

Study of Adverse Effect of Drugs Due to Antiretroviral Therapy in Patients Of Hiv Infection



Medical Science

KEYWORDS : Antiretroviral therapy, HIV, Adverse drug reaction, zidovudine, lamivudine

Dr Madhuri Wahane

Resident in GMC,Nagpur, Medicine department, GMC Nagpur

Dr P.Patil sir

Associate Professor in Medicine, GMC, Nagpur

Dr Arun Janbandhu

Assistant Professor in Medicine, GMC,Nagpur.

ABSTRACT

Highly active antiretroviral therapy (HAART) is effective in reducing the plasma viral load, has dramatically reduced the morbidity and mortality associated with human immunodeficiency virus (HIV) infection and has improved the prognosis for people living with HIV infection/AIDS (PLHA) 8-10.

In recent years, excitement about the benefits of antiretroviral therapy and side effects associated with highly active antiretroviral therapy has become a major concern.

The present study has been undertaken to study the adverse effects and frequency of adverse effects of first line antiretroviral drug. The present study was conducted in ART centre of our parent institution. It was a prospective observational study. 130 HIV-1/AIDS patients eligible for first line antiretroviral therapy as per NACO guidelines filtered through following criteria, either hospitalized or coming to ART clinic were included in the study. The observations of our study are as follows.

Total 130 patients were studied, 92(70.76%) were males and 38(29.23%) were females. The most common mode of transmission of HIV-1 infection was heterosexual, 125 patients (96.15%), homosexual 2(1.53%), blood transfusion 2(1.53%) and IV drug user 1(0.76%). Most of the patients were in WHO stage III, 74 patients (56.92%), followed by stage II, 30 patients (23.07%), stage IV, 20 (15.38%) and stage I, 6 (4.61%).

Most of the patients were having CD4 count between 101-200/mm³, 71 patients (54.67%). Most commonly used initial ART regimen was Zidovudine + Lamivudine + Nevirapine, 83 patients (63.84%) received this regimen as initial regimen. Most common adverse drug effect due to ART observed was gastrointestinal disturbances like nausea, vomiting, diarrhoea observed in 39 (30%) patients.

Second most common adverse drug effect was anaemia seen in 32 patients (24.61%). Hepatotoxicity and skin rash seen in 19(14.61%), 14(10.76%) patients respectively. 7 patients (5.38%) had neuro psychiatric complaints.

Peripheral neuropathy 6 (4.61%) and lactic acidosis was seen in 3 (2.30%) patients receiving ART.

Steven Johnson's syndrome/Toxic epidermal necrosis and lipodystrophy were observed in 3(2.30%) and 2 (1.53%) patients respectively.

2 patients of lactic acidosis and 2 patients Stevens Johnson's syndrome died and death was attributed to adverse effect.

Overall, 40 patients required change in the initial HAART regimen, 37(28.46%) were due to drug toxicity while only 3 (2.30%) were due to tuberculosis.

Out of 37 patients who required change in the initial HAART therapy due to drug toxicity, 4 patients died and these deaths were attributed. 25 (30.12%) patients out of 83 patients who received Zidovudine+lamivudine+nevirapine as initial regimen required to change the regimen due to adverse effects.

9 patients (39.13%) had to change the initial regimen of Stavudine+lamivudine+nevirapine.

Out of 21 patients who received Zidovudine+lamivudine+efavirenz as initial therapy, 2 patients (9.52%) required to change the therapy.

1 patient required to change the therapy due to adverse drug effect of Stavudine+lamivudine+efavirenz regimen.

INTRODUCTION

AIDS, the Acquired Immuno Deficiency Syndrome or Slim Disease, is the disease known to be scourge for our century has had an impact like no other disease. Highly active antiretroviral therapy (HAART) is effective in reducing the plasma viral load, has dramatically reduced the morbidity and mortality associated with human immunodeficiency virus (HIV) infection and has improved the prognosis for people living with HIV infection/AIDS (PLHA) 4-6. In recent years, excitement about the benefits of antiretroviral therapy has been tempered by a growing awareness of the problem that accompany the use of ART. In addition to drug resistance and difficulty of adherence to complex regimen, side effects associated with highly active antiretroviral therapy has become a major concern. 1

AIMS:

The present study has been undertaken to study the adverse effects and frequency of adverse effects of first line antiretroviral drug.

