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Pattern Of Use Of Highly Active Antiretroviral Therapy Regimens And Pattern Of Occurrence Of Adverse Drug Reactions In An Indian Human Immunodeficiency Virus Positive Patients

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Shortened running title: R.Rajesh et al. Pattern of use of HAART regimens and ADRs

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ABSTRACT

Background: In India, Human immunodeficiency (HIV) infected patients with highly active antiretroviral therapy (HAART) are at higher risk of developing adverse drug reactions (ADRs).

Objectives: The aim of this study was to characterize the pattern of use of HAART, occurrence, incidence, severity and causality of ADRs to HAART in Indian HIV positive patients.

Methods: This was a prospective observational study conducted between August 2009 and May 2012. Enrolled HIV positive patients were intensively monitored for ADRs with fixed dose antiretroviral therapy as per National AIDS Control organization (NACO).World Health Organization (WHO) definition of ADR was adopted to detect ADRs to HAART and classified based on WHO adverse reaction terminologies. Naranjo's scale was used for causality assessment of ADRs. Preventability was assessed using Thornton and Schuman criteria and severity was assessed using the modified Hart wig and Siegel scale. Pattern of ADRs was assessed with patient demographics, ADRs characteristics, and pattern of drug and reaction characteristics. P-value <0.05 was considered as statistically significant.

Results: A total of 426 ADRs to HAART were evaluated from 1982 HIV positive patients during the study period. The overall incidence of ADRs to HAART was 21.4%. Significant difference was seen in the incidence of ADRs in the age group of 41-60 years (p <0.001), $CD4^+$T-cell counts of 350-500 cells/µl (p <0.001), females (p <0.001). Three fatal ADRs of with cutaneous drug eruptions of Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) was 1.1%. Anemia (31.7%) accounted for majority of the reports followed by vomiting (15.5%), skin rash (12.9%) and peripheral neuropathy (10.7%). The suspected drug was withdrawn for the management of the ADRs in majority (27.9%) of the reports. Higher incidence rate of ADRs was noted with lamivudine (3TC) + nevirapine (NVP) + stavudine (D4T) (22.9%). In, naranjo's causality assessment, majority of the ADR reports were rated as possible (69%). Symptomatic treatment for ADRs was given in 91.8% of the reports and 86.4% of the reports the patient recovered from the suspected adverse reaction at the time of evaluation.

Conclusion: In India, occurrence of ADRs to HAART in HIV infected patients was found to be higher with zidovudine induced anemia (31.7%). The higher percentage of ADRs to HAART was seen with female patients, age 41-60 years; $CD4^+$ T-cell counts 350-500 cells/µl. Physician must focus for monitoring all lab investigations for early detection and prevention of adverse effects associated with HAART.

Introduction

Human immunodeficiency virus (HIV) infected patients with highly active antiretroviral therapy (HAART) have led to substantial reductions in morbidity and mortality. Pattern of use of HAART regimens result in developing adverse drug reactions (ADRs).[1] Worldwide, 33 million people are infected with HIV infection and around 3 million people have access to HAART.[2] India as a developing country stands at second position in having highest burden of HIV/Acquired immunodeficiency syndrome (AIDS) and related opportunistic infections.[3] In India, HIV infected patients receive a fixed dose of antiretroviral therapy (ART) regimen consisting of either zidovudine (ZDV) or stavudine (D4T) with lamivudine (3TC) in combination

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with either efavirenz (EFV) or nevirapine (NVP). Most often under reporting of ADRs was observed among Indian clinicians due to inadequate training on use of drugs and patient safety monitoring, with increase in use of antiretroviral increases the risk for ADRs, resulting in humanistic and economic burden to the HIV infected patients as well as to the society.[4] The aim of this study was to assess patterns of use, occurrence, incidence, severity and causality of ADRs to HAART in Indian HIV positive patients.

