EFFECTIVENESS OF FIXED DRUG COMBINATION ANTI-RETROVIRAL THERAPY IN HIV INFECTED CHILDREN: AN EXPLORATIVE STUDY

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ABSTRACT: Over 90 per cent of HIV infected babies were born to HIV positive mothers in Sub-Saharan Africa and worldwide. It is estimated that currently 2.3 million i.e 5.9% are children less than 15 yrs of age infected with HIV. Worldwide, children under age 15 who were newly infected with HIV, more than 90 percent were babies were born to HIV-positive women. An estimated 1500 children get newly infected with HIV each day globally. The scenario is similar at home in Andhra Pradesh, India. This present exploratory study is to find out the effectiveness of fixed drug combination of antiretroviral therapy in children. The results are encouraging and are similar to results from such studies elsewhere.

KEYWORDS: Virus: Fixed Drug Combination HIV Children, AIDS, CD4, Weight Gain.

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INTRODUCTION: HIV infection rate seems to be at steady state in terms of percentage increase. The Physiology of retro virus makes it unique posing challenges.[1] in complete curing of the disease and eradication is not to think of in present discovery and research level. Three decades ago treatment started with single antiretroviral drug and research kept moving as the retrovirus guided our scientists. By the time virus became resistant research found us a way in by introducing new molecule to counter act.

The pace of output of new drugs decreased while at same time there is tremendous increase in time and various resources in discovering apt antiretroviral therapy. This has led to fixed dose combination therapy.[2] Treatment with antiretroviral therapy (ART) has reduced mortality of persons living with HIV-infection.[3] Regulators in developed countries are actually against to combination drugs. As there was no option left we landed up in combination therapies for HIV treatment. This is one part.

Coming to the other part of the issue–controlling-everyone won over HIV by educating and making people to use necessary precautions so as to arrest the transmission of disease. The story is different in children as over 90 per cent of HIV infected babies were born to HIV positive mothers in Sub-Saharan Africa and worldwide. It is estimated that currently 38.6 million people live with HIV/AIDS world over of which 2.3 million i.e. 5.9% are children less than 15 yrs. of age.[4] Though children represented 6% of all these cases they accounted for 18% of the 3.1 million AIDS deaths in 2006 and this is because only 40,000 or 4% of the 1 million people who are on Anti-Retroviral therapy are children Worldwide, children under age 15 who were newly infected with HIV, more than 90 percent were babies were born to HIV-positive women.[5]

An estimated 1500 children get newly infected with HIV each day globally. The scenario is similar *a*t home where this study was carried out. According to NACO, Indian state Andhra Pradesh has 400,000 HIV/AIDS patients-the second highest after Maharashtra and 10% of the total number of cases in India. Of these 3-5% cases are contributed by children. The HIV prevalence at antenatal clinics was 1.26% in 2006-higher than in any other state-while the general population prevalence was 0.97% in 2005-2006.[6]

So, instead of waiting for research outcome we as torch bearers of treating ailments-medical practitioners, have to make a decision to challenge and give HIV infected children their desired normal life. This thought came out as this research work. Antiretroviral therapy with three or more medications has become international standard of care for patients with the Acquired Immunodeficiency Syndrome (AIDS). Effectiveness of the treatment is normally measured in complete curing of disease which is not possible in AIDS as of now that has made us choose parameters like control in secondary infections, immunological parameters (CD4 count), weight gain in HIV infected patients.

AIM OF THE STUDY: The aim of this study is to assess the effectiveness of a combination of 3 antiretroviral drugs (2 NRTIs+1 NNRTI), available as Fixed Drug Combinations in weight-specific doses for pediatric use, with respect to effect on clinical and immunological status of HIV-infected children who are treated consecutively at ART center, King George Hospital, Visakhapatnam.

SUBJECTS & METHODS: This interventional prospective study was carried out at the ART center, King George Hospital, Visakhapatnam.

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Inclusion Criteria: All the HIV infected children enrolled between January 2007 and April 2008 in ART centre, KGH, Visakhapatnam were included in the study who were diagnosed to be HIV positive according to the strategy III testing as recommended by WHO.

- Children above 18 months to below 13 yrs.
- Eligible for Anti-Retroviral therapy according to WHO guidelines and CDC immunological categories.

Exclusion Criteria:

- Children aged less than 18 months were excluded from the study because of unavailability of diagnostic techniques in the resource poor setting.
- Patients above 13 yrs are excluded because the treatment guidelines are similar to that of adults.
- HIV negative children.

