Whether this sort of activity will become widespread in South Africa is questionable, given the lack of incentives. The CHC and the community it serves received no financial benefit from the more economical prescribing during this study. Perhaps one way to encourage more cost-effective prescribing is to learn from the UK experience with fundholding GPs[24] and to allow all or a proportion of savings from drug costs to be used to fund improvements in services and facilities of the institution making the savings.

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Survival of children in Cape Town known to be vertically infected with HIV-1

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Objective. To determine the survival patterns of children in Cape Town known to be vertically infected with HIV.

Design. Retrospective record review of children diagnosed with symptomatic HIV infection during the period 1 December 1990 - 31 May 1995.

Setting. Hospitals in the Cape Town metropolitan area.

Patients. 193 children were known to be vertically HIV-infected. HIV diagnosis was based on the following criteria: two positive HIV enzyme-linked immunosorbent assays (ELISAs) in children older than 15 months and a positive ELISA together with a positive polymerase chain reaction (PCR) in younger children. The mothers of the children were known to be HIV-positive. On the basis of the presenting clinical findings children were assigned to a disease severity category (A, B or C) according to the Centers for Disease Control and Prevention (CDC)'s 1994 revised classification system for HIV infection in children.

Outcome measures. Survival was analysed according to the Kaplan-Meier method. Survival time was defined as the length of time between clinical diagnosis of HIV and death or last contact with the health services. Mortality risk in relation to specific variables at diagnosis such as age and clinical manifestations was determined by calculation of odds ratios (ORs) with 95% confidence intervals (CIs).

Results. The median age at diagnosis was 5 months; 72% of children were aged less than 1 year at diagnosis. According to the CDC clinical classification, 47 (24%) fell into category A, 111 (58%) into category B and 35 (18%) into category C. Of the 193 patients 85 (44%) were alive at the time of review, 65 (34%) had died and 43 (22%) were lost to follow-up. Risk of death was significantly associated with age less than 6 months (OR 4.7,

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CI 2.1 - 10.3) and severe disease, i.e. CDC category C (OR 2.7; CI 1.1 - 6.9) at time of diagnosis. The median survival for all the children from time of diagnosis was 32 months. Infants diagnosed before 6 months of age had significantly shorter median survival (10 months) compared with 36 months for those diagnosed at 7 - 12 months of age. For the children over the age of 12 months the cumulative proportion surviving at 48 months was 78%. Children with severe disease (category C) had a median survival of 21 months, significantly lower than that in category B (32 months). For the children in category A the cumulative proportion surviving at 48 months was 66%.

Conclusion. The median survival of children with HIV was 32 months from time of diagnosis, and survival was influenced by age and disease severity.

HIV infection is having a major impact on child health and survival, particularly in Africa. In a study from 10 countries in Central and East Africa AIDS is projected to cause between a quarter and half a million additional deaths in children under 5 years of age by the year 2000. The projected under-5 mortality rates of between 159 and 189/1 000 will be significantly higher than the previous target of 98 - 132 set by the United Nations.[1] In recent studies from Abidjan[2] and Uganda[3] the infant mortality rates for children born to HIV-infected women were 151 and 163/1 000, respectively, compared with 34/1 000 (in both studies) for children of seronegative mothers. In addition, studies from Lusaka and Abidjan[4] have shown that the risk of an infected child dying in hospital was more than twofold greater than that for a non-infected child. It has been estimated that up to 75% of all HIV-infected children in Africa will die before their 5th birthday.[5] The HIV epidemic in Africa has also resulted in an additional burden to health services, with increasing numbers of sick children presenting to facilities at all levels of care.[6]

In South Africa vertically acquired HIV infection has become a major public health problem. The most recent national seroprevalence survey (1995) indicated that 10.4% of women attending antenatal clinics were infected.[7] This translates to approximately 40 000 HIV-infected infants for 1995. Published data on disease and survival patterns of vertically HIV-infected children are lacking in South Africa.[8,9] Such data are essential in planning and evaluating rational strategies for intervention and resource allocation, particularly in relation to provision of secondary and tertiary care.

The purpose of this study is to report the natural history of children in Cape Town known to have perinatally acquired HIV infection, with a focus on survival patterns.

