

Mother-to-child transmission of HIV: positive impacts



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Mother-to-child-transmission (MTCT) of HIV remains the major mode of paediatric HIV infection. Advances in the prevention of MTCT over the past decade and a half represent a major public health achievement. Strategies to prevent MTCT are now the standard of care for countries rich enough to afford the interventions. As such, perinatally acquired HIV in countries like the USA and Europe is now a rare event.

With clearly documented declines in MTCT rates in resource rich countries, the focus is shifting towards any downsides of these strategies in pregnant women and for fetuses exposed *in utero* to antiretroviral (ARV) drugs and to infants postnatally. Cumulative evidence still supports the benefits of these strategies in preventing MCTC of HIV, with continued benefits for HIV pregnant women and their infants, and with minimal adverse outcomes. Knowledge of HIV infection status in pregnancy is critical for identifying the need for MTCT prevention. However, antenatal testing rates to identify HIV infected women is variable and an area that warrants attention. The overwhelming challenge in the 21st century is up scaling the availability of MTCT interventions in resource poor areas where more than 90% of the world's HIV infected children now reside, and to develop optimal MTCT regimens that can be practically adopted in these settings.

The milestones leading to the current successful MTCT intervention programmes has been a journey over more than 2 decades. The first was the recognition that the human immunodeficiency virus was not limited to transmission among the homosexual population but was also acquired via heterosexual contact, and transmissible from infected women to infants¹. The identification of risk factors associated with MTCT transmission, including the first report from Australia documenting the role of breast milk as a significant mode of HIV transmission², and more recently, the estimates of the timing of MTCT transmission³ have set the stage for studies on methods to interrupt transmission. The major risk factors associated with MTCT transmission viz. virus burden to which the child is exposed, duration of exposure and factors facilitating transfer

of HIV from mother to child became the basis for studies on strategies for interrupting transmission⁴.

In 1994, the landmark trial on the use of the first licensed ARV, zidovudine (AZT), to prevent the transmission of HIV from mother to infants was halted early. Preliminary findings were so overwhelmingly in favour of its efficacy that continuing the study was unethical. PACTG 076 was a three part ARV approach to the interruption of HIV transmission from mother-to-child where pregnant women received AZT from 14 weeks of gestation, then intravenously during labour followed by 6 weeks of AZT to the infant. MTCT transmission was reduced by two thirds (from 22.6% to 8%)^{3,5}.

Since then, progress has been such that the three proven intervention strategies regarding ARV use to decrease maternal viral load antenatally and postnatal ARVs to infants – a component of which may be post-exposure prophylaxis, minimising duration of exposure to HIV by cesarean section before labour and before rupture of membrane and avoiding continued postnatal exposure to HIV by formula feeding infants – now achieves a phenomenally low rate of MTCT transmission. Historical MTCT rates of 20-30% are now in the order of 1-2%⁶⁻⁹. The success of these measures in resource rich settings has been measurable and sustained. Perinatal HIV incidence in the USA has fallen by about 95% since 1992¹⁰, similar to patterns in the UK and Ireland, and a selected Italian cohort⁶⁻¹⁰.

It appears that, overall, the benefits continue to outweigh potential risks¹¹. HIV does not adversely affect the clinical course of women¹². Combination therapy with highly active antiretroviral therapy (HAART) during pregnancy is efficacious, with the majority of women achieving viral suppression¹³. Recent medium-term follow-up supports evidence for healthy maternal survival after use of ARVs during pregnancy, be it zidovudine monotherapy or HAART¹⁴. Longer follow-up to 21 years in an Italian cohort is in further support of this⁸. Concerns that ARVs are associated with prematurity has not been a consistent finding¹⁵. Whilst concerns about mitochondrial toxicity in infants exposed to zidovudine *in utero* have been raised, evidence from large clinical trials do not support a significant risk of severe congenital anomalies, increase in malignancy or impaired growth and development in children exposed *in utero* to ARVs¹⁶.

However, strategies to prevent transmission can only be implemented if the diagnosis of HIV infection is known antenatally. Routine antenatal screening for HIV infection has long been a controversial issue, with those who argue against routine antenatal testing basing concerns on human rights issues, impact of false-positives results, the adequacy of counselling and appropriate post-test care of the woman¹⁷.