Materials and Methods

A prospective study was conducted in HIV-infected hospitalized in-patients and out-patient visit during follow-up from August 2009 to May 2012 at National AIDS Control organization (NACO) approved; Antiretroviral therapy (ART) Centre, district government hospital, Udupi, India. The study protocol was approved by the University ethics committee. The World Health Organization (WHO) definition[5] of ADRs was adopted to detect ADRs with respect to red blood cell disorders, skin and appendages disorders, gastro-intestinal system disorders, central and peripheral nervous system disorders, liver and biliary system disorders, urinary system disorders, body as a whole, general disorders, psychiatric disorders, metabolic and nutritional disorders and resistance mechanism disorders by using system organ classes and codes using WHO adverse reaction terminologies [WHO-ART][6]. By active follow-up after treatment and the adverse event was detected by asking patients directly or by screening patient's case records. HIV-infected patients of either sex who were receiving fixed dose of first-line ART combination regimens as per national treatment guidelines were included and HIV-infected patients treated with "traditional medicines" practiced in India like ayurveda, yoga, naturopathy, unani, siddha and homeopathy were excluded. Study procedure was explained and informed consent was obtained. The enrolled patients with average number of ten days of hospital stay as in-patient were followed for short term ADRs during ward rounds in collaboration with the clinicians and long term intensive monitoring of ADRs with their pattern of use of HAART regimens was documented by the clinical pharmacist at every six months of regular follow-up at out-patient visit. Suspected ADRs to HAART was documented by the department of pharmacy practice where the national pharmacovigilance programs for reporting of ADRs exist. The enrolled patients were followed for investigation for anemia i.e. (baseline hemoglobin level) and baseline symptoms of peripheral neuropathy i.e. (numbness, pins - and needles, burning and aching sensation, sensation of temperature in the legs and feet and cramping) before initiation of HAART and thereafter at every six months of regular follow-up was documented. Clinical pharmacist reviewed patient's treatment chart and case notes was made on demographic details, past medical history, diagnosis of HIV status, time of initiation of ART, duration of HAART, type of opportunistic infections and HAART regimen implicated. The laboratory investigations such as liver function tests, lipid profile, blood sugar level and renal function test along with the pattern of occurrence of ADRs to HAART was documented using ADR documentation forms with details of suspected antiretroviral drugs involved, treatment of management of ADRs and their outcome. Necessary intervention to the treatment for prevention of ADRs was made by the clinical pharmacist in cooperation with the treating physician. Naranjo's algorithm[7] was used for causality assessment of ADRs. The ADR was documented as "not predictable" if the drug had previously been well tolerated by the patient at the same dose and route of administration. The ADR was recorded as "predictable" If there was a previous history of allergic reactions to the drugs or history of exposure. Reported ADR with a literature incidence of ≥1/100 was documented as "predictable." The severity of suspected ADRs was assessed using the modified Hart wig and Siegel scale.[8] Modified Shumock and Thornton criteria[9] were used to assess the preventability of ADRs.

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Statistical Analysis

Frequencies with their percentage were used to represent demographic details of the patient. Statistical analysis was carried out using Statistical Package for Social Science (SPSS) version 17.0 (Systat Software, Inc., Chicago, Illinois).

Results

A total of 1982 HIV positive patients were enrolled with inclusion criterion 1181(59.6%) males, 801 (40.4%) females from NACO approved ART Center. Out of which 426 ADRs to HAART were reported and documented during the study period. Of the 426 ADRs, majority of female patients 236 (55.4%) developed ADRs compared to males 190 (44.6%). The overall incidence of ADRs to HAART in our study was 21.4% (426/1982). Higher incidence rate of ADRs was noted with 3TC + NVP + D4T (22.9%) and 3TC + NVP + ZDV combinations (22.5%) while the incidence rate of ADRs was lowest with 3TC + D4T + EFV combination (16.8%). Incidence of ADRs to HAART was significantly higher in the age groups 41-60 years [p <0.001], (25.7%) than in other age groups. Incidence of ADRs to HAART was significantly higher with $CD4^{+}$T-cell counts of 350-500 cells/µl [p <0.001], (47.2%).The incidence of ADRs in our study was higher in female population [p <0.001], 11.9 % (236/1982 compared to males [9.5% (190/1982)]. Patients' demographic details are shown in Table 1.

HAART regimen commonly implicated in ADRs was noted with 3TC+NVP+ZDV 226 (53%). The suspected antiretroviral drug was withdrawn for the management of the ADRs in majority 119 (27.9%) of the reports. Symptomatic treatment was instituted in 91.8% of the ADR cases. Most (86.4%) of the patients were recovered from ADRs on the last day of hospital discharge. Three fatal ADRs of NVP induced cutaneous drug eruptions of Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (1.1%) were observed during the study period. A total of 7.3% of patients with ADRs were discharged from the hospital against medical advice, which led to loss to follow-up and resulted in an unknown outcome of ADRs.

