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Original Research Paper

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A CROSS-SECTIONAL STUDY OF ADVERSE DRUG REACTIONS TO ANTI-RETROVIRAL THERAPY IN PEDIATRIC PATIENTS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Aim of the study: To assess the adverse drug reactions (ADRs) to antiretroviral therapy (ART) among paediatric patients of HIV. **Materials and methods:** After obtaining approval from the institutional ethics committee, a cross-sectional, observational study was conducted among 134 HIV/AIDS patients aged < 15 years. Patients who were on ART since 6 months were included in the study. Written and informed consent was obtained from the participant or the guardian. The study was conducted in the Department of Paediatrics, KIMS, Hubballi. The data was collected by self report by the care giver or the child regarding treatment adherence over the past month and ADRs experienced by them during the course of therapy, using a questionnaire. Confidentiality of patients was maintained throughout and after the study. **Results:** The most common time of occurrence of ADR was within the first 2 months of initiation of ART and the most common ADR was nausea and vomiting. 76.9% ADRs were 'probable' on Naranjo causality assessment and 92.3% were mild in nature. A statistically significant association was seen between adherence and ADRs. Occurrence of ADRs was higher with patients who were on ZDV+LMV+ EFV regimen. **Conclusion:** Occurrence of ADRs was seen to significantly influence the adherence to ART. As efforts continue in the development of medications with more favourable adverse effect profiles, treating physicians must remain aware of new and developing syndromes associated with the use of these drugs.

KEYWORDS : Adverse Drug Reactions; Paediatric; Antiretroviral Therapy.

INTRODUCTION:

Acquired immunodeficiency syndrome (AIDS) is one of the most destructive epidemics the world has ever witnessed. According to the India HIV estimates 2020, 81,430 children were estimated to be living with HIV, and are on active care with antiretroviral therapy (ART) by the national programme. Around 10% of the total new HIV infections in 2020 were estimated among children aged <15 years[1]. With the availability of antiretroviral drugs, there has been a decline in mortality and morbidity due to AIDS and these drugs have changed the disease pattern to a chronic manageable infection. Despite the great progress made in the last 15 years in the field of pediatric HIV diagnosis and treatment, pediatric antiretroviral treatment (ART) failure is an under-recognized issue that needs to be addressed[2]. The current goals of HIV treatment in children include restoring, enhancing and preserving immune function, suppressing viral replication, preventing the emergence of viral drug-resistance mutations, reducing drug-related toxicity and improving long-term outcomes and quality of life[3].

Antiretroviral therapy (ART) for HIV disease is often highly demanding, which includes multiple medications that require frequent dosing[4]. Adherence to antiretroviral therapy is critical for reducing the disease burden particularly among the children with HIV. The effects of non-adherence range from individual disability to global threat due to development of treatment-resistant viruses. ART drugs are highly toxic and are associated with various adverse drug reactions (ADR) and can often cause significant morbidity among the patients receiving the therapy. Unfortunately, up to 25% of patients discontinue their initial highly active antiretroviral therapy (HAART) regimen[5] due to various reasons, of which intolerance to adverse drug reactions is an important cause. Treatment limiting drug toxicities can add to the complexity in the management of HIV by impairing patient adherence to treatment, leading to inferior clinical outcomes and higher cost to the public health system[6]. Hence, monitoring and reporting of ADRs in pediatric HIV/AIDS patients receiving ART assumes great importance. A physician should be well equipped to identify and treat ART toxicity. Lack of ADR monitoring and reporting system in developing nations underestimates the burden of ADRs due to ART. The aim of the current study is to study and assess the adverse drug reactions to ART among patients of HIV aged less than 15 years.

MATERIALS & METHODS:

The study was conducted in the Department of Pediatrics at KIMS Hospital, Hubballi. Pediatric HIV patients aged less than 15 years who are accessing ART centre, KIMS Hubballi and fulfilling the inclusion criteria, constituted the study. 134 HIV/AIDS patients aged below 15 years who visited the Department of Pediatrics were to be included in the study.

MATERIALS & METHODS:

Inclusion criteria:

(I) All patients below 15 yrs of age, diagnosed with HIV/AIDS on antiretroviral therapy visiting KIMS hospital, Hubballi.
(ii) Patients on ART for a period of 6 months or more.
(iii) Patients or the legal guardian of patients willing to give consent for the study.

Exclusion criteria:

(i) Patients on ART for a period of less than 6 months.

Clearance from the institutional ethics committee, was taken before starting the study. Written and informed consent was taken after explaining the study, in their native language, from the participant / the legal guardian. A questionnaire was used to collect the data. The participants along with their guardians were interviewed separately in private, in their vernacular language. The name of the participant was not recorded in the questionnaire in order to maintain the confidentiality.

