% of pregnant women living with HIV had access to antiretroviral medicines to prevent transmission of HIV to their child in 2018 [1]. All HIV infected pregnant women have to be detected and provided with timely ART in order to reduce mother to child transmission and ultimately to eliminate paediatric HIV [8]. According to the latest guidelines of ACOG, the treatment of HIV-infected pregnant women with combined ART can achieve a 1-2% or lower risk of mother-to-child transmission if the maternal viral load of 1000 copies/ml or less can be sustained, independent of the route of delivery [9]. This study was aimed to evaluate the safety and efficacy of the TLE regimen in the PMTCT of HIV. The efficacy of TLE was found to be 98.65% with no without major adverse effects.

The mean age of the study subjects was 25.4±3.66 and ranged from 19 to 39, similar to previous studies [10,11]. In this study, majority of the women (66.67 %) were illiterate, similar to study done by Saha S at al., [12]. A higher illiteracy rate in this study may be explained by the fact that the majority of women were from low socioeconomic class (53.47 %). Illiterate women are susceptible to HIV/AIDS because of the inability to have adequate knowledge for protection from sexually transmitted diseases [13]. Poverty and illiteracy increase susceptibility to HIV/AIDS particularly in developing countries like India [13-16].

In terms of parity, 34.48% of women were nullipara, 41.38% were primipara, 24.14% were multipara, similar to previous studies [10,14]. A family obligation, social pressures like the stigma of infertility and inability to terminate the pregnancy seems to be important for the repeated pregnancies in seropositive women [9,13]. Out of 87 women, 54 women were detected seropositive in the present pregnancy as part of PPTCT while 33 women were diagnosed preconceptionally. Of these, 14 women were diagnosed as a part of the PPTCT program during previous pregnancies, 11 women were detected after the husband was diagnosed as seropositive, while eight women were detected seropositive while being investigated for other medical conditions. Hence, 78.16% of the total subjects were diagnosed due to the reach of the PPTCT program. In contrast, a study done by Daver RG and Chhabra M. showed that 64.5% of cases were diagnosed as part of the PPTCT program and Izzo I et al., reported that 43.1% of patients were detected antenatally, whereas 53.9% were detected preconceptionally [11,16]. As antenatal clinics are a woman's first point of contact with the health care system in developing countries, HIV testing integrated with such clinics is the main reason for the detection of HIV in women who would not otherwise get tested.

In this study, out of 69 couples 64 (92.75%) were seroconcordant, and five (7.25%) were serodiscordant. Daver RG and Chhabra M. and Darak S et al., reported 64.5% vs 30.1% and 79.4% vs 7.7% seroconcordant and serodiscordant couples, respectively in their studies [11,17]. In a study from India, Shah I reported prevalence of serodiscordance among HIV infected pregnant women of 6.7% [18]. Serodiscordance was found which could be because the spouses were in the window period.

In this study, majority of women 68 (78.16%) had a CD4 count of ≤500/mL, similarly to other previous studies [5,17]. Contrary to this in study done by Onoya D et al., majority of women had CD4 count >500/mL [19]. In this study, 33 (37.93%) women were already on ART, and majority of women started ARV in the second and third trimester. Hence, a large number of patients have started ARV regimen as a result of the PPTCT program, minimising the risk of transmission significantly. This finding is similar to a study done by Daver RG and Chhabra M. where 30.1% of women were already on ART and 41.57% of women started ARV in the second trimester. Similarly, in study done by Gupta A et al., 39.4% of gravidas were found seropositive during antenatal check-up [5]. Izzo I et al., reported that 75% and 42.8% women were already on ART, and 25% and 57.2% women started ARV during pregnancy in Italian and migrant population respectively [16]. Early start of ARV related with the reduction of perinatal morbidity and mortality for seropositive mothers [4]. Those patients who started ARV late in pregnancy, the total duration of ARV received were less than those who started earlier, thereby increasing the chances of vertical transmission [11]. In contrast, a study conducted by Berhan Z et al., in Ethiopia reported that 63.4% of the women were already on ART and 30.3% were started ARV as a part of the PMTCT program and 6.2% women not received ARV, with 10.1% transmission rate as 19.1% infants not received ARV prophylaxis at birth [20].

