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SAFETY AND EFFICACY OF PEDIATRIC FIXED DOSE COMBINATIONS (FDCS) OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN HIV INFECTED CHILDREN IN A DEVELOPING COUNTRY

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ABSTRACT

Objective: *Pediatric fixed dose combinations antiretroviral tablets have been developed in accordance with pediatric recommendations. We studied feasibility and effectiveness of pediatric fixed dose combination of lamivudine, nevirapine and stavudine in HIV infected children in developing country.*

Design: *Randomized interventional non comparative prospective study*

Methods: *This study was conducted at Anti Retroviral Treatment clinic of a tertiary care centre. Thirty vertically infected HIV positive children older than 18 months were started on weight-appropriate doses of the pediatric fixed dose combination and followed up for 6 months. Weight, CD4 counts, absolute lymphocyte count and number of episodes of illness were assessed before and after HAART. Adherence and barriers to adherence were studied.*

Results: *Mean weight increased from 16.6±1.1 to 20±2.2 kg (p<0.001) while mean CD4 counts increased from 226/cmm to 584/cmm (p<0.001). One child developed minor skin rash in the initial two weeks of starting nevirapine. Improvement in Centre for Disease Control immunological classification as well as World Health Organization clinical staging was statistically significant. Adherence to the regimen was >95 %, and there were no treatment failure.*

Conclusions: *Use of pediatric fixed dose combination in weight specific dosages is safe and effective for treatment of Pediatric HIV in resource scarce setting. Our study provides additional evidence of the effectiveness of highly active antiretroviral therapy for children with good clinical and immunologic recovery.*

KEYWORDS : *HIV, CD4 count, Pediatric fixed drug combination, HAART, Adherence, WHO clinical staging.*

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INTRODUCTION

Fifteen per cent of India's 2.5 million HIV-positive are children. Some 50,000 of them are born infected or become infected each year [1]. Highly active antiretroviral therapy (HAART) has shown reduction in circulating viral load. Protease inhibitor based regimens although highly potent but have a high pill burden, quite expensive and beyond reach of most HIV affected families in India and other developing countries. One of the biggest obstacles to reaching ART to children was the lack of paediatric formulations. When liquids preparation of ART are available, they are costly having short shelf lives and are difficult to transport and store [2]. As a result of the lack of availability of affordable and appropriate pediatric ART formulations, divided adult fixed-dose combinations (FDCs) tablets are frequently provided for children. In addition to unequal distribution of drugs in tablets and difficulties with accurate cutting, a major problem with such a approach is that the ratios of drugs in adult FDCs are according to adult recommendations and do not allow easy dose adjustment as a child grows because rate of drug metabolism is likely to vary with age. Children receiving divided adult FDCs demonstrated a risk of nevirapine under dosing [3]. Under dosing results in development of mutations, particularly against drugs with a low genetic barrier to resistance such as nevirapine and lamivudine because of lack of potency in suppressing viral replication and thus a major threat to the long-term success of ART [4,5].To solve this problem small, dispersible, crushable, scored FDCs for HIV-infected children have been developed in accordance with paediatric dosing recommendations. Generic split dose adult FDCs have been used to treat HIV-infected pediatric patients in resource-limited countries. [6,7] There is a paucity of reports on pediatric FDCs 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 in a tertiary care hospital in northern India.

METHOD

This interventional non comparative prospective study was carried out in Department of Pediatrics, Pandit Bhagwat Dayal Sharma Post Graduate Institute Medical Sciences (PGIMS), a tertiary care hospital in Rohtak, Haryana after obtaining ethical clearance. The study was conducted during a period from May 2008 to December 2009. Thirty vertically infected pediatric HIV patients above 18 months of age admitted in indoor pediatric ward or presented in ART (Anti Retroviral treatment) clinic of PGIMS, Rohtak were enrolled. Children fulfilling the WHO clinical staging criteria and diagnosis of HIV-I infection confirmed by two positive ELISA (enzyme linked immunosorbent Assay) tests were included and children less than 18 months of age unless diagnosis is confirmed by HIV-DNA PCR estimation or patient already on antiretroviral treatment from outside were excluded.