In Australia, paediatric HIV has always been rare. However, of concern is that children diagnosed with perinatal infection in the MTCT prevention era (post-1994) reflect missed opportunities for prevention strategies due to the lack of an antenatal diagnosis in pregnant HIV infected women. National surveillance data from 1994-2003 report a total of 206 perinatal exposures identified, 34 of

which resulted in an HIV infected child. A disturbing proportion, 68% (23/34) of infants, were offspring of women whose HIV diagnosis was not made antenatally (Table 1). Cumulative data from 1982 – 2006 on the number of perinatally infected children in Australia show a substantial increase in mother-to-child-transmission rates if HIV infection is made postnatally compared to antenatally, reflecting the missed opportunities for prevention of MTCT (Figure 1).

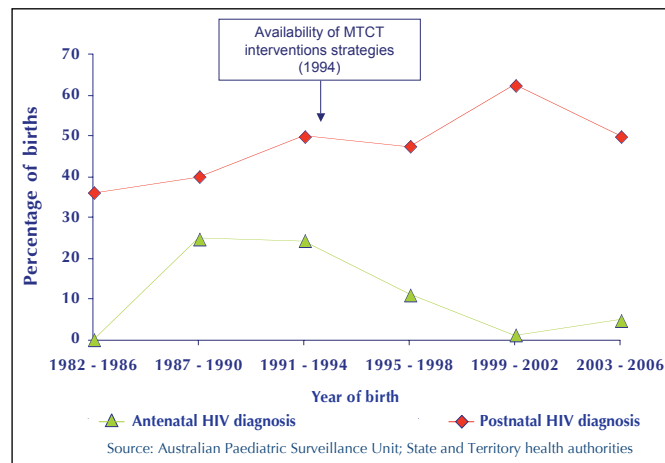
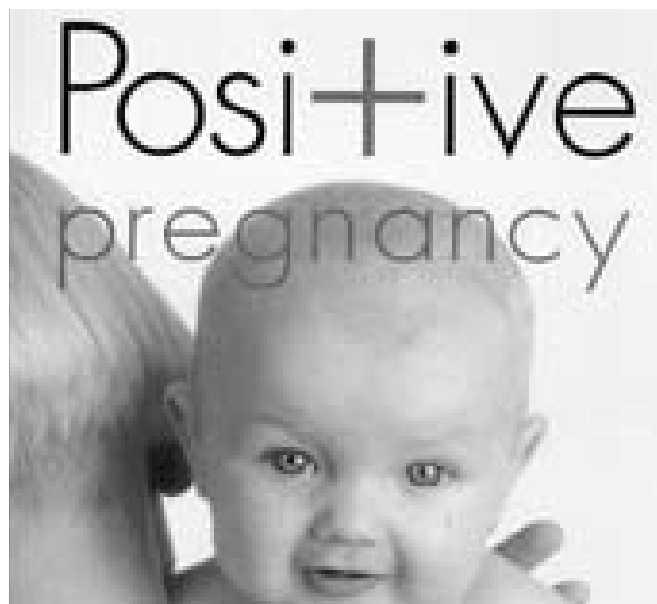


Figure 1: Perinatal HIV infection in Australia (1982 – 2006), by year of birth and timing of mother's HIV diagnosis.
Acknowledgement: Ann McDonald, National Centre in HIV Epidemiology and Clinical Research (NCHECR).

The Royal Australian and New Zealand College of Obstetricians (RANZCOG) recommend routine testing (a 'universal testing' approach) as part of antenatal care, whilst the 2006 National HIV testing policy recommends routine testing with essentially an 'opt-out' approach¹⁸. The extent of antenatal HIV screening in Australia is not known but studies indicate that only 50-60% of obstetricians offer HIV tests antenatally^{19, 20}. The variable rate of antenatal HIV testing is also reflected in other centres in countries resourced to support testing^{8, 21, 22}.

Overall, the public health challenge for the 21st century is up scaling access to workable MTCT prevention strategies in resource poor settings. Simple, successful interventions could mean preventing millions of HIV infected infants per year. The news is somewhat encouraging, for example access to ARVs for MTCT programmes appear to have increased in recent estimates, although progress is slow, and access to interventions still remains dismal in areas of greatest need (Figure 2)²³. Recent focus on how to best to minimise transmission of HIV via breast milk by feeding practice and ARV regimens may provide part of



From *Positive Pregnancy*, a resource booklet for pregnant women living with HIV. Paediatric HIV Service, Sydney Children's Hospital, Randwick, revised 2008.

a workable solution to impact on the current transmission rates in countries where infants are dependent on breast feeding for survival²⁴.

