Efficacy of Highly Active Antiretroviral Therapy in HIV-Infected Children Participating in Thailand's National Access to Antiretroviral Program

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Background. Programs for access to antiretroviral treatment were only recently implemented in developing countries. This study aimed to describe the effect of highly active antiretroviral therapy (HAART) in treating human immunodeficiency virus (HIV)–infected children in Thailand's National Access to Antiretroviral Program for People Living with HIV/AIDS.

Methods. From August 2002 to July 2003, a total of 107 children were enrolled in the study. They received HAART consisting of either nevirapine or efavirenz, together with lamivudine and stavudine. Generic drugs and/ or adult formulations were used. CD4 lymphocyte count, plasma HIV RNA level, and weight-for-age and height-for-age z scores were measured before, 2 months after, and every 6 months after initiation of HAART. A genotypic resistance assay was performed for patients with poor virological response.

Results. The mean age of the patients was 7.7 years (range, 2.1–13.8 years). At baseline, the median CD4 cell percentage was 3%, and the plasma HIV RNA level was 5.4 $\log_{10}$ copies/mL. Four patients died from HIV-related illness. After 72 weeks of HAART, the median CD4 cell percentage was 21%, and 76% of patients had HIV RNA levels of <50 copies/mL. The mean weight-for-age and height-for-age z scores increased from −1.9 to −1.3 ($P < .0001$) and from −2.3 to −2.0 ($P < .0001$), respectively. The percentage of patients who took ≥95% of prescribed medications during the interval between every follow-up visit was 86% For patients with suboptimal virological response, the most common resistance mutations among HIV isolates were associated with lamivudine and with nonnucleoside reverse-transcriptase inhibitors.

Conclusion. In this resource-limited setting, HAART is safe and effective for HIV-infected children despite initiation of treatment during the advanced stage of disease. The use of generic and nonpediatric drug formulations is feasible.

HAART prolongs survival of HIV-infected persons [1], but until recently, the drugs were too expensive for most patients in developing countries. The World Health Organization estimates that 1.1 million Asians are currently in need of HAART, with only 6%–7% having access [2]. In Thailand, 120,000 of the estimated 570,000 HIV-infected people currently need HAART [3]. In the past few years, there have been several reports of antiretroviral treatment initiatives for adults in re-source-limited countries [4–7]. There were few such reports for children [8–10].

In 2002, the Thai Ministry of Public Health launched the National Access to Antiretroviral Program for People Living with HIV/AIDS (NAPHA) with the aim of providing treatment to all Thai patients with HIV infection. The program used 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and 1 nonnucleoside reverse-transcriptase inhibitor (NNRTI) as a first-line HAART regimen [11]. To reduce the cost and to facilitate drug supply management, a fixed-dose combination of generic drugs was used, and the use of nonpediatric formulations was encouraged for children. NAPHA relies heavily on a fixed-dose combination of generic stavudine, lamivudine, and nevirapine (known as "GPO-VIR") produced by the Thai Government Pharmaceutical Organization (TGPO) [12]. The

NAPHA enabled us to assess the safety, effectiveness, and feasibility of NNRTI-based HAART regimens in HIV-infected, antiretroviral drug–naive children in a resource-limited setting.

PATIENTS AND METHODS

This study was conducted at the following 4 government hospitals in northern Thailand: Chiang Mai University Hospital (Chiang Mai province), Chiang Mai Provincial Hospital (Chiang Mai province), Lamphun Provincial Hospital (Lamphun province), and Sanpatong District Hospital (Chiang Mai province). These facilities form part of a network of government hospitals serving the adjacent provinces of Chiang Mai and Lamphun (combined population, ~2 million). The study was approved by the research ethics committee of Chiang Mai University. Written informed consent was obtained from each child's parent or guardian before enrollment.

Patients. From August 2002 through July 2003, HIV-infected children who participated in NAPHA were prospectively enrolled in the study. Eligibility criteria were age of <15 years, CD4 cell percentage of ≤15%, and no previous treatment with antiretroviral drugs. Exclusion criteria were active opportunistic infection and baseline serum transaminase and/or bilirubin levels >5 times the upper limit of normal.

