Comparative Study Of Adverse Drug Reactions Of Two Antiretroviral Regimens (Zidovudine+ Lamivudine + Nevirapine Vs Stavudine+ Lamivudine+ Nevirapine) In Hiv/Aids Patients

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Abstract: *AIDS (acquired immunodeficiency syndrome) is one of the most destructive pandemics in the history of medicine with 6800 people infected afresh with HIV virus and more than 5700 deaths everyday across the globe. In India 2.39 million people are suffering with HIV/AIDS . Death rate is dropping down due to the availability of treatment freely in ART centres under NACO. The HIV/AIDS patients are treated with combination of 3 antiretroviral drugs as one regimen in all ART centres. The two regimens commonly used in ART centres are ZIDOVUDINE +LAMIVUDINE +NEVIRAPINE (Category A) and STAVUDINE+LAMIVUDINE+NEVIRAPINE (Category B). Though these drugs have been decreasing death rate, they have many side effects. So we studied and compared the side effects of two regimens. We have enrolled 650 patients visiting ART centres at Siddhartha medical college,Vijayawada and Guntur medical college,Guntur from october 2006 to march 2008. The results showed category A has less side effects than category B.*

Keywords: *AIDS, ART centre, HIV, NACO*

I. Introduction

AIDS, the acquired immunodeficiency syndrome is a fatal illness caused by a retrovirus known as the human immunodeficiency virus(HIV)which breaks down the body"s immune system, leaving the victim vulnerable to a host of life-threatening opportunistic infections, neurological disorders, or unusual malignancies.[1] AIDS was first recognized in the United States in the summer of 1981, The human immunodeficiency virus was isolated in 1983[2]. HIV disease is one of the most destructive pandemics in recorded history with 6800 people infected afresh and more than 5700 deaths everyday across the globe . In India more than 2.39 million people are suffering with HIV/AIDS[3,4,5]. The first effective antiretroviral agent , Zidovudine was approved in 1987. The use of single drug (mono therapy) has been discontinued due to the high mutation rate of HIV.[6] and three drug regimens are used as they are more effective[7,8,9,10,] which is called as Highly Active Antiretroviral Therapy (HAART).

Government of India has started free ART centers across the country through National AIDS Controlling Organization (NACO) on 1st April 2004. Currently there are about 127 ART centers in India by 2007 and 24 ART centres in Andhra Pradesh by 2007.[3]

Today globally around 25 antiretroviral drugs are available to prolong the life of HIV/AIDS patients. At present in India NACO is providing only 4-5 drugs in two regimens through ART centers[11,12]. In this scenario, as there are very little number of studies on their side effects,we take this opportunity of comparing two regimens i.e., Zidovudine, Lamuvudine and Nevirapine under one arm (regimen A)and Stavudine, lamivudine and Nevirapine under the another arm (regimen B) about the occurrence of potential adverse drug reactions caused by such regimens. This study is done within the framework of facilities of laboratory investigations, other methods available at ART centers affiliated to Siddhartha medical college, Vijayawada and Guntur medical college ,Guntur.

II. Materials And Methods

It is a longitudinal, prospective, observational study, carried at ART centres of siddhartha medical college, Vijayawada and Guntur medical college, Guntur from october 2006 to march 2008, after the approval of college ethical committee. An informed consent was taken from each patient.

2.1. Inclusion Criteria:-
2.1.1. Patients were declared as HIV + ve as per NACO guidelines in the VCTCs under the departments of Microbiology, Siddhartha Medical College, Vijayawada and Guntur Medical College, Guntur.
2.1.2. Both males and female patients aged above 13 years.
2.1.3. Patients enrolled at ART centers, Vijayawada and Guntur are included.

2.1.4. Patients with CD4 + cell count less than 200cells/cumm and between 200cells/cu.mm and 300 cells /cu.mm with symptomatic HIV disease .

2.1.5. Patients who were intiated with Highly active antiretroviral therapy(HAART) by two regimens i.e Tab.Zidovudine +Tab.Lamivudine+Tab.Nevirapine and Tab. Stavudine + Tab.Lamivudine + Tab. Nevirapine.

2.2.Exclusion Criteria:

2.2.1. Children below 13 years

2.2.2. Pregnant women .

2.2.3. Patients already used/ using ART outside and attending ART clinic

2.2.4. Patients with chronic renal, hepatic and heart failure.

All patients were asked to visit ART centres if they developed any symptoms or on a monthly basis. They were screened clinically and investigated suitably for all ADRs periodically.

