

Hepatitis B or hepatitis C co-infection in individuals infected with human immunodeficiency virus and effect of anti-tuberculosis drugs on liver function

Padmapriyadarsini C, Chandrabose J*, Victor L, Hanna LE, Arunkumar N, Swaminathan S

Tuberculosis Research Centre, Chetput, Chennai - 600031 and *Department of Zoology, Madras Christian College, Tambaram, Chennai - 600059, India.

Correspondence: Soumya Swaminathan, E-mail: doctorsoumya@yahoo.com

ABSTRACT

Background: Tuberculosis (TB) and hepatitis are the two common co-infections in patients infected with human immunodeficiency virus (HIV). Anti-tuberculosis treatment (ATT) may have an effect on the liver enzymes in these co-infected HIV patients.

Aims: To determine the prevalence of Hepatitis B and C virus coinfection in HIV infected patients in Tamilnadu and assess effects of anti-tuberculosis drugs on their liver function.

Settings: HIV positive subjects referred to the Tuberculosis Research Centre, Chennai

Materials and Methods: All HIV infected patients referred to the Tuberculosis Research centre, from March 2000 to May 2004, were screened for Hepatitis B surface antigen (HBsAg) & Hepatitis C virus (HCV) antibodies by enzyme linked immunoabsorbent assay (ELISA). HIV infection was confirmed using two rapid tests and one ELISA. Patients were given either short- course anti-tuberculosis treatment or preventive therapy for tuberculosis, depending on the presence or absence of active TB, if their baseline liver functions were within normal limits. None of these patients were on antiretroviral therapy during the study period.

Statistical Analysis: Paired t-test was used to find the significance between baseline and end of treatment liver enzymes levels, while logistic regression was done for assessing various associations.

Results: Of the 951 HIV-infected patients, 61 patients (6.4%) were HBsAg positive, 20 (2.1%) had demonstrable anti HCV antibodies in their blood. Serial estimation of liver enzymes in 140 HIV patients (81 being co-infected with either HBV or HCV) showed that 95% did not develop any liver toxicity while they were on anti-tuberculosis treatment or prophylaxis.

Conclusions: The prevalence of hepatitis B and C coinfection was fairly high in this largely heterosexually infected population supporting the use of more careful screening for these viruses in HIV positive persons in this region. Anti-tuberculosis therapy as well as TB preventive therapy can be safely employed in HIV and hepatitis coinfecting patients, if baseline liver function tests are within normal limits.

KEY WORDS: HIV, Hepatitis B, Hepatitis C, antituberculosis therapy

Tuberculosis and viral hepatitis are two of the commonest co-infections, seen among HIV-positive patients worldwide. Infection with hepatitis B (HBV) and hepatitis C viruses (HCV) are especially common and more significant in HIV patients. Though there is some data on the prevalence of these infections in the general population in India,^[1] there is limited information from HIV infected individuals.^[2,3] The main mode of spread of HIV in India is heterosexual, with blood products and intravenous drug use accounting for less than 5% of the infections.

Tuberculosis (TB) is the commonest opportunistic infection

in HIV-infected patients in India and most of the drugs used in anti-tuberculosis treatment (ATT) cause varying degrees of hepatotoxicity. Fatal hepatotoxicity although rare, has been reported.^[4] One study has demonstrated that in patients with pre-existing liver injury due to hepatitis C virus, the relative risk of developing drug-induced hepatitis was increased 14.4 fold ($P < 0.002$).^[5] However, the impact of anti tuberculosis treatment on the liver enzymes in patients co-infected with HIV and hepatitis in India has not been described. We therefore sought to determine: (i) the prevalence of hepatitis B and C infection in patients infected with HIV in Tamilnadu, and (ii) the risk of hepatotoxicity with antituberculosis drugs

in these coinfecting patients.

