Rajesh R, Vidyasagar S, Nandakumar K. Highly active antiretroviral therapy induced adverse drug reactions in Indian human immunodeficiency virus positive patients. Pharmacy Practice (Internet) 2011 Jan-Mar;9(1):48-55.

Original Research

Highly active antiretroviral therapy induced adverse drug reactions in Indian human immunodeficiency virus positive patients

Radhakrishnan RAJESH, Sudha VIDYASAGAR, Krishnadas NANDAKUMAR.

Received (first version): 9-Aug-2010 Accepted: 24-Dec-2010

ABSTRACT*

Objective: To assess the incidence, severity pattern, causality, predictability and preventability of adverse drug reactions (ADRs) and to identify risk factors for adverse drug reactions in highly active antiretroviral therapy.

Methods: Enrolled patients were intensively monitored for ADRs to highly active antiretroviral therapy. Predictability was assessed based on history of previous exposure to the drug or literature incidence of ADRs. Preventability was assessed using Schumock and Thornton criteria and severity was assessed using modified Hartwig and Siegel scale. Multivariate logistic regressions were used to identify the risk factors for ADRs.

Results: Monitoring of 130 retropositive patients by active pharmacovigilance identified 74 ADRs from 57 patients. Anemia and hepatotoxicity were the most commonly observed ADRs. The organ system commonly affected by ADR was red blood cell (21.4%).The ADRs were moderate in 77% of cases. Type A reactions (77%) were more common. A total of 10.8% ADRs were definitely preventable. The incidence rate of ADRs (65.9%) was highest with Zidovudine + Lamivudine + Nevirapine combination. A total of 84% interruptions to highly active antiretroviral therapy were due to toxicity. CD4 less than 200 cells/µl, female gender and tuberculosis were observed as risk factors for ADRs.

Conclusion: Incidence of ADRs in intensively monitored patients was found to be 43.8%. Anemia in HIV patients is an influential risk factor for occurrence of ADRs. With the increasing access to antiretroviral in India, clinicians must focus on early detection and prevention of ADRs to highly active antiretroviral therapy.

Keywords: Drug Toxicity. Antiretroviral Therapy, Highly Active. India.

REACCIONES ADVERSAS INDUCIDAS POR TRATAMIENTOS ANTIRETROVIRALES ALTAMENTE ACTIVOS EN PACIENTES INDIOS POSITIVOS AL VIRUS DE LA INMUNODEFICIENCIA HUMANA

RESUMEN

Objetivo: Evaluar la incidencia, gravedad, causalidad y preventabilidad de las reacciones adversas medicamentosas (RAM) e identificar los factores de riesgo de esas RAM en terapias de antiretrovirales altamente activos.

Métodos: Se monitorizó intensamente a los pacientes incluidos a la búsqueda de RAM. La predecibilidad se evaluó con base en la historia de exposiciones previas al medicamento o a la incidencia de RAM en la literatura. La preventabilidad se valoró usando los criterios de Schumock y Thornton y la gravedad se evaluó utilizando la escala modificada de Hartwig y Siegel. Se utilizaron regresiones logísticas multivariadas para identificar los factores de riesgo de RAM.

Resultados: La monitorización retrospectiva de 130 pacientes mediante farmacovigilancia activa identificó 74 RAM de 57 pacientes. Anemia y hepatotoxicidad fueron las RAM más comúnmente observadas. El sistema comúnmente afectado por las RAM fueron las células rojas sanguíneas (21,4%).

Las RAM fueron moderadas en el 77% de los casos. Las reacciones tipo A fueron las más comunes. Un total del 10,8% de RAM fueron definitivamente prevenibles. La incidencia de RAM más alta fue con la combinación Zidovudina + Lamivudina + Nevirapina. Un 84% de las interrupciones de terapias antiretrovirales altamente activas fue debido a la toxicidad. Se observaron como factores de riesgo de RAM un CD4 en menos de 200 cel/µl, el género femenino y la tuberculosis.

Conclusión: La incidencia de RAM en pacientes intensivamente monitorizados fue del 43,8%. La anemia en pacientes con VIH es u7n factor d e riesgo de influencia en la aparición de RAM. Con el creciente uso de antiretrovirales en India, los clínicos deben centrar la atención en la detección temprana y la prevención de RAM de terapias antiretrovirales altamente activos.

* Radhakrishnan RAJESH. M.Pharm, Senior Grade Lecturer. Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal University. Manipal (India).
Sudha VIDYASAGAR. MD. Professor and Head of the department of Medicine, Kasturba Medical College, Manipal University. Manipal (India).
Krishnadas NANDAKUMAR. M.Pharm, PhD, Associate Professor. Department of Pharmacology, Manipal College of Pharmaceutical Sciences, Manipal University. Manipal (India).

Palabras clave: Drug Toxicity. Antiretroviral Therapy, Highly Active. India.

