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A Prospective Study to Evaluate Adverse Drug Reaction Following HAART Therapy in a Tertiary Care Teaching Hospital

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Abstract: ***Background: Highly active antiretroviral therapy (HAART) is usually effective in reducing plasma HIV RNA levels and in gradually increasing CD_4 cell counts. The present study was undertaken with the special focus on adverse drug reaction due to the ART drug. Methodology: 328 consecutive AIDS patients included for the study and they were registered for ART drug treatment. All patients were informed about the adverse reactions to the ART drugs and all the adverse effects developed by patients were noted. Results: Stavudine combinations were preferred (80%) more than Zidovudine combinations. Nevirapine was withdrawn due to one or other adverse reactions or due to hepatic illness in about 10% of cases. The predominant system involved was Gastro intestinal tract 25.6% followed by central nervous system (16.5%), Dermatological system (3.9%), Reticuloendothelial system (3%) and miscellaneous manifestations (12.2%).***

Keywords: Anti-retroviral drugs, Stavudine, Nevirapine, Acquired Immuno Deficiency Syndrome, Adverse drug reaction

1. Introduction

Human Immuno Deficiency Virus infection was first identified in India during 1986 by Dr. Sunithi Solomon, Professor of Microbiology, Madras Medical College, Chennai. When the world was alerted to the first case of AIDS, no one could have imagined that it would claim more than 20 million lives in a matter of 20 years. According to United Nations Acquired Immuno Deficiency Syndrome estimate, 36.1 million people are now living with HIV / Acquired Immuno Deficiency Syndrome (AIDS) and 5.3 million are infected every year. Today our nation has about 4 million HIV / AIDS patients, the second highest number among all nations [1].Recognizing it as a serious threat to humanity, today researchers are working hard in many ways to find out remedial measures. In some of the developed countries greater awareness and modern antiretroviral drugs are bringing about a sharp and sustained decline in the incidence of AIDS and AIDS related mortality. However like many other developing countries, India has a long battle ahead. Wide spread implementation of these interventions, however, continues to be hampered by personal, social, political and economical barriers

Today anti-retroviral therapy has turned AIDS into a chronic infection that patients live with and not necessarily die of. A large and increasing number of anti-retroviral agents are currently available for treatment of HIV infected patients. A combination of highly active antiretroviral therapy (HAART) is usually effective in reducing plasma HIV RNA levels and in gradually increasing CD_4 cell counts, particularly in Anti-retroviral naive patients. Also important in selection of agents is optimization of adherence, tolerability and convenience. Many patients will ultimately experience at least one treatment failure, close monitoring of viral load and CD_4 cell counts is critical to trigger appropriate changes in therapy. Pharmacological aspects and therapeutic issues with regard to ART though known to doctors from literature, they have not personally experienced in this area. Hence the present study was undertaken with the special focus on adverse drug reaction due to the ART drug.

2. Aims

To find out the pattern of Adverse Drug Reactions among AIDS cases receiving Highly Active Anti-Retroviral Therapy (HAART)

3. Materials and Methods

Study was carried out in AIDS patients attending the outpatient department of ART Centre, attached to Department of Medicine, Government Rajaji Hospital, Madurai. The study was carried out in Collaboration with Institute of Pharmacology and Department of Medicine and Dermatology, Madurai Medical College, Madurai. Study was designed as a cross sectional study. Institutional Ethical Clearance was obtained from the ethical committee, Government Rajaji Hospital, Madurai. Informed consent was obtained from all the patients included for the study. All those cases referred to ART centre for treatment were evaluated following National Aids Control Organization guidelines. Patients of both sexes diagnosed as Human Immuno Deficiency Virus positive by voluntary counselling and Testing Centre and cases referred from various places, attending the ART centre of Government Rajaji Hospital were selected for ART drug treatment as per NACO guidelines. Inclusion criteria for present study were HIV positive patients with CD_4 cell count less than 200/mm^3 CD4 cell count was determined by Flow cytometric (automated) methodology. Flow cytometry is the gold standard method

for the estimation of CD4 counts due to its accuracy, precision and reproducibility. Patients who come under the WHO staging III or IV were included.HIV patients who are free from opportunistic infection were included. Exclusion criteria for study were mentally abnormal patients and patients not able to adhere ART drugs, Non Co-operative patients were excluded, Non supportive patients, pregnant patients were excluded. Debilitated and Terminally ill patients were excluded from the study and those taking other drugs like Ayurveda and Siddha were excluded. Patients with other co-morbid conditions like Tuberculosis, Hypertension, Diabetes Mellitus, Renal, Hepatic, Dermatological and neurological illnesses were excluded from the study.

