"FACTORS ASSOCIATED WITH SHORT TERM SURVIVAL OF HIV INFECTED CHILDREN IN NAIROBI, KENYA."

A dissertation presented in part fulfillment for the

Degree of Masters of Medicine (Pediatrics)

in the University of Nairobi.

By:

Dr. Njenga S Njoroge

Department of pediatrics

University of Nairobi

DECLARATION

I declare that this dissertation is my original work and has not been published elsewhere or presented for a degree in any other University.

Signed: _____ Date: 14/10/2002

Dr. Njenga S Njoroge

MBChB (NBI)

This dissertation has been submitted to the University of Nairobi with our approval as University Supervisors.

Signed: _____ Date: 14/10/2002

Dr. Ruth Nduati,

MBChB., M. Med. (paed), MPH

Senior Lecturer

Department of Pediatrics

University of Nairobi

Signed: _____ Date: 14/10/2002

Prof. Frank Plummer, MD

1. Visiting scientist

   Department of Microbiology,

   University of Nairobi

2. Chairman Department of Medical Microbiology,

   University of Manitoba, Canada.

3. Medical Research Council of Canada Senior Scientist

Acknowledgements

I would like to express my sincere appreciation to:

1. My supervisors Prof. Plummer F. A. and Dr. Nduati R. W. for their guidance, encouragement, support and patience through the study.
2. The Principle Investigators of the University of Nairobi Paediatric AIDS Study for allowing me to use the clinic for this study.
3. Mr. Fred Oyugi, of Department of Microbiology U.O.N for his tireless help in the entire preparation of the manuscript.
4. Mr. Ochieng' J., of Department of pediatrics U.O.N for his valuable statistical input.
5. All the children and their mothers who participated in this study.

Table of Contents

LIST OF ABBREVIATIONS

AIDS	Acquired Immune-deficiency Syndrome
ARV	Anti-Retroviral
BOH	Bad Obstetric History
EIA	Elisa
GC	Gonococci
HAZ	Height for Age Z-score
HIV-1	Human Immunodeficiency Virus Type –1
KDHS	Kenya Demographic Health Survey
KEPI	Kenya Expanded Program for Immunization
MCH	Mother Child Health
MTCT	Mother-To-Child-Transmission
NHCS	National Center for Health Statistics
PCR	Polymerase Chain Reaction
ROM	Rapture of Membranes
RR	Relative Risk
RPR	Rapid Plasmin Reaction
STD	Sexually Transmitted Disease
WHO	World Health Organization
WAZ	Weight for Age Z-score
WHZ	Weight for Height Z-score

LIST OF FIGURES AND TABLES

Figures **Page**

Tables

Abstract

Background and objectives:
There is limited report on natural history of HIV-1 infection in African children, and much more so on long-term observational cohort studies. The literature on natural history may differ from the western world due to lack of anti-retroviral drug use and other infectious disease burdens in the resource poor sub Saharan Africa. From 1986, a collaborating team of researchers from the University of Nairobi and the University of Manitoba, Canada has been conducting a cohort study on mother-to-child HIV-1 transmission. While following up the children, we noted a sub-group of children who died before reaching 3 years of age. The study objective is to describe the factors associated with survival of HIV-1 infected children to <3 years.

Methods:
Data was abstracted from the main study on HIV-1 infected mothers and their children those who were born between 1992 and 1997. The data included maternal socio-demographic and clinical factors at delivery of the index child, the clinical and anthropometrical measurements of the infant at delivery, and clinical and laboratory follow-up evaluation on scheduled visits.

Results:
There were 52 HIV-1 infected children within complete follow-up data from delivery. Twenty-eight of the 52 children (53.8%) died before age 3 years. The mothers and the children had no access to anti-retroviral drugs. Significant factors associated with early mortality included: illnesses during pregnancy with no medical treatment being sought (P0.02), low birth weight <2500grams (P=0.02), occurrence of diarrhoeal disease as early as 6 weeks of life (P=0.06) and failure to thrive by 6 months (p=0.001). Significantly higher incidences of common signs of HIV-1 infection; fever (P=0.02), cough (p<0.000), diarrhoea (P=0.002) and thrush (P=0.0002) were seen in the children who died before 3 years of age.

Conclusion:
There was a high (53.8%) mortality in this cohort in the first three years of life. Diarrhoeal disease and failure to thrive were the main factors associated with early mortality in this cohort of children without antiretroviral drug exposture.

INTRODUCTION AND LITERATURE REVIEW

In the year 2000, it was estimated that there were over 36 million HIV-1 infected individuals worldwide (1), 68% residing in sub-Saharan Africa. There are about 2 million reported AIDS cases in Kenya of whom 10% are children under five years of age. The male to female ratio of the HIV-1 infection is 1:1.

Maternal HIV-1 infection has far reaching effects on health. In the general population, the effects range from loss of labor force to loss of a caregiver. In the pediatric age groups, the effects include increased pediatric AIDS, rising child mortality, and increase of orphans with all their attendant health problems. The Kenya Demographic Health Survey (KDHS) 1998 (2) shows that the mortality rates for women aged 20-34 years exceeded their mortality rates estimates of the 1989 census and suggests this could be explained by the recent deterioration in adult survival prospects due to the AIDS epidemic. That survey also shows a 33.3% increase in post-neonatal and child mortality (2). The trends in infant mortality rates and under-five mortality rates by KDHS 1993 (3) and 1998 showed there was a steady improvement (decline) through the early 1980s, a plateauing in the mid 80s and then a remarkable rise during the period between early and mid 1990s; infant mortality rates were 69 in 1978-82, 63 in 1983-87, 62 in 1988-93 and 73.7 in 1994-98 with corresponding child mortality "first birth day to fifth birthday" of 35, 28, 37 and 40.8 respectively (2,3). The rise in Infant Mortality Rate (IMR) and Child Mortality Rate (CMR) has been attributed to HIV and the rise is most accentuated in parts of Kenya where HIV-I is very prevalent.

Over the last decade or so, the approach to pediatric AIDS has focussed on prevention/reduction of infection. Use of anti-retroviral drugs together with breast-feeding substitutes has almost eradicated MTCT of HIV in developed countries (4). In developed countries, short course ARV drug therapies have been found to be 38-50% effective in preventing MTCT of HIV in breast-feeding populations. Although these interventions are effective, their widespread application is limited by unavailability of financial resources and technical knowledge. Therefore many children continue to be infected with HIV.

The relationship between the course of HIV infection in the person who transmits the virus and the course in the person who becomes infected is difficult to establish in the case of sexual transmission. This relation has been studied, however, in cases of transmission by blood transfusion in adults. Mother-infant transmission is another instance in which this type of correlation can be established. The evolution of HIV infection to AIDS acquired by vertical transmission is more rapid in children than the evolution of the disease in the adults who have different modes of HIV acquisition. Most adult HIV literature indicates the median survival with HIV infection is 8-10 years. Rouzioux C. et al found mean survival ranges of 75 to 90 months with only 70% of French HIV-1 infected children reaching age 6 years, and 15 to 20% dying within the first three years of life before introduction of anti-retroviral drug therapy. The findings were consistent with an earlier report that documented a survival rate of 48% at 3 year.

It has been postulated that those acquiring the disease by vertical transmission early in foetal life constitute the early mortality group. Those who acquire the disease close to

birth constitute the late mortality group. There is a direct relationship between the severity of maternal illness as measured by low CD4 cell counts, rapidly declining CD4 cell count or elevated plasma viral material load and the risk that the child will acquire opportunistic infections and die in the early years of life (6,7). The viral load is probably the factor that best predicts the course of infection but a linear relation cannot be established between it and the risk of progression. Low CD4 cell count or rapid decline in CD4 cell count is associated with rapid disease progression (7). In Zimbabwe, Katzenstein et al found that, a tenfold incremental increases in maternal HIV RNA were associated with a 2.1-fold increase in infant mortality. In addition maternal CD_4 cell count below the median ($400/mm^3$) were significantly associated with infant mortality (8). In resource – poor settings, viral load and CD4 cell count estimation is not feasible. It is therefore important to describe the clinical predicator of the disease progression that would guide the care of HIV infection children.

The median duration of survival in rapidly progressing and slowly progressing disease were 4.1 months and 6.1 years in developed countries before the advent of anti-retroviral therapy. Data on the natural history of HIV-I infection in children followed prospectively from birth to death is scarce in developing countries. Available reports show a high variability in mortality and morbidity indicators according to the study setting and a probable bimodal evolution of pediatric HIV disease.

Bobat et al, in a South African cohort, noted that mortality among children with vertically acquired HIV infection is high in the first year of life (9). Within 26 months of follow up, the mortality of the infected children was 35.4%, with 76% of the deaths occurring in the first year. The mean age at death of HIV-related cases was 10.1

months, with 83%of HIV-related deaths occurring before the age of 10 months. A combination of diarrhea, pneumonia, failure to thrive and neurological abnormalities often presaged rapid deterioration and death (10). However, that was only for the vertically infected and did not include postnatally infected children. Taha et al, in Malawi, followed children who had survived beyond one year to three years of age. In that cohort, cumulative survival of the HIV infected to 24 months was 70%, and survival to 36 months was 55% while by 32months of age none of the severely immunosuppressed (CD4 cell count %< 15) children was alive. Wasting and respiratory conditions were the major causes of mortality (11).

Spira R. et al, in a prospective cohort study in Kigali, Rwanda, reported a bimodal evolution of HIV-1 pediatric disease, as in industrialized countries, but a poorer prognosis in the developing African country (12). The estimated risks of death of the infected children at 2 and 5 years were 45% and 62% respectively. Among the risk factors of death were failure to thrive and generalized lymphadenopathy. Notably, there were no specific combinations of clinical manifestations associated with differences in survival and biologically, neither the maternal CD4 cell count at day 15 nor the child's CD4/CD8 ratio at six months of age was predictive of death.

