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Outcomes Of Third Line Antiretroviral Therapy In Treatment Experienced HIV Patients In A National Program: A Prospective Observational Study

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Abstract

Background

Demand for third line ART regimens is increasing due to increase in access to viral load monitoring and increase in the number of patients experiencing second line treatment failure. There is limited data on the outcomes of these drugs in a resource limited setting. We here describe virological, immunological and clinical outcomes on third line ART.

Methods

We conducted a prospective observational study on people living with HIV (age >12 years) who had treatment failure on second line ART and were switched to third line ART under national public sector ART program in western India. Third line ART consisted of Darunavir / ritonavir and Raltegravir. Viral suppression was defined as viral load. Viral suppression was defined as viral load <1000 copies/ml.

Results

The Median CD4 count at the start of third line ART was 235 cells/mm^3, which significantly increased to 377 cells/mm^3 after 6 months on third line ART (p value - <0.001) with a median CD4 gain of + 142 cells/mm^3. Median viral load at third line initiation was

61876.5 copies/ml which drastically reduced to 25 copies/ml after 6 months on third line ART (p value-<0.001). Among all the 198 patients, 64.6% (128/198) were alive in care with viral suppression after 6 months on third line ART. However among patients alive in care with viral load measured at 6 months, 81.5% (128/157) achieved viral suppression (VL<1000 copies/ml). Younger age (<30 years) and high baseline viral load were independent predictors of virological failure on third line ART.

Conclusion

Third line Antiretroviral therapy consisting of Darunavir/ritonavir and Raltegravir has high degree of effectiveness in treatment experienced patients with minimal adverse effects.

Keywords

Third-line, Antiretroviral therapy, Darunavir, Raltegravir, Virological outcomes, NACO, HIV.

Introduction

HIV-AIDS which was once considered a virtual death sentence at the time of initial epidemic in 1980's is now a chronic manageable disease with tremendous advancements in field of HIV prevention, diagnosis, treatment and innovative service delivery. The government of India launched free antiretroviral therapy (ART) initiative in April 2004[1], since then there has been a massive scale up and decentralization of ART services with the aim of universal access to life saving ART for all. India's ART programme implemented by National aids control organization (NACO) is one of the best public health programsproviding HIV care services free of cost.

With the removal of CD4 count thresholds for initiation of ART, there has been an increase in people living with HIV (PLHIV) on ART. Due to expanded access to treatment and longer duration of ART exposure, there has been emergence of resistance to first line ART, consisting of NNRTI and NRTI [2] . Consequently there is increase in patient being switched to protease inhibitor (PI) based second line ART, which are more difficult to adhere due to tolerability issues and higher pill burden. As a result of suboptimal adherence, there is an acquisition of multiclass drug resistance leading to treatment failure on second line ART.

In 2013, WHO recommended that national ART programs should develop policies for third line ART consisting of new drugs (like INSTIs and second generation NNRTI and PI) with minimal risk of cross resistance to previously used regimens [3] . In 2016, NACO approved third line ART for patients failing on second line ART [1] . NACO provides boosted Darunavir/ritonavir and Raltegravir under third line therapy.

Effectiveness of these drugs as salvage therapy in treatment experienced patient's is proved in several randomized controlled trials (RCT) and observational studies conducted in middle to high income settings [3-10] . There is limited data on the efficacy of these drugs when used in resource limited settings and low/middle income countries. So we here describe the outcomes of third line ART in treatment experienced patient's in national public sector ART program in western India.

Materials And Methods

Study Design

Prospective observational study.

Study Subjects and Setting

This study was conducted on people living with HIV (PLHIV) with age >12 years who had treatment failure on second line ART and were switched to third line ART consisting of Darunavir/ritonavir and Raltegravir twice daily. This study was conducted in Centre of excellence (CoE) for HIV care, Sir JJ Group of

hospitals, Mumbai, India. This centre follows NACO guidelines for HIV treatment.

