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# Risk factors for HIV infection among patients infected with hepatitis C virus

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## ABSTRACT

**OBJECTIVE:** Human immunodeficiency virus and hepatitis C virus share the same routes of transmission. Currently, there is a high frequency of co-infection worldwide, especially among users of injectable drugs and in subjects with history of blood transfusions. The aim of the present study was to evaluate risk factors associated to human immunodeficiency virus infection in patients infected with hepatitis C virus.

**METHODS:** We carried out an epidemiological case-control study, including 118 patients (cases) infected by both viruses and 233 patients (controls) infected only by the hepatitis C virus. Between January 1999 and November 2001, patients responded to a questionnaire assessing sociodemographic and professional characteristics, and major risk factors for virus infection. After description and initial comparison, variables were evaluated by univariate analysis and then by multivariate logistic regression for variables selected through the maximum likelihood test.

**RESULTS:** Co-infection was associated with female sex (OR=2.89; 95% CI: 1.16-7.08), being divorced/widow (OR=3.91; 95% CI: 1.34-11.35), past or current use of illegal drugs (OR=3.96; 95% CI: 1.55-10.13) and to the habit of sharing pipes or needles (OR=10.28; 95% CI: 4.00-6.42).

**CONCLUSIONS:** Among patients infected with hepatitis C virus, female sex is a risk factor for HIV infection after adjustment for the habit of sharing pipes and needles. Being divorced/widow, use of illegal drugs, and the habit of sharing pipes and syringes were associated to co-infection.

**KEYWORDS:** Risk factors. Acquired immunodeficiency syndrome, epidemiology. Acquired immunodeficiency syndrome, transmission. Hepatitis C, epidemiology. Hepatitis C, transmission. Case-control studies. Questionnaires. Socioeconomic factors. Sexual behavior.

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## INTRODUCTION

The human immunodeficiency virus (HIV) – the etiological agent of Acquired Immune Deficiency Syndrome (AIDS) – and the hepatitis C virus (HCV) share the same mechanisms of transmission (parenteral, sexual, and mother-to-child). This epidemiological similarity accounts for the high frequency of co-infection by both viruses, which is more common among patients with history of injectable drug use and blood transfusions.<sup>2,14</sup> Prevalence varies according to the risk factors present in the studied population.<sup>6,8,13,10</sup> A study<sup>5</sup> conducted in 1996, including 1,457 HIV-infected patients, showed 17.7% prevalence of co-infection with HCV, and 16.3% of co-infected subjects reported as risk factors only having HIV-positive sexual partners, without any other risk factor for the transmission of HIV and HCV.

Mortality and morbidity among HIV-infected patients is constantly declining, as a result of highly-active anti-retroviral therapy (HAART) and of the prevention of opportunistic diseases. The survival of patients without progression to AIDS is thus constantly increasing. However, morbidity and mortality due to co-infection with HCV are increasing in this population. The importance of co-infection becomes clear when we consider its high prevalence, and its impact on morbidity and mortality.

HIV/HCV co-infection is still marked by the impact of HIV on the course of HCV infection, and vice-versa. HIV determines faster progression of liver disease in persons infected by HCV, increasing risk of cirrhosis and leading to higher HCV viremia. HCV has an important impact on the management of HIV, increasing risk of liver toxicity due to antiretroviral drugs. Recent studies<sup>3,9,11</sup> show also that HCV accelerates the progression of HIV disease, and may delay the immunological reconstitution of HIV-infected patients following HAART. Therefore, according to the United States Public Health Service<sup>12</sup> (USPHS) and the Infectious Diseases Society of America<sup>12</sup> (IDSA), hepatitis C is considered as an opportunistic disease in persons infected by HIV, due to its increased incidence among this population, and also to its accelerated progression in co-infected persons.

The aim of the present study was to investigate risk factors associated with HIV infection in patients infected with HCV.