CD4 + cell count measured with machine made by Beckson and Dickinson company, made in USA and Beckson and Dickinson kits, available at Department of Microbiology, GMC,Guntur. Hemoglobin percentage was estimated with Sahli's method, SGOT with Kinetic method, SGPT with kinetic method (rapid kit), sr.creatinine with Jafes method and S.bilirubin with Diazo method (manual) at department of Biochemistry, Siddhartha medical College, Vijayawada and Guntur Medical College, Guntur.

2.3. Normal ranges of the parameters:

2.3.1. Hemoglobin:

Males :-14.5gm-16.5gm.

Females:-13.5gm-15.5gm.

 (Anemia = < 8gm. Or < 50% ;1 gm.=6.5%)

2.3.2. Total leucocyte count:-7000-11000 cells/cumm

2.3.3. Platelet count:- 1.5 lacs ʙ 4 lacs

2.3.4. SGOT:-5-45i.u.

2.3.5. SGPT:-5-35i.u.

2.3.6. S.creatinine:-0.7-1.5

2.3.7. S.bilirubin:- <1mg.

650 patients were enrolled into study. Out of 650, 325 patients were received Tab.Zidovudine +Tab.Lamivudine+Tab.Nevirapine (Regimen A) and 325 patients were received Tab. Stavudine + Tab.Lamivudine + Tab. Nevirapine (Regimen B) in fixed drug combination.The study is designed for a Period of 12 months by recording above observations at 0 months, 6months and 12months.

An informative questionnaire in the local language (telugu) regarding adverse drug reactions is collected from patients.All the cases enrolled had been studied prospectively at the ART centres and the data entered into the case sheets.The adherence to the ART is assessed by asking the patients to get the empty drug bottles and checking the number of remaining tablets.

The chi-square test is applied for all the parameters after 6 months data and after 12 months data with degree of freedom (df) of >1= and >P= value as 0.05 (p=0.05) and the level of significance as x^2 >3.84.

Limitations of study:-

1. The period of study was not sufficient to assess long term adverse effect profile as HIV / AIDS patients living longer with ART.
2. We were unable to assess the coinfection and influence of hepatitis B and C & syphilis on ADRs as diagnostic tests for them were not carried out in our centre.

III. Results

Distribution of cases according to age:

Graph No.1
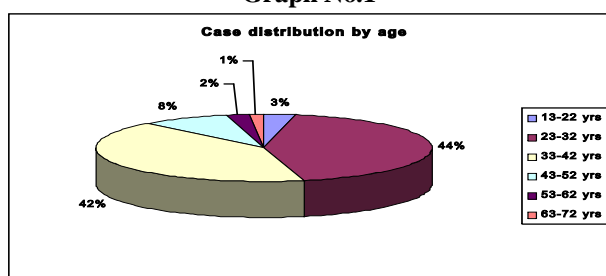
Six hundred and fifty patients were enrolled into the study. Out of 650 patients, 3% [n=19] were belonged to 13-22 years, 43% [n=279] were belonged to 23-32years, 42% [n=273] belonged to 33-42 years, 8.4% [n=55] were belonged to 43-52 years, 2.2% [n=14] were belonged to 53-62 years and 1.4% [n=10] belonged to 63-72 years. Maximum number of patients i.e. 43% [n=279] and 42% [n=273] belonged to 23-32 years and 33-42 years respectively.

Distribution of cases according to gender:

Graph No.2
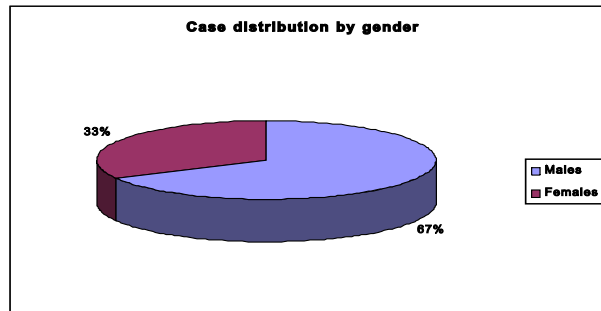
Out of 650 patients, 67.2% [n=437] were males and 32.8% [n=213] were females. So more no. of males were attending ART centre.