Methods

The medical records of all children with clinically symptomatic vertically acquired HIV infection seen in Cape Town hospitals during the 54-month period 1 December 1990 - 31 May 1995 were reviewed. Approximately 85% of the patients were known to the Red Cross War Memorial Children's Hospital infectious diseases clinic, which was set up in 1991 in order to follow up these children. The rest were followed up at a similar clinic at Tygerberg Hospital. None of the children reviewed had received routine antiretroviral or immunoglobulin therapy. Children infected via horizontal transmission of the virus, patients with doubtful or incomplete laboratory data and asymptomatic vertically infected infants were excluded from the study.

The diagnosis of vertically acquired HIV infection was based on the following criteria: two positive HIV enzyme-linked immunosorbent assays (ELISAs) in children older than 15 months and a positive ELISA together with a positive polymerase chain reaction (PCR) in younger children. In addition, the mothers of children included in the study had to be known to be HIV-positive.

Sociodemographic details, age and clinical findings at first diagnosis were documented. On the basis of the presenting clinical findings children were assigned to a disease severity category (A — mild, B — moderate and C — severe) according to the Centers for Disease Control and Prevention (CDC)'s 1994 revised classification system for HIV infection in children.[10] Date of death or last contact with health services was recorded.

Data analysis

Data were collated and analysed on computer using Epi-Info version 6 and Statistica programs. Categorical and continuous data were assessed by the c^2 test and the non-parametric Kruskal-Wallis test, respectively. Mortality risk in relation to specific variables such as age and clinical manifestations was determined by calculation of odds ratios (ORs) with 95% confidence intervals (CIs). Survival analysis was done according to the Kaplan Meier method and stratified according to age and clinical stage at diagnosis. The log rank test was used to determine whether statistical differences existed between the groups. Survival time was defined as the length of time between clinical diagnosis of HIV infection and death or last contact with the health services.

Results

Virtually all the 193 patients enrolled in the study were from a disadvantaged socio-economic background. Nearly one-third live in Khayelitsha, a sprawling peri-urban area outside Cape Town. The male/female ratio was 1.2.

The age distribution of the children at diagnosis is shown in Fig. 1. The median age at diagnosis was 5 months, with a range of less than 1 month to 58 months; 72% were aged less than 1 year at diagnosis. In 52% of cases the diagnosis was made on first admission to hospital. The median number of hospital admissions following HIV diagnosis was 2, and 12% of patients had 5 or more hospital admissions.

At diagnosis, 30.4% of the children were marasmic (< 60% of expected weight for age), 64.2% were underweight for age (between 60% and 80% of expected weight for age) and only 7.4% were above the third percentile. No cases of kwashiorkor were noted. Diarrhoeal disease and acute respiratory tract infections were the most common presenting complaints, occurring in 47% and 44%
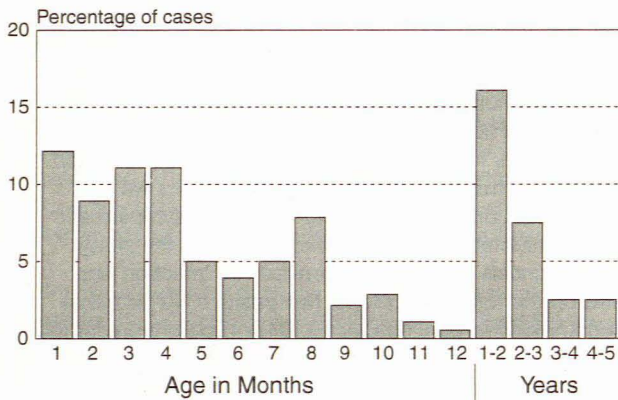
Fig. 1. Age distribution of children at diagnosis of HIV infection.

of cases, respectively. The most common clinical finding was hepatomegaly (83% of cases), followed by lymphadenopathy (67%), splenomegaly (50%), dermatological problems (45%) and oral thrush (34%). Tuberculosis was diagnosed in 49% of children at the time of HIV diagnosis. According to the CDC's clinical classification 47 (24%) fell into category A, 111 (58%) into category B and 35 (18%) into category C.