## METHODS

We conducted an epidemiological case-control study including 351 patients, of which 118 were cases and 233 were controls.

We defined as cases patients co-infected with HIV and HCV, seen at an outpatient facility specializing in hepatitis. Eligible patients had two positive serological tests for anti-HIV antibodies by ELISA, confirmed by one positive Western Blot, as well as one positive ELISA for anti HCV-antibodies (second or third generation).

The control group included patients infected with HCV seen in another specialized outpatient facility. Eligible patients had one positive ELISA for anti-HCV antibodies by ELISA (second or third generation) and one negative ELISA for anti-HIV antibodies.

None of the patients in any of the groups had serological markers of current infection by hepatitis B virus.

Patients of both groups were selected without distinction from among patients regularly seen at the facilities, and were recruited between January 1999 and November 2001. After listening to a verbal description of the study's objectives and signing a term of free informed consent, patients from both groups answered a questionnaire addressing risk factors for HIV/HCV co-infection.

Sample size calculation was based on the following considerations: 0.95 confidence level, 0.80 statistical power, 5% prevalence of sexual transmission of HCV,<sup>10</sup> and an odds ratio (OR) of 3.5. These parameters led to a sample size of 116 in the case group and 232 in the control group. Our final sample included 118 cases and 233 controls. Data were entered into a digital database using Epi Info 6.04b software.

We investigated sociodemographic variables (sex, schooling, age, marital status, and income); work-related variables (occupation, manipulation of blood); sexual behavior (sexual orientation, age at first sexual intercourse, number of sexual partners in life, practice of oral and anal sex); sexual partner's status (HIV+, received blood transfusion); co-habitation with HIV+ persons; use of illicit drugs (current or past use of drugs, use of marijuana, inhaled drugs, crack, sharing of pipes or needles); alcohol use; blood transfusion; hospital admission; surgeries; acupuncture; tattoos; and body piercing.

After the description and comparison of variables by group, we carried out univariate analyses to estimate crude ORs, followed by logistic regression analysis. Variables included in the model were selected using the maximum likelihood test, and in the final model, all variables with p-values  $\leq 0.10$  were included. We used a backward modeling strategy, with variables being included in increasing order of importance. The goodness

**Table 1** - Distribution of cases and controls according to sociodemographic characteristics, after univariate analysis and estimated odds ratios. São Paulo, Brazil, 1999-2001.

Variable	Cases		Controls		OR	95% CI	p*
	n	%	n	%			
Sex							
Male	83	70.3	116	49.8	1	-	-
Female	35	29.7	117	50.2	0.41	0.26-0.66	<0.001
Color							
White	88	76.5	177	76.0	1	-	-
Black/mixed	27	23.5	56	24.0	0.96	0.57-1.64	0.909
Age group							
≤29	10	8.5	61	26.2	1	-	-
30-39	60	50.9	46	19.7	7.95	3.67-17.20	<0.001
40-49	38	32.2	77	33.1	3.01	1.38-6.52	0.005
>49	10	8.5	49	21.0	1.24	0.47-3.23	0.653
Schooling							
University	18	15.5	26	11.4	1	-	-
Secondary	30	25.9	111	48.5	0.39	0.18-0.80	0.011
Primary or less	68	58.6	92	40.1	1.06	0.54-2.10	0.85
Origin							
Other States	24	21.4	63	27.5	1	-	-
Sao Paulo State	88	78.6	166	72.5	1.39	0.81-2.37	0.227
Marital Status							
Married	27	22.9	103	44.2	1	-	-
Single	44	37.3	53	22.8	3.16	1.76-5.67	<0.001
Living with partner	21	17.8	40	17.2	2	1.01-3.94	0.044
Divorced/widow	26	22.0	37	15.9	2.68	1.39-5.16	0.003
Monthly income							
>R\$2,000	12	11.4	11	6.3	1	-	-
R\$1,000-2,000	20	19.1	41	23.6	0.44	0.16-1.18	0.107
R\$500-1,000	29	27.6	70	40.2	0.37	0.15-0.95	0.04
≤R\$500	44	41.9	52	29.9	0.77	0.31-1.92	0.585

\*Wald test

of fit test was used to evaluate how well the model fit the data.<sup>4</sup> The significance level of  $p < 0.05$  in the Wald test was used to evaluate risk factors, and precision was given by 95% confidence intervals, calculated for each category of variables present in the model.

