ADHERENCE TO ANTIRETROVIRAL THERAPY IN PREGNANT AND LACTATING WOMEN WITH HIV INFECTION AND ITS RELATION TO INFANT HIV STATUS

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ABSTRACT **Introduction:** Mother to child transmission of HIV accounts for over 90% of new infections among children. Transmission can occur during pregnancy, childbirth and breastfeeding. As on March 2013, 0.1 million HIV positive children had been registered under the antiretroviral therapy (ART) programme and 38,579 are receiving free antiretroviral therapy (ART) in India.
Materials and Methods: In this study we will talk to you to find how well you are taking your medicines. We will also try to find out what difficulties you face in taking your medicines regularly on time. We will examine you for any illness and provide you with appropriate treatment. Same will be done for your baby. And if they are causing any side .After getting written informed consent from the candidate detailed history and clinical evaluation will be done. Few routine blood investigations will be performed. Adherence will be assessed by pill count method and 3 day recall method.
Results: Our study was carried out at the Paediatric ART Centre, Kalawati Saran Children's Hospital from November 2016 to March 2018. A total of 71 HIV infected mothers on ART were enrolled, out of which 68 constituted of lactating mother and rest 3 of pregnant women. All the study subjects were interviewed using a structured proforma after obtaining written informed consent.
Conclusion: Maternal education status and husband as primary caregiver were significant predictors of maternal adherence to ART. Most mothers had a healthy BMI and absence of comorbidities at assessment. However, anemia was present in >80% of enrolled subjects. All infants tested negative for HIV at 6 weeks assessment. 43 reached 6 months assessment and all tested negative for HIV on that assessment.

KEYWORDS : child transmission, HIV, Maternal education, BMI.

INTRODUCTION

Mother to child transmission of HIV accounts for over 90% of new infections among children. Transmission can occur during pregnancy, childbirth and breastfeeding. As on March 2013, 0.1 million HIV positive children had been registered under the antiretroviral therapy (ART) programme and 38,579 are receiving free antiretroviral therapy (ART) in India.[1] Prevention of mother to child transmission (PMTCT) programme provides antiretroviral treatment to HIV positive pregnant women to stop their infants from acquiring the virus ,without which the likelihood of HIV passing from mother to child is 20-45%.[1] Effective antiretroviral treatment and PMTCT interventions reduce the risk to below 5%.[1] Maternal risk factors influencing PTCT are high viral load, HIV subtype, resistant strains, advanced clinical stage, concurrent sexually transmitted diseases, recent infection.[2]

Maternal viral load is a key determinant of MTCT risk and triple drug antiretroviral therapy (ART) is highly effective in reducing viral load, in turn reducing MTCT risk and promoting maternal health. Use of ART by HIV positive pregnant women is currently the standard of care worldwide. The success of Antiretroviral therapy (ART) for both maternal health and PMTCT hinges on timely initiation of ART during pregnancy and maintenance of high levels of adherence throughout pregnancy and postpartum when breastfeeding.[6]

Adherence to antiretroviral therapy (ART) is crucial in preventing mother-to-child transmission of human immunodeficiency virus (HIV) and ensuring the long-term effectiveness of Antiretroviral therapy (ART). Inadequate adherence to Antiretroviral therapy(ART) is associated with loss of viral suppression, increased risk of transmitting HIV, therapeutic failure, viral resistance and maternal HIV disease progression. Several studies have suggested that levels of ART adherence was good among pregnant women as compared to non pregnant women.

MATERIALS AND METHODS

In this study we will talk to you to find how well you are taking your medicines. We will also try to find out what difficulties you face in taking your medicines regularly on time. We will examine you for any illness and provide you with appropriate treatment. Same will be done for your baby. And if they are causing any side .After getting written informed consent from the candidate detailed history and clinical evaluation will be done. Few routine blood investigations will be performed. Adherence will be assessed by pill count method and 3 day recall method.

Expected Duration of the Subject Participation: 60 minutes

Benefits: The mothers will be helped overcome various barriers to adherence to ART. This will help improve their own health apart from preventing HIV transmission to their babies.

