

HBV co-infection in HIV infected patients and its effect on progress of the disease

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Abstract

Introduction: Co-infection of Human Immunodeficiency Virus (HIV) and Hepatitis B Virus (HBV) is a common event due to similar routes of transmission, with significant clinical implications. Progression to liver disease is more rapid in HIV-HBV co-infected patients. The present study was designed to find the sero-prevalence of HBV in newly diagnosed HIV positive patients.

Materials and Methods: 200 newly diagnosed HIV positive cases were enrolled in present study. 3-5 cc blood was collected from these patients and HBsAg ELISA was carried out on serum obtained. HBsAg positive samples were processed further to detect HBeAg and anti-HBeAg by ELISA. Liver Function Tests (LFTs) and CD4 T cell count were noted.

Results: Out of 200 HIV positive patients, 4% were co-infected with HBV. Out of the 4% co-infected cases 37.5% were HBeAg positive and 62.5% were anti-HBe positive. None of the HIV-HBV co-infected case had a CD4 T-cell count >500 cells/ μ L whereas 55.2% of HIV mono-infected cases had CD4 T-cell counts > 500 cells/ μ L. 37.5% HIV-HBV co-infected cases had CD4 T-cell count \leq 200 cells/ μ L whereas only 11.4% HIV mono-infected cases had CD4 T-cell count \leq 200 cells/ μ L. HIV-HBV co-infected cases had more deranged liver enzymes. 50% of HIV-HBV co-infected cases belonged to WHO stage II, whereas majority (91.6%) of HIV mono-infected cases belonged to WHO stage I.

Conclusion: This study highlights that, routine screening of HBsAg should done in all HIV infected patients and virological markers of HBV, Liver Function Tests and CD4 T cell count of HIV-HBV co-infected patients should be assessed for appropriate management.

Keywords: HIV-HBV Co-infection-Correlation: CD4 Count, WHO staging, LFT.

Introduction

Human Immunodeficiency Virus (HIV) is one of the common infections in medical realm today. HIV is most commonly transmitted through blood which is also the most common route for spread of Hepatitis B Virus (HBV).¹ Hence individuals at risk of acquiring HIV are also at risk of acquiring hepatitis B viral infection.² According to WHO, chronic HBV infection affects an estimated 5–20% of people living with HIV, majority of them acquire the infection through sexual route and through infected blood and body fluids. In India, the prevalence of co-infection of HIV-HBV ranges from 9-30%.³⁻⁵ With upgraded treatment of HIV, life expectancy of HIV infected patients has increased. Due to improved life expectancy of HIV positive patients, liver disease has become an important cause of morbidity and mortality in HIV-HBV co-infected patients.^{3,6}

HIV-HBV co-infection has a deleterious effect on the outcome of patients especially if co-infected patients have chronic hepatitis B. These co-infected patients greatly complicate their management. HIV-positive individuals with chronic hepatitis B have more liver mortality than those infected with HIV alone.⁴

HIV promotes chronicity of Hepatitis B infection and increases the risk of liver fibrosis and hepatocellular carcinoma in HIV-HBV co-infected patients especially when CD4T cell counts are low.⁷ Co-infection of HBV with HIV infection results into considerable impairment of cell mediated responses and

augments the mechanisms of viral replication of HIV. It results in significant decline of CD4 T cell count in HIV-HBV co-infected patients.⁸ There is a quicker progression of HIV to AIDS-defining illness when HIV is co-infected with HBV.⁹

Co-infection with HBV may complicate the antiretroviral treatment of HIV. It fastens the progression of liver related pathogenicity which leads to increased risk of drug induced hepatotoxicity when ART is started in these patients.¹⁰

With this background the present study was particularly focused on sero-prevalence of HIV-HBV co-infection in newly diagnosed HIV infected patients. The cases enrolled in the study were HIV infected adults which were not started with Antiretroviral Therapy (ART). The study also throws light on the fact whether HIV-HBV co-infected cases had less CD4 count and more deranged levels of Liver Function Tests (LFT) than HIV mono-infected cases. Another important aspect of this study is to look for combined effect of HIV-HBV on WHO staging of HIV. In the present study, virological markers of Hepatitis B Virus like HBeAg and anti HBe were also assessed in HIV-HBV co-infected patients.

