Prevention of mother-to-child transmission of HIV - An overview

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With the human immunodeficiency virus (HIV) epidemic showing a shift towards women and young people, the increasing seroprevalence among women will result in an increase in the mother-to-child transmission of HIV. The vast majority of HIV-positive children worldwide acquire the infection through vertical transmission. The discovery of successful interventions that interrupt this transmission has been one of the greatest successes in AIDS research. The transmission of HIV from an infected mother to her child can be reduced to less than 2 per cent by intensive interventions in the antenatal, intranatal and postnatal periods. To achieve this low rate, primary prevention of HIV infection in parents-to-be, early identification of seropositivity in pregnant women, prevention of unwanted pregnancies, prevention of mother-to-child transmission of HIV by appropriate antiretroviral therapy, special interventions in maternal management during labour, appropriate care and follow up of the newborn, all play an important role. However, these approaches are not always possible in developing countries wherein currently 95 per cent of vertical transmission occurs. Several questions and challenges remain. These include choice, availability, affordability, duration, long-term safety of optimal antiretroviral agents to be used during pregnancy and early neonatal life and the issue of transmission via breastfeeds in situations where alternatives to breastfeeding are not available. The challenge is to find the most cost-effective and feasible intervention to achieve zero per cent transmission of HIV from an infected mother to her child.

Key words  Interventions - paediatric HIV - preventing mother-to-child transmission - vertical transmission

The HIV epidemic is showing a shift towards women and young people. In India, 39 per cent of adults living with HIV/AIDS are women. The increasing HIV prevalence among women will show an increase in mother-to-child transmission of HIV. Until 2002, over 4.3 million children have succumbed to the AIDS epidemic worldwide and in 2003 an estimated 7,00,000 children under the age of 15 yr became infected with HIV. The vast majority (>90%) acquired the infection from their mother through mother-to-child transmission (MTCT). In the absence of any intervention, rates of MTCT of HIV can vary from 15 to 30 per cent in the developed countries and can reach as high as 30 to 45 per cent in developing countries. This difference is mainly attributable to infant feeding practices in the developing world. Transmission during the peripartum period accounts for one to two-thirds of the overall transmission rate, depending on whether breastfeeding occurs or not. The peripartum and breastfeeding period has thus become the focus for efforts to prevent MTCT. The discovery of successful interventions that interrupt this transmission has been one of the greatest successes in AIDS research. Currently 95 per cent of vertical transmission occurs in the developing countries and the challenge in these...
settings is to find the most cost-effective and feasible intervention to prevent MTCT. The transmission of HIV from an infected mother to her child can be reduced to less than 2 per cent by intensive interventions that include combination therapy of potent antiretrovirals, obstetrical interventions including elective caesarean section at 38 wk and complete avoidance of breastfeeding. Throughout this document, HIV refers to HIV-1 since cases of mother-to-child transmission of HIV-2 are extremely rare.

**Vertical transmission**

Magnitude of the problem: In India, about 28 million deliveries occur annually, of which 84,000 deliveries would occur in HIV-positive women considering a national average of 0.3 per cent prevalence of HIV in pregnant women. Without any intervention, about 30-45 per cent of these babies will become infected with HIV. In the high prevalence states of Maharashtra, Tamil Nadu, Andhra Pradesh, Karnataka, Manipur and Nagaland, with more than 1 per cent HIV prevalence amongst pregnant women, there could be a much higher number of vertically infected babies being born annually. In developing countries, WHO/UNICEF’s child survival programmes on immunization, oral rehydration therapy, and effective case management of acute respiratory infections, promotion of breastfeeding, good weaning practices, family planning and growth monitoring achieved much. But the HIV/AIDS pandemic has reversed these gains to a large extent.