INTRODUCTION

An estimated 33 million people are living with human immunodeficiency virus (HIV) infection and around 3 million people have access to highly active antiretroviral therapy (HAART) worldwide.[1,2] The introduction of highly active antiretroviral therapy (HAART) has led to a significant reduction in AIDS-related morbidity and mortality.[3-5] Unfortunately, up to 25% of patients discontinue their initial HAART regimen because of treatment failure (inability to suppress HIV viral replication to below the current limit of detection, 50 copies/ µl), toxic effects or noncompliance within the first eight months of therapy.[6,7] There is considerable experience in the developed world with the use of antiretroviral medicines. These medicines are associated with significant safety concerns including serious ADRs, with both short and long term effects. The outcome of these long-term adverse effects is unknown. In India, often adverse drug reactions (ADRs) go unnoticed or are not reported. Monitoring and reporting of ADRs to HAART in the Indian population is very important. The Indian government has continued efforts to expand access to highly active antiretroviral therapy. Phase-III of the Indian national AIDS control programme is estimated to spend INR 13340 million (USD266 million) for HAART by 2011.[8]

The Indian National Pharmacovigilance Programme lacks continuity. There is a lack of awareness and inadequate training about drug safety monitoring among healthcare professionals in India. To our knowledge, this systematic study conducted in India concerning ADRs to HAART in retropositive patients will help physicians gain a working knowledge of these adverse effects, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment, promoting the early recognition and reversal of potentially serious adverse effects, and reducing the potential for adverse drug interactions. This study was conducted to assess the incidence, prevalence, severity pattern, causality, predictability, preventability of ADRs to HAART, and to identify risk factors for ADRs in HIV positive patients receiving HAART.

METHODS

The study was conducted at the medicine department, Kasturba Hospital, Manipal, India. The study was approved by the Institutional Ethics Committee of Kasturba Hospital, Manipal. Active pharmacovigilance (intensive monitoring by active follow-up after treatment and the event may be detected by asking patients directly or screening patient records) were adopted. HIV positive patients with fixed dose of highly active antiretroviral therapy were included. Written informed consent was obtained from these patients. Between August 2009 and March 2010, these patients were intensively monitored on a daily basis by a graduate trainee clinical pharmacist for ADRs during Hospitalization and at follow-up visit at the outpatient department (an initial outpatient visit after a 4 week period, followed by monthly visits).

Demographic details, medical history, diagnosis, drugs used during hospital stay and duration of stay in hospital was recorded in a data collection form. The details of suspected ADRs including drugs involved, treatment given for ADRs and patient's outcome was documented in a suitably designed ADR documentation form. ADR notification forms were used to report suspected ADRs. ADRs were identified by an interview with the patient and/or their attendants, as well as a review of in-patient case records, laboratory reports, clinician's notes and prescriptions at each follow-up visit. Suspected ADRs documented with necessary information were reviewed and assessed by a senior academic clinical pharmacist. Wherever appropriate, suspected ADRs were discussed with the clinicians.

The World Health Organization (WHO) ADR probability scale and Naranjo's algorithm were used for causality assessment.[9,10] Severity of ADRs was assessed using the modified Hartwig and Siegel scale.[11] If the drug had previously been well tolerated by the patient at the same dose and route of administration, the ADR was considered as 'not predictable'. If there was a history of allergy or reactions to the drug during previous exposure, the ADR was considered 'predictable'. In patients who had never received the drug previously, any ADR with a literature incidence of 1/100 was considered 'predictable'. Modified Shumock and Thornton criteria were used to assess the preventability of ADRs.[12] Adverse drug reactions were coded using WHO-Adverse Reaction Terminologies (WHO-ART).[13] Seriousness of the ADRs was assessed as defined by International conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH).[14] Anaemia occurred in patients receiving zidovudine containing regimen were graded according to the WHO/ACTG criteria. Prevalence was calculated by considering the ratio of number of patients with ADRs and total number of HIV positive patients involved in the study. Incidence rate was calculated by considering the ratio of ADRs and the exposure (person – time at risk).

Patients who had experienced and had not experienced ADRs were compared with Pearson Chi Square tests for categorical variables and by Mann Whitney U test for continuous variables. Risk factors for ADRs were determined at a P value <0.05 by investigating the effects of gender, age, body mass index, CD4 count, concomitant drugs, and opportunistic infections. Multivariate logistic regression was used to evaluate the influence of these risk factors on development of ADRs. All statistical calculations were performed using Statistical Package for Social Science (SPSS) Version 17.0. A p-value of <0.05 was considered as statistically significant.

Table 1. Demographic detail of the patients.

