

Prevention of mother-to-child transmission

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INTRODUCTION

Mother-to-child transmission (MTCT) is the most important source of human immunodeficiency virus (HIV) infection in children below the age of 15 years. It affects approximately 5,00,000 infants per year all over the world and is responsible for 1800 new infections in children daily, the majority of which are in developing countries. The rate of perinatal transmission is 15-25% in developed countries, and 25-45% in developing countries.^[1] In India, the Joint Technical Mission (2006) estimated that out of 27 million annual pregnancies, 189,000 occur in HIV-positive, pregnant women. An estimated cohort of 56,700 infected babies will be born annually in the absence of any intervention. The most affected states are Andhra Pradesh, Karnataka, Maharashtra, Tamil Nadu, and Manipur.^[2]

In 1994, the Pediatric AIDS Clinical Trials Group (PACTG) protocol 076 reported a decrease in the risk of MTCT by nearly 70% due to the administration of zidovudine (AZT) to women from the fourteenth week of pregnancy onwards and during labour, and to the newborn in the absence of breastfeeding.^[3] In non-breastfeeding populations, this regimen along with elective caesarean section decreased the transmission rate to $\leq 2\%$.^[4,5] Similar low vertical transmission has resulted with the use of highly active antiretroviral therapy by pregnant women.^[6] Still in resource-poor settings, the limitations for these regimens are the cost and complexity. The regimens should be cost-effective, easily approachable, with high efficacy and should cause no or lesser side effects without any risk of resistance.

In developing countries like India, it was believed that

husbands were mostly responsible for transmission of HIV in mothers through the sexual route and therefore, they are considered to be equally responsible for the transmission of HIV to their children. In India therefore, PMTCT is termed as PPTCT (prevention of parent-to-child transmission) so that mothers alone should not be blamed for HIV in their children. In India, the PPTCT program was started in 2002. Currently, there are more than 4000 Integrated Counselling and Testing Centres (ICTCs) in the country, most of these in government hospitals, which offer PPTCT services to pregnant women.

RATE OF TRANSMISSION OF HIV FROM MOTHER TO INFANT

The rate of perinatal transmission without intervention is 19-36%.^[7] Prenatal, intranatal and postnatal factors are responsible for MTCT. The rate varies in each scenario and these rates are important for the development of protective measures. Twenty-five to thirty-five per cent of total transmission occurs during the prenatal period, mainly in late pregnancy;^[8] while 70-75% of total transmission occurs during the intranatal period. Postnatal transmission is via breast milk and accounts for 10-16% of all transmission.^[9] The proposed mechanisms for intrapartum transmission are uterine contractions during labour that are responsible for micro-transfusion from constant massage of the placental bed and during labour exposure of the baby's mucocutaneous surface to maternal blood and cervical secretions. As per the Pediatric Virology Committee of the AIDS Clinical Trials Group in the United States, a child with a positive PCR within 48 h of birth has been infected *in utero* and a child who is PCR-negative at 48 h but positive 7-90 days after delivery indicates an intrapartum infection.^[10]

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FACTORS AFFECTING MOTHER-TO-CHILD HIV TRANSMISSION^[1]

Mother-to-child transmission of HIV-1 is multifactorial. Factors responsible for mother-to-child can be divided into five categories: (1) maternal factors, (2) virological factors, (3) obstetric factors, (4) fetal factors and (5) infant factors [Table 1]

STRATEGIES FOR MTCT PREVENTION:^[20]

The three-pronged approach to the prevention of MTCT is:

1. Primary prevention of HIV among parents.
2. Prevention of unwanted pregnancy in HIV-infected females
3. Core interventions to prevent MTCT by HIV-positive mothers

Primary prevention of HIV infection includes HIV education; safe-sex practices; avoidance of intravenous drugs and sharing contaminated needles; prevention, diagnosis and early treatment of sexually transmitted diseases; change in moral behavior and attitude of the community. This is the only method that is 100% effective in preventing HIV transmission to infants.

Prevention of unwanted pregnancy in HIV-infected females, which is the most effective means of preventing MTCT, requires the provision of voluntary counseling testing (VCT) services and voluntary, safe, and effective contraception, sterilization, or pregnancy termination.