Efficacy of transmission: MTCT is by far the most significant route of transmission of HIV infection in children below the age of 15 yr. This can occur during pregnancy especially in the last trimester, during delivery, and postnatally during breastfeeding. The foetus can get infected in utero through maternal blood, transplacental haemorrhage, and infection via umbilical cord or via the gastrointestinal mucosa while swallowing infected amniotic fluid. Contact with the mother’s blood and/or secretions during labour and delivery increases the risk of HIV transmission to the infant. The efficiency of transmission through breast milk ranges between 16-29 per cent. Of the 30% of babies who get infected vertically, the relative frequency of timing of transmission is said to be as follows: 2 per cent early in gestation, 3 per cent late in gestation, 15 per cent during labour, 5 per cent in early postpartum period, and 5 per cent in late postpartum period. In the absence of any intervention, rates of MTCT of HIV-1 can vary from 15 to 30 per cent in developed countries and can reach as high as 30 to 45 per cent in developing countries. This difference can mainly be attributed to infant feeding practices in the developing world that comprise almost universally of breastfeeds for prolonged duration.

Factors affecting transmission: Maternal factors like seroconversion during pregnancy, advanced stage of the disease, concomitant malnutrition, micronutrient deficiencies, sexually transmitted diseases in the mother, poor adherence to antiretroviral therapy after initiation, are some important factors which increase the transmission in the antenatal period. In the intranatal period, factors like vaginal delivery, prolonged contact with maternal blood and cervico-vaginal secretions, prolonged rupture of membranes, chorioamnionitis, procedures that increase exposure of infant to maternal blood like instrumentation during delivery, episiotomy, foetal scalp electrode, are associated with increased risk of transmission. Prematurity is a risk factor for increased transmission probable due to thin skin, susceptible mucous membranes, immature immune functions and low levels of maternal antibodies in the premature infant. In the postnatal period breast feeding, feeding in the presence of cracked nipples or mastitis, feeding by both breast feeds and top feeds, continuation of breastfeeds for prolonged periods of time, seroconversion of the mother during postnatal period, high viral load, low CD4 cell count, all increase the risk of transmission of HIV. Prolonged breastfeeding continues to expose the child to HIV, and estimates of the additional risk of infection after three months (known as late postnatal transmission) range from is considerably high.

**Prevention:** For the large scale implementation of prevention of mother-to-child transmission, UNAIDS, UNICEF and WHO have identified 5 phases (Fig.):
termination of pregnancy, appropriate infant feeding recommendations, goes a long way in the prevention of unintended pregnancies in HIV-positive women and all women at risk. This requires strengthening of family planning services. Women considering pregnancy should be encouraged to determine their HIV status and the implications of pregnancy when infected with HIV.

**Phase 2**: This consists of antiretroviral prophylaxis to the mother antenatally and intranatally and to the baby postnatally. These antiretrovirals act by reducing the viral load in the mother (a lesser quantity of virus goes to the infant) and preventing the virus from “fixating” itself in the child (post-exposure prophylaxis).

**Phase 3**: This phase deals with issues related to replacement feeds versus breast feeds in the context of maternal HIV. It supports the mother-infant pair in conducting a successful method of feeding.

**Phase alpha**: This phase deals with the primary prevention of HIV through sex education, family planning education and avoidance of high risk behaviour. The best way to prevent MTCT is by preventing HIV infection in girls and women of childbearing age and the society at large.

**Phase omega**: This phase deals with support-care-protection package to the HIV infected mother, child and the family. Issues like *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis, early detection of tuberculosis and management, weaning food supplements, vitamin A supplementation, are considered.

**Main interventions for decreasing mother-to-child transmission:**

(i) **Antiretroviral therapy**

Antiretroviral therapy (ART) recommendations for HIV infected pregnant women are based on the principle that therapies of known benefit to women should not be withheld during pregnancy unless the risk of adverse effects to the mother, foetus or infant outweighs the expected benefit to the woman concerned. Antiretroviral therapy to the mother antenatally and intranatally, and to the baby postnatally has been one of the interventional strategies studied extensively in prevention of vertical transmission. The largest body of experience relating to efficacy and maternal and foetal safety has been gained with zidovudine (ZDV/AZT). Consequently, first-line treatment regimens in pregnant women should include ZDV whenever possible. On World AIDS Day 2003, WHO and UNAIDS released a detailed and concrete plan to reach the “3 by 5” target of providing antiretroviral treatment to three million people living with AIDS in developing countries and those in transition by the end of 2005. This is a vital step towards the ultimate goal of providing universal access to AIDS treatment to all those who need it. According to the “3 by 5 initiative” of the WHO, the key recommendations are:

(i) **Women who need ART for their own health should receive it**, following revised ART guidelines recently posted by WHO. The use of ART when indicated during pregnancy will improve the health of the mother and substantially decrease the risk of transmission of the HIV to the infant.

