Natural History of Human Immunodeficiency Virus Disease in Perinatally Infected Children: An Analysis From the Pediatric Spectrum of Disease Project

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ABSTRACT. **Objective.** To describe the progression of human immunodeficiency virus (HIV) disease through clinical stages from birth to death among a large number of perinatally infected children.

**Methods.** The Pediatric Spectrum of Disease (PSD) project, coordinated by the Centers for Disease Control and Prevention (CDC), has conducted active surveillance for HIV disease since 1988 in seven geographic regions. PSD data are collected from medical and social service records every 6 months through practitioners at each participating hospital clinic. We analyzed data from perinatally HIV-infected children born between 1982 and 1993. The natural history of HIV disease was divided into five progressive stages using the clinical categories in the CDC 1994 pediatric HIV classification system: stage N, no signs or symptoms; stage A, mild signs or symptoms; stage B, moderate signs or symptoms; stage C, severe signs or symptoms; and stage D, death. A five-stage Markov model was fitted to the PSD data. To compare the estimates from the PSD project with the published estimates, we also fitted an alternative Markov model using acquired immunodeficiency syndrome (AIDS) 1987 case definition in place of stage C and also calculated standard Kaplan-Meier estimates.

**Results.** A total of 2148 perinatally HIV-infected children were included in the analysis. The estimated mean times spent in each stage were: N, 10 months; A, 4 months; B, 65 months; and C, 34 months. We estimated that a child born with HIV infection has a 50% (95% confidence interval [CI], 40%-60%) chance of severe signs or symptoms developing by 5 years of age and a 75% (95% CI, 68%-82%) chance of surviving to 5 years of age. For a child in stage B, there is a 60% (95% CI, 49%-71%) chance of severe signs or symptoms developing within the next 5 years and a 65% (95% CI, 56%-73%) chance of surviving 5 more years. The estimated mean time from birth to stage C was 6.6 (95% CI, 5.7-7.5) years, and the estimated mean survival time from birth was 9.4 (95% CI, 8.1-10.7) years. From the alternative Markov model, the estimated mean time from birth to AIDS was 4.8 (95% CI, 4.5-5.2) years.

**Conclusion.** Markov modeling using the revised pediatric classification system allowed us to describe the natural history of HIV disease in children before diagnosis of AIDS. On average, children progress to moderate symptoms in the second year of life and then remain moderately symptomatic for more than half of their expected lives, underscoring their need for clinical care before the onset of AIDS. The results from the Markov model are useful in family counseling, health care planning, and clinical trial designs. Pediatrics 1996;97:710–716; pediatric HIV and AIDS, natural history, Markov model.

Initial reports of the clinical manifestations of human immunodeficiency virus (HIV) infection in perinatally infected children described a rapidly progressive disease with short survival. However, because these observations were made early in the epidemic on small numbers of children whose HIV infection had been ascertained because of their severe illness, they were biased toward including HIV-infected children with the most rapidly progressive disease. Later descriptions were more comprehensive, because larger numbers of children had been observed, the duration of follow-up was longer, and the development of HIV antibody testing allowed asymptomatic infected children to be included. As a result, recent estimates of the time to acquired immunodeficiency syndrome (AIDS) and death in perinatally HIV-infected children are much longer than the initial estimates.

Until recently, no systematic method for describing the course of HIV infection in children was available. The 1987 classification system for HIV-infected children categorized HIV-related diseases but was not designed to describe disease progression. However, the 1994 revision of this classification system allows children to be classified into mutually exclusive categories based on severity of disease. With this

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new classification system and more cumulative follow-up time, an even more accurate description of the course of pediatric HIV infection, especially during the early stages, is now possible.

An accurate understanding of the timing of the progression of HIV infection in children has important clinical, research, and public health benefits. For clinicians, such knowledge contributes to prognostic information that can be communicated to patients and their families. For researchers designing clinical trials, knowledge of the rates of occurrence of various defined stages of disease assists in calculating sample sizes and planning trial durations. For health planners, the length of each stage of disease is important for estimating the resource needs of HIV-infected children.

