

A Prospective Study to Evaluate Prescription Pattern of Second Line Antiretroviral Therapy Given to HIV Patients

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ABSTRACT

Aims: To evaluate prescription pattern during second line Antiretroviral Therapy (ART) at tertiary care hospital. Despite a very large number of patient being covered under ART, there are limited data in Indian population regarding second line ART. Therefore, the present study was undertaken.

Methods: After consultation with physician of ART plus centre, patient was interviewed and details of the patient's case record was obtained. At each encounter on every 30th day patient's investigations, opportunistic infections, adherence level, associated medical conditions, second line ART and other drug prescription was recorded in preformed case record form for the study. **Results:** Out of 70 patients, 16 patients [22.86%] had history of 2nd line ART from Private ART clinics and 54 patients [77.14%] were transferred from other government ART centers. Mean time to switching from first line to second line ART was 3.67±2.29 years in 63 patients. Most common ART regimen prescribed at the initiation of second line ART was tenofovir+ lamivudine+ atazanavir /ritonavir in 45 patients [64.29%] with 264 encounters. Most common opportunistic infection was ARI [recur-

rent respiratory infection] with 28.84% incidence. **Conclusion:** Irrational practice by private hospitals limits treatment options with increasing the chances of drug resistance. On the other hand NACO sponsored second line ART was given with a proper treatment protocol causes good compliance in patients.

Key words: Human Immunodeficiency Virus, Antiretroviral Therapy, Prescription pattern, Adherence, NACO.

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INTRODUCTION

Human Immunodeficiency Virus [HIV] infection has been a growing challenge worldwide for the past three and half decades. Since the first cases of acquired immunodeficiency syndrome [AIDS] were reported in 1981, infection with human immunodeficiency virus [HIV] has grown to pandemic proportions.¹ According to the World Health Organization [WHO] there were approximately 35 million people worldwide living with HIV/AIDS in 2013. India has the third largest HIV epidemic in the world. HIV prevalence in India was an estimated 0.3 percent.

It is estimated that around 2.1 million people are currently living with HIV in India.²

The advent of highly active Antiretroviral therapy [HAART] has been a boon for human immunodeficiency virus [HIV] infected patients by reducing morbidity and extending lifespan.³ However, with increasing exposure to first line ART the risk of viral resistance and subsequent treatment failure has become more important, and switching to second-line regimens is increasingly needed. WHO estimates that the average switch rate from first to second line ART is 2-3% per year for adults.⁴

In order to expand the access to second line treatment, 37 "ART Plus" centers started and capacitated to provide second line/alternative first line treatment to eligible Patients. Till Sept.2014, 10,223 patients were received second line ART drugs from ART Plus Centers.⁴

Prescription of multiple drugs are common in HIV positive individuals particularly after initiation of ART. Therefore, they are at a higher risk of drug interactions and adverse drug reactions. The principal aim of drug prescription research is to facilitate rational use of drugs in populations.

So monitoring of prescription pattern can be helpful to change or design future treatment protocols. Despite a very large number of patients being covered under ART, there are limited data in Indian population regarding second line ART. Therefore, the present study was undertaken to evaluate prescription pattern during second line ART at tertiary care hospital.

METHOD

Patients selected on the basis of inclusion and exclusion criteria were explained in detail about this study. Written informed consent of all the patients was obtained before enrollment into the study as participant. Patients were explained about the nature of HIV infection, importance of ART and adherence to ART during treatment.

In our ART plus centre antiretroviral therapy is usually provided for 30 days. The patient had to come after 30 days of last visit to refill antiretroviral therapy for next month. At each encounter patient has to consult physician in charge of the ART plus centre. Line of management, ART and other drug prescription was carried out by physician. Patient coming for follow up before monthly interval either because of adverse events or any other health related condition; follow up data was recorded for that. After consultation with physician of ART plus centre, patient was interviewed and details of patient's case record was obtained. At each encounter opportunistic infections, adherence level, associated medical conditions, second line ART and other drug prescription was recorded in preformed case record form for the study.

Statistical analysis

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Recorded data was analyzed by Microsoft Office Excel 2013 and software Graphpad prism 6.

Normal distribution of study data was analyzed using D'Agostino - pearson omnibus test.

RESULTS

In this study, based on inclusion and exclusion criteria, total of 70 patients were enrolled during the study period. Out of these 70 enrolled patients, 63 patients were completed six months of second line ART. A 7 patients did not complete six months of treatment at ART plus center because either they were died or lost to follow up before completion of 6 months second line ART. Hence, further analysis was carried out on these 63 patients' data.

