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A cross-sectional study on co-infection of hepatitis B and hepatitis C among people living with HIV/AIDS from a tertiary care hospital of Central India

Riddhi Pradhan[1], Kirti Hemwani[2], Vidit Khandelwal[3], Bamboriya BL[4], Yogyata Marothi[5], Varsha Saxena[6]

[1,2]Associate Professor, [5]Professor and Head, [6]Demonstrator, Department of Microbiology, [3]Associate Professor, Department of Community Medicine, [4]Professor, Department of Medicine, R. D. Gardi Medical College, Ujjain, Madhya Pradesh, India

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ABSTRACT

Background: Hepatitis B virus (HBV), hepatitis C virus (HCV), and Human immunodeficiency virus (HIV) infections are prevalent throughout the world. HIV infection increases the risk of HBV and HCV liver disease especially when HIV-associated immunodeficiency progresses. **Aims and Objectives:** This study was carried out with the objectives as follows: Estimation of the prevalence of HIV- Hepatitis co-infection, determine CD4 + T lymphocyte count in co-infected patients, identify most common opportunistic infections in HIV – Hepatitis co- infection. **Materials and Methods:** A hospital-based, prospective, cross-sectional, and observational study was carried among people with confirmed HIV infection. HIV antibody, hepatitis B surface antigen (HBsAg), and HCV antibody tests were done in all patients visiting to integrated counseling and testing center. HIV, HBV, and HCV viral load were done in all serologically confirmed patients. In HBsAg positive patients various markers for hepatitis such as hepatitis B envelop antigen (HBeAg), anti-hepatitis B core antibody (HBcAb), and anti-hepatitis B envelop antibody were also done. **Results:** Out of 357 people living with HIV/AIDS (PLHA) patients 15/357 (4.20%) were co-infected with HBV, 03/357 (0.84%) were co-infected with HCV. The overall seroprevalence of Hepatitis virus (HBV + HCV) in PLHA patients was found to be 5.04% (18/357). CD4 + T lymphocyte count < 200 cells/μL was seen in 66/339 (19.4%), 04/15 (26.6%), and 03/03 (100%) patients of HIV mono-infected, HBV co-infected, and in HCV co-infected patients, respectively. HIV Viral load ≤ 1000 copies/mL was seen in 324 and 15 patients in HIV mono-infected and HIV- hepatitis co-infected patient, respectively. Among PLHA patients who were positive for HBsAg; 46.7% (n = 7) patients had HBV viral load > 2000 IU/mL. All hepatitis B co-infected patients were positive for HBcAb test; HBeAg was positive in 40% (n = 06). All HBeAg positive were having viral load > 2000 IU/mL. **Conclusion:** HIV-infected patients are more prone to hepatitis associated liver diseases and exposure to the HBV infection than the general population.

Key words: People living with HIV/AIDS; CD4 + count; HIV-Hepatitis virus co-infection; HIV-HBV and TB coinfection; Viral load

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INTRODUCTION

Hepatitis B virus (HBV), Hepatitis C virus (HCV), and Human immunodeficiency virus (HIV) infections are prevalent throughout the world. The prevalence is high not only in India but also in world.[1] The modes of transmission of HBV, HCV and HIV are similar due to overlapping of the common hematogenous route transfer. Therefore, it is a matter of public health concern throughout the world. However, the prevalence of HBV, HCV infection in AIDS

