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A RETROSPECTIVE STUDY OF HIV/HBV CO-INFECTION AND HIV/HCV CO-INFECTION WITH ITS EFFECT ON DISEASE PROGRESSION AND ITS OUTCOME: AN EXPERIENCE AT TERTIARY CARE ART CENTRE

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Abstract- *Introduction*: The advent of highly active antiretroviral therapy has brought with it a great sense of optimism for people living with HIV and their clinicians. It has been estimated that approximately one third of deaths of patients with HIV infection are in some way related to liver disease co-infections such as hepatitis B or C. And these continue to present challenges in the overall management of the HIV-infected patient. The prevalence of HIV and viral hepatitis co-infection has considerable geographic and demographic variability. In western world, 9-12% & 9-16% of HIV patients have HBV & HCV co-infection respectively. The literature regarding the prevalence of co-infection with HBV/ HCV in India is sparse. Hence the present study was conducted to find out prevalence of HBV/HCV co-infection in HIV patients in Gujarat.

Objectives: To study the prevalence, epidemiological and biochemical profile of HIV/ HBV and HIV/ HCV co-infection in PLHA along with study of HBV/HCV as a co-factor in HIV disease progression & vice versa.

Materials and Method: Study of 80 HIV/ HBV co infected, 66 HIV/ HCV co infected patients out of 2397 PLHA was conducted who visited to ART Center, Civil Hospital Ahmedabad, over the period of two years. Evaluation of each patient for HIV & HBV/HCV co-infection, medical care & provision of HAART is free of charge to all patients at ARTC, Ahmedabad as per NACO guide lines. Patients were considered to have HBV co-infection when HBsAg could be detected in Plasma & considered to have HCV co-infection when anti HCV was present. PLHA with negative HBsAg and negative anti-HCV were considered HIV monoinfected.

Results: In present study total male patients were 66.45% and female patients were 33.08%, which is comparable to GSACS having total, male patients 71.7% and female patients 28.8 % and NACO having male patients 70.7% and female patients 29.3%. It shows males are more affected than females in HIV. Male to female ratio is nearly 2:1. Out of 2397 HIV patients, 166 (6.92%) belonged to age </= 20 years, 1864 (77.76%) belonged to age group 20-45 years and 367 (15.31%) belonged to age >45 years. Out of 80 HIV/ HBV co-infected patients 64 (80%) patients and out of 66 HIV/ HCV co-infected patients 50 (75.75%) patients belonged to the age group 20-45 years.

Conclusion: Out of 2397 PLHA screened in present study total male patient were 66.45% and females patients were 33.08%. It shows males are more affected than females in PLHA. In present study HIV/ HBV co-infection is more prevalent in male than in female (M: F- 7:1). While in HIV/ HCV co-infected patients, prevalence in male is nearly same as in female (M: F-1.2:1). The Seroprevalence of HBV (3.34%) is 1.36 times higher than Seroprevalence of HCV (2.75%) in our population of PLHA (2397).

Keywords- Seroprevalence, CDC Criteria, *S. Billirubin*, S. AST

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Introduction

The advent of highly active antiretroviral therapy has brought with it a great sense of optimism for people living with HIV and their clinicians. It has been estimated that approximately one third of deaths of patients with HIV infection are in some way related to liver disease co-infections such as hepatitis B or C. And these continue to present challenges in the overall management of the HIV-infected patient. There are several reasons to highlight hepatitis co-infection in HIV-positive individuals. Not only is there more severe HBV/HCV-related liver damage in these patients, there is also the higher risk

of hepatotoxicity using antiretroviral drugs in these patients. In this sense, HIV and viral hepatitis co-infection and antiretroviral therapy-related hepatotoxicity are areas of emerging clinical concern.