Materials and methods;

The present study was conducted in ART centre of our parent institution.

STUDY DESIGN –

Prospective observational Study

STUDY SETUP –

In the present study, patients were included only after pre and

post HIV test counseling at VCTC and pre and post Antiretroviral Therapy counseling at the ART clinic.

130 HIV-1/AIDS patients eligible for first line antiretroviral therapy as per NACO guidelines filtered through following criteria, either hospitalized or coming to ART clinic were included in the study. 2,3

Inclusion criteria

1. Patients more than 15 yrs of age.
2. All the WHO stage 1 and stage 2 patients with CD4 count less than 200 cells/ μ L.
3. All the WHO stage 3 and stage 4 patients irrespective of CD4 count.

Exclusion criteria

1. All HIV-1 infected pregnant patients.
2. HIV-1 infected patients of less than 15 year.
3. Patients having pre-existing diabetes, dyslipidemia, coronary artery disease.
4. Patients with medical constraints like active malignant disease (except for mucocutaneous Kaposi's sarcoma), active psychiatric disorders and patients receiving anticancer chemotherapy (Immunomodulators or other trial drugs) or radiotherapy.

The diagnosis of HIV infection was confirmed by two serially reactive ELISA tests in symptomatic individuals and three tests in asymptomatic individuals. All patients had several (two to three)

counselling sessions before initiating HAART to assess treatment readiness and educate them regarding the need for life-long treatment, stringent adherence to therapy and potential adverse effects of drugs. 7,8.

All the 130 HIV-1 positive patients fulfilling the inclusion criteria were studied after taking written informed consent.

OBSERVATIONS:

Total 130 HIV-1 infected patients who were on first line antiretroviral drugs registered in ART clinic were studied. The observations of our study are as follows.

Total 130 patients were studied, 92(70.76%) were males and 38(29.23%) were females. The most common mode of transmission of HIV-1 infection was heterosexual, 125 patients (96.15%), homosexual 2(1.53%), blood transfusion 2(1.53%) and IV drug user 1(0.76%).

Most of the patients were in WHO stage III, 74 patients (56.92%), followed by stage II, 30 patients (23.07%), stage IV, 20 (15.38%) and stage I, 6 (4.61%).

Most of the patients were having CD4 count between 101-200/mm³, 71 patients (54.67%). 31 patients (23.84%) patients were having CD4 count between 50-100/mm³, 19 patients (14.61%) were having CD4 count >200/mm³ and 9 patients (6.92%) were having CD4 cell count <50/mm³ at presentation. 9,10

Distribution of different Initial HAART regimen

Sr. no.	ART regimen	No. of patients (n=130)	Percentage
1.	Zidovudine + Lamivudine + Nevirapine	83	63.84
2.	Stavudine + Lamivudine + Navirapine	23	17.69
3	Zidovudine + Lamivudine + Efavirenz	21	16.15
4.	Stavudine + Lamivudine + Efavirenz	03	2.30

Most commonly used initial ART regimen was Zidovudine + Lamivudine + Nevirapine, 83 patients (63.84%) received this regimen as initial regimen. 12

23 (17.69%) patients received Stavudine + Lamivudine + Nevirapine as initial ART regimen, 21 (16.15%) received Zidovudine + Lamivudine + Efavirenz as initial regimen.

Stavudine + Lamivudine + Efavirenz was used in 3 (2.30%) patients.

Adverse effects of antiretroviral therapy

Sr. no.	Adverse drug effect of ART	No. of patients (n=130)	Frequency
1.	GI intolerance (nausea, vomiting, diarrhoea)	39	30%
2.	Anaemia	32	24.61%
3.	Hepato toxicity	19	14.61%
4.	Neuropsychiatric complaints (vivid dreams, headache, loss of sleep)	7	5.38%
5.	Peripheral neuropathy	06	4.61%
6	Lactic acidosis	03	2.30%
7.	Steven Johnsons syndrome/TEN	03	2.30%
8.	Skin rash	14	10.76%
9.	Lipodystrophy	02	1.53%

Most common adverse drug effect due to ART observed was gastrointestinal disturbances like nausea, vomiting, diarrhoea observed in 39 (30%) patients.

