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ABSTRACT

OBJECTIVE. Increasing access to highly active antiretroviral therapy to reach all those in need in developing countries (scale up) is slowly expanding to HIV-positive children, but documented experience remains limited. We aimed to describe the clinical, immunologic, and virologic outcomes of pediatric patients with >12 months of highly active antiretroviral therapy in 2 routine programs in Cambodia.

METHODS. Between June 2003 and March 2005, 212 children who were younger than 13 years started highly active antiretroviral therapy. Most patients started a standard first-line regimen of lamivudine, stavudine, and nevirapine, using split adult fixed-dosage combinations. CD4 percentage and body weight were monitored routinely. A cross-sectional virologic analysis was conducted in January 2006; genotype resistance testing was performed for patients with a detectable viral load.

RESULTS. Mean age of the subjects was 6 years. Median CD4 percentage at baseline was 6. Survival was 92% at 12 months and 91% at 24 months; 13 patients died, and 4 were lost to follow-up. A total of 81% of all patients had an undetectable viral load. Among the patients with a detectable viral load, most mutations were associated with resistance to lamivudine and non–nucleoside reverse-transcriptase inhibitor drugs. Five patients had developed extensive antiretroviral resistance. Being an orphan was found to be a predictor of virologic failure.

CONCLUSIONS. This study provides additional evidence of the effectiveness of integrating HIV/AIDS care with highly active antiretroviral therapy for children in a routine setting, with good virologic suppression and immunologic recovery achieved by using split adult fixed-dosage combinations. Viral load monitoring and HIV genotyping are valuable tools for the clinical follow-up of the patients. Orphans should receive careful follow-up and extra support.

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Dr Janssens prepared the manuscript and design of the programs and the study; Dr Raleigh was project coordinator in Siem Reap and contributed to the manuscript; Dr Soeung, Ms Akao, Dr Te, and Dr Gupta contributed to the collection of data; Dr Gupta provided statistical analysis and reviewed the manuscript; Dr Vun contributed to the project design and reviewed the manuscript; Mr Ford provided editorial support to the manuscript; Mr Nouhin provided genotyping analysis; and Dr Nerrienet contributed to design of the study, managed the laboratory work of the viral loads and genotyping, and reviewed the manuscript.

Key Words
HIV, children, Cambodia, HAART, viral load, genotyping

Abbreviations
HAART—highly active antiretroviral therapy
WHO—World Health Organization
MSF—Me´decins Sans Frontie`res
CI—confidence interval
IQR—interquartile range
NNRTI—non–nucleoside reverse-transcriptase inhibitor
NNRTI—non–nucleoside reverse-transcriptase inhibitor
FDC—fixed-dosage combination

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275. Copyright © 2007 by the American Academy of Pediatrics
Access to antiretroviral treatment for patients with AIDS in resource-limited settings has increased dramatically in the past few years, with >1.6 million currently estimated to be receiving treatment. Despite these efforts, however, <5% of the 800,000 children who are in need of antiretroviral therapy are receiving it.\(^1\) Of the 39.5 million people who were estimated to be living with HIV/AIDS in 2006, 2.3 million were children who were younger than 15; more than half a million children died of HIV/AIDS that year.\(^2\) In the West, good outcomes are achieved for children who are on highly active antiretroviral therapy (HAART),\(^3\) and studies indicate that similar outcomes can be achieved in resource-limited settings.\(^6\)–\(^11\) However, documented experience of treating large numbers of children remains limited.

Cambodia is 1 of the poorest countries in Asia, ranking 130th on the human development index with an annual gross domestic product per capita of $2078.\(^12\) Generally the prevention response has been good in Cambodia, with HIV prevalence falling from 3% in 1997 to 1.9% in 2003. However, national efforts to prevent mother-to-child transmission only began in 2003.

Antiretroviral therapy has been provided in Cambodia since 2001. By December 2005, government and nongovernmental actors supported ~12,000 patients with HAART, which allowed the country to reach its World Health Organization (WHO) 3 by 5 target, which aims to start HAART for 3 million patients with AIDS worldwide by the end of 2005. Children have benefited from treatment since it has been available, with Médecins Sans Frontières (MSF) and the Cambodian Ministry of Health providing HAART to children since 2002. This was given additional priority in 2004, when the Ministry of Health released a policy package of treatment guidelines, training, and drug supply devoted to the management of pediatric HIV. This article provides outcomes of providing HAART for 212 children within a cohort of >800 HIV-positive children who were under care in 2 district hospitals in Cambodia.

