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Hospitalization and Mortality among HIV-Infected Children after Receiving Highly Active Antiretroviral Therapy

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Abstract

Background— Pediatric antiretroviral therapy programs have recently been implemented in resource-limited settings. Their impact in a prospective cohort is not well documented. The aim of this study was to evaluate the rates and causes of hospitalization and mortality among human immunodeficiency virus (HIV)–infected Thai children after receiving highly active antiretroviral therapy (HAART).

Methods— Children who started receiving HAART from August 2002 to March 2005 were prospectively observed. The patients included in the study were antiretroviral-naive HIV-infected children who had CD4 cell percentages ≤ 15% before treatment. All patients were observed for at least 48 weeks.

Results— One hundred ninety-two children were included. The mean age at HAART initiation was 7.6 years (range, 0.4–14.8 years). At baseline, the mean CD4 cell percentage (±SD) was 5.2% ± 4.9%, and the mean plasma HIV RNA level (±SD) was 5.4 ± 0.5 $\log_{10}$ copies/mL. Sixty-seven children (35%) were hospitalized a total of 108 times. The hospitalization rate decreased from 30.7% during the first 24-week period to 2.0% during weeks 120–144 after initiation of HAART. Fifty-nine hospital admissions (54.6%) occurred during the first 24 weeks of HAART. Causes of hospitalization were pneumonia and other bacterial infections (61.7%), immune reconstitution syndrome (23.4%), noninfectious illness (6.5%), opportunistic infection (5.6%), and drug-related events (2.8%). The mortality rate decreased from 5.7% in the first 24 weeks to 0%–0.6% in the subsequent 24-week intervals.

Conclusion— Hospitalization and mortality rates significantly decreased among HIV-infected children receiving HAART. Most hospitalizations and deaths occurred during the first 24 weeks of HAART.

HAART has been shown to slow the progress of disease and prolong survival in HIV-infected adults [1–3]. The incidence of common opportunistic infections (OIs), such as *Pneumocystis jiroveci* pneumonia, *Mycobacterium avium* complex disease, and cytomegalovirus retinitis, has also decreased [1]. HAART has similarly changed the course of HIV disease in children. Studies in developed countries have shown that rates of mortality, morbidity, and hospitalization decrease significantly among HIV-infected children who receive HAART [4–9]. Researchers in Romania and Haiti who reported their experiences with HIV-infected children who had access to HAART found similar decreases in morbidity and mortality [10, 11].

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In 2002, the Thai Ministry of Public Health launched the National Access to Antiretroviral Program for People Living with HIV/AIDS program, with the aim of providing universal access to treatment for all HIV-infected Thai patients who meet national-guidelines criteria for the initiation of antiretroviral therapy. This program enabled us to evaluate hospitalization and mortality among HIV-infected Thai children after receipt of HAART [12].

PATIENTS AND METHODS

From August 2002 to March 2005, we prospectively observed all HIV-infected children who started receiving HAART in the National Access to Antiretroviral Program for People Living with HIV/AIDS program a 4 hospitals in northern Thailand: the Chiang Mai University Hospital, Chiang Mai; Chiang Mai Provincial Hospital, Chiang Mai; Lamphun Provincial Hospital, Lamphun; and Sanpatong District Hospital, Chiang Mai. The patients included in the study were HIV-infected children who were antiretroviral naive (except for exposure to antiretroviral drugs as part of the prevention of mother-to-child HIV transmission) and had a baseline CD4 cell percentage ≤15%. HIV infection in children >18 months of age was documented by HIV antibody test; in children <18 months of age, HIV infection was documented by HIV DNA PCR or HIV RNA PCR test. All patients were observed for at least 48 weeks and were censored at 144 weeks after initiation of HAART. The study was approved by the research ethics committee of Chiang Mai University.

