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Adverse Drug Reactions in Children Living with HIV/AIDS Receiving First Line ART

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ABSTRACT
Optimal adherence to anti-retroviral therapy can be improved by early detection, differentiation of self-limiting from potentially serious ADRs, and treatment of ADRs. The medical literature contains numerous studies in adults related to these complications; however, data in children is relatively sparse. The present study is designed to identify and document the common ADRs associated with ART in children. A total of 72 children receiving first line antiretroviral therapy at the Department of Pediatrics in a medical college, were included in the study. Adverse effects of the drugs and their effect on physical development of the patients were noted. Forty three patients (59%) had developed side effects with the start of first line ART regimen. Rashes (39.7%), lipodystrophy (26.4%), anemia (22) and abnormal liver function (8.3%) were the common side effects noted. Also noted were gastritis, altered lipid profile and hyperpigmentation. Nevaripine-induced rash and Stavudine-induced lipoatrophy are the most common ADRs in children. Close monitoring and regular follow up of these patients are important for early identification and treatment. This will help to substitute them with less toxic antiretroviral agents, if needed, and also to improve treatment adherence. It may also assistin preventing interactions with other drugs needed for various comorbidities in these children.
Keywords –*Adverse drug reactions, anti-retroviral therapy, HIV infection, Children.*

INTRODUCTION

Antiretroviral therapy (ART) has revolutionized HIV treatment, and in India more than 35,000 children are on this therapy (NACO, 2014)[(1)]. ART is not curative in nature, but prolongs life and the treatment is lifelong and expensive. ART is associated with a range of adverse drug reactions (ADRs), and children receiving combination ART regimens should be monitored for short- and long-term adverse events. Clinical monitoring includes monthly clinical evaluation, monthly treatment adherence evaluation and, monitoring for adverse effects and drug interactions. Immunological monitoring is done with CD 4 counts every six months.

A high level of adherence is critical (>95%) for good prognosis. Adverse effects to ARV drugs is a major obstacle to good adherence.Optimal adherence to treatment regimen can be improved by early detection, differentiation of self-limiting

from potentially serious ADRs, and treatment of ADRs. In the new era of highly active ART (HAART), physicians must be trained to identify and manage the toxicities associated with HAART as well [Srikanth *et al*., 2012][(2)]. The medical literature contains numerous studies in adults related to these complications; however, the data in children is relatively sparse [Gil *et al*., 2007][(3)]. As such no definitive study on adverse effects associated with HAART in children has been carried out till date from South India .Hence the present study is designed to identify and document the profile of the common ADRs associated with ART in children.

METHODOLOGY

A total of 72 children diagnosed to have HIV infection and receiving first line antiretroviral therapy, who regularly attended the pediatric HIV care clinic at the Department of Pediatrics, Govt. Medical College Hospital, Thrissur, were included in the study. These children were studied in detail for the history of side effects(from the records), persisting side effects and the side effects that appeared over 1.5 years (January2012-June2013). Indication for starting ART regimen, change in the regimen (if any) and the reason for change were documented in a pretested proforma. Among the adverse effects which occurred in the past, only the documented ones and those that persisted were included; the subjective and transient symptoms recollected by the patient were not documented. Effects of ART on the growth and nutrition of these children were documented. Weight measurement was done using a uniform single standard calibrated bathroom scale for children. Accurate measurement of height was done for each patient using staediometer and recorded at the time of examination. These measurements were then plotted on the WHO growth charts.

Documents from ART Centre were verified for drug compliance, ART regimen, and recent CD4 count.CD4 count estimation was done for all patients by flow cytometry using a BD FACS count system, with kits supplied by National AIDS control organization of India (NACO) to the ART center, Medical College.

Each child was examined for the physical findings related to known ADRs of ART, including general and systemic examination. Child was also investigated with hematological and biochemical parameters for the known side effects of these drugs. Staging of the disease was done according to revised WHO clinical staging of the disease. The clinical and biochemical toxicities seen in these patients were classified into mild (grade1), moderate (grade2), severe (grade3) and severe and life-threatening (grade4) based on the severity grading as per WHO 2010 guidelines on antiretroviral therapy [WHO, 2010][(4)]. Other comorbid illnesses and features of vitamin and iron deficiency were documented. In children on anti-tuberculosis treatment, side effects of these drugs were also looked for and documented.

