**ACKNOWLEDGMENTS**

The authors thank Nathan Litman, MD, and Frederick Kaskel, MD, PhD, Department of Pediatrics, Albert Einstein College of Medicine, Children’s Hospital at Montefiore, Bronx; Vasudha Reddy, MPH, New York City Department of Health and Mental Hygiene, Bureau of Communicable Disease, New York; and Mel Backer, New York City Department of Health and Mental Hygiene; Public Health Laboratory, New York, NY.

**REFERENCES**


**SUSTAINED IMMUNOLOGIC AND VIROLOGIC EFFICACY AFTER FOUR YEARS OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN HUMAN IMMUNODEFICIENCY VIRUS INFECTED CHILDREN IN THAILAND**

Thanyawee Puthanakit, MD,* Linda Aurpibul, MD,* Peninnah Oberdorfer, MD, PhD,† Noppadon Akaratham, MD,‡ Suparat Kanjanavanit, MD,§ Pornphun Wannarit, MD,¶ Thira Sirisantha, MD,*, and Virat Sirisantha, MD†

**Abstract:** We report the long-term efficacy of highly active antiretroviral therapy (HAART) in 107 antiretroviral-naive human immunodeficiency virus (HIV)-infected Thai children. In an intention-to-treat analysis, 70% of the children had undetectable HIV RNA titers after 192 weeks of HAART. The mean CD4 cell percentage increased from 5.3% to 26.6%. HAART is effective for HIV-infected children in this resource-poor setting despite initiation of treatment in the advanced stage of disease.

**Key Words:** HAART in children, NNRTI-based HAART, HIV, resource-limited settings, Thailand

Accepted for publication May 24, 2007.

From the *Research Institute for Health Sciences, †Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; and ‡Ministry of Public Health, Bangkok, Thailand.*

Address for correspondence: Dr. Virat Sirisantha, Division of Infectious Diseases, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Thailand 50200. E-mail: vsirisan@mail.med.cmu.ac.th.

DOI: 10.1097/INF.0b013e318125720a

**There have been several reports of antiretroviral treatment (ART) initiatives for children in resource-limited countries.**""""Most studies report short-term efficacy at 48 weeks. Therefore, little is known about the durability of the viral suppression and the reconstitution of the immune system in children. A report from the Swiss adult cohort study showed that at 4 years after highly active antiretroviral therapy (HAART), 84.5% of human immunodeficiency virus (HIV)-infected adults had HIV RNA titers <400 copies/ml in an as-treated analysis.**""""There is no consensus among...""""
workers in the field regarding the ability to restore immune function to near normal values (CD4 >25%) among children who initiate treatment in advanced stage. Some think that younger age and higher baseline CD4 concentration are associated with better chance to reach near normal CD4% values. Some studies reported that children can restore their CD4 T cell levels independent of age and baseline CD4% values.

The objective of this report is to describe the long-term virologic efficacy of HAART and its ability to restore immune function in HIV-infected children after 4 years of treatment. This information is important for clinicians and policymakers for scaling-up ART programs especially for children in resource-limited settings.

