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## Original article

# Hepatitis C viral load in HCV-monoinfected and HCV/HIV-1-, HCV/HTLV-1/-2-, and HCV/HIV/HTLV-1/-2-co-infected patients from São Paulo, Brazil

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## ABSTRACT

Co-infections of hepatitis C virus (HCV) and either human immunodeficiency virus type 1 (HIV-1), human T-cell lymphotropic virus type 1 (HTLV-1) or type 2 (HTLV-2) have been described as having an impact on HCV viremia and subsequent disease progression. HCV load in serum samples from 622 patients (343 males, 279 females; median age 50.8 years) from São Paulo/southeast Brazil was analyzed using the Abbott Real Time HCV assay (Abbott Molecular Inc., IL, USA). Samples were obtained from HCV-monoinfected ( $n = 548$ ), HCV/HIV-1- ( $n = 41$ ), HCV/HTLV-1- ( $n = 16$ ), HCV/HTLV-2- ( $n = 8$ ), HCV/HIV/HTLV-1- ( $n = 4$ ), and HCV/HIV/HTLV-2-co-infected ( $n = 5$ ) patients, and results were compared among the groups and according to sex. The median HCV load in HCV-monoinfected patients was  $5.23 \log_{10}$  IU/mL and  $0.31 \log_{10}$  higher in men than in women. Increases in viral load of  $0.51 \log_{10}$ ,  $0.54 \log_{10}$ , and  $1.43 \log_{10}$  IU/mL were detected in HCV/HIV-1-, HCV/HTLV-1- and HCV/HIV/HTLV-1-co-infected individuals, respectively, compared with HCV-monoinfected counterparts. In contrast, compared to HCV/HIV co-infected patients, HCV/HTLV-2-co-infected patients had an HCV load of  $5.0 \log_{10}$  IU/mL, whereas HCV/HIV/HTLV-2-co-infected patients had a median load  $0.37 \log_{10}$  IU/mL lower. Significant differences in HCV loads were detected, with males and HCV/HIV-1- and HCV/HIV/HTLV-1-co-infected patients presenting the highest values. Conversely, females and HCV/HTLV-2-co-infected patients exhibited lower HCV loads. Overall, HCV viremia is increased in HIV and/or HTLV-1-co-infection and decreased in HTLV-2 co-infection.

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## Introduction

Hepatitis C virus (HCV) infection is an important health problem both in Brazil and worldwide because a considerable number of infected patients progresses to chronic liver diseases (cirrhosis and hepatocellular carcinoma) and require liver transplantation.<sup>1</sup> In Brazil, mandatory notification of HCV infection has been implemented since 1998. From 1999 to 2015, the Brazilian Ministry of Health (MH) recorded 289,459 cases, 64.2% of which occurred in the southeast region.<sup>2</sup> In addition, a cross-sectional population-based survey conducted in Brazil from 2005 to 2009 revealed an overall prevalence of 1.38% and estimated 1.3 million HCV-infected individuals in the country.<sup>3</sup>

Associations between HCV infection and old age, injected-drug use, sniffed-drug use, hospitalization, lack of sewage disposal, and injection with glass syringes have been described, and these associations depend on the socio-demographic characteristics of patients and regions.<sup>3</sup> Located in the southeast region, São Paulo is the most populous and wealthy state in Brazil, where HCV has been detected in 0.9% of individuals aged 10–19 years, and in 1.63% of those aged 20–69 years.<sup>3</sup>

HCV-infected patients are reported to the Brazilian MH, which provides free universal access to treatment, HCV genotyping and viral load determination.<sup>4</sup> Furthermore, the Brazilian MH recommends that HCV loads be measured for diagnosis confirmation and after six months of follow-up. Moreover, in patients without spontaneous HCV clearance and/or in those who have started treatment, genotyping and subsequent viral load measurements are recommended four times a year.<sup>4</sup>

Human T-cell lymphotropic virus types 1 and 2 (HTLV-1 and HTLV-2) are endemic in Brazil,<sup>5</sup> with an estimated 2.5 million individuals infected with HTLV.<sup>6</sup>

HTLV-1 is associated with at least two diseases of high morbidity and mortality: adult T-cell leukemia/lymphoma (ATLL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP).<sup>5</sup> Despite their endemicity and high morbidity, HTLV-1 or HTLV-2 notification is not compulsory in Brazil.