We found that 'no-de-challenge' and "no- re-challenge" accounted for 9.6% and 80.5% of the reported ADRs, respectively. The causality assessment was performed using Naranjo's scale, out of 426 ADRs reported, 294 (69%) were possible, 92 (21.6%) were probable. As per modified Schumock and Thornton scale, 31(7.3%) were 'definitely preventable ADRs. zidovudine induced anemia were considered under "preventable ADRs" and 4(0.9%) 'Probably preventable', 391(91.8%) were 'non-preventable'. The majority of ADRs 387 (90.8%) were 'non-predictable' and 39 (9.2%) were 'predictable and preventable ADRs' which includes zidovudine induced vomiting. The characteristic details of the reported ADRs to HAART are shown in Table 2.

The commonly observed ADRs to HAART were anemia 135 (31.7%), vomiting 66 (15.5%) followed by skin rash 55 (12.9%) and peripheral neuropathy 45 (10.7%). Pattern of adverse drug reactions reported with highly active antiretroviral therapy are shown in Figure 1. Severity of ADRs was assessed using modified Hart wig and Siegel scale and reported 'mild ADRs' i.e. level 1 and level 2 accounted for 0.5% and 50.2% respectively. 'Moderate ADRs' i.e. level 3, level 4a and level 5 accounted for 10.3%, 31% and 7.3% respectively. Only three (0.7%) of level 4b ADRs related to hospital admissions that was lead to level 7 'severe ADRs' or fatal ADRs. Results are shown in Figure 2.

Discussion

In our study, female HIV positive patients were found to be more susceptible to ADRs to HAART with higher incidence of 11.9% compared to male HIV positive patients. This result confirms the findings of various studies[10,11] that female gender have increased incidence for the development of ADRs. Most of ADRs to HAART were observed with 3TC + NVP + ZDV and 3TC + NVP + D4T. This may be due to large number of naïve HIV positive patients were diagnosed and initiated with first-line HAART similar to another study.[12] In this

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Table 1 Demographic detail of the patients

Characteristic	Gender group	Number of Patients n=1982 (%)	Total n=1982(%)	Number (%) of ADRs to HAART	Number of patients with ADRs / total number of patients, Incidence (%)	Number of patients with ADRs / total number of patients, Incidence (%) [p-value]
Number of Patients	Male	1181 (59.6)	1982	190 (44.6)	190/1982,(9.5)	426/1982, (21.4)
	Female	801(40.4)		236(55.4)	236/1982, (11.9)	[p <0.001]
HAART treatment regimen: Lamivudine+Nevirapine+ Zidovudine	Male	618(61.6)	1004(50.7)	102(24)	102/1004,(10.1)	226/1004, (22.5)
	Female	386(38.4)		124(29)	124/1004,(12.4)	
Lamivudine+Nevirapine +Stavudine	Male	314(54.6)	575(29)	54(12.7)	54/575,(9.3)	132/575, (22.9)
	Female	261(45.4)		78(18.3)	78/575,(13.6)	
Lamivudine+ Stavudine+Efavirenz	Male	139(59.9)	232(11.7)	17(4)	17/232,(7.4)	39/232, (16.8)
	Female	93(40.1)		22(5.1)	22/232,(9.4)	
Lamivudine+ Zidovudine+Efavirenz	Male	110(64.1)	171(8.6)	17(4)	17/171,(10)	29/171, (17)
	Female	61(35.9)		12(2.9)	12/171,(7)	
Age (Years) Less than 10 years	Male	37(1.9)	57(2.9)	2(0.4)	2/57,(3.5)	6/57, (10.5)
	Female	20(1.0)		4(0.9)	4/57,(7.0)	
11-20 years	Male	35(1.7)	65(3.2)	4(0.9)	4/65,(6.2)	8/65, (12.4)
	Female	30(1.5)		4(0.9)	4/65,(6.2)	
21-40 years	Male	720(36.3)	1266(63.9)	105(24.6)	105/1266,(8.3)	262/1266, (20.7)
	Female	546(27.5)		157(36.8)	157/1266,(12.4)	
41-60 years	Male	370(18.6)	568(28.6)	75(17.6)	75/568,(13.2)	146/568, (25.7)
	Female	198(9.9)		71(17)	71/568,(12.5)	
Above 60 years	Male	19(0.9)	26(1.4)	4(0.9)	4/26,(15.3)	4/26,
	Female	7(0.7)		----------		
$CD4^+$ T-cell counts (cells/µl) ≤ 350	Male	1122(56.7)	1879(94.9)	176(41.3)	176/1879,(9.3)	395/1879, (21)
	Female	757(38.1)		219(51.4)	219/1879,(11.7)	
350-500	Male	28(1.4)	55(2.7)	11(2.5)	11/55,(20)	26/55, (47.2)
	Female	27(1.3)		15(3.5)	15/55,(27.2)	
> 500	Male	28(1.4)	48(2.4)	3(0.7)	3/48,(6.2)	5/48, (10.4)
	Female	20(1.1)		2(0.6)	2/48,(4.2)	

