**Prevention of Perinatal HIV I Transmission by Protease Inhibitor Based Triple Drug Antiretroviral Therapy Versus Nevirapine as Single Dose at the Time of Delivery**

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**Abstract**

In India, parent to child transmission is the most important source of HIV infection in children below fifteen years of age. Transmission of HIV from mother to child can occur even at low or undetectable HIV virus levels. CD4 count or HIV RNA levels should not be the determining factor when deciding whether to use antiretroviral drugs for prevention of perinatal transmission of HIV. Use of single dose nevirapine during labour, in prevention of parent to child transmission (PPTCT) programme for pregnant females with CD4 count > 250 cells/cumm has less efficacy in reducing perinatal transmission. And there are high chances of development of nevirapine resistance to both mother and baby after single dose nevirapine exposure. Short course Protease inhibitor(PI) based triple drug combination ART from 28 weeks till delivery for perinatal prophylaxis is effective in reducing perinatal HIV transmission. PI’s are safe in pregnancy and also have less chances of development of resistance when used for perinatal prophylaxis and stopped post delivery. Hence, it is opined that PI based combination ART should be offered to pregnant females in PPTCT programme, thereby preventing occurrence of paediatric HIV infection in India. This can have significant impact on the society at large.

**Introduction**

In India the National AIDS Control Programme (NACP) was launched in 1992, and is being implemented as a comprehensive programme for prevention and control of HIV/AIDS in India. India has the third largest number of people living with HIV/AIDS, with an estimated adult prevalence of 0.29 %.

The prevalence of HIV infection has shown a declining trend indicating the possible impact of sustained programme interventions. Currently Phase 3 of NACP (2007 – 2012) has the overall goal of halting and reversing the epidemic in India over the 5 year period and has placed highest priority on preventive efforts.

Parent to child transmission is the most important source of HIV infection in children below fifteen years of age. Pregnancy is a special situation which provides a unique opportunity for prevention of vertical transmission of HIV using various interventions. Parent to child transmission accounts for 5.4 % of HIV cases detected in India (NACO). The prevalence of HIV infection among pregnant women in the age group of 15 to 24 years is considered proxy for incidence of new infections in general population in India. The prevalence of HIV positive pregnant females is showing a declining trend (0.49 % prevalence among ANC clinic attendees, 2008 – 2009). Preventive needs of children are addressed under universal provision of prevention of parent to child transmission (PPTCT) services. The aim is to offer HIV testing to every pregnant woman in the country so as to detect all HIV positive pregnant women in the country, and eliminate transmission of HIV from mother to child. Between April and Dec 2009, 44 lac pregnant women have been tested for HIV under PPTCT programme of which 15, 089 were detected HIV positive. Among those detected positive pregnant women, 9398 (62.28 %) mother baby pairs received nevirapine prophylaxis, to prevent mother to child transmission of HIV.

According to current NACO guidelines, pregnant females with CD4 more than 250 cells /cumm and not eligible for ART, are given single dose nevirapine during labor to reduce perinatal transmission of HIV. Data from clinical trials have shown that maternal to child transmission rate with single dose nevirapine is about 12%, (Table 1).

Considering the transmission rate with single dose nevirapine about 12%, the estimated number of babies likely to be born with HIV infection will be around 1127 babies for 9398 pregnant women.

**Strategies for Use of Anti-Retroviral Drugs in Pregnancy**

Recommendations regarding HIV screening and treatment of pregnant women and prophylaxis for perinatal HIV transmission is rapidly evolving throughout the world reflecting changes in the epidemic and the science of prevention.

Anti-retroviral drug recommendations in pregnancy are divided into sections depending upon anti-retroviral status of women at the time women presents for care, as follows:

- **Maternal risk of disease progression and the benefits and risks of initiation of therapy for her own health**
- **Benefit of combination antiretroviral regimens for**