Adverse effects after six months of treatment:
(df =1, P value =0.05, $X^2 \exists 3.84$)

In the first 6 months of treatment, 4% [n=13] deaths and 6% [n=22] lost for follow ups (LFPs) on regimen A and 3% [n=10] deaths and 6% [n=19] LFPs on regimen B were occured. So 290 cases in regimen A and 296 cases in regimen B were available for evaluation.
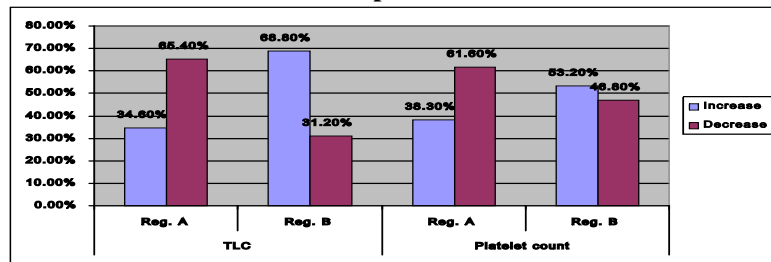
I. HEMATOLOGICAL Adrs:-

Graph No.3
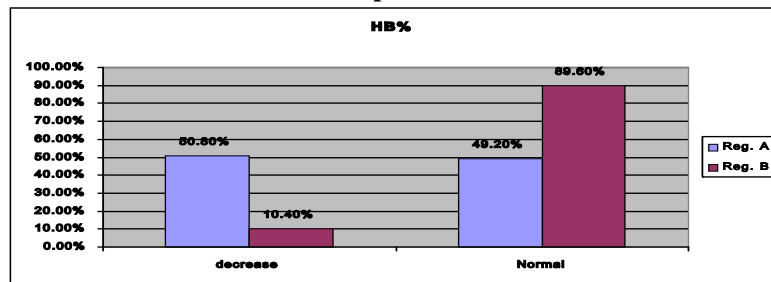
After 6 months of treatment with regimen A, 50.8% [n=147] had anemia, with regimen B 10.4% [n=31] had anemia,
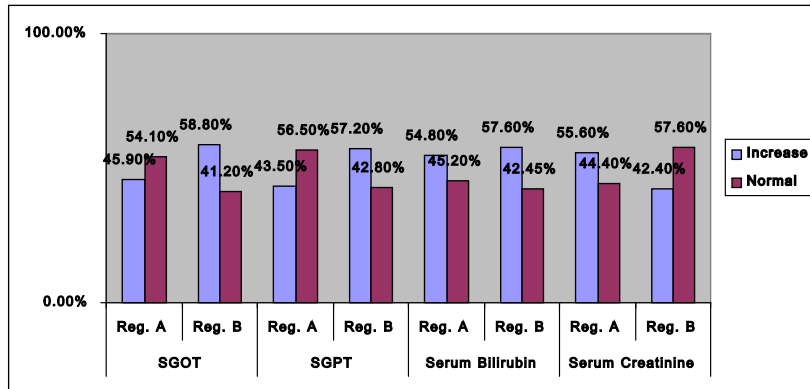
Graph No.4

With regimen A, 34.6% [n=101] had increased TLC, 38.3% [n=111] had increased platelet count, and with Regimen B, 68.8% [n=204] had increased TLC, 53.2% [n=157] has increased platelet count,

II.Hepatic And Renal Adrs:

Graph No.5

With regimen A,45.9%[(n=133)] had elevated SGOT levels, 43.5%[(n=126)] had elevated SGPT levels, 54.8%[(n=159)] had elevated serum bilirubin Levels, 55.6%[(n=161)] had elevated serum creatinine Levels, with regimen B, 58.8%[(n=174)] had elevated SGOT levels, 57.2%[(n=169)] had elevated SGPT levels, 57.6%[(n=170)] had elevated serum bilirubin levels, 42.4%[(n=126)] had elevated sr.creatinine levels,