It has been observed that even in studies to reduce MTCT of the HIV, the mortality of HIV-1 exposed but not infected children is high. For example, in a randomized clinical trial in Nairobi, Kenya, evaluating the effect of breast-feeding and formula feeding on postnatal transmission of HIV-1, "infants assigned to breast feeding and formula feeding arms had similar mortality rates through their first 24 months of 24.4% (95% CI 18.2%-30.7%) in the breastfeeding arm and of 20.0% (95 CI 14.4%-

25.6%) in the formula feeding arm (P= .30). There was a non-statistically significant increase in mortality in the formula arm during the first 6 weeks, 1.0% breastfed vs 3.9%formula-fed, P=0.06) when infants may be at a particular risk of serious infectious disease morbidity." (13). However, the 24-months mortality rates were much higher than those for Nairobi population were as a whole, reported as 4.1% in 1998, but similar to those seen in other cohorts of children of HIV-1 infected women in Africa. Whether formula feeding influences the survival of the child beyond 1year of life would be interesting to know for public health reasons.

Lepage et al summarized the findings of an international working group on MTCT on the care for HIV-1 infected children in developing countries (14). Among the findings were that the rates of morbidity and mortality were generally higher than in industrialized countries and prognostic studies were not available. Listed among research priorities was long-term observational cohort study.

From 1986, a collaborating team of researchers from the University of Nairobi and the University of Manitoba, Canada has been conducting a prospective cohort study on the natural history of mother-to-child transmission of HIV. This study found a MTCT rate of 38% (15). Further studies based on this data have shown that CD4 cell counts of HIV-1 perinatally infected children had distinguishable differences in lymphocyte subset percentages by three months of age mean CD4+% was 29.4% (5^{th} to 95^{th} %tile 27.2-31.6%) for infected versus 35.0% (32.3-37.7%) for uninfected and 39.4% (37.2-41.8%) for control children $p<0.001$.Differences between uninfected and control children disappeared after one year of age (16). The pattern of infectious diseases in infected and uninfected exposed children has been similar.

Objectives

The overall goal of this project is to describe the factors associated with survival of HIV-1 infected children to ≤3 years.

Specific Aims:

1. Describe the survival pattern of HIV-1 infected children born in Nairobi, between January-1992 and December-1997.
2. Determine demographic and clinical correlates of HIV-1 infected children who succumb before 3 years of age.

Study Justification.

Adult natural history studies of HIV have identified a sub-category of individuals with a slow disease progression without treatment. Similarly, among HIV-1 infected children survival to > 3 years is considered to be long-term survival. As seen in the literature review above, achieving the age of 3 years seems to be widely accepted as an indication of better survival (although this maybe an arbitrary cut off point). Identification of clinical factors associated with rapid progression may help in prioritization of intervention such as initiating anti-retroviral therapy or prophylaxis for opportunistic infections. From 1986, a collaborating team of researchers from the University of Nairobi and the University of Manitoba, Canada has been conducting a prospective cohort study on the natural history of mother-to-child transmission of HIV. We have observed that there are HIV infected children who die very early and others who survive beyond their third birthday. We would like to determine the clinical factors associated with short-term ("less than 3 years of life") survival in this population.

METHODOLOGY

Study design

Retrospective nested case control study.

Study population

The study population includes mothers and children who were recruited in the MCH pediatric AIDS study, from January 1992 to December 1997.

Cases: HIV-1infected (HIV-DNA PCR positive within 6 weeks of delivery) children dying before the age of three years of life.

Controls: HIV-1 Infected (HIV-DNA PCR positive within 6 weeks of delivery) children who lived to their third birthday and beyond.

Exclusion criteria:

Subsequent children and second twin are excluded from the analysis.

Recruitment/selection

From 1992 to December 1997 samples of maternal and cord blood of women who came to deliver at Pumwani Maternity Hospital were collected screened for HIV-1 antibodies on the day of delivery after obtaining informed consent for HIV testing. On the day after delivery, post-test counseling was carried out. Women with positive screening tests and randomly selected seronegative women were approached and asked to participate in the study along with their newborn infants. At that point a written consent was obtained. All the mother/child pairs HIV-1 DNA-PCR positive within six weeks of delivery were selected for this study.

For women enrolled in the study, maternal HIV-1 serological status was subsequently confirmed with repeated EIA testing and immunoblot. At enrollment, the women were interviewed to determine their demographic characteristics and clinical data of the index pregnancy. The delivery records were reviewed and data on labor, delivery and maternal problem during pregnancy and maternal illness were abstracted.

The baby was evaluated using standardized instruments for weight, length and head circumference at birth. The infant outcome (alive or stillbirth), maturity and clinical status were determined.

Study area

Subjects were recruited at Pumwani Maternity Hospital. This Hospital is located on the East side of the city in a low-income area and primarily serves this community. It also serves as the referral center for high-risk mothers identified in the different Nairobi city council clinics. It is the largest maternity hospital in Kenya with about 25,000 deliveries per year.

Laboratory specimen collection and evaluation

From each mother and each infant at already scheduled visit, five milliliters of blood were collected. For each sample, complete blood count as well as CD_4 and CD_8 cell counts and ELISA were done immediately while some blood sample portions were stored for later analysis for HIV-1 using PCR techniques. For HIV-1 serologic testing, an enzyme-linked immunosorbent assay (ELISA) (Behring, Ausgabe, Germany) was used for screening and a second ELISA (Cambridge, Biotec, Rockville, Md) for confirmation. The CD4 and CD8 cell counts were determined using monoclonal antibodies (Becton Dickinson, Erembodegem-Aalst, Belgium) and flow cytometry.

Peripheral blood monocytes were harvested for HIV-1 PCR testing. Standard HIV-1 DNA PCR (an in-house PCR in Manitoba) testing was done on infant samples using *vif, nef* and *env* primers.

The mother- infant pairs were not always seen on scheduled dates. Nevertheless data at time of birth was within 24 hours of delivery; at 6 weeks measurements were taken between 34 to 48 days of age; at 3 months' measurements were taken between a week before or after age of 3months. Subsequent measurements were between 2 weeks before or after the reference age. The women were assessed for STDs within 2 weeks of delivery for gonorrhoea (GC), Group-B streptococci (by culture and microscopy), Chlamydia (by antigen testing), and Syphilis by RPR screening.

Follow up process.

Mothers were requested to bring their children to the research clinic when the infant was two weeks old. Thereafter, mothers and children were seen at monthly intervals until 6months of age, then three monthly until 3years of age, then 6 monthly until 5years of age and then yearly thereafter. At the initial clinic visit, the mothers were informed of their HIV-1 serology results and counseled. Women were counseled to breast-feed according to the existing World Health Organization infant feeding guidelines and Ministry of Health policy at the time of enrollment. Neither children nor mothers received specific antiretroviral therapy.

At every scheduled visit, a standard questionnaire was administered to collect data on medical problems experienced since the last visit. A physical examination was carried out. Weight (Kg) was taken on a sit on (for children less than 2years) and stand on

(for those older than 2 years) electronic Seca scale; length (cm) lying on a stadiometer (for children less than 2years) and standing for those older than 2 years were taken.

Not all mothers were constant residents of Nairobi; some had travelled from the rural homes (upcountry) to join their husbands for delivery. All mothers and their children had free well-child and sick child (out-patient) care which included: growth monitoring, review of nutritional problems, diagnosis of illness and provision of necessary medications, immunizations, antihelminths therapy every 6 months after 1 year of age. Vitamin supplements were provided on clinical grounds. Malaria prophylaxis was provided if participants were to travel to malaria endemic areas.

Mortality

The participating women were encouraged to come and report any adverse events. Death of a child was recorded as reported to the research clinic. The date of death, the interval from the last follow-up to time of death, and health events one month before death were recorded. The researchers sought to establish the circumstances preceding death including type and duration of illness. The cause of death was recorded either as AIDS, AIDS-related, other or unknown, as documented in the institution records of death or as perceived by the clinic doctor (for the duration 1992-1997 in this analysis, the investigator) in case of no medical documentation.

The investigator worked in the research clinic for the duration of study as the project doctor. The responsibilities included attending to the clients medical problems, examining the clients, collecting specimens and collecting the clinical data on the research questionnaire as well as the day-to day administration of the research clinic

activities. A trained nurse counsellor administered the immunizations to the infants, dispensed drugs and in conjunction with the doctor conducted counselling to the clients. The socio-demographic information was collected by a social scientist in conjunction with a data clerk.

Data Management and Analysis

For the main study, all data was entered using file manager upto 1994 and from then to date using paradox file. For this analysis, data was transformed into computer SPSS file. The investigator abstracted data collected on mothers' Social demographic characteristics and immune status at delivery (CD4, CD8 cell count absolute).

Data on the child's social demographic characteristics, birth weights, completeness of immunizations, and serial Total WBC and CD4/CD8 cell count was also abstracted. Data was analyzed to describe pattern of mortality and to determine the correlates of survival. Measures of central tendency and dispersion were used to describe the cohorts and Chi-square tests and *t*-tests were used to examine differences between means. The program EPI-INFO was used for the calculation of Relative Risk (RR), 95% Confidence Interval (CI) and P Value.

Children who died before 3 years of age were compared to those who survived to ≥ 3 years to determine maternal and infant characteristics that were predictive of early mortality at birth, 6 weeks, and six months postnatal life.

We used National Center for Health Statistics (NHCS) charts (10) to assess growth patterns. NHCS charts are representative of a population of well-nourished and healthy children in the United States. Although this population is dissimilar to much of the rest of the world, the NHCS charts have been accepted by the W.H.O as the

international standards of growth for the first five years of life. Disparities between the developed and developing countries reflect nutritional rather than genetic differences (17).

Sample size

The sample size was calculated using Epi-Info version 6.0.

To have 80% power and 5% significance level, assuming

1. Lowest mortality of 15% at three years (5) of age and
2. Highest mortality of 54% at three years of age (12)

The sample size was N=54, 27 cases and 27 controls.

