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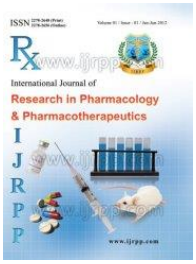

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Study of efficacy and safety of second line art regimen in HIV/AIDS patients in a tertiary care centre

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ABSTRACT

Background

The advent of HAART has decreased the progression to AIDS and AIDS related mortality and prolonged the survival .On the other hand, advances in the antiretroviral therapy have increased life span of HIV positive patients significantly. However, 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.

Aims and objectives

To assess the therapeutic response of second line ART regimen consisting of tenofovir + lamivudine + atazanavir and ritonavir by CD4 count and plasma viral load in HIV patients.

Methods

This was a longitudinal, prospective, observational study carried out in HIV positive patients attending ART centre, government general hospital, Vijayawada. Patients receiving first-line ARV drugs for at least six months were evaluated clinically, immunologically (CD4 count) and virologically (plasma viral load) for failure and started on second-line ART from November 2011 to November 2012 were included in the study.

Results

Out of 100 patients, 52 patients developed ADRs. In this 52, 34 patients had CD4+ count <250 cells/cu.mm and the remaining 18patients had CD4+ count >250 cells/cu.mm. The observed difference was statistically significant ($p<0.0001$). The plasma viral load after six months of therapy were decreased compared to the initial mean values.

Conclusion

The ADRs were most common in those patients whose CD4+ count is <250 cells/cu.mm. Early treatment outcome with second line ART in terms of immunological improvement and viral suppression was good in treatment experienced patients. Though atazanavir containing regimen is more efficacious but produces more serious adverse effects.

Keywords: HAART, CD4 count, Plasma viral load, AIDS.

INTRODUCTION

Highly Active Antiretroviral Therapy (HAART) has become the backbone for control of HIV infection since almost 15 years after its introduction. Further, the year 1996 proved to be a landmark in the treatment of HIV/AIDS, when highly active antiretroviral therapy (HAART) was first introduced. HAART constitutes the combination of three or more different antiretroviral drugs, taken simultaneously and regularly. This was found to significantly delay the onset of AIDS in people living with HIV and prolong lifespan. [1] Once infected, the HIV becomes integral part of host cell and survives for the full lifespan of the infected cells.

Despite the success of HAART, AIDS-related issues/problems still persist and some new challenges with respect to HIV, ARV drugs and HIV infected patients have emerged. HIV infection is now recognized as chronic persistent infection. [2] There are increasing reports of multi-drug resistant (MDR) virus in treatment experienced patients. [3] All these patients require new regimen for continual viral suppression. The problem of drug resistance has led to the concept of second line anti retroviral therapy (ART).

The CD4+ T cell count is one of the best indicators of the immunologic competence of the patient with HIV infection and determines the extent of damage done by HIV. Plasma Viral Load indicates the amount of viral RNA/DNA particles per ml of blood and is best predictor of long term prognosis, whereas CD4 count is best predictor of short term prognosis like opportunistic infections. [4] The two most commonly used techniques are RT-PCR assay and the bDNA assay, generate data in the form of number of copies of HIV RNA per milliliter of serum or plasma. Standard assays can detect as few as 40–50 copies of HIV RNA per milliliter of plasma.[5] Measurement of changes in HIV RNA levels over time have been of great value in delineating the relationship between levels of virus and rates of disease progression, the rates of viral turnover and the time to development of drug resistance. In general, most guidelines suggest that therapy be considered in patients with >100,000 copies of HIV RNA per milliliter. Effective therapy reduces HIV RNA to <50 copies per milliliter within 6 months of the initiation of treatment. [6]

This regimen includes- TDF + 3TC (Fixed dose combination of Tenofovir 300 mg + Lamivudine 300 mg once daily in tablet form) and ATV/r (Tab. Atazanavir 300 mg, Tab. Ritonavir 100 mg- Each tab to be taken once daily simultaneously). [7]

It has been observed that 2-3% patients on first line ART develop treatment failure or irreversible/fatal adverse drug reactions (ADRs). [8] To counteract the problem of treatment failure, WHO recommended inclusion of second-line ART in national ART programs for successful treatment of HIV infection. Second line ART is therefore an essential part of any national ART programme. In India, second line ART was introduced in the national programme in a phased manner since January, 2008.

Since drugs used in second line ART are new, we have very little experience regarding their use for treatment failure to first line ART. Further, the 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 efficacy and safety of second line ART in HIV positive patients receiving second line ARVs attending ART centre, GGH, Vijayawada.

