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The prevalence of hepatitis B virus infection markers and socio-demographic risk factors in HIV-infected patients in Southern Brazil

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ABSTRACT

Introduction: Hepatitis B virus (HBV) and human immunodeficiency virus (HIV) infections are two of the world's most important infectious diseases. Our objective was to determine the hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) prevalences among adult HIV-infected patients and identify the associations between socio-demographic variables and these HBV infection markers. **Methods**: This study was performed from October 2012 to March 2013. Three hundred HIV-seropositive patients were monitored by the Clinical Analysis Laboratory of Professor Polydoro Ernani de São Thiago University Hospital, Santa Catarina, Brazil. The blood tests included HBsAg, anti-HBc immunoglobulin M (IgM) and total anti-HBc. Patients reported their HIV viral loads and CD_4+ T-cell counts using a questionnaire designed to collect socio-demographic data. **Results**: The mean patient age was 44.6 years, the mean CD4 T-cell count was 525/mm^3, the mean time since beginning antiretroviral therapy was 7.6 years, and the mean time since HIV diagnosis was 9.6 years. The overall prevalences of HBsAg and total anti-HBc were 2.3% and 29.3%, respectively. Among the individuals analyzed, 0.3% were positive for HBsAg, 27.3% were positive for total anti-HBc, and 2.0% were positive either for HBsAg or total anti-HBc and were classified as chronically HBV-infected. Furthermore, 70.3% of the patients were classified as never having been infected. Male gender, age >40 years and Caucasian ethnicity were associated with an anti-HBc positive test. **Conclusions**: The results showed an intermediate prevalence of HBsAg among the studied patients. Moreover, the associations between the anti-HBc marker and socio-demographic factors suggest a need for HBV immunization among these HIV-positive individuals, who are likely to have HIV/HBV coinfection.

Keywords: Prevalence. Hepatitis B. Human immunodeficiency virus. Coinfection. Brazil.

INTRODUCTION

Hepatitis B virus (HBV) infection and human immunodeficiency virus (HIV) infection are two of the world's most important infectious diseases. HBV infection constitutes a major public health problem in many countries. More than two billion people have been infected with HBV worldwide, and 350 to 400 million people are chronic carriers[1]. It is estimated that nearly 600,000 people die annually from complications related to hepatitis B[2]. Approximately 70 million people have been infected with HIV; 35 million death shave occurred among individuals with acquired immunedeficiency syndrome (AIDS), and there are approximately 35 million HIV carriers[3]. Among the people currently living with HIV worldwide, approximately 8%, or 3 million, are chronically infected with HBV[4].

Coinfection with HBV and HIV is commonly observed because these viruses share common routes of transmission[5,6]. The prevalence of HBV/HIV coinfection reflects geographical variations[7], and the predominant routes of HBV transmission often correlate with the degree of endemicity. Most new infections occur among adults and are acquired sexually or through injectable drug use in minimally endemic settings. Conversely, exposure to chronically infected household members and perinatal transmission are the horizontal transmission routes that result in greatest amount of disease transmission in highly endemic countries. Countries with an intermediate endemicity exhibit a mixture of these transmission routes[8].

HBV coinfection may increase morbidity and mortality in HIV-seropositive patients. In addition, HIV infection increases the risk of chronic HBV infection and promotes a faster progression to cirrhosis and its complications, particularly when HBV replication is high[9-11].

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The seropositivity of HBV infection markers among HIV-infected individuals ranges from 4.2% to 19.4% for hepatitis B surface antigen (HBsAg)[5,12-18] and 22.9% to 70.4% for hepatitis B core antibody (anti-HBc)[12,14,16,17,19,20]. Studies have reported positive associations between HIV/HBV coinfection and such factors as sex, age, education level, intravenous drug use and homosexual activity[21,22]. In this study, the aim was to determine the prevalence of HBsAg and anti-HBc among an adult population infected with HIV regardless of antiretroviral therapy use to evaluate the different socio-demographic profiles of HIV/HBV coinfected subjects and to evaluate the presence of HBsAg and anti-HBc-associated factors in HIV-positive patients.

