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Mother-to-Child Transmission of HIV Infection: Nutrition/HIV Interactions

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Introduction

An estimated six million people were newly infected with HIV in 1997, approximately 10% of whom were children. Most of these infected children live in sub-Saharan Africa and approximately 90% were infected through transmission from mother to child. In developed countries the impact of interventions to reduce vertical transmission is already apparent and there has been a marked reduction in the number of children born infected with HIV. By contrast, in developing countries, where the prevalence of HIV infection is highest and where most infected children are found, the scope of prevention remains limited owing to cost and a lack of infrastructure. Nevertheless, there is an international effort to prevent vertical transmission in these countries as well as to develop more feasible interventions in settings where HIV prevalence is high and where it is impractical to test all pregnant women for HIV infection. Pilot implementation projects have been set up to monitor the impact of interventions in these settings.

It is perhaps surprising that vertical transmission of HIV infection is not much higher in parts of the world where rates of malnutrition and prematurity are high and associated infections are common than in countries where this is not the case. This might be explained by the fact that poor nutrition status and progression of HIV in pregnant women are associated with adverse pregnancy outcome but not necessarily with vertical transmission of HIV. In a systematic review of the literature and a meta-analysis based on fairly limited data, an association was found between maternal HIV and adverse fetal outcome. Vitamin A deficiency is common among African populations and data suggest that very low serum or plasma vitamin A levels are independent risk factors for morbidity in HIV infection. In addition, a deficiency of vitamin A, as well as other micronutrients, in pregnancy may contribute to an increase in mother-to-child transmission of HIV. In a study of 338 HIV-infected women in Malawi, more than half of the women had vitamin A deficiency and HIV transmission was significantly associated with vitamin A status. This association is plausible because vitamin A deficiency impairs T and B cell function, which could cause increased viral load and result in reduced maternal antibody concentrations. Alternatively, vitamin A deficiency could merely be a marker of advanced maternal disease, which could explain the higher rate of vertical transmission. Vitamin A supplementation could reduce chorioamnionitis in late pregnancy and improve immune function of the infant. Although it seems unlikely, a potentially harmful effect of vitamin A supplementation on maternal infection, and therefore on vertical transmission, could be through increasing HIV replication.

Preliminary findings from a trial in Tanzania comparing supplemental vitamin A with multivitamins that did not contain vitamin A or no supplementation in pregnancy showed a 40% reduction in fetal death and a reduction in adverse pregnancy outcome among the women taking multivitamins compared with those receiving no supplementation. Vitamin A alone had no significant effect. Multivitamins, but not vitamin A, also had a beneficial effect on T-cell subset counts. The efficacy in reducing vertical HIV transmission was not reported. In a similar trial in Malawi a benefit was reported with respect to fetal death and birthweight outcomes.

The Risk of Vertical Transmission

In the absence of any interventions, the rate of transmission from mother to child is 25–35%. The figure quoted for developing countries is usually higher than that for developed countries with the increased risk probably owing to breast-feeding. The estimated transmission rate was 15–25% in Europe and the United States, where few HIV-infected women choose to breast-feed, and rates in Africa, where breast-feeding is the norm, range from 25% to 40%. In Thailand and Brazil, transmission rates of 20% and 15% were reported in nonbreast-fed infants, which infers that most of the increased transmission seen in African populations is associated with breast-feeding. Similar
maternal risk factors for vertical transmission of HIV infection were reported from studies throughout the world and the consistency of transmission rates across geographic areas, when allowance is made for breast-feeding, would suggest that the maternal nutrition status does not play a major role in vertical transmission. Nevertheless, on an individual basis, factors such as maternal nutrition status or different HIV subtypes cannot be excluded.

