

# Epidemiological and Molecular Profile of Blood Donors Infected with HTLV-1/2 in the State of Pará, Northern Brazil

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## Research

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# Abstract

**Background:** The Human T Cell Lymphotropic Virus (HTLV) is a retrovirus of the genus *Deltaretrovirus*, which belongs to the family *Retroviridae*. The most important types are HTLV-1 and HTLV-2. It is estimated that between five and 10 million individuals are infected with HTLV-1, worldwide. Studies in the state of Pará indicate that it has the third highest prevalence of HTLV infections of any Brazilian state. The present study describes the epidemiological, serological, and molecular profile of blood donors from the state of Pará, that were classified as unfit due to infection by HTLV-1 and 2.

**Methods:** The present study is based on a descriptive, retrospective, and cross-sectional review of the epidemiological, serological, and molecular data on blood donations, between January 2015 and December 2019. The data were obtained from the blood bank system and were digitalized to form a database in the Statistical Package for Social Sciences program, version 20. Descriptive statistics were used to determine the absolute and relative frequencies of the qualitative variables. For the quantitative variables, the mean, standard deviation, and minimum and maximum values were calculated. A  $p \leq 0.05$  significance level was adopted for all analyse.

**Results:** A total of 632 samples were analyzed. The HTLV proviral DNA was detected primarily in females (69.1%), with a mean age of 40 years, with the highest frequencies of detection being recorded in single individuals (66.2%), first-time donors (74.3%), and individuals that had graduated high school (44.1%). The molecular confirmation of HTLV showed that three-quarters (78%) of the serologically reactive individuals were negative for either types 1 or 2, so the epidemiological profile of these individuals was significantly different from their detectable profile.

**Conclusions:** The HTLV is neglected in Brazil, there is thus a clear need for further research in the area of regional hemotherapy and hematology services, in order to contribute to the definition of regional infection profiles, that will be fundamental to the development of effective prophylactic practises for the prevention of the infection and the dissemination of knowledge on the dangers of HTLV in the community.

## Background

The Human T cell Lymphotropic Virus (HTLV) is a retrovirus of the genus *Deltaretrovirus*, which belongs to the family *Retroviridae* [1] and has tropism for T lymphocytes, with four types, HTLV-1, HTLV-2, HTLV-3, and HTLV-4. The HTLV-1 is the most relevant pathogen, being associated with severe diseases, such as Tropical Spastic Paraparesis/HTLV-1-Associated Myelopathy (HAM/TSP), while the HTLV-2 type is also epidemiologically important, but is not associated systematically with other pathologies [2, 3, 4].

The estimated number of individuals infected with HTLV-1 worldwide is between five and 10 million [5], with the most prevalent regions being Japan, Africa, the Caribbean islands, and Central and South America. In Brazil, the number of individuals infected with HTLV-1 is estimated to be approximately 2.5 million, with a lower prevalence in the south of the country, increasing toward the northern and

northeastern regions [6]. The northern Brazilian state of Pará is ranked third in the prevalence of HTLV in the country's states [7].

The routes of infection by HTLV-1 and 2 include the sexual route, most commonly from man to woman, vertical transmission, which is the most frequent route, mainly through breastfeeding, and the parenteral route, through the transfusion of contaminated blood elements, the most efficient transmission route [8, 9, 10]. In Brazil, like the rest of the world, hemotherapy has evolved in recent years through the introduction of new technologies that minimize the risks of blood transfusion, in particular through the prevention of the dissemination of infectious agents. Screening for HTLV in blood banks became mandatory in Brazil, in November 1993, through ordinance no. 1376 of the Brazilian Ministry of Health [8].

The present study describes the epidemiological, serological, and molecular profile of blood donors from Pará classified as inapt due to infection by HTLV-1 and 2. The definition of the infection profile of the blood donors from this state represents an importance advance in the understanding of infection patterns in Brazil, especially considering the major regional variation found in this country in socioeconomic, demographic, and cultural conditions, which may all influence the epidemiology of HTLV, which will be fundamental to the development of effective prophylactic practises for the country-wide combat of the infection.