Address for Correspondence:
Dr. Riddhi Pradhan, Associate Professor, Department of Microbiology, R. D. Gardi Medical College, Ujjain, Madhya Pradesh, India.
Mobile: +91-9826074088. **E-mail:** riddhipradhan@yahoo.co.in

patients varies according to the risk factors involved and the initial burden of the disease in the local community.[2,3] This may differ not only from country to country but also in different regions of the same country. HBV and HCV co-infection in AIDS patient has emerged as a leading cause of morbidity due to liver disease throughout the world in the last two decades.[4] The HIV infected individuals, co-infected with HBV and/or HCV not only carry an increased risk of progression to severe liver disease which decreases their life expectancy but also have a high susceptibility toward antiretroviral therapy induced hepatotoxicity. HIV infection increases HBV and HCV associated liver disease especially when HIV-associated immunodeficiency progresses.[5,6] The current status regarding the incidences of HIV co-infection with HCV and/or HBV in Madhya Pradesh is very limited. Therefore, the aim of this research was to determine the occurrence and risk factors of Hepatitis virus infection in AIDS patients in urban and rural patients coming to our Tertiary Care Hospital, Ujjain. This study will be beneficial in predicting the risk of co-infection in AIDS patients and their effective management.

Aims and objectives

The present study was designed to estimate the prevalence of HIV-hepatitis coinfection, to determine CD4+T lymphocyte in HIV-hepatitis coinfection and to identify the most common opportunistic infections in these patients.

MATERIALS AND METHODS

This study was carried out during January 2021–June 2022, in the Department of Microbiology, R.D. Gardi Medical College (RDGMC) Ujjain, India. The research was approved by the ethics committee (IEC Ref no.- 491) of the RDGMC Institution. This was a hospital-based, prospective, cross-sectional, and observational study carried among people with confirmed HIV infection and attending the hospital for follow-ups at integrated counseling and testing center and antiretroviral treatment (ART) center of RDGMC.

Study population

All people living with HIV/AIDS (PLHA) who came for counseling, CD4+cell count and viral load at ART center of our hospital, and those who were ready to give a written consent were included. However, PLHA patients with co-infection of Hepatitis B/C and on treatment of Hepatitis infection or those who had Hepatitis B/C before the diagnosis of HIV were excluded from the study.

Sample size

The sample size was calculated based on the prevalence with an approximate 95% confidence level, we used the following formula:

$$n=z^2\times P\times(100-P)/d^2$$

Prevalence of=50%, (the prevalence of 50% will produce the largest sample size within the range of 10% and 90%)

Hence, the required sample size was calculated to be 384.

Methods

Detection of HIV infection

ErbaLisa® HIV Gen 3 (Transasia Bio-Medicals Limited, India) was used initially for detection of HIV as per manufacturer's instruction. It is a 3rd generation enzyme-linked immunoassay for the detection of total antibodies against HIV 1 and 2. It is based on principle of Sandwich ELISA. It detects the presence of total antibodies (IgM, IgG and IgA) against HIV-1 and HIV-2 (HIV antigens – gp36, gp41 and gp120) with diagnostic sensitivity of 100.00% and specificity of >99%. All reactive specimens were further confirmed by Abbott Real-Time HIV-1 assay. Abbott Real-Time HIV-1 assay (Abbott USA) is an *in vitro* reverse transcription-polymerase chain reaction (RT-PCR) assay for the quantitation of HIV-1 in whole blood spotted on cards as dried blood spots (DBS) (i.e., obtained through venipuncture or capillary blood) or human plasma from HIV-1 infected individuals.

Detection of HBV infection

ErbaLisa® SEN hepatitis B surface antigen (HBsAg) (Transasia Bio-Medicals Limited, India) was used initially for detection of HBV as per manufacturer's instruction. It is a third generation qualitative enzyme linked immunoassay for the detection of HBsAg using polyclonal anti-HBsAg antibodies for better sensitivity. All reactive specimens were further confirmed by Truenat HBV assay. Truenat HBV assay (Molbio Diagnostics Private Limited India) is a Chip-based Real Time PCR Test for HBV. It is used for quantitative estimation of the HBV in human blood/serum/plasma specimen and aids in the diagnosis of infection with HBV and in the estimation of viral load. All HBsAg positive patient were further tested for hepatitis B e antigen (HBeAg) and antibodies (Anti- hepatitis B envelop antibody [HBeAb] and Anti- Hepatitis B core antibody [HBcAb]) Insight (Tulip Diagnostics) by Rapid Immunochromatography Method.