(ii) **Women who do not need treatment, or do not have access to treatment, should be offered antiretroviral prophylaxis to prevent MTCT using one of the drug regimens known to be safe and effective.**
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<tr>
<th>Study</th>
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<th>Post-partum infant</th>
<th>Median maternal CD4+ count /mm³ by arm at enrolment</th>
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<tr>
<td>PACTG 076/ ANRS 024 trial USA, France¹⁵</td>
<td>ZDV vs placebo</td>
<td>Long (from 14 wks), intravenous intrapartum</td>
<td>Long (6 wk)</td>
<td>538,560</td>
<td>Formula feeding</td>
<td>VTR 7.6% in intervention arm versus 22.6% in placebo arm at 18 m (68% efficacy) [363 infants]</td>
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<tr>
<td>Bangkok CDC short-course ZDV trial Thailand¹⁶</td>
<td>ZDV vs placebo</td>
<td>Short (from 36 wk), oral intrapartum</td>
<td>None</td>
<td>411,427</td>
<td>Formula feeding</td>
<td>VTR 9.4% in intervention arm versus 18.9% in placebo arm at 6 m (50.1% efficacy) [392 infants]</td>
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<td>Thai Perinatal HIV prevention trial Thailand¹⁰</td>
<td>ZDV different regimens, no placebo</td>
<td>Long (from 28 wk), Short (for 36 wk)</td>
<td>Long (for 6w), Short (for 3 days)</td>
<td>350,380</td>
<td>Formula Feeding</td>
<td>Short-Short arm was stopped. VTR 6.5% in long-short arm versus 4.7% in short-long arm at 6 m (statistical equivalence) [1079 infants]</td>
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<td>Ivory Coast CDC short-course ZDV trial Cote D’Ivoire²³, ⁵¹</td>
<td>ZDV vs placebo</td>
<td>Short (from 36 wk)</td>
<td>None</td>
<td>528,548</td>
<td>Breastfeeding</td>
<td>VTR 15.7% in intervention arm versus 24.9% in placebo arm at 3 m (37% efficacy) [230 infants]</td>
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<td>DITRAME / ANRS 049a trial Cote D’Ivoire, Burkina Faso²², ⁵¹</td>
<td>ZDV vs placebo</td>
<td>Short (from 36 wk)</td>
<td>Short (1 wk)</td>
<td>535,568</td>
<td>Breastfeeding</td>
<td>VTR 18.0% in ZDV arm, 27.5% in placebo at 6 m (38% efficacy), 21.5% versus 30.6% (30% efficacy) at 15 m; 22.5% versus 30.2% (26% efficacy) in pooled analysis with other Ivory Coast trial at 24 m [276 infants]</td>
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<tr>
<td>PETRA trial South Africa, Tanzania and Uganda¹⁰</td>
<td>ZDV + 3TC in 3 regimens vs placebo</td>
<td>Short (from 36wk)</td>
<td>Short (7 days)</td>
<td>435,475</td>
<td>Breastfeeding</td>
<td>VTR 14.9% at 18 m for antenatal/intrapartum/neonatal ZDV + 3TC, 18.1% for intrapartum/neonatal ZDV + 3TC, 20.0% for intrapartum ZDV + 3TC only and 22.2% for placebo [1413 infants]</td>
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<tr>
<td>French AZT + 3TC/ ANRS 075 trial France¹²</td>
<td>Open label, non randomised ZDV + 3TC</td>
<td>From 32 wk</td>
<td>3TC and ZDV for 6 wk</td>
<td>426</td>
<td>Formula feeding</td>
<td>VTR 1.6% [437 infants]; 5-fold lower than in controls receiving ZDV only</td>
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<td>Study</td>
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<td>Antenatal / Intrapartum</td>
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<td>Thai ZDV + 3TC trial Thailand⁶⁶</td>
<td>Open label, non randomised ZDV + 3TC</td>
<td>Short (from 34wk)</td>
<td>Long (ZDV 4 wk), 274</td>
<td>Formula feeding</td>
<td>VTR 2.8% at 18m [106 infants]</td>
