ISSN: 2319-5967
ISO 9001:2008 Certified
International Journal of Engineering Science and Innovative Technology (IJESIT)
Volume 2, Issue 2, March 2013

Statistical Models of Postnatal Transmission of HIV Type I Infection from Mother to Child–An Indian Perspective

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Abstract:
Objectives: To characterize the Peadiatric HIV epidemic in India using a Statistical model, and to use this model to determine the reasons for the high HIV prevalence in infants and children up to 15 years age groups. Trends in Peadiatric HIV prevalence are significantly influenced by prevention of mother-to-child transmission (PMTCT) and HAART (Highly active antiretroviral therapy) programmes, and this study, therefore, also aims to assess the impact of the PMTCT and ART programmes.
Methods: Cohort data were secondarily collected from ART centers of Karnataka State, India. Inclusive criteria were applied for the model setting. A statistical model of HIV incidence in children and HIV survival has been created, using CMIS -data sources. The model projects the size of the population under the monthly intervals, non-AIDS mortality rates and annual numbers of births to mothers who are HIV-positive and HIV-negative are obtained from the ASSA model.
Results: Since rates of vertical transmission of HIV are dependent on the maternal CD4 count, and since uptake of HAART relative to short-course ARV prophylaxis will also depend on the pregnant women's CD4 count, it is necessary to estimate rates of vertical transmission that would be expected at different CD4 counts, and to re-express the effect of the short-course ARV regimens in terms of percentage reductions in transmission. Based on a review of CD4 distributions in pregnant HIV-positive Indian women, and relative rates of vertical transmission at different CD4 intervals, we estimate that the average rate of transmission at or before birth, in the absence of PMTCT, is 46.0% if the mother has a CD4 count less than 100-200 µ/dL, 19.80% if the mother has a CD4 count of 201 to <250 µ/dL, 8.60% if the mother has a CD4 count of 251 to350 µ/dL, and 2.5% if the mother has a CD4 count greater than >500 µ/dL
Conclusion: Research Study suggests that the PMTCT programme in India had a significant pediatric impact on HIV incidence, and that the recent adoption of new PMTCT protocols can be expected to lead about 75% reduction in Peadiatric HIV incidence by 2015.

Key Words: **ART, HAART, Prophylaxis, HIV, PMTCT, ASSA, PCR.**

I. INTRODUCTION

Several recent studies in India have suggested a higher level of HIV prevalence in children than is estimated by statistical models. A number of potential explanations for this high HIV prevalence in children have been suggested, including nosocomial transmission of HIV, HIV transmission as a result of sexual abuse, false positive reactions on HIV antibody tests, lower-than-expected rates of mortality in children infected with HIV, and higher rates of mother-to-child transmission NACO- 2009). This study aims to characterize the Peadiatric HIV epidemic in India using a statistical model, and to assess which of these explanations are most likely. A further objective is to evaluate the prevalence and impact of the prevention of mother-to-child transmission (PMTCT) and the Peadiatric antiretroviral treatment (ART) programme in Karnataka, and to assess how the impact of these programmes may change in the future.

II. MATERIALS AND METHOD

A statistical model of HIV incidence in children and HIV survival has been created, using ART Karnataka CMIS data sources. The model projects the size of the population under the age of 15 and infants , at monthly intervals, starting from 2005, non-AIDS mortality rates and annual numbers of births to mothers who are HIV-positive ,as well as HIV-negative are obtained from the ASSA, AIDS and Demographic model, a widely used model of the HIV epidemic. Estimates of HIV incidence in mothers are also obtained from the ASSA model, so that the model can allow for vertical transmission from mothers who seroconvert after their antenatal HIV screening visit. The model allows for two modes of HIV transmission in children under the age of 15: transmission from infected mothers at or before birth (Intrapartum or intrauterine transmission) and transmission from infected mothers after birth, as a result of breastfeeding. In the absence of PMTCT, women who are HIV-seropositive at the time of their first antenatal screening visit are assumed to have an average probability of transmitting the virus at delivery equal to 0.2, with the probability varying according to the mothers CD4 count.

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ISO 9001:2008 Certified
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A higher transmission probability applies if the mother becomes infected prior to delivery and seroconverts after her first antenatal visit. In the absence of PMTCT, women who are HIV-seropositive at delivery are assumed to have a constant HIV transmission probability per month of breastfeeding. If the woman acquires HIV while breastfeeding, a higher transmission probability is assumed to apply during the acute phase that follows HIV acquisition.(NACO 2007), it is assumed that 66.70% of undiagnosed HIV-positive mothers breastfeed and the median duration of breastfeeding is 21 months (CI 18.65-23.54%).

