

# Mother-to-Child Transmission of Human Immunodeficiency Virus (HIV) in Ireland: A Prospective Study

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## Abstract

Symptomatic HIV infection was first diagnosed in an Irish child in 1985. A prospective study was initiated to determine the vertical transmission rate (VTR) of HIV and the average age of infant seroreversion and to monitor clinical, immunologic and virologic evidence for HIV infection in seroreverters. Ninety three HIV positive infants have been prospectively identified since 1985. The predominant underlying maternal risk factor for HIV infection is intravenous drug use (IVDU) (96 per cent). Of 93 infants, median gestational age was 40 weeks and median birth weight 3125 grams. Ninety-four per cent of infants were bottle fed. Currently 72 (77 per cent) infants are uninfected, 12 (13 per cent) are infected, 4 (4.5 per cent) are indeterminate and 5 (5.5 per cent) have been lost to follow up. The intermediate estimate of vertical transmission rate (VTR) is 14.3 per cent. The median age at documented seroreversion was 12 months. There are no significant differences between infected and non-infected children in male/female ratio, gestational age, mode of delivery or birth weight. Strategies to reduce the transmission of HIV among drug users in combination with routine antenatal screening and antiretroviral prophylaxis of vertical transmission are all measures which can reduce HIV infection in our children.

## Introduction

Perinatal or vertical transmission (VT) of human immunodeficiency virus (HIV) was first reported in 1982<sup>1</sup>. Three years later, in 1985, the first Irish child with symptomatic HIV infection was diagnosed. As of March 1997, 128 HIV positive children have been identified. HIV infection has been confirmed in 37, of whom 19 have been diagnosed with acquired immunodeficiency syndrome (AIDS). Thirty-two (86 per cent) of these children have acquired HIV as a result of maternal transmission during the pregnant or perinatal period. This study was initiated in 1985. The data presented is based only on the cohort of infants followed prospectively from birth and therefore does not include all HIV infected children in the Republic of Ireland.

## Methods

### Enrolment and follow up

Notice was given from adult HIV services and from each of the 3 Dublin maternity hospitals of expectant HIV infected women. Epidemiological information was collected for these mothers and infants were referred to the Paediatric HIV service. Evaluations were scheduled at birth, 3, 6, 9, 12, 15 & 18 months of age according to HIV status and 3 monthly or yearly thereafter. Clinical evaluation and, where possible, immunologic and virologic evaluation were carried out at each time point.

### HIV testing

HIV testing was carried out at the virus reference laboratory, University College Dublin using testing methods available at the time. HIV antibody was detected using 2 tests; an ELISA (Wellcozyme, Wellcome Diagnostics) and either an alternative ELISA or a particle agglutination assay (Serodia HIV, Fujirebio Inc. Tokyo). Antibody is currently detected using an antigen sandwich enzyme immune assay (Murex HIV 1+2, Murex Diagnostics, Dartford, Britain and a particle agglutination assay (Serodia HIV, Fujirebio Inc, Tokyo). Confirmation assay was performed initially with HIV-1 Western blot assay (Cambridge Biotech) and is now performed with Inno-Lia confirmation assay (Innogenetics, Zwijndrecht, Belgium).

p24 Antigen is detected using Murex HIV antigen Mab and Murex HIV antigen ICD (Murex Diagnostics, Dartford, UK) (Previously performed by Abbott EIA assay). HIV DNA from the pol region of the genome is amplified from DNA extracted from peripheral blood mononuclear cells in a nested PCR assay similar to that described by Ou et al 1988<sup>2</sup>. HIV RNA levels in plasma are quantified using the HIV monitor assay (Roche Diagnostics). Virus cultures were performed on a subset of infants at the Department of Virology, St. Thomas's Hospital, London.

