Effect of highly active antiretroviral therapy in treating children with advanced HIV disease.

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Abstract

Objective: To describe the effect of highly active antiretroviral therapy (HAART) on HIV infected children at Orotta Pediatric National Referral Hospital.

Method: Follow-up descriptive study was conducted on one hundred and one consecutive children with advanced HIV disease who were put on antiretroviral therapy from September 2005 to October 2006. These patients were followed up at the antiretroviral therapy (ART) clinic of the hospital.

Results: Out of the 270 HIV infected patients who were under follow up at miscellaneous follow-up clinic of the hospital 101(37.4%) were eligible for antiretroviral therapy based on the national antiretroviral therapy guidelines. These consecutive patients were under follow- up from one month to fourteen months. Majority of patients 68.3 %(n=69) were in the age group six years and above and 79.3 %(n=80) were in the advanced stage of the disease. In those patients who were under HAART for six months, the six months median CD4 % increase by 14% for children ≤6 years of age, and by 9.4% for children > 6 years age is significant (95% CI using the Wilcoxon sign rank test : at p value= 0.000). Similarly the median weight for height z-score increment from base line of -0.85 to 0.1 at six months is significant. (95% CI using the same test: at p value=0.000).

Conclusions: Despite the initiation of HAART at late clinical stages of HIV/AIDS and advanced immune suppression, the clinical and immune response was satisfactory. Therefore, treatment should be started to all eligible patients irrespective of disease severity and immuno-suppression.

Introduction

The first AIDS case in Eritrea was reported in 1988 in the port city of Assab. Up to the end of October 2006, the cumulative number of AIDS cases has reached 24,534. Out of this total number the proportion of pediatric cases (children under the age of 15) is 6 % [1]. Recent antenatal sentinel surveillance in the country has demonstrated seroprevalence rate of 2.38% in pregnant women [2]. In a country with 120,000 expected live births and vertical transmission rate of 24.7% [3] the estimated number of children born infected with HIV every year is 705.

Since 2002, a total of 350 HIV infected and exposed children have been followed up at Orotta Pediatric National Referral Hospital miscellaneous clinc. In this clinic provision of voluntary counseling and testing (VCT), cotrimoxazole prophylaxis and prevention of mother to child transmission (PMTCT) care and support were routine clinical activities. Recently antiretroviral therapy was introduced by the Ministry of Health as part of the comprehensive care provided to patients with advanced HIV disease. Following the introduction of antiretroviral therapy in August 2005, one hundred and one antiretroviral treatment eligible HIV infected children without history of previous antiretroviral exposure were started on first line highly active antiretroviral therapy according to the national anti retroviral therapy guide lines. The guidelines allow a combination of 2 NRTI and 1NNRTI as well as substitution of stavudine for zidovudine and efavirenze for nevirapine and vice versa [4]. Therefore, the aim of the study was to describe the effect of HAART in treating HIV infected children at the Orotta Pediatric National Referral Hospital.

Patients and Methods

After the introduction of CD4 value determination services by FACS count machine (Becton and Dickson, Mount View, Carlifornia, USA) at the National Health Laboratory in September, 2004, patients who were on a regular follow up had been evaluated for eligibility to be started on antiretroviral treatment based on Eritrean Antiretroviral Therapy Guidelines.

As a result 101 antiretroviral treatment eligible patients without previous ARV experience were put on first line highly active antiretroviral therapy according to the national guidelines with a combination of 2 NRTI and 1NNRTI. Substitution of Stavudin for zidovudin and efavirenze for nevirapine and vice versa was possible. Data on pre-treatment age, sex, weight, height, clinical stage, social background, CD4 values, base line hemoglobin, liver function tests, hepatitis markers and chest x-rays was recorded on the standard initial clinical form on every clinic day.

These consecutive patients were under follow up from one month to fourteen months (September 2005– October, 2006). Adherence to HAART was supported by ongoing counseling and pill counting at every visit. Patients were referred for nutritional support when indicated. After initiation of HAART, all children were followed up on monthly basis. Exception was during the first month in which the clinical follow up was weekly and bi-weekly for zidovudine and nevirapine containing regimens respectively. Body weight was measured in kgs monthly; height was measured in centimeters at three months, six months and one year interval.

CD4 values were determined at three months, six months and one year interval after initiation of

treatment and in the event of immune reconstitution inflammatory syndrome. Hemoglobin, liver function tests, other laboratory tests and chest x-ray were done depending on the ARV regimen and development of specific clinical conditions. The results of clinical assessment and laboratory investigations were documented similarly on standard clinical and laboratory follow- up forms.

Data analysis was performed using the Statistical Package for Social Science software (SPSS version 12.0). Epi-info software was also part of the analysis tool used to calculate the nutrition indices (weight for height). Since Epi-info software provides two alternative references, NCHS/WHO 1978 and CDC 2000, the first reference was used in this study for comparing cohorts.

