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Original Article

Pharmacology Section

Modification of First-line Antiretroviral Therapy in Treatment-naive, HIV Positive Patients

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ABSTRACT

Introduction: Modification of initial Antiretroviral Therapy (ART) program is an important issue in HIV infected patients as the number of ART regimens available is limited. Hence, there is a need to understand the factors that affect modification and therefore, the durability of the initial antiretroviral regimen.

Aim: To study the type of modification of first line ART in treatment-naive HIV positive patients and factors influencing it.

Materials and Methods: A retrospective observational study was carried out in the HIV clinic of a tertiary care hospital, using data obtained from the case records of the subjects who were initiated on ART between January 2012 to December 2014. Data on patient baseline characteristics, proportion of patients who required modification, type and time of modification was collected. The determinants of time to modification were analysed using Chi-square test. Binomial logistic regression was utilized to assess independent risk factors for change in regimen.

Results: Out of 200 case records analysed, 54 patients had to undergo a modification in their initial regimen. The mean age of patients was 44.68 ± 11.31 years. Majority of the patients were males. The most common reason for modification was Adverse Drug Reactions (ADRs) (79.63%) followed by treatment failure (9.25%). In 85.18% cases, modification involved substitution. Occurrence of ADRs and non-tenofovir based first-line regimens were associated with higher likelihood of substitution in regimen ($p<0.05$). The median time (IQR) to modification was 173 (152.25, 293.50) days.

Conclusion: ADRs and the use of non-tenofovir based regimens resulted in significantly higher rates of modification of antiretroviral therapy. There should be monitoring of patients on ART to detect ADRs at the earliest and to obtain increased use of single tablet containing tenofovir based regimen to improve durability of first line regimens.

Keywords: Adverse drug reactions, AIDS, Durability, Tenofovir

INTRODUCTION

The ART program of the Government of India in 2004 was an important step in the fight against Acquired Immuno-Deficiency Syndrome (AIDS). Over the past few years, efforts have been made to increase access of HIV positive patients to ART [1]. The currently used classes of drugs inhibit replication of virus, reduce morbidity and mortality, improve immunity and quality of life [2].

An important issue after start of ART in a treatment-naive patient is modification in the regimen [3]. The change in ART could range from substituting a drug in a regimen to changing the entire regimen [3]. As per NACO guidelines, change of entire regimen from first to second line (switch) is done in treatment failure. It is diagnosed by clinical and/or immunological criteria and confirmed by virological testing. Substitution refers to change in a drug due to toxicity or drug interactions. If toxicity is mild, treatment is symptomatic and patient is monitored. If it is moderate to severe, a change in drug is needed [3].

The durability of initial ART regimen is important as number of ART regimens available is limited [4]. The duration of initial ART regimen can be affected by Adverse Drug Reactions (ADRs), opportunistic infections, comorbidities, treatment failure, cost and patient compliance. Therefore, it is essential to recognize and modify factors that can have an impact on the duration of the initial ART regimen at the earliest to obtain increase in durability and better treatment outcome.

The aim of present study was to describe the type of modification of ART within 12 months of treatment initiation in treatment-naive HIV positive patients and factors associated with it.

MATERIALS AND METHODS

Following approval from the Institutional ethics committee, a retrospective observational study was done. It was conducted at HIV clinic and medical records section of the tertiary care hospital.

Inclusion criteria: Adult HIV positive patients who were initiated on first line ART between January 2012 and December 2014 were included in the study.

Exclusion criteria: HIV positive treatment-naive pregnant women initiated on ART during the above specified period.

Follow up: Follow up time started at initiation of ART. The study endpoint was time until either: (i) modification; (ii) completion of 12 months of therapy whichever was earliest [4].

Data collection: The case records of the selected patients were studied. No personal identification details were collected. All collected data was kept confidential. The following data was collected - age, gender, baseline haemoglobin (Hb), weight andCD4 count, WHO stage at start of therapy, initiated ART regimen, reason for modification of treatment, coexisting diseases which caused modification in ART, HIV RNA load (if available), ADRs which resulted in ART modification, modifications made- substitution/switch to second line regimen, date of modification, and relevant laboratory data.