PATIENTS AND METHODS

In 2002, the Thai Ministry of Public Health launched the National Access to Antiretroviral Program for People Living with HIV/AIDS (NAPH) aimed at providing treatment to all Thai HIV-infected patients. It used 2 nucleoside reverse transcription inhibitors (NRTI) and 1 non-NRTI (NNRTI) as first-line HAART regimen. From August 2002 to July 2003, 107 perinatally acquired HIV-infected children who participated in NAPH were prospectively enrolled at 4 government hospitals in northern Thailand: the Chiang Mai University hospital, Chiang Mai provincial hospital, Lampang provincial hospital, and Sanpatong district hospital. Eligibility criteria were an age <15 years, a percentage of CD4 cells ≤15%, and no previous treatment with antiretroviral drugs. Patients received either nevirapine (NVP) or efavirenz (EFV) in combination with stavudine and lamivudine. 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. 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. The study details and 72-week efficacy have been reported. Briefly, patients attended study visit at weeks 0 (start of treatment), 2, 4, 8, 12, 18, 24, and then every 12 weeks thereafter. All patients were followed for at least 192 weeks. During each visit we reviewed the patient’s medical history and performed a physical examination and blood tests. Hematologic tests, blood chemistry, CD4 cell count, and plasma HIV RNA (viral load) determinations were performed at baseline and every 24 weeks thereafter. CD4 cell counts were assessed with FACSCount apparatus (Becton-Dickinson, Mountain View, CA). Plasma HIV RNA titer was measured using the Roche Ultraviolet Amplicor assay, version 1.5. Virologic success was defined as plasma HIV RNA value <50 copies/mL. In the intention-to-treat analysis, patients who discontinued primary treatment regimen or died were counted as virologic failure. Categorical variables were tested with a χ² and continuous variables were tested with independent t test. Data were analyzed with the SPSS version 11.5 (SPSS Inc., Chicago, IL). A 2-sided P value of less than 0.05 was considered significant.

RESULTS

Characteristics of Study Population. From August 2002 to July 2003, 107 antiretroviral-naive HIV-infected children were enrolled. Mean age was 7.7 years (range, 2.1–13.8). The mean baseline CD4% was 5.3% (SD 4.9), and mean plasma HIV RNA titer was 5.4 log₁₀ copies/mL (SD 0.5). Fifty-six children received the NVP-based regimen whereas 46 received the EFV-based regimen.

Clinical Outcomes. During the 192 weeks of follow-up, 5 patients (5%) died of HIV-related illnesses. Five patients (5%) who received the NVP-based regimen were changed to the EFV-based regimen because of early severe adverse drug reactions. Ten patients (9%) subsequently changed to a protease inhibitor (PI)-based regimen because of virologic failure. The remaining 87 patients (81%) were still taking their primary drug regimen at week 192. One adolescent girl was married and had a healthy HIV-negative child.

The percentage of patients who took >95% of prescribed medications during first, second, third, and fourth year of treatment were 87%, 95%, 96%, and 95% respectively. There is no statistically significant difference between the 2 regimens.

After HAART initiation, their weight and height increased to catch up with normal children of the same age and gender by weeks 48 and 144, respectively. Mean weight-for-age Z-scores (±SD) increased from −1.9 ± 0.9 at baseline to −1.3 ± 1.0 at week 48 (P < 0.001 compared with baseline) and to −1.1 ± 0.9 at week 192 (P < 0.001), respectively. Mean height-for-age Z-scores (±SD) increased from −2.3 ± 1.5 at baseline to −1.5 ± 1.0 at week 144 (P < 0.001) and to −1.4 ± 1.2 at week 192 (P < 0.001), respectively.

Virologic Outcomes. In the intention-to-treat analysis, the proportions of patients with virologic success are shown in Table 1. At week 192, 20 children discontinued primary treatment because of change to PI-based regimen (10 children), adverse drug reactions (5 children), and death (5 children). Of the remaining 87 patients, 75 (70%) had viral loads of <50 copies/mL, 4 (4%) had viral loads between 50 and 1000 copies/mL, and 8 (7%) had viral loads of >1000 copies/mL. The virologic efficacy of the EFV-based regimen is better than the NVP-based regimen. The peak of virologic efficacy was reached at week 72 of treatment. There is no statistically significant difference in terms of age, gender, baseline CD4 values, and baseline viral loads between children who had viral load <50 copies/mL at week 192 and those who did not (data not shown).

Immunologic Outcomes. The mean CD4 cell percentage increased with time on HAART as shown in Table 1. The immunologic efficacy of the EFV-based regimen was better than that of the NVP-based regimen at weeks 72 and 96 (P = 0.03 and 0.01, respectively). However, this difference disappeared at week 120 when treatment of the children with virologic failure was changed to PI-based regimen and they were censored from the analysis.

