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Original Research Article

Comparative study of adverse effect profile of first line drugs Zidovudine (ZDV) + Lamivudine (3TC) + Nevirapine (NVP) Vs Tenofovir (TDF) + Lamivudine (3TC) + Atazanavir (ATV) + Ritonovir (RTV) in HIV/AIDS patients

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ABSTRACT

Background: The biggest threat to mankind from the health perspective is probably the virus Human Immunodeficiency Virus (HIV) responsible for a serious disease known as Acquired Immune Deficiency Syndrome (AIDS). To compare the adverse effect profile of two antiretroviral regimens i.e, Zidovudine (ZDV) + Lamivudine (3TC) + Nevirapine (NVP) [regimen A] Vs Tenofovir (TDF) + Lamivudine (3TC) + Atazanavir(ATV) + Ritonavir (RTV) [regimen B] by clinical and biochemical methods.

Methods: This prospective, observational study was carried out in 200 HIV positive patients receiving first line and second-line antiretroviral therapy (ART) at ART centre, GGH, Vijayawada. Out of 200 patients, 100 patients received regimen A [(ZDV) + (3TC) + (NVP)] and 100 patients were treated with regimen B [(TDF) + (3TC) + (ATV) + (RTV)]. The collected data has been analysed and presented.

Results: Out of 200 patients, 110 patients developed ADRs. In this 110, 38 patients received regimen A and 18 patients received regimen B and had CD4 + count <250 cells/mm^3. In the remaining 54 patients, 20 patients received regimen A and 34 patients received regimen B who had CD4+ count >250 cells/ mm^3.

Conclusions: The ADRs were most common in those patients whose CD4+ count is less than 250cells/cu mm. Though the patients on second line showed significant increase in CD4+count, number of patients with ADRs were also more with regimen B. Though atazanavir containing regimen is more efficacious than zidovudine containing regimen, but regimen B produces more serious adverse effects. So, second line drugs are reserved for treatment failures to first line, drug resistance and for those not tolerating first line drugs.

Keywords: AIDS, ADRs, HIV, Atazanavir, ART

INTRODUCTION

HIV is a retrovirus that causes chronic persistent infection with gradual onset of symptoms leading to immunosuppression, leaving the victim vulnerable to a host of life threatening opportunistic infections, neurological disorders and unusual malignancies.[1] At the end of 2016, an estimated 36.7 million people [34.0 million-39.8 million] were living with HIV worldwide. Globally there were 1.8million new HIV infections and 1.1 million people died of AIDS-related causes in 2016.[2] HIV/AIDS is the world's sixth largest cause of death in humans, accounting 3.1% of all deaths.[3] India ranks third among the countries having most number of HIV-infected people and HIV related deaths in the world.[4]

The basic principles of treatment of HIV disease are long term suppression of HIV replication and repletion of peripheral CD4 cells.[5] Treatment of HIV with monotherapy has been associated with high mutation rates and the use of multiple drugs that act on different viral targets is known as highly active antiretroviral therapy (HAART).[6] HAART decreases the patient's total viral load of HIV, maintains function of the immune system, and prevents opportunistic infections that often lead to death. Second line ART drugs are initiated in those patients who are showing immunological failure to first line drugs and those who are not tolerating first line regimen. The common second line regimen advocated in this set up includes tenofovir + lamivudine + atazanavir + ritonavir.[7]

HAART significantly delays the onset of AIDS in people living with HIV and decrease the progression to AIDS and AIDS related mortality and prolongs the survival.[8,9] There are increasing reports of multi-drug resistant (MDR) virus in treatment experienced patients.[10] The problem of drug resistance has led to the concept of second line anti-retroviral therapy (ART).

Currently, first line ARVs are prescribed for treatment-naïve patients, that includes nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and nucleotide analogues, while protease inhibitors (PIs) are reserved as the second line ARVs for treatment-experienced patients and treatment failure with first-line of drugs. Treatment failure to first line therapy is identified by clinical, immunological and virological monitoring. In India, second line ART was introduced in the national programme in a phased manner since January 2008. As second line ART is recently introduced in India, so data of its effectiveness and safety in Indian patients is not available. Therefore, the present study was undertaken to evaluate the safety of second line ART in HIV positive patients in comparison with the patients receiving first line ART attending ART centre, GGH.