Children having lipodystrophy as adverse effect were interviewed for the impact of this side effect in their lives, whether they experienced any discrimination due to the physical appearance. Statistical analysis was performed using appropriate statistical tests such as t test, Chi square and ANOVA and the quantitative relation was assessed using simple linear regression.

RESULTS

The mean age of the participants was 10.6 years, ranging from 1.5-18 years. About 50% of the participants were in the age group of 10-14.9 years. Gender distribution shows that more than 50% of the study participants were males (58.3%), and the rest females (41.7%). About 69% of the children were HIV orphans, that is, either or both of their parents had died of HIV/AIDS. Of this, 22(30%) children had lost both their parents due to the disease.

Retroviral therapy

In our study population, 33 (45.8%) children were started on Zidovudine-based regimen, whereas 39 (54.1%) were initiated on Stavudine-based regimen. One patient was put on Lopinavirbased

regimen due to prior exposure to Nevirapine. Antiretroviral drugs started in the study subjects are shown in Table 1.

Of these 53% were started based on clinical criteria, 42% based on immunological criteria and 5.6% based on age criteria regardless of clinical/ immunological staging as per the existing guidelines. A total of 35 children (48.6%) had their initial regimen changed atleast once (drug substitution). Among them, ADR was the reason for the change in 10 patients (28.6%). Starting of ATT was the reason for the change in 5 (14.3%) and non-availability of drug or change in Government policy was the reason in 20 patients (57%). None of the patients needed ART regimen switch due to treatment failure.

ADR profile

ADRs recorded in the participants are given in Table 2.

Fortythree patients (59%) had developed side effects with the start of first line ART regimen. Rashes, lipodystrophy, anemia, and abnormal liver function were the common side effects noted. Also noted were gastritis, altered lipid profile and hyperpigmentation. No patient had lactic acidosis or peripheral neuropathy in the study period.

Anemia

Anemia was mostly observed withZidovudine-based regimen (9; 12.5%). Of these, one (1.4%) had severe anemia characterized by Hb levels ranging from 6.5-7.5 g. Five of the patients (7%) had moderate anemia (Hb range: 7.5 –8.5g), while 3(4%) had mild anemia (Hb range: 8.5 - 10g). Only one patient had macrocytic anemia, while the rest had microcytic hypochromic (2; 2.8%) and normocytic normochromic anemia.Life-threatening form of this condition was not seen in any of them. Six patients (8.3%) had to change the initial treatment regimen due to anemia. No statistically significant association was found between number of patients in Zidovudine-based regimen and occurrence of anemia (P<0.37). None had pancytopenia.

Rashes

Rashes were common in Nevirapine-based ART regimen with 15% of the patients in this regimen reporting this ADR. Rash was mild in 8 participants (11.1%), while it was moderate in the rest (4.2%). Three children in this regimen had to change the regimen because of this side effect. Rashes were also induced by Efavirenz-based regimen, with 4 (5.6%) patients reporting this ADR. Three of them (4.2%) had mild rash, while one patient had moderate form of rash. There was no statistically significant relationship between the type of regimen and rash as a side effect (χ= 1.12; p<0.242).

Lipoatrophy

There were 39 patients on Stavudine-based regimen, 17 (43.5%) had lipoatrophy as side effect. There was a statistically significant association between Stavudine-based regimen and lipoatrophy as ADR (χ= 14.37; p<0.001). Most of the patients with this ADR were of higher age group (10-18 years). None of the children below 5 years developed lipoatrophy when on Stavudine-based regimen. Lipoatrophy was statistically related to the duration of Stavudine therapy, but the initial count of CD4 was not significantly associated with occurrence of this adverse reaction. This ADR caused significant effect on the emotional state of the patient (χ= 6.05; p=0.048).