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<tr>
<td>PACTG 316 trial (USA, Europe, Brazil, Bahamas)⁶</td>
<td>NVP vs placebo in women already receiving ZDV or ZDV plus other ART</td>
<td>Non-study ART antenatal Intrapartum; single NVP dose 200 mg versus ZDV (mother and infant)</td>
<td>Single dose 2 mg/kg within 72 h of birth plus non-study ART including ZDV</td>
<td>423,441</td>
<td>Breastfeeding</td>
<td>Trial stopped early due to very low VTR in both arms. VTR 1.4% in intervention arm versus 1.6% in placebo arm [1248 infants]</td>
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<tr>
<td>HIVNET 012 trial Uganda²⁵²⁷</td>
<td>NVP vs ZDV</td>
<td>No antenatal ART Intrapartum: single dose NVP 200 mg versus oral ZDV</td>
<td>Single dose NVP 2 mg/kg within 72 h of birth versus short ZDV (7 days)</td>
<td>426, 461</td>
<td>Breastfeeding</td>
<td>Placebo arm was stopped, VTR 15.7% in NVP arm versus 25.8% in ZDV arm (41% efficacy), at 18 m [451 infants]</td>
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<tr>
<td>SAINT trial South Africa⁶⁶</td>
<td>NVP versus ZDV + 3TC</td>
<td>No antenatal ART Intrapartum: single dose NVP 200 mg versus short ZDV (48 h of birth versus short ZDV)</td>
<td>Single NVP dose within 48 h of birth versus short ZDV + 3TC (7 days) (mother and infant)</td>
<td>384,404</td>
<td>Breastfeeding and formula feeding</td>
<td>VTR 12.3% in NVP arm versus 9.3% in ZDV + 3TC arm at 8 wk [1301 infants]</td>
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<tr>
<td>DITRAME Plus/ANRS 1201.0 trial Abidjan, Cote D'Ivoire²⁸</td>
<td>Open label, ZDV boosted by single dose NVP</td>
<td>ZDV from 36 wk, NVP one dose at onset of labour</td>
<td>Infant single dose NVP, plus one week ZDV</td>
<td>370</td>
<td>Breastfeeding and formula feeding</td>
<td>VTR at 6 wk 6.4% [331 infants]</td>
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<tr>
<td>DITRAME Plus/ANRS 1201.1 trial Abidjan, Cote D'Ivoire³⁰</td>
<td>Open label, ZDV + 3TC boosted by single dose NVP</td>
<td>ZDV + 3TC from 32 wk (stopped at day 3 post partum), NVP one dose at onset of labour</td>
<td>Infant single dose NVP, plus one week ZDV</td>
<td>439</td>
<td>Breastfeeding and formula feeding</td>
<td>VTR at 6 wk 4.6% [99 infants]</td>
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<td>SIMBA trial Rwanda, Uganda⁵³</td>
<td>NVP vs 3TC postnatally in neonates exposed antenatally to ZDV + ddI</td>
<td>ZDV + ddI from 36 wk to 1 wk postpartum</td>
<td>NVP once then twice daily versus 3TC twice daily while breastfeeding</td>
<td>423, 432</td>
<td>Breastfeeding for 3-5 months</td>
<td>VTR at 6 months 7.8% (no difference between the two arms) Postnatal (6 wk - 6 months) transmission rate 0.9% [397 infants]</td>
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<tr>
<td>NVAZ trial Malawi¹¹</td>
<td>Neonatal NVP vs NVP + ZDV</td>
<td>None (late comers)</td>
<td>Single dose NVP right after birth; ZDV twice daily for one week</td>
<td>Not reported</td>
<td>Breastfeeding</td>
<td>Overall VTR at 6-8 wk, 15.3% in NVP + ZDV arm and 20.9% with ZDV only. VTR at 6-8 wk in infants who were negative at birth 7.7% and 12.1%, respectively (36% efficacy) [952 infants]</td>
</tr>
</tbody>
</table>
(iii) The most efficacious regimen among those recommended for prevention of MTCT for women with HIV who do not need ART is zidovudine from 28 wk with single dose nevirapine (NVP) at onset of labour for the mother and single dose NVP plus one week ZDV for the infant.