Each child underwent a thorough clinical examination (including anthropometry). Baseline laboratory investigations including estimation of hemoglobin, absolute lymphocyte count (ALC), alanine/aspartate aminotransferase (SGOT/PT), serum creatinine, serum cholesterol were performed. All patients were subjected to chest radiography and ultrasound of abdomen. Screening for tuberculosis was done in all patients. A baseline CD4 count was performed in all cases by fully automated two laser BD FACS flow cytometer, usually at the same time of the day, to avoid diurnal variations. Each child was classified according to the WHO clinical staging as well as the CDC immunological staging. Anti retroviral therapy will be initiated for children in WHO clinical stage 3 or clinical stage 4 and CD4 guided in stage 1 and 2. HAART, as Fixed Dose Combinations (FDCs) comprised of one non nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine(NVP) and two nucleoside reverse transcriptase inhibition (NRTI) lamivudine and stavudine. During the lead-in period, patients take NVP in small evening dose for two weeks and then shifted over in the

continuation phase to the standard three-drug FDC formulation Children swallowed the tablets wherever possible. In younger age group the tablet was split and dissolved in water and administered. ART centre of our institution provided drugs free of cost. 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 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 patient's well being as assessed by caregiver, weight / height gain, episode requiring outpatient or in patient attendance, follow up rate, CD4 count, ALC and changes in WHO clinical staging and immunological staging. Adherence was checked by asking the patient/guardian whether he/she missed any dose. Bottle was also checked.

Episodes requiring inpatient treatment during 6 month on ART were compared with number of episodes in 6 months prior to starting ART and data was analysed by using paired t-test. Changes in weight, height, CD4 count were analysed using paired t-test. These changes in WHO clinical and immunological category was compared using Fischer's exact test. SPSS 17 software was used for the statistical analysis

RESULTS

Thirty perinatally infected HIV patients (21 boys, 9 girls) with a median age of 7 years and 3 months, who had never taken ART previously were initiated on treatment and followed for six months.Out of 30 patients, mode of delivery was vaginal in 28 while 2 patients were delivered through caesarean section. Weight loss was most common symptom present (27) followed by generalized weakness in (24), fever (23), diarrhoea (22), cough (11), hepatomegaly (15), generalized lymphadenopathy in 16 (53.3%),splenomegaly (12), molluscum contagiosum (1), herpes zoster (1) patient.

At enrollment of study, maximum number of children (22) were in stage III and 3, 1 and 4 were placed in Stage I, II and IV of WHO clinical classification, respectively. The effect of ART on various clinical and hematological parameters is shown in *Table II*. Regularity of follow-up visits was taken as a surrogate marker for adherence. Of the 210 visits expected from the cohort, 205 were completed on schedule giving a follow up rate of 97.6%. Individually the follow-up was excellent in 28 cases and good in 2 cases. While studying various factors influencing adherence and follow up, it was found that 18 children had a single surviving parent as the caregiver while both the parents were alive in 11 cases. In the remaining one case the relative were the caregivers for the child. Before initiation of therapy total number of episode requiring hospital admission were six but during therapy there was no hospital admission One child developed minor papular skin rash in the initial 2 weeks of starting nevirapine, which subsided completely; nevirapine was continued. All the patients in both the groups had SGPT / SGOT, serum cholestrol values within normal limit at the end of follow-up period. There were no treatment failures.

DISCUSSION

The limited availability of pediatric formulations acts as an additional barrier to treatment for children in the developing countries for a long time. With the arrival of generic pediatric FDCs, the problem was solved to some extent in the pediatric patients. Pediatric FDCs found to be appropriate for children in previous studies [8,9] This observational, prospective study addressed the efficacy of a simplified, standard, triple-drug antiretroviral regimen among HIV-1–infected children in India. The results showed an overall excellent clinical response to HAART.The drugs were made available free of cost in this study. Growth failure is a common feature of children with HIV infection (10). Weight gain has been used as a parameter for assessing improvement in health status. The weight for age increased during the follow-up period. Our study shows that a

significant weight and height gain can be achieved after initiation of HAART (6,11,12,13,14,15,16,17,18,19,20).

The effectiveness of three-drug (2 NRTI + 1 NNRTI) regimen for children are of crucial importance for resource-limited setting. We came across only three such studies in the Indian literature[6,21,22] however in these studies adult FDCs in split doses was used ,this is first study in which effectiveness of pediatric FDCs assessed. The effectiveness judged by clinically (improvement in WHO clinical staging) and immunologically (CD4 counts and change in immunological staging) .

The significant increase in CD4 count observed in this study replicates the findings of some Indian and other studies [6,13,14,15-25].The rise in CD4 count was paralleled by a similar rise in ALC. Moreover, the correlation between ALC and CD4 count in this study improved after treatment.

Also in present study there is significant improvement in WHO and CDC immunological staging as observed in previous studies [6,22].

The improvement in 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 indian and other studies on pediatric HAART [6,14,18,22,26]. An untreated HIV infected child tends to have repeated illnesses, which often are resistant to treatment.

