

REVIEW

ORIGIN AND PREVALENCE OF HUMAN T-LYMPHOTROPIC VIRUS TYPE 1 (HTLV-1) AND TYPE 2 (HTLV-2) AMONG INDIGENOUS POPULATIONS IN THE AMERICAS

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SUMMARY

Human T-lymphotropic virus type 1 (HTLV-1) is found in indigenous peoples of the Pacific Islands and the Americas, whereas type 2 (HTLV-2) is widely distributed among the indigenous peoples of the Americas, where it appears to be more prevalent than HTLV-1, and in some tribes of Central Africa. HTLV-2 is considered ancestral in the Americas and is transmitted to the general population and injection drug users from the indigenous population. In the Americas, HTLV-1 has more than one origin, being brought by immigrants in the Paleolithic period through the Bering Strait, through slave trade during the colonial period, and through Japanese immigration from the early 20th century, whereas HTLV-2 was only brought by immigrants through the Bering Strait. The endemicity of HTLV-2 among the indigenous people of Brazil makes the Brazilian Amazon the largest endemic area in the world for its occurrence. A review of HTLV-1 in all Brazilian tribes supports the African origin of HTLV-1 in Brazil. The risk of hyperendemicity in these epidemiologically closed populations and transmission to other populations reinforces the importance of public health interventions for HTLV control, including the recognition of the infection among reportable diseases and events.

KEYWORDS: HTLV-1; HTLV-2; Indians; Origin; Americas.

INTRODUCTION

The human T-lymphotropic virus type 1 (HTLV-1) and type 2 (HTLV-2), although closely related, have different geographical distributions^{8,21,23,35,59,63,72,93,110,119}, pathogenesis^{10,95,97,98}, and clinical manifestations^{8,10,21,23,35,59,63,97,110}. Although types 3 (HTLV-3) and 4 (HTLV-4) have been found in populations of central Africa, they have not yet been associated with disease in humans^{19,133}.

HTLV-1, the causative agent of HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), uveitis, infective dermatitis, and other inflammatory disorders^{21,35,59,110}, is endemic in many parts of the world, including southwestern Japan, some of the Caribbean islands, South America, and foci in western and central Africa and Australo-Melanesia⁵⁹. In turn, HTLV-2, despite there being no clear indications associating it with well-defined clinical manifestations, has been associated with sporadic cases of neurological disorders similar to HAM/TSP^{8,63}, and has been observed as prevalent in native populations, such as the indigenous peoples of the Americas, certain tribes of pygmies in Africa^{23,63,72,93,119}, and injection drug users (IDUs) in urban areas of the United States, Europe, and Latin America^{27,42,45,82,89,114,124,138}.

In Brazil, approximately 517,000 Indians live in officially recognized indigenous lands, with an estimated additional 380,000 living outside

these areas (78% of whom live in urban areas), for an estimated total population of 896,917 counted as indigenous by the 2010 census²⁹. Both HTLV-1 and HTLV-2 are prevalent among Brazilian indigenous populations, with HTLV-2 being the most predominant among these individuals^{14,51,52,69,72,91,93,100,102,119,126}.

The search strategy adopted in this review was intentionally broad so as to ensure the identification of all relevant studies published between 1980 and 2014 relating to infection by HTLV in indigenous populations in Latin America. Searches were made via the PubMed, Lilacs and Google Scholar electronic databases using the following terms: "HTLV", "Indians", "natives", "Americas". Lastly, multiple relevant articles were used to carry out the 'Snowball' method to supplement the review. However, the results of most of the studies published on this thematic should be taken with caution since the majority of them include rather small populations and not all the studies were carried out using stringent criteria of positivity, Western blot or PCR. In addition, HTLV prevalence tends to increase with age and is higher in women, but frequently information pertaining to age and sex of the studied populations has not been specified.

ORIGIN OF HTLV-1 AND HTLV-2 IN THE AMERICAS

HTLV-1 is endemic in South America, present in all 13 countries

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and prevailing in all ethnic populations^{22,26,59}. In Brazil, for example, HTLV-1 is found in immigrants from other endemic foci, such as Africa and Japan^{53,79}, and in those who are descended from Amerindians who have inhabited South America for thousands of years^{46,9,72,100,119}.

