Rev. Inst. Med. Trop. Sao Paulo
2016;58:80
http://dx.doi.org/10.1590/S1678-9946201658080

ORIGINAL ARTICLE

SEROPREVALENCE OF HTLV IN A POPULATION OF HIV1-INFECTED PATIENTS IN MIDWESTERN BRAZIL

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SUMMARY

Human T-cell lymphotropic virus (HTLV) may affect the clinical course of human immunodeficiency virus 1 (HIV1). Both infections are common in endemic areas because these viruses share similar routes of transmission. The aim of this study was to estimate the seroprevalence of HTLV1/2 in a population of HIV1-infected patients in the state of *Goiás*, Midwestern Brazil. Of the 505 studied patients, four (0.79%) were positive for anti-HTLV1/2 by enzyme-linked immunosorbent assay (ELISA), with HTLV1 infection confirmed by line immunoassay (LIA) and polymerase chain reaction (PCR) in all of the ELISA-positive samples. No cases of HTLV2 infection were observed. The prevalence of HTLV1/HIV1 coinfection was 0.79% (4/505; 95% CI: 0.25-2.16). All the coinfected patients reported sexual risk behaviors and only one reported intravenous drug use. Sequencing of the viral long terminal repeat (LTR) region and phylogenetic analysis revealed that the four HTLV1 isolates belonged to the Transcontinental (A) subgroup of the Cosmopolitan (1a) subtype, the most frequent subgroup detected in Brazil. This study shows a low prevalence of HTLV1/2 in HIV1-infected patients in Midwestern Brazil.

KEYWORDS: HTLV; HIV-1; Coinfection; Prevalence; Subtype.

INTRODUCTION

Human T-cell lymphotropic virus type 1 (HTLV1), the causative agent of adult T-cell leukemia/lymphoma (ATLL) and tropical spastic paraparesis/ HTLV1-associated myelopathy (TSP/HAM), is also related to uveitis and other inflammatory diseases[1]. Worldwide, it is estimated that 5-10 million people are infected with HTLV1. This virus is endemic in Japan, sub-Saharan Africa, the Caribbean and some parts of South America[2,3]. Based on genetic analyses of the viral long terminal repeat (LTR) region, HTLV1 has been classified into seven subtypes (1a-g). The 1a or Cosmopolitan subtype Transcontinental subgroup is the most widespread[1,2]. Human T-cell lymphotropic virus type 2 (HTLV2) has also been associated with myelopathy and other neurological disorders[4]. HTLV2 is largely present in indigenous populations in the Americas, as well as in intravenous drug users. This virus is subdivided into four subtypes (a-d). HTLV2c is the most prevalent subtype in Brazil[3].

Coinfection between HTLV1/2 and human immunodeficiency virus 1 (HIV1) is common in endemic areas, because these viruses share similar routes of transmission such as sexual contact, breastfeeding, blood transfusion and intravenous drug use (IDU). Although HTLV and HIV1 coinfection remains poorly understood, higher rates of myelopathy and other neurological disorders have been observed[5].

In Brazil, a South American country, few data have been reported on the prevalence of HTLV infection among HIV1-positive patients in recent years[6-10], and no studies regarding HTLV/HIV coinfection in Midwestern Brazil has been published so far. Therefore, the aim of this study was to estimate the seroprevalence of HTLV1/2 in a population of HIV1-infected patients in the state of *Goiás*.

MATERIAL AND METHODS

A cross-sectional study was conducted in a population of HIV1-positive patients at the *Hospital de Doenças Tropicais (HDT) Dr. Anuar Auad*. This hospital is located in the state of *Goiás* (6,610,681 inhabitants), the most populous state in Midwestern Brazil. The HDT is the largest public referral hospital for infectious diseases in the region, receiving an average of 600 new HIV1 cases per year. From April 2009 to March 2010, all the patients were invited to participate in the study during regular medical visits at the outpatient unit of the HDT. Individuals were eligible if they were adults (18 years old or older),

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infected with HIV1, antiretroviral drug therapy-naïve, and agreed to answer a structured questionnaire and have a blood sample collected. After the signature of the informed consent, they were interviewed so as to record their demographic and behavioral characteristics. Clinical data, T CD4+ lymphocyte counts, and HIV1 viral load measurements were obtained from medical records using the most recent data available at the time of the interview.

