

Viral Hepatitis in Patients Infected With Human Immunodeficiency Virus

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From 1992 to 1995 we studied 232 (69% male, 87% Caucasian) anti-human immunodeficiency virus (anti-HIV) positive Brazilian patients, through a questionnaire; HIV had been acquired sexually by 50%, from blood by 32%, sexually and/or from blood by 16.4% and by an unknown route by 1.7%. Intravenous drug use was reported by 29%; it was the most important risk factor for HIV transmission. The alanine aminotransferase quotient (qALT) was >1 for 40% of the patients, 93.6% had anti-hepatitis A virus antibody, 5.3% presented hepatitis B surface antigen, 44% were anti-hepatitis B core antigen positive and 53.8% were anti-hepatitis C virus (anti-HCV) positive. The anti-HCV test showed a significant association with qALT>1. Patients for whom the probable HIV transmission route was blood had a 10.8 times greater risk of being anti-HCV positive than patients infected by other routes. Among 30 patients submitted to liver biopsy, 18 presented chronic hepatitis.

Key Words: Hepatitis C virus, human immunodeficiency virus, alanine aminotransferase quotient, anti-hepatitis A antibody, hepatitis B surface antigen, anti-hepatitis B core antigen (anti-HBc).

Acquired immunodeficiency syndrome (AIDS) is characterized by a profound defect in cell-mediated immunity [1], which results in opportunistic infections and neoplasms that frequently involve the liver [2]. Risk factors and forms of transmission for human immunodeficiency virus (HIV) and hepatotropic viruses are often the same, which explains the high frequency of co-infection involving these two agents.

Hepatitis A virus (HAV) infection is common in both homosexual men [3] and intravenous drug users (IVDU) [4]. Like HIV, hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis delta virus (HDV) can be spread both by needles and sexually [5].

The prevalence of HCV infection among HIV-seropositive subjects ranges from 4% to 67% [5], and although the sexual transmission of HCV is uncommon it can occur in patients co-infected with HIV [6-7], although, unlike HBV and HIV, HCV is not easily transmitted by homosexual intercourse [8]. Some studies have indicated that HIV infection accelerates the natural course of HCV infection and causes rapid progression to cirrhosis [9].

We investigated the etiologic agent, risk factors, clinical features, biochemical and immunological test results, liver biopsies and histopathological lesions of viral hepatitis in HIV-infected patients in order better understand the interaction between these two viral agents in Brazilian patients.

Materials and Methods

The study group consisted of 232 Brazilian patients from the city of Campinas (São Paulo state, Brazil) who had been assessed as positive at least twice in anti-HIV EIA-2 tests between 1992 and 1995. More

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than 2/3 (69.4%) were men and 30.6% were women, with ages ranging from 17 to 63 years (mean = 30.8 years); 87% were Caucasian and 13% were Afro-Brazilian. According to the Center for Disease Control (CDC) criteria, 49.5% of the patients belonged to Group II, 30.2% to Group III and 20.3% to Group IV.

All patients were interviewed using a standard questionnaire designed to identify a series of parameters, including known risk factors for HIV infection, such as previous blood transfusion, intravenous drug use (IVDU), sexual habits, sexual intercourse with HIV-infected or HIV-suspected partners, tattoos, previous acupuncture, previous surgeries and use of intravenous medication. Symptoms related to viral hepatitis were also evaluated, e.g. fever, nausea, vomiting, previous jaundice, fat intolerance, diarrhea, hematemesis, alcohol abuse and contact with hepatotoxins. All group members also underwent a complete physical examination.

At the first clinical evaluation a hemogram was made, and the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), bilirubin, albumin and gammaglobulin were assessed. Prothrombin activity was also evaluated. ALT activity was determined in each serum sample by the COBAS-MIRA automated assay (ROCHE) and the results expressed as the ALT quotient (qALT), calculated by dividing the ALT level in the sample by the maximum normal value for the method. When the ALT value was elevated, qALT was always >1.

The serum samples were also assessed for immunoglobulin-G (IgG) and immunoglobulin-M (IgM) anti-HAV using the "HAVAB-EIA"/"HAVAB-M" kit; HBsAg was quantified using the Auszyme Monoclonal kit, anti-HBcAg with the Corzyme kit, anti-HBsAg with the Ausab kit (Abbott) and anti-HCV with a second generation HCV EIA (All kits were from Abbott Laboratories, North Chicago, IL., USA).