(iv) Alternative but less efficacious regimens include one based on ZDV alone (from 28 wk of pregnancy and through labour for the mother and for one week for the infant), one using the combination of ZDV plus lamivudine (3TC) (from 36 wk of pregnancy, through labour and one week postpartum for the mother, and for one week for the infant), and a regimen comprising a single dose of NVP to the mother and to the infant (which does not need to be initiated until labour).

(v) The selection of the ART regimen should be made at the national level based on issues of efficacy, safety, drug resistance, feasibility, and acceptability.

In February 1994, the Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076\textsuperscript{15} demonstrated that a three-part regimen of ZDV could reduce the risk for mother-to-child HIV-1 transmission by nearly 70 per cent. Studies conducted in Thailand using short course ZDV regimen for MTCT have indicated that this regimen could prevent many HIV-1 infections during late pregnancy and labour in less-developed countries unable to implement the full 076 regimen and can be successful if effectively implemented and complemented with other preventive interventions\textsuperscript{16}. However, keeping in mind the practical difficulties of offering HIV testing and counselling in overcrowded antenatal clinics in Indian hospitals compounded by the apprehension that this procedure may expose the antenatal women to the risk of social discrimination leading to poor acceptance of the intervention, the National AIDS Control Organisation (NACO), Ministry of Health and Family Welfare, Government of India (GOI), initiated a feasibility study on prevention of mother-to-child transmission using the short course regimen of ZDV\textsuperscript{17}. Between April 2000 and July 2001, intervention for PMTCT was initiated among consecutive antenatal attendees at 11 institutions selected from the 5 high prevalence states namely Maharashtra, Tamil Nadu, Karnataka, Andhra Pradesh and Manipur. During 173 months (average of 15.7 months at each institution) of the study, active group education, counselling of women and their husbands, HIV testing, cost-free ZDV for seropositive women, intra- and post-partum services were offered. Out of 103,681 women tested for HIV-1/2, 1724 (1.7\%) tested seropositive. Despite efforts of project staff at these institutions only 43.6\% of seropositive women took ZDV prophylaxis, the major reasons for lower recruitment for ZDV being: intention of women to return to their parents’ town during the third trimester as is the custom in most communities, refusal of women/family to take ZDV, etc. 82 per cent of seropositive women delivered a full-term normal baby vaginally. Only 18 per cent women had a lower segment caesarean section (LSCS) delivery due to indications other than as a mode of reducing MTCT. Informed choices were offered at counselling sessions and only 22 per cent opted for breast feeding at birth and the number remained consistent even at 2 months of age. The women who breastfed their babies for 2 months did not encounter any infant mortality as compared with those babies who were top fed. The predominant cause of death among top fed babies was diarrhoeal diseases. The study showed that the MTCT rate was reduced to 8.4 per cent at birth or 10.1 per cent at age two months. The cost effectiveness of the programme, as measured by the number of HIV infections averted in the babies born to seropositive women, may not be high since the prevalence of HIV in the community in most parts of the country is still low, hence, the number of new born HIV infections averted would also be very low. However, as seen in this study, the programme becomes cost-effective when primary prevention among 98.3 per cent HIV seronegative antenatal women is considered as an important outcome indicator. The cost of the intervention was determined at Rs.175 per woman. Since the feasibility study has established that PMTCT is a cost-effective strategy for prevention and control of the epidemic, it is recommended that NACO, GOI should expand the strategy to a programme level across the country\textsuperscript{17}.

The only combination drug prophylaxis that has been assessed to date for long-term efficacy at
18 months is ZDV + 3TC in three different regimens\(^1\). The antepartum + intrapartum + postpartum ZDV + 3TC regimen was the only one to show a sustained effect. NVP is the only non-nucleoside reverse transcriptase inhibitor (NNRTI) that has been studied in pregnancy. In recent years, the use of nevirapine has attracted considerable attention because of its demonstrated efficacy in clinical trials in reducing MTCT, its low cost and ease of use as also for the fear of high rates of mutations associated with resistance to NNRTIs following its use in PMTCT protocols. Further, Boehringer Ingelheim and FDA have notified healthcare professionals of new safety information added to the warnings for viramune (nevirapine) cautioning about severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure\(^\,19\). Women with CD4 counts >250 cells/mm\(^3\), including pregnant women receiving chronic treatment for HIV infection, are at considerably higher risk of these events\(^\,19\). Ritonovir (RTV), nelfinavir (NFV), indinavir (IDV) and saquinavir (SQV) have been studied pharmacokinetically in pregnant women and shown to be well tolerated. NFV, followed by SQV, are the most common protease inhibitors (PI) used to treat HIV infected pregnant women in resource-rich countries\(^\,20\). The design and efficacy of the various short course ARV drug regimens evaluated to date for the prevention of peripartum MTCT are presented in Table\(^\,21\).