Of the 193 patients 85 (44%) were alive at the time of review (June 1995), 65 (34%) had died and 43 (22%) were lost to follow-up. The outcome of children according to year of diagnosis and age and clinical category at diagnosis is outlined in Table I. None of the children diagnosed in 1990 have survived and at least 30% of those diagnosed between 1991 and 1994 are known to be dead, while 20% of those diagnosed in 1995 have died. Risk of death was significantly associated with age less than 6 months (OR 4.7; CI 2.1 - 10.3) or severe disease, i.e. CDC category C (OR 2.7; CI 1.1 - 6.9) at time of diagnosis. The mortality risk remained significant (but with a lower OR) if children who were lost to follow-up were regarded as having died.

Table I. Outcome of HIV-infected children according to age, year of diagnosis and CDC clinical category

	Dead	Alive	Lost to follow-up	Total
No. of children	65	85	43	193
Year of diagnosis				
1990	4	0	0	4
1991	7	6	6	19
1992	11	9	15	35
1993	11	11	11	33
1994	27	36	11	74
1995*	5	23	0	28
Age at diagnosis†	4	8	5	5
	(2, 7)	(3, 18)	(2, 16)	(2, 18)
< 6 mo.	48	33	23	104
7 - 12 mo.	12	18	7	37
> 12 mo.	5	34	13	52
Clinical category				
A	9	25	13	47
B	39	50	22	111
C	17	10	8	35

* Refers to the first 5 months of the year only.
† Median age (25th, 75th centiles) at diagnosis for dead and alive children were significantly different (P < 0.001).

The median (25th, 75th centiles) age at diagnosis of children known to have died was 4 (2, 7) months, with a range of less than 1 month to 49 months. The median time from diagnosis to death was 3 months, with a range of between less than 1 month and 46 months. Seventy two per cent of those who died did so by 12 months of age, and 88% were dead by 2 years of age. In contrast the median age at diagnosis of children known to be alive (at June 1995) was 8.5 (4, 18) months, with a range of less than 1 month to 54 months. Children who died were therefore significantly younger at diagnosis than the survivors (P < 0.001).

Analysis of survival patterns (utilising the Kaplan-Meier method) from diagnosis of HIV in relation to age and clinical category are shown in Figs 2 and 3, respectively. The median survival for all the children from time of diagnosis was 32 months. Young infants (age < 6 months) had a significantly shorter median survival period (10 months) compared with 36 months for children aged 7 - 12 months (P < 0.001). For children over the age of 12 months the cumulative proportion surviving at 48 months was 78% (Fig. 2.). Children with severe disease (category C) had a median survival of 21 months, significantly less than that in category B (32 months) (P = 0.02). For the children in category A the cumulative proportion surviving at 48 months was 66% (Fig. 3).
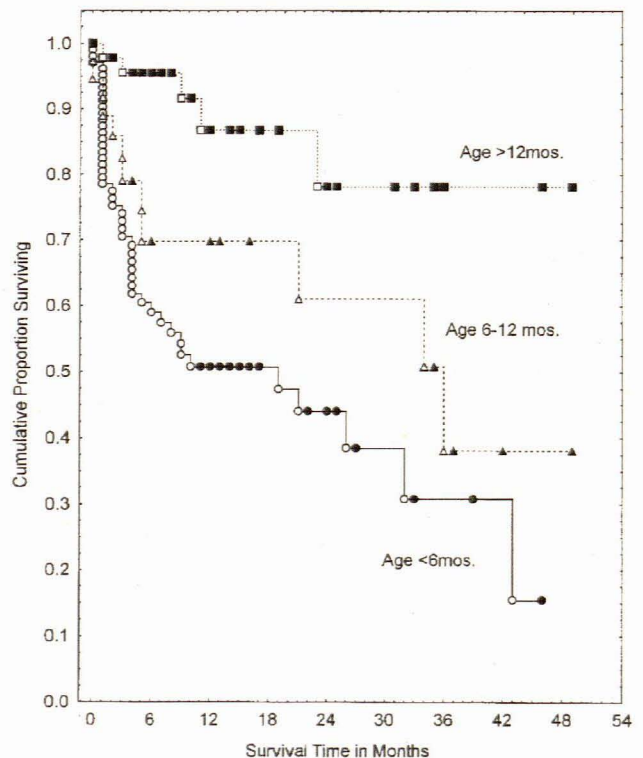

Fig. 2. Survival of children according to age at diagnosis of HIV.

