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Review Article

Recent Trends in Mother To Child Transmission of HIV in Pregnancy

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Introduction

Although vertical transmission has been largely eliminated in the developed world & there is plenty of evidence to show that Prevention of Mother To Child Transmission (PMTCT) services can be provided through existing public health systems even in the most poor parts of the world, this continues to remain an elusive goal, as evidenced by an estimated 430, 000 new HIV infections (240, 000–610, 000) occurring among children under the age of 15 in 2008. Almost all of these new infections in children are believed to stem from transmission in utero, during delivery or post-partum as a result of breastfeeding. Reducing this burden of pediatric morbidity and curbing the prevalence of HIV in the community is important if we want to ensure that the results of reproductive and child health programs are not to be nullified swiftly.

Magnitude of the Problem in India

In India, of the estimated 1.8 – 2.9 million people living with HIV, 39 % are women with a national average antenatal prevalence being 0.48 %[1]. Also, India is a country where breast feeding is a norm and a large majority of infants continue to breast feed till about two years of age, posing an enormous challenge of safe breast feeding practices in the context of HIV. Heterosexual transmission is by and large the most common route of transmission. The HIV seroprevalence among the pregnant women primarily attending the public hospitals has been reported to be between 0.5-3.3 % in various parts of the country. Earlier reports had suggested that HIV infection in women seeking antenatal care may be as high as Six percent.[2] The HIV prevalence among people aged 15-24 years is showing a declining trend and is currently estimated at 0.57 percent and with the exception of Andhra Pradesh with HIV Prevalence of 1%, all other states have shown less than 1% median HIV prevalence among ANC clinic attendees1

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Screening

It is now accepted that pregnant women should be offered screening universally because appropriate interventions can reduce mother-to-child transmission (MTCT)[3]. If testing has been performed early in pregnancy and the woman is thought to be at high risk of HIV infection, a repeat screening may be offered at 28 weeks of pregnancy.

Diagnosis of HIV infection

The diagnosis of HIV infection is made on the basis of two positive results of enzyme immunoassays which employ different antigens (ELISA, EIA, Rapid or Simple). The positive result of an enzyme assay test is confirmed by a Western Blot. This also differentiates

between HIV-1 and HIV-2 infection, which has implications for prognosis and therapy. When a patient presents in labor without an HIV report, a rapid test using a single ELISA may be appropriate.

Rates of MTCT

Mother to child transmission rates have been shown to have wide variations in different populations. Transmission rates ranging from 15% and 20% have been reported in the USA and Western Europe in untreated populations. In developing countries rates as high as 40% have been reported.4 As compared to HIV – 1, transmission of HIV – 2 from mother to child appears to be low with very few reports of pediatric HIV – 2 infections from perinatal transmission. Incidentally, the seroprevalance of HIV-2 in India appears to be low with a probability of still lower prevalence amongst pregnant women.[1]

Timing of MTCT

HIV transmission from mother to child can occur antenatally (in utero), intrapartum (during labor and delivery) or postpartum (breast-feeding)[5]. 25 to 35% of transmission occurs antenatally, mainly in the later part of pregnancy. 70% to 75% of vertical transmission occurs during labor and delivery. Dunn et al in a meta-analysis have estimated that the proportion of transmission attributable to breast feeding worldwide from HIV is 14% (95%CI 7% to 22%).[6]

Factors affecting MTCT

Table 1: Factors affecting MTCT

Maternal Factors
• Primary infection
• HIV-1 RNA levels
• CD4 lymphocyte count
• STD, Hepatitis C, CMV
• Drug abuse, tobacco, sexual practices
• Deficiency of Vitamin A / Anaemia
• Breastfeeding & duration / pattern / health
• Preventive interventions – antenatal/ intranatal / postnatal
Obstetrical Factors
• Prolonged rupture of membrane (>4hrs)
• Intrapartum haemorrhage
• Obstetrical procedures
• Mode of delivery
• Invasive fetal monitoring
Infant Factors
• Birth weight < 2.5 KG
• Prematurity
• Multiple pregnancy
• Oral factors – cuts/ abrasions/ oral thrush
• Gastro Intestinal factors - Low gastric acidity/ Thin mucosa and microvilli /deficiency of IgA secreting cells.