The prevalence of HIV and viral hepatitis co-infection has considerable geographic and demographic variability. In western world, 9-12% & 9-16% of HIV patients have HBV & HCV co-infection respectively [1]. Countries, in particular those with larger proportions of injecting drug use-related HIV, have a higher prevalence of co-infection. An understanding of the natural history of HIV and hepatitis co-infection underpins clinical management. Several hepatitis B antiviral therapies, some of which have dual activity against HIV and hepatitis B, have either been recently introduced or are in development. These advances in hepatitis B therapeutic management will undoubtedly enhance prospects for clinical management of HIV and hepatitis B co-infection. Despite improved hepatitis C antiviral therapy, efficacy remains suboptimal particularly for people with hepatitis C genotype 1 and those with advanced immune deficiency. Interactions between hepatitis C antiviral therapy and antiretroviral therapy increase the difficulty in therapeutic decisions. For these reasons, a strategy of clinical management based on an assessment of HIV and hepatitis C prognosis, and the likelihood of response to hepatitis C antiviral therapy is required.

The literature regarding the prevalence of co-infection with HBV/ HCV in India is sparse. Hence the present study was conducted to find out prevalence of HBV/HCV co-infection in HIV patients in Gujarat.

Materials and Method

Study of 80 HIV/ HBV co infected, 66 HIV/ HCV co infected patients out of 2397 PLHA was conducted who visited to ART Center, Civil Hospital Ahmedabad, over the period of two years. Evaluation of each patient for HIV & HBV/HCV co-infection, medical care & provision of HAART is free of charge to all patients at ARTC, Ahmedabad as per NACO guide lines. Patients were considered to have HBV co-infection when HBsAg could be detected in Plasma & considered to have HCV co-infection when anti HCV was present. PLHA with negative HBsAg and negative anti-HCV were considered HIV monoinfected.

Detailed clinical history was noted in each patient with special emphasis on presenting complaints, family history, personal history & past history of jaundice, blood transfusion, multiple sexual partners, occupational exposure, drug abuse, etc. Detailed physical & systemic examination was carried out in all patients looking especially for clinical evidence of hepatobiliary involvement & opportunistic infections. Routine hematological investigations in form of complete hemogram, PT, Biochemistry in form of liver function tests, renal function tests, S.Proteins, urine routine and microscopy examination; Radiological investigations in form of chest x-ray & ultrasonography of abdomen, & Serological investigations in form of S. HBsAg, IgM Anti HCV, IgM S. Toxoplasmosis, S. VDRL were carried out in all patients. CD_4 & CD_8 were also carried out.

The special investigations like S.HBeAg, HIV viral load, HBV DNA, HCV RNA (quantitative/qualitative) and Biopsy of Liver were not performed as resource limitation and cost constraints. All patients who presumed to have hepatitis co-infection were appropriately investigated according to their presentations. All the patients were managed as per standard NACO guidelines.

Data of each patient were recorded at time of enrollment & during follow up.

Results

In present study total male patients were 66.45% and female patients were 33.08%, which is comparable to GSACS having total, male patients 71.7% and female patients 28.8 % and NACO having male patients 70.7% and female patients 29.3%. It shows males are more affected than females in HIV. Male to female ratio is nearly 2:1. Out of 2397 HIV patients, 166 (6.92%) belonged to age </= 20 years, 1864 (77.76%) belonged to age group 20-45 years and 367 (15.31%) belonged to age >45 years. Out of 80 HIV/ HBV co-infected patients 64 (80%) patients and out of 66 HIV/ HCV co-infected patients 50 (75.75%) patients belonged to the age group 20-45 years. That indicates most of our patients were in active reproductive age group between 20-45 years [Table-1].

Table 1- Age & Sex distribution of HIV patients (n=2397)

Age groups	Present study	Sex	Present study
</= 20	6.92%	Male	66.46%
20-45	77.76%	Female	33.08%
>45	15.31%	TG/TS	0.46%

In male HIV patients, prevalence of HBV is more than HCV (nearly double). While in female HIV patients, prevalence of HCV is more than HBV (three times). It also points out that HIV/ HBV co-infection is more prevalent in male than in female (male: female-7:1). While in HIV/ HCV co-infected patients, prevalence in male is nearly same as in female (male: female-1.2:1).

In our study of 2397 HIV seropositive patients tested for HBsAg & Anti HCV. Out of them 80 (3.34%) patients were found positive for HBsAg & 66 (2.75%) patients were positive anti-HCV. This data suggests Seroprevalence of HBV (3.34%) is 1.36 times higher than Seroprevalence of HCV (2.75%) in our population [Table-2].

