ORIGINAL REPORT

Hepatitis-C and Hepatitis-B Co-Infections in Patients with Human Immunodeficiency Virus in Tehran, Iran

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Abstract- We carried out a study to determine the seroprevalence of HBV and HCV infections in HIV positive patients at a main referral center for HIV/AIDS in Iran. Serum samples from 201 HIV positive patients referring to a referral center for HIV/AIDS were analyzed for the presence of some hepatitis B (HBsAg, anti-HBc, anti-HBs) and Hepatitis C (anti-HCV) markers, during 2004- 2005. HBsAg was positive in 27 patients (13.4%), anti-HBc was positive in 60 patients (29.8%) and anti-HBs in 23 patients (11.4%). Anti-HCV Ab was positive in 135 of 201 (67.2%). HBV and HCV coinfection was observed in 73 of 201 (36.3%). The maximum prevalence of HBV-HIV and HCV-HIV coinfections were seen in intravenous drug users; 61.2% and 85.1%, respectively (P<0.0001). The minimum prevalence of HBV-HIV and HCV-HIV were seen in HIV patients´wife (HIV^+ patients who were infected by monogamous sexual contact with their HIV positive husband) both of them were 8% (P<0.0001). This study showed that HBV-HIV and HCV-HIV coinfections are significant in patients with HIV/AIDS in Iran. A greater relevance was observed in the association between HCV and HIV. This study suggests that it is necessary to investigate risk factors and risk groups for these infections in Iran.

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Introduction

The worldwide epidemic of hepatitis B, hepatitis C and HIV have led to new understanding of the complicated interactions between these viruses. Coinfection with HIV has a major impact on the natural history, diagnosis, progression and morbidity and mortality. An estimated one-third of death in HIV patients are directly or indirectly related to liver disease. Liver disease in HIV patients can occur due to hepatitis B virus and hepatitis C virus coinfections, chronic alcoholism, hepatic tuberculosis or due to the effects of anti-retroviral therapy (1, 2).

Coinfection of HBV and HCV with HIV has been associated with reduced survival, increase risk of progress to liver disease and hepatotoxicity associated with anti- retroviral therapy. Hepatitis B and C viruses and HIV share the same routes of transmission, as a consequence, infection with HBV and HCV are expected in HIV infected patients. Worldwide, HIV is responsible for around 38.6 million infections as estimated at the end of 2005 (3). While HBV and HCV account for around 370 million and 130 million chronic infections, respectively moreover among the HIV infected patients, 2-4 million are coinfected with HCV (4). Chronic HBV affects approximately 10 percent of HIV infected patients worldwide (5). In a study of 16248 HIV infected patients in USA found that prevalence of chronic HBV was 8% among unvaccinated patients (6).

The reported co-infection rates of HBV and HCV in HIV patients have been variable worldwide depending on the geographical region, risk groups, and types of exposure involved (4, 7-10). In USA, approximately 30% of the estimated 800000 patients who are HIV infected are also co-infected with HCV (11). Similar rates have been reported from Europe. In USA and Europe, HIV-HBV coinfection is reported in 6%-14% of all patients infected with HIV (4, 7), while HIV-HCV coinfection has been variably reported ranging from

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25% to almost 50% of these patients (8, 9). Evidence of exposure to HBV and HCV has been found in 8.7% and 7.8%, of HIV patients from Thailand retrospectively (10). In Southeast Asia, in India coinfection of HIV-HBV is reported from 6%-16 % (2, 12, 13). Similarly HIV-HCV coinfection rates also vary from 4.8%-21.4% in south India to 30% in western India to as high as 92% in northeast (2, 12, 14, 15).

Anti-HCV antibody testing on 1649 CAESAR (Canada, Australia, Europe, South Africa) study participants demonstrated an HIV-HCV coinfection prevalence of 16.1% which varied from 1.9% in south Africa to 48.6% in Italy (16). Prevalence of HCV-HIV coinfection was 16.9% in Slovenia (17). In other investigations, the prevalence of HBV markers (HBsAg, anti-HBc, anti-HBs) were 4.6%, 38.5%, 26%, respectively, and prevalence of HIV-HCV coinfection was 38.2% (18). In Portugal, the rate of HCV-HBV coinfections in HIV patients was 2.4% (18). In Germany 9% of HIV patients had HBV chronic infection, and 23% had anti-HCV antibodies (19).

While HIV-HBV coinfection has been linked to both sexual and intravenous injection route of transmission, the HCV-HIV coinfection has predominantly been associated with non sexual parental route of transmission. In Iran, HIV infection is predominantly acquired through drug injection. To our knowledge, there is no published study from Iran to evaluate transmission aspects of these two hepatitis viruses in HIV positive patients, so we set out to determine the seroprevalence of hepatitis B and C virus infection in HIV positive patients at a main referral center hospital for HIV/AIDS located in Tehran, capital of Iran.