Assumptions about access to PMTCT and PMTCT uptake are based on CMIS System data collected from 2005 to 2010. The HIV transmission probability at birth is assumed to reduce by 82% if the mother receives single-dose nevirapine during labor. Women who are initiated on highly active ART (HAART) during pregnancy are assumed to have a 0.03 probability of transmitting the virus to their infants at birth. It is assumed that 50% of women who receive positive test results prefer formula feeds, 45.6% initially practice exclusive breastfeeding (which is assumed to reduce the risk of transmission per month of breastfeeding), and the remaining prefer mixed feeding from birth, for a median duration of 8-10 months. In women who know themselves to be positive and prefer practice exclusive breastfeeding (EBF), the median duration of EBF is assumed to be 4 months, after which women either practice abrupt weaning or switch to mixed feeding. If women receive HAART while breastfeeding, the monthly postnatal transmission risk is assumed to be reduced by 86%. If the mother does not receive HAART while breastfeeding, but the infant receives extended nevirapine (NVP) prophylaxis, the rate of transmission is assumed to be reduced by 60%.

III. RESULTS AND DISCUSSION

Demographic features of HIV infected women: Over 18 years of pregnant women and children from1- 18 months infants 15 years were considered for the study.78%were illiterate, 63.35% below poverty line, 10.65% were in high income group. The mean age of the pregnant women was 24.65±4.8 years with (IQR 21.25-26.14). 25% Pregnant women's families migrated from other parts of the state for seasonal employment .80% of the patients were heterosexual.Primigravida (55.26%), Gravida-II(13.26%) remaining were Gravida III and IV.Discordent couples (31.26%) was recorded. 82.36%patients husbands had seroconversion. Mean base line CD4 Count was 116.35±56.25 µ/dL (CI 102.23-123.65 %) before Initiation of HAART and increasing trend of CD4 Count were shown after one year of completion of HAART and at the onset of pregnancy CD4 count mean was 289±45.22 µ/dL(CI 265.20-301.28%), CD4 count was least for manifestation of Opportunistic infections and non AIDS defining illnesses . Lallemant M., et al.,(2004) found that if CD4 count <100 at initiation of HAART then there are more chances of transmission of HIV from mother to child.

IV. MODEL DESCRIPTION

AIDS vertical transmission rates in children are obtained from the ASSA model. The model produces estimates of, the annual MTCT probability for children aged *a* (in years) in year *t*. For children aged up to 1 year and older (2-15 years), the monthly transmission rate is assumed to be one twelth of the annual transmission rate, i.e at "q"

$$-\frac{1}{12}\ln(1-qat) \qquad (1.1)$$

However, for children under the age of 1 year, the annual MTCT probability is high and much of the mortality risk is concentrated in the first month of life. We therefore follow the approach of Nagelkerke *et al.*, (1995) and use a Weibull distribution to calculate the monthly MTCT rate from the mother receive single dose nevirapine with or without after delivery in the ASSA model. Suppose that *r* and *b* are the rate and shape parameters respectively for the Weibull distribution describing transmission of HIV from infected mother to child up to 18 months of age, i.e. the proportion of infants HIV transmit to age *a* (in years) is

$$\exp(-rab) \qquad (1.2)$$

Suppose that $q0t$ and $q01t$ represent the infant and children (2-15years) MTCT rates respectively in year *t*, i.e. the probabilities of HIV transmit infected mother to child by 12 months and 1 month respectively, then

$$q0t = 1 - \exp(-r) \qquad (1.3)$$

$$qo1t = 1 - \exp[(-r(1/12)b] \qquad (1.4)$$

From which it follows that

$$r = -\ln(1-qot) \qquad (1.5)$$

$$b = ln\left[\frac{\ln(1-q01t}{\ln(1-qot))}\right]\left[ln\frac{1}{12}\right]^{\frac{-1}{\leftarrow}} \qquad (1.6)$$

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ISO 9001:2008 Certified
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Substituting the values of $q0\ t$ and $q0\ t$ □ estimated from the Nagelkerke *et al* (1995) (0.0454 and 0.0198 respectively, for births in the preceding five years), gives $r = 0.0265$ and $b = 0.43$. For convenience, we use this value of b for all years, although the parameter might be expected to vary slightly over time. This makes it possible to estimate the monthly transmitting probabilities in each year, given only the $q0\ t$ values estimated by the ASSA model and the assumed value of $b = 0.43$.