Materials and Methods

A Prospective, observational type of study was carried out in adult HIV infected patients attending to Integrated Testing and Counselling Centre (ICTC) of a tertiary care hospital over a period of two years. A total

of 200 newly diagnosed HIV infected cases not on ART were enrolled in the study after approval of Institutional Ethical Committee. HIV positive cases which were diagnosed with other opportunistic infections were excluded from the present study.

Written informed consent was taken from every participant. From each of the enrolled patient, 3-5 ml venous blood was collected using aseptic precautions. After clotting the serum was obtained was centrifuged at 3000 rpm for 10 minutes. The clear serum was then stored at -20°C till the serological tests were performed. All the serum samples were further processed to detect HBsAg by ELISA (Erba Lisa™ - Transasia). HIV positive patients who were HBsAg positive were considered as HIV-HBV co-infected. Serum samples of patients who were HIV-HBV co-infected were further investigated for presence of HBeAg or anti-HBe ELISA (MBS HBe Ag/Ab). Both ELISA tests were performed as per the manufacturer’s kit instructions. CD4+ T cell count of all the patients was noted. Liver function tests consisting of serum bilirubin, AST, ALT, ALP were recorded. Data was statistically analyzed using Microsoft Excel and SPSS 21.0 software. Appropriate statistical tests were applied to the data.

Results

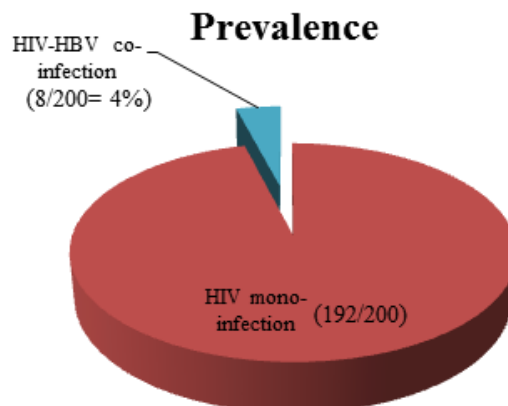


Fig. 1: Prevalence of HIV-HBV co-infections in study subjects (n=200)

Table 1: Virological markers of HBV in HIV-HBV co-infected cases (n=8)

Virological markers	Number (Percentage)
HBeAg	3 (37.5)
Anti-HBe	5 (62.5)
Total	8 (100)

3 out of 8 (37.5%) cases showed HBeAg positivity and 5 out of 8 (62.5%) cases showed presence of anti-HBe.

Table 2: CD4 T-cell counts in HIV-HBV co-infected and HIV mono-infected study subjects (n=200)

CD4 T-Cell count	Mean ± SD	≥500/mm ³	350-499/mm ³	200-349/mm ³	≤200/mm ³	‘t’ test P=0.01 Statistically significant
HIV-HBV co-infected n=8	291.8±121.1	0	3 (37.5%)	2 (25%)	3 (37.5%)	
HIV mono-infected n=192	529.2±273.1	106 (55.2%)	31 (16.1%)	33 (17.1%)	22 (11.4%)	

None of the HIV-HBV co-infected case had a CD4 T-cell count >500 cells/μL whereas maximum (55.2%) HIV mono-infected cases had CD4 T-cell counts > 500 cells/μL.

37.5% HIV-HBV co-infected cases had CD4 T-cell count ≤200 cells/μL whereas only 11.4% HIV mono-infected cases had CD4 T-cell count ≤200 cells/μL.

Table 3: Liver function tests in HIV-HBV co-infected and HIV mono-infected subjects. (n=200)

LFTs	Sr. bilirubin (mg/dl) Mean±SD	ALT (IU/L) Mean±SD	AST (IU/L) Mean±SD	ALP (IU/L) Mean±SD
Co-infected (n=8)	0.86 ± 0.31	58.37± 37.19	36.67± 32.91	129.25± 28.75
Mono-infected (n=192)	0.67± 0.44	37.26± 21.95	25.23± 11.73	70.61± 26.87
t test	P=0.22	P=0.01	P=0.01	P <0.0001

Serum Bilirubin levels were higher among HIV-HBV co-infected cases than HIV mono-infected cases though the difference was not statistically significant. (p=0.22).

