

Maternal HIV-1 and HIV-2 infection and child survival in The Gambia

Martin O.C. Ota, Diarmuid O'Donovan, Abraham S. Alabi, Paul Milligan, Lawrence K. Yamuah, Pa Tamba N'Gom, Elizabeth Harding, Koya Ariyoshi, Andrew Wilkins and Hilton C. Whittle

Objective: To compare the survival of children born to HIV-1 or HIV-2 seropositive mothers with that of children born to HIV-seronegative mothers and to evaluate risk factors for mortality.

Design: Physician-blinded prospective study.

Methods: One hundred and one HIV-1-seropositive, 243 HIV-2-seropositive pregnant women, and 468 HIV-seronegative women (control group) matched by age, parity, and health centre, were followed up in a study of mother-to-child transmission of HIV. Mothers and children were seen at 2 and 6 months of age and subsequently followed at 3-monthly intervals up to 18 months of age. HIV infection in children was diagnosed by polymerase chain reaction at 2, 9 or 18 months and by antibody assays at 18 months.

Results: Fifteen per cent of children born to HIV-1-infected mothers died compared with 7% of children born to HIV-2-infected mothers [hazard ratio, 2.3; 95% confidence interval (CI), 1.1–4.7; $P = 0.02$], and 6% of HIV-seronegative mothers (hazard ratio, 2.6; 95% CI, 1.4–5.0; $P = 0.003$). Six of the 17 children known to be HIV-1 infected died compared with none among the eight HIV-2-infected children ($P = 0.13$). High proviral load in the babies, high antenatal maternal RNA plasma viral load, and maternal death increased child mortality significantly.

Conclusions: More children born to HIV-1-infected mothers died in comparison with those born to HIV-2-infected mothers or to mothers from the control group. This effect was due to excess death in HIV-1-infected infants which was associated with a high viral load in the affected mother and child.

© 2000 Lippincott Williams & Wilkins

AIDS 2000, **14**:435–439

Keywords: HIV-1 and HIV-2, perinatal HIV transmission, proviral load, survival

Introduction

The high rise in HIV-1 infection in women in Africa has resulted in an alarming increase in child mortality due to mother-to-child transmission of the virus [1]. Thus, the hard won reduction in child mortality achieved by child survival strategies such as infant

immunization and improved mother and child care [2] is being rapidly undermined [3].

Most reports on the impact of maternal HIV infection on child survival deal with HIV-1 infection [4–6]; there is a dearth of information on the effect of maternal HIV-2 infection on the offspring. HIV-1 and

From the Medical Research Council Laboratories, The Gambia.

Sponsorship: This study was funded by the Medical Research Council, UK, the World Health Organization, the World Bank and the Japanese Foundation for AIDS Prevention.

Correspondence to Dr. Martin O.C. Ota, Medical Research Council Laboratories, Fajara, P. O. Box 273, Banjul, The Gambia.

Tel: +220 495442/6; fax:+220 495919; e-mail: Mota@mrc.gm

Received: 25 June; revised: 24 November 1999; accepted: 2 December 1999.

HIV-2 infections are present in The Gambia. Thus, in order to understand the dynamics of HIV-1 and HIV-2 mother-to-child transmission and its relation to disease progression in children we designed a cohort study to evaluate survival of infants born to HIV-1- and HIV-2-infected, and to uninfected mothers.

Materials and methods

A cohort of pregnant women consisting of HIV-1-, HIV-2-, dually-seropositive and seronegative controls, were recruited to evaluate mother-to-child transmission of HIV [7]. Field assistants visited babies born to these women in their homes at birth or soon after. Further visits in their homes by field assistants and physicians were at 2 and 6 months after birth, and thereafter every 3 months until 18 months of age. At each of these visits, a basic morbidity (or mortality) questionnaire was completed, a complete physical examination of mother and child was carried out, and a 1 ml venous blood sample was collected from the child. All mothers routinely breast-fed their babies. Physicians and field assistants remained blinded as to the HIV status of the subjects until completion of follow-up.

Ethical approval was obtained from The Gambia Government/MRC Ethics committee for this study and full details of the design, recruitment of subjects, laboratory and statistical procedures are provided in O'Donovan *et al.* [7].

Results

Mothers

One hundred and forty four HIV-1-infected, 294 HIV-2-infected, 15 dually seropositive women and 565 seronegative women (control group) were enrolled into the follow-up study. Dually seropositive women and their babies, none of whom were infected, have been excluded from the analysis.