A total of 328 consecutive AIDS patients included for the study and they were registered for ART drug treatment. Counseling was given to the patients individually. Counselling was also given to the family members and to the members of supportive systems / agencies or organization. Counseling regarding the disease, drug and diet to the selected patients individually. There were counseled regarding the disease in simple easily understandable language with examples. They were counselled about the fearlessness of normal activities like sharing the utensils and feeding their children that HIV virus is not transmitted by these activities. They were advised about modification of their behavioral habits regarding the sexual activities since HIV viruses transmitted mainly by sexual contacts and drug injections in drug addicts. All patients were informed about the adverse reactions to the ART drugs. So they were advised to immediately report of any complaints on reactions, on ART drug treatment. After giving counselling the following data were collected as per guidelines of NACO and Tamilnadu State AIDS Control Society. Sociodemographic data, base line clinical evaluations including assessment of clinical stage of HIV infection, identification past HIV related illnesses, identification of current HIV related illness that would require treatment Identification of co-existing medical conditions and medical treatment. Blood samples were collected from each patients for determination of the following parameters. Complete Blood count TC, DC, Hemoglobin%, Blood Sugar, Blood Urea, Serum Creatinine, Urine Analysis, Liver Function Test (LFT), Microbiological examinations like sputum for AFB and gram stain, X-ray chest PA view taken to rule out Tuberculosis, Ultra Sonogram abdomen, ECG done to assess the cardiac status, Ophthalmic examination

ART drugs were given on the first day of starting ART treatment under the supervision of the investigator and observed for any immediate drug reactions like urticaria, itching, and anaphylaxis. Initially patients were advised to attend ART centre daily for 15 days for ART drug collection. After 15 days, they were advised to attend the ART centre at regular intervals. Each and every visit the patients were counseled individually Each and every complaint was noted. Each system in the body was examined in detail to identify the adverse drug reaction including lipodystrophy and for Immune Reconstitution Inflammatory Syndrome (IRIS) during follow up. [2] The data was entered in Microsoft excel spread sheet and analyzed by simple descriptive statistics.

4. Results

Of the 328 cases included for the study, there were 206 males and 122 females. Females were predominant among the age group 10 and 29 and males among 30 and 39 years and this was statistically significant. Their age ranged from less than 12 to 61 years. The mean age was 34, (SD±7.9), median was 34.31 years.

Table 1: Distribution of cases in relation to age and gender

Age in years	Male	Female	Total
< 9	0	3	3
10 – 19	1	5*	6
20 – 29	37	55*	92
30 – 39	130*	40	170
40 – 49	31	16	46
50 and above	7	3	10
Total	206	122	328
Mean	35	30	34
SD	6.47	6.30	7.9
Median	35.87	31.67	34.31

* significant P < 0.05

They all hailed from urban, semiurban and rural areas in and around Madurai. During the study period significant number of females in WHO stage II had low CD_4 cell count than their male counter parts. The drugs distributed were in a combination of Zidovudine, Lamivudine and Nevirapine in 60, Stavudine, Lamivudine and Nevirapine in 235, Zidovudine, Lamivudine and Efavirenz in 3 and the rest had a combination of Stavudine, Lamivudine and Efavirenz.

Table 2: Drug regimen in relation to gender

No	Drugs	Male	Female	Total
1	Zidovudine Lamivudine Nevirapine	40	20	60 (18.29%)
2	Stavudine Lamivudine Nevirapine	144	91	235 (71.65%)
3	Zidovudine Lamivudine Efavirenz	2	1	3 (0.914%)
4	Stavudine Lamivudine Efavirenz	20	10	30 (9.15%)
		206	122	328

Over all 80% received stavudine preparations and 10% received Efavirenz instead of Nevirapine.

Table 3: Drug reactions among patients on ART

Various Systems	Male	Female	Total	%
Skin (Dermatology)	5	8*	13	3.96
Gastro Intestinal Tract	57	27	84	25.60
Central Nervous System	39*	15	54	16.46
Reticulo Endothelial System	6	4	10	3.04
Miscellaneous	23	17	40	12.19

* significant P < 0.05

Adverse drug reactions noticed were in the form of gastro intestinal manifestations in 84 (Nausea 61, Vomiting 35, Diarrhea 28, Loss of appetite 21, Epigastric discomfort or pain 17, Acid belching 6, Central nervous system manifestations in 54 (headache 23, sleep disturbances 17, numbness 9, fatique 6, psychosis 1, encephalopathy 1), Reticulo Endothelial system manifestations in the form of fall in hemoglobin level in 10 patients, skin manifestations

in 13 (itching 12, rashes 10, SJS 2, urticaria 1) and other manifestations in 40 patients (fever 26, myalgia 15, arthralgia 3, malaise 3, black discolouration of lips 2). [3].Over all central nervous system manifestations were noticed significantly more among males. Female showed more of skin manifestations and miscellaneous manifestations which were significant statistically.

