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PROFILE OF PATIENTS ON SECOND LINE ANTIRETROVIRAL THERAPY

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ABSTRACT

There are more than 35 million people at present living with Human immunodeficiency virus infection (PLHIV) who will require second-line therapy as a result of first line failure in future. Limited access to further therapeutic options requires evaluation of the current treatment outcome. Aims and objects: To describe the clinical, immunological and virological profile of patients on second line antiretroviral therapy. Method: A longitudinal cohort study was carried out in 53 patients eligible for second line ART. CD4 counts, viral load, haemoglobin and weight at baseline and 6 months after treatment were compared using appropriate statistical methods. A P value of<0.05 was taken as significant. Result: The maximum viral load of 5.83logcopies/ml decreased to 3.98logcopies/ml after six months, CD4 count increased from 13cells/µl to 55cells/µl (P value of 0.000) and mean difference in weight was 1.29 kg (P value of 0.000).Conclusion: Though the rates of switch to second line ART was low (4.9%), the treatment outcomes of patients started on second line ART were good.

Introduction

The rapid scale up of first-line treatment for Human immunodeficiency virus (HIV) infection has led to increased rates of treatment failure in the past few years .[3]However the lack of HIV-1 RNA monitoring in resource-poor settings results in continuation on first-line anti-retroviral therapy (ART) until virologic failure progresses to a 50% decrease in CD4 T cell count (immunological failure) or the recurrence of symptomatic HIV disease (clinical failure).[7] This leads to a delay in initiation of second line treatment.

Protease inhibitor (PI) boosted with ritonavir are recommended in second-line treatment as they have a high barrier to genetic resistance, are highly potent and generally well tolerated. However the need for life-long therapy, HIVs prodigious replication rate, and error- prone reverse transcriptase and selective pressure from drugs and from immune system has led to natural evolvement of drug resistance and second line failure (33% – 40%).[8]

A limited access to further therapeutic options necessitates evaluation of patients' clinical, immunological and virological response after starting on second line ART to make the best use of the currently available treatment options.

Aims and objects

To evaluate the clinical, immunological and virological profile of patients on second line antiretroviral therapy.

Subjects and Methods

This longitudinal cohort study was carried out from October 2016 to September 2019 with a follow up of 6 months. Fifty three (53) patients who were eligible for second line treatment were included. The decision to switch patients to second-line ART were taken based on National AIDS Control Organization (NACO) guidelines (2010) by the state AIDS clinical expert panel (SACEP) in the Centre of Excellence (COE), Regional Institute of Medical Sciences (RIMS). The second line therapy includes one new nucleoside reverse transcriptase inhibitor (NRTIs) and a protease inhibitor (lopinavir/ atazanavir boosted with ritonavir).

The following case definitions were applicable:
Virological failure: HIV RNA concentration (viral load) of >5000 copies/ml after at least 6 months of ART.

Immunological failure: decrease in CD4 cell count to pre-therapy baseline level (or below); 50% decrease from the peak value during treatment; and persistent CD4 cell counts of <100 cells/µl after 6 months of ART.

Clinical failure: occurrence of a new WHO stage IV condition after at least6 months of ART. For the purpose of this study, a CD4 cell count increase ≥50% of the value at the time of switch was regarded as a good immunological response to second-line ART.ART non-adherence was based on clinic attendance record or patient based report of missing antiretroviral medications or ART clinic pharmacy record of treatment interruption.

A comprehensive medical history was taken with emphasis on drug adherence, drug toxicity, and duration on ART and a thorough clinical examination including measurement of body weight was carried out. Laboratory investigations (Routine tests, serum lipid profile, CD4 count, HIV Viral load study) were done. CD4 cell count was calculated by using automated analyzer, Fluorescence activated cell sorter (FACS). Viral load was measured by real time RNA PCR technique.

Statistical Analysis: Data was analysed using IBM SPSS version 21 for Windows. Descriptive statistics like mean, SD, median, range and percentages were used. Wilcoxon rank sum test was used to compare CD4 counts and viral load at baseline and 6months.Paired t test was used to test the significance between haemoglobin (Hb) and weight before and after 6 months of initiation of second line ART. A P value of<0.05 was taken as significant.

Ethical approval: Approval for conducting the study was obtained from the institutional ethics committee, RIMS.