Serum ALT and AST levels were higher among HIV-HBV co-infected cases than HIV mono-infected cases. The difference was statistically significant. (p=0.01).

Serum ALP levels were significantly raised levels among co-infected cases than HIV mono-infected cases. (p= <0.0001).

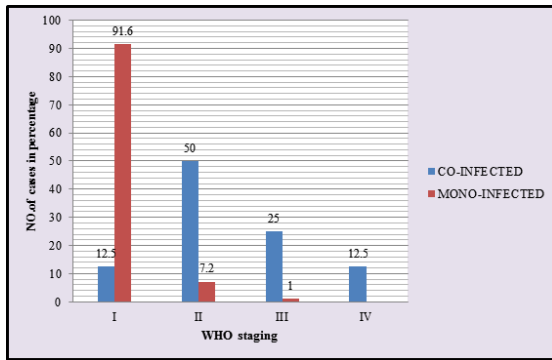


Fig. 2: WHO stages of HIV-HBV co-infected and HIV mono-infected subjects

91.6% of the HIV mono-infected subjects presented as WHO stage I, while only 12.5% subjects with HIV-HBV co-infection presented as WHO stage I. Only 7.2% mono-infected subjects presented as WHO stage II whereas 50% of the co-infected subjects presented as WHO stage II. Only 1% of mono-infected cases had a presentation of WHO stage III as compared to 25% of HIV-HBV co-infected cases.

None of the mono-infected case presented as WHO stage IV whereas, 12.5% co-infected cases presented as WHO stage IV.

Discussion

The co-infection with HBV composes a major health problem in patients infected with HIV. As HBV and HIV share a similar transmission pathway; they are often diagnosed in the same patient. Co-infection of HIV with HBV bring about higher viral load of hepatitis virus, decreasing the rate of HBsAg clearance and increased liver damage. HIV-HBV co-infected patients have a tendency of faster progression towards hepatic fibrosis. Another important concern is the effect of co-infection on liver. HIV-HBV co-infection has a hostile impact on liver disease. (10,1). In case of HIV-HBV co-infection, about 20% of patients develop chronic HBV infection.¹¹ The impact of HBV results in failure in immunological recovery in HIV positive patients. The treatment of co-infection is always challenging because Antiretroviral Therapy is often hepatotoxic in these patients.^{4, 12} As a result, assessment of HIV-HBV co-infection is very important so that therapeutic decisions are made correctly.^{7, 13}

The present study was aimed to know the seroprevalence of HBV co-infections in 200 randomly selected HIV positive patients before initiating ART, who attended an ICTC of a tertiary care hospital. HIV positive patients which demonstrated presence of HBsAg by ELISA were considered as having HIV-HBV co-infection. HIV-HBV co-infected patients were further assessed for presence of virological markers like HBeAg and anti-HBe by ELISA. As hepatic system is an important target of these viruses, we assessed the

participants for derangement of liver functions. Co-infections frequently complicate the immunological responses of host. CD4 T cell count of all HIV-HBV co-infected and HIV mono-infected cases was noted as well. A relation of HIV-HBV co-infection with clinical stages of HIV, LFTs was assessed.

The overall prevalence of HIV-HBV co-infection in HIV positive patients in the present study was 4%. The seroprevalence of HIV-HBV co-infection in similar studies by Padmapriyadarsini C et al,¹⁴ Swarn K et al,¹⁵ Lodenyo H et al,¹⁶ Mendes-Correa MCJ et al¹⁷ and Tripathi AK et al¹⁸ ranged from 2.25-6.4% which was comparable with the prevalence of present study.

Studies done by Hooja S et al,¹⁹ Jabbari H et al,²⁰ Denis F et al,²¹ Mohammadi M et al,²² Barth RE et al,²³ Alo M et al,²⁴ Sonth SB et al,²⁵ reported high prevalence of HIV-HBV co-infection than present study ranging from 12-30.4%. Tankhiwale SS et al⁴ (30.4%), Sonth SB et al²⁵ (21%), Chandra N et al²⁶ (15%), Hooja S et al¹⁹ (12%) studies from India also showed high sero-prevalence of HIV-HBV co-infection than present study. Tripathi et al¹⁸ (89%) concluded that seroprevalence of HIV-HBV depends on high or low risk of study population. In the present study HIV seropositive patients enrolled were not on ART and randomly selected. High risk group such as IDUs was not the selection criteria for enrolling the patient in present study. This could be the reason for low seroprevalence of HIV-HBV co-infection observed in present study than similar some of the other studies. Tripathi et al¹⁸ (89%) concluded that HIV-HBV prevalence of co-infection also depends on availability of better diagnostic facilities, increased awareness among physicians and patients and increased life span of HIV infected individuals due to availability of better treatment options. Geographical variation is one of the major determinants of difference in seroprevalence of HIV-HBV in various studies.²⁷