The following data were recorded: date of birth, sex, date when HAART was initiated, HAART regimen, CD4 cell count and percentage, plasma HIV RNA level, number and cause of hospital admissions, and number of days per hospitalization, as well as death and cause of death. Reasons for admission were divided into 5 categories: OI, immune reconstitution syndrome (IRS), drug-related events, other infections, and noninfectious illnesses. Admissions for diagnostic procedures and nonmedical causes were excluded. For the purpose of this article, an OI is defined as an infection caused by organisms listed as causing diseases in Centers for Disease Control and Prevention clinical category C [13]. When IRS was determined to be the cause of hospitalization and/or death, it was defined by (1) evidence of a favorable response to HAART, defined as a reduction in HIV RNA levels of at least 2 $\log_{10}$ copies/mL or an increase in CD4 cell percentage ≥5%; (2) a temporal association between the initiation of HAART and the onset of disease; and (3) the identification of microorganisms or a condition previously reported to be associated with IRS [14]. Drug-related events were defined as abnormal signs and symptoms possibly related to antiretroviral agents received at that time. “Other infections” were defined as infections other than OI. They were diagnosed mainly by assessment of clinical signs and symptoms with or without laboratory confirmation. Noninfectious illnesses were other causes of hospital admission, such as hematological, psychological, or cardiovascular diseases.

The 24-week hospitalization and mortality rates were calculated by dividing the number of hospital admissions and deaths, respectively, in each 24-week interval by the number of children at risk in that interval. The overall hospitalization rate and death rate were calculated for the whole duration of the study and are expressed as the number of hospitalizations and deaths per 100 person-years.

Comparisons of continuous variables were analyzed by independent sample *t* test and multivariate analysis, and those of categorical variables were analyzed by χ^2 test. Statistical significance was set at $P < .05$ (2-tailed). Statistical analyses were performed using Statistical Package for Social Science version 11.5 software (SPSS).

RESULTS

Characteristics of the study population

One hundred ninety-two HIV-infected children who were followed at Chiang Mai University Hospital (*n* = 119), Lamphun Provincial Hospital (*n* = 39), Chiang Mai Provincial Hospital (*n* = 14), and Sanpatong District Hospital (*n* = 20) were included in the study. Ninety-four children (49%) were male. All except 2 children were infected perinatally; 1 child was infected by blood transfusion, and 1 was infected by heterosexual transmission.

The mean age at a time of HAART initiation was 7.6 years (range, 0.4–14.8 years). There were 10 children who initiated antiretroviral therapy before 2 years of age. The mean baseline CD4 cell percentage (± SD) was 5.2% ± 4.9%, and the mean CD4 cell count (± SD) was 171 ± 289 cells/μL. The mean baseline plasma HIV RNA level (± SD) was 5.4 ± 0.5 $\log_{10}$ copies/mL. The HAART regimens used were the combination of stavudine, lamivudine, and nevirapine in 113 patients (59%); the combination of stavudine, lamivudine, and efavirenz in 73 patients (38%); and the combination of zidovudine, lamivudine, and nevirapine in 6 patients (3%).

At 24 weeks after HAART initiation, the mean CD4 cell percentage (±SD) increased to 13.2% ± 6.8%, and the mean CD4 cell count (± SD) increased to 431 ± 425 cells/μL. Of the 192 children, 104 (54.2%) achieved plasma HIV RNA levels < 50 copies/mL.

At 48 weeks after HAART initiation, the mean CD4 cell percentage (SD) was 17.2% ± 7.5%, and the mean CD4 cell count (± SD) was 922 ± 492 cells/μL. Of the 192 children, 130 (67.7%) achieved plasma HIV RNA levels <50 copies/mL. As of April 2006, the mean follow-up time (± SD) was 125 ± 44 weeks after initiation of HAART. The total follow-up time was 460 person-years.