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Table 1: Maternal to child transmission rate of HIV with single dose nevirapine prophylaxis.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drugs and Dose</th>
<th>Mother to child transmission rate (MTCT) and efficacy</th>
</tr>
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<tbody>
<tr>
<td>HIVNET 012 trial Uganda</td>
<td>sdNVP vs ZDV</td>
<td>MTCT was 11.8% in sdNVP arm vs 20.0% efficacy;</td>
</tr>
<tr>
<td></td>
<td>No AP ARV</td>
<td>in ZDV arm at 6 to 8 weeks (42% efficacy);</td>
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<tr>
<td></td>
<td>Intrapartum:</td>
<td>Oral IP: sdNVP vs oral ZDV 25.8% in ZDV arm</td>
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<tr>
<td></td>
<td>Infant:</td>
<td>at 18 months (41%) efficacy).</td>
</tr>
<tr>
<td></td>
<td>sdNVP within 72 hours of birth (infant only) vs ZDV (1 week), infant only</td>
<td></td>
</tr>
<tr>
<td>SAINT trial South Africa Breastfeeding and formula feeding</td>
<td>sdNVP vs ZDV + 3TC</td>
<td>MTCT was 12.3% in sdNVP arm vs 9.3% in ZDV + 3TC arm at 8 weeks</td>
</tr>
<tr>
<td>No AP ARV</td>
<td>Oral IP: sdNVP vs ZDV + 3TC Infant: sdNVP within 48 hours of birth (mother and infant) vs ZDV + 3TC (1 week), mother and infant</td>
<td></td>
</tr>
</tbody>
</table>

sdNVP-single dose nevirapine; AP-antepartum; IP-intrapartum; ZDV-zidovudine; 3TC-lamivudine

- Preventing perinatal HIV transmission;
- Potential adverse effects of antiretroviral drugs for mother, fetus, and infant;
- The limited long-term outcome data for both infants with in utero antiretroviral exposure and for women who temporarily use antiretroviral drugs during pregnancy for prophylaxis of transmission; and
- The possibility of development of antiretroviral resistance, including the need for strict adherence to the prescribed drug.

The durability, tolerability, and simplicity of the medication regimen is of particular importance in order to preserve options in the future for those women who will be stopping medications following delivery; and for those women who meet standard criteria for initiation of antiretroviral therapy as per adult guidelines and will continue the regimen after pregnancy.2

A. Pregnant Women already on ART2

1. Pregnant women who are receiving and tolerating an antiretroviral treatment regimen that is currently effective in suppressing viral replication should continue on the same ART regimen; however, the use of efavirenz should be avoided in the first trimester of pregnancy due to risk of its fetal teratogenic effects.

2. Pregnant women who are receiving nevirapine-containing regimens with viral suppression and are tolerating the regimen well should continue therapy, regardless of CD4 count. Although hepatic toxicity is a concern in women who have CD4 count more than 200 / mm² when they first start a nevirapine containing regime, an increased risk of hepatic toxicity has not been seen in women who are already receiving nevirapine based therapy and have immune reconstitution with therapy.

3. If the pregnant woman has detectable viremia (e.g., > 500–1,000 copies/ml) on therapy, HIV antiretroviral drug resistance testing should be recommended.

B. Treatment Naive Pregnant Women eligible for ART2

HIV-infected pregnant women who meet standard criteria for initiation of antiretroviral therapy as per adult antiretroviral treatment guidelines (NACO) should receive standard potent combination antiretroviral therapy as recommended for non-pregnant adults, taking into account what is known about the use of specific drugs in pregnancy and risk of teratogenicity. For women who require initiation of therapy for their own health, treatment should be started as soon as possible including first trimester because the potential benefits of treatment for the mother outweighs potential fetal risk.

Efavirenz should be avoided in the first trimester of pregnancy due to fetal teratogenic effects.

C. Treatment Naive Pregnant Women with CD4 count > 250 cells/ cumm to prevent perinatal HIV transmission:

1. Perinatal HIV transmission and maternal HIV RNA copy number

Data from studies regarding the correlation of viral load with risk of perinatal transmission is conflicting. In Paediatric AIDS Control Trial group(PACTG 076), an HIV RNA threshold below which there was no risk of transmission was not identified.7 Although the risk of perinatal transmission in women with undetectable HIV RNA levels appears to be extremely low, transmission from mother to infant has been reported among women with all levels of maternal HIV RNA.8,10 Additionally, although HIV RNA may be an important risk factor for transmission, other factors also appear to play a role.11,12,13 Although there is a general correlation between viral load in plasma and in the genital tract, discordance has also been reported, particularly between HIV proviral load in blood and genital secretions, especially in the presence of other genital tract infections.14

If exposure to HIV in the maternal genital tract during delivery is a risk factor for perinatal transmission, plasma HIV RNA levels might not always be an accurate indicator of risk. However, because transmission can occur even at low or undetectable HIV RNA copy numbers, HIV RNA levels should not be a determining factor when deciding whether to use antiretroviral drugs for prevention of perinatal transmission.15-18

2. Mechanism of action of ART in reducing perinatal transmission

There are a number of mechanisms through which antiretroviral drugs can reduce perinatal transmission. One important mechanism is by decreasing maternal viral load in the blood and genital secretions via antenatal drug administration, particularly in women with high viral loads. However, antiretroviral drugs have been shown to reduce the risk of transmission even among women with HIV RNA levels <1,000 copies/mL.6,17,19