In accordance with current recommendations<sup>3</sup>, children were considered infected if they fulfilled 1 of the following criteria:

- HIV antibody positive  $\geq$  18 months of age
- HIV antibody positive plus other virologic evidence of infection (p24 antigen, PCR or culture) documented on at least 2 occasions separated by a 2 week interval and < 18 months of age

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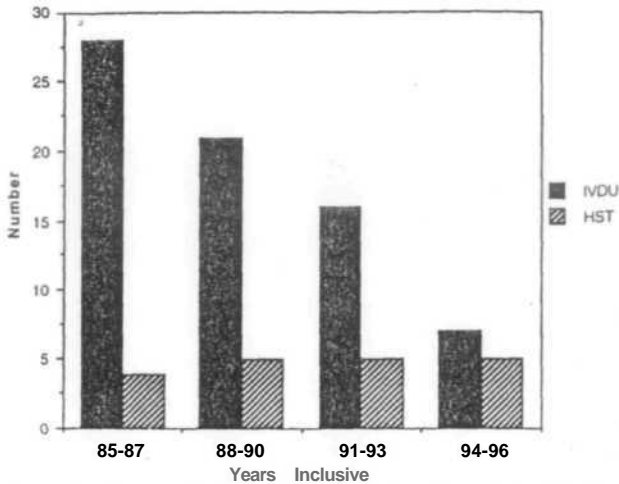


Figure 1 - Prospectively identified infants born to HIV infected mothers and infant status by year of birth (1985-1996).

• CDC AIDS case definition criteria

Children were considered uninfected if they were  $\geq 9$  months of age, antibody negative, and had no clinical evidence of infection. All other children are considered to be of indeterminate status<sup>4</sup>.

The vertical transmission rate (VTR) was calculated as recommended by the Ghent conference on mother to child transmission of HIV infection<sup>4</sup>. The numerator is the number of infected children and the denominator the number infected plus the number uninfected. An intermediate estimate of VTR assumes that indeterminate cases provide no information on HIV infection status. A lower estimate of VTR assumes that indeterminate cases are not infected. The age at seroreversion is defined as the midpoint between age at the last positive antibody test and age at the first negative test.

Results

Ninety-three infants born to 71 HIV infected women were identified between August 1985 and March 1997 (Figure 1). Most women had other children with parity ranging up to 6 at the time of delivery.

Maternal Characteristics

The median age of mothers at delivery was 24.8 (range 20-36.3) yr. The risk factors underlying infection in the mothers were intravenous drug use (IVDU) by the woman

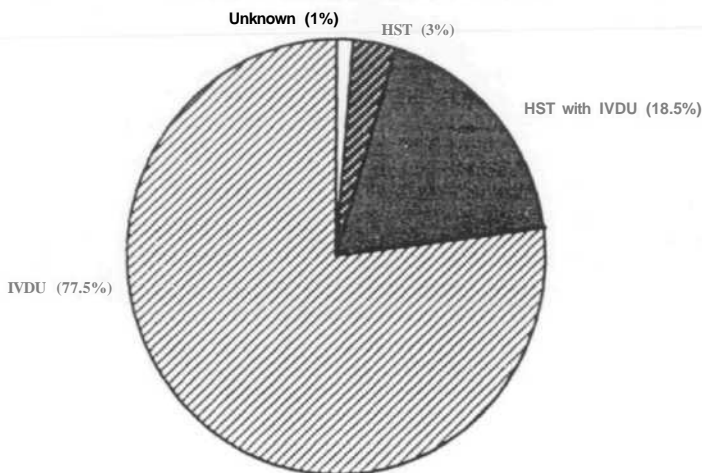


Figure 2 - Maternal risk factors for HIV infection.

TABLE I  
Mode of delivery and infection status of 71 mothers and 93 infants (August 1985 - March 1997)

	n(%)
Mode of Delivery	
Vaginal	77 (82.8)
Instrumented Vaginal	6(6.5)
Caesarean Section	9 (9.7)
Not recorded	1 (1.0)
Maternal Status at Delivery	
Asymptomatic	64 (68.8)
Symptomatic	13(14.0)
Not recorded	16(17.2)
Current Infection Status of Infants	
Uninfected	72 (77)
Infected	12(13)
Indeterminate	4 (4.5)
Lost to follow up	5(5.5)

herself (n=72; 77.5 per cent), heterosexual contact with an IV drug user (n=17; 18.5 per cent) or heterosexual contact with a partner not identified as being an IV drug user (n=3; 3.2 per cent). In one case risk factors were unknown (Figures 2 and 3).

