A COMPARATIVE STUDY OF CLINICO-IMMUNOLOGICAL RESPONSE TO HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN HIV AND HIV-HCV CO-INFECTION IN MANIPUR

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ABSTRACT

BACKGROUND
HIV-HCV co-infection is common in Manipur because of the increase in number of intravenous drug users (IDUs) and being eastern border state of India. HIV-HCV patients die of liver complications in spite of highly active antiretroviral therapy (HAART). The aim of the present study is to compare the clinico-immunological response to highly active antiretroviral therapy in HIV and HIV-HCV co-infection in Manipur.

MATERIALS AND METHODS
The present study was conducted in 45 HIV mono-infected (Group-I) and 45 HIV-HCV co-infected (Group-II) patients who were on first line antiretroviral treatment (ART).

RESULTS
In the present study, the clinico-immunological (CD4) response to ART in both the groups was recorded. The commonest route of transmission is heterosexual (62.2% and 53.3%) activity followed by IDUs (31% and 37%). The trend of CD4 is almost coinciding at initial 188.86± 104.27 Vs. 179.00 ± 98.19 cells/mm³ but mean CD4 for HIV group is higher at 6th month, at 12th month and at 18th month with 502.82± 272.22 Vs. 412.47± 229.48 cells/mm³ after ART as compared to HIV-HCV group significantly P<0.05 (P=0.032). Further, the CD4 response was better in HIV-HCV with treatment of both HIV and HCV than without HCV treatment.

CONCLUSION
The present study showed that the immunological response to ART to both HIV and HIV-HCV co-infection groups is good, but better in HIV group. Further, amongst the HIV-HCV co-infection the immunological response was better to those who had undergone HCV treatment. So routine screening for HCV in HIV infected patients and starting HCV treatment early will result in better quality of life.

KEYWORDS
Highly Active Antiretroviral Therapy, Antiretroviral Treatment, Intravenous Drug Users.

BACKGROUND
Worldwide, hepatitis C virus (HCV) accounts for approximately 185 million chronic infections, with an overall 3% prevalence and 4 to 5 million persons are co-infected with HIV. Due to shared risk factors, human immunodeficiency virus (HIV) infection influences the natural evolution of chronic HCV infection by higher rate of viral persistence, accelerating fibrosis, cirrhosis progressing to end-stage liver disease.[1] Further, as HIV has become a chronic illness due to the effectiveness of highly active antiretroviral therapy (HAART), HCV related liver disease has emerged as a major cause of morbidity and mortality among HIV infected patients in the developed world.[2] In Manipur

most of HIV-HCV cases are having a longer and better quality of life than before after starting free HAART by NACO through state AIDS Control Society (SACS) since April 2004. But the mortality rate of HIV-HCV is still increasing in Manipur as most of them cannot afford HCV treatment because of poor socioeconomic condition and die of liver complications. So, the present study is undertaken to know if there is any difference of clinico-immunological response between HIV mono-infection and HIV-HCV co-infection on HAART.

Aims and Objectives
To assess and compare clinico-immunological response (CD4 count) to Highly Active Antiretroviral Therapy in HIV and HIV-HCV co-infection patients.

MATERIALS AND METHODS
The study was carried out in the Department of Medicine, Regional Institute of Medical Sciences, Imphal from October 2014 to March 2016. The study was a single centre prospective cohort study. Out of total 1420 registered patients, 1360 were HIV mono-infected and 60 were HIV-HCV co-infected patients. Of these 90 patients who fulfilled

inclusion and external criteria, 45 HIV mono-infected (Group-I) and 45 HIV-HCV co-infected (Group-II) who were on first line treatment were included in the study. The sample size was calculated based on the mean CD4 count and standard deviation of HIV mono-infected and HIV-HCV co-infected patients from the previous study.[Ref: Taye S et al[3]].

Thorough clinical examination, laboratory investigations such as complete blood count, liver function test, kidney function test, random blood sugar, chest x-ray and CD4 count were done. The presence of HIV infection was confirmed as per the National AIDS Control Organization (NACO) guidelines using 3 (three) ER (ELISA Rapid) HIV test kit. CD4 cell count was calculated by Fluorescence Activated Cell sorter (Manufacturer: BD Biosciences 2350 Qume Drive, San Jose, CA 95131-1807, USA) and HCV viral load was measured by Real Time PCR (Manufacturer: ROCHE and Thermo Scientific). All the patients gave written informed consent and approval was taken from institutional ethical committee before the study.

