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Research Article

A prospective observational study of adverse drug reactions to antiretroviral therapy: type and risk factors in a tertiary care teaching hospital

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ABSTRACT

Background: To collect demographic details of patients receiving antiretroviral therapy (ART) and study type of adverse drug reactions (ADRs) and risk factors for ADRs to ART and to assess causality, severity, and preventability assessment of the reported ADRs.
Methods: A prospective observational study was conducted for 6 months from January 2012 until June 2012 at ART Center, KR Hospital of Mysore Medical College & Research Institute, Mysore. Data were evaluated for patient demography, risk factors for ADRs, type of ADRs. ADRs were also assessed for their causality, severity, and preventability as per the standard algorithm, using SPSS for windows (version 16.0).
Results: Out of 158 patients evaluated, majority were of age group of 21-40 years (66.5%). More number of illiterate patients (55.7%) showed ADRs to ART. Most patients were of CD4 count <250 cells/µl (65.82%). Most common regimen which caused ADRs was zidovudine + lamivudine + nevirapine. Most common type of ADRs was anemia (55.06%) and rash (25.31%). On evaluation of the causality of ADRs, majority were found to be possible (89.24%). The severity assessment showed that most of the patients ADRs were of level 3 (93.05%). The preventability assessment showed that 30.38% patients ADRs were preventable.
Conclusion: Identifying risk factors are of crucial importance to optimize the initial choice of ARVs regimen before initiating therapy and to prevent severity and complications caused by ART, thereby improving the quality of care to patients on ART.

Keywords: Adverse drug reactions, Antiretroviral therapy, Causality assessment, Severity assessment, Preventability assessment

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a global problem. It has now been reported from more than 190 countries around the world and a pool of human immunodeficiency virus (HIV) infected persons in Africa and Asia is large and expanding.[1] Today, around 4.87 million people are living with HIV in South, East, and South-east Asia. In India, an estimated 0.1% of adults aged 15-49 years are living with HIV; however, with a population of around 1 billion, this actually equates to 2.3 million adults living with HIV in India.[2,3]

Growing socio-economic burden of the disease in India led to the inception of National AIDS Control Organization (NACO) in the year 1986 and subsequently in the formation of National AIDS program in the year 1987. Antiretroviral therapy (ART) became the keystone of National AIDS program. Highly active antiretroviral therapy (HAART) presently is a lifelong therapy. Most of the drugs which are available and approved for use in HAART have some or the other adverse effects, thus treatment of HIV infection has become a complicated balancing act between the benefits of durable HIV suppression and the risks of drug toxicity.[4]

Although current antiretroviral regimens are potent from an antiviral perspective, they often fail because of patient non-adherence. To optimize adherence and hence efficacy, clinicians must focus on preventing adverse effects whenever possible, and distinguishing those that are self-limited from those that are potentially serious.[5] An estimated 33 million people are living with HIV infection and around 3 million people have access to ART worldwide. Unfortunately adverse effects of these drugs are of serious concern.[6]

The introduction of HAART has led to a significant reduction in AIDS related morbidity and mortality. Unfortunately, up to 25% of all patients discontinue their initial HAART regimen because of treatment failure, toxic effects or noncompliance within the first 8 months of therapy.[7] The major individual toxicities include bone marrow suppression (zidovudine [AZT]), pancreatitis (didanosine), hypersensitivity (abacavir), hepatic necrosis (nevirapine [NVP]), neuropsychiatric complaints (efavirenz), and nephrolithiasis (indinavir).[8]

There is a lack of awareness and inadequate training about drug safety monitoring among health care professionals in India. Often ADRs go unnoticed or are not reported. Monitoring and reporting of ADRs to ART is very important. Hence, the study will be conducted with the following objectives:

1. To collect demographic details of patients receiving ART and study risk factors for adverse drug reactions (ADRs) to ART.
2. To assess causality, severity, preventability assessment of the reported ADRs.

METHODS

The study protocol along with the proforma and informed consent in vernacular language was approved by the Institutional Ethical Committee before starting the study. A prospective observational study was conducted for 6 months from January 2012 to June 2012 at ART Center, KR Hospital of Mysore Medical College & Research Institute, Mysore.