Lipodystrophy was noticed among patients on Stavudine therapy [4]. They were abdominal obesity and in drawing of cheeks in 7 and 2 cases respectively. Immunere constitution inflammatory syndrome (IRIS) was noticed in 8 cases (2.1%) [5], [6].

5. Discussion

The introduction of highly active Anti-Retroviral Therapy HAART has led to a significant reduction in AIDS related morbidity and mortality. Unfortunately upto 25% of patients discontinue their initial HAART regimen because of toxic effects or non-compliance and treatment failure within the first 8 months of therapy. In this study none discontinued ART because of intense counseling and motivation. ART can have a wide range of adverse effects on the human body. Common but mild adverse effects occurring early in most Anti-Retroviral Regimens include gastro intestinal effects such as bloating, nausea, diarrhea which may be transient or may persist throughout the therapy as noticed in our study. Other common adverse effects were fatigue and head ache caused by Zidovudine, and nightmares associated with Efavirenz. Several uncommon but more serious adverse effects associated with Anti-Retroviral Therapy including Zidovudine associated anemia, Stavudine associated peripheral neuropathy can occur. Among the study subjects some of them showed adverse response to Zidovudine, Stavudine and Efavirenz.

Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) associated hypersensitivity reactions are treated symptomatically these patients had a satisfactory response to supportive and symptomatic treatment. Other serious adverse effects noticed among those on ART are Lacticacidosis, Hepaticsteatosis, Hepatotoxicity, Hyperglycaemia, Fatmaldistribution, Hyperlipidemia, Bleeding disorders, Osteoporosis and Skin rashes [7].

Lactic acidosis has been associated with Zidovudine (AZT) and Stavudine (d4T) therapy [8].Skin rash is common adverse effect of NNRTIs particulary Nevirapine. 16% experienced mild to moderate maculopapular rash, with or without pruritus, on the trunk, face and extremities, within the first 6 weeks on therapy [9]. If the rash occurs during the initial 2-week dose lead-in period, the dose should be held at 200mg daily until the rash resolves. Although most rashes are self – limited, Nevirapine should be permanently discontinued if the rash is severe or accompanied by constitutional symptoms. Severe rashes occur in about 6.5% of NVP-treated patients, mainly during the first 4 weeks of treatment, including Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis in less than 1% of all patients treated with NVP. In this study SJS was observed in 2 cases only.[10], [11].In view of the adverse reactions noticed among the patients on ART, every Health workers and those providing care and support to AIDS patients should be well informed about adverse effects of HAART. Accordingly, the patients may be provided adequate counseling on side effects of drugs before starting HAART. Unless and until patients and their family members are well motivated one cannot achieve good compliance. The strength of the study is prospective study and good compliance. The limitations are lack of detailed biochemical work up and pharmacokinetics of ART among those on ART. No attempt was made to work on genetic predisposition among those developed adverse effects following HAART. We conclude our study that the study objectives have been achieved and we found female preponderance was noticed among the age group 10 and 29 in contrast male predominance among the age group 30 and 39 years, there by indicating innocent female victims who get married in young age were susceptible to AIDS in view of their in a poor health status. Patients hailed from urban, semi urban and rural areas, and their economical status was far from satisfactory.CD_4 cell count was significantly low among female patients.

Stavudine combinations were preferred (80%) more than Zidovudine combinations. Nevirapine was withdrawn due to one or other adverse reactions or due to hepatic illness in about 10% of cases (33/328).Adverse Drug Reactions were seen in one form or other or a combination of them in (50.9%) 167 patients. The predominant system involved was Gastro intestinal tract 25.6% followed by central nervous system (16.5%), Dermatological system (3.9%), Reticuloendothelial system (3%) and miscellaneous manifestations (12.2%).

Among the Adverse Drug Reactions, skin manifestations were significantly more among females and central nervous system manifestations in men. Lipodystrophy was noticed in 9 patients. (2.8%).Immune Reconstitution Inflammatory Syndrome was noticed in 8 cases (2.1%) and they were cytomegalo virus Retinitis in 1, Herpes labialis in 2, Herpes genitalis in 3, and esophageal candidiasis in 2 individuals. In view of the adverse reactions noticed among the patients on ART, every health worker and those providing care and support to AIDS patients should be well informed about adverse effects of HAART. Accordingly the patients may be provided adequate counselling on side effects of drugs before starting HAART. To achieve the goals of HAART among AIDS cases, the patients, their family members, care takers, support organizations and care providers are all should work together as a team without difference or conflict among themselves

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