There are two hypotheses about the origin of HTLV-1 in the Americas. The first considers the prehistoric migration of infected populations about 11,000 to 13,000 years ago across the Bering Strait into North America. These people migrated through Central America and spread into South America, where they settled mainly in the Andes and along the Amazon. The other hypothesis suggests that HTLV-1 originated in Africa and was brought to the Americas (including the Caribbean islands, United States, and South America) through the slave trade between the 16th and 19th centuries.

It is estimated that the separation of African and non-African human populations occurred around 75,000 to 287,000 years ago^{28,112}, with gene flow occurring from pygmies to neighboring populations²⁸. HTLV-1 and HTLV-2 infections among pygmies are the oldest, and although frequent transmission of simian T-lymphotropic virus type 1 (STLV-1) from apes to humans in Africa could suggest that these infections were the result of interspecies transmissions over the years^{87,90,115,130}, the absence of non-human primates in Melanesia and Australia suggests that HTLV-1 existed among the Australoid people who first populated Australo-Melanesia around 60,000 years ago^{56,135}.

The transcontinental migration of HTLV-1 is supported by studies showing that two strains of human leukocyte antigen (HLA)-A alleles are associated with HTLV-1 in endemic regions around the world. Both strains (HLA-A*26 and HLA-A*36) originally evolved in Africa and dispersed through Asian populations and indigenous North and South Americans¹²⁰. This transcontinental dispersal of HTLV-1 partially overlapped the migration pattern of southeastern Asian mongoloids^{120,123}. Interestingly, these alleles are associated with adult T-cell lymphoma (ATL), and phylogenetic analysis revealed that the ancestral genes of these alleles came from primate major histocompatibility complex genes, including those of gorillas, chimpanzees, and monkeys¹¹³. Taking this into consideration, it is possible that the HLA-A*26 and HLA-A*36 evolved > 50 million years ago and that carriers have become natural hosts of HTLV-1 due to a low immune responsiveness to the virus¹²⁰.

Phylogenetic analysis of bone marrow samples from the femur of a mummified specimen revealed that the isolated clones were similar to those of the Indians of South America and belonged to a transcontinental subgroup closely related to HTLV-1 carriers, the Ainu of northern Japan, and some mongoloid Asian subgroups. These observations suggest that the Andean mummy's HTLV-1 could have originated from Asian paleo-mongoloids⁸⁶.

The debate over the origin of HTLV-1 has primarily focused on empirical-level molecular phylogenetic analysis, particularly on how to better explain the phylogenetic origin of the cosmopolitan subtype of HTLV-1, to which the indigenous strains found in South America belong and which is the predominant subtype among the other isolates from various endemic and non-endemic areas of the Americas²². The subtypes, which do not appear to differ in pathogenicity, likely reflect the geographical origins and migrations of ancient populations^{77,80,118}. Analysis of genetic sequencing has divided HTLV-1 into subtypes Ia

(cosmopolitan), 1b (Central African), 1c (Melanesian), and 1d, 1e, 1f, and 1g (found in Central Africa). The cosmopolitan subtype is divided into five subgroups, depending on geographical location: transcontinental (A), to which most strains of HTLV-1 isolated from South America belong; Japanese (B); West African (C); North African (D)^{55,94}; and Afro-Peruvian (E)¹²⁸.

The transcontinental subgroup (A) has been characterized both in North America (United States and Canada) and South America (Argentina, Brazil, Chile, Colombia, French Guiana and Peru)^{23,53,59,77,118,122,127}. The Japanese subgroup (B) has been found in the north, northeast, and southeast regions of Brazil; Canada; Colombia; and Peru and can be explained by the thousands of years of migration from Asia to the Americas and by recent Japanese immigration^{53,59,118,127,129}. The West African subgroup (C) was identified in the Caribbean and French Guiana but not in Brazil, despite its introduction being associated with slave trafficking from West Africa and the high rate of infection among black South Americans^{23,53,59,122}. The Afro-Peruvian subgroup (E) was characterized in two black individuals presenting a type of mitochondrial DNA identical to that found in some populations of West Africa^{55,128}.

