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Various Immunologic and Virologic Responses to Second line Antiretroviral Therapy in Tambaram, India

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Abstract

Introduction: We studied the prevalence and associated factors for various immunologic and virologic responses to second line antiretroviral therapy (SLA) in patients enrolled in a government tertiary care hospital in Chennai , India

Methods: A cross-sectional study of human immunodeficiency virus patients who have failed first line antiretroviral therapy and subsequently initiated on SLA .Concordant favourable response (CFR) or (CD4+/VL+) was defined as: increase in CD4 count of >=50 cells/mL and achievement of plasma viral load<400 copies/mL after 6 months. Concordant unfavourable response (CUR) or ($CD4^-/VL^-$) defined as increase in CD4 count of <50 cells/mL and achievement of plasma viral load>400 copies/mL. Various clinical and demographic factors were analyzed between different response groups using Chi-Square test, t-test, and One way ANOVA

Results: From January 2008 to February 2009, 60 patients initiated on SLA. In those 76.7% experienced CD4+/VL+, 10% $CD4+/VL^-$, 5% $CD4^-/VL+$ and 8.3% $CD4^-/VL^-$ response. The characteristics of CFR and CUR groups were: 97.8% and 100% males (p- value>0.05), mean baseline CD4 count of 100 and 198 cells/mL (p-value<0.05), mean baseline viral load of 187754 and 265580 copies/mL (p- value>0.05), mean CD4 count at 6 months (313 vs. 147 cells/mL; p-value<0.05), adherence>95% (100% vs. 40%; p-value<0.05). Immunologic only response ($CD4+/VL^-$) was associated with sub optimal adherence.

Conclusion: 76.7% of patients after 6 months on SLA indicated CFR and 8.3% experienced CUR. CUR associated with poor adherence.

Keywords: Adherence; CD4 counts; Discordant response; Second line ART

Introduction

The World Health Organization (WHO) statistics reports that the number of people living with HIV/AIDS (PLHA) at the end of 2011 was 34 million (31.4-35.9 million) [1]. As per the 2011 estimates released by the Ministry of Health and Family Welfare and National AIDS Control Organization (NACO), the estimated adult HIV prevalence in India is approximately 0.27% (0.22%-0.33%). The total number of PLHA (adults and children) in India is estimated to be 20.88 lakhs (17.20–25.30 lakhs) in 2011 [2]. Implementation of free antiretroviral therapy (ART) programme began in India from April 2004 [3]. The number of people receiving ART in India as of 2014 is 785161 [4]. The NACO started providing second-line ART (SLA) since January 2008 in India [5]. Not many studies have been done on immunologic and virologic responses to SLA and its associated factors in Indian context. Hence we wanted to study the various immunologic and virologic outcomes of patients initiated on SLA after a period of 6 months.

SACEP (State Aids Clinical Expert Panel)

SACEP is a panel of experts for NACO pilot programme who evaluates and initiates patients on SLA based on NACO guidelines [6]. In the government programme patient initiated on first line antiretroviral therapy (FLA) are monitored by doing a CD4 count testing once in 6 months. They are also monitored clinically on monthly basis. A patient on FLA is considered to be having treatment failure when he has immunological failure or clinical failure after a period of 6 months on FLA, Immunological failure is identified by [7-10]. a) Fall of CD4 count to pretherapy baseline. b) 50% fall from on treatment peak value. c) Persistent CD4 Count below 100 cells/mm3. Clinical failure is defined as recurrent stage 4 illness after 6 months of FLA. SACEP Eligibility criteria for viral load testing to patients on FLA: In the government programme viral load testing for patients on FLA is not done routinely. Viral load is done only to patients who are having treatment failure either by clinical failure or by immunological failure inspite of adherence to drugs >95% and should have been on FLA atleast for a period of 6 months. Subsequently after viral load testing patients who are having viral load >10,000 copies/ml will be initiated on SLA [8-10]. The NACO SLA consists of two regimens. Regimen 5: Zidovudine/Lamivudine/

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Lopinavir/Ritonavir/Tenofovir and Regimen 5 a: Lamivudine/Lopinavir/Ritonavir/Tenofovir. Patients with haemoglobin >8 mg/dl will be initiated on Regimen 5. Patients initiated on SLA will get a repeat CD4 Count after 6 months of therapy [7].