### Risk Factors Associated with Transmission

Maternal factors shown to increase the risk of mother-to-child transmission include advanced maternal HIV clinical disease, low CD4 counts and CD4:CD8 ratio, and high viral load (Table 1). In a multivariate analysis including viral load, CD4 count was no longer found to be associated with vertical transmission. Maternal viral load at delivery is highly predictive of transmission and in a recent trial of short course oral zidovudine monotherapy in Thailand, 80% of the vertical transmission rate was explained by maternal viral load at delivery and events surrounding labor and delivery that result in increased exposure of the infant to mother’s infected blood or vaginal secretions were shown to be associated with increased vertical transmission. Genital shedding of HIV associated with vitamin A deficiency and severe vitamin A deficiency, which could impair the integrity of the epithelial surfaces and increase vaginal viral shedding, was identified as a cofactor for increased risk associated with delivery in some, but not all studies. HIV RNA was also detected in oropharyngeal and gastric aspirates of both infected and uninfected infants born to HIV-infected mothers and infants who were not breast-fed. The significance of this finding for transmission, however, is not known.

### Timing of Transmission

The infant may become infected in utero, during labor and delivery or through breast-feeding. Knowledge of the timing of mother-to-child transmission is important because it has a direct impact on the design of preventive strategies to reduce transmission. A significant proportion of perinatal HIV transmission occurs during the intrapartum period. This is supported by the finding that delivery by an elective caesarean section before the onset of labor and rupture of the membranes reduces transmission by more than 50% and that prolonged rupture of the membranes increases the risk of transmission. Based on the detection of the HIV-1 genome within 48 hours of delivery by polymerase chain reaction (PCR) or virus isolation, 35–40% of nonbreast-fed infants are infected before birth and 60–65% are infected in late pregnancy or during delivery. In a recent review of the timing of mother-to-child transmission of HIV infection, approximately one-third of nonbreast-fed infants were assumed to have acquired HIV infection in utero, whereas in breast-feeding populations, this figure was less than a quarter (Table 2).

### Postpartum Transmission Through Breast-feeding

Transmission of HIV infection through breast-feeding is well documented; results from prospective studies of infants born to women with HIV infection demonstrated that

<table>
<thead>
<tr>
<th>Route of acquisition</th>
<th>% Acquiring HIV</th>
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<tbody>
<tr>
<td>Intrauterine period</td>
<td>33</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>67</td>
</tr>
<tr>
<td>Postpartum</td>
<td>33</td>
</tr>
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Source: Adapted from Newell.
breast-fed infants were more likely to be infected than those who were formula fed, even when allowing for other factors associated with mother-to-child transmission. The risk of infection is high for infants whose mothers acquire HIV infection postnatally (i.e., when they are breast-feeding). In a meta-analysis based on four studies of 42 mothers who acquired HIV infection while lactating and six studies of 1772 women with established infection before the birth, the estimated additional risk of transmission from breast milk, was approximately 29% (CI 16 to 42%) and 15% (CI 7 to 22%), respectively.25 Five of the six studies on which these latter estimates were based, however, were from developed countries where the duration of breast-feeding was brief.

The acquisition of HIV through breast milk is of particular concern in the developing world where there are no safe alternatives to breast-feeding and infant mortality caused by diarrhea is high. In these settings, approximately one-third of infected infants become infected with HIV through breast-feeding; however, additional data are required to identify the time of transmission through breast-feeding more precisely, to quantify the attributable risk of breast-feeding, and to determine associated factors.

Transmission through breast milk can occur at any stage of lactation but it is not known whether the risk is higher in the neonatal period, or from exposure to colostrum, than it is later on. In a study in Haiti, HIV DNA was detected more frequently in colostrum than in breast-milk samples collected at 6 months and 1 year.28 In a study in Rwanda, the detection rate was lower in samples collected at 6 months postpartum than at 15 days.29 By contrast, in a small study in Kenya, HIV DNA was found to be lower in colostrum than in breast milk collected between 1 week and 6 months.30 In view of the persistence of maternal antibodies and the presence of a window period during which infection is not detectable, it is not possible to distinguish infection acquired in the intrapartum period from that acquired through early breast-feeding. Nor is it possible to quantify the risk of infection through early breast-feeding. Results from observational cohorts in developing countries where breast-feeding is common and of longer duration show that prolonged breast-feeding continues to expose the child to HIV. In an international pooled analysis that included 902 children from Africa who were breast-fed by an HIV-infected mother, the risk of infection for infants known to be uninfected at 3 months of age was estimated to be 3.2 per 100 child years of breast-feeding.31 In a subgroup of 429 of these children, for whom detailed information was available, cumulative rates of transmission during breast-feeding were 2.5%, 7.4%, and 9.2% at ages 12, 24, and 36 months, respectively. In a subsequent study of Malawi infants with negative PCR results at 7 weeks of age or later, the cumulative estimated rate of seroconversion was 9.6%32 and not significantly different from the above estimate.

