

Morbidity Among Human Immunodeficiency Virus-1-Infected and -Uninfected African Children

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ABSTRACT. *Objective.* To assess patterns of morbidity and associated factors in late infancy and early childhood among human immunodeficiency virus (HIV)-infected and -uninfected African children.

Design. Prospective study.

Setting. The Queen Elizabeth Central Hospital, Blantyre, Malawi.

Participants. Children with known HIV status from an earlier perinatal intervention trial were enrolled during the first year of life and followed to ~36 months of age.

Outcome Measures. Morbidity and mortality information was collected every 3 months by a questionnaire. A physical examination was conducted every 6 months. Blood to determine CD4⁺ values was also collected. Age-adjusted and Kaplan-Meier analyses were performed to compare rates of morbidity and mortality among infected and uninfected children.

Results. Overall, 808 children (190 HIV-infected, 499 HIV-uninfected but born to infected mothers, and 119 born to HIV-uninfected mothers) were included in this study. Of these, 109 died during a median follow-up of 18 months. Rates of childhood immunizations were high among all children (eg, lowest was measles vaccination [87%] among HIV-infected children). Age-adjusted morbidity rates were significantly higher among HIV-infected than among HIV-uninfected children. HIV-infected children were more immunosuppressed than were uninfected children. By 3 years of age, 89% of the infected children died, 10% were in HIV disease category B or C, and only ~1% were without HIV symptoms. Among HIV-infected children, median survival after the first occurrence of acquired immunodeficiency syndrome-related conditions, such as splenomegaly, oral thrush, and developmental delay, was <10 months. These same conditions, in addition to frequent bouts of fever, were the main morbidity predictors of mortality.

Conclusions. The frequency of diseases was high, and progression from asymptomatic or symptomatic HIV disease to death was rapid. Management strategies that effectively reduce morbidity for HIV-infected children are needed. *Pediatrics* 2000;106(6). URL: <http://www.pediatrics.org/cgi/content/full/106/6/e77>; children, human immunodeficiency virus, morbidity, mortality, perinatal HIV infection.

ABBREVIATIONS. HIV, human immunodeficiency virus; PCP, *Pneumocystis carinii* pneumonia; DTP, diphtheria, tetanus, and pertussis; OPV, oral poliomyelitis vaccine; AIDS, acquired immunodeficiency syndrome; CI, confidence interval; LTFU, lost to follow-up; AHR, adjusted hazard ratio.

Although data on mortality of human immunodeficiency virus (HIV)-infected African children exist,^{1,2} morbidity data are sparse.^{3,4} Recently, 2 studies were reported. A natural history study among Rwandan children followed 54 HIV-infected children until 5 years of age and reported that HIV-related morbidity conditions were consistently higher and more severe among HIV-infected compared with HIV-uninfected children.⁵ A hospital-based study in Malawi described the clinical presentation and outcome of *Pneumocystis carinii* pneumonia (PCP) in young children. Among 150 children with radiologically confirmed severe pneumonia, 16 cases of PCP were identified and 10 of these cases died.⁶ All cases of PCP were <6 months of age. The underlying patterns of HIV-related disease in late infancy and early childhood are not well studied. Knowledge of these morbidity conditions may assist in providing appropriate clinical care and designing potential interventions.

We previously reported mortality rates and related risk factors among a group of HIV-1-infected and -uninfected children born to mothers who participated in a birth canal cleansing trial (the wash study) conducted in Blantyre, Malawi from June to November 1994.^{2,7} In this article, we examine rates of morbidity and associated risk factors among the same group of children. As in many African countries, antiretroviral drugs are not generally available in Malawi, and none of these children received antiretroviral therapy. Prophylaxis against opportunistic infections is also not the standard of care in Malawi for HIV-infected children.

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METHODS

Recruitment

The Queen Elizabeth Central Hospital is a tertiary care facility in Blantyre, Malawi, Southeast Africa. As described in detail elsewhere,^{2,8} children participating in this study were recruited from a cohort of infants who had been under follow-up to determine rates of mother to child transmission of HIV in the wash study. Briefly, 1371 children had HIV status determined by polymerase chain reaction testing at a postnatal visit in the wash study. Of these, 355 tested positive (26%) and 1016 tested negative (74%).

Enrollment into this study started in April 1995 (~5 and 12 months, respectively, after the birth of the last and first child in the wash study) and continued through October 1995. All children from the wash study (both HIV-infected and HIV-uninfected children) who attended the clinic during this 6-month period were eligible for enrollment. However, infants of mothers who were not residents of Blantyre or its surrounding townships and infants of mothers not willing to sign an informed consent to participate and return for follow-up visits were excluded. Overall, 689 of the 1371 children (50%) tested for HIV were enrolled. Infant death or loss to follow-up before enrollment, not attending the study clinic from April to October 1995, and not satisfying the inclusion criteria were the primary reasons for not being recruited into the current study. Of the 1371 HIV-tested children, the proportions enrolled were 190/355 (54%) of those infected and 499/1016 (49%) of those uninfected. These were not significantly different ($\chi^2 = 1.87$; $P = .17$).