Detection of HCV infection

ErbaLisa HCV Gen 3 v2 (Transasia Bio-Medicals Limited, India) was used initially for detection of HBV as per manufacturer's instruction. The kit utilizes a mixture of recombinant proteins of HCV, that is, Core, NS3, NS4, and NS5 for detection of anti-HCV antibodies with diagnostic sensitivity of 100% and Specificity of 100%. All reactive specimens were further confirmed by Truenat HCV assay. Truenat HCV assay (Molbio Diagnostics Private Limited

India) is a chip-based Real-Time RT-PCR test for the quantitative detection of HCV RNA in human plasma, serum, and whole blood samples. It aids in the diagnosis and confirmation of HCV infection (in conjunction with HCV antibody test) and in estimation of viral load.

Detection of hepatitis B viral markers

1. HBeAg (insight): HBeAg is based on the principle of agglutination of antibodies with respective antigen in an immunochromatography format along with use of nano-gold particles as agglutination
2. HBeAb (insight): HBeAb is based on the principle of agglutination of antibodies with respective antigen in the competitive immunochromatography format along with use of nano gold particles as agglutination
3. HBcAb (insight): HBcAb is based on the principle of agglutination of antibodies with respective antigen in the competitive immunochromatography format along with use of nano gold particles as agglutination.

Statistical analysis

SPSS version 22 was used to analyze the data. Chi-square test was used to find out the prevalence of HIV and co-infection with Hepatitis B and C. $P<0.05$ was considered statistically significant.

RESULTS

Socio-demographic and clinical characteristics of study participants

A total of 384 PLHA patients were enrolled in the present study over the period of one and half year. Twenty-seven subjects were excluded later as they were not ready to give the written consent because of some unknown reasons. Hence, out of 357 PLHA patients, 15/357 (4.20%) were co-infected with HBV, 03/357 (0.84%) were co-infected with HCV. However, none of the participants was co-infected with both HBV and HCV.

As shown in Table 1, majority of study participants were in the age group of 21–30 years (123/357; 34.45%). The mean age of participants was 37.62 years with standard deviation of 13.87.

Males accounted for the majority of the participants, that is, 219/357 (61.34%), whereas female participants were 136/357 (38.09%). There were only 02/357 (0.56%) transgender participants enrolled in this study.

The primary mode of transmission was found to be the heterosexuality. Among PLHA/HIV mono-infected patients, sexual route of transmission was 228/339 (67.26%); however, 11/15 (73.33%) HIV-HBV co-infected patients and 01/03 (33.3%) HIV-HCV co-infected patients acquired infection through sexual route as shown in Table 1.

Pulmonary TB was seen among 26/339 (7.7%) PLHA/HIV mono-infected patients. Only 02/15 (13.3%) of HIV-HBV co-infected patients were found to be TB positive, that is, HIV/HBV/TB co-infection, and 2/3 (66.6%), HIV-HCV co-infected patients found to be positive for TB infection, that is, HIV/HCV/TB co-infection and was statistically significant ($P=0.003$) as shown in Table 1.

The mean CD4+T lymphocyte count among PLHA patients was recorded as 452.19 cells/μL, whereas it was 336.40 cells/μL among HIV-HBV co-infected patients and 173.67 among HIV-HCV co-infected patients. Among PLHA-HBV co-infected patients, 273/339 (80.5%), 11/15 (73.3%) and patients had CD4+T lymphocyte count >200 cells/μL count, respectively, while none of HCV co-infected patient had CD4+T lymphocyte count >200 cells/μL. More than 95% ART adherence was observed among all the participants (100%). However, 66/339 (19.4%), 04/15 (26.6%), and 03/03 (100%) patients had <200 CD4+cells/μL, respectively, and it was statistically significant ($P=0.002$) as shown in Table 1.

Mean SGPT was 31.69U/L among PLHA patients, whereas it was 70.0 U/L in HBV co-infected patients and 37.57 U/L in HCV co-infected patients which was statistically significant ($P=0.000$) as shown in Table 1.

