

# Antiretroviral Therapy in Children: Indian Experience

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**Background :** There is a paucity of reports on Highly Active Antiretroviral therapy (HAART) in children. We studied feasibility and effectiveness fixed dose combination (FDC) of lamivudine, nevirapine and stavudine in HIV infected children. **Design:** Interventional study. **Setting:** A Tertiary care center. **Subjects:** Twenty five consecutive HIV positive antiretroviral naïve children older than 18 months. **Methods:** The study subjects were started on weight-appropriate doses of the FDC and followed up for 6 months. Weight, CD4 counts, absolute lymphocyte count (ALC) and number of episodes of illness were assessed before and after HAART. Adherence and barriers to adherence were studied. **Results:** Mean weight increased from 15.2 to 16.8 kg ( $P < 0.001$ ) while mean CD4 counts increased from 488/cmm to 765/cmm ( $P < 0.001$ ). Only 2 cases of drug associated adverse event were encountered. Improvement in Center for Disease Control (CDC) immunological classification of the subjects was significant while that in World Health Organization (WHO) clinical staging was not statistically significant. Follow up visits were 95% of the expected 175 visits. The average distance traveled by the patient for every visit was 72 km (one way). **Conclusions:** Use of FDC in weight specific dosages is feasible and effective for treatment of Pediatric HIV in resource scarce setting. These preliminary results need to be tested in a different setting.

**Key words:** Absolute lymphocyte count, Nevirapine, Adherence, Fixed drug combination, Pediatric HAART.

IT is estimated that 30,000 children are born in India every year with HIV infection(1). Highly active antiretroviral therapy (HAART) has shown reduction in circulating viral load. Protease inhibitor based regimens, while highly potent, have a high pill burden and poor palatability(2). The limited availability of pediatric formulations acts as an additional barrier to treatment. Fixed drug combinations (FDC) promote better adherence and tend to be cost-effective. Generic FDCs have been prequalified by the WHO to treat HIV-infected patients in resource-limited countries(3). There is a paucity of reports on HAART in children from resource poor settings. We assessed the effectiveness of a combination of stavudine, lamivudine and nevirapine, available as an FDC in weight-specific doses, with respect to effect on clinical and immunological status of HIV-infected children.

## Subject and Methods

This interventional prospective study was carried out at the BJ Medical College and Sassoon

General Hospital, a tertiary care hospital in Pune after obtaining ethical clearance. Twenty-five HIV positive, antiretroviral naïve children older than 18 months were enrolled. HIV infection was diagnosed by two positive ELISA (enzyme linked immunosorbent assay) tests. Each child underwent a thorough clinical examination. Baseline laboratory studies included estimation of hemoglobin, absolute lymphocyte count (ALC), alanine transaminase (ALT) and serum cholesterol. All children were subjected to chest radiography and ultrasound of abdomen. A baseline CD4 count was performed in all cases, by flow cytometry with a fully automated two-laser BD FACS calibur flow cytometer (USA) usually at mid-day, to avoid diurnal variations.

Probable tuberculosis was diagnosed based on the criteria detailed by Osborne(4) and anti-tuberculosis therapy (ATT) was started according to the Indian Academy of Pediatrics consensus guidelines(5). Each child was classified according to the WHO clinical staging(6) as well as the CDC clinical and immunological staging(2). Antiretroviral therapy (ART) was initiated for

children in WHO stage 3; CDC clinical category B or C and /or immune category 2 or 3; or on parental insistence despite being in CDC or WHO category 1. In patients diagnosed with tuberculosis, the ART was initiated 15 days after starting the anti-tubercular therapy. Pneumocystis carinii pneumonia prophylaxis was started in all cases. HAART comprised of one Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI), nevirapine and two Nucleoside Reverse Transcriptase Inhibitors (NRTI), lamivudine and stavudine. A fixed dose combination containing stavudine 30 or 40 mg, lamivudine 150 mg and nevirapine 200 mg was used. The tablets were administered as one half or one quarter twice a day so as to ensure a dose of one mg/kg of stavudine twice a day (*Table I*).