Concurrently, a sample of 119 children born to HIV-negative mothers who were part of the wash study were enrolled to mask the HIV status of participants and to provide an additional comparison group. Approximately, 1 child born to an HIV-negative mother was enrolled for every 6 children born to HIV-positive mothers. The median age of all children at enrollment was 8 months.

Participating mothers were counseled and requested to sign a consent form. A full-time pediatric clinical officer in the study clinic provided routine clinical care for both infants and mothers at no cost. This included treatment of simple chest infections, diarrheal diseases, anemia, and malaria. Referral to the hospital wards for specialized pediatric care was also available. The appropriate ethical committees in Malawi and the United States approved the study.

Study Visits and Procedures

Sociodemographic and clinical history and physical examination data were collected at baseline. Children were seen in clinic every 3 months after enrollment. At each visit, trained research nurses completed structured questionnaires to document morbidity associated events since the previous visit. A thorough physical examination was conducted every 6 months by trained research nurses. An on-site pediatric clinical officer provided clinical evaluation when necessary, and a consulting pediatrician was available for further evaluation and management. Mothers who missed their scheduled appointments were contacted at home and encouraged to return.

Child immunization history was obtained from the mother (or the care taker) and verified by checking the immunization card. In Malawi, BCG is given at birth, 3 doses of diphtheria, tetanus, and pertussis (DTP) are given at 6 weeks of age and at 1-month intervals after the first injection, and 3 doses of oral poliomyelitis vaccine (OPV) are given concurrently with DTP. Measles vaccine (mainly Schwarz strain) is given after 9 months of age. All children also routinely receive a single dose of vitamin A (100 000 IU) supplementation at age 6 months.

Peripheral blood samples were collected at enrollment or in a subsequent visit from 122 of 190 infected children (64%), and from a sample of uninfected children to determine white blood counts and differential (using a Coulter counter), percent CD4⁺, percent CD8⁺, percent T-lymphocytes, and CD4⁺ counts (using FACScan flow cytometry, Becton Dickinson, San Jose, CA) as described in a previous report.⁹ As many HIV-uninfected children as possible were sampled based on availability of monoclonals to perform the test on the day of the visit and willingness of the mother to permit infant blood draw. Overall, 171 HIV-infected and HIV-uninfected children had CD4⁺ values determined; 80% had these tests performed during the second year of age and the rest were tested

between the time of enrollment and age 12 months. Based on recommendations in the United States¹⁰ for children 1 to 5 years of age, we stratified values of CD4⁺ counts (cells/mm³) and percentages as follows: <500 cells or <15% severe immunosuppression, 500 to 999 cells or 15% to 24% moderate immunosuppression, and ≥ 1000 cells or $\geq 25\%$ no immunosuppression. The HIV status of the infant was determined by DNA polymerase chain reaction using Roche Amplicor HIV-1 test (Roche Diagnostic systems, Branchburg, NJ) as described elsewhere.¹¹ Testing was performed at the Frederick Cancer Research Center (Frederick, MD).

Morbidity and Mortality Outcomes

Based on the 1994 CDC Revised Classification systems for HIV infection,¹² HIV-infected children were classified into 4 mutually exclusive clinical categories as follows: N, not symptomatic; A, mildly symptomatic; B, moderately symptomatic; and C, severely symptomatic. Once classified, a child cannot be reclassified into a lesser severe category if the clinical status improves. In the survival analysis we defined deaths separately, regardless of the HIV clinical status of the child, because it is the severest outcome. We considered the following conditions as nonspecific acquired immunodeficiency syndrome (AIDS)-related conditions^{12,13}: prolonged fever, chronic diarrhea, chronic cough, weight loss, developmental delay (loss of developmental milestones¹³), oral thrush, chronic dermatitis, repeated ear infections, hepatomegaly, splenomegaly, and generalized lymphadenopathy (≥ 1 cm).

Statistical Analysis

For this analysis children were classified into 3 groups: group 1 were HIV-infected children; group 2 were HIV-uninfected children born to HIV-seropositive mothers; and group 3 were children born to HIV-seronegative mothers. Descriptive and stratified analyses were conducted to study morbidity among these 3 groups of children.

Kaplan-Meier survival curves were fit to estimate the cumulative proportion of HIV-infected children who reached a specific clinical category. We also used Kaplan-Meier analysis to estimate survival time after development of first AIDS-related morbidity in HIV-infected children. For purposes of comparison, we performed the same analyses on HIV-uninfected children. Multivariate proportional hazards analysis was performed to identify morbidity conditions (as time-dependent events) that could predict child mortality.