Seroprevalence of HIV, HIV-HBV and HIV-HCV

The overall seroprevalence of Hepatitis virus (HBV+HCV) in PLHA patients was found to be 5.04% (18/357).

HIV-HBV co-infection

Among Hepatitis co-infected participants, the prevalence of HBV was 4.20% (15/357). Among HIV-HBV co-infected participants, females were 53.33% (08/15), followed by males 33.33% (05/15) and transgenders were 13.33% (02/15). The highest HBV co-infection was seen in the age group of 31–40 years (06/15; 40%).

HIV-HCV co-infection

Among hepatitis co-infected participants, the prevalence of HCV was 0.84% (03/357). Only females (03/357; 0.84%) were found to be HIV-HCV co-infected. However, none of the male and transgender participants were co-infected with HCV infection. The highest HCV co-infected age group was 21–30 years (02/03; 66.67%).

HIV, HBV, and HCV both co-infection

Among the 357 PLHA participants, none were positive for all HIV, HBV, and HCV.

Table 1: Socio-demographic and clinical characteristics among PLHA, co-infected with HBV and HCV infection, n=357

Characteristics	PLHA; HIV mono-infected	Co-infected with HBV only	Co-infected with HCV only	Co infected with both HBV and HCV	Total	P-value
Clinical status	339	15	03	00	357	
Age group (years)						
≤10 years	13	00	00	-	13	
11–20 years	17	01	00	-	18	0.221
21–30 years	117	04	02	-	123	
31–40 years	84	06	01	-	91	
41–50 years	59	01	00	-	60	
51–60 years	36	00	00	-	36	
>60 years	13	03	00	-	16	
Gender						
Female	125	08	03	-	136	
Male	214	05	00	-	219	0.000
TG/TS	00	02	00	-	02	
Mode of transmission						
Sexual	228	11	02	-	241	
Vertical	16	00	00	-	16	0.000
Blood transfusion	02	00	01	-	03	
Drug abuse	00	01	00	-	01	
IDU	06	00	00	-	06	
MSM	03	00	00	-	03	
Probable unsafe injection	05	01	00	-	06	
Trucker	02	00	00	-	02	
Unknown	77	02	00	-	79	
Pulmonary TB	26	02	02	-	30	0.003
Extra pulmonary TB	16	02	00		18	
Baseline CD4 count (Mean)	452.19	336.40	173.67	-	-	0.047
SGPT levels (mean)	31.69	70.11	37.57	-	-	0.000
HB	11.74	8.74	8.17			0.107
CD4 (cells/mm^3)						
>200	273	11	00	-	284	0.002
<200	66	04	03	-	73	
Viral load						
>1000	15	03	00	-	18	0.007
≤1000	324	12	03	-	339	
Status of ART						
Yes	339	15	03	-	-	
No	00	00	00	-	-	
ART adherence (>95%)						
Yes	Yes	Yes	-	-		

HIV viral load count among study participants

Among all 339 mono-HIV infected participants, the HIV viral load count was >1000 copies/mL in 15 patients; however, viral load count s1000 copies/mL were seen in 324 patients. Among all 18 Hepatitis infected participants, the viral load count was >1000 copies/mL in 03 patients; however, viral load count atiti copies/mL were seen in 15 patients.

HBV viral load count and hepatitis marker

PLHA patients who were co-infected with HBV (HBsAg positive) were further tested for HBV viral load and various hepatitis markers such as (HBcAb), HBeAg, and HBeAb (Antibody against HBeAg). The average viral load for HBV was 5.38×10^7 IU/mL; 53.3% (n=8) patients were having viral copies <2000 IU/mL; and >2000 IU/mL viral load was found in46.7% (n=7) patients. All HBV co-infected patient tested positive for HBcAb. HBeAg was positive in 40% (n=06) HBsAg positive patients and was statistically significant (P=0.000) as shown in Table2 (b); all were having viral load >2000 IU/mL. HBeAb was positive in 40% (n=06); out of which 83.3% (n=5) were having HBV viral copies <2000 IU/mL.

