Original Article

Outcomes of Second Line Anti-Retroviral Therapy in Cases of Confirmed First Line Treatment Failure

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ABSTRACT

Aim and Objectives : The present research was undertaken to study the outcomes of second-line antiretroviral therapy (ART) in cases of confirmed first line antiretroviral treatment failure and also identify the factors associated with the outcomes.

Methods : A hospital-based descriptive cross-sectional analytical study was conducted in 70 HIV positive cases, who were registered for second-line ART at tertiary care center during a period of around 2 years from November 2017 to October 2019. One study subject died shortly after starting the study. So, the remaining 69 subjects were analyzed to find out different outcomes of second line ART and factors associated with these outcomes.

Results : Mean duration of first line ART exposure was 5.67 ± 2.57 years. At baseline 23 (33.33%) subjects were in WHO clinical stage 3 or 4. The most common cause of switching to second line ART was virological only failure (55%). The baseline mean value of weight, BMI, CD4 count, BREF score, Hb level, TG, TC, LDL levels, SGPT and ALP levels were statistically increased at 12 months of follow up. There was statistically significant improvement in the WHO clinical stage and the WAB functional status after 12 months. Mean viral load of the subjects was significantly reduced after 12 months. 45(65.22%) patients achieved CFR, whereas CUR and IOR achieved by 6 (8.70%) patients each. 12 patients (17.39%) achieved VOR. 45(65.22%) patients had adequate responses and 24(34.78%) had inadequate responses. The most of the subjects i.e., 60 (86.9%) had >95% adherence on second line ART.

Conclusion : The second-line ART has satisfactory early treatment outcomes at 12 months follow up. Also, timely switching of the patients to second-line ART after the first-line ART failure benefits the patient. The adherence is an important factor associated with the outcomes. So, adherence counselling should be done more frequently.

Key-words : Antiretroviral, Virological, Adherence, Outcomes, Viral load

Introduction :

Worldwide Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) is a major public health issue and in 2017, over 36.9 million people were living with HIV/AIDS[1-3]. The first case of HIV infection in India was discovered in 1986 in female sex workers in Chennai[4]. India has the third largest HIV epidemic in the world and is driven by sexual transmission, which accounted for 86% of new infections in 2017/2018[5]. In 2017, HIV prevalence among Indian adults (aged 15-49) was an estimated 0.2%. This figure is small compared to most other middle-income countries but because of India's huge population (1.3 billion people) this equates to 2.1 million people living with HIV[6,7].

The global antiretroviral therapy (ART) coverage increased progressively from 7% in 2005 to 59% in 2017[1-3]. Government of India started the free ART program on 1st April 2004, which is one of the largest in the world. The program initiated a number of new initiatives like, in 2006, CD4 count testing was made free[8]. In 2017, 79% of people living with HIV were aware of their status, of whom 56% were on antiretroviral treatment (ART). The proportion of people on ART who are virally suppressed is not reported[6]. Overall, India's HIV epidemic is slowing down. Between 2010 and 2017 new infections are declined by 27% and AIDS-related deaths more than halved, falling by 56%. Because of this extensive ART scale-up, treatment failure has become an emerging problem[9,10]. The prevalence of first-line ART failure differs significantly across countries

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depending on the criteria (clinical, immunological or virologic) used for its diagnosis. In India, the second line ART program for patients failing first-line ART was introduced in January 2008, initially at the JJ Hospital, Mumbai and GHTM, Tambaram[8].

The concept of ART plus was devised in October 2010 to increase access to second-line ART.As the data regarding the second-line ART is limited, present study was undertaken to find out the outcomes of second-line ART in Indian settings and the factors associated with these outcomes.

Materials and Methods :

After obtaining Institutional Ethical Committee approval and written informed consent from all the patients, this hospital-based descriptive cross-sectional study was conducted in 70 HIV positive cases with confirmed first-line treatment failure (virological/ immunological/ clinical) who were registered for second-line ART at tertiary care center during a period of around 2 years from November 2017 to October 2019. The approval from the Maharashtra State AIDS Control Society (MSACS) was also obtained. Patients with age less than 15 years, HBV/HCV co-infection, ANC women, patients who had not given consent were excluded from the study.