Numerous factors influence HIV perinatal transmission and these are often responsible for the observed variability in transmission rates. The strongest predictor of transmission is the maternal viral load. Garcia et al showed that there is no MTCT when maternal viral load is below 1000 copies/ml.[7] A meta-analysis of seven prospective studies demonstrated the risk of MTCT to be about 3.6% in a similar population[8]. Therefore, there is insufficient evidence for a plasma load threshold below which MTCT never occurs. Maternal immune depletion appears to co-relate with vertical transmission. An increased risk of vertical transmission is noted with lowered CD4 T cell counts or maternal AIDS.[9] Identifying generalized lymphadenopathy and a clinical search for opportunistic infections is even more important in developing countries where every patient cannot have a CD4 count or maternal viral load performed. Background genital tract infections irrespective of genital lesions increase the risk of MTCT. In the Women and Infant transmission study, clinical vaginitis or vaginosis of any etiology at the last antenatal visit was associated with MTCT.[10] Some studies have shown that transmission rates are higher when nutritional deficiencies co-exist. This possibly is an important factor responsible for the geographical differences in transmission rates. An example of this is the reduction of perinatal transmission by Vitamin A supplementation as demonstrated by Semba et al in a rural African population.[11] Use of drugs (cocaine, heroin, opiates, methadone, injecting drugs) by HIV positive women in pregnancy has shown to increase perinatal transmission. Increased transmission rates in this group are probably due to lowered immunity and increased incidence of preterm births in this group.[12] There has been documented an association between cigarette smoking in pregnancy and an increased risk of mother to child transmission.[13] Unprotected sexual intercourse, probably leading to a higher chance of genital infection, has also been found to increase perinatal transmission. [12]

Intrapartum events are crucial factors governing MTCT

since this is the period where the risk is highest. Duration of membrane rupture more than four hours, preterm births, chorioamnionitis, invasive procedures during labor and delivery have all been associated with an increased risk of perinatal transmission.[14] An elective caesarean section (before the onset of labour) prevents perinatal transmission[15] but an emergency caesarean section performed in labor for prolonged or difficult labor has been associated with increased transmission rates.[16]

Postnatally, breast feeding increases the risk of MTCT. This is further increased with recently acquired HIV infection in the mother and presence of mastitis (clinical and subclinical).[6]

Management Goals

The immediate concerns of a woman informed of HIV infection in pregnancy are perhaps support and counseling especially regarding her own health, probability of fetal infection, ways and means of preventing the same and disclosure to her partner. This pregnancy should be classified as high-risk and managed by a multi-disciplinary team. The primary goal is to reduce the risk of MTCT and the morbidity to the woman and her fetus from HIV associated diseases and their treatments. The broader goals should also address the issues of nutrition, monitoring the social environment and vocational guidance.

Antenatal Investigations

In addition to the routine antenatal investigations, disease progression needs to be monitored by the CD4 count and viral load. Some authors have proposed the use of total lymphocyte count as a surrogate marker for CD4 counts in resource-limited settings[17], however it is not the recommendation. Patients on antiretroviral therapy will also require periodic hematological, liver and renal profiles. Screening for sexually transmitted infections (Syphilis, Hepatitis B, Chlamydia, Gonorrhoea) should be offered. Other tests which may be performed as required are a pap smear, toxoplasma serology and X Ray chest with abdominal shield. Any risk from ionizing radiation is far outweighed by the diagnosis and treatment of pulmonary infections especially tuberculosis.

