Safety, Tolerability and Effectiveness of Generic HAART in HIV-Infected Children in South India

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Summary

HIV-infected children in resource-limited settings are increasingly gaining greater access to highly active antiretroviral therapy (HAART) but documented longitudinal data remains limited. We aimed to study the clinical and immunological outcomes among 67 South Indian HIV-infected children with >18 months of follow-up on HAART at a tertiary HIV care program. The median CD4 cell count at enrolment was 290 cells μl⁻¹ and at treatment initiation was 225 cells μl⁻¹. Patients demonstrated a significant rise in their CD4 cell counts between treatment initiation and after 6 months (701 cells μl⁻¹; p = 0.007), 12 months (741 cells μl⁻¹; p = 0.037), and 18 months of therapy (718 cells μl⁻¹; p = 0.005). The most common adverse events to therapy were nausea (20.9%) and rash (25.4%). Over one-fifth of patients (25.4%) substituted therapy due to toxicities and 19.4% of patients switched to second-line protease inhibitor-containing regimens. In this South Indian pediatric cohort, generic HAART was safe, effective and relatively well tolerated.

Introduction

It is estimated that between 2 and 3.1 million Indians are currently infected with HIV, of which 70 000 are children below the age of 15 years [1]. Despite recent efforts to scale-up perinatal HIV prevention services, 21 000 Indian children are infected each year with HIV through mother-to-child transmission (MTCT) [2]. Despite a relatively low population prevalence nationally, certain populations, such as clients of STI clinics and mothers reporting for antenatal care, have reported with higher rates of HIV. Since 2004, the Indian government has scaled up the provision of generic antiretroviral therapy and the next phase of the program has the goal of placing 40 000 children on ART by 2010.

The clinical efficacy of highly active antiretroviral therapy (HAART) has been well documented among children in the developed world [3, 4]. Despite the high burden of cases of pediatric HIV in resource-limited settings, there is still a paucity of longitudinal data documenting the clinical effects of increased accessibility of generic HAART [5–8]. The immune restorative effects of HAART in children may be compromised in resource-limited settings where poverty, malnutrition, limited access to care and tuberculosis (TB) are rampant. Earlier studies at our center have documented the changing natural history of HIV among South Indian adults after the introduction of generic HAART [9, 10]. An earlier study at our center documented the clinical manifestations of HIV disease among 58 children prior to the era of greater access to ART [11].

The current study was undertaken to determine the clinical and immunological outcomes among South Indian HIV-infected children initiating HAART. The findings of the current study providing 18 months of treatment follow-up is timely as more Indian children initiate HAART as part of the expanded government treatment scale-up.

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Methods

Setting
Since 1996, YRG Center for AIDS Research an Education (YRG CARE)-Voluntary Health Services, Chennai, has provided a continuum of care for over 10,000 HIV-infected individuals. All patients are treated according to World Health Organization (WHO) treatment guidelines [4]. Nevirapine (NVP)-based regimens, which are the least expensive and most widely available, are generally used as first-line therapies. Patients are seen every 3 months or as clinically indicated. CD4 monitoring is done every 3–6 months. Plasma viral load (PVL) monitoring is currently not standard care.

Patients
Between February 1996 and March 2008, 214 HIV-infected children were evaluated at the outpatient clinic. Of these children, 14 were already receiving HAART at enrolment and were not included in the current analyses. Eight patients were initially started on dual-therapy and four patients were initially started on monotherapy but were then later initiated on HAART. Only therapy-naïve children at enrolment to care who consequently initiated HAART with a minimum follow-up period of 18 months (N = 67) are included in the current study. The mode of HIV transmission was ascertained through establishing maternal HIV status, evaluating history of blood/blood product transfusion and history of sexual abuse. The initial patient assessment included a thorough pediatric history and physical examination as well as determination of clinical disease stage by CDC criteria [12].