Characteristic	Number of Patients n=130 (%)	Number of ADRs to HAART n=74 (%)	Number of Patients with ADR / Total no. of patients; Incidence (%)	Overall Incidence of ADRs (%)
Gender				(43.8)
Male	100 (76.9)	51 (68.9)	42/100; (42)	
Female	30 (23.0)	23 (31.0)	15/30; (50)	
Age (years)				
18-40	58 (44.6)	38 (51.3)	29/58; (50)	
41-60	67 (51.5)	32 (43.2)	24/67; (35.8)	
≥ 60	5 (3.8)	4 (5.4)	4/5; (80)	

RESULTS

A total of 130 retropositive patients with highly active antiretroviral therapy [100 males (76.9%)] and [30 females (23.0%)] were admitted to the hospital during this period. Out of 130 retropositive patients enrolled, number of patients with ADRs were 57 [males (42)] and [females (15)].Number of ADRs to highly active antiretroviral therapy during the eight month study period were 74 [51males (68.9%)] and [23 females (31.0%)]. The majority of patients with ADR were adults (51.3%), but patients aged 60 years and above (5.4%) were also included. The prevalence of ADRs in our study was higher in female population [50% (15/30)] compared to males [42% (42/100)].The incidence rates of ADRs was higher in age group greater than 60 years (80%). In our study, the overall incidence of ADR to highly active antiretroviral therapy was found to be 43.8% (Table 1).

Of the 57 suspected ADRs 42(73.6%) developed one ADR, 13(22.8%) developed two ADRs, 2 patients (3.5%) developed three ADRs (Figure 1). The CD4 count in the majority of patients (79.8%) with ADR was ≤200 cells/µl. HAART regimen commonly implicated in ADRs was noted with Zidovudine + Lamivudine + Nevirapine combination (39.1%).Type A adverse drug reactions (77%) were more common compared to Type B adverse drug reactions (22.9%). In the majority of ADRs, occurrence was reported during hospital stay (44.5%) followed by ADRs that required hospitalization or increased the hospital stay (35.1%) included Steven Johnson syndrome, hepatitis and anaemia. During the study, (59.6%) ADRs to antiretrovirals were observed due to polypharmacy as presented in (Table 2).

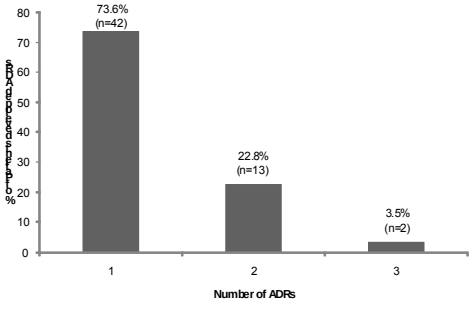

Figure 1. Number of Adverse drug reactions reported vs. % of Patients.

Table 2. Characteristic details of the adverse drug reactions (ADRs).

Characteristic (n=74)	N (%)
CD4 Count (Cells/µl)	
≤ 200	59 (79.8)
>200	15(20.2)
Classification of ADRs	
Type A	57(77)
Type B	17(22.9)
Occurrence of ADRs	
ADRs during hospital stay	33(44.5)
ADRs at the time of admission	26(35.1)
Previous exposure of ADRs	15(20.4)
Polypharmacy	
Minor (Two to three drugs)	5(6.7)
Moderate (Four to five drugs)	25(33.7)
Major (Greater than five drugs)	44(59.6)
Common HAART regimen implicated in ADRs	
Zidovudine+Lamivudine+Nevirapine	29 (39.1)
Zidovudine+Lamivudine+Efavirenz	11 (14.8)
Tenofovir+Emtricitabine+Efavirenz	9 (12.1)
Stavudine+Lamivudine+Nevirapine	8 (10.8)
Stavudine+Lamivudine+Efavirenz	7 (9.4)
Tenofovir+Lamivudine+Efavirenz	3 (4.0)
Tenofovir+Emtricitabine+Indinavir+Ritonavir	2 (3.2)
Tenofovir+Emtricitabine+Lopinavir+Ritonavir	2 (2.7)
Stavudine+Lamivudine+Tenofovir	1 (1.3)
Tenofovir+Emtricitabine+Atazanavir+Ritonavir	1 (1.3)
Abacavir+Lamivudine+Atazanavir+Ritonavir	1 (1.3)

The organ system affected in the majority of ADRs was red blood cells (21.4%) followed by gastro-intestinal (GI): (15.4%), white cell and RES; (14.2), skin and appendages; (10.7%). Psychiatric disorders and Urinary system disorder (2.3%) were the least observed (Table 3). Higher incidence rate of ADRs was noted with Zidovudine + Lamivudine + Nevirapine combination (65.9%), while the incidence rate of ADRs was lowest with Tenofovir + Lamivudine + Efavirenz (21.4%) (Table 4). The commonly observed ADRs were hepatotoxicity (10) followed by anaemia (9), pancytopenia (7) and peripheral neuropathy (6) (Table 5).

In the majority of ADRs, causality was 'probable' (63.5%) and 'possible' (35.2%) by WHO probability scale. Using Naranjo's algorithm, causality was 'possible' and 'probable' in 63.5% and 35.2% cases, respectively (Table 6). Of the 74 ADRs, 69 (93.2%) were 'predictable' and 5 (6.8%) were 'non predictable'. The majority of ADRs (45.9%) were 'probably preventable' and 10.8% ADRs were 'definitely preventable' while 43.3% of ADRs were 'non-preventable' (Table 7).