AIM

Primary Outcome

To evaluate the efficacy or therapeutic response to second line ARV's by CD4 count and plasma viral load.

Secondary Outcome

To evaluate safety or adverse drug reactions (ADR's) related to second line regimen.

MATERIAL AND METHODS

The study was conducted to evaluate the safety of second-line antiretroviral therapy in HIV positive patients attending antiretroviral therapy (ART) centre, at government general hospital, Vijayawada, a tertiary care teaching hospital in an urban setting. This was a continuous, longitudinal, prospective, observational study. Prior permission to conduct the study was obtained from Andhra Pradesh State AIDS Control Society (APSACS) and Institutional Ethics

Committee (IEC) of Siddhartha medical college, Vijayawada. Informed consent was obtained from all patients enrolled in the study.

The 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). The patients started on second-line ART from November 2011 to November 2012 and fulfilling inclusion and exclusion criteria were included in the study. Patients in the age group of 18-70 years who were started on 2^{nd} line ART therapy after failure of 1^{st} line therapy as per NACO guidelines.[3] were included and patients who were pregnant, lactating, having pre-existing abnormal liver, renal function tests, lipid profiles were excluded.

Laboratory Data

The data was entered in a case record form at the time of initiation of 2^{nd} line therapy consisting of Tenofovir + Lamivudine + Atazanavir + Ritonavir and at the end of 6 and 12 months of treatment.

- CD_4 Count.
- Plasma Viral Load.
- Haemoglobin values.
- Liver Function Tests.
- Renal Function tests.
- Lipid Profiles.

Statistics

The data was analysed using Microsoft excel and Graph pad prism version 5.0. Chi square and 't' test were applied. P value <0.01 considered as statistically significant.

RESULTS

Demographic details

Table no. 1: Basic Parameters.

S.No.	Parameter	Second line ARVs (TDF+3TC+ATV/r)
1.	No. of patients	100
2.	Mean age in years (range)	39 (36-42)
3.	Gender	
	Men	74
	Women	26
4.	Weight in kgs (mean ± SD)	56.57± 11.57
5.	Socioeconomic status	
	Low income group	75
	Middle income group	25

Age and gender wise distribution

One hundred patients were enrolled into the study. Out of 100 patients, 7% (n=7) belonged to 15 – 25 years, 34% (n=34) belonged to 26 – 35 years, 41% (n=41) belonged to 36 – 45 years, 15% (n=15) belonged to 46 – 55 years and 3% (n=3) patients belonged to age group 55 – 65 years. Maximum number of patients i.e 41% (n=41) and 34% (n=34) belonged to age groups 36 – 45 years and 26 – 35 years. The median age for patients being 39 years.

Socioeconomic status

Out of 100 patients receiving second line ART, 75 patients belonged to low socioeconomic status and 25 belonged to middle income group.

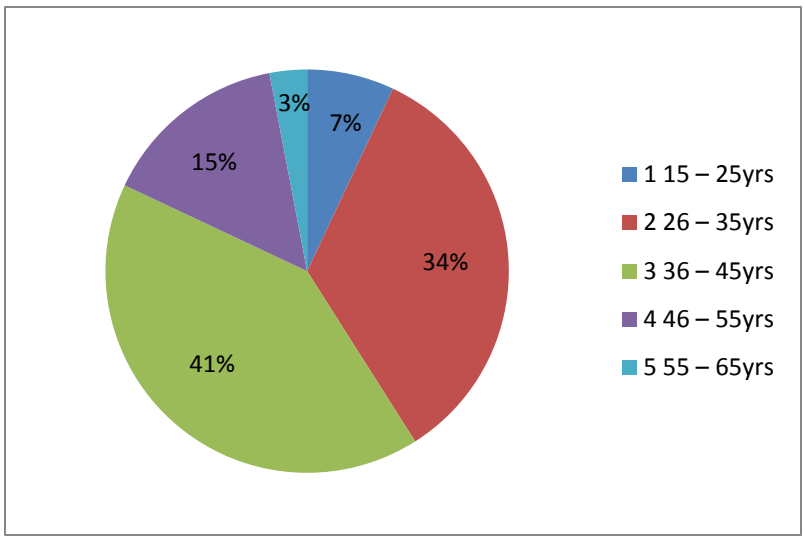

Figure no.1: Age wise distribution of cases.

Out of 100 patients, 74% (n=74) were males and 26% (n=26) were females. So more number of male patients were attending the ART centre.

