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REVIEW ARTICLE

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Prevention of mother to child transmission of HIV infection

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Introduction

The National AIDS Control Organization (NACO) of India reported an upper estimate of 4.58 million people living with HIV/AIDS in the country [1]. In India heterosexual transmission is by and large the most common route of transmission. The HIV seroprevalence among pregnant women attending the public hospitals has been reported to be between 0.5 and 3.3% in various parts of the country. However, recent trends suggest that the incidence of HIV infection in women seeking antenatal care may be as high as 6% [2]. India can expect 75,000 HIV infected neonates to be born every year. Reducing this burden of pediatric morbidity and the prevalence of HIV in the community is important for ensuring that the results of reproductive and child health programs are not nullified swiftly.

Counseling, screening and diagnosis

History taking and physical examination alone are grossly insufficient parameters to identify persons who may be HIV positive. It is now accepted that pregnant women should be offered universal screening because appropriate interventions can reduce mother to child transmission (MTCT). To balance this with the woman's civil liberties, named voluntary testing should be implemented with appropriate pre- and posttest counseling. The use of visual aids and individualized sessions are more effective than group education and counseling (GEC). Sastry et al [3] showed that 96% of women were able to comprehend key issues with the former approach as compared to only 38% with the latter approach. In public hospitals with a large number of antenatal registrations, such an individualized counseling by trained counselors is not feasible. In these circumstances, GEC still plays an important role. It is necessary for women and their partners to understand the issues involved in perinatal transmission to enable them to choose an approach towards preventing perinatal transmission which is best suited for their circumstances.

The diagnosis of HIV infection can be made on the basis of detection of antibody to HIV by an enzyme immunoassay test (ELISA, Rapid EIA, or Simple EIA). A Western Blot confirms the positive result of an enzyme assay test. This also differentiates between HIV-1 and HIV-2 infection, which has implications for prognosis and therapy as discussed later. In resource constraint settings the diagnosis of HIV infection can be made on the basis of three positive results of an enzyme immunoassay (ELISA, Rapid EIA, or Simple EIA), each of which should employ different antigens or different test principles. When a woman presents in labor without an HIV report, a rapid test using a single ELISA may be appropriate.

Rates of MTCT

MTCT rates have been shown to have wide variations in different populations. Transmission rates ranging from 15 to 20% have been reported in the USA and Western Europe. In developing countries rates as high as 40% have been reported [4]. Within India too, due to inherent economic diversity MTCT rates range from 24% in Mumbai [5] to as high as 48% amongst tribal women [6]. As compared to HIV-1, perinatal transmission of HIV-2 appears to be low with very few reports of pediatric HIV-2 infections from MTCT. Incidentally, the seroprevalance of HIV-2 in India appears to be low with a probability of still lower prevalence amongst pregnant women [1].

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Timing of MTCT

HIV MTCT can occur antenatally (in utero), intrapartum (during labor and delivery) or postpartum (breast feeding) [7]. While 25 to 35% of transmission occurs antenatally, mainly in the later part of pregnancy 70 to 75% of transmission occurs during labor and delivery. Dunn et al [8] in a metaanalysis have estimated that the proportion of MTCT attributable to breast feeding worldwide from HIV is 14% (95% CI 7 to 22).

Factors affecting MTCT

Numerous factors influence HIV perinatal transmission and these are responsible for the variability observed in transmission rates. The strongest predictor of transmission is the maternal viral load. Garcia et al [9] showed that there is no MTCT when maternal viral load is below 1000 copies/mL. A metaanalysis of seven prospective studies demonstrated the risk of MTCT to be about 3.6% in a similar population [10]. Therefore, there is insufficient evidence for a plasma load threshold below which MTCT never occurs. Maternal immune depletion appears to corelate with vertical transmission. An increased risk of vertical transmission is noted with lowered CD4 T cell counts or maternal AIDS [11]. Identifying generalized lymphadenopathy and a clinical search for opportunistic infections is even more important in developing countries where not every patient can have a CD4 count or maternal viral load estimation. 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 [12]. Some studies have shown that transmission rates are higher when nutritional deficiencies coexist. This possibly is a important factor responsible for the geographical differences in transmission rates [13]. The use of drugs (cocaine, heroin, opiates, methadone, drugs taken by injection) 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 [14]. An association between cigarette smoking in pregnancy and an increased risk of MTCT has been documented [15]. Unprotected sexual intercourse, probably leading to a higher chance of genital infection, has also been found to increase perinatal transmission [14].