Second most common adverse drug effect was anaemia seen in 32 patients (24.61%).

Hepatotoxicity and skin rash seen in 19(14.61%), 14(10.76%) patients respectively.

7 patients (5.38%) had neuro psychiatric complaints.

Peripheral neuropathy 6 (4.61%) and lactic acidosis was seen in 3 (2.30%) patients receiving ART.

Steven Johnson's syndrome/Toxic epidermal necrosis and lipodystrophy were observed in 3(2.30%) and 2 (1.53%) patients respectively.

2 patients of lactic acidosis and 2 patients Steven Johnsons syndrome died and death was attributed to adverse effect.

Reasons for treatment change of initial HAART regimen -

Sr.No.	Event	Frequency (n=130)
1	Drug toxicity	37(28.46%)
2	Opportunistic infections (tuberculosis)	03(2.30%)
3	Total	40

Overall, 40 patients required change in the initial HAART regimen, 37(28.46%) were due to drug toxicity while only 3 (2.30%) were due to tuberculosis. (12)

Out of 37 patients who required change in the initial HAART therapy due to drug toxicity, 4 patients died and these deaths were attributed.

Substitute of drug due to adverse drug effects to adverse effect.

Sr. no.	Adverse drug effect	Total No. of patients (n=130)	No of patients re-quired substitute or change of regimen	Probable drug causing adverse drug effect	Percentage Of patients re-quired substitute of drug
1.	GI intolerance (nausea, vomiting, diarrhea)	39	02	Zidovudine/ not specified	5.12%
2	Anaemia	32	16	Zidovudine	50%
3.	Hepatotoxicity	19	06	Nevirapine	31.5%
4.	Neuropsychiatric complaints	07	00	Efavirenz	00
5.	Peripheral neuropathy	06	06	Stavudine	100%
6.	Lactic acidosis	03*	03	Stavudine	100%
7.	Steven Johnsons syndrome	03*	03	Nevirapine	100%
8.	Skin rash	14	00	Nevirapine	00
9.	Lipodystrophy	02	01	Stavudine	50%
10	Total	125	37		29.60%

Distribution of change of regimen due to adverse drug effect

Sr. no.	Initial regimen	No. of patients on initial ART	No of patients requiring change of initial ART regimen
1.	Zidovudine+lamivudine+nevirapine	83	25(30.12%)
2.	Stavudine+lamivudine+nevirapine	23	09(39.13%)
3.	Zidovudine+lamivudine+efavirenz	21	02(9.52%)
4.	Stavudine+lamivudine+efavirenz	03	01(33.33%)

25 (30.12%) patients out of 83 patients who received Zidovudine+lamivudine+nevirapine as initial regimen required to change the regimen due to adverse effects.

9 patients (39.13%) had to change the initial regimen of Stavudine+lamivudine+nevirapine .

Out of 21 patients who received Zidovudine+ lamivudine+ efavirenz as initial therapy , 2 patients(9.52%) required to change the therapy.

1 patient required to change the therapy due to adverse drug effect of Stavudine+lamivudine+efavirenz regimen.

Distribution of adverse drug effects among initial ART regimen

Sr. no.	Adverse drug effects	AZT +3TC +NVP	4dT +3TC +NVP	AZT +3TC +EFV	4dT +3TC +EFV	Total no.of patients (n=130)
1.	GI intolerance	31	01	07	00	39
2.	Skin rash	09	04	01	00	14
3.	Steven Johnsons	03*	00	00	00	3
4.	Neuropsychiatric complaints	00	00	06	01	7
5.	Hepatotoxicity	18	01	00	00	19
6.	Anaemia	26	00	06	00	32
7.	Lactic acidosis	00	03*	00	00	3
8.	Peripheral neuropathy	00	05	00	01	6
9.	Lipodystrophy	00	02	00	00	2
10.	Total	87	16	20	02	125

DISCUSSION

Among 130 patients studied, 92 (70.76%) were male and female patients were 38 (29.23%)

In the present study heterosexual route was the most predominant mode of transmission of HIV infection observed in 125 patients(96.15%) ,homosexual route and blood transfusion in 1.53% each .

