Original Research Article

Profile of highly active antiretroviral therapy failure human immunodeficiency virus patients at a tertiary health care centre of India: a success story of NACP

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ABSTRACT

Background: Although HAART has successfully controlled the progression of HIV and helped to prevent the disease significantly, new challenges are heading up and ART failure despite of good adherence is becoming a major hurdle in the way of HIV control. Considering these facts present study was planned with an objective to study clinical and immunological profile of antiretroviral therapy failure HIV patients.
Methods: This observational study was conducted at ART plus centre of one of the tertiary health care centre of India from February 2018 to September 2019. Patients satisfying inclusion and exclusion criteria were interviewed by using semi-structured questionnaire and were examined and investigated for any opportunistic infections and their CD4 counts were studied.
Results: Among total 4098 patients alive on ART at present study centre 90.6% were responding well to the 1st line of ART, while 8.7% had failed to 1st line of ART but responding well to the 2nd line whereas 0.7% had failed to 2nd line and were initiated on 3rd line of ART. Failure of ART was the cause for change in regimen among 84.9% of patients. Median of rise in CD4 count at 6 months from switch to 2nd line was 137 cells/mm^3.
Conclusions: Antiretroviral therapy has significantly improved outcome of the disease. Failure of ART is the major cause for change in ART regimen. Majority of patients in failure had WHO clinical stage 1 and 2.

Keywords: ART failure, CD4, Clinical profile, HIV, Immunological profile

INTRODUCTION

Human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS) is pandemic, with infected patients has been reported from nearly every country in the world. Unlike other epidemics, AIDS falls most heavily on young adults in their prime, posing a grave challenge in the areas of health, social and economic development.[1] National adult (15-49 years) HIV prevalence in India was estimated at 0.22% in 2017. Estimated adult HIV prevalence of Maharashtra was 0.33% which is higher than that of national prevalence.[2]

ART centre of present tertiary care centre was established in 2006 and was upgraded as ART plus centre in 2011. This ART plus centre has been connected with network of ART centres as well as Linked ART centres (LACs). Till the end of this study almost 15874 patients were registered under pre ART at this centre and 10953 patients were registered under ART out of which 4098 patients were alive on ART. Highly active antiretroviral therapy (HAART) has become a major turning point in response to the HIV/AIDS epidemic. HAART treatments effect is clearly evident, as increased survival, decreased HIV associated mortality and vastly improved quality of life. An infectious disease which was previously used to be considered to have almost universally fatal outcome

has been transformed into a manageable chronic infectious disease.[3] In India demographic, geographic, economical and resource related problems has posed great difficulty on providing HAART but national programme of India has achieved great success overcoming these hurdles and has globally acclaimed as a success story. The National AIDS Control Programme (NACP) is being implemented as a comprehensive programme for prevention and control of HIV/AIDS in India.[4]

Although HAART has successfully controlled the progression of HIV, new challenges are heading up and ART failure despite good adherence is becoming a major hurdle in the way of HIV care. The present study was conducted with the objectives to study sociodemographic, clinical and immunological profile of antiretroviral therapy failure HIV patients.

METHODS

The present study was a hospital based observational descriptive study and was carried out in the Department of General Medicine of tertiary health care centre. Approval from the Institutional Ethical Committee was taken before start of the study. The present study was carried out from February 2018 to September 2019.

Inclusion criteria

We included those HIV infected patient older than fifteen years and were failing on ART (as defined by WHO guidelines), registered under ART plus centre and also admitted to medicine wards of present study teaching institute.

Exclusion criteria

Pregnant females, patients lost for follow up, Patients transferred out under linked ART centre, newly diagnosed along with patients on ART for less than 6 months and those who were not willing to participate were excluded from the study.
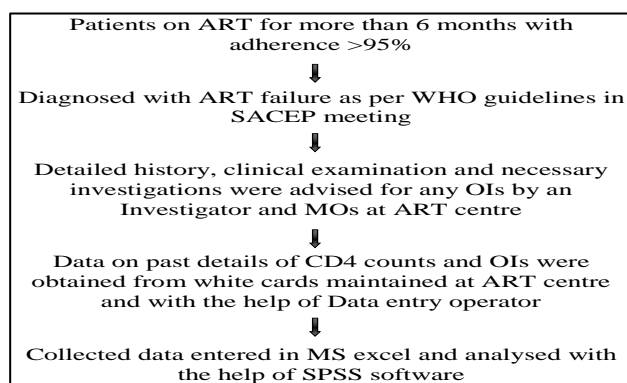

Figure 1: Study flow chart.