Strategies to prevent perinatal HIV transmission

Earlier, options for preventing mother to child transmission were limited. Termination of pregnancy was probably the only solution to prevent vertical transmission. Although this option is relevant even today, most HIV positive mothers in our country opt to continue pregnancy due to social pressures and longing for motherhood. Also, registration for antenatal care and subsequent diagnosis of sero positivity takes place late in pregnancy, well beyond the possible limit (up to 20 weeks) for a medical termination of pregnancy.

Advances in our understanding of risk factors and pathogenesis involved in vertical transmission have led to evolution of various strategies to prevent mother to child transmission.

These strategies can broadly be grouped into:

Antenatal
Antiretroviral Therapy
Correction of Risk Factors

Intrapartum
Antiretroviral Therapy
Optimizing obstetric practice

Postnatal
Antiretroviral Therapy
Breast-feeding / Substitutes

Antiretroviral Therapy (ART)

The mode of action of antiretrovirals in preventing vertical transmission probably lies in their ability to reduce maternal viral load and thereby decreasing viral exposure to the fetus. In resource rich countries, highly active antiretroviral therapy (HAART) has reduced the vertical transmission rates to around 1- 2 % but unfortunately HAART is not yet widely available in low and middle income countries, where various simpler and less costly antiretroviral regimens are being offered. With HIV drug resistance testing becoming an essential component of HIV management in developed countries, pregnancy presents some special concerns related to the development of drug resistance. Pre-existing resistance to a drug in an ART prophylaxis regimen or development of resistance to drugs used during pregnancy may diminish efficacy of that regimen in preventing perinatal transmission in the current pregnancy or future pregnancies. Drug resistance also limits future maternal treatment options and infant treatment options if a resistant virus strain is transmitted. Although perinatal transmission of resistant virus has been reported, it appears to be unusual as studies have suggested that drug resistance mutations may diminish the fitness of the virus possibly

leading to a decrease in transmissibility. Factors associated with the development of resistance mutations from PMTCT prophylaxis include high viral load, viral subtype C, low CD4 count, suboptimal drug levels and increased exposure to the drugs. It is unfortunate that the drugs that are used so commonly for PMTCT are the drugs that could lose efficacy following the development of a single resistance mutation, such as Nevirapine (NVP); not to forget the development of cross-resistance with other agents in the NNRTI class such as Efavirenz (EFV) and Lamivudine (3TC). The high genetic barrier to resistance of boosted Protease Inhibitors (PIs) and their short plasma half-life make them a more attractive option for short term ART than Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs). In the light of more & more reports emerging pertaining to development of resistance in the short, suboptimal viral suppressive courses of antiretrovirals, there is a major cause for concern, given that not all drugs for optimal therapeutic regimens are available easily in the resource limited settings, where these preventive regimens are largely being implemented and single-dose Nevirapine (SD-NVP) still continues to remain the corner stone of PMTCT services in many resource limited settings including India.

Antiretroviral therapy should be initiated based on maternal assessment. Women with a CD4 count lower than 350/ml or in WHO Stage 3 or 4 should receive antiretroviral therapy for their own health.[18,19] The components of the ART have to be individualized and generally three drugs are used. Zidovudine (ZDV) should be included as one of the drugs in the combination as far as possible. Women who have been exposed to a SD-NVP regimen without a dual Nucleoside Reverse Transcriptase Inhibitor (NRTI) tail in the previous twelve months should avoid having a NNRTI in their ART regimens due to the high probability of drug resistance.[19] Before starting a pregnant woman on ART, due consideration must be given to factors such as effects of these drugs on the unborn fetus, development of drug resistance, pill-burden and compliance and last but not the least, affordability. Presentations of drug toxicity can be in the form of liver dysfunction. This should be distinguished from the hepatic dysfunction associated with preeclampsia or cholestasis. Women who are on ART may have an increased risk for preeclampsia, gestational diabetes and preterm labor especially when taken for prolonged periods and have to be monitored for these.