Materials and Methods

It is a cross sectional study of 70 HIV infected adults initiated on SLA by SACEP from January 2008 to February 2009 at Government Hospital of Thoracic Medicine (GHTM), Tambaram, Chennai. Of the 70 patients initiated on SLA by SACEP only 60 patients were eligible for evaluation depending upon the inclusion and exclusion criteria mentioned below.

Inclusion criteria

a) Adult patients initiated on SLA after SACEP assessment in GHTM, Tambaram, India.

b) Patients who have continued SLA atleast for 6 months after initiation of SLA and have undergone repeat CD4 count and viral load test.

Exclusion criteria

a) Patients already initiated on SLA from private sectors and being referred to GHTM for further treatment.

b) Patients not initiated on FLA from government programme are excluded

Working Definitions for Responses or Outcomes to SLA After 6 Months on SLA

Concordant responses were categorized into two types

Concordant favourable response (CFR) or (CD4+/VL+): Increase in CD4 count of >=50 cells/mL and achievement of plasma HIV RNA level <400 copies/mL.

Concordant unfavourable response (CUR) or (CD4-/VL-): Increase in CD4 count of <50 cells/mL and achievement of plasma HIV RNA level >400 copies/mL.

Discordant Responses were Categorized into Two Types

Immunologic only response (IOR) or (CD4+/VL-)

Increase in CD4 count of >=50 cells/mL and achievement of plasma HIV RNA level>400 copies/mL.

Virologic only response (VOR) or (CD4-/VL+)

Increase in CD4 count of <50 cells/mL and achievement of plasma HIV RNA level<400 copies/mL.

Data Collected

The details like age, sex, CD4 cell count and viral load at the time of initiation of SLA and after 6 months on SLA, type of SLA regimen at the end of 6 months, change of SLA regimen, level of adherence to SLA, concomitant history of anti-tuberculosis therapy (ATT) are collected from the hospital information system and patient treatment card. Adherence is measured by monthly pill counts done by ART Counsellors while the patient visits the ART centre for drug collection. The adherence is recorded based on the missed doses by patients on monthly basis. we measured the percentage of adherence levels in these 3 categories

95% adherence: The 95% adherence means that if the patients have missed less than 3 pills in a month.

80-95% adherence: If the patient has missed 3 to 12 pills in a month we categorised them less than 80-95%.

<80% adherence: If the patient has missed more than 12 pills in a month we categorized them under <80% adherence

While doing analysis we categorised the level of adherence only into 2 categorise as >95% adherence and <95% adherence and did the chi square test. All the details regarding the level of adherence are collected only from patient's treatment card entered by the ART counselor.

Ethical Clearance

The study is approved by institution ethical committee and Institutional Review board of GHTM. Informed consent to collect the above mentioned data are obtained from all the study participants.

Statistical Analysis

The data collected is entered into excel sheet and analysed using SPSS (Statistical Package for Social Sciences) version 14 .The frequency tables for all collected variables is computed. The mean baseline CD4 Count, mean CD4 Count after 6 months of SLA, mean baseline viral load at the time of initiation of SLA are cross tabulated against the CFR and CUR groups and Independent sample test is used .For comparing other variables against the two groups of CFR and CUR chi square test is used. One way ANOVA is used for analyzing variables against the 4 response groups (CFR, CUR, IOR &VOR)

Results

Baseline characteristics

Of the 60 participants nearly 98.3% of the study population is males. The median age is 38 years (Inter-quartile range 35 to 40). Other baseline characteristics like concomitant history of ATT, median CD4 count before initiation of SLA and after 6 months on SLA, median baseline Viral load and median CD4 gain after 6 months on SLA are shown in Tables 1 and 2 respectively.