Liver biopsy was performed on all patients (n=30) with qALT > 1.5 times the normal value, or

who presented hepatomegaly in the physical examination, or who were anti-HCV positive with elevated ALT, or HBsAg positive with elevated ALT or to investigate patients with fever of unknown origin. Diagnoses were: normal liver (NL), chronic persistent hepatitis (CPH), chronic active hepatitis (CAH), chronic lobular hepatitis (CLH), minimal changes (MC), liver cirrhosis (LC) or other non-related lesions. CAH was classified as mild, moderate or intense. Hematoxylin-eosin, Grocott-Gomori, Masson's trichrome, Ziehl-Neelsen and Perls's Prussian staining was also used.

Statistical analysis. Chi-squared analyses (or Fisher's exact test when indicated) were used to compare the risk factors for HIV infection and serological tests for HCV and HBV. The EPI INFO program was used to calculate the results, with $p \leq 0.05$ being considered statistically significant. The relative odds ratio was calculated to compare the strength of the association of a positive anti-HCV result with the different risk factors. A logistic regression model (SAS program) was used to assess risk factors for qALT > 1. All percentages were calculated using n=232 patients, unless otherwise indicated.

Results

The questionnaire completed by the 232 patients showed that the most likely HIV acquisition routes were as follows: sexual intercourse for 50% of the patients, from infected blood for 32%, sexually and/or from infected blood for 16.3% and by unknown routes for 1.7%. In 29% of the patients IVDU was the most important risk factor found. Other risk factors were: heterosexual intercourse with an HIV-infected partner for 17%, homosexual intercourse for 13.4%, promiscuous heterosexual practices for 11%, promiscuous heterosexual practices and IVDU for 7%, male bisexuality for 5% and sexual intercourse with a person at risk of HIV infection for 3.4%. Together these factors accounted for 86% of all cases.

Table 1. Biochemical results for HIV infected patients (n)

Biochemical tests	Abnormal ¹		Normal		Total	
	n	%	n	%	n	%
Alanine aminotransferase (ALT)	92	40.0	140	60.0	232	100
Aspartate aminotransferase (AST)	49	21.0	182	79.0	231	100
Alkaline phosphatase (AP)	17	8.0	195	92.0	212	100
Total bilirubin	9	5.6	153	94.4	162	100
Albumin	10	5.0	92	95.0	202	100
Gamma-globulin	131	66.0	67	34.0	198	100

¹All values were above the upper normal value for the method, except for albumin which was below the lower normal value for the method.

Table 2. Serological tests for hepatitis virus A, B and C (HAV, HBV, HCV, respectively) in HIV-infected patients (n)

Serologic tests	Positive		Negative		Indeterminate		Total	
	n	%	n	%	n	%	n	%
IgM anti-HAV	01	0.6	155	99.4	—	—	156	100
IgG anti-HAV	146	93.6	10	6.4	—	—	156	100
HbsAg	12	5.3	211	93.4	3	1.3	226	100
Anti-HbcAg	100	44.0	126	56.0	—	—	226	100
Anti-HbsAg	79	35.3	145	64.7	—	—	224	100
Anti-HCV	119	53.8	100	45.2	2	1.0	221	100

Table 3. Positive serological tests for hepatitis virus B (HBV) and C (HCV) according to HIV transmission route

Positive serologic test	Blood transmission		Sexual transmission	
	n	%	n	%
Anti-HbcAg	5	15.6	26	66.7
Anti-HCV	27	84.4	13	33.3
Total (n)	32	100.0	39	100.0

Table 4. Probable risk factors involved in hepatic lesions based on the alanine aminotransferase quotient (qALT) of patients (n)

Risk Factor for hepatic lesion	q ALT > 1		q ALT ≤ 1		Total	
	n	%	n	%	n	%
No risk factors	5	5.4	49	35.0	54	23.3
One risk factor	42	45.6	50	35.7	92	39.6
HBV(HbsAg+)	2	2.2	—	—	2	0.9
HCV(anti-HCV +)	27	29.3	27	19.3	54	23.3
Hepatotoxic drugs	12	13.0	17	12.1	29	12.5
Use of illicit drugs ¹	1	1.1	1	0.7	2	0.9
Alcohol abuse	—	—	5	3.6	5	2.1
Two risk factors	29	31.5	22	15.7	51	22.0
HBV + HCV	—	—	1	0.7	1	0.4
HBV + other	—	—	1	0.7	1	0.4
HCV + other	29	31.5	20	14.3	49	21.1
Two or more non-viral risk factors	2	2.2	5	3.6	7	3.0
HBV + HCV + other ²	4	4.4	3	2.1	7	3.0
All factors	1	1.1	—	—	1	0.4
Serological tests not made	9	9.8	11	7.8	20	8.6
Total	92	100.0	140	100.0	232	100.0

¹Illicit drug = cannabis or cocaine (as snuff or intravenously).

