Review Article

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PROFILE OF PATIENTS ON SECOND LINE ANTI-RETROVIRAL THERAPY AT RIMS, IMPHAL, MANIPUR

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ABSTRACT:

Anti-retroviral therapy (ART) has virtually transformed the outcome of patients infected with HIV. In tandem with various global initiatives against the menace of HIV/AIDS, the Government of India launched free first line ART service in the year 2004.First line antiretroviral therapy (ART) is the first regimen given to a patient when one qualifies the national criteria for initiation of ART. Many patients on first line ART eventually fails to sustain the anti-viral action and require consideration for second line ART. It is reported that 3%of patients on first line ART will fail and ultimately need second line ART .In response NACO initiated second line ART in 2008 and issued guidelines to define first line failure. In due course of second line ART many patients have developed failure necessitating 3rd line ART. In June2016 the NACO has initiated 3rd line ART under the national ART program. It is therefore very essential to detect second line ART failure timely so that early switch tothe 3rd line ART can be done. The clinical, immunological and virological status are the monitoring mechanisms of ART response. The viral load study is the cornerstone of critical clinical decision making in formulating appropriate ART in the program. There is need for understanding the overall profile of second line ART patients especially the virological response to the second line ART.

Result: Majority of the subjects (88.55%) are 25 to 44 years of age which is a productive age group. Male to female ratio being 43:27. Fifty (71.42%) of the subjects were married. IDU [38(54.28%)] and Heterosexual [28(40%)] were the main modes of HIV infection. 8(11.28%)subjects developed failure within 1year of first lie ART but majority [45(64.31%)] of the study subjects developed failure within 1 to 4 years of first line ART. 45 patients (64.28%) were initiated with Atazanavir based regimen for the 2nd line ART and 25 patients (35.7%)were on Lopinavir based regimen.Second line antiretroviral therapy regimen is the ART regimen given next in sequence after the first line failure under the national program. It is effective and reliable as the immunolo-virological response is significantly improved. However, there are concerns about the dyslipidaemia (more in LPV regimen 44%) and unconjugated hyperbilirubinaemia (more in ATV regimen 48.88%). Vomiting, pancreatitis, renal failure and hypokalemia were also encountered as side effects. There is improvement of viral load at 6th and 12th month and also the CD4 counts. The finding of the study helps to understand the profile of patients on second line ARTwith an insight on the immuno-virological response. The outcome will help in managing the second line ART effectively, reassure all stakeholders about the effectiveness of 2nd line ART and gauge the extent of second line failure, hence understand the requirement for 3rd line ART which has been rolled out under the NACO program in June 2016.

Key words: HIV virological, 2nd line ART,3rd line ART, Anti-retroviral therapy,CD4

INTRODUCTION

The National AIDS Control Organization (NACO),Government of India, initiated free 2nd line ART in August 2008 and subsequently launched 3rd line ART in June 2016.Second line anti-retro viral therapy (ART) is defined as the regimen

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given next in sequence immediately after first line ART has failed .It started as pilot projectin a few ART centers andfurther expanded to cover the ten designated Coe for ART service and few ART plus centers. The second line regimen recommended by the national guideline are one newnucleoside/nucleotide reverse transcriptase inhibitors (NRTI) plus Lamivudine plus one protease inhibitor [either Atazanavir (ATV) or Lopinavir (LPV) boosted by Ritonavir (RTV)].Once the regimen is initiated after the recommendation of the State AIDS Expert Pane(SACEP),the response is followed by clinical, immunological and virological status.CD4 cell count is a surrogate marker for the immunological response and as per NACO guideline CD4 count is done every 6 months after the initiation. Assessment of Virological response (viral load) is recommended 6 months after initiation of the second line ART. Many patients on 2nd line ART have shown failure to the regimen and thereby necessitates initiation of next line of ART regimen (3rd line).NACO has issued guideline that viral load >1000 copies /cu mm at 6months of initiation and CD4 count less than baseline of 2nd line initiation, more than 50% drop from the highest value during the treatment, less than 100/cumm should arouse suspicion of 2nd line failure. If viral load is 1000 to 10000 repeat the viral load after 3months.Failure is defined if viral load is more than 100000/cumm. The 3rd line regimen of NACO comprises of Raltegravir(400mg)+Darunavir (600mg)+Retonavir (100mg);one tablet each twice daily.The present study is an attempt to analyze the different profiles of subjects on 2nd line ART and assess the immuno- virological response over the subsequent 12months following the initiation of 2ndlineART. This will help to understand the quantum of second line ART failure, its associated characteristics and hence will help to quantify the requirement for3rdlineART.[1-8]

