

Seroprevalence of HCV markers among HIV infected patients from Curitiba and metropolitan region

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SUMMARY

Objective: to determine the prevalence and epidemiological factors associated with hepatitis (HCV) coinfection in human immunodeficiency virus (HIV) patients from Curitiba and the metropolitan region.

Methods: a study with 303 HIV+ patients, mean age 41.2 years (18-73); 50.5% men, followed at the Hospital de Clínicas, Universidade Federal do Paraná, between April 2008 and March 2009. Clinical and epidemiological data were obtained through questionnaires and retrospective analysis of medical records. Anti-HCV antibodies were detected by chemiluminescence immunoassay.

Results: a total of 12.9% of HIV+ patients were positive for anti-HCV antibodies, 64.1% were men and 35.9% women, with mean age of 44.5 years (24-66). The frequency of HCV among men was 16.7% and among women 9.1% ($p=0.06$). HCV prevalence was associated to HIV infection when compared to the general population ($p<10^{-6}$, OR=100.4; 95CI=13.7-734.9). The parenteral route of transmission was the most frequent among coinfecting patients (46.1%), and the sexual transmission among HIV+/HCV- (71.8%) ($p=0.02$, OR=0.2; 95CI=0.1-0.7). The frequency of intravenous drug users was higher among the coinfecting patients (61.5%) compared to the non coinfecting (12.6%) ($p<10^{-6}$, OR=11.1; 95CI=4.5-27.7). **Conclusion:** the prevalence of coinfection with HCV in HIV+ patients is 12.9%, 88 times higher than in the general population in Curitiba. The most frequent route of transmission in the coinfecting patients is parenteral, but the sexual route is also representative (34.6%).

Keywords: HIV, acquired immunodeficiency syndrome, coinfection, hepatitis C.

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INTRODUCTION

Infection with the human immunodeficiency virus (HIV), which causes Acquired Immune Deficiency Syndrome (AIDS), and hepatitis C virus (HCV) are among the major challenges to public health in the world. Both are RNA viruses and share common transmission routes, including parenteral, sexual and vertical. This epidemiological similarity results in a high prevalence of HIV/HCV co-infection and represents an important factor of morbidity and mortality for the individuals affected.¹⁻⁴

Liver diseases are one of the most frequent causes (9%) of hospitalization and death in HIV infected patients, with co-infection with HCV an important cofactor for worsening the clinical picture.^{3,5} The prevalence of HIV/HCV co-infection varies widely in different pop-

ulations, according to the associated risk factors, distinct epidemiological characteristics and methodological differences.

HIV/HCV co-infection significantly alters the clinical course of these infections and is associated with unfavorable outcomes. In addition to liver damage, HCV enhances the activation of the immune system, chronic inflammation, and increased cardiovascular risk, kidney diseases and cancer. Furthermore, it can slow down the reconstitution of the immune system after highly active anti-retroviral treatment (HAART), and increase the risk of progression to AIDS.^{3,5,6} Concomitant treatment of these viruses may cause drug interaction between HAART and direct-acting antiviral agents (DAA), used in the treatment of HCV, increasing liver damage by up to three

times.^{5,7,8} Furthermore, co-infected patients have lower HCV clearance and greater viral load, and thus more rapid progression of liver disease compared to HIV patients that are not co-infected.^{1,4,9-11} HIV patients classified as rapid progressors have a higher HCV viral load than long-term progressors, suggesting that immunological and/or genetic factors also contribute to control of viremia in both viruses.¹²

Given the complexity of treatment in co-infected patients, it is necessary to identify HCV co-infection in individuals with HIV early in order to establish therapeutic measures and even primary prevention that alters the progression to chronicity. In such patients, treatment for HCV with DAA should be prioritized.^{5,13}

The present study analyzed some epidemiological factors involved in the co-infection of HIV/HCV in patients from Curitiba and the metropolitan region under monitoring at the Infectious and Parasitic Diseases Outpatient Clinic of the Hospital de Clínicas da Universidade Federal do Paraná (HC/UFPR) in order to determine the prevalence and associated risk factors.

METHODS

Patients and clinical data

303 HIV positive individuals of both sexes were analyzed during monitoring at the Infectious and Parasitic Diseases Outpatient Clinic of the HC/UFPR from April 2008 to March 2009.