Graph No.6
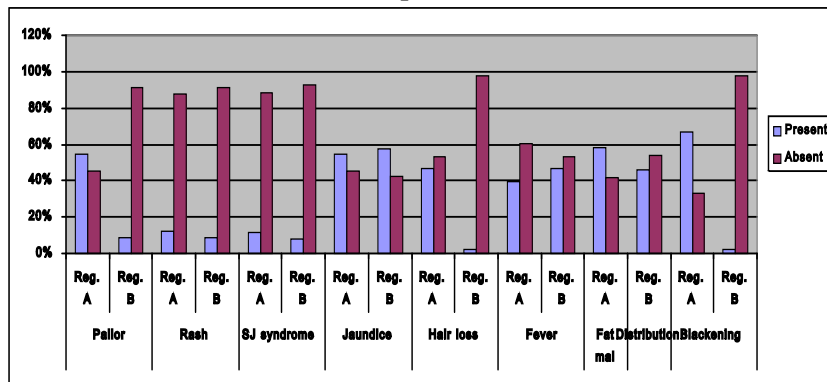
With regimen A,54.8%[(n=159)] had pallor, 12.4%[(n=36)] had rash, 11.3% [(n=33)] had SJ syndrome, 54.8% [(n=159)] had jaundice, 46.7% [(n=135)] had hairloss, 39.5% [(n=115)] had fever, 58.4%[(n=169)] had fat maldistribution, 66.8%[(n=194)] had Finger nail blackening and with regimen B , 8.4%[(n=25)]had pallor 8.8%[(n=26)] had rash, 46%[(n=136)] had fat maldistribution and 6%[(n=23)] had SJ syndrome, 57.6% [(n=170)] had jaundice, , 2.4% [(n=7)] had hairloss, 46.8% [(n=139)] had fever and 2.4%[(n=7)] had finger nail blackening,
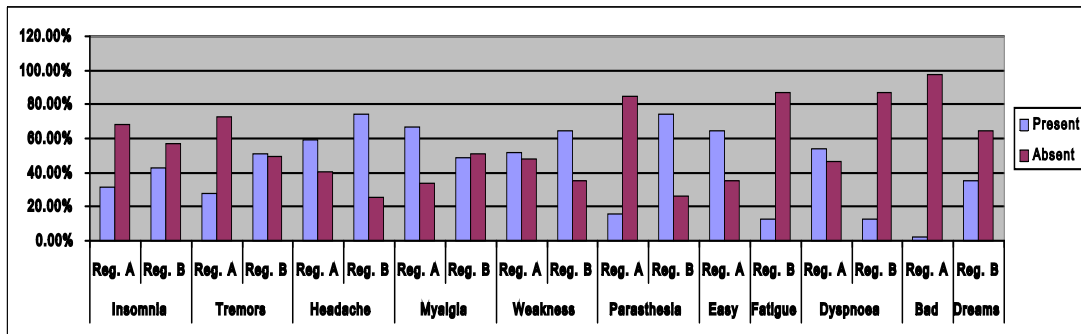`

III.GIT Adrs:-

Graph No.7
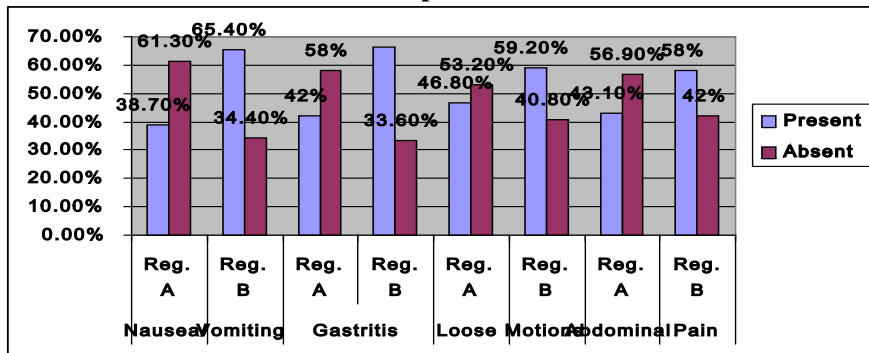
With regimen A ,38.7%[(n=112)] had nausea and vomiting, 46.8%[(n=136)] had diarrhoea, 43,1%[(n=125)] had pain abdomen, 42%[(n=122)] had gastritis,90%[(n=156)] and With regimen B 65.6%[(n=194)] had nausea and vomiting, 59.2%[(n=175)] had diarrhoea, 58%[(n=172)] had pain abdomen 66.4%[(n=197)] had gastritis,