METHODS

This cross-sectional study was performed at the Clinical Analysis Laboratory of Professor Polydoro Ernani de São Thiago University Hospital in the State of Santa Catarina, Brazil between October 2012 and March 2013. The cohort consisted of 300 patients aged ≥18 years who were infected with HIV-1, were treated with or without antiretroviral therapy and were monitored clinically and by the laboratory.

The patients answered a self-administered questionnaire that consisted of the following modules: socio-demographic characteristics, including sex, age, ethnicity, annual income, and the highest level of education achieved; HIV-related risks; cluster of differentiation for (CD_4) T-cell count; HIV viral load; time (in years) since HIV infection diagnosis; and years of antiretroviral therapy.

Antiretroviral therapy, CD_4T-cell count, HIV viral load, time since diagnosis of HIV infection and length of treatment time were included as variables to investigate whether they are associated with the prevalence of HBV infection markers.

A cut-off of 500 cells/mm^3 for the CD_4 T-cell count was utilized according to the Protocol and Therapeutic Guidelines for the Clinical Management of HIV Infection in Adults[23], which recommends initiating antiretroviral therapy when CD_4 lymphocyte counts are ≤500 cells/mm^3.

A blood sample was collected from each patient for the qualitative determination of HBsAg and anti-HBc. Anti-HBc immunoglobulin M (IgM) tests were performed using samples obtained from HBsAg-positive patients. After the serum was separated, HBsAg and anti-HBc were detected using a chemiluminescence microparticle immunoassay (CMIA) commercial kit (ARCHITECT®, Abbott Diagnostics, Sligo, Ireland) according to the manufacturer's instructions. These results were categorized as either positive or negative according to the provided cut-offs.

Using bivariate analysis, we compared the HBsAg-positive and HBsAg-negative individuals to identify the socio-demographic variables that were likely to be associated with the presence of these markers in anti-HBc-positive and anti-HBc-negative patients. The variables included in the analysis were age, gender, ethnicity, education level, monthly income, time since HIV infection diagnosis, years of antiretroviral therapy, HIV transmission route, HIV viral load, and CD_4T-cell count. Pearson's chi-square test was used to compare the proportions. Statistical significance was set as $p<0.050$. To identify the parameters associated with anti-HBc, variables with $p<0.200$ in the bivariate analysis were evaluated with multiple logistic regression using the stepwise method. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS®) for Windows version 17.0 (SPSS, Chicago, IL, USA) and MedCalc® version 12.4.0 (MedCalc Software bvba, Ostend, Belgium).

Ethical considerations

This study was approved by the Ethics Committee of the Federal University of Santa Catarina (Protocol 94.398). Informed written consent was obtained from all participants.

RESULTS

A total of 300 patients were enrolled in this study (179 males and 121 females), and the average age of the subjects was 44.6 years (range: 18 to 81). The patients' mean CD4T-cell count at the time of HBV testing was 525/mm^3 (range: 90 to 1,446), and the average total antiretroviral therapy time and time since HIV diagnosis were 7.6 years (range: 0 to 25) and 9.6 years (range:1 to 27), respectively.

The overall prevalences of HBsAg and total anti-HBc were 2.3% (7/300) and 29.3% (88/300), respectively. Among the individuals analyzed, 0.3% (1/300) were positive for HBsAg, 27.3% (82/300) were positive for total anti-HBc, and 2% (6/300) were positive either for HBsAg or total anti-HBc. All of the HBsAg-positive patients who tested positive for total anti-HBc had negative anti-HBc IgM results and were classified as chronically infected. None of the patients had positive anti-HBc IgM test results. The absence of HBsAg and anti-HBc was observed in 70.3% of the examined patients (211/300), who were classified as never having been infected **(Table 1)**.