In the present study, maximum number of patients had prolonged fever as presenting complaint,83 patients(63.84%),70 patients (53.64%) had significant weight loss,46 (35.38%) had chronic diarrhoea ,43(33.07%) had chronic cough,27 (20.76%) had recurrent upper respiratory tract infections and 21(16.15%) had lymphadenopathy as presentation.

In our study ,most common oportunistic infection was candidiasis in 26 patients(20%) followed by tuberculosis in 22 patients (16.92%),cryptococosis 7 (5.38%),pneumonia 3 (3.84%),cryptosporidiosis 5(3.84%) and herpes zoster 3 (2.30%).

Most of the other studies also reported candidiasis and tuberculosis as common opportunistic infection

In present study majority of the patients were in advanced stage of the disease,72.30% were in ststage III and stage IV.

Majority of the patients 71 (54.67%) were having CD4 count between 101-200/mm3. 31 patients (23.84%) were having CD4 count in 50-100/mm3, 19 patients (14.61%) had CD4 count >200/mm3 ount and 9 (6.92%)had CD4 count <50/mm3.

In the present study out of 130 patients, as per WHO guidelines most of the patients 83(63.84%)received AZT+3TC+NVP as initial regimen. 23 patients (17.69%) received 4dT+3TC+NVP, 21 patients (16.15%) were started on AZT+3TC+EFV and 3 patients (2.3%)were started on 4dT+3TC+EFV as initial ART regimen.

In the present study higher incidence of AZT+3TC+NVP used as a initial first line regimen as this is the preferred first line ART regimen to be used as per NACO and WHO guidelines.

Adverse effects of antiretroviral therapy-**1) Gastrointestinal intolerance-**

In the present study we reported gastrointestinal intolerance like nausea ,vomiting, diarrhoea in 39 patients (30%).Most of the gastrointestinal disturbances are in the initial period in 1- 4 weeks of starting the HAART. Almost all these GI intolerance was managed by advising patients to take medication after food or symptomatically treating with antacids and metocholpropamide. Christina menezes et al 11(2007) in their study of 361 patients of HIV -1 infection on antiretroviral therapy reported nausea in 51.2%, vomiting 36%, diarrhea in 33.2% of patients.2 patients had to change the initial ART regimen due to severe GI intolerance and both were due to Zidovudine

2) Neuropsychiatric complaints-

The overall frequency of neuropsychiatric manifestations vivid dreams, dizziness, headache, loss of sleep seen in 7 patients (5.38%) patients. Most of these manifestations are in the first month of the therapy with mean duration of weeks. All these adverse effects are due to efavirenz .Christiane A. et al11(2008) reported neuropsychiatric complaints like nightmares in 27.2%, dizziness in 22.2%, insomnia (32.1%) patients.

In present study the incidence of neuropsychiatric complaints are low because only 23 patients in our patients received Efavirenz containing regimen.

3)Skin rash-

The present study reported mild to moderate skin rash in 14 patients (10.76%).

In 13 patients ,skin rash was due to Nevirapine and 1 patient was on Efavirenz containing regimen.

All these skin rash were managed symptomatically or disappeared of their own and none patients required to change the initial regimen not required to change the therapy and managed by taking the drug at bedtime and symptomatic therapy .Tom Egwang et al 17(2007) reported skin rash in 10% of the patients and that were due to Nevirapine

4) Steven Johnsons syndrome/Toxic epidermal necrosis-

In our study ,3 patients (2.30%)had Steven Johnsons syndrome/ TEN,2 patients. Ajith Sivadasan et al 15(2009) in their study of 230 HIV-1 infected patients on ART reported Stevens Johnsons/ TEN in 9 patients(3.9%) of their patients. 1 patient died due to TEN. The time for the adverse effect was 2 weeks.

