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RESEARCH ARTICLE

ADVERSE DRUG REACTIONS OF ANTIRETROVIRAL TREATMENT (ART) IN PEOPLE LIVING WITH HIV/AIDS (PLHI)

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ABSTRACT

Background: Highly active antiretroviral therapy (HAART) is effective but at the same time is associated with several adverse drug reactions affecting various organ systems of the body posing a constant challenge, authors conducted a study on adverse drug reactions of ART at tertiary care centre
Methods: The criteria for the diagnosis of ADR was defined as per WHO guidelines. All cases were periodically subjected to clinical and laboratory monitoring for drug toxicity on each follow up during on one year period. CD4 count was done as and when required.
Observations: Anemia was observed as commonest side effect 19.13% (31/162), followed by rashes 15.44% (25/162), hepatitis 3.68% (5/162), peripheral neuropathy 11.11% (18/16), dyslipidemia 9.87% (16/162), gastrointestinal manifestations 4.32%(7/162) and neuropsychiatric manifestations 1.23% (2/162).
Conclusion: Though ADR are associated with HAART it has to be stressed that majority of patients are able to tolerate HAART well. The monitoring of treatment and associated toxicity by clinician is recommended in at least three monthly intervals, even in asymptomatic patients, and more often at the initiation of HAART.

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INTRODUCTION

Highly active antiretroviral therapy (HAART) has improved the prognosis for people living with HIV-infection/AIDS (PLHA), changing the disease course from life threatening infection to chronic disease but at the same time posing a clinical challenge with adverse drug reactions (ADR). The risk of ADR arises because of the disease itself and the effect of complex ART on the different organ systems of the infected person. World Health Organization (WHO) defines adverse drug reaction (ADR) as "A response to a drug which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy for a disease and for the modification of a function, excluding, failure to accomplish the intended purpose". (Esch, 1972) HIV-infection/AIDS disease is a global pandemic with 35 million people living worldwide. (Fauci and Lane, 19thed) An estimated 2.3 million people were living with HIV in 2015 with adult HIV prevalence of ~0.36% in India. (NACO INDIA Annual Report 2015) There has been reduction in mortality with increased use of potent ARV drugs generally administered in a combination of three or four agents. (Fauci and Lane, 19thed) Most of the drugs available and approved for use in HAART have some or the other adverse effect. One thus should have the knowledge of drugs having more modest and non-fatal adverse effect profile. The newer additions in the nucleoside reverse transcriptase inhibitor (NRTI) class like ten of ovir and abacavir offer such options. Side-effects are more varied with nucleoside analogues, including mitochondrial damage that can lead to hepatic steatosis and lactic acidosis as well as peripheral neuropathy and pancreatitis, anemia being the common challenge. Recently recognized problem has been a syndrome of hyperlipidemia, glucose intolerance/insulin resistance, and fat redistribution often referred to as lipodystrophy syndrome. (Nderitu *et al*., 2013) Nonnucleoside inhibitors of HIV-1 reverse transcriptase, nevirapine and efavirenz, are used in combination with nucleoside analogues for the treatment of HIV-infected adults and are associated with the development of a maculopapular rash, generally seen within the first few weeks of therapy, in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure have been reported in patients treated with nevirapine. Efavirenz causes feeling of light-headedness, dizziness.

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Sometimes complain of vivid dreams. Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. (Fauci and Lane, 19th ed) Therapeutics of HIV patient is further complexed because of the other adjunctive medications which most of these patients are prescribed when suffering from other conditions such as tuberculosis, fungal infections, P. jeroveci pneumonia, lymphoma etc. One has to consider drug-drug interactions between ART and drugs given to treat concomitant illnesses. This leads to further increase in incidence of side effects of ART and decrease in compliance. Clinical dilemmas of noting the exact culprit drug producing toxicity may be intriguing. Pharmaco-vigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects, or any other medicine related problem. (www.whoindia.org) Every country needs to have its own pharmaco-vigilance programme due to differences in the pattern, presentation and incidence of ADRs. Even the data derived from within a country has relevance for that particular population and may be helpful for making rational regulatory decisions. Present study was undertaken to monitor ADR in people living with HIV and AIDS and to report causality assessment of ADRs that reflects the association of the drug with the adverse effects.