The sera of HBsAg positive cases were also evaluated further for presence of HBeAg or anti-HBe by using HBe Ag/Ab ELISA. Out of these 8 HIV-HBV co-infected cases, 3 cases (37.5%) showed presence of HBeAg. These results were analogous with similar studies done by Geretti AM et al²⁸ and Chandra N et al.²⁶ The presence of HBeAg in chronic infection indicates that HBV is actively replicating and there is a high probability of liver damage.²⁹ Presence of HBeAg correlates with the high levels of HBV replication and infectivity.²⁹ The present study demonstrated presence of anti-HBe in 5/8 (62.5%) cases. This result was in agreement with the results found by Chandra N et al,²⁶ Saravanan et al.³⁰ Loss of HBeAg and appearance of anti-HBe is a favourable serological marker during acute hepatitis B, indicating the initiation of recovery.²⁹

In the present study, the mean CD4 T-cell count among HIV mono-infected subjects was 529.2±273.1 cells/μL. This was statistically significantly higher than HIV-HBV co-infected cases (291.8±121.1cells/μL)

($p=0.01$). The low CD4 T cell count in HIV- HBV co-infected patients as compared to HIV mono-infected patients was also found by Alo M et al (69), Idoko J et al,³¹ Sarkar J et al,³² Adewole OO et al,⁹ Wondimeneh Y et al.⁷ They indicated that HIV-HBV co- infection is associated with rapid decline in CD4 T-cell counts. Study by Wondimeneh Y et al⁷ suggested that the difference in CD4 T-cell count of HIV-HBV co-infected and HIV mono-infected was due to high viral replication of hepatitis B contributing for the impairment of an immune system of the patients in case of co-infection.

In present study, (55.2%) of the mono-infected cases had their CD4 T-cell counts ≥ 500 cells/ μ L, whereas none of the co-infected cases had CD4 T-cell counts ≥ 500 cells/ μ L. Only 11.4% of mono-infected cases showed CD4 T-cell counts ≤ 200 cells/ μ L, as compared to 37.5% of HIV-HBV co-infected cases. The severe immunosuppression in HIV-HBV co-infected cases was reflected by CD4 T-cell counts below 200 cells/ μ L. The results of studies carried out by Chandra N et al,²⁶ Tripathi AK et al¹⁸ and Das R et al³³ on comparison of CD4 T-cell count in HIV-HBV co-infected and HIV mono-infected were comparable with the present study. Sarkar J et al²⁷ have explained the possible mechanism for lower CD4 T-cell count in HIV-HBV co-infected patients than HIV mono-infected patients. They suggested that there is an immune activation due to chronic hepatitis B infection in HIV-HBV co-infected cases which increases apoptosis of CD4 T-cells. Olawumi HO et al¹³ concluded that determination of CD4 T-cell count is essential in HIV-HBV co-infected patients as the patients who have low CD4 T-cell count have accelerated hepatic complications such as hepatocellular carcinoma. Hence from present study we can suggest that detection and frequent monitoring of CD4 T-cell count is essential in HIV-HBV co-infected patients.

All HIV mono-infected and HIV-HBV co-infected cases were evaluated for liver enzymes. The mean serum bilirubin levels among HIV mono-infected and HIV-HBV co-infected participants were 0.67 mg/dL and 0.86 mg/dL, respectively. It was higher in HIV-HBV co-infected cases as compared to HIV mono-infected cases though the difference was not statistically significant. ($p=0.22$). Study done by Iroezindu MO et al³⁴ also observed higher mean bilirubin (10.91 \pm 10.37mmol/L) in HIV-HBV co-infected patients as compared to HIV mono-infected patients.

