Original Article

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Clinical and Immunological Outcomes after Initiation of Second Line Antiretroviral Therapy in People Living with HIV

Internal Medicine Section

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ABSTRACT

Introduction: Resistance to first-line Antiretroviral Therapy (ART) has been a major concern in People Living with HIV (PLHIV), which necessitates a switch to second-line therapy. Data regarding the outcomes of second-line ART, especially in patients receiving Lopinavir/Ritonavir and Atazanavir/Ritonavir based therapy in a resource-limited setting like India is limited.

Aim: To determine the clinical and immunological response to second-line ART as measured by change in mean body weight, change in WHO staging and change in CD4 cell count respectively.

Materials and Methods: This facility based cross-sectional was done on PLHIV who were initiated on second-line ART following first-line therapy failure between January 2010 and March 2015. The patients were followed up for a minimum duration of one year after initiating on second-line therapy. The data was collected using a semi-structured proforma. Data regarding the CD4 cell count, body weight and WHO clinical staging at second-line ART initiation, at six months and one year after second-line ART was collected. Statistical analysis was done using ANOVA with Bonferroni test and proportions were compared using chi-square test.

Results: A total of 110 patients who received second-line ART following first-line therapy failure were analysed. Majority 75 (68.2%) were males. The mean baseline body weight at the start of the second-line therapy was 50.65±7.9 kg which increased to 53.02±7.93 kg and 54.69±8.16 kg at 6 and 12 months of therapy respectively. The number of patients categorised as WHO Stage 3/Stage 4 reduced to 25 and 6 at the end of 6 and 12 months of therapy respectively. The mean baseline CD4 count at the start of the therapy was 210.95±104.53 cells/mm^3 which increased to 352.15±149.78 cells/mm^3 and 417.01±147.80 cells/mm^3 at 6 and 12 months respectively. There were a total of nine deaths in present study.

Conclusion: Second-line ART has a satisfactory outcome in terms of clinical and immunological improvement following first-line failure in PLHIV.

Keywords: Lopinavir, Protease inhibitors, Ritonavir

INTRODUCTION

HIV is a global health problem. India has the third highest PLHIV population in the world [1,2]. WHO statistics suggest that 59% of HIV positive patients i.e., 21.7 million are receiving ART at the end of 2017 [3]. In 2017, 9,40,000 PLHIV died from AIDS-related illnesses worldwide, compared to 1.4 million in 2010 [3]. ART reduces HIV replication hence it increases the survival of PLHIV.

Treating HIV infected patients is challenging in resource-limited settings. National ART programme in India was launched in April 2004 and there are 9.97 lacs patients receiving first-line ART at the end of September 2016 [4]. The National AIDS Control Organisation of India has been providing free second-line ART since 2008. First-line ART in resource-limited settings includes combining two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and one Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) [5,6]. HIV drug resistance is a concern in treatment-experienced patients [7]. This has been one of the most important reasons to switch over to a second-line, PI-based regimen. Other reasons for the switch being adverse drug reactions to first-line drugs [8]. A 3% of patients on first-line therapy fail the regimen annually and need switch to protease inhibitor-based second-line ART for survival. Approximately, three million PLHIV will receive second-line, boosted PI-based ART by 2020 [9].

Second-line ART is being provided free through National AIDS Control Organisation (NACO) since 2011 and about 15500 patients are receiving free ART and many are taking it in the private sector [4]. Second-line ART regimen in resource-limited settings consists of Ritonavir boosted-Lopinavir (LPV/r) or Atazanavir/Ritonavir (ATV/r) with two nucleoside/nucleotide reverse transcriptase inhibitors. The criteria to switch to second-line ART includes immunological and/or virological and/or clinical failure [10].

In resource limited settings, the data regarding the efficacy of second line ART is limited [5,11-13]. A pilot study done in at the present study institute mainly consisting of Indinavir based second line therapy did show a good clinical and immunological short term outcome over six months period [14]. Indinavir based regimens are not routinely used in clinical practice now. In resource, limited settings genotypic resistance testing, on every patient is not feasible and without the resistance testing the outcomes of second-line ART are unclear. The present study describes the clinical and immunological outcomes of PLHIV on PI-based second-line ART regimens in Southern India.

MATERIALS AND METHODS

Study Design and Setting

This cross-sectional study was done at Kasturba Medical College (KMC), Mangalore, Karnataka, India. KMC Mangalore is a Tertiary Care referral Hospital of Southern India.

Sample Size, Sampling Technique, Study Duration and Study Population

The sample size was calculated using the formula:

$$n=4pq/d^2$$

taking 'p' as 82% of HIV positive patients on second line ART who show clinical and immunological response as defined by previous studies [15] and taking 10% as relative precision and 95% as confidence interval (p=82, q=100-p, d=10% of p), the sample size

came to be 88, considering 20% as non response [16], the total sample size came to be 104. Study participants were selected by non-probability sampling. The study population comprised of HIV positive patients of age >18 years of either gender started on second-line ART after first-line therapy failure from January 2010 till March 2015. Pregnant women and patients whose CD4 cell counts were unavailable were not included in the study. The study protocol was approved by the Institutional Ethics Committee of KMC Mangalore.