5) Hepatotoxicity-

The overall incidence of hepatotoxicity in our study was 19 (14.61%) .In the present was diagnosed in patients who had symptoms and elevated liver enzymes >2times and in asympto-

matic patients elevated liver enzymes >5 times.

All of them were on Nevirapine containing regimen. 6 patients of hepatotoxicity had to change the initial ART regimen due to severe hepatotoxicity died and death was attributed due to adverse effect.

N. Kumarsamy et al 13(2008) reported hepatotoxicity in 3.5% of patients. In their study three fourth of the patients were treated with nivrapiene containing regimen and four fifth experienced hepatitis

6) Anaemia-

In present study, anaemia was reported in 32 patients (24.61%). In our study, anaemia was diagnosed clinically and Hb<7gm%.

Anaemia was due to zidovudine and observed most commonly in AZT+3TC+ NVP regimen.

Out of 32 patients who were diagnosed as anaemia due to ART, 16 patients had severe anaemia and required to change the initial ART regimen while others were managed with iron and folic acid supplementation.

Ajith Sivadasan et al 15(2009) in their in 230 HIV-1 infected patients on ART reported severe anaemia in 16 (7%). The mean duration of anaemia was 8 weeks (3-36 weeks).

6) Peripheral neuropathy-

In present study, peripheral neuropathy was diagnosed if patient complaints of tingling, numbness in distal limbs and absent or depressed reflexes. In our study, peripheral neuropathy was noted in 6 patients (4.61%). All of these patients were on Stavudine containing regimen. All 6 patients required to change their initial regimen and Stavudine was replaced by Zidovudine. Sharma et al 14(2007) reported peripheral neuropathy in 39.6% of patients with mean CD4 count of 69 in males and 144 in females.

7) Lactic acidosis-

In present study lactic acidosis was diagnosed if patient has nausea, vomiting, abdominal pain, breathlessness and serum lactate level >5mmol/l. We reported lactic acidosis in 3 patients (2.30%). All of them were on Stavudine containing regimen. 2 patients of lactic acidosis died due to severe metabolic acidosis and death was attributed to adverse effect.

N. Kumarsamy et al 13 (2008) in their in 3154 patients on first line HAART reported lactic acidosis in 0.8% of patients with mean CD4 count of 514/mm3.

8) Lipodystrophy-

In the present study, we observed lipodystrophy in 2 patients (1.53%) and the mean duration was ---(48-72 weeks). The drug responsible was stavudine.

A. Sharma et al 14(2007) reported lipodystrophy in 22.9% of their patients on ART. They also found that lipodystrophy was more common in women than in males (41.8% Vs 29.5%).

Change in the initial HAART regimens-

In the present study, at the end of 18 months follow up 125 patients who reported adverse effects due to antiretroviral therapy, 40 patients required to change the initial HAART regimen.

Drug toxicity was the major reason for the initial HAART, 37 patients (28.46%) required to change the initial ART regimen, 3 patients required change in the initial HAART due to opportunistic infections (tuberculosis).

In the present study only 2 patients (n=39) who experienced gas-

trointestinal disturbances required to change the therapy.

16 patients (50%) of severe anaemia had to change the regimen (n=32)

Hepatotoxicity was seen in 19 patients and 6 patients (31.5%) patients required to change the initial HAART regimen.

All 6 patients of peripheral neuropathy were required to change the initial HAART regimen.

Among 3 patients of lactic acidosis, all were required to change the therapy, 1 patient of lactic acidosis died and death was attributed to adverse effect.

CONCLUSION-

AZT+3TC+NVP is the most commonly used initial ART regimen in ART clinic. Most of the patients on antiretroviral therapy had at least one adverse effect. Most of the adverse effects of drugs due to antiretroviral therapy are mild and can be managed symptomatically or by adjusting the doses and do not require change in the ART regimen. Gastrointestinal intolerance, anaemia, hepatitis and skin rash are the most common adverse effects of drug due to antiretroviral therapy and often reported in first 12 weeks of starting the ART.