The clinical and epidemiological data were obtained during medical visits by filling in a questionnaire on the risk factors associated with HIV acquisition, and through a retrospective analysis of medical records. The following variables were analyzed: age, sex, date of first positive serology for HIV, possible form of acquisition of the virus and associated risk factors such as use of injectable drugs, number of sexual relations and history of blood transfusion and/or blood products.

This study was approved by the Ethics Committee for Research on Human Beings (CEP) at the HC/UFPR under n° CEP/HC 1409.074/2007-04.

Collection of blood and laboratory analysis

The patients treated at the Infectious and Parasitic Diseases Outpatient Clinic of the HC/UFPR in Curitiba, with HIV positivity determined according to the protocol of the National Coordination of STD/AIDS of the Ministry of Health (CNDST/AIDS-MS), were contacted and, after proper clarification and signing of the informed consent (IC) form, 5 mL of venous blood with anticoagulant was collected from each patient. After centrifuga-

tion, the *serum* was suitably separated, aliquoted and stored at -80°C until tested for the presence of anti-HCV antibodies.

Anti-HCV antibodies were determined by enzyme immunoassay with micro chemiluminescence (MCL), using the Architect® (Abbott, USA) commercial systems of the clinical analyses service of the HC/UFPR, according to manufacturer's instructions.

Statistical analysis

The data collected and results obtained were tabulated in an Excel spreadsheet and comparisons between groups were performed using the two-tailed Fisher's exact test, Student's t-test or chi-square test. The odds ratio value and confidence interval of 95% were calculated when appropriate. P-values <0.05 were considered significant.

RESULTS

The results of the characterization of the sample are presented in Table 1. Among the 303 HIV patients studied, 153 (50.5%) were male and 150 patients (49.5%) were female, with a mean age of 41.2 years (18 to 73 years). In relation to the predominant ancestry, 289 (95.4%) were Euro-Brazilians and 14 (4.6%) were Afro-Brazilians.

39/303 patients were identified (12.9%) as seropositive for HCV, a total of 25/39 (64.1%) of whom were male and 14/39 patients (35.9%) female, with a mean age of 44.5 (24-66 years); 37 (94.9%) were Euro-Brazilians and 2 (5.1%) Afro-Brazilians. Among the remaining 264 (87.1%) HIV patients, 139/264 (52.7%) were female and 125/264 (47.3%) were male, with a mean age of 40.7 years and variation of 18 to 73 years. The prevalence of HCV infection was significantly higher in HIV patients (12.9%) than in the general population of Curitiba (0.15%)¹⁴ ($p < 10^{-6}$, OR=100.4; 95CI=13.7-734.9).

The age and descent were similar in the two groups of HIV and HIV/HCV patients. In relation to sex, women represented 52.7% of cases in patients not co-infected and 35.9% in co-infected patients, suggesting a trend, albeit not significant ($p=0.059$), towards a higher frequency of co-infected males.

Only 193 (63.7%) of the 303 patients analyzed informed their supposed route of HIV infection. Therefore, in 110 (36.3%) of patients it was not possible to trace the route of infection of the virus. The co-infected patients differed from those not co-infected in relation to the frequency of sexual transmission and parenteral routes ($p=0.02$, OR=0.2, 95CI=0.1-0.7), with the sexual route most frequent among HIV/HCV- and parenteral among those with HIV/HCV. Regarding injectable drug use ($p < 10^{-6}$, OR=11.1,

TABLE 1 Characterization of the sample.