Procedures. Patients received either a nevirapine- or efavirenz-based treatment regimen. The choice of the regimen was made by the attending pediatrician. In most instances, this decision was based on the availability of drugs at the time. However, for children <3 years old, efavirenz-based regimens were not prescribed because no data about the appropriate dosage were available [13]. For the nevirapine-based regimen, GPO-VIR (30 mg of stavudine, 150 mg of lamivudine, and 200 mg of nevirapine) was used. The dosage was calculated to deliver a nevirapine dose of 150–200 mg/m² q12h [13]. To minimize the adverse effects of nevirapine, we gave patients only one-half of the daily nevirapine dose for the first 14 days. This was done by using GPO-VIR in the morning dose and separate pills of stavudine and lamivudine in the evening dose. After the first 14 days, GPO-VIR was given as one-half of a tablet, three-fourths of a tablet, and an entire tablet q12h for children with body weights of 12–17 kg, 18–24 kg, and ≥25 kg, respectively. The efavirenz-based regimen consisted of stavudine, lamivudine, and efavirenz. The formulation used was stavudine (30-mg capsules; TGPO), lamivudine (150-mg tablets; TGPO), and efavirenz (50-mg and 200-mg capsules; Bristol-Meyers Squibb). The dosages of stavudine and lamivudine were 1 mg/kg and 4 mg/kg q12h, respectively [13]. Therefore, lamivudine and stavudine were given as one-half of a tablet or capsule, three-fourths of a tablet or capsule, and an entire tablet or capsule q12h for children with body weights of 12–17 kg, 18–24 kg, and >25 kg, respectively. The dosage for efavirenz was 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, and 600 mg q24h in the evening for children with body weights of 10 to <15 kg, 15 to <20 kg, 20 to <25 kg, 25 to <32 kg, 32 to <40 kg, or ≥40 kg, respectively, as recommended in the US guidelines [13].

GPO-VIR and generic lamivudine tablets can easily be divided into halves or quarters by a pair of small scissors, and contents of generic stavudine capsules can be divided in halves with reasonable accuracy. In cases in which three-fourths of a capsule was to be administered, the content of 1 capsule was combined with 4 mL of water in a plastic syringe; 3 mL of this mixture was administered, and the rest was discarded. Doses of efavirenz were administered by appropriate combinations of 50-mg and 200-mg capsules.

Patients attended study visits at weeks 0 (start of treatment), 2, 4, 8, 12, 18, 24, 32, 40, 48, and 72. All children and care givers were counseled initially and at each visit to recognize side effects, seek appropriate care, and adhere closely to the regimens. During each visit, we reviewed the patient's medical history, did a physical examination, and assessed adverse events and adherence to treatment. The clinical stage of disease was determined according to the 1994 US Centers for Disease Control and Prevention revised classification [14]. Weight and height were expressed as weight-for-age and height-for-age z scores with reference to Thai children in the general population [15]. Adverse events were graded according to the US National Institutes of Health Division of AIDS [16]. Treatment was discontinued if a child had events of grade 3 or 4. The rate of adherence was defined as the number of doses taken divided by the total number of doses prescribed during each visit. Adherence was monitored by counting returned medication and by questioning the children and care givers. An adherence problem was defined as an adherence rate of <95% recorded at any scheduled visit [17].

Hematologic tests, blood chemistry tests, and CD4 cell count and plasma HIV RNA load determinations were done at weeks 0, 8, 24, 48, and 72. CD4 cell counts were assessed with use of a FACSCount apparatus (Becton-Dickinson). Plasma HIV RNA levels were measured by the Roche Ultrasensitive Amplicor assay, version 1.5 (Roche). All laboratory tests were done at Chiang Mai University. In patients with suboptimal virological response, HIV genotypic resistance tests were done at the HIV Netherlands Australia Thailand Research Collaboration Center (Bangkok) [18].

Statistical analysis. Weight-for-age and height-for-age z scores, CD4 lymphocyte counts, and virus loads before and after HAART were compared by use of Student's t test or Wilcoxon's rank-sum test, as appropriate. Virological success was defined as a plasma HIV RNA level of <50 copies/mL. In the intention-to-treat analysis, patients who discontinued their primary treatment regimen or died were counted as having ex-

perienced virological failure. Categorical variables were tested by means of χ^2 analysis or with Fisher's exact test, as appropriate.

We used a logistic regression model to assess the importance of risk factors in predicting the likelihood of virological success at week 72. Data were analyzed with Stata software, version 6.0 (Stata). A P value of <.05 for 2-sided tests was considered to be statistically significant.

