Perinatal exposure to HIV among children born in Australia, 1982–2006

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ABSTRACT

Objective: To describe the pattern of perinatal HIV exposure and outcomes among children born in Australia, 1982–2006.

Design and setting: National surveillance for perinatal HIV exposure.

Participants: Women with HIV infection and their perinatally exposed children.

Main outcome measures: Trends in the age-standardised rate of perinatal exposure, uptake of interventions by women with an antenatal HIV diagnosis, and rate of mother-to-child transmission.

Results: Between 1982 and 2006, there were 354 reported cases of perinatal HIV exposure among children born in Australia. The age-standardised rate of perinatal exposure per 100 000 live births increased from 2.3 (1982–1986) to 5.1 (1991–1998), 9.9 (1999–2002) and 8.3 (2003–2006). Among children whose mother was diagnosed antenatally, the mother-to-child transmission rate declined significantly, from 25% (4/16; 95% CI, 7%–52%) in 1987–1990 to 5% (4/82; 95% CI, 1%–12%) in 2003–2006 ($P < 0.001$). The rate declined from 8% (4/51; 95% CI, 2%–19%) in 1987–1998 to 1% (2/151; 95% CI, 0.2%–5%) in 1999–2006 among children whose mother used at least two interventions. Mother-to-child transmission remained high among children born to women diagnosed postnatally (39/87, 45%; 95% CI, 34%–56%) and to women diagnosed antenatally who used no interventions (7/15, 47%; 95% CI, 21%–73%).

Conclusion: The increasing rate of perinatal exposure and the decreasing rate of mother-to-child transmission among children whose mothers' HIV infection was diagnosed antenatally were temporally associated with use of interventions for minimising mother-to-child transmission. Mother-to-child transmission remained high when the mother's HIV infection was not known during pregnancy.

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In 1994, it was reported that the risk of mother-to-child transmission of HIV is substantially reduced by treating the mother during pregnancy and delivery, and the infant after birth, with zidovudine.[1] The use of highly active antiretroviral therapy (HAART) during pregnancy has reduced the risk even further.[2] Delivery by elective caesarean section is also associated with lower transmission risk than vaginal delivery.[3] Observational studies indicate that a mother-to-child transmission rate of less than 0.5% can be achieved for non-breastfed children whose mothers have an undetectable viral load at term through use of HAART during pregnancy and delivery.[4-8]

Previous reports of the pattern of perinatal exposure to HIV in Australia indicate increasing use of antiretroviral therapy during pregnancy and avoidance of breastfeeding by women diagnosed with HIV infection before delivery.[9-11] Here, we describe the pattern and outcome of perinatal HIV exposure in children born in Australia, including those born during the HAART era.

METHODS

Reporting of perinatal HIV exposure

Children born to women with diagnosed HIV infection were notified from 1982 to a national registry of perinatal exposure to HIV through an informal network of clinicians coordinated by the Sydney Children's Hospital, and, from May 1993, by paediatricians through the Australian Paediatric Surveillance Unit (APSU), using previously described methods.[12] Cases were also notified after retrospective assessment of perinatal HIV exposure among children born to women with new diagnoses of HIV infection from July 1995.[9,10]

Case definitions

Women with HIV infection diagnosed before or at an exposed child's birth (ie, during the hospital admission for the birth) were classified as having an antenatal diagnosis. Women with HIV infection diagnosed after a child's birth were classified as having a postnatal diagnosis.

Children born before their mothers' HIV diagnoses were included as cases of perinatal exposure if no exposure other than mother-to-child transmission was documented for the child and one of the following criteria was satisfied:

- the child was diagnosed with HIV infection;
- the mother was documented as having acquired HIV infection on a specified date before 1985 following receipt of HIV-infected blood or tissue;
- the mother's HIV infection was diagnosed in an antenatal specimen or dried blood spots collected through newborn screening programs; or
- the mother had a documented history of exposure on a specified date, either before the birth or while breastfeeding.