Blood was collected (10 mL) from all the participants. HTLV infection was detected by enzyme-linked immunosorbent assay (ELISA) (anti-HTLV, Murex HTLV–I+II, Murex Biotech, Dartford, UK) and confirmed by immunoassay (INNO-LIA HTLV I/II, Innogenetics Biotechnology for Healthcare, Ghent, Belgium).

Whole blood samples of anti-HTLV seropositive patients were subjected to DNA extraction using the QIAamp DNA Blood Mini kit (QIAGEN Inc., Hilden, Germany) according to the manufacturer's instructions. Polymerase chain reactions (PCR) targeting the *tax* and LTR regions of HTLV1 and HTLV2 were performed[11-13]. PCR products were purified using the QIAamp PCR purification kit (QIAGEN Inc., Hilden, Germany) and were submitted to direct nucleotide sequencing reaction in both directions using the Big Dye Terminator v 3.1 Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Foster City, CA, USA) in a 3100 Automated DNA Sequencer (Applied Biosystems, Foster City, CA, USA).

The HTLV1-LTR sequences were aligned using the ClustalW program, implemented in the MEGA version 5.2 software package[14], and edited using the BioEdit v5.0.9 program (Department of Microbiology, North Carolina State University, USA). A neighbor-joining (NJ) tree was constructed by PAUP* software version 4.0b10[15]. The Hasegawa, Kishino & Yano (HKY) model with gamma distribution was selected using the Modeltest 3.7 software[16]. The reliability of the NJ tree was evaluated by bootstrap analysis of 1,000 replicates. Novel nucleotide sequences identified from the present study were deposited in GenBank under accession numbers KM875549 to KM875552.

HTLV-positive samples were tested for hepatitis B virus (HBV), presence of hepatitis B surface antigen (HBsAg), using the Hepanostika HBsAg Ultra (BioMérieux, Marcy l'Étoile, Lyon, France); antibody to hepatitis B core antigen (anti-HBc), Hepanostika anti-HBc Uni-form (BioMérieux, Marcy l'Étoile, Lyon, France) and hepatitis C virus (HCV, anti-HCV-ELISA, Hepanostika Ultra, Biomedical, Shanghai, China).

This study was approved by the Ethics Committee of the Anuar Auad Tropical Disease Hospital, *Goiânia, Goiás*, Brazil.

RESULTS

A total of 520 treatment-naïve HIV1-infected patients were eligible for inclusion in this study. Of these, 505 (97.1%) agreed to participate. As shown in Table 1, most patients were male (60.2%). The mean age was 37.6 years (standard deviation (SD): 10.2). Almost half of the study population (45.4%) was single, 78.6% were non-Caucasian (Afro-descendants 77% and Asian 1.6%), 69.7% reported a monthly income of US$ 700 or less and 60.8% had less than 10 years of education.

Behavioral characteristics such as history of blood transfusion with blood bags that were not screened for anti-HTLV (before November 1993; 5.7%), IDU (2.2%), multiple sexual partners (> 10 during lifetime, 61.8%), non-use or occasional use of condoms (during lifetime, 89.9%) and history of sexually transmitted infections (at least one STI in lifetime, 36.6%) were reported by the study population.

Table 1
Sociodemographic characteristics of HIV1-infected patients in Midwestern Brazil (n = 505)

Characteristics	n	%
Age (mean ± SD: 37.6 ± 10.2)		
< 30 years	116	23.0
30-39 years	201	39.0
40-49 years	117	23.2
≥ 50 years	71	14.0
Gender		
Male	304	60.2
Female	201	39.8
Marital status		
Single	229	45.4
Married	201	39.8
Divorced/widowed	75	14.8
Ethnicity		
Caucasian	108	21.4
Non-caucasian	397	78.6
Monthly income[a]		
< 1 minimum wage	178	35.2
1-2 minimum wages	174	34.5
> 2 minimum wages	121	30.3
Education		
< 5 years	73	14.5
5-9 years	234	46.3
10-12 years	153	30.3
> 12 years	45	8.9

SD - standard deviation. [a]Minimum monthly wage was approximately equal to US$ 350.