Methods

Study Sites and Patients

Outcome data were pooled from 2 district hospitals: Angkor Hospital for Children in Siem Reap province (population 700,000) and Takeo district hospital in Takeo province (population 800,000). Angkor Hospital for Children is a charity-run 50-bed pediatric hospital that started to provide care for HIV-positive children in collaboration with MSF in February 2003. The Takeo district hospital is a 164-bed public referral hospital that started providing HIV care for children in February 2004, also with support from MSF. Both hospitals attract children from across the province as well as from neighboring provinces. Services in both sites are comparable and are provided primarily by Cambodian medical staff. The support of MSF was limited to technical assistance, the supply of most of the medicines, and the organization of the laboratory tests.

By March 2006, a total of 805 HIV-positive children (478 in Siem Reap and 327 in Takeo) had been enrolled in these 2 sites, 428 of whom had started HAART. Of the remainder, 82 (10%) patients were eligible for HAART but had died or were lost to follow-up before initiation and 295 (37%) did not meet eligibility criteria for HAART (see “Antiretroviral Therapy” below). All children at both sites who were aged ≤13 years and on HAART for >12 months were included in a cross-sectional evaluation of the virologic status, with an intention-to-treat analysis of the virologic efficacy performed on all children who started HAART between June 2003 and March 2005.

Antiretroviral Therapy

Criteria to commence HAART followed national guidelines: HIV-positive status (serology or reverse transcriptase polymerase chain reaction for children younger than 18 months) and CD4 count (<20% for children younger than 5 years or <200 cells per mL for children older than 5 years). The majority of the patients started on a standard first-line regimen of stavudine, lamivudine, and nevirapine, as recommended by the WHO.\(^13\) Zidovudine and efavirenz were used as alternatives in case of intolerance or interaction with other drugs. Adult generic fixed-dosage combinations (FDCs) were used for the children who were on the first-line regimen: before December 2003, GPOvir (GPO, Bangkok Thailand) was used; patients were then switched to Triviro (Ranbaxy, Dewas, India) on prequalification of this treatment.\(^14\) Tablets were cut in half to obtain the most appropriate dosages, and for some body weights, nevirapine syrup was added to achieve the correct dosage, according to a standardized drug-dosage table.\(^15\) For the patients in whom treatment failure was diagnosed, an individual evaluation was made to decide on a switch to a second-line HAART regimen. All patients received at least 3 HAART-preparation counseling sessions before commencement of the treatment. For younger children, counseling was given in the presence of the parents or the caregivers; for older children, a part of the sessions were given to the patients alone. Disclosure of HIV status was not a condition to start HAART, but the counselors developed an individual plan for each patient to follow a process of disclosure. Adherence to HAART was not systematically recorded, but several steps were taken to provide support for adherence. After commencement of HAART, adherence support was provided by the counselors at every visit to the clinic. Home visits were conducted for patients who arrived late for appointments or were suspected of needing more social support (although this was not always feasible for all patients who...
lived in another province. For patients who could not afford the travel to the clinics, financial support for transportation cost was provided.

**Clinical, Immunologic, and Virologic Evaluation**

Body weight was measured at every visit. CD4 cell count was measured at baseline and every 6 months after HAART initiation by flow cytometry (Facscount; Becton Dickinson, San Jose, CA). For children who were younger than 5 years, CD4% was used as the standard follow-up indicator; for the older children, both CD4% and the absolute CD4 cell count were used as recommended by the WHO. Hemoglobin and alanine aminotransferases were measured at week 2; months 1, 2, 3, and 6; and every 6 months thereafter to monitor for toxicity.