RESULTS

Between October 2016 to September 2019, 53 patients were switched to second line ART. There were 42 males (79.2%) and 11females (20.8%) in the study group. The regimens used on second line were regimen IV [tenofovir(TDF)+lamivudine(3TC)+ATV/r)] in 58.5% , regimen IVa (TDF+3TC+LPV/r) in 34% and regimen V[stavudine(d4T)+3TC+ATV/r] in 7.5% of patients.The reason for switch to second line ART was treatment failure (virological/immunological failure) in 79.2% of patients and clinical failure in 20.74% of patients. Two patients required a change in protease inhibitors, from atazanavir to lopinavir due to hyperbilirubinemia .More than half of the patients (54.6%) were in the age group of 41-50, 5.7% of patients were below 20 years of age, 1.9% between 21-30years,18.9% between 31-40 years and 18.9% above 50 years group.The mean age of the patients was 43.2±8.1 years. The mean weight at initiation was 53.15kg and at 6 months was 54.33kg, the mean difference being 1.29 kg with a P value of 0.000 (Table1).Injection drug use was the most common mode of transmission contributing for 54.7% of the total cases followed by heterosexual route in 34%, mother to child in 7.5% and blood transfusion in 3.8%.

Table 1: Comparison of weight at the time of initiation and after six months of therapy

	Mean (kgs)	SD (kgs)	Mean difference	P Value
Weight at initiation (n=53)	53.04	8.31	1.29	0.000*
Weight after six months(n=48)	54.33	8.03		

Paired t test*

In the study population, 35.8% had taken first line ART for ≥10 years, 30.2% had taken for≥ 5years, 18.9% had taken for 2-5 years and 15.9% had taken for less than two years. At the time of analysis after 6 months of therapy, 48 (90.5%) were in active follow up, 2(3.8%) had been lost to follow up and 3(5.7%) had died. Low CD4 count at initiation and poor adherence were the reasons for mortality but the cause of death was not medically certified. There was a mean increase in CD4 cell count of 235.13 at six months from the time of initiation and it was found to be statistically significant. At initiation 71.6% had CD4 count <100cells/µl., 26% had CD4 between 100-200cells/µl and 3.7% of patients had CD4 >200cells/µl. At 6months, 7.5% had CD4<100cells/µl, 22 % had CD4 of 100-200cells/µl, 20.7% had CD4 count >200cells/µl, 15.9% had CD4>350cells/µl and 24.5% had CD4>500cells/µl. (table 2)

The maximum viral load at initiation was 5.83logcopies/ml and minimum was 4.07logcopies/ml with a standard deviation of 0.54. The maximum viral load at 6months was 3.98logcopies/ml and minimum was 4.07logcopies/ml with a standard deviation of 0.54 which was statistically significant (0.000). 39.6% had undetectable viral load at 6months of therapy. (table 2).Second line ART reduced the number of patients categorized as WHO stage III/IV from 11to 3 after 6 months of treatment.

Oral candidiasi was seen in 47.16% of the study patients followed by 5.6% of pulmonary tuberculosis , 3.7% of cryptococcal meningitis and 1.8% each of pneumocystis carinii pneumonia, progressive multifocal leukoencephalopathy (PMLE) and non- Hodgkin's lymphoma. Most of the OIs were cured by six months of therapy.

Table 2: Comparison of CD4 count and viral load at the time of initiation and after six months

CD4	Minimum (Cells/ l)	Maximum (Cells/µl)	Mean (Cells/µl)	SD (Cells/µl)	P value
CD4at initiation (n=53)	13	376	112.74	70.96	0.000*
CD4 after six months (n=48)	55	973	360.02	215.82	
Log10 Viral load at initiation(n=53) (log Copies/ml)	4.07	5.83	5.02	0.54	
Log10 Viral load after six months(n=48) (logCopies/ml)	2.26	3.98	3.36	0.46	

*Wilcoxon sum rank test

Table 3: Clinical, immunological & virological characteristics after first line failure

Characteristic	Frequency	Percentage
Baseline CD4 cells/µl		
<200	46	86.8
200-499	7	13.2
CD4 at six months(n=48)		
<200	15	31.3
200-499	21	43.8
>500	12	25
Baseline log10viral load, Median(range)	5.24	1.95
Log10 viral load at six months, median(range)	3.36	1.56
WHO clinical stage		
II	42	79.2
III	4	7.5
IV	7	13.2

DISCUSSION

This longitudinal cohort study was undertaken to describe the profile of patients on second-line ART as scale-up of ART has resulted in patients experiencing treatment failure and thus increasing demand on second-line regimens.[13]

In our study, patients with treatment failure were identified mostly by immunological criteria (79.2%) following which they were subjected to virological test to confirm virological failure. Atazanavir/r was used in 66% of patients while lopinavir/r was used in 34% of patients. Among the NRTIs, tenofovir based regimen was used in 92.5% of patients, stavudine in 7.5% of patients with lamivudine as backbone. A study showed high rates of virologic suppression and immune reconstitution in patients on lopinavir/r based protease inhibitor.[9,17]Our study did not analyze any such association. Out of the total 53 patients, 42 were males (79.2%) and 11 were females (20.2%). The higher incidence in males can be attributed to the high prevalence of intravenous drug abuse in Manipur which matches with the study conducted by Ramachandra P et al.[22]