²Other = hepatotoxic drug, illicit drug or alcohol abuse.

Table 5. Liver biopsy results for HIV positive patients (n).

Histopathological Features	n	%
Chronic active hepatitis (CAH)	17	56.7
Chronic persistent hepatitis (CPH)	1	3.3
Cholestasis	3	10.0
Liver carcinoma	1	3.3
Minimal changes	6	20.0
Tuberculosis	1	3.3
Normal liver	1	3.3
Total	30	100.0

Other factors that were associated with HIV and viral hepatitis were: use of non-disposable needles (55.6%), previous surgery (55.6%); tattoos (31.5%), blood transfusion (14.6%) and acupuncture (2.2%). Daily alcohol consumption was reported by 14%. Abuse of non-alcohol drugs was cited by 13% of the patients, 13 of 30 of whom were intravenous users, while 23 of 30 used inhalation as the administration route. Hepatotoxic drug use was reported by 33.2%. However, there was no significant association between these factors and $qALT > 1$ ($p > 0.05$). Prior hepatitis was reported by 15% of the patients, but the etiological agents were unknown.

We found that 28.4% of the patients had some symptoms of digestive tract disorder, nausea (23.7%) being the most frequently reported symptom, while 10.3% complained of diarrhea and 9.5% complained of vomiting. Jaundice was cited by 4.3% of the patients, but only two complained of hematemesis. Only 3.5% presented moderate to intense grade hepatomegaly (liver > 3 cm), while in 54.3% the liver was 0-3 cm from the right costal margin and in 42.2% the liver was not palpable. The presence of a palpable liver was significantly correlated with $qALT > 1$ ($p = 0.0001$). The spleen was palpable in 12.5%, jaundice was found in 1.3%, 37.5% had cervical adenomegaly and one patient had the clinical features of portal hypertension.

Table 1 shows the results of the biochemical tests. Of the 49 patients with elevated AST levels, 22 used some kind of hepatotoxic medication, while among the 182 patients with normal AST, 55 (30%) also used hepatotoxic medication; patients who used hepatotoxic medication were significantly more likely to have high AST levels. Of the 17 patients with elevated AP levels, three had tuberculosis. Ten subjects with elevated AP levels were submitted to abdominal ultrasound but neither adenomegaly nor cholestasis were found. Among the 10 patients with hypoalbuminemia, five were classified in group IV of the CDC classification.

Table 2 shows the results of the serological tests for HAV, HBV and HCV. Of the 156 patients tested, 93.6% were anti-HAV IgG positive while one patient

was anti-HAV IgM positive. Among the 226 patients, 5.3% were HBsAg positive and 44.2% anti-HBcAg positive. Seventy-nine of 224 (35.3%) patients were anti-HBsAg positive and 119 of 221 (53.8%) of the patients were anti-HCV positive.

Table 3 shows the distribution of only anti-HBcAg or only anti-HCV positive patients, with respect to HIV transmission route. There was a significant association ($p = 0.001$) between these factors, and we observed that patients whose probable HIV transmission route was by blood had a 10.8 times greater risk of being anti-HCV positive than those whose probable HIV transmission route was sexual intercourse.

Table 4 shows the probable risk factors involved in hepatic lesions based on $qALT > 1$ values. Among 92 patients with $qALT > 1$, 4% had no detectable hepatic lesions, although one presented cervical adenomegaly that later was diagnosed as ganglionic tuberculosis and one had syphilis (VDRL=1/128). Table 4 also shows that 45.6% of the 92 patients with $qALT > 1$ had only one casual risk factor for hepatic lesion, i.e. HBV or HCV infection, use of hepatotoxic or illicit drugs or alcohol abuse. One of the 92 patients had all the risk factors that we investigated. If we consider all the individuals with $qALT > 1$ and that presented a viral hepatitis marker, we see that 66.3% were positive for anti-HCV and four (4%) were co-infected with HBV and HCV. The factor that gave a significant association with patients who had a $qALT > 1$ was a positive anti-HCV test ($p = 0.0001$).

