Perinatal Transmission of HIV and Diagnosis of HIV Infection in Infants: A Review

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Abstract

Paediatric HIV infection has become a major burden on families, communities and health services worldwide. The vast majority of children now acquire HIV as a result of mother to infant (vertical) transmission. Recent major advances have occurred following the greater understanding of the risk factors for perinatal transmission and the role of antiretroviral therapy in preventing transmission. Now that interruption of vertical transmission is possible, early identification of HIV-infected pregnant women is critical. As of June 1997, HIV infection has been diagnosed in 37 children under 15 yrs of age in the Republic of Ireland; 32 as a result of maternal to infant transmission. The exact timing of HIV transmission during pregnancy is unclear but it is estimated that 60-70 per cent of infants may be infected at the time of delivery with approximately 30 per cent infected earlier in gestation. Vertical transmission rates vary from 15-40 per cent in different global areas. Antenatal and perinatal zidovudine treatment can reduce this rate by 60-70 per cent. Risk factors for the vertical transmission of HIV-1 are multifactorial. These factors include maternal disease status, in particular maternal viral load, route of delivery, duration of membrane rupture, presence of obstetric complications and infant feeding practices. Definitive diagnosis of HIV infection in infancy has been difficult in the past. Direct viral detection methods now allow the reliable diagnosis of HIV infection in the first few months of life.

The most effective intervention to reduce perinatal HIV infection will be the better identification of HIV positive pregnant women with the subsequent introduction of measures to interrupt vertical transmission of HIV.

On a global basis, the incidence of paediatric HIV infection and AIDS is increasing rapidly. By the year 2000, 5 million children will be infected and 5 to 10 million will have been orphaned as a result of maternal AIDS deaths[1,2]. With the advent of effective donor blood and blood product screening the vast majority of children now acquire HIV as a result of mother to infant (vertical) transmission.

Epidemiology

Perinatal or vertical transmission of HIV was first reported in 1982[3]. As of 31 December 1996, 1,731 persons in Ireland had been infected with HIV, approximately 20 per cent of whom were women (Department of Health HIV/AIDS statistics). Of HIV positive individuals, IV drug users constitute the majority (46 per cent) with homosexuals being the second largest risk group (22 per cent).

As of June 1997, HIV infection has been diagnosed in 37 children in the Republic of Ireland under 15 yrs of age. Of these, 7 have died from HIV related illness and 12 children currently have AIDS. One child has contracted the virus through receipt of blood products, 32 as a result of maternal to infant transmission and 3 were born in countries with a high prevalence of childhood HIV infection.

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HIV prevalence in pregnant women

The prevalence of HIV infection in women of childbearing yrs varies from 0 to 0.1 per cent of pregnant women in the United Kingdom, Canada and Australia[4-8] to more than 30 per cent in the more severely affected African nations[9-12].

In Ireland, results of anonymous, unlinked antenatal screening carried out between the last quarter of 1992 and the last quarter of 1995 inclusive reveal an HIV positive rate amongst pregnant women of 0.016 per cent (1/6,427), with an estimate of 0.037 per cent (1/2,675), in the Eastern Health Board area and a rate of 0.005 per cent in all other areas combined.

HIV infection and pregnancy outcome

Reports from African countries have demonstrated an increased incidence of prematurity, growth retardation and fetal death in HIV infected mothers[13-15]. Findings from studies in the developed world report generally good outcomes[16] with only occasional reports of low birth weight[17] and premature delivery[18].

Vertical transmission

Vertical transmission rates vary by geographical area[13,19-26]. Rates are higher in Africa (30-40 per cent) and lowest in Western Europe (15-20 per cent). The vertical

transmission rate is between 12 and 14 per cent in the Republic of Ireland (Nourse et al, in press).

Timing of Vertical Transmission

The exact timing of HIV transmission during pregnancy is unclear. Evidence exists for intrauterine, intrapartum and immediate postnatal transmission. Based on viral culture, p24 antigen and viral load in infants at delivery, it is estimated that 60-70 per cent of infants may be infected at the time of delivery with approximately 30 per cent infected earlier in gestation[27-31]. Proposed definitions for in-utero versus intrapartum transmission of HIV-1 have been published by the Paediatric Virology Committee of the AIDS Clinical Trials Group[28] where it is suggested that an infected infant whose peripheral blood mononuclear cells (PBMC) are positive by culture or by the polymerase chain reaction (PCR) within 48 h of birth is classified as having intrauterine transmission, whereas transmission is classified as intrapartum if diagnostic studies are negative during the first week of life and become positive at a later date.

