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# A Retrospective Cohort Study on Protective Efficacy of Intrapartum Nevirapine Prophylaxis to Prevent Parent to Child Transmission of Human Immunodeficiency Virus in West Bengal.

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## ABSTRACT

**Background: :** In Prevention of Parent to Child Transmission (PPTCT) program in India, single dose Nevirapine was used for prevention of intrapartum transmission of HIV, but the protective efficacy of this regimen in Indian population is not beyond question. Objective: To analyze the protective efficacy of single dose Nevirapine prophylaxis in preventing mother to child transmission of HIV and comparing the effect of Nevirapine prophylaxis in different types of infant feeding practices and modes of delivery. **Methods:** A retrospective cohort study was carried out through analysis of secondary data during October 2010 to September 2011 from 16 Integrated Counseling and Testing Centers (ICTCs) having DNA-PCR (Polymerase Chain Reaction) collection facility in West Bengal among 224 babies born of HIV infected mothers, 168 unexposed (covered with intrapartum Nevirapine) and 56 exposed (not covered with intrapartum Nevirapine) to risk of transmission. HIV reactivity in babies was confirmed by DNA PCR of Dry Blood spot from 6 weeks age onwards. Data was entered and analyzed using Epi Info version 3.5.1 and Statistical Package for Social Sciences software version (SPSS 16.0). **Results:** About 10.12% of those received Nevirapine were found HIV reactive compared to 26.79% of those who did not. Overall Relative Risk of non coverage of Nevirapine for vertical transmission of HIV was 2.65 (95% CI : 1.42 – 4.95). Overall Attributable Risk was 62.22%. **Conclusion:** Since in 62.2% cases vertical transmission of HIV was prevented, additional regimen may be thought of for rest 37.8% cases.

***Keywords:*** HIV, Intrapartum transmission, Nevirapine.

## INTRODUCTION

The transmission of HIV from a HIV-positive mother to her child during pregnancy, labour, delivery or breastfeeding is called mother-to-child transmission. In the absence of any interventions; transmission rates range from 15-45%. This rate can be reduced to levels below 5% with effective interventions.

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The global community has committed itself to accelerate progress for the prevention of mother-to-child HIV transmission (PMTCT) through an initiative with the goal to eliminate new paediatric HIV infections by 2015 and improve maternal, newborn and child survival and health in the context of HIV.[1]

In 2013, about 67% of all pregnant women living with HIV in low- and middle-income countries received medicines that prevent transmission to their babies; which was increased from 47% in 2010, 56% in 2011 and 62% in 2012 respectively.[2]

The Prevention of Parent to Child Transmission of HIV/AIDS (PPTCT) programme was launched in India in the year 2002 following a feasibility study in 11 major hospitals in the five high HIV prevalence states. The National AIDS Control Organization (NACO) Technical Estimate Report (2012) estimated that out of 27 million annual pregnancies

in India, 34,675 occur in HIV positive pregnant women. In the absence of any intervention, an estimated cohort of 13,000 infected babies born annually. The PPTCT programme aims to prevent the perinatal transmission of HIV from an HIV infected pregnant mother to her newborn baby.[3]

To minimize mother-to-child transmission of HIV, several critical steps are required. The woman must present at an antenatal care unit; there must be continuity of care to ensure that pre-test counseling and HIV testing are offered and accepted; women must return for their test results; antiretroviral prophylaxis must be administered correctly; women must be screened and offered treatment for other possible risk factors for transmission; safe obstetric practices must be used; appropriate counseling about infant feeding must be offered; and there must be postnatal follow-up.[4]

As a part of ARV Prophylaxis in PPTCT program (under NACO), single dose Nevirapine was used for prevention of intrapartum transmission of HIV; a single dose of 200 mg oral tablet was given to the mother at the onset of labour and newborn babies receive 2 mg /Kg Nevirapine suspension within 72 hours of birth, or before discharge, whichever is first.[5]

The various studies conducted in different parts of the world revealed reduced transmission rates using different ARV prophylaxis regimen. Out of the multiple regimes that have been tested for prevention of vertical transmission of HIV, single-dose Nevirapine has emerged as one of the most convenient, cheap, and efficacious regimes.[5-12]

In India, perinatal single dose Nevirapine Prophylaxis is being practiced, but the protective efficacy of this regimen in the Indian population is not beyond question. The protective efficacy of this single dose Nevirapine is restricted to intrapartum HIV transmission. This hardly takes care of transmission occurring during antepartum and postpartum period (through breastfeeding).