Core MTCT prevention intervention consists of comprehensive maternal and child health services (antenatal, postnatal, and child health); voluntary counseling and testing

Table 1: Factors affecting mother-to-child HIV transmission

<i>Maternal factors</i>	
Maternal viral load ^[12-14]	Increased transmission risk with high maternal viremia, such as at the time of seroconversion and in advanced disease. But there is no viral load that can be regarded as safe. Local viral load in cervico-vaginal secretions may also be an important determinant of transmission risk during the intranatal period
Maternal immune status ^[15]	Lowered CD4+ cell counts or advanced disease increases the risk of transmission
Genital tract infections ^[16]	Genital lesions particularly due to ulcerative STDs, cause increased viral shedding leading to higher risk of transmission
Caesarean section	Unprotected sexual intercourse Increases the risk of genital infection and increases transmission
Antiretroviral treatment	Described in detail below
Nutritional factors	Antiretrovirals received during pregnancy or at the onset of labor decreases chances of transmission
Behavioral factors ^[17]	Low levels of vitamin A which maintain integrity of the vaginal mucosa or placenta may increases the risk
	Unprotected sexual intercourse with HIV-positive partner during pregnancy and cigarette smoking increase the risk
<i>Virological factors</i>	
Virus type	Risk is more with HIV-1 than with HIV-2 due to low infectivity and low viral load of HIV-2 virus
Viral prototype	Monocyte-macrophage tropic maternal virus is transferred more as compared to T-cell tropic phenotype
<i>Obstetric factors</i>	
Prolonged rupture of membrane ^[18]	Duration of labour does not appear to be as important as the duration of rupture of membranes, and the transmission risk is doubled with membranes ruptured for longer than four hours. There is a linear relationship of transmission with the duration of rupture of membrane with a 2% increase in risk for each hour increment
Invasive procedures	Episiotomy, vaginal tear and fetal blood sampling increases the risk
Other factors ^[19]	Chorio-amnionitis, abruption placenta, preterm delivery, traumatic delivery, use of fetal scalp electrodes and forceps delivery
<i>Fetal factors</i>	
Prematurity and twinning	Premature infants have immature immune systems and low levels of maternally derived HIV antibodies. Hence, they have increased susceptibility to intrauterine acquisition of infection. First-born twins have higher rates of infection than second-born twins
<i>Infant factors</i>	
Breastfeeding	Described in detail below
Other factors	Decreased acidity, decreased mucus, lower immunoglobulin A activity and thinned mucosa in gastro-intestinal tract and deficient in macrophage and T cell immune response may facilitate transmission

(VCT), antiretroviral prophylaxis; counseling and support for safe infant feeding and optimal obstetrical practices. The major focus is on antiretroviral prophylaxis in this article.

Antiretroviral regimens for prophylaxis

Due to the success of the Pediatric AIDS Clinical Trials Group (PACTG) protocol 076, various regimens have been developed [Table 2a and b]. In India, National AIDS Control Organization (NACO) has started to implement the single-dose-of-nevirapine (NVP) program in all the states beginning with the states with a high prevalence of HIV after the success of the HIVNET-012 study.^[21] PPTCT services cover about 10% of the pregnancies in the country and 2.1 million pregnant women accessed this service in 2001. Of these, more than 16,500 pregnant women were HIV-positive.

Recommendations for use of antiretroviral prophylaxis in various clinical situations^[29]

The following four scenarios should be considered while discussing HIV during pregnancy:

Scenario 1: HIV-1-infected pregnant women who have not received prior antiretroviral therapy: Recommendation

Standard clinical, immunological, and virological evaluation should be carried out. Recommendations for initiation and

choice of antiretroviral therapy should be based on the same parameters used for persons who are not pregnant, although the known and unknown risks and benefits of such therapy given during pregnancy must be considered and discussed. If the viral load is >1000 c (copies)/mL HAART including the three-part AZT regimen of PACTG 706, should be started. If the viral load is <1000 c/mL, HAART or only AZT may be given according to the PACTG 706 protocol [Table 2a]. In the first trimester of pregnancy, one may consider delaying the initiation of therapy until after 10-12 weeks' gestation because the risks associated with various agents taken during organogenesis are largely unknown.^[30]

Scenario 2: HIV-1-infected women receiving antiretroviral therapy during the current pregnancy: Recommendation

Women receiving antiretroviral therapy and whose pregnancy is recognized during the first trimester, should be counseled regarding the benefits and potential risks of antiretroviral administration during this period, and continuation of therapy should be considered. Women receiving antiretroviral therapy and whose pregnancy is identified after the first trimester, should continue therapy. AZT should be a component of the antenatal antiretroviral treatment regimen after the first trimester whenever possible, although this may not always be feasible.^[31] If