Materials and Methods

This study was carried out at the outpatient department and inpatient ward for infectious diseases at Imam Khomeini hospital which holds 1000 beds and is the largest governmental referral hospital in Iran. The study was conducted with the approval of the institutional review board of Tehran University of Medical Sciences. The study period was during March 2004-2005.

Patients attending at clinic were screened for HIV based on clinical subsection after pretest counseling and achieving the informed consent as a routine checkup. Our laboratory follows the world health organization (WHO) diagnostic strategies for HIV testing. Only the positive serum samples were included in this study and were anonymously tested for HBsAg, anti-HBc, and anti-HBs.

Viral diagnosis

The serum samples which were found to be HIV positive according to WHO testing strategies were coded and stored at -20 degree Celsius. The coded samples anonymously tested using enzyme linked immunosorbent assay (ELIZA) kit at a late date for presence of HBsAg, anti-HBc, anti-HBs (Cat. No.B9 280252, bio Merieux, France) and anti-HCV (DETECT-HCVTM Third generation, Cat. No. HCA 702B/700B, Adaltis, Italy). All serum samples were tested in duplicate.

Statistical analysis

Data was analyzed by using statistical software SPSS version 11.5 for windows (SPSS Inc. Chicago). Comparison of proportion was done using chi-square test. $P<0.05$ was taken as significant.

Results

Sera from a total of 201 HIV positive patients were collected in this study. The demographic data of these subjects showed that out the 201 patients, 172 (85.6%) were males and 29 (14.4%) were females. The mean age of study group was 36 years (SD=9.2, SE=0.65).

The majority of HIV infected patients comprised the 31-40 years old (41.7%), followed by 41-50 years (26.8%) and 21-30 years (26.3%). Mean age of HIV positive men was 36 years old (SD=9.2, SE=0.6) with the range of 3-62 years. The prominent mode of HIV transmission in these patients was intravenous drug use (IDU); 67 of 201 (33.3%) followed by HIV patients´ wife 25 of 201 (12.43%) (HIV^+ patients who were infected by monogamous sexual contact with their HIV positive husband), unsafe sex with multiple partners 15 of 201 (7.5%), blood transfusion; 8 of 201 (4%), more than one risk factor; 72 of 201 (35.7%). Overall the seroprevalence of hepatitis B in HIV patients was 44.3% (89 of 201). Among the coinfected HBV-HIV patients, there were 86 males and 3 females. HBsAg was positive in 27 of 201 (13.43%), anti-HBc was positive in 60 of 201 (29.85%) and anti-HBs was positive in 23 of 201(11.44%). Among males, HBV-HIV coinfection was seen in 86 of 172 (50%) while HBV was positive in only 3 of 29 females (10.3%). HBV coinfection rates were significantly higher in HIV positive men than women ($P<0.0001$). Anti-HCV Ab was detected in 135 of 201 (67.2%) of all patients. The rate of HCV-HIV coinfection was 135 of 201 (67.2%); among these 135 cases there were 133 males and 2 females. Among males, HCV-HIV coinfection was seen in 133 of 172

(77.3%), while only 2 of 29 females (6.9%) were HCV positive. Also HCV coinfection rates were significantly higher in HIV positive men than women (*P*<0.0001) (Table 1).

The maximum prevalence of HBV-HIV coinfection was seen in 61-70 years age group (100%) followed by 31-40 years age group (52.4%). The mean age of HBV-HIV coinfected patients was 37.18 (SD=8.6, SE=0.92) (Figure 1).

HCV-HIV coinfection was seen highest in the 51-60 years age group (75%), followed by 31-40 years age group (69%) (Figure 1).

The mean age of HIV-HCV coinfected patients was 36.5 years (SD=8.4, SE=0.72). The maximum prevalence of HBV-HCV coinfection was seen in 31-40 years age group (47%) followed by 41-50 years age group (30%) and the mean age of patients with HBV-HCV coinfection was 36.51 years (SD=8.4, SE=0.72) (Figure 1).

Details about seroprevalence of hepatitis B and hepatitis C coinfections according to the route of HIV transmission were seen in Table 2.

Maximum prevalence of HBV–HCV coinfection in HIV positive patients was in IDUs, and minimum was in HIV patients' wife. History of intravenous drug use was associated with both HBV and HCV coinfections (*P*<0.0001).

We divided CD4 count of patients into three groups 1: CD4≤200, 2: 200<CD4 count<500, 3: CD4≥500. Seroprevalence of hepatitis B, hepatitis C and hepatitis B, C were similar in different CD4 level (Figure 2) and there was no association between CD4 count and seroprevalence of hepatitis B, hepatitis C and hepatitis B, C in HIV positive patients (*P*=Not Significant).