Out of 70 patients, majority of the patients were male [75.71%] as compared to female [24.29%]. Most common age group [50%] was 37-55 years. Mean age of patients was 38.58 ± 9.20 [mean \pm SD] years. Age and gender and distribution of the study participants were summarized in Figure 1. Out of 70 patients, 8 were smoker while 9 and 4 patients had habit of consume tobacco chewing and alcohol respectively.

A total of 44.29% patients suffering from AIDS were educated up to primary level while 14.29% patients were illiterate (Table 1) and marital status of patients of the study participants were summarized in Table 2. Distribution of the patients based on duration of first line ART was summarized in Table 3. Total of 54 patients had started second line ART from government ART plus center. While 16 patients [22.86%] had started their second line ART in private and then they were either referred or transferred to government ART plus center. Distribution of the patients based on duration of second line ART was summarized in Table 4. Treatment substitutions [within second line ART regimens] and treatment hold and restart summarized in Table 5 and 6 respectively. Distribution of patients according level of adherence to second line art presented in Table 7.

Out of 70 patients, 42 patients [71.42%] were initiated and 20 patients [28.57%] were not initiated co-trimoxazole prophylaxis at start of ART. In spite of starting co-trimoxazole prophylaxis at start of treatment there were 42 [80.76%] incidences of opportunistic infections (Table 8). Most common opportunistic infection recorded was ARI [recurrent respiratory infection] with 28.84%.

DISCUSSION

In this study, among 70 enrolled patients having HIV, majority [92.86%] were falling in age group of 18-55 years [Figure 1]. This is in concordance with other study performed in India which showed 89.3% of study population was of age group 20-50 years.⁵ HIV/AIDS is a disease of reproductive age, as evident from the HIV prevalence being higher [86%] in the age group of 15-49 years.⁴ In this study mean age of study population was 38.58 ± 9.20 [mean \pm SD] years that is again in concordance with study of Jimenez-Nacher *et al* with mean age of 35 ± 7 [mean \pm SD] years.⁶ In this study most common age group was 37-55 years. Male [49.05%] and female [52.94%] were in almost equal proportion in this age group

In this study majority, 75.80% of the patients were males while only 24.20% were females. Our findings correlate with two other studies conducted in India which observed 78% male patients.⁷ However, national data shows that 61% of the total HIV infected patients are male, which is lower than observed in our study [NACO annual report, 2013-14]. Males are more likely to be infected by HIV because of the greater likelihood of being indulged in promiscuous activities.

In this study, majority, 85.71% of the study population was literate. [Table 1] 44.29% of the patients were educated up to primary level. This was in

concordance with other study in Indian population in which 41.2% patients were educated up to primary level.⁵ A similar trend was observed in other epidemiological studies.^{8,9} In this study, illiteracy rate was almost thrice among female patients [29.41%] in comparison to male patients [9.44%]. However, the recently observed changing trend for new HIV infection is more towards less educated groups.^{9,10} Education is important for HIV care, regular clinical visits and better understanding of importance of adherence to ART.

In this study 88.57% [n=62] of the patients were married while 11.42% were single. Out of 88.57 % of married patients 66.57% [n=46] were male. Since majority of patients were married, husband to wife transmission was common among spouses. The problem becomes even worse in a nuclear family where both husband and wife are HIV positive, it has been estimated that the average cost of treatment in the low-income population is 49% of total household income for a single HIV positive

Table 1: Distribution of education status and adherence level in patients who completed six months of second line art.

Education status	Male [% of total males]	Female [% of total female]	Total [% of total patients]
Illiterate	5[9.44%]	5[29.41%]	10[14.29%]
Primary	27[50.94%]	4[23.53%]	31[44.29%]
Secondary	19[35.84%]	7[41.17%]	26[37.14%]
College	2[3.78%]	1[5.89%]	3[4.28%]
Total	53	17	70

Majority of the patients [n=60] had their mean adherence level >95%.

Table 2: Marital status of patients.

Education status [n=63]	Adherence Level Of Patients [Mean %]		
	<80%	80-95%	>95%
Illiterate [n=10]	0	1	9
Primary[n=26]	0	1	25
Secondary[n=24]	0	1	23
College[n=3]	0	0	3
Total	0	3	60

88.57% [n=62] of patients were married in this study. Out of 88.57 % of married patients 66.57% [n=46] were male

Table 3: Distribution of the patients based on duration of first line art.

Duration	No. of patients [n=70]	Percentage of total
<2 years	18	25.72
2-4 years	19	27.14
4-6 years	17	24.28
6-8 years	8	11.42
>8 years	2	2.86
Data not available	6	8.58
Total	70	100

patient which may reach as high as 81% in advanced stage of disease. Thus, this can cause a great financial burden on a family having more than one HIV positive member.

