Review

Vertical transmission of human immunodeficiency virus

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Summary

We discuss the interactions between mother and infant that influence the transmission of HIV. Potential routes of infection are identified, and maternal and infant risk factors for transmission are explored. The role of the immune system in controlling HIV infection in the infant is discussed. Finally, preventive measures for reducing vertical transmission are proposed and evaluated.

Introduction

Infants born to mothers infected with human immunodeficiency virus (HIV) are at high risk of HIV exposure: vertical transmission is the primary route of HIV-1 and HIV-2 infection in children. The number of children at risk from HIV-1 perinatal transmission has increased in recent years. The World Health Organisation (WHO) estimated that at the end of 1992, more than 5 million women of childbearing age were infected; 4 million of these were African. WHO has also predicted that by the year 2000, 13 million women worldwide will be HIV-positive. By improving our understanding of vertical HIV transmission, it may be possible to control the paediatric AIDS epidemic.

Routes of infection

There is evidence to support three distinct routes of infection: transplacental, intrapartum, and from breast feeding.

Transplacental infection

Evidence for HIV transmission in utero comes from studies in which fetuses aborted from HIV-1-positive women had virological signs of HIV-1-infection. A recent study by Brossard and colleagues examined 100 consecutive aborted second trimester fetuses from HIV-1-infected women. Thymic tissue was tested for the presence of HIV DNA by the polymerase chain reaction (PCR). Only two of the fetuses tested positive, and this was confirmed by the presence of viral DNA in other organs. Of interest, both positive fetuses had died in utero following major complications in pregnancy (advanced AIDS with systemic toxoplasmosis, and recurrent antepartum haemorrhage); in contrast, none of the 92 electively terminated fetuses were HIV-positive. This suggests that vertical transmission rates of HIV in early pregnancy are low compared with overall transmission rates. Although placental macrophages, which can sustain a productive HIV-1 infection in vitro, may have a role in HIV transmission in utero, it seems likely that additional adverse factors are required for HIV to breach the placental barrier.

Intrapartum

Indirect evidence suggests that the most common time for transmission may be during the intrapartum...
period. Studies of twins show that there is a discrepancy in vertical transmission rates between the two infants. First-born twins, who spend more time in the birth canal in contact with cervicovaginal secretions, had an increased risk of HIV-1 infection.\textsuperscript{8} Cervical epithelial cells support a productive infection in vitro,\textsuperscript{9} and virus has been detected in the cervical secretions of 40% of HIV-positive pregnant women.\textsuperscript{10} The European Collaborative Study estimated that caesarean section halved the risk of perinatal transmission,\textsuperscript{11} supporting the idea that a major factor in vertical transmission is contact with cervicovaginal secretions. The length of time in contact with these secretions may also increase transmission: recent data from the Women and Infants Transmission Study suggest that infants born to women in whom membranes ruptured more than 4 h before delivery had a higher rate of transmission than those born after shorter periods between membrane rupture and delivery.\textsuperscript{12}

Other work has provided more direct evidence in favour of intrapartum transmission. In a prospective study of 50 infants born to HIV-1-seropositive mothers, peripheral blood mononuclear cell samples were tested for HIV-1 (by PCR, viral culture and p24 antigen measurements) at birth, and at the ages of 4–9 weeks and 5–9 months.\textsuperscript{13} Sixteen infants were diagnosed as HIV-infected by 4–9 weeks, but only five of those infants were positive for PCR or virus culture at birth. The authors noted that the HIV-1 viral load at birth in the other infants subsequently found to be infected was thus below the resolution of their assays, and this suggested active viral replication in the first weeks of life. In addition, the results suggested that these infants may have been infected late in pregnancy or during delivery.

In a study of non-breast-feeding HIV-infected French women, mathematical modelling was used to estimate that 65% of transmitting mothers infected their infants during delivery.\textsuperscript{14} Of the infants infected in utero, it was further estimated that 95% had been infected during the 59 days prior to delivery. The study also showed that the timing of vertical transmission was dependent on the mother’s immunological status: those with worsening immune deficiency at delivery were more likely to have transmitted HIV-1 to their infant in utero.