Possible risk factors that have been associated with postnatal transmission are shown in Table 3. These include maternal immune deficiency and the presence of virus-infected cells in breast milk.29 Other potential risk factors are cracked nipples9 and breast abscesses.33 Subclinical mastitis is common among women in developing countries, which might lead to increased permeability of the mammary epithelium and possible increase in virus in the breast milk. This could be associated with increased vertical transmission; however, evidence is lacking to confirm or quantify this effect.

HIV-1 has been isolated from cell-free breast-milk supernatants34 and from the cellular fraction of breast milk.35,36 However, the mechanisms for HIV transmission through breast milk, in particular the role of cell-free and cell-associated virus that is present in both colostrum and mature breast milk, are still not fully understood. Although HIV DNA and p24 antigen are present in the breast milk of infected women, their presence cannot be assumed to correspond with infectiousness.24 There is some evidence from animal studies that cell-free virus in breast milk can infect intestinal mucosal cells.37 It was proposed that highly specialized epithelial cells in the Peyer's patches of the intestinal mucosa, M cells, may provide a mechanism for infectious agents such as HIV to cross the intact mucosa.38,39

Disruption of the mucous membrane epithelial integrity of the infant's mouth or intestinal tract, whether caused by nutrition factors or infections such as oral thrush, could theoretically increase the transmission of HIV infection through breast milk. There is recent evidence from Brazil9 and South Africa40 that breast milk taken with other milk, tea, or fruit juices (i.e., mixed feeding) may be more risky than exclusive breast-feeding with no other food or drink. This observation is plausible because damage to the intestinal epithelium resulting from cow's milk or an allergy to complementary foods, as well as from infections, could facilitate entry of the virus. The observation among lactating women in Kenya that vitamin A deficiency was associated with an increase in the prevalence of HIV DNA in

Table 3. Possible Risk Factors Associated with Breast-feeding Transmission

<table>
<thead>
<tr>
<th>Possible Risk Factor</th>
<th>Description</th>
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<tbody>
<tr>
<td>Maternal acquisition of HIV during breast-feeding</td>
<td>High plasma viral load</td>
</tr>
<tr>
<td>Immune deficiency</td>
<td>Cell-associated/cell-free HIV in breast milk</td>
</tr>
<tr>
<td>High viral load in breast milk</td>
<td>Vitamin A deficiency</td>
</tr>
<tr>
<td>Cracked nipples</td>
<td>Mixed feeding (breast milk plus other type of milk, tea, or fruit juice)</td>
</tr>
<tr>
<td>Breast abscess</td>
<td>Damaged mucosal surface of the mouth or intestinal tract</td>
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breast milk cells in women with CD4 counts of less than 400/mL suggests that vitamin A could also influence vertical transmission through breast milk.12 It was suggested that supplementation of lactating women with vitamin A could reduce the viral load in breast milk and thereby reduce vertical transmission. Some antinfective substances in breast milk such as maternal immunoglobulins, lactoferrin, and mucins may provide some protection against HIV transmission. Breast milk from seropositive women contains antiHIV IgG, IgM, and IgA,29 but the role of these immune factors in preventing infection is not known. Breast milk from both infected and uninfected women was also shown to contain a factor, sulfated glycosaminoglycan, which inhibits the binding of CD4 to HIV envelope glycoproteins;41 however, the implication of this finding is unclear.