Results

Enrollment: Between September 2005 and October, 2006 a total of 101 patients, who were eligible for antiretroviral treatment were started on HAART. Two patients (1.98%), one due to social problem and the other opting for alternative treatment, were lost for follow up..

Age and sex distribution at enrollment: Out of the total 101 patients 49.5% (n=50) were females and the rest 50.5% (n=51)) were males with male to female ratio of 1:1.02. In these patients the majority 68.3 % (n=69) were in the age group six years and above. The median age at which treatment started was 90 months the interquartiles range being 63 to 114 months.

Clinical stages during initiation of treatment: 64.4% (n=65) were in WHO clinical stage 3 at enrollment. The remaining 20.8% (n=21) and 14.9% (n=15) were at stage 2 and 4 respectively. Accordingly majority of the patients 79.3 % (n=80) were in the advanced stage of the disease.

Care takers: About 10.5 %(n=11) of the patients were cared by both parents while 50.5% (n=51) were cared by one parent and the rest by relatives

Base line socio demographic characteristics and Clinical stages of the patients are summarized in table 1.

Table 1 Age, clinical stage, care takers and address of the patients on treatment, 2005-2006

Patients characteristics	Male	Females	Total
Age group			
≤ 6 years	17	15	32(31.3)
> 6 years	33	36	69(68.7)
Total	50	51	101
Clinical stage			
II	12	9	21(20.8)
III	31	34	65(64.4)
IV	8	7	15(14.9)
Care Takers			
One parent	27	24	51(50.5)
Two parents	6	5	11(10.9)
Other than parents	18	21	39(38.6)
Address			
Anseba Zone	-	3	3(3.0)
Debub Zone	4	6	10(9.9)
Gash Barka Zone	2	-	2(2.0)
Central Zone	44	41	85(84.2)
Northern Red Sea Zone	1	-	1(1.0)
Total	50	51	101

NB. Numbers in parenthesis are percentages.

CD4 T cell response by age, duration of treatment : In children younger than 6 years of age, the baseline median CD4 percentage rose from 10% (interquartile range 7 to 12 %) to 18% (interquartile range 13.8 to 25%) at three months and to 24.2% (interquartile range 17.8 to 31.9 %) at six months after starting treatment. In children older than 6 years of age, the baseline median CD4 percentage increased from 8% (interquartile range, 5 to 10.1 %) to 13.7 (interquartile range 9.3 to 18%) and to 17.4% (interquartile range 13 to 23.5%) at three and six months respectively.

For children (n=32)who were under treatment for one year the median CD4 rose from that of base line 8.3 percent (interquartile range 5.1 to 10.7%) to 22% (interquartile range 12.3 to 32.5) .

In this study it is noted that the increased in the median CD4 is higher in the younger children than in the older ones.

The six months median CD4 increase after treatment by 14% for children ≤6 years age and by 9.4% for children > 6 years age is statistically significant (95% CI using the Wilcoxon Sign Rank test at p value=0.000).

Table 2: Median and Quartile CD4 percentage for the two age groups at different follow up periods, 2005-2006

Time period	Children ≤6 years age			Children > 6 years age		
	Median	75 Quartile	25 Quartile	Median	75 Quartile	25 Quartile
Base line	10	12	7	8	10.1	5
3 months	18	25	13.8	13.7	18	9.3
6 months	24.2	31.9	17.8	17.4	23.5	13

Weight for Height gain after treatment: In order to determine clinical success, weight for height z-score was used. In this study the weight for height z-score showed marked increase from the baseline median value of -0.85 (interquartile range -1.89 to -0.14) to 0.1 (interquartile range -0.97 to 0.72) after six months of treatment.

The median weight for height z-score increment from base line of -0.85 to 0.1 at six months is statistically significant. (95% CI using the Wilcoxon Sign Rank test: at p value=0.000).

In patients (n=32) who were followed for one year, their median weight for height z-score of -0.54 (interquartile range of -1.39 to -0.15) at base line, increased to a median z-score of 0.38 (interquartile range -0.42 to 1.22) at one year.

Toxic effects and first line drug substitution: In this study 12.9 % (n=13) patients developed severe side effects requiring substitution of one of the first line drugs. In one patient there was a substitution of first line drug as a result of pulmonary TB following immune reconstitution inflammatory syndrome. The most frequently observed drug toxicity was rash due to Nevirapine and anemia due to Zidovudine, in 15% and 10% respectively.

Occurrence of Immune reconstitution inflammatory syndrome (IRIS): Worsening of symptoms of opportunistic infections that were under effective treatment shortly after starting HAART was observed in eighteen patients within fourteen weeks after initiation of treatment. The total number of events was 20. The most frequent IRIS in this study was pneumonia followed by herpes zoster. In two of the patients 2 conditions developed at a time. In another two patients their skin warts got worse after initiation of HAART. Only one patient developed pulmonary TB during treatment.