Information was collected by personal interview and with the help of preset proforma from each patient. Demographic data about age, sex, residence, marital status, addiction, comorbidities, duration of first-line ART, type of failure on first-line ART were obtained. Physical examination was done and baseline weight, BMI, presence of opportunistic infection and WHO clinical stage was assessed. The baseline values for CD4 count, HIV RNA levels were recorded and baseline BREF score was calculated. Baseline data about CBC, LFT, KFT, Lipid profile was obtained. Functional status was noted as working / ambulatory / bedridden. These patients were followed every monthly. During each visit, patients were clinically assessed by weight gain, subjective well-being, new symptoms and evidence of opportunistic infections. They were also counselled for adherence during each visit. At the end of 12 months of the study period, each of these study subjects underwent CD4 cell count and virological assessment by the HIV RNA level. In addition to this, investigations CBC, LFT, KFT, and Lipid profile were repeated after 12 months. WHO BREF score was reassessed at 12 months. 6 monthly CD4 count and viral load testings were not feasible in this study setting. Data about adherence was collected by monthly pill counts as follows and the average adherence of the last 3 months of study was considered as final adherence.

- 95% adherence: patient missed less than 3 pills in a month
- 80 to 95% adherence: missed 3 to 12 pill in a month
- < 80% adherence: missed more than 12 pills in a month

During the 3rd month of study, 1 patient died. As the values of this patient after 12 months of study were not available, we did not consider this patient in the final analysis. So, at the end of 12 months of study duration, outcomes of remaining 69 study subjects were categorized into four groups, i.e.

1) CFR (Concordant Favorable Response),

2) CUR (Concordant Unfavorable response),

3) VOR (Virological Only Response),

4) IOR (Immunological Only Response)

This categorization was based on viral load and CD4 count after 12 months of study.

Table 1 : **Outcomes of second line ART**

Increase in CD4 cell counts	Viral load after 12 months	Inference
>50 cells/cmm	<1000 copies/ml	CFR
	>1000 copies/ml	IOR
<50 cells/cmm	<1000 copies/m	VOR
	>1000 copies/m	CUR

These four outcomes were grouped into two response groups' i.e. adequate and inadequate response group. The adequate response group included CFR. The inadequate response group included CUR, IOR, and VOR. The association between these two response groups and various factors was analyzed by appropriate statistical analysis to find out the predictors of these outcomes.

Statistical Analysis :

Data was analyzed in statistical software STATA, version 10.1, 2011. Data analysis included both Descriptive and Inferential statistics. Descriptive statistics were used to summarize quantitative variables with mean, standard deviation (SD), while frequency and percentages were used to summarize categorical (qualitative) variables. Inferential statistics mainly included two-independent samples (Unpaired t-test) and Chi-square test for assessing the significance of the difference in various parameters expressed as means or proportions in two outcome groups (e.g. adequate and inadequate). The Significance of within-the-group differences in means from baseline to 12 months was also assessed by paired t-test. The role of baseline characteristics in the association of outcome and other covariates was assessed using Binary Multiple Logistic Regression (MLR) Analysis. Adjusted odd''s ratios were calculated along with 95% Confidence Intervals. A p-value < 0.05 was considered statistically significant for all the comparisons.

Observations and Results :

Total 70 patients were enrolled in the study, of them 1 patient died before completion of the study, so observation and results were obtained from 69 patients, after exclusion of the death. Mean age of patient was 38.12 ± 8.65 years, ranged from 15-54 years. Male patients predominated over females with a ratio of 4.75. Mean duration of first line ART exposure in the study was 5.67 ± 2.57 years. A detailed demographic data including age, sex, residence, marital status, addiction, comorbidities, duration of first-line ART and type of failure on first-line ART are shown in ***Table 1.***

Table 1 : **Demographic profile of the patients**

Characteristics		No. of Patients (%)
Age group (years)	11-20	4 (5.79%)
	21-30	9 (13.04%)
	31-40	27 (39.13%)
	41-50	27 (39.13%)
	51-60	2 (2.89%)
Gender	Male	57 (82.60%)
	Female	12 (17.40%)
Residence	Rural	23 (33.33%)
	Urban	46 (66.66%)
Marital status	Married	59 (85.50%)
	Unmarried	10 (14.49%)
Addiction	Yes	38 (55.07%)
	No	31 (44.92%)
Comorbidity	COPD	1 (1.45%)
	Asthma	1 (1.45%)
	Bronchitis	1 (1.45%)
	Depression	1 (1.45%)
	Hypertension	2 (2.90%)
	CVE	1 (1.45%)
	DM	1 (1.45%)
	No comorbidity	62 (89.86%)
1st line ART duration (years)	1	3 (4.34%)
	2	4 (5.79%)
	3	6 (8.69%)
	4	4 (5.79%)
	5	19 (27.53%)
	6	1 (23.18%)
	7	7 (10.14%)
	8	3 (4.34%)
	9	1 (1.44%)
	10	3 (4.34%)
	12	2 (2.89%)
	14	1 (1.44%)
Failure type	Virological only	38 (55.07%)
	Clinical + virological	10 (14.49%)
	Clinical + Immunological + virologica	14 (20.29%)
	Immunological + Virological	7 (10.14%)

At baseline, maximum (42.02%) patients were in WHO clinical stage I followed by stage II (24.63%), stage III (18.84%) and stage IV (14.49%). The most common cause of switching to second line ART was virological only failure (55%).