In summary, the news is good for MTCT of HIV in rich countries where new cases of paediatric HIV are rare, and the downsides of these programmes minimal. An identified area of concern is the missed opportunities to prevent cases of HIV infected infants in these countries for lack of antenatal testing. Significant challenges exist for extension of the same success in preventing children from acquiring HIV in poorer countries.

Figure 2: Percentage of pregnant women living with HIV and HIV exposed infants receiving antiretroviral prophylaxis for MTCT from seventy one middle and low income countries, 2004 - 2005²³.

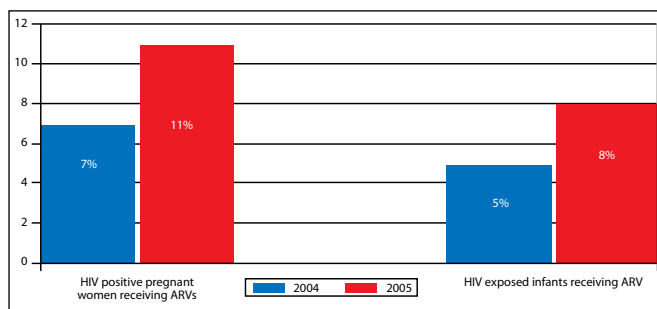


Table 1. No. infected infants in Australia identified by timing of maternal HIV testing 1994-2003¹⁸.

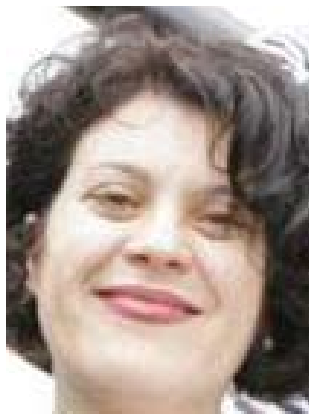
	Before birth:		At or after birth :		Total:	
	No. exposed	No. with HIV	No. exposed	No. with HIV	No. exposed	No. with HIV
1994-1995	24	7	20	8	44	15
1996-1997	16	3	10	7	26	10
1998-2001	46	0	7	5	54	5
2002-2003	38	1	1	0	39	1
Total	160	11	45	23	206	34

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Intrauterine infection: preterm birth and pulmonary impact



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... chorioamnionitis is a condition that cannot be diagnosed accurately until after the event, its cause appears multifactorial and non-specific, and treatment cannot be designed until after the cause is found – and then it is too late. Where are we going wrong? There is a long road ahead that must be taken because, in a time of low perinatal morbidity and mortality, the disorder is rapidly assuming an important role, if only by default. No longer is chorioamnionitis merely an interesting finding for pathologists to demonstrate to their colleagues¹.

This is an excerpt from a letter published anonymously in the *Lancet* in 1989. Acute chorioamnionitis is the histological hallmark of intrauterine infection and remains today the focus of intense, and increasing, research interest. This interest is underpinned by the association of chorioamnionitis with preterm delivery. Extreme prematurity is the fundamental, unresolved problem in perinatal medicine, has associated high morbidity and mortality, and accounts for a significant proportion of the

health expenditure in the developed world². The preterm delivery rate is increasing in Australia, from 6.8% in 1991 to 8.1% in 2005¹. Advancement in intensive care practice has increased survival of very preterm neonates, and this has meant an increase in diseases that are directly related to prematurity, such as cerebral palsy and neonatal chronic lung disease (CLD).

Epidemiology

Histological studies of the placenta of live-born infants consistently report chorioamnionitis to be most common in preterm populations, with the highest rates in the lowest gestational age groups, and the predominance in pregnancies less than 32 weeks' gestation. A recent Australian study of 3928 preterm infants between 20-34 weeks' gestation demonstrated the clear inverse relationship between histological chorioamnionitis and gestation, with the incidence of chorioamnionitis in those born at 20-24 weeks 66%, decreasing to 16% at 34 weeks².

Pathogenesis of intrauterine infection

There are four potential pathways for intrauterine infection. The first and most common route is ascending infection from the lower genital tract. Infrequently, infection can occur via retrograde passage of organisms from the peritoneal cavity via the fallopian tubes, haematogenously from the maternal circulation and from invasive antenatal diagnostic procedures, such as amniocentesis².

Ascending intrauterine infection

After overgrowth in the vagina and cervix, organisms gain access to the space between the amniotic membranes and the uterus to cause localised inflammation, and this can cause rupture of the membranes. Further extension of infection may