Risks and Discomfort:
No risk is anticipated for the candidate. The candidate will be examined and tests will be don

Maintenance of confidentiality of records:
Complete confidentiality of records will be maintained.

Compensation for participation: You will not have to make any additional visits to the hospital or pay for the purpose of the study. You will not receive any monetary compensation for your participation in this study.

Statement that consent is voluntary: Your participation in the study is purely voluntary.

Right to withdraw: You can withdraw from the study any time you wish, without any penalty. Your non- willingness or withdrawal will not affect your treatment in the hospital and will continue to receive the same care and treatment that your receiving prior to the study.

Costs and source of investigation:
For the study routine blood sampling as required for your health will be done in the hospital. You will not have to bear any extra cost due to the study.

RESULTS

Our study was carried out at the Paediatric ART Centre, Kalawati Saran Children's Hospital from November 2016 to March 2018. A total of 71 HIV infected mothers on ART were enrolled, out of which 68 constituted of lactating mother and rest 3 of pregnant women. All the study subjects were interviewed using a structured proforma after obtaining written informed consent.

Out the 68 lactating women enrolled majority was constituted by women of the younger age group (<30 years). The median age of enrolled subjects was 25 years (IQR 22-29.75). of the 3 pregnant women enrolled the median age was 30 (IQR 21-32).Table 5.1 and figure 2 show age wise distribution of enrolled subjects.

Table 1: Age wise distribution of enrolled subjects

Age (years)	Lactating n (%) (n=68)	Pregnant n (%) (n=3)
<20	0	0
20-25	35(51.4%)	1(33.3%)
25-30	20(29.4%)	0
30-35	11(16.1%)	2(66.6%)
>/=35	2(29.4%)	0
Median (IQR)	25(22-29.75)	30(21-32)

A total of only 12 (16.9%) women out of the 71 study subjects were illiterate and 15 (21%) of them graduates. 67(94.4%) of the enrolled mothers were homemakers, 3(4.2%) had private jobs, 1(1.4) woman was working as a domestic help.

At initiation of ART 69(97.1%) enrolled subjects were in WHO stage 1 and 2(2.9%) were in WHO stage 2. At the point of enrollment all subjects were in WHO stage 1. CD 4 counts of subjects at start of ART and at assessment are depicted in the Table 5.3.

Table 2: CD4 counts of enrolled subjects

Time of assessment	Mean+/-SD (cell/mm 3)	Range (cell/mm 3)
Start of ART (n=71)	522.9+/-186.53	172-1029
At enrolment (n=71)	588.1+/-162.06	204-975

Most of the enrolled subjects (52.1%) started ART in pre-pregnancy.

Table 3: Time of ART initiation

Time of ART initiation	Number of women(n=71) n (%)
Pre-pregnancy	37(52.1%)
First trimester	8(11.2%)
Second trimester	15(21.1%)
Third trimester	7(9.8%)
Labour	2(2.8%)
Lactation	1(1.4%)
Total	71(100%)

Average duration of ART in subjects at the time of enrollment was 2.39+2.15 years (Range 0.29-10 years). 65(91.5%) mothers were on Tenofovir, Lamivudine, Efavirenz (TLE) regimen and remaining on Zidovudine, Lamivudine, Efavirenz (ZLE) regimen.

70(98.6%) mother experienced mild ART side effects (nausea, vomiting, giddiness) during early days of ART initiation and 1(1.4%) mother had moderate side effect (excessive vomiting, rashes, anxiety, giddiness) which required medical care on outpatient basis. No derangement of liver function test (LFT) or hemogram was noted in any subjects. None required stopping ART drugs.

At the time of initiation of ART 3 out of the 71 enrolled subjects had pulmonary tuberculosis, all of whom had completed treatment with antitubercular therapy and successfully cured by the time of enrollment.1(1.4%) was diagnosed with hypothyroidism at initiation of ART and is currently euthyroid on oral thyroxine supplements. All enrolled subjects had no comorbidities at the pointof assessment and enrolment. None of subjects had any major medical illness or hospitalization after initiation of HIV care and ART.