Base Line Evaluation: Each child underwent a thorough clinical examination at all visits. Baseline laboratory studies included the measurement of hemoglobin, complete blood counts, renal parameters, liver function tests and a chest x-ray. A baseline CD4 count was performed in all cases, by flow cytometry with a fully automated two-laser Becton Dickinson FACS caliber flow cytometry usually at mid-day, to avoid diurnal variations.

Probable tuberculosis was diagnosed based on the Revised National Tuberculosis Control Program protocol and Anti Tuberculosis Therapy (ATT) was started according to the RNTCP guidelines. Each child was classified according to the WHO clinical staging as well as the CDC immunological staging.

Treatment: Antiretroviral therapy was initiated for all HIV infected children according to World Health Organization (WHO) guidelines for resource limited settings (2005).[7] which states that: if the child is confirmed to have HIV disease and is in:

- WHO Stage IV disease- treat all children irrespective of CD4 cell count
- WHO stage III disease- treat all children irrespective of CD4 cell count; in children aged over 18 months treat guided by CD4 where available.
- WHO stage II HIV disease-CD4 guided or if CD4 is not available, based on the total lymphocyte count.
- WHO stage I HIV disease: treat only guided by CD4; where CD4 is not available children should not be initiated on ART.

Depending on the CD4 count ART can be started as follows[8]:

- <11 months: if CD4 <1500cells/mm3 (<25%)
- 12 – 35 months: if CD4 <750cells/mm3 (<20%)
- 36 – 59 months: if CD4 <350cells/mm3 (<15%)
- 5 yrs – follow adult guidelines i.e. start ART if CD4 count is <350/mm3 especially if symptomatic or initiate ART if CD4 is < 200/mm3 (<10%) irrespective of the clinical status.

First and second-line antiretroviral-therapy regimens followed WHO guidelines, as recommended by the National Aids Control Society (NACO) of India.

The first-line antiretroviral therapy regimen for all children is d4T+3TC+NVP. The alternate first-line combinations are: d4T+3TC+EFV, taken as EFV once per day plus d4T/3TC as BID FDC which was used in children co infected with tuberculosis and in those who had adverse reactions to Nevirapine.

As Zidovudine based regimens were not available for use in children in the ART centers they were not given to the children in this study.

All children with tuberculosis were given ATT along with ART and the regimen was changed from d4T+3TC+EFV to d4T+3TC+NVP after completion of ATT.

Co-trimoxazole prophylaxis was given to all children as per NACO guidelines.[9]

Adherence to therapy was encouraged by counseling the parents or care givers and the children (In older children) by counselors at the ART centers, people with AIDS, pill counts, and by phone calls.

Monitoring and Follow up: 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. Developmental and nutritional status was assessed at every visit. The child was screened for opportunistic infections and treated accordingly. WHO clinical staging[10] and immunological staging based on the CD4 count was done at every visit. Adherence to treatment was also checked at all visits. The child was considered as Lost to Follow Up if he/she had missed the treatment for consecutive 3 months

Laboratory monitoring included the baseline CD4 T-cell count by flow cytometry (Becton Dickinson) and measurement of hemoglobin, complete blood counts, renal parameters, liver function tests and a chest x-ray. The CD4 T-cell count was determined at six months interval. Follow-up hemoglobin measurements, blood counts liver-function tests, lipid profile and other serum chemical analyses were performed if clinically indicated.

OBSESRVATIONS: Age distribution.[11,12,13] Mean age of presentation is 6.5 (Standard deviation–2.9) constituted by 40% in the age of 1-5years; highest in 6-9 years with 41% and least in the Age group of 10-12 years with 19%. These observations are similar to earlier published data.

Sex Distribution: The Male preponderance (males at 62% to that of 38% females) was significant according to the standard error difference between proportions which was 2.9 as > 2 is indicated by significant p-value (<0.001).

Statistically significant male preponderance was observed with a male to female ratio of 1.6:1 which was an invariable finding in most studies (1.2:1 in the study from Cambodia.[11] 1.3 in the study from Pune.[12, 1.1]: 1 in a study from Malawi.[14])

Mode of transmission: Highest number of cases (97.6%) was with perinatal transmission then by (2%) with blood transfusion.

STATISTICAL ANALYSIS: Out of the 125 children

- 18 children were registered in the first 6 months of the study period. Of these
- 11 were still taking ART, i.e. they have a follow up data up to 18 months.