Proforma contained patient identification data, personal history, family history, risk factor details, antiretroviral treatment history, antiretroviral treatment, laboratory investigations, ADR details & its assessment, and patient follow-up details.

Inclusion criteria

1. Both newly and previously registered HIV positive patients who were on ART.
2. Patients of either sex.
3. Patients who gave written informed consent.

Exclusion criteria

1. Patients unable to respond to verbal questions.
2. Pregnant/lactating females.
3. Patients with concomitant disorders such as diabetes mellitus and hypertension.

Essential laboratory investigations such as hemoglobin, total leukocyte count, differential leukocyte count, erythrocyte sedimentation rate, serum creatinine, blood urea, serum bilirubin, SGOT, SGPT, blood sugar, VDRL, HBsAg, anti-HCV, and CD4 count. Additional laboratory investigations like chest X-ray was done, whenever needed.

Data were evaluated for patient demography, risk factors for ADRs and type of ADR.

Demographic details of patients (Table 1) with the following characteristic such as:

1. Age.
2. Gender.

Table 1: Demographic details of the patients.

Sr. no.	Characteristic	n=158	%
1.	Gender		
	Male	80	50.6
	Female	78	49.4
2.	Age (years)		
	<20	8	5.1
	21-40	105	66.5
	41-60	44	27.8
	>60	1	0.6
3.	Weight (kg)		
	<35	22	13.9
	36-55	107	67.7
	56-75	28	17.8
	>75	1	0.6
4.	Residence		
	Urban	73	46.2
	Rural	85	53.8
5.	Literacy		
	Literate	70	44.3
	Illiterate	88	55.7
6.	Employment		
	Employed	110	69.6
	Unemployed	48	30.4
7.	CD4 count (cells/µl)		
	<250	104	65.82
	>250	54	34.18
8.	Regimen		
	AZT+3TC+NVP	105	66.45
	d4T+3TC+EFV	7	4.43
	AZT+3TC+EFV	32	20.25
	d4T+3TC+NVP	13	8.22
	Emtricitabine+tenofovir	1	0.63

3. Literacy.
4. Employment.
5. Marital status.
6. Residence.
7. CD4 count.
8. ART.

ADRs were also assessed for their causality, severity, and preventability using Naranjo's algorithm, Hartwig and Seigel scale, and modified Shumock and Thornton criteria respectively (Table 2).

Statistical analysis was performed using SPSS for windows (version 16.0). Methods applied were frequencies, crosstabs, and Chi-square test.

RESULTS

Out of 158 patients evaluated, majority were of age group of 21-40 years (66.5%). More number of illiterate patients (55.7%) showed ADRs to ART. Most patients were of CD4 count <250 cells/µl (65.82%).

Most common regimen which caused ADRs was AZT + lamivudine (3TC) + NVP. Most common types of ADRs were anemia (55.06%) and rash (25.31%).

On evaluation of the causality of ADRs, majority were found to be possible (89.24%). The severity assessment showed that most of the patients ADRs were of level 3 (93.05%). The preventability assessment showed that 30.38% patients ADRs were preventable.

Most common regimen which caused ADRs was AZT + 3TC + NVP and AZT + 3TC + EFV.

Table 2: Type of ADR and its assessment.

Sr. no.		n=158	%
1.	ADR type		
	Anemia	87	55.06
	Rash	40	25.31
	Hepatotoxicity	11	6.99
	Vomiting	17	10.75
	Lichenoid rash	1	0.63
	Rash, vomiting	2	1.26
2.	Causality assessment		
	Possible	141	89.24
	Probable	17	10.75
3.	Severity assessment		
	Level 1	9	5.69
	Level 3	147	93.05
	Level 4	2	1.26
4.	Preventability assessment		
	Preventable	48	30.38
	Not preventable	110	69.62

DISCUSSION

AIDS is a global problem. Many drugs have been approved for the treatment of HIV, but the adverse effects of HAART has become a complicated balancing act between the benefits of durable HIV suppression and the risks of drug toxicity.

