Editorial

Prevention of Vertical Transmission of Human Immunodeficiency Virus

From time to time a new disease strikes the world. In the fourteenth century, bubonic plague killed a quarter of the world's population, this was followed by the potent pandemics of small pox, cholera and influenza. The din of our celebrations of victory over small pox had barely settled when a relatively complacent mankind was struck by a deadlier and more virulent infection- the Human Immunodeficiency Virus (HIV).

Although there is no dearth of literature on HIV in adults, the status' and natural history of HIV in children has not been extensively studied particularly in the Indian population. The increase in pediatric HIV infection has had a substantial impact on childhood mortality both in industrialized countries(l) and developing nations(2). In some areas of Sub-Saharan Africa 10-30% of pregnant women are HIV infected and infection has now spread to many parts of South-East Asia. The reporting of HIV infected children and testing of antenatal and neonatal blood samples make it possible to monitor the prevalence and pattern of HIV infection in pregnant women and children in different geographical areas(3). The health scenario in India is frightening as reported HIV cases represent only a minuscule of the actual numbers.

Maternal to infant transmission is the primary mode by which infants and young children get infected with HIV. From 15-35% of infants born to infected mothers become infected *in utero* during labor and delivery or by breastfeeding(4,5). Current evidence suggests that most transmission occurs late in pregnancy or during labor and delivery(6,7). Most infants who get HIV through their mother's succumb to their illness in the first few years of life.

There is hence an urgent need to describe mother to child transmission of this infection and the natural history of the illness in children. There is also an urgent need to evolve low cost strategies to identify cases and prevent transmission of infection from a mother to her infant. This manuscript focuses on the current status of prevention of vertical transmission of HIV infection with particular emphasis on our experience.

Risk Factors for Transmission

1. *Viral Characteristics*: An important determinant of transmission is maternal viral load. Several studies have demonstrated that a high viral load as measured by plasma RNA by PCR(8) or by DNA copy number(9) is associated with increased transmission. Other factors associated with increased transmission include low maternal CD4 cell count and advanced clinical disease(10).

2. *Neutralizing Antibodies*: High levels of maternal neutralizing antibodies to the V3 loop have been shown to be associated with reduced transmission(11). It seems plausible that high affinity antibodies that react against a wide range of epitopes may confer some protection.

3. *Pregnancy and Delivery*: The mode of delivery, duration of labor, interval from time of rupture of membrances to delivery and

events during delivery that can expose an infant to mother's blood may all be important contributing factors(12-14).

4. *Breast feeding:* HIV is present in breastmilk. Two large European prospective studies showed breastfeeding to be independently associated with an approximate doubling of the risk of transmission (10,15). Research is needed to determine the mechanism and timing of HIV transmission through breastfeeding. Although bottle feeding is recommended for HIV infected women in developed countries, this is not appropriate in settings with high rates of infectious diseases and poor sanitation. The pernicious synergistic effect of non-breast feeding and poor sanitation would increase infant mortality and could be disastrous. For this reason the WHO recommends breastfeeding for all mothers in developing countries regardless of their HIV status(16). In a recent study on a group of HIV-1 seropositive Ugandan women no correlation was found between the detection of HIV in breastmilk or duration of breast feeding and the transmission of HIV-1 infection(17).

Reduction of Vertical Transmission

Antiretroviral therapy and avoidance of breastfeeding are recommended to reduce the risk of transmission. It is also advisable to avoid unnecessary use of invasive procedures such as amniocentesis and fetal blood sampling and to ensure that any sexually transmitted diseases are treated.

1. *Antiretroviral Therapy:* In a randomized placebo controlled trial the AIDS Clinical Trials Group Protocol 076 (ACTG-076) investigators noted that in pregnant women between 14-34 weeks gestation with CD4 counts greater than 200/cu mm, a regimen of antepartum and intrapartum zidovudine (AZT) to the mother and a six weeks course of AZT to the newborn reduced the risk of transmission by about two-thirds(18). In this trial anti-retroviral therapy was intended only to decrease mother to child transmission and therapy was not prescribed to stabilize the health of women with HIV infection (18). This protocol recommends a daily oral dose of 100 mg of AZT five times a day (500 mg daily dose) until labor followed by intrapartum AZT 2 mg per kg IV over a one hour period and then 1 mg per kg per hour until delivery. The newborn then receives oral AZT suspension 2 mg/kg/dose four times a day (8 mg/kg/day) for a period of six weeks. For women who present after 34 weeks gestation oral AZT therapy differs only in the duration of antenatal treatment. Unfortunately, the socioeconomic situation of numerous developing countries make it nearly impossible to utilize this treatment regimen. Therefore, shorter and more simplified AZT treatment that would benefit women in developing countries should be evaluated.

The optimal time to initiate antepartum AZT is unknown. Further analysis and trials would be needed to determine whether the duration of antepartum AZT therapy is predictive of the success of this treatment regimen. The safety of first trimester AZT therapy during the period of embryogenesis remains a serious concern and is not recommended. The ACTG-076 study was not designed to assess the relative contribution of ante-intra-post partum (neonatal) treatment in achieving this result. Some HIV investigators believe that as much as 50 to 70% infants acquire HIV during the intrapartum period and hence intrapartum and neonatal therapy may be helpful even if the mother has not received antepartum AZT.