Reported or confirmed (by physical examination) morbidity events were analyzed starting at the date of enrollment. Because these events were recurrent, we calculated age- (visit) adjusted point estimates and 95% confidence intervals (CIs) based on an extension of the life table to repeating and changing events.¹⁴ Age adjustment was to a uniform distribution of age from 9 months to 36 months. One-way analysis of variance was used to test statistical significance for continuous variables (for which we did not have repeated measurements) among the 3 groups of children. Logarithmic transformations were used to normalize the CD4⁺ and CD8⁺ counts when comparing the means of these values among the different groups of children.

RESULTS

Enrollment and Follow-Up

A total of 808 infants (190 group 1, 499 group 2, and 119 group 3) were enrolled during the study, April to October 1995. These children were subsequently followed for a median of 18 months (range: .03–30.1 months) after enrollment; the oldest child was 39 months at study closure. Of these children, 184 (22.8%) were lost to follow-up (LTFU) during the entire study: 81 (10.0%) before the child was 1 year old, and 103 (12.7%) after the first year of life. A Kaplan-Meier analysis of time to LTFU, which censored children who died, showed that LTFU was statistically higher ($P = .02$; log-rank test) among HIV-infected (group 1) children. A total of 109 children (70 group 1, 31 group 2, and 8 group 3) died during this study. Of these, 26 died between time of

enrollment and age 12 months, while 83 died after 1 year of age.

Demographics

The 3 groups of children had similar maternal age, education of the mother or father, and socioeconomic status (Table 1). However, HIV-infected children had lower mean birth weight, severe disease symptoms (category C), and their mothers had lower parity. These differences were statistically significant (Table 1). Among the children who survived 18 months, 64% of 50 group 1 children, 56% of 274 group 2 children, and 59% of 61 group 3 children were weaned after age 18 months. Supplemental foods were introduced at approximately the same time for all children (at age 4.5 months for group 1 children, 4.4 months for group 2 children, and 4.6 months for group 3 children).

Immunization History

Immunization coverage was high (Table 1). However, the proportion of children who received the third dose of DTP was significantly lower among HIV-infected compared with HIV-uninfected children ($P = .0001$; log-rank test). Measles vaccine coverage was lowest (87.1%) among HIV-infected children (group 1) compared with uninfected children: group 2 (92.3%) and group 3 (94.8%). These differences were not statistically significant when Kaplan-Meier analysis of time to vaccination that censored deaths and losses to follow-up was performed ($P = .18$; overall log-rank test). Among 689 children born to HIV-seropositive mothers (ie, groups 1 and 2), 603 received measles vaccine and 80 did not receive the vaccine (information was missing on 6 children). Of children born to HIV-seropositive mothers, measles

was reported among 18 (3.0%) of the vaccinated children and 4 (5.0%) of the unvaccinated children (odds ratio for vaccinated vs unvaccinated: .59; 95% CI: .19–2.44). Of the 18 children who developed measles after being vaccinated, 5 were HIV-infected (3 died) and 13 were HIV-uninfected (none died). All of these 18 children received measles vaccine at ~12 months (with the exception of 1 uninfected child who had vaccine at ~15 months). Age at reported measles onset in these 18 children ranged between 15 and 24 months (with the exception of 1 uninfected child who had measles at 30 months of age).

T-Lymphocyte Subsets

T-lymphocyte subsets were determined in 122 group 1 children, 37 group 2 children, and 12 group 3 children. The median age of testing for all children was 15 months, and the range was 5 to 27 months for group 1, 6 to 19 months for group 2, and 11 to 21 months for group 3 children. As shown in Table 2, the mean CD4⁺ values (CD4⁺% and counts) and the CD4⁺:CD8⁺ ratio were significantly lower among HIV-infected (group 1) children. For example, CD4⁺% values were 19 among group 1, 38 among group 2, and 40 among group 3 children ($P < .0001$). Mean CD8⁺% was significantly higher (46%) in HIV-infected (group 1) compared with HIV-uninfected children; group 2 (28%) and group 3 (29%; $P < .0001$). However, there were no significant differences among the 3 groups in mean T-lymphocyte percent, total lymphocyte percent, or white blood cell counts. Of the 122 infected (group 1) children tested, 33% were severely immunosuppressed (CD4⁺ cells: <15%), 42% were moderately immunosuppressed (CD4⁺ cells: 15%–24%), and 25% had no immunosuppression (CD4⁺ cells: ≥25%).

TABLE 1. Sociodemographic, Clinical, and Immunization Characteristics of HIV-Infected and -Uninfected Children