Statistical Analysis

Statistical analysis was done by using the Statistical Package for Social Sciences (SPSS) 20 version. Numerical continuous variables are presented as Mean ± SD (Standard deviation) and qualitative/categorical variables are again described as number of cases and percentages. The two means for each parameter between HIV and HIV+HCV groups are compared by Independent Sample Test (t-test); the variation of two means at two different stages for each parameter within group are tested by Paired t-test; the variation of more than two means at different stages for each parameter within group is tested by Friedman's Two-Way ANOVA; and χ^2-test is applied for categorical variables. All comparisons are two-sided and the P - values of < 0.05 and < 0.01 are treated as the cut-off values for significance and highly significance respectively.

RESULTS

The clinico-immunological (CD4) response to highly active antiretroviral therapy on both the groups were recorded. In group I and group II, the ratio of male: female was 60:40 and 84.4: 15.6 respectively thereby showing the higher prevalence of males in both the groups (P = 0.010). The number of married persons in both group I and group II were 69% and 86% showing the importance of sexual route of transmission. The average age of patients in HIV group was around 40 years and 43 years in HIV-HCV group which shows that both HIV and HIV-HCV are common in the fertile period. In both the groups, highest mode of transmission was found to be heterosexual (62.2% and 53.3%) activity followed by intravenous drug usage (31% and 37%). However, in the HIV group, infections due to blood transfusion, mother to child, and unsafe injections were very less with same percentage i.e., 2.2% each. In HIV-HCV group, unsafe injection (6.7%), blood transfusion (2.2%) and no case of mother to child transmission was found.

Mean ± SD: mean and standard deviation; t: independent sample test; d.f.: degree of freedom; P: Probability of difference due to chance factors; n: number of cases.

Parameters - cells/mm³	Groups				t value	d. f.	P-value
	N	HIV (Group I)	N	HIV-HCV (Group II)			
CD4 (baseline)	45	188.86 ± 104.27	45	179.00 ± 98.19	0.462	88	0.645
CD4 after 6 months	45	393.82 ± 195.54	45	310.64 ± 173.09	2.137	88	0.035
CD4 after 12 months	45	449.78 ± 249.48	45	368.71 ± 230.59	2.601	88	0.013
CD4 after 18 months	45	502.82 ± 272.22	45	412.47 ± 229.48	2.702	88	0.032
Table 1. Group-wise Distribution of Mean ± SD of CD₄ at Various Stages							

Table 1. Shows that there is no variation of mean CD4 between the groups in initial but after 6th, 12th and 18th month of ART, mean CD4 between the groups are found to be significant at 5% probability level as corresponding P <0.05 (P = 0.032).
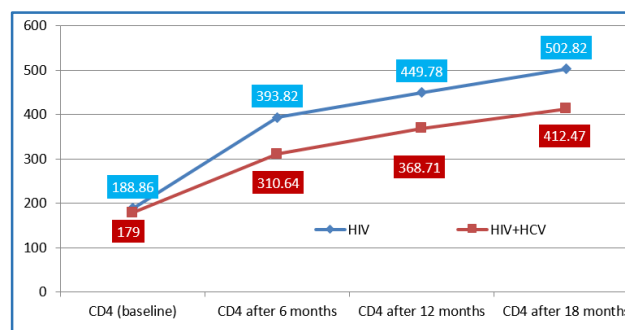

Figure 1. Shows the Trend of CD4 is almost Coinciding at Initial but Mean CD4 for HIV Group is higher at 6th month, at 12th month and at 18th month after ART as Compared to HIV-HCV Group Significantly.

Para-meters cells/mm³	Group II				t - value	d.f.	P - value
	N	HCV, No Treatment	N	HCV Treatment			
CD4 (Baseline)		198.84 ± 98.09		154.20 ±94.90	1.539	43	0.131
CD4 after 6 months	25	338.28± 182.15	20	276.10 ± 158.79	1.203	43	0.235
CD4 after 12 months	19	499.10 ± 318.86	16	476.81 ± 293.17	.214	33	0.832
CD4 after 18 months	6	389.25 ± 77.13	4	556.33 ± 271.35	1.589	8	0.632
Table 2. Treatment-wise Comparison of Mean ± SD of CD₄ for HIV-HCV at Various Stages (with and without HCV treatment)							

Table 2. Shows that the CD4 increased variations are not significant even at 5% probability level (P=0.632).