Short-term efficacy, as determined by infant infection status at 6-8 wk of life, has been demonstrated for short course prophylactic to ARV drug regimens comprising: ZDV alone\(^\,16,22,23\), ZDV together with 3TC\(^\,18,24-26\), NVP alone in two single-dose regimens to the mother and the infant\(^\,25,27\), ZDV boosted by single-dose NVP\(^\,28,29\), and ZDV+3TC boosted by single-dose NVP\(^\,30\).

In a recent trial from Malawi evaluating post-exposure prophylaxis (PEP) of either single-dose NVP or single-dose NVP plus 1 wk ZDV given to infants born to mothers who had not received antenatal or peripartum ARV prophylaxis, showed that the combination of NVP+ZDV was significantly more effective as PEP than NVP alone\(^\,31\). With the exception of this trial, all other regimens evaluated to date include an intrapartum component, and varying durations of antepartum and/or neonatal and sometimes maternal postpartum prophylaxis. There are conflicting data as to whether receipt of combination antiretroviral therapy during pregnancy is associated with adverse pregnancy outcomes such as preterm delivery. The potential harm to the foetus from maternal ingestion of a specific drug depends not only on the drug itself, but on the dose ingested, the gestational age of the foetus at exposure, the duration of exposure, the interaction with other agents to which the foetus is exposed and to an unknown extent, the genetic makeup of the mother and foetus. Because the period of organogenesis (when the foetus is most susceptible to potential teratogenic effects of drugs) is during the first 10 wk of gestation and the risks of antiretroviral therapy during this period are unknown, it is advisable to delay initiation of therapy until after the first trimester of pregnancy is over. Until more information is available, HIV-1 infected pregnant women who are receiving combination therapy for their HIV-1 infection should continue their provider-recommended regimen. They should receive careful, regular monitoring for pregnancy complications and for potential toxicities. Although mitochondrial dysfunction has been found to be associated with perinatal antiretroviral exposure in rare instances, it should be compared against the clear benefit of antiretroviral prophylaxis in reducing transmission of a fatal infection by 70% or more\(^\,4,32,33\). Mitochondrial dysfunction should be suspected in HIV uninfected children with perinatal antiretroviral exposure who present with neurologic findings of undetermined etiology. This emphasizes the importance of long-term follow up for any child with in utero exposure to antiretroviral drugs. The clinical significance of the emergence of resistance in the context of MTCT prevention programmes is as yet unknown, particularly with regard to future treatment options for the mother or the child, or to the outcome of prophylaxis during a subsequent pregnancy if the same drug is used. The WHO Technical Consultation in October 2000 carefully reviewed the available information and concluded that the benefit of decreasing mother-to-child HIV transmission with these antiretroviral drug prophylaxis regimens greatly outweighed concerns related to development of drug resistance\(^\,34\).
(ii) Elective lower segment caesarean section (LSCS)

Labour and delivery management of HIV infected pregnant women should focus on minimizing the risk for both perinatal transmission and the potential for maternal and neonatal complications. Caesarean delivery (elective or scheduled) performed before onset of labour and rupture of membranes has been found to be associated with a significant decrease in perinatal HIV-1 transmission. In a prospective study conducted in the perinatal clinic of a university affiliated maternity hospital in Mumbai, which included a four-pronged intervention consisting of the use of a shorter course with a lower dose of ZDV (as compared to the original ACTG 076 protocol) 400mg/day for the last 6 wk of antenatal period, coupled with elective caesarian section before the rupture of membranes, oral ZDV powder to the infant for 6 wk following delivery (due to unavailability of oral suspension at the time of the study) and complete omission of breast milk, a striking success in reduction of perinatal transmission was noted. (Transmission rates of 5.8% as against 24% in those who had not received any form of perinatal intervention) However few centres in the developing countries will have the capacity to perform safe operative deliveries on a large scale and hence may not be justifiable solely for the purpose of preventing HIV transmission. Nonelective cesarean delivery (performed after onset of labour or rupture of membranes) is not associated with a significant decrease in transmission compared with vaginal delivery.

