Immune Response to First Line HAART Therapy in A Tertiary Care Centre of Northern India

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ABSTRACT

Introduction: The prime aim of UNAIDS Treatment 2.0 initiative is to enhance effectiveness of HIV treatment through optimizing antiretroviral regimens for efficacy, simplicity of administration and reduced toxicity. This minimizes laboratory monitoring and enhances the efficiency of antiretroviral delivery. Thus primary goal of HAART therapy is reinstitution of immune response with safest toxicity profile. The aim of the present study was to evaluate the efficacy and toxicity profile of first line HAART in context of rendering quality treatment and patient care.

Material and methods: This study was conducted on patients taking first line HAART therapy, through the national AIDS control program of India. The study was conducted on 100 patients who were started on first-line ART between May-July 2013 at ART centre PGIMS Rohtak (Haryana).They were monitored for duration of six months, by recording various clinical and laboratory parameter regarding immune response and toxicity profile. The data collected was analyzed by appropriate statistical tests.

Results: The cohort of 100 patients was having mean age of 34.4 ± 10.1 years, consisting of 54 males and 46 females. The Mean Weight of the cohort was increased from 48.9 ± 10 Kg to 57 ± 10.7 Kg, Mean BMI increased from 22.2 ± 4 Kg/m^2 to 25.9 ± 4.3 Kg/m^2,and Mean haemoglobin increased from 10.6 ± 2 gm% to 12.8 ± 1.2 gm%, ($P < 0.0001$). The parameter of immune reinstitution, the mean CD4 count of the cohort was increased from 233.33±151 cells/cumm to 434.8 ± 217cells/cumm after six month of the treatment, ($P < 0.0001$). The side effects of HAART were reported in 70 % of the patients, The most common toxicity reported in our study was nausea and vomiting (59%),followed by Anaemia (15%), Hyperpigmenation (11%), Neurological (8%), Oral ulcers (10 %), Rash (9%), Peripheral neuropathy (4%), Hepatotoxicity (3%) which were generally self restricted or normalised after withdrawal of the causative agents.

Conclusion: The study demonstrated that first line HAART is efficacious and well tolerated.

Keywords: Immune Response, Haart Therapy

INTRODUCTION

The treatment of HIV is revolutionised in past two decades. This has lead to enormous decline in HIV related mortality and morbidity.[1] There are still challenges in the form of inherited and acquired resistance by the HIV virus. The global goal is to provide universal access to appropriate therapy to everyone living with HIV/AIDS.[2] The recognition of the related financial, social and technical obstacles in providing universal access therapy is the main obstacle in providing appropriate care. The UN agency responsible for HIV/AIDS (UNAIDS)in 2010 launched an ambitious proposal called Treatment 2.0, which aims to simplify the way HIV treatment is currently being provided. The core focuses of Treatment 2.0 are to simplify drug regimes for the treatment of HIV and to make it less toxic.[3,4] World Health Organization, in order to implement UNAIDS Treatment 2.0, currently recommends that antiretroviral regimens for the early treatment of HIV should include two nucleoside reverse transcriptase inhibitors and a non nucleoside reverse transcriptase inhibitor. The NRTIs in these regimens can comprise of zidovudine or tenofovir disoproxil fumarate [DF] with lamivudine or emtricitabine. The NNRTI component can be nevirapine (NVP) or efavirenz (EFV). This combination is also known as HAART (highly active antiretroviral treatment), a combination of effective drugs that attack the HIV virus in various mechanism.[4,5]

The nationwide ART programme was launched by the Government of India on 1st April 2004. As on March 2013, there were approximately 18.13 lakhs People living with HIV (PLHIV) registered at the 400 ART Centres functioning all around the country. The recent statistics suggests that nearly 6.5 lakhs patients are on first line ART. The first line HAART according to NACO guidelines consist of 2 NRTI + NNRTI regimen.[6] There are a number of new drugs that have been discovered in last decade. Therefore, the present study evaluated the efficacy and toxicity profile of first line HAART in context of rendering quality treatment and patient care. We, in the present study, followed and collected data of 100 patients who were given first line HAART according to NACO guidelines at PGIMS, Rohtak.