| Characteristic | Group 1* <i>n</i> = 190 | Group 2* <i>n</i> = 499 | Group 3* <i>n</i> = 119 | <i>P</i> Value† |
|-------------------------------|----------------------------|----------------------------|----------------------------|-----------------|
| Mean maternal age (y) | 23.8 | 24.1 | 24.7 | |
| Mother illiterate (%) | 8.4 | 12.4 | 12.7 | |
| Father illiterate (%) | 18.4 | 16.0 | 16.1 | |
| Electricity in the house (%)‡ | 30.3 | 31.2 | 32.1 | |
| Mean parity | 2.6 | 2.9 | 3.3 | .02 |
| Mean birth weight (g) | 2771.9 | 2903.0 | 2979.5 | .004 |
| Clinical category (%)§ | | | | .005 |
| N/A | 7.4 | 9.6 | 15.1 | |
| B | 86.2 | 88.2 | 84.0 | |
| C | 6.4 | 2.2 | 0.9 | |
| Immunized: coverage (%) | | | | |
| BCG | 100.0 | 100.0 | 100.0 | |
| First DTP | 98.4 | 99.4 | 100.0 | |
| Second DTP | 95.7 | 98.2 | 99.1 | |
| Third DTP | 91.4 | 95.7 | 99.1 | .0001 |
| First OPV | 100.0 | 100.0 | 100.0 | |
| Second OPV | 98.9 | 99.8 | 99.1 | |
| Third OPV | 97.9 | 98.2 | 99.1 | |
| Measles | 87.1 | 92.3 | 94.8 | |

* Group 1, HIV-infected children; group 2, HIV-uninfected children born to HIV-seropositive mothers; group 3, children born to HIV-seronegative mothers.

† Only statistically significant ($P < .05$) values are shown (1-way analysis of variance test for continuous variables, χ^2 test for categorical variables, and Kaplan-Meier analysis log-rank test for immunization coverage).

‡ Index of high socioeconomic status.

§ Based on CDC 1994 Revised Classification (see "Methods"). The clinical classification for groups 2 and 3 should not be related to HIV because these children were not infected (other clinical causes should be considered).

|| Immunization history (including verification of records—see "Methods").

TABLE 2. Values of Selected Immunologic Characteristics of HIV-Infected and -Uninfected Children*

| Parameter | Group 1† | Group 2† | Group 3† | P Value‡ |
|--|-----------------|-----------------|-----------------|----------|
| | <i>n</i> = 122 | <i>n</i> = 37 | <i>n</i> = 12 | |
| CD4 ⁺ percent | 19 (± 9) | 38 (± 11) | 40 (± 6) | <.0001 |
| CD4 ⁺ count | 1323 (± 907) | 2369 (± 1862) | 2105 (± 705) | <.0001§ |
| CD8 ⁺ percent | 46 (± 11) | 28 (± 10) | 29 (± 13) | <.0001 |
| CD4 ⁺ /CD8 ⁺ ratio | .44 (± .29) | 1.57 (± .78) | 1.65 (± .72) | <.0001§ |
| WBC count | 12 827 (± 5193) | 11 392 (± 4615) | 10 775 (± 6066) | .27 |
| Lymphocyte percent | 56 (± 11) | 54 (± 13) | 54 (± 14) | .61 |
| T-lymphocyte percent | 65 (± 10) | 64 (± 9) | 66 (± 10) | .79 |

WBC indicates white blood cell.

* Values are means (± standard deviation) per cubic millimeter of blood. Approximately 80% of the children were tested after 1 year of age; the rest were tested at enrollment at a median age of 8 months.

† Group 1 were HIV-infected children; group 2, HIV-uninfected children born to HIV-seropositive mothers; group 3, children born to HIV-seronegative mothers.

‡ One-way analysis of variance test.

§ Based on log₁₀-transformed data.

Morbidity

Tables 3 and 4 show that age-adjusted recurrent fever, chronic diarrhea, vomiting, ear infections, skin conditions, oral thrush, and cough were significantly ($P < .05$) more commonly reported among HIV-infected (group 1) children than among HIV-uninfected (group 2) children (Table 3). On clinical examination, otitis media, dermatitis, oral candidiasis, signs of active chest problems, lymphadenopathy, and developmental delay were significantly more frequent among HIV-infected (group 1) children (Table 4). The frequencies of symptoms and diseases among group 2 and group 3 children were comparable (no statistical difference).

Stratification of the overall age-adjusted morbidity by the percentage of CD4⁺ in group 1 children who had this measurement available (122 of 190) showed that the clinical conditions were most common among the severely immunosuppressed children (CD4⁺: <15%), intermediate among moderately immunosuppressed children (CD4⁺: 15%–24%), and lowest among children with no immunosuppression (CD4⁺: ≥25%; data not shown). For example, age-adjusted rates for recurrent conditions as suggested

by the response “child gets sick often” were 56.4% for CD4⁺ <15%, 34.1% for CD4⁺ 15% to 24%, and 21.5% for CD4⁺ ≥25%.

Survival

Figure 1 shows the cumulative proportion of infected children (group 1) at a given age who have died or reached a specific HIV clinical category. None of the infected children were in clinical category A. Children who were lost to follow-up were censored in these analyses. By 2 years after birth, ~35% of children died, 45% were in category B, and 20% had no symptoms (category N). By 3 years after birth, however, ~89% of the infected children had died, 2% were in category C, 8% were in category B, and only ~1% had no symptoms.