Discussion

This retrospective study provides survival data and the relationship of survival with age and clinical findings at the time of diagnosis for a large number of children who were vertically infected with HIV in the Cape Town metropolitan area. The clinical manifestations of children with HIV disease
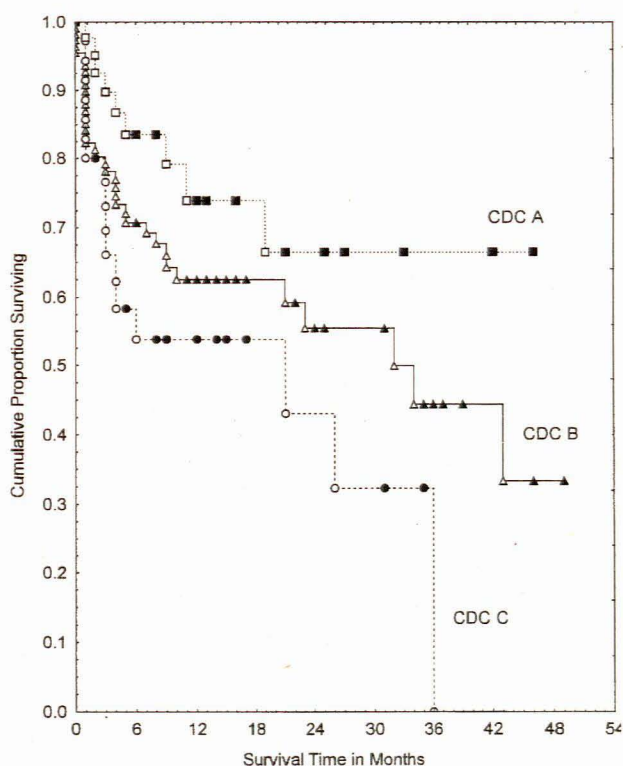
Fig. 3. Survival of children according to CDC clinical criteria at diagnosis of HIV.

in this study is similar to that described in the rest of Africa.[8,11] Acute respiratory tract infections, diarrhoea, malnutrition, lymphadenopathy, splenomegaly or dermatitis were present in over 40% of cases at initial diagnosis. One of the shortcomings of this study was that the true extent of AIDS-defining conditions such as lymphoid interstitial pneumonitis, *Pneumocystis carinii* pneumonia, encephalopathy and opportunistic infections other than tuberculosis could not be quantified, because investigations for such conditions were not part of routine clinical practice in the period under review. In addition the study focused on the common clinical findings at presentation and outcome and did not include a formal evaluation of radiological findings. Since most of these conditions would result in the classification of patients into CDC clinical category C, our clinical categorisation probably underestimates the true extent to which children presented with severe signs and symptoms.

The other major limitation of our study was that it was a retrospective record review of children known to be HIV-positive. As such it does not represent a true picture of the survival pattern of all children with vertically acquired infection. Nevertheless, it does provide useful epidemiological data on the evolution of the epidemic in our area. The median time period from birth to diagnosis was 5 months, with 72% presenting before the age of 1 year. This probably reflects the early stage of the epidemic in the area, and what we are currently seeing is the severe end of the spectrum. In the early 1980s the published data from the USA reported short incubation periods (6 - 9 months).[12,13] These studies were also biased in that they focused on

children whose HIV infection had been recognised because of their severe illness and who had presented to health facilities. More comprehensive recent data obtained from prospective cohort studies in developed countries suggest that the incubation period may be in the region of about 4 - 5 years.[14-18] What is significant about our data is the finding that children with severe disease or children who were aged less than 6 months at diagnosis had a higher risk of death (ORs 4.7 and 2.7, respectively) which is similar to findings reported previously.[13,15] In the New York study the relative risk of death in the most severe versus the least severe group was 3.3 and for children under 6 months old compared with older children the risk was 1.8.[13]