Materials and Methods

The study was undertaken after the protocol was approved by the Institutional Ethics committee. A retrospective review of case records of all the HIV seropositive patients, enrolled in 2 controlled clinical trials, between March 2000 and May 2004, namely chemotherapy for TB in HIV positive patients and the other chemoprophylaxis for TB in HIV positive individuals was carried out after obtaining consent from these subjects. For all clinical trials in our institution, the case records of all trial participants are stored in safe lockers/cupboards for a minimum of 7 years after the end of a trial. All case records had details of clinical history (including history of intravenous drug use, other risk behavior), physical examination findings and laboratory investigation results. The latter included complete blood counts, liver function tests (Serum bilirubin, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) Alkaline phosphatase, total protein, serum albumin and globulin) and renal function tests measured by clinical autoanalyser, (Model: ACE, Schiapparelli Biosystems. INC, Netherlands). All serum samples were screened for hepatitis B surface antigen (HBsAg) by ELISA (Hepalisa, J. Mitra & Co. Ltd/Biotech INC, India), and for anti-HCV antibodies by ELISA (Micro Lisa, J. Mitra & Co. Ltd/Biotech INC, India) and the cut off values were calculated as per the manufacturer's instructions manual. Any value above the cut off was taken as positive for HBsAg/ HCV. Positive results on ELISA were confirmed by a second test (Hepacard for Hepatitis B and RIBA assay for hepatitis C from Biotech INC, India). HIV infection was confirmed using a combination of two rapid tests namely Combaids (Span Diagnostics, India) and Tridot (J. Mitra & Co.Ltd/Biotech INC, India) and one ELISA (Lab systems, U.K.) as per the guidelines of National AIDS control organization (NACO). Pre-test counseling was done and informed consent obtained from the patient before performing an HIV test.

Tuberculosis was diagnosed on the basis of sputum smear and culture results for *M. tuberculosis* with clinical and radiographic evidence of tuberculosis. Patients with bacteriologic or radiographic evidence of tuberculosis were started on anti-tuberculosis treatment (ATT) with a directly observed short course (DOTS) intermittent regimen with isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z) as per the Revised National Tuberculosis Control Programme (RNTCP) guidelines,^[6] (2EHRZ₃/4RH₃ or 2SEHRZ₃/1EHRZ₃/

5EHRZ₃). They were monitored clinically every month and liver function tests were done at second month, at the end of treatment and at any time, in case of suspected toxicity. Patients who were asymptomatic and had no evidence of active TB were enrolled into a randomized trial of preventive therapy for TB with either Isoniazid (300 mg) daily or Ethambutol (800 mg) and Isoniazid (300 mg) daily. They were monitored clinically once a month and liver function tests performed once in 6 months, unless they developed symptoms suggestive of hepatotoxicity. Patients with a history of seizures, pregnancy, jaundice in the recent past, those who were seriously ill and those with abnormal liver function tests (i.e. AST or ALT >2 times ULN i.e. > 80 i.u) at the initial assessment period, were excluded from the clinical trial. Due to the non-availability of free antiretroviral drugs at that time, none of the patients in this study were on anti-retroviral drugs.

Statistical analysis

The characteristics of HIV positive patients with hepatitis co-infection and those without co-infection were compared. With categorical variables the chi-square test was applied. Paired t-test was used to test the difference between zero and six month levels of liver enzymes. 95% confidence intervals were constructed for AST and ALT. To find out the association between the enzymes (AST and ALT) with other variables namely age, sex, alcoholism and coinfection, logistic regression was used. Statistical analysis was performed using SPSS 10.0.

Results

Of the 951 HIV infected patients (286 with TB, 473 without TB and 192 who were not enrolled into the trials), 81 patients were co-infected with hepatitis and HIV (61 were HBsAg positive in addition to being HIV positive, 20 were HCV and HIV positive; 4 amongst HIV Infected patients were positive for both HBV and HCV tests). There were 62 males and 19 females, their age ranging from 20 to 40 years. Sixty seven were infected through sexual transmission, while intra-venous drug abuse was responsible for transmission in 13. One subject acquired infection through blood transfusion. The baseline characteristics of these co-infected patients are shown in Table 1. Among the dually infected patients, 22 patients received ATT as per RNTCP guidelines and 59 patients received prophylaxis for TB.