A description of the progression of pediatric HIV disease through the clinical stages can be developed from clinical data. Ideally, the clinical data would come from prospective clinical observations. However, most prospective clinical series have limited numbers of children under observation. The Pediatric Spectrum of Disease (PSD) project has collected longitudinal clinical data from more than 2000 HIV-infected children born to HIV-infected mothers. These children were diagnosed at various ages and followed for varying lengths of time. The Markov model can be used to model these longitudinal data to describe the progression of HIV disease. This method complements prospective cohort studies by estimating progression times based on larger numbers of infected children using the newly designed classification system. In addition, the Markov model is uniquely suited to estimating progression time, because even in prospective studies, the exact time of development of signs and symptoms that indicate progression to a more severe stage is not precisely known and is dependent on the frequency of medical evaluations. For example, documentation of liver and spleen enlargement moves a child from no-signs or symptoms stage to the mild–signs and symptoms stage. However, the precise age at which the child entered the mild–signs and symptoms stage is often not known (it occurred at some point in time between the two clinical evaluations). Therefore, the age at transition between disease stages is best estimated by mathematical models.

In this article, we describe the age-specific natural history of HIV disease from birth to death among children enrolled in the PSD project. To best describe the course of HIV disease among these large numbers of HIV-infected children, we applied Markov modeling techniques that are specifically suited for modeling short portions of individual disease histories and for evaluating transitions between clinical stages, such as those in the new classification system.

METHODS

PSD Project

The PSD project has conducted active surveillance for HIV infection and perinatal HIV exposure among children in seven geographic regions: Los Angeles County, New York City, three cities in Texas, Massachusetts, Washington, DC, Puerto Rico, and the San Francisco Bay area. In most sites, the surveillance is population based, enrolling essentially all children who have been clinically identified as HIV exposed or infected in those geographic areas. In New York City and Washington, DC, the surveillance is hospital based, enrolling only children identified in the participating hospitals and their associated clinics. The project started in 1988, but all children born after January 1, 1976, who were HIV infected or HIV exposed and who had been seen at one of the participating institutions were eligible for inclusion in the PSD project.

Children eligible for enrollment are identified through practitioners at each participating hospital clinic. Study personnel visit these institutions on a regular basis to collect data on children eligible for the project. All available inpatient and outpatient medical records on each child are abstracted at the initial evaluation. Records on each enrolled child are then reviewed every 6 months.

Data are collected on standard forms and entered into a Centers for Disease Control and Prevention (CDC)-designed software system at each site. Each participating site is responsible for establishing a provider-specific data management plan, compatible with local status, which ensures strict confidentiality of all medical records, surveillance registries, data collection forms, and computer files. Detailed data collection instructions and intensive technical support help ensure uniformity in data abstraction across sites. The information collected on each child includes demographic characteristics, mode of HIV exposure, diseases indicative of AIDS and other HIV-related conditions included in the Public Health Service pediatric HIV classification system, laboratory data, treatment for HIV infection, prophylaxis and treatment of opportunistic infections, and date and cause of death if the child died.

Data for Analysis

All data collected through year-end 1993 on children born since 1982 were included in the analysis. Children born before 1982 were excluded to avoid biases; HIV infection was not recognized in children until 1982, and short-term survivors born before 1982 would have been missed. The analysis presented here uses months of age as the smallest time unit, because the dates of symptoms were collected only by month and year of occurrence.

Classification System

The CDC's 1994 revised pediatric HIV classification system categorizes children by clinical status and CD4 T-lymphocyte count. We used these clinical categories to define the stages of disease. The clinical categories recorded on each child include: A, no signs or symptoms; B, mild signs or symptoms; C, moderate symptoms or signs; and D, severe symptoms or signs (see "Appendix"). All AIDS-defining conditions in the CDC 1987 definition are included in category C, except lymphoid interstitial pneumonia (LIP), which is less severe and associated with longer survival when compared with other AIDS-defining illnesses. LIP is classified in category B. The categories are mutually exclusive, and once a child has met the criteria for a more severe category, that child is not reclassified in a less severe category, even if the signs or symptoms resolve.

