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Early Immunological Response To Second Line Anti-Retroviral Therapy: An Institutional Experience

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Abstract

Background: *It is reportedthat 3%of patients on first line Antiretroviral therapy (ART) will fail and ultimately need second line ART.There is no thirdlineART at present under the national ART program and secondlineART isthe ultimate optionforthe HIV/AIDS patients.The clinical,immunological and virologicalstatus arethe monitoringmechanismsof ART response.Though the viral load study is the cornerstone of critical clinical decision making in formulating appropriate ART, in the resource limited setting it is prohibitively expensive therefore CD4 is used as the surrogate marker to determine the immunological status of a patient. As the knowledge about the early CD4 response to the second lineART will help in managing second line ART this study is being attempted .*

Objective:*To study the early CD4 cell count response to second line antiretroviral therapy and to compare the CD4 response between Lopinavir (Ritonavir boosted) vsAtazanavir (Ritonavir boosted) based regimens.*

Methods: *It is an observational cross sectional study conducted at Medicine OPD, and pathology hematology OPD, Regional Institute of Medical Sciences, Imphal. With informed consent forty (40)Patientstaking second line ART and having baseline,6th month and 12th month post second line ART initiation CD4 reports are interviewed, treatment records reviewed and clinically examined. The data is recorded in predesigned proforma .CD4 cell count/cumm at baseline(at the time of second line ART initiation), 6th month, 12th month after initiation of the second line ART were recorded. Regimens prescribed as per NACO guideline i.e either ATV/LPV boosted with Ritonavir. Adverse reaction encountered during the first 12 months of the second line ART were listed from and analyzed.*

Results: *Majority of the subjects are in the productive age group.Thirty five of the subjects aremarried and all their spouses are retro-reactive.IDU and Heterosexual are the main modes ofinfection.12 patients(30%) develop failure within 5 to 7 years of first line ART and equal number of patients(30%) weredetected failure within 7 to 9 years of first line ART. As second line ART thirty one patients(77.5%) were initiated with Atazanavir based regimen and 9 patients (22.5%) were on Lopinavir based regimen.Hyperbilirubinemia (70.9% in ATV v/s 0% in LPV),Dyslipidemia (67.7%in ATV v/s 44.4% inLPV),vomiting (19.3% in ATV v/s 44.4% inLPV),renal insufficiency (25.8% in ATV v/s 55.5% in LPV),hypokalemia (19.5% in ATV v/s 55.5% in LPV),hyperglycemia(39.6% in ATV v/s 11.1% in LPV)were the sideeffect profile.There is satistically significant raised in the CD4 count at the 6th and 12th months of second line ART initiation.*

Conclusion: *Second line antiretroviral therapy regimenis effective and reliable as the early immunological response is significantly improved .However, there are concerns about the Triglyceridemia and unconjugated hyperbilirubinaemia.The finding of the study helps to understand the early CD4 trend and hence the immunological response of the patients and the side effect profile.*

Keywords: *Immunological, second line ART, Anti-retroviral therapy,CD4 count,*

I. Introduction

Antiretroviral therapy (ART) has changed the outlook of HIV/AIDS, which was earlier considered to be a dreaded disease without any effective treatment. The first line ART which is the first regimen given to a patient when one qualifies the national criteria for initiation of ART. It is reported that 3%of patients on first line ART will fail and ultimately need second line ART. There is no third line ART at present under the national ART program and second line ART is the ultimate option for the HIV/AIDS patients. It is therefore very essential to carefully manage second line ART to maximize the benefits of the ART. The clinical, immunological and virological status are the monitoring mechanisms of ART response. Though the viral load study is the cornerstone of critical clinicall decision making in formulating appropriate ART in the resource

limited setting , it is prohibitively expensive therefore CD4 is used as the surrogate marker to determine the immunological status of a patient. There is scant report about the early CD4 response to the second line ART.

Secondline anti retro viral therapy (ART) isdefined as the regimen given next insequence immediately afterfirstline ART has failed.The National AIDS Control Organization (NACO) initiated free 2nd line ART in August 2008.It started as pilotprojectin a few ART centers andlateron in designated 10 CoE and ART plus centers.At present the regimen recommendedby the national guideline are one new NRTI plus Lamivudine plus one protease inhibitor [either Atazanavir (ATV) or Lopinavir (LPV) boosted by Ritonavir (RTV)].Once initiated after State AIDS Expert Pane(SACEP) recommendation ,the response toART is assessed by clinical,immunological and virological status.CD4 cell count is a surrogate marker for the immunological response and as per NACO CD4 is done every 6 months after the initiation of ART. In addition to analyzing the different profile of subjects on 2nd line ART. The present study is an attempt to assess the CD4 response over the subsequent 12months following the initiation of 2ndlineART.