Another recent study examined the relationship between maternal HIV viral load and the likelihood of vertical transmission.\textsuperscript{15} Quantitative competitive reverse transcriptase PCR was used to measure the level of HIV-1 RNA in the plasma of 30 infected pregnant women, during gestation and at the time of delivery. The infants were followed prospectively for a minimum of 6 months, and their HIV infection status determined by virus culture and by PCR. Eight of the 10 women with the highest levels of plasma HIV-1 RNA transmitted HIV-1 to their infants, whereas none of the 20 women with the lowest levels did (p = 0.0002). From further statistical analyses, the authors projected an approximate threshold for mother-to-child transmission of about 100 000 viral RNA copies per ml of maternal plasma. Although larger studies are awaited to refine these estimates, this is the first work to demonstrate an apparent maternal viral load threshold for vertical transmission.

**Breast feeding**

Following initial observations by Ziegler and colleagues,\textsuperscript{16} it is now well established that HIV can be transmitted from mother to infant via breast milk.\textsuperscript{17} HIV-1 can be isolated from breast milk in up to 70% of HIV-infected mothers. The risk of transmission from breast feeding alone may be as high as 29%,\textsuperscript{19} and this is related to duration of breast feeding.\textsuperscript{20} The causal link between infected breast milk and HIV transmission is demonstrated by reports of a previously uninfected child acquiring HIV-1 from its infected wet nurse,\textsuperscript{21} and of HIV-1 transmission to an infant from unpasteurised pooled breast milk.\textsuperscript{22}

There has recently been considerable debate about the relative risks to the infant of breast feeding from HIV-infected mothers. In countries with a reliable supply of cheap bottled milk, the advice is clear: it is safer to bottle feed than breast feed. But in less developed countries where bottle milk formula is in short supply and relatively expensive, and water is frequently contaminated,\textsuperscript{23} the infant mortality from malnutrition and other infections may exceed that from HIV infection. Several groups have attempted to evaluate this dilemma using mathematical models. The critical variables are: the relative risks of mortality in children who are not breast fed compared with those who are; the total under-five mortality, and the mortality attributable to HIV infection; and the risk of HIV infection from breast feeding. Results from earlier analyses suggested that for rural populations in less developed countries, breast feeding should be promoted, even with respect to known HIV-positive mothers.\textsuperscript{24,25} More recently, results from a refined model, which included the duration of breast feeding as an independent risk factor for HIV infection, suggested that beyond 7 months of life, the mortality risk of HIV transmission probably outweighs the mortality benefit from breast feeding.\textsuperscript{26} As the conclusions from these continuing studies evolve, it is important that their recommendations lead to coherent guidelines from health policy organizations.
Maternal factors affecting vertical transmission

Vertical transmission rates of HIV-1 and HIV-2

Quoted rates of vertical transmission of HIV-1 range from 14.4% (European Collaborative Study) to 20–30% in African and Haitian studies. The rate of sexual and vertical transmission of HIV-2 is lower than HIV-1. A prospective study of female sex workers from Senegal found that the incidence of HIV-2 remained stable over eight years and estimated the prevalence doubling time to be 31 years, compared to 5.7 years for HIV-1. Vertical transmission of HIV-2 is rare and studies (albeit with low sample sizes) have as yet failed to show vertical transmission in populations with low HIV-2 incidence. However, individual cases of vertical transmission of HIV-2 have been reported.

Maternal risk factors for transmission

Maternal factors that increase the risk of vertical transmission are not fully understood. A more advanced stage of HIV infection, with low CD4+ lymphocyte counts and high p24 antigenaemia, appears to favour vertical transmission. Obstetric complications, which increase fetal exposure to maternal blood, also increase vertical transmission of HIV-1. Other modifiable factors during pregnancy can significantly influence the risk of vertical transmission of HIV-1. A retrospective analysis of data obtained from the New York Mothers and Infants Cohort Study found that cigarette smoking after the first trimester, and premature rupture of membranes, adversely modified the effect of CD4+ lymphocyte count on vertical transmission.

Other possible factors affecting vertical HIV transmission include acquisition of HIV infection during pregnancy and the presence of other sexually-transmitted diseases. Newly-acquired HIV infection during pregnancy would expose fetuses to high virus titres before the infection could be controlled by the maternal immune system. Sexually-transmitted diseases, such as syphilis and herpes simplex virus infection, may cause genital ulceration, thus increasing infant contact with maternal blood during vaginal delivery.