Thirty patients agreed to have a liver biopsy (table 5); 18 presented chronic hepatitis and one had a normal liver.

Discussion

In 50% of our patients, sexual intercourse was the principal risk factor for HIV infection. This route of transmission is associated with about half of the cases of AIDS in adults in Brazil [10-11]. HIV transmission by blood probably occurred in 32% of our patients, with 29% being associated with IVDU. Official figures

for the state of São Paulo [11] show that 35% of the AIDS cases in this region are related to IVDU, which indicates that the population studied by us was representative of the HIV-infected adult population in our part of Brazil.

Neither alcoholism nor IVDU was significantly associated with high ALT levels in our group of patients, although elevated ALT levels did significantly correlate with HCV infection, and hepatomegaly and high AST levels were associated with hepatotoxicity. We consider that all HIV-positive patients with elevated ALT levels are at risk of HCV infection and should be investigated. A large number of AIDS patients are at present undergoing potentially hepatotoxic highly active antiretroviral therapy (HAART) therapy, and these patients must have their AST levels periodically measured.

About 28% of the patients in our study complained of gastrointestinal symptoms, nausea and vomiting being the most common (about 33%) with previous jaundice (4.3%) and hematemesis (1%) being uncommon, while at clinical evaluation only 1.3% were diagnosed as having jaundice and about 0.5% had portal hypertension. In our clinical experience, about 94% of the anti-HCV positive blood donors who are anti-HIV negative have no symptoms of jaundice, and only 2% report previous jaundice [12]. In the group of HIV-positive patients investigated in our current study, there were usually no symptoms of viral hepatitis (a few patients showed mild symptoms), just as was the case in HIV-negative patients with chronic viral hepatitis C seen in our general practice.

In general, HIV and HCV positive patients have a higher frequency of hepatomegaly when compared with patients infected only with HCV [2]. This may be explained by the presence of another hepatotropic virus, opportunistic infections, or the use of medication. Elevated ALT levels are frequently observed in HIV-infected subjects and may also be associated with hepatotoxic drugs, bad nutrition, cardiac insufficiency, hypoxia, medical procedures and blood transfusions. The majority of these factors were absent from our group of patients with elevated ALT levels.

In 17 (8%) of our patients, AP levels were

elevated, probably due to intrahepatic cholestasis or hilar adenomegaly (each of which may be present in cases of tuberculosis), tuberculosis being detected in three of 17 of these patients. In our opinion all HIV-infected patients with elevated AP levels should be submitted to liver biopsy, especially if they have fever.

Hypoalbuminemia was present in 5% of our patients, this being common in AIDS patients, due to bad nutrition, and 50% of our patients had opportunistic infections. It appears that both AIDS and opportunistic infections were important factors in patients' hypoalbuminemia, which was itself made worse by concomitant HBV or HCV infections. Elevated gamma-globulin levels were very frequently observed in our group of AIDS patients, but it was not associated with advanced liver disease.

About 94% of our patients had anti-HAV IgG in their serum. There is a higher risk of HAV infection among homosexual men [3] and IVDU [13], both of these being high risk groups for HIV infection. A high prevalence of anti-HAV has also been observed among HIV-negative adults in developing and newly industrialized countries, such as Brazil [14].

There were 12 (5.3%) HbsAg-positive patients in our group, this being about three times higher than the frequency found in a group of blood donors previously studied by us [15]. Six (50%) of our HbsAg-positive patients were IVDU, two (16.7%) were homosexual males, one (8%) was a bisexual male, one (8%) was a promiscuous heterosexual and two (17%) presented more than one risk factor. Different values have been found in other studies, e.g. in Spain 5% of homosexual men were HBsAg positive, 13% were IVDU and 2% of the patients' sexual partners were also HBsAg positive [16]; these values were similar in both HIV-positive and negative patients.