Hospitalization after initiation of HAART

During the study period, 67 children (35%) were hospitalized a total of 107 times, giving an overall hospitalization rate of 23.0 admissions per 100 person-years. The median number of admissions per child was 1 (range, 1–8). Twenty-three children (34%) required >1 hospital admission. The percentage of children who had at least 1 hospitalization after initiation of HAART was higher among children >2 years of age than among those in the older age group (50.0% vs. 33.5%; *P* = .29). The 24-week hospitalization rate decreased significantly, from 30.7% during the first 24-week period after initiation of HAART to 2.0% during the last 24-week period of observation (table 1). The median length of hospital stay was 7 days (range, 1–230 days); it was longest among those admitted because of OI (38 days; range, 13–73 days) and shortest among those admitted because of noninfectious illnesses (4 days; range, 1–19 days).

The details of hospitalization are shown in table 2. Causes of hospital admission were pneumonia and other bacterial infections (61.7%), IRS (23.4%), OI (5.6%), drug-related events (2.8%), and noninfectious illness (6.5%). The IRS that most frequently resulted in hospitalization was mycobaterial infection. Three children experienced moderate to severe adverse events due to nevirapine. They presented with acute onset of fever and erythematous rash spreading from the face to the trunk and extremities after a mean duration of 8.7 days of HAART. After 48 weeks of HAART, the hospitalizations were mostly attributable to pneumonia and other bacterial infections. OI, IRS, and antiretroviral drug toxicity rarely occurred.

Mortality after initiation of HAART

Thirteen patients died. The mortality rate was 5.7% (11 deaths) during the first 24 weeks after the initiation of HAART, but it decreased to 0%–0.6% in the subsequent 24-week intervals (table 1). The overall mortality rate was 2.8 deaths per 100 person-years. The mortality rate was significantly higher among children <2 years of age than among those in the older age group (30.0% vs. 5.5%; $P = .003$).

Demographic and clinical data on the patients who died are shown in table 3. The mean age at initiation of HAART was 7.0 years (range, 0.6–13.6 years). The mean baseline CD4 cell percentage (± SD) was 3.2% ± 3.7%, and the mean CD4 cell count (± SD) was 109 ± 217 cells/μL. The mean plasma HIV RNA level (± SD) was 5.3 ± 0.4 $\log_{10}$ copies/mL. The median duration of HAART was 7 weeks (range, 4–74 weeks). Ten (77%) of the patients who died had a history of ± 1 AIDS-related illness before initiation of HAART. Four (31%) of the 13 deaths were due to IRS.

Predictors of death or hospitalization

In the univariate analysis, the mean plasma HIV RNA level (± SD) before initiation of HAART was significantly higher in the group of children who required hospitalization or died (5.5 ± 0.4 vs. 5.3 ± 0.6 $\log_{10}$ copies/mL; $P = .02$). The mean age (± SD) before initiation of HAART was significantly lower in the group of children who required hospitalization or died (8.9 ± 3.7 vs. 9.9 ± 3.2 years; $P = .04$). There was no significant difference between the mean CD4 cell percentages (±SD) before initiation of HAART between the 2 groups (4.5% ± 4.4% vs. 5.7% ± 5.1%; $P = .09$). However, in the multivariate analysis, there were no statistically significant differences in age ($P = .23$) or baseline plasma HIV RNA level ($P = .07$) between the 2 groups.

DISCUSSION

Studies of the efficacy of HAART in HIV-infected children have usually assessed its impact on immunologic and virologic status and/or mortality rates among patients [5,6,11,12,15,16]. Few have reported the impact of HAART on hospitalization rate [4,7–10] or on the specific cause(s) of hospitalization or death [9] among these HIV-infected children after the initiation of HAART. This information is important for public health authorities. Training programs targeted at these specific causes of morbidity and mortality would enable health care workers to make diagnoses and give treatment in a timely manner. In the present study, we have demonstrated that the hospitalization rate decreased from 30.7% during the first 24-week period after initiation of HAART to 2.0% during weeks 120–144 after initiation of HAART.