SLA regimens

As you can see from Table 3, during the period of 6 months most number of patients nearly 91.7% is on Regimen5 (Zidovudine/Lamivudine/Lopinavir/Ritonavir/Tenofovir) and 25% (15) patients

Variables	N (%)	95% Confidence Limits
Male	59 (98.3%)	81.9-96.2
Female	1 (1.7%)	0.0-8.9
Concomittant history of ATT	9 (15.0%)	7.1-26.6

ATT: Anti Tuberculosis Therapy; N: Numbers; (%): Percentage

Table 1: Baseline characteristics N=60.

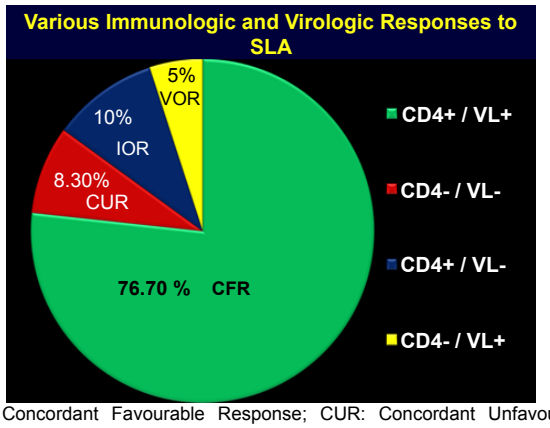
Variables		Interquartile Range
Median Age (Years)	38	35 to 40
Median CD4 Count before initiation of SLA (cells/mL)	83.50	40 to 145.50
Median CD4 Count after 6 months on SLA (cells/mL)	275	176 to 351.50
Median CD4 gain after 6 months on SLA (cells/mL)	190.50	134 to 275
Median baseline Viral Load before initiation of SLA (copies/mL)	143000	58100 to 281500

Table 2: Baseline characteristics.

SLA Regimen	N (%)	95% Confidence limits
Regimen 5 Zidovudine/Lamivudine/Lopinavir/Ritonavir/ Tenofovir	55 (91.7%)	81.6- 97.2
Regimen 5 a Lamivudine/Lopinavir/Ritonavir/Tenofovir	15 (25%)	14.7- 37.9
Patients who have undergone change of Regimens	10 (16.7%)	8.3- 28.5

SLA: Second line antiretroviral therapy; **N:** Numbers; **(%):** Percentage.

Table 3: SLA regimen during the period of 6 months.



CFR: Concordant Favourable Response; CUR: Concordant Unfavourable Response; IOR: Immunologic Only Response; VOR: Virologic Only Response

Figure 1: Various immunologic and virologic responses to SLA.

Variables	CFR	CUR	P-Value
Mean Age in Years	37	36	>0.05
Males	97.8%	100%	>0.05
Mean Baseline CD4 Count (cells/mL)	100	198	0.033*
Mean CD4 Count at 6 months (cells/mL)	313	147	0.004*
Mean baseline Viral Load (copies/mL)	187754	265580	>0.05
Change of SLA	13%	40%	>0.05
Concomitant history of anti tuberculosis therapy	10.9%	20%	>0.05
Adherence >95%	100%	40%	0.000*

CFR: Concordant Favourable Response; **CUR:** Concordant Unfavourable Response; *: Significant P-Value <0.05

Table 4: Variables analysed between CFR and CUR.

are on Regimen 5 a. of the 55 patients started on Regimen 5 nearly 10 patients are shifted to Regimen 5 because of the drop in haemoglobin levels below 8 g/dl.

Immunologic and virologic outcomes

Nearly 76.7 % of the study population showed CFR and 8.3% showed CUR. Remaining 15% showed discordant responses of which 10% were IOR and 5% were VOR. The various immunologic and virologic responses to SLA after 6 months on SLA are given in Figure 1.