The present study was approved by the *Comissão de Ética para Análise de Projetos de Pesquisa* (Ethics Committee for the Analysis of Research Projects - CAPEsq) of the Clinical Board of the *Hospital de Clínicas* of the *Faculdade de Medicina, Universidade de São Paulo*.

## RESULTS

Table 1 presents a description of sociodemographic variables by group and the results of univariate analysis and crude ORs.

The majority of patients studied was of white skin color, and came from the state of São Paulo. There was no statistically significant difference in terms of income between the two groups.

Regarding occupation, although univariate analysis showed that the majority of co-infected patients were retired or away from their jobs, while the majority of HCV-infected patients was in the unqualified labor category, this difference was not statistically significant ( $p > 0.10$ ; data not shown). Professional activity involving manipulation of blood was found to be a protective

factor for co-infection in univariate analysis ( $p < 0.10$ ), but this association was not confirmed in multivariate analysis (data not shown). Tattoos were risk factor for co-infection in univariate analysis, but again this was not confirmed in multivariate analysis (data not shown). Surgeries, hospital admission, acupuncture, and body piercing were not associated with HIV infection among HIV infected patients ( $p > 0.10$ ).

There was no statistical difference in terms of co-habitation with HIV-infected persons between the two groups. Regarding alcohol consumption, moderate or heavy drinking were associated with co-infection in univariate analysis, but this association was not confirmed in multivariate analysis.

Results regarding sexual behavior, with univariate analysis and estimated ORs, are presented in Table 2; sexual partner status is presented in Table 3.

Regarding sexual behavior, the following risk factors were found to be associated with HIV infection among HCV-infected patients: first sexual intercourse at age 15/16 or before age 15 years; having had between 4 and 11 or more than 11 sexual partners in life; male homosexuality; reported anal or oral sex; and having had at least one STD in life. However, none of these factors remained statistically significant in the logistic regression model of multivariate analysis.

As to sexual partner status, having had an HIV-in-

**Table 2** - Distribution of cases and controls according to sexual behavior, after univariate analysis and estimated odds ratios. São Paulo, Brazil, 1999-2001.

Variable	Cases		Controls		OR	95% CI	p*
	n	%	n	%			
Age at onset of sexual relations							
>16 years	18	25	115	50.9	1	-	-
15/16 years	30	41.7	69	30.5	2.77	1.44-5.35	0.002
<15 years	24	33.3	42	18.6	3.65	1.80-7.39	<0.001
Number of sexual partners in life							
≥3	13	12.8	94	42.0	1	-	-
4 to 11	31	30.7	60	26.8	3.73	1.81-7.70	<0.001
>11	57	56.4	70	31.3	5.88	2.99-11.58	<0.001
Sexual orientation							
Heterosexual	101	85.9	228	99.1	1	-	-
Homosexual	17	14.4	2	0.8	19.18	4.35-84.61	<0.001
Anal sex							
No	45	40.2	160	71.1	1	-	-
Yes	67	59.8	65	28.9	3.66	2.27-5.89	<0.001
Oral sex							
No	23	20.5	103	45.4	1	-	-
Yes	89	79.5	124	54.6	3.21	1.89-5.44	<0.001
At least one STD in life							
No	42	41.6	126	69.2	1	-	-
Yes	59	58.4	56	30.8	3.16	1.90-5.24	<0.001

\*Wald test

STD: sexually transmissible disease

fect partner or not knowing the partner's HIV serological status, and not knowing whether the partner had received blood transfusions were risk factors for co-infection in univariate analysis. These associations too were not confirmed in multivariate analysis.