The most frequent cause of hospital admission was pneumonia and other bacterial infections, which accounted for 66 admissions (61.7%). Twenty-five admissions (23.4%) were due to IRS, 6 (5.6%) were due to OI, and 3 (2.8%) were due to drug-related events. Although the methods of study were different, our results were similar to those reported by Viani et al. [9]. In that study, children receiving care during 1994–2001 at 3 HIV clinics in southern California were observed longitudinally for several clinical and laboratory parameters, including cause of hospital admission. The use of HAART increased from 0% in 1994 to 93% in 2001. Fifteen percent of the cohort was admitted for AIDS-defining illnesses in 1994, whereas no patient was admitted for this reason in 2001. Pneumonia and other bacterial infections were the principal causes of admission in the pre-HAART era (1994–1995) and continued to be the leading causes until 1999. During 2000–2001, antiretroviral toxicity and IRS emerged as leading causes of hospitalization, in addition to pneumonia and other bacterial infections [9].

In the present study of 192 Thai children with advanced-stage HIV infection (mean baseline CD4 cell percentage, 5.2%) who began receiving HAART, the overall mortality rate was 3.0

deaths per 100 person-years. In our previous study, of 353 symptomatic HIV-infected children who were admitted to the Chiang Mai University Hospital between January 1989 and December 1994, before the availability of HAART, 42% of the patients died during the first hospitalization [17]. In another study, conducted in a tertiary-care hospital in northeastern Thailand and involving 90 HIV-infected children who received care between January 1989 and December 1997, the 1-year survival rate from the time of the first symptom was 75.3% [18]. A similar reduction in mortality with the availability of HAART was shown in several studies, both from developed countries [5–9] and resource-limited countries [10,11]. In this cohort, the mortality rate was significantly higher among children <2 years of age than in the older age group (30.0% vs. 5.5%; $P = .003$). This probably reflected the fact that early diagnosis of HIV infection in infants (by HIV DNA PCR or HIV RNA PCR) was not routinely available in primary-care hospitals in Thailand. Thus, only HIV-infected infants who manifested as "rapid progressors" were identified and referred to antiretroviral treatment facilities.

There were 13 deaths in our study: 8 due to pneumonia, septicemia, and/or other bacterial infections; 4 due to IRS; and 1 due to OI. The fact that pneumonia and sepsis were the major causes of death in our study was similar to findings reported in the study conducted in southern California. In that study, of the 98 children who received care during 1994–1997, 9 died. The principal causes of death were sepsis and pneumonia, followed by AIDS-defining illnesses. Two of the 110 children who received care during 1998–2001 died, with pneumonia being the principal cause of death [9]. Our finding that 4 of the 13 deaths were due to IRS was consistent with the high incidence of IRS documented in our cohort. Between May 2002 and April 2004, we conducted a study to determine the incidence and spectrum of IRS in 153 children with late-stage HIV infection after initiation of HAART [14]. All patients were followed for 48 weeks. The incidence of IRS was 19% (95% CI, 13.1%–26.1%). The median time of onset was 4 weeks after the initiation of HAART (range, 2–31 weeks). There were 32 episodes of IRS, including 14 caused by mycobacterial organisms, 7 caused by varicellazoster virus, 7 caused by herpes simplex virus, 3 caused by *Cryptococcus neoformans*, and 1 episode of Guillain-Barré syndrome.

In our study, the mortality rate during the first 24 weeks after HAART initiation was 5.7%. The 24-week mortality rate decreased to a mean of 0.24% in the following five 24-week intervals (table 1). This finding of a high mortality rate in the first 6 months after HAART is similar to that reported from another developing country, the Ivory Coast, where 78 children receiving HAART were followed for a mean duration of 21 months [15]. The probability of survival in this cohort was 92.3% at 6 months, 91.0% at 12 months, and 88.1% at 18 and 24 months. However, the causes of death were not identified in the study.