When women require antiretroviral therapy only for preventing perinatal transmission, a choice exists between initiating multi drug antiretroviral therapy or using zidovudine monotherapy (Table 2). The first option (ART) is recommended to be started at 14 weeks of pregnancy and continued through labor and postpartum if the woman is breastfeeding. This approach is combined with infant prophylaxis and is associated with very low viral loads permitting a larger number of women to be eligible for vaginal delivery. However, it also has the constraints of multidisciplinary care, toxicity, cost and risk of developing drug resistance if taken in suboptimal dosages / combinations / duration. The second option is to use ZDV monotherapy. In the developing world, where patients usually have to pay for their own treatment, monodrug therapy with ZDV is the mainstay of antiretroviral therapy in pregnancy. Conventionally, ZDV is prescribed in the dose of 100 mg 5 times / day antenatally and 2 mg / kg as a loading dose followed by 1 mg/kg/hg in labor. The ACTG 076 trial20 categorically demonstrated its usefulness in preventing vertical transmission. The drug was administered antenatally after 14 weeks of gestation and continued throughout pregnancy. In labor it was administered intravenously and a syrup formulation was given to neonates for 6 weeks. Perinatal transmission was 68% lower in a non-breast fed population. In a systematic review, the efficacy of preventing MTCT with ZDV in a non breast fed population was maintained if the mother took ZDV from 28 weeks or if the baby was given ZDV for 6 weeks after birth.[21] The use of ZDV for shorter periods has been attempted but resulted in a compromise of its efficacy. Most studies using this time bound ZDV monotherapy has found that the drug was well tolerated by the mother with no adverse effects on the infants. The only short term problem observed in the ACTG 076 study was a transient self resolving anemia noted in infants who had longer exposure in utero and received ZDV as newborns. However, there have been concerns that the use of ZDV monotherapy in pregnancy may lead to the emergence of drug-resistant virus as studies have demonstrated ZDV associated resistance mutations in these women [22, 23] Other retroviral drugs such as Lamivudine (3TC) have been used in combination with ZDV in the PETRA trial.24 and various combinations have been tried with an efficacy ranging from 37 to 42%.

A pregnant patient presenting in labor with a HIV positive report is not unheard of in our circumstances. In such cases, NVP, a NNRTI, has been used. In the

Table 2: ARV-prophylaxis options recommended for HIV infected pregnant women who do not need treatment for their own health – New WHO Recommendation

Option A	Option B
Maternal ZDV	Maternal triple ARV prophylaxis
MOTHER	**MOTHER**
• Antepartum ZDV (from as early as 14 weeks gestation) • SD - NVP at onset of labour* • ZDV + 3TC during labour and delivery* • ZDV + 3TC for 7 days postpartum* * SD - NVP and ZDV + 3TC can be omitted if mother receives > 4 weeks of ZDV antepartum	Triple ARV from 14 weeks until one week after all exposure to breast milk has ended • ZDV + 3TC + LPV/r • ZDV + 3TC + ABC • ZDV + 3TC + EFV • TDF + XTC + EFV
INFANT	**INFANT**
Breastfeeding infant Daily NVP from birth until one week after all exposure to breast milk has ended	**Breastfeeding infant** Daily NVP from birth to 6 weeks
Non-breastfeeding infant ZDV or NVP for 6 weeks	**Non-breastfeeding infant** ZDV or NVP for 6 weeks

AZT: zidovudine; 3TC: lamivudine; NVP: nevirapine; SD – NVP: Single dose Nevirapine;
EFV: efavirenz; TDF: tenofovir; FTC: emtricitabine; XTC: 3TC or FTC;
LPV-r: lopinavir/ ritonovir; ABC: abacavir;

Source: http://www.who.int/hiv/pub/mtct/rapid_advice_mtct.pdf.