Intrapartum events are crucial factors governing MTCT since this is the period where the risk is highest. More than 4 hours duration of membrane rupture, preterm births, chorioamnionitis, and invasive procedures during labor and delivery have all been associated with an increased risk of perinatal transmission [16]. An elective cesarean section (before the onset of labor) prevents perinatal transmission [17] but an emergency cesarean section performed in labor for prolonged or difficult labor has been associated with increased transmission rates [18].

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) [8].

Management goals

The immediate concerns and needs of a pregnant woman informed of HIV infection are perhaps support and counseling especially regarding death, fetal infection, and disclosure to her partner. 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, proper social environment and vocational guidance. In addition to the routine antenatal investigations, disease progression needs to be monitored by CD4 counts and viral load. Viral load can be estimated by HIV RNA assay or a polymerase chain reaction (PCR) assay. Some authors have proposed the use of total lymphocyte count as a surrogate marker for CD4 counts in resource limited settings [19]. Patients on antiretroviral therapy will also require periodic hematologic, hepatic, and renal profiles. Such patients with disease progression should be classified as highrisk and managed by a multidisciplinary team. Screening for sexually transmitted infections (syphilis, hepatitis B, chlamydia, gonorrhea) should be offered. Other tests which may be performed as required are a pap smear, toxoplasma serology, and chest x-ray 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 MTCT 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 seropositivity takes place late in pregnancy, well beyond the safe limit of 20 weeks for a voluntary termination of pregnancy. Antiretroviral treatment remains the main backbone strategy for preventing MTCT all through pregnancy. Other strategies adopted during different periods of pregnancy are equally important. These strategies can broadly be grouped as shown in Table 1.

Table 1. Strategies to prevent MTCT.

Antenatal	Intrapartum	Postnatal
Antiretroviral therapy	Antiretroviral therapy	Antiretroviral therapy
Correction of risk factors	Optimizing obstetric practice	Breast feeding substitutes

Antiretroviral therapy

Antiretrovirals reduce MTCT by reducing maternal viral load and thereby decreasing viral exposure to the fetus. In situations where resources are not constrained, highly active antiretroviral therapy (HAART) is recommended for pregnant women with CD4 counts lower than 200 to 350/ mL or HIV-1 RNA copy number exceeding 1000/mL [20,21]. The components of the HAART have to be individualized and generally three drugs are used. The usual combination in pregnancy is a protease inhibitor (indinavir, nelfinavir, ritonavir) or a nonnucleoside reverse transcriptase inhibitor (nevirapine) with two nucleoside reverse transcriptase inhibitors (zidovudine, lamivudine, stavudine). Zidovudine should be included as one of the drugs in the combination as far as possible. Before starting a pregnant woman on HAART, due consideration must be given to factors such as effects of these drugs on the unborn fetus, development of drug resistance, pillburden, compliance, and last but not the least, affordability. Drug toxicity can be in the form of liver dysfunction. This should be distinguished from the hepatic dysfunction associated with preeclampsia or cholestasis. HAART is generally continued as a long term therapy for the woman's health. An alternative is to use HAART only for the duration of the pregnancy. However, this may have implications in the development of drug resistance and is not widely recommended.