We use a lead in period for Nevirapine in our study to prevent side effects of NVP in spite of fact that lead in period leads to regimens that require multiple FDCs as well as increased cost. Only one patient had adverse effects in form of skin rashes which resolved by itself and HAART was not stopped and leads us to believe that routine biochemical monitoring may not be necessary.[15,18,21,22].

Adherence to HAART was found more than 95% in all patients during study period. The sense of well-being in the child played a major part in ensuring adherence to treatment and regular follow up. Use of FDC resulted in better tolerance, simplification of treatment, reduction in number of pills, less frequent visits and thus better adherence.

The main drawbacks to our study are the short follow-up period and the relatively small number of patients. Studies in a larger cohort with a longer follow-up period are needed to determine the duration of the clinical, virologic, and immunologic responses and evaluate treatment compliance during a longer period of time. Another potential confounding factor in our study is the age of the patient population. The average age of children who were started on treatment was high at 7 years and 3 months. Same is true for the majority of published reports on treatment outcomes of HIV-infected children in the developing world [6,13,21] The mortality rates of untreated HIV-infected Indian children are extremely high, especially within the first 5 years of life. That the majority of our study patients survived past that age without ART suggests that most of the patients were pediatric slow progressors, which may in part explain the excellent clinical, virologic, and immunologic outcomes of the study. Studies in younger cohorts are essential to understand better the full spectrum of treatment responses in the developing world.

CONCLUSION & SUMMARY

Though, the study was done in a small number of patients within a short period, and results indicate that pediatric Fixed Dose Combinations (FDCs) is safe and significantly improves the clinical as well as immunological outcomes in HIV positive children. High percentage of children with excellent follow up indicate good adherence. In conclusion, present study demonstrated that pediatric FDCs are more appropriate and safe with better compliance to treat HIV infected children in resource limited setting .A relatively small sample size and short duration of follow up were some of limitation of present study.

NVP Lead-in period for first 2 weeks:

Weight band (kg)	Stavudine 6 mg containing FDCs		Stavudine 10 mg containing FDCs		Adult FDCs (Stavudine -30)	
	Morning 2-drug FDC-6 Sta 6 + Lam 30	Evening 3-drug FDC-6 Sta 6 + Lam 30 + NVP 50	Morning 2-drug FDC-10 Sta 10 + Lam 40	Evening 3-drug FDC-10 Sta 10; Lam 40 + NVP 70	Morning 2-drug FDC-30 Sta 30 + Lam 150	Evening 3 drug FDC-30 Sta 30 + Lam 150 + NVP 200
5-5.9	1	1				
6-6.9	1	1				
7-7.9	1.5	1				
8-8.9	1.5	1.5				
9-9.9	1.5	1.5				
10-10.9	2	2				
11-11.9	2	2				
12-13.9			1.5	1		
14 -16.9			1.5	1.5		
17-19.9			2	1.5		
20-24.9					1	1
25-29.9					1	1
30-34.9					1	0.5

Subsequent follow-on regimen for NVP

Weight band (kg)	FDC-6 Sta 6; Lam 30; NVP 50		FDC-10 (tab) Sta 10; Lam 40; NVP 70		Adult FDC-30 Sta 30; Lam 150; NVP 200	
	Morning	Evening	Morning	Evening	Morning	Evening
5-5.9	1	1				
6-6.9	1	1				
7-7.9	1.5	1				
8-8.9	1.5	1.5				
9-9.9	1.5	1.5				
10-10.9	2	2				
11-11.9	2	2				
12-13.9			1.5	1		
14 -16.9			1.5	1.5		
17-19.9			2	1.5		
20-24.9					1	0.5
25-29.9					1	1
30-34.p					1	1

Parameters	Before initiation of therapy (mean±SD)	After 6 month of therapy (mean ±SD)	P value
Mean hemoglobin (gm%)	9.4±1.3	11.05±0.93	<0.05
Mean weight (kg)	16.6±1.1	20±1.2	<0.01
Mean height (cm.)	114.6±3.7	117.6±3.8	<0.01

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WHO clinical staging

WHO clinical stage	No. of patients (%) Before initiation of therapy	No. of patients (%) After six months of therapy	P value
I	3 (10%)	13 (40.4%)	<0.05
II	1 (3.3%)	0 (0%)	
III	22 (70.4%)	15 (50%)	
IV	4 (10.3%)	2 (6.6%)	

CDC Immunological classification

Immunological stage	Before initiation of therapy No. of patients (%)	After six months of therapy No. of patients (%)	P value
Not significant	1 (3.3%)	13 (40.4%)	<0.05
Mild	1 (3.3%)	7 (20.3%)	
Advanced	10 (33.4%)	7 (20.3%)	
Severe	18 (60%)	3 (10%)	

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