Data were collected under the approval of YRG CARE’s free-standing institutional review board. Analysis was executed using the YRG CARE Chennai HIV Natural History study Observational Database. This database that is updated daily collects data on demographics; clinical assessments including data related to the occurrence of new opportunistic infections; current treatment regimens and adverse events (AEs) as well as laboratory data, including hemoglobin, liver, and renal function tests, CD4 cell counts; PVL and genotypic testing, if available. TB diagnosis was based on consistent history and physical exam and culture yielding Mycobacterium TB or positive sputum or aspirate tests for acid-fast bacilli, radiological features suggestive of TB, or clinical and radiological improvement in response to anti-TB treatment. Current WHO pediatric definitions of immunologic failure were used [4]; WHO weight-for-height tables were used to calculate z-scores [13].

Statistical analysis
Descriptive statistics were calculated with mean and standard deviation for variables that were normally distributed and the median and interquartile range (IQR) were calculated for variables influenced by extreme values. To compare proportions, chi-square (χ²) statistics were used and the Mann–Whitney U-test was used to compare median durations. Statistical analyses were performed with SPSS software (version 13.0; SPSS, Chicago, IL). A p-value <0.05 was considered statistically significant.

Results

Characteristics of the study population
Close to two-thirds of patients were male (61%); mean age (±SD) was 6.28 (±4.18) years (Table 1). Most patients were infected with HIV via MTCT (vertical) (87%) and 13% were infected via blood transfusion. Over one-third of the patients had both parents alive (37%), 34% had only one parent alive and 12% had no parents alive. Over half of the patients had two parents infected with HIV (58%), 27% had one parent infected with HIV and 4% had neither parent infected with HIV. At enrolment, half of the patients (50.8%) were classified as Stage 1 (asymptomatic), 40.3% as Stage 3 (moderate) and 9.0% as Stage 4 (severe).

The mean weight-for-height z-score increased from 0.53 (SD±1.41) at enrolment to care to 0.58 (SD±1.22) after 12 months of therapy. The median time before patients initiated HAART was 4.17 months (IQR: 0.03–22.6). Two-fifths of patients (41.8%) started on lamivudine, stavudine and NVP (3TC+d4T+NVP) as their first-line ART; 16.2% on lamivudine, zidovudine and NVP (3TC+AZT+NVP) and 20.9% on lamivudine, stavudine and efavirenz (3TC+d4T+EFV). The median time that patients were on HAART was 34.5 months (18.3–22.6).

Treatment outcomes
At enrolment to care, the most common opportunistic infections were oral candidiasis (26.9%), pulmonary TB (13.4%) and herpes zoster (7.5%). The median CD4 cell count at enrolment was 290 cells μl⁻¹ (IQR: 91–656) and at treatment initiation was 225 cells μl⁻¹ (IQR: 95–411). The median CD4% at enrolment to care was 14% (IQR: 7–20) and at treatment initiation was 12% (IQR: 7–18). The median hemoglobin at enrolment was 10.4 g dl⁻¹ (IQR: 9.1–11.6) and at treatment initiation was 10.7 g dl⁻¹ (IQR: 9.7–11.7).

Patients demonstrated a significant rise in their CD4 cell counts between treatment initiation and after 6 months (701 cells μl⁻¹; IQR: 296–918) (p = 0.007), 12 months (741 cells μl⁻¹; IQR: 334–1108) (p = 0.037) and 18 months of therapy (718 cells μl⁻¹; IQR: 411–1123) (p = 0.005) (Fig. 1). Additionally, patients demonstrated a significant rise in their CD4% between treatment initiation and 12 months (23%; IQR: 15–31) (p = 0.04). Patients did not demonstrate a significant rise in hemoglobin
between treatment initiation and after 6 months ($p = 0.4$), 12 months ($p = 0.1$) or 18 months of therapy ($p = 0.9$).

The most common AEs to therapy were nausea (20.9%) and rash (25.4%). Over one-fifth of patients (25.4%) substituted therapy due to toxicities and 19.4% of patients switched to second-line protease inhibitor-containing regimens. No patients died or discontinued therapy.