Between February 2006 and June 2006, viral load measurements were performed together with routine CD4 tests (flow cytometry, Facscount) for all patients who were on HAART for ≥12 months. HIV-1 RNA viral load was quantified by real-time reverse transcriptase polymerase chain reaction as developed by the French “Agence Nationale de Recherche sur le SIDA et les Hépatites Virales.” For patients with a detectable viral load (ie, >400 copies per mL), a genotype resistance test was done. For the genotype resistance study, viral RNA was extracted (QIAampViral RNA minikit; Qiagen, Hamburg, Germany) and amplified for reverse transcriptase genes, sequenced automatically (CEQ DTCS Quick start kit; Beckman Coulter, Fullerton, CA), and corrected manually using CEQ 8000 software (Beckman Coulter). Nucleotide sequences were compared against known reference strains of group M of the HIV-1 gene bank (www.hiv-web.lanl.gov). Genotype resistance interpretation was performed according to algorithms developed by the “Agence Nationale de Recherche sur le SIDA et les Hépatites Virales” (www.hivfrenchresistance.org) and the International AIDS Society (www.iasusa.org). All viral load and genotype resistance tests were performed at the Pasteur Institute (Phnom Penh, Cambodia).

This cohort evaluation received ethical approval of the Angkor Hospital for Children ethics committee; all patients were informed about the objectives of the laboratory tests during the routine counseling sessions. The results of all of the tests were made available to the clinicians as soon as possible to guarantee optimal benefits for the patients.

**Statistical Analysis**

All data regarding medical background and follow-up of patients were collected on FUCHIA 1.5 monitoring software (Epicenter, Paris, France). The $z$ score for weight for height to evaluate growth was used from the WHO (Geneva, Switzerland) reference curves. The probability of survival and remaining in care was calculated with Kaplan-Meier with all patients analyzed on an intention-to-treat basis. Patients who were alive and in care or transferred out on March 31, 2006, were censored on the date of their last visit before this date. Patients with >3 months’ delay with respect to the scheduled follow-up visit were regarded as lost to follow-up. A survival analysis to estimate the probability of patients’ remaining in care was done with events (uncensored) counted as patients who died or who were lost to follow-up. Confidence intervals (CIs) around the proportions of patients whose treatment was successful or failing were calculated with Mantel-Haenszel test with 95% limits. Logistic regression analysis was used to identify factors that were associated with virologic failure (viral load > 400 copies per mL). For all listed baseline factors, both univariate and multivariate analyses were calculated. All statistical analyses were performed by using Epi Info 2002 software (Centers for Disease Control and Prevention, Atlanta, GA).

**RESULTS**

**Characteristics of the Study Population**

A total of 212 patients had started HAART between June 2003 and March 2005. Baseline characteristics are presented in Table 1. Sixteen patients had started HAART in 2003, 131 in 2004, and 65 in the first quarter of 2005. Median age at start of HAART was 6 years (interquartile range [IQR]: 4.2–7.9), and only 7 (3%) children were younger than 18 months. The primary caregivers were biological parents (64%); grandparents (30%); or relatives, neighbors, or orphanages (6%). A total of 76 (36%) of the children were orphans. Only 8 (10.5%) of the 76 orphans were cared for in a structured orphanage. Median CD4% before starting HAART in all patients was 6% (IQR: 2.6–13.0), and the median absolute CD4 count for the children aged ≥5 years ($n = 134$) was 100 cells per mL (IQR: 22–273). In January 2006, 193 of the patients were alive and could be included in the cross-sectional virologic evaluation.

**Treatment Outcomes**

Of 212 children who had started HAART before March 2005, 13 had died, 4 were lost to follow-up, and 2 were transferred to another treatment site. Tuberculosis was responsible for 8 deaths; the remainder were attributed to severe sepsis (2 deaths), pneumonia, bacterial meningitis, and wasting syndrome. According to the survival analysis, 92% of the children were alive and in care at 12 months and 91% at 24 months of treatment (Fig 1). Median time on HAART of the patients who were alive was 16.8 months (IQR: 13.9–21.2). Thirty-six (17%) patients were on HAART for ≥24 months. Mean weight-for-height $z$ score increased by 0.81 to $-0.78$ (SD: $\pm 1.17$) at 12 months of HAART. HAART was generally well tolerated, with only 7 patients having to switch to...
an alternative regimen for reasons of intolerability for nevirapine (2), zidovudine (2), and stavudine (3).