Children swallowed the tablets wherever possible. In younger age group the tablet was split and dissolved in water and administered. ART was provided either through the ART center in the Sassoon general hospital (n = 16) or from local Non Governmental Organizations (n = 9).

First follow-up visit was after 15 days and then at monthly interval. Thus, seven visits were expected over a six-month period. Six or seven visits were

**TABLE I**—*Weightwise Dosing of Fixed Drug Combination (FDC)*

Weight (kg)	FDC used	Dose
5 - 8.5	Stavudine 30 mg Lamivudine 150 mg Nevirapine 200 mg	¼ tablet twice daily
8.6 – 12.5	Stavudine 40 mg Lamivudine 150 mg Nevirapine 200 mg	¼ tablet twice daily
12.6 – 17.5	Stavudine 30 mg Lamivudine 150 mg Nevirapine 200 mg	½ tablet twice daily
17.6 – 22.5	Stavudine 40 mg Lamivudine 150 mg Nevirapine 200 mg	½ tablet twice daily
22.6– 35	Stavudine 30 mg Lamivudine 150 mg Nevirapine 200 mg	1 tablet twice daily
>35	Stavudine 40 mg Lamivudine 150 mg Nevirapine 200 mg	1 tablet twice daily

taken as excellent follow up, three to five as good and less than three as poor follow up. Clinical examination and nutritional status was assessed at every visit. Biochemical investigations were performed if indicated. Intercurrent infections and adverse drug effects were recorded. A CD4 count along with an ALC was repeated 6 months after starting ART.

Outcome variables studied included the patient's well-being, as assessed by the caregiver, weight gain, episodes requiring out-patient or in-patient attendance, follow up rate, CD4 count, ALC and changes in the WHO clinical staging and CDC clinical and immunological staging, if any. Factors influencing adherence and follow-up like caregiver profile and average distance traveled to reach the hospital were also studied.

#### *Statistical analysis*

Episodes requiring out-patient and in-patient treatment during 6 months on ART were compared with the number of episodes in the 6 months prior to starting ART and were analyzed using paired t test. Changes in weight, CD<sub>4</sub> counts and ALC were analyzed using paired t test. The changes in CDC and WHO categories were compared using the Fisher's Exact test. Co-relation between CD<sub>4</sub> counts and ALC was studied using simple linear regression. Stata software was used for the statistical analysis.

#### **Results**

Twenty five subjects (14 boys, 11 girls) with a median age of 6 years and 8 months were part of this study. Of these, 2 were asymptomatic and 6, 14 and 3 were placed in Stage A, B and C of CDC clinical classification, respectively. The effect of ART on various clinical and hematological parameters is shown in *Table II*. ALC and CD4 count had a 48% correlation before ART while correlation increased to 84% after ART.

Regularity of follow-up visits was taken as a surrogate marker for adherence. Of the 175 visits expected from the cohort, 167 were completed on schedule giving a follow up rate of 95.4%. Individually the follow-up was excellent in 22 cases and good in 3 cases. While studying various factors influencing adherence and follow up, it was found

**TABLE II**—Differences in Various Parameters after 6 Months of ART

Parameter	Before initiation of therapy	After 6 months of ART	P value
Mean weight (kg) (SD)	15.2 (4.4)	16.8 (4.6)	<0.001
Mean CD4 count/mm <sup>3</sup> (SD)	488 (412)	765 (596)	<0.001
Mean ALC/mm <sup>3</sup> (SD)	2664 (957)	3479 (1968)	0.01
CDC immunological classification			
Category 1	8	13	
Category 2	7	10	<0.001
Category 3	10	2	
WHO clinical staging			
Stage 1	4	11	0.11
Stage 2	14	12	0.11
Stage 3	7	2	
Mean number of unscheduled OPD visits/ patient in 6 months (SD)	2.68 (1.1)	0.92 (0.86)	<0.001
Mean number of episodes requiring admission to hospital/ patient in 6 months (SD)	0.56 (0.77)	0.24 (0.52)	0.003

that 13 children had a single surviving parent as the caregiver while both the parents were alive in three cases. In the remaining nine cases the grandparents were the caregivers for the child. The average distance traveled by the child and caregiver to reach our hospital was found to be about 72 km one-way. Adverse effects of the drug were monitored and only one case each of gastritis and hepatitis was detected.

