

Survival, Disease Manifestations, and Early Predictors of Disease Progression Among Children With Perinatal Human Immunodeficiency Virus Infection in Thailand

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ABSTRACT. *Objective.* To describe survival and signs of human immunodeficiency virus (HIV) infection in perinatally infected children in Thailand.

Methods. At 2 large Bangkok hospitals, 295 infants born to HIV-infected mothers were enrolled at birth from November 1992 through September 1994 and followed up with clinical and laboratory evaluations every 1 to 3 months for 18 months. Infected children remained in follow-up thereafter. For the infected children, we used data collected through October 2000 to estimate survival times and compare characteristics among those whose disease progressed at rapid (died within 1 year), intermediate (died at 1–5 years), and slow (survived at least 5 years) rates.

Results. None of the 213 uninfected children died during the follow-up period. Of the 68 infected children, 31 (46%) died; median survival was 60 months (95% confidence interval: 31–89 months). The most common cause of death was pneumonia (52% of deaths). Thirty-two children (47%) started antiretroviral therapy. Six children died in their first year before developing specific signs of HIV infection; all others developed signs of HIV infection between 1 and 42 months old (median: 4 months). Severe clinical (Centers for Disease Control and Prevention Class C) conditions were diagnosed in 23 children at a median age of 12 months, 15 (65%) of whom died a median of 3 months later. Compared with children whose disease progressed slowly, those whose disease progressed rapidly gained less weight by 4 months old (median 1.7 vs 2.6 kg), and their mothers had higher viral loads (median 5.1 vs 4.5 log₁₀ copies/mL) and lower CD4⁺ counts (median 350 vs 470 cells/μL) at delivery.

Conclusions. Among HIV-infected Thai children, survival times are longer than among children in many African countries, but shorter than among children in the United States and Europe. Signs of HIV develop early in most children. Growth failure and advanced maternal disease can predict rapid HIV disease progression and

may be useful markers for treatment decisions. *Pediatrics* 2002;110(2). URL: <http://www.pediatrics.org/cgi/content/full/110/2/e25>; vertical human immunodeficiency virus transmission, children, human immunodeficiency virus infection, Thailand.

ABBREVIATIONS. HIV, human immunodeficiency virus; PCP, *Pneumocystis carinii* pneumonia; PCR, polymerase chain reaction; CDC, Centers for Disease Control and Prevention.

The epidemic of perinatal human immunodeficiency virus (HIV) infection in Thailand began in the early 1990s, when the median HIV seroprevalence, by province, among women in antenatal care jumped from 0% in 1990 to >2% by 1995.¹ In Thailand, >30 000 children have been perinatally infected with HIV, and >7000 cases of AIDS or symptomatic HIV infection in children have been reported.^{2,3} Although Thailand's national perinatal HIV prevention program, which recommends short-course zidovudine and formula replacement feeding, should reduce the incidence of HIV infection in children, ~15 000 HIV-infected children are living in Thailand and more will continue to be identified through systematic HIV testing now provided for children born to HIV-infected mothers.⁴

Despite increasing availability of antiretroviral treatment for HIV-infected children, illness and death caused by the progression of perinatal HIV infection will place a substantial burden on the health care system in Thailand. Caring for these HIV-infected children requires an understanding of the manifestations of perinatal HIV infection in Thailand, where most HIV infections in children are with subtype E.⁵ Knowing the expected duration of survival after perinatal infection helps with counseling families of HIV-infected children. Identifying predictors of disease progression can help indicate prognosis and guide treatment.

Despite the magnitude and duration of the HIV epidemic in Thailand, there has been little systematic description of the manifestations of HIV in perinatally infected Thai children. In this study, we describe manifestations of HIV infection, estimate survival times, and identify predictors of disease

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METHODS

Population

From November 1992 through March 1994, we enrolled 342 HIV-infected pregnant women into a prospective cohort study of perinatal HIV transmission at Rajavithi and Siriraj Hospitals in Bangkok. Children born at Rajavithi Hospital were followed up at the adjacent Queen Sirikit National Institute of Child Health (formerly known as Children's Hospital). Women who provided their informed consent were enrolled during antenatal care, and their children were followed up from birth. The enrollment procedures for this study and analysis of perinatal transmission have been published.^{5,6} The study was conducted before the AIDS Clinical Trials group 076 study ended⁷; antiretroviral prophylaxis was not yet used to prevent mother-infant transmission, although HIV-infected mothers were advised not to breastfeed and were provided infant formula and ongoing infant feeding counseling. During the course of this study, primary prophylaxis against *Pneumocystis carinii* pneumonia (PCP) was not used routinely for HIV-exposed infants, but was used for children with signs of HIV infection. Antiretroviral treatment was starting to be used for symptomatic HIV-infected children, at first monotherapy and later dual nucleoside therapy. Because treatment usually was started once children developed HIV-related symptoms, we could not analyze the impact of treatment on disease progression.