	HIV n=264 (%)	HIV/HCV n=39 (%)	p	OR (CI95%)
Descent			n.s. ²	
Euro-Brazilians	252(95,5)	37(94,9)		
Afro-Brazilians	12 (4.5)	2 (5.1)		
Gender			n.s. ²	
Female	139 (52.7)	14 (35.9)		
Male	125 (47.3)	25 (64.1)		
Age			n.s. ²	
Mean (±SD ³)	40.7 (±11.0)	44.5 (±11.4)		
Median (min-max)	39.4 (18-73)	41.7 (24-66)		
Progression time			n.s. ²	
< 2 years	131 (49.6)	13 (33.3)		
2-5 years	45 (17.0)	11 (28.2)		
6-10 years	33 (12.5)	6 (15.4)		
≥ 10 years	6 (2.3)	0 (0)		
N.I. ¹	49 (18.6)	9 (23.1)		
Risk group			0.02	0.21 (0.06-0.71)
Sexual	120 (45.4)	9 (23.1)		
Sexual/parenteral ⁴	14 (5.3)	5 (12.8)		
Parenteral ⁴	33 (12.5)	12 (30.8)		
N.I. ¹	97 (36.7)	13 (33.3)		
Transmission routes			0.01	0.27 (0.10-0.74)
1 route	152 (57.6)	19 (48.7)		
2 routes	13 (4.9)	7 (17.9)		
More than 2 routes	2 (0.8)	0 (0)		
N.I. ¹	97 (36.7)	13 (33.3)		
Risk group for IDU⁵			<10 ⁻⁶	11.12 (4.46-27.72)
IDU	21 (7.9)	16 (41.0)		
Non-IDU	146 (55.3)	10 (25.6)		
N.I. ¹	97 (36.7)	13 (1.4)		

¹Not informed.

²Not significant.

³Standard deviation.

⁴The parenteral route includes patients who reported receiving transfusions and/or being drug users.

⁵The risk group for IDU included patients who reported being injectable drug users, regardless of whether they reported other routes or not.

95CI=4.5-27.7), this was significantly higher among co-infected patients (61.5%) than those not co-infected (12.6%) and also in relation to the number of transmission routes to which they reported being exposed (p=0.01, OR=0.3, 95CI=0.1-0.7).

Among patients not co-infected, 167/264 (63.3%) informed the supposed route of infection. 15/167 (9.0%) of these cases had two or more overlapping transmission routes, 120/167 (71.9%) reported sexual contact only, 19/167 (11.4%) reported the parenteral route by blood transfusion, and 13/167 (7.8%) intravenous injectable drug use (IDU). Among individuals with overlapping routes, the sexual route was reported in 14/15 and the parenteral route was involved in all cases.

Among HIV patients co-infected with HCV, 26/39 (66.7%) informed the supposed route of infection. 7/26 of these presented overlapping routes, 10/26 (38.5%) reported only IDU and 9/26 (34.6%) only the sexual route. No cases of isolated infection via transfusion were reported. Among individuals with overlapping routes, the sexual route was reported in 5/7 and the parenteral was involved in 7 cases. Therefore, the parenteral route was the most frequent among patients co-infected with HIV/HCV 12/26 (46.1%), while the sexual transmission route was more frequent among HIV patients without co-infection 120/167 (71.9%).

There was no difference between the route of infection between men and women and between age groups,

both in the co-infected group and the group with HIV alone. In relation to the time for progression to AIDS, among co-infected patients, the analyses were not conclusive because the majority of the patients were unable to inform the approximate date of the start of infection.

DISCUSSION

The prevalence indexes for HIV infection remain alarming. According to the World Health Organization (WHO), approximately 3% of the world population is infected with HIV and Brazil has one of the highest rates in South America, from 2.5 to 10%.¹⁵

With the introduction of HAART therapy in 1996 there was a significant decrease in mortality of individuals infected with HIV. However, in the last 10 years, despite the efficiency of this therapy, we have seen a worsening of the clinical condition of these patients in relation to liver disease, such as decompensated cirrhosis and hepatocellular carcinoma, mainly due to co-infection with HBV and HCV. These clinical symptoms have been the main cause of hospitalization, accounting for 9% of deaths among HIV infected individuals.^{16,17} Various strategies have been proposed for the reduction of mortality in these individuals, such as vaccination against HBV and optimization of HIV and HCV therapies; screening for alco-

hol abuse; and diagnosis and treatment of underlying diseases, such as diabetes.¹⁸

The prevalence of HCV infection was significantly associated with HIV infection compared with the prevalence of HCV in the general population of Curitiba, which justifies screening for HCV in HIV patients. Co-infection with HCV is a major etiological cause of liver disease in HIV-infected individuals, with a negative impact on these patients. Liver damage induced by the immunosuppression caused by the presence of HIV is boosted by the presence of HCV, which also causes chronic inflammation in the liver, leading to an increased risk of cardiovascular and kidney diseases.^{4,19}