Newly diagnosed HIV infections, including diagnoses of mother-to-child transmission and AIDS in children, are notifiable in Australia.[13] Diagnoses are based on standardised laboratory tests and procedures.[14] An exposed child was confirmed to be without infection if HIV antibody testing of a specimen from the child at age 18 months or older gave a negative result. From 1998, the absence of HIV infection was also diagnosed using polymerase chain reaction (PCR) testing for detection of HIV RNA.

Data collection and analysis

Information sought on women whose children were perinatally exposed included the date of HIV diagnosis, the reported source of HIV exposure, mode of delivery, and mode of infant feeding. For women with an antenatal HIV diagnosis, information was also sought on use of interventions to minimise mother-to-child transmission. The available interventions were:

- before 1994, avoidance of breastfeeding alone;[4]
- from 1994, avoidance of breastfeeding plus antiretroviral therapy during pregnancy and delivery, and treatment of the newborn;[1,2] and
- from 1999, delivery by elective caesarean section in addition to other interventions, if appropriate.[3]

1 Age-standardised rate of perinatal HIV exposure among Australia-born children, by place of mother's birth

Year of birth	Australia	Oceania (excluding Australia)	High-prevalence countries in: Sub-Saharan Africa	High-prevalence countries in: South-East Asia	Other	Total
Total no. of births with exposure	124*	14*	37*	41*	24*†	267
Exposure rate (per 100 000 live births)						
1982–1986	nc	nc	nc	nc	nc	2.3
1987–1990	nc	nc	nc	nc	nc	2.6
1991–1994	nc	nc	nc	nc	nc	5.1
1995–1998	0.2	0.3	2.0	1.0	nc	5.2
1999–2002	0.4	0.4	9.3	1.6	nc	9.9
2003–2006	0.2	1.1	7.4	1.3	nc	8.3

nc = not calculated because of small numbers in the groups.
* Totals by place of mother's birth are for the period 1995–2006 (total number = 240).
† Including Europe (9), low-prevalence countries in Asia (5), the Middle East/North Africa (4), South and Central America (2), North America (1), and not reported (3). ◆

Information sought on perinatally exposed children included the date and country of the child's birth, and HIV infection status.

Rates of perinatal HIV exposure by state/territory and year of the child's birth were age-standardised, using the Australian population of women aged 15–49 years who delivered a live baby in 2001 as the standard.[15] Rates of perinatal HIV exposure were also age-standardised by the mother's region of birth using the population of Australian-born women in 2001 as the standard.[16] The pattern of perinatal HIV exposure was assessed by year of the child's birth, timing of the mother's HIV diagnosis with respect to the child's birth, and use of interventions by women diagnosed antenatally.

Univariate (χ^2 tests) and multivariate logistic regression analyses were performed to identify factors associated with mother-to-child transmission. The project was approved by the Ethics Committee of the University of New South Wales.

RESULTS

A total of 392 cases of perinatal HIV exposure, including 86 cases of mother-to-child HIV transmission, were reported by 31 December 2007 among children born between 1 January 1982 and 31 December 2006. Of these children, 354 (90.3%) were born in Australia, including 61 children with mother-to-child transmission. These 354 were born to 273 women, and included 25 children born to 19 Aboriginal and Torres Strait Islander women. Further analysis of the pattern of perinatal HIV exposure was limited to the children born in Australia.

Rates of perinatal HIV exposure

The age-standardised rate of perinatal HIV exposure in Australia increased from 2.3 per 100 000 live births in 1982–1986 to 8.3 per 100 000 live births in 2003–2006 (Box 1). Between 1995 and 2006, the exposure rate was stable for children of Australian-born women (0.2 per 100 000 live births). However, it increased for children of women born elsewhere in Oceania and in high-prevalence countries in South-East Asia (to 1.1 and 1.3 per 100 000 live births, respectively, in 2003–2006), and particularly for children of women born in high-prevalence countries in sub-Saharan Africa (to 9.3 per 100 000 in 1999–2002, dropping slightly to 7.4 per 100 000 in 2003–2006).