With this background the present study was carried out with the objectives of to analyze the protective efficacy of single dose Nevirapine prophylaxis in preventing mother to child transmission of HIV infection; to compare the effect of Nevirapine prophylaxis in different types of infant feeding practices and in different types of delivery practices.

## MATERIALS AND METHODS

- Study type and design – Retrospective record based cohort study carried out through the analysis of secondary data.
- Study period and duration – One year (October 2010 to September 2011)
- Study Population – HIV exposed babies (i.e. babies born of HIV infected mothers) who were screened for HIV in 16 ICTC centers of West Bengal, equipped with DNA PCR sample collection facilities at that time and also geographically well distributed to cater the representative study population of the state.
- Study tools**:** A pre designed schedule; PPTCT register.
- Data source – Secondary data collected from records of Early Infant Diagnosis (EID) from 16 PPTCT centers mentioned.
- Study variables: Data regarding types of infant feeding practices (breast-feeding or replacement feeding) and types of delivery (normal delivery or caesarian section) were collected in addition to data of Nevirapine coverage of Mother –Baby pair and HIV reactivity of child.
- Screening technique:-All babies born of HIV infected mothers were screened by either DNA PCR of DBS (Dry Blood Smear) at 6 weeks age onward or Antibody detection (Rapid test) at 6 months of age onward. A negative result on either of the test excludes the presence of infection but positive result on rapid test is further confirmed by DNA PCR of DBS for the presence of HIV infection
- **Sample size : -** 224 out of which 168 unexposed (covered with Nevirapine Prophylaxis) and 56 exposed (not covered with Nevirapine Prophylaxis) to the risk of intrapartum HIV infection
- **Calculation of sample size:** - The sample size has been calculated by Epi Info, Version 3.5.1; considering 95% confidence Interval, 80% Power, 30% risk among exposed [3] and 12% risk among unexposed. A 3:1 ratio of unexposed to exposed has been considered for study, depending on available exposure status.
- Analysis tool: – Data was entered and analyzed using Epi Info version 3.5.1 and Statistical Package for Social Sciences software version (SPSS 16.0). Results were presented as percentages; Relative Risk (RR); Attributable risk (AR); and Chi-square test. P values less than 0.05 were considered statistically significant.
- Ethical consideration:- Anonymous data was used for analysis i.e. client`s registration code was used instead of name for collection of data and follow up. Confidentiality of data was maintained. Also, all the HIV screening under the PPTCT programme was done with the written consent as per NACO guideline
- Operational case definition:

1. **Exposed cohort**: Babies of HIV infected mothers where Mother-Baby pair did not receive intrapartum single dose nevirapine prophylaxis.
2. **Unexposed cohort**: Babies of HIV infected mothers where Mother-Baby pair received intrapartum single dose nevirapine prophylaxis.
3. **HIV reactive child**: A child who is diagnosed by DNA – PCR of dry blood spot for the presence of HIV infection (HIV 1 – DNA)
4. **HIV non-reactive child**: A child diagnosed either by DNA PCR of dry blood smear or Rapid Test

(Antibody detection) for the absence of HIV infection (HIV 1-DNA / anti HIV antibody).

## RESULTS

About 10.12% of those received Nevirapine were found HIV reactive compared to 26.79% of those who did not receive Nevirapine. Overall Relative Risk of non-coverage of Nevirapine for vertical transmission of HIV was 2.65 (95% CI: 1.42 – 4.95). Overall Attributable Risk Percent was found to be 62.22% [Table 1].

