



MORTALITY IN A COHORT OF CHILDREN BORN TO HIV-1 INFECTED WOMEN FROM DURBAN, SOUTH AFRICA

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Objectives. To describe mortality in a cohort of infants with vertically transmitted HIV-1 infection.

Patients and methods. Children of HIV-1 infected women were followed up from birth and a record was made at each visit of growth, development and all illnesses. Details surrounding death were obtained from hospital records.

Results. The final cohort comprised 48 infected and 93 uninfected children; there were 25 deaths, 17 of which (35%) were regarded as being HIV-related. The mean age at death of HIV-related cases was 10.1 months (range 1 - 48 months), with 83% of HIV-related deaths occurring before the age of 10 months. The commonest diagnoses at the time of death were diarrhoea, pneumonia, failure to thrive and severe thrush. These findings, together with neurological abnormalities, often presaged rapid deterioration and death.

Conclusions. Mortality among children with vertically acquired HIV infection is high in the first year of life. Death in these subjects was due to the common causes of morbidity and mortality among all children in developing countries. A combination of diarrhoea, pneumonia, failure to thrive, and neurological abnormalities should alert one to the possibility of rapidly progressive disease and death.

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Children with vertically acquired HIV-1 infection appear to progress at different rates towards severe disease and death.¹ While some, approximately 23 - 26%, have a rapidly progressive course and die within the first year, others follow a less turbulent path and remain well into late childhood.² Use of antiretroviral drugs, prophylaxis against *Pneumocystis carinii*

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and other infections in developed countries, and better nutritional and anti-infective measures during care, mean that children are now surviving longer and in a better general state of health. In Africa, which bears the brunt of the disease, these interventions are generally not available because of lack of resources. Knowledge of the patterns and causes of death in HIV-infected children would enable the development of suitable management programmes targeted at these diseases. In addition, the prognostication and identification of HIV-infected children who will progress to early death would be possible. Some information is available on the causes of death in HIV-infected children from Africa,^{3,5} but these data are limited for a number of reasons, including low autopsy rates in general and a particular reluctance to undertake postmortems on HIV-infected individuals.

We present the causes of these early deaths in a cohort of children followed up from birth.

METHODS

These data derive from a hospital-based prospective cohort study conducted at King Edward VIII Hospital in Durban, South Africa, between October 1990 and April 1993. Details of the patient population and study methods have been described previously.⁶ Briefly, women were tested for HIV-1 at the hospital's antenatal clinic by a trained research worker who provided education and pre- and post-test counselling. The newborn infants of those for whom the test was positive were entered into the study. Informed consent was obtained at each stage. Infants were seen immediately after birth, and were then followed up at regular intervals to early infancy. At each visit a record was made of growth, development and morbidity, as well as of feeding and all current and interim illnesses. The recommendations of the Ghent workshop⁷ were used for classifying infection status as well as for the classification of deaths.

Most deaths occurred either in the study hospital's outpatient department or in the paediatric wards, with information for these children obtained from the hospital records. Sufficient data on the deaths were not available for all the patients since some died at home; in these cases the only available information was that obtained from the mother subsequent to the child's death. These children were classified as indeterminate as the actual cause of death and the relationship to HIV could not be established.

Postmortems were not conducted if the child was known to be HIV-positive, as this was the policy of the pathology department at the study hospital.

RESULTS

The initial cohort comprised 234 infants and their 229 mothers. Fifty-three of the infants were not brought back for a single

follow-up visit and were excluded from the study. This group was no different from the rest of the cohort with regard to risk factors analysed, which included mode of delivery and maternal syphilis serology.⁶ The final cohort comprised 181 infants, with 48 classified as infected, 93 as uninfected, and 40 as indeterminate. The median vertical transmission rate was 34% (CI 26 - 42%). The children were followed up for varying periods, ranging from 1 to 48 months. The mean follow-up period was 28.5 months for infected infants and 23.6 months for the uninfected group.