MATERIAL AND METHODS

The study was initiated after taking approval from the institutional ethics committee. Patients were explained about the study design and a written informed consent was obtained from all the study participants.

The study was conducted in the Department of Medicine/A. R. T. Centre, Pt. B.D. Sharma, Post Graduate Institute of Medical Sciences, Rohtak. The study group was selected from HIV positive patients attending A.R.T clinics and medicine O.P.D during the month of May-July 2013.The study group consisted of 100 patients, who were aged more than 18 years, eligible for the treatment according to NACO guidelines and were willing to participate in the study. Patient's demographic and personal details were recorded. Meticulous history including targeted general and systemic examination was taken. Also, any changes in weight, BMI, Haemoglobin, Platelets, Total Lymphocyte

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Counts, Blood Sugar, Lipid Profile and any possible side effects were assessed for immune response to HAART at baseline (initial visit) and every monthly thereafter for six months. All the data were recorded systematically. All drug modifications including initial doses, participant initiated, protocol mandated interruptions, substitutions, and permanent discontinuation and reasons for modification were assessed and documented at each visit.

STATISTICAL ANALYSIS

Data was collected, entered in the SPSS version 19 and analyzed using Paired t test.

RESULTS

The mean age of the study cohort was 34.4 ± 10.1 years. The study cohort comprised of 54 male patients and 46 female patients, of which, 14 patients were unmarried and 86 patients were married. Amongst them, partners of 74 patients were also reactive. The most common presenting symptom was fever (87%) followed by anorexia (59%), headache (47 %), Cutaneous infection (34 %), glandular enlargement (27 %), weight loss (23%), loose motions (21%), dysphagia (16%) and cough (15%). The most common clinical finding was pallor which was present in 29 patients followed by Lymphadenopathy which was present in 22 patients and oral candidiasis in 33 patients. The cohort had many patients with opportunistic infections such as oral candidiasis being most common in 33 patients and 4 patients were also found to be HbsAg positive. Tuberculosis was diagnosed in 17 patients who included 9 patients of pulmonary tuberculosis and 8 patients of extra pulmonary tuberculosis including 5 patients of lymph node tuberculosis, 2 patients of CNS and 1 patient of abdominal tuberculosis.

Treatment response

Patients were treated with the first line HAART therapy i.e. two NRTI and one NNRTI according to UNAIDS Treatment 2.0. Four regimens were designated as first line HAART according to NACO which includes ZLN, TLN, ZLE and TLE.[2] The numbers of Patients treated with ZLN were 59, ZLE were 12, TLN were 17, and TLE were 12 patients. At the end of six months, 91 patients remained in the study. ZLN was given to 50 patients, ZLE to 4 patients, TLN to 23 patients and TLE to 14 patients. The number of patients given PCP prophylaxis was 43 patients and MAC Prophylaxis was 8 patients at the initiation of study. After six months of therapy, their CD4 counts improved. Thus, at the end of six months, the number of patients given PCP prophylaxis and MAC prophylaxis reduced to 8 and 3 respectively.

The cohort was followed up for six months, during which eight patients died due to opportunistic infections and one patient was lost in the follow up. Hence, at the end of the study, ninety one patients remained in the cohort with complete follow up.