## Discussion

HAART in Pediatric age group remained a difficult proposition for children in the developing countries for a long time because of lack of pediatric formulations and cost of therapy. With the arrival of generic FDCs, the problem was solved to some extent in the adult patients. The WHO recognizes that until appropriate formulations can be made more widely available the splitting of adult-dose solid formulation antiretrovirals, while sub-optimal, may be the only way a severely ill child can receive therapy, and should be considered when no alternatives are available(6). Hence, we decided to utilize the same FDCs in children using half or even one fourth tablet due to lack of other options although not an ideal proposition. Dispersible FDCs with the concentration of the drugs suited for the pediatric population will be the ideal alternative for treatment

of pediatric HIV. The drugs were made available free of cost in this study. However, an assured supply of drugs beyond six months was not guaranteed. Hence we decided to follow the patients for six months only.

Growth failure is a common feature of children with HIV infection(7). Weight gain has been used as a parameter for assessing improvement in health status(7,8). Our study shows that a significant weight gain can be achieved after initiation of HAART. The caregiver noticed a sense of well being with the child even before weight gain occurred. This was an important change although difficult to quantify.

The effectiveness studies of three-drug (2 NRTI + 1 NNRTI) regimen for children are of crucial importance for resource-limited setting. We came across only one such study in the Indian literature(9). The effectiveness is commonly judged by CD<sub>4</sub> counts and viral load assays. The significant increase in CD<sub>4</sub> count observed in this study replicates the findings of some Indian and Thai studies(9,10). Thus, the use of adult FDCs in children after calculating weight-specific dosages is feasible and useful.

The rise in CD<sub>4</sub> count was paralleled by a similar rise in ALC. Moreover, the correlation between

ALC and CD<sub>4</sub> count in this study improved after treatment. Studies have demonstrated that a reliable relationship exists between ALC and CD<sub>4</sub> counts(11) as well as the suitability of the use of ALC in the absence of CD<sub>4</sub> counts(12).

The improvement of immune status is also clinically visible by the significant decrease in episodes of minor illnesses as well as major illnesses. A substantial reduction in the rates of hospitalizations and infections has also been documented in some Spanish and French studies on pediatric HAART(13-15). An untreated HIV infected child tends to have repeated illnesses, which often are resistant to treatment. The management of these puts extra strain especially on single parents or grandparents.

We did not use a lead in period for Nevirapine in our study because a lead in period leads to regimens that require multiple FDCs as well as increased cost. Only two cases of drug associated adverse events in this study leads us to believe that routine biochemical monitoring may not be necessary. Testing wherever there are signs/symptoms of adverse event seems more justifiable. Two of the subjects developed herpes zoster during the course of the study period. This may be attributed to immune re-constitution with HAART. Three patients in our study were simultaneously receiving ATT as well as nevirapine based ART because of high cost of efavirenz-based regimen and unavailability of a suitable FDC. None of these patients had any drug associated adverse event and all of them showed an increase in CD<sub>4</sub> counts. The clinical significance of the drug interaction between nevirapine and rifampicin, whereby nevirapine levels are reduced, needs to be studied in depth in children.

The sense of well-being in the child played a major part in ensuring adherence to treatment and regular follow up. Medical adherence is fundamental to successful ART. In our study, the high percentage of children with excellent follow up may indirectly indicate good adherence. Besides, practical difficulties in adherence also need consideration. Easy availability, simplified monitoring and less frequent visits for expert opinion are sure to enhance effectiveness of HAART.

In conclusion, our study demonstrated that it is feasible to treat HIV-infected children with available FDC meant for adults. A relatively small sample size and a short duration of follow up were some of the limitations of this study.

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*Competing Interests:* None.

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