Brief Reports

Antiretroviral Therapy in HIV-1 Infected Children

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Highly active antiretroviral therapy is beyond reach of most HIV-infected children in developing countries. There is paucity of data on more affordable regimens such as ones based on nevirapine and 2 nucleoside reverse transcriptase inhibitors. We report our experience with the use of antiretroviral therapy in children with HIV-1 infection at a tertiary care hospital in north India. The study subjects were HIV-1 infected children, who were receiving 3-drug antiretroviral therapy for a period of three or more months. The children were regularly followed up for any complications, changes in anthropometry, and changes in CD4 counts. The mean age of children at diagnosis (n=26; 22 boys) was 68.5 ±33.4 months. These children were followed up for a mean of 19.7 ± 18.7 months. Twenty four children received nevirapine based regimen. There was statistically significant improvement in weight for height and body mass index on follow up. The mean CD4 count changed from baseline (n=24) of 584.3 ± 685.9/ mm^3 to 614.4 ± 455.7/ mm^3 (n=15) at last follow up. One child developed minor skin rash in the initial two weeks of starting nevirapine. One child developed pancreatitis. We conclude that administration of nevirapine based ART for HIV-1 infected children is feasible in resource poor setting. There is improvement in growth parameters with use of this therapy.

Key words: *Antiretroviral, HIV-1, Nevirapine.*

IN less than 3 decades, HIV infection has become a global problem(1). Children also have not been left unaffected. A curative treatment for HIV infection should eliminate the virus replication; at present this appears elusive. Current evidence indicates that the highly active antiretroviral therapy (HAART), which is based on a protease inhibitor along with 2 nucleoside reverse transcriptase inhibitors, can lead to prolonged suppression of circulating viral load. However, this therapy is quite expensive (monthly cost for a child weighing 15 kg is approximately Rs. 2500). This is well beyond reach of most HIV-afflicted families in India and other developing countries. Substitution of protease inhibitor with nevirapine/ efavirenz (Non-nucleoside reverse transcriptase inhibitor) is an alternative. There are limited data on use of nevirapine in children(2,3). We report here our experience with use of 3-drug anti-retroviral therapy in HIV-infected children in a tertiary care hospital in northern India.

Subject and Methods

All HIV-infected children diagnosed at our

tertiary care hospital in north India and those referred to us are followed in a specialty outpatient clinic. The study subjects were HIV-1 infected children who were receiving 3-drug antiretroviral therapy for a period of three or more months.

In children over 18 months of age, the diagnosis of HIV-1 infection was confirmed by three positive ELISA (enzyme linked immunosorbent assay) tests according to the WHO strategy III(4). We recorded the demographic details, clinical features at presentation, and diagnostic information. The details of management and follow-up were recorded. The presumed mode of transmission was arrived at on the basis of confidential interview with the parents regarding sexual behavior, history of blood transfusion in parents and child and the HIV serology status of parents.

All children underwent the following investigations: complete blood counts, serum chemistry, chest radiograph and tuberculin test (considered positive if the induration was more than 5 mm). CD4 counts were estimated by multiplatform two color flow cytometry (Becton Dickinson flow cytometer).

The children were managed as per standard guidelines for children with HIV infection(5-7). Children with tuberculosis were treated with two months of intensive therapy (iso-niazid, rifampicin, pyrazinamide, ethambutol) followed by four to seven months of daily isoniazid and rifampicin. Antitubercular therapy was completed before starting the antiretroviral regimen. Based on the published treatment guidelines, antiretroviral therapy was offered to HIV-infected children with clinical symptoms of HIV infection (clinical category B or C) and/ or evidence of immune suppression (Immune category 2 or 3)(5-7).

Immunizations, antitubercular prophylaxis with isoniazid, *Pneumocystis carinii* pneumonia (PCP) prophylaxis with cotrimoxazole were advised as per to the available guidelines(8,9). Nutritional counselling formed an important component of management.

The most commonly used regimen was based on nevirapine along with 2 nucleoside reverse transcriptase inhibitors (Zidovudine + lamivudine or stavudine + lamivudine). All drugs were administered in doses recommended in standard treatment guidelines (6,7). The doses of various drugs used were: Zidovudine 90-160 mg/ m^2 every 6- 8 hours or 180- 300 mg/ m^2 every 12 hours (when administered as fixed drug combination); Lamivudine 4 mg/kg 12 hourly; Stavudine 1 mg/kg 12 hourly; Didanosine 90- 150 mg/ m^2 every 12 hours; Nevirapine 120- 200 mg/ m^2 every 12 hours; Indinavir 500 mg/ m^2 every 8 hours, Efavirenz 300 mg once a day for body weight 20- 25 kg and 350 mg for body weight 25-32.5 kg. Most children were administered combination of stavudine, lamivudine and nevirapine. However those children who could not swallow tablets/capsules, were started on combination of zidovudine, lamivudine, and nevirapine as syrup formulations of these drugs were available. In 19 children fixed drug combinations were used at appropriate fractions so as to meet the dosing requirement. The FDCs used were:

- Combination of Stavudine 30 mg + Lamivudine 150 mg + Nevirapine 200 mg
- Combination of Stavudine 40 mg + Lamivudine 150 mg + Nevirapine 200 mg
- Combination of Zidovudine 300 mg + Lamivudine 150 mg + Nevirapine 200 mg

Children were followed up regularly. At each visit, history about any infection, use of antibiotics, and need for hospitalization were

recorded. The children were examined and anthropometry performed at each visit. 'z' scores were calculated for 'weight for age', 'height for age' and 'weight for height' using the statistical package EPI-NFO 2000 (Centers for Disease Control and Prevention, USA). CD4 counts were repeated at about 6 month intervals. Complete blood counts and serum chemistry were performed every 6 months to assess any adverse effects of the therapy. We also looked for any clinical manifestations of adverse effects. Viral load estimations were performed wherever parents could afford it. These children were admitted in general pediatric ward if required.

Statistical analysis

Descriptive analysis was performed. The annual rates of pneumonia, acute diarrhea, antibiotic usage and hospitalization were calculated. CD4 counts at baseline were compared with those performed at last follow up visit. We also classified the CD4 counts into various groups according to reference values for CD4 counts(10). Changes in "z" scores for various anthropometric parameters were calculated.

Results

Over a 8 years period (from 1996-2003), 109 children (82 boys, 27 girls). were diagnosed to have HIV-1 infection. ART was indicated in 100 children; parents of 34 (28 boys, 6 girls) agreed for therapy. Of these, 26 children (22 boys) had a follow up of greater than 3 months. Further details are described for these 26 children.

The mean age of children at diagnosis was 68.5 ± 33.4 months (range: 18-147 months). These children were followed up for a mean of 19.7 ± 18.7 months (median (95% CI): 11.5 (7-24 months)]. The total months of follow up were 512 months. The details regarding mode of transmission, categorization is provided in *Table I*. Sixteen (61.5%) children were diagnosed on the basis of clinical suspicion; 8 (31%) were diagnosed on screening children of HIV infected parents; and two had been diagnosed elsewhere and referred.

Fifteen children received a combination of stavudine, lamivudine and nevirapine (14 of these received appropriate fixed drug combination). Seven children received zidovudine, lamivudine and nevirapine (5 of these received fixed drug combination); two children received didanosine, stavudine and nevirapine. One child each received combination of lamivudine, zidovudine and indinavir; and lamivudine, stavudine and indinavir. In 19 children, fixed drug combinations were used at

TABLE I–*Baseline Characteristics of Patients (n=26).*

1. Age (months)	
Mean ± SD	68.5 ± 33.4
Median (95% confidence interval)	69 (48.9- 87.28)
2. Sex	
(Male/Female)	22/4
3. Mode of infection	
Perinatal	19 (73.1%)
Blood products	5 (19.2%)
Unknown	2 (7.7%)
4. CDC classification	
Clinical: N	5 (19.3%)
A	8 (30.8%)
B	4 (15.3%)
C	9 (34.6%)
Clinical + Immune*	
N 2/3	4/1
A 1/2/3	3/3/1
B 2/3	1/3
C 1/2/3	2/2/4
5. Prior treatment	
Zidovudine + lamivudine	4
Zidovudine alone	2
6. Mean CD4 counts (/mm^3) (n=24)	584 ± 685.9

*: Data for 24 children

appropriate fractions so as to meet the dosing requirement.

The mean annual rates of acute gastroenteritis were 0.93 ± 1.6 and pneumonia 0.43 ± 1.3. These children received a mean 0.8 ± 1.5 courses of antibiotics per year. The mean annual hospitalization rates were 0.21 ± 0.8. Nine children (34.6%) were treated for tuberculosis. Two children each developed chickenpox and herpes zoster; 2 of these children received acyclovir. Two children developed chronic diarrhea. One child developed mumps, 2 sinusitis, and 1 otitis media during the follow-up. There were no documented cases of *Pneumocystis carinii* pneumonia.