Maternal HIV-1 variants and vertical transmission

The in vivo genetic variation of HIV-1 significantly affects the biological characteristics and pathogenicity of the virus. One study found that HIV-1 sub-types capable of generating more proviral copies per cell resulted in increased vertical transmission rates. Another group studied characteristics of HIV-1 obtained from transmitting and non-transmitting mothers. HIV-1 from transmitting mothers replicated more efficiently in human peripheral blood mononuclear cells (PBMC), compared to HIV-1 from non-transmitting mothers, and was capable of infecting one or more human T-lymphocytic cell lines.

Vertically-transmitted HIV-1 sub-types may retain their virulence in the infant. An investigation of two mothers who had each infected three infants found multiple HIV-1 sub-types in each mother. All infants were infected with multiple HIV-1 variants similar to those isolated from their mothers. Another study found that rapid disease course in mothers correlated with the rate their infants developed AIDS.

Unprotected sexual intercourse with multiple partners may expose a woman to a range of HIV variants. A Rwandan study showed that HIV-1-infected women with more than one sexual partner during the first trimester were at higher risk of transmitting HIV-1 to their infants. In addition, unprotected intercourse with multiple partners during the 5 years prior to pregnancy increased vertical transmission rates. This risk was independent of CD4/CD8 ratio, parity, history of sexually transmitted diseases and evidence of genital infection during pregnancy.

Thus, the sexual behaviour of a woman before and during pregnancy may determine the characteristics of the HIV sub-types she carries, which in turn may profoundly affect the outcome in her child.

Maternal nutrition and health

Nutritional status has an important effect on susceptibility to infections. In particular, vitamin deficiency may adversely affect mucosal integrity. One study of 567 HIV-infected pregnant Malawian women examined serum vitamin A concentrations and the transmission rate of HIV-1. Women with low vitamin A concentrations (<0.7 mmol/l) had a vertical transmission rate of 32.4%, compared to 7.2% in the high vitamin A group (>1.40 mmol/l). Other work has shown that vitamin A deficiency in HIV-1-infected adults may increase progression to AIDS. Vitamin A has stimulatory effects on T-cell and B-cell function, and may thus be important for a continued and appropriate immune response to HIV.

Vitamin A deficiency could increase vertical HIV-1 transmission rates in a number of ways: (i) decreased T cell activity may result higher viral titres, which is known to increase transmission rates; (ii) the integrity of the placenta may be impaired by pathological changes in the fetal membranes and the uterine mucosa, and (iii) the susceptibility of the birth canal to trauma may be increased.
It is well recognized that other sexually-transmitted diseases (STD), such as gonorrhoea, syphilis, and herpes simplex virus infection, may increase the transmission of HIV. Likely mechanisms include the impairment of genital mucosal integrity, and local and systemic effects on host immunity. Thus, identifying and treating common sexually transmitted diseases may reduce HIV transmission.

A recent prospective randomized controlled community-based trial in Tanzania investigated the effect of treating STDs on HIV incidence. More than 12,000 individuals were recruited into the study from six intervention and six pair-matched communities. The intervention consisted of five components: establishment of an STD reference clinic; training of existing staff from health centres in diagnosis and treatment of STDs; regular supply of appropriate drugs for STD treatment; regular review of the community clinics by a program officer; and periodic visits by health educators to provide information on STDs and encourage prompt attendance for treatment of symptoms. A random cohort of about 1,000 adults from each community was surveyed at the beginning of the study and at follow-up 2 years later. Baseline HIV prevalences were 3.8% and 4.4% in the intervention and comparison communities, respectively. The proportions of HIV-seronegative individuals seroconverting during the 2 years were 1.2% in the intervention communities and 1.9% in the comparison communities; the estimated relative risk ratio for the intervention was 0.58 \( (p = 0.007) \). There was no reported difference in the sexual behaviour (number of partners; condom use) between the intervention and comparison communities, suggesting that the reduction in HIV incidence was a result of prompt and appropriate treatment of intercurrent STDs. Although the study did not specifically examine vertical transmission of HIV, it would seem reasonable to expect a reduction in infant HIV incidence as well because of (i) reduced maternal HIV prevalence; (ii) reduced genital ulceration and hence intrapartum HIV exposure.