Following infection by vertical transmission, the children's mortality rate is variable over time. Rouzioux C. et al (5) found a mortality rate of 15 to 20% within the first three years of life among European children vertically infected by HIV-1. Blanche S. et al, (6) demonstrated bimodal pattern of mortality with a rate of survival at 3 years of 48% in children whose disease progressed rapidly (early mortality group) and a rate of survival beyond 3 years of 97%in those whose disease progresses slowly (late mortality group). Spira R. et al (12), reported estimated risk of death of the infected children at 2 and 5 years were 45% and 62% respectively in a prospective cohort study in Kigali, Rwanda. Assuming uniform distribution of mortality between 2 and 5 years (9% increments per year) the total mortality at 3 years would have been 54% in the Rwanda cohort. She also reported a bimodal evolution of HIV-1 pediatric disease, as in industrialized countries, but a poorer prognosis in the developing African country.

Ethical considerations:

Approval to carry out this retrospective sub-study was granted by the department of paediatrics. The approval to carry out the parent study "Perinatal transmission of HIV-1 Impact of infection on maternal and child health and social economic well being of the family" was granted by the Ethical Committee of the Kenyatta National Hospital in 1992.

RESULTS

Characteristics of the study population.

In our cohort study, there were 77 mother-child HIV-1 positive sets who participated in the study between January 1992 and December 2000. The subjects were a subset of children drawn from "Perinatal transmission of HIV-1 Impact of infection on maternal and child health and social economic well being of the family", a University of Nairobi prospective cohort study in Pumwani Maternity Hospital, Nairobi, Kenya. All the children were HIV positive on HIV-DNA PCR testing.

The median age of the 77 mothers was 22 years (range 16 to 35 years), while teenage mothers were 27% and none of the women was over 35 years. The marital status, gestational age at the start of antenatal care and clinical problems experienced during the pregnancy were as shown below.

Table 1: Characteristics of all the women

Marital status	Married	75%
	Single	22%
	Divorced or separated	3%
Gestation at starting of antenatal care	First trimester	4.4%
	Second trimester	67.5%
	Third trimester	19.1%
Reported Problems which occurred during pregnancy	Fever of >one month	22%
	Hospitalization	18.6%
	Genital discharges/ulcers	13%
	Diarrhea of ≥one month	7.8%
	Pneumonia	1.5%
	Persistent bleeding	1.4%

The women had a median number of lifetime sex partners of 2 (range 1-99). Only one woman reported prostitution and she had 99 partners in the past. The median gestation at initiation of prenatal care was 5 months (range 1-9 months). Nine percent of the women did not receive any care during the pregnancy under review. Majority of the women (78%) had experienced no problem that made them seek medical attention during pregnancy. In all 51.5% reported general malaise/asthenia during pregnancy for which they did not seek medical care or self-medicate.

Characteristics at delivery

The parity of the mothers was generally low, with para 4 and less contributing 81.1%, (median parity=1, Range 0 to 6) of the population, and primigravidas 34.3% of the total population. There was a frequent history of poor pregnancy outcome in this population with 22.5% of the mothers reporting a prior prenatal death, stillbirth or abortion. The gestational age at delivery (as calculated from the mothers last menstrual period), the duration of labor and the duration between rapture of membranes (ROM) to delivery were as below.

Table 2: Characteristics at delivery

Characteristic N=77	Median	Range(min max)
Gestation (weeks) 69	39	16 (28 to 44)
Duration of labor(hr) 63	9	24 (<1 to 24)
Duration of ROM(hr) 63	1	24 (<1 to 24)

Most of the deliveries were at term (39weeks), without prolonged labor (9hours) or prolonged rapture of membranes (1 hour). The median duration of labour was 9 hours (range less than 1-24) while the median duration of rapture of membranes was 1 hour (range less than 1-24). Ninety-eight percent of the mothers had a vaginal delivery. Episiotomy was performed on 19.4% of all women and Caeserian-section was done on 1.5%. All the Caeserian sections were for emergency indications.

Postnatal period

The immune status (by CD4 levels) within 6 weeks of delivery was done on 43 (86.7%) of the 52 mothers with complete follow-up data. Twenty (46.5%) of the 43 women had CD4 cell counts of more than 500/ml, and 46.5%(20) had between 200-499/ml; and 7%(3) had less than 200/ml. The median CD4 cell count was 464/ml (range70-1051).

Sexually transmitted disease (STD) infections

The mothers were screened for sexually transmitted infections within two weeks of delivery. The prevalence of HIV-1 seropositivity in the parent cohort was 12.8%. The prevalence of STD infections as detected by laboratory testing of the 69 mothers in this study were as shown below.

Table 3: Prevalence of STD infections during postnatal period

Gonorrhea	6.3%
Group-B streptococci	5.9%
Chlamydia	3.2%
Syphilis	1.8%
Other STDs (excluding HIV)	11.4%

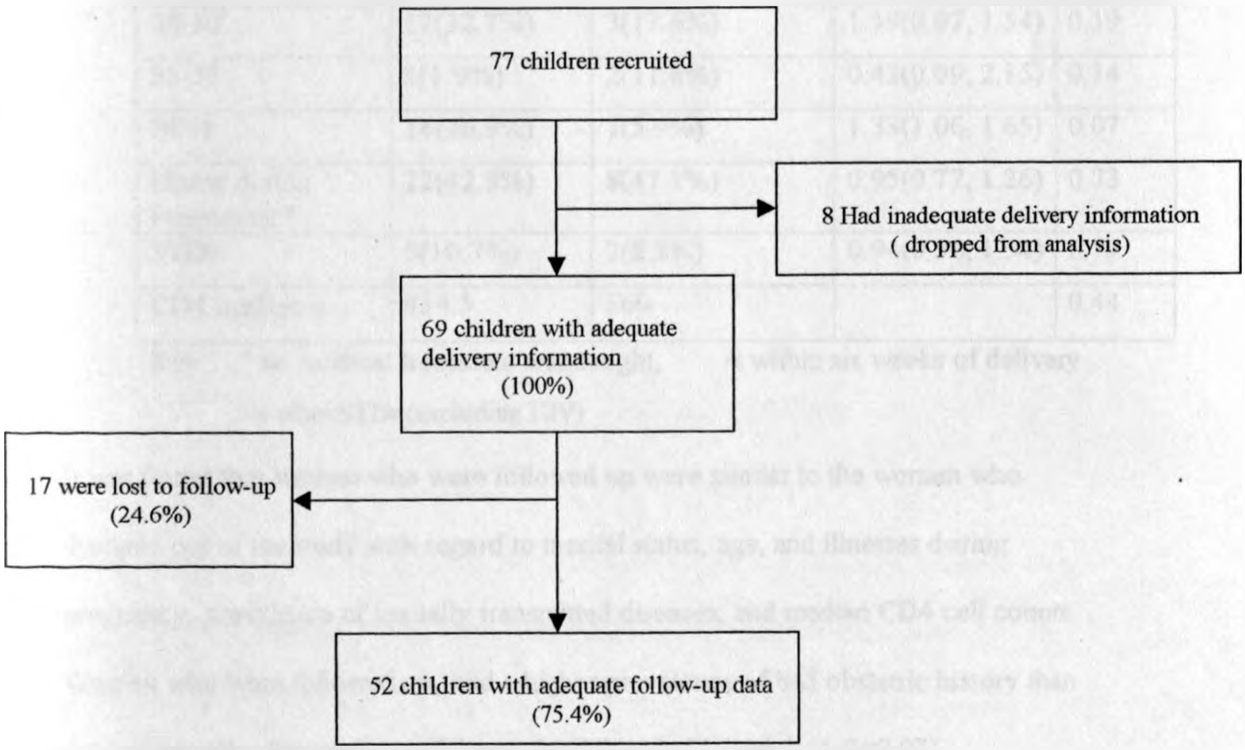
The prevalence of other STD (excluding HIV) was 11.4% (some mothers had more than one infection concurrently). The most frequent STD was gonorrhea (6.3%), while the least frequent was syphilis (1.8%).

Characteristics of the children

There were 77 HIV-1 positive children of whom 52.7% were females and 47.3% were males. There was one neonatal death (1.4%); and only one set of twins (first twin was taken for analysis). Gestational age was not determined by the Dubowitz scoring system but, according to their mothers last menstrual period, 48.2% of the infants were born at term 37-42 weeks, 41% post term >42 weeks, and 8.6% borderline premature (34-36 weeks). Only one mother delivered at less than 34 weeks, a baby that survived only two days.

For eight 8 children, the delivery information was inadequate, leaving 69 children with adequate delivery information; Seventeen children (22%) were lost to follow up (i.e. were not reported dead nor followed to the age of three years), leaving a total of 52 children with adequate follow-up data.

Figure 1: Follow-up diagram of the study.



Eleven of the 17 children (64.7%) were lost to follow-up in the first six months of life, 3 children (17.6%) were lost to follow-up between 6 and 12months and 3 children (17.6%) were lost to follow-up after 12 months of age. The main reason for loss to follow-up was movement from the city back to the rural home.

With regard to socio-demographic and bad obstetric data, a comparison of the 17 who dropped out and the 52 mothers who were followed up was made.

Table 4: Comparison of mothers followed up and those lost to follow up.

	On follow-up N=52	**Lost to follow-up N=17**	**Relative risk (95% CI)**	**P Value**
Marital status				
Single	10(19.2%)	5(29.4%)	0.36(0.58, 1.26)	0.3
Married	40(76.9%)	12(70.6%)	1.09(0.77, 1.55)	0.4
Separated/divorced	2(3.8%)	-	1.34(1.17, 1.54)	0.5
Age in years				
<20	16(30.8%)	8(47.1%)	0.83(0.61, 1.65)	0.2
20-24	18(34.6%)	4(23.5%)	1.13(0.87, 1.47)	0.39
25-30	17(32.7%)	3(17.6%)	1.19(0.97, 1.54)	0.19
31-35	1(1.9%)	2(11.8%)	0.43(0.09, 2.15)	0.14
BOH	14(26.9%)	1(5.9%)	1.33(1.06, 1.65)	0.07
Illness during Pregnancy *	22(42.3%)	8(47.1%)	0.95(0.77, 1.26)	0.73
STD+	5(10.7%)	2(8.3%)	0.94(0.58, 1.54)	0.79
CD4 median α	434.5	560		0.44

Key: * no medical treatment was sought, α within six weeks of delivery

+ other STDs (excluding HIV)

It was found that women who were followed up were similar to the women who dropped out of the study with regard to marital status, age, and illnesses during pregnancy, prevalence of sexually transmitted diseases, and median CD4 cell counts. Women who were followed up, had a higher prevalence of bad obstetric history than the women who dropped out of the study (RR1.33, CI 1.06-1.65 P=0.07).