Variables analysed between CFR and CUR

We analysed factors like mean age in years, sex, mean baseline CD4 Count, mean CD4 count at 6 months, mean baseline Viral load, change of SLA, concomitant history of ATT and adherence levels with respect to CFR and CUR groups. The Table 4 shows the various variables analysed between CFR and CUR groups.

Variables analysed between 4 different response groups

We analysed various factors like age, baseline CD4 counts, CD4 counts after 6 months on SLA, mean baseline viral load, adherence level and concomitant history of ATT against the four different response groups, which are shown in Table 5.

Discussion

Our study showed that nearly 76.70% had good immunological and virological improvement. So from this study we can say that the success rate to SLA is nearly 76.7% after 6 months on SLA inspite of high pill burden. We say high pill burden because the number of tablets to be consumed by each patient in a day for regimen 5 and regimen 5a was 7 and 5 [11].

This result is comparable with a study done by Patel et al. [11] on 126 patients. Their study was also done in India and the patients are started on similar SLA regimens. The Patel et al. study showed a success rate of 82% and the patients are followed up for a period of 12 months, while in our study we followed up the patients only for 6 months.

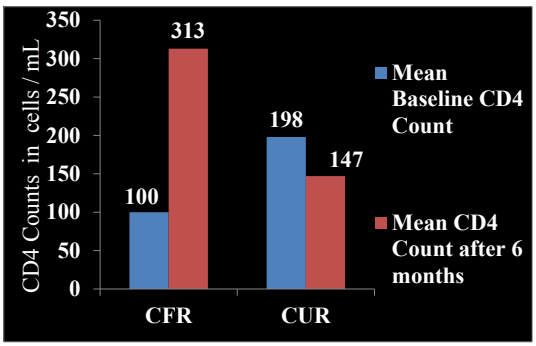
In our study the median CD4 gain after 6 months on SLA is 190.50 cells/mL which is slightly higher than the Patel et al. study which is 163.5. The virological outcomes are also similar when compared with Patel et al., showing a virological response of 81.70% in our study vs 82% in their study [11].We could not compare other similar studies done in Thailand [12] and South Africa [13,14] as those studies definition for virological failure was >1000 copies/ml while our studies definition for virological failure is >10, 000 copies/ml. So in a way the other studies [12-14] could have detected treatment failure earlier than our study because of the difference in the definitions for viral Load.

We can see from Figure 2, even though the mean baseline CD4 count is low in CFR group (100 cells/mL) when compared with CUR group (198 cells/mL), but still the CFR groups mean CD4 count after 6

Variables	CFR	IOR	V0R	CUR	P-Value
Mean age in Years	37	41	43	36	>0.05
Mean Baseline CD4 Count (cells/mL)	100	40	105	198	0.042*
Mean CD4 Count at 6 months (cells/mL)	313	297	129	147	0.006*
Mean baseline Viral Load (copies/mL)	187754	413133	116466	265580	0.055
Adherence level > 95%	100%	83.3%	100%	40%	0.000*
Concomittant history of Anti tuberculosis therapy	10.9%	50%	-	20%	>0.05

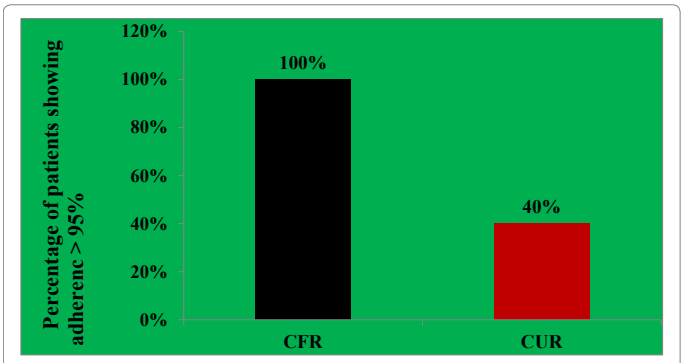
CFR: Concordant Favourable Response; **IOR:** Immunologic Only Response; *: Significant P-Value <0.05; **VOR:** Virologic Only Response; **CUR:** Concordant Unfavourable Response

Table 5: Variables analysed between 4 different response groups.