HCV viral load in HCV Ab positive patients

PLHA patients who were co-infected with HCV (n=3) were further tested for HCV viral load. The average viral load was found to be 3466 IU/mL.

Table 2: HBV viral load and result of various hepatitis markers

(a)			
Hepatitis marker	**Viral load<2000 IU/mL**	**Viral load>2000 IU/mL**	
HBeAg positive (n=6)	0	6 (100%)	
Anti-HBcAb positive (n=15)	8 (53.4%)	7 (46.6%)	
Anti-HBeAb positive (n=6)	5 (80%)	1 (20%)	
(b)			**P-value**
HBeAg positive	0	6	0.000
HBeAg negative	09	0	
(c)			**P-value**
HBeAb positive	5	1	0.132
HBeAb negative	4	5	

HBeAg: Hepatitis B envelop antigen, HBcAb: Anti-hepatitis B core antibody, HBeAb: Hepatitis B envelop antibody, HBV: Hepatitis B virus

DISCUSSION

Hepatitis virus infection, especially HBV and HCV, is frequently found as a co-infection in HIV-positive patients; causing complications and leading to death. Globally, about 10% of HIV-infected individuals developed chronic HBV co-infection. But in hepatitis-endemic areas up to 20% of HIV infected individuals have developed HBV co-infection.[7] Therefore, this study determined the seroprevalence and associated factors of hepatitis co-infection in PLHA patients of Central India. In this study, the overall prevalence of HBV or HCV or both with HIV co-infection was about 5.04% (18/357). Among these, the proportions of co-infections for HIV-HBV, HIV-HCV were 4.20% and 0.84%, respectively; and none of the patients were all three (HIV-HBV-HCV) positive. However, Bhattarai et al.,[8] reported the prevalence of HIV-HBV, HIV-HCV and HIV-HBV-HCV was 3.62%, 2.93%, and 0.34%, respectively; and Shrestha et al., reported prevalence of 2.95% HIV-HBV, 18.14% HIV-HCV, and 2.53% HIV-HBV-HCV cases.[9] In a study by Ionita et al., the prevalence rate of HBV-HCV co-infection among PLHA in Nepal was 4.4% and 19%, respectively, in 2017.[10] In North India, the prevalence of HBV and HCV co-infection among PLHA was 5.32% and 2.43%, respectively.[11] In the present study, the true prevalence of co-infection of HIV-HBV as well as HIV-HCV among the study participants might be higher than the reported, if PCR test would have been performed in all PLHA patient along with HBsAg and HCV antibody.

HIV infected patients are more prone to exposure to the HBV infection than the general population. The following could be the reasons for the co-infection such as the two diseases have a similar route of transmission, similar risk groups and HIV patients are immunocompromised, which makes them susceptible to other opportunistic infections.[12]

In our study, all PLHA at age equal to and more than 40 years were less likely to be infected with HIV-HBV co-infection than those under 40 years. This finding is in contrast to the study by Choy et al., which showed that age 30–49 years and more than 50 years was significantly associated with HIV-HBV co-infection.[13] This lower proportion of HIV-HBV co-infection among elder HIV patients could be because of minor frequency of higher aged (≥40 years) HIV patients in this category. But the exact reason needs to be explained from other prospective studies. Moreover, it is consistent with the study reported by Yemanebrhane et al.[14]

The present study also reported HIV-HBV and HIV-HCV co-infections higher in male as compared to female (P=0.000). The reason could be the working profession of the males such as drivers who more often travels outstation.

In our study, HIV patients who acquired HIV through sexual route were more likely to have HIV-HBV co-infection as compared to those with other mode (P=0.000). Similarly, HIV patients infected through sexual mode were more likely to have HIV-HCV and HIV-HBV-HCV co-infections as compared to those with other mode. However, Shrestha et al.,[9] reported that patients who acquired HIV through intravenous drug use route were more likely to have HIV-HBV or HIV-HCV co-infections as compared to those with sexual mode.