Outcome of pregnancy

The outcome of pregnancy was known for 101 (70%) of HIV-1-infected, 243 (83%) of HIV-2-infected, and 468 (83%) uninfected women (Table 1). The main reasons for loss of follow-up were incomplete or wrong addresses or migration to an unknown destination. As most of the deliveries were at home, we used weights recorded within 72 hours of delivery as birth weights. A higher proportion (nine of 83) of babies born to HIV-1-infected mothers were of low birth weight (< 2.5 kg) compared with (11 of 199) children born to HIV-2-infected [odds ratio (OR), 2.1; 95% confidence interval (CI), 0.83–5.2] or to control (18 of 396) mothers (OR, 2.6; 95% CI, 1.1–5.9) (Table 1). The mean birth weight of the 17 HIV-1-infected and eight HIV-2-infected children did not differ significantly from that of uninfected babies (data not shown).

Follow-up and outcome of all children

We followed up 98 children born to HIV-1-infected mothers, 228 babies born to HIV-2-infected mothers, and 448 babies born to mothers in the control group. Table 1 shows that the proportion of babies lost to follow-up during the study period did not differ significantly between the study groups. The mortality rate was significantly higher in children born to HIV-1-infected mothers compared with those born to HIV-2-infected (hazard ratio, 2.3; 95% CI, 1.1–4.7; $P=0.02$) and uninfected mothers (hazard ratio, 2.6; 95% CI, 1.4–5.0; $P=0.003$), who had similar mortalities.

Figure 1 shows the Kaplan–Meier survival curve of children according to the maternal HIV status. The probability of survival at 18 months of age was 83% (95% CI, 73–89%) for babies born to HIV-1-infected mothers. This was significantly lower than that of babies born to HIV-2-infected mothers and HIV-seronegative mothers whose probability of survival was 92% (95% CI, 88–95%) and 94% (95% CI, 91–96%), respectively. However, after the exclusion of the 17 HIV-1-infected and the eight HIV-2-infected children (see below) there was no significant difference in the survival of the uninfected children according to mater-

Table 1. Maternal HIV infection in relation to morbidity and mortality of offspring.

	HIV-1	HIV-2	HIV negative
Women studied, n (%)	101	243	468
Women died, n (%)	3 (3.0)	2 (0.8)	1 (0.2)
Children (including twins), n (%)	103	246	473
Stillbirths, n (%)	5 (5.0)	18 (7.4)	25 (5.3)
Low birth weight (< 2.5 kg) ^a	9/83 (10.8)	11/199 (5.5)	18/396 (4.5)
Children lost to follow-up, n (%)	20 (20.4)	43 (18.9)	111 (24.8)
Children that died ^a	15/98 (15.3)	16/228 (7.0)	27/448 (6.0)
Mortality rate (per 100 child years), n (95% CI)	12.7 (7.7–21.1)	5.4 (3.3–8.8)	4.8 (3.3–6.0)
No. of HIV-infected children that died ^a	6/17 (35.3)	0/8 (0)	–

^aValues given are n/total in category (%). CI, confidence interval.

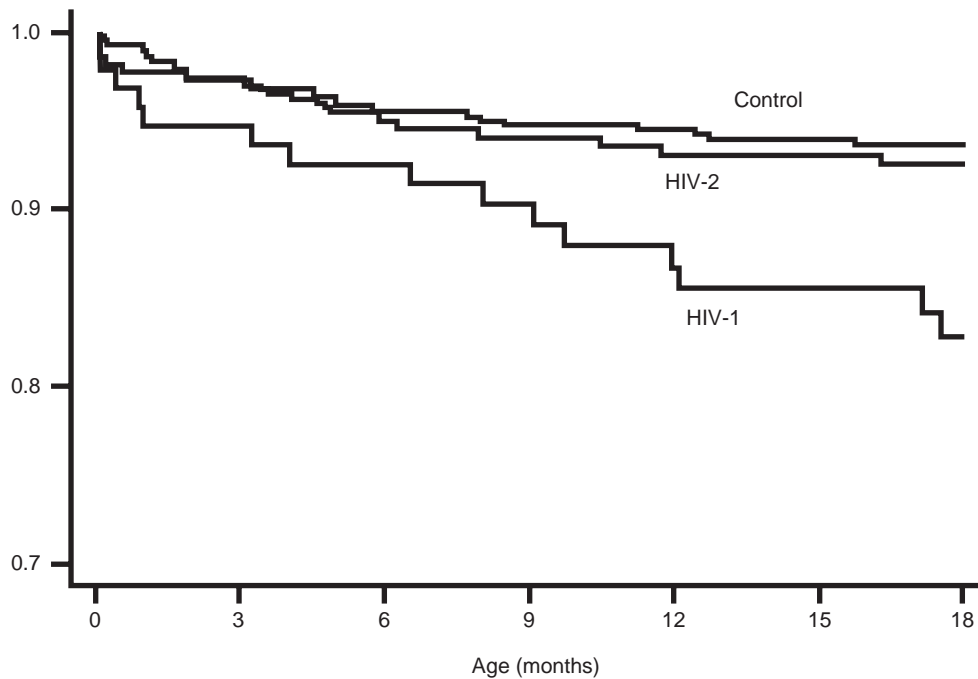


Fig. 1. Survival of children according to maternal HIV status.

nal HIV status: nine of 98 (9.2%) for HIV-1-infected versus 16 of 228 (7.0%) for HIV-2-infected and 27 of 448 (6.0%) for control mothers.