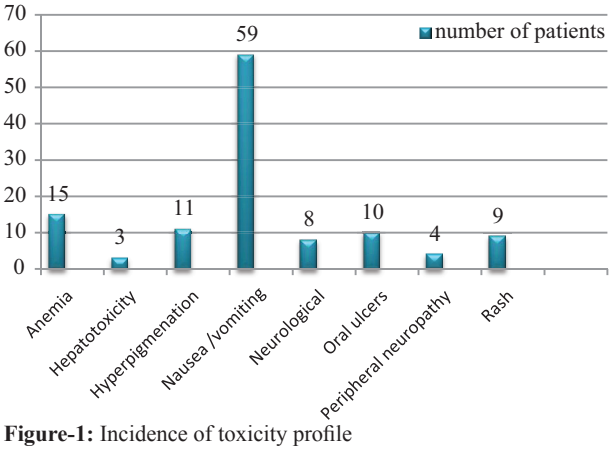

Figure-1: Incidence of toxicity profile

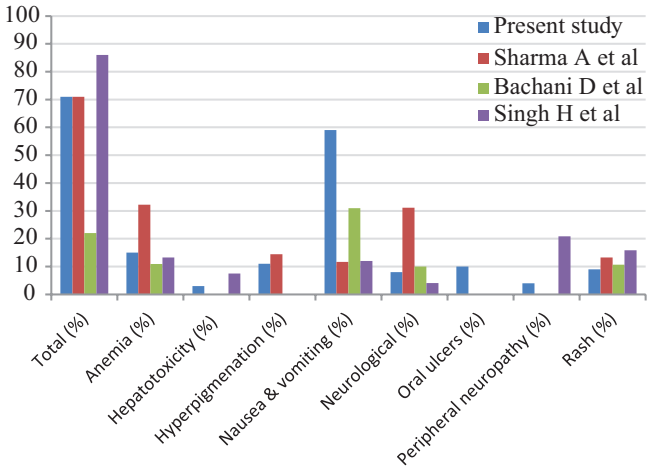

Figure-2: Comparison of toxicity profile with other similar studies

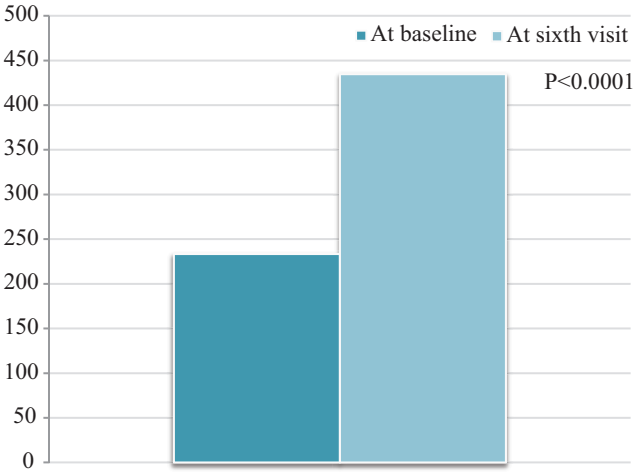

Figure-3: Comparison of CD4 count at baseline and at 6 months

Characteristics	At initiation	First visit	Second visit	Third visit	Fourth visit	Fifth visit	Sixth visit	P - value for baseline and six month
Haemoglobin (gm%)	10.6±2	10.6±1.9	10.6±1.2	11.3±1.5	11.6±1.4	12.1±1.3	12.8±1.2	<0.0001
Total Lymphocyte Count (cells/cumm)	785±291	909±247	954±323	943±286	833±240	980±252	862±217	0.213
Platelet (Lakh/cumm)	2.5±0.9	2.2±0.6	2.6±0.7	2.3±0.5	2.7±0.4	2.4±0.4	2.4± 0.7	0.25
Blood Sugar (mg %)	88.5 ±16	90 ± 13	90±15	89±11	93±11	92±11.7	86 ±11	0.868

Table-1: Comparison of various parameters at baseline and at subsequent visits

The cohorts parameters recorded at the end of study were mean weight which increased from 48.9 ± 10 Kg to 57 ± 10.7 kg, mean BMI which increased from 22.2 ± 4 Kg/m^2 to 25.9 ± 4.3 Kg/m^2 and mean haemoglobin which increased from 10.6 ± 2 gm% to 12.8 ± 1.2 gm% ($p < 0.0001$). Total Lymphocyte Counts increased whereas blood sugar and platelet counts decreased throughout the study duration ($p > 0.005$).

The mean CD4 count of the cohort was increased from 233.33±151 cells/cumm to 434.8 ± 217cells/cumm at six months ($p < 0.0001$). The number of patients in the group having CD4 count < 300 reduced eventually whereas it increased in groups having CD4 count > 300. The number of patients in group having CD4 count of 1-99 cells/cumm reduced from 14 to 3, with 100-199 cells/cumm from 29 to 8 and with 200-299 cells/cumm from 32 to 10. The number of patients with CD4 count range of 300-399 cells/cumm increased from 18 to 22, with 400-499 cells/cumm from 4 to 18 and with ≥ 500 cells/cumm from 3 to 30. The above observation showed that that the number of patients was elevated in higher CD4 count groups.