Table 2 Characteristic details of the ADRs to HAART.

Characteristic	Number of ADRs n=426(%)
HAART treatment regimen	
Lamivudine+Nevirapine +Zidovudine	226(53)
Lamivudine+Nevirapine +Stavudine	132 (31)
Lamivudine+ Stavudine+Efavirenz	39 (9.2)
Lamivudine+ Zidovudine+Efavirenz	29 (6.8)
Management of ADR	
Drug withdrawn	119(27.9)
Dose altered	273 (64.1)
No change	34 (8.0)
Treatment given for ADR	
Symptomatic	391(91.8)
No change in treatment	4(0.9)
Specific	31(7.3)
Outcome of ADR	
Recovered	368(86.4)
Continuing	24 (5.6)
Fatal	3 (0.7)
Unknown	31 (7.3)
Dechallenge of ADR	
No dechallenge	41 (9.6)
Definite improvement	385(90.4)
Rechallenge of ADR	
No rechallenge	343(80.5)
Recurrance of symptoms	49 (11.5)
No occurrence of symptoms	3(0.7)
Unknown	31 (7.3)
Causality : (Naranjo's Scale)	
Definite	9(2.1)
Probable	92 (21.6)
Possible	294(69.0)
Unlikely	31 (7.3)
Predictability of ADR	
Predictable	39(9.2)
Not predictable	387 (90.8)
Preventability: (Schumock & Thornton's Scale)	
Definitely preventable	31 (7.3)
Probably preventable	4(0.9)
Not preventable	391 (91.8)

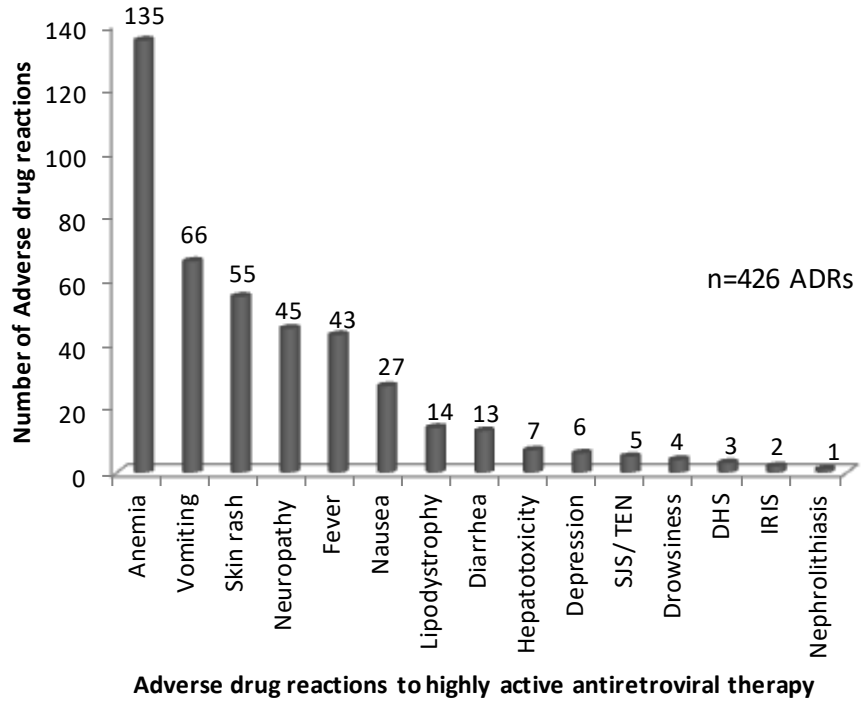

Figure 1. Pattern of adverse drug reactions reported with highly active antiretroviral therapy.