Data Collection

The study subjects were enrolled after obtaining written informed consent. Data were collected using a semi-structured proforma. Data were collected using the medical records of the patients and by interviewing them. The patients were followed-up for a minimum duration of one year after initiation of second-line ART. The CD4 cell count was measured every six months. Data regarding the CD4 cell count, body weight and the WHO clinical staging at second-line ART initiation, at six months and one year after starting second-line therapy was also collected.

Data regarding reasons to switch to second-line ART was captured. {The criteria to switch to second-line ART included clinical and/or immunological failure in a patient who had received six months or more of standard first-line therapy. The patients qualified for second-line ART if there was CD4 decline to pre-ART values, drop in the CD4 to <50% of on-treatment peak value, failure to attain CD4 >100 cells/mm^3 (immunological failure), or develop a new WHO Stage 3/Stage 4 AIDS-defining illness (clinical failure) [16]. In the present study second-line, ART regimen consisted of Ritonavir boosted protease inhibitor (Atazanavir/Ritonavir or Lopinavir/Ritonavir or Indinavir/Ritonavir) plus 2 nucleoside/nucleotide reverse transcriptase inhibitors like Zidovudine+Lamivudine or Stavudine+Lamivudine or Tenofovir+Lamivudine or Tenofovir+Emtricitabine.

The adequate clinico-immunological outcome was defined as the following for the purpose of this study:

- Increase in CD4 count above 200 cells/mm^3 or Doubling of CD4 cell counts from baseline (whichever was higher).
- Improvement in WHO clinical stage for HIV from Stage 3/Stage 4 to Stage 2/Stage 1.

STATISTICAL ANALYSIS

Data collected were analysed using SPSS Version 11.5 statistical software. For continuous variables, the mean (standard deviation) and median were calculated. For categorical variables, authors calculated proportions. Continuous data were compared with ANOVA with Bonferroni test; proportions were compared with chi-square test. Friedman test with post-hoc analysis by Wilcoxon signed rank test was applied for the analysis of CD4 count and WHO clinical staging. The p-value <0.05 was considered to be significant.

RESULTS

Baseline Characteristics

Authors analysed 110 PLHIV on second-line ART. The mean age of the patients was 43.79±6.98 years Majority 75 (68.2%) were males. Most of them 56 (50.9%) were in the age group of 41-50 years [Table/Fig-1]. In the present study 44 (40%) patients were receiving Zidovudine+Lamivudine+Nevirapine and 25 (22.7%) patients got Tenofovir+Lamivudine+Efavirenz as first-line ART [Table/Fig-1]. The most common opportunistic infection was Tuberculosis 28 (25.4%) followed by Pneumocystis pneumonia 8 (7.2%), Candidiasis 6 (5.4%), Toxoplasmosis 4 (3.6%), CMV Oesophagitis 2 (1.8%) and Cryptococcal meningitis 1 (0.9%).

Mean baseline CD4 count at the initiation of second-line ART was 210.9±104.5 cells/mm^3. The mean body weight was 50.6±7.9 kg. Majority 49 (40.5%) of the patients were in WHO clinical Stage 1. The most common reason to switch to second-line ART was combined clinical and immunological failure (44%) followed by immunological failure (30%) alone and clinical failure (26%) alone.

Variables	n (%)
Gender	
Female	35 (31.8)
Male	75 (68.2)
Age (years)	
≤40	34 (30.9)
41-50	56 (50.9)
>50	20 (18.2)
WHO staging (baseline)	
Stage 1	49 (44.5)
Stage 2	7 (6.3)
Stage 3	23 (20.9)
Stage 4	31 (35.5)
First line treatment	
AZT+3TC+NVP	44 (40)
TDF+3TC+EFV	25 (22.7)
TDF+3TC+NVP	15 (13.6)
d4T+3TC+EFV	10 (9.1)
d4T+3TC+NVP	8 (7.3)
AZT+3TC+EFV	8 (7.3)
Second line treatment	
AZT+3TC+ATV/r	25 (22.7)
TDF+3TC+ATV/r	54 (49.1)
TDF+FTC+ATV/r	14 (12.7)
TDF+3TC+IDV/r	2 (1.8)
TDF+3TC+LPV/r	6 (5.5)
AZT+3TC+LPV/r	9 (8.2)

[Table/Fig-1]: Demographic and clinical profile of study population (n=110). AZT=Zidovudine, 3TC=Lamivudine, NVP=Nevirapine, EFV=Efavirenz, TDF=Tenofovir, d4T=Stavudine, FTC=emtricitabine, LPV/r-lopinavir/ritonavir, ATV/r-atazanavir/ritonavir, IDV/r-Indinavir/ritonavir)

Outcomes of Second-Line ART

Atazanavir/Ritonavir+Tenofovir+Lamivudine 54 (49.1%) were the commonest second-line ART in the present study. In the present study, 25 patients (22.7%) received Atazanavir+Ritonavir+Zidovudine+Lamivudine [Table/Fig-1]. During the study period, there were nine deaths and four patients were transferred to other ART centres.