Data Collection

Women had study visits during each remaining trimester of pregnancy, at delivery, and at 6 and 12 months' postpartum. All children were evaluated at birth and scheduled for study visits at 1, 2, 4, 6, 9, 12, 15, and 18 months of age. Infected children have been followed up indefinitely every 3 months. At each visit the child was examined, and the child's interim medical history was recorded along with information on hospitalizations, outpatient visits, medication use, and the child's diagnoses. Venous blood specimens were taken within 72 hours of birth, at 2, 6, 12, and 15 months of age, and every 6 months thereafter for lymphocyte phenotyping according to published methods.⁵ Plasma HIV RNA concentration (viral load) was measured retrospectively for selected specimens.

Infection Definition

The child's infection status was determined from the results of HIV DNA polymerase chain reaction (PCR) tests done at birth and at 2 and 6 months of age.⁵ Infants were considered HIV-infected if they had positive test results from 2 separate samples or one positive test result and a Centers for Disease Control and Prevention (CDC) Class C HIV condition.⁸ Children were considered not infected if 2 separate samples, including 1 obtained at >6 months of age, had a negative PCR result or if 1 specimen was negative for HIV antibody by enzyme immunoassay testing. Children were considered to have indeterminate infection status if none of these conditions was met.

Analysis

We analyzed data collected through October 2000. We estimated time of survival to death and to death or CDC Class C disease⁸ using the Kaplan-Meier method.⁹ Survival times of children lost to follow-up were censored at the time of last available information on clinical and vital status. To determine whether loss to follow-up affected the results, we compared factors found to be significant for early disease progression and time to Class C disease between children lost to follow-up and those who died or remained in follow-up. We used the χ^2 or Fisher exact test to compare categorical variables and the Student *t* test to compare continuous variables among groups. We defined rapid progression as death within 1 year of birth, intermediate progression as death between 1 and 5 years of birth, and slow progression as survival for at least 5 years.

RESULTS

Population Characteristics and Follow-up

Of the 295 children born in the cohort from November 1992 through September 1994, 68 were infected with HIV, 213 were not infected, and 14 had indeterminate HIV infection status. The estimated mother-infant HIV transmission rate in this cohort was 24.2%; 66 (97%) of the infected children were infected with HIV subtype E.⁵ Only 1 mother breastfed her child. Among the children not infected, 193 (91%) completed 18 months of follow-up, and none was known to have died during follow-up. Three of the children with indeterminate HIV status died, all in the first month of life (sepsis, pneumonia, gastrochisis).

As of October 2000, 31 (46%) HIV-infected children had died, 21 (31%) were lost to follow-up, and 16 (24%) were still in follow-up. The median time of follow-up was 28 months (range: 2–84 months). Of the 21 children who were lost to follow-up, the age at last visit ranged from 2 to 57 months; the median age was 24 months. The main reason for loss to follow-up was family relocation outside of Bangkok. Children lost to follow-up were similar to those remaining in follow-up on most characteristics; however, children lost to follow-up had a higher median weight at 4 months old (5.6 kg vs 5.2 kg, *P* = .008, Table 1).

Morbidity and Mortality Among HIV-Infected Children

Of the 31 children who died, the age at death ranged from 2 to 69 months, the median age was 22 months, and 22 (71%) had started antiretroviral therapy.

The estimated median survival time after infection (ie, birth) was 60 months (95% confidence interval: 31–89 months), with an estimated 82%, 74%, 61%, 56%, 49%, and 43% surviving for 1, 2, 3, 4, 5, and 6 years, respectively. The estimated median survival time free from Class C disease or death was 33 months (95% confidence interval: 16–50 months), with 73%, 59%, 49%, 45%, 40%, and 34% surviving without Class C disease for 1, 2, 3, 4, 5, and 6 years, respectively. Survival free of Class C disease was similar for children who were lost to follow-up and those who were not. Infectious causes of death were most common: pneumonia (52%), diarrhea (19%), and other infectious causes (sepsis and/or fungal esophagitis, 10%). Causes of death, stratified by age, are shown in Fig 1.

Of the 68 infected children, 6 died at 4 to 8 months of age without having had any clinical signs of HIV infection recognized by the time of their last study visit, which was a median of 1.5 months before death. Four of these children had CD4⁺ cell counts <1500 cells/ μ L at 2 months old; 3 died from pneumonia.