In this study 11.42 % of the subjects were smokers while 12.85% had habit of chewing tobacco. Four patients [5.71%] were habitual or social alcoholics. Several studies were done which shows heavy smoking may predispose to, or increase the risk of OIs in the respiratory tract, and alcohol drinking may hasten disease progression, compromise treatment adherence and may also increase the risk of drug induced hepatotoxicity, the morbidity and mortality rate may be higher in the presence of these habits.^{11,12,13,14}

In this study, Out of 70 patients, 16 [22.86%] had history of 2nd line ART from Private ART clinics and 54 [77.14%] patients were transferred from other government ART centers. Successful long-term treatment of HIV/AIDS requires at least 95% adherence to HAART in order to prevent emergence of drug-resistant HIV variants that lead to regimen failure and limit options for future therapy. Drug cost is a major reason for discontinuation of HAART.¹⁵ This is particularly important in developing countries like India. The second line ART costs nearly Rs.32, 000 per patient per year as compared to Rs.5000 for first line ART per patient per year,¹⁶ this much cost of HAART may not be afforded by many Indian patients in private ART clinics.

Table 4: Utilization pattern of second line art regimens.

ART regimen	No of patients [n=70]	Percentage of total patients	No. of encounters with ART prescription	Percentage of total encounters
TDF+3TC+ATV/r	45	64.29	264	66.49
D4T+3TC+ATV/r	15	21.42	75	18.89
AZT+3TC+ATV/r	6	8.57	34	8.56
AZT+3TC+LPV/r	2	2.86	12	3.022
ABC+3TC+ATV/r	2	2.86	12	3.022
Total	70	100	397	100

TDF- Tenofovir; D4T- Stavudine; AZT- Zedovudine; 3TC- Lamivudine; ABC-Abacavir, ATV/r- Atazanavir/Ritonavir LPV/r-Lopinavir/Ritonavir

Table 5: Treatment substitutions [within second line ART regimens].

2 nd line ART regimen before substitution	Specified reason for substitution	Number of substitutions [n=4]	2 nd line ART regimen after substitution
AZT+3TC+ATV/r	Anemia	1	D4T+3TC+ATV/r
TDF+3TC+ATV/r	Hyperbilirubinaemia	2	TDF+3TC+LPV/r
D4T+3TC+ATV/R	Lactic acidosis	1	ABC+3TC+ATV/R

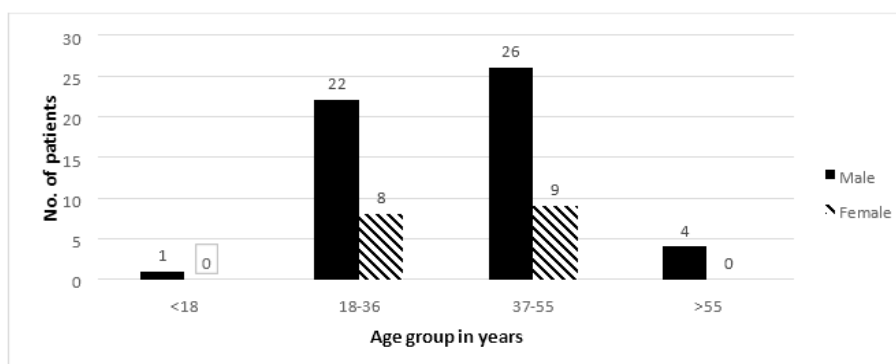


Figure 1: Age and gender distribution of study participants.

Table 6: Treatment hold and restart.

2 nd line ART regimen hold	Reason for treatment hold	Number of treatment hold [n=1]	Regimen at restart of treatment
AZT+3TC+ATV/R	hyperbilirubinaemia	1	AZT+3TC+ATV/R

Successful long-term treatment of HIV/AIDS requires at least 95% adherence to HAART in order to prevent emergence of drug-resistant HIV variants that lead to regimen failure and limit options for future therapy. The barriers to adherence observed in HIV treatment resemble barriers to the successful treatment of other chronic diseases: regimen complexity, side effects resulting in poor tolerability, patient lifestyle factors, and patient-provider relationships.¹⁷

In this study, 52.86% of patients were initiated second line ART within 4 years after starting first line ART. Mean time to switching from first line to second line ART was 3.67±2.29 years in 63 patients.