- 2 cases had a follow up data up to 6 months only
- The remaining 5 had no follow up.
- 69 children were registered in the next 6 months. Of these
- 37 were still taking ART, i.e. they have a follow up data up to 12 months.
- 7 cases had a follow up data up to 6 months only
- The remaining 25 had no follow up.
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- 38 children were registered in the last 4 months of the study period. Of these
- 21 were still taking ART, i.e. they have a follow up data up to 6 months.
- The remaining 17 had no follow up.

To summarize, out of the 125 cases:

- 47 cases have no follow up data (5+25+17).
- 11 cases have follow up data up to 18 months
- 37 cases have follow up data of 12 months
- 30 cases have follow up data of 6 months.
- i.e. 78 children have follow up data of at least 6 months.

Tuberculosis: Of the 125 patients, 13 (11%) had tuberculosis. 3 had extra pulmonary tuberculosis in the form of abdominal tuberculosis (2 cases) and TB lymphadenopathy (1 case) whereas the other 10 had pulmonary tuberculosis. All received Anti Tuberculosis Therapy according to the RNTCP guidelines. Along with ATT all received ART but with substitution of Nevirapine with Efavirenz. After completion of ATT the child was again put on Nevirapine based regimen. Of the 13 children with tuberculosis 4 (31%) completed the treatment and were cured, 4 (31%) expired, 2 (15%) children were transferred out to another ART center while on ATT, 1 (8%) child was using ATT at the time of analysis and the remaining 2 (15%) have lost to follow up.

Tuberculosis was the most common single opportunistic infection accounted for 13 cases (11%) and 4 out of 8 (50%) deaths in the study were found to be due to tuberculosis. A study from Prachomklao Hospital, Petchburi, Thailand.[14] shows that 25% of the study subjects had tuberculosis and it accounted for all deaths in the study.

First-Line Medication Changes and Toxic effects: Of the 125 patients, 11 (8 percent) required a change in a first-line medication. The reasons for the change were toxic effects in 5patients, skin rash was the most common (in 4) followed by Hepatitis (in 1) and tuberculosis in the rest of 6 patients. 2 children had gastro intestinal side effects.

Mortality: Of the 125 patients, 8 (6.4%) died. Among these 6 (75%) were males and 2 (25%) were females. The age distribution is as follows:

1.5 – 5 yrs.	-	4 (50%)
6 – 9 yrs.	-	1 (12%)
10 – 12 yrs.	-	3 (38%)

4 (50%) were in WHO stage IV and the remaining 4 (50%) were in Stage III at the time of presentation. According to CDC staging 6 (75%) were in stage 3 and the other 2 (25%) in stage 2. the mean CD4 count was 234.

Of the 8 deaths, 4(50%) to tuberculosis, 1 (12%) to bacterial pneumonia, 1 was due to severe sepsis and the causes of death in the other 2 (12%) was not known. 7 deaths (87%) occurred within six months after the initiation of antiretroviral therapy. The mean period of follow up in these patients was 3.6 months.

Lost to Follow Up (LFU) & Transfer out: If a child who is on ART misses treatment for 3 consecutive months he/she is considered to be lost to Follow Up. In this study 14 (11.2%) of the 125 patients lost to follow up for which the reasons are not known. The mean follow up period was 3.7 months.

Care giver profile: Out of the 125 children 42 (33%) are cared by both parents, 38 (31%) by at least one parent and out of the 47 orphans 20 (16%) by Grandparents, 9 (7%) by other relatives and 16 (13%) by Orphanages. This has got significance because 9 (64%) of the 14 children who lost to follow up were orphans and cared by grandparents, relatives or orphanages. Of the 8 expired children 3 (37%) were orphans.

DISCUSSION: ART 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. As Fixed Drug Combinations (FDCs) with the concentration of the drugs suited for the pediatric population were available for use, we decided to study the effectiveness of ART in children in relation to the clinical and immunological improvement. The drugs were made available free of cost to all children under the funding of NACO.

CONCLUSIONS: The rapid and effective large-scale introduction of antiretroviral therapy in the developing countries like India has reduced mortality of persons living with HIV.s

Growth failure is a common feature of children with HIV infection. Weight gain has been used as a parameter for assessing improvement in health status. Our study shows that a mean weight gain was statistically significant and is more significant in long duration of therapy.

