STUDY OF THERAPEUTIC RESPONSE TO SECOND LINE ART REGIMEN IN TERTIARY CARE TEACHING HOSPITAL OF SOUTH INDIA

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ABSTRACT

BACKGROUND

The widespread use of HAART therapy resulted in marked decline in the incidence of most AIDS defining conditions and mortality, both in the developed and developing world. As the scope of ART in developing countries continues, the number of patients failing in first line therapy and switching to second line therapy will inevitably increase. The aim of the study is to assess the therapeutic response by CD4 count and plasma viral load in HIV patients who received 2nd line regimen consisting of tenofovir, lamivudine, Ritonavir and atazanavir.

METHODS

This was a retrospective observational study. The data was collected retrospectively from the case sheets of the 50 patients of ART Centre of King George Hospital, Visakhapatnam, a tertiary care teaching hospital in South India. Patients in the age group of 18-70 years who were started on 2nd line ART therapy after failure of 1st line therapy as per NACO guidelines were included. The data analysis was carried out using Graph pad prism version 5.0. P value <0.01 considered as statistically significant.

RESULTS

It was observed that mean levels of CD4 after six months of therapy were elevated compared to the initial mean values. The observed difference was statistically significant (p<0.0001). Mean levels of viral load after six months of therapy were decreased compared to the initial mean values. The observed difference was not statistically significant (p=0.17) (Table 10).

CONCLUSION

Patients who were initiated on second line therapy after the failure of first line regimen had high rates of immunologic and virologic success and low rates of mortality. This is evident by the increase in CD4 count and decrease in viral load in our study.

KEYWORDS

HAART, CD4, AIDS, HIV.

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INTRODUCTION

Highly Active Antiretroviral Therapy (HAART) is the cornerstone of management of patients with HIV infection. The widespread use of antiretroviral therapy resulted in marked decline in the incidence of most AIDS defining conditions and mortality, both in the developed and developing world.[1] Results of three large clinical end point studies demonstrated that combination therapy significantly delayed progression of HIV disease and improved survival.[2]

As the scope of ART in developing countries continues, the number of patients switching to second line therapy will inevitably increase. Divisions about the use of second line regimen in these areas will depend in part on the success of these regimens, but to date there has been little evidence to assess the effectives of these regimens in patients failing in first line therapies.

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ATV/r) aims to achieve viral suppression for as long as possible, so that survival can be prolonged. 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).[3]

Measuring Plasma Viral Load (PVL) and CD4 counts are crucial for initiating and modifying ART therapy. While PVL indicates the magnitude of viral replication; CD4 counts indicate the extent of immune system damage. PVL 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] In fact, the very goal of therapy has been redefined as the achievement of maximal durable suppression of virus replication on a long term basis.[5,6]

Number of drugs available for therapy is limited and moreover cross-resistance between specific drugs has been documented. In this present situation, any change in ART regimes increases future therapeutic constraints like virologic failure, adverse drug side effects and impact on adherence and mortality.

So this study was conducted to assess therapeutic efficacy of second line ART drugs and their side effects at ART centre of King George Hospital, Visakhapatnam, a Tertiary Care Teaching Hospital of South India.

AIM

Primary Outcome

To study therapeutic response by CD4 count and plasma viral load in HIV patients who received 2nd line regimen consisting of tenofovir, lamivudine, ritonavir and atazanavir.

Secondary Outcome

To study the effect of 2nd line regimen on Renal Function Tests, Liver Function Tests, Lipid Profile and Haemogram.

MATERIAL AND METHODS

This was a retrospective observational study. The data was collected retrospectively from the case sheets of the 50 patients of ART Centre of King George Hospital, Visakhapatnam, a Tertiary Care Teaching Hospital in South India. The permission of the institutional head and approval of Institutional Ethics Committee was obtained. Patient confidentiality was maintained. Patients in the age group of 18-70 years who were started on 2nd line ART therapy after failure of 1st 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.

The following Data was collected

Demographic Data

- Age.
- Gender.
- Family History.
- Marital Status.
- First Line ART initiation Date.
- Second line ART initiation Date.
- Opportunistic infections.
- Adherence to therapy.

Laboratory Data: At the time of initiation of 2nd line therapy consisting of tenofovir, lamivudine, ritonavir, atazanavir and at the end of 6 months of treatment,

- CD_4 Count.
- Plasma Viral Load.
- Complete Blood Picture.
- Liver Function Tests.
- Renal Function tests.
- Lipid Profiles.

The data analysis was carried out using Graph pad prism version 5.0. P value <0.01 considered as statistically significant.