IV.CNS Adrs:-

Graph No.8

With regimen A,31.6%[(n=92)] had insomnia, 27.6%[(n=80)] had tremors,59.3%[(n=172)] had headache, 66.4%[(n=193)] had myalgia, 52%[(n=151)] had weakness,15.6%[(n=45)] had parasthesia, 64.5%[(n=187)] had easy fatigue2.4%[(n=7)] had bad dreams and with regimen B, 42.8%[(n=127)] had insomnia, 50.8%[(n=150)] had tremors,12.8%[(n=38)] had easy fatigue, 74%[(n=219)] had parasthesia, 64.4%[(n=191)] had weakness, 48.8%[(n=144)] had myalgia, 12.8%[(n=38)] had dyspnoea, 74.4% [(n=220)] had headache, , 35.6% [(n=105)] had bad dreams,
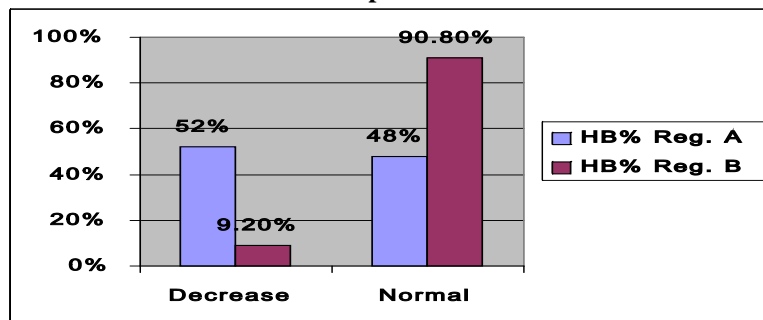
Adverse effects after twelve months of treatment:-
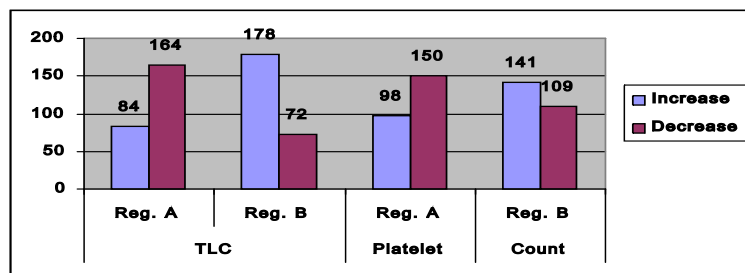(df =1, P value =0.05, $X^2 \exists 3.84$)

In the second 6 months of treatment, 6%[(n=17)] deaths and 8%[(n=25)] LFPs in regimen A and 7%%[(n= 20)] deaths and 10%[(n=26)] LFPs in the regimen B were lost . So 248cases in regimen A and 250cases in regimen B were available for evaluation .
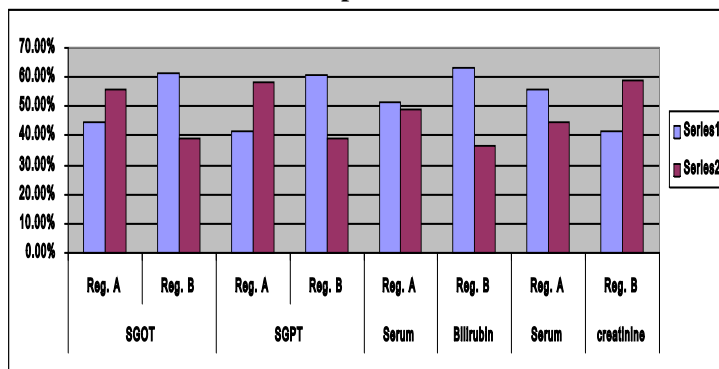
I.Hematological Adrs:-

Graph No.9

GRAPH NO.10

After twelve months of treatment with regimen A, 91.2%[(n=227)] had anemia, 34%[(n =84)] had increased TLC, 39.6%[(n=98)] had increased platelet count, After twelve months of treatment with Regimen B, 9.2%[(n=23)] had anemia, 71.2%[(n =178)] had increased TLC, 56.4%[(n=141)] has increased platelet count,

Hepatic And Renal Adrs:

Graph No.11

With regimen A,44.3%[(n=110)] had increased SGOT levels, 41.6%[(n=103)] had elevated SGPT levels, 51.2%[(n=127)] had elevated serum bilirubin levels, 55.6%[(n=138)] had elevated serum creatinine levels and With regimen B, 61.2%[(n=153)] had elevated SGOT levels, 60.8%[(n=152)] had elevated SGPT levels, 63.2%[(n=158)] had elevated serum bilirubin levels, 41.6%[(n=104)] had elevated sr.creatinine levels,