All the information collected was based on patient's self report. Patients were asked for any adverse reactions experienced during the course of treatment. The causality of reactions was analyzed by Naranjo causality scale. Severity of ADRs was assessed using modified Hartwig & Siegel scale. Data was entered in Microsoft Excel 2007 and was analyzed as numbers & percentages. Chi square test, paired and unpaired student's t test were used for comparing attributes and variables of study. Probability value of <0.05 was considered as significant. Data was described in form of

tables and graphs. IBM SPSS software version 21 was used for calculations.

RESULTS:

Figure-1 shows the number of study participants with different levels of ART adherence in 1 month prior to the interview. 99 (73.8%) participants had taken 95% and more of the prescribed medications for that month, 18 (13.4) participants had taken 90% to 95% of the prescribed medications for that month and 17 (12.8%) participants had taken 90% and less of the prescribed medications for that month. The mean adherence in the study population was 94.2% with a standard deviation of 15.6%.

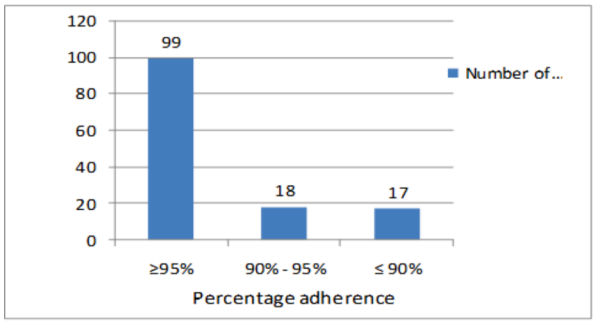

Fig-1 Degree of adherence to ART over the previous 1 month

Of the 134 study participants, 39 (29.1%) participants reported to have experienced adverse drug reactions to ART. Majority of these i.e. 34 (87.2%) occurred in the first 2 months of therapy, while 4 (10.2%) reported ADRs after 6 months of ART therapy.

The study participants were asked to list the ADRs experienced by them since the initiation of their therapy with ART. Some participants listed multiple reactions. 89 such responses were recorded. Out of the 89 responses, the most common ADR was nausea, which was experienced by 32 (36%) participants, followed by vomiting, experienced by 29 (32.6%) participants. 6 (6.7%) participants experienced diarrhea, while 4 (4.5%) had experience rashes and itching. Other ADRs experienced are listed in Table- 1

Table-1 Adverse drug reactions experienced by the study participants

Adverse drug reactions experienced	Number	Percentage
Nausea	32	36
Vomiting	29	32.6
Diarrhea	6	6.7
Rash & itching	4	4.5
Lack of appetite	4	4.5
Burning sensation in stomach	3	3.4
Dizziness	3	3.4
Impaired concentration	2	2.2
Fever with chills	2	2.2
Excessive sleep	1	1.1
Abdominal pain	1	1.1
Headache	1	1.1
Others	1	1.1
Total	89	100

Association of adherence to the factors determining adherence was checked by independent sample t test. Significant statistical association with a p value of 0.04 was found between adherence and adverse reactions. Higher mean percentage of adherence was seen among participants with no adverse reactions to the therapy. Table-2

Adverse drug reaction	SD	P value
Yes	89.8 (25)	0.04*
No	95.9 (8.9)	

Table-2 Association Of Adherence And The ADR

p value based on independent sample t test, SD-standard deviation

Of the 134 study participants, the number and percentage of participants who experienced ADRs while on various ART regimens was tabulated. On evaluating the association of ADRs with various ART regimens, the p value obtained was 0.10, which was not statistically significant.

Out of 134, 39 study participants reported to have experienced ADRs to ART. These ADRs were assessed for causality by Naranjo scale and was found that the reactions experienced by 30 (76.9%) participants were "probable" and 9 (23.1%) reactions were possible. There were no definite or doubtful reactions to the use of ART in this study.

The reported ADRs were assessed for severity by Hartwig and Siegel scale. ADR experienced by 35 (89.7%) participant was of level I and 1 (2.6%) participant experienced level II ADR. Thus 36 participants had mild ADR to ART. 3 (7.7%) participants experienced level IV ADR which was of moderate degree. No severe reactions were seen due to the use of ART in the present study.

DISCUSSION:

This study makes an effort to look into the the adverse effects experienced by pediatric patients of HIV on which not many studies have been conducted in India. Our study showed that 73.8% participants had taken more than 95% of the medication in the previous month and were well adherent to treatment. 26.2% participants were non adherent and they are at higher risk of failure of therapy. In a study conducted at New Delhi by Bhattacharya et al, good adherence was seen among 65.6% participants[7], while good adherence was seen among 73% children in a study conducted in Cape Town by Davies et al[8]. Nachega et al in his study found that, compared to adults, adolescents were less adherent to combination ART[9].