Median CD4% gain at 12 months was 17.0% (IQR: 16.3%–30.7%); among the children who were older than 5 years at that time (n = 164), median CD4 cell count gain from baseline was 490 cells per mL. Viral load was measured for all 193 patients who were alive and on HAART at 12 months. A total of 156 (81% [95% CI: 74.0%–85.0%]) of the samples showed an undetectable viral load (<400 copies per mL), 7 (3.7% [95% CI: 1.6%–7.5%]) of the patients had a viral load between 400 and 1000 copies per mL, and 30 (15.5% [95% CI: 11.0%–21.4%]) of the patients had a viral load of >1000 copies per mL.

In an intention-to-treat analysis, 156 of 212 (73.6% [95% CI: 67.0%–79.0%]) of all patients who started HAART before March 2005 had an undetectable viral load. Of these, 36 had been on HAART for 24 months, and among this subgroup, 24 (66.6% [95% CI: 50.0%–80.0%]) had an undetectable viral load. The proportion with an undetectable viral load in the intention-to-treat analysis for this group was 24 of 38 (63.0% [95% CI: 47.0%–76.6%]). Of the 30 children with a viral load of >1000 copies per mL, 16 (53%) were in immunologic failure at the moment of the viral load according to the criteria of the guidelines from the National Institutes of Health. In the analysis of baseline characteristics as predictors of virologic failure (Table 2), being an orphan was found to be a statistically significant predictor of virologic failure (P = .001). For all 37 samples with a viral load of >400 copies per mL, genotype resistance testing was performed. Genotyping could not be amplified in 1 case. In 34 samples, at least 1 mutation was found. Of the 2 samples in which none was detected, viral loads were 16 637 and 689 copies per mL. Mutations in 31 of 34 patients showed a nucleoside reverse-transcriptase inhibitor (NRTI) mutation, the most common being M184 (n = 26), D67 (n = 7), T215 (n = 7), and T69 and L210 (n = 4). Twenty-seven patients had developed resistance to lamivudine, 9 to zidovudine, and 11 to stavudine. Resistance to abacavir was found in 4 patients, to tenofovir in 3 patients, and to didanosine in 3 patients. Thirty-two of 34 had developed non–nucleoside reverse-transcriptase inhibitor (NNRTI) resistance, 3 of them had no NRTI resistance. Of 31 patients with NRTI resistance, 2 showed no NNRTI resistance.

### DISCUSSION
The experience of these 2 pediatric HIV/AIDS care programs shows that antiretroviral therapy is feasible for children at the district level in Cambodia, with very good results obtained after 2 years on treatment. A total of 92% of patients were alive at 12 months, and median CD4% rose from 6% at baseline to 25% at 12 months. A cross-sectional survey of viral load of all patients who were receiving HAART at 12 months showed that 81% had an undetectable viral load using a threshold of detection of 400 copies per mL as treated and 74% in intention-to-treat analysis.

The proportion of patients who achieved virologic success is equal to or better than all of the clinical trials in Western settings before 2002 as summarized in a review article by Van Rossum et al. Among the best results cited in the review, 3 trials are comparable; they report the proportion of patients with a viral load of <400 copies per mL at 48 to 72 weeks of HAART as 69%, 70%, and 87%, respectively, on a population as treated. One result is available on an intention-to-treat population, and that showed 61% with a viral load of <400 copies per mL. In the comparison with the results of our Cambodian cohort, it has to be acknowledged, however, that in a number of these studies, no patients were included that were naïve to NRTI. The outcomes in this study generally also compare favorably
with the published cohort studies in other resource-limited contexts such as Thailand, Romania, and Ivory Coast.8,10,11

The majority of patients in our cohort were treated with split adult FDC of 2 NRTIs and 1 NNRTI, confirming other findings that good outcomes can be achieved with this treatment strategy.18,19 It should be noted, however, that this practice is a suboptimal interim strategy13 pending prequalification of pediatric formulations of FDCs. The majority of the patients were in an advanced stage of HIV infection, similar to many settings where HIV/AIDS care for children has been commenced. We also note that the 2 different settings offer similar results, demonstrating that a well-organized public hospital (Takeo) with targeted support can achieve a quality of care equal to a private, nonprofit setting. In Takeo, all consultations and nursing support was done by Ministry of Health hospital staff, and MSF provide psychosocial support and technical support.

Being orphaned was found to lead to a greater risk for virologic failure, and this is likely because of poorer adherence support, although this cannot be said with certainty given that adherence was not recorded systematically. Most of these orphans are cared for in the family of the grandparents or neighbors. The results of this evaluation should encourage paying a greater attention to adherence support for this group, for example, through more intensive home-based care, specific counseling sessions for grandmothers, or the development of better adapted tools and approaches for adherence support.