Table 1. Seroprevalence of hepatitis B and hepatitis C in HIV positive patients by sex

	Male	***Female***	***P* Value**
Hepatitis B	86 (50%)	3 (10.3%)	*P*<0.0001
Hepatitis C	133 (77.3%)	2 (6.9%)	*P*<0.0001
Hepatitis B, C	73 (42.4%)	0 (0%)	*P*<0.0001

Table 2. Prevalence of hepatitis B, hepatitis C in HIV positive patients by the route of HIV transmission

Route of HIV Transmission	**Hepatitis B Number (%)**	**Hepatitis C Number (%)**	**Hepatitis B,C Number (%)**	***P* Value**
Blood Transfusion	2(25%)	6 (75%)	2 (25%)	NS
Unsafe Sex (multiple sexual partners)	5 (33.3%)	6 (40%)	3 (20%)	NS
IDU	41(61.2%)	57(85.1%)	38 (56.7%)	P<0.0001
Other (Tattoo, Vertical)	6 (42.9%)	6 (42.9%)	3 (21.4%)	NS
Unsafe Sex (monogamous HIV infected husband)	2 (8%)	2 (8%)	0 (0%)	*P*<0.0001
More than one Risk Factor	33 (45.8%)	58 (80.6%)	27(37.5%)	*P*<0.003

***NS*:** Not Significant

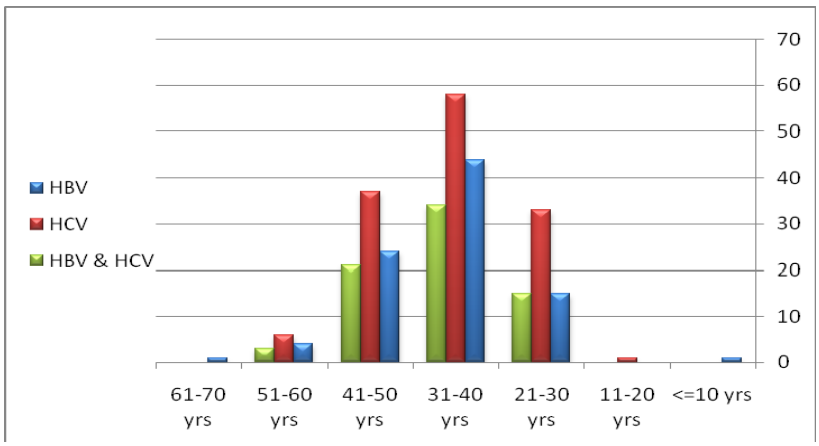

Figure 1. Prevalence (No.) of hepatitis B, hepatitis C in HIV patients by age groups

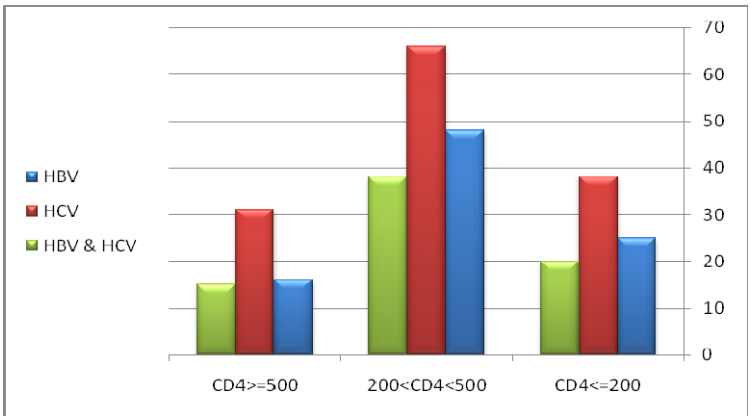

Figure 2. Prevalence (No.) of hepatitis B, hepatitis C in HIV patients by CD4 count

Discussion

The joint United Nations program on HIV/AIDS (UNAIDS) estimated that 38.6 million people were living with HIV globally at the end of 2005 (3) globally around three million people died of acquired immunodeficiency syndrome (AIDS) related disease in 2005 (3). It has been estimated that about on third of these deaths are in someway related to liver disease while this is predominantly a reflection of the problem encountered in the setting of coinfection with hepatitis B or C (20). Liver damage maybe directly related to HIV infection or may result from alcoholism, prior viral hepatitis or intravenous drug abuse (2). In addition, sepsis, malnutrition, or the administration of possibly hepatotoxic antiretroviral medication may also lead to liver damage. Due to declining opportunistic infection as a result of highly active antiretroviral therapy a new focus has emerged on the morbidity and mortality related to hepatitis B, hepatitis C and end stage liver disease. The interactions between HCV, HBV and HIV influence the diagnosis, evaluation, treatment and overall management of these patients.