Markov Models

The natural history of HIV infection in perinatally infected children can be considered as a progression of stages from birth to death. Markov models have been successfully used to describe progression of adults through stages of HIV infection and other diseases, including cancer. The natural history of HIV disease in perinatally infected children was divided into five progressive stages; clinical categories N, A, B, and C were defined by the HIV classification system and a fifth stage, D (death), was included as the final stage. Using the methods of Longini et al, we fit a five-stage Markov model to the PSD data. Like the classification system, the model allowed children to progress when they met the criteria for the next category, but not regress when signs or symptoms improved. Figure 1A depicts the progressive stages; stage-specific rates of transition (hazard rates) are represented by λ. We assumed that all children were in stage N at birth, because perinatally infected children rarely have signs or symptoms of HIV infection at birth. This Markov model assumed that every infected child moved to stage A, then to stage B, then to stage C, and finally to stage D in sequence as the disease progressed. 

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However, all stages may not have been observed because of the timing of medical evaluations and the rate of disease progression. In addition, the time of the observation may not be the exact time when the child entered the stage. Thus, the data required models, such as Markov models, that were capable of estimating both the time of entry and the time of exit for a stage and, hence, the time spent in each stage.

To compare the results from the PSD data with published data, an alternative five-stage Markov model was also fit to the PSD data (Fig 1b). By placing LIP with category C rather than category B, the revised category (C including LIP) in this model becomes identical to the 1987 AIDS case definition. In addition, we also calculated Kaplan-Meier estimates for time from birth to diagnosis of AIDS, time from birth to death, and time from diagnosis of AIDS to death.

RESULTS

Clinical data from 2148 perinatally HIV-infected children born between 1982 and 1993 were included in the analyses. Of these children, 11% were white, 45% were African-American, 41% were Hispanic, and 3% had other or unrecorded race or ethnicity. The mother’s risk of HIV transmission was sexual contact in 30%, injected drug use in 40%, and other or unrecorded risk in 30%. Of the children included in the analysis, 36% were from New York City, 16% were from Puerto Rico, 13% were from Massachusetts, 10% were from Los Angeles, 9% were from Washington, DC, 9% were from Texas, and 7% were from San Francisco. One hundred twenty-four (6%) of the children were born in 1982 and 1983, 247 (12%) were born in 1984 and 1985, 386 (18%) were born in 1986 and 1987, 521 (24%) were born in 1988 and 1989, 609 (28%) were born in 1990 and 1991, and 261 (12%) were born in 1992 and 1993. At year-end 1993, 458 (21%) had died, 357 (17%) were in stage C, 1157 (54%) were in stage B, 143 (7%) were in stage A, and 33 (2%) were in stage N. The mean age of living children at the time of the most recent clinical evaluation was 50 (median, 43) months. The mean age at death for the children who had died was 32 (median, 23) months. Three hundred forty-eight (16%) children died in the first 4 years of life, and 876 (41%) survived beyond 4 years of age. Thus, substantially more children have less rapidly progressive disease, and the resulting model primarily reflects this population.

Table 1 displays the number of paired observations for every two consecutive observation times (including birth). The months between the two consecutive observation times range from 1 to 127 months, with a median of 6 months. These numbers, together with the observation times, contributed to the estimate of transition time from one stage to the next stage. Of the 2148 HIV-infected children who began in stage N at birth, 2115 (98%) were observed in other stages (row N, columns A–D) at some time. The largest frequency in Table 1 is row B, column B, which indicates that many children remained in stage B for several observations without progressing to stage C or D. Relatively small numbers in row A show that many children progressed to stages B through D quickly without being observed in stage A. Of the 458 deaths observed, 388 (85%) occurred in children with severe signs or symptoms at previous observations (row C, column D).

The estimated mean and median times spent in each stage from the five-stage Markov model are given in Table 2. The estimated mean times spent in stages N and A were relatively short (10 and 4 months, respectively), and the time spent in stage B was the longest (mean, 65 months). Table 3 shows the estimated mean and median times from the beginning of stages N, A, and B to the beginning of stages A without LIP, B or LIP (AIDS), and C or LIP (AIDS).
stage C. The estimated mean time from birth (stage N) to stage C was 6.6 years (95% confidence interval [CI], 5.7–7.5 years). We estimated that a child with HIV infection has a 50% chance of severe signs or symptoms developing by 5 years of age. For children who have just entered stage B, the chance of severe signs or symptoms developing in the next 5 years is 60%.

