

Original Article**Clinical profile and response to first-line anti-retroviral therapy in Human Immunodeficiency Virus infected patients in Manipur**Rao A¹, Singh NB², Ninsheng R³, Singh TB⁴

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ABSTRACT

Background: Knowledge of demographic profiles and baseline characteristics of HIV infected patients is essential for devising prevention strategies. Analysis of factors influencing improvement in CD4 cell count will help to determine prognosis and better implementation of ART.

Objectives: This retrospective study was conducted on HIV patients in Manipur, to assess clinical profile and factors influencing baseline immunological status and response to ART.

Methodology: 1231 patients were enrolled. Baseline demographic and laboratory parameters were recorded. CD4 cell counts were recorded at baseline and 6 months after ART initiation.

Results: 66.3% patients were male, 74.6% aged 21-40 years, 65.6% were Hindus and 52.9% of urban residence. 17.5% patients had Haemoglobin ≤ 9 grams/dl. Prevalence of HIV-HBV and HIV-HCV coinfection was 3.4% and 20.5% respectively. Male sex (141.51 ± 96.21 vs. 169.92 ± 111.2 cells/mm³; $p=0.001$), age >20 years and Haemoglobin ≤ 9 g/dl (127.5 ± 99.5 vs. 153.8 ± 99.1 cells/mm³; $p=0.001$) were associated with lower baseline CD4 count. Females (219.01 ± 187.2 vs. 161.79 ± 153.35 cells/mm³; $p=0.001$), age group 1-20 years and those without HIV-HCV coinfections (188.72 ± 170.81 vs. 154.20 ± 155.88 cells/mm³; $p=0.004$) had significant improvement in CD4 count at 6 months-post ART initiation. CD4 response in HIV-HBV coinfecting patients was lower (188.59 ± 170.65 vs.

162.39 ± 139.8 cells/mm³; $p=0.324$) but not statistically significant.

Conclusion: Majority of HIV patients in Manipur were - Males, Hindus, aged 21-40 years and of urban residence. Males, age >20 years and haemoglobin ≤ 9 g/dl were associated with lower baseline CD4 count. HIV-HBV/HIV-HCV coinfection wasn't associated with lower baseline CD4 count. Females, age <20 years and absence of HIV-HBV/HIV-HCV coinfections were associated with superior immunological response to ART.

Keywords: Hepatitis B virus, hepatitis C virus, HIV-HBV coinfection, HIV-HCV coinfection, CD4 count, response to ART, HIV

Introduction

Since the detection of the first case of Human Immunodeficiency Virus (HIV) 29 years ago, our understanding of HIV/ Acquired Immunodeficiency Syndrome (AIDS) has come a long way. In 2009 National AIDS Control Organisation (NACO) estimated that there were a total of 2.39 million people infected with HIV in India and total deaths due to AIDS related illnesses were 170,000. With an HIV prevalence of 1.4%, Manipur is one of the

states with the high prevalence of HIV in India.^[1]

Untreated HIV infection involves gradual depletion in the peripheral blood CD4 lymphocyte count from normal levels of around 900 cells/mm³ to as low as < 10 cells/mm³, which results in risk of AIDS defining diseases and death.^[2, 3] The rate of decline in CD4 count is largely determined by the rate of HIV replication.^[4] Antiretroviral therapy (ART) induces immunological response thereby

producing substantial reductions in plasma HIV Ribonucleic Acid (RNA) levels, which reverses the downward trend in CD4 lymphocyte cell counts. [5-8] Progressive improvement in ART efficacy has changed the world's outlook on AIDS from that of a "virtual death sentence" to one of a "chronically manageable disease". Knowledge of the demographic profile and baseline characteristics of the HIV infected patients in the population is essential for devising prevention strategies. An analysis of the factors influencing the improvement in CD4 cell count will be of help in providing feedback, for making appropriate alterations for the better implementation of ART.

