

**HUMAN IMMUNODEFICIENCY VIRUS-1 INFECTION
AND THE ACQUIRED IMMUNODEFICIENCY SYNDROME
IN AFRICAN CHILDREN : NATURAL HISTORY FROM
BIRTH TO EARLY CHILDHOOD**

by

RAZIYA AHMED BOBAT

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DECLARATION

**This thesis is the author's own work and has not been submitted previously
to this or any other university**


RA BOBAT

DEDICATION

for Seema and Natasha

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Bobat RA, Moodley D, Coutsooudis A, Coovadia HM, Gouws E. Growth in early childhood in children born to HIV-1 infected women from Durban, South Africa. Provisionally accepted for publication: *J Acquir Immune Defic Syndr Human Retrovir* .

SUMMARY

Background: in 1987, the first child with HIV-1 infection was identified in the paediatric wards at King Edward VIII Hospital in Durban. This made paediatricians aware that the epidemic had spread to the children of KwaZulu/Natal. Although information on transmission and natural history was becoming available from developed countries, little was known about the disease in developing countries. It was important to determine transmission rates and disease patterns in the local population, in order to appropriately counsel women, and for management of infected infants. In addition, with resources for laboratory diagnoses being limited in developing countries, much emphasis had to be placed on clinical findings for identification of infected children.

In 1989, a retrospective analysis was made of the HIV-infected children seen over a 2-year period, between 1987 and 1989. Nine such children were identified and their clinical and biochemical features were described. It was concluded that HIV infected children presented with an identifiable pattern of signs, fairly similar to that described for children in industrialised countries.

With these findings, a prospective study was undertaken, to determine the vertical transmission rate, the factors affecting this rate, and natural history of vertically transmitted HIV-1 infection.

KwaZulu/Natal, being at the epicentre of the epidemic in South Africa, was a natural site for the study.

Patients and Methods: a trained research worker was placed in the antenatal clinic at King Edward VIII Hospital for the specific purpose of educating, counselling, and testing of all women attending the clinic. Women attending the clinic for the first time in the index pregnancy were offered HIV testing if informed consent was obtained. Blood for HIV serology was drawn at the same time as sampling for the obligatory syphilis serology. The acceptance rate for sampling was > 95%. The majority of the women attending the clinic were black, and first attendance was generally late, into the third trimester. The same research worker was responsible for post-test counselling which was offered to all the women, not only those who tested positive. This research worker was also responsible for obtaining maternal consent for entering the newborn infant into the study.

All newborn infants were seen within 48 hours of birth. At this time they were examined, growth parameters were recorded, and initial blood samples taken. These infants were then followed-up at 1 month, 2 months, 3 months, then at 3-month intervals up to 18 months, then at 6-month intervals. At each visit, a thorough clinical examination was performed, growth measurements taken, and development assessed. Record was made of any interim illness and visits to health centres, and of hospital admissions. Method of feeding was noted; and details on immunisation obtained from the child's immunisation card. The children received all the

routine childhood immunisations according to the national regimen, based on WHO recommendations.

Mothers were asked to bring the child to the follow up clinic for any problem, so that episodes of illness would not be missed. The women were reimbursed for transport costs to encourage follow up visits.

Calculation of transmission rate and classification of infection status were made according to the recommendations of the Ghent workshop. Children were regarded as infected if they were antibody positive at 18 months or had an HIV related death. They were classified as uninfected if the antibody test was negative at 9 months of age. Those infants who were lost to follow up before the age of nine months whilst still antibody positive and those whose cause of death could not be determined, were classified as indeterminate. The diagnosis of AIDS was based on the WHO criteria.

Blood samples were taken at birth, at age one and three months, then at three month intervals to 18 months; thereafter at six month intervals. Sera were tested for HIV1 antibodies by a commercial enzyme-linked immunosorbent assay, ELISA. Samples that tested positive were confirmed by two tests, a Roche Elisa and by an immunofluorescent assay (IFA). A sample was regarded as being positive if both the second ELISA as well as the IFA or the Western Blot tested positive.

Results: between October 1990 and March 1993, 234 infants and their 229 mothers were entered into the study. Those who did not attend a single follow up after birth were excluded from the study. The final cohort comprised 181 infants, of whom 48 were classified as infected (including 17 deaths); 93 not infected, and 40 as indeterminate (including 8 deaths).

Maternal Data: about 60% of the mothers were under 30 years of age and were multiparous; 18% tested positive for syphilis serology; 22.9% were anaemic during pregnancy, and 37% were delivered by caesarean section. Most women lived in urban areas, and 16% chose to bottle-feed exclusively.

Vertical Transmission Rate and Factors affecting this Rate: the median vertical transmission rate was 34%, (95% confidence intervals, CI 26%-42%). This figure is similar to that found in most parts of Africa, but much higher than those for Europe and USA. The maternal factors found to be associated with an increased risk of transmission were vaginal deliveries and a low haemoglobin level during pregnancy.

Breastfeeding, Transmission, and Outcome: breastfeeding was found to have an increased risk of transmission, by 15 % (CI 1.8-31.8). On assessing growth and morbidity, it was noted that breastfed infants were not protected against such common childhood infections as pneumonia

and diarrhoea, and that failure to thrive occurred with equal frequency in both those breastfed as well as those receiving artificial feeds.

Newborn Data: when comparing newborn data between those infants who were subsequently found to be infected with those who were uninfected, it was found that there were no major differences between these groups with regard to growth parameters and neonatal complications. However, those infants with rapidly progressive disease (those who died within 24 months), were noted to have lower mean birth weights and lengths, a higher frequency of low birth weights, and tended to have more neonatal problems.

Clinical Manifestations: the first differences between the infected and the uninfected infants generally manifested from about 3 months of age. HIV infected children were identifiable by higher frequencies of thrush, lymphadenopathy, skin rash, and hepatosplenomegaly in the early stages, and later on with a higher tendency to neurological and developmental abnormalities, as well as of diarrhoea. Pneumonia was found with equal frequencies in both the infected and uninfected children. The HIV infected child could be distinguished fairly early in life by the combination of the manifestations described above.

Progression to AIDS: AIDS was diagnosed in 44% of all the infected children during the study period. Ninety five percent of these children were identified by 12 months of life, showing a rapid progression of the disease.

Longitudinal Growth: when longitudinal growth parameters were analysed in this cohort, it was found that HIV infected children were stunted from as early as 3 months of age, and remained below the international standards into early childhood. Infected children were also found to be malnourished (i.e. weight for age below international means), from an early age, and this persisted throughout early childhood. Of note, the uninfected childrens' weights, although comparable to international means initially, dropped after the first year of life. However, both groups did not have significant wasting, when compared to international means.

Mortality: there were 25 known deaths during the study period. Of these, 17 were classified as HIV-related, and 8 as indeterminate. The mean age at death was 10.1 months, with 83% of all the HIV-related deaths occurring within the first year of life. The commonest diagnoses at the time of death were diarrhoea, pneumonia, and failure to thrive; also, thrush was common, as were neurological abnormalities.

SECTION 1

CHAPTER 1

CHAPTER 1

BACKGROUND

1.1 The Epidemic

The first persons with AIDS were described in 1981, in the United States. Since then, the epidemic has risen to a global pandemic, with staggering figures of numbers of infected persons. In 1983 the human immunodeficiency virus was established as the cause of the new syndrome, and was noted to have a tropism for the CD4⁺ T lymphocyte (Amman 1983). The first cases of AIDS in children were described in 1982, and the link between infected mothers and their infants was established (CDC 1982). In 1985, an antibody assay was established for laboratory diagnosis (Barre 1983). Reporting of AIDS cases in Africa began in 1983, with a sharp increase from 1986 (Rosenberg 1992). In South Africa the first AIDS cases were reported in 1982, occurring in white homosexual males (Epidemiological comments 1987).

The HIV pandemic has undergone four main phases in its evolution (Quinn 1996):

- emergence: the infection emerged from rural populations and spread to urban areas, spreading silently among sexually active populations;
- dissemination: the virus spread rapidly to different regions of the world, through migration and international travel, as well as due to enormous social disruption in Sub-Saharan Africa;

- escalation: this occurred mainly in the eighties, as the infection spread into other high risk populations and to the general population;
- stabilisation: this phase has become evident in some regions, such as North America and western Europe, Uganda, Thailand, and whilst this may represent positive preventive measures, it may also mean transition to an endemic status.

Spread of the epidemic has varied considerably between the developed and the developing countries, depending on social, cultural and behavioural differences. Incidence rates have been the highest in developing countries. At present 21 million of the total global number of 30.6 million adults and children living with HIV/AIDS are in sub-Saharan Africa (UNAIDS 1998). In South Africa, the prevalence of HIV-1 infection rose from 0.76% in 1990 to 16.01% in 1997. It has been estimated that, at the end of 1997, there were 3 million South Africans infected with HIV (Dept of Health, unpublished surveillance data).

Tables for South Africa in Annexure 1.

1.2 Transmission of the virus

There are three chief modes of transmission of the virus:

- sexual transmission: which may be heterosexual, bisexual, or homosexual;

- parenteral transmission: contaminated blood and blood products, contaminated needle and syringes;
- vertical transmission from mother to infant: this may occur in- utero, during labour and delivery, or postnatally through breastfeeding.

1.2 (a) Sexual transmission

Worldwide, heterosexual transmission is the chief mode of spread of the virus, accounting for over 75% of all infections. In Africa, heterosexual transmission has always been the chief mode of transmission, and, in some regions, 10-20% of 20-40 year old persons are infected with the virus (Quinn 1996). Women are infected in equal numbers as men, leading to a major problem of vertical transmission. In some regions of Africa, the seroprevalence rates at antenatal clinics is as high as 30%.

1.2 (b) Vertical transmission

Vertical transmission of HIV-1 accounts for more than 90% of all infection in childhood. The virus is transmitted from the infected mother to her infant, either antenatally, perinatally, or postnatally. The exact contribution of each mode is not well established; however, most

contribution during pregnancy, and some transmission occurring from breastfeeding.

Numerous studies have been done, which have established the transmission rates as well as some of the factors which determine this rate (ECS 1992, Hira 1989, Lepage 1993). The rate of transmission varies between different regions, from a low of 14% in the European Collaborative Study, to a high of 52% in Africa. Most reports from Africa show a higher transmission rate compared to countries from Europe and America. Whilst the exact reasons for the variation in the transmission rate between regions is not certain, there are many possible explanations for this. These include :

- breach of the placental barrier
- the stage of the HIV infection in the mother during pregnancy
- viral load in the mother during pregnancy
- maternal sexually transmitted diseases
- maternal nutrition and micro-nutrient deficiency during pregnancy
- anaemia during pregnancy
- advanced maternal age and increased parity
- inadequate facilities for labour and delivery
- breastfeeding
- maternal co-infections such as tuberculosis and malaria

Several studies have shown that the mode of delivery may be significant in reducing transmission; caesarean deliveries have been found to be protective against transmission (ECS 1992, Dunn 1994). Further reductions may occur if the caesarean section is carried out whilst membranes are intact (Kuhn 1996). However, caesarean deliveries are not without morbidity and complications may be increased in women who are HIV infected.

Sexually transmitted diseases are prevalent among women in Africa, and co-infection with syphilis may lead to the breaching of the protective placental barrier, leading to an increased risk of HIV infection. This increased risk, with active syphilis infection, has been reported in some studies, but has not been found in others (Andiman 1991, Boyer 1994).

Poor nutrition in the mother as well as micro-nutrient deficiency may lead to an increased risk of transmission. Studies have shown that transmission is increased if the mother is vitamin A deficient (Semba 1994, Bridbord 1994, Mostad 1997). This may reflect general maternal poor health as the risk factor, with the vitamin A acting as a surrogate marker. Similarly, it has been shown that women who have lower haemoglobin levels have an increased risk of transmission (St.Louis 1993). Again, the anaemia may be a surrogate marker for poor maternal nutrition, or may be a marker for advanced stage of the HIV infection.

Increased risk of transmission by breastfeeding is now widely accepted. A meta-analysis established the increased risk as being between 7-20%, depending on the stage of the HIV infection in the mother (Dunn 1992). In women with established infection at the time of pregnancy, the risk is lower compared to women who become infected during pregnancy. Much controversy surrounds the association between the duration of breastfeeding and the risk. It is generally accepted that risk increases as the length of exposure increases, i.e. women who feed for longer periods are more likely to transmit the virus than those who breastfeed for shorter periods (Leroy 1998). The risk of late postnatal transmission varies from 5-32% (Leroy 1998, Ehounou 1997). Infants who are documented as being uninfected in the first three months, but become seropositive thereafter, are deemed to have late postnatal transmission. Acceptance of the role of breastfeeding as a potential source of transmission, led to the WHO/UNICEF issuing a statement of recommendations, depending on the region in which the woman lived (WHO 1992); in Annexure 11.

In 1996, the UNAIDS revised this policy and issued an interim statement which recognised that women had the freedom of choice, no matter where they resided (UNAIDS 1996); in Annexure 11.

1.3 Viral Structure and Immunopathogenesis

(a) *The virus*

The human immunodeficiency virus is an RNA virus, belonging to the lentivirus family. HIV virions contain a virus capsid, which consists of the major capsid proteins; the virion envelope, and the matrix protein. There are two sub-types, HIV-1 and HIV-2. HIV-2 shares 40% genomic similarity with HIV-1, is geographically restricted to the west coast of Africa, and causes a milder disease with slower progression (Bryant 1991).

HIV isolates show extensive genetic variability, with sequence variation even within patients. During the course of infection, the distribution of virus variants changes, providing the basis for the continuous emergence of new virus variants. HIV isolates can differ in their tropism for cells from different lineages. While the CD4 molecule is required for the entry of all HIV variants, some variants are able to infect macrophages, and others show a preferential tropism for T cells.

Extensive genetic analysis has revealed that HIV-1 isolates fall into two main groups, designated M and O (Janissens 1997). Most isolates belong to the M group, which has at least 10 different sub-types (A-J). Subtype B is predominant in western Europe and USA; Africa has several different subtypes, with subtypes B and C being predominant in South Africa (Table 1.1).

Table 1.1 The main viral subtypes in different regions

Region	Common Viral subtype/s
Europe	B
USA	B
Africa :	
Cote d'Ivoire	A
Zaire	A
Uganda	A, D
Rwanda	A
Malawi	C
South Africa	B, C
Thailand	E

1.3 (b) *Immunopathogenesis*

Infection with the human immunodeficiency virus results in a profound immunosuppression, so that the host is susceptible to various opportunistic infections and neoplasms. Effects of the virus on the host may be particularly dramatic in children as many of the organ systems are still developing.

The principal target of the virus is the CD4⁺ T lymphocyte, due to the presence of the CD4 molecule on the surface of the cell. Infection with the HIV leads to a rapid cytopathic effect on the CD4 cells. Some cells survive and maintain a low grade infectivity. The destruction of the CD4⁺ cells leads to the profound immunosuppression which is characteristic of AIDS. HIV can also infect cells from the monocytic lineage, which express the CD4 molecule on their surface. Thus HIV can infect monocytes and macrophages. Infection of these cells does not lead to a decrease in their total numbers, nor are the cells destroyed. It is thought that they function as a reservoir for the virus in various organs (Rosenberg 1992).

The precise mechanisms of HIV induced immunosuppression are not well understood. HIV can directly and indirectly infect CD4⁺ T cells, cause functional impairment of CD4⁺ T cells, as well as of B cells and other antigen-presenting cells.

A period exists between infection and manifestation of disease, during which viral replication occurs without any symptom manifestation (Perelson 1996). What causes activation from this latent stage is under investigation. Numerous factors can induce HIV activation. These include: mitogens, cytokines, and soluble factors such as interferons and TGF- β .

In 1993, the emerging group of small chemotactic-cytokines was designated "chemokines" (Lindley 1993). In 1995, the first link between chemokines and the HIV virus was established, with the discovery of the specific antiviral effect of regulated on activation of

normal T-cell expressed and secreted (Rantes), macrophage inflammatory protein (MIP-1) α and MIP-1 β (Cocchi 1995). These were found to be major components of the HIV-suppressive activity produced by CD8 + T-lymphocytes. Following this, several chemokine receptors, in particular CXCR4 and CCR5 were shown to serve as co-receptors for HIV on the cellular surface membrane (Deng 1996). The differential usage of such co-receptors, that is critically dependent on the sequence of the V3 domain of the major viral envelope glycoprotein, gp 120, is emerging as the physiological basis for the diversity among the HIV isolates recovered at different stages of the disease. Moreover, a homozygous deletion within the coding sequence of the CCR5 gene has been linked to resistance to HIV infection in some individuals with multiple high risk exposure. The rapid progress in this field may ultimately lead to the development of novel therapeutic approaches for AIDS.

Viral load: there has been a proliferation of information on viral load and disease progression (McIntosh 1996). In children, of particular significance, is the relationship between viral load in the mother and transmission of HIV, as well as viral load and disease progression in the infant (Lambert 1997). Several studies have shown that a higher viral load in the mother is associated with increased transmission, and that the risk is increased further if the mother has high viral loads together with low CD+4 counts (Lambert 1997). In addition, infected children with higher viral loads were found to progress more rapidly to AIDS and death, than infected children with low viral loads (Pollack 1997). In antiretroviral therapy,

viral loads are being used, together with CD+4 counts, for the monitoring of response to treatment, and to monitor disease progression. It is important to remember that infants with vertically acquired HIV infection have high viral loads in the first year (Palumbo 1995), with levels falling off and reaching a steady state thereafter (Mcintosh 1996).

1.4 Diagnosis of HIV Infection

1.4 (a) *Laboratory diagnosis*

HIV infection is diagnosed by finding antibodies specific to the virus, or by detecting the virus itself.

In adults, HIV antibodies are detected 6-8 weeks after the infection. HIV infected women produce antibodies which cross the placental barrier to the fetus, so that all infants born to HIV positive women will have anti-HIV IgG antibodies. The enzyme linked immunosorbent assay (ELISA) is used for the detection of these antibodies. Confirmatory tests which are used include: radioimmunoprecipitation (RIA), indirect immunofluorescent assay (IFA), and the immunoblot (or western blot).

Diagnosis of infection comprises a positive ELISA plus a positive confirmatory assay, or two positive ELISA based on different methods, done on the same sample.

The virus can be detected by the following tests: p24 -antigen, nucleic-acid based assays (polymerase chain reaction, isothermic amplification), and virus culture.

1.4 (b) *Diagnostic problems*

In infants, maternal antibodies which cross the placenta can persist for up to 15 months of age; therefore, diagnosis which depends on a positive HIV antibody test can be a problem as all the infants would test positive. Diagnosis is further complicated by wide spread breastfeeding in developing countries. The most suitable tests would be those that detect the virus itself.

However, the difficulty in developing countries is that these tests are extremely costly, and therefore not generally available.

Since the anti HIV antibodies which cross the placenta are of the IgG class, detection of the other classes, i.e. IgA and IgM would indicate infection in the infant. These assays are being used and have been described in detail in the thesis on laboratory diagnosis by D. Moodley (Moodley 1996).

As a result, in most of the developing countries, the ELISA is used together with clinical criteria for the diagnosis of HIV infection and AIDS.

1.5 Clinical Manifestations

The effects of vertically acquired HIV infection in the infant are widespread and multi-system. Patterns of disease expression and progression differ among HIV infected children. It is generally accepted that there are two major categories of infants: those who are rapid progressors (about 25 %) and those who progress more slowly (Auger 1988, Duliege 1992). Rapid progressors may have been infected in-utero or received a higher viral load, therefore manifest earlier and progress more rapidly to symptomatic disease, AIDS, and death (Mayaux 1996).

Onset of manifestations may depend on the timing of the infection, i.e. in-utero vs peri/postnatal. At birth, only a small proportion of infants of HIV positive women show signs of infection, but most infants who are HIV- infected will manifest features of the disease by 6 months of age (Galli 1995). Age at onset of disease predicts length of survival.

The clinical manifestations of HIV disease have a wide spectrum. Some infants will present with features of immunodeficiency, whilst others have non-specific signs. Non-specific features include:

- hepato-splenomegaly
- failure to thrive
- persistent fever

- persistent/recurrent diarrhoea
- generalised lymphadenopathy

About 30-50% of children present with opportunistic infections at an early age (Scarlati 1996). These include pneumocystis carinii infection, candidiasis, cytomegalovirus infection, and tuberculosis. The survival rate in children with opportunistic infection is much worse.

Serious bacterial infections, lymphoid interstitial pneumonitis (LIP) and encephalopathy occur frequently in HIV infected children. The prognosis is worse in those children with encephalopathy than in those without this complication.

HIV-related malignancies, although uncommon in children, include non-Hodgkins lymphoma, Kaposi's sarcoma, and MALT (Mucosal associated lymphoid tissue).

The natural history of vertically transmitted HIV-1 infection : at the time that this study was conducted, little was known about the natural history of the infection in infants and children. Subsequently, much information became available, chiefly from industrialised countries (Johnson 1989, Scott 1989, Blanche 1990, ECS 1991). Information from Africa remains minimal (Lepage 1990, Jackson 1992).

The natural history studies from various regions are discussed in Chapter 8.

1.6 Classification of Disease

There are two widely used systems for the classification of HIV disease, the CDC (Centres for Disease Classification, Atlanta, USA) and the WHO (World Health Organisation) classification systems.

The WHO classification system for AIDS was established as the CDC criteria were considered to be too sophisticated for most third world countries, which bear the brunt of the disease. For reporting purposes, either one of the two systems is used.

The WHO classification system, which was modified in Geneva in 1989, includes the following:

Major criteria

- weight loss or failure to thrive
- chronic diarrhoea (> 1 month)
- prolonged fever (> 1 month)
- severe or repeated pneumonia

Minor criteria

- generalised lymphadenopathy
- oro-pharyngeal candidiasis
- repeated common infections
- generalised pruritic dermatitis
- confirmed maternal HIV infection

For the diagnosis of AIDS, the infant must have at least two major in association with two minor criteria.

The CDC classification system is used for the classification of disease, thus enabling uniformity for the purposes of treatment and reporting (CDC 1994). Parts of the system can be used by many regions; however, due to the lack of availability of CD4+ counts in most developing countries, this part of the classification system would be impossible to utilise, (Table 1.2).

Table 1.2 CDC Revised Paediatric HIV Classification†

Immune Categories	Clinical Categories#			
	N	A	B	C
	No Signs / Symptoms	Mild Signs / Symptoms	Moderate Signs / Symptoms *	Severe Signs / Symptoms *
(1) No evidence of suppression	N1	A1	B1	C1
(2) Evidence of moderate suppression	N2	A2	B2	C2
(3) Severe suppression	N3	A3	B3	C3

* Category C and lymphoid interstitial pneumonitis (LIP) in Category B are reportable to state and local health departments as AIDS (MMWR 36 : 15, 1987).

† Children whose HIV infection status is not confirmed are classified by using the above grid with a letter E (for perinatally exposed) placed before the appropriate classification code (e.g., EN2).

For explanation of each category and symbols, refer to Annexure 1V.

CHAPTER 2

CHAPTER 2

AIMS/OBJECTIVES

2.1 Aim

The aim of the study was to describe the natural history of vertically transmitted HIV-1 infection, from birth to early childhood, in a cohort of infants followed prospectively from birth.

2.2 Specific objectives

- to determine the vertical transmission rate
- to determine maternal factors which might affect the vertical transmission rate
- to determine the effect of breastfeeding on the transmission rate and on the outcome in the infant
- to determine the age at which maternal antibodies were lost in the infants
- to describe the neonatal characteristics and complications of the group, according to infection status
- to determine onset of specific morbidity in the cohort
- to describe overall morbidity in the cohort
- to describe longitudinal growth in the cohort
- to determine the rate, onset and progression of AIDS in the infected infants
- to determine the rate and causes of mortality in the infants

CHAPTER 3

CHAPTER 3

METHODS

3.1 Study site and patient population

The study was conducted at King Edward VIII Hospital, situated in Durban, South Africa. This is a large, urban hospital, where at least 99% of the patient population is black. The hospital's obstetric unit handles approximately 16000 deliveries per annum.

Patients were recruited into the study between October 1990 and March 1993. A research worker was trained in HIV education and counselling and was based at the hospital's antenatal clinic. All women who were attending the clinic for the first time in the index pregnancy were given education and counselling on HIV, as a group. If signed consent was obtained for HIV testing, a sample of blood was taken at the time blood was drawn for syphilis serology, which is obligatory at the study hospital. There was > 95% acceptance for testing. When results for the test became available, personal counselling was offered to each woman. The possibility of participating in the newborn and infant study was discussed only with the women who tested HIV positive.

When an HIV positive woman delivered a liveborn infant, permission was sought, by the same research worker, to enter the infant into the study. Once written permission was obtained, the infant was enrolled.

3.1 (a) Retrospective Study

The first children with vertically transmitted HIV-1 infection at King Edward VIII hospital were recognised in late 1987 and early 1988. Based on the available data, we identified a few children in our wards who fitted the given descriptions, tested them for HIV-1 antibody, and collected their data retrospectively. Details on methods are included in the manuscript in Chapter 4.