Table (1): Probabilities of transmitting HIV, at of before birth by ASSA model. (N=100)

Antenatal care	Probability of Transmission
HIV-seropositive at 1st antenatal visit, no prophylaxis	0.621
Receiving single-dose nevirapine	0.140
Receiving AZT from 28 weeks	0.338
Receiving single-dose nevirapine and AZT from 28 weeks	0.245
Receiving highly active HAART –Started during pregnancy	0.446
HIV Seronegative at 1st ANC Visit	0.743
Not receiving ARV Prophylaxis	0.845

Table (2): Probabilities of transmitting HIV of African infants infected at 4-6 weeks, after birth to mothers on HAART.

Study	**Location**	**Timing of HAART initiation**	**HAART initiation criteria**	**n**	**% HIV+**
Peltier *et al* (2009)	Rwanda	28 weeks	None	532	1.1%
Homsy *et al* (2009)	Uganda	Before conception	CD4 <250, WHO stage III/IV	118	0.0%
Tonwe-Gold *et al* (2007)	Abidjan (Côte d'Ivoire)	During pregnancy	CD4 <200, WHO stage IV, CD4 <350 + stage III	107	1.0%
Palombi *et al* (2007)	Mozambique, Malawi, Tanzania	During pregnancy	None	809	0.8%
During pregnancy		None	341	1.2%	
Bera *et al* (2010)	East London (South Africa)	During pregnancy	CD4 <250, WHO stage IV	495	2.8%
Before conception		172		1.2%	
*Average transmission rate if HAART initiated during pregnancy			2.1%		
*Average transmission rate if HAART initiated prior to conception			0.6%		

V. INTRAUTERINE AND INTRAPARTUM TRANSMISSION

This section begins with a review of estimates of mother-to-child transmission at birth, in the absence of any intervention, and the effects of short-course antiretroviral prophylaxis, as well as antiretroviral treatment (ART) initiated for the mothers with CD4 Count >250µ/dL. Evidence on the probability of vertical transmission from mothers who acquire HIV in late pregnancy is also reviewed. Single dose NVP was given to the mothers after delivery in 1-6 hours. The DBS and Polymerase chain reaction test (PCR) were conducted at different intervals for screening of HIV.

ISSN: 2319-5967
ISO 9001:2008 Certified
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VI. TRANSMISSION PROBABILITY AT OR BEFORE BIRTH, IN THE ABSENCE OF ARV-PROPHYLAXIS.

Although there have been several studies in India that have estimated the proportion of pregnant women ,who transmit HIV to their children before or soon after birth, it is difficult to estimate the proportion of children who are infected intrauterine/intrapartum on the basis of these studies. This is because the PCR test typically does not yield a positive result until 18 months after HIV transmission has occurred. It is therefore necessary to wait for at least a month before one can reliably identify almost all of the infants who have been infected before or at birth. However, over this time period, some infants would have acquired HIV through breastfeeding, and might also be PCR-positive at the time of testing. This makes it difficult to identify the infants who were truly infected at or before birth. It is possible to estimate the proportion of children who become infected at or before birth, based on what is known about the rate of transmission through breast milk and the rate at which newly infected infants develop detectable virus. Suppose that $R(a)$ is the proportion of infants born to HIV-positive mothers, who test positive at age *a* (in months) on a PCR test, and further suppose that π is the proportion of infants, who acquire HIV at or before birth, in the absence of any antiretroviral prophylaxis (ARV), if *f* is the proportion of HIV-positive mothers who formula-feed exclusively $\beta(a)$ and is the probability that a breastfed child acquires HIV postnatally and has PCR-detectable virus by age *a*, then

$$R(a) = \pi + (1-\pi)(1-f)\beta(a) \quad (1.7)$$

if it is assumed that all of the infants infected at or before birth have PCR-detectable virus by age *a* (this would generally be the case for $a \geq 1.5$ (Newell et al.,1998)). From this it follows that

$$\pi = \frac{R(a) - (1-f)\beta(a)}{1-(1-f)\beta(a)} \quad (1.8)$$

Suppose that breast-fed infants acquire HIV at rate *h* and newly infected infants develop PCR-detectable virus at rate γ. Then

$$\beta(a) = \int_0^a h \exp(-ht)\,(1 - \exp\,(-\gamma(a-t))\,\mathrm{dt} \quad (1.9)$$