In Northern India, KGMU, Lucknow [1] study prevalence of HBV and HCV co-infection was 2.25% and 1.61% respectively. Another study on HIV patients from India reports the prevalence of HBV and HCV co-infection as 6.4% and 2.1% respectively. While in the Euro-SIDA and MACS cohort study the prevalence of HIV / HBV co-infection was reported as 9% and 12.7% respectively. In the CAESAR STUDY and CPCRA STUDY the prevalence of HIV/ HCV co-infection was found to be 9% and 16.1% respectively [1].

So, we can consider that the prevalence of co-infection may vary according to the geographical difference.

Table 2- Seroprevalence of HBV (HBsAg) & HCV (Anti HCV)

Group of patients	No. of patients (n= 2397)	Present study (n=2397)	KGMU, Lucknow [1] (n =620)
HIV monoinfection	2254	94.03%	95.98%
HIV/ HBV co-infection	80	3.34%	2.25%
HIV/ HCV co-infection	66	2.75%	1.61%
HIV/HBV/HCV co-infection	3	0.13%	0.16%

Out of 2397 HIV patients 1541 (64.28%) patients had history of high risk sexual behavior & 313 (13.05%) had a history of Blood Transfusion (BT) and Blood Transfusion products (BT Products). Out of 1541 HIV patients with history of high risk sexual behavior, 49 (3.17%) were HBV co-infected, & 28 (1.81%) were HCV co-infected. Out of 313 HIV patients with history of transfusion, 11 (3.51%) were HBV co-infected and 27 (8.62%) were HCV co-infected. Out of 80 HIV/ HBV co-infected patients, 49 (61.25%) had history of high risk sexual behavior and 11 (13.75%) had history of

transfusion. Out of 66 HIV/ HCV co-infected patients, 28 (42.4%) had history of high risk sexual behavior and 27 (40.90%) had history of transfusion.

In Northern India, KGMU, Lucknow [1] study mode of transmission in HIV/ HBV co-infection was heterosexual & in HIV/ HCV co infection 50% had heterosexual mode of transmission, 40% had blood transfusion, 10% had intravenous drug use as the mode of transmission which is comparable to our results [Table-3].

Table 3- Possible Source of Transmission of Infections in Present Study

Route of Exposure*	HIV monoinfection (n=2254)	HIV/ HBV co-infection (n=80)	HIV/HCV co-infection (n=66)	Total (n=2397)
Sexual route	1466	49	28	1541
Blood & Blood Transfusion products	276	11	27	313
IV Drug User	5	0	0	5
Vertical transmission	101	2	3	106
Multiple routes	47	3	0	50
Unknown routes	359	15	8	382

*Route of exposure was derived from detailed history for personal exposure

As per Definition of AIDS, based on revised (1993) CDC classification system HIV infected patients in categories A3, B3, C3, C1 & C2 are defined to have AIDS. As shown in the [Table-4]. out of 2254 HIV monoinfected patients 853 (37.84%) were in B3 category and 748 (33.18) were in C3 category. In HIV- HBV co-infected group, 35 (43.75%) out of 80 patients were in C3 category and 25 (31.25%) were in B3 category. In HIV/ HCV co-infected group of patients, 34 (51.51) were in B3 category out of 66. These data points out, Hepatitis co-infected patients were more commonly presets in B3/C3 category at the time of diagnosis in our patients. As our study was conducted at tertiary care Centre patients we could explain more cases in higher categories.

Table 4- Distribution of Patients According to CDC Classification

Category	No. of Monoinfected patients			No. Of HIV/ HBV Co infected Patients			No. Of HIV/HCV Co infected Patients		
CDC stage	1	2	3	1	2	3	1	2	3
A	12	74	99	1	0	2	0	1	2
B	27	273	853	1	9	25	1	7	34
C	26	142	748	1	6	35	1	6	14

From the [Fig-1] We can observe that incidence of commonest OIs were nearly similar in all groups. Prevalence of other OIs in these groups was also comparable but higher than general HIV population as most of the patients were of higher HIV-category than large population based survey like from GSACS or NACO. Most common OI observed in these groups were candidiasis & tuberculosis.