Table 3 Organ System affected due to Adverse drug reactions to HAART (system organ class codes WHO-ART)

	% of ADRs
Skin and Appendages (0100)	10.7
Vascular (1040)	1.1
Central peripheral nervous system (0410)	9.5
Gastro intestinal (0600)	15.4
Red blood cell (1210)	21.4
White cell and RES(1220)	14.2
Platelet, bleeding and clotting (1230)	1.1
Urinary system disorder (1300)	2.3
Liver and biliary disorder (0700)	15.4
Psychiatric (0500)	2.3
Metabolic and Nutritional (0800)	1.1
Body as a whole (1810)	3.5
Resistance mechanism disorders (1830)	1.1

Table 4. Incidence rate of ADRs to Individual HAART regimens.

HAART regimen implicated in ADRs (No. of ADR n=74 /)	Total no. of Prescriptions; Incidence (%)
Zidovudine+Lamivudine+Nevirapine	29/44 ; (65.9)
Stavudine+Lamivudine+Nevirapine	8/14 ; (57.1)
Zidovudine+Lamivudine+Efavirenz	11/24 ; (45.8)
Tenofovir+Emtricitabine+Efavirenz	9/30 ; (30)
Stavudine+Lamivudine+Efavirenz	7/24 ; (29.1)
Tenofovir+Lamivudine+Efavirenz	3/14 ; (21.4)
Stavudine+Lamivudine+Tenofovir	1/1; (100)
Tenofovir+Emtricitabine+Indinavir+Ritonavir	2/1 ; (200)
Tenofovir+Emtricitabine+Lopinavir+Ritonavir	2/4 ; (50)
Tenofovir+Emtricitabine+Atazanavir+Ritonavir	1/2; (50)
Abacavir+Lamivudine+Atazanavir+Ritonavir	1/1 ; (100)

Almost all the ADRs that were 'moderate' in severity were required discontinuation of suspected drug(s). The suspected drug was withdrawn in 73% (54/74) of ADRs. Symptomatic treatment was given in most of the ADR cases. The majority of the patients recovered from the ADR at the time of discharge [83.8% (62/74)] while a small but notable number [8.1% (6/74)] continued to suffer even at their last follow-up visit. Out of 130 patients followed for 8 months, 6 adverse drug reactions with unknown outcome of management to ADRs were noted as these patients discharged from hospital against medical advice, resulted in lost to follow up. (Table 8).

Among 130 retropositive patients, 50 patients was observed on discontinuation of highly active antiretroviral therapy due to toxicity of antiretroviral therapy (84%) followed by treatment failure (12%) and to toxicity of other drugs (4%).

Zidovudine use was observed as a risk factor for ADRs like anaemia and vomiting. Stavudine use was identified as a risk factor for peripheral neuropathy while nevirapine use and female gender were the risk factors for skin rashes. Regression analysis identified, CD4 count <200 cells/µl, female gender, concurrent tuberculosis as risk factors for ADRs (Table 9).Concurrent tuberculosis was the only influential risk factor for development of ADRs identified in a logistic regression. Age, Body mass index, concomitant drugs, candidiasis, herpes zoster and syphilis were not significantly associated with the development of ADRs.

Table 5. Adverse drug reactions to antiretroviral in intensively monitored patients.

Adverse drug reaction	Number of ADRs n=74 (%)
Hepatotoxicity	10 (13.5)
Grade 1(1.25-2.5×ULN)	1(1.3)
Grade 2(2.6-5×ULN)	4(5.4)
Grade 3(5.1-10×ULN)	2(2.7)
Grade 4(>10×ULN)	3(4.0)
Anaemia (Hb in gm/dl)	9 (12.1)
Grade 1(9.5-10.5)	2(2.7)
Grade 2 (8.0-9.4)	5(6.7)
Grade 3 (6.5-7.9)	1(1.3)
Grade 4 (<6.5)	1(1.3)
Pancytopenia	7 (9.4)
Vomiting	7 (9.4)
Peripheral neuropathy	6 (8.1)
Skin rash	4 (5.4)
Drug hypersensitivity syndrome	4 (5.4)
Diarrhoea	3 (4.0)
Bicytopenia	2 (2.7)
Hyperbilirubinemia	2 (2.7)
Renal failure	2 (2.7)
Rash maculopapula	1 (2.5)
Depression	1 (1.3)
Dyslipidemia	1 (1.3)
Erythrema multiform	1 (1.3)
Headache	1(1.3)
Hepatic Infiltration	1 (1.3)
Hyper pigmentation	1 (1.3)
Gastritis	1 (1.3)
Giddiness	1 (1.3)
Insomnia	1(1.3)
Immune reconstitution inflammatory syndrome	1(1.3)
Itching	1 (1.3)
Leucopenia	1 (1.3)
Neutropenia	1 (1.3)
Pancreatitis	1 (1.3)
Spongiotic dermatitis	1 (1.3)
Vasculitis	1 (1.3)
Steven Johnson Syndrome	1 (1.3)