The statistical analyses indicated that none of the socio-demographic or clinical variables studied were associated with positive HBsAg **(Table 2)**. However, caucasians (p=0.049), men (p<0.001), people with incomes ≥US$1,300 (p=0.032), patients over 40 years old (p=0.001), men who had sex with men and patients who were part of an intravenous drug use (IDU) risk group (p=0.005) were more likely to have an anti-HBc positive test compared with patients with African ancestry, members of non-intravenous drug user riskg roups, females, patients with an income <US$1,300 and those aged ≤40 years old **(Table 3)**. In the stepwise logistic regression analysis, non-Caucasian individuals and women had a significantly lower risk of being anti-HBc positive. Conversely, individuals older than 40 years had an increased risk of being anti-HBc positive **(Table 4)**.

DISCUSSION

The HBsAg and anti-HBc prevalences confirmed in this study were lower than those found in studies of HIV-seropositive patients in different Brazilian cities, such as Belém (7.9% and 51%)[24], Cuiabá (3.7% and 40%)[25], Campinas (5.3% and 44%)[26],

TABLE 1- Prevalence of the HBV infection markers HBsAg and anti-HBc among 300 HIV-infected patients in Southern Brazil from October 2012 to March 2013.

	HBsAg (-) Total anti-HBc (-)		HBsAg (-) Total anti-HBc (+)		HBsAg (+) Total anti-HBc (-)		HBsAg (+) Total anti-HBc (+)		Total	
Gender	n	%	n	%	n	%	n	%	n	%
Male	109	36.3	64	21.4	1	0.3	5	1.7	179	59.7
Female	102	34.0	18	6.0	-	-	1	0.3	121	40.3
Total	211	70.3	82	27.3	1	0.3	6	2.0	300	100.0

HBV: hepatitis B virus; **HBsAg**: hepatitis B surface antigen**; anti-HBc**: hepatitis B core antibody; **HIV:** human immunodeficiency virus.

Ribeirão Preto (8.5% and 40.9%)[27] and São Paulo (5.7% and 38.6%)[28].

Taking into account the seropositivities of 0.3% for HBsAg and 2% for HBsAg and total anti-HBc, this study revealed an overall seropositivity of 2.3% for HBsAg. The prevalence of HBsAg carriers identified in this study can be considered intermediate[29]. In addition, the prevalence of HBsAg in our study is lower than the continental HBsAg prevalence of 9.1% that was estimated for HIV-seropositive patients by the EuroSIDA Study Group in 1998, which included the United Kingdom, Ireland, Norway, Sweden, Denmark, Germany, Holland, Luxembourg, France and Switzerland[30] and countries in which the HBV infection prevalence in the general population was estimated to be less than 1%.

When we compared our results with those from a 1999 study performed in the same region that also examined HIV seropositivity[31], we found reductions in the prevalences of HBsAg, anti-HBc and HBV chronic infection from 28.8%, 95.5% and 24.3% to 2.3%, 29.3% and 2%, respectively.

Studies performed in southern Brazil between 2009 and 2010 showed that the vaccination coverage of children and adolescents who were born after the hepatitis B vaccination was introduced was over 92%[32] and that the HBsAg and anti-HBc prevalences were less than 1% and 10%, respectively[32-35]. Hepatitis B virus vaccination began in 1992 for children younger than five years of age and subsequently expanded to health professionals, students, firefighters, police and the military in 1994 and to adults under 20 years old in 2001[36]. Considering that the marked reduction in the prevalence of HBV infection markers among the general population is primarily a result of immunization against hepatitis B, vaccination may have also contributed to the decreased prevalences of HBsAg and anti-HBc that were observed in HIV-infected individuals between 1999 and 2013.

Studies performed in the United Kingdom and the United States among HIV-infected children and adults[14,37] also found a significant decrease in the prevalence of HBV infection markers (HBsAg and anti-HBc) ten and fifteen years after hepatitis B vaccinations were introduced. Considering the expanded availability of the hepatitis B vaccine to people in older age groups and the expansion of risk groups, which resulted in the near-universalization of the vaccine[36,38], it is possible that the prevalence of HIV/HBV coinfection and the prevalence of HBsAg and anti-HBc in the general population may decline significantly over the next decade, resulting in true therapeutic reductions in pathologies caused by HBV infection, such as hepatocellular carcinoma and liver cirrhosis.