CFR: Concordant Favourable Response; CUR: Concordant Unfavourable Response

Figure 2: Comparison of mean CD4 counts before and after 6 months in 2 response groups.



CFR: Concordant Favourable Response; CUR: Concordant Unfavourable Response

Figure 3: Percentage of adherence levels >95% between CFR and CUR.

months of SLA are higher than CUR group (313 vs. 147 cells/mL). This finding is probably because the CFR group showed a 100% adherence level >95%, while the percentage of adherence level >95% is shown only in 40% of CUR group (Figure 3). So adherence plays an important role in the effectiveness of improvement in CD4 counts irrespective of the baseline CD4 counts.

Our study showed the overall discordant response is 15% (IOR+VOR) as shown in Figure 1. This is comparable with other studies [15-21] which showed the approximate discordant response to ART is nearly 15 to 40%. A study done by Prabhakar et al. [22] in Indian settings showed 13.59% has discordant responses to FLA which is similar to our discordant response percentage. Our study showed the IOR is associated with low mean baseline CD4 counts, and poor adherence. Even though IOR group showed high mean baseline viral load when compared with other groups and also showed nearly 50% of this group has a history of concomitant history of ATT, these findings are not statistically significant.

Some of the other studies also showed that IOR is associated with low baseline CD4 counts [22-24]. Study done by Moore et al. [17] showed poor adherence is associated with both IOR and VOR. The role of Tuberculosis therapy and tuberculosis infection in IOR could be because of the additional pill burden of ATT along with SLA, but the reason behind increased percentage of concomitant history of ATT in IOR group has to be studied further even though it is not statistically significant finding .VOR is associated with slightly low mean base line CD4 counts ,and good level of adherence (>95%) when compared with other groups (Table 5). VOR is associated with baseline CD4 counts in another study [25].

In our study 100% of VOR group has taken only Regimen 5. Regimen 5 is a Zidovudine based regimen. Zidovudine has been attributed to poor CD4 count increase inspite of good viral suppression [26]. Even a study done by Prabhakar et al. [22] showed that VOR is associated with Zidovudine based regimen as nearly 71% of VOR group is on Zidovudine in their study. A study have shown that both IOR and VOR is associated with infection of multi resistant viral strains [27], which we could not confirm because our programme does not have the facility to do resistance testing.

Conclusion

In this population, 76.70% experienced CFR, 10% IOR, 5% VOR, and 8.3% CUR after 6 months on SLA. The CFR is associated with adherence levels >95%. CFR is associated with low baseline CD4 count when compared with CUR. The CUR is associated with adherence levels <95%. Even though the mean baseline CD4 counts are low in the CFR group when compared with the CUR group, they are able to produce good CD4 gain and viral suppression after 6 months because of good levels of adherence. Low baseline CD4 count is not associated with CUR. Considering the limited drug options available in the Government Programme, the adherence counselling should be enhanced to patients on SLA. Our study showed both the discordant responses have been associated with baseline CD4 counts and baseline viral load. It is high time that our policy makers start to reconsider the guidelines for viral load testing , as the definition for treatment failure is viral load >10, 000 copies/ml and it has to be revised to >400 copies/ml. Hence early deduction of treatment failure can vary the baseline CD4 count values and baseline viral load values, which in turn can reduce the number of patients with both type of discordant responses (IOR & VOR).

Next Step: The study should be continued for assessing the long term responses to SLA in GHTM. The risk factors of IOR and VOR have to be studied further.Clinical outcomes of different response groups needs to be followed up.

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Authors Contribution

Dr Ganesh S.A carried out study design as well as data collection, and wrote manuscript. Dr Chandrasekar C, Dr Manoharan, Dr Raja K and Patrick Nadol designed the study, reviewed the manuscript and approved the final version. Ezhil R carried the statistical analysis and data management.

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