$$1 - \frac{\gamma \exp(-ha) - h\exp(-\gamma a)}{r-h} \quad (1.10)$$

The parameters *h* and γ have been estimated to be 0.014 × 1/12 and 2.0 per month respectively (see section1.3). In all of the studies considered here, *a* is 1.5 months, and hence is 0.012. relate only to women who were not receiving any antiretroviral prophylaxis. For all studies except the (Nduati *et al*, 2000), the results presented are based on a meta-analysis published by Leroy *et al* (2005) rather than the originally published results (Dabis *et al*, 1999; Wiktor *et al*, 1999; Coutsoudis *et al*, 1999b; Petra Study Team 2002). The average estimate of the proportion of infants who acquire HIV intrauterine or intrapartum is 19.7%, only fractionally lower than the proportion of infants who have detectable virus at the age of 4-6 weeks.

VII. INCLUDED IN THE UNCERTAINTY ANALYSIS (MEAN OF 0.35, STANDARD DEVIATION 0.08)

Since rates of vertical transmission of HIV are dependent on the maternal CD4 count, and since uptake of HAART compared to short-course ARV prophylaxis will also depend on the pregnant woman¨s CD4 count, it is necessary to estimate rates of vertical transmission that would be expected in each CD4 stage, and to re-express the effect of the short-course ARV regimens in terms of percentage reductions in transmission. Based on a review of CD4 distributions in pregnant HIV-positive Indian women, and relative rates of vertical transmission in different CD4 intervals, we estimate that the average rate of transmission at or before birth, in the absence of PMTCT, is 46.0% if the mother has a CD4 count less than 100-200 µ/dL, 19.80% if the mother has a CD4 count of 201 to <250 µ/dL, 8.60% if the mother has a CD4 count of 251 to350 µ/dL, and 2.5% if the mother has a CD4 count greater than >500 µ/dL, and 1.4% if the mother has a CD4 count greater than 500. The proportions of pregnant HIV-positive women in the CD4 <200, 200-349, 350-500 and >500 categories are estimated to be 14.0%, 24.9%, 24.5% and 36.6% respectively. Single-dose nevirapine is assumed to reduce the transmission probability by 40%, and when combined with AZT from 28 weeks (previous guidelines NACO), is assumed to reduce the probability by 80%. The efficacy of AZT alone is assumed to be 35%. It is assumed that the

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percentage reduction due to short-course ARV prophylaxis is the same regardless of the maternal CD4 count, as there is little consistency in the relationship between efficacy and CD4 count between different studies (Sperling *et al*, 1996; Shaffer *et al*, 1999; Lallemant *et al*, 2004).

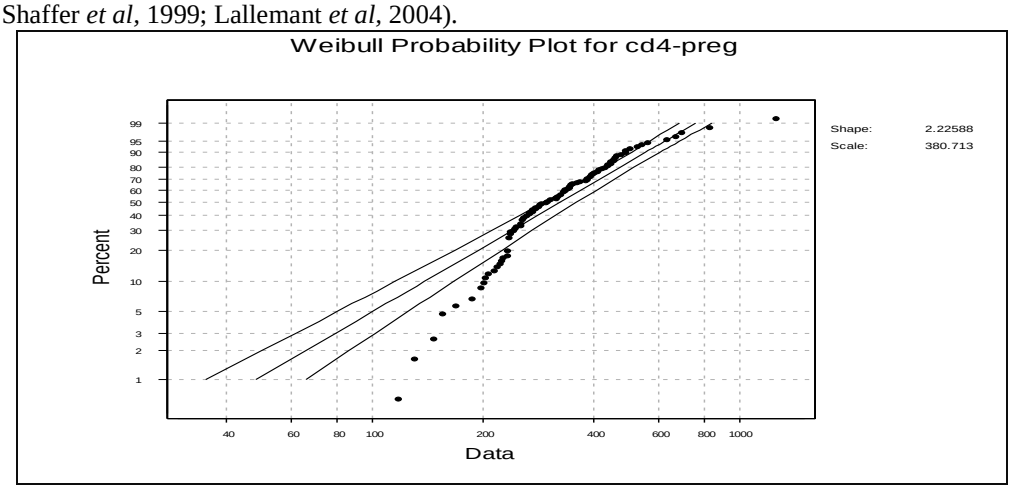

Fig (1): Shows Probability plot for base line CD4 count at the time of HAART Initiation of pregnant women (n=100)