Mortality data

Among the 69 children, 52 children (75.4%) had good follow-up data and 17 children (24.6%) were lost to follow-up. The median survival time was 1585 days (4.3 years), standard error of 440 days (1.2 years), and 95% confidence 723 to 2447 days (2 to 6.7 years).

Of the 52 children with follow-up data, 28(53.8%) died before 3 years of age. The cumulative mortality was 28.8% at 1 year and 44% at 2 years. Fifty-four percent of all deaths were in the first year of life; 7(25%) died in their first 6 months of life, 8(28.6%) in the ages 6-12 months, 8(28.6%) in their second year of life and 3(17.3%) in their third year of life. Twenty-four children (46.2%) survived to the age of ≥ 3 years. The median survival of the 52 children on follow-up is 994 days (2.7 years). This data implies that the sicker children remained on follow-up.

Figure 2: Survival curve of the study cohort

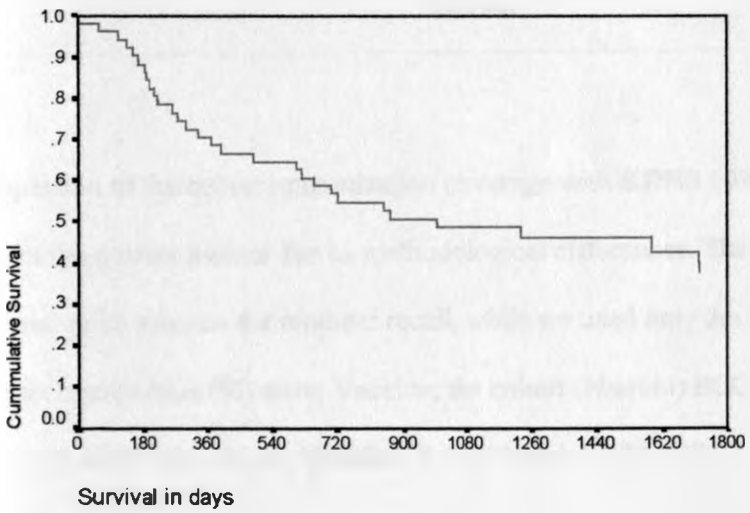
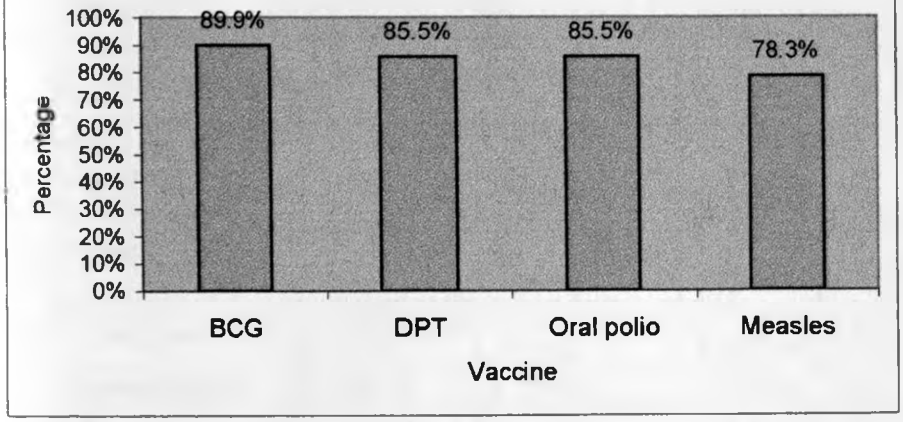


Figure 2 is the survival curve of the 52 children with adequate follow-up. There were many deaths in the first 180 days (1.5years) of life. We have plotted survival in days to avoid data loss that would occur when one expresses the survival in months. This gives a clearer picture of the death pattern of these children.

Vaccinations

In the research clinic, the children were provided with their primary health care, which included primary immunizations with BCG, DPT, Oral POLIO and Measles according to Kenya expanded program of immunizations. In all, 78% of the children were fully vaccinated.

Figure 3: Immunization coverage rates of the study population



Comparison of the cohort immunization coverage with KDHS 1998 figures may not present the correct picture due to methodological differences. The KDHS used the card and in its absence the mothers recall, while we used only the card. Nevertheless the vaccination rates (%) were: Vaccine; the cohort (Nairobi) BCG; 89.9 (97.7), Polio 85.5 (75), DPT 85.5 (86.4), Measles 78.3 (93) and All 78.3 (72.7).

Clinical characteristics of the children

In all, there were 28 female children and 24 males who were followed up. The male to female ratio was 1:1.1. Children who died before 3 years of age were compared to those who survived to 3 years and beyond with regard to the maternal demographic and obstetrical characteristics during the index pregnancy and mother's immune-status at delivery.

Table 5: Comparison between children who died under 3 years and those who to survived to 3 years and beyond.

	Died at < 3 years N = 28	Survived to ≥ 3 years N = 24	Relative risk (95% CI)	P Value
Maternal characteristics				
Mother is married	20 (71%)	20 (83%)	0.75 (0.45, 1.24)	0.3
Age in years				
< 20	9 (32%)	7 (29%)	0.83 (0.61, 1.65)	0.2
20-24	9 (32%)	9 (38%)	1.13 (0.87, 1.47)	0.39
≥ 25	10 (36%)	8 (33%)	1.59 (0.89, 1.84)	0.17
Bad obstetric history	19 (68%)	19 (79%)	0.78 (0.47, 1.29)	0.3
General malaise/asthenia in pregnancy*	12 (43%)	18 (75%)	0.55 (0.33, 0.91)	0.02
STD+	3 (11%)	2 (8%)	1.13 (0.89, 2.42)	0.8
Median CD4	409	409		
Infant characteristics				
Female baby	18 (64%)	10 (50%)	1.54 (0.89, 2.67)	0.2
Birth weight < 2500gms	8 (9%)	1 (4%)	1.19 (1.29, 2.84)	0.02
Orphaned	7 (25%)	3 (12%)	1.4 (0.84, 2.3)	0.2
Immunization				
BCG	25 (89%)	20 (83%)	1.30 (0.53, 3.57)	0.5
Polio	23 (82%)	19 (79%)	1.10 (0.56, 2.16)	0.8
DPT (any)	6 (21%)	5 (21%)	1.02 (0.55, 1.87)	1.0
Measles+	12 (75%)	18 (78%)	0.55 (0.33, 0.91)	0.8

Key: * no medical treatment was sort, + < 3yrs n = 16, ≥ 3 years n = 23
+ other STDs (excluding HIV)

Maternal characteristics; age, parity, marital status, and immune-status at delivery as assessed by CD4 cell count at 6weeks after delivery were similar in the two groups of

children, those who died before three years of age and those who survived to 3years and beyond

Ten (19.2%) of the 52 children were orphans, the male to female ratio and prevalence of orphans was comparable in the two groups of children. The children who died before age of 3 years had a significantly higher likelihood of having been born with low birth weight. Eight (9%) of the 28 children who died before 3 years had a birth weight of <2500gms compared to 1 (4.1%) of 24 children who survived to and beyond 3years (RR=1.19 95% CI 1.29-2.84, P=0.02). Vaccine completion rates were similar in the two groups of children, those who died before three years of age and those surviving to 3years and beyond

Characteristics of the children on scheduled visits

We then examined the infant characteristics at six weeks of life and six months of life to determine whether there are any factors predictive of early mortality or survival to 3 years of age and beyond. The children were compared with regards to whether they ever had symptoms of fever, cough, diarrhoea, rash or signs of otitis media, lymph node enlargement, hepato/splenomegaly, and URTI. Oral thrush and mouth ulcers were grouped together.None of the children developed parotitis, and hence it is not included in the analysis

Table 6: Characteristics of the infants at six weeks of age

	Died at < 3 years N = 23	Survived to ≥ 3 years N = 11	Relative risk (95% CI)	P Value
Sign				
Fever	8 (34.8%)	5 (45.5%)	0.86 (0.52, 1.43)	0.55
Cough	10 (43.5%)	2 (28.2%)	1.41 (0 .92, 2.17)	0.1
Diarrhea	6 (26.1%)	0 (0%)	1.65 (1.22, 2.22)	0.06
M/rash	1 (4.3%)	1 (9.1%)	0.73 (0.18, 2.97)	0.6
Thrush	4 (26.4%)	0 (0%)	1.58 (1.2, 2.07)	0.14
Otitis	1 (4.4%)	1 (9.1%)	0.7 (0.18, 2.97)	1
Lymphnodes	7 (34.4%)	2 (9.1%)	1.22 (0.77, 1.92)	0.7
H/S megaly	5 (21.7%)	1 (9.1%)	1.30 (0.8, 2.8)	0.4
URTI	1 (4.3%)	0 (0%)	1.50 (1.2, 1.9)	1

Key: Diarrhea = ≥3 loose stools persistent/recurrent in a day for two or more weeks, Fever = >37.5°c, URTI=upper respiratory tract infection
M/p rash = maculo-papular rash, H/S = Hepato-splenomegally

At the age of 6 weeks 34 children were seen (i.e 18 children did not turn up on schedule for the 6 weeks visit). Twenty-three of these died before 3 years age and 11 survived to and beyond 3 years of age. Reported were fever in 13 children (38.2%), cough in 12 children (35.3%), diarrhoea in 6 children (17.6%) and rash in 2 children (5.9%). The prevalence of these conditions was similar in the children who died before age three compared to those who survived to reach 3 years and beyond except for diarrhoea. All the 6 cases of diarrhoea reported at 6 weeks were in children who died before the age of 3 years. Children who died before 3 years of life had an increased risk of diarrhoeal disease of RR 1.6 (95% CI 1.22-2.22), thrush RR 1.58(95% CI 1.2-2.07) and an increased risk of upper respiratory tract infections RR1.50(95% CI 1.2-1.9).