3.1 (b) Maternal Data

Information on the mother was obtained either from the newborn infants' charts, or retrospectively from the antenatal and labour records. The following information was recorded:

Antenatal history:

- age
- parity
- past obstetric history
- medical examination
- haemoglobin level
- syphilis serology
- other STDs
- urinalysis
- pap smear
- ultrasound gestational assessment
- any complications

Labour and delivery:

- duration of labour
- method of delivery
- duration of ruptured membranes
- indications for assisted deliveries/ caesarean sections

- complications in labour: fever
bleeds
hypertension
meconium in liquor
fetal tachy/bradycardia
- maternal medical complications

3.1 (c) Neonatal data

every neonate was examined within 48 hours of birth. A full clinical examination was performed including general and systemic examination, growth parameters were measured, and initial blood samples were taken. The following were recorded at this time:

- weight (at birth)
- gender
- apgar scores at 1 and 5 minutes
- need for resuscitation
- meconium staining
- length
- head circumference

- dysmorphic features
general examination including skin, eyes, umbilicus, genitalia,
lymphadenopathy, jaundice, anaemia
- systemic:respiratory /abdomen/neurological/cardiac/renal
- gestation, and whether small or appropriate for gestation
- sepsis
- surgical problems

Subsequent to discharge, the neonatal records were reviewed for any late complications, particularly infections, jaundice, and neurological events. The duration of stay depended on the presence of complications, and ranged from 12 hours to 30 days.

3.1 (d) Follow-up of infants

A follow-up clinic was established specifically for the follow-up of this cohort of infants and comprised : paediatrician, 2 research scientists, and 2 research assistants (one of whom was the same person based in antenatal clinic and therefore had the most contact with the mother).

(i) timing of visits : the infants were followed up from birth at the following times:

- 1 month
- 2 months
- 3 months
- 6 months
- 9 months
- 12 months
- 15 months
- 18 months
- 24 months

thereafter at 6 monthly intervals if available.

(ii) clinical assessments : at each visit, the following were recorded:

- age
- weight, length, head circumference
- temperature
- skin rash
- lymphadenopathy: presence, sites, size

- eye, ear and throat examination
- thrush: presence and sites
- systems: respiratory/abdomen/neurological/cardiac
- development
- feeding
- history of diarrhoea/fever
- any interim illnesses/ visits to health care centres
- immunisation (from record card)

Growth parameters were plotted on NCHS (National Centre for Health Statistics) growth charts.

Mothers were encouraged to bring the infants to the follow-up clinic for any complaint, so that episodes of illness would not be missed, and to inform the team of any hospital admissions. Where possible, the inpatient records for these admissions were obtained.

Transport costs were paid for all hospital visits, and the visits to the hospital were free, to encourage follow-up. Defaulters were visited by one of the two research assistants, where possible, to try and encourage revisits.

(iii) Immunisation:

all the infants were immunised according to the immunisation schedule developed for South Africa, based on WHO recommendations. All the infants received BCG as well as oral polio drops at birth, prior to discharge. Subsequent immunisation was done at community clinics. At each scheduled hospital visit to the follow-up clinic, the immunisation records were checked and information recorded. Mothers were encouraged to attend immunisation clinics if they had lagged behind.

(iv) Blood testing:

- blood samples for HIV serostatus were taken at birth, 1,3,6,9,12,15,18,24,36 months.
- at these times, additional samples were taken for serum globulin levels
- samples for full blood counts were taken at 3-month intervals
- during episodes of illness, additional tests were undertaken as necessary. These included: cultures of blood, urine, stool and csf, full blood counts, viral serology, pus swabs, and radiology.

3.1 (e). Classification of infection status:

The infants' infection status was classified using the recommendations of the workshop on methodology held in Ghent, Belgium, in 1992. The reasons for this were:

- (i) maternal antibody may persist in the infant for up to 15 months of age; therefore, in regions which use the antibody test alone, diagnosis is delayed
- (ii) they allowed for classification of those infants who were lost to follow up early on in the study, and for classifying early deaths
- (iii) the same system could be used for the calculation of the vertical transmission rate.

Using this system, infants were classified as infected, uninfected, and indeterminate: Tables 3.1 to 3.4. Some modifications were made to allow for local differences in testing.

Table 3.1

Ghent classification of children born to seropositive mothers according to their probable HIV infection status (1992)

HIV-infected

HIV WB-antibody positive at 15 months

or

HIV-related death

or

AIDS

HIV-non-infected

HIV WB-serum-antibody-negative at 15 months

or

HIV WB-negative ≥ 9 months in a child lost to follow-up without AIDS

or

HIV WB-negative ≥ 9 months in a child who died from probable non-HIV-related cause

Indeterminate HIV infection status

Death before 15 months with indeterminate relation to HIV infection

or

Child died of probable not HIV-related cause while WB-positive or indeterminate before 15 months or WB-negative < 9 months (when last seen)

or

Child lost to follow-up while WB-positive or indeterminate before 15 months or WB-negative < 9 months (when last seen)

or

Child with indeterminate WB and alive at 15 months

Table 3.2

HIV-related signs and symptoms in children born to HIV-seropositive mothers used for the Ghent classification of paediatric HIV infection.

Persistent diarrhoea (≥ 15 days)

Oral candidiasis (beyond the neonatal period)

Generalized lymphadenopathy (enlarged lymph nodes in at least two independent anatomic sites)

Failure to thrive (no weight gain for a period of 3 months or crossing two percentiles lines on the growth chart)

Chronic parotitis (> 1 month)

Herpes zoster infection ('shingles')

Recurrent pneumonia (two or more episodes)

Table 3.3

Definitions for children born to HIV-seropositive mothers who died before infection status could be determined by serology. Ghent classification, 1992.

Probable HIV-related death

Either AIDS

or

At least one HIV-related sign/symptom when last seen

and

Dying from severe infection or persistent diarrhoea beyond the first 4 weeks of life

Probable non-HIV-related death

No HIV-related sign/symptoms when last seen

and

Dying from cause other than severe infection or persistent diarrhoea after the first 4 weeks of life

Death with indeterminate relation to HIV infection

All deaths occurring within the first 4 weeks of life

or

Beyond this period, all the deaths not classified above

Table 3.4

 Modified WHO clinical case definition for paediatric AIDS (1989)

Major signs

- Weight loss or failure to thrive
- Chronic diarrhoea (>1 month)
- Prolonged fever (> 1 month)
- Severe or repeated pneumonia

Minor signs

- Generalized lymphadenopathy
 - Oro-pharyngeal candidiasis
 - Repeated common infections
 - Generalized pruritic dermatitis
 - Confirmed maternal HIV infection
-

Paediatric AIDS is suspected in a child presenting with a least two major signs and two minor signs in the absence of known causes of immunosuppression.

3.2 Laboratory methods

HIV serology: the following methods were applied to all samples from mothers and infants, for HIV serostatus determination. All samples were initially tested using a commercial enzyme-linked immunosorbent assay, ELISA (Abbot Laboratories, N. Chigaco, IL). Those samples which tested positive were then confirmed with two tests, a Roche ELISA (Cobus Core, Besel, Switzerland), and an immunofluorescent assay, IFA, (Virion, Cham, Switzerland). Samples which tested negative with the IFA, were then tested by a Western Blot assay(diagnostic biotechnology). Samples were regarded as positive if the second

ELISA was positive, or if either the IFA or Western Blot was positive. These methods were applied to both the maternal and infants' blood samples.

More details on laboratory methods are described in the various chapters, according to the investigations used therein.

3.3 Statistical methods

Details on statistical methods used are provided in each chapter. However, some salient details are highlighted below:

3.3 (a) Calculation of vertical transmission rate:

the recommendations of the Ghent methodology workshop were used for this. Three different transmission rates are calculated, an upper, a lower, and an intermediate estimate. These calculations take into account those infants lost to follow-up, whose infection status was indeterminate:

the upper estimate: assumes that all indeterminate infants were infected;

the lower estimate: assumes that all indeterminate infants were uninfected; and

the median estimate: assumes that all indeterminate infants do not contribute to the calculation of the vertical transmission rate.

The intermediate estimate is used for reporting purposes.

The method used for the calculation:

upper estimate: $TR = (n+) + (n?) / N$

lower estimate: $TR = n+ / N$

intermediate estimate: $TR = (n+) / (n+) + (n-)$

where TR= transmission rate; N= total number in cohort;

n+ = positives; n- = negatives; n? = indeterminates

The 95% confidence intervals were calculated thus:

$$95\% \text{ CI} = TR \pm 1.96 \times \sqrt{\frac{TR \times (1-TR)}{D}}$$

where TR = transmission rate, and D is the denominator used in calculation.

3.3 (b) Factors affecting vertical transmission rate:

maternal risk factors which could impact on the vertical transmission rate were analysed in a univariate analysis; the results are presented as relative risks and 95% confidence intervals.

These were then included in a multivariate analysis to determine whether the effect of those found significant would remain; again results are presented as relative risks and 95% confidence intervals.

3.3 (c) Effect of breastfeeding on outcome of infants:

described in chapter 7.

3.3(d) Neonatal characteristics and outcome:

described in chapter 8.

3.3(e) Morbidity, natural history, and progression to AIDS:

described in chapter 9.

3.3(f) Growth:

described in the chapter 10.

3.3(g) Mortality:

described in chapter 11.

3.4 Ethical Approval

This study was approved by the Ethics committee of the Faculty of Medicine, University of Natal.

Permission for conducting the study was obtained from the medical superintendent of King Edward VIII Hospital, Durban.

CHAPTER 4

CHAPTER 4

RETROSPECTIVE STUDY

SOME EARLY OBSERVATIONS ON HIV INFECTION IN CHILDREN

4.1 Summary

Nine black children aged between 3 months and 30 months of age, with human immunodeficiency virus I (HIV-I) infection are described to draw the attention of health professionals in Southern Africa to special clinical characteristics useful for recognising this problem, which has many shared features with common diseases of infancy and childhood in the Third World. The main presenting complaints were chronic cough and persistent diarrhoea and vomiting. These children frequently had diarrhoea (8 of 9 patients), mucocutaneous candidiasis (8), pneumonia (7), hepatosplenomegaly (9), significant lymphadenopathy (5) and wasting (5). All were infected by common bacteria, such as Gram-negative organisms, *Mycobacterium tuberculosis* and *Campylobacter jejuni*, or by opportunistic infections such as *Candida* or cytomegalovirus (CMV), or by both bacterial and opportunistic organisms. A raised total serum globulin level, anaemia, lymphopenia and a cerebrospinal fluid (CSF) pleocytosis were frequent findings. Incomplete data on parental HIV status suggest perinatal transmission. Three of the children were HIV-antigen positive. The diagnosis of full-blown acquired immunodeficiency syndrome (AIDS), using the stringent Centers for Disease Control

criteria, is difficult in our situation because of limited diagnostic resources; however, using these criteria, and the clinical case definition for AIDS recommended by World Health Organisation, it is thought that probably 4 of these children could be considered as having AIDS.

Any child with an elevated serum globulin level, CMV infection, an unexplained abnormal CSF, an unusual or unresponsive form of tuberculosis, long-standing symptoms of common childhood illnesses and found to have diarrhoea, pneumonia, mucocutaneous candidiasis, hepatosplenomegaly, lymphadenopathy and wasting should be evaluated for the presence of HIV infection.

4.2 Introduction

There are increasing numbers of children with human immunodeficiency virus type I (HIV-I) infection and the acquired immunodeficiency syndrome (AIDS) throughout much of the world and in South Africa (Update: AIDS 1988, Aids update 1988). By October 1989, there were 12 reported cases of AIDS in South African children (AIDS advisory group 1989), and this figure is expected to increase annually in geometric leaps.

Since early 1988, an increasing number of children with HIV infection have been diagnosed in the paediatric wards at King Edward VIII Hospital Durban. While information is steadily becoming available about clinical features, management,

mortality, morbidity and outcome of HIV infection and AIDS in children in Western countries (Falloon 1989, AIDS:update 1989, Connor 1987) little is known about these aspects in children in Africa. Among adults in Africa, AIDS has been shown to be different from the disease in the West (Schoub 1986).

There is considerable overlap between the features of HIV infection/AIDS described among children in rich industrialised countries and the common diseases occurring among children in the Third World, e.g. protracted diarrhoea, chronic chest infections, malnutrition and tuberculosis. It is therefore important for clinicians to be able to distinguish children with these common conditions from those with HIV infection/AIDS, for appropriate prophylaxis, close observation and monitoring, as well as prompt treatment of intercurrent infections.

4.3 Patients and Methods

This retrospective study was carried out at King Edward VIII Hospital, Durban. Data were collected on all those children found to have a positive HIV-antibody test between April 1988 and July 1989. Only children with positive results on both the enzyme-linked immunosorbent assay (ELISA) and Western blot were included. Initial HIV-antibody testing had been done if the mother was known to be HIV-positive or if the

attending clinician suspected HIV infection/AIDS. One child was tested three times - at 1 month and 12 months after initial test.

These children had detailed clinical assessments and varying degrees of investigations were performed. The investigations included : HIV-antibody testing (by ELISA and Western blot); HIV antigen test (by ELISA); a full blood count and a differential count; cultures of blood, urine, stool and cerebrospinal fluid (CSF); examination of the CSF by microscopic and chemical methods; liver function tests; the TORCH screen; chest radiography; and Mantoux tests. Lymph node and liver biopsies and computed tomography (CT) had been done only where indicated. Cytomegalovirus (CMV) infection was diagnosed on the basis of a specific IgM antibody in serum, by liver biopsy, and by microscopic examination of the urine. In order to define lymphopenia, values for age-matched normal black children were used (Kiepiela 1989).

Parents' HIV status was tested where one or both parents were available and consent was obtained. The patients were categorised according to the classification system for HIV infection in children under 13 years of age recommended by the Centers for Disease Control (CDC) in Atlanta, Georgia, USA (Classification 1987). The total serum globulin levels were compared with those in age-matched patients with the following diagnosis: CMV infection without HIV infection (5 patients), tuberculosis (10), protein-energy malnutrition (20), and diarrhoeal illness requiring admission to hospital (20).

4.4 Results

During the study period of 15 months, 9 black children were identified as being HIV-antibody positive.

Table 4.1 shows their age at time of diagnosis, gender, presenting complaints and duration, place of residence, the CDC classification for HIV exposure, and outcome. Patient 3 was tested 3 times, and the positivity of the antibody test had increased with each subsequent testing. The mean age of these children was 13,2 months (range 3-30 months). There were 5 boys, and 7 patients came from urban areas. their main presenting complaints were chronic cough (6 of 9 patients), diarrhoea and vomiting (5) and loss of weight (2). Four children died (patients 1, 5, 7, and 9), their duration of stay in hospital varying from 1 day (patient 9) to 9 months (patient 1). Four children (patients 1, 3, 4 and 8) were aged > 15 months, the cut-off age used for presence of maternal antibodies.

The main clinical features of these patients are shown in Table 4.2. Six children were below the 3rd percentile for weight (National Center for Health Statistics (NCHS) standards). The patients nearly always has diarrhoea (8 of 9 cases), candidiasis (8), pneumonia (7), hepatosplenomegaly (7) and often had significant lymphadenopathy (5) and wasting (6). The significant laboratory results and radiographic findings are shown in Table 4.3. All the children had bacterial and/or opportunistic infections. Bacterial

infection was due to common organisms such as Gram-negative *Escherichia coli*, *Mycobacterium tuberculosis*, and *Campylobacter jejuni*. One child (patient 1) had massive tuberculous lymphadenopathy with no response to conventional antituberculosis drug therapy and died after 9 months' treatment in hospital. The most common opportunistic infection was candidia (8 of 9 patients) followed by CMV (5). CMV was diagnosed by a positive IgM (in 5 of 5 patients tested) and in 1 child (patient 7) CMV was also found in the urine and on liver biopsy. The CSF was found to be abnormal in 6 of the 9 children, the main abnormality being a pleocytosis; the total protein was elevated in 1 child.

Anaemia was present in 8 children, 6 had lymphopenia, while none had thrombocytopenia. The total serum globulin level was markedly elevated in all those tested, with a mean level of 56,8 g/l (range 37 - 78 g/l). In contrast, the means for the other conditions investigated were: CMV infection - 29 g/l (range 25 - 37 g/l); gastro-enteritis - 27,4 g/l (range 17 - 49 g/l); protein energy malnutrition - 26,2 g/l (range 8 - 38 g/l) and tuberculosis - 35,7 g/l (range 23 - 48 g/l).

Immune function testing had been done on only 3 children (patients 1, 2 and 4). The results of these showed a depressed CD4:CD8 ratio of 0,07, 0,09 and 0,20, respectively (Kiepiela 1989). The T-cell function (phytohaemagglutinin transformation) was impaired in patient 4, normal in patient 2, and was unsuitable for comment in patient 1.

CT was performed on 1 patient, No. 7, and this showed generalised cerebral atrophy.

All the children's sera was tested for the presence of HIV antigen. This is not yet a sensitive test in our laboratory (I.M. Windsor - unpublished observation). Three of the 9 were found to be positive (patients 2, 6, 9) and they were all < 15 months of age.

The mothers of 2 children were known to be HIV-antibody positive at the time the patients were admitted to hospital. Three sets of both parents were available for HIV-antibody testing; of these 2 sets of both parents were HIV-positive, while in 1 set only the mother was positive. The social and sexual histories were available for the parents of 2 children. One set of parents were both teenagers, were still at school and each of them admitted to having had several sexual partners. In the other set of parents, the father had 2 wives and 6 children, 2 from the mother of the patient and 4 from the other wife. He himself was antibody negative. The mother refused to give a history regarding her sexual contacts.

TABLE 4.1 PATIENT DETAILS AND OUTCOME

Patient	Age at time of diagnosis (months)	Sex	Residence	Presenting complaints and duration (months.)	CDC classification for HIV infection	Outcome and duration of stay (mo.)
1	24	M	Urban	Cough (2) Swelling in neck (1)	P II D I	Died 9/12
2	13	F	Urban	Failure to thrive, cough, vomiting (2) Diarrhoea : recurrent (5)	P I D I	Discharged
3	15 Repeated at 16 and 24	F	Urban	Cough, fever, vomiting (1) Persistent pneumonia (6)	P II D I	Discharged
4	30	F	Rural	Cough, loss of weight, fever (2)	P II D I	Discharged
5	8	M	Urban	Recurrent diarrhoea (3)	P 0	Died 1/12
6	3	M	Urban	Cough, fever (1)	P II D I	Discharged
7	5	M	Rural	Cough, failure to thrive, unresolving pneumonia (2)	P II B	Died 2/12
8	16	F	Urban	Recurrent diarrhoea (7)	P II D II	Discharged
9	5	M	Urban	Cough, diarrhoea, vomiting fever 1 wk	P II D I	Died 1 day

* Refers to duration of hospital stay from admission to death

TABLE 4.2 CLINICAL FEATURES

no.	Diarrhoea present	Significant lymphadenopathy	Mucocutaneous candidiasis	Chest: pneumonia	Abdomen: Hepatomegaly	Splenomegaly	Admission weight in kg*
1	+	Generalised	+	+	+	+	9,3 (< 3rd)
2	+	Generalised	+	+	-	-	7,1 (< 3rd)
3	+	Axillary	+	+	+	+	6,4 (< 3rd)
4	-	-	-	-	+	+	12,3 (25th)
5	+	Generalised	+	+	+	+	2,7 (< 3rd)
6	+	-	+	+	+	+	5,5 (50th)
7	+	Generalised	+	+	+	+	3,7 (< 3rd)
8	+	-	+	+	+	+	7,9 (3rd)
9	+	-	-	-	-	-	8,0 (75th)

* (NCHS centile)

+ = present; - = absent

TABLE 4.3 RESULTS OF INVESTIGATIONS

Patient	INFECTIONS										CEREBROSPINAL FLUID*			HAEMATOLOGICAL		CONSOLIDATION : CHEST RADIOGRAPH	BIOPSY SITE AND REPORT
	HIV-Antigen (ELISA)	Organism	Site	Opportunistic Infections	Total serum globulin (g/l)	P	L	R	Hb (g/d)	Lymphocyte count (/ul)*							
1		M. Tuberculosis Campylobacter	Lymph nodes chest stool	CMV, Candida	76	2	0	0	6.2	2736(↓)		Bilateral	Lymph node: active tuberculosis				
2	+	Nil		Candida	Not done	16	12	10	7.8	6656(N)		Not done					
3	NEG	Pseudomonas	Ear, nose	CMV, Candida	64	Not available			8.3	3024(N)		Bilateral	Liver : consistent with HIV infection				
4	NEG	E. coli, Campylobacter	Stool	CMV	78	8	4	0	7.0	5372(N)		Bilateral	Liver : consistent with HIV infection				
5	NEG	Nil		Candida	42	Unsuitable			7.9	10 650(↑)		Bilateral					
6	+	E. coli Campylobacter	Stool	CMV, Candida, toxoplasmosis	40	46	12	0	10.3	2392(↓)		Bilateral	Liver : normal				
7	NEG	Nil		CMV, Candida	61	0	0	20	9.7	3552(B)		Unilateral	Liver : features of CMV hepatitis				
8	NEG	E. coli Pseudomonas	Urine Ear	Candida	37	Not available			7.7	2574(↓)		Unilateral					
9	+	Gram-negative	Blood	Candida	Not done	4	0	0	8.4	2528(↓)		Not done					

NEG = NEGATIVE

L = LYMPHOCYTES

R = RED BLOOD CELLS

+ = POSITIVE

P = POLYMORPHONUCLEAR CELLS

*↓ = LOW

N = NORMAL

B = BORDERLINE LOW

↑ = INCREASED

4.5 Discussion

With the expected increase in the number of infants and children with HIV antibodies, HIV infection and AIDS, especially among blacks, there is an urgent need for health professionals caring for children to become aware of those features of this condition which might apply in the local situation. This preliminary account of a small sample of 9 hospitalised black infants and children with HIV infection attempts to do this; it draws attention to a few characteristics that are useful for recognising this syndrome, which has many features shared by the common diseases of infancy and childhood in poor countries.

The presenting symptoms were indicative of respiratory and gastro-intestinal problems; since these two conditions are the most frequent causes of morbidity and mortality among children in the Third World, these symptoms did not in themselves signal the likelihood of a background HIV infection. The protracted duration of the complaints may have given a hint about the seriousness of the underlying process; However, this is a highly subjective factor in our environment and was therefore of doubtful value. The patients almost always had diarrhoea, pneumonia, mucocutaneous candidiasis and enlargement of the liver and spleen; they often had significant lymphadenopathy and wasting. It is this combination of clinical features, rather than any individual problem, which should alert the health professional to the probability of HIV infection. Diarrhoeal disease, respiratory tract infections and protein-energy malnutrition, taken separately, may occasionally each show evidence of all these above findings, but very often do not.

Stronger support for the diagnosis of HIV infection is provided by the additional detection of an elevated serum globulin level, CMV infection, CSF pleocytosis and unusual manifestations of tuberculosis. Such an assembly of clinical problems increases the likelihood of HIV infection even further. Overt CMV infection, especially the intra-uterine type, is exceedingly uncommon among black children in our experience. The extent of serum globulin elevation in AIDS among the children reported here was far in excess of that seen in common chronic diseases, such as tuberculosis, malnutrition and diarrhoea. It was also higher than that in CMV infection without concomitant HIV infection. The presence of raised globulins has been noted in other studies of paediatric HIV infection and AIDS (Oleske 1983, Mok 1989, Pahw 1986), and may accordingly be the single most important simple test for supporting this diagnosis.

In Western countries, the main clinical features in children with HIV infection are failure to thrive, recurrent fever, thrush, diarrhoea and lymphadenopathy (Falloon 1989, Connor 1987). Our patients had nearly all these features and, in addition, hepatosplenomegaly was a common finding. Pulmonary disease accounts for most of the morbidity and mortality associated with HIV infection in American children, with *Pneumocystis carinii* being the most common opportunistic infection (Connor 1987). Lymphoid interstitial pneumonia (LIP) also occurs frequently (Connor 1987).

Disseminated CMV infection is the second most frequent opportunistic infection, followed by *Candida* (Schoub 1986). The cause of pneumonia in our patients remains unknown.

Although we did not look for *P. carinii* or LIP, there was a high incidence of persistent or recurrent pneumonia; in 1 child the chest radiograph was suggestive of LIP (Rubinstein 1986). As in children from industrialised countries, anaemia was a consistent feature (Oleske 1983). Thrombocytopenia, which is frequently found (Saulsbury 1986, Shannon 1985), was not seen in any of our patients whereas lymphopenia, which is not described as a common finding in children in the USA (Pahw 1986), was frequently found in our patients.

Central nervous system involvement includes encephalopathy, developmental delay, microcephaly, cerebral atrophy and CSF abnormality (Connor 1987, Epstein 1986, Epstein 1985). Our results show that CSF abnormality occurred frequently among our patients. One child had CT and this showed generalised atrophy. The children were not adequately assessed for developmental delay.

Cardiomyopathy, arteriopathy and the nephrotic syndrome have been described in American children (Connor 1987). None of our patients had cardiac or renal involvement. Kaposi's sarcoma was not found in any child and, in all reports to date, is said to be rare (Falloon 1989). The overall mortality given for American children with AIDS is 50-65% (Falloon 1989, Connor 1987). The mortality in our series was 45%. The causes of death were disseminated, unresponsive tuberculosis and extensive pneumonia.

Although 5 of our 9 patients were < 15 months of age (which is the cut-off age used for the persistence of maternal antibodies), 3 of them were antigen-positive, and the other 2 had other

criteria consistent with making the diagnosis of HIV infection as described by the CDC (Classification 1987). Diagnosis of AIDS, as proposed by the CDC (Revision 1987), is difficult in our situation because of limited diagnostic resources and the stringent criteria. However, on the basis, possibly patients 1 and 8 would match the required criteria. Using WHO criteria (WHO 1986) for the clinical case definition of AIDS where diagnostic resources are limited, then patients 2 and 4 would probably also fulfil the criteria.