MATERIALS AND METHODS

It is an observational cross sectional study conducted at Medicine OPD,and pathology hematology OPD, Regional Institute of Medical Sciences, Imphal, Manipur. After obtaining proper informed consent seventy (70)Patients (>18 years,both genders) taking second line ART and having baseline,6th month and 12th month post second line ART initiation viral load and CD4 count reports are interviewed, treatment records reviewed and clinically examined. The data is recorded in predesigned proforma .Demographics: Age, sex, marital status, educational qualification, mode of transmission. Time duration from the initiation of first line ART to the initiation of second line ART is assessed. Viral load by nucleic acid PCR (CobasTechman 48) and CD4 count by automated analyzer, Fluorescence Activated Cell Sorter(FACS)at baseline(at the time of second line ART initiation), 6th month, 12th month after initiation of the second line ART(the frequency as per the NACO guideline)done by at Microbiology Department, RIMS, Imphal.

Regimens prescribed for the patients are studied. The basic principle being as per NACO guideline i.e one new(not taken in first line) NRTI+ Lamivudine+ Protease Inhibitor (ATV/LPV boosted with Ritonavir).Regimen specific adverse drug reaction (ADR) encountered during the first 12 months of the second line ART are listed from the history and treatment records of the subjects and analyzed.Exclusioncriteria:1.Unwilling patients,2. Patients without complete record and requisite viral loadreport,3. Pregnant and lactating women,4. terminally ill patients.All the data collected will be analyzed using the social sciences software statistical Package for the Social Sciences sofware(IBMSPSS) and draw scientific conclusions from the study.

RESULTS

Table 1.Showing gender distribution of the subjects

Variable	No of subjects (70)
Male	43
Female	27
Transgender	0

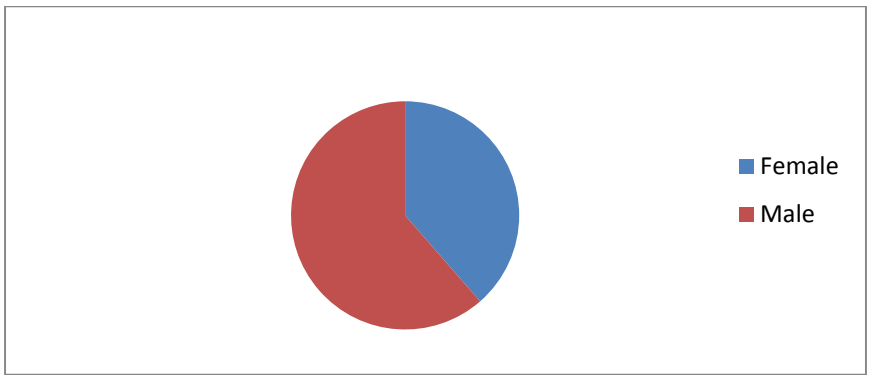


Table2. Showing age distribution of subjects:

Age in years	No ofsubjects(70)
<15	1 (youngest 13yrs)
15-24	0
25-34	18
35-44	44
45-54	5
55-64	2 (oldest 64yrs)

Table 3.showing educational qualification

Level of education	No of subjects (70)			
	Unemployed	Employed		Total
		Private sector	Government	
Illiterate	7	0	07	
Under matric	65011			
Matric	54	09		
Undergraduate	66618			
Graduate	610925			

Table 4. Showing marital status of subjects

Marital status	No of subjects
Married	50(71.42%)
Unmarried	20(28.57%)

Table 5. Showing distribution of route of infection(HIV) of subjects

Route of infection	No of subjects (70)
IDU	38(54.28%)
Heterosexual	28(40%)
Homosexual	0
Mother to child /vertical	2(2.85%)
Blood transfusion	2(2.85%)
Needle stick/professional injury	0

Table 6.showing duration between initiation of first line ART and second line ART

Duration (years)	No of subjects (70)
<1	8(11.42%)
>1-2	13(18.57%)
>2-3	16(22.85%)
>3-4	16 (22.85%)
>4-5	12(17.14%)
>5-6	5 (7.14%)
>6-7	0

Table 7.Showing distribution of second line ART regimens among the subjects

Regimen	No of subjects (70)
TDF+LAM+LPV(RTV boosted)	25 (35.71%)
TDF+LAM+ATV(RTV boosted)	45(64.28%)