In present study, mean ALT in HIV mono-infected patients was 37.26 \pm 21.95 IU, whereas the mean ALT in HIV-HBV co-infected patients was 58.37 \pm 37.19 IU. The level of mean ALT in HIV-HBV co-infected cases was raised as compared to mean level in HIV mono-infected cases. This difference was statistically significant. ($p=0.01$). Chandra N et al²⁶ and Tripathi AK et al¹⁸ also found significantly raised ALT levels in

HIV-HBV co-infected patients than HIV mono-infected cases. In a study done by Olawumi HO et al,¹³ also recommended that raised ALT at baseline is an indication of the liver damage and hence in management of such patients the hepato-toxic drugs should be escaped in ART.

In present study, the mean AST in HIV mono-infected and HIV-HBV co-infected was 25.23 \pm 11.73 IU and 36.67 \pm 32.91 IU respectively. The mean level of AST was higher in HIV-HBV co-infected cases than HIV mono-infected cases. The difference in the levels of AST in HIV mono-infected and HIV-HBV co-infected was statistically significant. ($p=0.01$). The results were similar with the results of studies performed by Adewole OO et al,⁹ Mukherjee T et al,¹² Sarkar J et al.³²

The mean ALP in HIV mono-infected and HIV-HBV co-infected cases of the present study was 70.61 \pm 26.87 IU and 129.25 \pm 28.75 IU respectively. The difference was found to be statistically significant. ($p < 0.0001$). A study by Wondimeneh Y et al⁷ concluded that HIV can infect the kupffer cells which further participate in the development of liver fibrosis and this could be the cause for raised liver enzymes.⁷ Duration of viral hepatitis plays an important role in fluctuations in levels of liver enzymes in HIV-HBV co-infected cases. Other factors such as chronic alcoholism and hepato-toxicity due to other drugs also have impact in levels of liver enzymes.^{7, 35} Assessment of liver function tests is reasonably priced and is a non-invasive technique to evaluate extent of liver damage in HIV-HBV co-infected patients. Hence, we suggest that every patient of HIV-HBV co-infection should undergo an assessment for liver enzymes. This would facilitate the clinicians to settle on an effective management of such patients.

WHO stages were assigned to all the participants enrolled in the study. 91.6% of the HIV mono-infected subjects presented as WHO stage I, while only 12.5% subjects with HIV-HBV co-infection presented as WHO stage I. Only 7.2% mono-infected subjects presented as WHO stage II whereas 50% of the co-infected subjects presented as WHO stage II. Only 1% of mono-infected cases had a presentation of WHO stage III as compared to 25% of HIV-HBV co-infected cases. None of the mono-infected case presented as WHO stage IV whereas, 12.5% co-infected cases presented as WHO stage IV. This indicates that in HIV-HBV co-infected cases rapid progression of WHO stages of HIV occurs, from stage I to stage IV. This progression is comparatively less in HIV mono-infected cases. These results were in line with the similar studies by Sarkar J et al,³² Adewole OO et al⁹ Recent molecular studies have demonstrated that the HBx gene present in hepatitis B virus promotes a faster evolution of Acquired Immuno Deficiency Syndrome (AIDS) in HIV-HBV co-infected individuals. Hence these patients are liable to have advanced WHO stages.¹²

The limitation of the present study was small sample size. Larger multicentre studies are needed to get an appropriate estimate of the burden of HIV-HBV co-infection in the community. There is a necessity for a responsiveness among patients and health-care providers about this co-infection. Accessibility of hepatitis B screening at ICTCs may perhaps be useful in identifying undiagnosed hepatitis B co-infection in HIV infected individuals.

Conclusions

In present study, prevalence of HIV-HBV co-infection was 4%. Among the co-infected cases, 37.5% were HBeAg positive and 62.5% were anti-HBe positive. Mean CD4 count among these co-infected cases was less than HIV mono-infected cases.

Serum ALT, AST and ALP were raised in HIV-HBV co-infected patients as compared to HIV mono infected patients. HIV-HBV co-infection leads to worsening of WHO clinical staging of HIV.

We recommend screening of all HIV positive patients for HBV co-infection before commencement of ART. In case of HIV-HBV co-infection, LFT, CD4 count and WHO clinical staging and virological markers such as HBeAg and anti-HBe should be looked for an appropriate management.

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