The co-infection rates vary widely in different populations, probably due to differences in the population groups and methodologies used (Table 2). The prevalence of co-infection varies in different populations, from 10% and possibly reaching 85% in IDU.¹ In the United States and Europe, it is estimated that approximately 30% of HIV patients are co-infected with HCV,¹⁷ which may reach up to 95% if one considers blood as the route of transmission, both IDU as well as blood transfusion.²⁰ In Brazil, the prevalence varies from 5 to 54% depending on the region investigated and the study design,²¹⁻²⁶ and may reach 84% in IDU.^{21,27} In this study, we observed a preva-

TABLE 2 Prevalence of HCV/HIV co-infection in different Brazilian geographical regions

Geographical regions	N	HCV-HIV prevalence (Anti-HCV)	References
Florianópolis, SC	99	53.8%	Treitinger et al., 1999 ³⁴
São Paulo, SP	1,457	17.7%	Mendes-Corrêa et al., 2001 ⁴¹
Rio de Janeiro, RJ	238	8.9%	Ferraz et al., 2002 ⁴²
Campinas, SP	232	53.8%	Pavan et al., 2003 ³⁵
Santos, SP	495	36.2%	Segurado et al., 2004 ²¹
Londrina, PR	784	21.0%	Morimoto et al., 2005 ²²
Manaus, AM	704	5.0%	Braga et al., 2006 ²³
Porto Alegre, RS	330	38.2%	Tovo et al., 2006 ²⁵
Cuiabá, MT	1,008	10.9%	Mussi et al., 2007 ²⁶
Botucatu, SP	150	14.7%	Corvino et al., 2007 ⁴³
Belo Horizonte, MG	824	9.2%	Carmo et al., 2008 ⁴⁴
Belo Horizonte, MG	300	15.7%	Rodrigues et al., 2008 ⁴⁵
Londrina, PR	778	21.0%	Reiche et al., 2008 ²⁹
São Paulo, SP	8,019	12.9%	Farias et al., 2008 ²⁸
Recife, PE	343	4.1%	Carvalho et al., 2009 ⁴⁶
São Paulo, SP	2,024	16.7%	Mendes-Corrêa et al., 2010 ⁴⁰
Santa Maria, RS	250	31.2%	Santos et al., 2010 ³⁰
CE	1,291	25.4%	Távora et al., 2013 ³²
Curitiba, PR	303	12.9%	Present study

lence of 12.9% co-infection with HCV among patients monitored at the Infectious and Parasitic Diseases Outpatient Clinic at the HC/UFPR in Curitiba. This rate was similar to that found in São Paulo by Farias et al.,²⁸ but lower than that observed in patients in Londrina (PR) by Reich et al.²⁹ (21%) and in Santa Maria (RS) by Santos et al.³⁰ (31.2%). The prevalence of co-infection with HCV observed in Curitiba was lower than those reported in Eastern European countries and the United States, which ranges from 20-40%.^{5,18}

Although some authors, such as Greub et al.⁷ and Lakus et al.¹ report rapid progression to AIDS in the presence of co-infection with HIV/HCV, this evidence was not found in our study, possibly due to the limited number of sampling of co-infected cases (39 cases). However, a meta-analysis by Chen et al. characterized that the increased mortality in these patients was not associated with AIDS defining events.¹⁹

According to the Ministry of Health, the Brazilian profile of HIV infection in 2012 was 1.7 cases of men for every case in women,³¹ while in the present study the proportion found was 1:1. In relation to the frequency of HIV/HCV co-infection with regard to sex, there was a greater proportion of men (64.1%) compared to women (35.9%) among co-infected patients. Although the difference is not significant ($p=0.06$), these data are similar to those reported by Távora et al.³² in northeastern Brazil (77.8 and 22.2%, respectively) and Reiche et al.²⁹ (71.1 and 28.9%, respectively) in Londrina (PR).

The descent profile characterized in our study is directly related to the profile of the population of the metropolitan region of Curitiba, according to the last census by the Brazilian Census Bureau (IBGE - Instituto Brasileiro de Geografia e Estatística),³³ with a higher frequency of Euro-Brazilian individuals.