Follow up and outcome of HIV-1- and HIV-2-infected children

In order to evaluate the role that HIV infection in the children had on their survival a sub-analysis of the survival according to HIV status of the children was carried out. It was restricted to those who survived beyond 5 months of age (data not shown). Of the 16 children of HIV-infected mothers who died before 5 months of age only one had an HIV test, whereas of those children surviving to at least 5 months of age, only 3% were not tested. Among the 16 children that died before 5 months of age without being tested, seven of 98 (7.1%) were born to HIV-1-infected mothers compared with nine of 228 (4.0%) born to HIV-2-infected mothers ($P = 0.26$ Fisher exact test); these were omitted from the analysis.

Six of the 17 (35%) HIV-1-infected children died whereas, surprisingly, none of the eight HIV-2-infected children died during the 18 months of follow-up (Table 1). The hazard ratio for an HIV-1-infected child compared with an uninfected child born to HIV-1-infected mother (given survival to 5 months of age) was 15 (95% CI, 3–74; $P = 0.001$). For those children whose HIV status was known, the mortality rates (per 100 child-years) were 30 (95% CI, 13–66) for HIV-1-infected children; 2.1 (95% CI, 0.5–8.6) for uninfected children born to HIV-1-infected mothers, 0 (95% CI, 0–23) for HIV-2-infected children, 2.6 (95% CI, 1.2–

5.4) for uninfected children born to HIV-2-infected mothers and 4.8 (95% CI, 3.3–7.0) for control children.

Survival of HIV-1-infected children in relation to maternal plasma viral load or child's proviral load

Of the six HIV-1-infected children that died and 11 HIV-1-infected children that lived, antenatal maternal plasma viral load was available from five and nine mothers, respectively. The geometric mean antenatal maternal plasma viral load of the babies who died was 60 000 copies/ml (95% CI, 8700–420 000) compared with 19 000 copies/ml (95% CI, 9600–37 000) for mothers whose children lived. The hazard ratio for death for a 10-fold increase in maternal viral load was 2.9 (95% CI, 1.1–7.9; $P = 0.042$).

Six children infected with HIV-1 that died and five children that did not die tested positive by polymerase chain reaction at 2 months of age. The geometric mean proviral load of the six that died was 260 (95% CI, 5.4–12 000) compared with 13 (95% CI, 0.43–410) copies per 10^5 peripheral blood mononuclear cells of the five survivors. The hazard ratio for death for a 10-fold increase in proviral load of the babies was 1.85 (95% CI, 1.1–3.1; $P = 0.021$).

Survival of the babies in relation to maternal death

Six mothers died during the period of study: three were HIV-1-infected, two were HIV-2-infected and one was seronegative. Five of six (83%) of their babies

died in comparison with 53 of 722 (7.3%) babies born to 712 women who lived (relative risk = 11.4; 95% CI, 7.3–17.7; $P < 0.001$). The only surviving child born to these mothers was born to an HIV-1-infected mother. None of these babies were HIV infected: thus death of mother independently and significantly adversely affected the survival of children.

Discussion

This community-based study like another study in Abidjan [8] showed that children born to HIV-1 seropositive mothers had a higher mortality in the first 18 months of life compared with children born to either HIV-2-seropositive or mothers in the control group. Surprisingly, neither mortality of uninfected nor infected children born to HIV-2-infected mothers differed significantly from that of controls. The markedly better survival of the HIV-2-infected children is further evidence that HIV-2 is less pathogenic than HIV-1 [8–10].

The increased mortality of children born to HIV-1-seropositive mothers was accounted for mainly by HIV-1 infection in the child. The majority of deaths in the HIV-1-infected children were in those with a high viral load whose mothers were found to have a high antenatal RNA plasma viral load. A similar association between high viral load in pregnant women and increased risk of rapidly progressive disease and death in the infected offspring has been demonstrated in New York City [11]. Our finding is also in agreement with earlier reports from multicentre studies in America and Puerto Rico [12,13] in which higher plasma viral load in the first months of life was associated with rapid progression of disease and consequently death. However, our study merits special attention as the only community-based study of perinatal HIV-1 and HIV-2 infection in Africa that relates maternal and child viral burden to the survival of the children.