The emergence of HIV infection has already reversed the gains that were made in child health during the past two decades through strategies, including the promotion of breast-feeding, which not only provides nutrition benefit but also protects against common childhood infections and contributes to family spacing. Of particular concern is the knowledge that HIV infection can be transmitted through breast-feeding. The introduction of different feeding modalities to reduce vertical transmission of HIV infection will therefore need to be carefully balanced against the potential increase in mortality associated with alternative feeding.

**Interventions to Reduce Vertical Transmission**

**Antiretroviral Therapy**

Antiretrovirals are an important option for reducing vertical transmission because they reduce maternal viral load, which is a major risk factor for infection. Zidovudine is the only preventive therapy with demonstrated efficacy. When given to women in the second and third trimester of pregnancy by intravenous infusion during delivery and orally to the newborn for 6 weeks, zidovudine was shown in a randomized trial to reduce the risk of vertical transmission by approximately two-thirds, in the absence of breastfeeding.42 Because this preventive approach is too expensive and not feasible for most developing countries, subsequent trials were set up in poor resource countries to evaluate shorter regimens of antiretroviral therapy. In these trials, prepartum therapy is generally given for the last 2–6 weeks of pregnancy and intrapartum treatment is given orally. Postpartum therapy is not usually administered and when it is, treatment of the mother or neonate is limited to a brief period of less than 1 week. Three different regimens of zidovudine, in combination with lamivudine given at 36 weeks of pregnancy during labor and delivery and for 1 week postpartum to the mother and infant, are also being evaluated in a large UNAIDS multicenter trial in Africa known as the Petra trial.43 The nonnuclear reverse transcriptase inhibitor, nevirapine, which is given once to the mother during labor and once to the newborn is also being investigated.

Recent results from trials of short-course regimens of antiretroviral therapy in developing countries showed a reduction in mother-to-child transmission (Table 4). In Thailand, oral zidovudine given during late-pregnancy and during labor reduced vertical transmission by 51% in formula-fed infants.12 In addition, the results from the two trials of short-course zidovudine in predominately breast-fed populations in the Cote d’Ivoire and Burkina Faso demonstrated a reduction of approximately 35% in transmission of infection in infants at 6 and 3 months of age, respectively.44,45 Preliminary results from the Petra study showed a 50% reduction in infection in infants 6 weeks of age among those who had received the three components (intrapartum, peripartum, and postpartum therapy) compared with those given a placebo.46 A 37% reduction was observed for those who received only intrapartum and postnatal treatment. Follow-up of the infants to identify those subsequently infected will provide additional information on the benefits of antiretroviral therapy in breast-fed infants. The findings from these trials are important and reassure that in breast-fed infants whose mothers receive prophylactic antiretroviral therapy, the reduction in transmission at the time of delivery is not negated by subsequent prolonged rebound in viral load or increased postnatal transmission of the virus. If breast-feeding is continued for long, however, the beneficial effect is likely to decrease.

**Table 4. Comparison of ARVT Intervention Trials**

<table>
<thead>
<tr>
<th>Trials</th>
<th>% Infected</th>
<th>Placebo</th>
<th>% Reduction</th>
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<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTG076</td>
<td>8.3</td>
<td>25.5</td>
<td>67 (no breast-feeding)</td>
</tr>
<tr>
<td>Thailand</td>
<td>9.4</td>
<td>18.9</td>
<td>51 (no breast-feeding)</td>
</tr>
<tr>
<td>Cote d’Ivoire (CDC)</td>
<td>15.7</td>
<td>24.9</td>
<td>37 (at 3 months)</td>
</tr>
<tr>
<td>Cote d’Ivoire (ANRS)</td>
<td>18.0</td>
<td>27.5</td>
<td>38 (at 6 months)</td>
</tr>
<tr>
<td>PETRAA*</td>
<td>8.6</td>
<td>17.2</td>
<td>50 (at 6 weeks)</td>
</tr>
<tr>
<td>PETRAB†</td>
<td>10.8</td>
<td>17.2</td>
<td>37 (at 6 weeks)</td>
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* A=antenatal, intrapartum, and postpartum.
†B=intrapartum and postpartum.