The median (95% CI) weight for age 'z' scores changed from –2.46 (2.8 to –2.1) at baseline to –1.7 (–2.4 to –1.0) [P = 0.059]. The median height for age 'z' score scores changed from –2.48 (–3.2 to –2.1) at baseline to -0.99 (–2.6 to 0.03) [P = 0.64]. The median weight for height 'z' score scores changed from –1.01 (–1.4 to –0.55) at baseline to 0.135 (–1.08 to 0.94) [P = 0.012]. The median body mass index 'z' score scores changed from 14.6 (13.7 to 15.3) at baseline to 16.2 (14.5 to 18.7) [P = 0.016]. There was statistically significant improve-ment in weight for height and body mass index on follow up.

The mean CD4 count at baseline (n = 24) was 584.3 ± 685.9/ mm^3. Counts first repeated after a mean of 6.9 ± 4.1 months increased to 699.8 ± 500.6/ mm^3 (n = 12). The mean last CD4 count available was 614.4 ± 455.7/ mm^3 (n = 15). In these 15 children, the baseline mean CD4 counts were 631 ± 803.1/mm^3. We compared the initial classification of CD4 counts (percentiles) (Ref 10) with that at last follow up visit for 15 children where both these values were available. These are shown in *Table II*. All children except two, either remained in the same percentile category or entered into a higher (better) percentile category for CD4 count.

Viral load (by PCR) could be performed in only 3 children. The initial value ranged from 23,550 to 320,000 copies/mL. There was reduction on follow up. However, value less than 20 copies/mL could be achieved in only one child; this child was on nevirapine based regimen and had not been exposed to these drugs earlier. In other two children there was a log decline but viral load did not drop to less than 20 copies/mL even after 6 months of therapy; these were children who had been exposed to inadequate ART earlier and are now on protease inhibitor based regimen.

TABLE II–*Changes in Classification on the Basis of CD4 Counts with Treatment.*

Initial classification* (percentiles)	n	Final classification* (percentiles) (at last follow up visit)					
		<5	5-10	10-25	25-50	50-75	75-90
<5	8	6	1	0	1	0	0
5-10	3	0	1	1	0	1	0
10-25	1	0	0	0	1	0	0
25-50	1	0	1	0	0	0	0
50-75	1	1	0	0	0	0	0
75-90	1	0	0	0	0	0	1

*percentiles of CD4 count (age specific) (Reference: 10).

The children were screened for any adverse effects of therapy during follow up. On repeated estimations of serum chemistry no abnormality was noted. One child developed minor papular skin rash in the initial 2 weeks of starting nevirapine, which subsided completely; nevirapine was continued. One child developed pancreatitis while on ART (stavudine, lamivudine and nevirapine); the child improved with conservative management. Thereafter ART was modified to indinavir, zidovudine and abacavir. No other significant side effects were noticed. In two children, ART was changed to protease inhibitor based regimen because of worsening of clinical and immune condition. One child died during the follow up; the cause of death was severe pneumonia and respiratory failure. Two children were lost to follow up.

Discussion

We observed that patients getting 3-drug antiretroviral therapy (all except two children received nevirapine based regimen) showed significant improvement in anthropometric parameters and tolerated medications very well. CD4 counts were well maintained but there was no significant increase. There were no major side effects.

The patients were prescribed antiretrovirals as per the available guidelines(5-7). However, 3 children with mild symptoms (clinical category A) were also started on the drugs after the families insisted on early therapy. One of these 3 children had a high viral load (320000 copies/ mL) at baseline. Early therapy is favored by a few experts to limit the damage to the immature immune system of the child.

There are studies to document antiretroviral activity of 3-drug protease inhibitor-based regimen. These studies have documented virologic, immunologic and clinical responses(3,11,12). There is some evidence about the prolonged and high degree of viral suppression with use of more than 3 antiretroviral agents(13). There have efforts to simplify antiretroviral regimen in HIV-infected children. McComsey, *et al*. studied substitution of protease inhibitor with efavirenz and observed that this was well tolerated and maintained virologic suppression(14). They also showed significant improvement in fasting total cholesterol, low-density lipoprotein cholesterol, triglycerides, and the cholesterol: HDL ratio.

Only a few studies have evaluated nevirapine-based regimen(2,3). Luzuriaga, *et al*. studied the safety and efficacy of a combination of zidovudine, didanosine, and nevirapine in 8 children with maternally acquired HIV-1 infection(2). They documented sustained efficacy of the combination against HIV-1. In study by Wiznia, *et al*. nevirapine was used along with nucleoside reverse transcriptase inhibitor and protease inhibitor(3). So, the efficacy of regimen containing nucleoside reverse transcriptase inhibitors and nevirapine alone cannot be judged.