### Role of the infant in vertical transmission

Perhaps surprisingly, vertical transmission of HIV does not occur in the majority of pregnancies. What role does the infant play in this complicated interaction? Evidence is accumulating to suggest that the immune system of the infant may influence the outcome of HIV transmission.

The immune system has two arms; (i) innate immunity: including neutrophils, macrophages and complement; and (ii) acquired immunity: T lymphocytes (cell-mediated) and B lymphocytes (humoral), where the response is adaptive and is directed towards specific antigens. Particular attention has focused on the role of cytotoxic T lymphocytes in HIV infection.

### Action of cytotoxic T lymphocytes

Cytotoxic T lymphocytes (CTL) have an important role in the control of many virus infections. CTL are a subset of T lymphocytes, which recognize short peptide fragments of endogenous proteins presented in association with autologous Class I major histocompatibility complex (MHC) molecules. When a virus infects a cell and replicates, new virus proteins are present in the cytoplasm, peptides from which are presented at the cell surface by MHC molecules. These virus-peptide-MHC complexes are recognised by mature CTL which initiate lysis of the infected cell.

Human HIV infection is usually associated with a persisting viraemia. However, most infected individuals remain asymptomatic for years, suggesting a constant and vigorous virus-host interaction. In adults, strong HIV-specific CTL responses are found during the asymptomatic phase of HIV-1 infection and decrease markedly with progression to AIDS. This association suggests an important role for CTL in the control of HIV infection in adults.

### Analysis of cytotoxic T lymphocytes in infants at risk of vertical transmission

HIV-specific CTL responses have also been demonstrated in infants born to HIV-infected mothers. One study examined activated HIV-specific CTL responses in 29 HIV-1 seropositive children. Twenty-four children produced HIV-specific CTL, and the response of freshly isolated CTL was weaker in symptomatic children. In this study, four of the children with no HIV-specific CTL responses became seronegative (sero-reverted) when maternal antibody decayed, suggesting that they had not been infected.

One complication of mother-infant immunological studies is that transplacentally transferred maternal antibody (IgG) may persist for several months in the infant. This makes serological confirmation of HIV infection in the infant unreliable. However, infection with live virus is an effective stimulator of the CTL response. The presence of HIV-specific CTL therefore suggests recent exposure to HIV (although not necessarily a productive infection, as defective virus may also stimulate CTL responses) even when other evidence of infection is obscure.

The observation that many children of HIV-infected mothers are not themselves infected thus raises the possibility that they have been exposed to the virus but have cleared the infection. One study...
found HIV-specific CTL responses in seropositive children, but also in four seronegative children born to HIV-1-positive mothers. Another group described an HIV-seronegative infant born to an HIV-1-infected mother, where the infant made a transient CTL response to an HIV-1 peptide epitope at 3 months of age. A similar case has been described, and a further study found HIV-specific CTL responses in 25% of uninfected children born to HIV-1-infected mothers.

Recovery from vertically acquired HIV-1 infection

Several studies of vertical HIV-1 transmission include unexplained reports of sero-reverting infants who had previous evidence of HIV-1 infection by virus culture or by PCR analysis. However, results must be interpreted with caution because the PCR reaction is so easily contaminated. In the best documented case so far, the infant was born to an HIV-1 infected mother. At 19 and 51 days post partum, peripheral blood samples were taken and HIV-1 was cultured. Serum at day 51 was also positive for HIV-1 by PCR. However, the infant was seronegative at 1 year and HIV-1 viral culture and PCR studies have also been negative on repeated occasions. However, it has been argued recently on the basis of phylogenetic analysis that the virus isolates from the infant were too distantly related to those from the mother to be the result of vertical transmission, and may thus have been the result of contamination. Although samples were thoroughly checked to ensure that no contamination had occurred, and that all samples were from the same infant, there still remains a small chance of contamination. Further studies are awaited from this and other mother-infant pairs to resolve this important debate.

Prevention of vertical transmission

Caesarean section

The evidence already discussed suggests that a majority of HIV-1-infected infants are infected either in late pregnancy or during labour. Several epidemiological investigations into the role of method of delivery and vertical transmission rates of HIV-1 have indicated that there may be some benefit to the infant if it were delivered by caesarean section.