Table 4 shows the estimated mean and median survival times from the beginning of each stage. For a child with perinatally acquired HIV infection, the mean survival time (birth to death) was estimated as 9.4 years (95% CI, 8.1–10.7 years), and the probability of surviving to 5 years of age was 75%. For children with moderate signs or symptoms (stage B), the estimated mean time from stage B to death was 8.2 years. For a child with severe signs or symptoms, the estimated mean time from stage C to death was 2.8 years (95% CI, 2.5–3.1 years), and the chance of surviving 5 years was 17%.

In the alternative five-stage Markov model with AIDS in place of stage C (Fig 1b), the AIDS incubation period was the time from birth (stage N) to stage C including LIP. The estimated mean times spent in each stage were 10 months for stage N, 4 months for stage A, 44 months (3.7 years) for stage B not including LIP, and 54 months (4.5 years; 95% CI, 4.1–4.9 years) for the AIDS stage. The estimated median time from AIDS to death was 3.1 years. From the cumulative distribution of the AIDS incubation period, we estimated that the median AIDS incubation period was 58 months or 4.8 years (95% CI, 4.5–5.2 years; median, 3.8 years).

For comparison, we also computed estimates from the Kaplan-Meier method using the same data. The estimated median survival time was 10.9 years. This estimate is biased, because no death was observed after 10.9 years, and the 95% CI is not available. However, the estimated probability of surviving 5 years was \( P = .76 \) (95% CI, .74–.78). The median time to AIDS was estimated as 4.9 years (95% CI, 4.2–5.5 years). We used 943 children with AIDS to estimate the survival time from AIDS. The median time from AIDS to death was 3.1 years (95% CI, 2.7–3.7 years).

Subgroup analyses were performed to address possible biases. We first selected infected children born between 1986 and 1989 to exclude those children born before the HIV enzyme-linked immunosorbent assay was developed and to avoid biases resulting from short follow-up times. A total of 907 infected children were included in subgroup 1. To address possible case ascertainment bias, subgroup 2 consisted of the 1171 children enrolled from the population-based project sites (i.e., excluding New York City and Washington, DC). The third subgroup contained the 486 children who were included in both subgroups 1 and 2. Table 5 gives the estimated mean times spent at each stage as well as the times from birth to stage C, mean survival times, AIDS incubation periods, and mean survival times from AIDS. The estimates from the subgroup analyses were similar to the estimates from the analyses that included all 2148 children.

### DISCUSSION

We have used a staged Markov model to describe the age-specific natural history of HIV disease in perinatally infected children from birth to death (Fig 2). Several authors have advocated using the Markov model over other methods, such as the Kaplan-Meier method, to analyze data on the natural history of HIV.

First, the Markov model allows the progression of a disease through different stages to be examined and, therefore, provides a comprehensive view of the disease process. Second, in contrast to the Kaplan-Meier method, the Markov model can handle data in which the exact transition times among stages are not known (right, left, or interval censored). Therefore, the Markov model can use incomplete longitudinal data on short portions of individual disease histories more efficiently than can the Kaplan-Meier method. However, when applying both methods to the PSD data, the estimates were similar.