In the developing world, where patients usually cannot afford to pay for such treatments and face the problems of non-availability of a specialist, drug resistance, and drug toxicity monodrug therapy with zidovudine is the mainstay of antiretroviral therapy in pregnancy. Conventionally, zidovudine is prescribed in the dose of 100 mg five times a day antenatally and 2 mg / kg as a loading dose followed by 1 mg/kg/hour during labor. The AIDS Clinical Trial Group 076 (ACTG) 076 trial [22] 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 nonbreastfed population. In a systematic review, the efficacy of preventing MTCT with zidovudine in a nonbreastfed population was maintained if the mother took zidovudine from 28 weeks or if the baby was given zidovudine for 4 weeks after birth [23]. The use of zidovudine for shorter periods has been attempted but it resulted in a compromise of its efficacy. Most studies using this time bound zidovudine monotherapy have 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 zidovudine exposure in utero and also received it as newborns. Other retroviral drugs such as lamivudine (3-TC) have been used in combination with zidovudine in the PETRA trial [24].Various combinations were tried with an efficacy ranging from 37 to 42%.

A pregnant woman presenting in labor with a HIV positive report is not unheard of in our circumstances. In such cases, nevirapine, a nonnucleoside reverse transcriptase inhibitor, has been used. In the HIVNET 012 trial,[25] it was used in a single dose of 200 mg given to the mothers with the onset of labor and a single dose of 2mg/kg given to the neonates within 72 hours of birth. The efficacy in reducing perinatal transmission was 49%. Nevirapine 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 zidovudine therapy or HAART, one must balance this against the relatively lower efficacy and the development of a major nevirapine resistant mutation in 75% of women in the first year after therapy. This may limit its use in subsequent pregnancy and the use of other nonnucleoside reverse transcriptase inhibitors. To overcome the problem of drug resistance with single dose nevirapine, it is now recommended to add a tail of zidovudine and lamivudine to the mother to be given for 7 days [26]. Though single dose nevirapine therapy is considered simple, only 30% of women eligible for its use received the complete treatment in Lusaka in Africa [27].

Correction of risk factors

Improving nutritional status especially in the developing world is an important aspect of 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 demonstrating benefit in preventing MTCT with any particular nutritional supplement [28]. Antepartum evaluation should be for searching and treating infections (STD's and opportunistic). A speculum examination done between 24 and 34 weeks of gestation can identify presence of asymptomatic vaginal infections which if present, can be appropriately treated.

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

Optimizing obstetric practice

Intrapartum care and the role of elective cesarean section

Since majority of infants acquire HIV infection during delivery, obstetric practices should be modified to include limiting duration of membrane rupture by late rupture of membranes, and 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 and often during labor. Labor itself being such an unpredictable event with respect to rupture of membranes or anticipation of difficulty, elective cesarean section (preferably at 38 weeks before onset of labor) 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 elective cesarean section as compared to vaginal delivery [29]. This translates into a 50% reduction of risk in women not on HAART or in those with a high plasma viral load. The benefit from elective cesarean section persists even when the groups are controlled for use of zidovudine. Recent recommendations of the RCOG include offering elective cesarean section to all HIV positive pregnant women with viral load greater than 1000 copies/mL [30]. In terms of maternal complications elective cesarean delivery for prevention of HIV-1 transmission poses a greater risk than vaginal delivery but lesser than that of emergency cesarean delivery. Recommending for the United States, the CDC guidelines suggest that these risks are not of significant frequency or severity to outweigh the potential benefits of reduced transmission and suggest that an elective cesarean delivery can be offered to women as long as they understand the risk and potential benefits [20]. 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. In India where facilities for cesarean delivery especially in rural centers may not exist or may be associated with high morbidity, the option to offer an elective cesarean delivery as an intervention strategy has to be individualized. Even if offered, its acceptance as an intervention modality in such centers may remain low.