Toxicity profile

71 patients reported toxicity of at least one type in follow up period of six months among the cohort of 100 patients. Nausea and vomiting was the most common side effect with overall incidence in 59 patients. It was more in initial months of therapy, was found to be more often in patients having oral candidiasis and who were also taking ATT. It usually resolved with symptomatic treatment.

Patients reported easy fatigability and tiredness in first three months. Anaemia was identified in 15 patients on Zidovudine but their haemoglobin values improved in an average span of one to two months after changing the regimen. Anaemia was the most common indication for the change of regimen amongst all adverse drug reactions.

Skin rash was reported by 9 patients, who were on Nevirapine therapy. The toxicity was more in the initial months of therapy and it was self resolving with due course of time. Patients had severe skin reaction which led to a change of drug regimen to Efavirenz containing regimen in 3 patients.

Peripheral neuropathy was reported by 4 patients, which was more commonly seen after three months of therapy. There was no increase in severity during the follow up. Neurological side effects in the form of vivid dreams, headache and insomnia were reported by patients on Efavirenz. It was more in first two months of therapy and it was self resolving. Oral ulcers were seen in first and second months in 6 and 2 patients respectively followed by one patient each in third and fourth months of follow up and they were self resolving with supportive care.

DISCUSSION

Treatment response

The present study followed a cohort of one hundred patients with mean age of the cohort 34.4 ± 10.1years, of which 54 patients were male and 46 patients were female. A similar study was conducted by Bachani D et al[8] on 972 patients with the median age of 35 years and 66% male patients. In another study by Akinboro O.A et al[9] on 140 patients, the mean age of the study cohort was 35.00 ± 8.8 years comprising of 96 females and 44 male patients. These study cohorts were comparable with our study cohort except for the gender ratio and a low median CD4 count in the study cohort of Bachani et al.[8]

The mean weight in our study cohort raised from a baseline value of 48.9 ± 10 Kg to 57 ± 10.7 Kg in a duration of six months. This increase in mean weight by 7.9 kg was statistically significant ($p < 0.0001$). This finding is in harmony with the study by Bachani D et al[8] wherein they demonstrated a median weight gain of 6 kg and the study of Akinboro O.A[9] et al wherein there was a rise of 6.15 kg. This may be due to increased patient care and availability of effective prophylaxis in previous years.

The mean BMI increased from the baseline value of BMI 22.2± 4 Kg/m^2 to 25.9 ± 4.3 Kg/m^2 with an estimated mean rise of 3.7 Kg/m^2 ($P < 0.0001$). In a study conducted by Akinboro O.A et al,[9] baseline BMI of the patients was 20.65 ± 2.89 Kg/ m^2 and a mean rise of 2.34 Kg/ m^2 was observed. This increase was comparable in both the studies.

The mean haemoglobin also increased from baseline value of 10.6 ± 2 gm% to 12.8 ± 1.2 gm% with a rise of 1.1g % ($P < 0.0001$). The study by Bachani D et al[8] reported median baseline haemoglobin of 10.9 gm% and a median increase in haemoglobin of 2 g/dl which was comparable in both the studies.

The baseline Total Lymphocyte Count was 785 ± 291 cells/cumm which increased during six months to Total Lymphocyte Count of 862 ± 217 cells/cumm but the rise was not statistically significant ($p = 0.213$). F. I. Buseri et al[10] in their study of 273 patients concluded that total lymphocyte count was a strong predictor of CD4 counts. Our result was not able to attain any significant results regarding this aspect.