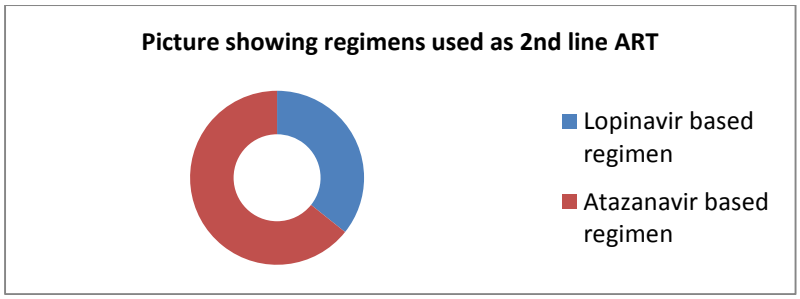


Table 8.Showing distribution of adverse reactions

Adverse reaction	No of subjects	
	LPV(R)+LAM TDF(No.25)	ATV(R)+LAM TDF(No.45)
Renal insufficiency	11(44%)	18(40%)
Hyperglycemia	4(16%)	9(20%)
Hyperbilirubinaemia	0	22(48.88%)
Hypokalemia	9(36%)	9(20%)
Pancreatitis	4(16%)	6(13.33%)
Anemia	3(12%)	8(17.77%)
Vomiting/nausea	7(28%)	12(26.66%)
Diarrhea	3(12%)	5(11.11%)
Lactic acidosis	3(12%)	3(6.66%)
Dyslipidemia	11(44%)	16(35.55%)
Peripheral neuropathy	4(16%)	4(8.88%)
Allergy /hypersensitivity	0(%)	4(8.88%)
Myositis	0	3(6.66%)

Table 9.showing distribution of viral load(copies/ml) at baseline, 6thmonth and 12th month of second line ART

Viralload(copies /cumm)	No. of subjects at Base line (70)	No.of subjects 6 months of 2ndline ART (68)	No.of subjects at 12 months of 2nd line ART (64)
Not detected	0	52	60
<1000	0	10	01
<1,000 to 10,000	02	06	01
>10,000 to 1,00,000	20	0	01
>1,00,000	48	0	01

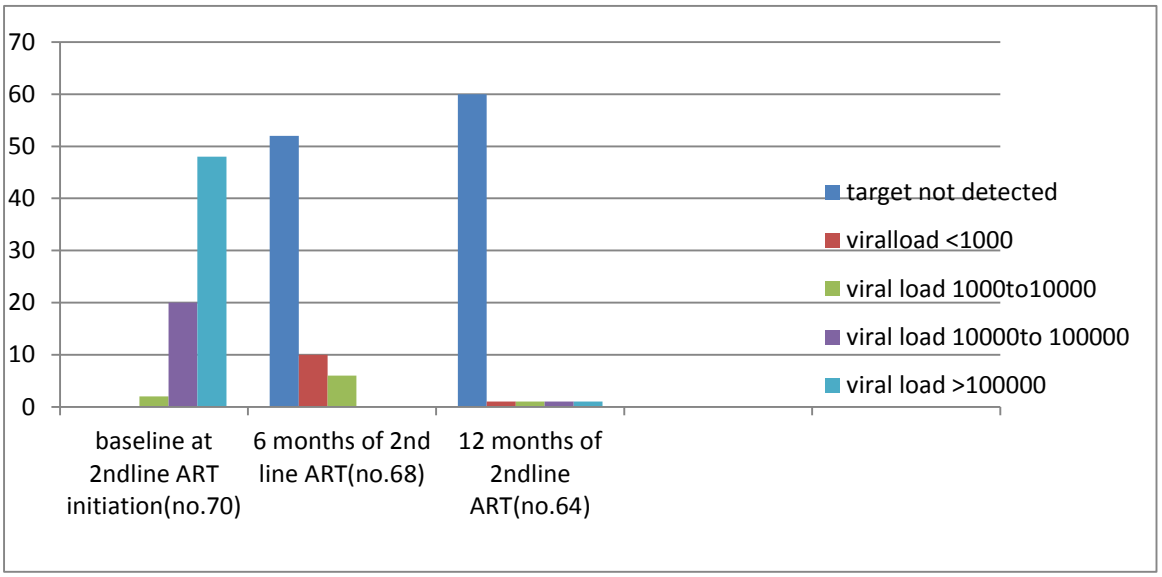
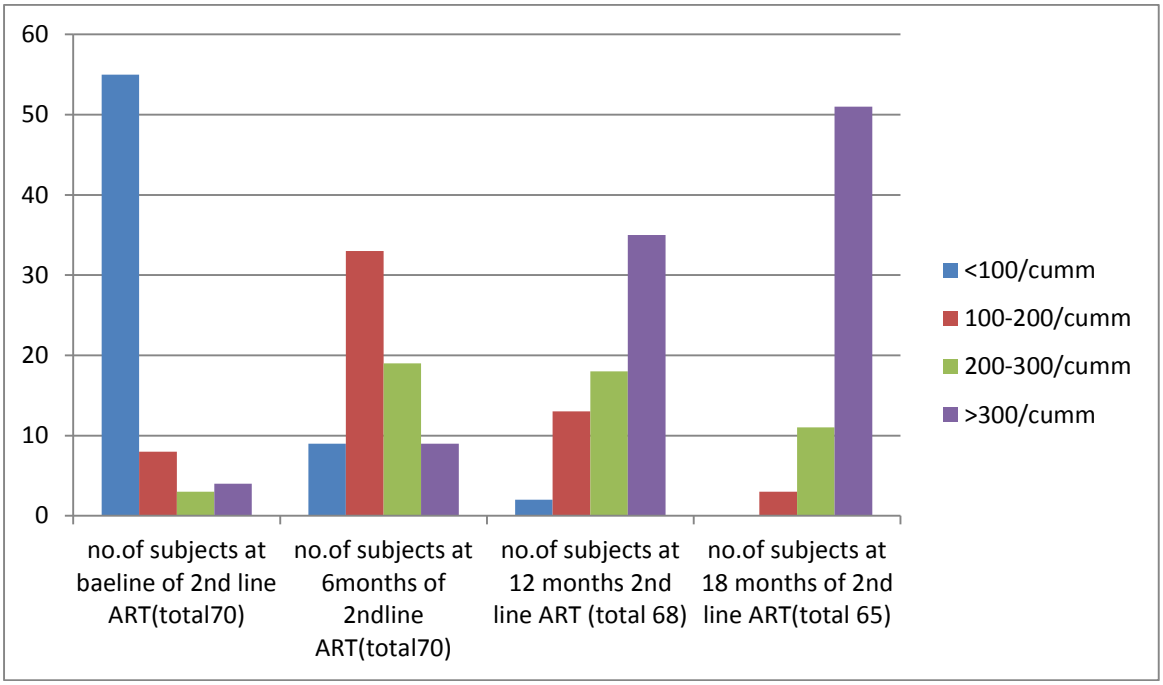