Table 5: Comorbidities of enrolled subjects at time of ART initiation

Comorbidities	Number of women (n=71) N (%)
Hypothyroidism	1(1.4%)
Pulmonary TB	3(4.2%)
None	67(94.4%)

Majority of the subjects [68 (95.7%)] had normal BMI (18.5-25 kg/m*2) at enrollment. out of the remaining 3(4.3%) had low BMI (BMI <18.5kg/m*2) .All pregnant women had MUAC >/= 24 cm (wasting </= 22 cm).None of women had BMI >25.

Table 6: Nutritional status of enrolled subjects

Anthropometry	Mean +/- SD	Range
Height in cm (n=71)	154.95+/-5.44	137.5-163
Weight in kg (n=71)	50.54+/-5.22	34-63
BMI in kg/m*2 (n=71)	21.07+/-1.85	16-25

Anemia was strikingly noted in 61(85.9%) out of 71 enrolled subjects, (Hb 7-11g/dl). About 10(14.1%) women had normal hemoglobin levels. Mean+/-SD hemoglobin was 9.87+/-0.88 and a range (7-12g/dl). Only 25(35.2%) husbands had up to middle school education, 3 were graduates and 1 was illiterate.

Majority was comprised of skilled 27(38%) followed by semiskilled 22(31%) and unskilled 10(14.1%) workers. clerical/shop owner/farmer comprised the remaining 12(16.9%).

Invariably all the spouses of the 71 enrolled subjects were HIV infected. 4 had succumbed to illness and expired while the remaining 67 husbands were on ART. All the 4 widows of the above-mentioned have remarried with current husbands being uninfected.

Average monthly family income was Rs37000 +14789, Range (Rs6000-Rs60000).Table 5.8 shows socioeconomic status of enrolled subjects based on modified Kuppuswamy classification.

In our study all 68 lactating women had singleton pregnancies.

Table 7: Birth details of present pregnancy/child (n=68)

Birth details	Number of children(n=68) N (%)
Mode of delivery -Vaginal delivery -LSCS	54(79.4%) 14(20.6%)
Sex of infant -Male -Female	42(61.8%) 26(38.2%)
Gestation -Term -Preterm	57(83.8%) 11(16.2%)
Birth weight -low birth weight(<2500g) -Normal birth weight(>/2500g)	22(32.3%) 46(67.7%)
Mean birth weight+/-SD (grams)	2647.19+/-449.17

As per our inclusion criteria all enrolled subjects (68) were breastfeeding their babies. 64(94.1%) children were exclusively breast fed for initial 6 months and 4(5.9%) children complementary feeding was initiated before 6 months of age. Average age at beginning of complimentary feeding:

5.89+0.79 months, minimum and maximum months were 3 months and 7 months. At the time of assessment all infants were still breastfed. All the 68 enrolled children, received ARV drug (Nevirapine) prophylaxis. 10(14.7%) children had received nevirapine prophylaxis for 12 weeks as mothers of these children received ART <6 months at the time of delivery (NACO guidelines). 58(85.3%) had received nevirapine prophylaxis for 6 weeks. Mean age at assessment was 21.34+/-15.34 weeks (Range 5 to 55 weeks).

Only 2 (2.9%) out of the 68 children had severe acute malnutrition (weight for length <-3SD), 3(4.41%) had moderate acute malnutrition (weight for length between -3SD to -2SD) and rest 63(92.6%) children had normal weight for length. Table 5.10 and 5.11 describes the anthropometry and nutritional status of child.

HIV status of children:
All 68 children, 68/68(100%) had undergone DBS 1 test done at 6

weeks of age and all the test results were negative. 43/68(71.6%) had reached 6 months of age and had undergone HIV serology testing and all test results were negative. Therefore, as per the NACO protocol DBS2 was not sent for these children, only 3/68(5%) children had reached 18 months of age and had undergone HIV serology, all of them tested negative.

Sibling details: 24 out of 71 mothers had one older child prior to the present child. 8 of them tested HIV positive. Of these 4 had expired while remaining 4 were on ART. 10/71 women had 2 older children.4 out 20 children whom were infected .0f them 3 were on ART and one expired.

Assessment of adherence to ART in enrolled subjects
Pill burden of enrolled subjects
Apart from the ART pills, some enrolled subjects are some other medications. Table 8 various types of medication.