A meta-analysis, which included six prospective cohort studies, concluded that the risk of HIV-1 infection was significantly affected by mode of delivery: 20.2% for vaginal delivery and 14% for caesarean section. The European Collaborative Study found that women who had caesarean sections had more advanced disease, as defined by CD4 count and clinical symptoms. These factors increase the risk of vertical transmission, and when accounted for, the risk of vertical transmission of HIV-1 was found to be 51% lower in caesarean sections than in vaginal deliveries. A randomized trial of caesarean vs. vaginal delivery is about to begin. However, caesarean section is not without its risks to the mother, and cleansing of the birth canal with virucidal agents prior to delivery may prove a more acceptable alternative.

Zidovudine therapy

Zidovudine (AZT) has become established as a first-line agent in the treatment of symptomatic AIDS. However, much controversy, both in the medical and in the popular press, has surrounded the use of zidovudine in asymptomatic HIV-1-infected adults. The Concorde group showed no benefit to symptom-free HIV-1-seropositive adults during a three year, randomized double-blind placebo-controlled trial, contradicting evidence from previous trials, which were smaller and were of shorter duration.

Recent work has investigated the role of zidovudine in prevention of vertical transmission of HIV-1. The ACTG trial of 409 infected pregnant women used oral zidovudine or placebo antenatally, starting between 14 and 34 weeks’ gestation. Intravenous zidovudine/placebo was administered throughout delivery and zidovudine/placebo syrup given to infants for a further 6 weeks. All mothers were symptom-free, had CD4 counts above 200/μl and none had previously received zidovudine. There was a significant reduction in vertical transmission in the zidovudine group (8.3% zidovudine, 25.5% placebo). Side effects were similar in both groups except for haemoglobin levels, which were slightly reduced in zidovudine-treated infants. The mechanism of this decrease in vertical transmission is probably by a zidovudine-induced reduction in maternal viral load. Further trials are needed to assess the optimum time to commence anti-retroviral therapy. Recent studies have suggested that antiviral drugs are most effective in reducing virus load during the first few days after therapy is initiated. Therefore, if most transmission occurs at birth, it may only be necessary to treat just prior to parturition.

The ACTG trial and another study, of 104 cases of zidovudine in pregnancy, failed to find any congenital abnormality or increase in spontaneous abortion and stillbirth that could be attributed to zidovudine. However, there is still unease over the long-term effects on infants treated with anti-retroviral drugs during fetal development. Follow-up of zidovudine-treated children, the majority of whom would not be infected with HIV-1 in the absence of
zidovudine, is necessary so that accurate risk-benefit analyses are available. A further concern over the widespread use of zidovudine in asymptomatic pregnant mothers is the risk of inducing zidovudine-resistant HIV. Exactly this phenomenon has been described in a mother previously treated with zidovudine for 15 months, who transmitted zidovudine-resistant HIV-1 to her infant. The generation of zidovudine-resistant HIV would have adverse implications for the longer term treatment of mothers and their infected infants, not to mention the general population.

Conclusions

Prevention of vertical HIV transmission on a worldwide basis faces many hurdles. An obvious and cost-effective plan would be to reduce the prevalence of HIV in pregnant women. Adult education programs to reduce HIV infection in women continue to develop, but in many parts of the world are confounded by established religious, political, and cultural beliefs. However, the recent report of reduction in HIV incidence by simple treatment of STDs (with no reported changes in sexual behaviour) offers hope for such achievable interventions worldwide.

Rates of transmission during parturition could be reduced in developed countries by judicious use of caesarean section, but this and other interventions are unlikely to become widely available in rural parts of less-developed countries, where HIV infection is most prevalent and those at risk unknown to medical services. Anti-retroviral therapy throughout pregnancy would in many countries be limited by expense, and in addition may carry a risk of inducing resistant strains of HIV. However, 'single shot' therapy at the time of delivery may be efficacious and would certainly be more affordable. Further work is needed to evaluate this approach in greater detail.

Breast feeding by HIV-infected mothers is a Damocles sword. In areas where bottled milk powder is cheap and plentiful, the risks to the infant of HIV transmission outweigh the benefits of breast feeding. However, in the majority of less-developed countries, the reverse is true, and breast feeding in these areas should continue to be encouraged.

The intriguing evidence that some infants are able to clear a productive HIV infection offers hope for the prevention and treatment of HIV infection in infants and in adults. Further research into the immune mechanisms for apparent resistance to, and recovery from, HIV infection may provide new approaches to control the paediatric AIDS epidemic.

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