METHODS

Study design

This was a continuous, longitudinal, prospective, observational study carried out in HIV positive patients attending antiretroviral therapy (ART) centre, government general hospital, Vijayawada.

Study method

The study protocol was approved by institutional ethical committee. Patients receiving first-line ARV drugs from National AIDS Control Organisation (NACO) for at least six months and suspected of having treatment failure were examined by State AIDS Clinical Expert Panel (SACEP). These patients were evaluated clinically, immunologically (CD4 count) and virologically (plasma viral load). Patients started on second-line ART from November 2011 to November 2012 and fulfilling inclusion and exclusion criteria were included in the study. At first visit, pre-treatment assessment data such as physical examination, baseline CD4 count, plasma viral load and laboratory investigations and details of prescribed drugs were recorded in case record form (CRF). The patients were followed up every month for clinical assessment and to monitor adverse drug reactions (ADRs) till completion of 1-year of second-line treatment.

Inclusion criteria

- Both males and females aged above 18 years enrolled at ART Plus centre, Vijayawada
- Patients with CD4 cell count < 350 cells/cubic mm.
- Patients initiated with HAART by two regimens i.e. Zidovudine +Lamivudine +
- Nevirapine and Tenofovir + Lamivudine + Atazanavir + Ritonavir.

Exclusion criteria

- Patients below 18 years, pregnant and lactating women.
- Patients with chronic conditions like renal, hepatic and heart failure.

NACO guidelines for second-line ART monitoring is given in Table 1.

Plasma viral load

Plasma viral load is estimated by two methods i.e. Polymerase chain reaction test (PCR) and Branched chain DNA assay (b-DNA) every 6months at the Centre of Excellence (COE), Gandhi Hospital, Secunderabad.

Table 1: Laboratory monitoring according to NACO guidelines second-line ART.

Visit parameters	Base line	Day 15	1 month	3 months	6 months	End of study
Hb,CBC	√	√	√	√	√	√
LFT	√			√	√	√
RFT	√			√	√	√
RBS	√					√
Lipid profile	√					√
Plasma viral load	√				√	
CD4 count	√				√	√

A total of 200 patients were enrolled in the study. Out of 200 patients, 100patients received regimen A [(ZDV) + (3TC) + (NVP)] and remaining 100 received regimen B [(TDF) + (3TC) + (ATV) + (RTV)]. The study was carried out for a period of 12 months and patients were examined every month.

Statistics

The data was recorded in Microsoft Excel Worksheet and analyzed using statistical package for social sciences (SPSS) for windows version 22. Descriptive statistics, percentages, proportions and chi square are applied where ever required. P value < 0.05 was considered to be significant (0.01).

RESULTS

Demographic details

Age and gender wise distribution

Two hundred patients were enrolled into the study. Out of 200 patients, 6.5% (n=13) belonged to 15-25 years, 34.5% (n=69) belonged to 26-35 years, 41% (n=82) belonged to 36-45 years, 15.5% (n=31) belonged to 46-55 years and 2.5% (n=5) patients belonged to age group 55-65 years. Maximum number of patients i.e. 41% (n=82) and 34.5% (n=69) belonged to age groups 36-45 years and 26-35 years. The median age for regimen A is 37 years and for regimen B it is 39 years. Out of 200 patients, 66.5% (n=133) were males and in these 133 males, 59 males belonged to regimen A and 74 belonged to regimen B. 33.5% (n=67) were females and in this 41 belonged to regimen A and 26 belonged to Regimen B. So, more number of male patients were attending the ART centre in both the regimens compared to number of females.

After 6 months of treatment with regimen A, 63.6% (n=63) had increase weight, 70% (n=70) had increased CD4+ count and with regimen B, 69.4% (n=66) had increased weight, 83.1% (n=79) had increased CD4+ count. The mean increase in CD4+ count in regimen A is 240cells/cu mm from 191cells/cu mm and in regimen B 180cells/cu mm from 66cells/mm^3 (Table 2).

Table 2: Weight and CD4+ count.