The effectiveness of three-drug (2 NRTI+1 NNRTI) regimen for children is commonly judged by CD4 counts. The mean raise in the CD4 count is extremely significant the raise is progressive with prolongation of therapy which is statistically extremely significant.

The improvement in the WHO clinical staging is statistically very significant with prolongation of therapy

The improvement in the CDC immunological staging is extremely significant even within the first 6 months. This improvement is more significant statistically than WHO staging.

In our study there are significant number of defaulters i.e. who lost to follow up after initiation of therapy (14–11%) which is alarming and needs intervention regarding program orientation.

The incidence of children who lost to follow up is more in those who are cared by persons other than the parents. This shows the need to have good facilities for the HIV infected children who became orphans. This is where NGOs and government has to play an effective role.

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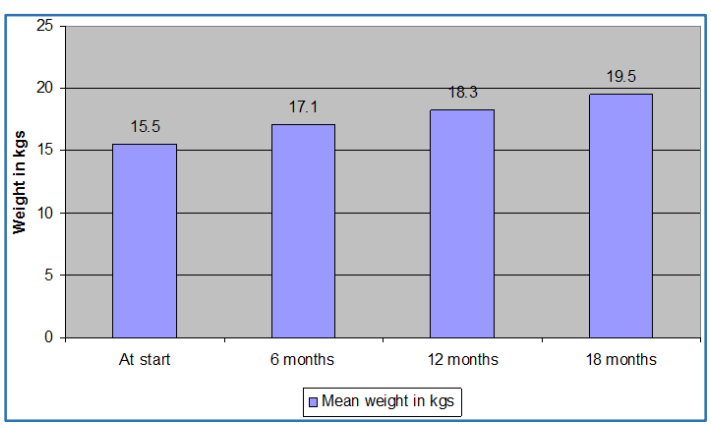
Weight Gain:

1) Weight gain in the children followed for 18 months.
Total No. of children -11

	Mean weight in kg	Standard Deviation	Mean weight gain
At start of therapy	15.5	5.7	
After 6 months	17.1	6.7	1.6 kg
After 12 months	18.3	6.5	2.8 kg
After 18 months	19.5	6.7	4.0 kg



According to the Student Newman Keuls multiple comparisons test & the one way Analysis Variance (ANOVA test) the p-value is 0.529 which is considered not significant and this may be due to small sample size.

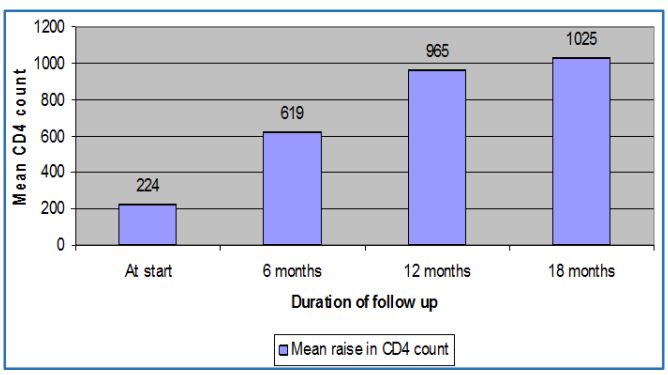
Paired t-test results (two tailed p-values) are as follows:

- From start to 6 months after therapy - p-value-0.1894–not significant
- From start to 12 months after therapy - p-value-0.0295–significant
- From start to 18 months after therapy - p-value-0.060–very significant.

CONCLUSIONS: The mean weight gain was statistically significant and is more significant in long duration of therapy.

CD4 Count: Raise in the mean CD4 count in the children followed for 18 months
Total No. of children - 11

	Mean CD4 count	Standard Deviation	Raise in CD4 count
At start of therapy	224	102	
After 6 months	619	292	395
After 12 months	965	469	246
After 18 months	1025	411	60



According to the Student Newman Keuls multiple comparisons test & the One way Analysis Variance (ANOVA test) the p-value is <0.0001 which is considered extremely significant.

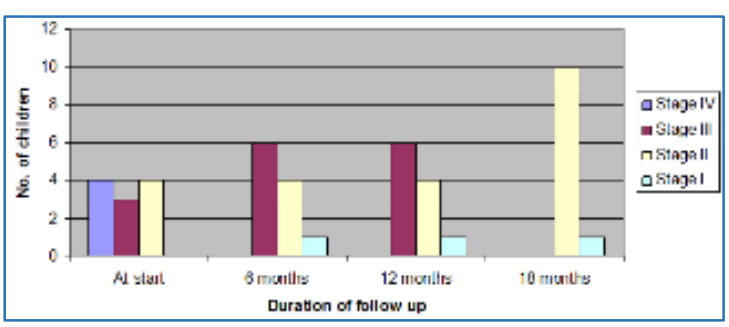
Paired t-test results (two tailed p-values) are as follows:

- From start to 6 months after therapy - p-value-0.0025– very significant.
- From start to 12 months after therapy-p-value-0.0003 – Extremely significant.
- From start to 18 months after therapy-p-value-< 0.0001 – Extremely significant.

