Efficacy of Second line Anti-retroviral therapy among HIV/AIDS patients in south India: A Prospective Observational study

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ABSTRACT

Background: Acquired immunodeficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). Because of treatment failure with first line ART, Roughly 4% of total patients on ART are on second line therapy. Second line ART is being instituted in 10 Centers of excellence in India, Gandhi hospital being one of them in south India. **Objective:** To detect efficacy of second line Anti-Retroviral therapy in HIV/AIDS patients. **Methods:** This prospective and observational study of 20 months was done in south Indian tertiary hospital. HIV/AIDS patients receiving second line Anti-Retroviral therapy (ART) due to failure of first line drugs were assessed for viral load and CD4 count before and after therapy and analyzed the same by Repeated Measures ANOVA followed by post hoc analysis by Dunnet's multiple comparison test, respectively. **Results:** Total One hundred and sixteen patients received second line ART. Mean viral load was 2, 31280 ± 50913 copies per milliliter and mean CD4 count was 75.03 ± 10.69 cells per cubic millimeter before treatment. After initiation of second line ART, Viral load reduced significantly to 1846 ± 621.4 ($p<0.001$) and 260.4 ± 183.7 ($p<0.001$) after six and twelve months of treatment, respectively and CD4 count increased significantly 181.8 ± 14.34 ($p<0.001$) and 235.7 ± 14.56 ($p<0.001$) after six and twelve months of treatment, respectively. **Conclusion:** Second line ART regimens are efficacious regimens as they improved CD4 counts and reduced viral load significantly.

Key words: CD4 counts, viral load, Second line anti-retroviral, HIV/AIDS

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INTRODUCTION

India has the third largest number of people living with HIV in the world—2.1 million (1.7 million–2.7 million) at the end of 2013-and accounts for about 4 out of 10 people living with HIV in the region. India recorded a 38% decline in AIDS-related deaths between 2005 and 2013 because of major scale up of access to Anti-HIV treatment. At the end of 2013, more than 700 000 people were on antiretroviral therapy, the second largest number of people on treatment in any single country.[1]

In Case of failure of first line ART (non-nucleoside reverse-transcriptase inhibitors [NNRTI] containing regimen), the WHO advises that second-line ART consist of a boosted protease inhibitor (PI) in combination with 2 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI), at least 1 of which is new to the patient.[2,3]

Identification of ART treatment failure can be done by clinically and detection of increasing viral load and decreasing CD4 counts. Identification of efficacy also can be done by decreasing viral load and increasing CD4 counts. [3]

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As second line ART, ritonavir boosted PIs in use are heat-stable fixed-dose combinations of ritonavir boosted atazanavir (ATV/r) and ritonavir boosted lopinavir (LPV/r) and NRTIs include zidovudine (AZT), Lamivudine (3TC), tenofovir (TDF), emtricitabine (FTC) and stavudine (d4T) as available options.[4]

The following sequence of second-line NRTI options is recommended: After failure on a TDF + 3TC (or FTC)–based first-line regimen, use AZT + 3TC as the NRTI backbone in second - line regimens. After failure on an AZT or d4T + 3TC–based first-line regimen, use TDF + 3TC (or FTC) as the NRTI backbone in second-line regimens.[5]

In a literature search, we found very limited data evaluating efficacy of second line antiretroviral therapy after failure of first line drugs in India.

The aim of this study was to know the effect of second line ARV drugs in HIV/AIDS patients. The objective of this study was to detect efficacy of second line ART in our setup and with the ultimate goal of improving the health status of HIV/AIDS patients.

METHODS

This prospective observational study was done from May 2010 to January 2012 at Centre of Excellence (C.O.E.) Gandhi Hospital, Hyderabad, India.

Inclusion criteria

All adult HIV/AIDS patients of either sex aged between 20 to 60 years who were registered for second line anti-retroviral treatment due to failure of first line drugs.

Exclusion criteria

Patients with known hypersensitivity reactions, neuropsychiatric disorders, liver failure and renal failure

Study was started after taking approval from the institutional ethics committee of the Gandhi hospital. Informed consent of the patient was also taken

Data Collection Procedure

Information on patient's details, the WHO clinical staging of the disease[6] at the start of ART, duration of treatment, drug details, outcome, and results of investigations performed were collected using a data collection format.

The study subjects were monitored for CD4 and viral loads before therapy, after 6 months and after 12 months of therapy.

CD4 count and Viral load analysis

Twenty μL of whole blood taken from all patients and CD4 count analysis was done by flow cytometric analysis[7] method using CD4 easy count kit (PARTEC Company). All samples were stained and analyzed within 2 hours. PCR of in vitro DNA synthesis uses a DNA template, polymerase, buffers, primers, and nucleotides to multiply the HIV in the blood sample. Then a chemical reaction marks the virus. The markers are measured and used to calculate the amount of virus. PCR is used to quantify integrated DNA.