Material and methods

It is a prospective study, carried out between 2004 and 2007, in which data was collected from the ART centre, Regional Institute of Medical Sciences, Imphal, Manipur, which is a centre of excellence for patients with HIV/AIDS. Treatment naive HIV positive patients newly registered at RIMS ART centre were included in the study. HIV status detected by presence of antibodies to HIV 1/ HIV 2 by the test performed at RIMS microbiology department (using S.D. Bioline 29.04.013). Patients were diagnosed to have hepatitis B and C coinfections by using the by presence of HBs antigen and Anti HCV antibodies respectively. All other investigations were carried out at department of biochemistry and pathology at RIMS. Written informed consent was taken from all the participants. The baseline data, including demographic details, laboratory parameters and CD4 cell counts were obtained at the date of enrolment of the patient to the ART centre for ART initiation. The ART regimen consisted of

two NRTI's (lamivudine combined with either zidovudine or stavudine) and one NNRTI (nevirapine or efavirenz). The follow up CD4 cell count was obtained 6 months after ART initiation.

Patients who had received prior ART as well as those who were lost to follow up either owing to death, transfer to another ART centre or other reasons were excluded from the study. Data was analysed using IBM statistical SPSS version 20. Values were expressed as either percentage or as mean \pm standard error. Independent t- test and ANOVA were used to compare the values, where appropriate. A p value $<$ 0.05 was considered significant.

Results

Out of 2527 patients who were registered and initiated on ART at our centre, a total of 1231 patients were selected for the study. The mean age of patients was 34.34 ± 9.262 years, and most of the patients belonged to the age group of 21-40 years (74.6%). Majority of the patients were Hindus (65.6%) and belonged to urban residence (52.9 %) as shown in figure 1. Other baseline characteristics are mentioned in the table 1.

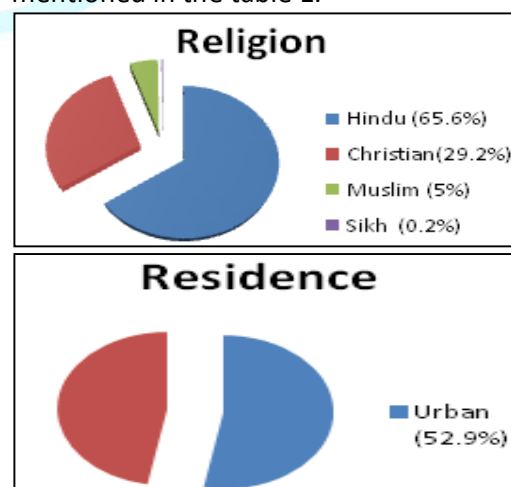


Fig.1 Distribution of religion and residence in the study population (n=1231)

Table: 1 Baseline laboratory parameters of study population

Parameters	Minimum	Maximum	Mean	STD deviation
Hemoglobin (g%)	3.90	18.00	10.768	1.884
Total leucocyte count (cells/mm ³)	2200	21020	6483.45	2218.220
Platelet count (lac cells/mm ³)	0.1	7.5	1.961	0.554
SGOT (IU/L)	40	430	62.95	44.591
SGPT (IU/L)	36	563	57.41	43.032
Random blood glucose (mg/dl)	54	221	97.73	32.24

Table: 2 CD4 count at baseline & its response to ART with respect to different characteristics

PARAMETER		NUMBER (%)	BASELINE CD4	P value	INCREASE IN CD4 ± SD (6 months)	p value
SEX	MALE	815(66.3)	141.51±96.21	0.001	161.79±153.35	0.001
	FEMALE	415(33.7)	169.92±111.2		219.01±187.2	
HBs Ag STATUS	NONREACTIVE	943(76.6)	128.9±101.5	0.159	188.59±170.65	0.324
	REACTIVE	42(3.4)	151.86±102.3		162.39±139.8	
ANTI HCV STATUS	NONREACTIVE	943(76.6)	156.9±86.9	0.311	188.72±170.81	0.004
	REACTIVE	252(20.4)	149.6±105.9		154.20±155.88	
Hb	< 9 g/dl	215(17.5)	127.5±99.5	0.001	187.81±151.7	0.322
	≥ 9g/dl	843(62.5)	153.8±99.1		175.58±164.1	
Age group (years)	1-20	81(6.6)	264.77 ± 201.6	0.001	320.26±140.08	0.001
	21-40	918(74.6)	143.73 ± 97.37		170.36±100.2	
	41-60	228(18.5)	143.06 ± 119.8		160.38±88.31	
	61-100	4(0.3)	141.19 ± 91.97		192.75±65.67	