Characteristics of the infants of 6 months of age

At the age of 6 months, 27 children were seen (7 children had already died while 18 children failed to turn up on schedule). 17 of these died before 3 years age and 10 survived to age 3 years and beyond. The findings obtained at the age of 6 months were similar to those obtained when the children were aged six weeks.

Table 7: Characteristics of the infants of six months of age

	Died at < 3 years N = 17	Survived to ≥ 3 years N = 10	Relative risk (95% CI)	P Value
Sign				
Fever	5 (29.4%)	4 (40%)	0.83 (0.43, 1.63)	0.6
Cough	8 (47.1%)	4 (40%)	1.2 (0.63, 1.97)	0.7
Diarrhea	7 (41.2%)	0 (0%)	2 (1.29, 3.10)	0.02
M/p rash	3 (17.6%)	0 (0%)	1.71 (1.22, 2.40)	0.2
Thrush	0 (0%)	0 (0%)		
Otitis	1 (0.06%)	0 (0%)	1.75 (1.27, 2.4)	0.4
Lymph nodes	8 (53.3%)	2 (25%)	1.49 (0.82, 2.68)	0.2
H/S megally	6 (40%)	2 (25%)	1.25 (0.70, 2.22)	0.5
URTI	3 (17.6%)	1 (10%)	1.23 (0.64, 2.37)	0.6

Key: Diarrhea = ≥3 loose stools persistent/recurrent in a day for two or more weeks, Fever = >37.5°c, URTI=upper respiratory tract infection
M/p rash = maculo-papular rash, H/S = Hepato-splenomegally

The children who died before the age of 3 years compared to the children who survived had a significantly higher likelihood of diarrhoeal disease RR 2 (95% CI 1.29-3.10), maculo-papular rash RR 1.7 (95% CI 1.22-2.40), otitis RR 1.75 (95% CI 1.27-2.4) and lymphadenopathy RR 1.49 (95% CI 1.82-2.68).

We then examined the incidence of the signs and symptoms to determine whether there are any differences in occurrence predictive of early mortality or survival to 3 years of age and beyond. The visits beyond three years of age were excluded so as to compare only the first three years of life.

Table 8: Comparison of the incidence of common signs and symptoms of Infection in children who died at<3 years compared to those who survived to ≥ 3 years

	Died at < 3 years	Survived ≥ 3years	Relative Risk (95% CI)	P Value
Number	28	24		
Follow-up months	388	864		
Fever	26 (101)	18.6 (161)	1.24 (1.1, 1.5)	0.02
Cough	32.7 (127)	18.9 (163)	1.41 (1.2, 1.7)	<0.000
Diarrhoea	17.8 (69)	10.5 (91)	1.39 (1.1, 1.7)	0.002
M/p rash	3.1 (12)	3.9 (34)	0.84 (0.5, 1.4)	0.5
Thrush	5.9 (23)	1.9 (16)	1.9 (1.9, 2.5)	0.0002
Otitis	4.1 (16)	2.9 (25)	1.26 (0.9, 1.9)	0.3
Lymph nodes	14.7 (57)	12.6 (109)	1.1 (0.9, 1.4)	0.4
H/s megally	16.5 (64)	13.4 (116)	1.2 (0.9, 1.4)	0.2

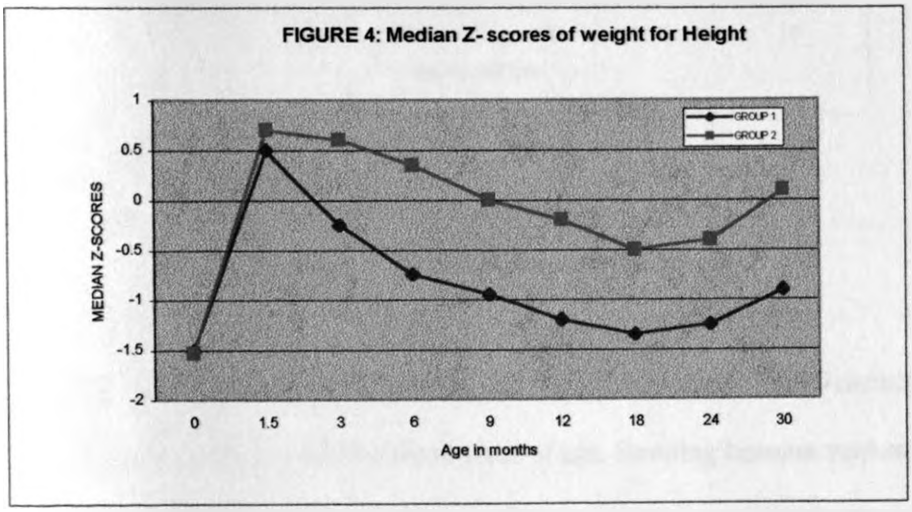
*Figures in parenthesis are actual number of events

Key: Diarrhea = ≥3 loose stools persistent/recurrent in a day for two or more weeks, Fever = >37.5°c, URTI=upper respiratory tract infection
M/p rash = maculo-papular rash, H/S = Hepato-splenomegally

Nutritional status

We carried out an in-depth analysis of the nutritional status of children who died before reaching the age of 3years and those who survived to reach 3 years of age and beyond. Using the National Center for Health Statistics (NHCS) charts, the median for the measures were used to assess growth patterns.

To compare the acute (wasting) nutritional status of the children who died before reaching the age of 3years and those who survived to reach 3 years of age and beyond, the median Z-scores of weight for height were plotted and the differences between the medians at different ages to check for significance of the differences.



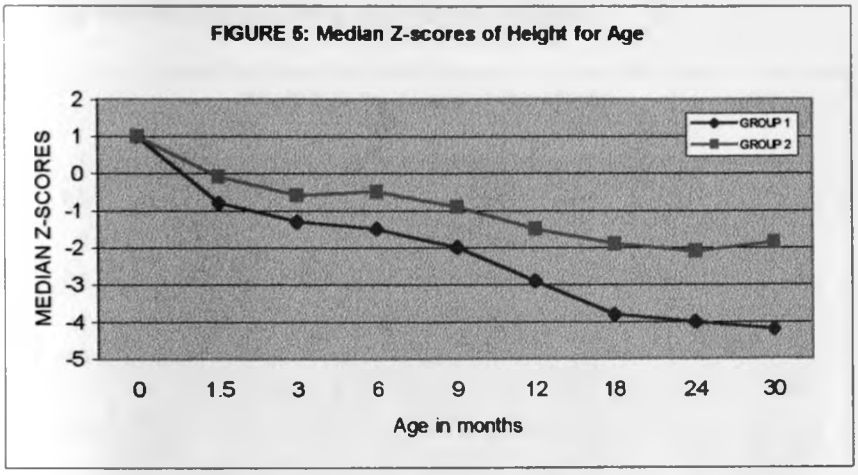
Key: Group 1= Children dying at < 3years

Group 2= Children surviving ≥ 3years.

The nutrition status in the two groups was similar at birth and at the age of 6 weeks. While none of the two groups had severe wasting (WHZ less than –2.0) the children who died before reaching the age of 3years were significantly more likely to be acutely malnourished (significant difference between the median weight for height Z scores **P= 0.027**) at six months of age than those who survived to reach 3 years of age and beyond.

To compare the chronic (stunting) nutritional status of the children who died before reaching the age of 3years and those who survived to reach 3 years of age and beyond, the median Z-scores of height for age were plotted and the difference between the medians at different ages to check for significance.

FIGURE 5: Median Z-scores of Height for Age

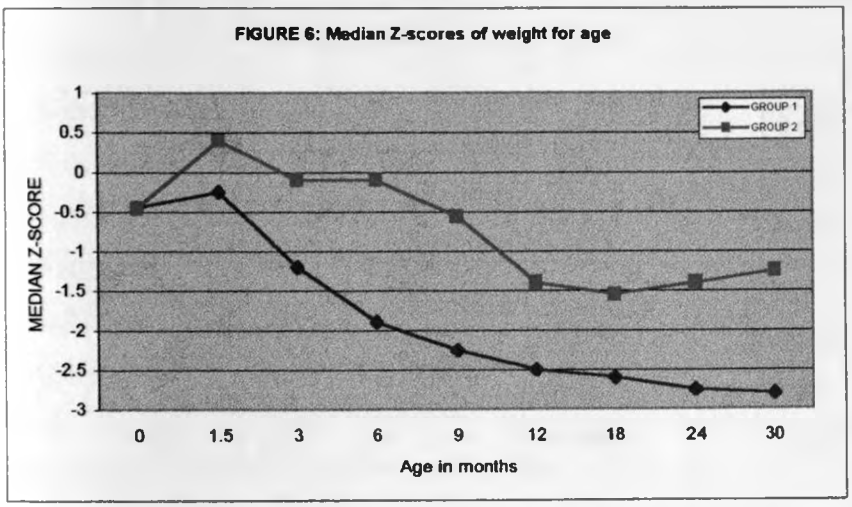


Key: Group 1= Children dying at < 3years
Group 2= Children surviving ≥ 3years

Stunting, as indicated by HAZ –score <-2.0, became apparent from 9 months of age in those who died before reaching three years of age. Stunting become evident at the age of one to one and a half years (and even then marginally so) in those who survived to reach 3 years of age and beyond. However the two groups were not statistically different at birth and at six weeks of age. However, at six months, children who died before reaching age of 3 years tended to be more stunted than those who survived to reach 3 years and beyond (HAZ –1.99 versus –0.9 p=0.075).