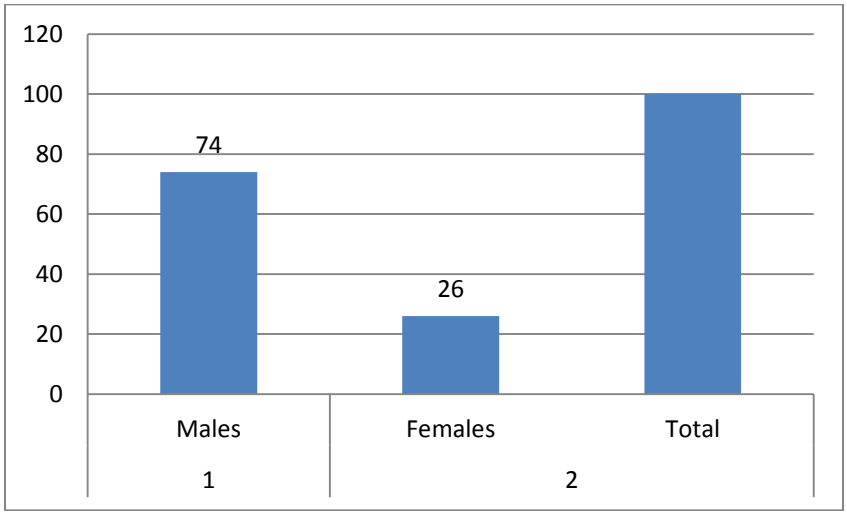

Figure no.2: Sex wise distribution of cases

In the first 6 months of treatment, 5 patients died on second line ART. After 12 months there were no deaths or lost to follow ups. So 95cases on second line ART were available for evaluation. There were zero dropouts and 5% deaths at the end of treatment.

Out of 100 patients 73 patients showed an improvement in CD4 count and 22 patients showed fall in CD4 count. Of these 52 patients developed ADRs. In this 52, 34 patients had CD4+ count >250 cells/cu.mm and the remaining 18patients had CD4+ count <250 cells/cu.mm.

Table no.2: CD4+ Count and ADRs

S.No	CD4 Count	ADR Present	ADR Absent	Number	Chi square	P Value
1	<250	18	4	22	6.6	0.0102
2	>250	34	39	73	1.99	0.1583

Second line ART significantly increased mean body weight of patients at 6 and 12 months of treatment. After 6 months of treatment with second line ART 69.4% (n=66) had increased weight. 77.8% (n=74) showed increased weight after 12 months of treatment. However, mean increase in body weight at 6 months of treatment was 57.9kgs and at the end of 12 months it is 59.26kg. ($P < 0.01$)

Immunologic improvement

It was observed that mean levels of CD4 after six months of therapy were elevated compared to the baseline values.There was a significant increase in mean CD4 count at 6 months (180.37/cu.mm) and 12 months (266.04/cu.mm) as compared to baseline (66.35/cu.mm) ($P < 0.0001$).However, an increase in mean CD4 count was significantly more at 12 months in patients treated with second line ART regimen [266.04 cells/mm] ($P < 0.05$)

After six months of treatment with second line ART , 26.3% (n=25) patients had anaemia but mean haemoglobin levels increased from 9.05 gm/dl to 10.36 gm/dl and after 12 months the mean haemoglobin increased to 10.7 gm/dl and 30.5% (n=29) developed anaemia. The increase in CD4 count and haemoglobin and decrease in plasma viral load were extremely statistically significant. ($P < 0.0001$)

Table no.3: Assessment of weight, CD4, PVL & Hb.

Parameters	Mean ± SD			't' test	'P' Value
	Baseline	6months	12months		
Weight	56.57±11.57	57.9±10.22	59.26±9.29	1.8129	0.0714
CD4 Count	66.35±40.55	180.37±45.05	266.04±74.07	23.647	0.0001
Plasma Viral Load	212068.40± 55641.41	----	164840.24± 86680.24	4.585	0.0001
HB (gm/dl)	9.05±1.12	10.36±0.562	10.70±0.617	12.842	0.0001

At the end of 12 months of treatment 51 patients showed an increased serum bilirubin levels with an elevated liver function tests. There was an increase in mean serum bilirubin (1.14 mg/dl) and SGOT and SGPT (39.0 IU/dl & 37.48 IU/dl) from baseline values (0.76mg/dl, 34.47 IU/dl, 28.53 IU/dl).

Table no.4: Hepatic ADRs.