DISCUSSION

HCV-HIV co-infection is common among the IDUs in Manipur, but longer life span seen after free ART was started by NACO through SACS since April 2004. However, these HIV-HCV co-infection patients die prematurely because of liver complications including HCC of HCV in spite of ART. The lesser number of patients on HCV treatment is because HCV treatment is costly and unaffordable. In the present study, males are affected than females (60% Vs. 40%) in Group I and (84.4% Vs. 15.6%) in Group II. The highest prevalence is

found in the age group 40-45 years in both the groups which is in agreement with the work of Taye S et al.[3] The mode of transmission in the present study is highest in both the groups with heterosexual (62% Vs. 53%) activity followed by intravenous drug users (37% Vs. 31%) respectively in contrast to other previous studies where HIV-HCV co-infection was found more among IDUs.[4,5,6]

The reason being HCV screening test was done routinely in all HIV patients in the present study before ART in contrast to other study by Rockstroh J et al[7] where HCV screening test was done only in the high risk group i.e. IDUs.

In the present study, there is no significant variation of mean CD_4 count between the two groups I and II before starting HAART (188.86 ± 104.27 Vs. 179.00 ± 98.19, P = 0.645). But after 6th (393.82 ± 195.54 Vs. 310.64 ± 173.09 P = 0.035), 12th (449.78 ± 249.48 Vs. 368.71 ± 230.59 P = 0.013), 18th (502.82 ± 272.22 Vs. 412.47 ± 229.48, P = 0.032) months of HAART, the range of revised CD4 count was higher in Group-I than in Group-II which is statistically significant. Taye S et al[3] found that the increased CD4 was higher in HIV than HCV co-infected group on HAART (426 Vs. 343; P <0.004). Braintstein P et al[8] also found that HCV negative patients had CD4 increase of an average of 75 cells in the absolute CD4 cell count and 4.4% in the CD4 cell fraction, compared with 20 cells and 1.1% in HCV positive patients, after 48 weeks of ART. Miller M et al[9] also found that the HIV-HCV co-infected patients had a mean increase in the CD4 cell count with 33.4 cells/mm³ (95% CI, 23.5–43.3 cells/mm3) less than that for HIV mono-infected patients. These findings are similar to previous studies where there was negative impact on immune recovery by HCV co-infection in HIV patients.[3,4,8,9,10,11,12,13,14] In our study, the adherence rate was high in both the groups (97%), so this could be one of the reason for good immune response. This is similar to the study conducted by Abrogoua D et al[15] as the baseline CD4 cell count was <200/mm³ in both the groups and the increased CD4 response after 6 months of HAART was >100/mm³ in both the groups during the 18 months period. In Group II only 20 patients could afford treatment of HCV. The increase of CD4 count was 198.84 ± 98.09 at baseline and at 389.25 ± 77.13 after the 18th month without HCV treatment.

But in HCV treated HIV patients (Injection Peginterferon and Tab. Ribavirin), the increase of CD4 count was 154.20 ± 94.90 at baseline and 556.33± 271.35 after the 18th month of HCV treatment. This shows that treatment of HCV in HIV-HCV had better immunological response than those with no HCV treatment. The genotypes were 2, 3, 1 and 6. There is a variation of liver enzyme SGPT and SGOT level between the two groups. The liver enzyme level was higher in HIV + HCV group as compared to mono-infected group (85.53 ± 12.55 Vs. 35.48 ± 13.59 and 72.08 ±11.59 Vs. 31.57 ± 11.75; P = .043) which suggests that HCV causes the chronic liver infection. There was no significant disparity of mean RBS level between two groups (101.71 ± 18.49 Vs. 111.96 ± 20.21; p = 0.952). None of the patients were diabetic though 03 cases in HIV group and 04 cases in HIV+HCV group were in the impaired glucose tolerance range. There was increase in weight in both HIV and HIV-HCV co-infected after 6 months of HAART (3.5 ± 1.6 kg and 3 ± 1.2 kg respectively). In the

present study, there was no death due to liver disease among the study population during the period of study as the other causes like alcohol, HBV infection were excluded. This study is in agreement with Carmo R et al[14] where there was no increased risk of progression to new AIDS-defining clinical events or death caused by AIDS after the initiation of HAART. In our study, maximum (95.6%) patients were on TLE regimen which was recently changed according to NACO guidelines 2013. There was no major serious adverse effect of the regimen though the renal toxicity is a common side effect of tenofovir but it will depend on the dose and duration of the treatment.

CONCLUSION

The present study showed that the immunological response to ART to both HIV mono-infection and HIV-HCV co-infection groups was good, though the response was better in HIV mono-infection group. Further, amongst the HIV-HCV co-infection, the immunological response was better to those who had undergone HCV treatment. The HCV seropositivity was not associated with an increased risk of progression to a new AIDS-defining opportunistic illness or death after the initiation of ART. So, routine screening for HCV in HIV infected patients and starting HCV treatment early will result in better quality of life.

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