Out of total 4098 patients 3714 (90.6%), 357 (8.7%) and 27 (0.7%) patients were on 1st, 2nd and 3rd line of ART respectively. Among all these, 303 and 27 of 1st and 2nd line failures respectively were fulfilling all the inclusive and exclusive criteria's. Thus we studied total 330 study subjects during the study period.

RESULTS

At the present study ART centre 10953 patients were initiated on ART since 2006 out of which 4098 patients were alive taking ART from the present study ART centre till the end of the study period, 1968 patients died on ART, 442 patients were lost to follow up, 383 patients opted out voluntarily and 4062 patients were transferred out to other ART and linked ART centres. Among 4098 patients on ART maximum no. of patients (n=3714; 90.61%) were responding well to the 1st line of ART, whereas 357 patients were on 2nd line of ART among which 303 were shifted to 2nd line of ART due to failure of ART and only 27 patients were on the 3rd line of ART.

In the present study maximum no. of patients belonged to the age group 31 years to 50 years. Present study population was predominantly composed of male patients, consisting of 63%, 74% of total patients of 1st and 2nd line failure respectively. From both 1st line and 2nd line failures (172(57%) and 20 (74%) patients respectively) maximum proportion of patients were from the rural areas. Maximum numbers of patients were married. Proportion of unmarried patients increased as line of failure progressed from 1st line failure to 2nd line failure as only 3% of 1st line failures were unmarried whereas proportion of unmarried patients increased to 11% of patients from 2nd line failure.

Almost 52 (17%) of 1st line ART failure patients were illiterate and maximum proportion of patients i.e. 44% and 41% from 1st and 2nd line ART failure respectively had acquired education upto secondary school. Interesting observation was maximum number of patients were from upper lower class as per Kuppuswamy socieo-economical classification. Among study population majority of patients had BMI within normal range i.e. 18.5-24.9 kg/m². Mean BMI of 1st line and 2nd line failure patients was normal. Also mean BMI of females was lower than that of males.

Heterosexual route was the predominant route of transmission among all lines of failure patients. 89% and 85% of 1st line and 2n d line failure patients respectively had acquired HIV by heterosexual route. Proportion of patients with mother to child transmission of HIV seen to be increasing as line of failure advances from 1st line to 2nd line failure as only 2% of 1st line failure patients had acquired HIV vertically which increased to 11% of 2nd line failures (Table 1).

Table 1: Distribution of study subjects according to sociodemographic profile.

Sociodemographic features	First line ART failure (%) (n=303)	Second ART line failure (%) (n=27)	χ^2, df, p value
Age group (in years)			
15-20	4 (1)	1 (4)	
21-30	34 (11)	2 (7)	
31-40	105 (35)	8 (30)	χ^2=16.51, df=10, p=0.085
41-50	106 (35)	12 (44)	
51-60	44(15)	4 (15)	
>60	10 (3)	0 (0)	
Gender			
Male	192 (63)	20 (74)	
Female	110 (36)	7 (26)	χ^2=1.49, df=4, p=0.82
Transgender	1 (0.3)	0 (0)	
Residence			
Urban	131 (43)	7 (26)	χ^2=4.82,df=2, p=0.089.
Rural	172 (57)	20 (74)	
BMI			
Mean BMI	20.92	21.36	
Underweight (<18.5)	80 (26)	4 (15)	
Normal (18.5-24.9)	188 (62)	18 (67)	χ^2=4.82, df=6, P= 0.56
Overweight (25-29.9)	31 (10)	5 (19)	
Obese (>30)	4 (1)	0 (0)	
Socioeconomic status (Kuppuswami scale)			
Upper	1 (0.3)	0 (0)	
Upper middle	71 (23.4)	6 (22.2)	
Lower middle	81 (26.7)	6 (22.2)	χ^2=1.53, df=8, p=0.99
Upper lower	142 (46.9)	15 (55.6)	
Lower	8 (2.6)	0 (0)	
Education			
Illiterate	52 (17)	3 (11)	
Primary school	51 (17)	8 (30)	
Secondary school	134 (44)	11 (41)	
College	37 (12)	3 (11)	χ^2=5.7, df=12, p=0.93
Diploma	10 (3)	0 (0)	
Degree	18 (6)	2 (7)	
Profession or honours	1 (0.3)	0 (0)	
Route of transmission			
Heterosexual	270 (89)	23 (85)	
Mother to child	6 (2)	3 (11)	
Blood transfusion	4 (1)	0 (0)	χ^2=14, df=8, p=0.6
Infected needle	1 (0.3)	0 (0)	
Unknown	22 (7)	1 (4)	
Duration between diagnosis and start of ART			
<15 days	69 (23)	2 (7)	
15 days to 1 month	37 (12)	5 (19)	
1-6 month	92 (30)	1 (4)	χ^2=27, df=8, p=0.00048
>6	98 (32)	16 (59)	
Not available	7 (2)	3 (11)	