Our data are incomplete in certain important respects, such as immune function testing, parental HIV status, history regarding risk factors and possible modes of infection. However, we felt it important to share our limited clinical experience at this stage with other clinicians caring for children, in order to alert them to the features of this condition in South African children. A prospective study is being planned in order to delineate some of the unanswered questions referred to above, and to compare local experience of paediatric AIDS with that reported from the West.

Addendum

By the end of August 1990, a further 21 children were diagnosed as being HIV-positive; 18 of them were regarded as having symptomatic HIV infection and would fall into the PII category of the CDC classification. Of these 18,5 children fulfil the WHO criteria for the diagnosis of AIDS. Our findings in these children consolidate the observations we made on the first 9 children.

SECTION 2

CHAPTER 5

CHAPTER 5

RESULTS

5.1 General Results

Infants were enrolled into the study between October 1990 and April 1993.

During this period, 234 infants and their 229 mothers were entered into the study. Fifty three infants were not brought back for a single follow-up visit after discharge from the neonatal unit, could not be traced by the research workers, and were excluded from the study. Unrest and political violence in the province of Kwa/Zulu Natal during the study period led to large numbers of people moving from one area to another, so that the original address changed; in addition, women sometimes returned to remote rural areas after delivery and therefore could not be reached. This group of patients was compared to the rest of the cohort with regard to maternal, labour and delivery data, and was found to be comparable to the rest of the cohort, and subsequently excluded from all analyses.

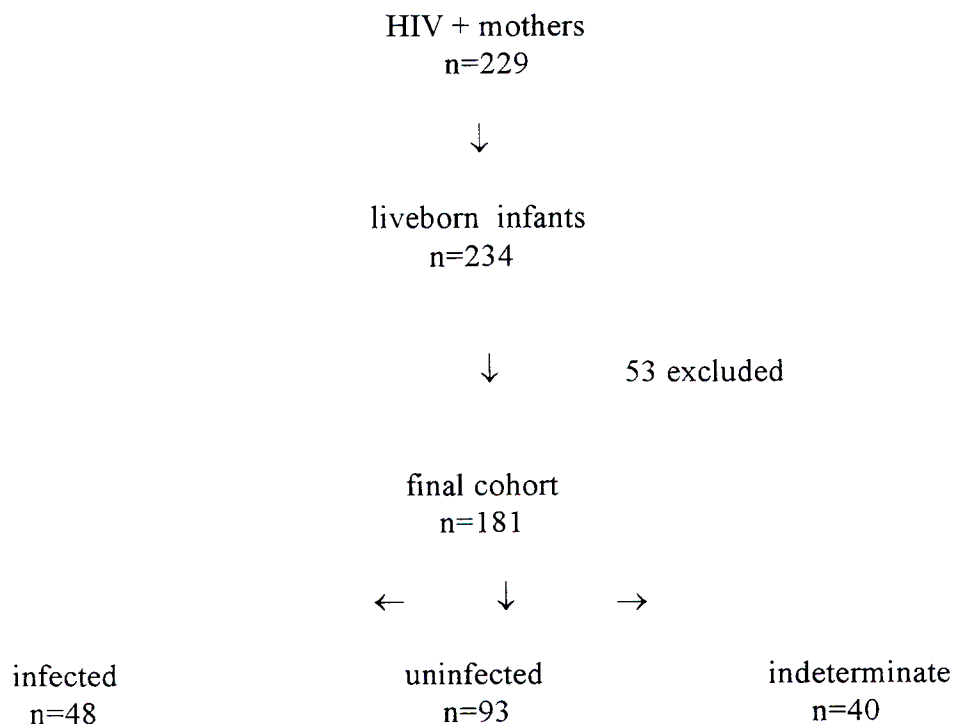
The remaining 181 infants were classified as follows (figure 5.1):

- 48 infected
- 93 uninfected
- 40 indeterminate.

The infected group included 17 deaths, and the indeterminate group included 8 deaths from unknown aetiology.

There were 5 sets of twins in the cohort. There was concordance in three sets, 1 set being infected and two uninfected; discordance occurred in one set, where twin 1 had an HIV related death and twin 2 remained uninfected; in the last pair, twin 1 was stillborn and twin 2 had an HIV-related death.

Figure 5.1



(5.2) Maternal Characteristics

Some of the maternal characteristics assessed are shown in Table 5.1

The mean age of the mothers was 24 years, (range 16 to 40 years). Forty four of the women, 33%, were primiparous. A positive syphilis serology was found in 23 (18%) of the women. Forty four women (37%) were delivered by caesarean section, of which 77% were emergency caesarean deliveries (this high rate is due to the study hospital being a tertiary referral centre, and black women having a greater tendency to cephalo-pelvic disproportion). Of those who delivered vaginally, 39% had an episiotomy or tear. Only 17 (13%) of the deliveries occurred before 36 weeks gestation. Twenty one of the mothers (16%) did not breastfeed at all.

At the time of delivery, only 5 women were symptomatic for HIV infection, and none was given the diagnosis of AIDS. There were two maternal deaths in the puerperium, both non-HIV related (one from cardiac disease and the other from puerperal sepsis).

Table 5.1 Characteristics of the maternal population

Characteristic		Number	(%)
age	≥ 30 years	54	40.3
	< 30 years	80	
parity	p 0	44	33.8
	p 1+	86	
syphilis serology	positive	23	18.1
	negative	104	
haemoglobin level	≤10 g/l	25	22.9
	>10 g/l	84	
delivery	caesarean	44	36.7
	vaginal	76	
feeding method	breast /mixed	110	84
	bottle only	21	
mean HIV-IgA (optical density)		1.62	
mean beta-2 microglobulin level (mg/l)		0.01	
residence	urban	148	
	rural	63	

CHAPTER 6

CHAPTER 6

DETERMINANTS OF MOTHER-TO-CHILD TRANSMISSION OF HIV-1 INFECTION IN A COHORT FROM DURBAN, SOUTH AFRICA

6.1 Summary

Objectives: To determine the vertical transmission rate of HIV-1 infection and to assess the influence of maternal risk factors on transmission in infants born to HIV-1 infected black women in Durban.

Design: A prospective, hospital-based cohort study conducted at King Edward VIII hospital, Durban. HIV-1 seropositive women were enrolled into the study and their infants followed up at regular intervals from birth to early childhood. Classification of infection status of the children and computation of transmission rate were done according to the recommendations of the workshop held in Ghent, Belgium(1992).

Results: The final cohort of 181 infants were classified as: 48 infected, 93 not infected and 40 indeterminate. Clearance of maternal antibodies was achieved by 12 months of age in virtually all infants who became seronegative. The intermediate transmission rate was 34% (95% C.I. 26%-42%). Deliveries by caesarean section were found to have significantly lower transmission, R.R.=0.46 (95%C.I. 0.23-0.91). Women with lower hemoglobin levels during pregnancy (less than 10 g/dl) had an increased risk of transmission, R.R.=1.99 (95%C.I. 1.18-3.34). Advanced maternal age, multiparity, positive

syphilis serology, duration of ruptured membranes, preterm delivery and breastfeeding* were not associated with an increased risk of transmission.

Conclusions: This study, the first from South Africa, has confirmed that the rate of vertical transmission of HIV-1 is as high as that reported from most African cohorts. Caesarean sections were protective against transmission, while low hemoglobin levels were associated with an increased risk of transmission. Twelve months could be used as the cut-off age for the diagnosis of vertical infection using antibody tests.

*N.B. In this observation, we had compared ever breastfed versus never breastfed. In the next chapter, we discussed breastfeeding in more detail, comparing exclusive, mixed, and formula fed infants.

6.2 Introduction

The Human Immunodeficiency Virus 1(HIV-1) epidemic which began later in South Africa than in the rest of the continent, is spreading rapidly in the country, especially among young black women of child-bearing age (Abdool Karim 1992, Kustner 1995). According to national surveys the prevalence rates at antenatal clinics in the country range from a low of 1.16% in Western Cape to a high of 14.35% in KwaZulu/Natal (Kustner 1995). Since more than 90% of HIV-1 infection in childhood occurs by vertical transmission, an increasing number of infected women will lead to large numbers of infected children. The magnitude of the problem depends on the vertical transmission rate in the local population and the factors influencing this rate.

The vertical transmission rate varies considerably among regions, with low rates reported from Europe(14%) to much higher rates from central and southern Africa (up to 45%) (ECS 1992, Lepage 1993, Hira 1989, Ryder 1989, Lallemand 1994). Why these differences exist is not yet fully understood and is the focus of many studies. One possible explanation is differences in methodology; this can be addressed by the use of standardized methods as recommended by the workshop held in Ghent in 1992 (Dabis 1992, The Working Group 1995).

It is now well accepted that infection of the infant can occur in utero, during labor and delivery, and in the postnatal period (Mofenson 1994), although the proportion of each is not known. Some of the risk factors that have been assessed in various studies include: low CD4 counts during pregnancy, presence of symptoms in the mother, maternal p24 antigenemia, disruption of the placenta, mode of delivery, and feeding practice (ECS 1992, Hira 1989, Lallemand 1994, Borkowsky 1992, Gabiano 1992, Dunn 1992). The European Collaborative Study found that caesarean sections decreased the risk of transmission (ECS 1994) and the first report of the same finding for an African cohort came from an interim analysis of the study cohort (Moodley 1994). A meta-analysis done on feeding methods found that breastfeeding could increase the risk of infection by 14% (Dunn 1992) in those mothers with established infection. This is of particular importance in developing countries where breastfeeding is widespread.

In order to counsel and care for HIV infected expectant mothers appropriately, it is necessary to establish the vertical transmission rate in the local population, and to assess the effects of a variety of risk factors. Thus a study was undertaken in Durban, in the province of Natal/KwaZulu, which is at the epicentre of the HIV-1 epidemic in South Africa (Kustner 1995).

6.3 Patients and Methods

This report derives from a prospective, hospital based, cohort study, on the natural history of vertically transmitted HIV-1 infection. The study was conducted at King Edward VIII Hospital, a large urban hospital in the city of Durban. At least 95% of the patients attending the hospital are black.

Approval for the study was given by the Ethics Committee of the University of Natal's Medical Faculty and the medical superintendent of the hospital.

6.3.1 Patient population

All the details on patient population have been provided in Chapter 3.

Data on maternal age and parity, obstetric history, antenatal care and circumstances around labor and delivery, as well as results of hemoglobin and syphilis serology were obtained from the newborn infants' records at delivery as well as retrospectively from the obstetric charts. Gestation was determined from ultrasonography done on every patient at the first antenatal visit.

The decision to perform caesarean section on the women was in no way influenced by the HIV-1 serology result. In addition, AZT was not being used on pregnant women at this hospital during the study period.

6.3.2 Laboratory Methods

Refer to Chapter 3.

6.3.3 Classification of infection and calculation of transmission rate

The recommendations of the Ghent Workshop on methodology were used for the classification of childrens' HIV-1 infection status and for the calculation of mother to child infection rates (Dabis 1992). Briefly, children were classified as positive if: they were antibody positive at 15 months, or if they fulfilled WHO criteria for AIDS, or if they had an HIV-1 related death. Children who became antibody negative after age nine months, as well as those who died of a non HIV-1 related illness, were classified as not infected; and

those infants who were lost to follow-up or died of an unknown cause before the age of 15 months, while still antibody positive, were classified as indeterminate.

6.3.4 Statistical methods

The data for the univariate analysis are presented using relative risks (R.R.) and 95% confidence intervals. Logistic regression was used to examine the simultaneous effects of several variables which included maternal age, parity, syphilis serology, hemoglobin, gestation, method of delivery, and feeding method. Twins were excluded from both the above analyses. The rate of loss of maternal antibody was calculated using life table methods.

6.4 Results

Between October 1990 and April 1993, 234 Black infants and their 229 mothers were entered into the study. All the children in the study were born at least 18 months prior to the time of analysis. Follow-up of the cohort was ongoing at the time of this analysis.

6.4.1 Classification and transmission rate

Fifty-three of the patients did not attend a single follow up visit after birth and could not be traced by field workers. Unrest and political violence in the province led to large numbers

of people moving from one area to another; in addition, patients sometimes returned to remote rural areas immediately after delivery and were lost to follow up. This group was no different from the rest of the cohort with regard to the risk factors analyzed and was excluded from subsequent analyses. The remaining 181 patients were classified as follows: 48 infected (including 17 deaths), 93 not infected, and 40 indeterminate (this includes 8 deaths from unknown causes and 32 losses to follow up between one and nine months of age, while still antibody positive). There were 24 known deaths at the time of analysis, of which 16 were HIV related. Of the 5 sets of twins in the cohort, there was concordance in 3 sets of twins, one set being infected and two sets not infected; discordance occurred in one set, where twin one had an HIV-1 related death and twin two has remained uninfected. In the last pair, twin 1 was stillborn and twin two had an HIV-related death.

Using the direct method for the calculation of the vertical transmission rate (Dabis 1992), the following results were obtained: the median estimate, which assumes that indeterminate children do not contribute to the vertical transmission rate, was 34% (95% CI 26%-42%). The upper estimate, which assumes that all indeterminate children are infected, was 48% (95% CI 40%-60%); and the lower estimate, which assumes that all indeterminates are not infected, was 26.5 % (95% CI 20%-33 %).

6.4.2 Maternal Data

The mean age of the mothers was 24 years (range 16-40 years); and 43(32%) of the women were primiparous; 23(18%) had a positive syphilis serology; 44(35%) were delivered by caesarean section, of which 77% were emergencies. Of those delivered vaginally, 39% had an episiotomy or tear. Only 17(13%) of deliveries occurred before 36 weeks' gestation. Twenty-one (16%) of the mothers did not breast feed at all (duration of breastfeeding ranged from one week to 30 months).

At the time of delivery, only 5 mothers were symptomatic for HIV infection. There were two maternal deaths in the puerperium, both due to non HIV related causes.

6.4.3 Analysis of risk factors

The univariate analysis of various risk factors is shown in (Table 6.1). The significant findings were: deliveries by caesarean section had a lower risk of transmission than vaginal deliveries, relative risk:0.46 (C.I. 0.23 to 0.91); women with a low hemoglobin during pregnancy were at increased risk of transmission, R.R.=1.99 (C.I. 1.18 to 3.34). No significant risk of transmission was noted for the following factors: advanced maternal age, multiparity, positive syphilis serology during pregnancy, delivery before 36 weeks' gestation, duration of ruptured membranes, and breastfeeding (Refer previous explanation). When duration of membrane rupture was analysed using 4 hour and 6 hour,

Table 6.1. Results of univariate analysis

Characteristic	Infected (n= 44)	Not infected (n=88)	R.R. [#]	95% C.I. ⁺
Maternal age ≥30 years	17	34	1.03	0.62-1.69
< 30 years	26	54		
Multiparous	29	57	1.04	0.61-1.75
Primiparous	14	29		
Syphilis serology: positive	6	17	0.73	0.35-1.53
negative	37	67		
Hemoglobin ≤10g/dl	13	12	1.99	1.18-3.34
>10g/dl	22	62		
Gestation ≤36 weeks	6	11	1.08	.0.54-2.16
>36 weeks	38	77		
Deliveries caesarean	8	36	0.46	0.23-0.91
vaginal	30	46		
Ruptured ≥12 hours	4	11	0.86	0.35-2.09
	29	64		
Ever breastfed	38	72	1.44	0.64-3.22*
Never breastfed	5	16		

⁺ C.I.=confidence intervals

[#] R.R. = relative risk.

Numbers do not always add up to 44 infected and 88 not infected because of missing data. Twins are excluded (4 infected and 5 not infected).

* Refer explanation in Summary (6.1).

instead of 12 hour cutoff times, no association was found with risk of transmission.

In a more detailed examination of the method of delivery, no significant difference was found between the 33 emergency and 11 elective caesarean deliveries; 7/33 infants delivered by emergency caesarean and 1/11 delivered by elective caesarean were infected. Similarly, no increased risk of infection was noted in those infants born vaginally with intact perineum (17/46) vs those delivered vaginally with episiotomy or laceration (13/30).

In the multivariate analysis, the decreased risk of transmission for deliveries by caesarean section as well as the increased risk for low hemoglobin values, remained significant.

When the analysis was repeated including the children whose status was indeterminate with the infected group or the uninfected group, the effects of low hemoglobin and caesarean delivery were similar (Table 6.2).

6.4.4 Clearance of maternal antibodies

Figure 6.1 shows the rate of loss of maternal antibodies according to age. At birth, 100% were antibody positive, with 98% remaining positive at 6 months. Thereafter, the rates changed rapidly with 63.9% positive at 9 months and 29.2% positive at 12 months. A plateau effect was seen from 12 months. For those infants becoming antibody negative,

Table 6.2. Results of multivariate analysis

Variable	Relative Risk (95% C.I.)					
	group A		group B		group C	
Low hemoglobin	3.20	(1.23-8.28)	2.74	(1.05-7.13)	2.88	(1.09-7.57)
Caesarean delivery	0.37	(0.14-0.95)	0.32	(0.12-0.84)	0.33	(0.13-0.88)

group A = infected + indeterminate vs not infected

group B = infected vs not infected + indeterminate

group C = infected vs not infected

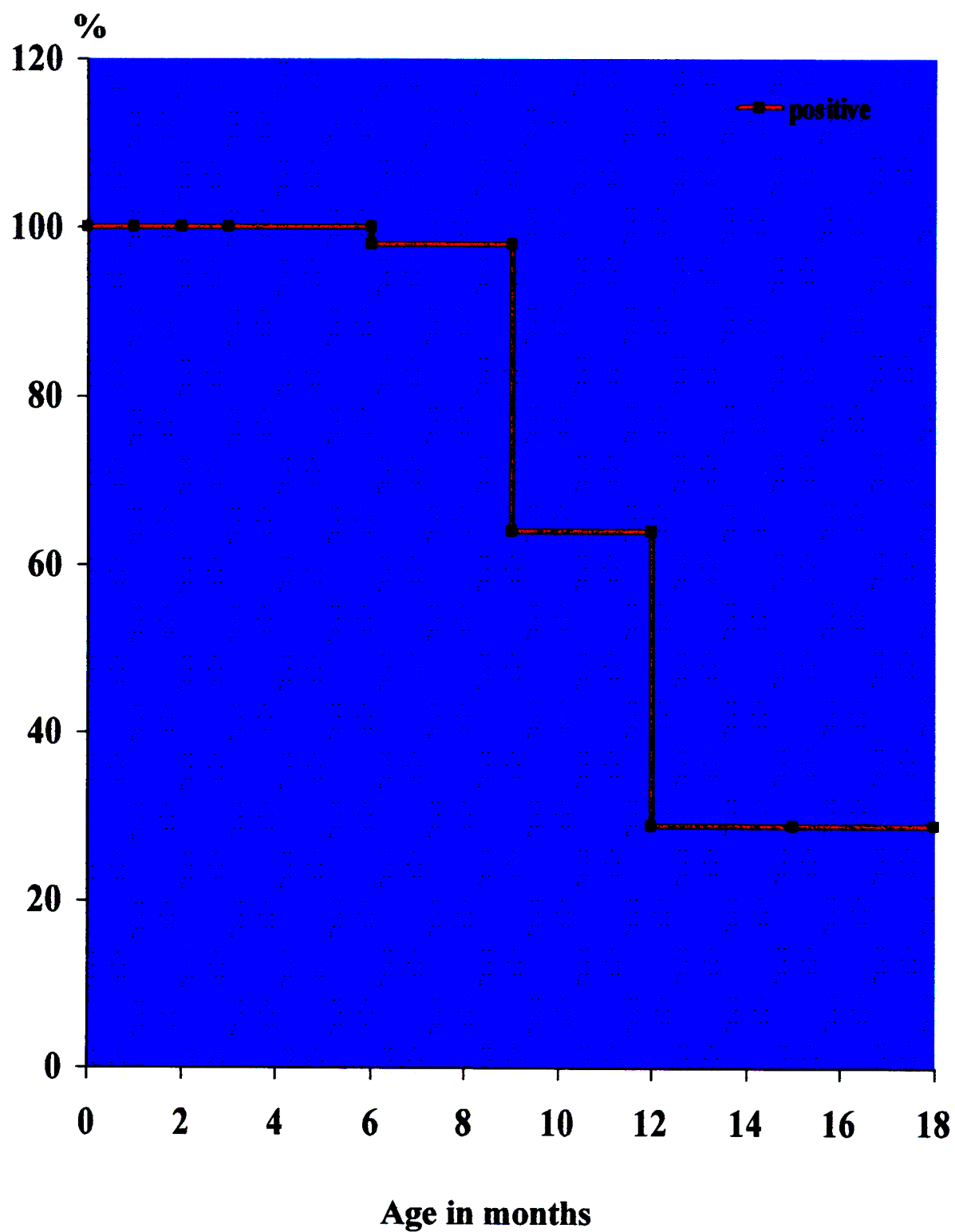


Figure 6.1 Clearance of Maternal Antibodies.

clearance was achieved by age 12 months in almost all (92/93). At the time of analysis no child who became antibody negative had subsequently seroreverted (with follow up ranging from 21 to 48 months).

6.5 Discussion

The transmission rate of 34% found in this prospective cohort study is within the range for cohorts from other parts of Africa, reported rates being between 20% to 45% (Lepage 1993, Lallemand 1994) and higher than the rates reported from studies in developed countries (ECS 1992, Gabiano 1992, Nair 1993). Comparison among studies is difficult because of differing methods for diagnosis of infection and for calculation of mother to child transmission rates. However, even with standardization, the rates for Africa are higher (The Working Group 1995). Comparison can be made between the rates for this study and those from two other African studies: from Kigali, Rwanda (Lepage 1993) and from Brazzaville, Congo (Lallemand 1994). These studies used the same criteria for defining infection status and the same method for calculation of transmission rates (Dabis 1992) although the numbers in the study cohort are smaller. The transmission rate for this study lies between the rate reported for Rwanda (25 %), and that for Congo (40.4%). Since the mothers in this study were mainly asymptomatic at the time of delivery, this could account for the lower rates than in studies from Congo (Lallemand 1994) and from Zambia (Hira 1989). In the Congo cohort, women who were symptomatic were more likely to transmit infection; while in the Zambian cohort, which had a very high transmission rate,

53% of the women were symptomatic.

The pattern of antibody clearance observed in the study cohort was similar to that found in other studies (Lepage 1993, Ryder 1989, Andiman 1990). Almost universal clearance was achieved by 12 months' age, which can be used as a cut-off for diagnosis of vertical transmission in this population. This is important since more sophisticated tests are not readily available in most developing countries, where the only available laboratory diagnosis is an antibody test.

The finding in this study that deliveries by caesarean section were less likely to transmit infection was previously reported from an interim analysis of this same cohort (Moodley 1994). That deliveries by caesarean section were protective against transmission has been shown by the large European Collaborative study (ECS 1992), but this has either not been reported in African cohorts (Hira 1989, Lallemand 1994) or has been shown to have no effect (Lepage 1993). While overall caesarean deliveries were shown to be protective in the study cohort, a comparison between elective and emergency caesareans showed no difference. However, the number of elective caesarean deliveries was small. A secondary analysis on caesarean deliveries in this cohort found that the protective effect was not increased if caesarean deliveries were undertaken prior to membrane rupture (Kuhn 1996).

Studies have reported that risk of transmission with vaginal deliveries was increased if deliveries occurred through an episiotomy or laceration where the infant was exposed to maternal blood (ECS 1992, Boyer 1994). This effect was not observed for the study cohort where a significant number of deliveries were associated with an episiotomy or tear. St. Louis et al (St. Louis 1993) from Zaire reported an association between risk of transmission and anemia in those women with low hemoglobin values, especially if the CD4 + lymphocyte count was high. The present study has found that women whose hemoglobin values were below 10g/dl during pregnancy were at an increased risk of transmission. This may reflect the effect of advanced subclinical disease, in which case it may serve as a marker of disease state. Alternatively, it may be due to poor nutrition and general poor health of the mother, in which case it presents the possibility of a simple intervention in pregnant HIV infected women. This finding needs to be evaluated further together with assessment of immune function during pregnancy. This would be of particular importance if AZT were to be used as a means of intervention during pregnancy.

It is now accepted that transmission of HIV-1 occurs via breast milk; the magnitude of the increased risk of breastfeeding, in women with established infection, is said to be 14% (Dunn 1992). This risk must be balanced against the increased morbidity and mortality associated with formula feeding in developing countries (Cutting 1993, Heymann 1990, Nicoll 1995). In Africa, breastfeeding is the norm and in all the reported cohort studies, breastfeeding was almost universal. In the study cohort, 16% of the women did not breastfeed at all, the main reason being the need to return to work immediately after

delivery. Although no significant protective effect from formula feeding was noted, the numbers were small and a larger study with equal numbers of women in each group is needed for clearer definition. In a study from Zaire breastfeeding did not increase risk of transmission, and it was protective against the morbidity attached to common childhood illnesses in developing countries (Ryder 1991). A similar observation was made in a study from Rio de Janeiro (Collareda 1993). Studies from developed countries have usually observed an increased risk, but in these countries, the proportions of women breastfeeding are small (ECS 1992, Gabiano 1992). Breastfeeding was generally prolonged in most infants in the present study, and it is significant that, to date, no child has seroreverted, although late seroreversion, which has been attributed to prolonged breastfeeding, was reported in other African studies (Bulterys 1995, Datta 1992). A recent study from India supports the finding of our cohort where no seroreversion occurred despite breastfeeding (Kumar 1995). Unless suitable conditions are met for the provision of formula feedings to infants of all infected women in developing countries (clean water, sterilization facilities for bottles and nipples, adequate funds to buy formulas, etc.) the recommendations of the WHO and UNICEF should be observed (WHO/UNICEF 1992, Nicoll 1995).