II. Materials and Methods

It is an observational cross sectional study conducted at Medicine OPD,and pathology hematology OPD, Regional Institute of Medical Sciences, Imphal. With proper informed consent forty (40)Patients (>18 years,all genders and transgenders) taking second line ART and having baseline,6th month and 12th month post second line ART initiation CD4 reports are interviewed, treatment records reviewed and clinically examined. The data is recorded in predesigned proforma .

Variables :Demographics: Age, sex, marital status, educational qualification, mode of transmission, HIV status of the spouse. Time duration from the initiation of first line ART to the initiation of second line ART is assessed. Adherence to drug is determined by pill counting method.CD4 cell count/cumm 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 the automated analyzer, Florescence Activated Cell Sorter (FACS) 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.
Exclusion criteria:1.Unwilling patients,2. Patients without the requisite reports of CD4 cell count,3. Pregnant and lactating women,4. Terminally ill patients,5. Patients having hypersplenism,malignancy,chemotherapy,aplastic anemia

All the data collected will be analyzed using the social sciences software (IBMSPSS) and draw scientific conclusions from the study.

III. Results

Table showing age distribution of subjects:

Age in years	No ofsubjects(40)
15-25	3(7.5%)
26-35	12(30%)
36-45	22(55%)
46-55	3(7.5%)
>55	0

Table showing gender distribution of the subjects

Gender	No of subjects (40)
Male	27(67.5%)
Female	13(32.5%)
Transgender	0

Table showing educational qualification

Level of education	No of subjects			
	Unemployed		Employed	Total
	Self	Government		
Illiterate	1	0	01	
Under matric	3	2	05	
Matric	2	1	03	
Undergraduate	4	4	4	12
Graduate	4 87	19		

Table showing marital status and HIV status of the spouse of subjects

Marital status	No of subjects
Married	35(87.5%) (all spouses.hiv +ve)
Unmarried	5 (12.5%)

Table showing distribution of route of infection(HIV) of subjects

Route of infection	No of subjects (40)
IDU	18(45%)
Heterosexual	17(42.5%)
Homosexual	0
Mother to child /vertical	3(7.5%)
Blood transfusion	2(5%)
Needle stick/professional injury	0

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

Duration (years)	No of subjects (40)
<1	0
>1-3	2 (5%)
>3-5	10 (25.5%)
>5-7	12 (30%)
>7-9	12 (30%)
>9-11	2 (5%)
>11-13	1 (2.5%)
>13-15	1 (2.5%)
>15	0

Table showing distribution of second line ART regimens among the subjects

Regimen	No of subjects (40)
TDF+LAM+LPV(RTV boosted)	9 (22.5%)
TDF+LAM+ATV(RTV boosted)	31(77.5%)

Table showing distribution of adverse reactions

Adverse reaction	No of subjects	
	LPV(R)+LAM TDF	ATV(R)+LAM TDF
Dyslipidemia	4(44.4%)	21(67.7%)
Hyperglycemia	1(11.1)	3(9.6%)
Hyperbilirubinaemia	0	22(70.9%)
Allergy/rash	0	2(22.2%)
Diarrhea	1(11.1%)	3(9.6%)
Anemia	1(11.1%)	6(19.3%)
Vomiting/nausea	4(44.4%)	6(19.3%)
Pancreatitis	1(11.1%)	3(9.6%)
Myositis	0	2(6.4%)
Renal insufficiency	5(55.5%)	8(25.8%)
Peripheral neuropathy	2(22.2%)	3(9.6%)
Hypokalemia	5(55.5%)	6(19.3%)
Lactic acidosis	1(11.1%)	2(6.4%)

Table showing distribution of CD4 count at baseline, 6^{th}month and 12^{th} month of second line ART

Case no.	CD4 at the initiation of 2^{nd} line ART (Base line)	CD4 at the 6 months 2^{nd} line ART	CD4 at 12 months 2^{nd} line ART
1	48	312	428
2	148	176	472
3	13	196	513
4	86	218	461
5	74	403	595
6	83	279	236
7	50	429	659
8	70	205	208
9	392	676	604
10	32	209	286
11	20	434	466
12	131	350	500

13	147	253	386
14	63	472	559
15	87	312	354
16	215	416	572
17	263	311	340
18	20	434	440
19	288	366	490
20	183	280	300
21	32	687	863
22	205	337	416
23	73	311	323
24	202	353	866
25	235	356	403
26	430	560	732
27	115	260	460
28	195	229	260
29	113	188	324
30	20	408	851
31	13	201	494
32	139	145	380
33	388	533	718
34	56	357	626
35	41	197	306
36	544	1013	1120
37	364	604	700
38	62	358	450
39	152	384	376
40	82	142	313