RESULTS

Characteristics of the study population. From August 2002 through July 2003, a total of 107 HIV-infected children were enrolled in the study, of whom 66 (62%) were at the hospital of Chiang Mai University, and 41 (38%) were at the 3 other hospitals. As of December 2004, all patients had been followed up for at least 72 weeks. The mean age at initiation of treatment was 7.7 years (range, 2.1–13.8 years). Only 5 children were <3 years of age at initiation of treatment. The baseline characteristics of these 107 children are presented in table 1. Sixty-one children received the nevirapine-based, fixed-dose combination regimen (GPO-VIR), and 46 received the efavirenz-based regimen. Five patients who received the nevirapine-based regimen had to switch to the efavirenz-based regimen because of severe adverse drug reactions. Four patients died from HIV-related illnesses during the study period (mortality rate, 3.7%; 95% CI, 1.0%–9.3%). The remaining 98 patients were still taking their primary drug regimen at week 72. The primary care givers were grandparents (for 36% of patients), biological parents (for 26%), relatives (for 20%), and orphanage staff (for 18%). The percentage of patients who took ≥95% of prescribed medi-

Table 1. Baseline characteristics of HIV-infected Thai children before receiving HAART regimens containing either nevirapine or efavirenz in combination with stavudine and lamivudine.

| | | HAART regimen | | |
Characteristic	All patients (*n* = 107)	Nevirapine based (*n* = 61)	Efavirenz based (*n* = 46)	*P*
Demographic				
Male sex	46 (43)	30 (49)	16 (35)	.14
Mean age, years ± SD	7.7 ± 2.7	7.1 ± 2.8	8.5 ± 2.5	.01
Clinical				
Weight, mean *z* score ± SD[a]	−1.9 ± 0.9	−1.9 ± 1.0	−1.9 ± 0.7	.68
Height, mean *z* score ± SD[a]	−2.3 ± 1.5	−2.2 ± 1.7	−2.5 ± 1.0	.20
CDC HIV disease class				
Class N (asymptomatic)	14 (13)	7 (12)	7 (15)	
Class A (mild)	16 (15)	10 (16)	6 (13)	
Class B (moderate)	23 (22)	10 (16)	13 (28)	
Class C (severe)	54 (50)	34 (56)	20 (44)	.40
Immunologic				
Median CD4 cell percentage (IQR)	3 (1–9)	4 (1–9)	3 (1–10)	.95
CD4 cell percentage ≤5%	65 (61)	38 (62)	27 (59)	.71
Median CD4 cell count, cells/μL (IQR)				
Age ≤6 years[b]	97 (44–307)	61 (38–314)	228 (42–538)	.26
Age >6 years[c]	46 (30–71)	46 (30–103)	47 (21–128)	.90
Virologic				
Mean plasma HIV RNA load, $\log_{10}$ copies/mL ± SD	5.4 ± 0.5	5.3 ± 0.5	5.4 ± 0.4	.71
Plasma HIV RNA level >5 $\log_{10}$ copies/mL	82 (77)	44 (72)	38 (83)	.21

NOTE. Data are no. (%) of patients, unless otherwise indicated. CDC, US Centers for Disease Control and Prevention; IQR, interquartile range.

[a] Age- and sex-adjusted with reference to Thai children in the general population.
[b] A total of 25 patients received the nevirapine-based regimen, and 8 patients received the efavirenz-based regimen.
[c] A total of 36 patients received the nevirapine-based regimen, and 38 patients received the efavirenz-based regimen.

Table 2. Immunologic responses of HIV-infected Thai children after receiving HAART for 72 weeks.

Parameter, time point	All patients[a] (n = 107)	HIV RNA level at week 72		
		<50 copies/mL[b] (n = 85)	≥50 copies/mL (n = 22)	P[c]
CD4 cell percentage				
Week 0	3 (1–9)	4 (1–10)	3 (2–6)	.48
Week 8	9 (5–15)	9 (6–16)	7 (3–12)	.13
Week 24	12 (8–18)	12 (8–18)	11 (7–19)	.62
Week 48	17 (11–20)	18 (13–20)	11 (9–19)	.03
Week 72	21 (15–26)	21 (18–27)	14 (11–20)	.002
Increase in CD4 cell count from baseline				
Week 8	126 (73–275)	143 (80–283)	95 (17–214)	.12
Week 24	226 (127–330)	218 (127–318)	240 (89–414)	.68
Week 48	332 (187–457)	353 (243–483)	209 (131–390)	.07
Week 72	532 (287–709)	565 (330–729)	274 (156–631)	.006

NOTE. Data are median values (interquartile range).

[a] Three patients died at weeks 12, 12, and 18 of HAART, leaving 104 patients available for evaluation at week 24. One patient died at week 26, leaving 103 patients for evaluation at weeks 48 and 72.