Disruption in the integrity of the placental barrier by co-infection with syphilis could increase the risk of transmission (Andiman 1991). Researchers from New York as well as from Baltimore have reported increased transmission associated with untreated syphilis (Borkowsky 1992) and with other sexually transmitted diseases (Nair 1993). Several other studies have not found this association (Lepage 1993, Boyer 1994, St. Louis 1993). In

our study no increased risk was found for women with syphilis. This could be explained by the policy of treating all women with syphilis during antenatal care. If the difference in observations of associated risk was due to the treatment factor, this presents another simple intervention for reducing transmission.

Goedert et al (Goedert 1989) reported an increased transmission risk for infants born before 37 weeks' gestation, and the European Collaborative Study reported an increased risk in those infants less than 34 weeks' gestation (ECS 1992). This association has not been observed in our study and in most other studies (Ryder 1989, Lallemand 1994, Boyer 1994, St. Louis 1993, Blanche 1989, Lindgren 1991).

A recent report by Minkoff et al (Minkoff 1995) found that the risk of transmission with vaginal deliveries was increased if membranes were ruptured for ≥ 4 hours; this association was not found in our cohort and in the small number of other studies where this has been reported (Boyer 1994, St. Louis 1993, Connor 1994). Similarly, the lack of association with parity in the study cohort is the same as that from several other studies (ECS 1992, Hira 1989, Lallemand 1994, Nair 1993, Boyer 1994, St. Louis 1993).

Intervention programs for the interruption of vertical transmission in the study population need to take into account the protective effect of deliveries by caesarean section.

However, deliveries by caesarean section are not without risks and morbidity. In addition, in a hospital where the number of caesarean deliveries is already high (25% at the study

hospital), the additional burden of delivering all HIV infected women by caesarean section must be considered. Ideally, intervention should be non-invasive and due consideration must be given to such simple measures as maintaining an optimal haemoglobin during pregnancy and treating sexually transmitted diseases such as syphilis. The use of a drug such as AZT which has been shown to decrease transmission (Boyer 1994, Minkoff 1995) is an option to consider, but needs to be weighed against cost, availability, and the necessity for close monitoring. Alternatively, the use of vitamin A, the deficiency of which may increase transmission (Semba 1994) needs to be evaluated further as it would be an additional simple and inexpensive intervention.

In conclusion, this study has found that the vertical transmission rate of HIV-1 for the black population in Durban is high; that deliveries by caesarean section were protective against transmission of infection, and that women with lower hemoglobins were more likely to transmit infection. In addition it has shown that clearance of maternal antibodies is virtually achieved by 12 months of age, and that this age could be used as a cut-off for the diagnosis of vertical infection in areas relying on antibody tests.

CHAPTER 7

CHAPTER 7

BREASTFEEDING BY HIV-1 INFECTED WOMEN AND OUTCOME IN THEIR INFANTS : A COHORT STUDY FROM DURBAN, SOUTH AFRICA

7.1 Summary

Background: Women in developing countries have the difficult choice of balancing the risk of transmitting the human immunodeficiency virus through breastmilk against the substantial benefits of breastfeeding. It is not known, however, whether the benefits of breastfeeding are the same when the mother is HIV infected. Therefore, we examined the impact of breastfeeding on infections, growth, and mortality in the infants of HIV-1 infected women.

Methods: Infants of HIV-1 positive women were followed up from birth and at each visit were examined, growth parameters recorded, note made of feeding method, and of current and interim illnesses.

Results: Of the 43 infected and 90 uninfected infants for whom feeding data was available, 36 infants (27%) were exclusively breastfed, 76 (57%) received mixed feeding, and 21 (16%) received formula only. The HIV transmission rate was 39% in those exclusively breastfed, 24% in those on exclusive formula, and 32% in those receiving mixed feeding (RR of 7.39, CI 1.67 - 32.6 between the exclusive breast and formula only groups). There

was a stepwise increase in the transmission rate with duration of exclusive breastfeeding of one, two, and three months (45%, 64%, and 75%, respectively). Among the infected infants, 7(50%) exclusively breastfed, 13(51%) of those on mixed feeds and none on formula only developed AIDS; exclusively breastfed infants had a slower rate of progression to AIDS (mean age 7.5 months compared to 5.0 months, $p=0.2242$) than those on mixed feeds. Mortality (which occurred in the infected infants only) was 19% in the exclusively breastfed infants; 13 % in those on mixed feeds, and 0% in those exclusively formula fed. The frequency of failure to thrive and episodes of diarrhoea and pneumonia were not significantly different between the three groups, in both the infected and uninfected infants.

Conclusions: Exclusive breastfeeding by HIV infected women does not appear to protect their infants against common childhood illnesses and failure to thrive, nor significantly delay progression to AIDS. The implication of the trend towards differential mortality rates according to feeding groups is uncertain and requires further investigation.

7.2 Introduction

One of the principal gains in maternal and child health during the past few decades has been the revival of breastfeeding. The immediate and long-term benefits of breastfeeding have been well documented (Howie 1990, Plank 1973, Victoria 1987, Cunningham 1977). The

HIV epidemic, however, has made it impossible to have a uniform policy on breastfeeding for rich and poor countries. There is clear evidence to show that HIV is transmitted through breastmilk (Douglas 1992, Van de Perre 1993, Van de Perre 1995) and the increased risk of vertical transmission by this route is estimated to be about 14% for women with established infection (Dunn 1992). Accordingly, in 1992, WHO made recommendations on breastfeeding based on whether infectious diseases and malnutrition were or were not the primary causes of infant deaths among populations (WHO 1992); in developing countries HIV infected women were encouraged to continue breastfeeding. In a more recent statement, UNAIDS has given far greater emphasis to ensuring individual informed choice (UNAIDS 1996). This accords with the recognition that there are circumstances in developing countries where alternatives to breastfeeding for HIV seropositive women are a safe option (Nicoll 1994). Such circumstances might apply to countries with intermediate economies, such as South Africa. Implications of breastfeeding under conditions of varying infant mortality rates, vertical transmission rates through breastfeeding, HIV prevalence and incidence, have been modelled, and these calculations may be useful to countries developing their own policies (Hu 1992). Although the dangers of transmission of virus have been recognised, there is little information on whether breastmilk of HIV seropositive women is as protective against common childhood infections, malnutrition, progression to AIDS, and early death, as that of HIV seronegative women. A recent editorial concluded that the lack of data on whether breast or bottle feeding by HIV seropositive mothers affected overall outcome in their babies, limited women's choices in deciding on feeding method (Ziegler 1993).

We report on the association between feeding practice and outcome in a cohort of children born to HIV-1 infected women from Durban, South Africa.

7.3 Patients and Methods

This report is derived from a prospective, hospital based, cohort study on the natural history of vertically transmitted HIV-1 infection. The study was conducted at King Edward VIII hospital, a large urban hospital in Durban, KwaZulu/Natal. About 99% of the patient population is black. The major causes of infant death in KwaZulu/Natal are infections, malnutrition, and perinatal problems (SA 1995, SA Vit A CONS. GROUP 1996,). South Africa is classified as a middle income country by the World Bank with a per capita income of \$2670.

7.3.1 Patient population: the sampling method has been described in detail in Chapter 3.

At no stage of the study were the mothers influenced against breastfeeding. The policy in the neonatal unit during the study period was to advise mothers on the advantages of breastfeeding. Women who chose to formula feed received advice on hygienic preparation of feeds and were not provided with any financial support for artificial feeding. Method of feeding was recorded in detail for the first twelve months; thereafter this assessment became difficult as the children were either fully on family diet or complementary feeds made up the major part of the diet. Feeding method was defined as: exclusive

breastfeeding: where the child was on breastfeeds only from birth (these infants received no supplementary milk feeds); mixed feeding: where the child was receiving both formula feeds and breastmilk (the period of exclusive breastfeeding and the age at which formula was commenced were noted, as well as the duration during which the infant received both breast and formula feeds); exclusive formula feeding: where the infant received formula feeds only. All groups of infants would have received other complementary foods, for varying periods. These definitions vary from those recommended (Labbok 1990).

The infants received no anti-retroviral or immunotherapy during the course of the study.

7.3.2 Classification

Classification of infection status was made according to the recommendations of the Ghent workshop (Dabis 1993). Children were regarded as infected if they were antibody positive at 15 months or had an HIV- related death. They were classified as uninfected if the antibody test was negative from 9 months of age, or if death was non-HIV related. Those infants who were lost to follow up before the age of nine months whilst still antibody positive and those whose cause of death could not be determined, were classified as indeterminate. The diagnosis of AIDS was based on the revised WHO criteria (WHO 1989).

7.3.3 Definition of morbidity

Diarrhoea, pneumonia, and otitis media were chosen as outcomes because these are the infections that breastfeeding appears to prevent in non-HIV-infected populations, and because diarrhoea and pneumonia are the common causes of morbidity and mortality in black South African infants and children. The following criteria were used to define morbidity :

Diarrhoea : three or more episodes of loose stool per day, present for at least three days.

Pneumonia : the presence of tachypnoea and crackles and/or radiological changes.

These three infections were chosen as they have been shown to be less common in breastfed infants. Failure to thrive: weight and length below the third percentile or crossing of percentile lines (NCHS 1976).

Otitis media : inflammation of the eardrum or a purulent discharge from the ear.

7.3.4 Laboratory methods

Blood samples were taken at regular intervals from birth. These were tested for HIV-1 antibodies by a commercial enzyme linked immunosorbent assay, ELISA, (Abbot Laboratories); by a confirmatory Roche ELISA (Cobus Core) or an immunofluorescent assay, IFA, (Virion). Samples were considered positive if the second ELISA or the IFA was positive. The same method was applied for maternal samples.

7.3.5 Statistical methods

Social and demographic characteristics were compared between the three feeding method groups using Analysis of Variance or Chi-square test. The association between feeding and rate of HIV infection was assessed for maternal risk factors which could impact on transmission, including age, parity, haemoglobin level, and mode of delivery (ECS 1992, Borkowsky 1992, Gabiano 1992). The latter two were included as these were found to be significantly associated with transmission in a previous report on this population (Bobat 1996). Logistic regression analysis was used to control for the effect of these variables on the transmission rate and feeding method.

For mortality and progression to AIDS, survival function estimates were computed using the product-limit (Kaplan-Meier) method. The curves were compared using the log-rank test.

Morbidity was expressed, according to feeding practice and HIV status, as incidence densities per 100 child months of follow-up.

7.4 Results

Between October 1990 and April 1993, 234 black infants and their 229 mothers were entered into the study. Fifty three patients did not attend a single follow up visit and were

excluded from the study. This group was not different from the rest of the cohort with regard to maternal characteristics used to compare the groups.

7.4.1 Classification and vertical transmission:

The remaining 181 children were classified as 48 infected (including 17 deaths); 93 not infected, and 40 indeterminate (including 8 deaths). The median vertical transmission rate was 34% (confidence intervals 26%-42%); the upper estimate, which assumes all indeterminates are infected, was 48%(40% - 60%); the lower estimate, which assumes all indeterminates are uninfected, was 26.5%(20% - 33%).

The mean follow-up period for the breastfed infants was 22.8 months, for those on mixed feeding was 22.5 months, and for those on formula only was 20.6 months.

7.4.2 Feeding and transmission:

There were no significant differences in the basic social and demographic characteristics between the women in the three different feeding-method groups (Table 7.1), as well as between their newborn infants. The first available CD4 counts in the infants was at three months of age; there was no significant difference in the means between those breastfed and those on mixed plus formula only (2154, SD 1001 compared to 2271, SD 746).

Table 7.1 Characteristics of HIV-1 seropositive expectant mothers and their newborn infants according to feeding method employed for the infants

	Exclusive breast n = 36	mixed feeding n = 76	formula only n = 21
<i>Maternal Data</i>			
mean age (years)	24 (4.6)**	25 (6.4)	23 (3.2)
mean parity	1.0 (1.2)	1.25 (1.2)	1.11 (1.0)
mean haemoglobin (g/dl)	10.8 (1.1)	10.8 (1.2)	10.2 (1.8)
mean β -2-M (mg/l) ##	1.24 (0.6)	1.53 (1.0)	1.65 (0.5)
% caesarean deliveries	30	56	14
% in safe environment#	72	60	79
<i>Newborn Data</i>			
mean β -2-M (mg/l)	1.7 (1.9)	2.17 (2.1)	1.00 (1.9)
mean HIV- IgA (OD)*	0.13 (0.2)	0.08 (0.2)	0.09 (0.1)

access to electricity, safe water and toilet facilities

beta-2-microglobulin

* optical density

** figures in parenthesis represent standard deviation

There were 133 infants for whom adequate feeding information was available.

Twenty one infants (16%) were exclusively formula fed, 36 infants (27%) received exclusive breastfeeds and 76 (57%) received both breast and formula (mixed) feeds. The median duration of exclusive breastfeeding for the whole group was 5.0 months (range 1 to 12 months), for those on exclusive breast was 12.0 months (1-12), and for those on mixed feeds was 2.0 months (1-12).

When the relationship between feeding and transmission was analysed more closely (Table 7.2), it was found that infants who were exclusively formula fed had a lower transmission rate (24%), as compared to those infants who received either mixed feeding (32%), or exclusive breastfeeding (39%); the relative risk for infection in the exclusively breastfed vs those on formula only, was 1.63 (CI 0.71- 3.76), p-value 0.24. The increased risk for transmission by breastfeeding compared to formula feeding was 15% (CI 1.8 - 31.8).

Maternal risk factors which could impact on transmission were compared and were found not to be different between the three groups. Mode of delivery, maternal age, and maternal hemoglobin level had no impact on transmission rate by feeding group. When these were controlled for in a logistic regression model, the association between increased risk and exclusive breastfeeding remained, but was of borderline significance (relative risk 10.7, CI 1.1 - 96.0).

To determine whether duration of breastfeeding affected transmission, we assessed the risk of infection according to the duration of exclusive breastfeeding, to the nearest month,

Table 7.2: The association between method of feeding and transmission in the infant

Feeding Method	Total N	HIV-Infected N (%)	HIV-Uninfected N (%)	Relative Risk# (95% CI)
Breast only	36	14 (39)	22 (61)	
Breast and formula	76	24 (32)	52 (68)	1.63 (0.71 - 3.76)
Formula only	21	5 (24)	16 (76)	
Total *	131	43	90	

* Numbers do not add up to 48 infected and 93 uninfected because of missing data

Relative risk for infection in the exclusive breastfeeding vs exclusive formula feeding

(Table 7.3). The infection rates were 45% of those infants receiving breast only for the first month, 64% of those receiving breast only for two months of life, and 75% of those receiving breast only for three months. However there were only 4 infants in the latter group. Thereafter the rate remained constant at $\pm 25\%$ for up to 12 months of exclusive breastfeeding. These figures are not statistically significant.

7.4.3 Feeding and mortality

Deaths occurred only in the infected infants. Of the 17 infected infants who died, 7 were exclusively breastfed and 10 had mixed feeding. No deaths occurred in the exclusively formula fed group during the study period, compared to a mortality of 19% (7/36) in the exclusively breastfed infants, and of 13% (10/76) in the infants receiving mixed feeding, Relative Risk 1.87 (CI 0.61 - 6.66). The relative risk of death in the exclusively breastfed compared to the exclusively formula-fed, could not be defined, as there were no deaths in those exclusively formula fed.

When we compared feeding vs mortality only in the HIV infected infants, we found mortality to be highest in the infants receiving exclusive breastfeeds (7/14, 50%), compared to 10/24 (42%) in the infants receiving mixed feeding and 0/5 (0%) in those infants receiving formula only. However, survival at 12 months was similar in both the exclusively breastfed and those on mixed feeding, 64% and 65%, (Figure 7.1).

Table 7.3. The association between duration of exclusive breastfeeding and HIV transmission from mother to infant

duration of exclusive breastfeeding (months)	total number of infants	number infected	transmission rate (%)
1	18	8	45
2	11	7	64
3	4	3	75
4-12	41*	15	25

*5 for <12 months and 36 for 12 months

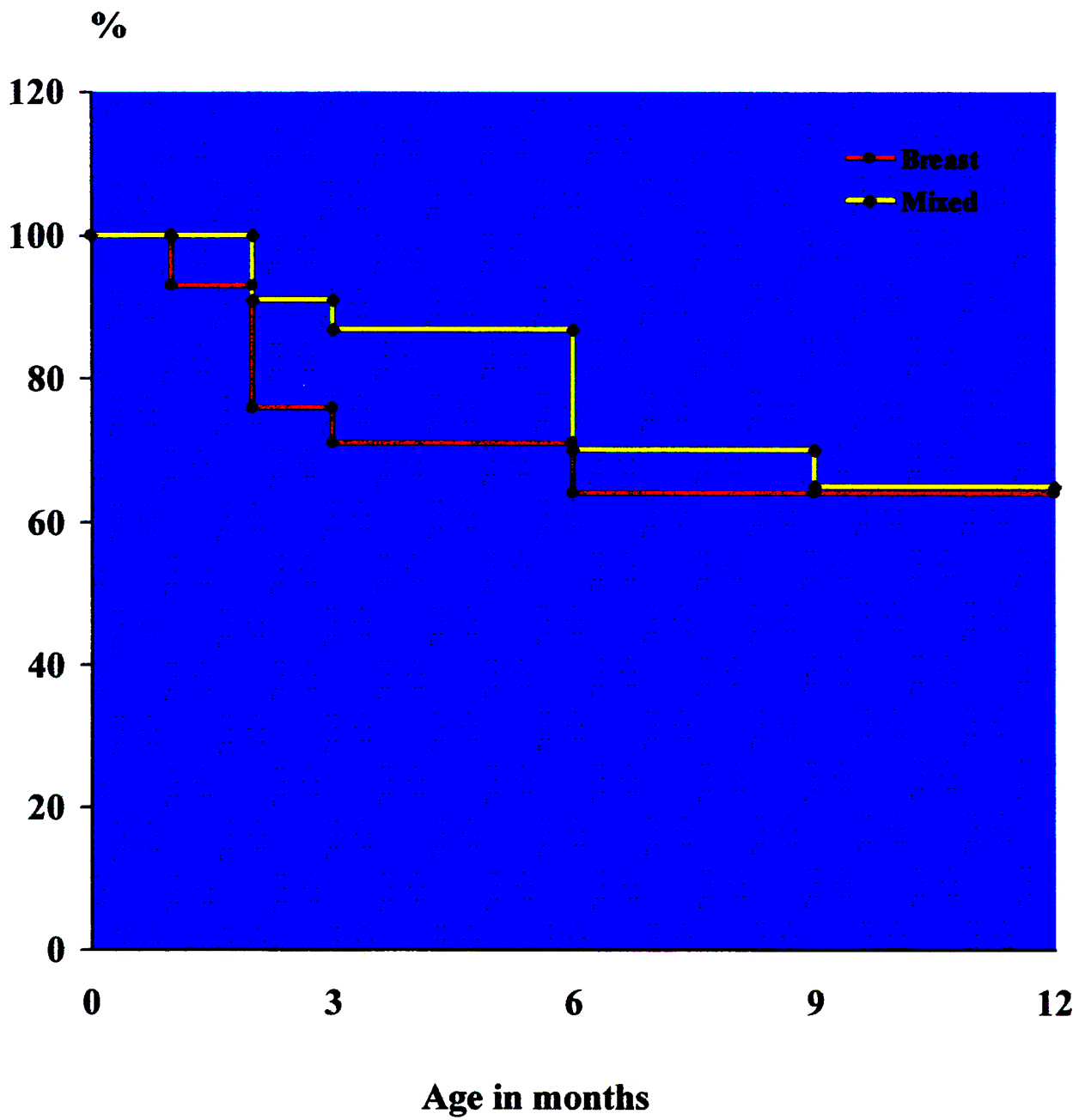


Figure 7.1 Mortality by feeding method

7.4.4 Feeding and morbidity

Table 7.4 shows the relationship between feeding method and morbidity. The data shown represents a total of 2924 child months of follow up. We found no significant difference between the group that was exclusively breastfed and those who received mixed feeding and exclusive formula feeding. This was similar for both the HIV infected as well as the uninfected children.

7.4.5 Feeding and AIDS

Among the infected infants, 7/14 (50%) of those exclusively breastfed, 13/24 (54.1%) on mixed feeding, and 0/4(0%) on formula only, developed AIDS during the study period (Figure 7.2). Infants who were exclusively breastfed appeared to progress to AIDS more slowly than those who received mixed feeds, mean age at diagnosis of AIDS was 7.5 months (SD 5.3, range 2-18 months), compared to 5.0 months (SD 2.0, range 3-10 months) in the mixed feeding group, p-val = 0.2242.

7.4.6 The indeterminate group of infants

A similar pattern for morbidity to that detected in the infected and uninfected groups as described above, was noted; little information was available for the 7 deaths in this group.

Table 7.4 Morbidity according to feeding practice and HIV-1 status in infants born to HIV-1 seropositive women

morbidity	breast fed	mixed feeding	formula fed	relative risk** (CI)*
<i>Infected infants</i>				
number	14	22	1	
follow-up (months)	287	437	24	
pneumonia#	6.27 (18)	8.70 (38)	0	0.76 (0.43-1.33)
diarrhoea#	10.5 (30)	13.5 (59)	0	0.81 (0.53 - 1.27)
otitis media#	3.8 (11)	3.60 (16)	0	1.10 (0.51 - 2.37)
failure to thrive (%)	57.1	68.2	0	0.88 (0.51 - 1.49)
<i>Uninfected infants</i>				
number	22	52	16	
follow-up (months)	537	1246	393	
pneumonia#	4.7 (25)	4.0 (54)	3.1 (12)	1.16 (0.73 - 1.83)
diarrhoea#	4.1 (22)	6.6 (82)	2.3 (9)	0.76 (0.48 - 1.21)
otitis media#	0.9 (5)	0.8 (6)	1.8 (7)	0.97 (0.32 - 2.98)
failure to thrive (%)	13.6	15.4	11.1	0.96 (0.29 - 3.18)

Figures are given as incidence densities per 100 child months of follow-up
 Figures in parenthesis are the total number of episodes

* CI : 95% confidence intervals

** since the number of episodes of morbidity in the formula fed infected infants was zero, calculation of relative risk would be meaningless; thus this group was combined with the mixed feeding infants for the calculation of relative risk

+ numbers do not add up to 48 infected and 93 uninfected due to missing data

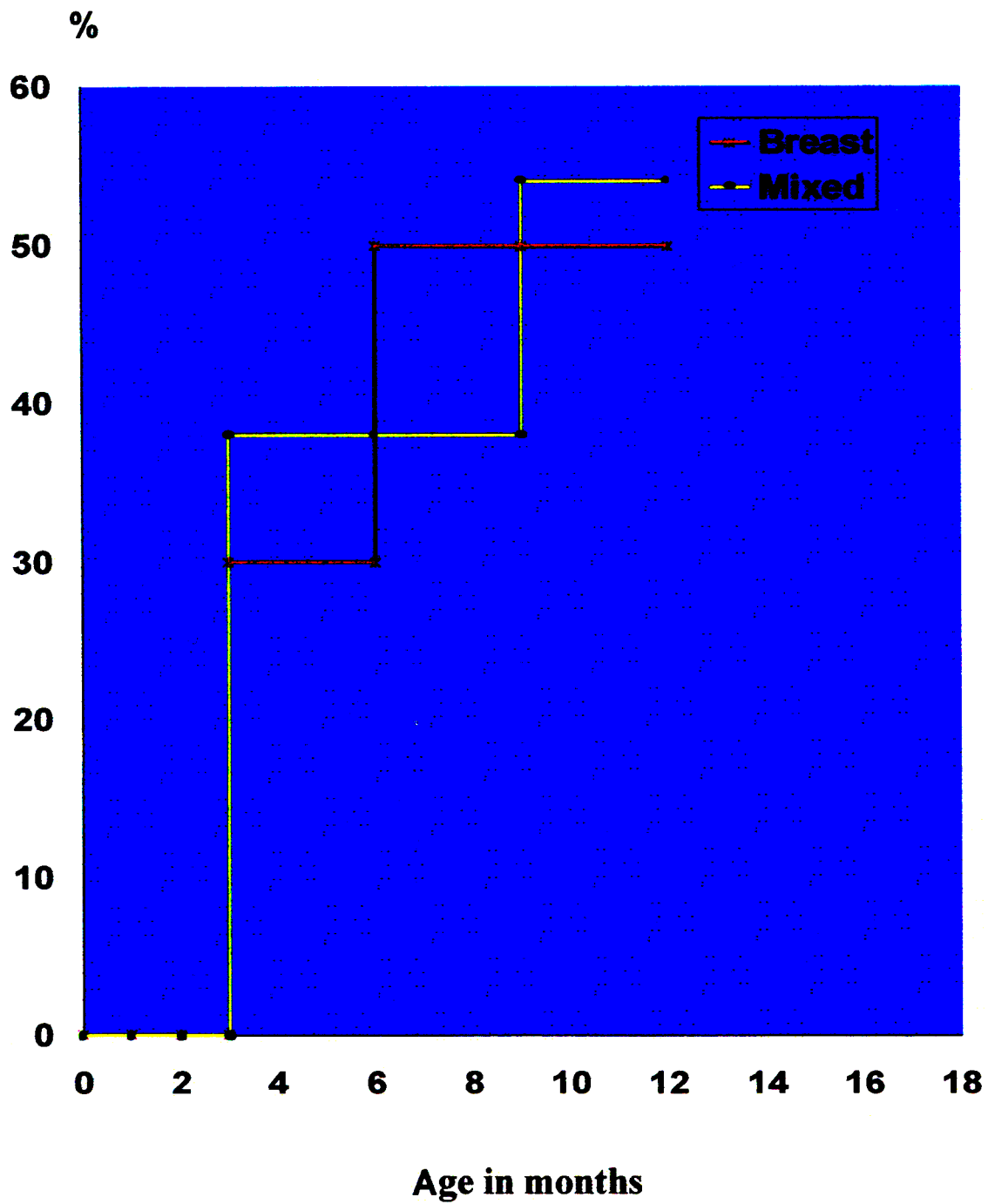


Figure 7.2 Progression to AIDS by feeding method

7.5 Discussion

In this prospective study of a cohort of babies born to black HIV-1 infected South African women, we did not find the expected benefits of exclusive breastfeeding. We employed four outcome criteria to measure benefit: mortality, infections, failure to thrive, and progression to AIDS. Of the HIV infected children who died during the study period, the mortality was highest in those exclusively breastfed, although it did not achieve statistical significance. Our study does not allow us to determine the cause of this finding. This ambiguity may be the result of research design: the study did not set out to test the effects of breastfeeding against formula by a randomised controlled method. We have calculated that the sample size in our population (ante-natal HIV-1 prevalence 20%) to detect differences in mortality between breast and formula fed infants of HIV seropositive mothers will be 2500 antenatal attendees (80% power, 5% significance level). Disturbances in breastmilk immune factors directed at common infections of infancy and the impact of HIV virions on gastrointestinal integrity require further investigation.