**Table 1: Distribution of Nevirapine coverage and HIV reactivity (n = 224).**

| Nevirapine coverage | Reactive N (%) | Non Reactive N (%) | Total N (%) |
|---|---|---|---|
| **Nevirapine not received(Exposed)** | 15 (26.79%) | 41 (73.21%) | 56 (25%) |
| **Nevirapine received (Unexposed)** | 17 (10.12%) | 151 (89.88%) | 168 (75%) |
| **Total** | 32 (14.29%) | 192 (85.71%) | 224 (100%) |

RR(Non coverage of nevirapine) = 2.65 (95% CI : 1.42 – 4.95); AR Percent = 62.22%

Statistically significant association (Chi Square = 9.53, df =1. p =0.002) was found between absence of single dose intrapartum Nevirapine coverage and HIV reactivity in children. Almost similar association (Chi Square = 9.51, df =1.p =0.002) was found between breast feeding and HIV reactivity. However, no statistically significant association (Chi Square = 0.55, df =1, p =0.457) was seen between type of delivery and HIV reactivity [Table 2].

**Table 2: Univariate analysis for determination of association (n = 224).**

| Variables | Chi Square | df | P value (2 – tailed) |
|---|---|---|---|
| Nevirapine Prophylaxis & HIV reactivity | 9.53 | 1 | 0.002 (Non-coverage of Nevirapine) |
| Infant Feeding Practice & HIV reactivity | 9.51 | 1 | 0.002 (Breast Feeding) |
| Type of Delivery & HIV reactivity | 0.55 | 1 | 0.457 |

Multivariate analysis also revealed that significantly increased risk of mother to child transmission of HIV was associated with non-coverage of intrapartum Nevirapine prophylaxis [Exp (B) = 2.71 (1.19 – 6.13)] as well as breast feeding [Exp(B) = 2.70 (1.21 – 6.02)] [Table 3].

In breast feeding cohort, 18.18% of those received Nevirapine were found HIV reactive compared to 34.48 % of those who did not receive Nevirapine. Relative Risk of non coverage of Nevirapine for vertical transmission of HIV was 1.90 (95% CI: 0.85 – 4.23) in this group and Attributable Risk was 47% [Table 4].

**Table 3: Multivariate Analysis (Binary Logistic Regression) for estimation of Odds (n = 224).**

| Variables | B | df | Sig | Exp (B) | 95% CI for Exp (B) |
|---|---|---|---|---|---|
| **Mode of Delivery (ref : Caesarian section)** | - 5 | 1 | 0.230 | 0.609 | 0.271 – 1.369 |
| **Nevirapine coverage (ref: nevirapine received)** | 0.997 | 1 | 0.017 | 2.71 | 1.197 – 6.137 |
| **Infant Feeding (ref: replacement feeding)** | 0.994 | 1 | 0.015 | 2.70 | 1.211 – 6.026 |
| **Constant** | -2.227 | 1 | 0.000 | 0.108 | |

**Table 4: Risk of vertical transmission of HIV vis-a- vis Nevirapine coverage in Breast Feeding Cohort (n = 73).**

| Breast feeding cohort | Reactive N(%) | Non Reactive N(%) | Total N(%) |
|---|---|---|---|
| Nevirapine not received | 10 (34.48%) | 19 (65.52%) | 29 (39.73%) |
| Nevirapine received | 08 (18.18%) | 36 (81.82%) | 44 (60.27%) |
| Total | 18 (24.66%) | 55 (75.34%) | 73 (100%) |

RR (Non coverage of Nevirapine) = 1.90 (95% CI : 0.85 – 4.23); AR Percent= 47.27 %

Similarly, in replacement feeding cohort, 7.26 % of those received Nevirapine were found HIV reactive compared to 18.52 % of those who did not receive Nevirapine. Relative Risk of non coverage of Nevirapine for vertical transmission of HIV was 2.55 (95% CI: 0.93 – 7.01). Here Attributable Risk was 60.5% [Table 5].