There was a total of 25 known deaths in the entire cohort during the study period. Of this number, 17 deaths were classified as HIV-related and 8 as indeterminate. In the HIV-related group, the mean age at death was 10.1 months (range 1 - 48 months). Only 3 HIV-related deaths occurred after 12 months of age. Eighty-three per cent of all deaths occurred before 10 months of age. The mean survival time for the infected group was 34.2 months (standard error 2.9 months).

Onset of symptoms in the infants who died occurred at a mean age of 3 months (range 1 - 5 months), compared with 5.1 months (range 1 - 21 months) in those infected infants who were still alive at the end of the study period. The main presenting complaints or symptoms just before death were cough, diarrhoea and fever; at least two of these symptoms were found in 16 of the 17 infants who died an HIV-related death. The main morbidity data are summarised in Table I.

Table I. Summary of the morbidity data on the 17 HIV-1-infected infants who died

Feature	No. of children	%	95% CI
Age at death			
0 - 6 months	11	64.7	
6 - 12 months	6	35.3	
Diarrhoea	13	76.5	56.3 - 96.3
Severe thrush	13	76.5	56.3 - 96.6
Failure to thrive/ marasmus	12	70.6	48.9 - 92.2
Pneumonia	12	70.6	48.9 - 92.2
Significant lymphadenopathy	10	58.8	35.4 - 82.2
Neurological abnormality/ delayed development	9	52.9	29.2 - 76.7

DISCUSSION

Mortality for the infected children in this cohort during the period of follow-up was 35.4%, with the majority of the HIV-related deaths occurring before the age of 1 year. It is clear from the complaints, symptoms and clinical findings that most deaths were related to either diarrhoeal disease or respiratory infection, or both (12/17, 70.5%). The majority of the infants showed failure to thrive or marasmus at the time of death, and half of them had neurological signs and/or developmental



delay. HIV-related disease developed early and was rapidly progressive in these children, with mortality being highest in the first year of life.

These children had illnesses similar to most other children in developing countries; diarrhoeal disease and respiratory infections *per se* cannot therefore identify the HIV-infected children who will develop rapidly progressive disease. However, most of these infants also had failure to thrive and a high proportion had neurological abnormalities. In an analysis of the newborn infants in this cohort it was noted that those HIV-positive infants who died early had lower birth weights, and were more likely to have complications in the newborn period.⁸

In an infant, a combination of diarrhoeal disease, respiratory infection, failure to thrive and neurological abnormalities, as well as low birth weight and neonatal complications, should alert one to the likelihood that the child is HIV-infected and may develop rapidly progressive disease, followed by early death.

These findings are similar to those reported from central Africa. In a report from Malawi,³ diarrhoeal disease, respiratory infections and failure to thrive were the commonest causes of death, and mortality in the first year was high. Similarly, in Lusaka, Zambia, it was found that mortality among vertically infected children was 44% at 2 years; the main clinical findings included pneumonia, diarrhoea, failure to thrive, and fever.⁴ A study from Kinshasa⁹ reported a 3-year mortality of 44% in children born to HIV-1-infected women, with diarrhoea and pneumonia among the chief causes of death.

The proposed new Integrated Management of Childhood Infections initiative incorporates the management of the major causes of illness and death in African children, i.e. diarrhoea, pneumonia, measles, malaria and malnutrition.¹⁰ The shortcoming of this protocol is that HIV infection has not been included among these diseases. Given the extent of the epidemic in Africa, and the increase in childhood mortality from HIV,¹¹ it would be crucial to include consideration of HIV in any management protocol dealing with childhood infections in Africa. In particular, attention must be given to the problem of repeated and often protracted diarrhoea, recurrent or chronic pneumonia, as well as a high frequency of failure to thrive and neurological abnormalities in children with vertically acquired HIV infection.

In conclusion, mortality among children with vertically acquired HIV-1 infection is high in the first year and the pattern of illness is similar to that reported in other parts of Africa. The combination of diarrhoea, pneumonia, failure to thrive and neurological abnormalities in HIV-infected children should alert one to the possibility of rapidly progressive HIV disease and early death. In addition, this study highlights the need for early and aggressive management of these infections in HIV-infected children as well as the need for early

interventions, e.g. antiretroviral therapy and nutritional support.

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