Parameters	Mean ± SD			't' test	'P' Value
	Baseline	6months	12months		
SGOT	34.47±13.37	42.01±10.61	39.0±8.14	2.820	0.0053
SGPT	28.53±10.12	37.75±7.20	37.48±7.92	6.788	0.0001
Bilirubin	0.752±0.21	1.27±0.26	1.14±0.23	12.34	0.0001

At the end of 6 months of treatment 27% (n=27) and 17% (n=17) showed an increase in blood urea and serum creatinine. But at the end of 12 months the number of patients showing an elevated renal function came down to 19% (S.Creatinine) and 11% (Blood urea).The mean serum creatinine levels after six and twelve months of therapy were 1.13mg/dl & 1.11 mg/dl (Table no.6). Mean BUN levels after 6 and 12 months of therapy were 31 mg/dl & 32 mg/dl. Blood urea not quite significant and s.creatinine extremely significant.

Table no.5: Hepatic ADRs.

Parameters	Mean ± SD			't' test	'P' Value
	Baseline	6months	12months		
Blood Urea	30.26±7.90	31.76±5.60	32.32±7.13	1.935	0.0543
S.creatinine	0.88±0.22	1.13±0.197	1.11±0.23	7.226	0.0001

Mean RBS levels after 12 months of therapy were elevated from 104 mg/dl to 114 mg/dl. The observed differences were statistically significant.

While comparing the changes in lipid profile (Table no.7), it was observed that mean levels of serum total cholesterols after 12 months of therapy were elevated from 185 mg/dl to 201 mg/dl. Mean levels of HDL (From 39 mg/dl to 50 mg/dl), LDL (From 67 mg/dl to 69 mg/dl), serum triglycerides and VLDL after 12 months of therapy were decreased compared to the initial mean values.

Table no.6: Metabolic ADRs

Parameters	Mean±SD		't' test	'P' Value
	Baseline	After 12months.		
RBS (mg/dl)	104.74±26.27	114.85±17.77	3.222	0.0015
Sr. Cholesterol (mg/dl)	185.05±51.67	201.15±79.91	1.613	0.1083
TG (mg/dl)	139.61±79.36	120.29±31.58	2.262	0.0248
HDL (mg/dl)	39.87±10.59	50.18±15.30	5.540	0.0001
LDL (mg/dl)	67.35±49.64	69.02±27.37	0.294	0.7686
VLDL (mg/dl)	35.7±13.9	39.59±12.84	2.203	0.0287

In spite of ART therapy, during this study 35%patients on regimen B developed opportunistic infections. Amongst all opportunistic infections candidiasis, diarrhea, and tuberculosis were most common.

Table no.7: Opportunistic infections

S.no	Opportunistic infections	Regimen B
1.	Candidiasis	9 (25.7)
2.	Diarrhoea/ Dysentery	9 (25.7)
3.	Herpes zoster	5 (14.2)
4.	Tuberculosis	4 (11.4)
5.	Herpes simplex	4 (11.4)
6.	Lower respiratory tract infections	4 (11.4)
	Total	35

DISCUSSION

Despite the success of HAART, AIDS-related issues/problems still persist and some new challenges with respect to HIV, ARV drugs and HIV infected patients have emerged. HIV infection is now recognized as chronic persistent infection. There are increasing reports of multi-drug resistant (MDR) virus in treatment experienced patients. All these patients require new regimen for continual viral suppression. The problem of drug resistance has led to the concept of second line anti retroviral therapy (ART). One hundred patients were enrolled into the study. The present study showed that the most common age group affected by HIV infection was 36-45 years 41% (n=41) followed by 26-35 years 34% (n=34). Thus, nearly 75% 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. [9] The median age for patients being 39 years which is comparable to Pujades-Rodríguez M et al (35 years). [10] Out of 100 patients, 74% (n=74) were males. There were

more male patients than females (M: F ratio = 2.8:1) indicating high HIV prevalence in males. However, national data shows that 61% of the total HIV infected patients are male, which is lower than observed in our study. [9]

Majority of patients with HIV who has shown immunologic failure to first line therapy achieved viral suppression after switching to second line therapy. This has been demonstrated in the present study by substantial mean increase in CD4 count in patients on second line therapy, an average of 180 cells/cu.mm over 6 months period. This is comparable to a median CD4 count increase at 12 months of 135 cells/cu.mm by Pujades Rodriguez M et al. [10] In comparison the average gain of 114 cells in 6 months on second line seen in our study represents substantial immune recovery. With second line regimen there was a significant increase in CD4 count at 6 and 12 month 83% (n=79) and 86% (n=82). This was also observed in study at Kolkata, India (Guha SK et al., 2011). [11]

The reported rates of mortality among patients on second line ART substantially ranging from 3% to 16% (Castelnuovo B et al). [12] In our study, 5% patients died on the follow-up.