Conclusions: The mean raise in the CD4 count is extremely significant the raise is progressive with prolongation of therapy which is statistically extremely significant.

WHO clinical staging: 1) Improvement in the WHO staging[9] in the children followed for 18 months
Total No. of children -11

	At start	6 months	12 months	18 months
Stage IV	4	0	0	0
Stage III	3	6	6	0
Stage II	4	4	4	10
Stage I	0	1	1	1



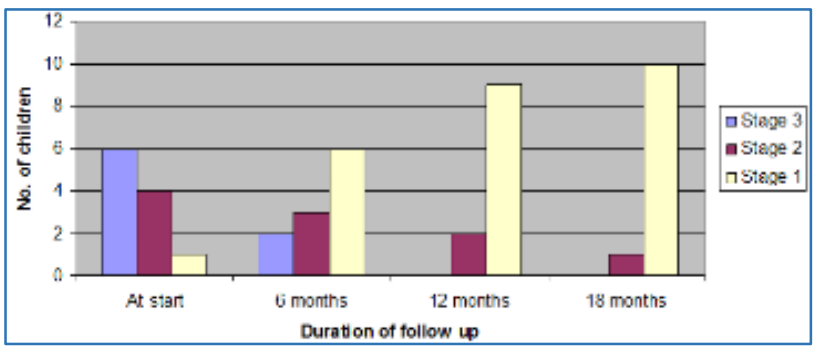
According to the Student Newman Keuls multiple comparisons test & the One way Analysis Variance (ANOVA test) the p-value is <0.0063 which is considered very significant.

Paired t-test results (two tailed p-values) are as follows:

- From start to 6 months after therapy - p-value-0.0061– very significant.
- From start to 12 months after therapy-p-value-0.0061 – very significant.
- From start to 18 months after therapy-p-value-0.0014 – very significant.

CDC immunological staging: 1) Improvement in the CDC staging in the children followed for 18 months
Total No. of children – 11

	At start	6 months	12 months	18 months
Stage 3	6	2	0	0
Stage 2	4	3	2	1
Stage 1	1	6	9	10



According to the Student Newman Keuls multiple comparisons test & the One way Analysis Variance (ANOVA test) the p-value is <0.0001 which is considered extremely significant.

Paired t-test results (two tailed p-values) are as follows:

- From start to 6 months after therapy - p-value-0.0047– very significant.
- From start to 12 months after therapy-p-value-0.0004 – extremely significant.
- From start to 18 months after therapy-p-value -< 0.0001 – extremely significant.

CONCLUSIONS: The improvement in the CDC immunological staging is extremely significant even within the first 6 months. This improvement is more significant statistically than WHO staging.[9]

Summary of the comparison of variables of this study with other comparable studies:

Parameter	Present Study	Bart Janessen et al Cambodia.[11]	Petdachai et al Thailand.[15]	S.A. Natu and S.R. Daga et al, Pune.[12]	Rakesh Lodha et al, Delhi.[13]	S. K. Khanna et al, Pune.[16]
Study period	18 months	24 months	15 months	6 months	18 months	7 months
Age group	1 ½ yrs to 12 yrs	<13 yrs	1 – 14 yrs	1 ½ yrs – 12 yrs	1 ½ yrs – 12 yrs	5 mon – 12 yrs
Mean age of presentation	6 yrs and 6 months	6 yrs and 9 months	7 yrs 2 months	6 yrs and 8 months	5 yrs and 8 months	6 yrs
Male: Female	1.6: 1	1.2 : 1	1.4 : 1	1.3 : 1	5.5: 1	1.1: 1
Mean weight gain after 6mon.	1.7 kg	-	-	1.6 kg	1.5 kg	1.7 kg
Mean raise in CD4 count after 6 mon	302	390	10%	277	125	15%
Adverse events	6.4 %	4%	-	8%	7%	-
Death rate	6%	6.1%	9%	-	3%	-