In the normal delivery cohort, 10.48% of those received Nevirapine were found HIV reactive compared to 19.51 % of those who did not receive Nevirapine. Hence, Relative Risk of non coverage of Nevirapine for vertical transmission of HIV was 1.86 (95% CI: 0.81 – 4.30) in this group. Here Attributable Risk was 46.30% [Table 6].

Similarly, in the caesarean section cohort, 9.52% of those received Nevirapine were found HIV reactive compared to 46.67 % of those who did not receive Nevirapine. Hence, Relative Risk of non-coverage of Nevirapine for vertical transmission of HIV was 4.90 (95% CI: 1.93 – 12.47). Here Attributable Risk was 79.6% [Table 7].

**Table 5: Risk of vertical transmission of HIV vis-a- vis Nevirapine coverage in Replacement Feeding Cohort (n = 151).**

| Replacement feeding cohort | Reactive N(%) | Non Reactive N(%) | Total N(%) |
|---|---|---|---|
| Nevirapine not received | 5 (18.52%) | 22 (81.48%) | 27 (17.88%) |
| Nevirapine received | 9 (7.26%) | 115 (92.74%) | 124 (82.12%) |
| Total | 14 (9.27%) | 137 (90.73%) | 151 (100%) |

RR (Non coverage of Nevirapine) = 2.55 (95% CI : 0.93 – 7.01), AR Percent = 60.80 %

**Table 6: Risk of vertical transmission of HIV vis-a- vis Nevirapine coverage in Normal Delivery Cohort (n = 146).**

| Normal delivery cohort | Reactive N(%) | Non Reactive N(%) | Total N(%) |
|---|---|---|---|
| Nevirapine not received | 8(19.51%) | 33 (80.49%) | 41 (28.08%) |
| Nevirapine received | 11 (10.48%) | 94 (89.52%) | 105 (71.92%) |
| Total | 19 (13.02%) | 127 (86.98%) | 146 (100%) |

RR (Non coverage of Nevirapine) = 1.86 (95% CI : 0.81 – 4.30), AR Percent = 46.30 %

**Table 7: Risk of vertical transmission of HIV vis-a- vis Nevirapine coverage in Caesarean Section Cohort (n = 78).**

| Caesarean Section Cohort | Reactive N(%) | Non Reactive N(%) | Total N(%) |
|---|---|---|---|
| Nevirapine not received | 7(46.67%) | 8 (53.33%) | 15(19.23 %) |
| Nevirapine received | 6 (9.52%) | 57 (90.48%) | 63 (80.77%) |
| Total | 13 (16.67%) | 65 (83.33%) | 78 (100%) |

RR (Non coverage of Nevirapine) = 4.90 (95% CI: 1.93 – 12.47), AR Percent = 79.6 %

Hence Attributable Risk reduction from replacement feeding to a breast feeding group was 13.5% (60.5 - 47 %) and from caesarean section to the normal delivery group was 33.3% (79.6 - 46.3 %).

## DISCUSSION

In the present study; out of 224 children, 168 (75%) received a single dose of Nevirapine; thereby remained unexposed to the risk of intrapartum transmission of HIV. Rest 56 (25%) did not receive Nevirapine prophylaxis; hence were exposed to the risk of intrapartum transmission of HIV. About 10.12% of those received Nevirapine were found HIV reactive compared to 26.79% of those who did not received Nevirapine. Similar findings were observed in various other previous studies in India and abroad.