Maximum cases were in the age group of 41-50 years (54.6%) with the mean age of 43.2±8.1years in our study. The mean age was within the average age of 30–45 years for patients receiving second-line therapy in various studies done in sub-Saharan Africa and Asia.[2]This distribution of age can be

explained by the declining trend in the prevalence among people with injection drug (PWID) use who reside in north-eastern states.[21] A significant (0.000) increase in mean body weight and marked reduction in number of patients categorized as WHO stage III/IV was observed at 6 months of second-line ART. Similarly a prospective observational study in India found significant increase in mean body weight (<0.0001) and reduction in number of patients categorized as WHO stage III/IV at 12 months of second-line ART.[12]

The average time interval from first-line ART initiation to switch in our cohorts was about 88.9±42.2 months. This is double of what was reported from various RLS which had a range from 11 to 35 months.[2] The long duration of patients on first line ART in our setting can be explained by the lack of routine virological monitoring.[3,9,19,20] Similarly a study in Pune, India, shows an average time duration of 53.75 months from diagnosis to second line initiation. The longer duration on first line ART in the absence of virologic monitoring also raises concerns for drug resistance.[8]

In our study it was also observed that 47% of the patients were clinically asymptomatic at the time of failure which indicates that clinical failure manifest at later stage as evidenced in a similar study.[12] Palombi et al[18] found immunological failure as the most common reason for switch, followed by virological failure, describing clinical failure is rare and our study also supports this study as in 79.2% of patients, the reason for switch was immunological failure. One study also evidenced that CD4 and WHO clinical criteria have low specificity and positive predictive value which means individuals with adequate virological suppression risk being incorrectly classified as treatment failure and unnecessarily switched to second line which underscores the importance of confirmation of virological failure by viral load testing.[6,11,20] In contrast; presence of OIs was the reason of failure and switch to second line as reported by Patrikar et al[1] in 65% of the patients. According to Johnston et al[14] more than 80% of switches to a second-line regimen in their cohorts in South Africa were on account of treatment failure, with toxicity accounting for 11–16%.Varying definitions of virologic suppression also has an impact in the delay in detecting virological failure in different study settings as demonstrated by other studies.[2,10] Our study demonstrated more than 50% rise in CD4 count 6 months post switch to second line. The mean CD4 at initiation was 112.74 and 347.87 at 6 months. A mean increase of 235.13 was seen and the value was statistically significant (0.000). Fox et al[18] reported that CD4 nadir on first line therapy used to be a predictor of success in European countries before genotyping became widely available. A study reported that CD4 count at second line therapy start is an important determinant of failure.[16] Substantial but variable virological and immunological responses to second-line therapy have been documented in other studies.[7]A study reported that females were at an increased risk of lack of virologic suppression during early second-line therapy which constitutes <1/3rd of our study population.[10]

Our study showed 18.2% mortality in females and the predictors of mortality were CD4+ Tcell< 100cells/µl and adherence <90% which was similar to a study conducted by Charles M et al.[4] Another study found association between severe immunosuppression and mortality.[15]

In our study viral load at initiation was 5.02 log $_{10}$copies/ml which reduced to 3.38 log$_{10}$ copies/ml at 6 months and it was statistically significant (0.000).

Adherence to second-line ART in our study was more than 95%. Studies have shown association between adherence and outcome. Time to improvement was most rapid among patients with 91-100% adherence. Similarly, another study has reported non adherence as a major cause of viremia.[14]This highlights the need for early detection of suboptimal adherence to first-line therapy. In settings in which viral-load monitoring is infrequent and changes to second-line treatment may occur late, there are likely to be accumulations of resistance mutations that compromise second-line regimens.[19]Our study supports previous studies which have shown good early outcomes with second line therapy and also emphasizes the need of routine virological monitoring as late switching of treatment increases drug resistance which can jeopardize long term prognosis due to accumulation of resistance .

Conversely if treatment is switched unnecessarily, resources may be wasted and further treatment options reduced. Therefore, cheap and robust methods of virological monitoring are a high priority in resource limited settings.

CONCLUSION

The present study showed that though the rates of switch to second line ART was low (4.9%), the treatment outcomes were good. Clinical failure is a poor criteria for first line failure detection .After 6 months of second line therapy, the numbers of patients categorized as stage III/IV were reduced and a significant rise in the CD4 count with virological suppression.

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