The baseline mean values of weight, BMI, CD4 count, BREF score, Hb level, TG, total cholesterol, LDL levels, SGPT and ALP levels were statistically increased at 12 months of follow up. There was statistically significant improvement in the WHO clinical stage and the WAB functional status after 12 months. Mean viral load of the subjects was significantly reduced after 12 months, ***(Table 2).***

45 (65.22%) patients achieved CFR, whereas CUR and IOR achieved by 6 (8.70%) patients' each. 12 patients (17.39%) achieved VOR, ***(Figure 1).*** The outcomes were divided into two responses; the adequate response group had 45 (65.22%) patients whereas the inadequate response group had 24 (34.78%) patients.

Table 2 : **Comparison of various parameters at baseline and after 12 months**

Parameters		**Baseline**	**At 12 months**	**P value**
Weight (In kg)		53.65 ± 11.02	58.26 ± 9.88	0.0001
BMI		20.49 ± 3.48	22.36 ± 3.12	0.0001
CD4 count		304.33 ± 178.60	409.31 ± 268.05	<0.001
Viral load		113060 ± 161888.4	10476.7 ± 68408.5	0.0001
BREF score		65.77 ± 9.52	91.52 ± 9.96	0.0001
Change in WHO clinical stage from baseline to 12 months				
Stage		**Baseline**	**At 12 months**	**P value**
1		29 (42.03%)	53 (76.81%)	0.0001
2		17 (24.64%)	14 (20.29%)	0.5406
3		13 (18.84%)	2 (2.9%)	0.0026
4		10 (14.49%)	0 (0%)	0.001
WAB status	Working	54 (78.26%)	68 (98.55%)	0.001
	Not working	15 (21.73%)	1 (1.44%)	
Laboratory parameters		**Baseline**	**At 12 months**	**P value**
Hemoglobin		9.97 ± 1.87	11.58 ± 2.32	<0.0001
Total bilirubin		1.23 ± 0.71	1.47 ± 0.72	0.0093
SGOT		27.53 ± 1.57	29.15 ± 17.13	0.4538
SGPT		21.07 ± 7.51	26.62 ± 11.68	0.0008
ALP		169.8 ± 118.28	206.34 ± 129.64	0.0178
Blood urea		33.53 ± 16.82	35.63 ± 19.10	0.2100
Creatinine		0.79 ± 0.30	0.87 ± 0.36	0.0998
Lipid parameters		**Baseline**	**At 12 months**	**P value**
TG		87.13 ± 28.7	181.45 ± 18.22	<0.0001
LDL		67.44 ± 30.14	87.4 ± 21.24	
HDL		40.11 ± 4.9	34.49 ± 4.69	
TC		141.4±22.01	167.42±30.39	