Risk factors for Maternal-Infant HIV transmission (Table I)

Numerous antenatal risk factors for vertical transmission of HIV-1 have been investigated including mother's disease status, route of delivery, duration of membrane rupture, presence of obstetric complications such as maternal haemorrhage or infection and perinatal feeding practices. A general consensus is that this risk is multifactorial. The European Collaborative Study (ECS)[20] found that vertical transmission rates were significantly associated with vaginal delivery, decreasing maternal CD4 count and gestation at delivery <35 weeks.

Much recent attention has focused on the clinical, virological and immunological status of the mother prior to and at delivery and the subsequent effect on HIV vertical transmission rates[32,33]. Advanced maternal disease, low CD4 cell count, high viral load as determined by p24 antegenemia or viral titers and the syncytium-inducing phenotype of the maternal virus have been associated with increased risk of mother-to-infant HIV transmission[13,32,34,35,35-37].

Of particular recent interest, maternal HIV-1 viral titer during pregnancy and at delivery has been found to significantly increase vertical transmission rates[36,38-44], with some researchers postulating a threshold RNA viral titer below which HIV transmission is unlikely to occur[42,45]. Specific viral subtypes are also thought to have different effects on vertical transmission[46]. Many of these issues have yet to be fully resolved.

Elective Caesarean section has a potentially protective effect on vertical transmission[47-49]. Theoretically, it may prevent infant contact with massive amounts of maternal blood and cervical secretions. It may reduce late ascending infection and maternal-fetal transfusion, both of which may occur during delivery. There is a need for controlled randomised trials, one of which is underway in Europe.

TABLE I
Factors postulated to increase mother to child transmission of HIV

Maternal Factors
Advanced clinical stage
Low CD4 lymphocyte counts
P24 antigenemia
Increased HIV-1 viral titer
Absence of protective antibodies against gp 120, principal neutralising domain and V_3 loop.
Presence of other sexually transmitted diseases.
Breast-feeding
Viral factors
Viral genotype and phenotype
Virulent strain of HIV eg. syncytium inducing
Host factors
Genetic
Premature delivery
Obstetric factors
Prolonged rupture of membranes
Vaginal delivery
Invasive procedures during labour

Postnatal viral transmission and breast-feeding

There is substantial evidence to support the transmission of HIV-1 via breast milk. HIV-1 has been isolated in the cell free fraction of human milk[50] as well as within cells of breast milk and colostrum of HIV-1 positive mothers[51,52]. Ziegler published the first report of an infant infected with HIV-1 via breast milk[53]. Despite this risk, in the absence of safe alternatives, one cannot advise all HIV positive mothers not to breast feed. Breast milk has the well known advantages of low cost, nutritional value and sterility. Additionally, its immunological properties may well protect against prenatally acquired virus infection and may minimise infections and prolong the incubation time in an HIV-infected infant[51]. The WHO consensus statement states that "where infectious diseases and malnutrition are the main causes of infant deaths and the infant mortality rate is high, breast-feeding should be the usual advice to pregnant women, including those who are HIV-infected"[54].

Interruption of Vertical Transmission

Zidovudine, a thymidine derivative has been demonstrated to be an effective treatment to decrease viral burden and delay disease progression in HIV infected adults and children.

In April 1991 a phase III randomised, double-blinded, placebo-controlled clinical trial (ACTG076)[55] was initiated by the Paediatric Aids Clinical Trials group to evaluate whether antenatal zidovudine therapy could reduce the risk of maternal-fetal transmission in HIV-infected women. Zidovudine treatment was associated with a 67.5 per cent reduction in the risk of HIV transmission; transmission occurred in 8.3 per cent of the treatment group versus 25.5 per cent of the placebo group. The only adverse effects noted were neonatal neutropenia, hyperbilirubinemia and anemia all of which resolved after treatment ceased.

Further reports suggest that antenatal oral zidovudine may be as effective as antenatal oral plus IV zidovudine during labour and the 3-component ACTG 076 regimen in decreasing maternal to infant HIV-1 transmission[56].

A phase 3 trial (ACTG 316) assessing the efficacy of oral nevirapine given in the third trimester in preventing mother to child transmission of HIV is underway. Initial results are encouraging (personal communication).

Immunoprophylaxis is another strategy by which it may be possible to alter transmission of HIV from the mother to the fetus or infant. A subgroup of the ACTG is currently conducting such a trial in the US; giving HIV positive mothers monthly hyperimmune globin (HIVIG) during the third trimester and likewise to the infant within 2 h of birth. A phase 1 safety and pharmacokinetic study has revealed that infusion of HIVIG or IVIG was well tolerated when administered to pregnant women and newborns[57]. Further results are awaited.

Despite the optimism surrounding ZDV prophylaxis, other strategies for reducing vertical transmission must not be forgotten. These include preventing HIV infection among women, identification of the HIV positive mother, attempting to establish the route and timing of fetal infection, minimising invasive intervention during labour and giving appropriate advice about breast-feeding.