Of the 505 study participants, four were found to be HTLV1/2-positive by ELISA. After confirmatory testing (LIA and PCR targeting the *tax* and LTR regions), these patients were confirmed to be positive for HTLV1. The prevalence of HTLV1/HIV1 coinfection was 0.79% (4/505; 95% CI: 0.25-2.16). No cases of HTLV2 infection were observed.

Although the number of coinfected individuals was small, a higher mean age and percentage of females were observed in this group. The four coinfected patients reported unprotected sex with multiple partners. Of these, two reported STIs and had also a positive serology to HBV.

One of them reported IDU and had also a positive serology to HCV. Mean CD4+ T cell counts for HIV1 mono-infected and HTLV1/HIV1 coinfected patients were 526.6 cells/μL and 599.7 cells/μL, respectively. Mean HIV1 viral load (log10) were 4.6 copies/ml and 4.9 copies/mL, respectively (Table 2).

The phylogenetic analysis of the HTLV1-LTR region (Fig. 1) revealed that the four HTLV1 isolates (V-89, V-162, V-359 and V-390) belonged to the Transcontinental (A) subgroup of the Cosmopolitan (1a) subtype.

DISCUSSION

In this study, we reported for the first time the HTLV seroprevalence in a population of HIV1-infected patients in Midwestern Brazil. The prevalence of HTLV1 was 0.79%, six times higher than the percentage found in local blood donors (0.13%) (A G Kozlowski, unpublished data). Nevertheless, relative to other Brazilian data regarding HIV1-infected patients published between 2010 and 2015, this prevalence was lower than those reported in *Piauí* (1.12%)[6], *São Paulo* (1.55%)[10], *Porto Alegre* (1.9%)[9] and *Feira de Santana, Bahia* (3.74%)[17]. Differences in regional endemicity, ethnic origin of the population, risk behaviors and study designs are the possible reasons for these differences in the observed rates.

These factors may also reflect the wide variation in HTLV1 and HTLV2 distribution in Brazilian HIV1-infected patients. In this study, HTLV1 was identified in the four HTLV/HIV1 coinfected patients. No case of HTLV2 infection was observed. Similarly, HTLV1 was also identified in the majority of HTLV/HIV1 coinfected patients in *Piauí*[6], *Porto Alegre*[9] and *Feira de Santana*[17], unlike those from *São Paulo*, where similar distribution of HTLV1 and HTLV2 was reported[10]. By contrast, some previous studies have demonstrated high HTLV2/HIV1 coinfection rates in *Belém*[18,19], where HTLV2 infection is known to be endemic, as well as in *Londrina*[20], *Ribeirão Preto* and *São Paulo*[21] where this coinfection was associated with IDU.

Sexual risk behaviors such as history of multiple sexual partners and non-use or occasional use of condoms were frequently reported among the study participants. These data are consistent with data reported in the Epidemiological Bulletin by the Ministry of Health, showing that the majority of HIV/Aids cases in 2013 (94.9% and 97.4% in men and women, respectively) among individuals older than 12 years old resulted from sexual transmission[22]. It is also an important route of HTLV1 transmission[1]. In fact, the four HTLV1/HIV1 coinfected patients reported unprotected sex with multiple partners. Two of them reported history of STIs and were also exposed to HBV. It is important to emphasize that sexual transmission is a major route for HBV infection in our region[23]. In this study, one HTLV1/HIV1 coinfected patient was seropositive to HCV and reported IDU. This behavior has been reported by others authors among HTLV1/HIV1/HCV coinfected patients[20,21,24], reflecting the high transmissibility of these viruses through direct blood contact resulting from the sharing of syringes and needles.

Table 2
Characteristics of HIV1 mono-infected and HIV1/HTLV1 coinfected patients in Midwestern Brazil (n = 505)

Variables	HIV-mono-infected (n = 501)	HIV1/HTLV1 coinfected (n = 4)
Age (years)		
Mean (range)	37.5 (18-74)	44 (36-53)
Gender, n (%)		
Male	303 (60.5)	1 (25)
Female	198 (39.5)	3 (75)
Risk behavior (lifetime), n (%)		
Number of sexual partners (>10)	308 (61.5)	4 (100)
Unprotected sex	450 (89.8)	4 (100)
Previous STI	183 (36.5)	2 (50)
Intravenous drug use	10 (2.0)	1 (25)
Blood transfusion*	29 (5.8)	0
CD4 counts (cells/μL)		
Mean (range)	526.6 (6-1800)	599.7 (264-916)
HIV viral load (log_{10} copies/mL)		
Mean (range)	4.6 (1.3-5.7)	4.9 (2.5-5.5)
HCV seropositivity, n (%)	22 (4.4)	1 (25)
HBV seropositivity, n (%)	122 (24.3)	2 (50)

*Blood transfusion not screened for anti-HTLV (before November 1993), STI: sexually transmitted infections, HBV: hepatitis B virus; HCV: hepatitis C virus.