Peripheral neuropathy and lipodystrophy are the long term adverse effects of ART due to Stavudine containing regimen. Some adverse effects like lactic acidosis, Stevens Johnsons Syndrome and severe hepatitis are life threatening and physician should be very vigilant to identify and treat these adverse effects. Regular follow up and monitoring of patients on antiretroviral therapy is mandatory. The examination for adverse effects may help physician to choose regimen better suited to the patients, thereby preventing irregular ART use and need for early change of therapy. Recognizing and managing the adverse effects of antiretroviral therapy is essential as they may compromise adherence and sometimes necessitate change in the regimen thereby exhausting the treatment options.

References :

1. K Park: Textbook Of Preventive and Social Medicine: 18th Edition
2. Joint United Nations Programme on HIV/AIDS (UNAIDS). AIDS epidemic update: December 2007. Geneva: WHO; 2007.
3. HIV Sentinel Surveillance and HIV Estimation in India 2007. A Technical Brief National Aids Control Organization, Ministry Of Health and Family Welfare. October 2008.
4. Mouton Y, Alfandari S, Valette M, et al. Impact of protease inhibitors on AIDS-defining events and hospitalizations in 10 French AIDS reference centers. Federation National des Centers de Luttele, SIDA. AIDS 1997; 11: F101-5.
5. Mocroft A, Vella S, Bevfield TL, et al. Changing pattern of mortality across Europe in patients infected with HIV-1. Lancet 1998; 352: 1725-30.
6. Gilks CF, Crowley S, Ekpini R, Gove S, Perriens J, Souteyrand Y, et al. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. Lancet 2006; 368 (9534):505-12.
7. National AIDS Control Organization. Epidemiology of HIV/AIDS : Specialist's training and reference module. New Delhi .www.nacoonline.com.
8. NACO: Antiretroviral Therapy Guidelines for HIV-Infected Adults and Adolescents Including Post-exposure Prophylaxis May 2007 Ministry of Health and Family Welfare, Govt. of India. Available from electronic information: www.nacoonline.org
9. Sanjay Pujari et al. Guidelines for Use of Antiretroviral Therapy for HIV Infected Individuals in India (ART Guidelines 2008) Journal of Association of Physicians of India (JAPI) vol.56; may 2008, 339-371.
10. Guidelines for HIV DIAGNOSIS and Monitoring of ANTIRETROVIRAL THERAPY WHO Project: online WHO website: www.who.com
11. 11 Cristiane A. Menezes de Pádua, Cibele C. César, Palmira F. Bonolo, Francisco A. Acurcio and Mark Drew C. Guimarães. Self-Reported Adverse Reactions Among Patients Initiating Antiretroviral Therapy in Brazil The Brazilian Journal of Infectious Diseases 2007; 11(1):20-26.

12. **12 Kumaraswamy N, Solomon S, Jayaker Paul SA et al.** Spectrum of opportunistic infections among AIDS patient in Tamil Nadu, India. *Int J STD AIDS* 1995; 6:447-9.
13. **13 N.Kumarsamy et al.** Spectrum of Adverse Events After Generic HAART in Southern Indian HIV-Infected Patients AIDS PATIENT CARE and STDs Volume 22, Number 4, 2008.
14. **14 Ajay Sharma, Megha Modi, Archana Sharma, YS Marfatia.** Stavudine Zidovudine as antiretroviral therapy. *India Indian journal of sexually transmitted diseases: 2007 | Volume : 28 | Issue : 1 | Page : 26-29.*
15. **15 Ajith Sivadasan,OC Abraham, Priscilla Rupali, Susanne A Pulimood, Joyce Rajan .**High Rates of Regimen Change due to Drug Toxicity Among a Cohort of South Indian Adults with HIV Infection Initiated on Generic, First-Line Antiretroviral Treatment, JAPI • MAY 2009 • VOL. 57:384-389.
16. **16 Department of Health and Human services (DHHS) USA , guidelines;** *Ann intern Med.*2002; 137:381
17. Tom Egwang .Toxicity of Nevirapine based ART differs in HIV infected Mozambian and Thai women with higher CD4 count .Abstract no.752,14th Conference on Retroviruses and opportunistic infections.25-28 Feb.2007.