The mechanism by which AZT reduces the risk of maternal-infant transmission is not established. Maternal AZT may reduce the viral load and hence diminish viral ex-

posure of the fetus *in utero*. In addition there is a significant transplacental passage of AZT(18/19) and therapeutic concentration of the drug in the fetus may reduce HIV infection. Some infants become infected despite therapy either because transmission has occurred before treatment or insufficient suppression of maternal viral replication or noncompliance with treatment regimen. It also remains unclear which component of treatment is most important. Future trials should determine the optimum timing of therapy with simpler shorter regimes using antiretroviral drug combinations. The possibility of long term adverse effects of AZT exposure to the fetus and newborn is yet to be ascertained and the follow up of such children is crucial. In general the short term toxicities observed with AZT therapy in adults include headaches, gastrointestinal intolerance, anemia and hepatitis. A recent ongoing trial in South Africa, Tanzania and Uganda is evaluating the efficacy of using AZT with Lamivudine (3TC) for reducing perinatal transmission of HIV.

2. Other Approaches: There is some data suggesting that for HIV infected women delivery by cesarean section may prevent viral transmission. A European collaborative study showed that the infection rate was 50% lower in infants delivered by cesarean section than in those delivered vaginally(12). A meta analysis suggested an overall benefit of cesarean section, but not all studies have found lower transmission rates(20). Todate, a policy of routine cesarean section for HIV infected women is not justified.

The Wadia Experience

At the Nowrosjee Wadia Maternity Hospital (NWMH) all pregnant women are subjected to HIV testing on their first antenatal visit, after informed consent, using a third generation ELISA test. In order to make mass screening cost-effective, given our economic conditions, we have resorted to pool sera testing of 5 blood samples as recommended(21). A pool that tests positive is subsequently subjected to individual sample testing. A patient whose blood sample tests positive is recalled with her spouse for retesting and counseling. Only patients who test positive by ELISA on recall are considered as positive cases and subjected to Western-blot testing for confirmation of diagnosis. Detailed information regarding HIV infection is then offered to the couple. Confirmed positive cases of less than 20 weeks gestation are offered the option of pregnancy termination, while those beyond 20 weeks are informed about the risk of vertical transmission and their pregnancy allowed to continue to term. Infants born to these HIV positive women are clinically examined at 1, 3, 6, 9, 12, 15 and 18 months and their blood samples subjected to ELISA testing at 9 and 18 months age.

Since January 1993, we have tested 48,579 pregnant housewives with no high risk sexual behavior for their HIV status and have noted a seroprevalence rate of 1.5% in these women. We have data on the pregnancy outcome of 350 women and are following up 240 infants. This is the largest HIV screening programme in our country.

A special protocol is offered to women presenting after 20 weeks gestation who can afford AZT therapy. This comprises daily oral administration of AZT capsules (100 mg qid) upto term. Of the 30 women so far treated with this regime the mean age for starting therapy was 32 weeks. As intravenous AZT is not available to us, these patients have not received IV therapy. All these cases have however, been delivered by cesarean section. As the suspension form of AZT is also not available in In-

dia, infants born to these women receive oral AZT powder in a dose of 8 mg/kg/day for a period of 6 weeks. We avoid giving these infants breastmilk. This interventional strategy has resulted in the prevention of vertical transmission in infants so far delivered using this therapeutic regime. All these infants have tested negative for HIV antibodies at 9 months.

Concluding Comments

Obstetric care providers should preferably offer and recommend HIV antibody testing for all pregnant women, which should be done as early as possible during pregnancy and patients should be informed about the risk of mother to child transmission. In developing countries, this could be feasible and work out economical if the technique of pool testing of sera is used, as advocated(21). This risk varies from 15 to 35% if no therapeutic interventional strategies are adopted.

Women below 20 weeks gestation should be offered the choice of pregnancy termination. For women between 20 to 34 weeks of gestation a combined antepartum, intrapartum and neonatal treatment regimen is recommended as per ACTG-076 protocol(18). Women receiving oral AZT during pregnancy should have monthly complete blood count and liver function tests. Dose interruption or modification should be considered if intolerance or side effects to the drug are noted. Although there is some data suggesting the beneficial effects of cesarean section in the transmission of vertical infection, this has not been conclusively documented and hence a policy for routine cesarean section is not justifiable. Infants exposed to AZT therapy should have routine monitoring of hemoglobin, white blood cell counts and monthly liver function tests.

Early diagnosis of HIV infection in infancy should be done by HIV-DNA polymerase chain reaction or P24 analyses as HIV antibody tests by ELISA or Western blot positivity under 15 months age is not diagnostic of active infection.

The transmission of HIV infection via breastmilk requires special consideration. There are indeed well documented cases of women with HIV, infecting their infants through breastmilk(22,23). The extent to which women with stable HIV infection and relatively low levels of circulating virus transmit the infection to their infant via breastfeeding has not been established. This potential risk can be eliminated in populations with access to breastmilk alternatives by refraining from breastfeeding. However, this is not feasible for most HIV infected women in developing countries where often no affordable or safe alternative exists. Given the substantial benefits of breastmilk, it may be reasonable to direct public health efforts towards preventing seronegative women and mothers from becoming infected with HIV, rather than preventing HIV infected women from breastfeeding.

Finally it has been suggested that in developing countries poor nutritional status of pregnant women might contribute to higher mother to child transmission, although little is known about the type of nutritional factors involved(24). Vitamin A may be an important factor because it has a , stimulatory effect on the immune system and helps to maintain mucosal integrity^). A strong association has been documented between maternal vitamin A deficiency and vertical transmission of HIV. Maternal vitamin A deficiency was associated with a three to four fold increased risk of transmission(26). The temporal relation noted between low vitamin A levels and an increased risk of perinatal transmission may suggest that improving vitamin A in-

take during pregnancy may lower the vertical transmission rate of HIV(26).

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