STATISTICAL ANALYSIS

Independent t-test was used to compare mean baseline age, weight and haemoglobin and Mann-Whitney U test for median CD4 count values between tenofovir and non-tenofovir based regimens. Factors assessed were age at start of treatment, gender, baseline

weight, haemoglobin, CD4 count, ART regimen, opportunistic infections and ADRs. Association between factors and modification was done using Chi-square test. A binomial logistic regression was used to identify independent risk factors for change in regimen.

RESULTS

Demographic Data

A total of 202 case records were assessed. Out of these, two patients did not come for follow up after ART initiation. So, they were excluded from analysis. Hence, case records of 200 patients were studied, of which 152 were males and 48 were females. The mean age of patients was 44.68± 11.31 years.

Modification in Treatment

Out of 200 patients, 54 (27%) had a modification in treatment regimen. Of these, 40 were males and 14 females. In 46 cases, modification involved substitution whereas in the remaining eight, there was a change of entire regimen. It was most common (30 patients) in the age group 31-45 years followed by 20 patients over 45 years of age. Rest was in the age group of less than 30 years.

Causes for Treatment Modification

The reasons for modification of ART were ADRs – 43 (79.62%); treatment failure – 5 (9.25%); physician decision due to patient non compliance- 3 (5.55%) and comorbidities (tuberculosis) –3 (5.55%).

ART Regimens Used

Overall, non-tenofovir based regimens were prescribed in 108 (54%) patients and tenofovir based regimens in 92 (46%) patients [Table/Fig-1]. Non tenofovir based ART included zidovudine (AZT) or stavudine-based regimens.

Time for First Modification of ART

Overall, the median (interquartile range, IQR; 25th, 75th percentile) time for modification was 173 (152.25,293.50) days. The median (IQR) time required for substitution in ART due to ADRs was 175 (170,341) days. It was 340 (172.50, 351) days due to treatment failure.

Determinants of Time to Modification

This is shown in [Table/Fig-2]. The time to modification was taken as within 6 months and between 6-12 months. Age, gender, baseline haemoglobin, weight, CD4 count and regimen did not show significant relation with time to modification.

Tenofovir and Non-tenofovir Based Regimens

There was no significant difference in baseline characteristics between tenofovir and non tenofovir based regimens [Table/Fig-3]. Comparison with WHO clinical stage could not be done as data was missing in lot of cases.

Adverse drug reactions

The ADRs causing modification in ART are shown in [Table/Fig-4]. A total of 43 ADRs resulted in modification of treatment. The suspect drugs for ADRs included Zidovudine, Stavudine, Tenofovir, Nevirapine and Efavirenz. Zidovudine induced anamia was the most common ADR. Central Nervous System (CNS) side effects of Efavirenz included sleep disturbances.

Mortality

There was no mortality; 2 patients were lost to follow-up following treatment initiation and they were not considered in this study analysis.

Gender wise distribution of change in regimen was studied. No statistical difference was seen between the groups [Table/Fig-5]. Change in regimen was analysed against whether patients had ADR or not. Occurrence of ADR was significantly associated with change in regimen [Table/Fig-6]. Out of the 200 patients in the study, 184 had

First line regimens	Total number of patients (n=200)	Number of patients requiring modification (n=54)
Zidovudine + Lamivudine + Nevirapine	59	16
Stavudine + Lamivudine + Nevirapine	20	17
Tenofovir + Emtricitabine + Efavirenz	70	11
Zidovudine + Lamivudine + Efavirenz	15	4
Tenofovir + Lamivudine + Efavirenz	16	2
Stavudine + Lamivudine + Efavirenz	9	2
Tenofovir + Lamivudine + Nevirapine	6	1
Didanosine + Lamivudine + Nevirapine	1	1
Stavudine + Lamivudine + Darunavir/Ritonavir	1	-
Zidovudine + Lamivudine + Emtricitabine	3	-

[Table/Fig-1]: Regimen wise distribution of ART modification.