## Methods

The present study was approved by the FIBRA Committee for Ethics in Research through protocol number CAAE 19004819.7.0000.8187 and was conducted at the Pará State Center for Hematology and Hemotherapy (HEMOPA), which has 10 blood donation centers, including its headquarters, in the state capital, Belém. The other centers are located in the towns of Ananindeua and Castanhal, in northern Pará, the city of Santarém, in western Pará, Marabá, Redenção, and Tucuruí, in the southeast of the state, Abatetuba and Capanema in the northeast, and Altamira, in the southwest.

The present study is based on a descriptive, retrospective, and cross-sectional review of the epidemiological, serological, and molecular data on blood donations, between January 2015 and December 2019. As inclusion criteria, the selected data of subjects were those who were over eighteen years and had samples considered as reagent on the serological screening and were sent to the confirmatory detection, by molecular biology. As exclusion criteria, subjects younger than eighteen years and samples that did not presented results for one of the tests have not been used in the research.

In the period of study, the HEMOPA foundation performed the serological screening using chemiluminescent microparticle immunoassay (CMIA), making use of the ARCHITECH rHTLV-I/II platform, with sensibility value of 100% and specificity of 99.95%, according to manufacturer. The confirmatory test that was performed in the study period was the Real-time Polymerase Chain Reaction (qPCR) method, using the TaqMan® (AppliedBiosystems) system, which consists of three targets, the albumin gene and the non-homologous regions of the HTLV-1 and HTLV-2 pol gene, being a highly specific test.

The data were obtained for the present study from the blood bank system (SBS and SBS web) and were digitalized to form a database in the Statistical Package for Social Sciences (SPSS) program, version 20. This database included information on the sex, age, geographical origin, education level, marital status, race (self-defined), the type of donor and donation, the quantity of donations, and the results of the serological testing (chemiluminescence) and qPCR.

Descriptive statistics were used to determine the absolute and relative frequencies of the qualitative variables. For the quantitative variables, the mean, standard deviation, and minimum and maximum values were calculated, according to the characteristics of each study variable. These means were compared between groups using Student's *t*, while the Chi-Square test of independence was applied to the qualitative variables. A  $p < 0.05$  significance level was adopted for all analyses.

## Results

A total of 453,626 blood donations were screened serologically in the state of Pará between January 2015 and December 2019. Overall, 1476 (0.3%) of these donations were found to be inapt due to the serological detection of HTLV, and 747 (51%) of these samples were submitted to a confirmatory test for HTLV-1 and 2 proviral DNA by real-time PCR. A total of 115 samples were omitted from the analyses due to the fact that they did not satisfy the selection criteria for the study population. The data on 632 samples were thus analyzed, of which 496 (78%) had no detectable proviral DNA and 136 (22%) had detectable HTLV. The HTLV-1 was detected in most (78%; 106/136) of these samples, while only 30 (22%) were detected for HTLV-2. The presence or the absence of proviral DNA was the basic criterion for the comparative analyses, that is, between detectable and undetectable groups (Table 1).

Table 1

– Association between the presence and absence of proviral DNA from donors classified as inapt due to HTLV infection in the Brazilian state of Pará.

Variables	Total	Undetectable		Detectable		p*
		n	%	n	%	
Sex						
Female	346	252	50.8	94	69.1	< 0.0001
Male	286	244	49.2	42	30.9	
Marital status						
Married	188	142	28.6	46	33.8	0.240
Single/divorced/widow	444	354	71.4	90	66.2	
Geographical origin						
Metropolitan Region of Belém	425	331	66.7	94	69.1	0.600
Interior of the state	207	165	33.3	42	30.9	
Education level						
Elementary school graduate	57	42	8.5	15	11.0	< 0.0001
Elementary school (unfinished)	44	24	4.8	20	14.7	
High school graduate	306	246	49.6	60	44.2	
High school (unfinished)	60	44	8.9	16	11.8	
College graduate	82	72	14.5	10	7.4	
College student	72	61	12.3	11	8.1	
Postgraduate	11	7	1.4	4	2.9	
Race (self-declared)						
White	105	82	16.6	23	16.9	0.979
Brown	502	394	79.4	108	79.4	
Black	25	20	4.1	5	3.7	
Type of donor						
First time	210	109	22	101	74.3	< 0.0001
Sporadic	256	232	46.8	24	17.6	
* <i>Chi-Square.</i>						