While mean time between confirmed HIV diagnosis and start of second line ART was 4.27±2.84 years in 70 patients. This type of study was done, which shows median time to switching from first line to second line was 1.81 years in 236 patients from programmers with viral load monitoring.¹⁸ Another study which was done in India shows similar results to our study. In which the mean duration of treatment with first line ART was 3.15±1.15 years.³⁰ The durability of first line regimen delays the treatment failure and account for late requirement of second line ART. Major reasons for switching was due to treatment failure, toxicity, adverse drug reactions and poor adherence to first line ART which develops resistance. Our study observed that the average duration of first line ART treatment was higher as compared to other studies.[Table 9] Probably this may be due to an effective first line ART regimen along with good compliance or this may be due to genetic variation according to study population across the world which can give different responses to first line ART.

Out of 70 patients 16 patients had started second line ART at private hospitals. According to NACO, experience had shown that the private sector concurrently uses second-line ART drugs, such as abacavir and PIs as first line, and this has resulted in a cohort of non-naïve treatment experience patients.²² Second line ART was started in some patients without following NACO guidelines by various private hospitals with a view to achieve rapid clinical improvement. Few patients were given drug regimens which include both first and second line ART in private hospitals. In such cases second line ART was continued by ART plus center to prevent treatment failure and resistance to drug regimens. Such irrational practice by private hospitals limits treatment options with increasing the chances of drug resistance and mortality. All these factors increases the prevalence of second line ART patients in society.

In this study, 5 second line ART regimens were used. Most common ART regimen prescribed at the initiation of ART was TDF+3TC+ATV/r in 64.29% patients [Table 4]. This is in accordance with the National guideline which recommends TDF+3TC+ATV/r should be preferred as first choice ART regimen.²²

According to NACO, second-line regimens should include at least three active drugs; one of them from a new class, in order to increase the likelihood of the success of the treatment and to minimize the risk of cross-resistance. The PI class should be reserved for second-line treatments. If AZT is used in first-line, NRTI choices in second-line could be TDF. If TDF is used in first-line, NRTI choices could be AZT. If both TDF and AZT can't be used, the last option is d4T. Thai national guidelines for antiretroviral therapy also suggest that zidovudine [AZT] or Tenofovir [TDF] in combination with lamivudine [3TC] is recommended as the preferred NRTI backbone.²³ A multi country survey by the WHO found highly variable rates of switching to second-line regimens.²⁴ It seems unlikely that this variability is explained by differences in primary resistance to NRTIs or NNRTIs. In another study which was held in Cambodia includes 70 patients, shows that the most frequent second-line regimen used was ddI+3TC+LPV/r [n = 46, 65.7%]. Some patients had to be switched to ddI+TDF+LPV/r [n=7, 10.0%]. The remaining patients were switched to TDF+3TC+LPV/r [n=5, 7.1%], ddI+AZT+LPV/r [n = 6, 8.6%] or AZT+3TC+LPV/r [n = 2, 2.9%]. So, which regimen should

Table 7 : Distribution of patients according level of adherence to second line art.

Level of adherence	No. of encounters [n=397]	Percentage
>95%	359	90.42
80-95%	24	6.04
<80%	3	0.75
Bottle not borrowed	11	2.77

>95%: <3 doses missed in a period of 30 days; 80-95%: 3-12 doses missed in a period of 30 days and <80%: >12 doses missed in a period of 30 days

Table 8: Incidence of opportunistic infections during study period.

Opportunistic infection	Incidence [n=52]	Percentage incidence
ARI [recurrent respiratory infection] with	15	28.84
Pruritic papular eruptions	7	13.46
Diarrhoea	7	13.46
Candidiasis	6	11.53
Extra pulmonary TB	3	5.76
UTI	3	5.76
Scabies	2	3.84
Pulmonary TB	2	3.84
Sexually transmitted disease	1	1.92
CMV retinitis	1	1.92
Herpes labialis	1	1.92
Herpes zoster	1	1.92
Perianal dermatitis	1	1.92
Cryptococcal meningitis	1	1.92
CSOM	1	1.92

be use in second line ART depends on the drugs used in first line ART, which can be differ according to genetic variability in HIV prevalent population worldwide. (For drug abbreviations kindly find Table 4)

In this study, most common cause for substituting/hold 2nd line ART regimen was adverse events, recorded in five patients [Table 5(A)(B)]. Out of five patients 2 were substituted from their regimen due to hyperbilirubinemia while in two patients the cause were anemia and lactic acidosis respectively for substitution. One study done in India, which shows 203 patients [16.2%] developed anemia out of 1256 in which zidovudine was initiated.²⁵ The high incidence of Anaemia mandates close monitoring of patients receiving second line ART. Another study of 250

Table 9: Comparison of Average duration of first line ART [months] in different studies across India, South-east Asia, Africa and MSF countries.