Gastrointestinal side effects

Gastritis was found in 5 patients (15%) in Zidovudine-based regimen. When compared to other non-AZT regimens, this relation was not statistically significant (χ= 3.708; p=0.087).

Abnormal liver function

In 2 (9%) patients undergoing Zidovudine-based regimen, abnormal liver function was noted. This ADR was also noted in Stavudine-based regimen, with 4 patients (10.3%) reporting abnormality in liver functions. When compared to non AZT-based regimens, this association was not statistically significant.

Hyperpigmentation

Hyperpigmentation was reported in one (3%) participant in AZT-based regimen, but this ADR was not significantly related to the intake of AZT (p=0.509).

Table 1: Antiretroviral therapy in study participants (ZDV – Zidovudine; d4T – Stavudine; NVP – Nevirapine; EFV – Efavirenz; LPVr - Ritonavir boosted Lopinavir)

ART REGIMEN STARTED	NUMBER OF CHILDREN (%)
ZDV- based	33 (45.8%)
d4T- based	39 (54.2%)
NVP- based	62 (86.1%)
EFV- based	9 (12.5%)
LPVr- based	1 (1.4%)

Table 2: Distribution of adverse drug reactions in the participants

Adverse drug reactions	No. of patients	Percentage (%)
Rash	28	39.7
Lipodystrophy	19	26.4
Anemia	15	22
Altered liver function	6	8.3
Gastrointestinal side effects	5	6.9
Altered lipid profile	5	6.9
Hyperpigmentation	1	1.4

DISCUSSION

ART is known to be associated with many toxicities ranging from mild to life-threatening ADRs. In HIV-infected children most of the ARTs have shown ADRs of different grades that limit possible safe doses and combinations (Piscitelli *et al*., 1996)[5]. In India there are very few studies which deal with ADRs of HAART in children exclusively. In the present study the prevalence of ADRs to ART was 59%. This value is higher than that reported from Eastern India on children undergoing first line ART (28%; Chatterjee *et al*., 2012)[6], and another that reported 30% in HIV-positive children from the age group of 5 months to 14 years (Shah, 2006)[7]. The percentage of reported ADRs in children from other countries ranges from 14.1% to 47.7% (Oumar*et al*., 2012; Oshikoya *et al*., 2012;Menezes *et al*., 2006)[8-10]. It is possible that the spectrum of ADRs to ART varies from one country to another. The difference in rates of ADRs can be attributed to the differences in ethnicity and the treatment regimens adopted.

ADR profile revealed in this study include short- or medium-term toxicities like anemia, rashes, gastrointestinal effects, abnormal liver function, hyperpigmentation and long term adverse effects like lipodystrophy. Rash, lipodystrophy and anemia were the common ADRs recorded.

Cutaneous adverse reactions to ART in children have been recorded in case reports (Kumar and Kiran, 2014)[11]. But these reactions were recorded only during the first six months of the treatment in a prospective study from Eastern India (Chatterjee *et al.,* 2012)[6]. Yet another prospective study in HIV-infected children showed rashes in 9% of the patients (Shah, 2006)[7].

Rashes were common (17.7%) in children on Nevirapine-based regimen in this study, but in most of them they were mild, according to the WHO 2010 classification. None had Grade 3 or 4 rash.The rashes subsided when the drug was temporarily stopped and could be continued on Nevirapine later. In about 4.2% cases, rashes were significant or recurred on challenging with Nevirapine and required substitution with Efavirenz. Efavirenz also caused rashes as side effects, but were not significant and did not necessitate change in regimen. The prevalence rate of rashes was comparable to that of adults undergoing this treatment regimen. (16-22%; Warren *et al*., 1998; Pollard *et al*., 1998; Montaner *et al*., 1998; Carr and Cooper, 2000)[12-15]. Studies show that nevirapine-based ART is feasible in HIV-infected children, particularly in developing countries (Luzuriaga *et al.,* 1997; Rakesh *et al*., 2005)[16,17]. Lack of statistically significant association between the type of treatment regimen and the prevalence of rash, along with the fact that it has lower treatment-limiting toxicity, supported the use of nevirapine-based regimen in children in our country.