Out of the 1231 patients, 542 were put on Zidovudine based regimen; out of which 376 patients received Nevirapine as the Non-Nucleoside Reverse Transcriptase

Inhibitor (NNRTI) and showed an improvement in CD4 count of a mean value of 180.09±156.495 cells/mm³, whereas 166 patients received Efavirenz

as the NNRTI with an improvement in CD4 counts of a mean value of 140.73 ± 147.902 cells/mm³. This difference was significant ($p=0.001$). Meanwhile another 687 patients were put on Stavudine based regimen; out of these, 537 received Nevirapine as the NNRTI and showed an improvement of CD4 count of a mean value of 194.68 ± 175.587 cells/mm³, while 150 received Efavirenz as the NNRTI and had a mean improvement in CD4 counts of 180.77 ± 180.116 cells/mm³. This difference was also significant ($p=0.002$). These findings reiterate the fact that ART regimens with Nevirapine are superior in efficacy to regimens with Efavirenz.

The baseline as well as improvement in CD4 cell count of patients with respect to different clinical and biochemical parameters and difference in other characteristics is mentioned in table 2. The mean baseline CD4 at presentation and improvement in CD4 cell count after 6 months of ART administration was significantly greater among the female patients compared to the male patients, and also greatest in the age group of 1-20 years. The Increase in CD4 count was also seen to be significantly greater in patients without Hepatitis C co-infection than those harbouring the virus. Also the prevalence rates of Hepatitis B and Hepatitis C co-infections with HIV were found to be 3.4 % and 20.4 % respectively.

Discussion

HIV already has 33.4 million victims globally, and in India, this figure is around 3 million patients.^[9] The clinical spectrum of HIV infection in India is different from rest of the world, and within India also there is a lot of variability as shown in different studies producing immunological response.^[10-15] So in resource limited settings, knowledge regarding the clinical profile of HIV patients can help to cut

down the cost burden of HIV disease. We conducted this study on 1231 HIV patients in Manipur to study their clinical and demographic profile and its impact on immunological response to ART.

In the present study, patients were mostly from the age group of 21-40 years (74.6%) which is consistent with other Indian studies.^[10-12] This is probably since it is the age group of maximum sexual activity and vulnerability to recreational intravenous drug use. The patients in the age group between 1-20 years comprised 6.6% of the study group; they had the highest mean baseline CD4 cell count of 264.77 ± 201.6 cells/mm³ and showed the maximum response to ART (320.26 ± 140.08 cells/mm³) in comparison to other age groups.

In most Indian studies, male patients have been predominant over female^[10, 11]; and this was true even in our study. Males were 66.3% of the study group, but this is lower than the value in studies from other parts of the country.^[10-12, 16] The baseline CD4 at initiation of ART was significantly higher among the female patients than male patients (141.51 ± 96.21 vs. 169.92 ± 111.2 cells/mm³; $p=0.001$). The subsequent improvement in CD4 cell count at 6 months after initiation of ART was also significantly greater among the females than males (161.79 ± 153.35 vs. 219.01 ± 187.2 cells/mm³; $p=0.001$). The reason for this may be due to greater awareness regarding personal health in general, and in particular regarding HIV/AIDS among women, thereby seeking early health care, as well as keeping better compliance to ART medications, allowing a better treatment response. Thus a greater emphasis may have to be placed on spreading awareness regarding HIV/AIDS illness in Manipur especially

among men, as well as on the importance of regular intake of ART medications.

There were 17.5% of the patients in the study group, who had haemoglobin values lower than or equal to 9 grams/dl, and these patients had a baseline CD4 count that was significantly lower (127.5 ± 99.5 vs. 153.8 ± 99.1 cells/mm³; $p=0.001$). This could be due to the effect of higher disease burden in these patients thereby leading to anaemia. Thus it may be inferred that the haemoglobin value at presentation may correspond inversely to the stage of the disease in HIV. Anaemia is associated with progression of HIV disease and it is associated with shorter survival of HIV-infected patients.^[17] HIV may lead to anaemia in many ways: changes in cytokine production with subsequent effects on haematopoiesis; decreased erythropoietin concentrations; opportunistic infectious agents; administration of agents such as zidovudine, ganciclovir, and trimethoprim-sulfamethoxazole; and cancers such as lymphosarcoma. But there was no significant difference in the response to ART with respect to increase in CD4 cell count between those patients with haemoglobin less than or equal to 9 g/dl and those with a value greater than 9 g/dl (187.81 ± 151.7 vs. 175.58 ± 164.1 cells/mm³; $p=0.322$). The patient group with haemoglobin lower than 9 g/dl was initiated on an ART regimen with Stavudine rather than Zidovudine as the Nucleoside Reverse Transcriptase Inhibitor (NRTI), since Zidovudine is known to cause bone marrow suppression and aggravate anaemia.

