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Original Research Article

A study of profile of patients failing first line NACO recommended ART

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ABSTRACT

Background: Failure of first line NACO recommended Therapy has been reported in 1-5% cases of HIV/AIDS. Various factors are associated with failure. This study describes the profile of patients failing first line ART (FLA) in a predominately lower socioeconomic population. The objective of the present study was to identify factors associated with failure of FLA.
Methods: Retrospective data analysis of patients failing first line therapy. Epidemiological information, clinical parameters and laboratory reports were taken into consideration. Data was analysed as per standard statistical analysis.
Results: Out of a total 3926 patients on first line ART for varying periods of time from our ART centre 54 patients were on second line ART. Males (2.20%) had a high failure rate than females (0.50%). The average time of failure was 64.11 months with a median of 56.50 months. 74.1% (40/54) of the patients had very low CD4 count at the time of initial diagnosis. Failure rate of FLA was higher in the patients having Stavudine based regimen (NRTI) (6.61%) and 3.64% in patients having Nevirapine based regimen (NNRTI).
Conclusions: Second line therapy is required only in a small number of patients at present, but as it is related to the duration on first line ART and also with initial low CD4 count, more and more patients will require SLA in the near future.

Keywords: FLA (first line antiretroviral), NNRTI (non-nucleoside reverse transcriptase inhibitor), NRTI (nucleoside/nucleotide reverse transcriptase inhibitors), SLA (second line antiretroviral), VL (viral load)

INTRODUCTION

The prevalence of HIV infection has declined in India from 0.41 in 2002 to 0.26 in 2005.[1] As per an estimation there are approx 21 lakhs peoples who have HIV infection. NACO (National AIDS Control Organization) started ART programme in 2004 and has since scaled up the programme with presently all patients with HIV infection being eligible for ART.[2] As with other viral infections, HIV has a property to mutate and develop drug resistance.[3-5] This led to initiation of second line ART in 2008 by NACO. Resistance to protease inhibitor used in NACO regimen has also been shown.[6] According to NACO, till August 2016, patients alive on ART are 9, 97,869 out of which 9,42,263 adults and 55,606 children are on ART, of these 15,500 patients are on second line ART. Several studies of patients in sub-Saharan Africa have shown that prolonged, undetected treatment failure is associated with accumulation of NRTI resistance.[7-9]

Variety of factors lead to resistance to the first line Therapy .The previous studies done on first line ART failure showed that the factors associated with increased failure were: Low CD4 at ART initiation (<50cells/cumm), Poor adherence of the patient, higher baseline HIV RNA measurement (viral load), missed

visits, and younger age, baseline drug resistance elevated viral load at ART initiation, higher WHO stage at ART initiation, previous exposure to short course ART for prevention of mother to child transmission (PMTCT), ART interruptions, use of nevirapine instead of efavirenz low general health score.[10-14] Of these, adherence to ART has been shown to be one of the most important predictors of virologic success and preventing disease progression.[15-19]

BRD medical college Gorakhpur caters to a periodically migrant population of HIV patients who are mostly socioeconomically backward and may have a combination of the above mentioned factors. The present work was done to study the profile of those patients who have failure of NACO recommended first line ART.

METHODS

The data was obtained retrospectively from the HIV patients on second line ART taking care and treatment from ART centre B R D medical college Gorakhpur. Data of a total of 54 patients who were switched from first line ART to second line ART was studied and patients were also interviewed. The study protocol was approved by institutional ethical committee. Socio demographic data including age, education, marital status and probable transmission route were documented. Baseline WHO clinical stage, CD4 count and viral load were studied along with first-line ART regimen initially introduced, its adherence and the reason for switch and components of the second-line ART regimen. CD4 count at diagnosis, on start of first line ART, at time of switch to second line ART, post 6 months and 12 months of second line ART were noted.

Case definitions

The following case definitions were applicable for switch to 2nd line ART: (as per NACO guideline 2013).

Virological failure

HIV RNA concentration (viral load) of 1000 copies/ml (i.e., 3log10 copies/ml) on two consecutive occasions after at least 6 months of treatment.[20]

Immunological failure

Decrease in CD4 cell count to pre-therapy baseline level (or below); 50% decrease from the peak value during treatment; and persistent low CD4 cell counts of less than 100 cells/mm3 after at least 12 months of ART.

Clinical failure

Occurrence of a new WHO stage III or IV opportunistic disease while on treatment.

Treatment failure

Presence of either virological, immunological or clinical failures.

ART non-adherence

Non-adherence was defined as <95% of drug intake over the duration of each month.

Statistical analysis

Categorical variables were expressed as proportions. Continuous variables were described using means± standard deviation (SD) and in terms of median (range) for skewed data.

The reliability of the parameters were given by 95% confidence interval (CI). Statistical analysis was carried out in SPSS 22.0.

RESULTS

Information was extracted for 54 patients who were on second line ART and analysed in detail. Out of 54 patients, 42(77.8%) were males and 12(22.2%) were females. The mean age of these patients was 36.67 years ±10.48years.