Further studies are needed to determine whether elective cesarean delivery provides significant benefit in infected women with a low or undetectable viral load who are receiving combination antiretroviral therapy. Any benefit must be weighed against the known increased risks to the woman with cesarean section compared with vaginal delivery, i.e., a several fold increased risk of postpartum infections, including uterine infections and pneumonia, anaesthesia risks, and surgical complications. Although the risk for perinatal transmission in women with HIV-1 viral loads below the level of assay quantitation appears to be extremely low, transmission from mother-to-infant has been reported among women with all levels of maternal HIV-1 viral loads. Results of epidemiologic and clinical trials suggest that women receiving ART regimens that effectively reduce HIV RNA to <1,000 copies/ml or undetectable levels have very low rates of perinatal transmission. Given the variability in quantification of HIV-1 RNA levels at low copy numbers, the variety of lower limits of quantification of the tests, and the similarly low levels of perinatal transmission of HIV-1 at levels <1,000 copies/ml, the American College of Obstetricians & Gynecologists (ACOG) has chosen 1,000 copies/ml as the threshold above which to recommend scheduled caesarean delivery as an adjunct for prevention of transmission. However, since transmission can occur even at low or undetectable HIV-1 RNA copy numbers, viral load levels should not be a determining factor when deciding whether to use ZDV for chemoprophylaxis.

(iii) Infant feeding

Breastfeeding is normally the best way to feed infants with its benefits going far beyond sound nutrition, unfortunately, both cell-associated and cell-free virus has been detected in breast milk from HIV infected mothers. The efficiency of transmission through breast milk ranges between 16-29 per cent. Colostrum has shown to have a higher viral load as also higher antibody levels. Some of the cellular and humoral factors are found to be reduced in colostrum samples obtained from HIV seropositive mothers as compared to seronegative mothers. Seroconversion during lactation, advanced stage of the disease in the mother, concomitant vitamin A deficiency, breast conditions like cracked nipples and mastitis, have shown to increase the risk of postnatal transmission of HIV through breastfeeds. Infant feeding practices in the developing world that comprises almost universally of prolonged duration of breastfeeds contribute to the higher rates of 30-45 per cent of MTCT as against 15-20 per cent in the developed countries, in the absence of any intervention. The least common route of vertical transmission in industrialized nations is breastfeeding. Current WHO/UNAIDS/UNICEF guidelines recommend that women with HIV infection should be fully informed of both the risks and benefits of breastfeeding and be supported in their decision about feeding practices.
If safe alternatives to breastfeeding are not available in resource-limited settings, exclusive breastfeeding for the first several months of life is recommended. The overall objective is to prevent HIV transmission through breastfeeding while continuing to protect, promote and support breastfeeding for HIV-negative women and those of unknown status. When children born to women living with HIV can be ensured uninterrupted access to nutritionally adequate breast-milk substitutes that are safely prepared and fed to them, they are at less risk of illness and death if they are not breastfed. However, when these conditions are not fulfilled, in particular in an environment where infectious diseases and malnutrition are the primary causes of death during infancy, artificial feeding substantially increases children’s risk of illness and death\(^4\). Replacement-fed infants born to HIV-infected mothers in India have a high early postpartum rate of hospitalization\(^4\). The risk of giving replacement feeds must be less than the risk of HIV transmission through breastfeeding in order to be justified. Essential requirements include knowledge and commitment on the part of caregivers, safe water, assured supplies of affordable fuel, easy access to quality health care for mothers and infants, and a good level of support from counselors and/or social workers. Women choosing not to breastfeed will need extra support and counselling in order to avert mixed feeding which can be more hazardous. The time immediately after delivery was noted as critical for recounselling about infant feeding and further support of the woman’s decision, thus lowering the risk of mixed feeding\(^4\). A policy recommendation that HIV infected mothers be counseled about considering not breastfeeding can have major implications for birth spacing, as such women are deprived of protection from lactational amenorrhoea. If they do not use an appropriate form of family planning, they may have a shorter interval between births with adverse consequences for their own health. Ultimately, a larger number of potentially HIV infected children will be born and will need to be cared for. Family planning information and services need to be made readily available to mothers and their partners.