Weight for age is a composite index of weight for height (measure for acute nutritional status) and height for age (measure for chronic nutritional status). Though it does not differentiate between the two, it is a good overall indicator of the

nutritional status for a population. To compare the overall nutritional status of the children who died before reaching the age of 3years and those who survived to reach 3 years of age and beyond, the median Z-score of weight for age were plotted. The difference between the medians of the groups were found and compared to determine whether the two groups were significantly different.



Key: Group 1= Children dying at < 3years

Group 2= Children surviving ≥ 3years.

At 3 months of age children who died before reaching 3 years of age had a significantly lower WAZ compared to those who survived to reach three years (P value **0.010).** Under-weight, as indicated by WAZ- score < -2.0 was quite apparent from 6 months in all those children who die before reaching 3 years of age. Wasting of this magnitude did not occur in those children who survived to reach 3 years and beyond. At 6 months of age, children who died before reaching 3 years of age were significantly less well nourished than those who survived to reach 3 years of age and beyond in all measures of nutrition. There was a significantly lower WAZ score – 1,502 versus –0.055 (p=0.001).

Table 9 summarizes in tabular form the data that is plotted in figures 4,5 and 6. A comparison of the difference between the median Z scores and survival between the two groups of children at birth, at age 6 weeks and at age 6 months.

Table 9: Comparison of median Z scores and survival

	Survived to ≥ 3 years	Died at < 3 years	Difference	P value
BIRTH				
Weight for height	–1.314	-1.313	0.001	0.853
Height for age	1.045	0.99	0.035	0.301
Weight for age	-0.46	-0.46	0.001	0.484
6 WEEKS				
Weight for height	0.529	0.354	1.256	0.662
Height for age	-0.16	-0.073	0.093	0.584
Weight for age	0.213	-0.049	1.256	0.280
6 MONTHS				
Weight for height	-0.259	-0.631	0.990	**0.027**
Height for age	-0.9	-1.99	1.09	0.075
Weight for age	0.055	-1.502	1.447	**0.001**

The key finding is that children who died before 3 years of age had significantly lower WHZ and WAZ at 6 months of age.

DISCUSSION

There are limited reports on natural history of HIV-1 infection in African children. Most published data concerning pediatric HIV-1infection in developing countries have been either prospective studies that focused primarily on mother-to-child transmission with limited follow-up of the infected children or, non-prospective studies focusing on HIV-1 infected children while long-term observational cohort studies are few (14).

This study describes factors associated with death before 3 years of life (short-term) among breastfed HIV-1 infected children with no antiretroviral drug exposture.

This study confirms previous observations of high mortality among HIV infected children. Twenty-eight (53.8%) of the 52 children died before age 3 years. Studies among African HIV infected children have looked at different time points and used different selection criteria for the study participants. As an example, Taha studied children who had survived the first year of life (11). The South African study reports only 26 months of follow-up while the Rwanda study reports mortality at 2 years and 5 years (9,12). Nevertheless, the mortality reported from this study is similar to the findings of these three studies on HIV infected African children who had not been exposed to anti-retroviral drugs. Environmental factors may be important determinants of this high mortality in HIV infected children living in resource-poor settings. Jean et al compared mortality of HIV Haitian children living in Haiti and the United States. The mortality of the HIV infected children in Haiti was 60% in the first 6 months of life compared to 10% in those living in the United States (23). Other possible explanations for high mortality may be prevalent HIV subtypes or host characterisitics such as nutritional status.

The second key observation is on the timing of death. Of the 28 deaths described in this study, 15 (54%) were in the first year, 8 (28.6%) in the second year and 3 (17.3%) in the third year of life and overall cumulative mortality of 28.8% in the first year and 44% in the second year. The cumulative mortality before reaching 3 years of age was 53.8%. Our findings are similar to other studies. In the Rwanda study the cumulative mortality was 26% in the first year and 45% in the second year of life (12).

The third observation was that we were able to identify one maternal clinical factor associated with index child's death before 3 years of age. Infants of women who reported general malaise/asthenia that did not require hospital admission were more likely to die before the age of 3 years. We were unable to find in published literature of any study that correlated malaise/ asthenia to risk of death in HIV infected children. General malaise/asthenia may be a marker of advanced maternal HIV disease, a factor associated with increased likelihood of infant HIV disease progression and death (7). In a cohort study of disease progression among HIV infected women, patient report of general asthenia and general malaise was significantly associated with HIV disease progression to death. (Allen). Surprisingly, low maternal CD4 cell counts within 6 weeks of delivery was not associated with early death in the HIV infected child, contrary to the study by Blanche et al (7) who found low CD4 cell count and elevated maternal plasma viral load was associated with rapid disease progression in the child.

We were also able to identify clinical characteristics of HIV – 1 infected children who were more likely to die in the first 3 years of life. At delivery, a birth weight of less than 2500g was significantly associated with death before three years of life. Low

birth weight has been identified as a risk factor for HIV infection in babies. However, we did not find any study that had identified low birth weight as a risk factor for HIV disease progression in children. Low birth weight is a well described risk for early mortality among HIV uninfected children. The most frequent cause of low birth weight is maternal malnutrition leading to foetal malnutrition. Other causes of low birth weight are premature births that are frequently caused by sexually transmitted diseases in the mother. The low birth weight observed in our study could also be attributed to HIV infection.

In this study maternal nutritional status was not evaluated and we therefore can not say to what extent maternal malnutrition contributed to the low birth weight. We evaluated the mothers of babies in this study for sexually transmitted diseases (gonorrhoea, chlamydia, group B streptococci and syphilis) and found that the prevalence was similar in mothers of babies who died before 3 years compared to those who survived to $\geq$ 3 years of age. Therefore in this population of HIV infected children prematurity could not be attributed to maternal infection with STD's (gonorrhoea, chlamydia, group B streptococci and syphilis).

During follow-up, children who died before 3 years of age were more likely to experience illness excluding AIDS. In this population of breastfed infants, children who died before 3 years were significantly more likely to experience diarrhoea, thrush and upper respiratory infections in the first 6 weeks of life and at 6 months of life.

The findings of this study are consistent with findings of Blanche et al. (6) who followed 94 HIV infected children and assessed them for 4 clinical symptoms; infection by opportunities micro-organism, infection by bacteria, clinical signs of

encephalopathy and signs of interstitial preumonitis. They found that in the 56 (60%) of the children who developed at least one of these symptoms, mortality was 28.7% compared to 5% among those that did not develop any of the symptoms. Unlike our study, the symptomatic children were on routine co-trimoxazole prophylaxis and this may partly explain the differences in the magnitude of mortality.

We also found that children who died before 3 years of life were more likely to be wasted and stunted. A previous study on this cohort of children found the nutritional status of HIV unexposed, HIV exposed seronegative and HIV exposed seropositive children to be similar. Sherry B. et al (18) found them better nourished at I year of age than the general Kenyan children. All the mothers had extensive health education, nutritional counselling and free access to medical care for their children. However, there were more malnourished children in the second year of life with a trend towards higher prevalence of malnutrition among HIV infected children. Similar trends in nutritional status have been reported in HIV exposed breastfed and formula fed infants (24). These seem to emphasize on the effects of environmental factors to which the children are exposed

The causes of malnutrition in HIV infected children are multiple and inter-related. The HIV infection associated Imnuinosupression predisposes children to repeated infections. The infections and drugs use to treat them interfere with appetite and absorption of nutrients. HIV and co-morbidities also increase obligatory energy requirements that are fulfilled by increased body catabolism when nutrition intake is inadequate and thus further aggravating malnutrition. In addition, malnutrition independent of HIV infection causes immunosuppression, compounding the

malnutrition vicious cycle. The immune system, gastrointestinal tract function, malnutrition, and chronic or recurrent infections interact and contribute to the nutritional deficiencies, problems of growth and mortality in the HIV-1 infected children (21).

We postulate that these children who died before three years probably had a more marked immunosuppression leading to the increased frequency of infections as we have observed. The immunosuppression is probably related to the severity of HIV disease. Several studies have shown more rapid disease progression of HIV infected children of women with advanced disease. Although our measure of maternal health status was fairly non-specific, mothers of children who died before three years were more likely to report symptoms of general malaise/aesthesia.

Comparison our cohort mortality with KDHS 1998 figures (/1000 live births) would difficult due to our small sample size. However there were 1(1.92%) neonatal, 14 (26.92%) post neonatal and 15 (28.85%) infant mortalities.

Mortality	National	Nairobi	Our cohort (extrapolated)
Neonatal	28.4	19.5	19.2
Post neonatal (1-12mo)	45.3	21.6	269.2
Infant	73.7	41.1	288.5

Our mortality rate in the first of year is 14.6% which is similar to (9-16%) the rates reported in Brazil and in the western countries. Our study reveals higher rates at 2 years of age (31.5%), only comparable to the Brazilian rate 25-36% at 5years. The increased mortality in this study may be explained, at least partly, by non-existent anti-retroviral treatments in this cohort (this is the usual scenario in resource poor Africa), which have been widespread in industrialized countries. These therapies are

however usually initiated after the first year of life and thus increased mortality after one year are likely to reflect the lack of these therapies in the resource poor countries.

The findings of the study are not generalizable to all children in developing countries, but rather represent the best-case scenario. All the mothers had extensive health education, nutritional counseling and free access to medical care for their children. The children had an overall better vaccination rate than national average figure 3, KDHS (6).

The main weakness of this study is that the clinical course of HIV in children was not the primary objective of the parent study and therefore only limited clinical assessment was carried out for example we did not collect data on encephalopathy or routinely assess for conditions like lymphoid interstitial pneumanitis that have been correlated with survival of HIV infected children (7). The other weaknesses were the small sample size from a "select" population and loss to follow-up.

The strength of the study is prospective follow-up cohort study though analyzed retrospectively. Another strength was the ability to determine the childrens' status by six weeks using DNA-PCR. This technology is not available for routine use in Kenya. We were able to provide quality primary healthcare to the children. The results in this study may thus not be representative of the general population of HIV infected children.