About 44% of our HIV-positive patients were also anti-HBcAg positive. In the group of blood donors that we had studied earlier [15], 11% were anti-HBcAg positive. In the current study there was no significant difference in the prevalence of anti-HBcAg in IVDU (40%) and homosexuals (44%),

but when the relationship between the presence of anti-HBcAg and mode of transmission was analyzed it was found that HIV-positive patients who had been contaminated by the sexual route had a significantly higher prevalence of anti-HBcAg than patients contaminated by blood. These results reflect the importance of the sexual transmission of HBV. In some patients anti-HBcAg may act as the only HBV infection for several reasons, e.g. undetectable levels of HBsAg in a serological test (the so-called immunological window), deficient production of anti-HBsAg caused by genetic factors, loss of HBsAg in very old infections, passive transmittance of anti-HBcAg by drug users, a false positive EIA test result, or interference caused by the presence of other viruses. In our study, 25 patients, 48% of whom were IVDU, presented anti-HBcAg as the only HBV marker. It appears that some patients co-infected with HIV are unable to produce anti-HBsAg during HBV infection. This atypical feature of HBV infection has been observed in 10.7% of IVDU in England and 35% in Italy [17].

The anti-HBsAg antibody was present in 35.3% of our patients, lower than the 65% found in patients with advanced HIV infection [18]. Another study [16] found anti-HBsAg in 88% of IVDU, 70% of homosexual men and 26% among sexual partners of IVDU. In our study, 15 patients presented only anti-HBsAg as a marker of previous HBV infection. These patients had not previously been immunized against HBV and it seems that they had lost the other anti-HBV markers due to HIV infection. No significant correlation was observed between the presence of HBV markers and elevated ALT levels. About 54% of our patients were anti-HCV positive, which is very much higher than the 2.6% anti-HCV positive found in blood donors from the region of Campinas [15]. When the probable route of HIV transmission was by blood we noted a higher rate of positive anti-HCV tests (84.4%) when compared to that observed in patients whose probable HIV transmission route was sexual intercourse (33.3%).

This correlation was significant and confirms that hepatitis C is very common when HIV infection is

acquired by exposure to infected blood. The prevalence of positive anti-HCV tests was high among IVDU (90%) and low among homosexual men (3.7%), while among promiscuous heterosexuals there was a higher prevalence of HCV (43.5%) than in homosexuals (3.7%). A study involving the sexual partners of patients with hemophilia [7] found that the rate of HCV transmission was five times higher in the presence of concomitant HIV transmission; it may be that HIV is an important cofactor for the sexual transmission of HCV.

Some authors [19,20,21] consider that anti-HCV tests can present false positives in patients with HIV infection due to the high levels of circulating antibodies, while others argue that anti-HCV tests can give false negative results in cases of advanced AIDS because of decreased antibody production [22]. Some studies have shown a good correlation between the results of anti-HCV tests by EIA-2 and tests involving HCV RNA using the polymerase chain reaction (PCR); one such study showed that in groups with high risk for HCV infection about 93% of the positive anti-HCV EIA-2 tests were positive for the immunoblot test for HCV (RIBA-2), and 85% of them were HCV RNA positive [23-24]. In our opinion, anti-HCV positive patients should always be considered as HCV infected, which may be confirmed by detecting HCV-RNA using PCR.

With regard to our findings concerning ALT, other authors have also observed an association between positive anti-HCV test and elevated plasma ALT [20-24]. We consider that the cytopathic effect of HCV in the liver may be amplified when the patient is co-infected with HIV.

We encountered chronic hepatitis in 60% of the liver biopsies from HIV patients (only 3.3% had a normal liver) and 70% of our anti-HCV positive patients had CAH, which demonstrates the importance of liver biopsy in co-infected patients. In the past a great number of opportunistic infections have been seen in liver biopsies of HIV-infected patients because such patients normally had advanced AIDS [25-26-27]. In more recent studies, patients without advanced AIDS have been

evaluated, and we have observed histopathological lesions similar to those found in patients with HCV but without HIV. In such cases, changes such as CAH and CH, which are associated with hepatotropic virus, predominate [28].

In HIV patients co-infected with HBV the liver biopsies showed mild lesions, when compared to the histopathological alterations present in anti-HIV negative patients [29]; it seems that HBV is not cytopathic for hepatocytes. The mild liver lesions observed in our HBV infected patients reflects a deficient cellular immune response to infected hepatocytes in patients with HIV infection. The occurrence of the more severe lesions, which were observed in HCV patients co-infected with HIV suggests, and perhaps confirms, the predominantly cytopathic action of HCV in the liver [9].

In conclusion, the occurrence of viral hepatitis in our group of Brazilian HIV-infected patients is common and it affects the clinical course of both infections. The advent of highly effective anti-HIV therapy has given AIDS patients both prolonged survival and a better quality of life, but an increased incidence of end-stage liver disease is now being observed among these patients and this will oblige us to find better ways to treat the chronic liver diseases caused by hepatotropic viruses.

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