Maternal HIV exposure

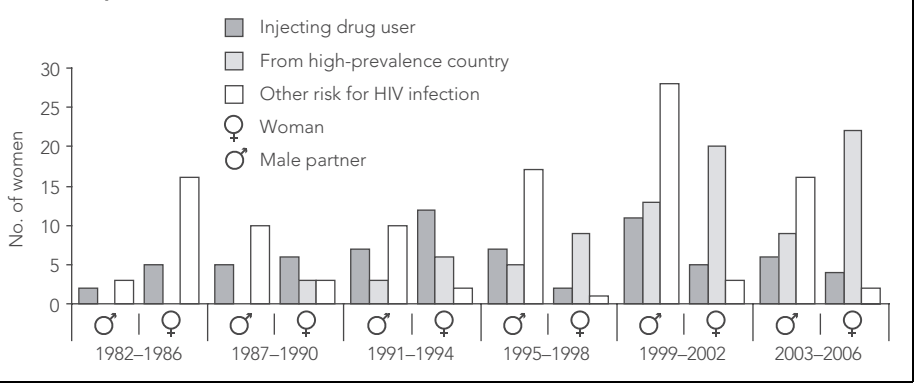
Sources of maternal HIV exposure are shown in Box 2. For women whose first exposed child was born in Australia in 1982–1986, the predominant source of exposure was receipt of HIV-infected blood or tissue before 1985 (16 of 26 women). In contrast, for those whose first exposed child was born in 2003–2006, heterosexual contact — in Australia or overseas — was the most frequent source (31 of 59 women). This included nine women who reported having a partner from a high-prevalence country, mostly in sub-Saharan Africa), and an increasing number who reported heterosexual contact in Australia with a partner with an HIV risk factor other than coming from a high-prevalence country or injecting drug use. Twenty-two women came from a high-prevalence country (12 from sub-Saharan Africa and seven from South-East Asia). Among 19 Aboriginal and Torres Strait Islander women, HIV exposure was attributed to heterosexual contact (17) or injecting drug use (2).

Timing of diagnosis and interventions

The mother had an antenatal HIV diagnosis in 75% of reported cases of perinatal exposure in children born in Australia 1982–2006, including 21 of the 25 children (84%) born to Indigenous mothers. The percentage of mother–child pairs with an antenatal diagnosis increased significantly over time ($P<0.001$), from 11% in 1982–1986, to 66% in 1991–1998, and 98% in 2003–2006 (Box 3).

Uptake of interventions by women with an antenatal diagnosis is shown in Box 4. Avoidance of breastfeeding was the only

2 Source of HIV exposure among women with HIV infection, by year of birth of first exposed child

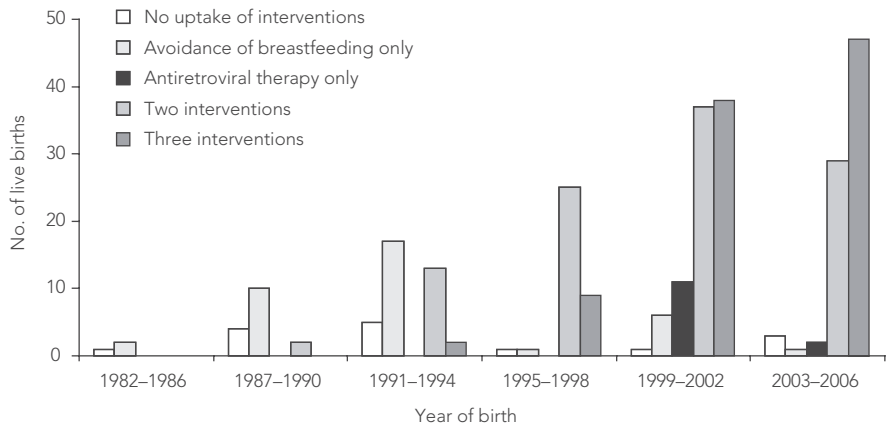


3 Number of Australian-born children reported with perinatal HIV exposure and number infected, by timing of the mother's HIV diagnosis with respect to the child's birth