Association of adherence to various factors by independent sample t test:

In the present study, statistically significant association was seen between adherence and adverse drug reactions experienced by the participants. Mean adherence was higher among participants who had not experienced any adverse reactions during the course of therapy (95.9%). This finding shows that occurrence of adverse events can significantly reduce the adherence to therapy and hence affect the clinical outcome. Similar to our finding, in a study by Nsheha et al, adherence was worse among children who developed side effects to ART[10]. Non-compliance due to ADRs was observed in 28.9% patients in a study by Nagpal et al[11].

Adverse drug reactions to ART among the study population

Out of 134 study participants, only 39 (29.1%) reported experiencing at least one adverse drug reaction since the start of therapy with ART. A study by Nagpal et al among adults with HIV, 90.64% patients reported ADRs[11]. At least one adverse drug reaction was reported by 89.8% of the participants in a study among adults with HIV by Tadesse et al[12]. On comparison with other studies, it was noted that the incidence of ADRs to ART is higher among adults than with pediatric patients. Many studies have found that ART among children, seems to be well tolerated, with few severe drug toxicities reported[13].

Out of all the participants who experienced ADR to ART, majority of ADRs were seen in the first 2 months of therapy in our study (87.2%), in contrast to a study by Sauvageot et al[13], where most reactions to ART occurred during the first 6 months of treatment. In the present study, maximum adverse drug reactions were seen among the participants who were on ZDV+LMV+ EFV regimen (33.3%). A majority of patients

(96.2%) were on the standard first-line ART regimen with of d4T+3TC+NVP in a study done among children with HIV in Malawi by Buck et al[14] . In a study by Williams et al there was an almost two fold increase in the odds of non-adherence among children and adolescents receiving 3 NRTIs as compared with those on HAART[4]. India has a wide variety of genetic make-up and hence holds a possibility of uncovering many new ADRs to ART that might not have been recognized in earlier studies. The most commonly reported ADR to ART in this study was nausea (35.9%), followed by vomiting (32.6%). Leonard et al in their review suggested that pediatric patients are more vulnerable than adults to metabolic side effects of ART because of its potential impact on growth and greater cumulative exposure among them[15] . In a study conducted by Shah among HIV-positive children in Mumbai, 16% developed hepatotoxicity, 12% had raised serum amylase without symptomatic pancreatitis, 12% had zidovudine induced anemia, 9% had nevirapine induced rash, 2% had didanosine induced pain in abdomen, 2% had stavudine induced angioedema, and 2% had hepatic steatosis[16] . Whereas the most common ADR observed in a study among adults with HIV by Vaghani et al. was peripheral neuropathy in 37.7% patients,which was similar to a study by Singh et al in which it was 31.6%[17] . This finding shows that ADR profile among children is different from that of adults.

Assessment of adverse drug reactions to ART

In our study, among the 39 patients who reported to have experienced ADR to ART, causality assessment of the ADRs showed that 76.9% of the ADRs were "probable", while 23.1% were "possible" on Naranjo scale. Severity assessment of these ADRs by Hartwig-Siegel scale showed that 92.3% reactions were mild and only 7.7% reactions were of moderate degree. There were no severe reactions due to ART in our study. In a study by Sauvageot et al, among HIV positive children aged less than 5 years, 3.8% participants changed their first-line antiretroviral agents because of severe toxicity. They also found that, in the first 6 months of ART, toxicities were more frequent in Asia than in Africa. Also, in Asia, toxicities tended to be more frequent with nevirapine containing regimens[13]. However, severe adverse drug reactions were seen in 32.5% patients aged less than 35 yrs in a study conducted in Chattisgarh by Singh et al[17]. In a study done among 143 HIV adults by Gagiya et al, 36 patients had severe ADRs, whereas 51 patients had mild to moderate ADR[5] . In a study by Nagpal et al, causality assessment of the ADR to ART revealed that 6.63% ADRs were probable and 93.3% ADRs were possible[11].

CONCLUSION:

While great progress has been made in the field of HIV diagnosis and treatment, pediatric HIV treatment related aspects are still an under-recognized issue. Adverse drug reactions to ART pose a significant challenge in maintaining adherence to ART. As efforts continue in the development of medications with more favourable adverse effect profiles, treating physicians must remain aware of new and developing syndromes associated with the use of these drugs. This study underscores the importance of Pharmacovigilance activities related to ART and the need to identify them as they affect adherence to the therapy significantly, thereby affecting the outcomes of ART.

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