The other 62 infected children developed an HIV-related sign⁸ at a median age of 4 months (range: 1–42 months). A Class C condition (recurrent serious bacterial infections) developed as the first sign of HIV infection in 2 children aged 4 and 11 months; 23 children had >1 sign at presentation (Table 2). The

TABLE 1. Comparison of Various Factors by Rate of Disease Progression in Children With Perinatally Acquired HIV Infection*

Factor	Rate of Disease Progression					P Value (Rapid Versus Slow)
	Overall (N = 68)	Rapid (n = 12)	Intermediate (n = 17)	Slow (n = 18)	Lost (n = 21)	
Maternal						
Median CD4+ cell count at delivery (cells/ μ L)	410	350	380	470	460	.006
Median viral load at delivery (log ₁₀ copies/mL)	4.8	5.1	4.8	4.5	4.8	.04
Newborn						
Median birth weight (g)	3030	2900	2900	3100	3010	.13
Median gestational age (wk)	39.5	38	39.5	40	40	.42
PCR+ within 72 h of birth	14/55	3/8	4/12	5/16	2/19	1.00
Early infancy (0–4 mo)						
Median viral load at 2 mo (log ₁₀ copies/mL)	6.5	6.6	6.5	6.5	6.4	.11
Median CD4+ cell count at 2 mo (cells/ μ L)	2280	1510	2210	2610	2410	.09
Median weight gain birth to 4 mo (kg)	2.2	1.7†	1.9	2.6	2.4	.004
Median weight at 4 mo (kg)	5.3	4.5†	5.0	5.3	5.6	.003

* Rapid = died within 1 year of birth; Intermediate = died at age 1 to 5 years; Slow = survived for >5 years; Lost = all other children. † Excludes 1 child who died before age 4 months.

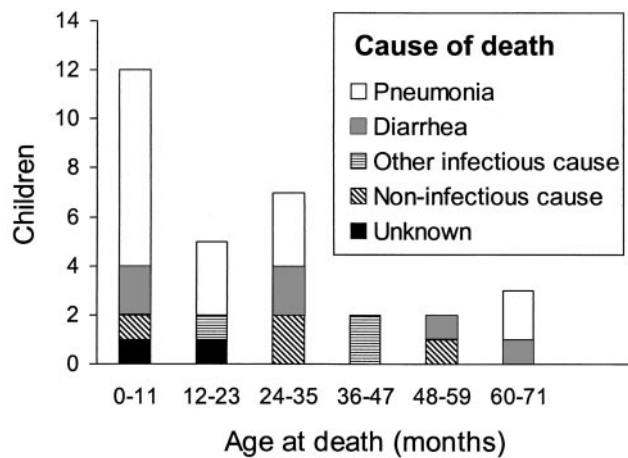


Fig 1. Primary causes of death, by age at death (n = 31).

most common first signs and median ages when first noted were lymphadenopathy (n = 25 [40%], median: 7 months old), splenomegaly (n = 19 [31%], median: 3 months old), and hepatomegaly (n = 18 [29%], median: 3 months old). A Class C condition was diagnosed in 21 children at a median age of 12 months; 14 (67%) died at a median of 5 months after diagnosis (Table 3). Two children were diagnosed with lymphoid interstitial pneumonitis at 63 and 69 months old. After signs of HIV infection appeared, 32 (52%) of the 62 children with symptomatic HIV infection were prescribed antiretroviral medications, and 36 (58%) were prescribed prophylaxis against PCP. Antiretroviral therapy had been prescribed for only 12 (22%) of the 55 children in follow-up at 1 year of age, but 19 (63%) of the 30 in follow-up at 3 years of age.

Predictors of Rapid Progression

Twelve infected children died within 1 year of birth (“rapid progression”), 17 children died between 1 and 5 years of age (“intermediate progression”), and 18 children survived for >5 years (“slow

progression;” Table 1). Children who gained fewer than 2 kg by 4 months old were 7 times more likely, and children whose CD4 count was <1500 cells/ μ L at 2 months old were 4 times more likely to have rapid progression (Table 4). Other significant predictors were low CD4 count or high viral load in the mother at delivery and high viral load in the infant at 2 months of age.

Status of Children Still in Follow-up

Of the 16 children still in follow-up in October 2000, the median age at last visit was 73.5 months and the age range was 62 to 84 months. At the last visit, 14 children (88%) were taking antiretroviral medications, and 15 (94%) were taking trimethoprim-sulfamethoxazole as prophylaxis against PCP. The median CD4+ cell count was 452 (range: 15–1131) cells/ μ L. The mothers of 6 (38%) children had died, and 7 (44%) children were still living with their biological mothers.