Steven Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN), Drug hypersensitivity syndrome (DHS), Immune reconstitution syndrome (IRIS)

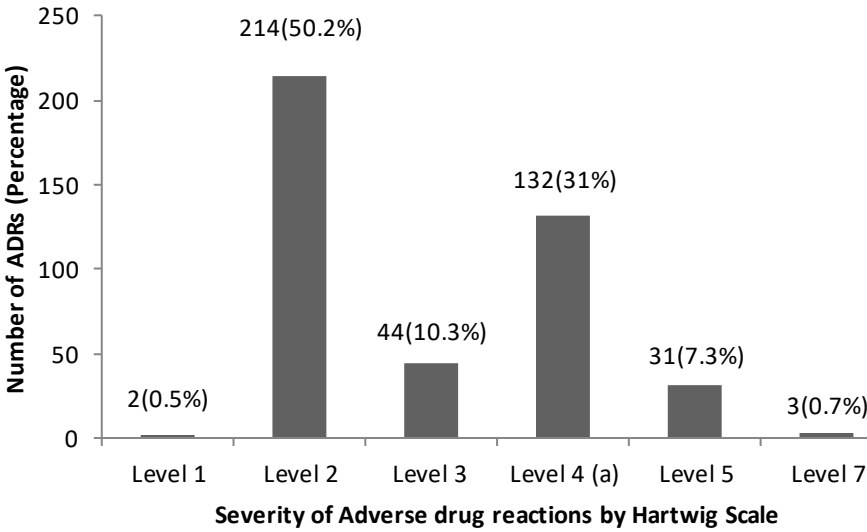

Figure 2. Severity of adverse drug reactions reported with highly active antiretroviral therapy.

study, we found that highest percentage of ADRs reported to HAART were among age group of 21- 40 years (61.5%) followed by 41-60 years (34.2%), a finding consistent with the study carried out by Obiako et al.[13] However, other study[10] that were carried out reported higher percentage of ADRs to HAART in children's and elderly patients. This may be due to the fact that in the present study, most patients 1266 (63.9%) who were admitted to the study site were in the age group 21- 40 years.

The occurrence of anemia had the highest percentage (31.7%) with ZDV containing HAART regimen during first four weeks of initiation of HAART. After replacement to ZDV with D4Tcontaining HAART regimen, an improvement in hemoglobin levels (8.0-9.4 g/dl) was observed with our patients. This finding is in accordance with previous published studies from our department where incidence of ZDV induced anemia was higher in comparison with D4Tcontaining HAART regimen in Indian HIV patients.[2] With the use of ZDV containing HAART regimen, gastrointestinal adverse effects such as vomiting was observed to be major cause for discontinuation of HAART regimen among Indian patients within 4 to 8 weeks of initiation of ZDV. This finding consistent with various studies.[11, 14, 15]

In our study dermatological manifestations of skin rashes was reported in patients with NVP therapy along with cutaneous drug eruptions of Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) was observed (1.1%). In few patients, erythematous macules that progressed to flaccid blisters along with symptoms of fever, stinging eyes and painful swallowing was observed with NVP therapy. In our study patients, with the occurrence of SJS and TEN was managed by discontinuation of NVP and with supportive measures of intravenous fluid administration, antimicrobial therapy, electrolyte maintenance, and with intensive skin care. Three patients were admitted to our study site, due to NVP induced SJS with level of 4b severity of Hart wig and Siegel scale. These three patients was not completely recovered from NVP induced SJS, even after discontinuation of NVP and resulted to level 7 severity of fatal adverse reactions. This is in accordance with published studies where NVP induced SJS and TEN has resulted in life threatening fatal ADRs in HAART treatment.[16, 17]

Drug Hypersensitivity Syndrome (DHS) with efavirenz (EFV) containing HAART regimen (12.9%) showed definite improvement after discontinuation of EFV. In our study, three cases of EFV induced maculopapular skin eruptions that prolonged into exfoliative erythroderma were presented with moderate in severity. Complete recovery from these ADRs was seen in our patients after four weeks of discontinuation of EFV. The onset of maculopapular skin eruptions due to EFV therapy ranged from 12 to 14 days after initiation of treatment. Our study findings are similar to observations in a published studies.[18, 19]