HIVNET 012 trial,25 it was used in a single dose of 200 mg to the mother at the onset of labor and a single dose of 2mg/Kg was given to the neonates, within 72 hours of birth. The efficacy of reducing perinatal transmission was 49%. NVP in the peripartum period has also been offered as a sole intervention for preventing transmission under the NACO program. Though it has the obvious advantages of being cheaper and simpler as compared to ZDV monotherapy or HAART, one must balance this against the relatively lower efficacy and the development of a major NVP resistance mutation in about 75% of women in the first year after therapy. This may limit its use in subsequent pregnancy and the use of other NNRTI based ART regimens for the mother's future treatment options. To reduce this risk, a tail of ZDV plus 3TC for 1 week postpartum to the mother is recommended. Though this therapy is considered "simple", only 30% of women eligible for its use received the complete treatment in Lusaka, Africa.[26]

Correction of Risk factors

Improving nutritional status especially in the developing world is an important aspect in improving overall health and obstetric outcome. An appropriate diet containing plenty of vegetables, fruits and grains but low in fats and cholesterol is desirable. It is important to avoid drinking unpasteurized milk or unsafe water. Supplementation with the usual prescribed dosages of iron and calcium is necessary. However, there is no clear evidence to demonstrate benefit in preventing MTCT with any particular nutritional supplement.[27] Antepartum evaluation should be to search and treat infections (STD's and opportunistic). A simple per speculum exam done between 24 to 34 weeks gestation can identify presence

of asymptomatic vaginal infections and if infections are present, they can be appropriately treated.

Tobacco use, as with cigarette smoking has shown to increase mother to child transmission. In our country, tobacco use amongst pregnant women is not infrequent, usually in the form of dentifrice (mesehri). Inquiring about its habit in pregnancy and subsequent intervention can reduce transmission risk and improve overall outcome.

Optimizing Obstetric practices: Intrapartum Care and the role of Elective Cesarian Section (ELSCS)

Since majority of infants acquire HIV infection during delivery, obstetric practices should be modified to include limited duration of membrane rupture by late rupture of membrane, avoiding invasive procedures like use of scalp electrode or fetal scalp blood sampling. A prolonged difficult labor associated with a traumatic delivery should best be avoided. Vaginal cleansing by virucidal agents such as chorhexidine has not been shown to be protective in reducing transmission.

Maximum transmission takes place late in pregnancy often during labor. Labor itself being such as unpredictable event with respect to rupture of membranes or anticipation of difficulty, an ELSCS (before onset of labor preferably at 38 weeks) has been advocated as a means of preventing intrapartum transmission. A systematic review has shown a clear benefit (RR 0.17, 95% CI 0.05-0.55) from ELSCS as compared to vaginal delivery.21 This translates into a 50% reduction of risk in women not on HAART or those with a high plasma viral load. The benefit from ELSCS persists even when the groups are controlled for use of zidovudine. The risk of cesarean section related complications to the mother are not increased when the pregnant woman is asymptomatic and not advanced in the disease. Recent recommendations of the RCOG include offering ELSCS to all HIV positive pregnant women with viral load greater than 50 copies/mL. Mothers already on HAART and having a viral load of less than 50 copies/ml at term can opt for a vaginal delivery since the chance of intrapartum perinatal transmission in these women is very low.[28]

In India where facilities for HIV-1 viral loads are unavailable or not affordable and that the cesarean delivery is associated with high morbidity especially in rural centers, the option to offer an elective cesarean delivery as an intervention strategy has to be individualized.

If a patient on ZDV opts for a vaginal delivery or local protocols do not offer viral load estimation at term and elective cesarean section, the AIDS Clinical Trial Group Protocol 076 regimen recommends intravenous ZDV given as a loading dose of 2mg/ kg followed by a continuous infusion of 1mg/ kg. Unfortunately, parenteral preparations of ZDV are not available in our country. Here, 300 mg of ZDV is given orally every 3 hours starting at the onset and through the course of labor. Even though a patient may not want to undergo Cesarean Section to prevent perinatal transmission, she should be advised of the possibility of the same for other medical or obstetric conditions. It may be useful to have a neonatologist standby at the time of delivery.