DISCUSSION

In this large systematic cohort study of perinatally HIV-infected children in Asia, the HIV subtype, demographics, disease prevalence, medical infrastructure, and racial composition differ from those in similar studies in America, Europe, and Africa. Thus, the results of this study may be more helpful than studies from elsewhere in guiding clinicians and public health officials in this region, especially Thailand.

By 5 years after birth, an estimated 49% of the HIV-infected Thai children in our study had died, a proportion higher than that reported from Europe (26% by 6 years)¹⁰ or the United States (25%–35% by 5 years)^{11,12} but lower than that reported from Rwanda (62% by 5 years)¹³ or Uganda (54% by 2 years).¹⁴ The 1-year survival rate in this cohort (82%) is similar to that reported from a more recent study (short-course zidovudine perinatal trial) in the same 2 Bangkok hospitals during 1996–1998 (85%).¹⁵ Sim-

TABLE 2. First Signs of HIV Infection Among HIV-Infected Children (*n* = 62)*

Sign	Number of Children			
	0–5 Months	6–11 Months	12–23 Months	≥24 Months
First manifestation of HIV recognized	39	13	8	2
Class C condition† as first sign	2	2	0	0
Other first sign†				
Lymphadenopathy	9	9	7	0
Splenomegaly	13	5	1	0
Hepatomegaly	11	4	3	0
Dermatitis	11	0	0	0
Thrush	4	1	1	0
Failure to thrive	4	0	0	0
Weight loss	2	1	0	1
Fever	1	1	1	0
Recurrent lower respiratory infections	2	0	0	0
Bacterial pneumonia	2	0	0	0
Chronic diarrhea	1	0	0	0
Recurrent diarrhea	0	0	1	0
Failure to reach milestones	0	0	1	0
Motor deficits	0	0	0	1
Herpes simplex virus infection	1	0	0	0
Anemia	1	0	0	0

* Six children died before signs of HIV infection; 23 children had >1 first sign.

† Definitions based on CDC classification.⁸

TABLE 3. Class C Clinical Conditions Among HIV-Infected Children (*n* = 21)

Condition*	Number†	Median Age (Months)	Number Died (%)	Median Time From Diagnosis to Death (Months)
Recurrent serious bacterial infections	13	11	8 (62%)	10.5
Wasting syndrome	8	26	7 (88%)	0.5
Encephalopathy	5	11	4 (80%)	17.0
PCP	4	7	4 (100%)	0.5
<i>Candida esophagitis</i>	4	20.5	4 (100%)	5.0
First Class C condition	21	12	14 (67%)	3.0

* Definitions based on CDC classification.⁸

† Includes 4 children with >1 Class C condition at time of first Class C condition and 6 children who had subsequent Class C conditions diagnosed.

TABLE 4. Risk of Rapid Disease Progression in Children With Perinatally Acquired HIV Infection*

Factors	Number (%) Rapid Progression		Relative Risk (95% CI)
	Factor Present	Factor Absent	
Maternal			
CD4+ cell count at delivery <400 cells/μL	9/27 (33%)	3/40 (8%)	4.4 (1.3–14.9)
Viral load at delivery >10 ⁵ copies/mL	7/22 (32%)	5/46 (11%)	2.9 (1.1–8.2)
Newborn			
Birth weight <2500 g	4/11 (36%)	8/57 (14%)	2.6 (0.9–7.1)
Gestational age <37 wk	1/7 (14%)	11/59 (12%)	0.8 (0.1–5.1)
PCR+ within 72 h of birth	3/14 (21%)	5/41 (12%)	1.8 (0.5–6.4)
Male	3/27 (11%)	9/41 (22%)	0.5 (0.2–1.7)
Early infancy (0–4 mo)			
Viral load at 2 mo >10 ^{6.5} copies/mL	9/32 (28%)	2/31 (7%)	4.4 (1.0–18.6)
CD4+ cell count at 2 mo <1500 cells/μL	4/9 (44%)	5/44 (11%)	3.9 (1.3–11.8)
Weight gain birth to 4 mo <2 kg	8/22 (36%)	2/41 (5%)	7.5 (1.7–32.1)
Hepatomegaly, and/or splenomegaly, and/or lymphadenopathy by 4 mo	2/25 (8%)	9/42 (21%)	0.4 (0.1–1.6)

CI indicates confidence interval.