Now that interruption of vertical transmission is possible, early identification of HIV-infected pregnant women is critical if any of these interventions are to succeed. Both voluntary (targeted or universal) and mandatory antenatal testing have been proposed. This is a controversial area but it is clear that HIV counselling and voluntary antenatal testing offer opportunities to identify HIV-infected women, begin therapy, and potentially prevent HIV infection in children.

Diagnosis of HIV infection in infancy (Table II)

Early diagnosis of the HIV-infected infant is important as both prophylactic and therapeutic interventions are currently available.

Definitive diagnosis of HIV infection relies on obtaining the relevant laboratory studies and most importantly, interpreting the results appropriately.

Elisa / Western Blot / Line immunoassay antibody (LIA) tests

The standard screening test for HIV antibodies is the enzyme-linked immunosorbent assay (ELISA) which primarily detects IgG antibodies to a limited number of HIV antigens. In adults it is extremely sensitive and specific (>99 per cent) and of relatively low-cost[90]. Western Blot analysis detects IgG antibodies to multiple HIV-specific antigens; is also highly sensitive and very specific, is significantly more expensive than an ELISA but is used as an excellent confirmatory test for HIV antibodies[91]. LIA tests result in less visual distraction and clearer antigenic profiles. Their performance is reliable for detection of HIV-1 and HIV-2 antibodies, and at a substantially lower cost[58].

TABLE II
Investigations available to diagnose HIV infection in infancy.

HIV IgG antibody assay (Elisa/Western Blot/Line immunoassay)
HIV IgM/IgA assay
HIV P24 antigen assay
HIV Blood culture
Polymerase chain reaction (PCR)
HIV RNA quantitation

These tests, however, do not reliably identify HIV infection in the infant born to an HIV-infected mother as all children born to an HIV-infected mother will have serum antibodies to HIV secondary to transplacental passage of maternal IgG for up to 18 months. Direct test for HIV include HIV P24 antigen assay, HIV blood culture, polymerase chain reaction (PCR) and quantitation of HIV RNA.

HIV P24 antigen

A new immune complex dissociated (ICD) method has improved this assay's sensitivity to 90 per cent (specificity >97 per cent) in specimens from children tested at 1-6 months of age. This is becoming one of the more popular tests for HIV infection in the young infant[59-61].

HIV culture

HIV culture from peripheral blood mononuclear cells of plasma remains the diagnostic gold standard against which newer techniques are measured. It is highly specific and indicates the presence of active HIV infection. Drawbacks include the need for biohazard facilities, its expense, limited availability, its lack of sensitivity in the first months of life (70-80 per cent), the relatively large blood volume required and the 2-6 week interval before availability of results.

HIV DNA Polymerase chain reaction (PCR)

Polymerase chain reaction (PCR) is an in vitro technique for the amplification of specific nucleic acid sequences to levels that are readily detectable in the laboratory. The test is rapid (a few days), automated, significantly less costly than HIV culture and is highly sensitive (100 per cent) and specific (>97 per cent) for detection of HIV DNA sequences in children aged 1-6 months[61-64].

As with HIV culture, PCR results may be falsely negative in infants younger than 1 month of age. This window of negativity is interesting. It may occur because the virus is transiently cleared from the newborn's circulation into regional lymphoid tissue, only to reappear after 1 month of age or it may reflect late acquisition of the virus during the intrapartum period[59,65].

Quantitative plasma HIV RNA testing

This technique has recently been shown to be more sensitive for early detection of HIV infection than other

diagnostic tests (sensitivity 98 per cent in infants between 14 days and 3 months of age with a threshold of test sensitivity at 103 copies/ml of plasma)[66]. If similar findings of high sensitivity and high specificity occur in future studies, determination of HIV infection status of perinatally exposed infants may occur earlier than currently possible and may improve the ability to distinguish the timing of intrauterine versus intrapartum HIV transmission.

At this time, most if not all infected infants can be identified by 8 to 12 weeks of age using a combination of the above tests.

Conclusion

Vertical HIV transmission is the primary mode of infection in children. Measures to better identify HIV positive pregnant women are crucial.

Much more needs to be known about the relative risks of transmission in different mothers and at different times during gestation. Early studies suggest that vertical transmission can be interrupted or at least reduced; more studies are necessary to define optimal drug use, optimal dosage and timing of intervention. Protocols for the early diagnosis of HIV infection in infancy need to be developed and the greater availability of testing is awaited. The use of newer drugs and immunotherapy may give reason for optimism in the interruption of vertical transmission and the treatment of the HIV-infected patient.

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