All patients on second line ART were subjected to viral load monitoring and all patients with suspected second line treatment failure (defined as viral load >1000 copies/ml) were thoroughly evaluated for treatment adherence and presence of any opportunistic infection [1]. Patients with good adherence (>95% in last 3 months) were referred to CoE. At CoE, state AIDS clinical expert panel (SACEP) thoroughly examined the patient for issues like clinical symptoms, signs, investigations, adherence, OI treatment and prophylaxis [1]. Viral load report were reviewed by SACEP and eligibility for third line ART was determined. All those with viral load>10000 copies/ml were switched to third line ART, but if viral load was between 1000-10000 copies/ml, CoE repeated the viral load after 3 months to confirm failure and exclude possible blips in viral load readings [1]. Those with viral load>1000 copies/ml after3 months were initiated on third line ART. Under NACO, third line regimen included INSTI (Raltegravir 400 mg BD) +Boosted PI (Darunavir 600 mg +ritonavir 100 mg BD).

Operational Definitions

Virological failure

Virological failure is identified by the detectable viral load count of 1000 or more copies/ ml, in targeted or routine viral load monitoring, at least 6 months after ART, with > 95% of treatment adherence for each of the last 3 months [1].

Lost to follow up (LFU)

Patients who did not pick up drugs for at least 3 months [1].

Alive in care

Patients who are alive and in follow up at ART centre.

Institutional ethics committee approval was taken and informed consent of the study subjects taken before enrollment.

Data Collection Methods

At the start of third line ART a detailed clinical profile, baseline CD4, viral load, details and duration of their first line and second line ART were noted. Subjects visited ART Center every month for collecting third line medications. We followed up subjects at 6months of third line ART. During this visit patient's clinical profile including presence of opportunistic infection, CD4, and viral load at 6 months after third line ART were noted along with routine investigations.

CD4 T cell count was done using POC FACS Presto and viral load testing was done using Abbott Real time PCR. For statistical analysis purposes results like TND (Target not detected) and <20 copies/ml was taken as 20 copies/ml. The above data was noted in case record forms and entered into Microsoft excel sheets.

Statistical Analysis

Data entered into Microsoft excel data sheet and was analyzed using spss22 version software. Continuous baseline descriptive variables will be expressed as mean with standard deviations and will be compared using the MannWhitney U test. Categorical variables will be expressed as absolute numbers and proportions. Bivariate relationship for categorical variables will be assessed using odds ratio (OR) calculated based on P earson's $\chi 2$ test or Fisher's exact test. Paired t test is the test of significance for paired quantitative data. P value of a<0.05 was considered statistically significant after assuming all the rules of statistical tests. Statistical software**:** MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

Results

A total of 198 Patients who were initiated on third line ART at CoE, JJ Hospital were followed up in this study. Median age at the time of third line ART initiation was 42 years and 65.2% (129/198) were males. 86.4% had heterosexual mode of transmission, 12.6% vertical mode followed by 0.5% each by blood transfusion and unknown mode respectively. The predominant subtype was HIV 1 in 99.5% of cases and 0.5% had both HIV 1 and 2 subtype.

While on second line ART 64.6% (128) patients were on TDF+3TC+ATVr followed by AZT+3TC+ATVr in 20.2% (40) and ABC +3TC+ATVr in 8.6% (17) subjects. All the subjects at the start of third line ART had virological failure (i.e 100%), 40.4% had immunological failure and 3% had clinical failure on second line ART.

At the start of third line ART, majority of our subjects i.e 83.8% were in WHO stage I followed by 12.1% in stage II, 3.1% in stage III and 1% in stage IV. Median CD4 count at the start of third line ART was 235 cells/mm3. Median viral load at start of third line ART was 61876.5 copies/ml, among which 47.5% had VL between 1000- 50000copies/ml and 52.5% had VL >50000 copies/ml.