Total 98 (32%), 16 (59%) patients from 1st, 2nd line ART failures respectively were started on ART after 6 months of delay from the detection of HIV. Median duration between detection of HIV and initiation of ART was 1 month among 1st line ART failure patients (Figure 2).
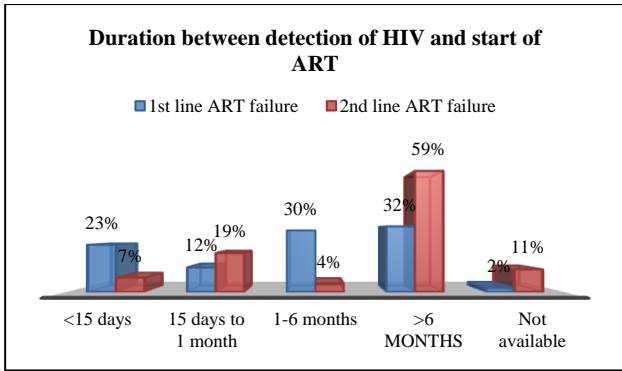
Figure 2: Duration between detection of HIV and start of ART.

till the end of study period) was 265.5 cells/mm^3 that after 12 months of shift was 350.5 cells/mm^3 (n=206, as only 206 patients had completed 12 months from the switch to 2nd line of ART). Rise in CD4 counts from the count at the time of failure was seen in 217 out of 242 patients at 6 months and median of rise in CD4 count at 6 months from switch to 2nd line was 137 cells/mm^3 whereas persistent fall in CD4 count was seen in 25 patients and median of fall in CD4 count was 14 cells/mm^3. Rise in CD4 counts from the count at the time of failure was seen in 192 out of 206 patients at 12 months and median of rise in CD4 count at 12 months from switch to 2nd line was 218 cells/mm^3 whereas persistent fall in CD4 count was seen in 14 patients and median of fall in CD4 count was 78 cells/mm^3 (Table 2).

Table 2: Showing immunological profile of ART failure patients.

Immunological profile	1st line failure		2nd line failure	
	No. of patients	Median CD4 count (cells/mm^3)	No. of patients	Median CD4 count (cells/mm^3)
Baseline CD4	296	156	27	298
CD4 count at the time of failure	303	146	23	180
CD4 count at 6 months of switch of ART	242	265	19	387
CD4 count at 12 months of switch of ART	206	350	3	412
Rise in CD4 count 6 months post switch	217	137	14	169
Rise in CD4 count 12 months post switch	192	218	3	299

Table 3: Showing correlation between WHO stage and CD4 count of 1st line failure patients.

CD4 (cells/mm^3) class at the time of failure to ART	No. n (%)	WHO clinical staging			
		1	2	3	4
<50	34 (11)	8 (24)	2 (6)	11 (32)	13 (38)
51-100	73 (24)	19 (26)	16 (22)	23 (32)	15 (21)
101-150	47 (16)	19 (40)	14 (30)	11 (23)	3 (6)
151-200	42 (14)	18 (43)	9 (21)	7 (17)	8 (19)
201-349	74 (24)	49 (66)	18 (24)	5 (7)	2 (3)
350-499	22 (7)	14 (64)	3 (14)	1 (5)	4 (18)
>500	11 (4)	8 (73)	0 (0)	1 (9)	2 (18)
Total	303 (100)	135 (45)	62 (20)	60 (20)	46 (15)