Even though study designs have differed, the available data from prospective cohort studies in developed countries indicate that the median survival of children with vertically acquired HIV infection from the time of diagnosis is in excess of 5 years, while in Africa it is significantly shorter. In one study from Italy 70% of perinatally infected children were alive at 6 years and 50% at 9 years.[14] In the USA it has been estimated that a child born with HIV has a 75% chance of surviving to 5 years of age.[17] On the other hand, the median survival in Uganda[3] was reported to be 21 months and in Kenya it was about 4 years,[19] which is similar to survival in this study. The difference in survival is clearly related to the availability and accessibility of medical and other supportive care. In addition, the rapid advances in antiretroviral therapy in developed countries promises to increase survival rates significantly. This option is not feasible in Africa at this moment, or for the foreseeable future, given the high cost of such interventions.

In our study, which was a retrospective study of children known to be HIV-infected, the median survival was 32 months. Survival was shorter in younger children and in those with severe disease. Of the 16 children under 6 months old who also had severe disease (CDC category C) 15 (94%) are known to have died, all except 2 within 6 months of diagnosis and before the age of 1 year. In the absence of specific antiretrovial therapy and within the context of scarce resources, these data suggest that we should provide only palliative care for these children, ideally within a primary care setting, and not subject them to hospital admission and intensive or high-care therapy.[20] On the other hand, current data indicate that there is a group of children who appear to have a good outcome. For these children, who were first diagnosed after their first birthday, the cumulative proportion surviving 48 months after diagnosis was 78%. This suggests that we should be looking at strategies to improve the quality and duration of life of these children as well as those who present with mild disease. Ensuring adequate nutrition, psychosocial support and accessibility to medical care, particularly for preventive interventions such as immunisation and prophylaxis for common paediatric illnesses, are important in reducing morbidity from the common complications of HIV. Evaluation of such strategies will be important, since as would be expected with the unfolding of epidemic, more older children will present to our health services. Ultimately the control of the paediatric HIV epidemic will be dependent upon reducing the heterosexual spread of HIV among the adult population and minimising perinatal transmission from infected mothers to infants.

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Review Article

Electron beam computed tomography for the diagnosis of cardiac disease
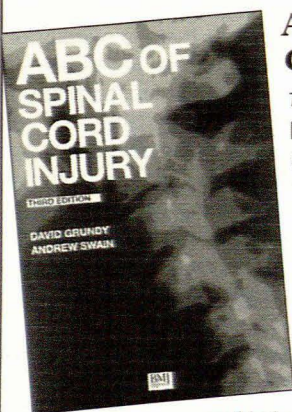
Yadon Arad

Electron beam computed tomography (EBCT) of the heart is a new modality which will alter the way cardiology is practised. It allows for the detection of early coronary artery disease (CAD) in asymptomatic individuals, regardless of their level of risk as assessed by traditional risk factor analysis. Compared with risk analysis based on risk factors alone, an assessment which also utilises quantitative measurements of coronary artery plaque by EBCT allows for more precise determination of the need for medical therapy. Non-invasive intravenous contrast EBCT coronary angiography can identify significant obstructive CAD, and should reduce the need for conventional coronary angiography. Incorporation of EBCT into routine medical practice is more cost-effective than other modalities currently available.

This paper reviews relevant original articles on EBCT and preventive cardiology published in peer-reviewed medical journals, and assesses the implications of EBCT for preventive cardiology.

Limitations of traditional evaluation of coronary heart disease

Coronary artery disease (CAD) is the leading cause of death in developed countries. Despite marked progress in the diagnosis and treatment of CAD, its detection is limited by the high incidence of silent, preclinical disease. In up to 50% of patients the first symptom of atherosclerotic cardiovascular disease is either an acute myocardial infarction (MI) or sudden death.[1] Furthermore, although subjects with a higher degree of obstruction may subsequently be more likely to suffer a cardiac event, angiography shows that half of those with a first or a fatal MI have less than 50% coronary obstruction. This apparent paradox is due to the much larger number of potential patients with less extensive disease. The correlation

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