Table I illustrates the mode of delivery and infection status of mothers and infants. As of March 1997, 29 (31 per cent) of mothers have died of HIV related causes; 29 are living with HIV infection and 13 have been lost to follow up.

Infant Characteristics

Forty-eight infants were male and 45 female. Ninety (94 per cent) infants were bottle fed. Median gestational age was 40 weeks (range 33-44 weeks) and median birth weight was 3125 g (range 1705-4250 g) (Table II). Details of the infection status of infants are included in Table I. Four infants are of indeterminate status and 5 infants have been lost to follow up.

Eighty-four infants have been tested at  $\geq 15$  months. Of these, 72 are HIV negative and 12 are HIV positive (Fig. 1). Thus the intermediate estimate of VTR for this group is 14.3 percent (95 percent C.I. 7.6-23.6 percent). Of all 93 infants the lower estimate of VTR is 12.9 per

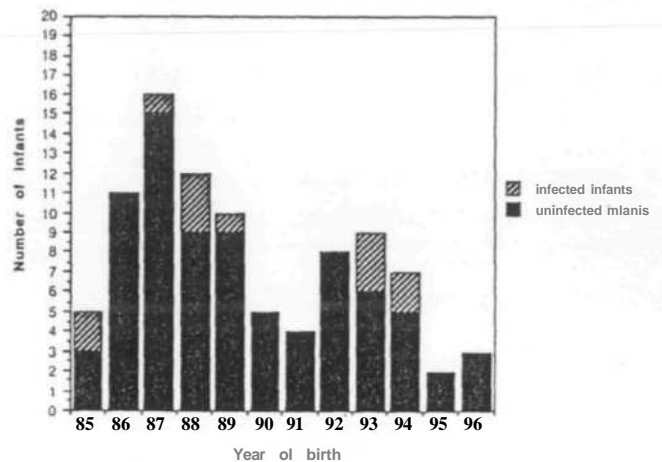


Figure 3 - Maternal risk factors for HIV infection by year of birth of infant (1985-1996).

TABLE II  
Comparison of characteristics between infected and non-infected children

	Seronegative (n=72)	Infected (n=12)
Male: Female ratio	1.5:1 (43:29)	1:1.4(5:7)
Proportion interventional delivery	14/72(19%)	1/12(0.8%)
*Gestational Age at birth (weeks)	40 [33-44]	39 [37-41]
*Birth Weight (g)	3076(1705-4250]	3450 [2892-3860]
*median values given		

cent (95 per cent C.I. 6.8-21.5 per cent). The median age at diagnosis of infected infants was 11 months (1 month to 2 yr).

Since the introduction of prenatal, intrapartum and postnatal (infant) administration of zidovudine prophylaxis in 1995, none of the 6 infants born to HIV infected mothers has evidence of infection to date (one born in 1997 not included in Figure 1).

The median age at documented seroreversion in 72 seroreverters was 12 months. The earliest documented seroreversion was at 4 months but because of poor compliance with protocol, seroreversion was documented as late as 34 months in 1 child. No seroreverting child had a documented positive test at  $\geq 15$  months of age. No positive tests were documented after seroreversion during a median follow-up period of 22.5 months (range 0-99.5 months). Thirteen failed to return for further testing once seroreversion was documented. None of these children have any HIV related illness.

Of 84 children with a definitive outcome (12 infected and 72 uninfected), the current median age of infected children is 66 months and of seroreverters is 75 months. There are no significant differences between infected and non-infected children in male/female ratio, gestational age, mode of delivery or birth weight (Table II)

### Discussion

From August 1985 to March 1997, 93 infants born to 71 HIV infected women have been prospectively identified (Fig 1). This number most likely under-represents the true number of infants born to HIV infected mothers as, in the absence of universal antenatal screening, all HIV infected mothers are not identified. Some women fail to disclose their status. Others are not aware of their status, and importantly, many do not perceive themselves to be at risk of infection. Most of the HIV infected children attending the paediatric HIV service have not been recognised to be at risk of infection at the time of birth (Nourse et al, Paediatric HIV infection in the Republic of Ireland and need for antenatal screening, in press).