Further, ZDV, 3TC and NVP have all been detected in the breast milk of HIV-infected women on treatment\(^44,45\). This could probably lower the viral load in breast milk and be associated with a reduced risk of HIV transmission. However, there is a possibility of only some drugs penetrating the breast milk, some only in sub-optimal concentrations that may not be sufficient to decrease viral replication, probably promoting the development of drug resistant virus in the milk, which could be transmitted to the infant. Moreover, the toxicity of chronic ARV exposure of infants via breast milk is unknown.

(iv) Other interventions

Vitamin A prophylaxis: Vitamin A is an essential micronutrient for normal immune function. Vitamin A deficiency is found to be common among HIV infected pregnant women and is associated with higher mother-to-child transmission of HIV-1 and increased infant mortality\(^46\). The biological mechanisms by which vitamin A deficiency could influence MTCT include impairment of immune responses in both mother and infant, abnormal placental and vaginal pathology and increased HIV viral burden in breast milk and blood\(^47\). However, there is no conclusive evidence to say that vitamin A supplementation can reduce MTCT.

Vaginal disinfection: Most HIV infections in children occur during the time of delivery. Both free and cell bound viruses have been found in cervical and vaginal secretions. Theoretically, cleansing the vagina with an antiseptic or viricidal agent such as chlorhexidine could reduce this mode of transmission. Again, there is scarcity of evidence to conclusively say that inexpensive modalities like cleaning/disinfection of the birth canal can reduce MTCT. However, the incidence of neonatal sepsis is definitely cut down by these strategies.

Immunotherapy: Although ART has significantly reduced the MTCT of HIV, it has its own drawbacks. The antiretroviral medications have a relatively short half-life and therefore have to be administered throughout the course of breast-feeding, to both the mother and the infant in order to optimally prevent infection in the infant. Additionally, the cost, the potential toxicities and the development of resistance are likely to limit the long-term efficacy of antiretroviral prophylaxis. Hence, a safe and effective active/passive immunoprophylaxis regimen, begun at
birth, and potentially overlapping with intrapartum or neonatal chemo prophylaxis, would therefore pose a more attractive strategy and might also provide the basis for a lifetime protection against HIV-1 infection. Various strategies for stimulating a protective immune response against HIV infection are being explored through basic research, animal models, and clinical trials. Vaccines capable of stimulating the mother’s and/or infant’s immune response or passive immunity therapies may be capable of reducing perinatal transmission. Vaccines also may serve as immunomodulators to improve immune function and diminish disease progression in HIV infected individuals and may potentially prevent transmission from the mother to her foetus or from one infected adult to another. Like Hepatitis B, the use of active, passive, or active/passive strategies to reduce transmission has the highest potential for reducing mother-to-child transmission in developing countries.

**Conclusion**

Mother-to-child transmission of HIV is a global problem. HIV can be transmitted from mother-to-child at various stages of pregnancy, i.e. ante, intra- and post-partum. A number of interventions have therefore been aimed at effectively administering antiretroviral drugs to the mother and to the baby, limiting the risk of newborn infection by elective caesarian section as the mode of delivery and providing alternatives to breastfeeding. However, these approaches are not always possible in developing countries wherein currently 95 per cent of vertical transmission occurs. Several questions and challenges remain, which include choice, availability, affordability, duration, long term safety of optimal antiretroviral agents to be used during pregnancy and early neonatal life to reduce transmission whilst also protecting treatment options to women and children who may need it in future and the issue of transmission via breastfeeding in situations where alternatives to breastfeeding are not available. A wider array of strategies for prevention of mother-to-child transmission of HIV-1 during breastfeeding including passive and active immunization, may offer much needed answers to the problem of continued HIV transmission. Evaluation of efficacy and tolerance of preventive interventions complementary to antiretroviral prophylaxis such as HIV perinatal vaccine, passive immunophrophylaxis, micronutrient supplementation and vaginal-cervical disinfection by means of microbicides should be actively continued and encouraged. The challenge is to find the most cost-effective and feasible intervention to achieve zero per cent transmission of HIV from an infected mother to her child.

**References**


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