It is clearly observed from the data in [Fig-2] that the incidence of liver injury in the form of Hepatomegaly, fatty liver or cirrhosis of liver, evidenced by USG is more in HBV co-infected patients followed by HCV co-infected group of patients.

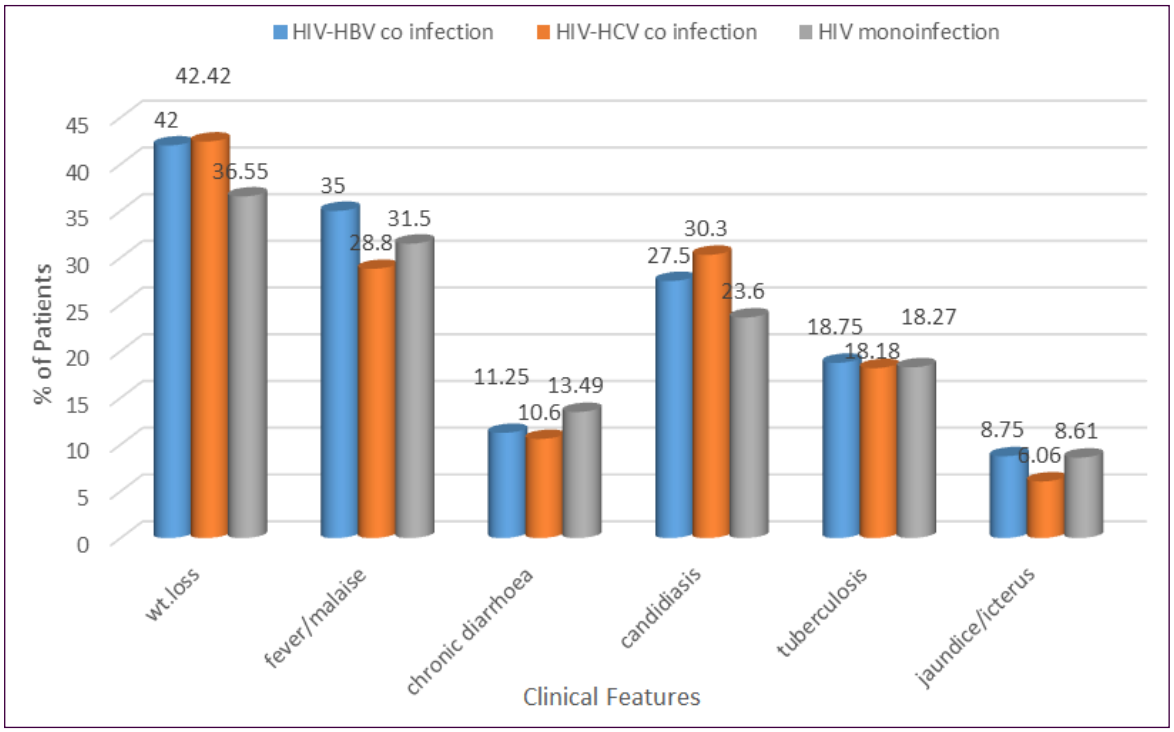

Fig. 1- Prevalence of Clinical Features in HIV/HBV Co-infected, HIV/HCV Co-infected & HIV Monoinfected Patients