Table 2a: Antiretroviral regimens: Non-breastfeeding populations^[21]

Regimens	Schedule	Efficacy/transmission rate/comments
PACTG076/ANRS024 AZT	<i>Pregnancy:</i> from wk 14 100 mg 5 times daily <i>Intrapartum:</i> 2 mg/kg intravenous infusion over 1 h, continuous hourly IV infusion of 1 mg/kg <i>Postpartum Infant:</i> 2 mg/kg orally 6 hourly for 6 wks	18 months efficacy 68% 18 months transmission rate 8% Original regimen
<i>Regimens starting in late pregnancy</i>		
'Thai short course' ^[22] AZT	<i>Pregnancy:</i> from wk 36 300 mg twice daily <i>Intrapartum:</i> 300 mg 3 hourly	6 months efficacy 50% 6 months transmission rate 9%
PHPT, Thailand ^[23] AZT	Long-Short, Long-Long <i>Pregnancy:</i> from wk 28 300 mg twice daily <i>Intrapartum:</i> 300 mg 3 hourly <i>Postpartum Infant:</i> 2 mg/kg 6 hourly for 3 days or 6 wks Short-Long	6 months transmission rate 6% May be slightly better than 'Thai short course'
	<i>Pregnancy:</i> from wk 35 300 mg twice daily <i>Intrapartum:</i> 300 mg 3 hourly <i>Postpartum Infant:</i> 2 mg/kg 6 hourly for 6 wks	6 months transmission rate 8% Similar to 'Thai short course'

Table 2b: Antiretroviral regimens: breastfeeding populations^[20]

<i>Regimens starting in late pregnancy</i>		
CDC, W. Africa ^[24] AZT	Pregnancy: from wk 36 300 mg twice daily Intrapartum: 300 mg 3 hourly	6 mths efficacy 37% 3 mths transmission rate 17%
DITRAME/ ANRS 049a W. Africa ^[25] AZT	Pregnancy: from wk 36 300 mg twice daily Intrapartum: 600 mg Postpartum mother: 300 mg twice daily for 1 week	6 mths efficacy 38%; 6 mths transmission rate 18% Pooled 24 mths W African data CDC/DITRAME: 28% efficacy and transmission rate 22%
PETRA Arm A AZT + 3TC ^[26]	Pregnancy: from wk 36 AZT + 3TC twice daily Intrapartum: AZT 3 hourly/ 3TC twice daily Postpartum mother: AZT + 3TC twice daily for 1 wk Postpartum Infant: AZT + 3TC twice daily for 1 wk	6 wk efficacy 54% 6 wks transmission rate 7%
<i>Regimens starting in labour</i>		
PETRA Arm B ^[26] and SAINT ^[27] AZT + 3TC	Intrapartum: AZT 3 hourly/ 3TC twice daily Postpartum mother: AZT/3TC twice daily for 1 wk Postpartum Infant: AZT + 3TC twice daily for 1 wk	PETRA: 6 wk efficacy 39% 6 wk transmission rate 10% SAINT: 6 wk transmission rate 10% Programmatically attractive because of simplicity and relatively low cost
HIVNET 012 ^[28] and SAINT ^[27] NVP	Intrapartum: 200 mg at start of labour (HIVNET) or at hospital intrapartum (SAINT) Postpartum mother: 200 mg stat (SAINT only) Postpartum Infant: 2 mg/kg stat within 48 hours (SAINT) or 72 hours (HIVNET 012)	HIVNET 012: 14-16 wk efficacy 47%; 6 wks transmission rate 12% 12 mths efficacy 42%; 12 mths transmission rate 16% SAINT: 8 wks transmission rate 13%; very attractive because of simplicity and very low cost. Concerns over drug resistance in women who have access to ARV therapy

therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid the development of drug resistance.^[32] In case of NNRTI based regimen, stop NNRTI and continue NRTIs for 3-7 days so as to prevent drug resistance. Regardless of the antepartum antiretroviral regimen, AZT administration is recommended during the intrapartum period and for the newborn.

Scenario 3: HIV-1-infected women in labor who have had no prior therapy: Recommendation

Several effective regimens are available for intrapartum therapy for women who have had no prior therapy [Table 3]. If single-dose nevirapine is given to the mother, alone or in combination with AZT, consideration should be given to adding maternal AZT/3TC starting as soon as possible (intrapartum or immediately postpartum) and continuing for 3-7 days, which may reduce the development of resistance to nevirapine. In order to plan continuation of therapy, the

mother should have appropriate assessments (*e.g.*, CD4+ cell counts and HIV1 RNA copy number) in the immediate postpartum period.