Regarding the 2% chronic HBV infection prevalence observed in this study, it is important to note that the worldwide prevalence of chronic HBV infection in HIV-infected patients is approximately 10%[39]. However, studies have shown that HBV-deoxyribonucleic acid (HBV-DNA) can be detected in patients with serological profiles that would traditionally be interpreted as previously infected or never infected[16,40] and in patients who are also seropositive for anti-HBc[41]. The prevalence of occult hepatitis B infection in HIV-positive patients with isolated anti-HBc ranges from 0% to 89%[42]. Thus, additional studies are required to better assess the prevalence of chronic hepatitis B infection among HIV-seropositive patients.

Importantly, we found that anti-HBc was most prevalent among males, people over 40 years old and people of Caucasian ethnicity. Moreover, non-Caucasian people and women had a significantly lower risk of being anti-HBc positive. The association between male gender and a high anti-HBc prevalence was also observed in previous studies[16,43,44] and can be explained by males' higher rate of promiscuity and more frequent exposure to risk factors for transmission[5]. The association between anti-HBc and age over 40 years that we observed in our study can be explained by the increased chance of HBV infection that results from a longer lifespan and life time exposure to unprotected sex, unprotected sexual relationships and mother-to-child transmission. Importantly, older patients are also less likely to have been vaccinated for HBV or to have contracted HBV before they contracted HIV because vaccinations for individuals over thirty years of age did not begin until 2013[36]. The significant association between Caucasian ethnicity and anti-HBc prevalence may be attributable to the socio-demographic characteristics of the study population. Our study's population differs from the populations of studies performed in the United Kingdom and Germany; in those countries, there were stronger associations between HBV infection markers and patients who were non-Caucasian patients or originated from endemic regions[14,16].

TABLE 2 – Socio-demographic and clinical variables potentially associated with isolated HBsAg prevalence in 300 HIV-infected patients in Southern Brazil from October 2012 to March 2013.

	HBsAg						
	negative		positive			Total	
Variable	n	%	n	%	p-value	n	%
Age (years)							
≤40	98	97.0	3	3.0	0.907	101	33.7
>40	195	98.0	4	2.0		199	66.3
Gender							
male	173	96.6	6	3.4	0.155	179	59.7
female	120	99.2	1	0.8		121	40.3
Ethnicity							
caucasian	252	97.7	6	2.3	0.982	258	86.0
non-caucasian	41	97.6	1	2.4		42	14.0
Highest level of education							
<high school	171	97.7	4	2.3	0.948	175	58.3
≥high school	122	97.6	3	2.4		125	41.7
Monthly income (US$)							
<1,300	196	97.5	5	2.5	0.801	201	67.0
≥1,300	97	98.0	2	2.0		99	33.0
Time since HIV infection diagnosis (years)							
<10	155	96.9	5	3.1	0.332	160	53.3
≥10	138	98.6	2	1.4		140	46.7
Time since the initiation of antiretroviral therapy (years)							
<10	183	97.3	5	2.7	0.628	188	62.7
≥10	110	98.2	2	1.8		112	37.3
Transmission route of HIV infection							
MSM	65	95.6	3	4.4	0.856	68	22.7
heterosexual	183	98.9	2	1.1		185	61.7
IDU	32	94.1	2	5.9		34	11.3
others	13	100.0	-	-		13	4.3
HIV viral load (copies/mL)							
<50	224	97.8	5	2.2	0.847	229	76.4
50 to 10,000	45	97.8	1	2.2		46	15.3
>10,000	24	96.0	1	4.0		25	8.3
CD4 T-cell count (cells/mm^3)							
<500	150	98.0	3	2.0	0.478	153	51.0
≥500	143	97.3	4	2.7		147	49.0

HBsAg: hepatitis B surface antigen; **HIV:** human immunodeficiency virus; **MSM:** men who have sex with men**; IDU:** intravenous drug user; **CD4:** cluster of differentiation 4.