Ii.Dermatological Adrs:-

Graph No.12
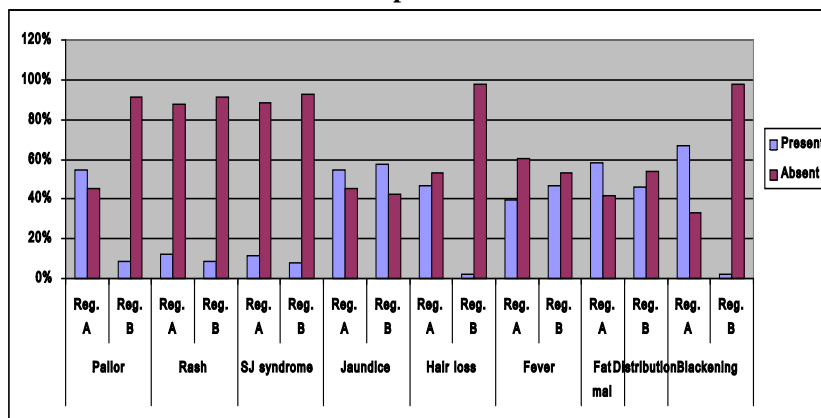
With regimen A,59.3%[(n=147)] had pallor, 25.6%[(n=63)] had rash, 65.2%[(n=162)] had fat maldistribution, 69.2%[(n=172)] had finger nail blackening, 51.2% [(n=127)] had jaundice,50.8% [(n=126)] had hairloss, 30.6% [(n=76)] had fever and with regimen B, 10.4%[(n=26)] had pallor, 23.6%[(n=59)] had rash, 63.2% [(n=158)] had jaundice, 2% [(n=5)] had hairloss, 43.6% [(n=109)] had fever,49.6%[(n=124)] had fat maldistribution and 2%[(n=5)] had finger nail blackening .
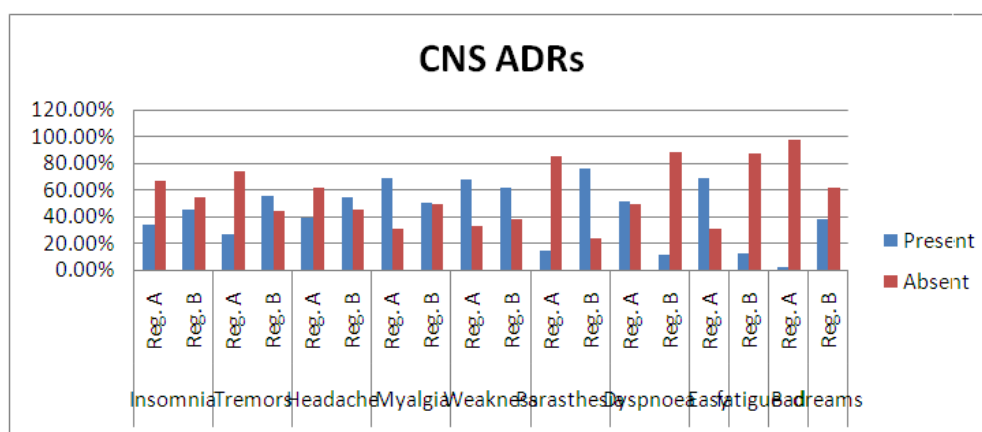
III.GIT Adrs:-

Graph No.13
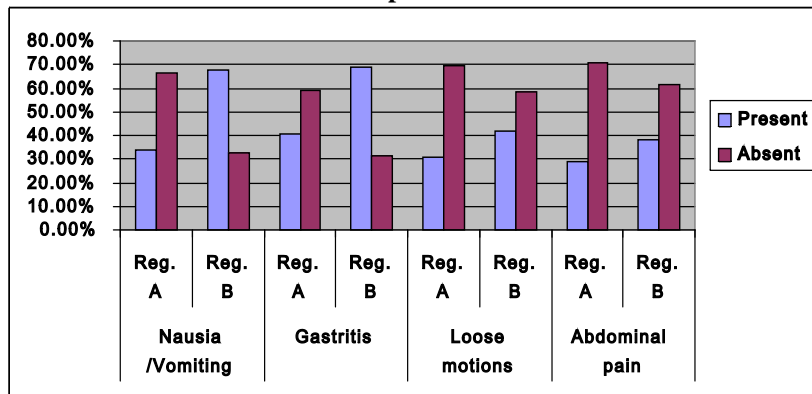
With regimen A, 33.8%[(n=84)] had nausea and vomiting,30.6%[(n=76)] had diarrhoea, 29%[(n=72)] had pain abdomen, 40.8%[(n=101)] had gastritis and with regimen B, 67.6%[(n =169)] had nausea and vomiting, 68.8%[(n=172)] had gastritis, 41.6%[(n=104)] had diarrhoea, 38.4%[(n=96)] had pain abdomen,