MATERIALS AND METHODS

This prospective cohort study was conducted at tertiary care centre over a period of one year after getting approved by Institutional Review Board and Ethical Committee. Eligible subjects were recruited from the Integrated Counseling and Testing Centre (ICTC) clinic which is dedicated outpatient service for People Living with HIV and AIDS (PLHA) working under the supervision of Department of Medicine which provides logistic support.

Subjects: The subjects under study included all HIV-positive cases, already on antiretroviral treatment (ART) and recently diagnosed put on ART. The subjects were enrolled after a written informed consent as per prescribed proforma. The protocol according to the international guidelines were followed in the present study.

Exclusion criteria: Patients having pretreatment haemoglobin <10 gram, liver dysfunction, renal dysfunction, diabetes mellitus, impaired fasting blood serum level and patients with age <18 years were excluded from the study. Patients complaining of distal weakness, parasthemia and numbness before initiation of treatment were also excluded.

Initially, a total of 162 subjects were included in the study. All subjects stratified the initiation of ARV therapy (WHO clinical stage III/IV or clinical stage I/II with CD4+T-cell counts less than 200 cells/μL).A detailed history of every patient was taken including past history of ART, history of fever, cough, breathlessness, past or present history of opportunistic infections i.e., pulmonary/extrapulmonary tuberculosis, skin lesions, mucosal lesions and sexually transmitted diseases (STD). Baseline laboratory investigations such as hemoglobin, total counts, differential counts, erythrocyte sedimentation rate, urine analysis, serum veneral disease research laboratory (VDRL) test, serum hepatitis B surface antigen (HBsAg). Subjects also underwent liver function tests (LFTs), renal function tests (RFTs), lipid profile and blood sugar tests. The criteria for the diagnosis of ADR was as per WHO definition which defines ADRs as "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy". (Esch, 1972)

Art regimens

Drug regimens given to subjects who underwent this treatment:

1. Nevirapine (200mg)+ Lamivudine (150mg) + Stavudine (30mg)
2. Ziduvudine (300mg) +Lamivudine (30mg) +Nevirapine (200mg)
3. Lamivudine (150mg) +Stavudine30mg)+ Efavirenz (600mg) Patients having haemglobin (Hb) >10 g% were initially put on ziduvudine + lamivudine + nevirapine (AZT + 3TC + NVP) combination, those having Hb <10 g% were put on stavudine + lamivudine + efavirenz (4dT + 3TC + EFV).

All cases on ART were periodically subjected to clinical and laboratory monitoring. They were screened for opportunistic infections and drug toxicity in each follow-up visit during one-year period. CD4 and T-cell count was done every three months or more frequently, if clinically indicated. In patients on zidovudine-containing regimens, haemoglobin was measured before initiation and at 4, 8 and 12 weeks of therapy or in response to their symptoms. LFTs was done at 4, 8 and 12 weeks in patients on nevirapine-based regimens. SGOT and SGPT > 5 time baseline were taken as significant event. Lipid profile, serum amylase and blood glucose estimates was done regularly at 3 months interval. Total cholesterol >240 mg%, LDL cholesterol level >200 mg%, triglycerides >200 mg% and HDL cholesterol <40 mg% were taken as significant events.
Detailed neurological examination was done along with dermatological examination depending upon the symptomatology as and when required.