Scenario 4: Infants born to mothers who have received no antiretroviral therapy during pregnancy or intrapartum: Recommendation

AZT should be initiated as soon as possible after delivery, preferably within 6-12 hours of birth as per the ACTG 076 protocol. Some clinicians use AZT in combination with other ARV drugs, particularly if a mother is suspected of having an AZT-resistant virus.^[33,34] Efficacy for infants is currently unknown. In the immediate postpartum period, the mother should have appropriate assessments (*e.g.*, CD4+ cell counts and HIV1 RNA copy number) to determine whether antiretroviral therapy is recommended for herself. Early HIV diagnostic testing should be done on infants so that if he or she is HIV-1 infected, treatment can be initiated as soon as possible.

Table 3: Regimens available for intrapartum therapy for women who have had no prior therapy

Regimen	Maternal	Infant
AZT	AZT 2 mg/kg IV 1 st hour, then 1 mg/kg IV until delivery	AZT syrup 2 mg/kg every 6 hourly for 6 weeks*
AZT/3TC	AZT: 600 mg orally at onset of labor, then 300 mg every 3 hourly 3TC: 150 mg orally at onset of labor, then 150 mg every 12 hourly	AZT 4 mg/kg every 12 hourly with 3TC 2 mg/kg every 12 hourly for 7 days
NVP/AZT	AZT: 2 mg/kg IV bolus, then 1 mg/kg/hr NVP: 200 mg at onset of labor	AZT 2 mg/kg every 6 hourly for 6 weeks with NVP 2 mg/kg at 48-72 hr (single dose)**
NVP	200 mg at onset of labour	NVP 2 mg/kg at 48-72 hr

*AZT (infants with < 35 weeks' gestation): 1.5 mg/kg IV or 2 mg/kg orally every 12 hr, then every 8 hourly and 2-4 weeks, **If NVP < 1hr prior to delivery, first infant dose should be given as soon as possible after birth and second infant dose at 48-72 hr

Special issues related to the transmission of HIV from mother to child

Pre-conceptional counseling and care for HIV-1-infected women of childbearing age^[35]

The Centers for Disease Control and Prevention (CDC), the American College of Obstetrics and Gynecology (ACOG), and other national organizations recommend offering preconception counseling and care as a component of routine primary medical care to all women of childbearing age. The purpose of preconception care is to improve the health of each woman prior to conception by identifying risk factors for adverse maternal or fetal outcome, providing education and counseling targeted to the patient's individual needs, and treating or stabilizing medical conditions to optimize maternal and fetal outcomes.

Mode of delivery

Elective cesarean section (CS) at 38 weeks of pregnancy before the onset of labor or rupture of membrane decreases transmission by 50-80%.^[36,37] This transmission rate is further reduced to 2% when elective CS is combined with AZT prophylaxis. However, in mothers who have viral load <1000 c/ml or have CS done after the onset of labor or rupture of membranes, there is no evidence of any benefit of CS in preventing perinatal transmission in fact, the risk of infectious complications increases 5-7 fold. So the decision of elective CS is based on the risk/benefit ratio.

Breastfeeding

The breast milk of HIV-infected mothers contains proviral HIV and free virus, as well as protective factors such as HIV antibodies and a glycoprotein that inhibits HIV binding to CD4+ cells.^[38,39] Despite the presence of these protective factors, a number of cases have been documented of transmission of HIV by breastfeeding.^[40] The risk appears to be more during the first 4-6 months.^[41] The risk of transmission is related to the duration of breast feeding, amount of virus in the breast milk, presence of HIV antibodies

in the milk and whether or not breastfeeding is exclusive or mixed with other supplementary feeds. Mastitis, breast abscess, cracked nipples; infants with thrush, prolonged breastfeeding, and primary infection during pregnancy are other risk factors. In developed countries, breastfeeding is discouraged, however, in developing countries where formula puts the infant at high risk for other infections, breastfeeding is critical for infant nutrition and survival.^[9]