Table 8: Type of medication enrolled subjects taking

Type of medications	No of subjects(n=71) N (%)
ART pills	71(100%)
Calcium tablets	10(14.1%)
Iron tablets	31(43.6%)

Table 9: Overall pill burden

Number of pills/day	Number of women (n=71) n(%)
1 pill/day	35
2 pill/day	25
3 pill/day	6
4 pill/day	5

Adherence to ART by pill count method: Average adherence during last 6 months: 95.49+5.8 %. Minimum and maximum adherence was 55% and 100%. Table 5.14 describes mean adherence among enrolled subjects.

Table 10: Mean adherence to ART during last 6 months of assessment

Adherence level	Number of women (n=71) n(%)
Good adherence (>/= 95%)	61(85.9%)
Average adherence (80-95%)	9(12.7%)
Poor adherence (<80%)	1(1.4%)

Adherence by 3-day Recall method: All enrolled women all were able to recognize ART drugs taken by them amongst those displayed, 69(97.2%) were able recall exactly the number of pills to be taken and 2(2.8%) mothers were not able to recall the exact number of pills to be taken.

Average adherence by 3-day recall method recall: 99.05+5.6 %. Minimum and maximum adherence were 66 percent and 100 percent respectively.

Overall adherence by two methods
Women who were found to be have good adherence by both methods were considered to have good adherence and women who were found to be nonadherent by any one of the method were nonadherent.

Association of various factors with adherence
To assess influence of various factors on ART adherence, subjects were divided into two groups, those adherent >95% (n=60) and those nonadherent <=95% (n=11)

Maternal age: Table 5.17 shows the level of adherence between two age groups. The results showed there was no significant difference among two groups.

Maternal education
Table 5.18 shows the relation between maternal education and level of adherence. The results showed. The results showed that women who had >/= high school education had significantly good adherence compared to women who had </= middle school education.

The results showed that there was no statistically significant difference among two groups. However, women whose husbands educational status >/= high school were good adherent compared to women whose husband educational status </= middle school. Table 5.19 shows the relation of level of adherence among women in relation to their husbands' educational background.

Duration on ART of mother:
The results showed that there is no significant difference between two groups. The relation between level of adherence and duration of ART depicted in table 5.20.

Socioeconomic status of family: The results showed that that there is no significant difference between two groups.

ART regime of mother: The results showed that that there is no significant difference between two groups.

Table 11: Relation between ART regime and adherence

ART regime	Total (n)	Adherent n (%)	Nonadherent n (%)	P value
ZLE	6	5(83.3%)	1(16.7%)	0.93
TLE	65	55(84.61%)	10(15.3%)	

Knowledge about the disease among mothers: In our study we found out that in adherent group 88.3% women had good knowledge about the disease. In nonadherent group 81.8% had good knowledge about the disease.

Table 12: Relation between tools used to remind drugs and adherence:

Tool used to remind ART drug intake	Adherent(n=60)	Nonadherent (n=11)	P value
Reminder alarm	39/60(65%)	7/11(63.6%)	0.93
Some other tool	12/60(20%)	0/11(0%)	0.10
Husband	33/60(55%)	3/11(27.2%)	0.09
Children	1/60(1.6%)	0/11(0%)	0.66
Other family member	3/60(5%)	1/11(9%)	0.59

Caregiver: The results showed that women were more adherent where husband was a caregiver compared to women where caregiver was other family members.

Table 13: Relation between caregiver and adherence:

Relation	Total (n)	Adherent	Nonadherent	P value
Husband	64	58(90.62%)	6(9.3%)	
Other family members	7	2(28.57%)	5(71.42%)	<0.001

Distance from home to ART center

The results showed no significant difference between two groups may be due to availability of good mode of transport. **Attitude of health staff:** The results show there is no significant difference between two groups. However most of women 48/71 felt average to good towards attitude of health staff.

Table 14: Relation between attitude of health staff and adherence:

Attitude	Total (n)	Adherent n (%)	Nonadherent n (%)	P value
</= good	48	41 (85.41%)	6(12.5%)	0.33
>/= very good	23	19(78.26%)	5(21.73%)	

Overall pill burden: The results show that there is no significant difference among two groups.