Morbidity due to common childhood infections (diarrhoea, pneumonia, otitis media) and failure to thrive, were as frequent in babies who were exclusively breastfed as in those who were given either exclusive formula or a mix of formula and breastmilk; this observation held true for both HIV infected and HIV uninfected infants and children.

To the best of our knowledge there are four other sets of similar data, some of which are comparable to the results given here. Results from an Italian study (Tozzi 1990) showed that breastfeeding was of short term advantage: progression to AIDS was slower and survival longer in breastfed as opposed to formula fed HIV infected children. This advantage of breastfeeding was lost when children were 5 years of age (De Martino 1992). However, data were retrospectively collected and the duration of breastfeeding was not known. In a study of relatively privileged Zairian women, breastfeeding was found to protect the infants from common childhood illnesses, in those born to both HIV infected and HIV negative women (Ryder 1991), but the HIV infected infants were not compared by feeding method and all those who died within the first six months were excluded from the analysis. The closest findings to ours are also from Africa. In a prospective study from Nairobi, breastfeeding by HIV infected women, for longer than 15 months, was more often associated with growth retardation than breastfeeding for shorter periods (Datta 1994). Gray et al have reported an increased transmission rate and an increased mortality in exclusively breastfed HIV infected infants from Soweto, South Africa (Gray 1996). In breast fed infants, mortality was 9/114(7.0%), compared to 1/49(2%), in infants on mixed feeding ($p=0.14$). Moreover, there were no adverse effects on growth or morbidity, and no increase in hospital admissions among breastfed over non-breastfed infants born to HIV seropositive women.

The higher transmission rate in the exclusively breastfed group compared to either the mixed breast and formula fed group or to those exclusively formula fed, is similar to

findings summarised in a recent meta analysis on this subject (Dunn 1992). There are several studies from the developed countries as well as from Africa that have reported on the association between breastfeeding and transmission of HIV infection (De Martino 1994, Ryder 1991, ECS 1992). An increased risk of transmission through breastfeeding has been reported from Brazil, a country with an intermediate economy (Collareda 1993). The Italian study also showed that the risk of transmission was increased with breastfeeding and that the risk increased with the duration of feeding (De Martino 1994). The data from Durban do not reach statistical significance but are suggestive of a similar direction in the relationship between HIV transmission and duration of breastfeeding.

The greater prevalence of infections and failure to thrive among the HIV infected patients was predictable and extends the results from other studies in developing (Mgone 1991) and industrialised countries (ECS 1991). It is essential that the trend towards an association between breastfeeding and HIV related mortality (detected in both Durban and Johannesburg) and the absence of data for HIV unrelated deaths (given the small number of deaths in the indeterminate group) be explored further.

Recent reviews of the available published data on the subject of breastfeeding have confirmed once again that breastfeeding protects against infections and reduces infant mortality; the conclusion was drawn that the relative risk for mortality of artificial feeding was from one to nine (Nicoll 1994). These findings generally apply to developing and developed countries. However, most studies on breastfeeding were undertaken in the pre-

HIV era. As the benefits of breastfeeding were well established, we did not include a control group of HIV seronegative pregnant women and their offspring.

This study has several shortcomings which require explanation. The women were not randomly allocated to breastfeeding versus no breastfeeding, they self-selected to feeding method. It has been argued, among key research scientists, that randomised studies in poor countries will be unethical (Nicoll 1994) given the undisputed public health benefits of breastfeeding and the prospects of allocating women without access to adequate sanitation and clean water to a non-breastfeeding group, and women with such access to breastfeeding with its concomitant risk of HIV transmission. Secondly, the number of women who chose exclusive formula feeding was small; therefore the number of HIV infected infants in the artificially fed group was minuscule. This, in fact, is the real position in Africa; very few women give only formula feeding. The pattern of feeding adopted by the women in this study is similar to that for most women in Africa (Nicoll 1994). In addition, we were unable to assess the possible role of other contributing factors to the results obtained; these include maternal viral load, CD4/CD8 counts, and p24 antigen levels (Peckham 1995). We could not assess whether the differences in time to AIDS between breastfed and formula fed infants were due to dissimilarities in the proportions infected in-utero, intra-partum, and postnatally. We have data which suggests that the proportions of infection in our cohort were: 27% in-utero and 72% during delivery and postnatally (Moodley D, Coovadia H, Bobat R, Sullivan J. Timing of vertical transmission of HIV by polymerase chain reaction. Submitted for publication.). The delay to AIDS in the breastfed infants may have been due

to these being infected by breastmilk in contrast to those on formula who could have been infected earlier. It should be noted that the comparison of time to AIDS by feeding method was limited, as we did not control for confounding factors.

The inclusion of the indeterminate group of infants is unlikely to have altered the main conclusions of the study. The proportion of these infants in the different feeding groups resembled that in the 141 infants classified as infected or uninfected. The maternal characteristics, newborn and early infancy features in this indeterminate group, were similar to those included for analysis. Moreover, morbidity patterns were similar, and the available information suggests that there were no differences in morbidity between those infants breastfed and those receiving formula or mixed feeds; the seven deaths in this group may have added clarity to the mortality differences between the groups.

In a recent workshop on breastfeeding in HIV positive women (held in Durban, South Africa), health professionals from central, east, and southern Africa, agreed that there was no conflict of purpose in safeguarding individual choice whilst promoting breastfeeding at population level. The results from this study do not contradict this consensus view, and they support the recent UNAIDS recommendations (UNAIDS 1996).

In conclusion, our findings have particular relevance to populations in countries with intermediate economies where the under five mortality rates straddle the division between high and moderate (The World Health Report 1996); and HIV infected women can choose

safe alternatives to breastfeeding. In these situations, all pregnant women should be offered counselling and HIV testing, and those found to be positive to be advised that breastfeeding may not provide the anticipated degree of protection against common infections and growth failure, and is associated with a higher risk of transmission. We expect that breastfeeding would regain its role as the pre-eminent method of infant feeding, in individual countries, as the epidemic declines.

CHAPTER 8

CHAPTER 8

NEONATAL CHARACTERISTICS AND OUTCOME IN A COHORT OF INFANTS BORN TO HIV-1 INFECTED AFRICAN WOMEN FROM DURBAN, SOUTH AFRICA

8.1 Summary

Background: Most newborns of HIV-1 seropositive women show little evidence of HIV disease. The early identification of vertically infected infants at risk of rapid progression and death enables appropriate management of these infants. In developing countries, where techniques such as viral load are unavailable, emphasis has to be placed on clinical manifestations.

Methods: HIV-1 seropositive women were identified antenatally, and their newborn infants followed up from birth to early childhood. At birth, the infants' growth parameters were measured, they were examined clinically, and note was made of any problems related to delivery and resuscitation measures. Complications arising during the neonatal period were recorded on discharge.

Results: The final cohort comprised 48 infected and 93 uninfected infants. There were no differences between the newborns who were later found to be infected, compared to those who were exposed, but uninfected, with regard to growth parameters, frequencies of preterm, low birth weight, and growth retardation rate, as well as for neonatal complications. However, when we compared the newborn data of those HIV-infected infants who died by 18 months, with that of those infected infants who survived, we found the former group had lower mean birth weights (2.90kg, 3.15kg, $p=0.096$) and lengths (46.5cm, 48.5cm, $p=0.041$), had a higher frequency of low birth weight (30.8%, 3.3%, $p=0.024$), were more likely to have been resuscitated (30.7%, 0%, $p<0.001$), and were more frequently jaundiced (46.2%, 13.3%, $p=0.044$).

Conclusions: As a group, vertically infected newborns of HIV-positive mothers cannot be differentiated from those who are exposed, but uninfected. However, infected newborns of HIV-positive women who are found to be growth retarded, or who develop complications in the neonatal period, are more likely to progress rapidly and die, and should therefore be monitored carefully and managed vigorously, and may be suitable for participation in trials using intensive drug therapy. Such infants probably represent intrauterine or early intra-partum transmission.

8.2 Introduction

In children, infection with the human immunodeficiency virus, type 1 (HIV-1) occurs chiefly by vertical transmission, either in utero, during labour and delivery, or post partum by breastfeeding (Mofenson 1994, Douglas 1992, Borkowsky 1992). The majority of transmission in developing countries occurs during labour and delivery and through breastfeeding, and therefore infected newborns of HIV-1 seropositive women show few, if any, abnormalities or evidence of HIV disease (Lepage 1991, Bulterys 1994, Lallemand 1989). Some studies from developed countries have found differences in growth parameters at birth, and higher frequencies of preterm deliveries and low birth weights (Spinillo 1994, ECS 1991). Less information is available for Africa, and data from Rwanda and Malawi show conflicting results (Lepage 1992, Taha 1995). It is clear from recent evidence that babies who have very high viral loads within 48 hours of birth and have probably been infected in-utero, have rapid progression of disease compared to those who have lower viral loads (Shearer 1997).

The detection of HIV infection in the newborn, which requires molecular amplification techniques, is beyond the resources of developing countries and most diagnoses during infancy are made on the basis of WHO clinical criteria and the presence of antibodies beyond 15 months of age. For many reasons (such as prophylaxis, early therapy, counselling, etc) it is advantageous to detect HIV infection in babies of seropositive women soon after birth, and to identify those at risk for rapidly progressive disease.

Therefore, we examined the neonatal characteristics of infants, born to HIV-1 infected black women from Durban, South Africa, who were followed-up from birth to early infancy, particularly to detect clinical features predictive of rapid progression.

8.3 Patients and Methods

Details of the sampling method have been previously described in Chapter 3.

8.3.1 Patient population:

All liveborn infants of those women testing HIV- positive were entered into the study, with maternal consent. Data on maternal age, parity, obstetric history, antenatal care and circumstances around labour and delivery, as well as results of haemoglobin and syphilis serology, were obtained from the newborn infants' records, and retrospectively from the obstetric charts. Gestational age was assessed from ultrasonography done at the first antenatal visit. The mothers received no antiretroviral treatment or vitamin A supplementation, either during pregnancy or post delivery.

All the newborn infants were examined within 48 hours of birth. A full clinical examination was performed, with assessment of each system, growth measurements recorded (weight, length, head circumference), and note made of any dysmorphism. Before discharge, any complications

occurring during the hospital stay were recorded. Initial blood samples were taken at this time. The infants were followed up at regular intervals to early childhood.

8.3.2 Classification of infection status

Refer Chapter 3.

8.3.3 Laboratory methods

Refer Chapter 3.

8.3.4 Statistical methods

Infected babies were compared to non-infected babies using Student's unpaired t-test for continuous data and Chi-square test (or Fischer's exact in the case of small cell sizes) for categorical data.

The same tests were used for comparing babies who died to those who survived. The significance level was set at 0.05.

8.4 Results

Between October 1990 and April 1993, 234 black infants and their 229 mothers were entered into the study. All the children were born at least 18 months prior to the analysis.

53 infants who were not brought for a single follow-up visit were excluded from the study.

The final cohort comprised 181 patients who were classified as: 48 infected, 93 not infected and 40 indeterminate. The vertical transmission rate was 34% (95% CI 26-42%).

The mean follow-up period for the infected infants was 28.5 months, and for the uninfected infants was 23.6 months.

8.4.1 Maternal data

The mean age of the mothers was 24 years (range 16 - 40 years), 32% were primiparous, 18% had a positive syphilis serology, and 35% were delivered by caesarean section. Sixteen percent of all deliveries occurred before 37 weeks' gestation. There was no history of intravenous drug abuse. The mothers were from uniformly poor socio-economic circumstances. At the time of delivery, only 5 mothers had any HIV- related symptoms, and none fulfilled the WHO criteria for AIDS. There were two maternal deaths in the puerperium, both non HIV- related.

8.4.2 Clinical and laboratory characteristics

There were no differences between infants who were later found to be infected, compared to those who were exposed but uninfected, with regard to the parameters shown in Table 8.1.

8.4.3 Neonatal complications

Complications occurring during the newborn period were compared in the two groups. These are shown in Table 8.2. There were no other substantial differences between the two groups.

8.4.4 Neonatal characteristics of those who subsequently died:

All the above clinical characteristics, complications, and laboratory data were compared in those infected infants who died by 18 months, with those who were infected, but survived, beyond 18 months (Table 8.3). The infants who subsequently died, had lower mean birth weights and lengths, were more likely to be low birth weight, were resuscitated more often, and more frequently had jaundice or sepsis than those who were alive at the end of 18 months. The rest of the features were not significantly different between the groups.

Table 8.1 Clinical and laboratory characteristics of newborns of HIV-1 infected women

characteristic	HIV-infected	HIV-uninfected	p-value
	n=48	n=93	
weight (kg)*	3.06 (0.37)	3.07 (0.64)	0.908
length (cm)*	47.7 (2.66)	48.5 (2.82)	0.163
head circumference (cm)*	34.2 (1.16)	34.5 (2.83)	0.459
preterm (<37 weeks)	3 (6.2%)	10 (10.9%)	0.542
% low birth weight (<2500 g)	10.4	16.1	0.357
small for gestational age	6 (12.5%)	14 (15.2%)	0.663
females	21 (45%)	53 (57%)	0.168
total globulin (g/dl)*	28.9 (2.77)	28.7 (3.30)	0.821

* figures are means and standard deviations

Table 8.2. Complications in the neonatal period in 48 infected and 92 uninfected infants of HIV-1 positive mothers

complication	infected		Uninfected		p-value
	n	(%)	n	(%)	
resuscitated at birth	5	(10.4)	14	(15.2)	0.431
dysmorphic features	2	(4.2)	4	(4.3)	1.000
sepsis	15	(31.3)	19	(20.7)	0.165
jaundice	12	(25)	22	(23.9)	0.887
respiratory problems	0	(0.0)	7	(7.6)	0.095
neurological abnormalities	1	(2.1)	3	(3.3)	1.000

Table 8.3. Neonatal characteristics and complications in those HIV-1 infected infants who died, compared to those infected infants who survived

Characteristic	died n=17	Survived n=31	p-value
mean weight(kg)	2.90 (0.48)	3.15 (0.30)	0.096
mean length(cm)	46.54 (2.72)	48.50 (2.61)	0.041
< 2500 gr	4 (30.7%)	1 (3.3%)	0.024
Resuscitated	4 (30.7%)	0 (%)	<0.001
mean APGAR @ 1 minute	7.6 (1.8)	8.8 (0.6)	0.112
Jaundice	6 (46.2 %)	4 (13.3%)	0.044
Sepsis	6 (46.2%)	6 (13.9%)	0.137

8.4.5 Comparison of neonatal data:

Neonatal data from studies done in both developed and developing countries are presented in Table 8.4, to show the similarities and differences between regions.

8.5 Discussion

It is important to detect abnormalities and HIV infection in the neonatal period as optimal utilisation of appropriate health and welfare services can be ensured, prophylaxis against common infections provided, likely clinical problems anticipated and effectively managed (diarrhoea, pneumonia, malnutrition), prognosis discussed, and advice on breastfeeding given. General birth data (perinatal and neonatal mortality, low birth weight and prematurity) for statistical, surveillance and monitoring purposes, can be adjusted to account for the impact of HIV infection.

In this prospective cohort study where we examined birth and neonatal characteristics of infants born to HIV-1 positive women, we found no significant differences between the infected and uninfected groups with regard to intrauterine growth, prematurity, and neonatal complications. These findings are similar to the available data from several other studies. Reports from Italy, France, Sweden, and USA (Spinillo 1994, Blanche 1989, Lindgren 1991, Nesheim 1994) found no differences in the growth parameters, preterm and low birth weight rates, and frequency of

Table 8.4 Comparison of neonatal characteristics and complications of HIV-infected (inf) and uninfected (n/inf) infants born to HIV-1 positive women from developed and developing countries

Newborn feature	South Africa (Durban)		Rwanda		USA (New York)		Italy		France	
	inf	n/inf	inf	n/inf	inf	n/inf	inf	n/inf	inf	n/inf
mean weight (kg)	3.06	3.07	2.68	2.91	2.53	2.86	2.91	2.96	2.96	3.04
mean length (cm)	47.7	48.5	47.3	48.0	n/a		n/a		48.4	48.7
mean OFC* (cm)	34.2	34.5	34.6	35.1	32.0	33.1	n/a		33.5	33.9
% preterm	6.2	10.9	42	32	33	19	15	16	15	11
% low birth weight	10.4	16.1	22	14	45	29	21	18	22	14
% growth retarded	12.5	15.2	n/a		26	16	n/a		n/a	

* ofc: head circumference

complications between infants who were HIV-infected and those who were exposed, but uninfected. However, there are other studies which did identify differences between such groups. In Miami, New York, and Baltimore (Hutto 1991, Abrams 1995, Nair 1993) infected infants were more likely to have evidence of growth disturbance, to be preterm, or to have higher frequencies of complications such as sepsis. The European Collaborative Study showed a strong correlation with extreme prematurity and increased risk of transmission (ECS 1992). Information on newborn characteristics from Africa is limited. Two studies, from central Africa, compared neonatal data of babies born to HIV-seropositive women, depending on whether or not the infant was later found to be infected. The study from Rwanda (Butlerys 1994) found that infected newborns were more likely to have lower birth weights and lengths, and were more frequently preterm and low birth weight, whilst the other, from Malawi (Taha 1995), compared only growth, and found no differences. What all the studies agree on is that there is no characteristic clinical syndrome which identifies the HIV- infected child at birth.

Several studies, mainly from Africa and Haiti, compared the outcomes of infants born to HIV-1 seropositive and HIV-1 seronegative mothers. Whereas the study from Congo found no differences in the neonatal characteristics of these two groups (Lallemant 1989), the reports from Rwanda and Malawi found that infants born to HIV-1 positive mothers were more likely to have lower birth weights and lengths, and had an increased frequency of preterm delivery and growth retardation (Lepage 1991, Taha 1995); in addition, the study from Malawi reported

a higher mortality rate in the children born to seropositive women. In the report from Haiti, it was found that newborns of HIV-1 seropositive women had lower birth weights and a higher frequency of preterm deliveries as compared to those born to HIV-1 seronegative women (Halsey 1990). In a community-based study done in Durban, South Africa, at a time when the HIV-1 seroprevalence was less than 5%, it was found that the mean birth weight for black babies was 3.3 kg (SD 0.5), and the rate of low birth weight was 5% (Ramkissoon 1991). In a report from the neonatal unit of the study hospital, the low birth weight rate was found to be 17.4% in 1990 (Adhikari 1995). Although these findings are not directly comparable to the cohort of babies born to HIV positive women described here, they reveal no marked differences between newborns of HIV positive and negative women.

When we compared infected infants who died with those infected infants who survived, we found lower mean birth weights and lengths, higher frequency of low birth weight , more frequent resuscitation at birth, and more cases of jaundice in the former. These differences, most of which were detected within 48 hours of birth, were unexpected, but are consistent with available data from developed countries. In a study from France, it was suggested that the infants who developed rapid onset of severe disease were likely to have been infected in-utero (Mayaux 1996). A recent study from the Women and Infants Transmission Study group, Baltimore, has suggested that a higher HIV viral load may be responsible for early, rapid progression of some vertically infected infants (Taha 1995). Studies from New York and

Malawi found that mortality in their cohorts was strongly associated with prematurity (Abrams 1995, Taha 1995). The explanations for this vary, but may be linked to early infection with high viral loads, or to an immature immune system at birth, enabling greater viral replication and rapid progression of disease.

The type of complications which these newborns had suggest an intrauterine, rather than an intrapartum or postpartum, insult. The limited information we have does not allow us to infer the nature of this damaging event. It could be a high viral load in the mother or foetus, placental dysfunction, or a concomitant sexually transmitted disease. When comparing studies from developed countries with those from Africa, it is worth noting that, in most studies from developed countries, large numbers of HIV-infected mothers were intravenous drug abusers, and many received antiretroviral therapy, which may be confounding factors. In Africa, intravenous drug abuse in young black women is rare; the majority of the women are HIV-infected by heterosexual transmission; and the use of antiretroviral therapy is virtually non-existent. However, African women are exposed to certain risk factors such as micronutrient deficiency, amniotic fluid infection syndrome and sexually transmitted diseases, which may increase the risk of intrauterine HIV transmission, and have negative effects on intra-uterine growth (Borkowsky 1992, Nair 1993, Semba 1994).

In summary, in this prospective cohort study of newborns born to HIV-1 infected women, we have found that, as a group, there were no significant differences in growth parameters and neonatal complications between the infants who were HIV-infected compared to those who were exposed but uninfected. However, when we examined the group of HIV-infected infants who subsequently died, we found that they had lower birth weights and lengths, were more likely to be low birth weight, and had higher frequencies of complications in the neonatal period. These simple clinical criteria may help to identify a group of HIV-infected infants born to seropositive women who may benefit from more aggressive interventions and appropriate drug trials.

CHAPTER 9

CHAPTER 9

THE EARLY NATURAL HISTORY OF VERTICALLY TRANSMITTED HIV-1 INFECTION IN AFRICAN CHILDREN FROM DURBAN, SOUTH AFRICA

9.1 Summary

Objectives: To determine the natural history of vertically transmitted HIV infection in South African children.

Patients and methods: Infants born to HIV infected women were followed up from birth to early infancy. At regular intervals, the infants were examined, growth and development assessed, all current and interim illnesses recorded.

Results: There were 48 infected and 93 uninfected infants; the mean period of assessment was 26 months. The mean age at onset of signs was 5.1 months for infected infants, and 9.2 months in uninfected infants; of the former, 70% were symptomatic by 6 months. The relative risks in the infected infants were highest for lymphadenopathy (4.56; CI 2.7-7.7), failure to thrive (4.48; 2.57-7.81), and neurological abnormalities (3.32; 1.96-5.58); the most frequent findings were diarrhoea (occurred in 78%), pneumonia(76%) and lymphadenopathy (70%). Thrush and pneumonia occurred early, but declined over time,

whereas diarrhoea and neurological abnormalities occurred later and increased in frequency; lymphadenopathy and hepatosplenomegaly remained constant. Of those who developed AIDS, the mean age at onset was 5.95 months, with 95% diagnosed by 12 months. The mortality in infected infants was 35.4%, and 76% of deaths occurred within the first year. About two thirds of HIV infected infants survived into early childhood, mean survival 34.1 months.

Conclusions: In South African children with vertically acquired HIV-1 infection, the onset of disease is early and deterioration to AIDS and death are rapid. Infected infants can be easily recognised clinically, the majority by 6 months of age, which is particularly useful in developing countries. Two thirds of infected infants survived beyond infancy; this has important implications for management and health care planning.

9.2 Introduction

Human Immunodeficiency Virus (HIV1) infection masquerades in the guise of such a multiplicity of disorders that it has raised the level of diagnostic uncertainty in clinical medicine as did tuberculosis and syphilis. Despite the substantially higher burden of sickness and death due to perinatally transmitted HIV in poor countries, we know more about these problems in industrialised countries than in the former. Descriptions from the European Collaborative Study (ECS 1994, ECS 1991) together with reports from the Italian multicentre study (Italian Multicentre Study 1988, Italian Register 1994) and from

France (Blanche 1990), and accounts from a few major cities in the USA (Johnson 1989, Scott 1989) and the United Kingdom (Mok 1989), have established a recognisable clinical picture of paediatric HIV infection in the western hemisphere. It is unclear whether factors such as differences in routes of transmission to women, in subtypes of the virus, in prevalence of sexually transmitted diseases and nutritional deficiencies, and genetic variation, influence the expression of HIV disease among children in developing countries. There are very few prospective cohort studies of the natural history and clinical profile of perinatally transmitted HIV from the latter. Those that have been undertaken in Africa have been largely restricted to central and east Africa (Datta 1994, Lepage 1990, Lallemand 1989) and are insufficient to enable clinicians to develop a consistent pattern of the disease. Indeed, a recent paper lamented the lack of studies which adequately documented the survival and experience of HIV infected children (Meyers 1994).