	Antenatal diagnosis		Postnatal diagnosis		Total	
Year of birth	No. exposed	No. infected	No. exposed	No. infected	No. exposed	No. infected
1982–1986	3	0	25	9 (36%)	28	9 (32%)
1987–1990	16	4 (25%)	15	6 (40%)	31	10 (32%)
1991–1994	37	9 (24%)	18	9 (50%)	55	18 (33%)
1995–1998	36	4 (11%)	19	9 (47%)	55	13 (24%)
1999–2002	93	1 (1%)	7	5 (71%)	101*	6 (6%)
2003–2006	82	4 (5%)	2	1 (50%)	84	5 (6%)
Total	**267**	**22 (8%)**	**86**	**39 (45%)**	**354**	**61 (17%)**

* Includes one mother whose date of HIV diagnosis was not reported. ◆

4 Uptake of interventions by women with an antenatal HIV diagnosis, by year of birth of the exposed child



5 Number of children born in Australia, 1982–2006, to women with an antenatal HIV diagnosis, and number infected, by interventions

Intervention	No. inf/exp	Transmission rate (95% CI)
None	7/15	47% (21%–73%)
Avoidance of breastfeeding	9/37	24% (12%–41%)
ARV in pregnancy	0/13	0
Avoid breastfeeding + ARV in pregnancy	4/101	4% (1%–9%)
Other combinations of two interventions	0/5	0
Three interventions*	2/96	2% (0.3%–7%)
Total	**22/267**	**8% (5%–12%)**

No. inf/exp = no. infected/no. exposed.
ARV = antiretroviral therapy.
* Three interventions = avoidance of breastfeeding, ARV during pregnancy and elective caesarean section. ◆

intervention used by 52% of women (29/56) whose child was born in 1982–1994. Use of antiretroviral therapy during pregnancy plus avoidance of breastfeeding more than doubled, from 30% (11/37) in 1991–1994 to 69% (25/36) in 1995–1998, and then declined, as the use of three interventions steadily increased — from 5% (2/37) in 1991–1994, to 57% (47/82) in 2003–2006.

Mother-to-child transmission

Mother-to-child transmission rates for women with an antenatal diagnosis, by uptake of interventions to minimise transmission are shown in Box 5. Transmission occurred in 47% of children (7/15) born to women who reported using no interventions, and 24% (9/37) whose mothers reported avoiding breastfeeding alone. Rates were much lower in children of women who used two interventions (4%; 4/106) or all three interventions (2%; 2/96). In the six cases where transmission occurred despite use of two or three interventions, the duration of antiretroviral therapy during pregnancy was 3 months or less. No cases of mother-to-child transmission occurred among 21 children born to Indigenous women diagnosed antenatally, including 15 whose mother used at least two interventions.

Among children born to women with a postnatal HIV diagnosis, the mother-to-child transmission rate remained high over the period 1982–2006, in comparison with the rate among women diagnosed antenatally (Box 3). Most of these women reported breastfeeding (62/72; 86%). Most were born in Australia (57; 66%), with smaller numbers born in high-prevalence countries (13; 15%) or another country (16; 19%).

Multivariate analysis, adjusting for year of birth, indicated that lack of use of antiretroviral therapy during pregnancy was associated with an increased risk of mother-to-child transmission (odds ratio [OR], 8.7; 95% CI, 2.9–26.2; $P < 0.001$). Breastfeeding was also associated with increased risk (OR, 2.3; 95% CI, 1.1–4.5; $P = 0.03$). When use of any antiretroviral therapy during pregnancy was excluded from the model, breastfeeding (OR, 2.29; 95% CI, 1.14–4.60; $P = 0.02$) and delivery by modes other than elective caesarean section (OR, 4.04; 95% CI, 1.13–14.37; $P = 0.01$) remained independent predictors of mother-to-child transmission, after controlling for year.

Outcomes of perinatal HIV infection

Of the 61 Australian-born children with perinatally acquired HIV infection, 26 had been diagnosed with AIDS, and 16 had died following AIDS by 31 December 2001. Most AIDS diagnoses (20; 77%) and deaths following AIDS (12; 75%) occurred before the introduction of HAART in mid 1996.