RESULTS

Of all patients, maximum patients belonged to the age group of 31-40 years (50%) (Table 1). The mean age of patients was 35 years; 33 were men and 17 were women (Table 2); 90% patients were married, 6% were unmarried and 4% were widowed (Table 3). Of 50 patients, 25 patients were seroconcordant (Table 4).

In our study, there were no opportunistic infections in 72% of patients, 24% were effected with TB and 4% were effected with other infections (Table 5). Of all patients enrolled in study, 34% patients were on 1st line regimen for 5-6 years following 28% for 1-2 years, 12% for 7 years and above and 26% for 3-4 years (Table 6). Different types of first line treatment regimens were available for HIV treatment, among which 68% received ZLN, 20% received SLN, 8% received ZLE, 2% received TLN and 2% received TLE 1st line regimens (Table 7). Compliance with therapy was good in 52% patients followed by 38% with excellent adherence, 10% with poor adherence (Table 8). There were 15% dropouts and 1.67% deaths (Table 9). It was observed that mean levels of CD4 after six months of therapy were elevated compared to the initial mean values. The observed difference was statistically significant ($p<0.0001$). Mean levels of viral load after six months of therapy were decreased compared to the initial mean values. The observed difference was not statistically significant ($p=0.17$) (Table 10).

On comparing the haemograms (Table 11), after six months the mean haemoglobin levels after six months of therapy increased from 10.32 gm/dL to 10.52 gm/dL. Mean total count levels after six months of therapy were elevated from 6277 cells/cumm to 6594 cells/cumm. Mean neutrophil levels decreased from mean of 62% to 60%. Mean ESR levels after six months of therapy were decreased from 46 mm/hr to 42 mm/hr. The observed differences were not statistically significant. Mean lymphocytes levels after six months of therapy were increased from 31% to 35%. The observed difference was statistically significant ($p=0.01$).

At the end of six months therapy (Table 12), there was increase in mean total and direct bilirubin, alkaline phosphatase and decrease in mean SGOT and SGPT. Similarly, the mean serum creatinine levels after six months of therapy were increased from 0.91 mg/dL to 1.0 mg/dL (Table 13). Mean BUN levels after six months of therapy were increased from 26 mg/dL to 27 mg/dL. The above differences were not statistically significant.

While comparing the changes in lipid profile (Table 14), it was observed that mean levels of serum total cholesterol after six months of therapy were elevated from 147 mg/dL to 157 mg/dL. Mean levels of HDL (from 39 mg/dL to 44 mg/dL), LDL (From 74 mg/dL to 84 mg/dL), VLDL after six months of therapy were elevated compared to the initial mean values. Mean RBS levels after six months of therapy were elevated from 98 mg/dL to 108 mg/dL. The observed differences were not statistically significant.

Age Group	Number of Patients	Percentage
11-20	01	2%
21-30	13	26%
31-40	25	50%
41-50	09	18%
51-60	02	4%
61-70	0	0%
Total	**50**	**100%**

Table 1: Age Distribution of Patients

Of all patients, maximum patients belonged to the age group of 31-40 years (50%).

Gender	Number of Patients	Percentage
Females	17	34%
Males	33	66%
Total	**50**	**100%**

Table 2: Gender Distribution of Patients

The mean age of patients was 35 years; 33 were men and 17 were women.

Marital Status	Number of Patients	Percentage
Married	45	90%
Unmarried	03	6%
Widow	02	4%
Total	**50**	**100%**

Table 3: Marital Status of Patients

90% patients were married, 6% were unmarried and 4% were widowed.

Spouse	Number of Patients	Percentage
Positive	25	50%
Negative	25	50%
Total	**50**	**100%**

Table 4: Serological Concordance

Of 50 patients, 25 patients were seroconcordant.

Type of Infection	Number of Patients	Percentage
Tuberculosis	12	24%
Other	02	04%
Without infection	36	72%
Total	**50**	**100%**

Table 5: Opportunistic Infections

There were no opportunistic infections in 72% of patients, 24% were effected with TB and 4% were effected with other infections.

Duration (yrs.)	Number of Patients	Percentage
1-2	14	28%
3-4	13	26%
5-6	17	34%
Above 7	06	12%
Total	**50**	**100%**

Table 6

Of all patients enrolled in study, 34% patients were on 1st line regimen for 5-6 years following 28% for 1-2 years, 12% for 7 years and above and 26% for 3-4 years.