The high mortality rate during the first months of HAART among patients in developing countries had also been reported in a study of 910 treatment-naive adult patients from Haiti, in which 80% of deaths occurred during the first 6 months [11]. It was also documented in a study comparing mortality among HIV-infected adults in the first year of HAART between low-income and high-income countries [19]. In 18 HAART programs in Africa, Asia, and South America, the number of deaths per 1000 person-years was reported to be 147 (95% CI, 105–207) during month 1, 106 (95% CI, 71–160) during month 2, 51 (95% CI, 33–77) during months 3–4, 51 (95% CI, 33–79) during months 5–6, and 27 (95% CI, 19–40) during months 7–12. The authors suggested that the higher mortality rates in low-income countries during the first few months of treatment, compared with those in Europe and North America, could be explained by the low CD4 cell counts, the more advanced clinical stage, and the prevalence of coexisting infection at the time of HAART initiation, as well as the occurrence of IRS in these patients with late-stage HIV infection. In our study, we also found that these factors, together with adverse events caused by antiretroviral drugs, were the principal causes of morbidity and mortality. Thus, in developing countries planning to start a HAART program, training

programs for health care workers that are targeted at these conditions are needed. This, together with training programs for drug adherence counseling and the building of infrastructure to promote voluntary counseling and testing and ensure uninterrupted access to HAART, are the key factors for a successful HAART program in a resource-limited setting.

In conclusion, the present study has demonstrated that the use of HAART has a significant impact on the reduction of hospitalization and mortality rates among HIV-infected children, even in resource-limited settings. A high mortality rate during the first 6 months of HAART was documented. Identification of the causes of hospitalization and death is essential to decrease the high early mortality rate.

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Potential conflicts of interest. All authors: no conflicts.

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Table 1

Hospitalization and mortality rates among HIV-infected children, by 24-week interval after initiation of HAART.

Variable	0–24 weeks	25–48 weeks	49–72 weeks	73–96 weeks	97–120 weeks	120–144 weeks
Patients at risk,[a] no.	192	181	180	177	157	146
Hospital adminissions, no.	59	17	15	9	4	3
24-Week hospitalization rate, %	30.7	9.4	8.3	5.1	2.5	2.1
Cause of hospitalization,[b] no. of admissions (%)						
OI	6 (10)	0	0	0	0	0
IRS	17 (29)	5 (29)	2 (13)	0	0	1 (33)
Drug-related adverse event	3 (5)	0	0	0	0	0
Other infection	32 (54)	9 (53)	11 (73)	9 (100)	3 (75)	2 (67)
Noninfectious illness	1 (2)	3 (18)	2 (13)	0	1 (25)	0
Deaths, no.	11	1	0	1	0	0
24-Week mortality rate, %	5.7	0.6	0	0.6	0	0

NOTE. IRS, immune reconstitution syndrome; OI, opportunistic infection.

[a] Number of patients decreased because of staggered enrollment.

[b] Details are given in table 2.

Table 2

Reasons for hospital admission among HIV-infected children, stratified by 24-week interval after initiation of HAART.