Table 3 : **Factors associated with outcomes**

Various factors		Outcomes		P value
		Adequate	Inadequate	
Age group (years)	11-20	3 (6.67%)	1 (4.17%)	0.717
	21-30	5(11.11%)	4 (16.67%)	
	31-40	20 (44.44%)	7 (29.17%)	
	41-50	16 (35.56%)	11 (45.83%)	
	51-60	1 (2.22%)	1 (4.17%)	
Gender	Male	36 (80%)	21 (87.50%)	0.434
	Female	9 (20%)	3 (12.50%)	
Residence	Rural	17 (37.78%)	6 (25%)	0.284
	Urban	28 (62.22%)	18 (75%)	
Marital status	Married	38 (84.44%)	22 (91.67%)	0.396
	Unmarried	7 (15.56%)	2 (8.33%)	
Addiction	Yeas	23 (51.11%)	15 (62.50%)	0.365
	No	22 (48.89%)	9 (37.50%)	
Mean weight (baseline)		53.80 ± 11.78	53.37 ± 11.69	0.8801
Mean BMI (Baseline)		20.63 ± 3.19	20.09 ± 4.01	0.5458
Mean CD4 count (baseline)		346.08 ± 203.86	226.04 ± 70.65	0.0037
Mean viral load (baseline)		92228.62 ± 129210.7	152119.6 ± 207615.2	0.0723
WHO clinical stage (baseline)	1	19 (42.22%)	10 (41.67%)	0.371
	2	13 (28.89%)	4 (16.67%)	
	3	6 (13.33%)	7 (29.17%)	
	4	7 (15.56%)	3 (12.50%)	
WAB status (baseline)	Ambulatory	6 (13.33%)	2 (8.33%)	0.749
	Bedridden	5 (11.11%0	2 (8.33%)	
	Working	34 (75.56%)	20 (83.33%	
Adherence	≤95%	1 (2.22%)	9 (37.50%)	0.001
	>95%	44 (97.78%)	15 (62.50%)	
1st line ART duration (years)	1	3 (6.67%)	0 (0%)	0.143
	2	2 (4.44%)	2 (8.33%)	
	3	5 (11.11%)	1 (4.17%)	
	4	2 (4.44%)	2 (8.33%)	
	5	13 (28.89%)	6 (25%)	
	6	12 (26.67%)	4 (16.67%)	
	7	2 (4.44%)	5 (20.83%)	
	8	3 (6.67%)	0 (0%)	
	9	0 (0%)	1 (4.17%)	
	10	2 (4.44%)	1 (4.17%)	
	12	0 (0%)	2 (8.33%)	
	14	1 (2.221%)	0 (0%)	

Failure type	Virological only	24 (53.33%)	14 (58.33%)	0.453
	Clinical + virological	5 (11.11%)	5 (20.83%)	
	Clinical +Immunological + virologica	6 (13.33%)	1 (4.16%)	
	Immunological + Virological	10 (22.22%)	4 (16.66%)	

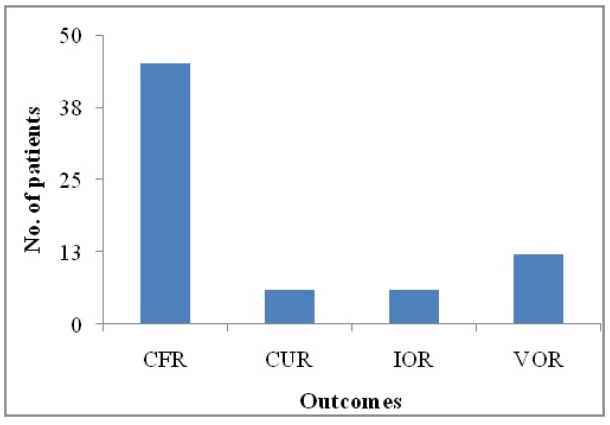
The multivariate analysis which indicate that the odds of Adherence was 1.7 times more in the adequate group versus Inadequate group, when adjusted for other characteristics like addiction, baseline weight, WHO clinical stage at baseline, CD4 count at baseline, viral load at baseline. Similarly, odds of CD4 count at baseline was 1.007 times more in the adequate group versus Inadequate group, when adjusted for other characteristics like addiction, adherence, baseline weight, WHO clinical stage at baseline, and viral load at baseline, ***(Table 4).***

The adherence level showed that the most of the subjects i.e., 60 (86.9%) had >95% adherence on second line ART.

Table 4 : **Multivariable analysis using binary logistic regression for association between the outcomes and other baseline characteristics**

Variables	Adj.OR	95% CI	P Value
Adherence	1.69	1.21-2.35	0.002
Weight at baseline	1.01	0.93-1.11	0.726
WHO Clinical Stage at baseline	1.54	0.66-3.65	0.318
Cd4 count at baseline	1.007	1.001-1.014	0.026
Viral load at baseline	0.999	0.999-1.001	0.210

Figure 1 : **Various outcomes in study population**



Discussion :

As HIV disease steps into the fourth decade, there are number of patients on lifelong ART, facing the threat of drug resistance and subsequent treatment failure. In the present study mean duration of first line ART was 5.67 ± 2.57 years; this is longer than mean duration reported in Desai et al[11] and Boettiger et al[12]. In the developing countries, the number of patients switching to second-line ART continues to increase. The most common cause of switch on second line ART was virological only failure (55.07%) followed by immunological + virological (20.29%) while in a study conducted by Desai et al[11] the most common cause to switch was combined immunological and virological failure (50.79%) followed by all three failure (34.92%). It is well known that the virological failure precedes immunological failure and clinical failure is last to appear[13]. Thus in current study, most of the patients was detected as first line ART failure before immunological and clinical failure occurred.