TABLE 3 - Socio-demographic and clinical variables potentially associated with anti-HBc prevalence among 300 HIV-infected patients in Southern Brazil from October 2012 to March 2013.

	Anti-HBc					Total	
	negative		positive				
Variable	n	%	n	%	p-value	n	%
Age (years)							
≤40	84	83.2	17	16.8	0.001*	101	33.7
>40	128	64.3	71	35.7		199	66.3
Gender							
male	110	61.5	69	38.5	<0.001*	179	59.7
female	102	84.3	19	15.7		121	40.3
Ethnicity							
caucasian	177	68.6	81	31.4	0.049*	258	86.0
non-caucasian	35	83.3	7	16.7		42	14.0
Highest level of education							
<high school	128	73.1	47	26.9	0.265	175	58.3
≥high school	84	67.2	41	32.8		125	41.7
Monthly income (US$)							
<1,300	150	74.6	51	25.4	0.032*	201	67.0
≥1,300	62	62.6	37	37.4		99	33.0
Time since HIV infection diagnosis (years)							
<10	115	71.9	45	28.1	0.623	160	53.3
≥10	97	69.3	43	30.7		140	46.7
Time since initiation of antiretroviral therapy (years)							
<10	137	72.9	51	27.1	0.277	188	62.7
≥10	75	67.0	37	33.0		112	37.3
Transmission route of HIV infection							
MSM	44	64.7	24	35.3	0.005*	68	22.7
heterosexual	139	75.1	46	24.9		185	61.7
IDU	17	50.0	17	50.0		34	11.3
other	12	92.3	1	7.7		13	4.3
HIV viral load (copies/mL)							
<50	157	68.6	72	31.4	0.269	229	76.4
50 to 10,000	37	80.4	9	19.6		46	15.3
>10,000	18	80.0	7	20.0		25	8.3
CD4 T-cell count (cells/mm^3)							
<500	109	71.2	44	28.8	0.461	153	51.0
≥500	103	70.1	44	29.9		147	49.0

Anti-HBc: hepatitis B core antibody; **HIV:** human immunodeficiency virus; **MSM:** men who have sex with men**; IDU:** intravenous drug user; **CD4:** cluster of differentiation 4.*Statistically significant at p<0.050.

TABLE 4 - Multiple logistic regression analysis of socio-demographic variables associated with anti-HBc prevalence among 300 HIV-infected patients in Southern Brazil from October 2012 to March 2013.

Variable	OR (95%CI)	p-value
Age(years)		
>40	2.9047 (1.5459 to 5.4577)	0.0009*
Ethnicity		
Non-caucasian	0.3539(0.1448 to 0.8050)	0.0027*
Gender		
Female	0.2825 (0.1555 to 0.5134)	<0.0001*

Anti-HBc: hepatitis B core antibody; **HIV:** human immunodeficiency virus; **OR:** odds ratio; **95% CI:** confidence interval.*Statistically significant at p<0.050.

One limitation of the present study is that the cohort is only representative of the population of HIV-infected patients of Florianópolis, State of Santa Catarina. However, the results of this study provide valuable data for targeting HBV immunization campaigns among HIV-infected patients, who are more likely to exhibit HIV/HBV coinfection, and may help to improve preventive actions.

The results of this study indicated an intermediate prevalence of HBsAg among HIV-infected patients in southern Brazil. In addition, the prevalence of the anti-HBc marker was significantly associated with the sex, age and ethnicity of the HIV-infected patients, suggesting the need for HBV immunization campaigns that focus on those HIV-positive individuals who are most susceptible to coinfection. Despite the observed decline in the prevalence of HBsAg and anti-HBc, prevention campaigns are important to encourage the adult population to vaccinate and to reaffirm that vaccination is the most effective way to avoid both HBV infection and diseases that result from infection, such as hepatocellular carcinoma.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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