Regimen	Number of Patients	Percentage
ZLN	34	68%
SLN	10	20%
ZLE	04	08%
TLN	01	02%
TLE	01	02%
Total	**50**	**100%**

Table 7: 1st Line Treatment Regimens used by the Patients

Different types of first line treatment regimens were available for HIV treatment among which 68% received ZLN, 20% received SLN, 8% received ZLE, 2% received TLN and 2% received TLE 1st line regimens.

Adherence	Number of Patients	Percentage
Excellent	19	38%
Good	26	52%
Poor	05	10%
Total	**50**	**100%**

Table 8: Adherence to Therapy

Compliance with therapy was good in 52% patients followed by 38% with excellent adherence, 10% with poor adherence.

	Number of Patients	Percentage
Dropouts	9	15%
Deaths	1	1.67%

Table 9: Assessment of Dropouts and Deaths

There were 15% dropouts and 1.67% deaths.

Parameters	Mean±SD		'P' Value
	Baseline	After	
CD4 Count (cells/mm^3)	104.18±84.70	225.93±148.19	<0.0001
Viral Load (copies/mL)	254085.96± 313690.14	156778.79± 397876.57	0.17

Table 10: Assessment of CD4 Count and Viral Load

It was observed that mean levels of CD4 after six months of therapy were elevated compared to the initial mean values. The observed difference was statistically significant (p<0.0001).

Mean levels of viral load after six months of therapy were decreased compared to the initial mean values. The observed difference was not statistically significant (p=0.17) (Table 10).

Parameters	Mean ± SD		'P' Value
	Baseline	After	
Hb (g/dL)	10.37±2.03	10.52±1.55	0.67
TC (cells/cumm)	6277.2±2213.16	6594±1826.40	0.43
Neutrophils (%)	62.08±7.73	60.56±11.09	0.93
Lymphocytes (%)	31.64±7.99	35.40±7.0851	0.01
ESR (mm/hr)	46.74±22.53	42.58±23.04	0.36

Table 11: Assessment of Complete Blood Count

On comparing the haemograms (Table 11) after six months, the mean haemoglobin levels after six months of therapy increased from 10.32 gm/dL to 10.52 gm/dL. Mean total count levels after six months of therapy were elevated from 6277 cells/cumm to 6594 cells/cumm. Mean neutrophil levels decreased from mean of 62% to 60%. Mean ESR levels after six months of therapy were decreased from 46 mm/hr to 42 mm/hr.

The observed differences were not statistically significant. Mean lymphocytes levels after six months of

therapy were increased from 31% to 35%. The observed difference was statistically significant (p=0.01).

Parameters	Mean±SD		'P' value
	Baseline	After	
Bilirubin (T) (mg/dL)	1.02±0.96	1.29±1.20	0.23
Bilirubin (D) (mg/dL)	0.36±0.39	0.43±0.43	0.42
Bilirubin (I) (mg/dL)	0.66±0.66	0.83±1.0	0.33
SGOT (IU/L)	42.17±29.97	38.92±20.77	0.52
SGPT (IU/L)	39.31±23.93	34.64±21.21	0.30
ALP (IU/L)	131.2±74.53	132.12±50.80	0.94

Table 12: Assessment of Liver Function Tests

At the end of six months therapy (Table 12), there was increase in mean total and direct bilirubin, alkaline phosphatase and decrease in mean SGOT and SGPT.

Parameters	Baseline Mean±SD	After Mean±SD	'P' Value
Sr. Creatinine (mg/dL)	0.91±0.33	1.0±0.31	0.21
BUN (mg/dL)	26.96±13.28	27.22±8.57	0.90

Table 13: Assessment of Renal Function Tests

Similarly, the mean serum creatinine levels after six months of therapy were increased from 0.91 mg/dL to 1.0 mg/dL (Table 13). Mean BUN levels after six months of therapy were increased from 26 mg/dL to 27 mg/dL. The above differences were not statistically significant.

Parameters	Mean±SD		'P' Value
	Baseline	After	
Sr. Cholesterol (mg/dL)	147.86±31.29	156.46±24.72	0.12
TG (mg/dL)	147.4±79.40	154.82±73.30	0.62
HDL (mg/dL)	39.54±11.24	44.28±12.89	0.05
LDL (mg/dL)	74.90±28.17	84.18±26.46	0.08
VLDL (mg/dL)	37.22±22.64	37.28±23.77	0.99
TC:HDL	3.70±1.25	3.47±1.10	0.34
RBS (mg/dL)	98.64±28.84	108.7±34.06	0.11

Table 14: Assessment of Lipid Profile and Blood Sugar

While comparing the changes in lipid profile (Table 14), it was observed that mean levels of serum total cholesterol after six months of therapy were elevated from 147 mg/dL to 157 mg/dL. Mean levels of HDL (From 39 mg/dL to 44 mg/dL), LDL (From 74 mg/dL to 84 mg/dL), VLDL after six months of therapy were elevated compared to the initial mean values.