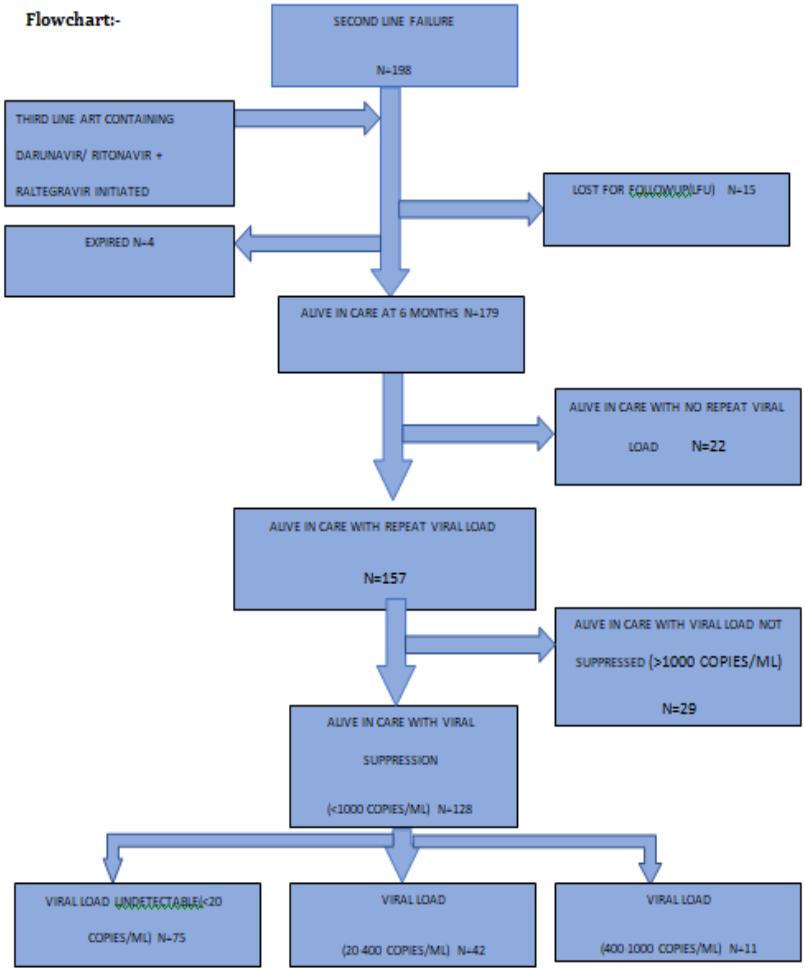

Table I: Characteristics of Patients started on third line ART

Characteristic at third line initiation	Number (%) or median
Gender Male Female	65.2% (129/198) 34.8% (68/198)
Age (Median years)	42 years
HIV subtype HIV1 HIV2 HIV1+2	99.5% (197/198) 0% (0/198) 0.5% (1/198)
Probable mode of transmission Heterosexual Vertical Blood transfusion Unknown	86.4% (171/198) 12.6% (25/198) 0.5% (1/198) 0.5% (1/198)
Second line regimen at the time of switch to third line. TDF+ 3TC+ ATVr AZT+ 3TC+ATVr ABC+3TC+ATVr TDF+3TC+LPVr Others	64.6% (128/198) 20.2% (40/198) 8.6% (17/198) 2.5% (5/198) 4.1% (8/198)
WHO Clinical stage at the start of Third lineI II III IV	83.8% (166/198) 12.1% (24/198) 3.1% (6/198) 1% (2/198)
CD4 count at the start of Third line ART (cells/mm3) <100 101-200 201-350 >350	 19.8% (39/198) 22.8% (45/198) 29.2% (58/198) 28.2% (56/198)
HIV viral load at the start of Third line ART (copies/ml) <1000 1000-50000 >50000	 0% (0/198) 47.5% (94/198) 52.5% (104/198)
Number of ART regimens prior to third line ART (Median)	3
Total Duration of ART Exposure prior to third line ART	7.62 years
Duration of PI (protease inhibitor) Exposure prior to third line ART	2.15 years