Majority of the patients were married (72.2%), single (22.2%) and divorced (5.6%). Education levels showed that 25.9% had studied only till the 5th standard, 29.6% of the patients had passed their 10th grade and almost 22.2% were 12th class pass and graduates. The mean BMI was 19.82±2.63, alcohol use was documented in 15(27.8%) patients, 19 (35.2%) patients also had tuberculosis as an opportunistic infections (OIs).

The failure rate of first line ART was higher among male (2.20%) than female (0.59%). The failure rate of first line ART was higher in MSM (10%) Mode of transmission than others. The failure rate of FLA was higher among literate (3.28%) than illiterate (1.34%). The failure rate of FLA was higher among trucker (5.60%) than others.

Duration of first line ART was 31-80 months in more than half of patients (53.7%) followed by 81-120 months (35.2%), 6-30 months (11.1%).

Failure rate of FLA was higher in the patients having Stavudine based regimen (NRTI) (6.61%). Failure rate was 3.64% in patients having Nevirapine based regimen (NNRTI).

25(46.3%) patients had CD4 count less than 100 in pre-ART and at SACEP 35 (64.70%) patients had CD4 count less than 100.

Table 1: Failure rate of FLA on the basis of gender, mode of transmission, education, occupation in this cohort of patients.

Parameters	Risk factors	Total no. of patients in first line ART	Total no. of patients in second line ART	Percentage failure rate of first line ART	Percentage of patients in second line ART
Gender	Male	1907	42	2.20	77.78
	Female	2004	12	0.59	22.22
Mode of transmission	Heterosexual	1876	45	2.39	83.33
	MSM	20	2	10	3.7
	MTC	230	7	3.04	12.96
Education	Illiterate	893	12	1.34	22.2
	Literate	1280	42	3.28	77.8
Occupation	Laborer	621	24	3.86	44.5
	Employed	488	15	3.34	27.8
	Trucker	59	3	5.08	5.6
	Housewife	977	12	1.23	22.2

Table 2: Distribution of patients according to duration of first line ART.

Duration of first line ART in months	No. (n=54)	%	Mean±SD	Median and (95% CI)
6-30	6	11.1	64.11±37.88	56.50 (53.77 -74.45)
31-80	29	53.7		
81-120	19	35.2		

Table 3: FLA failure rate in NRTI and NNRTI based regimen.

NRTI/NNRTI based regimen	Total no. of patients on first line ART	Total no. of patients on second line ART	Percentage of failure on first line ART
Zidovudine based regimen	1193	30	2.5%
Tenofivir based regimen	2597	15	0.58%
Stavudine based regimen	136	9	6.61%
Nevirapine based regimen	1043	38	3.64%
Efavirenz based regimen	2808	16	0.57%

Table 4: CD4 count of patients on SLA.

CD4 count range(cells/mm^3)	Baseline (pre-ART)		12 months before SACEP on first line ART		6 months before SACEP on first line ART		At the time of SACEP on first line ART	
	n=54	%	n=54	%	n=54	%	n=54	%
<50	10	18.5	8	14.8	13	24.07	16	29.62
50-100	15	27.8	22	40.7	16	29.62	19	35.18
101-200	15	27.8	9	16.7	19	35.18	14	25.92
201-300	7	13.0	11	20.4	5	9.25	5	9.25
301-500	4	7.4	4	7.4	1	1.85	0	0
>500	3	5.6	0	0	0	0	0	0
Mean±SD	123.45±93.42		121.50±91.30		94.67±61.53		82.05±63.10	

DISCUSSION

A growing proportion of patients on antiretroviral therapy even in resource limited settings will need to be switched on second-line regimen.[21] Failure of first line antiretroviral (FLA) therapy is inevitable sooner or later in a proportion of patients.

In present study centre total number of patients alive on ART are 3,926, out of these 1,907 are males, 2,004 are females and rest 15 are transgender. There are 3,864 patients on first line ART and 62 on second line ART (SLA). Authors found a 1.57% failure rate (62/3926), which is similar to NACO reported failure rate of (1.55%).[1]

In present study there were 77.8% male and 22.2% female on SLA. A study done by Johnston V et al, in South Africa, reported male predominance (91.7%).[22] In contrast to present study, Onyeduma CC et al, in Nigeria reported female predominance.[23] Men on ART are more likely to experience treatment failure compared to female patients. Kipp W et al, and Penot P et al, from Uganda and Burkina, reported that men on ART were vulnerable to treatment failure.[24,25] The possible reason for this is that males as compared to females had unhealthy behaviours like using alcohol and cigarettes etc. which might lead them to poor drug adherence and reduce the overall treatment success. As a percentage of total patients, failure rate in males was (2.2%) and female was (0.59%) in present study.