The migration of African people to the Americas through slave trade took place from mainly western and central Africa, and 40% of the approximately 10 million Africans arrived at Brazilian ports, making it intriguing that subgroup C is not found in Brazil⁵³. Aiming to clarify the origin of HTLV-1 in Brazil, GALVÃO-CASTRO *et al.*⁵³ analyzed 243 sequences of the long terminal repeat region of isolates from descendants of various ethnic groups and geographical regions of the country, all of which were classified as the cosmopolitan subtype. Of these, 98% were in the transcontinental subgroup (A) and 3.3% in the Japanese subgroup (B), which is discordant with historical data indicating that the majority of Africans who came through Salvador were the original carriers of the West African subgroup (C).

The migration of African populations comprised several cycles: Guinea Cycle during the second half of the 16th century; Angola and Congo Cycle in the 17th century; Mina Coast Cycle during the first three-quarters of the 17th century; and Bay of Benin Cycle in the 18th and 19th centuries. It is possible that the occurrence of multiple introductions of some sequences of HTLV-1 in the post-Columbian era are clustered in Latin American groups with sequences of southern African ancestry that were segregated from the same ancestor of another group with a central African string. Thus, this relationship of ancestry suggests that this group was first introduced in South Africa due to the migration of the Bantu people of Central Africa to South Africa about 3,000 years ago and then to Brazil during the slave trade period between the 16th and 17th centuries⁵³. Analysis of the distribution of haplotypes linked to the group of γ -globin genes demonstrated that 29.4% of the Bantu haplotype could explain why the majority of HTLV-1 isolates are grouped with those from southern Africa². It is known that Africans of Bantu ethnicity were brought to Bahia between 1678 and 1810 and that approximately 2,400 African Bantu (with 100 coming from Angola and 2,300 from Madagascar) were brought between 1817 and 1843³⁷. During the colonization of South Africa by the British in the 17th and 18th centuries, many Africans migrated to neighboring regions currently known as Angola, Madagascar, and Mozambique, where they were captured and transported to Salvador³⁷. In addition, there is evidence that the ports of departure of African slave ships often were not related to the ethnic

and geographic origins of African transportees³⁷. Thus, taken together, these results corroborate the hypothesis of multiple introductions of post-Columbian subgroup A in Brazil.

Most of non-indigenous persons infected by HTLV-1 in the Americas have probably been infected by virus strains originating from the African slave trade during the post-Columbian period^{2,37,44,53,57,59,75,122,128,130} and, it is today accepted that HTLV-1 in the Americas has more than one source: through migration from Asia through the Bering Strait^{86,94,104,134} during the Paleolithic era; the trafficking of slaves during the colonial period^{2,53,122,128,130}; and more recently, the Japanese immigration in the early 20th century (Fig. 1)^{79,127,128}.

HTLV-1 and HTLV-2 are similar, with approximately 60% of their structures based on the same sequence of nucleic acids and 70% on the same sequence of amino acids²⁰. Both viruses are very old and have evolved independently through transmission of STLV from nonhuman primates to the first humans⁶². HTLV-2 is divided into four subtypes: 2a, 2b, 2c, and 2d. Molecular studies confirm the presence of HTLV-2c in Brazil, the only country to identify this subtype⁴³. The Brazilian variant of HTLV-2 has a tax region similar to that of subtype 2b and the env-like subtype 2a genomic long terminal repeat region^{33,43,72}. Only the 2c variant was identified in Brazilian tribes, and this subtype of HTLV-2 is prevalent in IDU and non-IDU populations in Brazil^{3,43,69,70,72,119,125,126}. HTLV-2 is considered an ancestral virus in the Americas because it is endemic among isolated indigenous groups, having been inherited by the general population and transmitted to IDUs from indigenous populations (Fig. 1)^{3,43,70,72,125,126}.

The endemicity of HTLV-2 among various indigenous peoples of the Americas and the lack of evidence of infection with STLV-2 in New World monkeys have led to the conclusion that HTLV-2 has been present on the American continents since ancient times^{11,66,81,101,105}. The hypothesis of independent development of HTLV-1 and HTLV-2 from a common ancestor after human migration to the Americas has a very low possibility of support due to the fact that HTLV-2 has been identified in

isolates from pygmies in northwestern Zaire and Cameroon^{58,61}, where HTLV-1 has not been identified, as well as the above mentioned absence of STLV-2 in New World monkeys⁷⁵ and the slow evolutionary potential of HTLV-2¹¹⁶.