We found high childhood mortality was associated with maternal death which is to be expected as a close correlation between child morbidity/mortality and the quality of parenting has been documented in The Gambia [14] and in Rwanda and Zaire [15,16]. Thus another tragic consequence of the global AIDS pandemic is the death of infected mothers resulting in growing numbers of orphans who overwhelm the caring capacity of the extended family system. Consequently, the WHO targets of a reduction in infant mortality to 50 or less per 1000 live births by the year 2000 [17] may be difficult to achieve. Therefore interventions to decrease mother-to-child HIV transmission such as cheap short-term antiretroviral therapy and educational campaigns to curtail the spread of

sexually transmitted diseases including HIV should be urgently applied.

Acknowledgements

We thank Dr. Neil Berry for helping to set up the assays for viral measurement. We are grateful to Professor B.M. Greenwood, Professor Catherine Peckam and Dr. Maarten Schim van der Loeff for helpful comments and critical review of the manuscript. The field workers are also appreciated for their expert assistance in field work. This study would not have been possible without the help and support of Mr. Saihou Ceesay of the Department of State for Health of The Gambia, and the staff of the health centres where the mothers of the children in this study were recruited during the antenatal period. We are grateful to the parents who agreed to have their children enrolled into this study.

References

1. Blanche S, Rouzioux C, Guihard Moscato ML, *et al.* **A prospective study of infants born to women seropositive for human immunodeficiency virus type 1.** *N Engl J Med* 1989, **320**:1643–1648.
2. United States Agency for International Development. *Child survival – A fifth Report to Congress on the USAID program.* Washington, DC: USAID; 1990.
3. Boerma JT, Nunn AJ, Whitworth JAG. **Mortality impact of the AIDS epidemic: evidence from community studies in less developed countries.** *AIDS* 1998, **12** (suppl 1):S3–S14.
4. Valleroy LA, Harris JR, Way PO. **The impact of HIV-1 infection on child survival in the developing world.** *AIDS* 1990, **4**:667–672.
5. Lallemand M, Lallemand-Le-Coeur S, Cheyner D, *et al.* **Mother-child transmission of HIV-1 and infant survival in Brazzaville, Congo.** *AIDS* 1989, **3**:643–646.
6. Ryder RW, Nsa W, Hassig SE, *et al.* **Perinatal transmission of the human immunodeficiency virus type 1 to infants of seropositive women in Zaire.** *N Engl J Med* 1989, **320**:1637–1642.
7. O'Donovan D, Ariyoshi K, Milligan P, *et al.* **Maternal plasma viral RNA levels determine marked differences in mother-to-child transmission rates of HIV-1 and HIV-2 in The Gambia.** *AIDS* 2000, **14**:441–448.
8. Adjorlolo-Johnson G, De Cock KM, Ekpini E, *et al.* **Prospective comparison of mother-to-child transmission of HIV-1 and HIV-2 in Abidjan, Ivory Coast.** *JAMA* 1994, **272**:462–466.
9. Whittle H, Morris J, Todd J, *et al.* **HIV-2 infected patients survive longer than HIV-1 infected patients.** *AIDS* 1994, **8**:1021–1023.
10. Faye A, Burgard M, Crosnier H, *et al.* **Human immunodeficiency virus type 2 infection in children.** *J Pediatr* 1997, **130**:994–997.
11. Lambert G, Thea DM, Pliner V, *et al.* **Effect of maternal CD4+ cell count, acquired immunodeficiency syndrome, and viral load on disease progression in infants with perinatally acquired human immunodeficiency virus type 1 infection.** New York City Perinatal HIV Transmission Collaborative Study Group. *J Pediatr* 1997, **130**:890–897.
12. Shearer WT, Quinn TC, LaRussa P, *et al.* **Viral load and disease progression in infants infected with human immunodeficiency virus type 1.** *N Engl J Med* 1997, **336**:1337–1342.
13. Abrams EJ, Weedon J, Steketee RW, *et al.* **Association of human immunodeficiency virus (HIV) load early in life with disease progression among HIV-infected infants.** New York City Perinatal HIV Transmission Collaborative Study Group. *J Infect Dis* 1998, **178**:101–108.
14. Greenwood AM, Greenwood BM, Bradley AK, *et al.* **A prospec-**

-
15. **Survey of the outcome of pregnancy in a rural area of The Gambia.** *Bull WHO* 1987, **65**:635–643.
15. Taha TET, Miotti P, Liomba G, Dallabetta G, Chipangwi J. **HIV, maternal death and child survival in Africa.** *AIDS* 1996, **10**:112–113.
16. Ryder RW, Kamenga M, Nkusu M, Batter V, Heyward WL. **AIDS orphans in Kinshasa, Zaire: incidence and socioeconomic consequences.** *AIDS* 1994, **8**:673–679.
17. WHO. *The World Health Report 1995 – Bridging the gaps.* Geneva: WHO; 1995.