Table 5 shows that among HIV-infected children, the median survival time was shortest (<10 months) after occurrence of first AIDS-related morbidity conditions, such as splenomegaly, oral thrush, and developmental delay, and longest (>20 months) after the first occurrence of conditions, such as fever, cough, diarrhea, and lymphadenopathy. The proportion of children surviving to 12 months after occur-

TABLE 3. Age-Adjusted Frequencies of Selected Reported Morbidity Conditions Among HIV-Infected and -Uninfected Children*

| Reported History | Group 1† % (95% CI) | Group 2† % (95% CI) | Group 3† % (95% CI) |
|------------------------|------------------------|------------------------|------------------------|
| | <i>n</i> § = 733 | <i>n</i> § = 2190 | <i>n</i> § = 609 |
| Child gets sick often‡ | 34.2 (26.6–41.8) | 11.2 (8.9–13.6) | 10.7 (7.8–13.6) |
| Diarrhea in last month | 38.6 (31.7–45.5) | 28.0 (25.4–30.6) | 30.1 (25.0–35.2) |
| Since last visit had | | | |
| Fever | 56.1 (49.0–63.2) | 44.3 (40.9–47.6) | 39.0 (33.1–44.9) |
| Vomiting | 16.0 (11.1–20.9) | 5.4 (4.2–6.6) | 5.8 (4.0–7.8) |
| Cough | 51.3 (43.9–58.8) | 41.5 (38.0–45.0) | 41.2 (34.1–48.3) |
| Conjunctivitis | 18.4 (12.3–25.3) | 12.7 (10.5–14.9) | 12.9 (8.8–17.0) |
| Oral thrush | 20.1 (14.0–26.2) | 9.7 (7.5–11.9) | 8.2 (4.1–12.3) |
| Ear infection | 16.6 (11.9–21.3) | 5.5 (4.1–6.9) | 3.9 (2.3–5.5) |
| Skin disease | 28.0 (21.1–34.9) | 15.0 (12.5–17.6) | 19.5 (13.8–25.2) |
| Measles | 4.8 (4.0–5.6) | 2.6 (2.0–3.2) | 1.2 (.4–2.0) |
| Malaria | 8.6 (5.1–12.1) | 8.1 (6.1–10.1) | 6.5 (4.7–8.3) |
| Visited a clinic | 67.1 (60.6–73.6) | 54.3 (51.0–57.6) | 51.3 (44.4–58.2) |
| Been hospitalized | 8.2 (4.7–11.7) | 3.9 (2.5–5.3) | 2.6 (1.0–4.2) |

* Age adjusted to a uniform distribution between 9 months and 3 years of age as described elsewhere.¹⁴

† Group 1, HIV-infected children; group 2, uninfected children born to HIV-seropositive mothers; group 3, children born to HIV-seronegative mothers.

‡ Indicator of recurrence.

§ Overall number of visits made by 190 group 1, 499 group 2, and 119 group 3 children.

|| Statistically significant difference ($P < .05$) between HIV-infected and -uninfected children.

TABLE 4. Age-Adjusted Frequencies of Selected Confirmed Morbidity Conditions Among HIV-Infected and -Uninfected Children*

| Clinical Condition† | Group 1‡ % (95% CI) | Group 2‡ % (95% CI) | Group 3‡ % (95% CI) |
|--------------------------------|------------------------|------------------------|------------------------|
| | <i>n</i> = 387 | <i>n</i> = 1247 | <i>n</i> = 319 |
| Male gender | 47.4 (37.0–57.8) | 51.6 (46.3–56.9) | 50.0 (39.2–60.8) |
| Oral thrush | 10.3 (5.8–14.8)¶ | 1.9 (1.1–2.7) | .9 (.01–1.9) |
| Herpes simplex | 3.3 (.1–6.6) | .6 (.2–1.0) | .5 (.01–1.1) |
| Otitis media | 9.9 (5.2–14.6)¶ | 1.9 (.9–2.9) | 3.2 (1.0–5.4) |
| Dermatitis | 12.5 (7.8–17.2)¶ | 4.2 (2.6–5.8) | .9 (.01–1.9) |
| Coughing on examination | 55.1 (47.7–62.6)¶ | 33.8 (30.3–37.3) | 26.0 (19.9–32.1) |
| Chest examination: retractions | 1.7 (.5–2.9) | .9 (3–1.5) | .2 (.01–.6) |
| wheezes | 5.9 (3.5–8.3) | 4.0 (2.6–5.4) | 3.1 (1.5–4.7) |
| rales | 27.0 (19.2–34.8)¶ | 12.1 (9.4–14.3) | 11.1 (7.6–14.6) |
| Palpable lymph nodes§ | | | |
| Occipital | 37.2 (30.9–43.5)¶ | 19.2 (16.5–21.9) | 18.1 (12.8–23.4) |
| Submandibular/-mental | 13.8 (10.1–17.5)¶ | 3.8 (2.6–5.0) | 1.8 (.4–3.2) |
| Cervical/supraclavicular | 20.1 (13.6–26.6)¶ | 7.7 (5.7–9.7) | 12.2 (7.9–16.5) |
| Axillary | 27.3 (21.6–33.0)¶ | 7.8 (6.0–9.6) | 7.6 (4.1–11.1) |
| Inguinal | 38.6 (32.2–44.9)¶ | 24.7 (21.6–27.8) | 17.4 (12.9–21.9) |
| Splenomegaly | 3.7 (1.7–5.7) | 2.4 (.01–7.1) | .8 (.01–2.0) |
| Developmental delay | 15.4 (11.7–19.1)¶ | 3.4 (1.2–4.6) | 3.0 (1.2–4.8) |

* Age adjusted to a uniform distribution between 9 months and 3 years of age as described elsewhere.¹⁴

† Confirmed by examination.