[b] Includes 81 patients with virological success in the intention-to-treat analysis (table 3), as well as 4 of 5 patients who achieved virologic success after their regimens were changed from nevirapine-based HAART to efavirenz-based HAART.

[c] By Wilcoxon's rank-sum test.

cations during the interval between every visit was 86% (85% for the nevirapine-based regimen and 86% for the efavirenz-based regimen; P = .80). During the same 12-month period, NAPHA enrolled 867 children nationwide.

Clinical outcomes. Between week 0 and week 72, the mean weight-for-age and height-for-age z scores (±SD) increased from −1.9 ± 0.9 to −1.3 ± 0.9 (P<.0001) and from −2.3 ± 1.5 to −2.0 ± 1.4 (P<.0001), respectively. The mean hemoglobin level (±SD) increased from 10.1 ± 1.6 mg/dL to 12.5 ± 1.3 mg/dL (P<.0001). There were 4 cases of severe AIDS-related illness in the group that received the nevirapine-based regimen and 7 in the group that received the efavirenz-based regimen (4 cases of nontuberculous *Mycobacterium* infection, 3 cases of tuberculosis, 1 case of recurrent cryptococcal meningitis, 1 cases of herpes encephalitis, and 2 cases of clinical sepsis). Four of these 11 patients died. Two died from bacterial sepsis at week 12, one from herpes encephalitis at week 18 and the other from *Mycobacterium avium* complex infection at week 26. The CD4 cell percentages for these 4 patients at enrollment were 0%, 1%, 2%, and 6%. At the time of death, 3 of the 4 patients showed good virological response to HAART, although the CD4 cell percentage remained low.

Immunologic outcomes. Table 2 shows the median CD4 cell percentages and the median increases in the CD4 cell count at weeks 8, 24, 48, and 72. Patients with successful virological suppression had significantly higher median percentages of CD4 lymphocytes and median increases in CD4 cell counts at weeks 48 and 72 of treatment (table 2).

Virological outcomes. The proportions of patients with virological success at weeks 8, 24, 48, and 72 are shown in table 3. At week 72, a total of 81 patients (76%) had virus loads of <50 copies/mL, 3 patients (3%) had virus loads of 50–1000 copies/mL, 14 patients (13%) had virus loads of >1000 copies/mL, and 9 patients (8%) had died or changed primary treatment.

Table 3. Proportion of HIV-infected Thai children who had virological success after receiving HAART.

Analysis, time point	All patients	HAART regimen		
		Nevirapine based	Efavirenz based	P[a]
Intention-to-treat[b]				
Week 8	23/107 (21)	10/61 (16)	13/46 (28)	.139
Week 24	57/107 (53)	26/61 (43)	31/46 (67)	.011
Week 48	74/107 (69)	35/61 (57)	39/46 (85)	.002
Week 72	81/107 (76)	39/61 (64)	42/46 (91)	.001
As treated[c]				
Week 8	23/102 (23)	10/56 (18)	13/46 (28)	.21
Week 24	57/99 (58)	26/56 (46)	31/43 (72)	.01
Week 48	74/98 (76)	35/55 (64)	39/43 (91)	.002
Week 72	81/98 (83)	39/55 (71)	42/43 (98)	.0005

NOTE. Data are no. of patients who achieved virologic success/no. evaluated (%). Virological success is defined as achievement of a plasma HIV RNA level <50 copies/mL.

[a] By the χ² test.

[b] Patients who died or discontinued the primary treatment regimen were counted as having experienced virological failure.

[c] In the as-treated analysis, patients were censored at the time of death or discontinuation of the primary treatment regimen.

Table 4. Effects of baseline characteristics and adherence to treatment on the likelihood that plasma HIV RNA levels would be <50 copies/mL at week 72 of treatment.

Analysis, characteristic	Risk ratio (95% CI)	P^a
Univariate		
Male sex (vs. female sex)	0.4 (0.2–1.1)	.09
Age (per year of age)	1.0 (0.8–1.2)	.92
Adjusted z score for weight (per unit increase)	1.0 (0.6–1.7)	.99
CDC HIV disease class C (vs. all other classes)	0.6 (0.2–1.7)	.37
Baseline CD4 cell %		
Per unit increase	1.1 (1.0–1.2)	.26
>5% (vs. ≤5%)	2.0 (0.7–5.5)	.20
Plasma HIV RNA level >5 $\log_{10}$ copies/mL (vs. ≤5 $\log_{10}$ copies/mL)	0.7 (0.2–2.2)	.52
Adherence problem[b]	0.2 (0.1–0.6)	.006
Drug regimen (efavirenz vs. nevirapine)	4.4 (1.4–14.1)	.01
Multivariate		
Adherence problem[b]	0.2 (0.1–0.7)	.01
Drug regimen (efavirenz vs. nevirapine)	4.1 (1.2–13.5)	.02

NOTE. CDC, US Centers for Disease Control and Prevention.
[a] By logistic regression analysis.
[b] Defined as the failure to take ≥95% of prescribed medication during any interval between follow-up visits.