Table 10.showing no. of patients with CD4 count at baseline,6th ,12th& 18th month of 2nd line ART.

CD4 count/cumm	No.of pts. at baseline (70)	No.of pts. at 6months 2nd line (70)	No.of pts. at 12 months 2nd lineART (68)	No.of pts. at 18months 2ndlineART (65)
<50	38	0	0	0
50-100	17	9	2	0
>100-150	5	20	6	2
>150-200	3	13	7	1
>200-250	2	13	5	4
>250-300	1	6	13	7
>300-350	0	0	17	16
>350	4	9	18	35



DISCUSSION

Antiretroviral therapy has virtually changed the outlook of HIV/AIDS patients whichwas earlier considered to be a dreaded disease without any effective treatment.NACO,Government of India initiated free national ART service since April 2004 followed by launching of second-line ART in 2008.To deal with the evolving challenge of second-line ART failureNACO initiated 3rdline in june 2016. This has brought about significant headway in the fight against the menace of HIV. The first line ART which is the first regimen given to a patient when one qualifies the national criteria for initiation of art. Second line ART is the ART regimen given next in sequence to the failing first line ART.It is reported that 3%of first line ART will fail and ultimately need second line ART. Even though the national program has launched third line ART it is the ultimate national ART option and therefore there is a need to manage patients on second