Because this analysis is the first to use the 1994 revised classification system with Markov modeling to assess clinical progression among HIV-infected children, it is important to examine the validity and potential biases of the data and the model. The primary limitation of this Markov model was its assumption that children moved through the clinical stages in sequence, which may not be true for some children. A more complex model, which allows children to jump over one or more clinical stages, is being developed. The potential biases in the data are more numerous. Our analyses used data obtained by reviewing the medical records of all HIV-infected children.
TABLE 5. Subgroup Analyses: Mean Times in Stages and Between Stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Subgroup 1 (n = 907)*</th>
<th>Subgroup 2 (n = 1171)*</th>
<th>Subgroup 3 (n = 486)*</th>
<th>All (n = 2148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>mo (yr) 11 (0.9) 10-12</td>
<td>mo (yr) 9 (0.7) 8-10</td>
<td>mo (yr) 10 (0.8) 10-11</td>
<td>mo (yr) 10 (0.9) 10-11</td>
</tr>
<tr>
<td>A</td>
<td>mo (yr) 5 (0.4) 4-5</td>
<td>mo (yr) 3 (0.3) 3-4</td>
<td>mo (yr) 3 (0.3) 3-4</td>
<td>mo (yr) 4 (0.3) 3-4</td>
</tr>
<tr>
<td>B</td>
<td>mo (yr) 61 (5.1) 55-67</td>
<td>mo (yr) 61 (5.1) 56-67</td>
<td>mo (yr) 55 (4.6) 48-62</td>
<td>mo (yr) 65 (5.4) 60-70</td>
</tr>
<tr>
<td>C</td>
<td>mo (yr) 33 (2.8) 29-37</td>
<td>mo (yr) 32 (2.7) 28-36</td>
<td>mo (yr) 32 (2.7) 27-37</td>
<td>mo (yr) 34 (2.8) 31-37</td>
</tr>
<tr>
<td>N to C</td>
<td>mo (yr) 77 (6.4) 56-97</td>
<td>mo (yr) 73 (6.1) 58-89</td>
<td>mo (yr) 69 (5.7) 42-96</td>
<td>mo (yr) 79 (6.6) 68-90</td>
</tr>
<tr>
<td>N to D</td>
<td>mo (yr) 110 (9.2) 81-139</td>
<td>mo (yr) 105 (8.8) 82-128</td>
<td>mo (yr) 101 (8.4) 61-141</td>
<td>mo (yr) 113 (9.4) 97-128</td>
</tr>
<tr>
<td>N to AIDS</td>
<td>mo (yr) 55 (4.6) 48-61</td>
<td>mo (yr) 61 (5.1) 52-70</td>
<td>mo (yr) 54 (4.5) 38-70</td>
<td>mo (yr) 58 (4.8) 54-62</td>
</tr>
<tr>
<td>AIDS to D</td>
<td>mo (yr) 52 (4.3) 45-58</td>
<td>mo (yr) 44 (3.7) 39-49</td>
<td>mo (yr) 44 (3.7) 37-51</td>
<td>mo (yr) 54 (4.5) 48-59</td>
</tr>
</tbody>
</table>

*Subgroup 1 includes all infected children born between 1986 and 1989; subgroup 2 is the population-based group that includes all infected children born between 1982 and 1993 excluding New York and Washington, DC; subgroup 3 comprises infected children who are included in both subgroups 1 and 2.

Children at the seven sites born from 1982 to 1993. Because the capability for serologic diagnosis of HIV was limited before 1985, only symptomatic mothers and their children were identified during this period. We found that most of the deaths among younger children occurred among those born recently. This finding suggests that HIV-related deaths at an early age were not captured among children born early in the epidemic. Furthermore, one study site (New York City) did not systematically enroll children who died before the study began. In addition, children born in the early years of the epidemic may have entered the study at older ages, because data collection for the project began in 1988. Although all medical records of these children were examined, their disease status was not observed every 6 months. In our analyses, children born earlier contribute more information for disease progression at later ages, and children born recently contribute more information for disease progression at early ages. A potential bias may be present if infected children born earlier progressed differently than the children born more recently. For example, children born before the widespread availability of prophylaxis for Pneumocystis carinii pneumonia, antiretroviral therapy, and other various advances in treatment for opportunistic infections may have progressed more rapidly than children born more recently.

Another source of bias in these data is incomplete case ascertainment. HIV-infected children born to mothers not tested for HIV are generally not identified until either the mother or the child becomes symptomatic. Therefore, the PSD data are potentially biased toward more symptomatic children. Last, the time interval of data abstraction introduces a potential bias. Because the mean times spent in stages N and A are relatively short (10 and 4 months, respectively), and the data are collected in 6-month intervals, the estimates of the ages at transition from stages N to A and A to B may be less precise than the ones from stages B to C and C to D. As a result, the confidence bounds from the Markov model may overestimate our true confidence.