‡ Group 1 were HIV-infected children; group 2, uninfected children born to HIV-seropositive mothers; group 3, children born to HIV-seronegative mothers.

§ Lymphadenopathy of any size. Lymph nodes of >1 cm were also significantly more common among infected than among uninfected children.

|| Overall number of visits made by 190 group 1, 499 group 2, and 119 group 3 children.

¶ Statistically significant difference ($P < .05$) between HIV-infected and -uninfected children.

Cumulative mortality and clinical classification by age in infected children

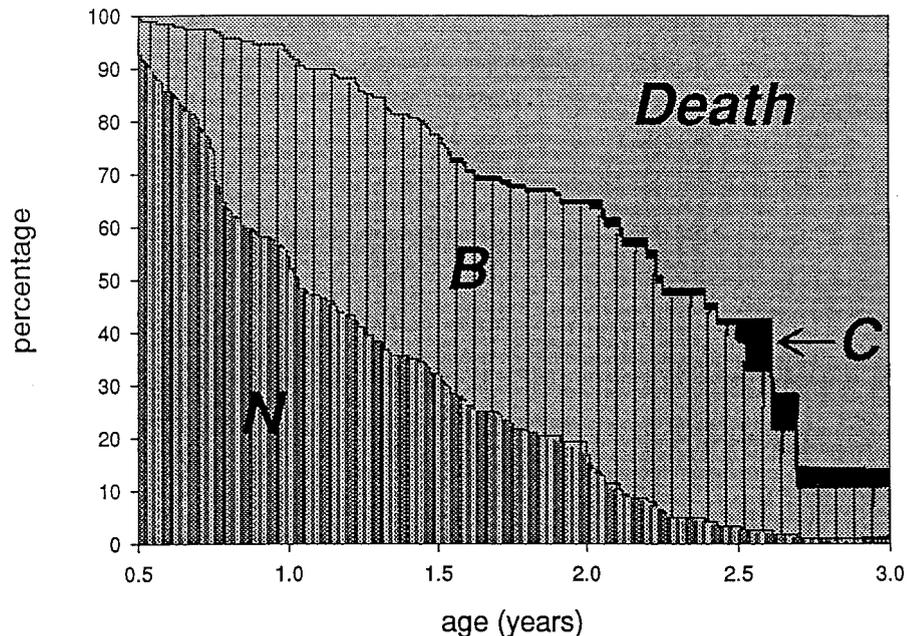


Fig 1. N indicates not symptomatic; B, moderately symptomatic; C, severely symptomatic.

rence of a first disease episode was consistently lower among HIV-infected children compared with HIV-uninfected children (Table 5). More than 50% of HIV-infected children who developed splenomegaly, oral thrush, or a developmental delay did not survive to 12 months, compared with <20% of HIV-uninfected children who developed the same conditions (Table 5). In proportional hazards models that simultaneously adjusted for the first occurrence of all the AIDS-related conditions, developmental delay (adjusted hazard ratio (AHR): 3.8; 95% CI: 2.3–6.4),

fever (AHR: 3.5; 95% CI: 1.6–7.6), oral thrush (AHR: 2.4; 95% CI: 1.4–4.7), and splenomegaly (AHR: 2.2; 95% CI: 1.2–4.1) were the major morbidity predictors of child mortality among HIV-infected children. Among HIV-uninfected children (groups 2 and 3 combined), the major predictors of mortality were splenomegaly (AHR: 4.9; 95% CI: 1.8–13.1), developmental delay (AHR: 3.9; 95% CI: 1.6–9.3), and cough (AHR: 2.7; 95% CI: 1.3–5.8). There were no significant differences related to morbidity or mortality among male and female children (data not shown).

TABLE 5. Median Survival Months and Proportion of Children Surviving to One Year After First Morbidity Condition Among HIV-Infected and -Uninfected Children*

| Disease | # Died | | Median survival | | % Surviving to 12 Months of Age | |
|-------------------------|--------|------|-----------------|------|---------------------------------|------|
| | HIV+ | HIV- | HIV+ | HIV- | HIV+ | HIV- |
| Fever | 59 | 27 | 25.9 | — | 62 | 95 |
| Cough | 46 | 27 | 22.3 | — | 68 | 93 |
| Diarrhea | 46 | 25 | 20.2 | — | 68 | 95 |
| Lymphadenopathy (>1 cm) | 25 | 3 | 20.2 | — | 68 | 96 |
| Dermatitis | 18 | 6 | 19.8 | — | 65 | 90 |
| Otitis media | 13 | 2 | 12.9 | — | 51 | 96 |
| Developmental delay | 34 | 7 | 9.1 | — | 47 | 87 |
| Oral thrush | 22 | 5 | 8.9 | — | 47 | 85 |
| Splenomegaly | 14 | 5 | 7.1 | — | 39 | 81 |

* Uninfected children (HIV-) include both groups 2 and 3 ($n = 618$).