* Includes 12 children with rapid progression (death within 1 year of birth) among 68 infected children.

ilar to that of other populations, the risk of dying was greater in the first 3 years of life than afterward, and pneumonia was a common cause of death, especially in the first year.¹² Although specific diagnosis was unavailable in most cases, it is likely that some of these early cases of fatal pneumonia were caused by *P carinii*, which has its peak incidence in the first year of life among HIV-infected children.^{16,17} Median survival after the diagnosis of Class C disease was short

(3 months), even shorter than the range of survival times reported from other studies (9–23 months).^{10,13} With earlier diagnosis and more effective treatment for both the Class C conditions and the underlying HIV infection becoming available, survival times in settings such as this are likely to become longer.

Except for 6 children who died in early infancy, all children developed HIV-associated signs, most appearing in the first 6 months of life, as reported in

other cohorts.^{10,13,18} The most common signs in our cohort were lymphadenopathy, splenomegaly, and hepatomegaly. Although nonspecific, such signs can be useful for making clinical decisions regarding the care of HIV-exposed children (eg, whether to start or continue treatments). Four of the 6 infants who died before signs of HIV were recognized were severely immunosuppressed, and 3 died of pneumonia. These findings of early, fatal pneumonia should be considered when deciding on strategies for preventing PCP in infants. In a separate cohort, we evaluated a PCP prophylaxis strategy in which all infants born to HIV-infected mothers were prescribed trimethoprim-sulfamethoxazole and clinical indicators were used at 6 months old to decide whether prophylaxis should be continued. This evaluation suggested that such a PCP prophylaxis strategy can prevent death from pneumonia and that clinical findings can be used for deciding about discontinuing prophylaxis.^{17,19}

Because understanding predictors of rapid disease progression provides useful information for counseling families about a child's prognosis and for making decisions about clinical management, we examined the relationships between early death and several maternal, birth, and early infant factors. Several factors were observed more frequently with regard to children who died within 12 months of birth: high viral load and low CD4⁺ cell count in their mothers at delivery, low CD4⁺ cell count and high viral load in the infants at 2 months old, and poor infant weight gain by 4 months old. These factors have been associated with HIV disease progression in other cohort studies in the United States, Europe, and Africa.^{10,13,14,18,20–29} Because CD4 count measurement is increasingly available in Thailand, maternal test results may be useful to guide interventions for both HIV-infected women and their children. For countries with more limited resources, an inexpensive and widely available prognostic marker such as early weight gain may be useful. Although it is unknown whether nutritional interventions would improve survival among poorly thriving children with HIV infection or whether poor weight gain itself is a manifestation of advanced HIV infection, children with poor weight gain would likely benefit from more intensive nutritional and medical interventions. A positive PCR test at birth, considered a proxy for in utero infection, was not a significant predictor of rapid progression in our cohort, although the number of children analyzed was small.

This study also indicates that avoidance of breastfeeding and use of infant formula from birth did not have any apparent adverse impact on mortality among the uninfected children born to HIV-infected mothers. Although there were several deaths among newborns with unknown status, there were none among the 213 infants known to be uninfected. These data support the safety of Thailand's policy of providing replacement feeding for infants born to HIV-infected mothers.⁴

Our study has several limitations. We studied a relatively small number of HIV-infected children, thereby limiting our statistical power to precisely

define survival risk or to conduct meaningful multivariable analyses of risk factors. Because antiretroviral therapy usually was started in response to disease progression, we could not adjust our analysis of risk factors for antiretroviral treatment and so cannot speculate as to the extent to which antiretroviral treatment (generally zidovudine monotherapy or dual nucleoside analog therapy) may have prolonged life. Moreover, it is likely that more potent antiretroviral regimens, such as those including a protease inhibitor, would have delayed clinical progression and death. Finally, whether the findings from these 2 large Bangkok tertiary hospitals can be generalized to other settings in Thailand or Asia is unknown.

Nonetheless, this cohort has several features that make these data useful for clinicians, counselors, and policymakers. Its prospective follow-up from birth, systematic collection of clinical and laboratory data, and relatively long follow-up period enhance the reliability of the data. The description of the manifestations of perinatally acquired HIV disease in Thailand can assist the growing number of clinicians caring for HIV-infected children in Thailand and Asia. Estimates of survival times can aid in appropriate counseling of families about the prognosis of HIV-infected children. Finally, estimates of survival times and incidence of severe disease can assist public health policymakers estimate the number of HIV-infected children requiring long-term health care and other support services. The finding that half of the HIV-infected children in Thailand may be surviving for 5 years or more even with limited antiretroviral therapy highlights the substantial resources that are needed to meet the long-term medical and social needs of these children, such as antiretroviral therapy, other health care, and psychosocial support.

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