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**Mode of Delivery**

Intrapartum transmission accounts for a substantial number of perinatal HIV infections, presumably by exposing the infant to infected blood and maternal secretions during passage through the birth canal and to micro-transfusions of maternal blood during contractions in labor. There is now good evidence that elective caesarean section delivery before the onset of labor and rupture of the membranes, alone and in combination with antiretroviral therapy, significantly reduces perinatal HIV transmission. Even among women with low viral load, elective caesarean section delivery reduces the risk of infection. This approach to intervention is clearly limited and not an option in most settings where the prevalence of HIV infection is pregnant is high.

**Cleansing of the Birth Canal**

Other approaches to reduce peripartum transmission include cleansing of the birth canal with an antiseptic or virucidal agent during delivery. If effective, such an approach would have great potential because these antisepsics are widely available, inexpensive, well tolerated, and their application may not require HIV testing of pregnant women. Chlorhexidine solution used during delivery was shown in a randomized controlled trial in Sweden to reduce infant morbidity owing to streptococcal infection. In a randomized controlled trial in Malawi, cleansing of the birth canal with chlorhexidine solution during labor had no effect on vertical transmission overall, although there was a reduction in a subset of women with prolonged rupture of the membranes. However, what emerged from this trial in the intervention arm was the significant reduction in overall neonatal and maternal morbidity and mortality owing to sepsis. Further trials using chlorhexidine are currently being evaluated in Africa.

<table>
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<tr>
<th>Table 5. Infant Feeding Options</th>
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<tbody>
<tr>
<td>Exclusive breast-feeding</td>
</tr>
<tr>
<td>Modified breast-feeding</td>
</tr>
<tr>
<td>Other breast milk</td>
</tr>
<tr>
<td>Breast milk substitutes</td>
</tr>
</tbody>
</table>

**Vitamin A**

If proven effective, supplementation with vitamin A could potentially greatly reduce vertical transmission of HIV infection; it is inexpensive, easy to administer, and does not require HIV testing. Several placebo-controlled trials were set up in countries where vitamin A deficiency is common in order to evaluate the effect of vitamin A supplementation during pregnancy on reducing vertical transmission. Studies reported a marked reduction in perinatal mortality and an increase in birth weight associated with the administration of vitamin A in pregnancy. None of these trials have yet published results on the effect of administration of vitamin A on vertical transmission, but preliminary reports suggest that there was no significant effect. In the United States, where vitamin A deficiency is rare, there was no association between maternal vitamin A levels and vertical transmission of HIV in nonbreast-fed infants in one study, whereas in another study, vertical transmission was associated with severe vitamin A deficiency.

**Avoidance of Breast-feeding**

The respective advantages and disadvantages of breast-feeding in African populations where HIV infection is endemic have been widely debated. A randomized trial was completed in Nairobi, Kenya to compare transmission rates in breast-fed and bottle-fed infants and results will be reported shortly. In situations where the prevalence of HIV is high and alternative feeding is not appropriate or safe, consideration must be given to different breast-feeding regimens (Table 5). These could include exclusive breast-feeding (with no additional milk, fruit juice, or water), discarding colostrum and early milk, earlier cessation of breast-feeding (e.g., after 6 months to avoid late postnatal transmission), and the pasteurization or treatment of breast milk (Table 4).

**Disease Progression in HIV-infected Infants**

Adequate sources of vitamin A through supplementation or adequate diet play a major role in preventing morbidity and mortality in developing countries. Extensive research into the role of micronutrients in child health and survival in developing countries established that supplementation of children’s diets with specific nutrients can result in significant reductions in childhood morbidity and mortality. The underlying mechanisms responsible for these outcomes are the changes that micronutrient deficiencies produce in the host immune response to infectious disease.