The mean weight was increased by 4.61 kg which was statistically significant (p-value=0.0001) and the number of patients with WHO stage III/IV were reduced from 23 to 5 after 12 months, these findings are similar to the study conducted by Desai et al[11]. The most common opportunistic infection (OIs) was

tuberculosis in 22 subjects (31.88%) and other OIs were fungal nail infections[6], herpes zoster[4] and candidiasis[3]. CD4 count was increased by 124.91 cells/cmm after 12 months. The decline in mean viral load was 1,02,583.6 copies/ml which was significant. 82.6% subjects achieved virological suppression (<1000 copies/ml) which is comparable with Desai et al[11] and later study had stricter virological suppression criteria. There was a significant improvement in Hb level (p<0.0001) and anaemia occurred in 26 (37.68%) patients. The hyperbilirubinemia occurred in 27 (39.13%) patients. Hyperbilirubinemia is an expected consequence of ATV/r as it is known to increase bilirubin via inhibition of UGT1A1; various previous studies report the occurrence of 40-49%[14]. It is more common in Indian patients which could be attributed to the higher frequency (35%) of UGT1A1 *8 allele among Indians[15]. However, this is only of cosmetic importance and not usually related to the hepatic injury. It was found that the level fall back to normal after discontinuation of drug [16]. SGOT levels increased in 10(14.49%) patients, but this increase was non-significant (p-value=0.4538). 6 (8.69%) patients had SGPT elevation and ALP was raised in 8(11.59%) patients. This increase in SGPT and ALP levels was statistically significant. However, this needs to be followed over longer time period.

The most common ADRs reported was dyslipidemia which occurred in 46 (66.7%) patients after 12 months. The most common among the dyslipidemia was decrease in HDL which occurred in 33 cases (47.82%) followed by increased TG levels which occurred in 28 (40.57%). The LDL levels were raised in 5 cases (7.24%).The total cholesterol was elevated in 2 patients (2.89%). The mean serum HDL level was decreased and mean TG level was increased, this decreased HDL level and increased TG level was statistically significant. The mean LDL level was increased with highly significant p-value <0.0001. The mean total cholesterol was also significantly elevated. HIV is now a chronic manageable disease. There is a need for managing these metabolic complications. Therefore, all the patients on second line ART should undergo regular lipid profile monitoring.

The adequate response (CFR) was obtained in 65.22% of patients after 12 months and concordant unfavorable response was found in 8.7% subjects. In study conducted by Anusuya, et al[17] 76.7% subjects had good immunological and virological improvement (CFR) after 6 months and concordant unfavorable response (CUR) was found in 8.3% subjects. So, present study had the lower success rate and similar CUR rate. CFR rate was also less and discordant responses (IOR+VOR) were more than the other studies[11,17].

There was no significant association of outcomes with the age, gender, baseline weight, BMI, baseline WHO clinical stage. Adherence level < 95% was found to be significantly associated with the inadequate response. the odds of Adherence was 1.7 times more in Adequate group versus Inadequate group, when adjusted for other characteristics like addiction, baseline weight, WHO clinical stage at baseline, CD4 count at baseline, viral load at baseline. There was significant association between the baseline CD4 count and the outcomes. These findings are correlated well with previous studies[18-21].

Limitations of the Study :

The present study has a lot of strengths, but we acknowledge a few limitations of the study which includes - it was a single center study, sample size was smaller, follow up time was short (1 year), the comparison was done only at 12 months. The 6 monthly CD4 count and viral load were not done in our study due to the lack of resources. The association of outcomes with the different second line regimens was not studied. Unequal number of patients in the adequate and the inadequate response groups had affected the association of certain factors (e.g., the association of mean baseline viral load with outcomes could have been significant if the numbers in these two groups were comparable). Resistance testing was not offered to patients due to economic constraints.

Conclusion :

The second-line ART has satisfactory early treatment outcomes at 12 months follow up. The timely switching of the patients to second-line ART after the first-line ART failure benefits the patient. The adherence is an important factor associated with the outcomes. So, adherence counselling should be done more frequently. It was found that the low baseline CD4 count was associated with inadequate outcome. As viral load starts increasing before the CD4 count decline starts, the national program should encourage the use of viral load monitoring for the detection of first-line ART failure. This will help to switch the patient on second-line ART before a drop in CD4 count. There are some adverse effects of second like ART like dyslipidemia, hyperbilirubinemia which should be monitored. Further studies are required to see for how long the beneficial effect of second-line ART persists.

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