OBSERVATIONS AND RESULTS

Subjects enrolled were followed for 1 year. Out of a total of 162 patients, 94 (58.55%) were male and 68 (41.45%) were female patients. Majority of the patients 115 (71.05%) had CD4+ T-cell counts < 200. Highly active antiretroviral therapy (HAART) regimens used were : Ninety five (59.21%) of the patients initiated treatment with combination of ziduvudine + lamivudine + nevirapine (AZT + 3TC + NVP), 47 (29%) patients received combination of stuvudine + lamivudine + nevirapine (d4T + 3TC + NVP) and 20 (11.18%) patients received combination of stuvudine + lamivudine + efavirenz (d4T + 3TC + EFV). A total of 162 HIV/AIDS patients were included in the study, comprising 94 (58.55%) males and 68 (41.45%) females.94 patients were <35 years of age and 68 patients>35 years of age.CD4+T-cell counts at base line observed was <200/mm^3 in 115 patients and >200/mm^3 in 47 patients. Ninety five patients were put on AZT +3TC +NVP regimen,47 patients on d4T +3TC+ NVP and 20 on d4T+3TC +EFV regimen. Anemia was observed as commonest ADR,IN 19.13 (31/162),followed by skin rashes 15.43% (25/162),

peripheral neuropathy 11.11%(18/162) and hepatotoxicity 4.93% (8/162). A total of 118 ADRs were reported. Severe ADR was reported in31.35% (37/118) patients and incidence of ADR was more common in female patients57.62% (68/118).CD4 count in patients with ADR was below 200/mm^3 in 72.88% (86/118) patients with ADR and >200 /mm^3 in27.18%(32) patients with ADR (Table 1). We analyzed the adverse drug reactions (ADRs) of the generic, fixed dose combination of antiretroviral therapy (ART) regimens recommended by the National AIDS Control Organization (NACO) in 162 adult people living with HIV/AIDS (PLHA) followed up at tertiary care teaching hospital in north India. The majority of patients were in WHO clinical stage 3 or 4 and CD4+T cell counts was <200 cells/µL. In the present study, adverse drug reactions were observed in 72.83% (118/162) patients. The incidence of ADR'S has been reported to vary between 60% to 86% in various studies. (Keneth and Azuka, 2013; Fellay *et al*., 2001) (Table 2 & 3) The most common side effect observed in present study was anaemia seen in 19.13%(31/152) patients and severe anaemia of grade III and IV was found in 7.23% (11/152) patients. Zidovudine related anemia usually occurs within 3 months after initiating therapy. It is a known myelosuppresive drug and anemia is more common in those with more advanced disease and possibly those receiving chemotherapy, pyrazinamide and interferon. Sivadasan *et al*. (2009) Anaemia has been reported as a common side effect and common ADR requiringtreatment modification in severe, grade III and IV. (Sivasdasan *et al*., 2009; Cesar *et al*., 2010) Zidovudine was associated with an increased association of treatment change in the present study. In the present study, rashes developed in 15.44% (25/162) patients, 6.17% (10/162) patients had grade III or IV rashes in which nevirapine (NVP) was replaced by efavirenz (EFV).Rashes attributed to NVPhas been reported between 15% to 26% in various studies and replacement of NVP in patients having grade III to IV rashes. (Singh *et al*., 2009; Sivasdasan *et al*., 2009; Maggiolo *et al*., 2007; Sharma *et al*., 2008) Drug hypersensitivity is known in form of erythematous maculo-papular pruritus rashes and confluent rashes with or without fever is known to occur with HAART usually occurring within six week of therapy. (Montessori *et al*., 2004) NNRTI's nevirapine, dilaviridine (ddI) and efavirenz and the NRTI abacavir and the protease inhibitor amprenavir are common drugs that cause hypersensitivity, which is rare with other NRTI's or protease inhibitors. Diagnosis is based on the clinical criteria. However, other causes such as infection, malignancy or immune reconstitution need to be considered. (Jha *et al*., 2015; Montessori *et al*., 2004)