An additional mechanism of protection is pre-exposure infant prophylaxis provided by administration of antiretroviral drugs that cross the placenta from the mother to the infant, resulting in adequate systemic...
Nevirapine has a low genetic barrier to resistance, is likely to be particularly important during the infant’s passage through the birth canal, a time of intensive exposure to maternal genital tract virus. Post-exposure infant prophylaxis is provided through administration of drug to the infant after birth. This mechanism protects the infant from cell-free or cell-associated virus that might have obtained access to the fetal/infant systemic circulation through maternal-fetal transfusion during uterine contractions occurring in labor or through systemic dissemination of virus swallowed by the infant during passage through the birth canal. It is likely that efficacy of antiretroviral drugs in reducing perinatal transmission is multifactorial, and each of these mechanisms is contributory.23,24

3. Combination antiretroviral regimen for perinatal prophylaxis

Lessons from international clinical trials of short-course regimens for prevention of perinatal transmission of HIV have shown that, combination antepartum antiretroviral drug regimens are more effective than single-drug regimens in reducing perinatal transmission and should be recommended for use for maternal prophylaxis and offered to all pregnant women with HIV infection irrespective of viral load or CD4 count.20,21

4. Significance of anti-retroviral drug resistance in pregnancy

Pregnancy presents some special concerns related to the development of drug resistance. Preexisting resistance to a drug in an anti-retroviral prophylaxis drug regimen may diminish the efficacy of that regimen in preventing perinatal transmission. Development of resistance to drugs used during pregnancy for the prophylaxis of perinatal transmission may limit future maternal treatment options, or decrease the effectiveness of prophylactic regimens in the current pregnancy or future pregnancy. Additionally, if maternal resistance is present or develops and the resistant virus is transmitted, infant treatment options may be limited.

Antiretroviral drugs may be used during pregnancy solely for prophylaxis of perinatal transmission and discontinued after delivery in women who do not require therapy for their own health. This may increase the chance of development of drug resistance. This is more likely if regimens used for prophylaxis include drugs with significant differences in half-life such as nevirapine or efavirenz. NNRTI’s have longer half-life and drug levels can persist up to 1 to 3 weeks after stopping the drug. Efavirenz levels persist longer than nevirapine.13 If NNRTI’s are combined with two nucleoside analogue drugs, discontinuation of all regimen components simultaneously postpartum may result in persistent sub-therapeutic drug levels and increase the risk of development of NNRTI resistance.23

5. Resistance pattern with single dose nevirapine prophylaxis

Nevirapine has a low genetic barrier to resistance, with 1 point mutation (K103N) conferring resistance to nevirapine and to other NNRTI drugs. Furthermore, its long half-life, with blood levels detectable up to 21 days after a single dose in labor, increases selection pressure and risk of resistance.25 The rate of genotypic resistance after exposure to single-dose nevirapine has varied in studies, ranging from 15% to 75%.26-28

A recent study has examined the presence of resistant mutations in HIV-1-infected women receiving antiretrovirals limited to pregnancy. All women evaluated received zidovudine and lamivudine with 76% receiving nevirapine and 8% nevirapine. In women receiving dual or triple prophylaxis, postpartum rates of the M184V/I mutations were 65% and 29%, respectively. The decreased replication capacity of M184V-carrying viruses may be of clinical benefit. NNRTI resistance was identified postpartum among 38% of nevirapine recipients, whereas only 1% of PI recipients developed resistance. Thus, short course PI based ART regimens have low chances of development of resistance as compared to NNRTI’s.29 In the PACTG 316 study, addition of single-dose nevirapine to other background regimens (77% of women received antenatal combination antiretroviral therapy) still resulted in nevirapine resistance in 14 of 95 (15%; 95% CI, 8%–23%) women.26

In a study of virus from 67 South African women, using a sensitive allele-specific resistance assay, the K103N mutation was seen in 87% of women at 6 weeks and in 11% at 12 months after single-dose nevirapine exposure.30 Because nevirapine resistance mutations can be detected in the postpartum period in a significant proportion of women receiving single-dose intrapartum/infant nevirapine prophylaxis, the response to non-nucleoside-based combination therapy when later required for maternal health reasons has been a concern.31-34

The Optimal Combination Therapy After Nevirapine Exposure (OCTANE)/A5208 trial conducted in Africa compared nevirapine versus lopinavir/ritonavir-based therapy in women requiring therapy who had prior exposure to single-dose nevirapine prophylaxis. The results suggest that prior exposure to single-dose nevirapine within 24 months of initiating therapy may be associated with higher risk of viral failure with nevirapine-based therapy compared to lopinavir/ritonavir-based therapy.