Parameter	Regimen	Increase (%)	Decrease (%)	Total	Chi-square
Weight	A	63(63.6)	36(36.3)	99	0.831
	B	66(69.4)	29(30.5)	95	
CD4+	A	70(70.7)	29(29.2)	99	4.069
	B	79(83.1)	16(16.8)	95	

In this study 110 patients developed ADRs and of these 38 patients received regimen A and 34 patients received regimen B who had CD4+ count <250 cells/mm^3. Of the remaining 38 patients, 20 patients received regimen A and 18 patients received regimen B who had CD4+ count >250 cells/mm^3 (Table 3).

Table 3: Relationship of ADRs with CD4+ count.

CD4 count	Regimen	No.	ADR present	ADR absent	Chi-square
<250	A	49	38	11	6.642
	B	38	34	4	
>250	A	50	20	30	0.545
	B	57	18	39	

Outcome of treatment after 6 months

After 6 months of treatment with regimen A 43% (n=43) had anemia and with regimen B 26.3% (n=25) developed anemia. The mean decrease in HB% in regimen A is 9.12gm/dl from 9.44gm/dl and in regimen B there is an increased mean from 9.04gm/dl to 10.36gm/dl (Table 4).

Table 4: Hematological ADRs.

Parameter	Regimen	Normal (%)	Decrease (%)	Total	Chi-square
HB%	A	56(56.5)	43(43.4)	99	4.78
	B	70(73.6)	25(26.3)	95	

In the present study patients on regimen A showed elevated liver functions [(n=9) SGOT levels, (n=11) SGPT and (n=23) serum bilirubin] when compared to [(n=34) SGOT levels, (n=29) SGPT and (n=34)] patients who received regimen B (Figure 1).

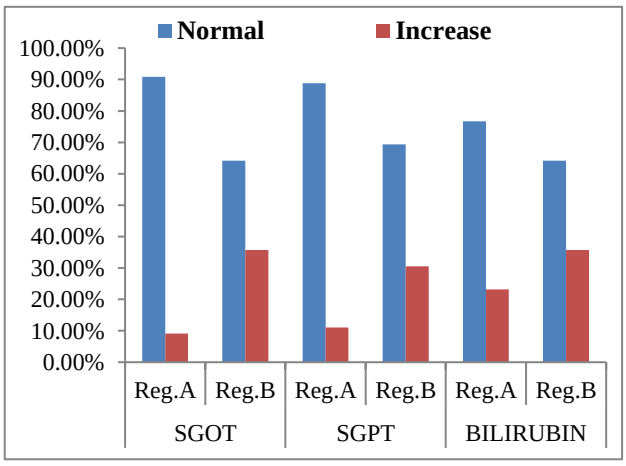

Figure 1: Hepatic ADRS.

Similarly, patients on Regimen A had elevated renal parameters and amongst this 29patients had elevated blood urea and 25 had increased serum creatinine levels. On Regimen B a total of 44pateints had renal function alterations i.e. 27 had elevated blood urea levels, and 17 had elevated serum creatinine levels (Figure 2).

After 12 months of treatment with regimen A, 59.5% (n=59) had increased weight, 66.6% (n=66) had increased

CD4+ count, with regimen B 77.8% (n=74) had increased weight, 86.3% (n=82) had increased CD4+ count. The mean increase in CD4+ count in regimen A and B are 259 cells/mm^3 and 391 cells/mm^3 from baseline and 6 months value (Table 5).

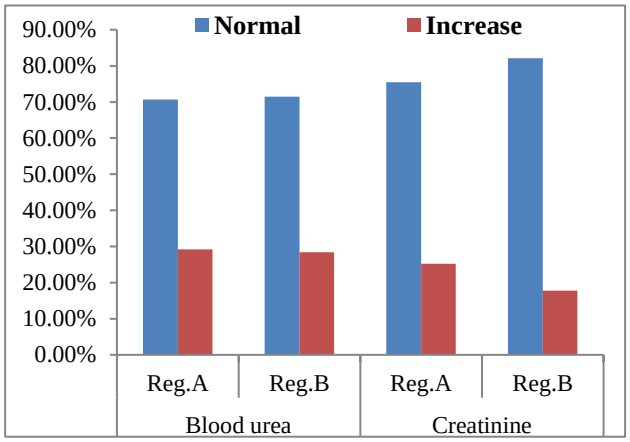

Figure 2: Renal ADRS.