Mothers already on HAART and having a viral load of less than 1000 copies/mL at term can opt for a vaginal delivery since the chance of intrapartum perinatal transmission in these women is very low [30]. When the woman opts for a vaginal delivery, labor should be conducted with sound obstetric judgment in the same way as that of a noninfected women. For a woman on zidovudine who opts for a vaginal delivery, the ACTG 076 Protocol regimen recommends intravenous zidovudine given as a loading dose of 2mg/kg followed by a continuous infusion of 1mg/kg. Unfortunately, parenteral preparations of zidovudine are not available in our country. Hence, 300 mg of zidovudine is given orally every 3 hours starting at the onset of and throughout the course of labor. Even if the mother has been on antenatal zidovudine, single dose nevirapine with lamivudine along with zidovudine has been recommended in labor [26]. Though a woman may not want to undergo cesarean section to prevent perinatal transmission she should be advised of its possible need for other medical or obstetric conditions. It may be useful to have a neonatologist present at the time of delivery. Data from randomized trials and their systematic reviews, suggest that perinatal transmission rates for nonbreastfed neonates who received zidovudine and underwent an elective cesarean delivery is around 2% [17,18,29]. This remains the benchmark perinatal transmission rate with which effectiveness of intervention strategies are compared today. In a clinical setting where such an intervention was offered in Mumbai, the perinatal transmission rate was 5.8% [5].

Current trials focus on the use of antiretroviral combinations to reduce MTCT to levels similar to those in women who have undergone an elective cesarean delivery or those in women with low viral loads. A study was conducted in Thailand on women receiving zidovudine 300mg twice daily in the antenatal period. They were given 300 mg of zidovudine every 3 hours during labor until delivery and the newborn received zidovudine 2 mg/kg every 6 hours for a week after delivery. In one of the arms of the study, women received 200 mg of nevirapine at the onset of labor and infants received a single fixed dose of 6 mg between 48 and 72 hours after delivery. MTCT occurred in only 1.9% of cases with such a regimen [31]. Adding zidovudine 300mg and lamivudine 150mg twice daily 'tail' for 1 week starting in labor will prevent nevirapine resistance. Such antiretroviral based strategies avoid the problems associated with cesarean delivery and still achieve effective reduction in transmission. Developing such intervention strategies with antiretrovirals, which remain effective even when taken for a short duration and have fewer problems of resistance and toxicity, will remain an ongoing process.

Breast feeding substitutes

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% risk per month [8]. A study by Coutsoudis et al [32] from Durban has shown that transmission rates are similar at the end of 3 months in populations who either breast feed or top feed exclusively. Mixed feeding significantly increased the risk of transmission. However results of this study hold true only if transmission rates are considered till the end of 3 months. Also, it may be practically difficult to abruptly shift from exclusive breast feeding to milk substitutes at the end of 3 or 6 months. Realizing the above, whenever alternative feeds are possible, the option to breast feed or not to breast feed should be explained. For an individual woman, who is educated, has resources, and understands safe milk substitute practices, breast feeding should be avoided. Early weaning of breast milk and expression with pasteurization are other possible interventions aimed at reducing transmission in breast feeding mothers.

Diagnosis of pediatric HIV infection

The gold standard for diagnosis of pediatric HIV infection is the detection of antibodies at 18 months of age. The routine HIV ELISA cannot distinguish between passively transferred HIV antibodies and those that are produced 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 6 months of age, may be used to exclude HIV infection in children with no clinical evidence of disease. The early diagnosis of HIV infection can be undertaken using PCR technic. The serostatus of the child can also be determined by performing a HIV DNA PCR at birth, and at 1 and 3 months of age. If two of these are positive, the child is 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 pregnancy and labor as safe as possible. The woman should be offered the various intervention strategies available. The freedom of choice should ultimately lie with her at all times. With rapid globalization of HIV research, this freedom of choice will become all the more precious and the rights of the underprivileged will become a major concern [33]. 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 areas where will and resources permit, interventional programs aimed at preventing MTCT can be set. In India, where diverse multiple factors play a role, interventional programs should be derived considering individual health care settings and environment. In such situations a Cafeteria Approach Strategy will be optimum [34]. The woman makes an informed choice of the intervention that is best suited to her. Such an Offer and Accept Program will gain better acceptance than a Prescribe and Take Protocol.

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