Reason for admission	0–24 weeks	25–48 weeks	49–72 weeks	73–96 weeks	97–120 weeks	121–144 weeks
OI[a]						
Mycobacterium avium complex infection	3	0	0	0	0	0
Mycobacterium kansasii infection	1	0	0	0	0	0
Intracranial tuberculoma	1	0	0	0	0	0
Cytomegalovirus myocarditis	1	0	0	0	0	0
IRS[b]						
M. avium complex infection	6	3	1	0	0	0
M. kansasii infection	1	0	0	0	0	0
Mycobacterium scrofulaceum subcutaneous infection	1	0	0	0	0	0
Pulmonary tuberculosis	5	1	0	0	0	0
Cryptococcal meningitis	3	1	1	0	0	0
Herpes simplex virus encephalitis	1	0	0	0	0	0
Cytomegalovirus and Epstein-Barr virus encephalitis	0	0	0	0	0	1
Drug-related adverse event[c]						
Fever with rash[d]	3	0	0	0	0	0
Other infection[e]						
Pneumonia	20	7	4	5	2	0
Septicemia	5	0	1	0	0	0
Otolaryngological infection	3	0	1	0	0	0
Skin/subcutaneous infection	2	0	2	1	0	1
Gastrointestinal tract infection	1	2	1	1	0	0
Fever/febrile convulsion	1	0	2	1	1	1
Bacterial meningitis	0	0	0	1	0	0
Noninfectious illness[f]						
Cerebral infarction	0	0	1	0	0	0
Immune thrombocytopenic purpura	0	1	0	0	1	0
Depression	0	0	1	0	0	0
Ciprofloxacin-induced allergic reaction	0	1	0	0	0	0
Peptic ulcer	1	0	0	0	0	0
Hypokalemic pseudoparalysis	0	1	0	0	0	0

NOTE. Data are no. of admissions. IRS, immune reconstitution syndrome; OI, opportunistic infection.

[a] Six admissions (5.6%).

[b] Twenty-five admissions (23.4%).

[c] Three admissions (2.8%).

[d] All were moderate to severe adverse events caused by nevirapine.

[e] Sixty-six admissions (61.7%).

[f] Seven admissions (6.5%).

Table 3

Details of HIV-infected children who died after initiation of HAART.

Patient	Sex	Age at initiation of HAART, years	HAART regimen[a]	Duration of HAART, weeks	History of AIDS-related illness before HAART	Diagnosis/ cause of death	Baseline CD4 cell percentage (CD4 cell count, cells/ mL)	Baseline plasma HIV RNA level, $\log_{10}$ copies/mL
1	M	1.6	NVP	4	None	Sepsis	5 (90)	5.83
2	M	4.7	NVP	4	*Penicillium marneffei* infection	*Mycobacterium avium* complex infection	0 (0)	ND
3	M	10.9	NVP	5	Disseminated *Mycobacterium scrofulaceum* infection	*Pseudomonas aeruginosa* pneumonia	0 (0)	4.86
4	F	7.6	NVP	6	Bronchiectasis, *P. marneffei* infection	Pneumonia	1 (ND)	ND
5	F	9.7	NVP	6	*Mycobacterium kansasii* infection	*Staphylococcus aureus* septicemia	5 (65)	ND
6	M	1.1	EFV	6	Oral candidiasis, chronic diarrhea	Diarrhea/sepsis	9 (314)	4.80
7	M	3.3	EFV	7	CMV retinitis, cryptococcal men ingitis, immune thrombocytopenic purpura, intracranial mass (presumptive tuberculoma)	IRS (postcraniotomy intracranial hemorrhage)	1 (5)	5.33
8	M	0.6	NVP	9	CMV retinitis and colitis	IRS (CMV) presenting as myocarditis	11 (740)	5.88
9	M	13.6	EFV	12	None	Sepsis	1 (23)	4.82
10	M	8.3	EFV	21	*P. marneffei* infection, autoimmune hemolytic anemia and hepatitis	*Salmonella* septicemia	0 (4)	5.88
11	F	11.3	EFV	22	CMV retinitis, HIV nephropathy, enteropathy, and encephalopathy	IRS (herpes simplex) presenting as encephalitis	2 (12)	5.09
12	F	8.7	NVP	26	None	IRS *(M. avium* complex)	6 (44)	5.57
13	M	9.5	NVP	74	*M. avium* complex infection	Chylous ascites with *Escherichia coli* septicemia	0 (5)	5.02

NOTE. CMV, cytomegalovirus; EFV, efavirenz; IRS, immune reconstitution syndrome; ND, not done; NVP, nevirapine.

[a] "NVP" denotes a regimen of nevirapine, stavudine, and lamivudine; "EFV" denotes a regimen of efavirenz, stavudine, and lamivudine.