Table II: Comparison of WHO Clinical staging at the start and end of 6 months on third lineART

WHO Clinical stage	At the start of third line ART (No of Patients)	%	After 6 months on third line ART (No of Patients)	%
I	166	83.8	145	81%
II	24	12.1	28	15.7%
III	6	3.1	1	0.5%
IV	2	1	5	2.8%
TOTAL	N=198	100	N=179 (15 cases lost for follow up)	100%

Table III : Comparison of CD4 count distribution before and after 6 months on third line ART

CD4 CELL COUNT (cells/mm^3)	At the start of third line ART (No of Patients)	%	After 6 months on third line ART (No of Patients)	%
<100	39	19.8	11	6.7
101-200	45	22.8	13	7.9
201-350	58	29.2	47	28.7
>350	56	28.2	93	56.7
TOTAL NO OF CASES	N=198	100%	N=164*	100%

*Out of 198 cases, 15 were lost for follow up and 4 expired. Hence 179 cases were in follow up . Out of 179 Patients in follow up / alive in care, 164 patients had repeat CD4 count at follow up before the end of Oct- 2019.

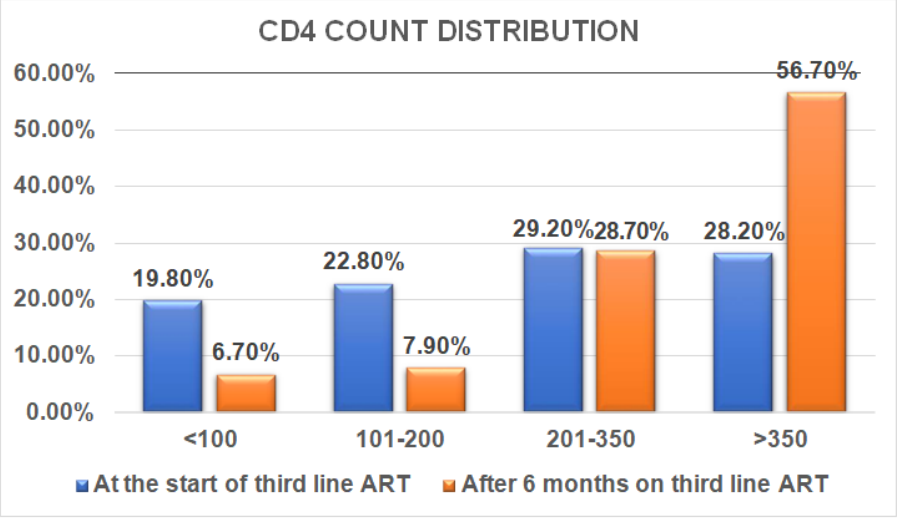

Fig 1: Comparison of CD4 count distribution before and after 6 months on third line ART

Table IV: Virological Outcomes at the end of 6 months on third line ART

	6 months (n = 198)	
	No of Patients	%
Alive In Care with viral Suppression	128	64.6%
Alive In Care with viral load Not Suppressed	29	14.6%
Alive In Care with No Repeat Viral Load at Follow Up	22	11.1%
Lost to Follow Up	15	7.6%
Death	4	2.0%

Table V: Viral load comparison before and after 6 months of Third line ART

Viral load	At the start of third line ART N =198	%	At 6 Months N= 157*	%
<1000	0	0%	128	81.5%
1000-50000	94	47.5%	12	7.6%
>50000	104	52.5%	17	10.9%

*Out of 198 cases, 15 were lost for follow up and 4 expired. Hence 179 cases were in follow up. Out of 179 patients in follow up, 157 patients had repeat viral load at follow up before the end of Oct 2019.