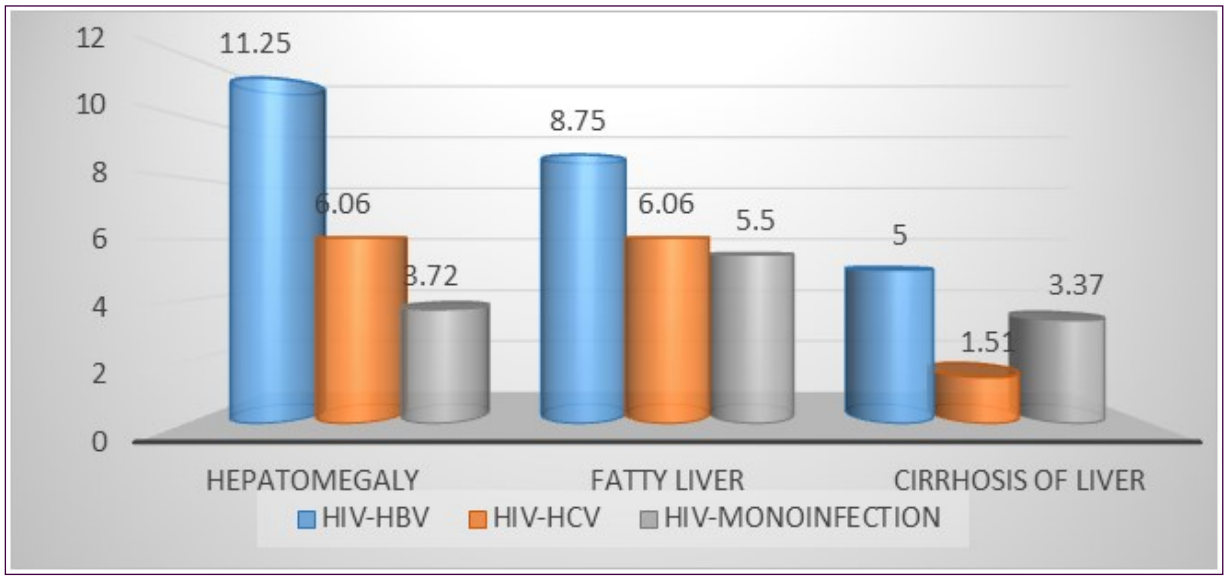

Fig. 2- Ultrasonography Changes in HIV/HBV Co-infected, HIV/HCV Co-infected & HIV Monoinfected Patients

During baseline evaluation of all patients, 2118(93.96%) patients out of 2254 HIV monoinfected patients, 72 (90%) patients out of 80 HIV/ HBV co-infected patients, and all 66 (100%) HIV/ HCV co-infected patients had serum bilirubin level within normal limits [Table-5]. During baseline evaluation 2098 (93.07%) patients out of 2254 HIV monoinfected patients, 71(88.75%) patients out of 80 HIV/ HBV co-infected patients and 64 (96.96%) patients out of 66 HIV/ HCV co-infected patients had serum ALT level within normal limits [Fig-3] & [Fig-4]. 4 patients of HIV/HBV co infection have S. Billirubin >4.5 & S.ALT >200 might be due to their h/o chronic alcoholism & presence of cirrhosis of liver as comorbid factor at time of baseline evaluation.

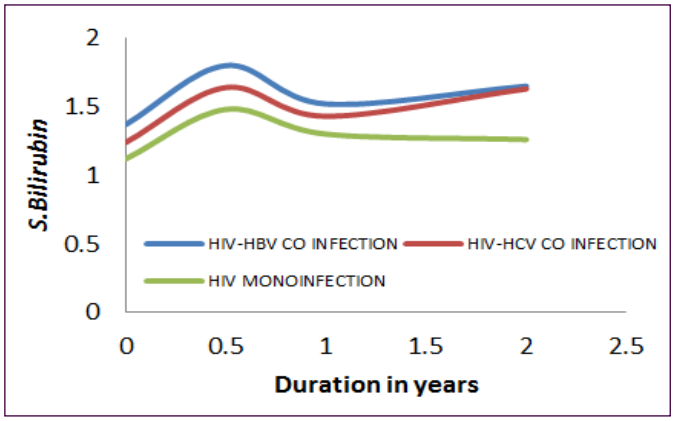

Fig. 3- Pattern of S. Bilirubin with Disease Progression

HIV disease progression here in this study is defined by CD4 value.

In present study, 1700 (75.42%) out of 2254 HIV monoinfected patients, 62 (77.50%) out of 80 HIV/ HBV co-infected patients, 50 (75.75%) out of 66 HIV/ HCV confected patients have CD4 count </ =200/mm^3.

In present study majority of patients have base line CD4 count of <200/mm^3 [Table-5] & [Fig-5]. Mean baseline CD4 count was 226.5/ mm^{3}in monoinfected group, 164.5/mm^3 in HBV co-infected group and 174/mm^3 in HCV co-infected group, which were 150.7/mm^3 and 288.6/mm^3 in HIV/ HBV &HIV/ HCV groups in KGMU study [1].