Human immunodeficiency virus type 1 (HIV-1) is responsible for the acquired immunodeficiency syndrome (AIDS) pandemic; notification is compulsory in Brazilian blood banks since 1988. From 1980 to 2016, the Brazilian MH reported 882,810 HIV/AIDS cases, with 52.3% in the southeast region.<sup>7</sup>

As all of these viruses share some common routes of transmission/infection, there is a tendency for co-infection.

HIV/HCV co-infection has been associated with poorer outcomes of subsequent diseases.<sup>4,8,9</sup> HIV/HTLV-1 co-infection induces rapid progression toward AIDS and death<sup>10,11</sup>; HIV/HTLV-2 slows the progression toward AIDS.<sup>12</sup>

Although HCV/HTLV-1/-2 co-infection has been associated with worse outcomes of HCV infection worldwide (higher HCV viremia, lower rate of sustained virological response to  $\alpha$ -interferon treatment, increased risk of chronic liver disease, and cancer), this is not the case in Brazil.<sup>13</sup> Indeed, in Brazil, HCV/HTLV-1 co-infection has been associated with spontaneous clearance of HCV, and less liver injury.<sup>9,13–16</sup>

The present study aimed to confirm or refute the positive influence of HTLV-1 on HCV viremia in co-infected patients in Brazil, and to add further information concerning the impact of HIV-1, HTLV-1 and HTLV-2 on HCV viremia in patients from São Paulo.

## Methods

### Study population

The Instituto Adolfo Lutz (IAL), a Public Health Laboratory located in São Paulo city, is a reference laboratory for viral hepatitis, HIV, HTLV-1, and HTLV-2 infections. IAL is responsible for the surveillance of these viruses and to assess trends of infections and co-infections. Blood samples are sent to IAL are from several Specialized Health Centers in the state of São Paulo, i.e., STD/AIDS and Viral Hepatitis Centers and Gastroenterology and/or Hepatology Services. A cross-sectional study was conducted using data obtained from serum samples collected from 622 patients analyzed for HCV viral load during the period of June to November 2014 at IAL.

For this study, samples were collected from the following health centers: Gastroenterology Service in the city of São Paulo ( $n=181$ ); several specialized services of Infectious Diseases, STD/AIDS and Viral Hepatitis, and Gastroenterology and Hepatology outpatients services, located in the Metropolitan area of São Paulo city; in two cities located south of São Paulo ( $n=124$  and  $n=8$ , respectively); and in cities situated in the eastern part of the state, up to 200 km away from São Paulo city ( $n=309$ ) (Fig. 1).

### Laboratory methods

After performing HCV load measurement using a Real-Time HCV assay (Abbott Molecular Inc., IL, USA), with a lower limit of detection of 12 IU/mL, samples were tested for HIV-1, HTLV-1 or HTLV-2 co-infection, as previously described.<sup>17</sup>

Briefly, anti-HTLV-1/-2 antibodies were detected by an enzyme immunoassay (EIA, HTLV-I/II, Gold ELISA, REM Ind. Com. Ltda, São Paulo, SP, Brazil) and confirmed by line immunoassay (INNO-LIA HTLV-I/II, Fujirebio, Europe N.V., Belgium). HIV-1 infection was evaluated by using an immunochromatographic assay (Rapid Check HIV 1+2, Universidade Federal do Espírito Santo, ES, Brazil) and an enzyme immunoassay (GS HIV-1/HIV-2 Plus O EIA, Bio-Rad Laboratories, USA). All assays were conducted according to the respective manufacturers' instructions. A prevalence of 7.9% of HIV-1 and 5.3% of HTLV-1/-2 were detected, revealing HTLV-1/-2 infection in patients with hepatitis C, regardless of their HIV-1 status.<sup>17</sup>

### Groups for analyses and data collection

Six groups were categorized according to the results (positive or negative) for the following HIV-1 and HTLV-1/-2 serological assays: HCV mono-infection ( $n=548$ ); HCV/HIV-1 ( $n=41$ ), HCV/HTLV-1 ( $n=16$ ), HCV/HTLV-2 ( $n=8$ ), HCV/HIV/HTLV-1 ( $n=4$ ), and HCV/HIV/HTLV-2 co-infection ( $n=5$ ).

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