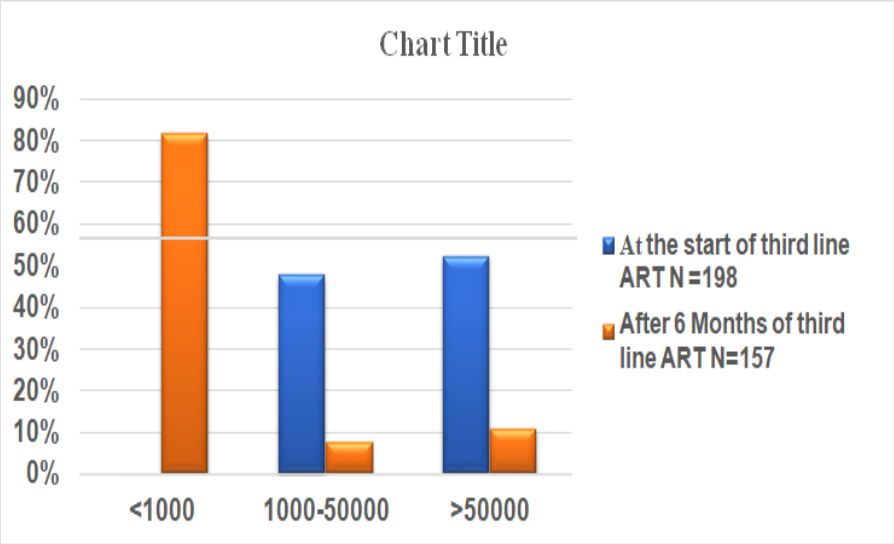

Fig 2: Bar diagram showing viral load at start of third line ART and at 6 months follow-up.

After 6 months on third line ART, 90.4% (179/198) were alive in care, 7.6% (15/198) were lost for follow up (LFU), 2% (4/198) had expired.

Median CD4 at 6 months on third line ART was 377 cells/mm3. There was significant increase in CD4 count from 235 cells/mm3 to 377 cells/mm3 after 6 months on third line ART and the data was statistically significant (p value- <0.001). We had a median CD4 gain of +142 cells/mm3 at 6months.

Median viral load at 6months follow up was 25 copies/ml, the decrease in viral load wad statistically significant (p value- <0.001).

In our study out of 198 Patients enrolled for study, at 6 months follow up 128 patients (64.6%) were alive in care with viral load suppressed, 29 patients (14.6%) were alive in care with viral load not suppressed, 22 patients as (11.1%) were alive in care with no repeat viral load value at follow up, 15 patients (7.6%) were lost for follow up (LFU) and 4 patients (2%) expired within 6 months of enrollment. However among all patients alive in care with viral load measured at 6 months, 81.5% (128/157) cases were viral suppressed (Table IV &V).

Among 128 patients who were alive and viral suppressed,75 patients had VL <20 copies/ml, 42 patients had viral load between 21-400 copies/ml and 11 had VL between 401-1000 copies/ml.

After 6 months on third line ART, patients in the age group of<30 years had lowest percentage of viral suppression (59.3%) and those with age >45 years had highest percentage of viral suppression (90.2%).Younger patients were more likely to fail third line ART (p value- 0.003). Patients who had viral load between 1000-50000 copies/ml at start of third line ART, 94.1% of them had viral suppression, while among those with viral load >50000 copies/ml 66.7% had viral suppression. High HIV viral load at baseline is a strong predictor of third line ART failure (p value- 0.001). There was no significant association between viral resuppression and sex, WHO clinical stage, baseline CD4 (p values 0.698, 0.15 and 0.770 respectively) (Table VI).

Mean duration of PI exposure (prior to third line initiation) in viral suppressed group was 1038 days, while it was 798 days in unsuppressed group. There was no significant association between duration of PI exposure prior to third line initiation and viral re-suppression on third line ART (p value-0.09).

Similarly there was no statistically significant association between change in PI regimen during second line ART and viral re-suppression on third line ART.