At week 72, the mean decrease ($\pm$SD) in the plasma HIV RNA level from baseline was 3.3 ± 0.9 $\log_{10}$ copies/mL. There was a statistically significant difference in the mean decrease ($\pm$SD) in HIV RNA level between the 2 groups (3.1 ± 1.0 $\log_{10}$ copies/mL for those who received the nevirapine-based regimen and 3.6 ± 0.5 $\log_{10}$ copies/mL for those who received the efavirenz-based regimen; $P = .007$).

We analyzed the effect of baseline characteristics and adherence to treatment on the likelihood of virological success at week 72 (table 4). Treatment regimen and adherence to treatment were statistically significant predictors of virological success.

Genotypic resistance mutation patterns. After week 24 of treatment, 14 children had HIV RNA levels of >1000 copies/mL. One child received efavirenz-based HAART, and the other 13 children received nevirapine-based HAART. The genotypic resistance patterns for isolates from these 14 children are shown in table 5. The most common mutation patterns were associated with lamivudine resistance (M184V, M184I, and V118I) and with NNRTI resistance (K103N, V108I, Y181C, G190A, G190S, and M230L). These mutations were detected as early as week 24 of treatment. Virus in 5 patients also developed multiple NRTI-based resistance mutations (F116Y, Q151M, D67N, V118I, T215F, K219E, and K219Q). All but 2 of these mutations were detected during or after week 48 of treatment.

Adverse drug reactions. The most common clinical adverse drug reactions were rash and transient CNS disturbance (i.e., headache, dizziness, somnolence, and vivid dreams). Seventeen children (16%) developed grade 2 rash (14 children [23%] who received the nevirapine-based regimen and 3 [7%] who received the efavirenz-based regimen). Thirteen children (12%) had grade 1 CNS disturbance (1 child [2%] who received the nevirapine-based regimen efavirenz and 12 children [26%] who received the efavirenz-based regimen), and all episodes occurred during the first 2 weeks of treatment. Five children who received the nevirapine-based regimen developed severe drug reactions. These included rash and drug fever (3 patients); rash, mucosal involvement, and drug fever (1 patient); and rash, grade 3 neutropenia, grade 2 elevated liver enzymes, and drug fever (1 patient). Treatment for these 5 patients was successfully switched to the efavirenz-based regimen. No potentially life-threatening adverse drug reactions occurred in any patients.

The adverse reactions to drugs affecting laboratory parameters were grade 1 and grade 2 elevated alanine aminotransferase levels in 14 patients (9 children [15%] who received the nevirapine-based regimen and 5 children [11%] who received the efavirenz-based regimen), grade 1 elevated aspartate aminotransferase levels in 8 patients (6 children [10%] who received the nevirapine-based regimen and 2 children [4%] who received the efavirenz-based regimen), and a grade 1 elevated alkaline phosphatase level in 1 patient (2%) who received the efavirenz-based regimen. No patient developed clinically apparent hepatitis.

DISCUSSION

Our study demonstrated the effectiveness of NNRTI-based HAART regimens in treatment-naive children with advanced-stage HIV infection from a resource-limited setting. At baseline, 61% of our patients had CD4 cell percentages of ≤5%. After 72 weeks of HAART, the median CD4 cell percentage increased to 21% (interquartile range, 15%–26%). Also, after 72 weeks of HAART, 76% of the patients had plasma HIV RNA levels of <50 copies/mL. Our cohort accounted for 12% of children enrolled in NAPHA from August 2002 through July 2003. NAPHA provides free antiretroviral drugs and performs free CD4 cell determinations and laboratory tests to monitor adverse drug reactions. Our study provided additional monitoring of plasma HIV RNA levels and HIV genotypic resistance. Although not prohibited by the study protocol, we did not have to make any changes in treatment based on the results of this monitoring. Thus, the result of our study could be generalized to the rest of NAPHA.