Statistical Analysis

Data entry and analysis was done using Microsoft excel sheet and graph pad prism statistical software. Viral load and CD4 count before and after therapy (after 6 and 12 months) was analyzed by Repeated Measures ANOVA followed by post hoc analysis by Dunnet's. P. values less than 0.05 is considered to be statistically significant.

RESULTS

116 cases were included in the study. The study group included 40 (34.49%) females and 76 (65.51%) males. The age of patients were ranging from 20-60 years. Highest numbers 90 (77.59) of the patients were between 30 to 50 years of age.

At the initiation of treatment, 48 (41.38%) patients were at WHO clinical stage II, while 46 (39.65%) patients at stage III, 14 (12.06%) patients at stage I and 8 (6.9%) patients at stage IV.

All Patients were given NACO regimen V (LPV/r + ZDV +TDF or LPV/r+ ZDV +3TC).

At the initiation of second line ART treatment, 86 (74.13%) patients had CD4 count less than 100 cell/mm^3, 30 (25.87%) patients had CD4 count more than 100 cells/mm^3.

68 (58.62%) patients had viral load more than 1 lakh. 48 (41.38%) had less than 1 lakh viral load.

Table 1 showed mean viral load was 2, 31,280 ± 50,913 copies per milliliter before treatment which reduced significantly to 1846 ± 621.4 ($p<0.001$) and 260.4 ± 183.7

Table 1: Viral load before and after treatment, n=116 (Repeated Measures ANOVA analysis)

	Viral load Mean ±SEM	95% CI	F value	Dunnett's multiple comparative test	p- value
Baseline Viral load	2,31280 ±50913	129328-333231	20.5	<0.05	<0.0001 (Compare to baseline)
After 6 months	1846±621.4	601.8-3090			
After 12 months	260.4±183.7	-107.4-628.2			

SEM= Standard Error of the Mean, CI=confidence interval

Table 2: CD4 count before and after treatment, n=116 (Repeated Measures ANOVA analysis)

	CD4 count Mean ±SEM	95% C I	F value	Dunnett's multiple comparative test	p- value
Baseline CD4 count	75.03± 10.69	53.62-96.45	37.07	<0.05	<0.0001 (Compare to baseline)
After 6 months	181.8 ±14.34	153.1-210.6			
After 12 months	235.7 ±14.56	206.2-265.1			

SEM= Standard Error of the Mean, CI=confidence interval

($p<0.001$) after six and twelve months of second line ART, respectively.

Table 2 showed mean CD4 count was 75.03 ± 10.69 cells per cubic millimeter before treatment which increased significantly 181.8 ± 14.34 ($p<0.001$) and 235.7 ± 14.56 ($p<0.001$) after six and twelve months of treatment, respectively.

DISCUSSION

Approximately 50,000 of the 1.25 million patients currently on ART in Asia are using a second-line regimen.[8] All eligible second-line patients used ritonavir boosted lopinavir (LPV/r) and two NRTIs include zidovudine (AZT) and Lamivudine (3TC) or tenofovir (TDF). As combination regimen that includes lopinavir–ritonavir is well tolerated and has antiviral activity superior to other PIs.[9] So given treatment was same as current WHO guidelines.[2] These standardized simplified second line regimens have been essential in expanding access to ART in resource limited countries.

Our study shows the outcomes of 116 patients treated with second line LPV/r-based ART regimens for 12 months at Gandhi hospital in Hyderabad, South India. After 6 and 12 months of follow-up, all 116 patients remained on treatment with no deaths or drop outs.

At the time of beginning of second line ART regimen, the Viral Load was similar and CD4 count was lower in our study as compared to similar study in Gujarat, India. [10] This finding suggest similar picture in India and this is due to prolong time require to diagnose treatment failure of first line Anti-retroviral treatment and switching to second line ART.

Similar study at South Africa[11] showed low viral load and more CD4 count as compared to our study, it may be because our National AIDS Control Organization (NACO) guidelines[12] defines virologic failure with plasma viral load more than 10,000 copies/ml, while in South Africa this is only more than 1000 copies/ml.

It guides us to revise definition of virologic failure to initiate second line anti-retroviral therapy.

It has been suggested by Ajose *et al.*, to initiate second line ART as soon as the PVL is more than 400 copies/ml in second line ART programs.[13]

The increase in CD4 count and decrease in viral load was more during first 6 months of therapy, which continued up to 12 months, albeit at a slower rate. Similar observation has been made by other study. [10] It may be because of LPV/r based regimen is more potent and efficacious in suppression of viraemia.

Median increase in CD4 count at 12 months treatment was higher as compared to similar study done at Cambodia and similar to study done in Gujarat.[10,14] Thus, our study observed better immunological outcome.

The immunologic and virologic data supports our observation that the patients' compliance was good despite taking more number of pills and difficulties to store LPV/r.

Limitations of the study was small sample size, Patients have been followed up for a period of one year only. Many of the patients were referred to their respective peripheral ART Centre's after a treatment period of 6 months. Finally, further prospective study is recommended to overcome the limitations of this study.

CONCLUSION

Our study concludes that the second line ART regimens are efficacious regimens as they improved CD4 counts and reduced viral load significantly

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