The mean baseline CD4 values for all groups of patients were marginally different & HIV monoinfected had higher CD4 count than HIV / HBV and HIV/ HCV co-infected group of patients.

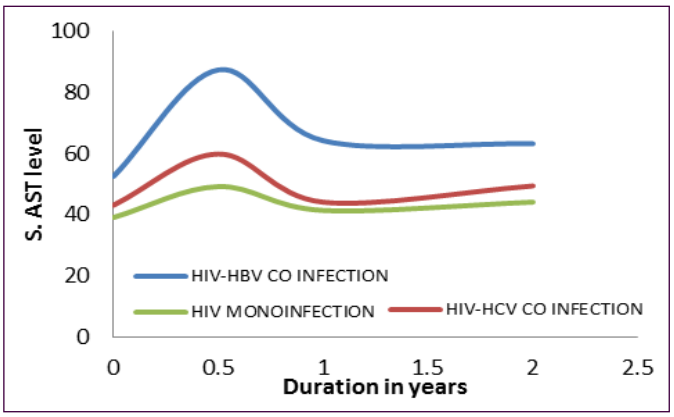

Fig. 4- Patterns of (mean) S. ALT with Disease progression

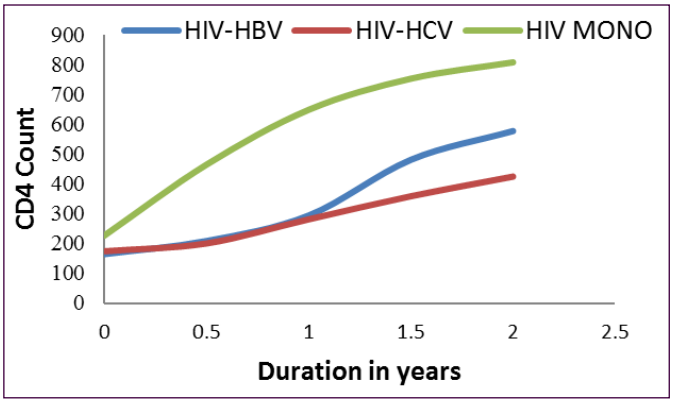

Table 5- Baseline CD4 count & their Correlation with Disease

Fig. 5- Mean CD4 counts with disease progression

No. of patients in each groups		HIV/ HBV co-infection (n=80)	HIV/HCV co-infection (n=66)	HIV mono- infection (n=2254)
CD4(mm^3)	<200	62	50	1700
	200-500	15	14	489
	>500	3	2	65

Discussion

We observed that maximum cases of HIV infected persons belonged to age group between 20-45 years followed by >45 years, Though our data is pooled from tertiary care centre as compared to community base survey in GSACS and NACO, it is nearly comparable to it. We observed that maximum cases of HIV infected persons were in age group between 20-45 years; suggest HIV is more common in reproductive age groups. Though our data is pooled from ARTC, Ahmedabad compared to large data of GSACS & NACO, it is comparable by age & sex of the patients. In present study of 2397 HIV patients1593 (66.45%) were male & 793 (33.08%) were female patients. Prevalence of HIV in male is more than female.

Out of 1593 male HIV patients 70 (4.39%) were HIV/ HBV co infected, & 36(2.25%) were HIV/ HCV co infected. Out of 793 female HIV patients 10 (1.26%) were HIV/ HBV co-infected, & 30 (3.78%) were HIV/ HCV co-infected. The data on mode of transmission indicates, HBV is more prevalent than HCV in HIV patients with high risk sexual behavior while HCV is more prevalent than HBV in HIV patients with history of BT or BT products. Jaundice, abdominal distension, oedema feet & s/o hepatic failure were more commonly observed in HBV-HIV co-infected patients than remaining groups. That might be due to comparably fast progression of hepatic injury in HBV co infected patients than other groups. Same incidence in clinical presentation of hepatocellular injury in HIV / HCV co-infected group & HIV monoinfected groups, which were lower than HIV / HBV co-infected group was observed. The cause might be, our study was of short period (2 years) & HCV remains dormant for longer periods of time (years) and had delayed liver injury. To know the incidence of liver disease in HIV / HCV co infected patients long duration of follow up is required.