The baseline values of liver enzymes along with serum bilirubin of all the co-infected patients are shown in Table 2 along with values for the age, sex and socio-economically matched HIV

Table 1: Baseline characteristics of HIV and hepatitis coinfecting patients

Groups	Total	Age (Years)	Sex		Probable route of transmission of HIV			Median CD4 count (cells/mm ³)	CDC status		
			Male	Female	Sexual	IV drug use	Bld transf		A	B	C
HIV+HBV	61	30.6±6	46	15	54	6	1	242 (432-90)	26	18	17
HIV+HCV	20	32.1±8	16	4	13	7		308 (412-120)	6	9	5
HIV alone	98	30.0±7	50	48	97	1	0	209 (400-112)	65	13	20

HIV: Human Immunodeficiency Virus, HBV: Hepatitis B virus, HCV: Hepatitis C virus, CDC: Centre for Disease Control, IV: Intra-venous Bd.trnsf: Blood transfusion

Table 2: Baseline values of liver enzymes among HIV and hepatitis co-infected patients

Co-infection	N	Serum bilirubin (mgs/dl)		Serum aspartate aminotransferase (U/l)		Serum alanine aminotransferase (U/l)		Serum alkaline phosphatase (U/l)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
HBV + HIV	57	0.5	0.3	39*	26	30	25	95	96.8
HCV + HIV	17	0.4	0.1	34	11	23	14	65	47
HBV + HCV + HIV	4			42.0	15.8	31.2	18.3		
HIV alone	95	0.6	0.3	30	18	23	17	99	105

HBV= hepatitis B virus, HCV=hepatitis C virus, HIV= human immunodeficiency virus, N = number of patients

positive controls, without hepatitis virus co-infection. Among the latter group, 20 patients received anti-tuberculosis drugs for TB and 78 were on prophylaxis for TB.

Serial estimation of hepatic enzymes (ALT, AST, SAP) in 74 patients while they were on ATT, showed that only 8 patients with HBV, 2 patients with HCV and 6 patients with HIV had more than two-fold elevations in the enzyme levels from the upper limit of normal, which did not require discontinuation of anti tuberculosis drugs [Figures 1 and 2]. Two percent of patients had a greater than three-fold elevation in AST and 5% of patients in ALT. Table 3 shows the enzyme levels at the baseline and at 6-months after introduction of ATT in patients, in whom paired data were available. Paired t-test was done to detect a significant change in levels between zero and six months in relation to hepatitis infection and anti-TB drugs and did not show any significant change in the levels of liver

enzymes in co-infected patients. Logistic regression analysis done among these co-infected patients did not show any significant association between liver enzymes and coinfection status, age, sex, alcoholism or route of transmission.

Two patients, who were negative for hepatitis serology before the initiation of ATT, subsequently developed acute hepatitis B, a few months after starting antituberculosis therapy. One patient developed jaundice, with a serum bilirubin of 8.5 mgs%, ALT of 900 I.U. and AST of 725 I.U., after 14 months of isoniazid (INH) therapy. The other patient developed jaundice with a serum bilirubin of 6.0 mgs%, ALT of 1725 I.U. and AST of 600 I.U., during the fourth month of ATT (while on rifampicin and isoniazid thrice weekly). In these two patients, antituberculosis drugs were withheld, till the liver enzymes returned to normal and they improved symptomatically. Anti-TB therapy was successfully restarted in both without further problems.