line ART to preserve the future ART option for the HIV/AIDS patients. Preservation of future ART option is an important consideration in HIV management. It is therefore very essential to carefully manage second line ART to maximize the benefits of the ART. Streamlining second line ART and properly understanding how it works is an important issue.The clinical, immunological and virologicalstatus are the monitoring mechanisms of second line ART response.CD4 is the surrogate marker to determine the immunological status of a patient. There are many fallacies of CD4 count assessment and in many clinical situations may not be a true reflection of the immune status of the patient. Viral load morethan 10000/cumm after 6months of secondline ART is defined as failure.There is scant report about the viral load trend of patients being given second line ART.Majority of the subjectstotaling 64(88.54%)are in the age group between 25 to 44 years .This age group being in the productive age group there is a need for due care for this patient group to sustain their families economy and maintainability. The youngest patient being a 13year old boy and the oldest being a 64year old man. Male to female ratio being 43:27. Fifty (71.42%) of the subjects weremarried indicating that majority of the patients do continue to live life ofpurpose and sustain their families. However,all their spouses are found to be retro-reactive. IDU (38 patients) and Heterosexual (28 patients) are the main modes of infection with 2 patient each for the blood transfusion and verticalmode of transmission. 63(90%) subjects are educated with 25 in the graduate level but only 15 (21.41%) of the study population are employed and 30(42.85%) being unemployed, therefore the need for programmatic support to sustain the anti-retroviral and comprehensive care of HIV associated problems.Majority of the subjects [32 (45.70%)] developed failure within 2 to 4 years of first line ART.8 patients(11.41%) had less than 1year of first line ART before developing failure.This elicits the importance of the consideration for the issue of primary HIV resistance to ARV drugs.None of the subject had more than 6 years of first line ART before being declared failure. Proper focus on adherence and effective management of co-morbidities might yeal an extendedfavourable experience with first line ART.Second line regimen most commonly prescribed is the Atazanavir (ATV)based along with lamivudine(LAM) and Tenofovir (TDF) . Forty five (64.28%) and twenty five (35.71%) subjects were found to be taking ATV and LPV based regimens respectively. Hyperbilirubinemia was found exclusively in patients taking ATV based regimen(48.88%) as againstnone in LPV based regimen.Proper explanation and reassuring the patients for the likely development of jaundice is needed for patients initiated on ATV .Dyslipidemia which is known to occur with protease inhibitors were prevalent in both regimens but more with LPV regimen

(35.5%in ATV v/s 44 % in LPV).Renal insufficiency was detected in 40% of patients on ATV v/s 44% in LPV based regimen which is to be interpreteded with the accompanying molecule of TDF which is well known for causing renal insufficiency. There is need for proper periodic follow up of the renal function once the TDF containing second line regimen is initiated. Vomiting (26.66% in ATV v/s 28% in LPV), hypokalemia (20% in ATV v/s 36 % in LPV)with patients on TDF and LAM as common molecule for both regimens. Hyperglycemia is a well reported adverse effect of Protease inhibitors and in this study it was detected in 20% in ATV v/s 16% in LPV which is in much lesser in frequency than the dyslipidemic effects. Pancreatitis (13.35% in ATV v/s 16 % in LPV) and rash (8.88% in ATV regimen but none reported with LPV regimen) were the adverse effects in the study. Immunological status (CD4 count/cumm) of the subjects were recorded at base line (time of 2nd line initiation), 6th,12th and 18th month of continuation of second line ART. 55 patients (78.57%) had CD4 count<100/cumm,whereas only 4 subjects had count >350/cummats baseline. After 6 months of therapy 61 (87.14%) subjects recorded CD4 count >100/cumm and at the end of 12months therapy 97.05% subjects recorded CD4 >100/cumm. The count of >100/cumm was achieved in 100% of the study subjects at the end of 18 months of 2nd line ART.Therefore majority of the subjects showed raised CD4 in the periodic assessment.There may beimitations of the study in terms of the limited number of subjects and the weaknesses of a cross sectional observational study but the findings suggest that second line antiretroviral therapy is an important, effective and reliable modality of antiretroviral therapy for patients of HIV/AIDS failing first line ART. Timely identification of first line ART failure and further the 2nd line regimen failure followed up with prompt and appropriate initiation of next line of ART regimen therapy is vital for good outcome. Now that NACO has initiated 3rdline ART timely 2ndline failure detection is very essential. Viral load count could be recorded for 70 patients at baseline, for 68 patients at 6months and for only 65 patients at 12months of 2nd line ART initiation. Majority of the subjects [48 subjects(68.57%)] had Viral load >1lakh/ml at the beginning of 2ndline and 52 subjects (76.47%) achieved Target not detected (TND)status at the end of 6 months therapy.60(93.75%) subjects recorded TND at 12th months of 2nd line. Thus the effectiveness of the regimen is established. Out of the 70 subjects in the study 2 already showed viral copies >10,000/ml,indicating failure to 2nd line and thus the need for 3rd line ART.The finding of the study will help to understand the trend of CD4 and viral load response to 2nd line ART and hence the immuno-virological response of the patients .The outcome will help in reassuring all stakeholders about ART efficacy even after failing first line ART, anticipate impending adverse effects

and thus deal effectively in time with the ultimate thrust to optimize second line ART. The study further highlights the clinical necessity to be alert about the eligibility for 3rd line ART. [9-18]

CONCLUSION

Second line ART is an effective option after first line failure under the prevailing National programmatic condition. The launching of 3rdline ART by NACO has further given a big boost in the fight against HIV/AIDS. The accompanying adverse effects of the regimens should be well anticipated and managed optimally to derive full benefit of the regimen.

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