Chi square=71.17; degrees of freedom=18; p-value= <0.0000001

Median CD4 of 1st line ART failure patients at the time of starting ART (n=296 as baseline CD4 of 7 patients was not available) was 156 cells/mm^3, which was fallen down to 146 cells/mm^3 at the time of failure. Median CD4 counts after 6 months of switch to 2nd line ART (n=242, as all patients had not completed 6 months from switch

Baseline median CD4 of 2nd line failure patients was 298 cells/mm^3 which was fallen to 180 cells/mm^3 at the time of failure to 2nd line of ART (n=23, as CD4 count at the time of failure of 4 patients was not available). After switch to 3rd line ART median CD4 count at 6 months was 387 cells/mm^3 (n=19, 19 out of 27 patients had completed 6 months from switch at the end of study

period) that at the 12 months was 412 cells/mm^3 (n=3, as only 3 patients had completed 12 months from switch to 3rd line). Rise in CD4 count was seen in 14 patients at 6 months out of 19 patients (data on CD4 count at the time of 2nd line failure was not available for 4 patients and 2 patients experienced persistent fall in CD 4 count despite of change in ART regime n) and median of rise in CD4 count at 6 month of switch to 3rd line ART was 169 cells/mm^3, all 3 patients who had completed 12 months after switch to 3rd line ART had increase in CD4 count and median of rise in CD4 count was 299 cells/mm^3. 2 patients had persistent fall in CD4 at 6 months of switch to 3rd line ART and median of fall in CD4 was 72 cells/mm^3 (Table 2).

Maximum number of patients had WHO stage 1 at the time of failure to ART [135 (45%) and 12 (44%) of 1st line and 2nd line ART failure respectively]. Only 16% and 11% of 1st line and 2nd line ART failures had WHO stage 4. Majority of patients at the time of failure to both 1st and 2nd line ART had CD4 counts less than 200 cells/mm³ [196 (55%) and 14 (51%) patients respectively]. Only 4% and 11% of 1st line and 2nd line ART failures had CD4 counts more than 500 cells/mm³.

Among patients from 1st line ART failure 38% and 32% patients of CD4 count less than 50 cells/mm³ had WHO stage 4 and 3 respectively i.e. 70% of patients with CD4 count less than 50 had WHO stage 3 and 4. The relationship between WHO clinical stage and CD4 counts was found statistically very significant as p value was <0.0000001 (Table 3).

Whereas among patients from 2nd line of ART failure, One of 2 patients with CD4 counts less than 50 cells/mm³ had WHO stage 1 and another had WHO stage 4 whereas out of 3 patients from CD4 counts between 51 to 100 cells/mm³, 1 had WHO stage 4, 2nd had WHO stage 3 and 3rd had WHO stage 2. 4 out of 7 patients with CD4 counts between 151-200 cells/mm³ had WHO stage 1. All patients with CD4 counts more than 350 cells/mm³ had WHO stage 1.
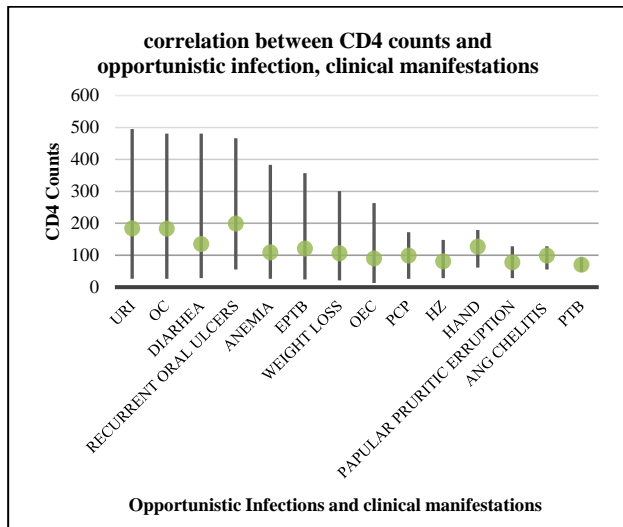

Figure 3: correlation between CD4 counts and opportunistic infection, clinical manifestations.
URI: upper respiratory tract infection; OC: Oral Candidiasis; EPTB: Extra Pulmonay TB; HZ: Herpes Zooster; PCP: Pneumocystis Carini Pneumoonia; OEC: Oro Esophageal Candidiasis; HAND: HIV Associated Neuronal Disorder; PTB: Pulmonay TB.