There were 13 patients (12%) aged <5 years, 68 patients (64%) aged 5–9 years, and 26 (24%) aged ≥10 years at the time of HAART initiation. At week 192, there was no difference in the CD4% gain from baseline among these different age groups (21.8%, 21.2%, and 20.7%; P = 0.94).

There were 65 patients (61%) with low baseline CD4% of ≤5% and 42 patients (39%) with high baseline CD4% from 6% to 15%. The CD4% during the follow-up period is shown in Figure 1. The CD4% gain in the first 24 weeks was similar between the 2 groups (7.8% versus 8.0%). Between week 24 and 120, the rate of CD4 cell gain was faster in the low baseline group. These results in both groups reaching similar CD4% level at week 120 (Fig. 1). At week 192 of HAART, 52 of 87 children (60%) reached CD4 >25%, and 56% and 65% of children in low and high baseline CD4 groups, respectively (P = 0.51).

DISCUSSION

Our study demonstrated the long-term efficacy of NNRTI-based HAART regimens in advanced-stage, antiretroviral-naive, HIV-infected children in a resource-limited setting. After 192 weeks of HAART, 70% of children had undetectable HIV RNA titers. The mean CD4 cell percentage increased from 5.3% at baseline to 26.6%. Sixty per cent of the children reached a CD4 cell percentage of >25%. These data support the World Health Organization recommendation to use NNRTI-based HAART regimen as a first-line regimen in resource-limited settings.

The long-term outcome using NNRTI-based HAART in this cohort is similar to reports from African countries. In a cohort of 787
ART-naive children in Botswana, the median baseline CD4 was 15%. After 3 years of HAART, the median CD4 value increased to 32% and 71% of the children had viral load <400 copies/mL. About 16% of children switched to second-line regimens because of virologic failure. In a South African cohort of 130 antiretroviral-naive children, the median baseline CD4 was 11%. After 3 years of HAART, the mean CD4 value increased by 21%, and 83% of the children had viral load <400 copies/mL. In this cohort, patients who received the EFV-based regimen had a higher rate of virologic success than those who received the NVP-based regimen. However, this study was not a randomized trial, and was not designed to compare the 2 treatment regimens. The data from the 2NN study, a

<table>
<thead>
<tr>
<th>Week</th>
<th>All Children (n = 107)</th>
<th>NVP-Based* (n = 61)</th>
<th>EFV-Based† (n = 46)</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 24</td>
<td>57 (53) 26 (43)</td>
<td>31 (67)</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td>74 (69) 35 (57)</td>
<td>39 (65)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Week 72</td>
<td>81 (76) 39 (64)</td>
<td>42 (91)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Week 96</td>
<td>79 (74) 38 (62)</td>
<td>41 (89)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Week 120</td>
<td>78 (73) 38 (62)</td>
<td>40 (87)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Week 144</td>
<td>76 (71) 38 (62)</td>
<td>38 (83)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Week 168</td>
<td>73 (68) 37 (61)</td>
<td>36 (78)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Week 192</td>
<td>75 (70) 37 (61)</td>
<td>38 (83)</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

* NVP-based denotes regimen containing nevirapine, lamivudine, and stavudine.
† EFV-based denotes regimen containing efavirenz, lamivudine, and stavudine.
‡ P values were calculated with y² test or independent t test.
§ Data shown as n (%). In the intention-to-treat analysis, patients who died (n = 5; 1 in NVP-based group and 4 in EFV-based group) or discontinued primary treatment regimen (adverse drug reactions, n = 5; all in NVP-based group, virologic failure, n = 10; all in NVP-based group) were counted as virologic failure.

Data shown as mean (SD), number. The number of patients declined over time due to change of antiretroviral regimen or death.
large randomized trial in adult, showed that after 48 weeks of treatment, there was no difference in virologic success between the 2 groups (NVP = 65.4% and EFV = 70.0%).