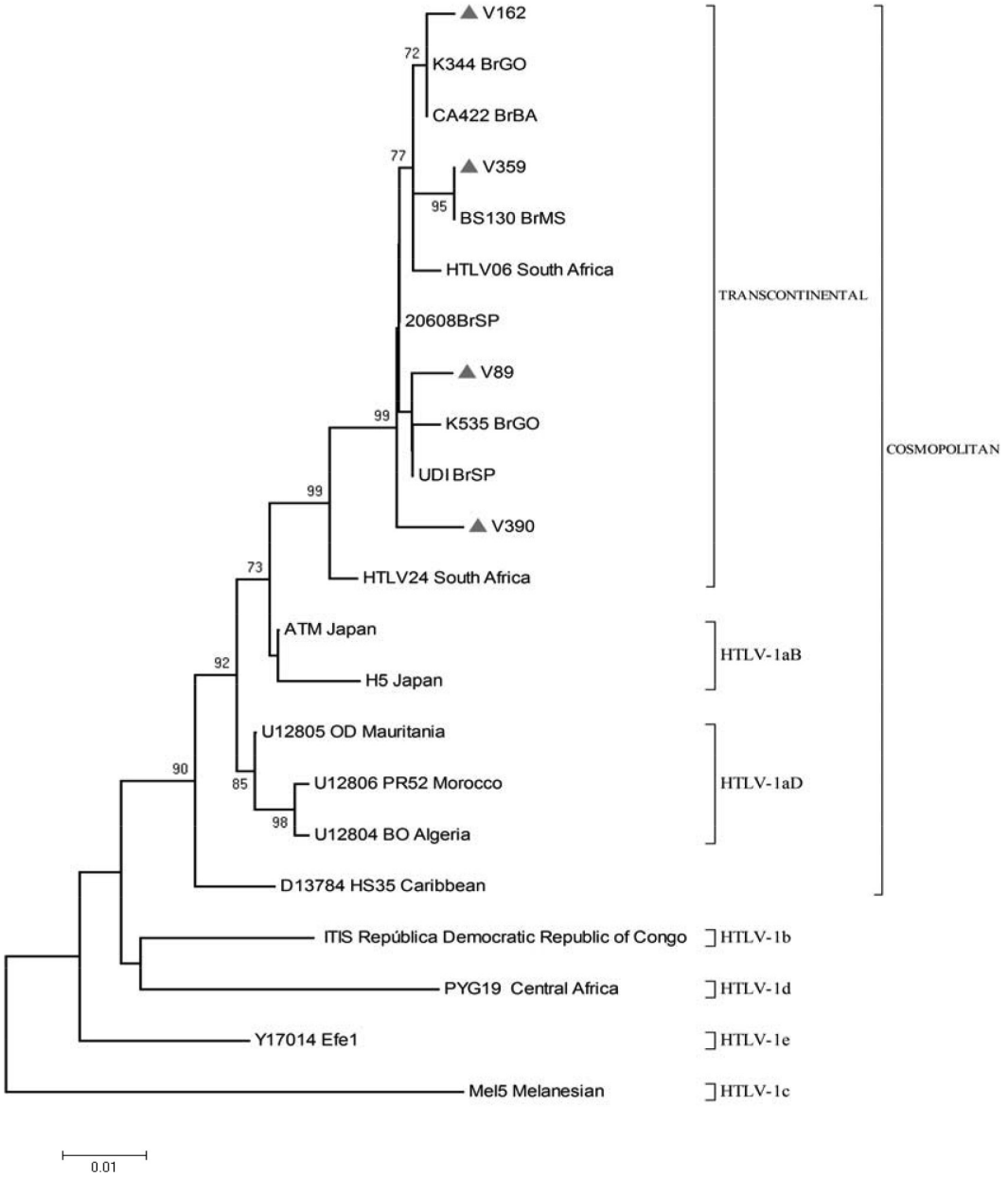

Fig. 1 - Phylogenetic tree of HTLV1 isolates based on the 640 bp fragment of the LTR region, including four sequences from treatment-naïve HIV1-infected patients (V) in Midwestern Brazil and 18 GenBank sequences of subtypes a-d. The phylogenetic tree was constructed using the neighbor-joining method based on the Hasegawa, Kishino & Yano model and γ-distribution. The number on the tree represents bootstrap values.