During the present study, the occurrence of drowsiness (0.9%) and severe depression (1.4) was observed in patients with EFV therapy. This patients developed aggressive reactions, agitation, emotional liability, neurosis, paranoid and mania. Such psychiatric symptom was greatly reduced by our clinical pharmacist intervention during ward rounds with physician for prescribing EFV therapy at bed time and all patience with EFV treatment at bed time was followed for adverse psychiatric symptoms at every six months of regular follow-up at out-patient visit. These observations are in agreement with the previously published study where EFV therapy resulted with higher incidence of central nervous system disorders.[20]

In our study, Forty five of our patients experienced D4T induced peripheral neuropathy. This patients developed pain in the hands and at feet with numbness, tingling sensation. The symptom associated with D4T induced peripheral neuropathy was resolved after two to eight weeks after discontinuation of D4T therapy. In our study the incidence of D4T induced peripheral neuropathy was found to be less i.e. 10.7%

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compared to Browne et al.[21] where they reported 55% incidence of D4T induced peripheral neuropathy.

In the present study, Lipodystrophy occurred in patients receiving a D4T containing regimen with the incidence of 3.2% which is similar to that of other studies[22, 23]. In most of our patients, central fat accumulation was observed within the abdomen as well as in the dorso-cervical spine region and upper trunk. Metabolic abnormalities such as elevated cholesterol, elevated triglycerides level, hyperlactataemia, low levels of high-density lipoprotein (HDL) cholesterol and type-2 diabetes mellitus was presented with lipodystrophy. Our study findings are similar to other studies[21, 23] where in most of the patients developed a greater increase in triglycerides and cholesterol level compared with patients who do not develop lipodystrophy.

In our study, the occurrence of hepatotoxicity was observed after 18 weeks with use of NVP therapy with elevated transaminase, prolonged partial thromboplastin time, with and without hyperbilirubinemia, liver tenderness, and hepatomegaly. Out of seven cases of NVP induced hepatotoxicity, six cases showed greater increase in serum AST and ALT levels more than five times the upper limit of normal values. Also we found that woman, including pregnant women was at a higher risk of developing NVP induced hepatotoxicity than men. Our study findings is agreement with various studies[24], [25,26,27,28,29] where they observed similar incidence of severe hepatotoxicity with NVP use.

In the present study, Immune reconstitution syndrome was reported in two patients, with 3TC + NVP + ZDV during initial eight months period of HAART, developed pneumocystis pneumonia and Guillain-Barre syndrome. The finding of our study supported with various studies [30,31,32,33,34] Nephrolithiasis was observed in one patient, who was receiving 3TC + ZDV combination along with additional protease inhibitor. The occurrence of nephrolithiasis in our study suggesting that renal effects was more likely associated with use of additional protease inhibitors rather than the reverse transcriptase inhibitors. This finding is agreement with the studies.[35, 36]

Strategies to either avoid or minimize the ADRs to HAART greatly influence quality of life in HIV infected patients. zidovudine induced anemia can be prevented either by careful monitoring of complete blood count, blood transfusion or use of epoetin alfa, use of myelosuppressive treatment with sulfamethoxazole-trimethoprim or gancyclovir and ultimately discontinuation of zidovudine containing regimen.[37] zidovudine induced vomiting can be prevented by taking medication with meals, nutritional counseling, knowing triggers for nausea/vomiting with specific food products, use of antiemetic drugs, acid reducing agents, tea with ginger or switching medications.[38] Skin rash can be managed by using antihistamines or corticosteroids, and discontinuing offended drug or switching therapy.[39] The main stays of management of peripheral neuropathy with use of amitriptyline, gabapentine or pre-gabalin, Non-Steriodal Anti-Inflammatory drugs (NSAIDs), opiate analgesics, acupuncture treatment and keeping the extremities warm.[40] Treatment for lipodystropy involves polylactic acid injections, exercise for fat accumulation, weight reduction, breast reduction surgery and liposuction for dorso-cervical fat accumulation.[41]

Conclusion

In India, the pattern of ADRs to HAART in HIV infected patients treated with lamivudine +nevirapine +zidovudine combination predicts higher incidence of anemia with zidovudine use.

HIV infected female patients, patients with age distribution of 41-60 years; $CD4^+$ T-cell counts 350-500 (cells/µl) need to be advised to monitor toxicity of HAART. Physician must focus for monitoring all lab investigations for early detection and prevention of adverse effects associated with HAART.

Competing Interests

The authors declare no conflicts of interest.

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