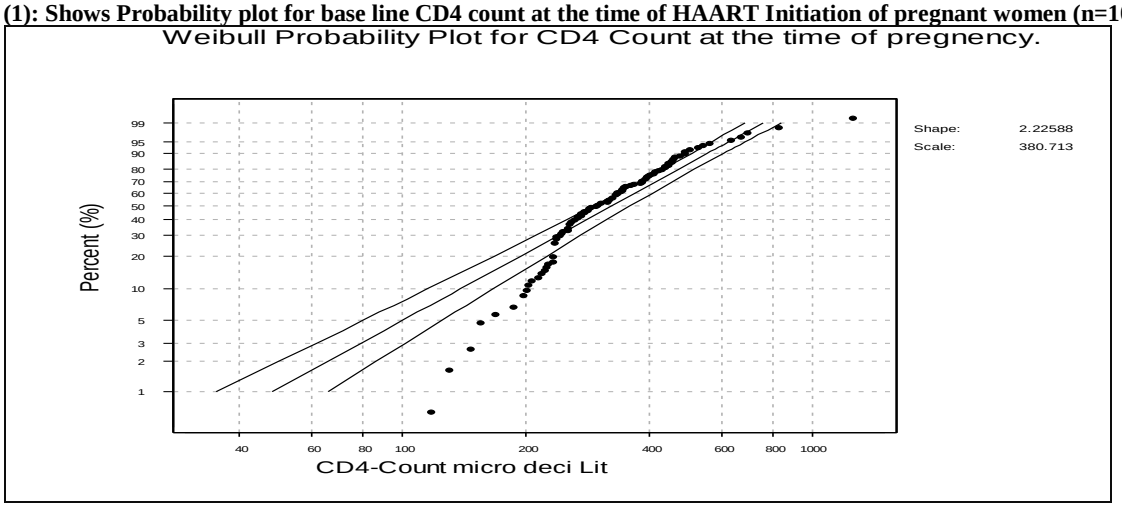

Fig (2): Shows Probability plot for CD4 count at the time of pregnancy (n=100)

VIII. DISCUSSION

In this research, a non-linear statistical model is proposed and analyzed to study the transmission of HIV/AIDS in a population of varying size with HAART treatments and vertical transmission under the assumption that due to with or without receive single dose NVP after birth and breast feeding, the infected babies are born to increase the growth of infective population directly. It is assumed that women in receiving PEP-single dose NVP classes are exposed and capable of producing children without HIV. By analyzing the model, we have found a parameter *h* newly infected infants develop PCR-detectable virus at rate "γ" and "a' is time interval.

The model equilibrium is also shown to be asymptotically stable under certain conditions. It is found that an increase in the rate of vertical transmission leads to increase the population of infectives which in turn increases the pre-AIDS and AIDS population. Thus, the vertical spread of the disease should be controlled by effective HAART treatment or promoting the condom use to keep the overall infective population under the control. This will help in reducing the transmission rate as well. Also by model simulation it is shown that by controlling the rate of vertical transmission, the spread of the disease can be reduced significantly consequently the equilibrium values of infective. Most other models have assessed the rate of mother-to-child transmission using the HIV prevalence in pregnant women at their first antenatal screening visit, and have ignored the very significant vertical transmission that can occur in women who seroconvert after their first antenatal visit, either before delivery or while breastfeeding. The high HIV prevalence estimated by our model is also partly due to the lower rate of transmission estimated in our analysis, particularly in children who acquire HIV at or before birth. Although it is possible that our model estimates of AIDS transmission rates are understated. This study

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concludes that, parameters of the model can be easily find out the prevalence rate and is an ability to derive the further algebraic treatment or derivation. Reliability, accuracy and the model equilibrium is consistently more adoptive. The outcomes of this study is help the Government and NGO's to establish policies, programmes and optimal plan for control of the disease by taking into account the aspect of treatment and vertical transmission. It helps the society in general to have an understanding on how the disease can be controlled through treatment of infectives with ARV. Also it is add more knowledge to the existing literature on HIV/AIDS and help Researchers to do more research on this disease.

ACKNOWLEDGEMENT

I grateful thanks to Karnataka State AIDS prevention Society, NACO-New Delhi for giving secondary data of ANC-Cases enrolled for ARV treatment and also I thanks to all the members of the scientific advisory group for their timely help in setting the model assumptions and in adding to the discussion of the model results.

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