Country	India	Thailand	South Africa	Cambodia	Me´decins Sans Frontie`res countries
Study	Present Study [n=70]	Sungkanupa -ph S et al., 2007 ^[18] [n = 98]	Fox MP et al., 2010 ^[19] [n=328]	Ferradini L et al., 2011 ^[20] [n = 70]	Pujades-Rodri´guez M et al., 2008 ^[21] [n = 370]
Average duration on first lineART [months]	44.04	20	15.6	26.6	19.8

patients shows, 41% [n=102] developed hyperbilirubinemia due to Atazanavir,²⁶ which was comparable to 67% in Rotger M *et al* study²⁷ and 44% in Castle study.²⁸

High-level adherence to antiretroviral therapy is associated with favorable patient outcomes.²⁹ In this study, in majority [90.42%] of encounters, >95% adherence level was reported. [Table 6]. In another clinical study, adherence level of optimal [95-100%], suboptimal [80-94%] and poor [<80%] was recorded with incidence of 62.9%, 28.3% and 8.8% patients respectively. Poor [<80%] adherence was associated with poor clinical and immunologic response among individuals in this group.²⁹ A meta-analysis of various second-line ART treatment studies have established the correlation between adherence and successful treatment outcome measured in terms of virological suppression. This meta-analysis showed that adherence of less than 80% is associated with significantly higher treatment failure rates [383.5/1000 person-years] compared to those with an adherence of more than 95% [176/1000 person years [P< 0.001].³⁰ The success of any adherence strategy depends on the education of patients before the initiation of ART, an assessment of their understanding of the therapy, and their readiness for treatment.³¹ In our study as shown in Table II majority of the patients were educated who had their mean adherence level >95% [n=60]. Majority of patients were educated up to primary level [n=25] followed by secondary level [n=23].

Co-trimoxazole should be implemented as an integral component of the HIV chronic care package and as a key element of pre antiretroviral therapy care. Co-trimoxazole prophylaxis needs to continue after antiretroviral therapy is initiated until there is evidence of immune recovery.³² Co-trimoxazole reduced mortality and the incidence of severe HIV related illnesses in patients with evidence of advanced immune suppression on clinical [WHO stages 3 and 4] or laboratory assessment of CD4 count <250 cells/mm³.³³

In this study, co-trimoxazole prophylaxis was initiated in 71.42 % patients at the time of initiation of ART. Major cause for not initiating co-trimoxazole prophylaxis was past history of allergic/hypersensitivity reactions to co-trimoxazole. In 28.57% patients' cotrimoxazole was not initiated. Other studies have reported similar pattern of drug therapy for OIs which mainly included co-trimoxazole [therapeutic dose for PCP] and other antibiotics depending upon the type of infections.^{34,35,36} In spite of starting co-trimoxazole prophylaxis at start of treatment there were 42 [80.76%] incidences of OIs in these patients during 6 months of treatment which made role of co-trimoxazole questionable.

Human Immunodeficiency viruses are the initial causative agents in AIDS, but most of the morbidity and mortality in AIDS cases result from opportunistic infections. Identification of such pathogen is very important for clinicians and health planners to tackle the AIDS epidemic in more effective manner.³⁷ HIV causes progressive decrease in immunity making the host vulnerable to number of infectious agents that increase

morbidity and mortality in HIV positive individuals. In this study, most common opportunistic infection recorded was ARI [recurrent respiratory tract infection] with 28.54% incidence. [Table 7]

Other studies carried out in India showed that pulmonary tuberculosis was the most common observed AIDS-defining illness.^{38,39} In another study oral candidiasis [59%] was found to be the most common opportunistic infection, followed by tuberculosis [56%], Cryptosporidium infection [47%].³⁷ Timely diagnosis of TB co-infection is crucial. HIV and Mycobacterium tuberculosis have a synergistic interaction; each accentuates progression of the other. The mortality of HIV-infected patients with TB is comparatively higher than that of HIV-negative TB patients. Anti-tuberculosis treatment is complicated by frequent drug-interactions with HAART and adverse drug reactions are more common among HIV-infected patients.⁴⁰

Limitations of the study

However, like any other study, there were few limitations.

First, it was an observational, single centre study.

Second, the patients were observed for 6 months. Considering the life-long treatment of ART, long term follow up is necessary.

CONCLUSION

So, the conclusion of this study is that mean time to switching from first line to second line ART was 3.67±2.29 years in 63 patients. Irrational practice by private hospitals limits treatment options with increasing the chances of drug resistance. On the other hand NACO sponsored second line ART was given with a proper treatment protocol which also causes good compliance in patients.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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