HTLV1 may impact the clinical course of HIV1 and vice-versa. In spite of evidence of increased morbidity, coinfected patients have normal or elevated CD4+ T cell counts. Even if the CD4 levels are elevated, most of the cells may be functionally impaired[5]. Although the design of this study does not allow us to evaluate the impact of HTLV1 on the clinical course of HIV1, the four coinfected individuals were asymptomatic and three of them had normal CD4+ T cell counts (higher than 500 cells/ mm^3, data not shown). In addition, similar CD4+ T counts were recorded between HTLV1/HIV1 coinfected and HIV1 mono-infected patients (599.7 versus 526.6 cells/μL, respectively; $p > 0.05$). Therefore, further clinical prospective investigations are necessary to elucidate the interaction of HTLV1 and HIV1 in coinfected patients.

The four HTLV1 isolates from this study were classified as Transcontinental (A) subgroup of the Cosmopolitan (1a) subtype. These data was in accordance with those reported in HIV1-infected patients in Brazil in whom this HTLV1 subgroup is predominant[6,17,19,21].

This study has limitations that should be taken into account. This was a hospital-based investigation and, therefore, the study population

does not represent all treatment-naive HIV1 patients in the state of *Goiás*. Another limitation of this study is the small number of patients studied, which may limit the statistical power of the results to detect differences between the groups (mono and coinfected) and the detection of HTLV2. On the other hand, only treatment-naïve HIV1 patients were included in the study because antiretroviral therapy may cause fluctuations in the HTLV proviral load and, thus, this condition may interfere with HTLV proviral DNA detection[25]. In addition, due to the lack of available data on the serological and molecular epidemiology of HTLV/HIV1 coinfection in Midwestern Brazil, this study provides the first data on HTLV1/2 in HIV1-infected patients in this region.

In spite of the importance of this coinfection, this status is underdiagnosed[5]. In fact, no HTLV1/HIV1 coinfected patients knew their HTLV status (data not shown). On the other hand, guidelines for the clinical management of HIV patients recommend the HTLV1/2 test, as well as the serology for viral hepatitis (B and C) before the initiation of the antiretroviral therapy[26]. Therefore, it is important to integrate and provide regularly diagnostic tests for these infectious diseases in the Brazilian public health services.

Although the public health system in Brazil provides prevention programs and free and universal access to antiretroviral treatment for HIV/AIDS, HTLV infection is considered a neglected infectious disease[22,27]. It is important to emphasize that HTLV infection is also lifelong and, although most of the infected patients remain asymptomatic for many years, these carriers are potential disseminators. In addition, there is no effective treatment or immunization for the HTLV infection and its complications. Thus, more research on HTLV infection is imperative for the elaboration of public policies on educational and prophylactic measures to increase the awareness of the infection and reduce the viral transmission and infection-related diseases.

In conclusion, this study shows a low prevalence of HTLV1/2 in HIV1-infected patients in Midwestern Brazil. In addition, the Transcontinental (A) subgroup of the Cosmopolitan (1a) subtype was detected in all the coinfected patients, highlighting the predominance of this subtype in Brazil.

ACKNOWLEDGEMENTS

The authors would like to thank Pollyanne S. Lemes and Nativa H. A. Del-Rios for their work in the sample and data collection; and Koko Otsuki and Ágabo Macedo da Costa e Silva for their technical assistance. They would also like to thank the staff of the *Hospital de Doenças Tropicais (HDT) Dr. Anuar Auad* for the fruitful collaboration. This study was supported by the *Fundação de Amparo à Pesquisa do Estado de Goiás* (FAPEG, process number 201210267001093/2012). Brian Ream edited this manuscript in English.

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Received: 02 November 2015
Accepted: 03 June 2016