The efficacy of these 2 NNRTI-based HAART regimens in children is comparable to that in adults. In the 2NN study [19], 65% and 70% of participants who received nevirapine- and efavirenz-based HAART, respectively, attained virological success. However, it took longer for children to achieve virus sup-

Table 5. Reverse-transcriptase genotypic resistance patterns at weeks 24, 48, and 72 after initiation of either nevirapine- or efavirenz-based HAART for HIV isolates from HIV-infected Thai children who had HIV RNA levels >1000 copies/mL.

HAART regimen	Sex (age in years)	Week 24	Week 48	Week 72	Baseline CD4 cell %	Baseline HIV RNA level, $\log_{10}$ copies/mL	Week 24 CD4 cell %	Week 24 HIV RNA level, $\log_{10}$ copies/mL	Week 48 CD4 cell %	Week 48 HIV RNA level, $\log_{10}$ copies/mL	Week 72 CD4 cell %	Week 72 HIV RNA level, $\log_{10}$ copies/mL
Nevirapine based												
Patient 1	F (7)	M184V, G190S, T215F	M184V, G190S	M184V, G190S, T215F	1	4.97	10	4.08	11	4.67	7	3.81
Patient 2	M (5)	M184V, G190A	M184V, G190A	M184V, G190A, T215F, D67N	2	5.16	20	4.49	19	4.58	12	4.88
Patient 3	F (6)	M184I, Y181C	M184V, Y181C	M184V, Y181C	2	4.82	11	3.47	11	3.97	13	3.82
Patient 4	F (4)	M184I, Y181C	M184I	M184I, Y181V	3	5.81	8	5.88	23	4.68	29	4.17
Patient 5	F (13)	M184V, Y181C	ND	M184V, Y181C	3	5.37	7	3.96	9	2.53	11	3.48
Patient 6	M (7)	M184I, Y181C	M184I, K103N, Y181C, Q151M	M184I, K103N, Y181C, Q151M, F116Y	4	5.88	13	3.19	11	3.64	9	3.89
Patient 7	F (6)	M184I, K103N, T215F	M184V, K103N, M230L, T215F	M184V, K103N, M230L, T215F, V118I	4	5.48	6	4.49	7	3.92	10	4.28
Patient 8	M (11)	K103N, Y181C	M184V, K103N, Y181C	NA	3	5.30	4	4.88	5	4.74	NA	NA
Patient 9	M (7)	Y181C, K219Q	M184I, Y181C, K219Q	M184I, Y181C, K219Q	6	5.34	4	4.97	9	3.85	18	4.19
Patient 10	M (10)	ND	M184I, K103N	M184V, G190A	0	5.71	6	2.46	9	3.56	13	4.00
Patient 11	F (8)	ND	M184V, Y181C, M230L, K219E	ND	2	5.88	15	2.20	10	3.49	18	2.90
Patient 12	M (13)	ND	M184V, Y181C, Q151M	M184V, Y181C, Q151M, F116Y	3	4.78	13	2.43	10	3.96	14	4.13
Patient 13	M (3)	ND	Y181C	M184V, Y181C, V108I	3	5.88	11	2.09	11	3.58	19	4.43
Efavirenz based												
Patient 14	M (9)	ND	M184V, K103N	M184V, K103N, M230L	10	5.35	21	1.70	20	4.05	21	3.37

NOTE. Mutations in the reverse-transcriptase gene associated with resistance to lamivudine are M184V, M184I, and V118I. Mutations associated with resistance to nonnucleoside reverse-transcriptase inhibitors are K103N, V108I, Y181C, G190A, G190S, and M230L. Mutations associated with resistance to multiple nucleoside reverse-transcriptase inhibitors are 151 complex (F116Y and Q151M) and nucleoside reverse-transcriptase inhibitor–associated mutations (D67N, V118I, T215F, K219E, and K219Q). NA, not available; ND, not done (plasma HIV RNA level of <1000 copies/mL).

pression. Of the 81 children who attained virological success at week 72 in our study, only 57 did so by week 24. In the 2NN study, most of the virological successes were achieved by week 24 [19]. This difference might be explained by the higher baseline virus loads in children, compared with adults.

In our study, patients who received the efavirenz-based regimen had a higher rate of virological success than did those who received the nevirapine-based regimen (91% vs. 64%; $P = .001$). This was confirmed by the multivariate analysis showing that use of the efavirenz-based regimen was a predictor of virological success. However, our study was not randomized, and the finding might have been confounded by several factors. For example, patients who received the nevirapine-based regimen were 1.4 years younger, and more children who received this regimen had stage C disease (table 3).