The subgroup analyses address these issues. The estimated times spent in each stage and between stages are very similar among the four groups. The subgroup analyses reassure us that the analyses using all children born between 1982 and 1989 are not substantially affected by the biases discussed. We postulate, specifically, that the children under care before routine use of effective therapies may have progressed differently. However, they contribute a small portion of the data used to fit the model and do not distort the estimate. Thus, the results of the analyses using all 2148 children are more reliable because the sample size is larger.

In the past several years, both statisticians and clinicians have observed that HIV-infected children fall into two distinct groups. The first group is smaller and has a more rapid disease course than the second group, but both groups have more rapid progression than adults. Auger and colleagues using a mixture model of two Weibull distributions, estimated that the median time to AIDS was 4 months for the first group and 6.1 years for the second group. In our analysis, 16% of the children died in the first 4 years of life (short-term survivors), 41% survived beyond 4 years of age (long-term survivors), and 43% are alive at ages younger than 4 years and may be short or long-term survivors. Describing disease progression in two distinct populations of HIV-infected children using the Markov model will require modeling the mixture of two Markov processes. The method for this modeling process has not been described but is currently being developed. However, the population that we analyzed has a larger number of long-term survivors than short-term survivors. We estimated that 72% of...
with approximately 72% long-term survivors, children progress to moderate symptoms in the second year of life and then remain moderately symptomatic for more than half of their expected lives, underscoring their need for clinical care before the onset of AIDS. The results have several important benefits for clinicians and health care planners. First, they provide data that clinicians can use to counsel families by predicting the age-specific clinical course of HIV-infected children. Second, the estimated times spent in each disease stage and progression rates between stages assist clinical researchers in calculating sample sizes and accrual rates for clinical trials. Third, these estimates also can be used to project future resource needs for HIV-infected children.

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Anemia (<8 g/dL), neutropenia (<1000/mm³), or

Category B: Moderately Symptomatic
Children who have two or more of the conditions listed below but none of the conditions listed in categories B and C.

Lymphadenopathy (>0.5 cm at more than two sites; bilateral is considered one site);
Hepatomegaly;
Splenomegaly;
Dermatitis;
Parotitis; and
Recurrent or persistent upper respiratory infection, sinusitis, or otitis media.

Category C: Severely Symptomatic
Children who have any condition listed in the 1987 surveillance case definition for AIDS, with the exception of LIP.

APPENDIX
Revised Pediatric Clinical Pediatric HIV Classification

Category N: Not Symptomatic
Children with no signs or symptoms considered the result of HIV infection or with only one of the conditions listed in category A.

Category A: Mildly Symptomatic
Children who have two or more of the conditions listed below but none of the conditions listed in categories B and C.

Recurrent or persistent upper respiratory infection, sinusitis, or otitis media.

Category B: Moderately Symptomatic
Children who have symptomatic conditions other than those listed for categories A and C that are attributed to HIV infection. Examples of conditions in clinical category B include, but are not limited to:

- Anemia (<8 g/dL), neutropenia (<1000/mm³), or thrombocytopenia (<100 000/mm³) persisting for more than 30 days;
- Bacterial meningitis, pneumonia, or sepsis (single episode);
- Candidiasis, oropharyngeal (thrush), persistent (>2 months) in a child older than 6 months of age;
- Cardiomyopathy;
- Cytomegalovirus infection, with onset before 1 month of age;
- Diarrhea, recurrent or chronic;
- Hepatitis;
- Herpes simplex virus stomatitis, recurrent (more than two episodes within 1 year);
- Herpes simplex virus bronchitis, pneumonitis, or esophagitis with onset before 1 month of age;
- Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome;
- Leiomysarcoma;
- LIP or pulmonary lymphoid hyperplasia complex;
- Nephropathy;
- Nocardiosis;
- Persistent varicella zoster;
- Persistent fever for more than 1 month;
- Toxoplasmosis, onset before 1 month of age; and
- Varicella, disseminated (complicated chickenpox).

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