A study at 3 sites of South Africa (Oct 2002-Nov 2004) revealed the 3-week HIV transmission rates ranged from 8.6% to 13.7% between sites; and the proportion of infants infected at 3-4 weeks among mothers who received nevirapine between 2 and 24 hours before delivery was 9.9% compared with 13.4% who took Nevirapine earlier or later and 14.2% who were not given nevirapine.[5]

In Pediatric, AIDS Clinical Trials Group (PACTG) 316 at several sites between May 13, 1997, and June 8, 2000;17 of 1174 infants were infected, giving a transmission rate of 1.5% and 5 (8%) of 64 evaluable women who had received single-dose nevirapine during labor had new nevirapine resistance mutations detected 6 weeks postpartum.[6]

In a study by Taha et al between April 1, 2000, and March 15, 2003, at 6 clinics in Blantyre, Malawi, Africa among all infants born to 894 women who were HIV positive, where 448 infants were assigned to NVP and 446 to NVP plus ZDV; mother-to-child transmission of HIV at birth was 8.1% in infants administered NVP only and 10.1% in those administered NVP plus ZDV; overall transmission at 6 to 8 weeks was 14.1% in infants who received NVP and 16.3% in those who received NVP plus ZDV.[7]

In another study by Taha et al (NVAZ study) in six clinics in the Blantyre area of Malawi between April 2000 and January 2002 among babies of 1119 Malawian women with HIV-1where 562 babies were allocated nevirapine and zidovudine and 557 were allocated nevirapine only; the overall rate of mother-to-child transmission at 6–8 weeks regardless of HIV status at birth was 15·3% in 484 who received nevirapine and zidovudine and 20·9% in 468 babies who received nevirapine only - a protective efficacy of 26·8%; and 34 (7·7%) babies who had nevirapine and zidovudine and 51 (12·1%) who received nevirapine only were infected —a protective efficacy of 36.4% among those who were positive at 6–8 weeks, but HIV negative at birth.[8]

In a multicentre study by Moodley et al from May 1999 to February 2000; HIV-infected pregnant women were screened at 11 maternity health institutions in South Africa; the overall estimated HIV-1 infection rates in 1307 infants by 8 weeks were 12.3% for Nvp; excluding infections detected within 72 h (intrauterine); new HIV-1 infections were detected in 5.7% of infants in the Nvp group; if Nevirapine intrapartum plus for 24–48 hours postpartum given. [9]

NIAID-sponsored HIVNET 012 randomized trial and 18-month follow-up of this trial at Uganda by Jacson et al, estimated risks of HIV-1 transmission was 8.2% at birth; 11.9% at 6-8 weeks postpartum; 13·1% by age 14–16 weeks and 15·7% by age 18 months respectively among babies of mothers receiving single-dose nevirapine.[10-11]

The Six-Week Extended dose Nevirapine (SWEN) studies were three separate clinical trials conducted

in Ethiopia, India and Uganda; 986 infants received single-dose NVP, and 901 received the six-week regimen; the six-week NVP regimen was found to be as safe as and more effective than single-dose NVP in reducing the rates of postnatal HIV transmission; at 6 weeks of age, SWEN infants had a 46% lower risk of HIV infection than the infants in the single-dose NVP arm (2.5% vs 5.3%) and at 6 months of age, SWEN infants had 20% lower risk of infection than single-dose NVP infants (6.9% vs 9.0%). The combined risks of post-natal HIV transmission in the SWEN arm *vs* the single-dose NVP arm were 3.7% vs 6.8% at 6 weeks and 8.0% *vs* 11.6% at 6 months, respectively.[12]

Most of the studies compared the efficacy of single dose nevirapine with another treatment arm such as Zidovudine and Nevirapine, Extended Nevirapine etc. Our study is unique in the sense that we have managed to capture the data of Nevirapine -naive HIV infected mother and her exposed child, hence our study has been able to estimate the efficacy (AR%) of single dose Nevirapine against complete absence of any prophylaxis.

## CONCLUSION

1. Intrapartum single dose Nevirapine was associated with a protective or risk lowering effect in regards to mother to child transmission of HIV.
2. Since by administration of single dose intrapartum Nevirapine, mother to child transmission of HIV infection can be prevented by 62.2% cases.
3. As breast feeding and normal delivery reduced the protective effect of Sd/- Nevirapine in 13.5% and 33.3% cases respectively, hence either additional ARV regimen may be used for these groups or replacement feeding and caesarian section may be practiced as much as possible.

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