Knowledge of the natural history of vertically transmitted HIV-1 infection is essential for appropriate care of infected children, for prognostication (Forsyth 1996), choice of patients likely to benefit from antiretroviral therapy and to enable the formulation of suitable management policies. This information is also necessary for the planning of clinical trials and immunisation against HIV infection.

9.3 Patients and Methods

This report is derived from a prospective, hospital based, cohort study conducted at a large urban hospital in Durban. All the children in the study were born at least 18 months prior to the analysis.

9.3.1 Patient population

The sampling method has been described in detail in Chapter 3.

Mothers were asked to bring the child to the follow up clinic for any problem, so that episodes of illness would not be missed. The women were reimbursed for transport costs to encourage follow up visits. At no time during the study did the children receive anti-retrovirals, immunotherapy, or prophylaxis against pneumocystis carinii.

9.3.2 Classification

Refer Chapter 3 for details.

9.3.3 Definition of morbidity

The following criteria were used to define morbidity:

Diarrhoea : three or more episodes of loose stool per day, present for at least three days.

Pneumonia : the presence of tachypnoea and crackles and/or radiological changes. Thrush: if both the hard and soft palate were involved and/or present in more than one site.

Lymphadenopathy: if present in more than one site and at least 0.5 cm in diameter.

Neurological abnormalities: the presence of static or delayed development/or regression of milestones, tone disturbances and seizures (in the absence of infection). Failure to thrive: weight and length below the third percentile on more than one occasion / or crossing percentile lines (NCHS 1976). Hepatosplenomegaly: if present on more than one consecutive visit. Fever: if present for more than three days/ or if recurrent. Skin rash: any significant rash other than impetigo and scabies.

9.3.4 Laboratory methods

Refer Chapter 3 for details.

9.3.5 Statistical methods

Relative risks were calculated for the comparison between occurrences of morbidity in the HIV infected children relative to uninfected children. The chi-square test was used to assess the significance of the associations. Incidence densities of morbidity per 100 child months of follow-up were estimated for the two groups and Relative risks and 95% confidence intervals were calculated. Kaplan-Meier estimates were calculated to estimate the average age at onset of morbidity, development of AIDS, and mortality, and were compared using a Log-rank test.

9.4 Results

9.4.1 The cohort: between October 1990 and April 1993, 234 black infants and their 229 mothers were entered into the study. All the children in the study were born at least 18 months prior to the time of analysis. Those who did not attend a single follow up after birth were excluded from the study; there were no differences between this group and the remaining cohort, as previously described (Bobat 1996). The final cohort comprised 181 infants. The children were followed up for varying periods, ranging from 1 to 48 months. The mean follow up period for the infected infants was 28.5 months, and for the uninfected infants was 23.6 months.

9.4.2 Classification

The children were classified as 48 infected (including 17 deaths); 93 not infected, and 40 indeterminate(including 8 deaths). The vertical transmission rate was 34% (95% CI 26% - 42%). There were no late seroconverters during the study period.

9.4.3 Onset of disease

In all the following analyses, children with indeterminate status were excluded. The data presented here represents a total of 3234 child months of follow up. The mean interval between birth and the onset of symptoms in infected infants was 5.1 months (range 1-21

months); in contrast, infants who were exposed but not infected manifested symptoms at a mean age of 9.2 months. By 3 months, 60% of infected infants showed some form of HIV related sign/symptom, by 6 months 70% manifested HIV related signs, whilst at age 1 year, 77% were symptomatic. The mean age at onset of the various morbidity criteria is shown in Table 9.1. Infected children had an earlier onset of lymphadenopathy, pneumonia, neurological disturbances and failure to thrive as compared to the children who were exposed but not infected.

9.4.4 Disease patterns

Morbidity is reflected in four formats: as the proportions of infants affected by the clinical signs, as frequencies of the specific signs, as frequencies per quartile in the first 12 months, and as incidence densities of signs per 100 child months. Table 9.2 shows the frequency of occurrence of the major morbidity criteria, the proportions of children affected by these criteria, and the relative risks for their development in the infected versus the uninfected children. There was a significantly increased risk for all the morbidity criteria, except fever and skin rash, in the infected children. Diarrhoea and pneumonia were the most common, occurring in 78% and 76% of all infected infants, with lymphadenopathy being found in 70% of those infected. Although infants who were exposed but not infected had high frequencies of diarrhoea and pneumonia, these were not as common as in the infected group. Failure to thrive occurred in 64% of infected infants, whilst only 14% of the uninfected infants failed to thrive. Overall, neurological abnormalities were found in 58% of

Table 9.1. Age at onset of signs of disease in infants born to HIV-1 infected women

Clinical Sign	Age in months [mean , (SD)*]				p - value
	infected		not infected		
thrush	2.14	(2.49)	1.8	(2.46)	0.660
hepatosplenomegaly	3.90	(3.47)	2.27	(1.17)	0.049
pneumonia	4.71	(1.77)	5.72	(5.63)	0.493
lymphadenopathy	5.08	(4.32)	6.50	(4.27)	0.331
neurological abnormality	5.44	(3.36)	9.07	(4.1)	0.009
diarrhoea	6.74	(6.05)	6.78	(5.95)	0.976
failure to thrive	7.26	(3.97)	12.46	(2.69)	0.0002

* **SD: standard deviation**

Table 9.2. Frequency of occurrence of signs of disease in children born to HIV-1 infected women

Clinical sign	Infected		Not Infected		Relative Risk (95% C I #)	p- value	PPV* %
	n=48	(%)	n=93				
lymphadenopathy	26	(70)	14	(15)	4.56 (2.70 - 7.75)	0.001	65
failure to thrive	25	(64)	13	(14)	4.48 (2.57 - 7.81)	0.001	65.8
neurological abnormality	21	(58)	16	(18)	3.32 (1.96 - 5.58)	0.001	56.8
hepato/splenomegaly	22	(61)	18	(20)	3.08 (1.89 - 4.52)	0.001	55
thrush	22	(61)	20	(22)	2.77 (1.75 - 4.44)	0.001	52.3
pneumonia	28	(76)	43	(47)	1.60 (1.20 - 2.12)	0.003	39.4
diarrhoea	29	(78)	52	(56)	1.38 (1.08 - 1.77)	0.020	35.8
skin rash	22	(61)	59	(64)	1.04 (0.77 - 1.42)	0.750	27.2
fever	28	(68)	56	(62)	0.79 (0.62 - 1.00)	0.081	33.3

confidence interval

*PPV positive predictive value

infected infants and in 17% of those uninfected. In both the infected and the uninfected, developmental disorders accounted for the majority of neurological problems after the first three months.

Figures 9.1a and 9.1b show the progression of the clinical signs over 3 monthly periods during the first year in the infected and uninfected groups. In the infected group, thrush was common initially but declined after 6 months age; lymphadenopathy and hepatosplenomegaly remained consistent findings throughout; the frequency of pneumonia declined after the first 6 months; whilst neurological problems and diarrhoea increased over the course of the year. A similar pattern was noted for the uninfected infants, although the frequencies were far lower for all the clinical signs assessed.

Table 9.3 compares the morbidity criteria as the incidence densities per 100 child months of follow-up, between the two groups. This shows the significantly higher incidence for all the criteria, except pneumonia, in the infected group.

9.4.5 Progression to AIDS:

The diagnosis of AIDS was made in 44.4% of infected infants by age 1 year and 46.8% by age 18 months (figure 9.2). Of those who developed AIDS during the course of the study, 95% were diagnosed by age 12 months, mean age at diagnosis 5.95 months (SD 3.61 months, range 2-18 months) with no new diagnosis of AIDS being made after the first 18 months. The estimated mean age at diagnosis of AIDS for the entire group, taking into

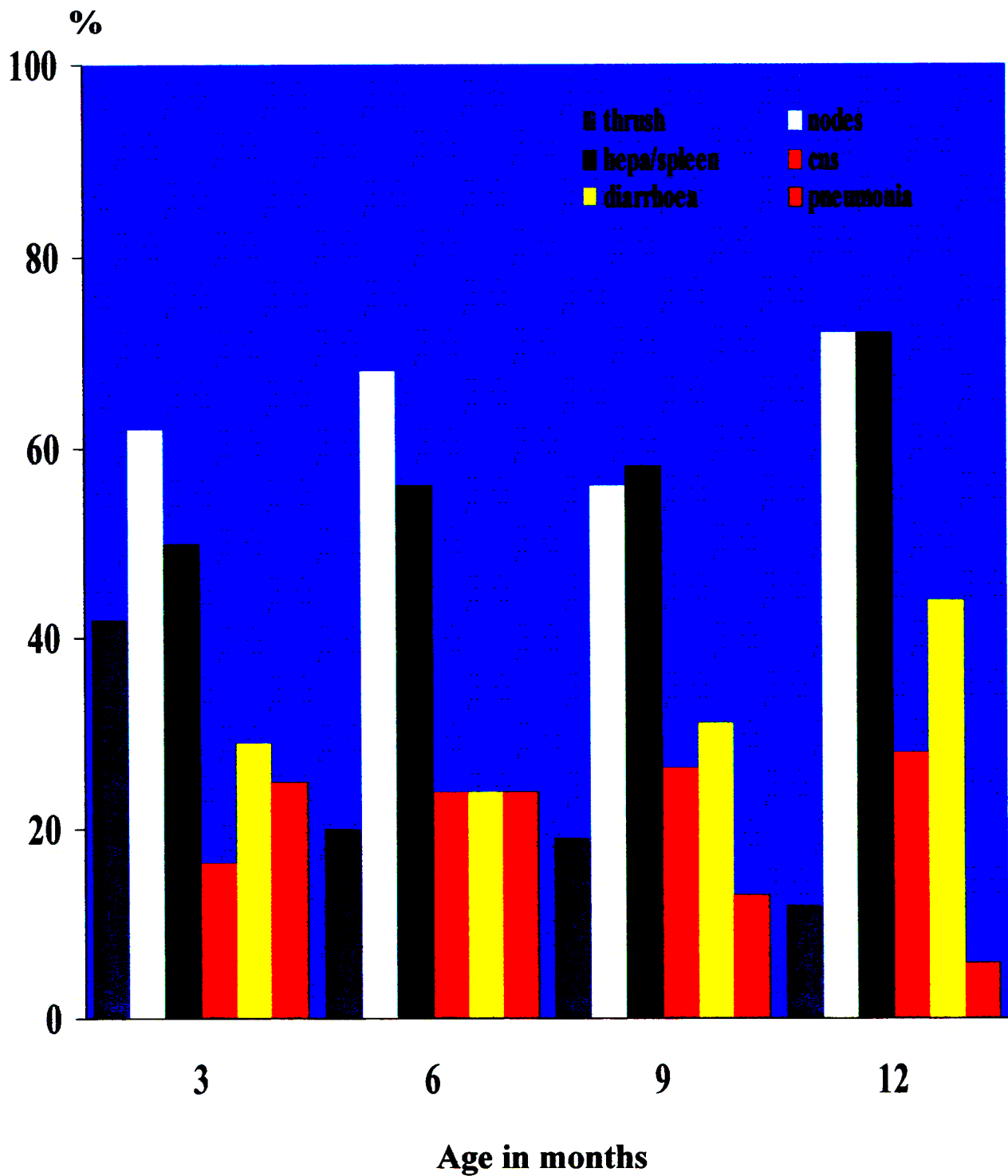


Figure 9.1(a) Frequencies of clinical signs in quartiles, over first year, in infected infants.

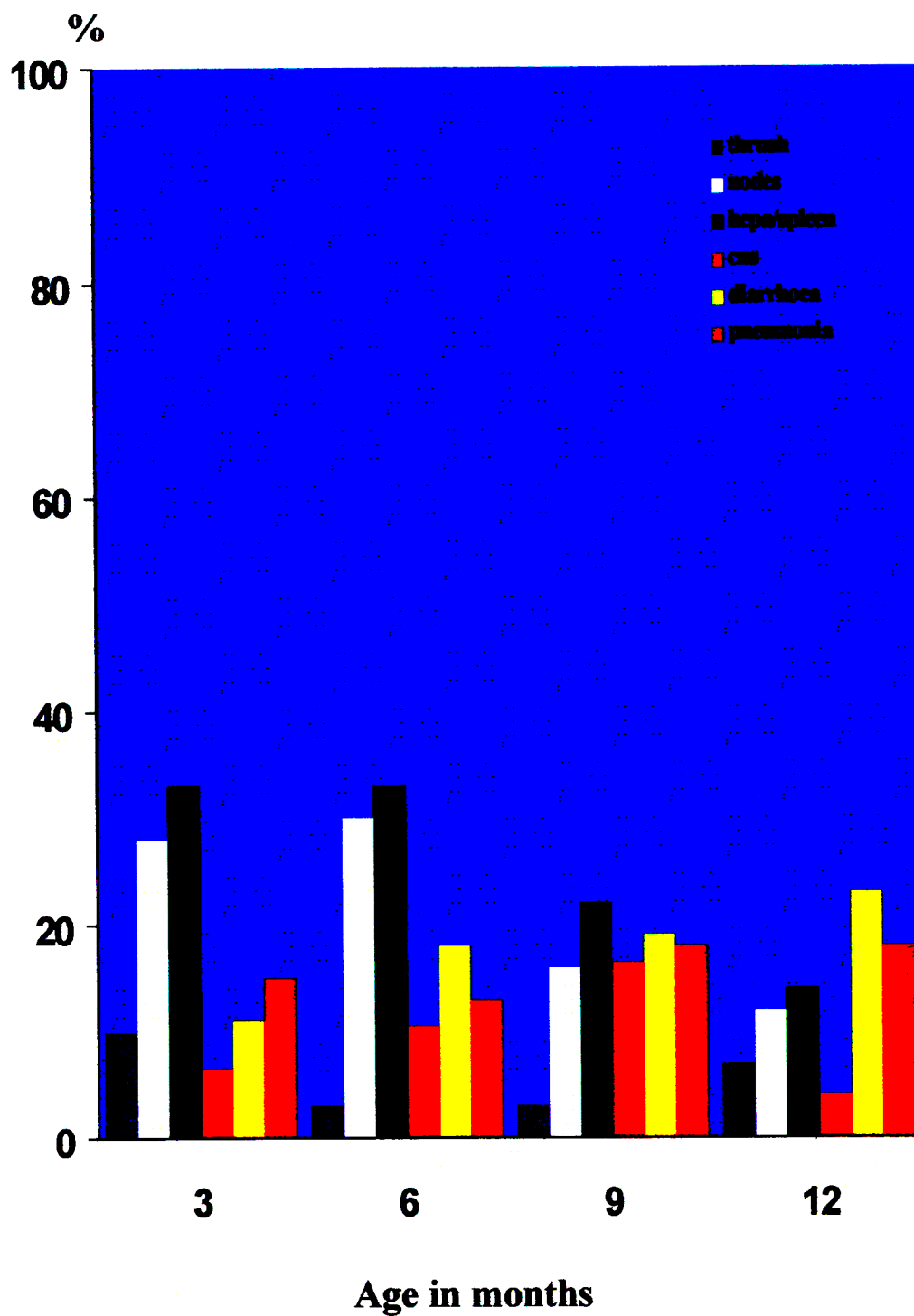


Figure 9.1(b) Frequencies of clinical signs, in quartiles, over first year, in uninfected infants.

Table 9.3. Incidence Density per 100 child months (number of episodes) of signs of disease in children born to HIV-1 infected women

Sign of disease	Infected n=1037 months		Not infected n=2197 months		Relative risk (95% CI)*
Thrush	6.94	(72)#	1.50	(33)	4.63 (3.07 - 6.98)
Failure to thrive	2.41	(25)	0.59	(13)	4.08 (2.09 - 8.00)
Lymph-adenopathy	2.41	(25)	0.64	(14)	3.77 (1.97 - 7.22)
Neurological abnormalities	1.93	(20)	0.73	(16)	2.64 (1.37 - 5.09)
Hepato-splenomegaly	2.12	(22)	0.81	(18)	2.59 (1.39 - 4.82)
Skin Rash	9.55	(99)	5.46	(120)	1.75 (1.34 - 2.28)
Diarrhoea	9.06	(94)	5.28	(116)	1.72 (1.31 - 2.25)
Fever	7.91	(82)	4.73	(104)	1.67 (1.24 - 2.24)
Pneumonia	5.49	(57)	4.09	(90)	1.34 (0.96 - 1.86)

* CI : confidence intervals

number of episodes

consideration those who had not developed AIDS during the follow-up period, was 12.4 months (SE 1.01 months).

9.4.6 Mortality

There were 17 deaths which occurred only in the HIV infected infants. The mortality rate was 35.4%, with 76% of the deaths occurring within the first year of life (figure 9.3). The mean age at death was 8.9 months (range 1-48 months). There were 4 late deaths which occurred at 24, 24, 25 and 48 months.

9.4.7 Features in early childhood

The mean survival time for the HIV-infected group was 34.17 months. 35 infected infants survived beyond the first 12 months. Of these, 25 were followed up beyond 2 years of age. Of the 9 infants who were asymptomatic at 12 months, 3 developed minor symptoms/signs during the second year of life (occasional diarrhoea or pneumonia, minimal lymphadenopathy) and six remained asymptomatic. Of the remaining 16 infants, 4 died, 1 developed AIDS and 12 stabilised and remained generally well, although most had persistent lymphadenopathy and/or hepatosplenomegaly.

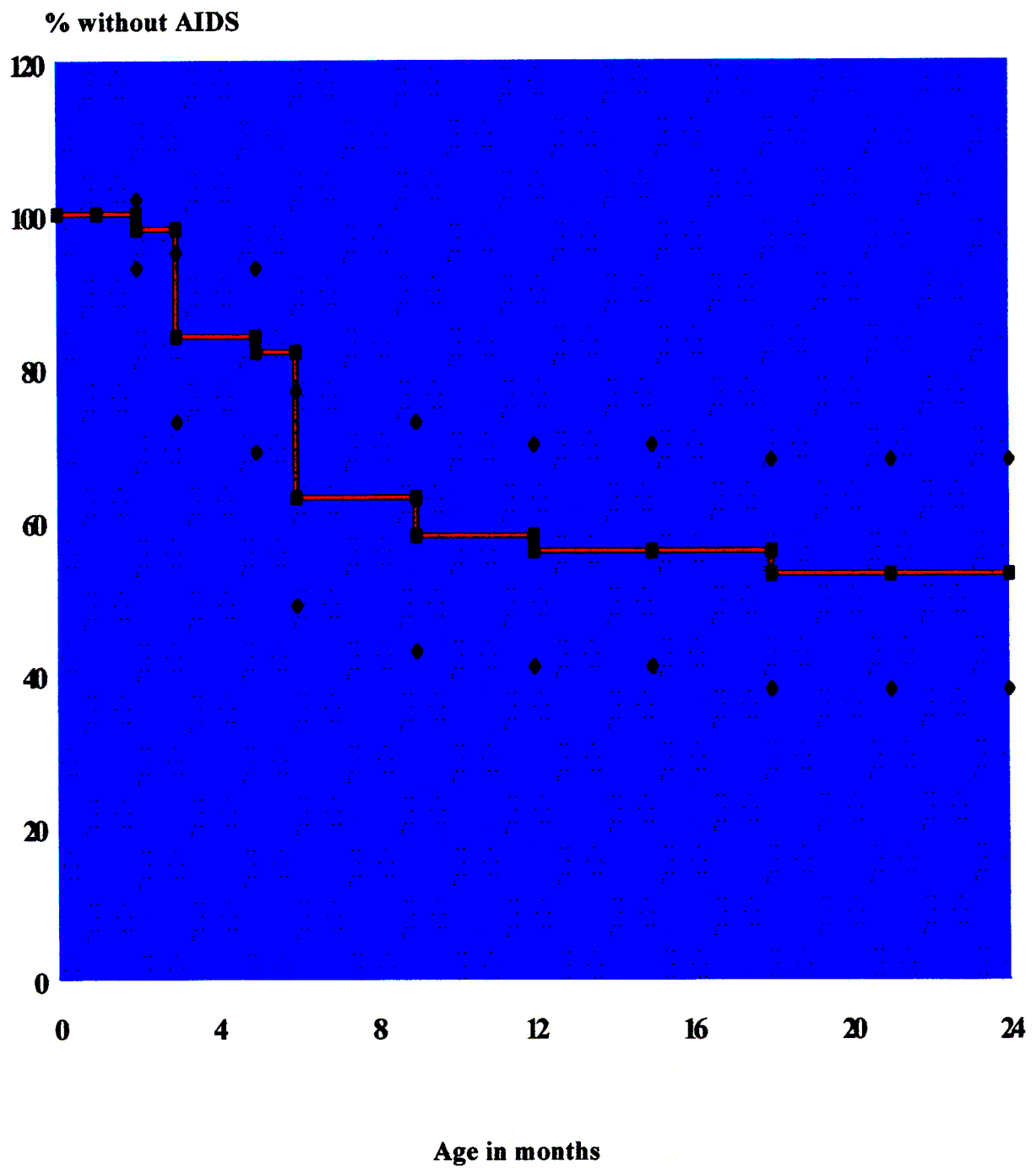


Figure 9.2 Progression to AIDS, with 95% confidence intervals, in infected children

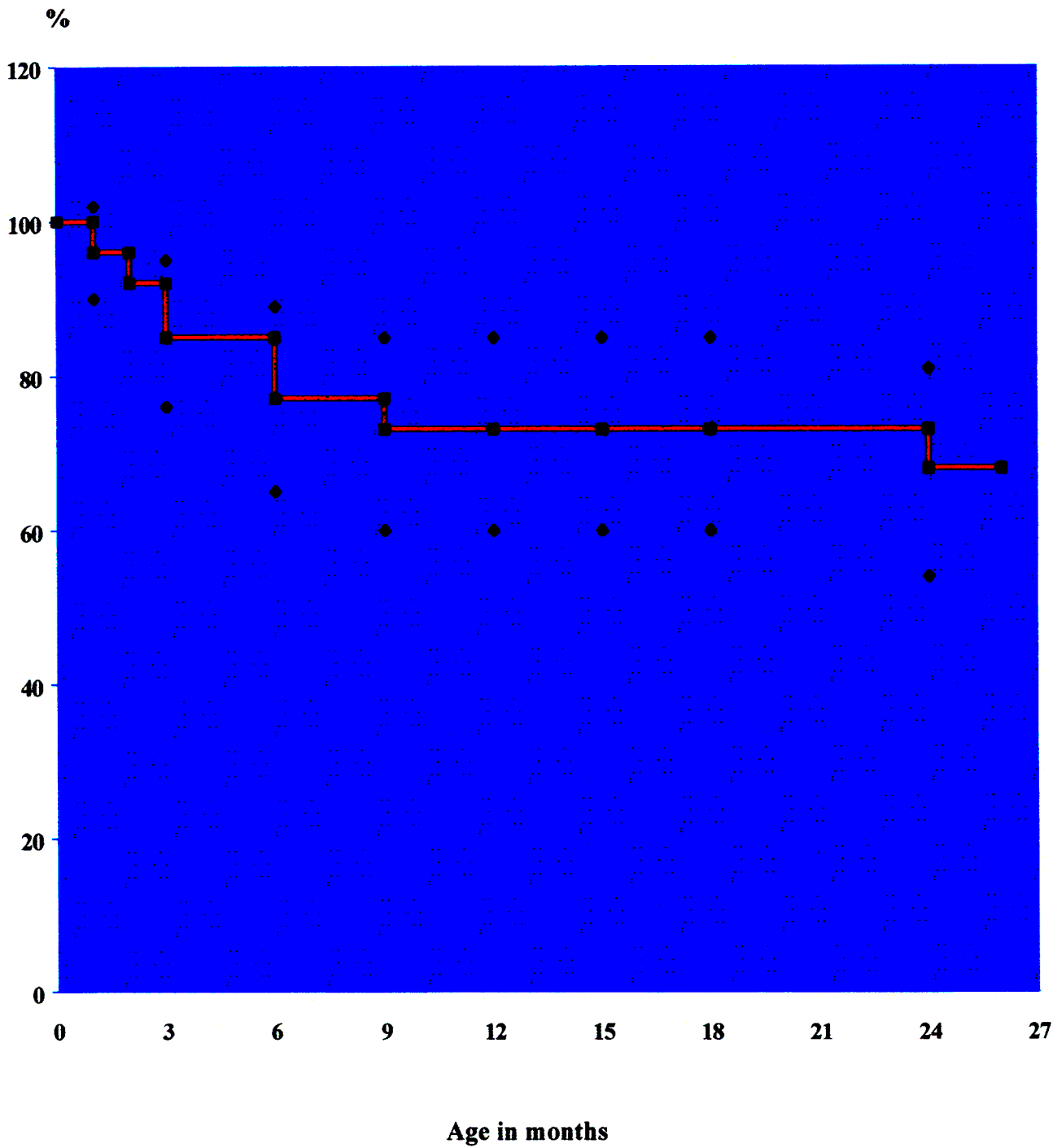


Figure 9.3 Survival from birth, with 95% confidence intervals, in infected children

9.4.8 *Indeterminate group of infants*

There were 40 infants in this group, including eight who died from unknown causes. Two infants, who were HIV negative at six months and subsequently lost to follow-up, could probably be regarded as uninfected, since, from our own experience we have found that there were no seroreverters in our cohort (Bobat 1996). 16 infants were followed-up for at least 6 months before being lost to follow-up whilst still antibody positive; of these, 5 would be classified as infected based on the onset and pattern of disease described above, and 11 others would be uninfected. The remaining 15 infants were less than 6 months when lost to follow-up and had insufficient information for further classification. We would then have a cohort of 53 infected and 106 uninfected infants, giving a vertical transmission rate of 33.3%, which is similar to that previously calculated for this cohort (Bobat 1996).