Table showing mean ofCD4 count (/cu mm) at baseline,6thand 12th month of different 2nd line ART regimen

ART regimen	Mean CD4 at baseline	Mean CD4 at 6th month	Mean CD4 at 12thmonth
ATV based	**137.90(SD-124.41)**	**350.29(SD-185.01)**	**520.32(SD-206.59)**
LPV based	**166.56(SD-156.8)**	**379.4(SD-135.3)**	**436.5(SD-141.8)**

IV. Discussion

HIV/AIDS was earlier considered to be a dreaded disease without any effective treatment .Antiretroviral therapy has virtually changed the outlook of HIV/AIDS patients. NACO,Government of India initiated free national ART service since April 2004. 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.Under the national program there is no third line ART at present and second line ART being the ultimate option for the HIV/AIDS patients. 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 one important issue.The clinical, immunological and virological status are the monitoring mechanisms of second line ART response.CD4 is the surrogate marker to determine the immunological status of a patient. There is scant report about the early CD4 response to the second line ART.

In the present study majority of the subjects are in the productive age group calling for the need for due care of this patient group to sustain their families economic and maintainibility. Male to female ratio being 27:13.Thirty five of the subjects married and all their spouses are found to be retro-reactive. IDU (18 patients) and Heterosexual (17 patients) are the main modes of infection. Majority are educated but only 11 of the study population are employed therefore the need for programatic support to sustain the anti-retroviral and comprehensive care of HIV associated problems. 12 patients (30%) develop failure within 5 to 7 years of first line ART and equal number of patients (30%) were detected failure within 7 to 9 years of first line ART. Regimens commonly prescribed as second line ART is the ATV based .In the present study 31 (77.5%) and 9(22.5%) subjects were found to be taking ATV and LPV based regimens respectively. Hyperbilirubinemia (70.9% exclusively in ATV v/s none in LPV),Dyslipidemia (67.7%in ATV v/s 44.4% in LPV),vomiting (19.3% in ATV v/s 44.4% in LPV),renal insufficiency (25.8% in ATV v/s 55.5% in LPV, where TDF and LAM are common for both regimens),hypokalemia (19.5% in ATV v/s 55.5% in LPV where TDF and LAM are common molecule for both regimens),hyperglycemia(39.6% in ATV v/s 11.1% in LPV)pancreatitis (9.6% in ATV v/s 11.1% in LPV) and rash (2% in ATV v/s none in LPV)were the side effect profile.The immunological response for the subjects taking ATV regimen as measured by CD4 (mean) at baseline, 6thand12th month of initiation being 139.5/cumm,353.3/cumm and 513.5/cumm respectively with a p value of extremelysignificant in first

6months(<0.0001)and very significant value at12months ART(0.0012). For the patients on LPV based regimen the mean CD4 at baseline,6th,and 12th month being 166.5/cumm,377.2/cumm and 436.5/cumm respectively with a p value extremely significant in 6th month (0.0009) and signioficant at 12 motn (0.0372).There is no statically significant difference in efficacy between the two regimens.Both the regimens showed comparable riseinthe first 6months (213.8/cumm for ATV and 210.7/cumm for the LPV) and the risein12months maintained from the baseline however the raise from the count of 6th month to the 12th month count is higher in ATV than LPV based regimen(160.2/cummvs 58.8/cumm).There are imitations of the study in terms of the limited number of subjects and the inherent weaknesses of a cross sectional observational study.Second line antiretroviral therapy is areliable modality of antiretroviral therapy for patients of HIV/AIDS failing first line ART. Timely identification of first line ART failure and prompt and appropriate initiation of therapy is vital for good outcome.Understaning the early CD4 trend and hence the immunological response of the patients and anticipating impending adverse effects will help optimize second line ART.

V. Conclusion

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 prompt and appropriate initiation of therapy is vital for good outcome. Both the regimens are effective and comparable in the early period but the long term response is superior with ATV. Both the regimen groups in which the common molecule being TDF and LAM shows renal insufficiency and hypokalemia.The finding will help to understand the early CD4 trend and hence the immunological response of the patients .The outcome will help in choosing appropriate regimen, anticipate impending adverse effects and thus deal effectively in with the overall thrust to optimise second line ART.Second line ART is effective and remains as the only option after first line failure at present under the National program. The accompanying adverse effects should be anticipated and managed optimally for full benefit of the regimen. Its place in the National program is paramount.

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