In this study, significantly more women in the nevirapine arm (29, 24%) failed to achieve undetectable viral load (25) or died (4) compared to women in the lopinavir/ritonavir arm (8, 7%; 7 virologic failures and 1 death; p < 0.0005). Of those women with documented nevirapine resistance at the start of therapy, 38% (5 of 13) either had detectable virus or died.35

Nevirapine resistance mutations were detected at 6 weeks postpartum in 19% of antiretroviral-naïve women in HIVNET 012 and 15% of a subset of women receiving additional antiretroviral drugs during pregnancy in PACTG 316 who received single-dose nevirapine during labor.26,28

6. Recommendation for combination anti-retroviral regimen for perinatal prophylaxis

The strategy of antiretroviral prophylaxis for perinatal transmission of HIV should be, to use and adhere to an effective combination drug regimen to maximally suppress the viral replication and minimize the risk
of perinatal transmission, and also to reduce the potential for development of resistance when the anti retro viral drugs are used during pregnancy solely for prophylaxis of perinatal transmission and discontinued after delivery in women who do not require therapy for their own health.

The combination regimen for perinatal prophylaxis should contain 3 agents; 2 NRTIs and 1 NNRTI or PI. The preferred NRTI regimen in pregnancy based on efficacy studies in preventing perinatal transmission with large experience of use in pregnancy is zidovudine plus lamivudine. In addition to 2 NRTI's either an NNRTI or a PI can be included.

7. Nevirapine toxicity in women with CD4 more than 250 cells / cumm

Women initiating nevirapine with CD4 more than 250 cells / cumm, have increased risk of development of severe rash and nevirapine related hepatotoxicity, which can be severe life threatening and in some cases fatal. The development of severe nevirapine-associated skin rash has been reported to be 5.5 to 7.3 times more common in women than men and has been reported in pregnant women.

Other studies have found that hepatic adverse events with systemic symptoms (predominantly rash) were 3.2-fold more common in women than men. The degree of risk of hepatic toxicity also appears to vary with CD4 count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with CD4 counts >250 cells/mm3 were 9.8 times more likely than women with lower CD4 counts to experience symptomatic, rash-associated, nevirapine-related hepatotoxicity.

Pregnancy itself is a risk factor for liver enzyme elevation. Several early reports of death due to hepatic failure in HIV-infected pregnant women receiving nevirapine as part of a combination antiretroviral regimen raised concerns that pregnant women might be at increased risk of hepatotoxicity from nevirapine, compared to other antiretroviral drugs.

Nevirapine should therefore be used as a component of a combination regimen in this setting only if the benefit clearly outweighs the risk. Women with CD4 counts less than 250/mm3 can receive nevirapine-based regimens, and women who enter pregnancy on nevirapine regimens and are tolerating the regimens well may continue therapy, regardless of CD4 count.

8. Recommendation for PI based combination regimen for women with CD4 count more than 250 cells/mm3 for perinatal prophylaxis

Ritonavir-boosted PI-containing regimens have a higher genetic barrier to resistance. Results from French Perinatal survey (ANRS C001-EPF) strongly suggest that; exposure to PI based ART for prevention of mother to child transmission has no negative impact on response to a PI based HAART during subsequent pregnancies. PI’s are safe in pregnancy. Although there is slight increased risk of preterm births in women who received PI based combination therapy, data from studies suggest that PI based therapy was no more likely than non PI based regimens to be associated with spontaneous preterm births.

Due to the chances of nevirapine related adverse effects in pregnant females with CD4 count more than 250 cells / cumm, and the chances of development of NNRTI resistance if the prophylactic combination regimen would be stopped post-delivery, a PI should be recommended for use in the combination regimen with dual NRTI. Based on data from clinical trials, PI based regimens have high efficacy in reducing perinatal transmission. Maternal to child transmission rate with PI based combination ART is significantly low, about 0.4%. Also PIs are safe in pregnancy with low toxicity and less chances of resistance when used solely for perinatal prophylaxis and stopped post-delivery.

Lopinavir/ ritonavir is the preferred PI regimen for pregnant women because of its efficacy studies with adults and experience of use in pregnancy.

9. Duration of perinatal prophylaxis

Although most perinatal transmission occurs during the intrapartum period, 30-35% of transmission may occur in utero and majority of in utero transmission of infection is thought to occur later in pregnancy.