Mean RBS levels after six months of therapy were elevated from 98 mg/dL to 108 mg/dL. The observed differences were not statistically significant.

DISCUSSION

As the scope of ART in developing countries continues, the number of patients switching to second line therapy will inevitably increase. Divisions about the use of second line regimen in these areas will depend in part on the success of these regimens, but to date there has been a little evidence to assess the effectives of these regimens in patients failing in first line therapies.

Our study showed that the most common age group was 21-40 years with 94% of our patients belonging to the reproductive age group (20-50 years). The mean age of patients was 35 years, which is comparable to studies of Pujades-Rodríguez M et al (35 years).[7] Men constituted 66% of our study subjects. This was comparable to national data that shows 61% of the total HIV infected patients are men.[8] Our study had 50% seroconcordance among couples, which is less than 66% noted by Dishank Patel et al[9], 72% of our study patients did not have any opportunistic infections. The most common opportunistic infection was tuberculosis in 12 (24%), which was more than the findings of Dishank Patel et al (14%).[9]

Findings of this analysis indicate that majority of patients with HIV drug resistance to first line therapy achieved viral suppression after switching to second line therapy. We have demonstrated substantial mean increase in CD4 count in patients on second line therapy, an average of 120 cells/UL over the observed period. This is again similar to the MSF cohort, where patients had a median CD4 count increase at 12 months of 135 cells/UL by Puades Rodriguey M et al.[7] Although not universally accepted, an increase of 100 cells/UL over the first year on therapy can be seen as a marker of treatment success on first line therapy, when most patients are initiated at CD4 counts below 200. In comparison the average gain of 124 cells in 6 months on second line seen in our study represents substantial immune recovery.

The reported rates of mortality among patients on second line ART substantially ranging from 3% to 16% (Castelnuovo B et al).[10] In our study, 1.67% patients died on the follow-up.

As more patients are initiated on second line regimens, being able to identify which patients fail these regimens and why will be critical to the long-term durability of these regimens. The data on adherence to second line therapy, the most predictor of achieving viral suppression. Overall adherence was high as treatment success rates were high, but overtime adherence rates may decline leading to more failures.

The effect of second line regimen on different laboratory parameters assessed was not statistically significant for this shorter duration of study, but on long-term follow the results may depict clearer picture.

Our study had few limitations. First, this was a small group of patients, so limited generalization of our findings. Also, ours is a retrospective analysis utilizing routinely available data, thus there might have been some unmeasured factors that influenced the outcomes.

CONCLUSION

In conclusion, we found that patients who were initiated on second line therapy after the failure of first line regimen had high rates of immunologic and virologic success and low rates

of mortality. This part is evident by the increase in CD4 count and decrease in viral load in our study. Further research is needed to determine if these findings can be extended to different settings and longer follow-up will be needed to determine if these early outcomes can be sustained over the long term treatment.

REFERENCES

1. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV out patient study investigators. NEJM 1998;338(13):853-60.
2. Feinberg MB, Carpenter C, Fauci AS, et al. Report of the NIH panel to define principles of therapy of HIV infection and guidelines for the use of antiretroviral agents in HIV infected adults and adolescents. Ann Intern Med 1998;128:1057-110.
3. National guidelines on second-line and alternative first-line ART for adults and adolescents. The National AIDS Control organisation 2013;1-105.
4. Saag MS, Holodniy M, Kuritzkes DR, et al. HIV viral load markers in clinical practice. Nat Med 1996;2(6):625-9.
5. Carpenter CCJ, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1998. Recommendations of an international panel. JAMA 1998;280(1):78–86.
6. Gazzard BG, Moyle GJ, Weber J, et al. British HIV association guidelines for antiretroviral treatment of HIV seropositive individuals. Lancet 1997;349(9058):1086–92.
7. Pujades-Rodríguez M, O'Brien D, Humblet P, et al. Second-line antiretroviral therapy in resource-limited settings: the experience of médecins sans frontières. AIDS 2008;22(11):1305–12.
8. NACO annual report 2010-11.
9. Dishank Patel, Mira Desai, Shah AN, et al. Early outcome of second line antiretroviral therapy in treatment-experienced human immunodeficiency virus positive patients. Perspect Clin Res 2013;4(4):215–20.
10. 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) 2009;8(1):52–9.