ULN, Upper limit of normal range

Table 6. Causality of adverse drug reactions.(n=74)

Causality	Number of ADRs, (%)
WHO scale	
Certain	1(1.3)
Probable	47(63.5)
Possible	26(35.2)
Naranjo's algorithm	
Definite	1(1.3)
Probable	47(63.5)
Possible	26(35.2)

Table 7. Preventability and Predictability of adverse drug reactions.(n=74)

	Number of ADRs, (%)
Preventability	
Definitely preventable	8(10.8)
Probably preventable	34(45.9)
Not preventable	32(43.3)
Predictability	
Predictable	69(93.2)
Not predictable	5(6.8)

DISCUSSION

This is the first study assessing the incidence, prevalence, severity pattern, causality, predictability, preventability and associated risk factors of ADRs to highly active antiretroviral therapy in HIV positive

Indian patients. Active surveillance methods were adopted. The study observed significant morbidity associated with the use of highly active antiretroviral therapy in the local population. In our study majority of ADRs to HAART were observed in adults. This may be due to large number of new HIV positive adult patients treated with HAART at our hospital. A finding of ADRs observed in adults, similar to another study.[15] However, other study[16] has reported larger percentage of ADRs in geriatric and pediatric populations.

Table 8. Severity, Management and Outcome of management of adverse drug reactions.(n=74)

	Number of ADRs,(%)
Severity	
Mild	17 (23)
Moderate	57 (77.0)
Management	
Drug withdrawn	54 (73)
Dose altered	19 (25.7)
No change	1 (1.3)
Outcome of management	
Recovered	62 (83.8)
Continuing	6 (8.1)
Unknown	6 (8.1)

During this study about 74% of patients showed at least one ADR and switching to another HAART drug regimen was done in 47% of them. Red blood cell complaints were the most prevalent reported ADRs in our study; however, ADRs were moderate in severity and need just symptomatic treatment in a few patients. Like other reports, these red blood cell effects were detected in first four weeks of treatment. Red blood cell adverse effects were reported to be more with Zidovudine containing HAART regimens. Anaemia occurred in patients receiving zidovudine containing regimens were graded according to the WHO/ACTG criteria. Majority of the cases, grade 2 anaemia [Haemoglobin (Hb) 8.0 - 9.4 g/dL] was observed with Zidovudine. In almost all cases (9/74), an improvement in Hb level was observed on discontinuation of zidovudine similar to the findings reported by Koduri and Parekh.[17] Results from the TAHOD study found that anaemia (Hb<10 g/dL) with zidovudine therapy was associated with low baseline Hb level, older age and female gender.[18] In our study, patients were initiated on a zidovudine-containing regimen only if Hb level was more than 10.5 g/dL at baseline, thereby avoiding the occurrence of zidovudine induced anaemia. Older age and female gender were not significantly associated with anaemia. However, we observed a highly significant association between the use of zidovudine and anaemia which is similar to other studies.[19,20]

In our study, the occurrence of hepatotoxicity was highly associated with nevirapine and efavirenz therapy and was graded according to the severity grades of toxicity[21] of National Institute of Allergy and Infectious Diseases. Severe hepatotoxicity (defined as a grade 2 or grade 4 changes in the serum levels of alanine amino transferase and aspartate amino transferase) suggesting that injury was hepatocellular in nature. Liver enzyme levels were raised by up to five times the upper limit of normal in all ten cases. Our study findings are similar to a Sulkowski study[22] where they observed similar rates of hepatotoxicity for nevirapine and efavirenz but found that elevation of CD4 cell count of more than 50/µL was most strongly linked to hepatotoxicity, perhaps due to adherence or immune reconstitution.

Peripheral neuropathy was observed in patients who were on stavudine-containing regimen for more than 7 months. In 8.1% (6/74) of these cases, stavudine was discontinued and the patient recovered. Six patients who experienced peripheral neuropathy were receiving concomitant antituberculosis (TB) drugs and pyridoxine with a stavudine-containing regimen. In four of these six cases, positive dechallenge to stavudine was observed suggesting a likely association of stavudine, however, a few patients who took zidovudine therapy also suffered peripheral neuropathy. There is sufficient data regarding stavudine induced neuropathy but in our study the incidence of stavudine induced peripheral neuropathy was less compared to von Giesen et al.[23] Also finding of our study supported stavudine as a risk factor for occurrence of peripheral neuropathy which was also suggestive from Scarsella et al.[24]

Vomiting was a common ADR observed among patients who were on regimens containing zidovudine. It was noted that a majority of these patients experienced vomiting an hour after ingestion of the drug. Most of the GI ADRs were observed in the first few weeks of therapy and symptoms were self limiting. GI disorders are one of the causes for medication non-adherence.[25] Patients receiving a zidovudine containing regimen had a greater risk of vomiting similar to that observed in an Iranian study.[26]