Hypersensitivity is known to resolve spontaneously despite continuation of therapy. Therapy need to be stopped/modified if there is mucosal involvement and blistering and exfoliation. (Carr and Cooper, 2000) Hypersensitivity manifesting as hepatitis (elevation of liver enzymes >5 times baseline was observed in 5 (3.08%) patient and all of them required modification of HAART. Nevirapine was found to be offending agent. The incidence of hepatitis attributed to nevirapine is reported between 3% to 5% in various studies (Sivasdasan *et al*., 2009; Maggiolo *et al*., 2007; Sharma *et al*., 2008; Patel *et al*., 2006) NNRTI's mainly nevirapine is known to cause hepatitis which is associated with elevation of aminotransferases greater than five times the baseline and tender hepatomegaly. The pathogenesis of hypersensitivity is unknown. Various causes and mechanisms suggested include degree of immunodeficiency or immune activation and co-existing HBV and HCV coinfection. Cytokines are probably involved with the IL-6, IL-1 and TNf-α contributed by CD4 lymphocytes and macrophages. (Carr and Cooper, 2000) Gastrointestinal toxicity observed in our study was mainly gastritis associated with nausea and vomiting in 4.32% (7/162) patients of the cohort, diarrhea was observedin 1.23% (2/162) patients. Gastrointestinal toxicity attributed to HARRT mainly in form of abdominal pain, diarrheaand gastritis incidence of>1% to10% in literature. Gastrointestinal toxicity manifesting as nausea, vomitingordiarrhea is caused by almost all antiretroviral drugs. Nausea is commonly associated with zidovudine and diarrhea is most common with protease inhibitors particularly tnefonavir. (Sharma *et al*., 2008; Maniar and Desai, 2000; Robinson *et al*., 2008) Peripheral neuropathy was observed in 11.11% (18/152) patients, 3.08% (5/162) patients had severe symptomatology which required treatment modification, stavudine was replaced by zidovudine.

Table 1. Characteristics of the patients enrolled

Characteristics	Number of patients (%) (n = 162)
Gender	
Male	94 (58.05)
Female	68 (41.98)
Age in years	
< 35	89 (58.55)
> 35	63 (41.45)
CD4+ T-cell counts at presentation	
< 200	108 (71.05)
> 200	44 (28.95)
Patients with ADR	118 (72.28)
Male patients with ADR	50 (42.37)
Female Patients with ADR	68 (57.62)
CD4 countin patients with ADR	
ART regimen	
AZT + 3TC + NVP	90 (59.21)
d4T + 3TC + NVP	45 (29.61)
d4T + 3TC + EFV	17 (11.18)

Table 2. Distribution of types of ADRs in the study (number of ADR events, n=118)

Types of ADRs	Total ADR events		Severe ADR events	
	Male No. (%)	Female No. (%)	Male No. (%)	Female No. (%)
Anaemia	13 (9.84)	18 (13.63)	4 (3.03)	7 (5.30)
Rashes	11 (8.33)	15 (11.36)	4 (3.03)	7 (5.30)
Hepatic	3 (2.27)	5 (3.78)	3 (2.27)	5 (3.78)
Gastritis	2 (1.51)	5 (3.78)	–	2 (1.51)
Diarrhoea	1 (0.75)	1 (0.75)	–	–
Peripheral neuropathy	7 (5.30)	11 (8.33)	2 (1.51)	3 (2.27)
Vivid dreams and sleep disturbance	1 (0.75)	1 (0.75)	–	–
Dyslipidemia	7 (5.30)	10 (7.57)	–	–
Lipodystrophy	5 (3.78)	2 (1.51)	–	–
Total	50(42.37)	68(57.62)	13(11.01)	24(20.33)

Table 3. Relationship of ADRs with CD4+ T-cell counts

CD4+ T-cell counts/ mm^3	No. of patients (n = 162) No. (%)	No. of ADR events (n = 118) No. (%)
< 200	115 (70.99)	86 (72.88)
> 200	47 (29.01)	32 (27.12)

In various studies the incidence of peripheral neuropathy has been reported between 3% to 22% with treatment modification insevere cases (WHO grade III and IV). (Sivasdasan *et al*., 2009; Maggiolo *et al*., 2007; Sharma *et al*., 2008; Maniar and Desai, 2000; Canestri *et al*., 2007) Peripheral neuropathy is a known side effect associated with HAART, and is mainly seen with didanosine, zalcitabine or stavudine. Various studies have shown that these agents inhibit nerve growth factor (NGF)-stimulated differentiation of a normal cell line. (Lieketseng *et al*., 2015; Maniar and Desai, 2000) Patients may get symptomatic relief with analgesics, tricyclic antidepressants with varying results. However, the patients who develop neuropathy while on HAART need to be carefully evaluated and the dosage may be decreased or the offending agent discontinued.