Some studies have evaluated the immune reconstitution that occurs with antiretroviral therapy. Johnston, *et al.* observed that moderately to severely suppressed HIV-1-infected children receiving HAART were able to reconstitute their immune systems to a degree that is indistinguishable from that of stable, CDC Class A1 HIV-1-infected children with regard to CD4+ and CD8+ T cell subsets, and expression of cellular maturation markers(15). Another study found that long-term non-suppressive antiretroviral therapy could induce limited improvement in immune function in pediatric AIDS patients. We observed that the CD4 counts improved slightly with therapy over a follow up period of 19.7 ± 18.7 months. Even this may be

Key Messages

- Administration of nevirapine based antiretroviral therapy for HIV-1 infected children is feasible in resource limited settings. It is feasible to use fixed three drug combinations in children.
- There is improvement in growth parameters with use of this therapy.
- The therapy prevents deterioration in immune status and may lead to improvement in the same.

significant as we expect the counts to decline without therapy over this period of time. We observed that "z" score for weight for age, height for age, weight for height and body mass index improved during the follow up; the changes in the latter two parameters were statistically significant. In published literature, there are no studies with which the above results can be compared. Verweel, *et al*. analyzed selected growth parameters, clinical data, and laboratory results as part of a prospective, open, uncontrolled, multicenter study to evaluate the clinical, immunologic, and virologic response to HAART consisting of indinavir, zidovudine, and lamivudine in children with HIV-1 infection(16). They documented a positive effect of HAART on the growth of HIV-1 infected children; particularly in children who had a greater virologic response to HAART. It is encouraging to note positive effects on anthropometric parameters with use of a less potent nevirapine based regimen.

There was some improvement in CD4 counts with time. Because of economic reasons, viral load was not estimated in the majority of patients. Complete suppression was documented in only one of the 3 children in whom viral load was estimated. It is important to study the viral load in children on nevirapine based regimen. An optimal ART regimen should suppress the viral replication effectively. There are concerns about development of resistance with use of nevirapine.

Because of economic reasons, only a small proportion of HIV infected children could be prescribed ART. The rest received supportive care in the form of nutritional counseling, early diagnosis and treatment of various infections and use of prophylactic antimicrobials. The monthly cost of nevirapine based regimen for a child weighing 15 kg is about nine hundred rupees (US$ 20), while that of PI based regimen about two thousand five hundred rupees (US$ 55). More often than not, multiple members in a family are infected. The earning members and adults get a priority for the money to be spent on health care, leaving the child at disadvantage. There is need for some support- either direct financially or indirect through subsidized treatment- for improving the care of HIV-infected children.

We used the adult fixed dose formulations in 19 children. This was done after calculating the doses of individual drugs and thereafter choosing an appropriate fraction of the adult fixed dose formulation. For example, a 15 kg child was prescribed half a tablet of combination (Stavudine 30 mg + Lamivudine 150 mg + Nevirapine 200 mg) twice a day. With this there is slight overdosing for lamivudine but appropriate dosing for the other 2 drugs. We had to resort to this as using individual drugs is often not feasible as some drugs like stavudine and zidovudine are available as capsules and cannot be divided into fractions easily. If syrups are used the volumes are large and children find it difficult to take such large volumes (example: for a 15 kg child if syrups of zidovudine, lamivudine

and nevirapine are used, the daily volume of medications will be more than 70 ml). Stavudine syrup is currently not available and needs to be stored in a refrigerator, making its use difficult. We did not encounter major complications except for 1 child who developed pancreatitis.

In view of the small number of patients, it is not feasible to compare changes in various parameters in different groups: *e.g.*, boys versus girls; different treatment categories of treatment provided. There is a limitation of non-availability of CD4 counts in all patients at all time periods.

We conclude that administration of nevirapine based ART for HIV-1 infected children is feasible in resource limited settings. There is improvement in growth parameters with use of this therapy and prevention of deterioration in immune status. There is need for more studies on the long-term safety and efficacy of affordable regimens of anti-retroviral therapy.

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Concomitant Use of Insulin Glargine and NPH in Type I Diabetes

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In a prospective study on 11 patients with Type 1 diabetes we evaluated the glycaemic control and hypoglycaemic episodes on a combination therapy of "pre-mixed" and glargine insulin. Glycosylated hemoglobin (HbA_{1C}), fasting (FPG) and Post Prandial blood glucose (PPG) levels were recorded at baseline and three monthly intervals for a period of 6 months. The mean HbA_{1C} reduced from 9.5 to 7.3%, incidence of hypoglycemias from 1.6 to 0.8, mean FPG from 146.5 to 90.4 and mean PPG from 258.4 to 184 over a six-month observation period. This regimen also helps to avoid injection of insulin before lunch so that child's school schedule is minimally disturbed and yet the incidence of hypoglycemia is not increased.

Key words: *Glycosylated hemoglobin, Insulin glargine, Type 1 diabetes.*