In present study the mean age of patients was 36.67±10.48 years. Another study done in India by Patrikar S et al, reported mean age of 40.58±8.57 years.[26] Authors found that more than half of the patients were above 35 years of age. These findings suggest that increasing age is associated with increased chance of failure. Another study from India by Singh A et al also reported similar trend.[27]

In present study the mean BMI of patients was 19.82±2.63. Patients in the study of Patrikar et al, on Second Line Antiretroviral Therapy had mean BMI 21.30±2.71, which is also comparable to studies on second-line therapy in sub-Saharan Africa and Asia.[26,28,29] A low BMI has been reported to be associated with treatment failure by various studies.[17,30] The possible reason for this is decrease in immunity and blunted immune response due to poor nutrition. Above studies indicate that the level of nutritional status determines the immune response, and poor nutritional status leads to treatment failure. Although in present study 63% patients on SLA had low BMI, but authors did not analyse data on all our HIV patients for BMI changes over time and hence cannot comment upon the relevance of these finding.

The modes of transmission in patients on SLA were not different from patients on first line ART. When authors compared failure of ART across various mode of transmission we found that failure rate was highest in MSM (10%), 2 out of 20.

In this study authors observed unemployed patients had slightly higher chance of treatment failure, compared to employed patients (3.97 vs 3.34). The possible explanation for this could be that, patients who were unemployed might have low income that hinders them from getting the opportunity for early and better care and support.

This is in agreement with a study by Melsew et al, who found that unemployed patients had about 1.7 times higher risk of immunological failure compared to employed patients.[31] This might be due to the reason that those employed patients may have better income, that in turn creates opportunity to get better care and support. Authors also found that house wife, has least chance of failure (1.23%) compared to other occupation and most possible explanation for this might be good adherence to ART.

Treatment failure rate in educated people appears to be a paradox but has been explained by various theories. Educated people are more liable to receive less interview, counselling on the assumption of them knowing more about the disease.

Educated people are more likely to be unemployed in developing countries where unskilled employee is in a higher demand, also the reason of unemployment could be associated stigma and discrimination. In present study authors found that treatment failure is more common in literate compared to illiterate. Studies by Teshome et al, and Babo et al, reported that treatment failure was more common in higher educational group as Compared to the illiterate.[30,32]

In present study authors found that average time of switch to second line ART from first line ART was 64.11±37.88 months with median 56.50 months. A study by Patrikar et al, has also shown that, the average time of switch to second line ART from first line ART was 53.75 months with median of 60 months.[26] Authors observed that 88.9% patients were switched to SLA after 30 months on FLA.

Result from present study revealed that duration of first line ART was an important determinant of treatment failure. Patients, who were on their first line regimen for longer duration, appear to have high risk of treatment failure. It is similar with a retrospective cohort analysis from Uganda which reported that failure is more common in those who are longer duration on FLA.[33]

A study by Prabhakar B et al, from India reported that immunological failure was more common in those who were on ART for more than 3 years.[34] In contrast to the present study, a cross sectional study by Meriki HD et al, from Cameroon found that duration of antiretroviral treatment was not associated with treatment failure.[35]

In the present study authors found that Stavudine based NRTI was associated with increased risk of treatment failure as compared to Zidovudine based NRTI. It is similar with the findings of Babo YD et al, from Ethiopia.[30] Present study findings were in contrast with

the study by Kowbah CM et al, from Kenya who showed that Zidovidine based regime was associated with more treatment failure.[36] Stavudine is more susceptible to develop drug resistance on prolonged therapy as compare to zidovudine. Resistance to stavudine arise through specific pathways that involve either selection of the 151M mutation or insertion of two serine or serine-alanine residues at amino acid residue 69.[37-40] Multi-resistance to two nucleoside analogue can also be achieved through changes that appears to map outside of the reverse transcriptase (RT) gene.[41] However in each case multi-resistance develops in patients who have been on sequential or combination nucleoside analogue therapy for a prolonged period. On the choice of NNRTIs (NVP vs. EFV) we found that Nevirapine was associated with increased risk of treatment failure in our study. A study by Datay MI et al, from South Africa revealed a 2.5 times increased risk of treatment failure in the NVP based group compared to EFV based group.[13] In contrast to our observation, Rajasekaran S et al, from India reported that failure was significantly higher in the EFV based regimen cohort.[17] Studies from Ethopia and Kenya reported that the choice of NRTI (NVP vs EVF) was not associated treatment failure.[30,36]

In the present study authors found that 74.1% (40/54) patients who had FLA, had very low baseline CD4 count (<100 cells/mm3) at initiation of ART. These patients might have very high baseline viral load as compared to the patients who had higher CD4 count at initiation. The high initial viral load may lead to greater chance of incomplete viral suppression, hence development of drug resistance. A study by Babo et al, reported that low base line CD4 count was associated with higher ART failure rate.[30]

CONCLUSION

To conclude authors found that male gender, low BMI, Educated, unemployed, MSM, duration of FLA, Stavudine, Nevirapine and low baseline CD4 count were factors which were associated with treatment failure. Second line therapy is required only in a small number of patients at present, but as it is related to the duration on first line ART and also with initial low CD4 count, more and more patients will require SLA in the near future.

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