During this study, adverse cutaneous reaction occurred in patients receiving lopinavir/ritonavir containing regimen. In the majority of patients, a definite improvement of skin rash was observed after discontinuation of the offending agent. Maculopapular drug eruption took two weeks to resolve after discontinuation of lopinavir/ritonavir. In one of these five cases of adverse cutaneous reactions, maculopapular drug eruption evolved into exfoliative erythroderma similar to findings of a study conducted by Revuz et al.[27] Stevens Johnson Syndrome (SJS) was observed in the first week of nevirapine therapy similar to that observed in a case control study wherein two thirds of patients developed SJS or toxic epidermal necrolysis in the first week of nevirapine treatment.[28] Cutaneous leucocytoclastic vasculitis was observed in one patient receiving efavirenz therapy, similar to the findings by Domingo.[29] Skin discoloration, which is typically reported as hyper pigmentation was observed only in patients receiving emtricitabine therapy. Discoloration of the soles of the feet was observed in 1 (1.3%) which resolved during continued treatment with emtricitabine. Our findings are similar to observations in a recently published study.[30] The occurrence of insomnia, depression, giddiness and headache was highly associated with efavirenz therapy Similar to the observations in the study by Fumaz et al.[31] The occurrence of this ADR was minimized by administering the efavirenz once a day at night.

Table 9. Risk factors for adverse drug reaction to antiretroviral in intensively monitored patients.

Characteristic		Total number of Patients n=130 (%)		p-value
		Cases (With ADR) n=57(%)	Control (Without ADR) n=73(%)	
Gender	Male	42 (73.7)	58 (79.5)	
	Female	15 (26.3)	15 (20.5)	<0.001
Age (years)	21–40	29(50.9)	29 (39.7)	0.929
	41-60	24 (42.1)	43 (58.9)	
	>60	4 (7.0)	1 (1.4)	
BMI (Kg/m^2)	<18.5	24 (42.1)	30 (41.1)	0.829
	18.5-24.9	31 (54.4)	41 (56.2)	
	>24.9	2 (3.5)	2 (2.7)	
CD4 Count (Cells/µl)	<200	42 (73.7)	57 (78.1)	<0.001
	>200	15 (26.3)	16 (21.9)	
Concomitant drugs Cotrimoxazole	Yes	47 (82.5)	54 (74.0)	0.249
	No	10 (17.5)	19 (26.0)	
ATT	Yes	11 (19.3)	19 (26.0)	0.366
	No	46 (80.7)	54 (74.0)	
Antifungal	Yes	8 (14.0)	13 (17.8)	0.562
	No	49 (86.0)	60 (82.2)	
Acyclovir	Yes	3 (5.3)	4 (5.5)	1.000
	No	54 (94.7)	69 (94.5)	
Opportunistic Infections				
Tuberculosis	Yes	26 (45.6)	26 (35.6)	<0.001
	No	31 (54.4)	47 (64.4)	
Candidiasis	Yes	21 (36.8)	24 (32.9)	0.637
	No	36 (63.2)	49 (67.1)	
PCP	Yes	7 (12.3)	5 (6.8)	0.288
	No	50 (87.7)	68 (93.2)	
Herpes zoster	Yes	3 (5.3)	10 (13.7)	0.145
	No	54 (94.7)	63 (86.3)	
Syphilis	Yes	1 (1.8)	4 (5.5)	0.385
	No	56 (98.2)	69 (94.5)	
CMV	Yes	2 (3.5)	0 (0)	0.190
	No	55 (96.5)	73 (100)	
Toxoplasmosis	Yes	1 (1.8)	1 (1.4)	1.000
	No	56 (98.2)	72 (98.6)	
TB Meningitis	Yes	0 (0)	1 (1.4)	1.000
	No	57 (100)	72 (98.6)	
Cryptococcal Meningitis	Yes	1 (1.8)	1 (1.4)	1.000
	No	56 (98.2)	72 (98.6)	
Cryptosporidiosis	Yes	1 (1.8)	0 (0)	0.434
	No	56 (98.2)	73 (100)	

In our study, the patients with abacavir-induced ADRs underwent prior screening for the HLA-B*5701 allele before their adverse events. Individuals who were test positive for HLA-B*5701 generally did not receive abacavir. However, we observed drug hypersensitivity syndrome (DHS) in patients who were on abacavir-containing regimen for more than 6 weeks. In 5.4% (4/74) of these ADRs, abacavir was discontinued and the patient recovered. This syndrome is characterized by exfoliative dermatitis, fever and potentially life threatening damage (hepatitis, nephritis and pneumonitis). Four patients who experienced drug hypersensitivity syndrome were receiving topical high-potency corticosteroids for treating cutaneous lesions. This finding is concurrent with the study carried out by Roujeau et al.[32]