DISCUSSION

The population rate of perinatal exposure to HIV in Australia increased substantially between 1982 and 2006, with increasing rates among women from countries with high HIV prevalence, but not among Aus-

tralian-born women. The decline in the mother-to-child transmission rate among children born to women whose HIV infection was diagnosed antenatally was temporally associated with uptake of available interventions. However, mother-to-child HIV transmission continued to occur among children whose mothers' HIV infection status was not known during pregnancy.

Cases of perinatal HIV exposure were initially reported through a network of HIV specialists. In 1993, reporting was expanded to include a national network of paediatricians, coordinated by the APSU. Because only a small number of specialists manage pregnancy in women diagnosed with HIV infection in Australia, or refer exposed children to paediatricians, APSU reporting is thought to be a reliable indicator of trends in perinatal HIV exposure among women with an antenatal HIV diagnosis. Among women with a postnatal diagnosis, the increasing rate of mother-to-child transmission over time suggests underreporting or underdiagnosis of perinatal exposure that does not result in infection. If mother-to-child transmission occurs in 16% of exposed children who are breastfed,[17] and 39 cases of infection have been diagnosed among 86 exposed children of mothers with a postnatal diagnosis, then an estimated 160 additional children have been exposed but not infected, bringing the total number of exposed children born in Australia by December 2006 to around 515.

The substantial increase in the population rate of perinatal HIV exposure from 1999 coincided with increases in the population of women of childbearing age from countries with high HIV prevalence in sub-Saharan Africa and South-East Asia. The percentage of the Australian population of women of childbearing age who were born in countries in sub-Saharan Africa and South-East Asia increased from 0.6% and 2.9%, respectively, in 1996, to 1.0% and 3.3%, respectively, in 2006.[16] The substantially higher population rate of perinatal HIV exposure among women from high-prevalence countries compared with Australian-born women may reflect differences in HIV prevalence among women of childbearing age by country of birth. The stable rate of perinatal exposure to HIV among Australian-born women suggests that HIV prevalence in this group changed little between 1982 and 2006.

The increase in the population rate of perinatal HIV exposure in Australia in 1999–2002 coincided with the availability of HAART for minimising the risk of mother-to-child transmission. Use of HAART has been associated with a decrease in AIDS diagnoses and death following AIDS among children with perinatal infection in both Australia and in other developed countries.[18-20] Since the development of HAART, women diagnosed with HIV infection may be electing to have children because of the possibility of substantially reducing the risk of transmission and adverse outcomes after perinatal HIV infection.

Use of all three interventions — antiretroviral therapy during pregnancy, elective caesarean section and avoidance of breastfeeding — was associated with a substantially reduced mother-to-child transmission rate in Australia, comparable with rates reported from large international studies.[5-8] In the six Australian cases of mother-to-child transmission that occurred despite the reported use of antiretroviral therapy during pregnancy, the duration of therapy was 3 months or less before delivery, also consistent with results of international studies. Short duration of antenatal antiretroviral therapy has been identified as a risk factor for mother-to-child transmission among women with an undetectable viral load at term.[5-7]

The use of antenatal HIV antibody testing has steadily increased in Australia, to around 60% of pregnant women seen by Fellows of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists in 2004,[21-23] suggesting increasing acceptance of testing among women of childbearing age. However, HIV infection remained undiagnosed during pregnancy for a substantial number of Australian-born women and women from high-prevalence countries. The national policy on antenatal HIV testing was revised in 2006 and recommends that it be offered to all women.[24] The impact of this policy on perinatal HIV exposure and its outcome in Australia is awaited.

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COMPETING INTERESTS

None identified.