Neuropsychiatric complications are also known to occur with ARV agents, particularly NNRTI's – efavirenz, delavaridine and nevirapine, particularly most commonly associated with efavirenz. (Maniar and Desai, 2000) In our study, only two patients had neuropsychiatric manifestations in form of vivid-dreams and disturbed sleep pattern which was mild and transient. Incidence of about 2.2% has been reported in literature. (Sharma *et al*., 2008) Dyslipidemia manifesting as hypercholesteremia and hyper-triglyceridemia was observed in 9.87% (16/162) of the patients. Two (1.23%) patients had significant dyslipidemia (serum cholesterol >400 mg%, serum triglyceride >400 mg%). Lipodystrophy was observed in 7 (4.32%) of the patients. In various studies the incidence of about 2% to 14% has been reported using NRTI and NNRTI based HARRT regimen. (Patel *et al*., 2006; Maniar and Desai, 2000) Metabolic dearrangements associated with the use of HAART calls for clinical concerns about their use. Dyslipidemia could lead to cardiac disease and other related vascular diseases. Protease inhibitors are most commonly associated with metabolic dearrangement and NRTI's especially stavudine. (Nderitu *et al*., 2013; Treisman and Kaplin, 2002) Lipodystrophy syndrome is associated with peripheral fat loss in the face, limbs and buttocks and accompanied by central fat accumulation in the abdomen and breasts and over the dorsocranial spine. Stavudine associated lipodystrophy commonly presents as lipoatrophy. The pathogenesis of lipodystrophy is poorly understood or most likely multifactorial with combined endocrine and metabolic abnormalities having profound effect on distribution of body fat. (Montessori *et al*., 2004) It has to be stressed that majority of patients are able to tolerate HAART well, even over the years. The monitoring of treatment toxicity by an HIV clinician is recommended in at least three monthly intervals, even in asymptomatic patients, and more often at the beginning of a new HAART. Standard evaluations (including drug allergies and other side effects), physical examination, measurement of vital signs and body weight, as well as routine investigations including a full blood count, liver, pancreas and renal function tests, electrolytes, fasting cholesterol, triglycerides and glucose levels have to be regularly monitored. At the same time, patient should be counseled in detail about potential side effects in order to be able to recognise them and to consult physician in some. In our study, we also graded the ADRs. The main aim of grading the severity of ADRs was to improve early detection and proper management of ADRs, so as to improve the compliance and decrease the associated morbidity and mortality. Therapeutic of HIV patient is further complexed because of other adjunctive medications which most of these patients are prescribed when suffering from other conditions such as tuberculosis, fungal infections, Pneumocystis jeroveci and lymphoma, etc. One has to consider drug-drug interactions between ART and drugs given to treat concomitant illness. This leads to further increase in incidence of side effects of ART and decrease in compliance. The newer additions in the HAART in NRTI class like tenofovir and abcavir, and protease inhibitors, the other class of ART, as a part of second line regimen in free ART programme also need consideration when NRTI use is not possible. There is always a balancing act for the physician when he starts patient on HAART. The initial regimen should be the best possible so as to be able to effectively suppress the virus and to improve compliance. The multiplications of present ART programme would lead to an educated, updated and efficacious implementation of free ART services, which would also lead to long term success of this programme and also help the PLHA to lead purposeful and productive life.Our study has several possible limitations. Cohort surveillance was not active. Plasma viral load and serum lactate testing were not performed. Our patients might not be complete representative of HIV infected patients in India. We studied patients who were followed up in a medical college. Therefore, care should be taken in extrapolating these results.

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