Extra pulmonary tuberculosis was found to be the most common opportunistic infection at the time of failure to ART and tuberculous pleural effusion was observed to be the most common form of extra pulmonary tuberculosis. In present study population extra pulmonary tuberculosis occurred at median CD4 count of 96 cells/mm³. Weight loss occurred at median CD4 count of 103 cells/mm³

whereas anaemia occurred at median CD4 count of 73 cells/mm³. Diarrhoea, recurrent upper respiratory tract infections, oroesophageal candidiasis, herpes zoster, oral candidiasis, pulmonary tuberculosis and pneumocystis pneumonia occurred at median CD4 counts of 114 cells/mm³, 158 cells/mm³, 71 cells/mm³, 75 cells/mm³, 126 cells/mm³, 72 cells/mm³ and 99 cells/mm³ respectively (Figure 3).

DISCUSSION

In our observational study we studied demographic, clinical and immunological profile of HIV patients failing on HAART.

Present study population was predominantly composed of male patients (63%), and most of studies done in India and all over the globe showed male predominance in HIV infection.[5-9] We observed that maximum proportion of patients were from middle age group and from earning population (70% and 74% of 1st and 2nd line failure respectively). Which is similar to the observations found by Kumaraswamy et al in their study at Chennai on 1443 patients (mean age was 35 years) and by Cao et al at China (mean age 47 years).[8,9] 87% of present study population had acquired HIV by heterosexual route which is very close to the finding of a study done by Hailu et al at Ethiopia (88.1% of study population had acquired HIV by heterosexual route).[10] Another study done by Kumarswamy et al had similar observation.[8] 80% patients of present study population were living married life. 74.20% and 71.38% of patients from studies done by Kumari et al and Deshpande et al respectively were married.[11,12] Illiteracy rate of present study population was 17% which is slightly lower than that of other similar studies carried out in India, which was 36.20% and 44.66% of population as indicated by Kumari et al (study of 5308 patients at Uttar Pradesh) and Kumawat et al (a study of 300 patients at Rajasthan) respectively.[11,13] This difference can be explained by the difference of literacy rate of these states as Maharashtra has comparatively higher overall literacy rate (82.91%) when compared with Uttar Pradesh (69.72%) and Rajasthan (67.06%).[14]

Once initiated on ART regimen can be changed due to different reasons and we found that failure of ART is the major cause for change in regimen followed by toxicity to different drugs of HAART, similar findings were observed by a study done by Cao et al at China.[9] ART failure can be defined as clinical, immunological and virological failure as per criterias led down by WHO. Among patients from failure of 1st line ART 43% of patients had immunological failure only while 23% of patients had virological failure only which was 30% and 63% respectively among patients with failure to 2nd line of ART suggesting that there is a need to increase viral load testing among patients on 1st line of ART.

Deshpande et al and Nayak et al observed in their studies that maximum proportion of patients had WHO stage 3 (42.45% and 48.3% respectively).[12,15] In contrast to these observations 45% of present study population had WHO stage 1 and only 16% had WHO stage 4 at the time of failure.

As during initial period of the study, viral load testing was not available at present study centre hence only suspected failure patients were advised viral load testing which is the major limitation in developing countries in the care of HIV patients.

CONCLUSION

Results of present study throw a light on the fact that antiretroviral therapy has significantly improved outcome of the disease caused by HIV infection in terms of improvement in clinical and immunological status even after failure of initial lines of ART. We also observed that Failure of ART is the major cause for change in ART regimen among patients with good adherence to treatment. Majority of patients in Immunological and virologic failure had WHO clinical stage 1 and 2 at the time of failure which is a sign of early detection of failing patients. We also observed that delay in initiating ART is more associated with failure of ART hence it is recommended that to start HAART as early as possible after diagnosis of HIV infection. Extra pulmonary tuberculosis was found to be most common opportunistic infection at the time of failure. ART centres and linked ART centres has contributed to reduce the prevalence of HIV and improved care of HIV infected patients in India by different ways telling the success story of NACP.

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