Table 5: Weight and CD4+ count after 12 months therapy.

Parameter	Regimen	Increase (%)	Decrease (%)	Total	Chi-square
Weight	A	59(59.5)	40(40.4)	99	7.748
	B	74(77.8)	21(22.1)	95	
CD4+	A	66(66.6)	33 (33.3)	99	11.398
	B	82 (86.3)	13 (13.6)	95	

Outcome of treatment after 12 months:

After 12months of treatment, 47 patients on regimen A had developed anaemia and with regimen B 30.5% (n=29) had anaemia. There is a mean decrease in Hb% of 9.22gm/dl with regimen A and an increased mean Hb% of 10.70gm/dl with regimen B (Table 6).

Table 6: Hematological ADRs after 12months therapy.

Parameter	Regimen	Normal (%)	Decrease (%)	Total	Chi-square
HB%	A	52(52.5)	52(52.5)	52(52.5)	5.533
	B	47(47.4)	47(47.4)	47(47.4)	

In this study patients on regimen A showed elevated liver functions [(n=11) SGOT levels, (n=13) SGPT and (n=17) serum bilirubin] compared to [(n=34) SGOT levels, (n=29) SGPT and (n=34)] patients who received regimen B (Figure 3).

After 12 months of treatment with Regimen A 19.9 % (n=19) had increased RBS values and 17.8 % (n=17) patients on regimen B had increased RBS values. The alterations in lipid profile values with both regimens A and B has been shown in Figure 5.

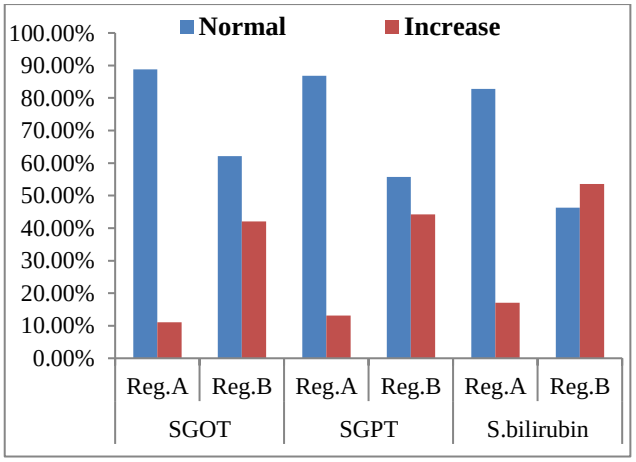

Figure 3: Hepatic ADRS after 12 months therapy.

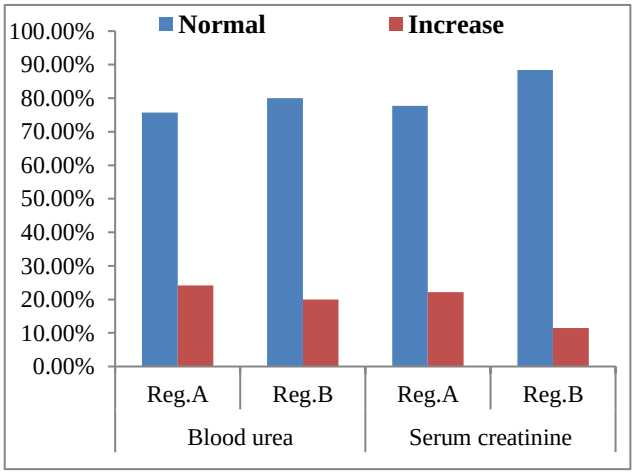

Figure 4: Renal ADRS after 12 months therapy.

In the first 6 months of treatment one patient died in regimen A and 5 patients died in regimen B. After 12months there were no deaths or lost to follow ups in both the regimens. So, 99 cases in regimen A and 95 cases in regimen B were available for evaluation.

DISCUSSION

Acquired immunodeficiency syndrome (AIDS) has been one of the leading causes of the death worldwide. Several classes of antiretroviral drugs (ARVs) are now available; however, none of them can successfully eliminate the Human immunodeficiency virus (HIV) from the body. The increased duration of antiretroviral treatment in such treatment-experienced patients is associated with the problems of adverse drug reactions (ADRs), drug interactions and emergence of drug resistant strains of HIV.