Conclusion

We found that, African HIV-1 children infected perinatally or in the intrapartum period have high mortality rates 53.8% in the first three years of life. The bimodal pattern evolution of disease reported in other countries was not observed within the first three years of life.

The study revealed poor nutritional status as monitored by weight and height for age as predictor for early childhood death of HIV-1-infected children.

Recommendations

We recommend routine use of anti-retroviral therapy and enhanced nutritional support in HIV-1 infected children to reduce both early morbidity and mortality.

References

1. Joint United Nations Programme on HIV/AIDS and World Health Organization. Report on the Global HIV/AIDS Epidemic, June 2000. UNAIDS, World Health Organization; Geneva, Switzerland. 2000.

2. Kenya Demographic Health Survey 1998. Published by National Council for Population and Development, Central Bureau of Statistics, Demographic and Health Surveys, Macro International Inc. Chapter 10,90-93.

3. Kenya Demographic Health Survey 1993. Published by National Council for Population and Development, Central Bureau of Statistics, Demographic and Health Surveys, Macro International Inc. Chapter 10,83-85.

4. Coutsoudis A, Pillay K, Spooner E, et al. Influence of infant-feeding patterns on early mother-to-child transmission of HIV-1 in Durban, South Africa. Lancet. 1999; 354: 471-76.

5. Rouzioux C, Blanche S, Mayaux M. J, et al. Morbidity and mortalty in European children vertically infected by HIV-1. The French Pediatric HIV Infection Study Group and European Collaborative Study. J Acquir Immune Defic Syndr Hum Retrovirol. 1997; 14(5): 442-50.

6. Blanche S, Tardieu M, Duliege A., et al. Longitudinal study of 94 symptomatic infants with perinatally acquired HIV-1 infection. Evidence for a bimodal expression of clinical and biological symptoms. Am J Dis Child 1990; 144(11): 1210-5.

7. Blanche S, Mayaux M. J., Rouzioux C, et al. Relationship of the course of HIV-1 infected children to the severity of the disease in their mothers at delivery. N Engl J Med. 1994; (30):308-312

8. Katzenstein D. A., Mbizvo M., Maldonado Y., et al. Serum level of maternal human immunodeficiency virus (HIV) RNA, infant mortality, and vertical transmission of HIV in Zimbabwe. J Infect Dis 1999; 179(6): 1382-7.

9. Bobat R, Moodley D, Coutoudis A. et al. The early natural history of vertically transmitted HIV-1 infection in African children from Durban, South Africa. Annals of Tropical Paediatrics 1998; 18: 187-96.

10. Bobat R, Moodley D, Coovadia H, Coutoudis A. et al. Mortality in a cohort of children born to HIV-1 infected women from Durban, South Africa. S Afr Med J 1999 jun; 89 (6): 646-8.

11. Taha TE et al. Mortality after the first year of life among HIV-1 infected and uninfected children. Pediatr Infect Dis J, 1998; 18(8):689-94.

12. Spira R. et al. Natural History of HIV-1 Infection in Children: A Five-year Prospective Study in Rwanda. Pediatrics 1999; 104 (5): 56-70

13. Nduati R., John G., Mbori-Ngacha D. et al., Effect of Breastfeeding and Formula feeding on Transmission of HIV-I. A Randomized Clinical Trial. JAMA 2000; 283 (9): 1167-74.

14. Lepage P, Spira R, Kalibala S., et al. Care of HIV-1 infected children in developing countries. Report of a workshop for clinical research. Pediatr Infect Dis J.1998; 17:581-6.

15. Data P, Embree J, Kreiss J., et al Mother-to-Child HIV-1 transmission: Report from the Nairobi Study. J Infect Dis 1994; 170:1134-1140.

16. Embree J, Bwayo J, Plummer F. et al. Lymphocyte subsets in HIV-1 infected and uninfected children in Nairobi. (In Press).

17. Behrman, R.E., Kleigman, R. M., Arvin A.m., (Eds). Assessment of growth In: Nelson's Textbook of Pediatrics, 15th Edition; W. B. Saunders CO.; 1997: 63 -65 Philadelphia,U.S.A

18. Bettylou Sherry *et al* Socio-demographic characteristics, care, feeding practices, and growth of children born to HIV-1 infected and uninfected mothers in Nairobi. Kenya. Tropical Medicine and International Health 2000 **5**(10)678-686.

19. Jeanne B, et al. Estimating the time of Mother-to-Child Transmission of HIV-1 in a Breast-feeding Population in Kinshasa, Zaire. *The journal of infectious diseases* 1996 :174:722-6

20. Leroy V, Newell ML, Dabis F et al (1998) International multicentre pooled analysis of late postnatal mother-to-child transmission of HIV-1 infection, *Lancet* **352**, 597-600

21. Philip, A. P., Catherine, M. W., (Eds). Abnormalities in Growth and Development In: Pediatric AIDS, 2nd Edition; A. Waverly CO.; 1994: 575-586. Baltimore,U.S.A

22. Njenga S, Embree E.E, Plummer F. A, et al Excess Morbidity and Mortality in the uninfected children of HIV-1 infected mothers. IXth International Conference on AIDS. 1993; PO-B37-2382: Abstract. Berlin,Germany.

23. Jean S. S, Pape J. W, Verdier R. I, et al. The natural history of HIV-1infection in Haitian infants. Pediatr. Infect Dis J 1999;18(1):58-63

24. Mbori-Ngacha. D, Nduati R. W, Kreiss J. et al. Morbidity and Mortality in Breastfed and Formula-fed Infants of HIV-1 infected women .A Randomized Clinical Trial. JAMA 2001; 286 (19): 2413-20.

Appendix 1 **QUESTIONAIRE**

-Initial Maternal Evaluation-

ID #MCH _____

Date(day/month/year)___/___/____

___ Number of babies this delivery: 1=singleton 2=twins

___ Age(years):

___ Marital status: 1=single 2=divorced/separated 3=married

___ Gravida(#pregnancies, including present)

___ Para(# live births, excluding present)

___ Number of previous children who have died:___

Give age _____, cause _____ year _____

___ Number of still births(>20 weeks)

___ Number of miscarriages(<20 weeks)

___ Number of induced abortions

___ Gestational age in weeks (date of last period:___/__/___)

___ Number of sex partners/past 5 years

___ Curent or past prostitution: 0=no 1=yes

___ Month of pregnancy prenatal care began 0=no 1=yes

___ Significant medical problem or infections during pregnancy:__

0=none 1=hypertension 2=hypertension and infection 3=infection 4=other

___ Vaginal bleeding last trimester? Premature labour?(what month?___)

0=none

1= yes, bleeding 2=premature labour 3=both

___ History of medical problem? __ 0=no 1=yes

Symptoms during pregnancy

__ Fever>1 month: 0=no 1=yes (if yes, confirm that fever lasted for longer than 1 month)

__ Diarrhoea>1 month:0=no 1=yes (if yes, confirm that diarhoea lasted for longer than 1 month)

__ Pneumonia 0=no 1=yes if yes, describe:_____

__ Genital lesions: 0=none 1=vaginal discharge 2=genital ulcers

3=vaginal discharge+genital ulcers 4=others

<u>At delivery</u>

__ Hours from raptured memberanes to delivery:

__ Hours from onset of labour to delivery:

__ Problems during labour and delivery:0=none; 1=laceration;

2=episiotomy; 3=C-section; 4=other _____; 5=C-section +fever; 6=fever

__ Skin lesions 0=none; 1=maculopapular rash; 2=zoster with active lesions; 3=zoster scar; 4=1+2; 5=1+3; 6=2+3;

7=1,2+3; 8=other

__ Oral lesions 0=none; 1=thrush; 2=ulcers; 3=leukoplakia;

4=1+2; 5=1+3; 6=2+3; 7=1,2+3; 8=other

__ Extrainguinal lymphadenopathy: 0=none; 1=1 site; 2=2 or more sites

__ Inguinal Lymphadenopathy: 0=none; 1=1 site; 2=2 sites

__ Hepatosplenomegaly: 0=none; 1=hepatomegaly; 2=splenomegaly;

3=both

__ Kaposi's Sarcoma : 0=none; 1=skin; 2=mouth; 3=both

Comments

_____

_____

_____

Notes including other physical exam abnormalities and missing specimens

Neonatal Evaluation

ID # MCH _____

Date of birth (Day/Mo/Yr) __/__/__

Birthweight (gm) _____

__ Sex: _____ 1=male; 2=female; 3=ambiguous

__ Apgar: _____

__ Maturity rating: _____wks.

__ Did infant survive? 0=no; 1=yes

If no, please fill out mortality/lost to follow-up questionnaire

__ If yes, length of stay: _____

__ Did infant receive polio at birth? 0=no; 1=yes (code on ***immunization form)

__ Did infant receive BCG at birth? 0=no; 1=yes (code on *** immunization form)

Infant follow-up Evaluation

_____

ID Mother_____ Child code_____

Visit #_____ code visit number correlating with scheduled visit otherwise code US

Date (day/month/year) ___/___/____

_____Child is now 0 = dead, 1=alive (if not already done, fill mortality form concerning details of illness and death).

Since the child's last visit to the MCH clinic, has the child been

____Hospitalized? 0= no 1= yes

If yes how many times?_____(code number of times, 9=>9)

	Hospital	Date of admission	Reason
1.	_____	____/___/_____	_____
2.	_____	___/___/_____	_____
3.	_____	___/___/_____	_____

___ Visited a doctor or clinic other than MCH Clinic? 0=no 1=yes, Reason_____

____ Received oral medication? 0=no1=antipyretics 2=antibiotics+/-antipyretics, 3=other
5= deworm 4= chloroquine+/-antipyretics, 6=2+4