IV.CNS Adrs:-

Graph No.14

With regimen A,33.6%[(n=83)] had insomnia, 68.8%[(n=171)] had easy fatigue, 14.4%[(n=35)] had parasthesia, 67.2%[(n=167)] had weakness, 26.4%[(n=65)] had tremors, 69.2%[(n=172)] had myalgia, 92%[(n=229)] had dyspnoea, 38.7% [(n=96)] had headache, 2.1% [(n=5)] had bad dreams and With regimen B, 45.2%[(n=113)] had insomnia, 12.4%[(n=31)] had easy fatigue, 76.4%[(n=191)] had parasthesia, 61.6%[(n=154)] had weakness, 55.6%[(n=139)] had tremors, 50.4%[(n=126)] had myalgia, 11.6%[(n=29)] had dyspnoea, 54.8% [(n=137)] had headache, 38.4%[(n=96)] had bad dreams,

IV. Discussion

AIDS / HIV patients had remarkable and drastic changes in mortality and morbidity of life with anti retroviral therapy. The selection of initiating regimen and shifting to alternate regimen depends upon the resource settings. The available studies today were mostly pertained to the resource rich settings. Due to the potential adverse drug reactions of ART, regimen selection plays a vital role in our resource poor settings.

ART is becoming increasingly effective but also increasingly complex. Adverse effects of therapy may cause symptoms that affect a variety of organ systems. Although current antiretroviral regimens are potent from an antiviral prospective, they often fail because of patient non adherence which is mostly due to adverse effects. 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.

650 cases were registered and 23.3%[(n =152)] cases were lost as deaths and lost for follow up (LFP) during 12 months study. So 498 cases were observed for a period of 12 months.

Dr.Senthil.R[(13)], convener, Indian parliamentarians forum reported 6%deaths and 8% LFPs occured after 6months of HAART and 8%deaths and 9% LFPs occurred after 12 months of HAART. While in this study it was observed that 4% [(n=13)]deaths and 6%[(n=22)] LFPs on regimen A and 3%[(n=10)]deaths and 6%[(n=19)]LFPs on regimen B were lost in the first 6 months of HAART and 6%[(n=17)]deaths and 8%[(n=25)]LFPs on regimen A and 7%[(n=20)]deaths and 10%[(n=26)] on regimen B were lost after 12 months of HAART.

Ajay Sharma et al [(14)] reported AZT induced finger nail blackening in 56% patients. While in the present study it was observed in 69%[(n= 172)] patients on Regimen A and 2%[(n=5)] patients on Regimen B.

Yogesh Marfatia et al[(15)] reported rash in 15% and 8% with regimen A and regimen B respectively and SJ syndrome in 3% of patients and the hairloss was reported in 30%. While in this study rash was observed in 25%[(n=63)] and 23%[(n=59)]patients, SJ syndrome was observed in 11.3%[(n=33)] and 7.6%[(n=23)] patients and hair loss was observed in 50.8% [(n=126)] and 2%[(n=5)] patients with regimen A and regimen B respectively. The most common cutaneous ADR observed was rash and hairloss.

O=Brien et al [(16)]reported ART induced gastritis in 44% patients While in this study it was observed in 40%[(n=101)] and 68%[(n=172)]patients with regimen A and regimen B respectively.

Maniar J et al[(17)] reported abdominal pain in 7% of patients and Y.Marfatia et al reported in 22% patients. While in this study it was observed in 29%[(n=72)] and 38%[(n=96)]patients with regimen A and regimen B respectively.

Ajay Sharma et al [(14)] reported diarrhoea in 11% patients. While in the present study it was observed in 30%[(n= 76)] patients on Regimen A and 41%[(n=104)] patients on Regimen B.

Y.Marfatia et al [15] reported nausea / vomiting in 30% and 70% patients. While in the present study it was observed in 33.8 % [n= 84] patients and 67.6% [n=169] p ` atients with Regimen A and Regimen B respectively.

The most common gastrointestinal tract ADR was gastritis 68% [n=172]. In a study by O=Brien et al[70], GI events were mentioned as the most common reason (4.4%) for a patient to discontinue ART.

Dournan et al [18] reported Azidothymidine induced anemia in 16.5% cases while in this study it was observed in 52% [n =128] with Regimen A and 9.2% [n =23] with Regimen B.

Ajay Sharma et al [14] reported increase in total leucocyte count in 10% patients. While in the present study it was observed in 34% [n= 84] patients and 71.2% [n=178] patients and the increase in platelet count was observed in 39.6% [n=98] patients and 56.4% [n=141] with regimen A and regimen B respectively.