**Discussion**

The current study demonstrates the effectiveness and tolerability of generic HAART among South Indian HIV-infected children. All patients were alive at 18 months and the median CD4% more than doubled from 12% at treatment initiation to 25% at 18 months. An earlier study from South India found that children initiated on HAART with a CD4 cell% $< 14\%$ had a significantly higher mortality rate [14]. Children who were therapy-naive at enrolment in the current study demonstrated significantly greater rises is CD% and CD4 cell count between initiation and 18 months of therapy compared with children who were on prior mono- or dual therapy. This can be explained by the development of resistance to dual NRTI regimens. The immunological recovery documented in the current study compares favorably with recent studies from other resource-limited settings, including Kenya, Cambodia, Thailand, Cote d’Ivoire and Zambia [5–8, 15]. The AEs to therapy were reversible and relatively minor, which is in line with

| TABLE 1
Demographic and clinical characteristics of HAART experienced children (N = 67) |
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<tbody>
<tr>
<td>Gender</td>
<td>Boys: 61.2, Girls: 38.8</td>
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<tr>
<td>Age (years)</td>
<td>Mean ± SD: 6.28 ± 4.18, Range (Minimum-Maximum): 0.06–15</td>
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<tr>
<td>Mode of transmission</td>
<td>Mother-to-child/Vertical: 86.6, Blood transfusion: 13.4</td>
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<tr>
<td>Parent status</td>
<td>Two parents alive: 37.3, One parent alive: 34.3, No parents alive: 11.9, Status not known: 16.4</td>
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<tr>
<td>Weight-for-height z score, mean ± SD</td>
<td>At enrollment: 0.53 ± 1.41, At 1 year after HAART: 0.58 ± 1.22</td>
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<tr>
<td>CDC Category at the time of initiation of HAART</td>
<td>Stage 1 (Asymptomatic): 50.8, Stage 2 (Mild): 0, Stage 3 (Moderate): 40.3, Stage 4 (Severe): 9.0</td>
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<td>Median CD4 cell count (cells/μl)</td>
<td>At enrolment: 290 (91–656), At treatment initiation: 225 (95–411), At 6 months: 701 (296–918), At 12 months: 741 (334–1108), At 18 months: 718 (411–1123)</td>
</tr>
<tr>
<td>Median CD4%</td>
<td>At enrolment: 14 (7–20), At treatment initiation: 12 (7–18), At 6 months: 20 (13–27), At 12 months: 23 (15–31), At 18 months: 25 (16–33)</td>
</tr>
<tr>
<td>Median hemoglobin (g/dl)</td>
<td>At enrolment: 10.4 (9.1–11.6), At treatment initiation: 10.7 (9.7–11.7), At 6 months: 11.4 (10.6–12.6), At 12 months: 11.6 (10.9–12.6), At 18 months: 11.7 (11.1–12.5)</td>
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(continued)
another study from Western India documenting AEs to ART [16].

Despite the fact that pediatric HIV is a completely preventable disease, children in the current study were infected via vertical transmission and to a lesser extent via blood transfusion at a time after the extensive rollout of voluntary counseling and testing services at antenatal centers and blood screening in the public sector. The mean age at presentation of children was over 6 years and at this point over half of the children were in Stages 3 or 4. This highlights the clinical reality that early diagnosis of HIV in children is complicated by a lack of effective maternal prevention services and that early symptoms, such as failure to thrive, bacterial infections and diarrhea are also prevalent conditions in non-HIV infected children [17].

More than half of the children in the current study had both parents infected with HIV and only a little over one-third of children had both parents living. HIV treatment models should encompass the whole family, both adult caregivers and children. The limited availability of pediatric-specific formulary of antiretroviral drugs has been a major barrier to wider access to treatment [18]. Initially generic adult fixed-dose regimens of 2 NRTIs and 1 NNRTI were split due to a lack of alternative pediatric regimens. The current study confirms that though this is a suboptimal treatment strategy, good treatment outcomes can be achieved. Later dispersible fixed-dose forms with drug concentrations suitable for a pediatric population were made available to study patients.

In this South Indian pediatric cohort, generic HAART was safe, effective and relatively well tolerated. Despite wider access to first-line antiretroviral therapy through the expanded government scale-up, a major challenge will be to provide adequate second-line treatment options for children failing first-line therapy. More proactive testing at antenatal centers and greater protection of the blood supply coupled with a wider formulary of antiretroviral therapy for HIV-infected children will require a multifaceted public health approach involving both the government and civil society.

References