Number of hospital admission: In order to examine the effect of antiretroviral treatment on the rate of hospital admission, the number of admissions of every patient one year before and after the start of treatment was documented. Accordingly the number of hospital admissions one year before and after initiation of HARRT is 67 and 25 respectively.

Survival after treatment: Out of the 99 patients who were followed-up only one died because of severe malnutrition and severe pneumonia two months after initiation of HAART. All children stayed on their first line treatment.

Discussion

Programmes for access to antiretroviral treatment were only recently implemented in developing countries. In Africa, few HIV infected children received highly active antiretroviral treatment [5].This is partly due to the limited experience with pediatric treatment and limited availability of pediatric formulations in resource constrained settings. In this paper the experience of treating children with ARV and the effect of treatment on the out come is discussed.

Antiretroviral therapy was initiated in 101 patients at Orotta Pediatric National Referral Hospital in a period of 14 months. During enrolment there was a high rate of severe malnutrition and advanced immune suppression in these patients which is similar to most developing countries children's HIV clinic population [6]. For the sake of close clinical follow up and to ensure adherence most of the patients enrolled in this study were from the central zone. It could be either due to this reason or due to the close follow up and proper adherence counseling of the care takers, only two patients were lost for follow up.

In this study only one patient under 18 months of age was started on treatment because the first line combination currently in use is less flexible for this age group (i.e. Substitution of Efavirenz for Nevirapine is not possible). Moreover, adherence to HAART was questionable as most care takers of the very young children were found to be less motivated.

Where the commitment of care takers is not reliable and in cases where pulmonary TB could not be ruled out confidently, convenient regimens were chosen for better adherence and presumed less toxic effects and drug interactions which need less follow-up by care takers.

In Eritrea no data is available on the survival rate of children without HAART. Nevertheless, during the last fourteen months follow up period only one patient died in comparison to a one year survival rate with out ART of about 30% in developing countries [7].

In this study HAART was shown to have an impact on reducing number of hospital admission one year after initiation of treatment. Nevertheless, before coming to conclusion it is imperative to know the rate of admission for every enrolled patients one year after initiation of treatment.

According to the Eritrean Antiretroviral Therapy Guidelines an increase in CD4 values and growth are good indicators of treatment success [4]. During the assessment made at enrollment, malnutrition and advanced immune suppression were common in these patients. Significant and sustained increase was documented in the weight for height Z-score at three and six months interval after initiation of HAART. There was also a remarkable effect of HAART on increasing CD4 values from that of base line at three and six months.

In literature the rate of post nevirapine rash in children was said to be low. In contrast the rate of skin rash in this study was 15% which is similar to findings from recent studies elsewhere [8,9] . In this study the rate of anemia due to zidovudine was 10% which is in agreement to current literature [10]. It should also be noted that there was no treatment limiting toxic effects in our patients.

Immune reconstitution inflammatory syndrome is said to be less frequent in children [11]. In the contrary this study has shown that immune reconstitution inflammatory syndrome was not rare. This needs further follow-up studies on newly enrolled larger number of patients.

Conclusion

Although most of the patients enrolled were in the late clinical stages and advanced immune suppression categories the immune and clinical response in these study was remarkable. Therefore, irrespective of the clinical stage and immune suppression those children who are eligible for antiretroviral should be treated based on the available treatment guidelines.

References

1. 2005 Annual report of the National HIV/AIDS Control Division, MOH
2. The state of HIV/AIDS in Eritrea 2005, Review, Reflection and Responses
3. Report of Eritrean 2005 round HIV sentinel Surveillance Survey on Women ANC attendees, NATCoD/MOH
4. Eritrean Antiretroviral therapy Guidelines February 2005 Asmara,Eritrea
5. Thanyawee Puthanakit, Aurmporn Oberdorfer, Noppadon Akarathum, Suparat Kanjanavanti etal, Efficacy of highly active antiretroviral therapy in HIV infected children participating in Thailand's National access to antiretroviral program
6. Patrice Severe, Paul Leger, Macarthur Charles, Francine Noel, etal Antiretroviral Therapy in a Thousand patients with AIDS in Hiti.
7. Jean ss,Pape JW,Verder RL,et al. The natural history of human immunodeficiency virus 1 infection in Haitian infants Pediatr infect dis J 1999;18:58-63
8. E.Luyirka.T. Finkbeiner L.Nabidda,E. Kikule,et al Antiretroviral therapy for HIV infected Children in Uganda, 2004-05
   .
9. P.C Karyo,M.J Mbuzenakamawe, E. Baramperya, L. Barutwanyo, S. Bahimanga. Antiretroviral treatment in a hundred Burundian children.
10. Medical management of HIV infection, John G. Bartlet, and Joel E. Gallant. (2004)
11. Antiretroviral treatment in infants and children in resource limited settings, towards Universal access : Final version (February, 2006)