It appears from this study that the number of prospectively identified infants born to HIV infected mothers in the Dublin area is declining. However updated figures for 1997 (9 women in total) and 1998 (4 women

in the first quarter) suggest that this trend is now being reversed.

Recently published results of an unlinked anonymous survey of HIV infection among antenatal women estimate the overall national prevalence of HIV infection in childbearing women at 0.016 per cent, (1/6,427) with an estimate of at least 0.037 per cent, (1/2,675) in the Dublin area (Surveillance Subcommittee of the National AIDS Strategy Committee, June 18, 1997) Early identification of HIV infected pregnant women is critical in order to facilitate strategies to halt mother to infant transmission of HIV. Antenatal testing can be voluntary, mandatory, targeted or universal and is a controversial issue. Decisions to test are made on an individual country basis and to date have been largely governed by prevalence rates in the population considered. Now that effective strategies for prevention of VT are available, where resources permit, unlinked routine antenatal testing should be introduced in any endemic areas of HIV infection. It is interesting to note that despite being aware of their status and the resulting risks of vertical transmission, 10 infected women in this report proceeded to have further children.

The study reveals the importance of drug use as a risk factor for HIV infection in Irish women. In 96 per cent of cases, infection in the mother was either directly or indirectly linked to intravenous drug use. However, the number of new cases with IVDU as a risk factor has shown a downward trend over the last 10 yr while the number of new cases with heterosexual transmission (HST) as a risk factor has remained constant. It would appear that HST is becoming a relatively more important risk factor for HIV infection in women in the Republic of Ireland (Figure 3).

In the cohort studied, vaginal deliveries were usual. Evidence has suggested that delivery by Caesarean section may result in less vertical transmission of HIV<sup>Sft</sup> but most centres are awaiting the results of further prospective studies before adopting a change in routine policy for delivery of the HIV positive mother.

Although 69 per cent of mothers were asymptomatic at the time of delivery, in this pre-triple therapy era, 29 (31 per cent) of the 71 mothers have since died from HIV related illness. This illustrates the enormous effect of HIV infection on a family, including those members uninfected by the virus.

The majority of women had full term deliveries and most infants were of average birth weight. HIV infection during pregnancy does not appear to have adversely affected the fetus. Findings from studies in the developed world report generally good outcomes<sup>7</sup>, with only occasional reports of low birth weight<sup>8</sup> and premature delivery<sup>9</sup>. In this study, only 3 women breast fed their infant, the last doing so in 1991. Due to the documented transmission of HIV from breast milk to infants, current WHO recommendations are that mothers in countries where safe alternatives to breast milk are readily available should not breast feed their babies<sup>10</sup>.

Whether based on all available information or restricting it only to those infants greater than 15 months

when last tested, the VTR of HIV infection in the Republic of Ireland lies around 12-15% with confidence intervals of 6-23% and is consistent with rates reported from other European studies<sup>1,3</sup>.

We found no significant differences between infected and non-infected children with regard to potential risk factors for vertical transmission. However our relatively small numbers would preclude such a finding. Importantly there have been no subsequent diagnoses of HIV infection among seroreverting children.

### Conclusion

Intravenous drug use is the main risk factor underlying HIV infection in this group. Increasingly we are witnessing the result of heterosexual spread of HIV infection to partners of drug users who have themselves never abused drugs. The impact of HIV infection on children (infected or uninfected) is huge and is exemplified by the significant number of mothers (31 per cent) who have died.

The VTR of 12-15 per cent is similar to that of other European studies and is lower than that reported from the U.S. and Africa. We are optimistic that antiretroviral prophylaxis will further reduce this rate. Current anecdotal reports of even more successful intervention when Caesarean section and antiretroviral therapy are combined leads one to hope that vertically transmitted HIV infection will be a completely preventable disease. In this study, lack of evidence of HIV infection among clinically well seroreverters followed for up to 99 months post seroreversion is reassuring.

As the greater number of options available to prevent VT of HIV can have an enormous impact on childhood HIV infection, the time for routine antenatal testing for HIV infection is now here.

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