Determinants	< 6 months (31 modifications)	6 – 12 months (23 modifications)	p-value*
Age (years) (Mean±SEM)	44.37 ± 12.43	44.04 ± 10.89	0.920
Gender	Male: 25, Female: 6	Male: 15, Female: 8	0.201
Baseline haemoglobin (g/dL) (Mean±SEM)	10.11± 1.86	10.96 ± 1.66	0.259
Baseline weight (kg) (Mean±SEM)	53.59 ± 10.24	53.49 ± 7.60	0.970
Baseline CD4, cells/mm^3 Median(IQR)	53 (32, 92)	72 (42, 111)	0.230
Zidovudine + Lamivudine + Nevirapine	14	2	p>0.05**
Stavudine + Lamivudine + Nevirapine	9	8	
Zidovudine + Lamivudine + Efavirenz	2	2	
Stavudine + Lamivudine + Efavirenz	-	2	
Didanosine + Lamivudine + Nevirapine	1	-	
Tenofovir + Emtricitabine + Efavirenz	5	6	
Tenofovir + Lamivudine + Efavirenz	-	2	
Tenofovir + Lamivudine + Nevirapine	-	1	

[Table/Fig-2]: Determinants of time to first modification of antiretroviral therapy.
*Chi-square test.
**Chi-square test for regimen (tenofovir/non-tenofovir) as determinant for time to modification.

Parameters	Tenofovir based	Non tenofovir based	p-value
Age (years) (Mean±SEM)	44.15 ± 11.46	45.14 ± 11.23	0.540*
Gender	Male: 72 Female:20	Male: 80 Female: 28	0.490***
Baseline weight (kg) (Mean±SEM)	52.63 ± 8.57	54.19 ± 9.30	0.221*
Baseline haemoglobin (g/dL) (Mean±SEM)	11.01 ± 2.26	10.81 ± 1.94	0.187*
Baseline CD4 (cells/ mm^3) Median (IQR)	58.50 (28,84.25)	65.5 (42, 94)	0.138**
Opportunistic infections	82	102	0.167***

[Table/Fig-3]: Comparison of baseline characteristics between tenofovir and non-tenofovir based regimens.
*Independent t-test; ** Mann Whitney test; *** Chi-square test.

Adverse drug reactions	Number of patients (suspect drug)
Anaemia	10 (Zidovudine)
Rash	5 (Nevirapine)
Peripheral neuropathy	6 (Stavudine)
Hepatotoxicity	5 (Nevirapine)
Lipodystrophy	5 (Stavudine)
Renal dysfunction	3 (Tenofovir)
Gastrointestinal intolerance	1 (Zidovudine)
Pancreatitis	3 (Stavudine)
Lactic acidosis	1 (Zidovudine)
CNS side effects	4 (Efavirenz)

[Table/Fig-4]: Occurrence of various Adverse Drug Reactions (ADRs) and the suspect drugs.

Chi-square	Male	Female	Total
Change in regimen	40	14	54
No change in regimen	112	34	146
Total	152	48	200

[Table/Fig-5]: Cross tabulation of change in regimen versus gender. $\chi^2 = 0.150$ and $p = 0.698$.

Chi-square	With ADR	Without ADR	Total
Change in regimen	43	11	54
No change in regimen	38	108	146
Total	81	119	200

[Table/Fig-6]: Cross tabulation of change in regimen versus Adverse Drug Reaction (ADR). $\chi^2 = 47$ and $p<0.001$.

Chi-square	With OI	Without OI	Total
Change in regimen	51	3	54
No change in regimen	133	13	146
Total	184	16	200

[Table/Fig-7]: Cross tabulation of change in regimen versus Opportunistic Infection (OI) $\chi^2 = 0.601$ and $p = 0.438$.