The immune reconstitution inflammatory syndrome (IRIS) was observed within the first 6 months of HAART. In one patient [1.35% (1/74)], IRIS manifested as TB. Our study findings are similar to a South African study wherein most of the IRIS cases (41%) manifested as TB.[33] Pancreatitis developed after 4 weeks to a year of starting therapy with stavudine-containing regimen. This ADR was specific to patients receiving stavudine and patients recovered from pancreatitis following discontinuation of stavudine as observed in a previously published case series.[34] The patients did not complain of pancreatitis symptoms after switch over from stavudine to zidovudine. Renal failure was observed with 2.7% of the patients who received treatment with tenofovir. A case of lichenoid eruption with eosinophilia was observed. The patient recovered from renal injury following dechallenge. This finding is agreement with the study carried out by Woolley et al.[35] HIV patients being treated for opportunistic infections (OIs) experience ADRs at a much higher rate.[36] Antibiotics (Cotrimoxazole) and antitubercul drugs, antifungal, acyclovir are implicated in two thirds of hospital-acquired ADRs. We observed that the probability of occurrence of ADRs to antiretrovirals in patients with HIV and tuberculosis [(45.6%) 26/57] was higher compared to HIV patients without any OIs.

The majority (93.2%) of the ADRs were predictable as they were common (incidence ≥1/100 and <1/10) or very common (incidence ≥1/10).[37] Findings of preventability (56.76%) were substantially higher than (46.2%) observed in a study conducted by Mehta et al.[38] In most of preventable ADRs, preventive measures for ADRs were prescribed or administered to patients: for example common instructions were given to patients to avoid fatty foods and dairy products for prevention of nausea and vomiting in patients receiving zidovudine. The finding of this study showed that the most common cause of highly active antiretroviral therapy cessation in these patients was due to predominant hematological adverse effects like anaemia, eosinophilia, leucopenia, neutropenia, bicytopenia, pancytopenia with zidovudine therapy.

CONCLUSIONS

This is the first active pharmacovigilance study that was designed to evaluate the antiretroviral induced ADRs in Indian HIV positive patients. The finding of this study showed that to optimize adherence and to maintain efficacy of highly active antiretroviral therapy, treating physicians must focus on early detection and prevention of ADRs. Highly active antiretroviral therapy with zidovudine + lamivudine + nevirapine and stavudine + lamivudine + nevirapine is a predictor of ADRs. The finding of this study showed that there is a need for intensive monitoring for ADRs in Indian HIV positive patients who are illiterate, of female gender, with CD4 count <200 cells/µl, with tuberculosis. The finding of this study also supported the pattern of adverse cutaneous reactions especially maculopapular drug eruption, Stevens Johnson Syndrome (SJS) and drug hypersensitivity syndrome with highly active antiretroviral therapy in Indian population.

ACKNOWLEDGEMENTS

The authors wishing to thank staff of Medicine department and administrative staff of Kasturba Medical College, Manipal University, Manipal for their technical support and encouragement.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

References

1. World Health Organization [home page on the internet]. 2008 [cited 2008 October 23]. Available from: URL: http://www.who.int/en/
2. Averting HIV and AIDS [home page on the internet]. 2008 November 26 [cited 2009 January 5]. Available from: URL: http://www.avert.org/
3. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhre J, Satten GA. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med. 1998;338:853-860.
4. Detels R, Munoz A, McFarlane G, Kingsley LA, Margolick JB, Giorgi J, Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. AIDS Cohort Study Investigators. JAMA. 1998;280:1497-1503.
5. Hogg RS, Yip B, Kully C, Craib KJP, O'Shaughnessy MV, Schechter MT. Improved survival among HIV-infected patients after initiation of triple drug antiretroviral regimens. CMAJ. 1999;160(5):659-665.
6. Arminio Monforte A, Lepri AC, Rezza G, Pezzotti P, Antinori A, Phillips AN. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naïve patients. I.C.O.N.A. Study Group. Italian Cohort of Antiretroviral-Naïve Patients. AIDS. 2000;14:499-507.
7. Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. Ann Intern Med. 1999;131:81-87.
8. Bachani D. 650 link ART centres planned under NACP-III. NACO News. 2009;5(1):8.
9. Mayboom RH, Hekster YA, Egberts AC, Gribnau FW, Edwards IR. Causal or casual. The role of causality assessment in pharmacovigilance. Drug Saf. 1997;17(6):374-389.
10. Naranjo CA, Busto U, Sellers EM. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-245.
11. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992;49:2229-2232.
12. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm 1992; 27(6): 538.
13. International monitoring of adverse reactions to drugs. WHO Adverse Reaction Terminology, The Uppsala Monitoring Centre: Uppsala, 2007.
14. ICH Harmonised Tripartite Guideline: E2a. [Online] 1994 Oct [cited 2010 April 9]; Available from: URL: http://adr.doh.gov.tw/doc/ICH%20E2a.pdf
15. Mehta U, Durrheim DN, Blockman M, Kredo T, Gounden R, Barnes KI. Adverse drug reactions in adult medical inpatients in a South African hospital serving a community with a high HIV/AIDS prevalence: prospective observational study. Br J Clin Pharmacol. 2008;65(3):396-406.
16. Melmon KL. Preventable drug reactions-causes and cures. N Engl J Med. 1971;284(24):1361-1368.
17. Koduri PR, Parekh S. Zidovudine-related anemia with recticulocytosis. Ann Hematol. 2003;82(3):184-185.
18. Huffam SE, Srasuebkul P, Zhou J. Prior antiretroviral therapy experience protects against zidovudine-related anaemia. HIV Med. 2007;8(7):465-471.