The magnitude of improvement in CD4% in our study is better than that in pretreated children reported from western countries. In the Pediatric AIDS Clinical Trial Group (PACTG) 219 study of 702 children who received PI-based HAART, only 33% and 26% of children with pre-PI CD4 of <5% and 5–14%, respectively, achieved CD4 values of >25% after 3 years of PI-based HAART. In a pretreated Spanish pediatric cohort, children with CD4 cell <5% at baseline did not achieve CD4 cell percentage of >25% after 6 years of HAART. In our study, 56% and 65% of children with baseline CD4 ≤5 and 6–15%, respectively, achieved CD4 values above 25%. The main difference between these studies and ours is previous exposure to ART. The CD4 lymphocyte recovery in this study is similar to that reported from the Swiss adult cohort, in which 48% of the patients achieved CD4 lymphocyte concentrations of >500 cells/μL after 4 years of HAART. The baseline CD4 level is also an important factor of CD4 cell recovery in adults; 70% and 50% of individuals who commenced HAART with baseline CD4 count of 300 to 400 cells/μL and CD4 count of <300 cells/μL, respectively, reached CD4 count >500 cells/μL. Our study did not show this difference.

In our study, there is no difference in immune recovery among children of different age groups. This is similar to the report from the Dutch pediatric cohort that the immune recovery is independent of age.

However, our finding is different from that of the PACTG 219 study, in which the mean increase of CD4% after 3 years of PI-based HAART was largest among the youngest age group (age <5 years, 5–9 years, and ≥10 years; 9.2%, 8.0%, and 4.3%, respectively; P = 0.001). There was no information on the adherence to treatment, especially in adolescents in the PACTG 219 study, which can contribute to the poorer treatment result in that group.

In conclusion, we have documented the long-term efficacy of NNRTI-based regimens as first-line HAART in advanced-stage, treatment-naive, HIV-infected children participating in a nationwide antiretroviral drug access program in a resource-poor setting.

ACKNOWLEDGMENTS

This work was supported by a grant from the Thai Government Pharmaceutical Organization, Chiang Mai University, and the Thailand Research Fund.

REFERENCES


DIAGNOSTIC VIROLOGY PRACTICES FOR RESPIRATORY SYNCYTIAL VIRUS AND INFLUENZA VIRUS AMONG CHILDREN IN THE HOSPITAL SETTING: A NATIONAL SURVEY

Hasan S. Jafri, MD,* Octavio Ramilo, MD,＊ Doris Makari, MD,† Deborah Charsha-May, PhD,‡ and José R. Romero, MD‡

Abstract: A survey was sent to the emergency room and laboratory directors of 400 randomly selected US hospitals to assess the diagnostic testing practices for respiratory syncytial virus and influenza virus in children. The results demonstrate that the majority of hospitals routinely perform viral testing for both viruses and use virology testing practices appropriate for the reasons reported for testing.

Key Words: respiratory syncytial virus, influenza virus, diagnostic testing, survey

Accepted for publication May 25, 2007.

From the *Division of Pediatric Infectious Diseases, The University of Texas Southwestern Medical Center at Dallas and Children’s Medical Center Dallas, Dallas, TX; †MedImmune, Inc., Gaithersburg, MD; and ‡Section of Pediatric Infectious Diseases, University of Nebraska Medical Center, Omaha, NE.

Address for correspondence: José R. Romero, MD, 982162 Nebraska Medical Center, Omaha, NE 68198-2162. E-mail: jrromero@ummc.edu. DOI: 10.1097/INF.0b013e31812718ac

Respiratory syncytial virus (RSV) and influenza virus infections occur in annual epidemics, resulting in considerable morbidity and mortality, particularly in infants, young children, and the elderly.1–6 Timely and accurate diagnosis of these infections provides guidance for appropriate infection control, may help avoid the improper use of antimicrobial agents, and in certain situations allows prompt initiation of antiviral therapy.7,8 Accurate diagnostic testing also generates useful information regarding the onset and duration of yearly epidemics to better define regional and national epidemiology. This survey was developed to evaluate testing practices for RSV and influenza virus at teaching and nonteaching hospitals across the United States.

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