Stephen A et al [13] reported 36% cases with protease inhibitor associated anemia which is comparable to 30% (n=29) in present study with patients on regimen B.

Sotirios Tsiodras et al [14] reported 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.

Robert L Murphy et al [15] reported 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.

Serum creatinine levels were elevated in 11%(n=11) in patients receiving regimen B. L Gerard et al [16] observe 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. According to L Gerard et al 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 in terms of efficacy, weight gain and decreasing opputunistic infections. The second line ARVs were highly effective but requires ADR monitoring for dyslipidemia and liver function tests and the patients should be regularly followed up.

A good number of patients were followed up for a period of 12 months. Thus, it can be concluded that the second line ART regimen has satisfactory early treatment outcome with respect to immune reconstruction and viral suppression. However, further research is needed to determine if these early outcome can be sustained over the following years of treatment.

Limitation of the study

The patients were observed for 12 months. Considering the lifelong treatment of ART, long term follow up is necessary to establish continual clinical, virological and immunological improvement/ deterioration and monitor ADRs.

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REFERENCES

[1]. History of HIV & AIDS in UK 1996 onwards. Available from: http://www.avert.org/ukaids.htm [Accessed 2012].

[2]. Anthony S Fauci, H.Engene Braunwald, Dennis L.Kasper, Stephen L, Hanser, Dan, L Longo, J.Lammy Jamson, Joseph Loscalzo, H.Chifford lane. "Human Immunodeficinecy virus disease: AIDS and related disorders"- Harrisons Principles of Internal Medicine, Chapter 17(182), 1137-1203.

[3]. Desai M et al., 2012. 'Advances in antiretroviral drugs.' *Indian Journal of Pharmacology*, 44(3), 2012, 288-98.

[4]. Saag MS, Holodniy M, Kuritzkes DR, et al. HIV viral load markers in clinical practice. Nat Med 2(6), 1996, 625-9.
[5]. Beuningen R et al. 'Development of a high throughput detection system for HIV-1 using real-time NASBA based on molecular beacons.' The International Society of Optical Engineering, 4264.
[6]. AIDS education and training centres 2012. 'CD4 and viral load monitoring.' Available from: http://www.aidsetc.org/aidsetc?page=cg-206_cd4_monitoring [Accessed 2012].
[7]. National guidelines on second-line and alternative first-line ART for adults and adolescents. The National AIDS Control organisation 2013, 1-105.
[8]. NACO, 2011. 'National guidelines on second line ART.' Ministry of health and family welfare. Government of India.
[9]. NACO annual report 2010-11. Available from: http://www.nacoonline.org/Quick_Links/ Directory_of_HIV_Data/ [Accessed 2012].
[10]. Pujades-Rodrı´guez M et al., 2008. 'Second-line antiretroviral therapy in resource-limited settings: the experience of Me´decins Sans Frontie`res.' AIDS, 22(11), 2008, 1305–1312.
[11]. Guha SK et al., 2011. 'Effectiveness of addition of zidovudine to second line antiretroviral regimen of tenofovir, lamivudine and lopinavir/ritonavir in patients failing thymidine analogue based first line antiretroviral therapy in India.' Available from: pag.ias2011.org/Abstracts.aspx?AID=3419 [Accessed on 2012].
[12]. Castelnuovo B, John L, Lutwama F, et al. Three-year outcome data of second-line antiretroviral therapy in ugandan adults: good virological response but high rate of toxicity. J Int Assoc Physicians AIDS Care (Chic) 8(1), 2009, 52–9.
[13]. Stephen A. Harrison, 2010." Management of Anemia in Patients Receiving Protease Inhibitors". *J. Gastroenterol Hepatol* (N Y). 8(4), 2012, 254–256.
[14]. Sotirios T et al, 2000. "Effects of protease inhibitors on hyperglycemia, hyperlipidemia and lipodystrophy". *Arch Intern Med*. 160, 2000, 2050- 2056.
[15]. Robert L. Murphy et al.. "Dose-ranging, randomized, clinical trial of atazanavir with lamivudine and stavudine in antiretroviral-naïve subjects". *AIDS* 17, 2003, 2603–2614.
[16]. Gerard L et al, 2007. Renal functions in antiretroviral experienced patients treated with tenofovir disoproxil fumarate associated with atazanavir/ritonovir. *Antiviral therapy*. 12, 2007, 31-39.