Safety and adverse effects of antiretrovirals in pregnancy

Short-term safety and tolerance of antiretroviral prophylactic regimens has been demonstrated in all controlled clinical trials but data on long-term safety and on patterns of resistance is still being compiled. The following antiretrovirals should be avoided during pregnancy: Efavirenz (EFV), hydroxyurea, didanosine + stavudine (ddI + d4T), liquid amprenavir.^[42] EFV causes neural tube defects in the first trimester while ddI + d4T causes severe lactic acidosis and/or hepatotoxicity. Nevirapine (NVP) causes fatal hepatic necrosis when given to pregnant women with CD4+ cells counts > 250/mm³, although it appears safe at delivery with only a concern for resistance with a single dose. Early pregnancy-associated nausea and vomiting may cause difficulty in antiretroviral administration or may exacerbate gastrointestinal side effects. Hyperglycemia and diabetes mellitus have been reported among patients taking protease inhibitors.^[43]

Resistance

The frequency of NVP resistance is 60-70% with a single dose^[44] with higher rates of NNRTI resistance mutations, especially K103N. In one trial, 15-24% of the mothers had NVP resistance six weeks postpartum with a single dose, which was no longer detected at 12 months.^[45] But the probability that they were archived is supported by a lower rate of response to subsequent treatment with NVP-based HAART.^[46] With AZT, development of resistance requires 4-6 months and AZT-resistant strains are infrequently transmitted.^[47]

CONCLUSION

With the increase in pediatric HIV infection, there is a substantial impact on childhood mortality. MTCT not only increases the load of HIV-positive children on society, but also causes social problems by increasing the number of single parent-children or orphans after the death of one or both parents due to AIDS. Therefore, all pregnant women with HIV infection should be handled with utmost care, as there is a great potential of preventing HIV through vertical transmission. Antiretroviral prophylaxis either by combination therapy or a single agent, is recommended for all pregnant women with HIV-1 infection with careful and regular monitoring of the pregnancy and potential toxicities. In order to provide universal access to these services, further scale-up is planned up to the level of Community Health Centre and the Primary Health Centre, as well as in the private sector by forming public-private partnerships. Through these measures, NACO hopes to achieve the target of reducing the proportion of infants infected with HIV/AIDS by 50% by 2010. Still, the challenge for the future is to find the most cost-effective and feasible intervention to achieve 0% transmission of HIV from an infected mother to her child.

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Multiple choice questions

1. The rate of perinatal transmission without intervention is
 - a. 19 to 36%
 - b. 20 to 48%
 - c. 5 to 10%
 - d. 70 to 80%
2. As per the Pediatric AIDS Clinical Trials Group (PACTG) protocol 076, AZT should be started to pregnant women from
 - a. 20 weeks of gestation
 - b. 12 weeks of gestation
 - c. 14 weeks of gestation
 - d. 10 weeks of gestation
3. Following antiretroviral drugs should be avoided during pregnancy except
 - a. Efavirenz
 - b. Didanosine and Stavudine combination
 - c. Lamivudine
 - d. Hydroxyurea
4. The frequency of NVP resistance with single dose is
 - a. 60-70%
 - b. 20-30%
 - c. 50-80%
 - d. 3-40%
5. Nevirapine (NVP) causes fatal hepatic necrosis when given to pregnant women with
 - a. CD4+ cell count >100/mm³
 - b. CD4+ cell count <250/mm³
 - c. CD4+ cell count >250/mm³
 - d. CD4+ cell count >400/mm³
6. The risk of HIV transmission through breastfeeding appears to be greater during
 - a. First 2-3 months
 - b. First 4-6 months
 - c. First 1-2 months
 - d. First 8-10 months
7. All are the risk factors for MTCT except
 - a. Chorio-amnionitis
 - b. Abruptio placenta
 - c. Prematurity
 - d. Increased acidity of infant GI mucosa
8. Efavirenz if given during first trimester causes
 - a. Cardiac defects
 - b. Neural tube defects
 - c. Cleft lip
 - d. Skeletal defect
9. Primary prevention of HIV infection includes all except
 - a. HIV education
 - b. Safe-sex practices
 - c. Avoidance of intravenous drugs and sharing contaminated needles
 - d. Antiretroviral therapy
10. Elective cesarean section (CS) at 38 weeks of pregnancy before the onset of labor or rupture of membrane decreases transmission by
 - a. 50-80%
 - b. 80-90%
 - c. 10-20%
 - d. 5-10%

ANSWERS: 1 - a, 2 - c, 3 - c, 4 - a, 5 - c, 6 - b, 7 - d, 8 - b, 9 - d, 10 - a