There is a lack of awareness and inadequate training about drug safety monitoring among health care professionals in India. Often ADRs go unnoticed or are not reported. Monitoring and reporting of ADRs to ART is very important to improve the quality of care to patients.

Majority were of age group of 21-40 years which indicates middle age group were affected. More number of illiterate patients showed ADRs to ART, which shows the ignorance and lack of knowledge and education regarding the disease.

Most patients were of CD4 count <250 cells/µl when ART was initiated and they experienced more frequent and severe ADRs to ART when compared to patients with higher CD4 count.

In our study, age group of 21-40 years (66.5%) has been affected with more ADRs to ART. A study from Kadapa, India showed age group of 17-40 years were more affected.[9] A study from Nigeria showed age group of 16-45 years were more affected.[10]

In our study, incidence of ADRs to ART in males and females did not show any significant difference (males 50.6%, females 49.4%) and CD4 count of <250 cells/µl were affected with more ADRs (65.82%) (Figure 1). A study from Kadapa, India showed the majority of ADRs were observed in males (60%) and CD4 count of <250cells/µl were affected with more ADRs.[9]

In our study, AZT + 3TC + NVP was the most common regimen which caused ADRs like the study from Nigeria.[10] A study from Chhattisgarh showed stavudine (d4T) + 3TC + NVP was the most common regimen which caused ADRs.[8]

In our study, anemia (55.06%) and rash (25.3%) were found to be most common type of ADR. A study from Vadodara, India unlike our study it showed that cutaneous ADR was most common (44.4%), then next was hematological

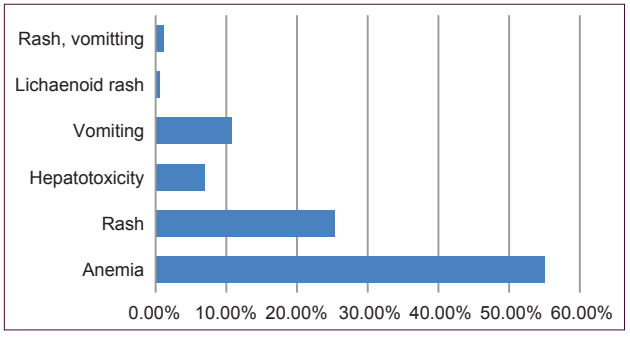

Figure 1: Type of ADR and its percentage.

ADR (32.2%).[5] In another study by Kumarasamy et al., the most common ADRs were peripheral neuropathy, anemia and nail hyperpigmentation.[11]

A study by Sivadasan et al. clearly showed that adverse effects of various drugs of the HAART regimen were one of the major reasons for treatment change.[12]

Anemia (55.06%) was seen with AZT + 3TC + NVP/EFV regimen, an improvement in the Hb level was observed on discontinuation of AZT, which was similar to other studies.[13,14] In our study, patients initiated on AZT based regimen only if they had Hb levels more than 9 g%. Initially, every 15 days monitoring was done recording Hb%, later monthly monitoring was done. AZT based regimen was substituted with d4T based regimen in patients who experienced anemia.

Rash (25.31%) was seen with the NVP based regimen. It was treated conservatively and regimen of AZT/d4T + 3TC + NVP was substituted with AZT/d4T + EFV regimen, when an improvement was observed on discontinuation of NVP and substituted with EFV.

Hepatotoxicity (6.96%) was associated with NVP and EFV and elevated levels of SGOT, SGPT, and bilirubin levels were seen.

Vomiting (10.75%) was associated with AZT. Cases were admitted, observed for 3 days and during that period discontinuation of AZT was done and cases were treated conservatively, which was similar to that observed in an Iranian study.[15]

Carrying out the causality assessment using standard methods is one of the best ways to establish the causal relationship between a drug and its effect. The Naranjo algorithm is widely used in carrying out the causality assessment of ADRs (Figure 2).[16] It is based on the scores calculated on the basis of points given for each of ten questions that comprise the algorithm. If the score is >9, then the adverse reaction is categorized as definitely caused by the particular drug. A score of 5-8 is categorized as probably caused by the drug and a score of 1-4 is categorized as possibly caused by the drug. On evaluation of the causality of ADRs, majority were found to be possible (89.24%).