We are aware of 7 patients who had previous antiretroviral experience (purchased drugs from private pharmacies or shared with their parents). All but 1 of these developed virologic treatment failure. We do not know for certain whether other children were also an-

TABLE 2
Effects of the Baseline Characteristics on the Likelihood That Plasma HIV RNA Would be >400 Copies per mL After ≥12 Months of HAART

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate Risk Ratio (95% CI)</th>
<th>Multivariate Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>&gt;6</td>
<td>1.200 (0.580–2.480)</td>
<td>—</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Male</td>
<td>1.900 (0.910–4.100)</td>
<td>1.800 (0.860–4.100)</td>
</tr>
<tr>
<td>Adjusted z score for weight</td>
<td>0.867 (0.612–1.230)</td>
<td>—</td>
</tr>
<tr>
<td>(per unit increase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>≤5</td>
<td>0.685 (0.330–1.400)</td>
<td>—</td>
</tr>
<tr>
<td>CDC stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other stages</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Stage C</td>
<td>1.700 (0.560–5.280)</td>
<td>—</td>
</tr>
<tr>
<td>Geographic origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients from the same province</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Patients from outside the</td>
<td>1.230 (0.558–2.730)</td>
<td>—</td>
</tr>
<tr>
<td>province of the clinic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children with at least 1</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>parent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orphan</td>
<td>3.850 (1.830–8.110)</td>
<td>3.800 (1.800–8.000)</td>
</tr>
<tr>
<td>Regimen at start</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZT/3TC/NVP</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>D4T/3TC/NVP</td>
<td>1.180 (0.315–4.450)</td>
<td>—</td>
</tr>
<tr>
<td>D4T/3TC/EFV</td>
<td>1.110 (0.411–2.970)</td>
<td>—</td>
</tr>
</tbody>
</table>

Multivariate values were only represented when univariate values showed a significant effect of the baseline characteristic.
tiretroviral experienced before they started follow-up in the clinics, so it is not possible to calculate the treatment success rate among antiretroviral-naïve patients. In the MSF cohorts of adult patients in Cambodia (>5000 patients), ~5% of all new patients are antiretroviral experienced, and a large proportion of pediatric patients have parents on HAART, so it is possible that more pediatric patients are antiretroviral experienced.

Sixteen of 30 patients with a viral load of >1000 copies per mL showed clear immunologic failure at the last CD4 measurement. Previous studies have concluded that CD4 monitoring is more appropriate than virologic monitoring because a decreasing CD4 count is a better predictor of disease progression. Early detection of treatment failure is important to limit the selection of resistance mutations, although it remains unclear at which level of detectable viral load patients should be switched.

All but 1 patient with a viral load of >1000 copies per mL had developed ≥1 resistance mutation indicating failure to the first-line HAART regimen. Seven patients had developed a profile of extensive resistance, leaving very few options for a HAART regimen that could be effective in achieving viral suppression. Five of these patients were known to be antiretroviral experienced. Five of the 30 patients in whom treatment failure was detected had virus strains that were sensitive to only 1 drug in the suggested standard second-line regimen in the 2006 WHO guidelines for infants and children. Three of these patients were known to be antiretroviral experienced, which suggests that the use of a standard second-line regimen will not be a good solution for all patients, and an expanded formulary is needed.

There are several limitations to this study. First, although a small group of patients have been on HAART for at least 24 months, the overall time under HAART is still short. Second, we do not have good information on antiretroviral experience for all of the patients; neither have we attempted to measure adherence in a systematic way. Third, only 7 children who started HAART at younger than 18 months are included in this cohort because of the unavailability of appropriate diagnostic tools to diagnose HIV/AIDS in infants in the first years of the clinics’ activities, and only rarely did children with suspected HIV infection reach the clinics before the age of 1.

Despite these limitations, these findings provide clear support for the feasibility of integrating pediatric care in a HAART clinic at the district level. Viral load is a valuable tool for detecting early treatment failure, and genotyping is useful for choosing the best second-line regimen, particularly for treatment-experienced patients. Orphans are at higher risk for developing treatment failure and need extra attention and support.

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