19. Sullivan PS, Hanson DL, Chu SY, Jones JL, Ward JW. Epidemiology of anemia in human immunodeficiency virus (HIV)-infected persons: results from the multistate adult and adolescent spectrum of HIV disease surveillance project. Blood. 1998;91:301-308.
20. Curkendall SM, Richardson JT, Emons MF, Fisher AE, Everhard F. Incidence of anaemia among HIV-infected patients treated with highly active antiretroviral therapy. HIV Med. 2007;8(8):483-490.
21. NIAID (National Institute of Allergy and Infectious Diseases), Section VIII: Appendices of Monitoring and Reporting Adverse Events.2003; 111-4. [Cited: 30 APR 2010]; Available from:URL:http://www.icssc.org/Documents/Resources/AEManual2003AppendicesFebruary_06_2003%20final.pdf
22. Sulkowski, M, Mehta S, Thomas D, Moore R. Hepatotoxicity associated with NNRTI use: role of drugs and chronic hepatitis [abstract 618]. 8th Conference on Retroviruses and opportunistic Infections; 2001 Feb 4–8; Chicago.
23. Von Giesen HJ, Hefter H, Jablonowski H, Arendt G. Stavudine and the peripheral nerve in HIV-1 infected patients. J Neurol. 1999;246(3):211-217.
24. Scarsella A, Coodley G, Shalit P. Stavudine-associated peripheral neuropathy in zidovudine-native patients: effect of stavudine exposure and antiretroviral experience. Adv Ther. 2002;19(1):1-8.
25. Cooper CL, Breau C, Laroche A, Lee C, Garber G. Clinical outcomes of first antiretroviral regimen in HIV/hepatitis C virus co-infection. HIV Med. 2006;7(1):32–37.
26. Khalili H, Dashti-Khavidaki S, Mohraz M, Etghani A, Almasi F. Antiretroviral induced adverse drug reactions in Iranian human immunodeficiency virus positive patients. Pharmacoepidemiol Drug Saf. 2009;18(9):848-857.
27. Revuz J, Valeyrie-Allanore L. Drug reactions. In: Bolognia JL, Jorrizo JL, Rapini RP. Dermatology. London: Mosby, 2003;333-353.
28. Fagot JP, Mockenhaupt M, Bouwes-Bavinck JN. Nevirapine and the risk of Stevens Johnson syndrome or toxic epidermal necrolysis. AIDS. 2001;15(14):1843-1848.
29. Domingo P, Barcelo M. Efavirenz-induced leukocytoclastic vasculitis. Arch Intern Med. 2002;162:355-356.
30. Mondou E, Quinn JB, Shaw A. Incidence of skin discoloration across phase 3 clinical trials of emtricitabine (FTC). In: Abstracts of the Fifteenth International AIDS Conference, Bangkok, 2004.Abstract WePeB5916.
31. Fumaz CR, Munoz-Moreno JA, Molto J. Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychological issues, and adherence. J Acquir Immune Defic Syndr. 2005;38(5):560-565.
32. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. Toxicology. 2005;209:123-129.
33. Murdoch DM, Venter WD, Feldman C, van Rie A. Incidence and risk factors for the immune reconstitution inflammatory syndrome in HIV patients in South Africa: a prospective study. AIDS. 2008;22(5):601-610.
34. Guyot S, Hayoz D, Telenti A, Cavassini M. Peripheral oedema and high arterial blood flow as a complication of antiretroviral therapy. AIDS. 2004;18(2):356-358.
35. Woolley IJ, Veitch AJ, Harangozo CS. Lichenoid drugeruption to tenofovir in an HIV/hepatitis B virus co-infected patient. AIDS. 2004;18:1857-1858.
36. Lin D, Tucker MJ, Rieder MJ. Increased adverse drug reactions to antimicrobials and anticonvulsants in patients with HIV infection. Ann Pharmacother. 2006;40(9):1594-1601.
37. Stephens MDB. Introduction. In Stephens' Detection of New Adverse Drug Reactions (5th ed), Talbot J, Waller P (eds). West Sussex, JohnWiley & Sons, Ltd: 2004;1-91.
38. Mehta U, Durrheim DN, Blockman M, Kredo T, Gounden R, Barnes KI. Adverse drug reactions in adult medical inpatients in a South African hospital serving a community with a high HIV/AIDS prevalence:prospective observational study. Br J Clin Pharmacol. 2008;65(3):396-406.