The present study showed that HIV patients with CD4+T lymphocyte cells count <200 cells/μL were at higher risk of having co-infections as compared to patients with CD4+T lymphocyte cells ≥200 cells/μL (P=0.002). This is in accordance with a study by Bhattarai et al.,[8] which showed that HIV patients with CD4+T lymphocyte cells >200 cells/μL were 81% less likely to have HIV-HCV co-infection. The depleting CD4+T lymphocyte cells count is a marker of immune dysfunction and HIV progression[15,16] and indicators of acquiring multiple opportunistic infections and co-infections.[9] The mean SGPT (70U/L) levels were high in HIV co-infection (HIV and HBV) than in HIV alone (P=0.000), which is concordance with the study conducted in Nigeria.[17] The HIV viral load, 94.96% (339/357) patients had viral load i1000 copies/mL. The most probable reason for this could be the continuous ART. However, approximately 5% (18/357) of PLHA patients had viral load of >1000 copies/mL. Regarding the result of viral load, our results are contradictory to the results by Ayelign et al.,[7] who reported 88.2% (15/17) of the hepatitis co-infected groups had an abnormal high viral load which was >1000 copies/mL. HIV infection also decreases the rate of HBeAg clearance and increases the level of HBV replication as manifested by higher HBV DNA levels >2000 IU/mL in HBeAg positive patients,

same findings were observed by Colin et al.,[18] and Gilson et al.[19] There are inadequate data in HIV- HBV co-infection to determine the appropriate cutoff value for HBV DNA level for treatment initiation, but recommended a level of 2000 IU/mL.[20] In our study, pulmonary TB was seen among 26/339 (7.7%) PLHA HIV mono-infected patients, only02/15 (13.3%) of HBV co-infected patients were found to be TB positive (HIV/HBV/TB co-infection), similar finding were noted by Sarkar et al.[21]

Limitations of the study

The first strength of this study is it determined the viral load count and its association with HIV-HBV and HIV-HCV co-infection. Second, both the HBV and HCV co-infection were assessed.

This study has certain limitations. The sample was limited to those with PLHA only. We did not assess the prevalence of other hepatitis viruses in the HIV positive patients, such as hepatitis A, D and E. We did not differentiate the sexual mode of transmission, that is, heterosexual or homosexual. Furthermore, we did not categorize the co-infections for HIV-HBV, HIV-HCV, and HIV-HBV-HCV patients based on marital status, ethnicity, and educational qualifications. HIV-HBV co-infected patient should also be screened for possible Hepatocellular Carcinoma using serum tests for alpha-fetoprotein and imaging of the liver every 6 month because after HBV infection, HIV- infected persons are up to six-fold more likely to develop chronic hepatitis B than are HIV- negative individuals.[22]

CONCLUSION

HIV infected patients are more prone to hepatitis associated liver diseases and exposure to the HBV infection than the general population.

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Authors Contribution:
RP, KH, VK, and YM- Were responsible for conceptualizing the study design and preparation of first draft of the manuscript; **RP, KH, VK, BBL, and VS**- For data collection and analysis. All authors contributed to the development of final MS and approved it.

Work attributed to:
R.D. Gardi Medical College, Surasa, Ujjain - 456 006, Madhya Pradesh, India.

Orcid ID:
Dr. Riddhi Pradhan - https://orcid.org/0000-0003-1848-2370
Dr. Kirti Hemwani - https://orcid.org/0000-0001-9885-0836
Dr. Vidit Khandelwal - https://orcid.org/0000-0003-4161-6381
Dr. Yogyata Marothi - https://orcid.org/0000-0002-6783-7871
Dr. Bamboriya BL - https://orcid.org/0000-0002-3602-2995
Dr. Varsha Saxena - https://orcid.org/0000-0001-6457-4298

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