Chi-square	CD4<100 cells / mm^3	CD4≥100 cells / mm^3	Total
Change in regimen	44	10	54
No change in regimen	126	20	146
Total	170	30	200

[Table/Fig-8]: Cross tabulation of change in regimen versus baseline CD4 range. $\chi^2 = 0.718$ and $p = 0.397$

Chi-square	Tenofovir based	Non tenofovir based	Total
Change in regimen	14	40	54
No change in regimen	78	68	146
Total	92	108	200

[Table/Fig-9]: Tenofovir and non-tenofovir based regimens vs change in regimen. $\chi^2 = 12$ and $p = 0.001$

Opportunistic Infections (OIs) whereas16 had no OIs. Occurrence of change in regimen was analysed against whether the patients had opportunistic infections or not. There was no significant difference between the two groups [Table/Fig-7]. There was no significant difference between baselines CD4 ranges versus change in regimen [Table/Fig-8].

Non tenofovir based regimen was significantly associated with change in regimen. A change in regimen was less common with tenofovir based regimens than non tenofovir regimens [Table/Fig-9].

Binomial Logistic Regression to Assess Risk Factors

The effect of age, gender, OIs, baseline haemoglobin, weight, CD4 count, ADRs and first line regimen on modification of ART was evaluated using binomial logistic regression. Occurrence of ADR and non-tenofovir based first-line regimens were associated with higher likelihood of modification in regimen ($p<0.05$). The logistic regression model was statistically significant $\chi^2= 53.073$ and $p< 0.05$ in predicting likelihood of modification.

DISCUSSION

The study was carried out to assess the type and factors determining modification in ART following its initiation in treatment-naive patients in a tertiary care hospital.

The age of patients enrolled on ART in the studies in India have ranged from 30-40 years, which was similar to studies reported from African countries [4]. The mean age of patients in our study was 44.68±11.31 years, which is higher than other studies where patients were in their early thirties. This could probably reflect the delay in start of ART which could be due to delayed diagnosis or patient's reluctance for treatment. Age was not associated with treatment modification in many studies. In a Brazil study, toxicity-related modifications within one year of initiation of ART showed a trend of increase with age, though it was not statistically significant [5]. In a Kenya study, there was an increased likelihood of modification in the older population. Another study in Nigeria reported lower risk in patients of more than 35 years [6,7]. But we did not find any relation between age and likelihood of modification in this study. This could be due to the small sample size.

Gender was not a risk factor for modification in this study. Similar findings have been reported from another study in Southern India [8]. In African countries, female to male ratio showed a slight female preponderance. This may be due to the large percentage of infected females in this region [4].

Tenofovir based regimens were commonly prescribed followed by Zidovudine and Stavudine in our study. A similar finding was observed in other studies in India [9]. Studies have shown that Stavudine and zidovudine based regimens were more frequently associated with modifications, unlike Tenofovir based regimens [10].

Most of the studies have reported ADRs to be the most common cause for ART modification. Gastrointestinal disturbances were the commonest side effect (28.9%), followed by hypersensitivity (18.3%), CNS effects and hepatotoxicity (11.5%) in an European study. Efavirenz therapy was changed due to CNS effects (44.4%) and nevirapine due to hypersensitivity reaction (40.7%). Drug-related toxicity was less with Tenofovir than Zidovudine-based regimens [11]. In this study, ADRs were the most common cause (79.62%) for modification of ART, as seen in most other studies. They included anaemia, rash, gastrointestinal intolerance, lipodystrophy, peripheral neuropathy, pancreatitis, lactic acidosis, renal dysfunction, and sleep disturbances. Anaemia was the most common ADR responsible for treatment modification. Haemoglobin levels are routinely monitored in patients on Zidovudine to detect drug toxicity and to assess clinical response. Anaemia due to Zidovudine can occur at doses used for treatment– it is reversible on stoppage of therapy [12]. Zidovudine can cause gastrointestinal intolerance and lactic acidosis. Gastrointestinal tolerance rarely requires modification but if severe, it can affect compliance and needs modification. Studies in USA and Kenya have shown ART modification due to gastrointestinal disturbances [10,13]. Nevirapine was discontinued due to development of rash and hepatotoxicity. The former accounted for 9.25% of modification, unlike a study in Kenya where it accounted for 20% change in regimen of the cases. Few patients had both rash and elevated liver enzymes, which indicate that it was a hypersensitivity reaction [14]. Stavudine has been commonly prescribed because it is cheap and efficacious. But, in the NACO