In order to take proper initiatives toward the management of ADRs, it is necessary to study the severity of ADRs. Hartwig's scale is widely used for this purpose.[17] This scale categorizes the reported adverse drug reactions into different levels. As shown in Figure 3, the severity assessment showed that most of the patients ADRs were of level 3 (93.05%).

The preventability assessment (Figure 4) done by using modified Shumock and Thornton criteria[18] showed that 30.38% patients ADRs were preventable.

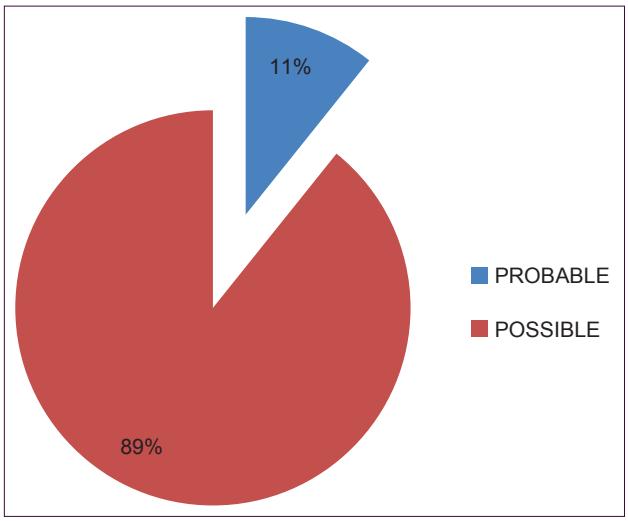

Figure 2: Causality assessment.

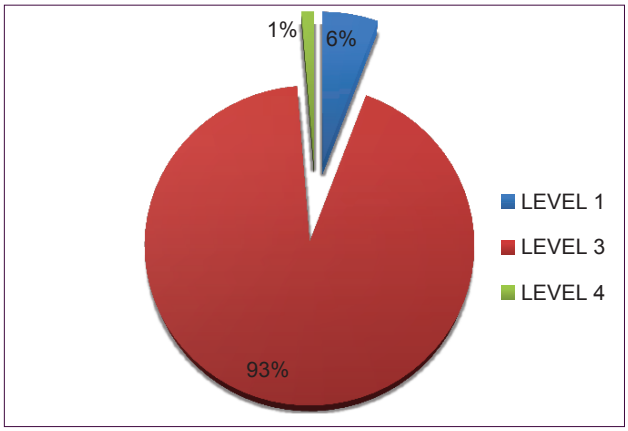

Figure 3: Severity assessment.

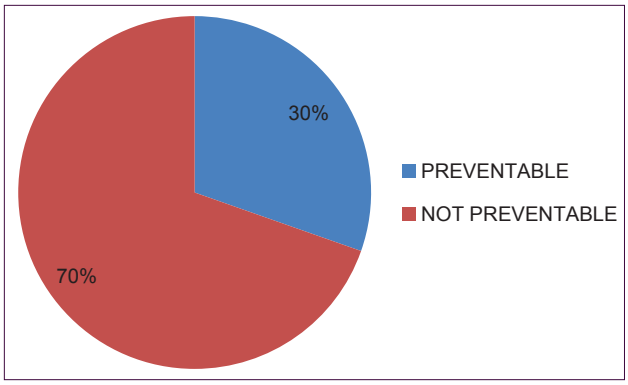

Figure 4: Preventability assessment.

CONCLUSION

Identifying risk factors such as age, sex, regimen, and CD4 count for the occurrence of ADRs is of crucial importance to optimize the initial choice of ARVs regimen before initiating therapy and to prevent severity and complications caused by ART.

ART with AZT+3TC+NVP/EFV is a predictor of ADRs. HIV patients who are of age group 21-40 years, illiterates,

CD4 count < 250 cells/µl need intensive monitoring of ADRs, thereby improving quality of care to patients on ART.

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