The drug resistance results into treatment failure to first line ARVs necessitating the need for second line ARVs in HIV positive patients. Thus, second line ARVs have become an important component for the effective management of treatment-failure patients.

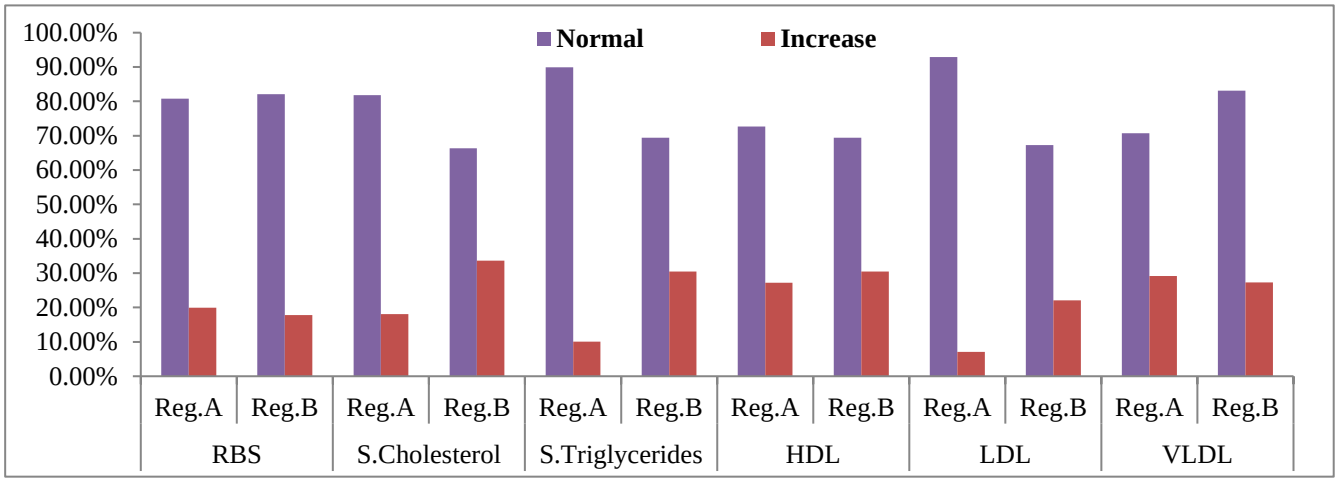

Figure 5: Metabolic ADRS.

Table 7: Comparison of immunological outcome of patients on second line ARVs at different time interval.

Time period	Median increase in CD4 count (cells/mm3)				
	Present study (n=100)	Ferradini L et al,[21] (n=70)	Pujades-Rodrıguez M et al,[17] (n = 370)	Fox MP et al,[18] (n=328)	Hosseinipour MC et al,[22] (n=109)
6 Months	146	80	90	63	---
12 Months	231	134	135	115	143

General characteristic of the patients

The present study showed that the most common age group affected by HIV infection was 36-45 years followed by 26-35 years. Thus, nearly 75% (n=151) of patients belonged to the reproductive age group (15-49 years). HIV/AIDS is a disease of reproductive age, as evident from the HIV prevalence being higher (83%) in the age group of 15-49 years.[11] Similar findings have been reported in HIV-related studies in India stating approximately 80% of total HIV population belong to reproductive age group.[12-14]

Secondly, the mean age of patients on first line ARVs was 37 years in present study while study done by Agu et al showed a mean age of 34.4 (IQR, 29 to 39.25) years.[15]

The mean age of patients on second line ARVs was 39 years. Similar studies at other countries reported mean age of patients on second line ARVs as 35.2±6.3 years, 35.1 years and 35.8±8.1 years.[14-16] Thus, the mean age of patients on first line and second line ARVs was higher in our study. This difference could be due to geographical variation in prevalence of disease in different age-groups.