DISCUSSION

This study examined morbidity rates and related factors among a cohort of children of HIV-infected mothers. This is one of the largest cohorts of HIV-infected children who have been followed in sub-Saharan Africa. In this cohort, mortality during the second and third years of life was substantially higher among HIV-infected than among HIV-uninfected children.² Consistent with the mortality findings, our current analyses show that HIV-infected children had higher disease frequency and severe immunosuppression.

T-lymphocyte subsets are rarely measured in sub-Saharan Africa, particularly in children. We were not able to conduct these tests on all HIV-infected children (64% or 122/190 children were tested) because of several factors, such as death of the child, refusal/inability to obtain a venous blood sample, and loss to follow-up. Estimates of CD4⁺ values for Malawian HIV-infected and -uninfected children, however, were similar to age comparable values reported from industrialized countries. For example, in a study of children 1 to 4 years of age in the United States, CD4⁺% was 21% among HIV-infected children and 40% among age-matched controls and CD8⁺% was 49% among infected children and 28% among controls.¹⁵ Among children 13 to 24 months old included in the Italian Registry study,¹⁶ the CD4⁺ counts were higher for both infected and uninfected children: CD4⁺ count was 2030 cells/mm³ among infected asymptomatic children, 1680 cells/mm³ among infected symptomatic children, and 2584 cells/mm³ among uninfected children. Because of variability of CD4⁺ counts, however, monitoring of CD4⁺ percentage has been preferred in practice.¹⁰ The percentage of CD4⁺ and the ratio of CD4⁺:CD8⁺ of Malawian children were slightly higher than in 16 HIV-infected Rwandan children 5 to 12 years of age.¹⁷

Although most of the HIV-infected children were either asymptomatic or moderately symptomatic, progression to death was rapid (Fig 1). By 3 years of age, 89% of the infected children alive at 6 months had died, 10% were alive in either clinical category B or C, and only 1% were symptom-free. Comparison of these data with morbidity and mortality patterns among vertically infected European and US children^{18,19} shows striking differences. For example, by 3 years of age in the European study, only 18% of the

children died, 12% were in category C, 36% in category B, 24% in category A, and 10% in category N (no symptoms). In the European study, mortality among HIV-infected children at 6 years of age was 4 times less than at 3 years of age in the current study. Among US children the probability of surviving to 5 years of age was 75%.¹⁹ The rapid progression to death among African children could be attributable to the high burden of infectious diseases and to difficulties in receiving timely and appropriate clinical care. Antiviral treatment is not available and prophylactic regimens against opportunistic as well as common bacterial infections are not routinely provided. It should be noted that the European and US children were followed from the time of birth, while children in this study were enrolled at a median age of 8 months.

The age-adjusted HIV-related morbidity conditions, such as chronic diarrhea, fever, oral thrush, otitis media, cough, dermatitis, and generalized lymphadenopathy were significantly higher among HIV-infected children compared with HIV-uninfected children. Age-adjusted rates of nonspecific infections (eg, conjunctivitis and malaria) were not associated with HIV infection. As has been observed in other studies on African children,⁵ morbidity conditions such as cough are common in all children (Table 3).

The observation that 18 children (including 13 uninfected but born to HIV-seropositive mothers) who were vaccinated against measles after 9 months as recommended in Malawi subsequently developed measles is of concern and favors immunization at an earlier age.²⁰ In countries where measles vaccine is routinely offered at 9 months of age, an earlier extra dose at 6 months of age is recommended for HIV-infected children. These data, however, should be interpreted with caution. We did not measure maternal measles antibody levels; these women, based on immunization practices in Malawi, have not been vaccinated in their childhood. Measles infection was identified only clinically and in the majority of cases from mothers' reports. The examining nurse verified history of immunization by checking the immunization card. Additionally, we have no information on logistic issues related to supply and storage of the measles vaccine used in these children. Measles vaccine failure in HIV-infected children has been re-

ported in the United States,²¹ and HIV-infected children were reported not to respond as well to measles or rubella components of the MMR vaccine, compared with HIV-uninfected children.²² It has been hypothesized that infants born to HIV-seropositive mothers (regardless of their own HIV status) may lose maternal measles antibodies earlier than children born to HIV-seronegative mothers and, therefore, may be more susceptible to early and severe measles infection.^{20,23,24}

Of the AIDS-related conditions, developmental delay, fever, oral thrush, and splenomegaly were the strongest predictors of mortality among HIV-infected children. With the exception of fever, which is common among all children (Table 3), median survival among children who developed these conditions was <10 months. Among HIV-uninfected children, splenomegaly, developmental delay, and cough could be attributed to malaria, malnutrition, and respiratory tract infections, respectively. These are the commonest causes of childhood deaths in Africa. These data are clinically relevant and could help clinicians to monitor growth and development and accordingly to guide the management of these children.