Regarding blood transfusions received by study subjects, univariate analysis showed an OR of 0.49 (95% CI: 0.32-0.76; p= 0.001).

Table 4 presents the results of univariate analyses and the estimated ORs for variables related to the use of illicit drugs.

Table 5 presents the results of the logistic regression model with the respective adjusted ORs for selected variables. As shown in the table, past or current use of illicit drugs (OR=3.96; 95% CI: 1.55-10.13) and the habit of sharing needles or pipes (OR=10.28; 95% CI: 4.00-26.42) were risk factors independently associated with HIV infection in patients with HCV.

## DISCUSSION

The importance of the study of risk factors involved

in HIV/HCV co-infection is related to the fact that the progression of hepatitis C is often accelerated when associated with HIV infection. This progression, which usually requires 30 years or longer in mono-infected individuals may require only half as much time in HIV-infected individuals. Likewise, the major causes of health among HAART-controlled HIV-infected patients in the developed world are hepatic insufficiency and/or liver cancer caused by HCV co-infection.<sup>11</sup>

Regarding the sociodemographic characteristics of patients, female gender was a risk factor independently associated with HIV infection among HCV-infected patients (OR=2.89; 95% CI: 1.16-7.08). The major forms of HIV transmission in women are heterosexual intercourse and use of injectable drugs. However, in the present study, the use of illicit drugs and the habit of sharing pipes and needles were characteristics related to male patients. This suggests that the risk HIV infection among women is related to the behavior of their sexual partners. Historically, over two-thirds of AIDS cases reported among women initially without known risk factors were later reclassified as by heterosexual transmission, and only one-

**Table 3** - Distribution of cases and controls according to sexual partner's status regarding HIV and blood, after univariate analysis and estimated odds ratios. São Paulo, Brazil, 1999-2001.

Variable	Cases		Controls		OR	95% CI	p*
	n	%	n	%			
HIV + Partner							
No	11	9.3	193	83.9	1	-	-
Yes	46	38.9	3	1.	269.03	72.12-1003.55	<0.001
Does not know	61	51.7	34	14.8	31.47	15.04-65.86	<0.001
Partner received blood transfusion							
No	28	23.7	115	49.8	1	-	-
Yes	8	6.8	17	7.4	1.93	0.75-4.92	0.168
Does not know	82	69.5	99	42.7	3.4	2.05-5.64	<0.001

\*Wald test

**Table 4** - Distribution of cases and controls according to use of illicit drugs, after univariate analysis and estimated odds ratios. São Paulo, Brazil, 1999-2001.

Variable	Cases		Controls		OR	95% CI	p*
	n	%	n	%			
Past or current use of illicit drugs					1	-	-
No	25	21,2	170	73,0			
Yes	93	78,8	63	27,0	11,48	5,92-17,01	<0,001
Past or current use of marijuana					1	-	-
No	25	21,2	176	75,5			
Yes	93	78,8	57	24,5	11,48	6,74-19,57	<0,001
Past or current use of inhaled drugs					1	-	-
No	38	32,2	203	87,1			
Yes	80	67,8	30	12,9	14,24	8,26-24,54	<0,001
Past or current use of crack					1	-	-
No	78	66,1	224	96,1			
Yes	40	33,9	9	3,9	12,76	5,92-27,50	<0,001
Past or current use of injectable drugs					1	-	-
No	52	44,1	210	90,1			
Yes	66	55,9	23	9,8	11,58	6,59-20,35	<0,001
Has shared pipes or needles					1	-	-
No	46	38,9	212	91,0			
Yes	72	61,0	21	9,0	15,8	8,83-28,25	<0,001

\*Wald test

quarter of these cases was attributed to the direct use of injectable drugs.