____ Received injections/infusions? 0=no1=vaccines 2=antibiotic 3=IVinfusions,4=other

If vaccines received at another clinic, record vaccine type and date

1. _____ _____/_____/_____

2. _____ _____/____/_____

3. _____ _____/___/_____

Does the child have now, or had since the last visit to this MCH clinic

_____ Fever? 0= no 1= yes, 2= yes documented

_____ Cough? 0= no 1= yes, 1= yes, documented

_____ Diarrhoea? 0= no 1= yes, 1= yes, documented

Physical Examination

Weight (gm) _____ Height (cm) _____ Head Circumference (cm)

_____ Temperature _____ degrees centigrade,
0=< 37.5 degrees centigrade 1>37.5 degrees centigrade

_____ Skin rash: 0=no 1=yes, describe_____

Mouth lesions: Mouth ulcers 0=no, 1= yes,
describe_____

Thrush: 0= no, 1= yes, describe
_____

_____ Lymphodenopathy: 0= no 1= 1 site 2=2 or more sites, describe

_____ Otitis media: 0=no 1=yes, acute, 2= yes, chronic, 3= yes, with draining

_____ Hepatosplesnomegaly: 0=no 1=hepatomegaly, 2= splenomegaly
3=other describe_____

_____ Upper Respiratory Signs: 0=no 1= cold, 2= cough,

3= other describe _____

_____ Gastroentritis: 0= no, 1= present 2= present with dehydration
3= present bloody, 4= 2+3 describe _____

_____ Parotitis: 0= no, 1= yes

Treatment antipyretic 0= no 1= oral antibiotics/antipyretics 2= topical therapy 3=
4= Other drugs 5= counselling only 6= hospital emergency
7= hospital clinic

Immunization _____

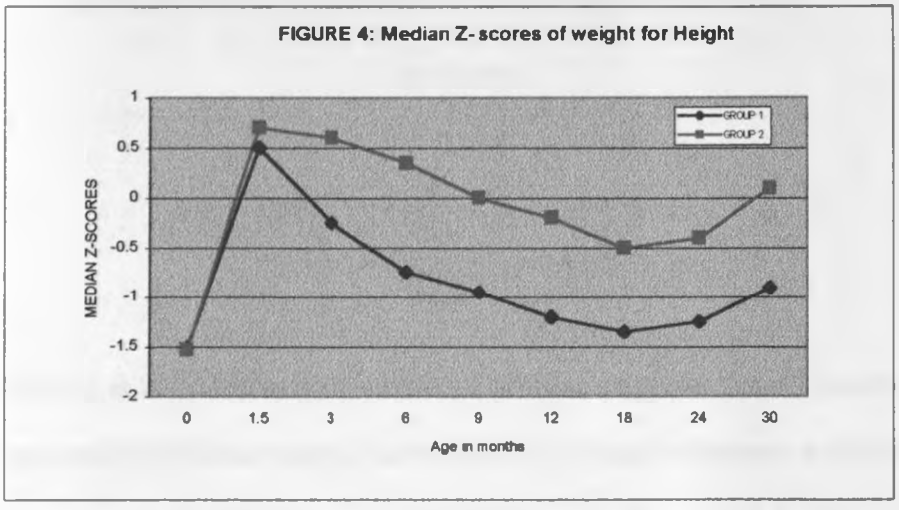
Appointment _____

Comments _____

Nutritional status

We carried out an in-depth analysis of the nutritional status of children who died before reaching the age of 3years and those who survived to reach 3 years of age and beyond. Using the National Center for Health Statistics (NHCS) charts, the median for the measures were used to assess growth patterns.

To compare the acute (wasting) nutritional status of the children who died before reaching the age of 3years and those who survived to reach 3 years of age and beyond, the median Z-scores of weight for height were plotted and the differences between the medians at different ages to check for significance of the differences.

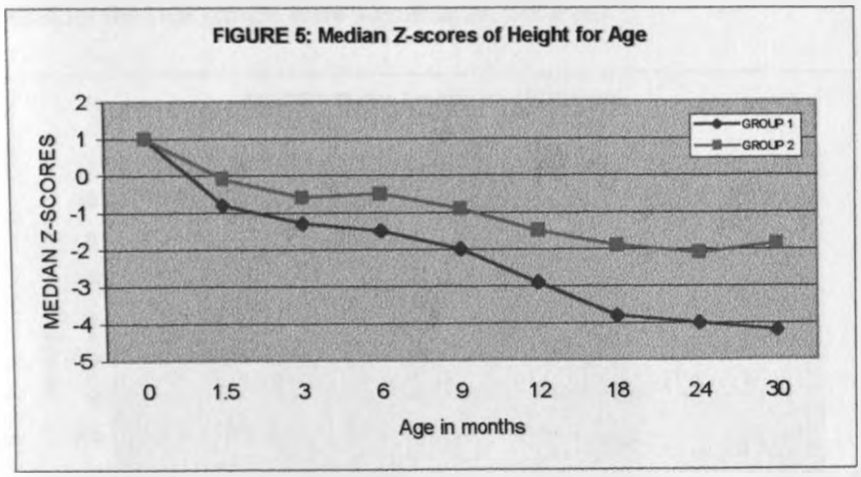


Key: Group 1= Children dying at < 3years

Group 2= Children surviving ≥ 3years.

The nutrition status in the two groups was similar at birth and at the age of 6 weeks. While none of the two groups had severe wasting (WHZ less than –2.0) the children who died before reaching the age of 3years were significantly more likely to be acutely malnourished (significant difference between the median weight for height Z scores P= **0.027**) at six months of age than those who survived to reach 3 years of age and beyond.

To compare the chronic (stunting) nutritional status of the children who died before reaching the age of 3years and those who survived to reach 3 years of age and beyond, the median Z-scores of height for age were plotted and the difference between the medians at different ages to check for significance.



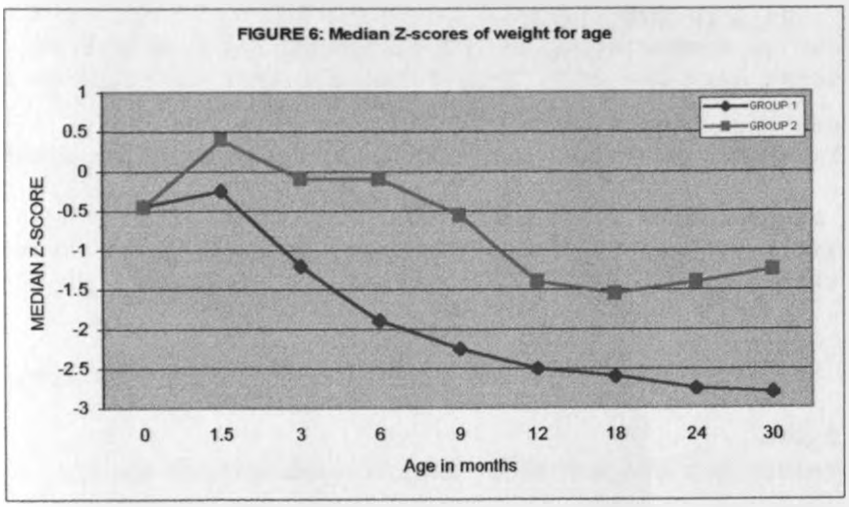
Key: Group 1= Children dying at < 3years

Group 2= Children surviving ≥ 3years

Stunting, as indicated by HAZ –score <-2.0, became apparent from 9 months of age in those who died before reaching three years of age. Stunting become evident at the age of one to one and a half years (and even then marginally so) in those who survived to reach 3 years of age and beyond. However the two groups were not statistically different at birth and at six weeks of age. However, at six months, children who died before reaching age of 3 years tended to be more stunted than those who survived to reach 3 years and beyond (HAZ –1.99 versus –0.9 p=0.075).

Weight for age is a composite index of weight for height (measure for acute nutritional status) and height for age (measure for chronic nutritional status). Though it does not differentiate between the two, it is a good overall indicator of the

nutritional status for a population. To compare the overall nutritional status of the children who died before reaching the age of 3years and those who survived to reach 3 years of age and beyond, the median Z-score of weight for age were plotted. The difference between the medians of the groups were found and compared to determine whether the two groups were significantly different.



Key: Group 1= Children dying at < 3years

Group 2= Children surviving ≥ 3years.

At 3 months of age children who died before reaching 3 years of age had a significantly lower WAZ compared to those who survived to reach three years (P value **0.010).** Under-weight, as indicated by WAZ- score < -2.0 was quite apparent from 6 months in all those children who die before reaching 3 years of age. Wasting of this magnitude did not occur in those children who survived to reach 3 years and beyond. At 6 months of age, children who died before reaching 3 years of age were significantly less well nourished than those who survived to reach 3 years of age and beyond in all measures of nutrition. There was a significantly lower WAZ score –1,502 versus –0.055 (p=0.001).

File: IDRC

UNIVERSITY OF NAIROBI

COLLEGE OF HEALTH SCIENCES

DEPARTMENT OF PHARMACY
POSTAL ADDRESS P O Box 19676 NAIROBI
KENYA

Telephone: 726770/1
Telegrams: Varsity

Our Ref

Your Ref

Dr. Ndinya Achola et al
Dept. of Microbiology
Faculty of Medicine
UON

27th July, 1992

REf: Research proposal "Perinatal transmission of HIV-1 Impact of infection on maternal and child health and social economic well being of the family. Paediatric AIDs Phase II
P 228/2/92

I am pleased to inform you that the KNH-ERC has reviewed and approved your above cited research study.

However the Committee has requested you to address the following issues:-

i. A sample of consent form should be provided.

ii Allowance for pre and post-testing counselling should be given.

iii. The clients should be given the opportunity to know their HIV status.

iv. An established referal system should be considered so that patients are not just refered to KNH but a specific area for management.

v. Care should be taken with regard to the volumes of blood drawn from babies to avoid anaemia.

As you proceed with the study make sure that your response to the above issues is communicated to the office of the undersigned not later than 30th Aug. 1992.

Thank you.

Dr. Anastasia N. Guantai
Secretary KNH-ERC

cc Prof. F.E. Onyango Chairman, KNH-ERC
Deputy Director - Clinical Services KNH