There were 4 deaths within 6months of initiation of ART, related to advanced stages of disease. 3 patients had CD4<100 cells/mm^3, 1 had between 100-200 cells/mm^3. Mortality was strongly associated with lower CD4 count (p value-0.026) (Table VII). There was no severe adverse effects of this regimen in our study.

Discussion

We present the clinical, immunological and virological outcomes and predictors of viral re-suppression on third line ART in a public sector program in a resource limited setting. Among patients enrolled into the third line ART program with viral load measured at 6 months, there is ahigh rate of viral suppression with 81.5% having VL<1000 copies/ml. Patients also had good immunological response with respect to increased CD4 count and no significant progression of the disease. We demonstrated effectiveness of third line ART consisting of boosted Darunavir/ritonavir and Raltegravir among patients failing second line ART.

Table VI: Predictors of re suppression on third line ART in patients failing second line ART

			Alive In Care				
		N=157	Alive in care with viral Suppression n=128 (81.5%)		Alive in care with viral load not suppressed n=29 (18.5%)		
			cases	%	cases	%	
Sex	Female	60	48	80.0%	12	20.0%	0.698
	Male	97	80	82.5%	17	17.5%	
Age(years)	<30	27	16	59.3%	11	40.7%	0.003*
	31 to 45	69	57	82.6%	12	17.4%	
	>45	61	55	90.2%	6	9.8%	
WHO clinical stage at start of third line	I	135	111	82.2%	24	17.8%	Chi-square value = 5.31, df = 3,p value = 0.15
	II	18	14	77.8%	4	22.2%	
	III	3	3	100%	0	0	
	IV	1	0	0	1	100%	
CD4 at Start of Third line ART	<100	25	19	76.0%	6	24.0%	0.770
	100 to 200	30	24	80.0%	6	20.0%	
	200 to 350	49	42	85.7%	7	14.3%	
	>350	53	43	81.1%	10	18.9%	
Viral load at start of third line ART	1000 to 50000	85	80	94.1%	5	5.9%	<0.001*
	>50000	72	48	66.7%	24	33.3%	

[Excluded LFU, EXPIRED, ALIVE IN CARE WITH NO REPEAT VIRAL LOAD AT FOLLOWUP subjects]

Table VII: Association between Mortality and Factors at the start of Third line ART:

		Group					P value
		Non survivors N=4		survivors N=179		Total N=183	
		cases	%	cases	%		
Sex	Female	1	1.5%	64	98.5%	65	0.657
	Male	3	2.5%	115	97.5%	118	
Age	<30 years	1	2.9%	33	97.1%	34	0.842
	31 to 45 years	2	2.6%	76	97.4%	78	
	>45 years	1	1.4%	70	98.6%	71	
WHO clinical stage at the startof third line ART	I	2	1.3%	152	98.7%	154	0.037*
	II	1	4.3%	22	95.7%	23	
	III	1	20%	4	80%	5	
	IV	0	0%	1	100%	1	
CD4 at the start of third line ART	<100	3	8.6%	32	91.4%	35	0.026*
	100-200	1	2.8%	35	97.2%	36	
	200-350	0	0%	56	100%	56	
	>350	0	0%	56	100%	56	
Viral load at the start of third line ART	1000-50000	2	2.2%	90	97.8%	92	0.982
	>50000	2	2.2%	89	97.8%	91	

[Survivors cohort includes all patients who are alive in care with viral suppression plus alive in care with viral load not suppressed plus alive in care with no repeat viral load. Excluded LFU subjects]

Among all the 198 patients started on third line ART 64.65% patients were alive in care with viral suppression at 6 months which was consistent with studies conducted by Evans et al(57.3%)[11] and Khan et al(61.1%)[12] . On further analysis, in our study only 157 patients of 179 who were alive in care had there viral load measured at 6 months and 15(7.6%)patients of the total 198 were lost for follow up. This subsequently underestimated viral suppression rates. So among those patients who were alive in care with viral load measured (157/198), 128/157(81.5%) were viral suppressed, which was consistent with Evans et al (78.3%)[11] and Moor house et al (83%)[13] .