In this study, no major adverse effects of ARV were noted except minor GI side-effects and all women continued TLE regimen till last follow-up. While Daver RG and Chhabra M. reported one case of tenofovir induced Nephritis and Gallant JE et al., reported two cases of acute renal failure and 2 patients with rash in their studies where TLE was used [11,21]. Hence, this study suggests that TLE appears to be better option for HIV reactive pregnant women.

In this study, 90.81% of women delivered vaginally while 9.19% were delivered by cesarean section due to obstetric indications. This finding was similar to the studies by Lussiana C et al., [22]. In study done by Gupta A et al., 66% infants were delivered by caesarean section and 44% by vaginal delivery and 2 infants found HIV reactive during follow-up and both were delivered by caesarean section [5]. While Daver RG and Chhabra M. and Thorne C et al., reported 31.2% and 37% of caesarean, and 68.8% and 63% vaginal delivery respectively [11,23]. In this era of triple-drug therapy, vaginal delivery is the safer option for HIV reactive women, with minimal risk of mother to child transmission.

Out of 87 women who delivered, there were 85 live births and two stillbirths. Out of 85 living born babies, four babies died in the infantile period. HIV reactive women, especially with advanced disease, have higher rates of pregnancy loss and neonatal mortality. Excess neonatal mortality in HIV reactive women may be due to low birth weight and prematurity [22,24]. Out of 85 live births, 30 (35.3%) babies were low birth weight (<2.5 kg).

Daver RG and Chhabra M. and Leroy V et al., reported 91.76% and 25.5% low birth weight baby, respectively [11,25]. Less number of low-birth weight babies in this study may be explained by the fact that most of the women in this study were in WHO stage I and II, as severity of disease increases as WHO staging increases from stage I to stage IV [6]. Kim HY et al., found a positive association between an advanced maternal HIV disease with adverse pregnancy outcomes [26]. Out of 85 live borns babies, 78 (91.76 %) were breastfed and seven (8.13%) babies were top-fed. This finding is similar to study by Edward M and Mofenson LM [27]. In study done by Daver RG and Chhabra M 75% babies were breastfed and 25% babies were top-fed [11]. In study done by Dash M et al., 82.6% babies were breastfed and 17.4% babies were on replacement feeding [28]. In the year 2009, WHO recommended babies of HIV-positive mothers can have a benefit of breastfeeding with very little risk of becoming infected with HIV [29]. In first six months of infant's life exclusive breastfeeding is associated decreased risk of HIV transmission compared to breastfeeding along with top-feeding [29].

Out of 74 infants followed, 73 were negative for HIV and one tested positive for HIV during follow-ups with a transmission rate of 1.35% and efficacy rate of the TLE regimen 98.65%. One baby who was found to be HIV reactive whose DBS 1, DBS 2 and final confirmation by HIV PCR technique at 18 months of age came out to be positive for HIV-1. HIV reactive baby was a girl and born to the mother who was already taking TLE regimen for last five years before pregnancy and was breast-fed. There may be poor adherence to treatment. Moreover, pregnant who were diagnosed antenatally were diagnosed coincidently and in early stage of disease as a part of the PPTCT program with better immune status than those who were already on ART. This can be the reason that there was no mother to child transmission occurred in antenatally detected women. Gupta A et al., Daver RG and Chhabra M, and Sumithra S and Manonmani R, reported 95.35%, 100%, and 93.3%, efficacy rate respectively of TLE regimen to prevent mother to child transmission of HIV in seropositive pregnant women [5,11,30].

Limitation(s)

Few limitations of this study need mention. First, the retrospective nature of the study design which may introduce bias. Second, the data used were tertiary care facility-based and might not be true presentation of the community.

CONCLUSION(S)

Vertical transmission is the predominant way children become infected with HIV worldwide. With improved access to ARV HIV can be significantly eliminated. The pregnant women should be offered universal screening because appropriate interventions with early initiation of ART can reduce mother to child transmission to a negligible level. In this study, the use of the TLE regimen led us to astonishing results with safety and efficacy rate of 98.65%. Fixed dose combination of TLE in pregnant women showed clear benefits for maternal health and reduction in perinatal transmission. The emerging drug resistance can be reduced with FDC-TLE compared to single dose nevirapine.

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