Clinical Outcome

The number of patients categorised as WHO Stage 3 or Stage 4 reduced to 25 and 6 at the end of six and 12 months [Table/Fig-2]. Wilcoxon signed ranks test value comparing the WHO staging at the start of second line therapy (0 month), at 6 months and at 12 months was found to be significant (p-0.001). The body weight increased to 53.02±7.93 kg and 54.69±8.16 kg at the end of 6 and 12 months of therapy respectively which was statistically significant (p-0.001) [Table/Fig-3].

	Stage 1 n (%)	Stage 2 n (%)	Stage 3 n (%)	Stage 4 n (%)	Mortality n
Baseline*	49 (44.5)	7 (6.3)	23 (20.9)	31 (35.5)	-
6 month	56 (53.8)	23 (22.1)	10 (9.6)	15 (14.4)	6
12 month	77 (79.4)	14 (14.4)	6 (6.2)	0	3

[Table/Fig-2]: Comparison of WHO staging of the study population. *During the study period nine patients died and four patients were transferred to other ART centres

	Weight (Kg) Mean±SD	p-value*
Baseline	50.65±7.9	0.001
6 months	53.02±7.93	
12 months	54.69±8.16	

[Table/Fig-3]: Weight comparison of the study population. *ANOVA

Immunological Response

The CD4 count increased to 352.15±149.78 cells and 417.01±147.80 cells at 6 and 12 months which was statistically significant (p-0.001) [Table/Fig-4].

	CD4 count (cells/mm^3) Mean±SD	Median=(IQR)	Friedman test value	p-value
Baseline	210.959±104.530	191 (142-271)	189.557	0.001
6 months	352.155±149.786	344 (257-397)		
12 months	417.010±147.803	401 (323-486)		

[Table/Fig-4]: CD4 count comparison of the study population.

DISCUSSION

The present study describes the clinical and immunological outcomes of PL-HIV on second line PI based ART regimen at the end of 12 months. After 12 months of follow-up, a good immune reconstitution (417±147 cells/mm^3) along with clinical improvement (weight) was observed in the study population. At the start of second-line therapy, out of 110 patients, 49 patients (44.5%) were categorised as WHO clinical Stage 1 which indicates that majority of the patients were asymptomatic at the time of switch to second line therapy and clinical failure manifests at the late stage. So, clinical failure is not a good indicator of first line therapy failure. The mean increase in CD4 count at 12 months of treatment was 206 cells/mm^3 which was higher when compared to similar studies done at Africa (206 vs 133) [17], but lower when compared to a similar study done in western India (206 vs 226) [15]. In a study done by Chakravarty J et al., the median CD4 count at the start of second line therapy was 78.50 (cells/mm^3 IQR 49.75-121.25) and at 12 months 273 cells/mm^3 (IQR 182-357) [18]. In the present study median CD4 count at baseline was 191 cells/mm^3 (IQR142-271) and 401 cells/mm^3 (323-486) at the end of 12 months. In a study done in Cambodia, the median CD4 cell gain on second-line regimen was 80 cells/mm^3 (IQR: 30-152) at 6 months and 134 cells/mm^3 (IQR: 71-204) at 12 months [19].

The clinical response to second-line therapy was equally good in the present study. The number of patients categorised as WHO Stage 3/4 significantly reduced from 54 to 25 and 6 at the end of 6 and 12 months respectively. In the present study 9 (8.2%) patients died within one year of switching over to second line ART, which is less when compared to study by Chakravarty J et al., published from Varanasi where 21 (12.35%) out of 170 patients died within first year [18].

LIMITATION

The present study had some limitations. Virological monitoring was not done. Identification of treatment failure in Asian countries is mainly determined by clinic immunological changes, which may occur long before or long after the loss of virological suppression [20]. Authors only assessed one year outcomes. Resistance testing was not done prior to switching to second line treatment. Data about adherence was not assessed. Adherence is an important determinant of treatment outcomes. Causes of death were not analysed. This was a single centre study done predominantly in an urban setting catering to Southern Indian population which might limit the generalisability of present results to rural settings. The main strength of present observational study is that it reflects programmatic conditions and not the rigid clinical trial environment.

CONCLUSION

In conclusion, the present study shows that second-line ART has a satisfactory outcome in terms of clinical and immunological improvement following first-line failure in resource-limited setting like India. Resource-limited settings must have access to viral load monitoring so that timely switch to second-line can be done. Further studies are required to know if these outcomes can be sustained over a longer period.

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