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REFERENCES

1 Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal–infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med* 1994; 331: 1173-1180.
2 Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr* 2002; 29: 484-494.
3 European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet* 1999; 353: 1035-1039.
4 Ziegler JB, Cooper DA, Johnson RO, Gold J; Sydney AIDS Study Group. Postnatal transmission of AIDS-associated retrovirus from mother to infant. *Lancet* 1985; 1: 896-897.
5 European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly

active antiretroviral therapy. *Clin Infect Dis* 2005; 40: 458-465.
6 Warszawski J, Tubiana R, le Chenadec J, et al; ANRS French Perinatal Cohort. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. *AIDS* 2008; 22: 289-299.
7 Townsend CL, Cortina-Borja M, Peckham CS, et al. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000–2006. *AIDS* 2008; 22: 973-981.
8 Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Trends in management and outcome of pregnancies in HIV-infected women in the UK and Ireland, 1990–2006. *BJOG* 2008; 115: 1078-1086.
9 McDonald AM, Cruickshank M, Ziegler JB, et al. Perinatal exposure to HIV in Australia, 1982–1994. *Med J Aust* 1997; 166: 77-80.
10 McDonald AM, Li Y, Cruickshank MA, et al. Use of interventions for reducing mother-to-child transmission of HIV in Australia. *Med J Aust* 2001; 174: 449-452.
11 Giles ML, McDonald AM, Elliot EJ, et al. Variable uptake of recommended interventions to reduce mother-to-child transmission of HIV in Australia, 1982–2005. *Med J Aust* 2008; 189: 151-154.
12 Zurynski YA, Peadon E, Bower C, Elliott EJ. Impacts of national surveillance for uncommon conditions in childhood. *J Paediatr Child Health* 2007; 43: 724-731.
13 Guy RJ, McDonald AM, Bartlett MJ, et al. HIV diagnoses in Australia: diverging epidemics within a low-prevalence country. *Med J Aust* 2007; 187: 437-440.
14 Communicable Diseases Network Australia. Interim surveillance case definitions for the Australian national notifiable diseases surveillance system. Canberra: CDNA, Australian Government Department of Health and Ageing, 2004. http://www.health.gov.au/internet/main/publishing.nsf/content/cdna-casedefinitions.htm (accessed Mar 2009).
15 Australian Bureau of Statistics. Births Australia. Canberra: ABS, 2007. (ABS Cat. No. 3301.0.)
16 Australian Bureau of Statistics. Migration, Australia, 2006–07. Canberra: ABS, 2008. (ABS Cat. No. 3412.0.)
17 Nduati R, John G, Mbori-Ngacha D, et al. Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial. *JAMA* 2000; 283: 1167-1174.
18 Lindegren ML, Byers RH, Thomas P, et al. Trends in perinatal transmission of HIV/AIDS in the United States. *JAMA* 1999; 282: 531-538.
19 Doerholt K, Duong T, Tookey P, et al, and the Collaborative HIV Paediatric Study (CHIPS). Outcomes for human immunodeficiency virus-1 infected infants in the United Kingdom and Republic of Ireland in the era of effective antiretroviral therapy. *Pediatr Infect Dis J* 2006; 25: 420-426.
20 Gibb DM, Duong T, Tookey PA, et al; National Study of HIV in Pregnancy and Childhood Collaborative HIV Paediatric Study. Decline in mortality, AIDS and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. *BMJ* 2003; 327: 1019.
21 Elford J, MacDonald MA, Gabb RG, et al. Antenatal HIV antibody testing in Australia. *Med J Aust* 1995; 163: 183-185.
22 Spencer JD, Tibbits D, Tippet C, et al. Review of antenatal testing policies and practice for HIV and hepatitis C infection. *Aust N Z J Public Health* 2003; 27: 614-619.
23 Giles ML, Garland SM, Grover SR, et al. Impact of an education campaign on management in pregnancy of women infected with a blood-borne virus. *Med J Aust* 2006; 184: 389-392.
24 National HIV Testing Policy 2006. Canberra: Ministerial Advisory Committee on AIDS, Sexual Health and Hepatitis, and Department of Health and Ageing, 2006. http://www.health.sa.gov.au/PEHS/PDF-files/hiv-testing-policy-2006.pdf (accessed Jul 2008).

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