Univariate analysis showed greater risk of HIV infection among patients infected with HCV in the 30-39 and 40-49 years age group, with complete elementary schooling or less, and who were single or divorced/widows. However, these associations were not confirmed in multivariate analysis, with the exception of being single or divorced/widow (OR=3.91; 95% CI 1.34-11.35), which remained independently associated with HIV-infection. We believe that this variable is correlated with other types of behavior, such as a greater number of sexual partners and other sexual behaviors, which would render these individuals more susceptible to HIV infection.

According to the Centers for Disease Control and Prevention<sup>15</sup> (CDC 2002), the use of injectable drugs has contributed, directly or indirectly, to over one-third (36%) of AIDS cases in the United States since

the beginning of the epidemic. This trend is apparently being maintained: 28% of the 42,156 new AIDS cases notified in 2000 were related to injectable drug use. Of the 807,075 cumulative cases of AIDS in adults and adolescents in the United States reported until December 2001, 145,750 men and 55,576 women acquired HIV through the use of injectable drugs.

The use of non-injectable drugs, such as snorted cocaine and crack, also contributes to the evolution of the epidemic, especially due to its relationship to unsafe sexual behavior. A CDC study<sup>17</sup> of 2 thousand youths showed that crack users show three times greater risk of acquiring HIV than non-users.

As to blood transfusions, the inverse or negative association found in multivariate analysis is far from meaning that this is a protective factor, given the biological implausibility of such an effect. However, this may be explained by a number of factors that we shall now discuss. Blood transfusion is one of

**Table 5** - Logistic regression model with estimated adjusted odds ratios for presence of HIV/HCV co-infection. São Paulo, Brazil, 1999-2001.

Variable	OR crude	OR adjusted	95% CI	p*
Sex				
Male	1	1	-	-
Female	0,41	2,89	1,16-7,08	0,022
Marital status				
Married	1	1	-	-
Single	3,16	2,17	0,85-5,49	0,101
Living with partner	2	2,7	0,89-8,17	0,078
Divorced/widow	2,68	3,91	1,34-11,35	0,012
Received blood transfusion				
No	1	1	-	-
Yes	0,49	0,48	0,27-0,86	0,013
Shared pipes or needles				
No	1	1	-	-
Yes	15,58	10,28	4,00-26,42	<0,001
Past or current use of illicit drugs				
No	1	1	-	-
Yes	11,58	3,96	1,55-10,13	0,004

\*Wald test

the major forms of HCV transmission, and is responsible for a large number of cases, especially before 1993, when screening for HCV among blood donors was implemented. With the introduction of highly sensitive screening for blood donors in the 1990's, the risk of contamination via the transfusion of blood and blood products (coagulation factors, immunoglobulins, and cryoprecipitates) fell dramatically. Currently, the risk of transmission by this route is around one per million transfused blood units when molecular biology methods are used. However, in the United States, an estimate of the prevalence of hepatitis C showed that 87% of patients with hemophilia treated with blood products before 1987 and 6% of those who received blood transfusions before 1990 were infected with HCV.

HIV transmission through blood transfusion is less important than that of HCV. Screening for HIV-1 in blood donation candidates preceded HCV screening

by almost a decade in the United States. In the US, almost all persons infected by HIV due to blood transfusion were infected before 1985, when screening for HIV was implemented.

It is estimated that between 1/450,000 and 1/660,000 blood donations a year are infected with HIV and fail to be detected by HIV screening. However, since 1995, the Food and Drug Administration (FDA) recommends that all donated blood and plasma be tested for anti-HIV-p24. With these measures, HIV transmission by the transfusion of blood and blood products is now extremely low.<sup>15</sup>

In conclusion, the present study has identified female sex as an independent risk factor for HIV infection among HCV-infected patients. Likewise, being divorced/widow, past or current use of illicit drugs, and the habit of sharing pipes or needles are also risk factors for HIV/HCV co-infection.

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