The prevalence of co-infection of hepatitis C (HCV) among those HIV patients receiving ART was 20.4% according to this study. The baseline CD4 in co-infected patients was not significantly different from those without

the co-infection, but the CD4 response to ART was significantly better in those without the co-infection than those harbouring HCV (188.72 ± 170.81 vs. 154.2 ± 155.89 cells/mm³; $p=0.003$). This finding is in agreement with studies that show that HCV does not appear to significantly influence HIV viral load or accelerate HIV disease progression, but may hamper response of HIV infection to anti retrovirals^[18, 19] The Swiss HIV Cohort Study in 2000 and Martin J et al at CROI in 2001, reported that coinfecting patients were significantly less likely to achieve CD4 cell gains of at least 50 cells/mm³ after one year of treatment. Other studies have shown similar results^[20, 21] People with HIV/HCV coinfection—especially those with advanced fibrosis or cirrhosis—are more susceptible to ART-related liver toxicity. Hence strong preference should be given to commence HCV treatment in patients with higher CD4 counts. For patients with lower CD4 counts (<200 cells/mm³), it may be preferable to initiate ART and delay HCV therapy until CD4 counts increase as a result of HIV treatment.^[22-25]

The seroprevalence of Hepatitis B (HBV) co-infection in HIV patients on ART was found to be 3.4%. There was no significant difference in the baseline CD4 cell count of those patients with, and those without HBV co-infection. The improvement in CD4 cell count in response to ART was higher in those without the co-infection than those with it (188.59 ± 170.65 vs. 162.39 ± 139.8 cells/mm³), but this was not statistically significant ($p=0.324$). This is in agreement with other studies,^[26-28] which have shown that HBV doesn't influence immunological response of HIV to ART. There have been previous studies,^[29, 30] that have shown that coinfection with HBV can accelerate immunological

deterioration in HIV coinfecting patients but these studies were done using HBV DNA viral load as well as HBe antigen as markers in addition to the presence of HBs antigen, in determining the impact of HBV on HIV.

In the study, 6 patients were found to have HIV, HBV & HCV coinfection together. Since HIV and hepatitis viruses share common modes of transmission there is high incidence of coinfection with these. Hence all HIV infected individuals should be tested for presence of HBV and HCV coinfections. Hence, along with awareness of HIV, efforts directed at prevention of HBV and HCV infections are essential.

In the state of Manipur, which has one of the highest prevalence of HIV/AIDS in India, our study of clinical profile and ART response of HIV patients found that the majority of the patients were males, though the percentage of females was higher than in studies from other states. Most of the patients were Hindus, and from the age group of 21-40 years, which is probably sexually most active and involved in recreational drug use. The seroprevalence of HBV and HCV coinfections were 3.4% and 20.4% respectively. The CD4 cell counts at presentation were significantly lower in males, patients with haemoglobin less than 9 g/dl and those above 20 years of age. The immunological response to ART was significantly better among female sex, those below the age of 20 years and in those not harbouring HCV coinfection. The CD4 response was also higher in those without HBV coinfection than those with it, but this wasn't statistically significant. The hepatitis viruses may hamper the treatment response of the HIV virus to ART drugs, and hence along with awareness of HIV, efforts directed at prevention of HBV and HCV infections are

essential. These data may help in planning awareness programmes, anti-retro-viral drug research as well as in future studies regarding factors influencing improvement in CD4 cell count.

As this study was conducted in a period when stavudine was still commonly employed as a part of first line ART regimens, majority of the patients received stavudine based anti-retro viral therapy. Stavudine has since been phased out of ART regimens. In studying the interaction between the hepatitis virus coinfection among the HIV patients, the level of viral replication of HIV and Hepatitis viruses, viral genotype and HBe antigen were not determined.

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