Breast feeding substitutes

Worldwide breastfeeding is an important route of HIV transmission from mother to child where safe feeding alternatives are not possible & the prevention of this transmission remains the focus of PMTCT research. Strategies being assessed include the use of short course antiretrovirals at labor/delivery; maternal HAART during the last trimester of pregnancy, at labor, and for up to 6 months following delivery with a goal of minimizing maternal viral load in plasma and breast milk; interventions directed at protecting the infant during 3-6 months of exclusive breastfeeding followed by weaning; and active or passive immune strategies that boost infant immune responses during the period of breast milk exposure. It is a well known fact that breast-feeding provides numerous health benefits to mothers and infants. Unfortunately breast milk contains the HIV virus and accounts for a 14% risk of transmission or 0.7 to 1% per month.[18] A study by Coutsoudis et al from Durban[29] has shown that transmission rates are similar at the end of three months in populations who either breast-feed or top feed exclusively. Mixed feeding significantly increased the risk of transmission. However, this study results hold true only if transmission rates are considered till the end of three months. Also, it may be practically difficult to abruptly shift from exclusive breast-feeding to milk substitutes at the end of three or six months. Rapid weaning programs are being assessed in trials in Zambia by Thea et al. [26]. Realizing the above, whenever alternative feeds are possible, the option to breast-feed or not should be explained. For an individual woman, who is educated, has resources and understands safe milk substitute practices, breast-feeding may be avoided. Early

weaning of breast milk and expression with pasteurization are other possible interventions aimed at reducing transmission in breast-feeding mothers.

Infants should receive daily NVP or a SD – NVP (within 12 hours of birth) plus daily ZDV for four to six weeks after birth. Ongoing studies evaluating antiretroviral prophylaxis in the infant or the mother during breastfeeding, and planned studies of active and passive immunoprophylaxis, will hopefully provide ways to tackle breastfeeding transmission of HIV to the infant and prevent millions of new paediatric HIV infections worldwide.

Diagnosis of pediatric HIV infection

The gold standard for diagnosis of pediatric HIV infection is by detection of antibodies at 18 months of age. The routine HIV ELISA cannot distinguish between passively transferred antibodies against HIV from the mother to her baby and those that are produced in the infected baby due to the infection itself. If HIV ELISA is used for diagnosis before 18 months of age, two negative HIV tests at least one month apart, if performed after six months of age, may be used to exclude HIV infection in children with no clinical evidence of disease. The early diagnosis of the HIV infection can be undertaken using polymerase chain reaction (PCR) technique. The serostatus of the child can also be determined by performing a HIV DNA PCR at birth, at one and three months of age. If two of these are positive, the child is considered to be infected with HIV-1.

Conclusions

It is indeed ironical that HIV infection - a harbinger of death and pregnancy - the generation of new life - should coexist so often. It should be the endeavor of the care provider to take care of the prospective mother and her unborn child and make the passage as safe as possible. The patient should be offered the various intervention strategies available. The freedom of choice should ultimately lie with the patient at all times. In developing countries where access to even basic antenatal care is unavailable, screening for HIV, which involves counseling with subsequent assessment and care may not be feasible. In India, where diverse and multiple factors play a role, intervention programs should be derived considering individual health care settings and environment. In such situation, a "Cafeteria Approach Strategy" will be optimum.[30] The patient makes an informed choice of the interventions that are best suited to them. Such an "Offer and Accept Program" will gain better acceptance than a "Prescribe and Take Protocol". What is of utmost importance is implementation of strategies to prevent the acquisition of a lifelong infection which largely is preventable, thereby negating not only an important burden of morbidity and mortality, but also tremendous social stigma

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