There were more male patients than females (M: F ratio = 1.9:1) indicating high HIV prevalence in males. Our findings correlate with two other studies conducted in India which observed 78% and 69% male patients.[14,12]

It was reported the increase in CD4 count was observed in 75% patients with first line regimen.[17] Present study observed a significant increase in CD4 count at 6 and 12 months as 70% (n=70) and 66 % (n=66) respectively as compared to baseline. The increase in CD4 count was more during first 6 months of therapy. With second line regimen there was a significant increase in CD4 count at 6 and 12 months 83% (n=79) and 86% (n=82). Increase in CD4 count continues even after the first 6 months, albeit at a slower rate as observed in all studies (Table 7).

Thus, it may be stated that regimen B is more effective than regimen A in improving immunological status of treatment failure patients although further studies are required to support this finding.

Adverse drug reactions

Out of 200 patients, 110 patients developed ADRs. In this 110, 38 patients received regimen A and 18 patients received regimen B and had CD4+count <250 cells/mm^3. In the remaining 54 patients, 20 patients received regimen A and 34 patients received regimen B who had CD4+ count >250 cells/mm^3. Thus, it can be inferred that ADRs were common in patients with CD4+count <250cells/mm^3. Being on HAART for long and low baseline CD4 counts also increased the risk of ADRs.[23-25]

an incidence of new-onset hyperglycemia, hypercholesterolemia, hypertriglyceridemia, and lipodystrophy as 5%, 24%, 19%, and 13%, respectively while in the present study it was found to be 17%, 32%, 29% and 15% with regimen B.[23] Dyslipidemia with

protease inhibitors (PIs) has been reported to be approximately 60%. The risk increases with combination of PIs compared to single PI.[24-26] AZT induced lipodystrophy 18.75% while in this study it is 6% with regimen A.[27]

The abnormal LFT's in 3% and 5% of cases, while in the present study the increase in SGOT and SGPT were 40% and 42% with regimen B.[31] Ajay Sharma et al reported 9% and 5% abnormal LFT's with regimen A while it is 11% and 13% in this study. Hyperbilirubinemia was observed in 24% patients while it is 51 % and 17% in patients on regimen B and A.[28]

Serum creatinine levels were elevated in 22% (n=22) and 11% (n=11) in patients receiving regimen A and regimen an increase in serum creatinine levels of 8% in patients receiving TDF containing regimen while in the present study it was 11% in tenofovir containing regimen.[29] Serum creatinine is a poor indicator of TDF induced nephrotoxicity while creatine clearance is confirmatory for nephrotoxicity. Because of lack of facilities for creatinine clearance the actual cause for rise in creatinine levels could not be made out.

Hence regimen B is superior to regimen A in terms of efficacy and weight gain. It was found that both the regimens were comparable in terms of adverse effects. The second line ARVs were highly effective but requires ADR monitoring for dyslipidemia and liver function tests. Though atazanavir has least effect on lipid profile the patients should be regularly followed up.

Limitations of the study, the patients were observed for 12 months. Considering the lifelong treatment of ART, long term follows up is necessary to establish continual clinical, virological and immunological improvement/deterioration and monitor ADRs. Lack of viral RNA estimation facility limits our study to assess efficacy and drug resistance accurately.

CONCLUSION

With increase in the understanding of viral replication and its pathogenesis a large number of antiretroviral (ARV) drugs have been made available. Antiretroviral drugs and treatment regimens (ART) have changed the HIV/AIDS scenario from being a virtual death sentence to a chronic manageable disease. In this study there was a significant improvement in CD4 count, weight gain and decreased opportunistic infections with regimen B. Further there is decreased incidence of anemia with regimen B.

The SGOT, SGPT, serum bilirubin, serum cholesterol, triglycerides are significantly increased. Raised serum creatinine levels, blood sugars and anemia, nausea/vomiting, diarrhoea, abdominal pain, easy fatigue and pallor were more common with regimen A.

The ADRs were most common in those patients whose CD4+ count is less than 250cells/cu.mm. Though the patients on second line showed significant increase in CD4+ count, number of patients with ADRs were also more with regimen B.

Though atazanavir containing regimen is more efficacious than zidovudine containing regimen, but regimen B produces more serious adverse effects. So, second line drugs are reserved for treatment failures to first line, drug resistance and for those not tolerating first line drugs.

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