Considering the risk factors associated with HCV transmission, the parenteral route was reported in 46.1% of co-infected patients HIV/HCV who reported a single route of infection. This frequency increased significantly (65.4%) when considering reports involving this associated with other routes of transmission. These findings corroborate the results obtained in other studies in Brazil^{34,35} and other countries, with data indicating a frequency up to 75%.^{4,5} This is due to the fact that it is often not possible to state which of the routes was responsible for transmission since these individuals also had sexual contact as an associated risk factor. Although the parenteral route is the most frequent in co-infection, in 34.6% (9/26) of the cases the sexual route was the only route of infection reported. When multiple transmission routes

were considered, the sexual route was involved in 53.8% (14/26) of cases. These data indicate that the sexual route is indeed an important route of transmission for HCV, a fact corroborated by other authors in Brazil and the United States.^{6,15} Some studies, such as those by Vandelli et al., Bradshaw et al. and Witt et al.,³⁶⁻³⁸ also reported the importance of this route. This fact has been the subject of discussion in the literature, with studies indicating the importance of this route mainly among men who have sex with men that do not use drugs.^{5,38,39}

The successful treatment of co-infection has reduced the morbidity and mortality of these patients, whose priority treatment should be for HCV.¹⁸ However, reports from different regions of the world have shown that only 30% of co-infected patients are eligible for standard therapy with pegylated interferon and ribavirin for treatment of HCV⁴⁰ and, in some cases, the choice of HAART therapy for the treatment of HIV and DAA therapy for HCV treatment will depend on the patient's response and the possible interactions between the drugs. This fact justifies the need for screening of co-infection with the HCV virus in HIV patients. The presence or absence of co-infection with HCV is crucial to the definition of treatment strategies, the choice of drugs and initiation of therapy that will directly impact the clinical progression and prognosis.

CONCLUSION

The prevalence of HCV infection in HIV patients in Curitiba is 12.9%, significantly higher than that found in the general population, which justifies the need for HCV screening in HIV patients. The parenteral route of transmission is the most prevalent in co-infected patients (46.1%), but the sexual route is also an important portion of the cases (34.6%). In HIV patients not co-infected with HCV, the most prevalent route was sexual, in 71.9% of the cases.

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RESUMO

Seroprevalência de marcadores do vírus da hepatite C (HCV) em pacientes infectados com HIV de Curitiba e Região Metropolitana

Objetivo: verificar a prevalência e caracterizar fatores epidemiológicos associados à coinfeção por HCV em pacientes HIV+ de Curitiba e Região Metropolitana.

Métodos: estudo envolvendo 303 pacientes HIV+, com idade média de 41,2 anos (18-73); 50,5% homens; acompanhados no Hospital de Clínicas da Universidade Federal do Paraná, entre abril de 2008 e março de 2009. Os dados clínico-epidemiológicos foram obtidos por meio de questionários e análise retrospectiva dos prontuários. Os anticorpos anti-HCV foram detectados por ensaio imunoenzimático quimioluminescente.

Resultados: dos pacientes HIV+, 12,9% apresentaram sorologia positiva para o HCV, sendo 64,1% homens e 35,9% mulheres, com idade média de 44,5 anos (24-66). A frequência nos homens foi de 16,7%, e nas mulheres, 9,1% ($p=0,06$). A prevalência do HCV foi significativamente associada à infecção por HIV quando comparada à população geral ($p<10^{-6}$, OR=100,4; IC95%=13,7-734,9). A via de transmissão parenteral foi a mais frequente entre os coinfectados (46,1%), e a sexual, a mais frequente entre os não coinfectados (71,8%) ($p=0,02$, OR=0,2; IC95%=0,1-0,7). A frequência de usuários de drogas injetáveis foi maior entre os coinfectados (61,5%) do que entre os não coinfectados (12,6%) ($p<10^{-6}$, OR=11,1; IC95%=4,5-27,7).

Conclusões: a prevalência da infecção por HCV nos pacientes HIV+ é de 12,9%, 88 vezes maior que a infecção na população geral de Curitiba. A via de transmissão mais frequente entre os coinfectados foi a parenteral, porém, a via sexual também é representativa para a transmissão do HCV (34,6%).

Palavras-chave: HIV, síndrome de imunodeficiência adquirida, coinfeção, hepatite C.

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