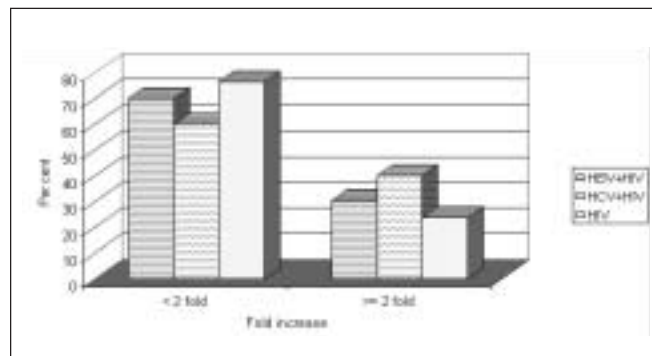


Figure 1: Proportion of patients on antituberculosis therapy, showing alterations in Alanine aminotransferase at 6 months

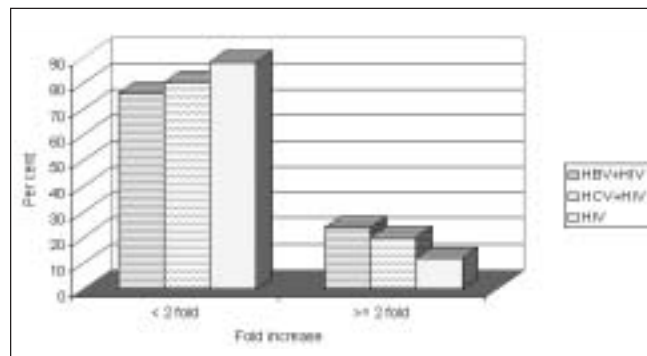


Figure 2: Proportion of patients on antituberculosis therapy, showing alterations in Aspartate aminotransferase at 6 months

Table 3: Changes in liver enzymes after 6 months of anti-TB therapy in HIV-Hepatitis coinfection

Groups*	Sr. Bilirubin 0 month (mgs/dl)	Sr. Bilirubin 6 month (mgs/dl)	P value	AST 0 month (U/l)	AST 6 month (U/l)	P value	ALT 0 month (U/l)	ALT 6 month (U/l)	P value	SAP 0 month (U/l)	SAP 6 month (U/l)	P value
HBV+HIV (n=35)	0.4 ± 0.2	0.5 ± 0.2	0.3	38 ± 25	42 ± 29	0.49	27 ± 18	41 ± 48	0.11	73 ± 102	71 ± 63	0.94
HCV+HIV (n=11)	0.3 ± 0.1	0.4 ± 0.2	0.3	33 ± 12	35 ± 28	0.79	23 ± 15	37 ± 33	0.17	61.3 ± 55.3	37 ± 36	0.18
HIV alone (n=94)	0.4 ± 0.3	0.7 ± 0.3	0.01	29 ± 18	29 ± 16	0.87	22 ± 16	25 ± 20	0.26	50 ± 61	123 ± 67	<0.001

*= all values are given as mean ± standard deviations

HBV= hepatitis B virus, HCV=hepatitis C virus, HIV= human immunodeficiency virus, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, SAP = serum alkaline phosphatase

Discussion

Co-infection with Hepatitis B virus (HBV) or Hepatitis C virus (HCV), in HIV infected patients complicates the clinical course, management and may also adversely affect therapy for HIV infection. The prevalence of hepatitis co-infection with HIV varies widely across different studies, mainly due to the variation in the distribution of risk factors, geographic location etc of the study population. In a study from Maharashtra,^[2] among 110 HIV seropositive patients, 30.4% and 7.27% of patients were positive for HBV and HCV respectively. A study from Manipur,^[3] reported a very high prevalence of HBV (100%) and HCV (92%) infection, amongst HIV seropositive intravenous drug users.

A cluster survey conducted in three randomly selected districts of Tamilnadu showed that the overall community prevalence of HIV and hepatitis B in Tamilnadu was 1.8% and 5.3% respectively.^[1] Another study^[7] reported a seroprevalence of HIV/HBV coinfection of 4% and HIV/HCV of 3%. Our study documents a hepatitis B infection rate of 6.4% in HIV positive individuals, which is slightly higher than that seen in the general population and hepatitis C virus infection of 2.1%. While in most patients in the HIV positive group, transmission was by the sexual route, 10% of HBV and 30% of HCV coinfecting patients had history of IV drug use.