The mean CD4 count of the cohort increased from 233.33±151 cells/cumm to 434.8 ± 217 cells/cumm at six months. The mean CD4 count of cohort increased by 201.1 cells/cumm as compared to baseline CD4 count ($p < 0.0001$). The number of patients in various groups of CD4 count less than 300 reduced such as the group having CD4 count range of 1-99 cells/cumm from 14 to 3, group with 100-199 cells/cumm from 29 to 8, group with 200-299 cells/cumm from 32 to 10 whereas the number of patients raised in the groups of CD4 count of more than 300 such as CD4 count range of 300-399 cells/cumm from 18 to 22, 400-499 cells/cumm from 4 to 18 and ≥ 500 cells/cumm from 3 to 30. In a study by Bachani D et al.[8] median baseline median CD4 count was 119 cells/cumm and the median increase in CD4 count at 6 months after initiation of treatment was 142 cells/cumm. In another similar study done by Akinboro O.A et al[9] mean CD4 count of the cohort increased from 121.5 ±84.83 cells/cumm to 267.8±151.8 cells/cumm and the mean CD4 count increased by 144 cells/cumm. This increase was found to be more profound in the present study because of high baseline CD4 counts in the current study and a low threshold of ART initiation recently.

71 patients reported atleast one toxicity in six months duration in the cohort of our study. Bachani D et al[8] reported that 214 patients (22%) had one or more minor or major side-effects in their study of 972 patients. Sharma A et al[11] in their study of 90 patients have reported toxicity in 71.1 % patients while Singh H et al[12] reported toxicity incidence in 86% patients in their study. The study by bachani et al[3] reported relative low incidence that may be attributed to their study being retrospective compared to other studies which were rather prospective.

The most common toxicity reported in our study was nausea and vomiting with overall incidence of 59 % patients. Bachani D et al[8] also reported that most frequent adverse effects were diarrhoea and gastrointestinal complained by 31% of the patients. Sharma A et al[6] in their study reported gastrointestinal toxicity in 11.7 % of patients whereas Singh HP et al[12] in their study reported gastrointestinal toxicity in 12 % of their patients. Anaemia was seen in 15 % (15/100) patients and severe anaemia was observed in 11 (11/100) patients. Of all the toxicities noteworthy, severe anaemia was found to be the most common reason for HAART regimen modification. Bachani D, Garg R, Rewari B.B[8] et al had also observed anaemia in 10.9 % of the patients in their study. Sharma A, Vora R, Modi M[11] et al, in

their study reported anaemia in 32.2 % of the patients whereas Singh H, Dulhani N, Tiwari P[12] et al reported anaemia in 13.3 % of their study patients. In some studies like our study and Sharma et al, Zidovudine was used as preferred agent and hence, incidence of anaemia was more common in these studies. The increased incidence of anemia in our study may be attributed to increased use of Zidovudine in contrast to other studies which used Stavudine as a first line regimen. Nevertheless, it is now being withdrawn as first line agent due to occurrence of disabling peripheral neuropathy.

Hyperpigmentation was reported in 11 patients. Sharma A et al[11] also showed an overall incidence of 14.4% pigmentation which was comparable in both studies. Skin rash was reported by 9 % patients, of which 3 patients had severe skin reactions on Nevirapine therapy which were eventually shifted to Efavirenz containing regimens of HAART regimen modification. In the study by Bachani D et al[8] skin rash was reported in 10.7 % of the patients whereas Sharma A,Vora R, Modi M[6] et al reported skin rash in 13.3 % of the patients in their study and Singh H et al[12] reported skin rash in 15.83 % of the patients.

In our study, 8 % patients reported neurological side effects, 4 % patients reported peripheral neuropathy and 3 % patients reported hepatitis. Bachani D et al[8] also reported neurological side effects in 10% patients. Sharma A[11] et al reported neurological side effects in 31.1% patients while Singh H et al[12] noted peripheral neuropathy in 20.83%, hepatitis in 7.5 % and neurological side effects in 4.1 % of the patients.

CONCLUSION

The study showed that first line HAART therapy after six months of treatment leads to significant increase in mean weight, mean BMI, mean Haemoglobin and mean CD4 counts. The side effects of HAART are reported in 70 % of the patients, which are usually self resolving or reversed after withdrawing of the offending agents. Total lymphocyte count was not significantly rise with rise in CD4 counts. The study showed that first line HAART is efficacious and well tolerated. Since this study was carried out on only hundred patients, a study with larger number of patients is considered necessary to explore the exact efficacy and toxicity of first line HAART in HIV patients

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