Women in the first trimester of pregnancy who do not require immediate initiation of therapy for their own health may consider delaying initiation until 10 to 12 weeks of gestation, because the fetus is most susceptible to the potential teratogenic effects of drugs during first 10 weeks of gestation and the risks of anti-retroviral therapy during that period are not fully known and the fact that most perinatal HIV transmission likely occurs late in pregnancy or during delivery. As per lessons from clinical trials, longer duration of antepartum antiretroviral prophylaxis (e.g. starting at 28 weeks gestation) is more effective than shorter duration (e.g. starting at 36 weeks gestation). Thus for women who do not require immediate initiation of therapy for their own health, prophylaxis should be provided from 28 weeks gestation till delivery.

10. Cost effectiveness of PI based combination ART for perinatal prophylaxis

The main concern while considering the implementation of use of PI based regimen for perinatal prophylaxis is the cost factor. We tried to calculate the cost of PI based prophylactic regimen per pregnant female. If we consider starting short course prophylactic regimen from 28 weeks to end of delivery, the effective duration of therapy would be about two months ART prophylaxis per pregnant female. The cost of the combination regimen of 2 NRTIs, zidovudine/ lamivudine combined with PI, lopinavir/ ritonavir in the dose of zidovudine 300 mg twice daily, lamivudine 150 mg twice daily and lopinavir/ ritonavir 400/100 mg twice daily will come around ₹ 6500 per month. If the prophylaxis is given from 28 weeks till delivery, i.e. about 2 months, the total cost of prophylaxis per pregnant female would be ₹ 13,000. As per data from clinical trials, MTCT rate is about 12% with use of single dose nevirapine for perinatal prophylaxis. So the number of babies likely to be born with HIV infection per 10,000 pregnant females who received single dose nevirapine prophylaxis during labour would be about 1200 HIV positive babies. If this is compared to PI based combination ART for perinatal prophylaxis
which has a low MTCT rate of about 0.4%, the likely number of HIV infected babies would be about 40 HIV positive babies, per 10,000 pregnant females. PI based combination ART has a greater potential of reducing vertical transmission, and can thus remarkably reduce the load of HIV positive children in the society. Also, children born with HIV infection, with prior nevirapine exposure during birth, have chances of nevirapine resistance and will require lifelong PI based ART if eligible for treatment. Considering the cost of lifelong ART for these HIV infected children, the cost of treatment of their opportunistic infections, the psychological and social impact on the children and their parents, and the problems faced by single parents in caring for their infected children; the cost of PI based prophylactic regimen stands meager.

**Conclusion**

The aim of PPTCT to eliminate the transmission of HIV from mother to child and thereby reduce pediatric HIV infection can be achieved by providing effective combination regimen to all pregnant females irrespective of their CD4 count or viral load.

Pregnant females already on ART should continue with the same regimen, but efavirenz should be avoided in first trimester. Pregnant females with CD4<250 cells/mm3 should be immediately started on ART, as per Adult NACO guidelines including first trimester, as maternal benefits outweigh fetal risks. Efavirenz should be avoided in first trimester due to fetal teratogenic risks. Pregnant females with CD4>250 cells/mm3 should be offered 3 drug combination PI based ART for perinatal prophylaxis to reduce mother to child transmission. NNRTI's should be avoided in PPTCT program in view of:

a. The chances of nevirapine toxicity in pregnant females with CD4>250 cells/mm3, and
b. The chances of NNRTI resistance when the regimen would be used for short course and stopped post-partum.

Zidovudine and lamivudine are the preferred NRTI's because of their efficacy and safety studies in pregnancy. Lopinavir/ritonavir is the preferred regimen in combination with NRTI's because of its efficacy studies in reducing maternal to child transmission and less chances of development of resistance when the regimen would be used solely for prophylaxis and stopped after delivery. As most perinatal transmission occurs late in pregnancy, the recommended duration of therapy effective in reducing perinatal transmission is from 28 weeks till delivery. The cost effectiveness of prophylactic regimen is supported by fact that, the regimen would be given for short course from 28 weeks till delivery (i.e. about 2 months); the PI based combination regimen is more effective than single dose nevirapine in reducing MTCT (PI, 0.4% MTCT, single dose nevirapine, 12% MTCT), thereby reducing the load of HIV positive children in the society; and thus reducing the cost burden of lifelong treatment of HIV positive children. The psychological and social problems faced by these HIV positive children and their families, the financial burden of treatment of these children on parents and society, can be avoided.

**Recommendations for ART in pregnancy**

1. Pregnant females on ART: Continue same ART. Efavirenz can be switched to Nevirapine or PI in first trimester.
2. Pregnant females with CD4 < 250 cells/cumm: Initiate ART as per adult ART guidelines by NACO, avoiding efavirenz in first trimester

**References**