Patients also had good immunological response after initiation of third line ART, as witnessed by median CD4 gain of+142 cells/mm3, this was consistent with studies conducted by Meintjes et al (+154 cells/mm3) [14] , Pujari et al(+211 cells/mm3) [15] and Chimbetete et al (+104 cells/mm3) [2] .

We also were able to demonstrate the success of routine viral load monitoring of patients in the public sector program. With access to routine viral load testing in ART Programs, these cohort of patients are under routine clinical, immunological and virological monitoring. So treatment failure was recognized early at the stage of virological failure which precedes immunological and clinical failure. This was demonstrated in our study with majority of patients were in WHO stage I at the start of third line ART (166/198) i.e. 83.8% and also after 6 months on third line ART (145/179) i.e. 81%. This also shows

effectiveness of third line ART in slowing clinical progression of HIV.

Predictors Of Viral Re-Suppression On Third Line Art

Factors independently associated with viral suppression on third line ART were age and baseline viral load. Our finding of younger patients(<30years) more likely to fail third line ART was discordant with the findings of Meintjes et al[14] but was consistent with meta-analysis study by Ghidei et al [16] . We believe that younger patients being occupied with work and also possibility of work place stigma associated with HIV leads to poor drug adherence leading to virological failure. Also older age is associated with better understanding of importance and value of adherence to cART.

Our finding of high Viral load at baseline or at the start of third line ART as a strong independent predictor of third line failure, has also been demonstrated by Meintjes et al [14] . The abovesame finding with respect to second line ART was demonstrated by Boettiger et al [17] and Cardoso et al[18] .

Acquisition of resistance mutations while replicating in the presence of failing ART (second line) leading to added drug resistance to PI and high viral load at third line initiation explains our findings[17]. High viral load at third line initiation can also be be taken as surrogate marker of poor drug adherence to second line ART. This leads to added drug resistance mutations to PI and subsequently to third line ART failure. Though we did not have data suggesting of poor drug adherence in patients who failed third line ART, usual adherence monitoring by pill counting (subject to pill dumping) and self reporting (subject to recall bias) used in NACO ART program overestimates adherence[19] .This underlines importance of appropriate adherence counselling prior to confirmation of virological failure. Other factors like sex, CD4 count, duration of exposure to PI based regimen were not associated with viral suppression. Major limitations of our study are small sample size, short duration of follow up, missing viral load data of few patients post third line initiation although they are alive in care (22/179). We had enrolled patients who were able to visit CoE for third line therapy from far flung areas, this might have introduced selection bias by excluding debilitated patients with advanced disease who could not travel. Unavailability of genotypic resistance testing (GRT) in our national programme is another major barrier for optimal management of patients failing second line ART. GRT can differentiate treatment failure due to poor adherence from that due to PI resistance. Thus unnecessary switch to more expensive third line treatment be averted. Unavailability of third line ART at all ART Centre's and need for patients to travel long distances to access third line treatment is major reason for lost for follow up (LFU). Though recently decentralization of third line ART has been started. Lack of unique patient identity makes it difficult to ascertain whether patients who are LFU have died or simply relocated and receiving treatment at private sector (silent transfers)[11] . Due to above limitations, our study findings may not be generalized to all HIV clinics.

Conclusion

Our findings highlight the effectiveness of third line ART provided in national public sector program in resource limited setting, suggesting that patients failing PI based second line ART can achieve high rate of virological suppression on third line ART

regimens containing boosted Darunavir/ ritonavir and Raltegravir with low adverse effects. Genotypic resistance testing and new strategies for adherence monitoring should be adopted in national program for optimal management of treatment failure. Decentralization of third line ART in national program is needed for an easy access and preventing lost for follow up. Future research is needed to access long term effectiveness of third line ART and feasibility of routine GRT in national program.

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