Variables	Total	Undetectable		Detectable		p*
		n	%	n	%	
Repeat	166	155	31.3	11	8.1	
Type of donation						
Spontaneous	415	321	64.7	94	69.1	0.338
Linked to a specific treatment	217	175	35.3	42	30.9	
* <i>Chi-Square.</i>						

The epidemiological profile of the samples confirmed with proviral DNA for HTLV-1 or 2 by qPCR included a predominance of female individuals (69.1%; 94/136) and individuals that were single, divorced or widowed (66.2%; 90/136) in comparison with married individuals. The mean age was 40.08 ± 12.07 years old, with a minimum of 18 years and a maximum of 65 years, and a peak in the 36–46 year age class (Table 2), which contained almost a third (30.9%: 42/136) of the group.

Table 2  
– Relative frequency by age class of blood donors diagnosed with HTLV proviral DNA in the Brazilian state of Pará.

Age class	Number of samples	%
18–24 years	16	11.8
25–35 years	32	23.5
36–46 years	42	30.9
47–57 years	32	23.5
> 57 years	14	10.3
Total	126	100

A majority of the samples (69.1%; 94/136) were provided by donors from the metropolitan region of Belém (Ananindeua, Belém, Benevides, Castanhal, Marituba, Santa Bárbara do Pará, and Santa Izabel do Pará), while only 30.9% (42/136) were collected in other regions (the interior) of the state. High school graduates made up the largest group of detectable donors (44.1%; 60/136), followed by individuals that did not graduate from elementary school (14.7%; 20/136). The vast majority of the detectable donors (79.4%; 108/136) also declared themselves to be of the brown race, followed by the white race, with 16.9% (23/136).

Almost three-quarters (74.3%; 101/136) of the individuals with detectable proviral DNA were first-time donors, while 17.6% (24/136) were sporadic donors, and 8.1% (11/136), repeat donors. The mean number

of donations provided by the sporadic donors was  $6.17 \pm 6.86$ , while it was  $9.45 \pm 5.82$  by the repeat donors. The vast majority of donations (69.1%; 4/136) were spontaneous.

The inapt blood donors with detectable HTLV were significantly older ( $p < 0.0001$ ), on average ( $40.08 \pm 12.07$  years old) than those with undetectable HTLV ( $32.93 \pm 9.96$  years old). The proportion of female donors was also significantly higher ( $p < 0.0001$ ) in the detectable group, in comparison with the undetectable group. The proportion of first-time donors was also significantly higher ( $p < 0.0001$ ) in the detectable group, while the sporadic and repeat donors predominated in the undetectable group.

In both groups, almost half of all donors were high school graduates, but whereas 37.5% of the detectable group had a lower education level, this was true of only 22.2% of the undetectable group. No association was found between the presence or absence of detectable HTLV proviral DNA and marital status, geographic origin, race or the type of donation.

## Discussion

The prevalence of HTLV varies according to sociodemographic factors, geographic region, and individual risk behavior. However, no epidemiological studies have yet demonstrated the real prevalence of HTLV in Brazil as a whole. Previous studies in the state of Pará have focused on specific groups, such as pregnant women [11, 12], riverside communities [13], indigenous populations [14, 15], and blood donors [7].