9.5 Discussion

This is one of few detailed descriptions of the evolution of clinical features and mortality in children born to HIV infected African women, derived from a cohort of babies prospectively studied from birth to a minimum of 18 months. It therefore contributes to the construction of a clearly discernible, and often distinct, pattern of morbidity and death in HIV-1 infected and HIV-1 exposed but uninfected children in Africa, which has the global burden of such infected children (Novelli 1996). The data also add to the existing body of information on this disease, which has in the main been obtained from studies of European and American children. The principal feature which distinguishes this disease in the African

children reported here from those in the industrialised countries is the faster tempo of disease progression. Indeed, given the substantial differences in the economic, social and health related backgrounds of the populations in which these children are born and grow up, it is surprising how closely the disease profiles, in most other respects, resemble each other. There are likely to be many reasons for the rapid onset of clinical deterioration and early deaths in this African cohort but it is important to reiterate that appropriate HIV directed health service interventions such as antiretrovirals, immunoglobulins and prophylaxis against pneumocystis carinii were not given. The first two were unavailable, and the role of pneumocystis in these children was unclear at the time of the study. South Africa is a middle income country and in the midst of an epidemiological transition for childhood diseases (S A Health Review 1995); therefore there may well be some differences between the HIV associated disease outcomes described here and those in the rest of Africa.

The onset of disease was early, with infected infants showing signs of disease by one month of age. The mean age at onset of HIV- related signs and symptoms is within the range of 5-8 months reported from major studies in the west (Italian Multicentre Study 1988, Scott 1989, Galli 1995). The age at onset is not precisely dated in the African studies, but appears to be within the first three months of life. In the Rwandan cohort (Lepage 1996) growth retardation was detected by 3 months of age. In Zaire, significant lymphadenopathy was detected by 6 months (Jackson 1992).

By the age of 6 months, 70% of the infected infants in our cohort had signs of disease, and by 1 year 77% were symptomatic. Similar findings were reported from the Italian group, the study from Yale, and that from Miami (Italian Multicentre Study 1988, Forsyth 1996, Scott 1989). In the European Collaborative Study, symptoms and signs were most frequent in the first 18 months of life (ECS 1994). Twenty three percent of the infected children in our cohort were asymptomatic at one year of age; similar figures were reported from Yale (Forsyth 1996) and from the Italian study (Italian Multicentre Study 1988).

The pattern of disease in the Durban cohort was similar to reports from other centres (ECS 1994, ECS 1991, Italian Multicentre Study 1988, Lepage 1990, Forsyth 1996, Galli 1995, Jackson 1992). Non-specific findings of lymphadenopathy, thrush, failure to thrive and hepatosplenomegaly occurred early and were the commonest findings in infected infants. Thrush and pneumonia occurred maximally in the first six months then declined, lymphadenopathy and hepatosplenomegaly were consistent findings, whilst neurological abnormalities and diarrhoea gradually increased in frequency. Not unexpectedly, diarrhoea and pneumonia were frequent problems in the infected infants. However, both conditions occurred in about half of the uninfected infants as well, and reflect the background problem of these two conditions in developing countries. Although pneumonia occurred more frequently in the infected group as a whole (Table 9.2), the number of episodes per child did not differ significantly between the infected and uninfected (Table 9.3). The aetiologies of pneumonia and diarrhoea were not documented for this study. Local reports from studies done subsequently, have shown that the commonest causes of death from severe respiratory

problems in HIV infected children were pneumocystis carinii and cytomegalovirus (Jeena 1996), and that tuberculosis was uncommon (Jeena 1996). The latter is surprising as the incidence of tuberculosis is high in South Africa (Dept Health SA 1996). In a separate study, among children with TB in Durban, 11% were found to be HIV positive. Similar findings have been reported from Abidjan (Lucas 1996) where pneumocystis was found in 31% of HIV infected children at post-mortem but tuberculosis was low. This issue requires further investigation of the epidemiology of co-infection but might simply mean that the sample size in the HIV infected groups was insufficient to detect exposure and infection by TB.

With regard to diarrhoea, a local study found that infectious diarrhoea in HIV infected children was due mainly to rotavirus (Rollins N, Wittenberg D, unpublished data). There was a high frequency of diarrhoea among the uninfected infants, similar to the finding from a Zairian study (Thea 1993); in addition, the researchers from Zaire noted that the risk for diarrhoea increased if the HIV positive mother was symptomatic or if she died. This would likely contribute to the prevalence of diarrhoea in our cohort.

Failure to thrive was a common finding in the infected infants, and occurred significantly more often than in infants who were HIV exposed but uninfected. Possible reasons for this include poor nutrition, recurrent diarrhoea and pneumonia, severe oro-pharyngeal thrush. Having a mother who was too ill to care for the child is another likely explanation; a report from Haiti showed that infants born to HIV infected women were more likely to be

malnourished at 3 and 6 months of age (Halsey 1990). In the Nairobi study, it was found that growth failure occurred more frequently in HIV infected children (Datta 1994); however a study from Rwanda showed that HIV infected children were more likely to have stunting but did not have wasting (Lepage 1996). In Europe the figures for failure to thrive ranged from 14% (ECS 1994, ECS 1991) to 56% (Italian Multicentre Study 1988).

Neurological problems in HIV infected children have been described with varying frequency in many studies from different parts of the world (Italian Multicentre Study 1988, Forsyth 1996, ECS 1990, Msellati 1993). In our study, neurological abnormalities occurred in approximately half of the infected infants and were found as early as 2.3 months of age. In the Rwandan study, neurological abnormalities were found in 15- 40% overall, with abnormal signs being detected by 6 months of age (Msellati 1993). Neurological deficits have been reported far more frequently in USA, i.e. in 60-90% of children, but this figure occurs in those with established AIDS (Belman 1988). In the European Collaborative Study, this figure was 8-13% overall (ECS 1990). Surprisingly, there was a high frequency of neurological problems even in the infants who were exposed but not infected. In a study from South Africa which looked at responses to acellular pertussis vaccines (Ramkissoon 1991), infants were examined by two pediatricians from birth to 9 months; the prevalence of neurological problems in this cohort of full term infants was found to be 2.6% (Ramkissoon 1991). The possible reasons for the high prevalence in the uninfected infants are not clear but may be related to a suboptimal home environment where one or both parents are HIV infected as has been previously postulated (ECS 1990), or may be due the fact that we did

not separate the infants into those with developmental problems versus those with tone disturbances/seizures.

Unlike most studies from the west, a large proportion of infants, 44.4%, developed AIDS in the first year of life, and a further 2% in the second year. Thereafter, no new case of AIDS was diagnosed during the study period. In the Italian study, AIDS was present in 23-26% of infants by the first year of life (Italian Register 1994), and in 40% by 5 years; whilst in the European Collaborative Study, 23% of infected infants developed AIDS in the first year, with no child developing AIDS after 20 months of age (ECS 1994, ECS 1991). The rates of progression to AIDS in Africa are unclear. Researchers from Rwanda have estimated that the progression to AIDS was 29% in the first 12 months of life and that the median incubation period was 18.56 months in their study population (Commenges 1992).

One third of the infected infants reported here progressed rapidly downhill, with the majority of deaths occurring within the first year of life. There were no deaths in the uninfected group. Mortality in the first year of life was far higher than that found in most other studies, both in developing and developed countries. In Africa, the frequency of deaths in the first year ranged from 14% in Kigali (Lepage 1990) to 39% in Brazzaville, Congo (Lallemont 1989). In Europe and USA this figure ranged from 17%- 25% (ECS 1994, Johnson 1989). The high mortality in our cohort might be attributed to several factors. At the time of the study, no prophylaxis against, or treatment for, pneumocystis carinii was used as the prevalence or presence of the organism in the study population was

not established; and no specific antiretroviral or immunoglobulin therapy was used. In addition, during this period, there was a great deal of political instability and families were unsettled.

Three patterns of disease progression have emerged from this study. The first group had rapidly progressive disease and died within the first year of life; the second group had slowly progressive disease and were either asymptomatic or mildly symptomatic at the end of the first year. The third group had rapidly progressive disease in the first 12 months of life, thereafter they stabilised and remained mildly symptomatic into early infancy and during the course of the study.

In summary, in this prospective natural history study of vertically acquired HIV-1 infection in black South African children who were not treated with either antiretrovirals or immunoglobulin therapy, we have found that signs and symptoms of disease develop early, progression to AIDS is rapid, and mortality is high in the first year of life. Infected infants can easily be recognised, even in early infancy, by the profile of HIV-1 associated clinical problems drawn in this account. This is particularly useful in developing countries, where diagnostic tests are either not available or are prohibitively costly. In addition, we have found that about two thirds of infected infants reached early childhood without much further progression of disease, and that few deaths occurred after the first year of life. Although we were unable to follow all our infants into late childhood, results from those who have been followed into early childhood, are similar to the findings of the European

Collaborative Study (ECS 1994) and the Rwandan study (Lepage 1991) where infected children beyond five years had few signs and symptoms. This has important health care implications as these children require long term care, and also has implications for the use of antiretroviral therapy.

CHAPTER 10

CHAPTER 10

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

10.1 Summary

Objectives: to describe growth in a cohort of black South African children with vertically acquired HIV-1 infection.

Methods: a prospective, hospital-based cohort study. Children born to HIV-1 seropositive women were followed-up from birth to early childhood, at regular intervals. At birth and each subsequent visit, growth parameters were measured. These children received no antiretroviral therapy.

Results: there were 48 infected and 93 uninfected children. There were no significant differences between the two groups at birth; thereafter, the infected group was found to have early and sustained low mean Z-scores for length-for-age and weight-for-age, but not

for weight-for-length. Although their means were always lower than those of the uninfected group, these only reached significance at certain ages: at 3,6, and 12 months for length, and at 3,6, and 9 months for weight. One third of the infected children had mean z-scores below -2SD for length at 3 months. Infected children who died early had more severe stunting, wasting and malnutrition, compared to infected children who survived.

Conclusions: infected children born to HIV-positive women have early and sustained linear growth failure, are malnourished, but are not wasted. Children with rapidly progressive disease have both stunting and wasting and are more severely affected. Uninfected children of infected mothers are also found to be mildly stunted, but not generally malnourished or wasted. Early nutritional intervention could be a means of preventing early progression or death in HIV- infected children, particularly in developing countries which do not have access to antiretroviral therapy.

10.2 Introduction

Growth in HIV infected children has been described in several studies from developed countries (ECS 1995, Miller 1993, Moye 1996, Saavedra 1995) and the major impact seems to be on attainment of normal height. Less information is available on longitudinal growth

in children from Africa, which has the largest number of HIV-1 infected children. Studies from Rwanda and Uganda found that HIV infected children had stunting, which began early, but had no wasting (Lepage 1996, Berhane 1997). Reports from other African countries have noted marasmus and kwashiorkor in association with HIV infection (Thea 1993). There are many reasons why infected children do not grow well; these include infections, poor nutrition, and hormonal effects (Thea 1993, Lepage 1991). Recently, a study from New York reported on an association between viral load and poor growth (Pollack 1997). This might explain the reported predictive value of malnutrition for mortality in HIV infected children (Forsyth 1996). Comparisons between HIV infected children in developed and developing countries are confounded by the availability of anti-retroviral therapy and adequate prophylaxis in the former.

There are differences in viral subtypes, stage of the epidemic, prevalence of malaria, socio-economic class, and availability of health services between central and east Africa and South Africa. These might affect growth of children.

We report on growth in the first 18 months of life in a cohort of children born to HIV-infected black women from Durban, South Africa, during the early stage of the epidemic.

10.3 Patients and Methods

Refer Chapter 3 for details.

10.3.1 Mothers and infants

The sampling method has been previously described in detail in Chapter 3.

10.3.2 Classification

Refer Chapter 3 for details.

10.3.2 Definitions

The anthropometric data was defined according to previously recommended terms. Children were classified as being wasted, stunted, or malnourished, depending on the weight-for-length, the length -for-age, or the weight-for-age (NCHS 1976).

10.3.3 Laboratory methods

Refer Chapter 3.

10.3.4 Statistical methods

Anthropometric indices, weight for age, length for age, and weight for length, were calculated using the growth reference curves developed by the National Centre for Health Statistics and CDC, as recommended by the WHO (WHO 1986, Dibley 1987). For each of these indices, the Z-score was estimated. The Z-score for weight for age, for example, is calculated by subtracting the median weight of the reference population at the child's age from the child's weight and dividing by the standard deviation of the weight of the reference population at that age. The Z-score results are reported as means and standard deviations at each age. HIV infected and uninfected infants were compared with relation to the mean Z-score using Student's unpaired t-test. The percentage of low anthropometric indices, using a cut-off value of $< -2SD$, was calculated and compared between infected and uninfected infants using a Chi-square test.

10.4 Results

Refer Chapter 3 for general results.

The mean follow up period for the infected infants was 28.5 months, and for the uninfected infants was 23.6 months.

10.4.1 Classification

The children were classified as 48 infected (including 17 deaths); 93 not infected, and 40 indeterminate (including 8 deaths). The 17 infected children who died during the first two years of life were regarded as rapid progressors; mean age at death was 10.1 months (range 1-48 months). All the children who died were receiving either predominant breastfeeds or mixed feeds (breast and formula).

10.4.2 Growth

Length for age: at birth, there were no significant differences between the infected and uninfected groups, and they compared well to international standards. Thereafter, the mean z-scores for length in the infected children fell below the international standards, and remained below those for the uninfected group (Table 10.1 and Figure 10.1). There was a significant difference in the length-for-age between the infected and uninfected children at the ages of three, six and 18 months. Stunting also occurred in the uninfected group from the age of three months; however, the means were always above those of the infected group. The proportion of infected children with length-for-age z-scores below -2SD were 27% at 3 months, 42% at 15 months, and 45% at 18 months.

Table 10.1 Mean weight-for-age, length-for-age, and weight-for-length z-scores in HIV-1 infected and uninfected children, born to seropositive mothers

Age (months)	Infected		Uninfected		p value
	Mean	(SD)*	Mean	(SD)	
Weight:					
Birth	0.101	(0.61)	0.397	(1.12)	0.379
3	-0.688	(1.21)	0.696	(1.57)	0.002
6	-0.611	(1.51)	0.412	(1.30)	0.006
9	-0.747	(1.48)	0.180	(1.40)	0.042
12	-0.529	(1.43)	-0.364	(1.53)	0.709
15	-1.031	(1.96)	-0.378	(1.42)	0.178
18	-0.899	(1.14)	-0.032	(1.43)	0.073
Length:					
Birth	0.132	(0.73)	0.239	(1.01)	0.574
3	-1.365	(1.74)	-0.200	(1.53)	0.014
6	-1.143	(1.38)	-0.079	(1.40)	0.006
9	-0.773	(1.01)	-0.733	(1.16)	0.913
12	-1.262	(1.50)	-1.005	(1.36)	0.526
15	-1.828	(1.58)	-1.098	(1.24)	0.079
18	-1.820	(0.61)	-1.058	(1.11)	0.006
Weight for length:					
Birth					
3	-0.431	(0.680)	-0.239	(1.01)	0.552
6	0.419	(1.10)	0.935	(1.25)	0.152
9	0.337	(1.56)	0.558	(1.43)	0.578
12	-0.202	(1.59)	0.997	(1.51)	0.015
15	0.498	(1.04)	0.535	(1.56)	0.931
18	0.133	(0.41)	0.456	(1.45)	0.514
	0.143	(1.30)	0.752	(1.62)	0.259

* standard deviation

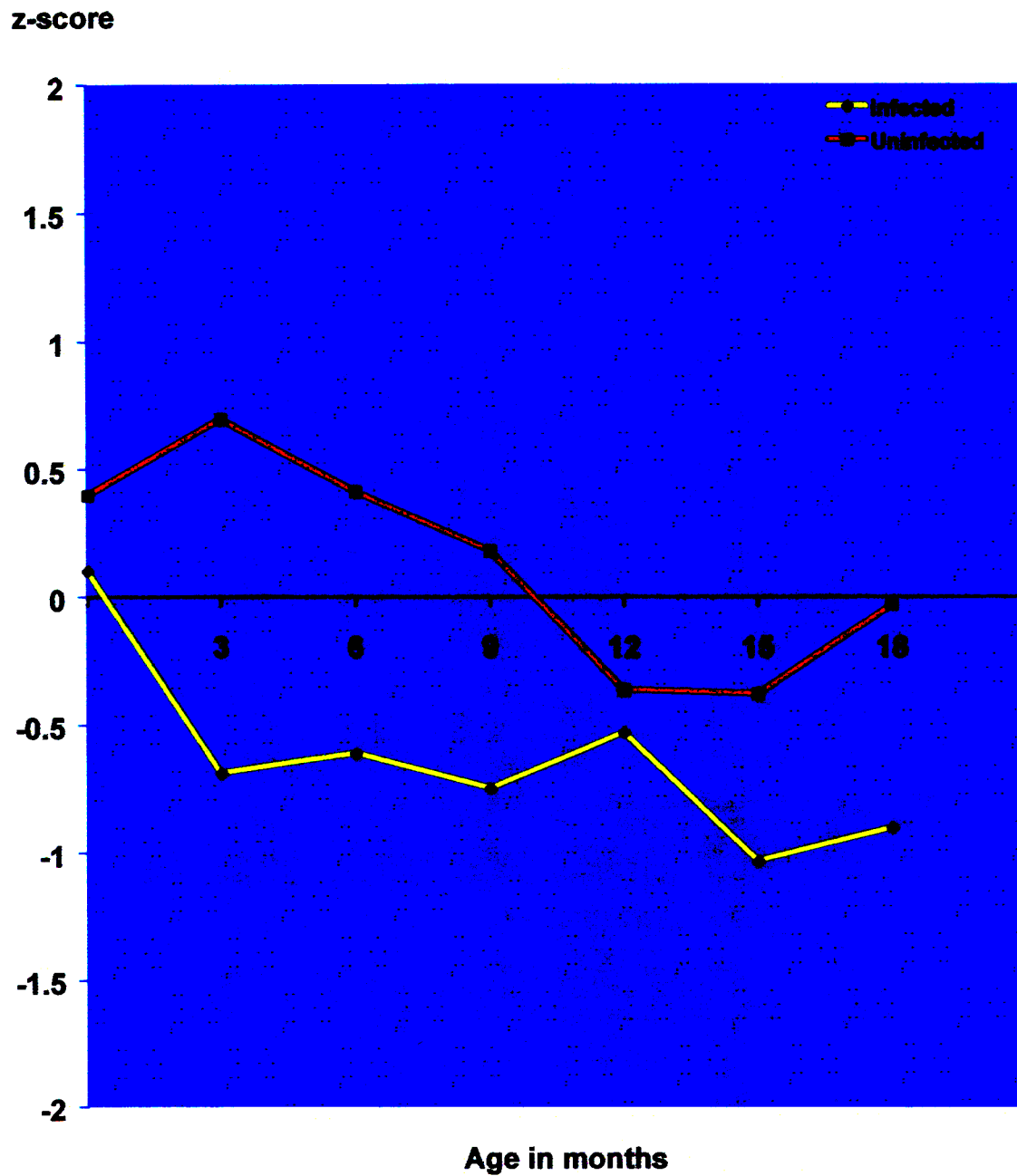


Figure 10.1 Mean length for age z-scores

Weight-for-age: at birth, the two groups compared well to international standards. Thereafter, the means for the infected group fell, and remained below those of the uninfected group (Table 10.1 and Figure 10.2). The differences were significant at ages 3, 6, and 9 months. Of note, in the uninfected group, weights were unaffected initially, but the means dropped after the age of 9 months.

Weight-for-length: at birth, the means for both the infected and uninfected group were low; thereafter, they remained comparable to international means, except at 9 months, when the means for the infected group were significantly lower than those of the uninfected group (Table 10.1 and Figure 10.3).

Growth parameters in the rapid progressors: we compared growth parameters between the 17 infected children who died with the 31 infected children who survived (Table 10.2). Although the numbers were small, a definite trend was noted. Differences in weight and length, which were noticeable from birth, persisted throughout in those infants who died. They had more severe stunting and malnutrition, and also had wasting. Seven of the 17 who died (42%), had length-for-age mean z-scores below -2SD.

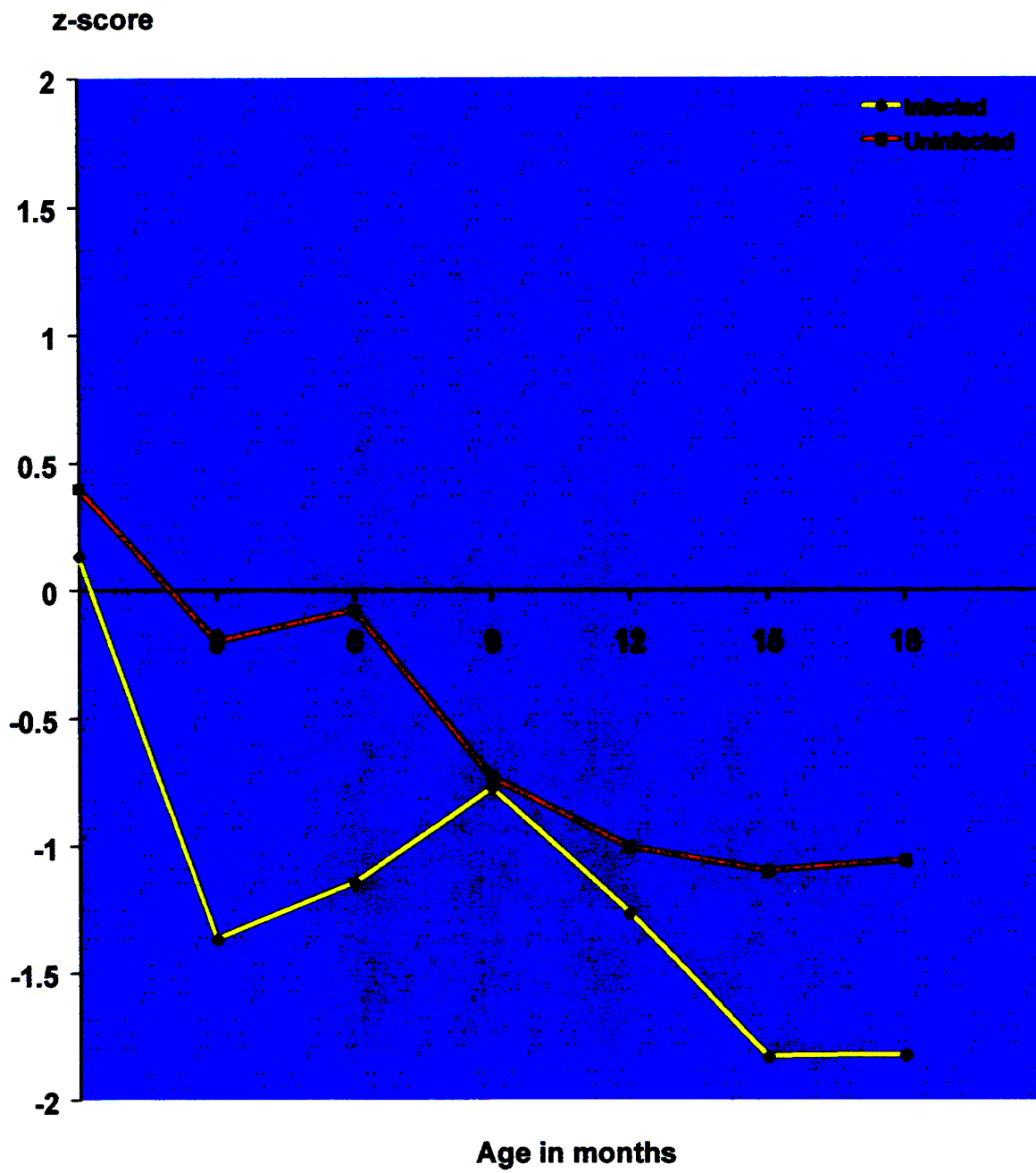


Figure 10.2 Mean weight for age z-scores

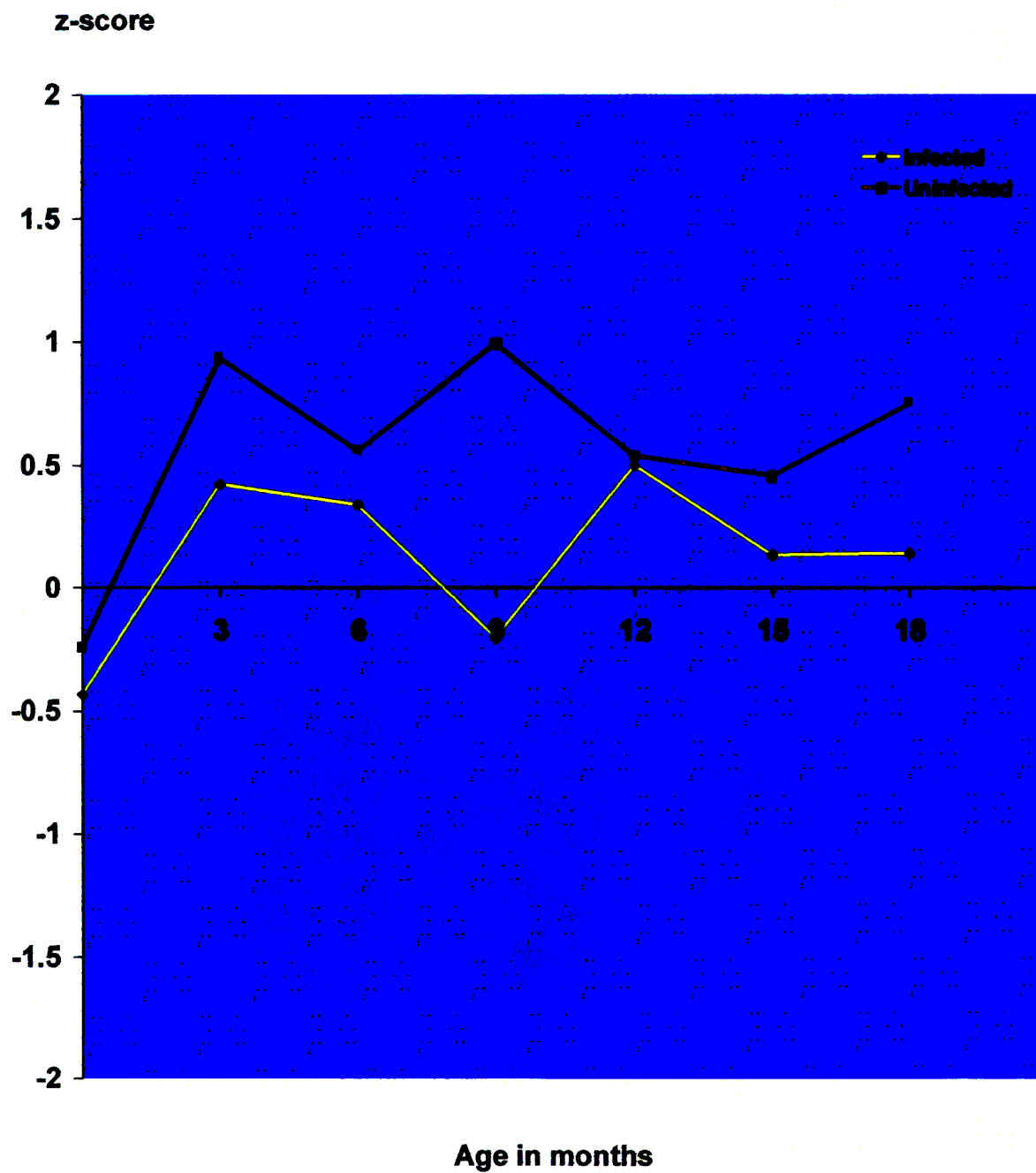


Figure 10.3 Mean weight for length z-scores

Table 10.2 Mean weight-for-age, length-for-age, and weight-for-length z-scores in HIV-1 infected children, comparing those who died with those who survived