The rise of S.Bilirubin/S.ALT during the first year of follow up might be possibly due to drug toxicities (HAART, AKT, OI management),IRIS, OI or other endemic causes which were more common in co infected patients. But in co-infected group of patients, persistently rising S.Bilirubin/S.ALT in follow up might be due to persistent progressive liver damage due to chronic hepatitis disease process, IRIS, or increased drug toxicities, etc. Our results are comparable with the study of Brinker M, Wit FW, Wertheim-van Dillen, et al [5].

As HAART includes lamivudine which acts on HBV also, the rise in CD4 count after one year in HIV / HBV co-infected was comparable to HIV monoinfected group of patients that might be due to clearance of HBV with lamivudine. Our findings are same as studied by Thio et al [12] & den Brinker et al [5].

Compared with HIV monoinfected group, HIV / HCV co-infected group had a marginally lower mean CD4 count. HIV/ HCV co-infected patients are compromised in their response to highly active antiretroviral therapy. Results are same as observed by Weis, et al. [16] & den Brinker, et al [5] But, a study by Rockstroh, et al [17] & Bica, et al [14] found no impact of HCV infection on the effectiveness of HAART in terms of changes in CD4+ cell counts.

Conclusion

In the present study we observed maximum cases of PLHA, HIV/ HBV, HIV/HCV co infected patients belonged to age group between 20-45 years. Suggest HIV & HIV-Hepatitis co-infection is more common in reproductive age groups. Out of 2397 PLHA screened in present study total male patient were 66.45% and females patients were 33.08%. It shows males are more affected than females in PLHA. In present study HIV/ HBV co-infection is more prevalent in male than in female (M: F- 7:1). While in HIV/ HCV confected patients, prevalence in male is nearly same as in female (M: F-1.2:1). Seroprevalence of HBV (3.34%) is 1.36 times higher than Seroprevalence of HCV (2.75%) in our population of PLHA (2397). High risk sexual behavior was major route of transmission of HIV followed by history of BT & BT products. HBV is more prevalent in sexually transmitted disease while HCV is more prevalent in PLHA with history of BT or BT products.

Rise in S.Bilirubin/S.ALT was more abrupt in co infected groups after starting HAART than in monoinfected patients. During the first year of follow up S.Bilirubin/S.ALT level decreased and almost return to normal baseline level and during the next follow up, value of s. bilirubin/S.ALT rise very slowly might be due to disease progression & chronic liver injury.

In the present study the mean baseline CD4 values for all patients were marginally different in HIV monoinfected group (226.5/$mm^{3)}$, HBV co-infected group (164.5/mm^3) and HCV co-infected group (174/mm^3) of patients.

Monoinfected patients on HAART have a higher increment in CD4 count (HIV suppression & immune recovery) as compared to HBV/ HCV co-infected patients during follow up.

Abbreviations

Ab: antibody

AHOD: Australian HIV Observational Database

AIDS : acquired immune deficiency syndrome

Anti-HBc: antibody to the hepatitis B core antigen

AST : aspartate aminotransferase

CAESAR: multicenter study conducted in Canada, Australia, Europe, and South Africa

ESR: Erythrocyte Sedimentation Rate

EuroSIDA: large cohort study of people with HIV infection in Europe

ELISA: Enzyme Linked Immunosorbant Assay

HAART: highly-active antiretroviral therapy

HAV : hepatitis A virus

HBsAg: hepatitis B surface antigen

HBeAg: hepatitis B envelope antigen

HBV : hepatitis B virus

HCV : hepatitis C virus

HIV: human immunodeficiency virus

LFTs: Liver function Test

MACS Multicenter AIDS Cohort Study

NACO: National AIDS Control Organization

PCR : polymerase chain reaction

PLHA: people living with HIV/AIDS

US ACTG: United States AIDS Clinical Trials Group

BT: Blood Transfusion

BT: Products Blood Transfusion Products

Conflicts of Interest: None declared.

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