There have been no head-to-head comparisons between nevirapine-based and efavirenz-based HAART in children, but data from 2 studies of antiretroviral-experienced children who received 4-drug regimens containing nevirapine or efavirenz, nelfinavir, and 2 NRTIs suggested the superiority of efavirenz over nevirapine [20, 21]. Three large cohort studies comparing efavirenz-based HAART with nevirapine-based HAART in antiretroviral-naive adult patients also suggested the superiority of efavirenz [22–24]. However, in the only adequately powered randomized trial comparing nevirapine- with efavirenz-based HAART, van Leth et al. [19] found that the rate of treatment failure in the nevirapine arm was 43.7%, whereas the failure rate in the efavirenz arm was 37.8%. This difference was not statistically significant. Thus, there is a need for a randomized clinical trial comparing nevirapine- with efavirenz-based HAART in children.

The immunologic efficacy in our cohort was comparable to that in pediatric cohorts from Romania and Cote d'Ivoire. In the report from Romania, a mean increase of 284 cells/μL in the CD4 cell count was found after treatment with a lopinavir-containing HAART regimen for 67 weeks [10]. In the Cote d'Ivoire cohort, the median CD4 cell percentage increased from 8% to 23% after treatment with nelfinavir- or efavirenz-containing HAART for 72 weeks [8]. In our study, the median CD4 cell percentage at week 72 was significantly lower among patients who did not achieve virological success (table 2). This was similar to data from a study involving adults that showed that patients who experienced virological failure had a blunted CD4 cell response after 48 weeks of treatment [25].

The frequency of clinical adverse reactions to drugs and of abnormal hepatic laboratory findings in our study was similar to that in other reports. In a cohort of 74 children treated with nevirapine in the United Kingdom [26], rash and elevated serum alanine aminotransferase level were reported for 20% and 9% of patients, respectively. In our study, efavirenz was well tolerated, and there was no discontinuation of efavirenz because of adverse reactions. Transient CNS disturbance and rash were found in 26% and 7% of patients, respectively. These percentages were lower than those reported by Teglas et al. [27] (36% and 15% of patients, respectively).

Adherence to treatment was good and comparable to that reported in the Cote d'Ivoire cohort [8]. A total of 86% of our patients took ≥95% of the prescribed medications during the intervals between study visits. This was because of the adherence counseling session given at each visit and because the clinical benefits were rapidly apparent to care givers, motivating them to adhere to the treatment. Care givers reported decreased incidence of HIV-related illness. Objectively, there were significant increases in the mean weight-for-age and height-for-age z scores and in the mean hemoglobin level. As in several other reports, we found that drug adherence is paramount to treatment success. In our study, patients with adherence problems were 5 times less likely to achieve virological success (table 4).

Drug-resistant virus emerged rapidly among children with incomplete virological suppression (HIV RNA level, >1000 copies/mL) after 24 weeks of HAART. The most common resistance mutations were associated with lamivudine and with NNRTIs, which were conferred by a change in a single amino acid. By week 72, a total of 13% of our patients developed isolates with resistance mutations. Because these patients were doing well clinically and were maintaining their CD4 cell counts and because the level of plasma HIV RNA at which therapy should be changed has not yet been determined [28], we chose to continue the primary drug regimens for these patients and to monitor the patients closely.

There were several limitations in our study. There were no infants <1 year old in our cohort. Because most cases of HIV infection in children in Thailand are still diagnosed by detection of serum anti-HIV antibodies, accurate diagnosis cannot be made in children <18 months old. Furthermore, our patients were followed up for only 72 weeks, and issues such as long-term toxicities and metabolic derangements, as well as the sustainability and duration of virological, immunologic, and clinical response, cannot be addressed at this time.

In conclusion, we have documented the safety, effectiveness, and feasibility of NNRTI-based regimens as first-line HAART in treatment-naive children with advanced stage HIV infection participating in a nationwide antiretroviral drug access program in a resource-poor setting.

Acknowledgments

References

1. Egger M, May M, Chene G, et al. Prognosis of HIV-1 infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet **2002**; 360:119–29.

2. World Health Organization (WHO). Treating 3 million by 2005: making it happen—the WHO strategy. Geneva: WHO, **2003**.

3. World Health Organization (WHO). UNAIDS/WHO epidemiological fact sheets on HIV/AIDS and sexually transmitted infections, 2004 update. Geneva: WHO, **2004**. Available at: http://www.who.int/GlobalAtlas/PDFFactory/HIV/EFS_PDFs/EFS2004_TH.pdf. Accessed 19 September 2004.

4. Farmer P, Leandre F, Mukherjee JS, et al. Community-based approaches to HIV treatment in resource-poor settings. Lancet **2001**; 358:404–9.