Age#	Infected, Died		Uninfected, Alive	
(months)	Mean n=17	(SD)*	Mean n=31	(SD)
Weight:				
3	-1.508	(0.79)	-0.278	(1.21)
6	-2.597	(1.10)	-0.043	(1.07)
9	-2.035	(1.04)	-0.489	(1.46)
15	-3.585	(0.33)	-0.520	(1.71)
Length:				
3	-2.086	1.95	-1.005	1.60
6	-1.917	2.17	-0.922	1.07
9	-0.900	1.05	-0.747	1.06
15	-3.320	0.48	-1.530	1.55
Weight for length:				
3	0.084	1.39	0.587	0.97
6	-1.465	0.89	0.852	1.35
9	-1.685	0.47	0.095	1.58
15	-2.080	0.04	0.575	1.12

***SD=standard deviation**

figures for birth, 12, and 18 months are not given as the numbers were insufficient for comparison

10.5 Discussion

In this prospective cohort study on children born to HIV-1 infected black women, we have found that children with vertically transmitted infection showed early onset of stunting, were generally undernourished, but did not have significant wasting. However, infected children with rapidly progressive disease had both wasting and stunting, with the differences in weight and length being present from birth. The uninfected group had mild stunting and malnutrition, which occurred later in infancy; but they had no wasting. This pattern was similar to that found in a population of black children, from Durban, prior to the HIV epidemic (Coovadia 1978).

Our results confirm and extend data from other studies. Other African studies, from Rwanda and Uganda, found that children with vertically acquired HIV-1 infection were frequently undernourished, were stunted, but not wasted (Lepage 1996, Berhane 1997). Similar results have been shown in New York, where infected children were found to have early and frequent stunting (Pollack 1997). Our cohort of children, like those from Rwanda, received no antiretroviral therapy, and are comparable, whereas in the New York study, 61% of infected children received antiretroviral drugs. In addition, the study from Uganda noted an increase in mortality in association with the severity of growth failure

(Berhane 1997). Similarly, in our cohort, children who died had more severe wasting and stunting.

It is not clear why HIV-infected children have growth failure. The study from New York has suggested that an increased viral load is a probable contributing factor (Pollack 1997). Children in their cohort had disturbed linear growth which corresponded to higher viral loads. They did not find a difference in growth related to the use of antiretroviral agents. Although we did not measure viral load, it is likely that this might have been associated with the growth disturbances we detected. Differences in length and weight in the HIV-infected group were present from birth (although not significant), but were profound by the third month of life. This parallels findings from recent studies on viral dynamics in which it has been established that the RNA viral burden peaks between 3 to 4 months of age from a relatively lower value at birth. The fact that HIV uninfected children also had a similar progression of stunting suggests that environmental conditions prevailing within families and communities are responsible. These factors have been discussed in a recent review on protein energy malnutrition in South African children (Glatthaar 1994).

In the cohort from Rwanda, an association was noted between growth failure and infections (Lepage 1996). Infected children with low weight and length for age were more likely to have had persistent diarrhoea, chronic fever and pneumonia. In a previous

description of our cohort, we have shown that the commonest causes for mortality in HIV infected children were either respiratory, diarrhoeal, or both. In addition, we showed a high proportion of failure to thrive (Bobat 1998). Persistent or recurrent diarrhoea and malabsorption have been associated with growth failure in HIV infected children (DuPont 1995). However, we did not find a significant difference in frequency of diarrhoea and respiratory infections between those infected children who were the most severely stunted, i.e. those who fell below -2SD for length, compared to the rest of the infected group.

Malnutrition has been shown to affect immunity (Gorbach 1993) and this predisposes to opportunistic infections. An association between growth failure and opportunistic infections has been shown in haemophiliac children (Bretler 1990). The combination of malnutrition and opportunistic infections would aggravate the problem of growth failure in HIV infected children.

There have been reports that endocrine dysfunction may be associated with the growth failure occurring in HIV infected children (Lepage 1991). Thyroid and adrenal abnormalities have been documented in HIV infection (Membreno 1997). What the exact role of these in HIV related growth failure is, remains uncertain. In South Africa,

endocrine dysfunction has been described in relation to malnutrition (Wittenberg 1998), and this may be one of the mechanisms for the growth failure.

The finding of growth failure in the children who were uninfected is interesting. It may be related to the problem of having an HIV- infected mother who is ill, as has been previously suggested (Halsey 1990); or be the consequence of dysfunctional families, or may be associated with the background poverty prevalent in South Africa. Figures from a randomised national sample of children in South Africa showed that the prevalence of underweight children was 9.3%, and that stunting occurred in 23% of children (SAVCG 1996).

We do not have an adequate explanation for the profound effect on stunting compared to the lack of significant wasting, found in our study, as well as in other African studies. Stunting probably reflects more than simple intake of food, and is likely a result of the combination of poor overall economic conditions, chronic or repeated infections, as well as inadequate nutrient intake (Dibley 1987). In addition, in the presence of HIV infection, it may be related to viral load (Pollack 1997); it has been shown that children who receive antiretroviral therapy grow better (McKinney 1991).

Growth failure in an infant born to an HIV-infected woman may be an indicator of infection in the child, or an indicator of rapidly progressive disease in an infected child, and should alert the physician to the need for possible intervention. Infected children with severe wasting and stunting are at particular risk for early death, and need to be monitored closely. The cause of growth failure in these children may be a combination of lack of food, frequent infections, and higher viral load. In most developing countries, where antiretroviral therapy is unavailable, early nutritional support may be an important intervention in preventing deterioration and possibly early death in HIV- infected children.

CHAPTER 11

CHAPTER 11

MORTALITY IN CHILDREN BORN TO HIV-1 INFECTED WOMEN

11.1 Summary

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 record 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, of which 17 (35%) were regarded as HIV-related. The mean age at death of HIV-related cases was 10.1 months (range 1-48 months), and eighty three percent of HIV-related deaths occurred 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. The combination of findings of diarrhoea, pneumonia, failure to thrive, and neurological abnormalities, should alert one to the possibility of rapidly progressive disease and death.

11.2 Introduction

Children with vertically acquired HIV-1 infection appear to progress at different rates to severe disease and death (Forsyth 1996). Whilst some, about 23-26%, have a rapidly progressive course with death within the first year, others follow a less turbulent path and remain well into late childhood (Scarlati 1996). With the use of antiretroviral drugs, prophylaxis against pneumocystis carinii and other infections in developed countries, and with better nutritional and anti-infective measures during care, 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 possibility of 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 (Taha 1995, Hira

1989, Vetter 1996) but these data are limited for a number of reasons including low autopsy rates in general and a particular reluctance to undertake postmortems in HIV infected individuals.

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

11.3 Methods

Details on methods and patient population have been described in Chapter 3.

Most deaths occurred either in the study hospital's outpatient department or in the paediatric wards, and information for these children was obtained from the hospital records. Sufficient data on the deaths was not possible for all the patients, since some died at home, and 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.

11.4 Results

The final cohort comprised 48 infected and 93 uninfected children. There was a total of 25 known deaths in the entire cohort during the study period. Of these, 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 month to 48 months). Only 3 deaths occurred after 12 months of age. If the 3 late deaths are excluded, then the mean age at death in the first 12 months was 3.8 months. Eighty three percent of all deaths occurred before 10 months of age.

11.4.1 Symptoms and clinical features at death:

The onset of symptoms in the infants who died was at a mean age of 3 months, (range 1 to 5 months). The main presenting complaints or symptoms just prior to death were cough, diarrhoea, and fever (Table 11.1); at least two of these symptoms were found in 16/17 of the infants who died from an HIV-related death. The main morbidity data are summarised in Table 11.2.

11.4.2 Laboratory data at death:

Of the 7 children for whom full blood counts were available, 5 (71.4%) had anaemia of varying degrees; thrombocytopaenia and leucopaenia were found in one child only. This infant had pancytopenia. The mean globulin level was 35.7 (range 21-74 g/l). Positive blood cultures were obtained in 4 children, of which 3 were gram negative organisms (Table 11.3).

Table 11.1. Presenting complaints and clinical features at death for each HIV-1 infected child who died

patient no.	presenting complaints	age at death: months	failure to thrive	thrush	Chest#	git*	cnsΦ	nodes ♣
18	fever, cough, diarrhoea	8	y	y	Y	y	y	y
72	fever, cough, tachypnoea	1	n	y	Y	n	n	n
79	cough, fast breathing, diarrhoea	1	n	y	Y	y	n	n
94	fever, cough diarrhoea	2	y	y	Y	n	n	y
104	diarrhoea	24	y	y	Y	y	n	y
105	diarrhoea	24	y	y	N	y	y	y
106	fever, cough diarrhoea	2.5	n	y	Y	y	y	n
111	fever, cough diarrhoea	3	y	y	Y	y	y	y
125	fever, cough diarrhoea	31	n	y	Y	y	y	y
138	fever, diarrhoea	5.5	y	y	Y	y	y	y
153	excessive crying	2.5	y	n	N	n	n	y
177	fever, diarrhoea	3.5	y	y	Y	y	y	n
179	fever, cough diarrhoea	6	y	y	N	y	n	n
181	cough, diarrhoea	9	y	n	Y	y	y	y
198	fever, cough	2.5	y	n	Y	n	n	n
203	fever, cough, diarrhoea	5.5	y	y	N	y	y	Y
220	fever, diarrhoea	1.5	n	y	Y	y	n	N

pneumonia

♣ lymphadenopathy

* diarrhoea

y=yes

Φ neurological abnormalities

n=not present

Table 11.2. Summary of the morbidity data on the 17 HIV-1 infected infants who died

Feature	Number of children	%	95% Confidence intervals
age at death:			
0-6 months	11	64.7	
≥ 6 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

Table 11.3. Laboratory data at death for HIV-1 infected patients who died*

patient no.	full blood count:			globulin g/l	blood culture	chest x-ray	Other
	Hb	wbc	plat				
18	n/a			67	no growth	bi-lateral extensive pneumonia	
72	12.6	11.9	290	n/a	no growth	bilateral broncho-pneumonia	pm # lung biopsy: pneumonia
79	n/a			29	pseudomonas	right broncho-pneumonia	
94	n/a			22	no growth	n/a	
106	n/a			21	no growth	clear	
111	9.1	22.6	624	21	no growth	bi-lateral broncho-pneumonia	CMV IgM positive
125	9.8	15.0	989	74	pneumococcus	bi-lateral bronchiectasis	csf: bacterial meningitis
138	8.3	15.7	322	50	no growth	right upper lobe pneumonia	ultra-sound head: cerebral atrophy liver biopsy: fatty changes
177	6.6	4.3	45	21	enterococcus	bi-lateral pneumonia	
179	10.4	8.3	317	27	n/a	n/a	
181	n/a				no growth	n/a	CMV IgM positive
198	7.2	20.7	399	25	pseudomonas	bi-lateral broncho-pneumonia	CMV IgM positive

* information was not available for every patient who died

11.5 Discussion

The 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 one 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 had 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 the highest in the first year of life.

These children had illnesses similar to most children in developing countries, and therefore diarrhoeal disease and respiratory infections, per se, cannot identify the HIV-infected child 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 on 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.

It would be the combination of features: diarrhoeal disease, respiratory infection, failure to thrive, and neurological abnormalities, as well as the findings of low birth weight and neonatal complications in the newborn of an HIV-positive mother, that would alert one to the child who is HIV-infected and who would develop rapidly progressive disease and early death.

These findings are similar to those reported from central Africa. In the report from Malawi, diarrhoeal disease, respiratory infections and failure to thrive were the commonest cause of death and mortality in the first year was high (Taha 1995). Similarly, in Lusaka, Zambia, it was found that mortality among vertically infected children was 44 % at 2 years, and the main clinical findings included pneumonia, diarrhoea, failure to thrive, and fever (Hira 1989). A study from Kinshasa reported a 3-year mortality of 44 % in children born to HIV-1 infected women, with diarrhoea and pneumonia being among the chief causes of death (Ryder 1994).

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 (IMCI 1997). The shortcoming of this protocol is that HIV infection has not been included among these. Our data highlights the role of diarrhoeal disease, respiratory infections, and malnutrition in HIV-related mortality and, given the extent of the epidemic in Africa, and the increase in childhood mortality from HIV (Nicoll 1995), it would be crucial to include the role of HIV in any management protocol dealing with childhood infections in Africa. In particular attention must be given to the problems of repeated and often protracted diarrhoea, recurrent or chronic pneumonia, as well as a high frequency of failure to thrive 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 illnesses are similar to those reported in other parts of Africa. The combination of findings in HIV infected children of diarrhoea, pneumonia, failure to thrive, and neurological abnormalities, should alert one to the possibility of rapidly progressive HIV disease and early death. In addition, it highlights the need for early and aggressive management of these infections in HIV-infected children, and the need for early interventions, (eg. antiretroviral therapy, nutritional support).

CHAPTER 12

CHAPTER 12

OVERVIEW OF RESULTS

This natural history study, conducted during the early phase of the epidemic in KwaZulu/Natal, has revealed some important observations which are important in the counselling of HIV positive expectant and new mothers; in the early recognition of infected infants; in the planning of appropriate management of infected children; and in the counselling of mothers with infected children.

This study has shown that the vertical transmission rate was high, 34%, and that there was an increased rate of transmission associated with vaginal deliveries and anaemia in pregnancy.

There was an increased risk of transmission, by about 15%, associated with breastfeeding. Exclusive breastfeeding by HIV-infected mothers did not appear to protect their infants against common childhood illnesses and failure to thrive, nor significantly delay progression to AIDS; and there was a trend towards higher mortality in those receiving exclusive breastfeeds.

As a group, vertically infected newborns of HIV-positive mothers could not be differentiated from those who were exposed, but uninfected. However, infected newborns of HIV-positive women who were found to be growth retarded, or who developed complications in the neonatal period, were more likely to progress rapidly and die. Such infants probably represented intrauterine or early intra-partum transmission.

In children with vertically acquired HIV-1 infection, the onset of disease was early and deterioration to AIDS and death were rapid. Infected infants could be easily recognised clinically, the majority by 6 months of age, which is particularly useful in developing countries. Two thirds of infected infants survived beyond infancy; this has important implications for management and health care planning.

Infected children born to HIV-positive women had early and sustained linear growth failure, malnutrition, but not wasting. This possibly reflects a combination of the effects of the disease and environmental factors, and has important implications for early nutritional interventions.

Mortality among children with vertically acquired HIV infection was 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. The combination of findings of diarrhoea, pneumonia,

failure to thrive, and neurological abnormalities, should alert one to the possibility of rapidly progressive disease and death.

Three patterns of disease have emerged from this study:

- rapidly progressive disease and early death
- initial rapid progression, followed by stabilisation
- slowly progressive disease

The results from this study provide health care workers in developing countries with additional information with regard to the factors contributing to vertical transmission and the effects of breastfeeding on vertical transmission and on morbidity. It provides the natural history of vertically transmitted HIV-1 infection during a period when no intervention was available; it provides clinical manifestations of the disease progress and the effects on growth. The study also provides information on the causes of mortality in vertically infected children. All this information contributes to improved care/management of HIV infected children, and provides direction for future research.

Much information is still required on the timing of vertical transmission and the effects of truly exclusive breastfeeding; the effect on vertical transmission of interventions such as the use of antiretroviral drugs and no breastfeeding. Future studies need to investigate, in depth, the effect of HIV on each system, and the effects of intervention, and provide management guidelines.

SECTION 3

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Table 1: National HIV surveys of women attending antenatal clinics of the public health services in South Africa, 1994 - 1996

	1996	1995	1994
	Est (HIV+) 95% CI	Est (HIV+) 95% CI	Est (HIV+) 95% CI
South Africa	14,17 (13,45 ; 14,89)	10,44 (9,86 ; 11,02)	7,57 (7,01 ; 8,12)
Provinces			
Western Cape	3,09 (2,34 ; 3,84)	1,66 (0,94 ; 2,38)	1,16 (0,76 ; 1,56)
Eastern Cape	8,10 (6,92 ; 9,28)	6,00 (4,89 ; 7,11)	4,52 (3,85 ; 5,19)
Northern Cape	6,47 (5,05 ; 7,89)	5,34 (4,10 ; 6,58)	1,81 (1,09 ; 2,53)
Free State	17,49 (15,57 ; 19,41)	11,03 (9,44 ; 12,62)	9,19 (7,94 ; 10,44)
KwaZulu-Natal	19,90 (17,68 ; 22,12)	18,23 (16,31 ; 20,15)	14,35 (12,22 ; 16,48)
Mpumalanga	15,77 (14,34 ; 17,20)	16,18 (14,40 ; 17,96)	12,16 (11,60 ; 12,71)
Northern Province	7,96 (6,24 ; 9,68)	4,89 (4,00 ; 5,78)	3,04 (2,40 ; 3,67)
Gauteng	15,49 (13,58 ; 17,40)	12,03 (10,36 ; 13,70)	6,44 (5,63 ; 7,25)
North West	25,13 (22,31 ; 27,95)	8,30 (6,67 ; 9,92)	6,71 (4,62 ; 8,80)
Age Group			
<20	12,90 (11,45 ; 14,35)	9,50 (8,15 ; 10,85)	6,47 (5,45 ; 7,49)
20 - 24	17,74 (16,49 ; 18,99)	13,12 (11,97 ; 14,27)	8,94 (8,02 ; 9,86)
25 - 29	15,33 (14,04 ; 16,60)	11,03 (9,81 ; 12,25)	8,63 (7,25 ; 10,01)
30 - 34	12,20 (10,73 ; 13,67)	8,05 (6,79 ; 9,31)	6,37 (5,28 ; 7,45)
35 - 39	9,71 (7,89 ; 11,53)	7,37 (5,47 ; 9,28)	3,72 (2,34 ; 5,11)
40 - 44	10,16 (5,95 ; 14,36)	4,36 (1,96 ; 6,76)	5,28 (3,21 ; 7,35)
45 - 49*	5,83 (2,24 ; 9,40)	7,45 (0,00 ; 19,36)	0,41 (0,00 ; 1,16)

Note:The estimate of HIV prevalence in the 45 - 49 year group is based on very small numbers.

* A correction to the first figure released.

Annexure 11**WHO/UNICEF STATEMENT ON BREAST-FEEDING****Recommendations**

1. In all populations, irrespective of HIV rates, breast-feeding should continue to be protected, promoted and supported.
2. Where the primary causes of infant deaths are infectious diseases and malnutrition, infants who are not breast-fed run a particularly high risk of dying from these conditions. In these settings, breast-feeding should remain the standard advice to pregnant women, including those who are known to be HIV-infected, because their baby's risk of becoming infected through breast milk is likely to be lower than its risk of dying of other causes if deprived of breast-feeding.
3. In settings where infectious diseases are not the primary causes of death during infancy, pregnant women known to be infected with HIV should be advised not to breast-feed but to use a safe feeding alternative for their babies.

4. When a baby is to be artificially fed, the choice of substitute feeding method and product should not be influenced by commercial pressures. Companies are called on to respect this principle in keeping with the International Code of Marketing of Breast-milk Substitutes.

5. In all countries, the first and overriding priority in preventing HIV transmission from mother to infant is to prevent women of childbearing age from becoming infected with HIV in the first place.

Annexure III

UNAIDS STATEMENT ON BREAST-FEEDING

1. Support breast-feeding

As a general principle, in all population, irrespective of HIV infection rates, breast-feeding should continue to be protected, promoted and supported.

2. Improving access to HIV counselling and testing

Access to voluntary and confidential HIV counselling and testing should be facilitated for women and men of reproductive age. Counselling for women who are aware of their HIV status should include the best available information on the benefits of breast-feeding, on the risk of HIV transmission through breast-feeding, and on the risks and possible advantages associated with other methods of infant.

3. Ensuring informed choice

Because both parents have a responsibility for the health welfare of their children, and because the infant feeding method chosen has health and financial implications for the entire family, mothers and fathers should be encouraged to reach a decision together on this matter. Women be empowered to make fully informed decisions about infant feeding, and that they be suitably supported in carrying them out. This should include

efforts to promote a hygienic environment, essentially clean water and sanitation, that will minimize health risks when a breast-milk substitute is used.

When children born to women living with HIV can be ensured uninterrupted access to nutritionally adequate breast-milk substitutes that are safely prepared and fed to them, they are at less risk of illness and death if they are not breast-fed.

However, when these conditions are not fulfilled, in particular in an environment where infectious diseases and malnutrition are the primary causes of death during infancy, artificial feeding substantially increases children's risk of illness and death.

4. **Preventing commercial pressures for artificial feeding**

Manufacturers and distributors of products which fall within the scope of the International Code of Marketing of Breast-milk Substitutes (1981) should be reminded of their responsibilities under the Code and continue to take the necessary action to ensure that their conduct at every level conforms to the principles and aim of the Code.

Annexure IV

Categories for CDC Classification of HIV Infection

Category N : Not Symptomatic

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in Category A.

Category A : Mildly Symptomatic

Children with two or more of the conditions listed below but none of the conditions listed in categories B and C.

- Lymphadenopathy (≥ 0.5 cm at more than two sites; bilateral + onesite)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

Category B : Moderately Symptomatic

Children who have symptomatic conditions other than listed for Category A or C that are attributed to HIV infection. Examples of conditions in clinical Category B include but are not limited to

- Anaemia (<8 g/dL), neutropenia (<1000/mm³), or thrombocytopenia (<100,000/mm³) persisting ≥30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children >6 months of age
- Cardiomyopathy
- Cytomegalovirus infection, with onset before 1 month of age
- Diarrhoea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (more than two episodes within 1 year)
- HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month of age
- Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Persistent fever (lasting >1 month)
- Toxoplasmosis, onset before 1 month of age
- Varicella, disseminated (complicated chickenpox)

Category C: Severely Symptomatic

- Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
- Candidiasis, oesophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhoea persisting >1 month
- Cytomegalovirus disease with onset of symptoms at age >1 month (at a site other than liver, spleen or lymph nodes)
- Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): a) failure to attain or loss of developmental milestone or loss of intellectual ability, verified by standard developmental scale of neuropsychological tests; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements

or brain atrophy demonstrated by CT scans or MR imaging (serial imaging is required for children < 2 years of age); c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance

- Herpes simplex virus infection causing a mucocutaneous ulcer that persists for >1 month; or bronchitis, pneumonitis, or oesophagitis for any duration affecting a child >1 month of age
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi's sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitts), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype
- Mycobacterium tuberculosis, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin or cervical or hilar lymph nodes)
- Mycobacterium avium-intracellulare complex or Mycobacterium kansasii, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)

- Pneumocystis carinii pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicemia, recurrent

Immune Categories:

Immune Category	Age of Child		
	<= 12 months	1 – 5 years	6 – 12 years
	Number/ ul/ %	Number/ ul/ %	Number/ ul/ %
Category 1: No suppression	>=1,500/ > 25%	>=1,000/ >25%	>=500/ >25%
Category 2: Moderate suppression	750-1,499/15-24%	500-999/ 15-24%	200-499/ 15-24%
Category 3: Severe suppression	<750/ < 15%	<500/ < 15%	<200/ < 15%