Table 15: Relation between pill burden and adherence:

Pill /day	Total (n)	Adherent n (%)	Nonadherent n (%)	P value
</= 2	60	50(83.3%)	10(16.7%)	0.52
>2	11	10(90.9%)	1(9.1%)	

DISCUSSION
In prevention of mother to child transmission of HIV not only timely initiation of ART but also adherence to therapy remains crucial. In India lack of antenatal visits and high prevalence of home deliveries amongst pregnant women increases the likelihood of missing a diagnosis of HIV infection in early stages of pregnancy. According to National Family Health Survey – 4 (NFHS-4, 2014-2015), 21% of Indian women had their deliveries at home. In women who were already on ART, change in residence and often caregiver at the time of delivery, change in lifestyle and ill health associated with delivery can all influence adherence to ART. Keeping the above factors in mind we conducted this study not only to study adherence to ART but also maternal health and its impact on infant's HIV status at a tertiary care Centre in North India.

Our study showed that most of the lactating mothers are doing well clinically and immunologically on ART at our Centre. Majority of the

mothers had good adherence to ART in our study and all the children were HIV uninfected till the point of assessment. However, anemia was predominant in our study population.

In our study majority of lactating women (80.8%) were < 30 year of age .The median age was 25 years (IQR 22-29.75). In the pregnant women the median age was 30(IQR 21-32). The age group is comparable to other studies conducted by Haas D et al at Malawi, Carter et al at Africa and Bailey H et al at Ukraine. There were 56.2% of enrolled subjects who have completed middle school education. In a similar study on pregnant women conducted at Ethiopia, by Ebuy H et al reported that 28.1% of pregnant women had completed middle school education which is less as compared to our study. We also found out in our study, 5.6% women were working. In India 28% of women were employed according to data from International labor organization (2013) (**57**).

Our study also showed 47.8% of husbands of enrolled mothers had >/= middle school education. Studies conducted by Maseko et al at Swaziland showed husbands of pregnant and lactating women on ART >/= Middle school education was 76% which is high compared to our study.

Most women in the study were healthy at time of enrollment and at the time of assessment. In our study 4.2% of enrolled women had Tuberculosis at the time of ART initiation. The national prevalence of TB in India among women in general population was 0.21%. The estimated HIV-TB co infection in India was 211/ lakh population. Mitku et al from Ethiopia in his study showed TB/HIV co-infection in adults on ART was 27.7%. Kamath R et al conducted a study in South India on HIV infected adults and observed 18.9% HIV positive cases were co-infected with tuberculosis in 2008-2012. Gupta et al at Maharashtra, India studied postpartum incidence of TB in lactating mother on ART and showed TB incidence of 5.0 cases per 100 person-years.

We also assessed nutritional status of pregnant and lactating women on ART and the results showed that most of women in our study were healthy except presence for the anemia. 85.29% of women in our study were anemic. Prevalence of anemia in women of reproductive age group in India is 53.1% and in pregnant women is 50.3% as per NFHS-4 report. In Tanzania, Isanaka et al in his study on pregnant women with HIV not on ART, the proportion of women who were anemic was 82% which is comparable to our study. The reason for such a high anemic prevalence in our study subjects may be lack of nutritional education, poor dietary intake and repeated childbirths.

Our study results show no HIV transmission among exposed infants at 6 weeks of age and in 43 children who completed 6 months of age. However, we cannot rule out further transmission of HIV in our infants as all of them continued to breastfeed at the point of assessment. Therefore, we cannot fully comment on final HIV status of infants. In Abidjan, Bequet et al in his study concluded early mixed feeding and EBF beyond 6 months increases the risk of mother to child transmission by 7.3% and 6.3%.

CONCLUSION
The enrolled pregnant and lactating women show a high level of adherence to ART. Even though most suffered from mild ART associated side effects, it did not affect adherence to ART. Maternal education status and husband as primary caregiver were significant predictors of maternal adherence to ART. Most mothers had a healthy BMI and absence of comorbidities at assessment. However, anemia was present in >80% of enrolled subjects. All infants tested negative for HIV at 6 weeks assessment. 43 reached 6 months assessment and all tested negative for HIV on that assessment.

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