A study of blood donors from donation centers in the 27 Brazilian state capitals, between 1995 and 2000, demonstrated a heterogeneous distribution of HTLV in Brazil, and estimated a seroprevalence of 0.9% in the state of Pará [7]. The much lower seroprevalence, of 0.3%, recorded in the present study, indicates a reduction in infection rates over the 15 years between the two studies, which may reflect changes in the behavior of the population in recent years, in relation to the prevention of sexually-transmitted infections. However, the difference between the studies may also have been determined, at least in part, by methodological differences.

In the donors in which either HTLV-1 or 2 was detected by molecular testing, HTLV infection was more prevalent in females and in middle-aged (36–46 years old) individuals. A similar pattern has been recorded in many previous studies [16, 5], which indicate a prevalence in females and older individuals, which may be related to the greater efficiency of the sexual transmission from man to woman and the increasing number of sexual encounters accumulated over the lifetime of the individual [6, 17]. The lower educational level, in general, of the individuals in the detectable group may reflect their reduced access to information on basic health, in general, and on the prevention of sexually transmissible infections, in particular [6, 18]. Unmarried individuals (single, divorced, widowed) predominated in both donor groups, which may be related to a greater exposure to the risk of sexual transmission, being associated with unprotected sex and multiple sexual partners [19, 20].

In Brazil, a considerable proportion of the potential blood donor population believes that blood banks are a convenient place for free testing for infections, and may thus not reveal their risky behavior at the clinical screening. This may have contributed to the fact that the number of detections was significantly higher among first-time donors. By contrast, regular donors, who are tested every time they donate blood, are likely to be a low risk group for infection [8, 21, 22].

In the present study, the profile (sex, age, education, and type of donor) of the donors varied considerably between in the groups in which the HTLV-1 or 2 proviral DNA was detected or not (undetectable). This indicates that the candidates for blood donation that were seropositive for HTLV had a distinct profile from those in which HTLV-1 or 2 was confirmed by qPCR. This difference may be related to the differential sensitivity and specificity of the screening and confirmatory tests, resulting in distinct outcomes between the two groups.

## Conclusions

The epidemiological profile recorded here is highly similar to that found in previous studies, with a predominance of infection in woman, a mean age of approximately 40 years, and a higher frequency of HTLV detection in unmarried individuals and first-time donors.

Neither HTLV-1 nor 2 was detected by qPCR in more than half of the serologically reactive individuals and the epidemiological profile (sex, age, education, and type of donor) of these individuals was significantly different from those in which the presence of HTLV proviral DNA was detected.

The Human T Cell Lymphotropic Virus is a neglected etiological agent in Brazil, and despite the many advances since its discovery, infection patterns are still relatively poorly understood by both healthcare professionals and the general population. There is thus a clear need for further research in the area of regional hemotherapy and hematology services, in order to contribute to the definition of regional infection profiles, that will be fundamental to the development of effective prophylactic practises for the prevention of the infection and the dissemination of knowledge on the dangers of HTLV in the community.

## List Of Abbreviations

CMIA - Chemiluminescent Microparticle Immunoassay

HAM/TSP - Tropical Spastic Paraparesis/HTLV-1-Associated Myelopathy

HEMOPA - Pará State Center for Hematology and Hemotherapy

HTLV - Human T Cell Lymphotropic Virus

qPCR - Real-time Polymerase Chain Reaction

## **Declarations**

### **Ethics approval and consent to participate:**

The present study was approved by the Faculdade Integrada Brasil Amazônia (FIBRA) Ethics in Human Research Committee number: 3.559.772 (CAAE: 19004819.7.0000.8187).

### **Consent for publication:**

Not applicable.

### **Availability of data and materials:**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### **Competing interests:**

The authors declare that they have no competing interests.

### **Funding:**

Not applicable.

### **Authors' contributions:**

CAM compiled the database and wrote the manuscript. KASB, JAAC, MKP, RBHC helped design the study and draft the manuscript. CEDMA helped design of the study, ran the statistical analyses, and helped to draft the manuscript. All the authors have read and approved the final manuscript.

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