The morbidity rates of infants who were not HIV-infected but who were born to HIV-seropositive mothers (group 2) were not different from those of children born to HIV-seronegative mothers (group 3). This finding is consistent with the results of a natural history study on Rwandan children.⁵ Birth weight, T-lymphocyte subset values, and frequency of disease were comparable between HIV-uninfected children born to seropositive mothers and children born to seronegative mothers. There were no differences in breastfeeding practices or in immunization history. These similarities suggest that there are no additional biological factors that could increase the risk of mortality among HIV-uninfected children of HIV-infected mothers. Maternal sickness from HIV disease, however, could limit maternal care and could lead to more child morbidity and mortality. In this study, the number of mothers who died was relatively small (5 mothers of group 1 and 23 mothers of group 2 children) and did not influence survival or follow-up of these children. In other cohorts in Malawi, where we studied a larger sample of mothers, we have shown that maternal death was significantly associated with child survival.²⁵

A few limitations of this study are worth mentioning. Children enrolled in this study were a subset of a larger perinatal intervention study.⁷ Therefore, biases related to selection of children for enrollment and their follow-up might have occurred. We do not have information about children who did not return to the clinic after the main trial. An analysis of the characteristics of children who did not return showed that they were more likely to be of lower birth weight and that their parents were more likely to be less educated²⁶; these factors are generally associated with higher infant mortality. However, we do not have estimates of mortality on these children. Likewise, early morbidity conditions such as PCP might have been missed. As in several cohort stud-

ies, some children were lost to follow-up after enrollment. The higher LTFU rate among HIV-infected children could be attributable to unreported deaths. Therefore, the observed mortality rates, although high, could be an underestimation. LTFU caused by sickness of the child (or mother) could have also led to underestimation of morbidity rates. As our Kaplan-Meier analysis indicated, the lower measles immunization rates among HIV-infected children (Table 1) were probably attributable to death of these children before being immunized. Although selection bias might have occurred at enrollment, it is unlikely that this bias could influence one group of children more than the others. There were no significant differences between HIV-infected and -uninfected children in several risk factors, such as maternal sociodemographic characteristics (Table 1), and there were no differences in proportions of children enrolled among those HIV-infected or -uninfected. Additionally, there were no statistically significant differences in demographic factors between this cohort of mothers and children and the original birth canal cleansing study cohort from which the current study participants were recruited (data not shown). We relied primarily on clinical diagnoses and did not perform blood cultures or chest radiographs to confirm clinical diagnoses. Therefore, misclassification, underestimation of diseases, or omissions of conditions such as PCP were possible. Use of maternal history might have overestimated or underestimated some conditions. Our stratified analyses, however, clearly showed excess morbidity among HIV-infected compared with HIV-uninfected children.

The strengths of this epidemiologic study include its prospective nature, its large size, and the ability to combine both clinical and immunologic findings to describe morbidity. Because our morbidity findings focus on late infancy and early childhood (from age 9 to 36 months), they are not confounded by other common determinants of morbidity and mortality, such as low birth weight, which predominate in early infancy.

Autopsy studies from the region have shown that pyogenic pneumonia and severe malnutrition are common in children over 1 year of age dying with HIV infection.^{27,28} However, autopsy data have inherent biases. For example, they are unreliable in establishing the frequency of specific illnesses in HIV-infected children and may bias toward infections that are important at a more advanced stage of disease. The most common bacterial isolate from the lungs at autopsy of HIV-infected Zimbabwean children was *Klebsiella* sp.²⁸ It was also the most common organism in HIV-negative children and was associated with malnutrition rather than with HIV infection. In broad diagnostic terms, the spectrum of diseases that we report is similar to that documented in other urban centers in Africa.^{29–31} In Blantyre, HIV-infected children presenting with signs and symptoms of infection are usually treated as HIV-uninfected children, because HIV testing is rarely performed (S. Graham, personal communication, 1999). Improved management of persistent diarrhea and of chronic suppurative otitis media is likely to

substantially reduce morbidity in HIV-infected children. Prophylactic antibiotics may improve morbidity by reducing the frequency of pneumonia or bacteraemia, which is more common among HIV-infected children.³² In contrast, antibiotic prophylaxis may accelerate the development of antimicrobial resistance to common childhood pathogens. To provide appropriate acute management or to consider the value of a prophylactic intervention, morbidity data of specific cause are required. The difficulties in establishing actual causes of morbidity and mortality should be realized. Efforts to make available simple diagnostic tests and procedures to help clinicians provide better care for the children of developing countries should be a priority.

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