5. Weidle PJ, Malamba S, Mwebaze R, et al. Assessment of a pilot antiretroviral drug therapy program in Uganda: patients' response, survival, and drug resistance. Lancet **2002**; 360:34–40.

6. Landman R, Schiemann R, Thiam S, et al. Once-a-day highly active antiretroviral therapy in treatment-naive HIV-1–infected adults in Senegal. AIDS **2003**; 17:1017–22.

7. Laurent C, Kouanfack C, Koulla-Shiro S, et al. Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1–infected adults in Cameroon: open-label multicentre trial. Lancet **2004**; 364:29–34.

8. Fassinou P, Elenga N, Rouet F, et al. Highly active antiretroviral therapies among HIV-1–infected children in Abidjan, Cote d'Ivoire. AIDS **2004**; 18:1905–13.

9. Eley B, Nuttall J, Davies MA, et al. Initial experience of a public sector antiretroviral treatment program for HIV-infected children and their infected parents. S Afr Med J **2004**; 94:643–6.

10. Kline MW, Matusa RF, Copaciu L, et al. Comprehensive pediatric human immunodeficiency virus care and treatment in Constanta, Romania. Pediatr Infect Dis J **2004**; 23:695–700.

11. World Health Organization (WHO). Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach—2003 revision. Geneva: WHO, **2003**. Available at: http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf. Accessed 19 September 2004.

12. Steinbrook R. After Bangkok—expanding the global response to AIDS. N Engl J Med **2004**; 351:738–42.

13. Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. 22 September **2003**. Available at: http://aidsinfo.nih.gov/guidelines/pediatric/archive/PED_092203.pdf. Accessed 25 September 2004.

14. Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. Official authorized addenda: human immunodeficiency virus infection codes and official guidelines for coding and reporting ICD-9-CM. MMWR Morb Mortal Wkly Rep **1994**; 43(RR-12):1–10.

15. Working Group on Using Weight and Height References in Evaluating the Growth Status of Thai Children. Manual on using weight and height references in evaluating the growth status of Thai children. Bangkok: Department of Health, Ministry of Public Health, **2000**.

16. Divisions of AIDS, National Institute of Allergy and Infectious Diseases. Toxicity table for grading severity of pediatric (> 3 months of age) adverse experiences. April **1994**. Available at: http://www.hptn.org/Web%20Documents/Regulatory_Resources/PediatricToxTables3months andUp.pdf. Accessed 6 September 2004.

17. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med **2000**; 133:21–30.

18. Sirivichayakul S, Ruxrungtham K, Ungsedhapand C, et al. Nucleoside analogue mutations and Q151M in HIV-1 subtype A/E infection treated with nucleoside reverse transcriptase inhibitors. AIDS **2003**; 17:1889–96.

19. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomized open-label trial, the 2NN study. Lancet **2004**; 363:1253–63.

20. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. N Engl J Med **1999**; 341:1874–81.

21. Krogstad P, Lee S, Johnson G, et al. Nucleoside analogue reverse transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. Clin Infect Dis **2002**; 34:991–1001.

22. Cozzi-Lepri A, Phillips AN, d'Arminio Monforte A, et al. Virologic and immunologic response to regimens containing nevirapine or efavirenz in combination with 2 nucleoside analogues in the Italian Cohort Naive Antiretrovirals study. J Infect Dis **2002**; 185:1062–9.

23. Matthews GV, Sabin CA, Mandalia S, et al. Virological suppression at 6 months is related to choice of initial regimen in antiretroviral-naive patients: a cohort study. AIDS **2002**; 16:53–61.

24. Keiser P, Nassar N, White C, et al. Comparison of nevirapine- and efavirenz-containing antiretroviral regimens in antiretroviral-naive patients: a cohort study. HIV Clin Trials **2002**; 3:296–303.

25. Deeks SG, Barbour JD, Martin JN, et al. Sustained CD4 T cell response after virologic failure of protease inhibitor–based regimens in patients with human immunodeficiency virus infection. J Infect Dis **2000**; 181:946–53.

26. Verweel G, Sharland M, Lyall H, et al. Nevirapine use in HIV-1–infected children. AIDS **2003**; 17:1639–47.

27. Teglas JP, Quartier P, Treluyer JM, et al. Tolerance of efavirenz in children. AIDS **2001**; 15:241–3.

28. Sharland M, Blanche S, Castelli G, et al. PENTA guidelines for the use of antiretroviral therapy 2004. HIV Med **2004**; 5:61–86.