Our study showed that the seroprevalence of hepatitis B (44.3%) and hepatitis C (67.2%) were significantly high. HIV-HBV coinfection has been reported in USA, and Europe in 6%-14% (4, 14) of all patients. While HCV-HIV coinfection has been variably reported from 25% to 50% (8, 9).

There are also different reports from Asia; HBV-HIV and HCV-HIV coinfections have been found in 8.7%to 7.8% in HIV positive patients from Thailand (10). In India prevalence of HIV-HBV is reported from 6-16% (2, 12-15) and HCV-HIV coinfection vary from 4.8-21.4% in South India also to 30% in Western India to as high as 92% in north east (16, 21). In South Africa in 9% of HIV positive patients were positive for HCV antibodies.

As noted before, we evaluated all HIV positive patients for HBV markers (HBsAg, anti-HBc, anti-HBs) that showed HBsAg in 13.4%, anti-HBc in 29.8%, and anti-HBs in 11.4% of all patients were positive.

Comparing results of a study from Portugal (HBsAg; 4.6%, anti-HBc; 38.5% and anti-HBs; 26%) (18, 19) with our study shows that the rate of HBV-HCV coinfection was 36.3% but in a study from Portugal was 2.4% (18) and 0% in India (22).

Also a significant risk for HBV was seen in men (50%) comparable with women (10.3%) (P<0.0001). This is similar to previous reports that male gender is associated with significant high risk for coinfection with HBV (4, 22).

HCV prevalence in our study group was higher than western countries (like USA and Europe) (8, 9). Saha *et al* reported that an HCV coinfection of 92% in IDUs from northeast India (15) while HCV-HIV coinfection in the report by Kumarasamy *et al.* was seen at 4.8% in HIV positive patients in south of India (12).

In present study seroprevalence of HCV-HIV and HBV-HIV coinfections were 67.2%, 44.3%, respectively. Also HCV Ab was detected in 67.2% of all patients. The most of HIV transmission risk factor was intravenous drug use followed by patients with more than one HIV transmission risk factor. The maximum prevalence of HCV-HIV coinfection was 85.1% in IDUs (P<0.0001) followed by 80.6% in patients with more than one risk factor, and 75% in patients with history of blood transfusion, but in HIV patients´ wife (HIV+ patients who were infected by monogamous sexual contact with their HIV positive husband), prevalence of HCV-HIV coinfection was minimum 8% (P<0.0001). As previously mentioned HCV-HIV coinfection has

association with HIV transmission risk factors. HIV is much more easily transmissible than HCV via intercourse (23, 24) among monogamous couples the risk of HCV transmission is exceedingly low (25). However the risk of HCV transmission appears to increase in multiple sexual partners (26).

There are some similar advantages in other studies: in Italy HBV-HIV coinfections was 82% in IDUs whereas anti-HCV prevalence was 72% in IDUs and only 7% in homosexuals (P<0.0001)(21) and also in a study from Portugal the main risk factor for HCV-HIV coinfection was intravenous drug injection (18). In an investigation from Thailand and also Slovenia, it was mentioned that history of intravenous drug abuse was associated with both HBV and HCV coinfections (P<0.0001) (10, 16).

In Iran, however, most of women are in monogamous relationship with their husbands and usually acquire HIV infection from their spouse, therefore while the risk for HCV acquisition in steady monogamous relationship is quite low (27). Also, there was no association between seroprevalence of HBV and HCV with age groups and CD4 count in HBV and HCV coinfections in HIV patients (P=Not Significant).

At present limited data is available about affects of HBV and HCV coinfections on HIV induced liver disease as a leading cause of significant morbidity and mortality in these patients (8, 9). HCV-HIV coinfection is more severe than HCV mono-infection and have a faster rate of liver fibrosis (28, 29).

There is some evidence that HIV can modify HBV infection course (5, 30). HIV subjects have higher rate of chronic HBV carriage. The impact of HIV on the outcome of HBV is controversial (31); some of the articles showed accelerated progression toward cirrhosis while others concerned decreased liver necro-inflammatory process (32). It's evident that early diagnosis and initiation of therapy before marked immunosuppression set in could be highly beneficial for HIV patients. Coinfection of HIV with HBV and HCV viruses were seen in 44.3% and 67.2% of all patients, respectively. A high percentage of HIV-infected patients in Iran were coinfected with hepatitis viruses, especially HCV. The prevalence of HBV-HCV coinfection was 36.3%. HIV transmission risk factors were associated with prevalence of HIV, HBV and HCV coinfections.

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