guidelines, it is reserved for use in special circumstances [3]. Since the study involved patients who were started on ART before 2013, a fairly good number of patients in our study were on Stavudine. Lipodystrophy and peripheral neuropathy were the main side effects of Stavudine. In another study, incidence of peripheral neuropathy and prevalence of dystrophy were 6%-37% and 10%-80% respectively [15]. Studies have shown modification of therapy may prevent progression of lipodystrophy [10]. Adverse effects related to CNS like sleep disturbances were observed with Efavirenz-containing regimens, which resulted in treatment modification in our study. Various studies have evaluated side effects of Efavirenz and the resultant discontinuation of the drug. In these studies, psychiatric symptoms were reported in 25%-40% of patients receiving Efavirenz which was the main reason for modification of therapy [16,17]. In another study, Efavirenz induced sleep disturbances was the reason for its discontinuation in 75.2% patients [18].

Renal dysfunction due to Tenofovir counted for 5.55% of modifications in our study as compared to 12% in another study [10]. According to a meta-analysis of studies done prospectively, the renal dysfunction caused by Tenofovir may not have a significant impact on the patient's clinical condition [19]. Contrary to this, retrospective studies have reported that renal dysfunction due to Tenofovir, can affect treatment continuation [20].

Treatment failure was the next common reason (9.25%) for modification. This was also seen in a few studies conducted in Africa [10]. Though, all patients are asked to do viral load testing, very few patients actually do so because of the costs involved. Therefore, decision is based on clinical and immunological outcome. Treatment failure as a cause for modification was less as compared to other studies in India where it was 14% [21].

Opportunistic infections increase the number of medications for a patient which could also have a potential for drug-drug interactions. Initiation of antitubercular therapy led to treatment modification in our study with Nevirapine being substituted with Efavirenz, to prevent hepatotoxicity, as the patient would also be on Rifampicin. Though, this was the reason for modification in a small (three) number of patients in our study, comorbidities have been an important cause of modification in another study in India [22]. Presence of comorbidities like tuberculosis has contributed to treatment modification in India, Africa and the West. Pregnancy and Hepatitis B were other reasons for modification in other studies [10,11,22,23].

Cost was an important reason for modification in treatment in some Indian studies [21]. In this study, this was not observed. A few patients in our study were switched over to fixed dose combinations to improve compliance.

The median time to modification ranged from 40 days in India, to 8-11.8 months in USA. It was 40,151 and 406 days due to adverse effects, cost and treatment failure respectively in an Indian study [21]. The median time to treatment modification due to ADRs was slightly longer: 173 days in our study. In developed countries, it is even earlier [10]. In a study in Kenya, it was 28 months (overall), with 5 months for tuberculosis, 20 months for pregnancy, 30 months for toxicity and 34 months for treatment failure related modifications. The long period in Kenya is probably due to an inability of the patient to understand the adverse effect or failure of diagnosis by the physician [10,11,13,21,24].

LIMITATION

There were some limitations in our study. Data like WHO stage of disease was missing in some case records. Treatment failure was based on CD4 count (immunological failure). Risk factors for individual ADRs were not assessed. Also, the duration of follow up was only for a year.

CONCLUSION

Occurrence of ADRs and use of non-tenofovir based regimens were significantly associated with modification of initial ART. ADRs may resemble symptoms of the disease itself, which can make its identification difficult. So, the treating physician needs to be vigilant, and patients should be educated and counselled about ADRs. Moreover, increased use of tenofovir should be favoured to decrease risk of modification.

Further studies can be done to assess how modifications affect treatment outcome. A comparison can be made on durability of initial ART between patients treated at ART centre and a private tertiary hospital.

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