Stavudine is known to cause lipodystrophy as a long-term adverse reaction in HIV-infected adults (Hawkins, 2010)[18]. The prevalence is reported to go up to 50 – 63% in some of the studies (Bernasconi *et al*., 2002)[19]. High prevalence of lipodystrophy was noted in an Indian cohort too (Pujari et al., 2005)[20]. In children, two cases of pure lipoatrophy due to Stavudine-regimen were reported from India (Parakh*et al*., 2009)[21]. Present study did show lipodystrophy as one of the most common ADRs among children on Stavudine-based regimen (46%). This association between the treatment regimen and the specific ADR was statistically significant. None of the children had lipohypertrophy or any mixed pattern of lipoatrophy and hypertrophy. Higher prevalence of this ADR was found in older children, but without any gender predilection. The prevalence was not associated with the CD4 count at the start of the treatment. About 27% of children with lipodystrophy reported an emotional impact of the adverse reaction, but it did not lead to any treatment substitution. Altered lipid profile due to Stavudine-based treatment is considered as one of the emerging complication in children undergoing ART in India (Parakh *et al*., 2009)[21]. Long term follow up is needed to study this further.

Zidovudine-induced anemia is one of the common ADRs in HIV-infected adults in some studies (Rajesh *et al*., 2014)[22].But some studies report low incidence of anemia exclusively in patients on this regimen (Eluva*et al*., 2012)[23]. About 12% of the children undergoing Zidovudine-based regimen had anemia as ADR in a study conducted by Shah (2006)[7], but this was seen after a mean duration of 2 years from the start of therapy. In Nigeria only 8.3% of children in ART showed clinically significant anemia (Oshikoya *et al*., 2012)[9]. Life threatening anemia that necessitates close monitoring and blood transfusion was not seen in this study. Only one among the 11.1% of children with anemia had macrocytic anemia, a feature of AZT induced anemia. Rest had either Iron deficiency anemia, more seen in children with malnutrition or normocytic anemia which could be due to Anemia of chronic disease. A statistically significant association was lacking between Zidovudine and anemia in the participants of the study. Zidovudine-based regimen was started only in patients with Hb> 8g and this might be one of the reasons for the reduced incidence of anemia. Further, a larger sample size would have given a meaningful depiction of the association between the two. Another factor that probably influenced the incidence of this ADR was the presence of malnutrition. About 28% of the patients with malnutrition showed symptoms of anemia in our study. Malnutrition is considered as a predictor for developing anemia in patients on ART (Lorna*et al*., 2013)[24]. Interventions aimed at correction of malnutrition should thus be an integral part of management of HIV-infected children.

Prognosis in HIV-infected children has definitely improved with the use of HAART. But the ADRs of ART may affect long-term prognosis, particularly in children where the treatment is initiated early. Moreover, the development of physical changes like lipodystrophy is likely to increase the stigmata, and may also affect the adherence to ART. Studies with longer follow ups are necessary to gain better understanding of these adverse reactions and their physical and psychological impact on patients.

This study shows that Nevaripine-induced rash and Stavudine-induced lipoatrophy as the most common ADRs in children. Close monitoring and regular follow up of these patients are important for early identification and treatment. This will help to substitute them with less toxic antiretroviral agents, if needed. This may also help to prevent interactions with other drugs needed for various comorbidities in these children. Understanding the ADR profile and their effect is thus important to ensure treatment adherence and improved quality of life for these children.

CONCLUSIONS

ART was well tolerated by HIV-infected children when compared to adults and has good prognosis. ART is associated with different types of adverse reactions in HIV-infected children, the most common being rash, lipodystrophy and anemia. Most of the ADRs are associated with Stavudine and Nevirapine-based regimen. Some of the ADRs like lipodystrophy are directly related to the duration of therapy. Malnutrition increases the risk of Zidovudine-based anemia in HIV-infected children and hence nutritional interventions are important to improve treatment adherence and improved quality of life.

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