Low intake of some nutrients such as vitamin A was also associated with disease progression to AIDS. Vitamin A and its active metabolites are necessary for normal T and B cell function, macrophage function, and antibody response to protein antigen, as well as maintenance of gastrointestinal and respiratory mucosal integrity (Table
Table 6. Vitamin A: Possible Mechanisms

Vitamin A and its active metabolites are necessary for normal T and B cell function, macrophage function, and antibody response to protein antigen.

Vitamin A is required to maintain gastrointestinal and mucosal integrity.

Severe vitamin A deficiency could impair integrity of epithelial surfaces and increase shedding of the genital tract and in breast milk.

6.1 Vitamin A deficiency is associated with impaired antibody responses, decreased CD4:CD8 lymphocyte ratio, decreased T lymphocyte function, and increased disease morbidity and mortality in children. It has an effect on HIV gene expression by enhancing virus production in acute infectious models and through an inhibitory effect in chronic infection models. Both high and low vitamin A intakes are associated with increased risk of disease progression to AIDS and mortality.

In Africa, low vitamin A was associated with increased infant morbidity, mortality, and growth failure but findings from the United States are conflicting. Vitamin A deficiency was associated with disease progression and mortality in HIV-infected adults and children. Because vitamin A deficiency is particularly severe among HIV-infected children in Africa, improvement of survival through vitamin A supplementation is advocated. Recent trials of vitamin A supplementation in HIV-infected children suggested that vitamin A supplementation improved disease morbidity and increased circulating natural killer cell and CD4 count. A larger trial is ongoing in Uganda and, if shown to be effective, vitamin A supplementation could potentially improve clinical outcome. By contrast, in the United States vitamin A was not associated with morbidity or mortality among children with relatively normal vitamin A concentrations. Because vitamin A could potentially modulate HIV replication, its use in the treatment of HIV infection is also under investigation.

Conclusion

Given the high rate of HIV infection in pregnant women in developing countries, with rates as high as 15–50% in some areas of sub-Saharan Africa, there is an urgent need to prevent infection in women, to develop interventions that will reduce mother-to-child infection transmission, and to improve the quality of life for women. These interventions must be feasible, affordable, and applicable for the target population. Although nutrition interventions were shown to reduce vertical transmission so far, they showed a benefit on maternal well-being, pregnancy outcome, and child health. Knowledge that HIV infection can be transmitted through breast-feeding is of particular concern and raises many difficult issues, because breast-feeding must continue to be promoted and supported as the ideal way to feed the majority of infants, particularly in developing countries. Nevertheless, appropriate and safe alternatives to breast-feeding should be made available to women infected with HIV.

Further research is needed to unravel the mechanisms associated with breast-milk transmission of HIV, such as the infectious activity of HIV in the various breast milk components and the role of HIV inhibitors in breast milk, and to find effective ways to reduce the risk of breast-milk transmission. Modifying infant feeding practices may be difficult, and perhaps harmful, in areas where infant mortality is high and women are poor. Studies are also necessary to examine the relative benefits of different infant feeding practices, such as the benefits of exclusive breastfeeding versus mixed feeding, dietary supplementation, and early cessation of breast-feeding, in populations where the prevalence of HIV infection is high. Although programs are currently being set up in several developing countries to evaluate specific intervention strategies at the local level, there is an urgent need to look at the wider impact of these programs on the entire population. The introduction of interventions to prevent mother-to-child transmission of HIV will challenge health care delivery systems and place an additional burden on health services that already lack resources. The introduction of interventions to reduce vertical transmission provides an opportunity to further enhance antenatal care. It will be important to monitor the impact of interventions on rates of breast-feeding and artificial feeding overall and to ensure that there are no adverse effects on child health and development. Any “spillover” effect of breast milk substitutes to women who are not infected or of unknown infection status will need to be carefully monitored. In addition, the safety of breast milk substitutes for HIV-infected women and the risks and benefits of intervention policies must be carefully weighed.

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