Serial estimation of Alanine aminotransferase (ALT) is an inexpensive and non-invasive means of assessing liver disease as it reflects the activity of hepatotropic viruses and status of liver during therapy with various hepatotoxic drugs. A substantial proportion of our patients had normal ALT and AST levels. The hepatitis B coinfecting group had higher baseline AST values and marginally higher ALT values than the HIV group. During serial estimation while on ATT, majority of coinfecting patients had normal ALT, if they had normal liver function at baseline. Studies have shown that the risk of isoniazid associated hepatotoxicity increases with age,^[8] and with daily alcohol consumption.

A previous study from TRC, Chennai in HIV negative patients on a daily dose of isoniazid and rifampicin for pulmonary tuberculosis, has shown a hepatotoxicity of 2-8% (drug dose based on body weight).^[9] In the present study an increase in hepatic transaminase values to more than 2 times the upper limit of normal (> 80 IU) occurred in 11.3% of HIV infected, 24% of HBV and 20% of HCV co infected patients who received concurrent ATT either as preventive regimen or as treatment regimen for TB. However, this required alteration/interruption of therapy in only 2 cases. Further, there was a statistically significant increase in serum bilirubin and alkaline phosphatase levels at 6 months compared to baseline, only in the HIV group but this was not clinically significant. HIV infection is known to cause a rise in alkaline phosphatase levels, and this has been linked to progression of the disease. While studies, in which transaminase levels were monitored regularly, regardless of symptoms, have shown an elevated transaminase levels in 10-22% of patients receiving isoniazid at least once during the course of therapy,^[5,10] other studies have shown higher

incidence of hepatotoxicity and appearance of cutaneous rash with pyrazinamide than with other first line anti TB drugs.^[11]

From a clinical perspective, the most important aspect is the incidence of discontinuation of INH therapy due to hepatotoxicity. In previous studies on INH preventive therapy, the rates of discontinuation of such therapy, because of hepatotoxicity, ranged from 0.1% to 10%.^[9,12] Although the height at which asymptomatic elevations of aminotransferase enzymes should necessitate discontinuance of INH is arbitrary, five times the baseline level is accepted as a reasonable cutoff.^[13] Most of the participants in this study, whose hepatic transaminase levels were elevated, were asymptomatic and did not necessitate discontinuation of INH therapy, except two patients, who developed acute hepatitis B infection.

Our study has its share of limitations. This was a retrospective analysis of case records. There could have been a selection bias of the sample as very ill and moribund patients with abnormal baseline liver enzymes were excluded from these clinical trials. Secondly, LFT was monitored only once in 6 months in patients on TB chemoprophylaxis and at the second and sixth month for patients on chemotherapy for TB. This infrequent monitoring could have missed a few short lasting episodes of liver enzyme elevations. Moreover, at the time of this study, HIV negative group was not available. Hence the effect of HIV itself on liver enzymes could not be studied. Further, our data may have underestimated the true prevalence of HCV among HIV positive patients as at least 4% of HIV-HCV co-infected patients have no detectable antibodies in the presence of HCV viremia.^[14,15] Another difficult issue associated with serological testing for HBV is that some individuals test positive only for antibodies to hepatitis B core antigen^[16] (anti HBc). However other potential hepatotoxic exposures were not quantified.

In summary, our study documents fairly high rates of hepatitis B and C coinfection among HIV infected persons suggesting more careful screening for these viruses in HIV positive persons. Further, we have shown that anti TB therapy as well as TB preventive therapy can be safely employed in patients coinfecting with hepatitis viruses, if baseline liver function tests are within normal limits and they are closely monitored, though these findings must be confirmed in larger studies of co-infected individuals. Future research questions that need to be addressed include the impact of HAART and anti-TB drug interactions in these dually infected patients.

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