Ajay Sharma et al [14] reported abnormal LFTs in 9% and 5% patients with regimen A and regimenB respectively. While in the present study increase in SGOT was observed in 44.3% [n= 110] patients and 61.2% [n=153] patients , increase in SGPT was observed in 441.6% [n= 103] patients and 60.8% [n=152] patients, increase in S.bilirubin was observed in 51.2% [n= 127] patients and 63.2% [n=15] patients, increase in S.creatinine was observed in 55.6% [n= 138] patients and 41.6% [n=104] patients with regimen A and regimen B respectively. The most common hepatic ADR is increase in LFTs (63.2%) [n =158] which is due to regimen B and common hematological ADR is anemia, (52%, [n =128] which is due to regimen A.

H forett Smith et al[19] reported AZT induced parasthesia in 24% and Stavudine induced in 40% while in this study it was observed that Regimen A induced parasthesia in 14.4% [n =35] and Regimen B induced in 76.4% [n =191] patients.

Ajay Sharma et al[14] reported headache in 9% and 3% patients with regimen A and regimen B respectively. While in the present study it was observed in 38.7 % [n= 96] patients and 54.8% [n=137] patients with regimen A and regimen B respectively.

Ajay Sharma et al [14] reported bad dreams in 1% and 6% patients with regimen A and regimen B respectively. While in the present study it was observed in 2.1% [n= 5] patients and 38.4% [n=96] patients with regimen A and regimen B respectively.

Tremors were observed in 26.4% [n=65] and 55.6% [n=139] patients, , myalgias insomnia was observed in 33.6% [n=83] and 45.2% [n=113] in 69.2% [n=172] and 50.4% [n=126] patients with regimen A and regimen B respectively.The most common central nervous system ADR was increase in parasthesia (76.4%, [n=191]) and tremors (55.6%, [n =139]) which are due to regimen B.

Dyspnoea was observed in 51% [n=126] patients and 11.6% patients, easy fatigue in 68.8% [n=171] and 12.4% [n=31] patients, pallor in 59.3% [n=147] and 10.4% [n=26] patients, weakness in 67.2% [n=167] and 61.6% [n=154] patients, fever in 30.6% [n=76] and 43.6% [n=109] patients was observed with regimen A and regimen B respectively. All the above are due to the anemia. Jaundice was observed in 51.2% [n=122] patients and 63.2% [n=158] patients with regimen A and regimen B respectively. This is due to abnormal LFTs.

Saint Marc et al[20] reported AZT induced Lipodystrophy in 18.75% and Stavudine induced lipodystrophy in 64% cases. While in this study it was observed that Regimen A induced in 65.2% [n =162] patients and regimen B induced in 49.6% [n =124] patients.

Van Leeuwen et al[21] reported change of regimen A to regimen B due to severe anemia in 34% cases and Ajay sharma et al reported this change in 7.4% cases ` While in this study it was observed that the regimen A was changed to regimen B in 17% [n=44] cases .
The severity of parasthesias and tremors needed a change of regimen B to regimen A in 21% [n=54] cases.

V. Summary & Conclusion

National Aids Control oganisation (NACO) is offeringtwo regimens of antiretroviral drugs for the needy HIV/AIDS patients all over India through established ART centres.The introduction of HAART has led to significant reduction in AIDS related morbidity and mortality. In this scenario, pertained to the available resources at our centre, we sought to study adverse drug reactions for these ART regimens in a period of one year.

This study showed that Zidovudine containing regimen A significantly lowers hemoglobin levels. The serum creatinine was significantly increased and anemia, easy fatigue, pallor, weakness, myalgia, rash, fat maldistribution, finger nail blackening, dyspnoea and hairloss were significantly observed in patients who were put on Regimen A.

The SGOT , SGPT serum bilirubin levels, the total leucocyte count and the platelet count were significantly increased and parasthesia, weakness, tremors, insomnia, gastritis, nausea / vomiting, diarrhea, pain abdomen, headache, bad dreams, jaundice and fever were significantly observed in patients who were put on Regimen B.

This study had 60 deaths and 92 lost for follow ups (LFPs). It is a serious problem. 23.3 % [n=152] patients losing in the form of deaths and LFPs was highly significant. The cause of deaths and LFPs could not be found as it was beyond the scope of this study. So we could not investigate. But yet the reasons could not be

ignored and left unexplained. The possible reasons might be the disease itself, due to nonadherence, increased opportunistic infections, lack of nuitrition, again nonadherence due to ADRs and drug resistance etc. So the death enquiry and auditing should be done.

To substantiate the results, though stavudine containing regimen B has better efficacy, but produces serious adverse effects. Hence, this study suggests zidovudine containing regimen A as it causes less severe side effects. But actually we need to substitute these regimens with better available agents to decrease adverse effect profile and increase the patient compliance.

Acknowledgements

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