HTLV IN INDIGENOUS GROUPS OF OTHER COUNTRIES OF THE AMERICAS

Among native populations, HTLV-1 is found in the Pacific countries, including Australia and Melanesia, as well as in North, Central, and South America¹⁰, whereas HTLV-2 is endemic and widely distributed among the indigenous peoples of North, Central, and South America, where it appears to be more prevalent than HTLV-1, and in some tribes of Central Africa.

The population of American Indians and Alaska Natives is estimated at 5.2 million or 2% of the general US population, of which approximately 49% are not mixed with other races⁵. There are 566 tribes and 325 Indian reservations recognized by the US federal government⁵. In Canada, about 1.4 million Indians make up 4.3% of the total population, with the most populous group being the First Nations (61%) followed by Métis (32.3%) and Inuit (4.2%)¹. In North America, there are few large, well-sampled studies of HTLV infection among Native Americans, and some have additional feature limitations, as shown by earlier serologic screening and confirmatory assays, or lack precise HTLV typing and molecular characterization of the virus²³. A database of 2,047,740 blood donors was examined in North America for the period of 2000 to 2009 for both viruses, suggesting a prevalence of HTLV in the general population of 0.1% to 0.2% and showed a higher prevalence of HTLV-2 (14.7/100,000) than HTLV-1 (5.1/100,000) in the western and southwestern United States³¹, which could be attributed to endemic foci among American Indians³⁰.

A previous study in blood donors had already demonstrated a rate of HTLV infection of 0.72/1,000 in New Mexico (most cases of which were attributed to HTLV-2) and, in turn, a higher prevalence among American

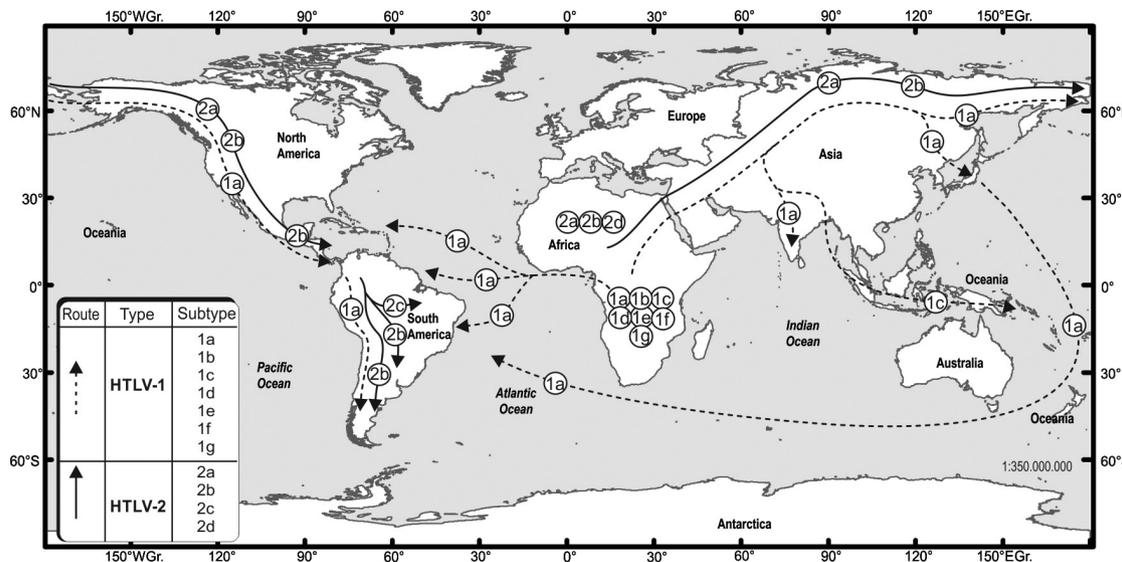


Fig. 1 - Origin of HTLV-1 and HTLV-2 in the Americas. Based on the references 53, 116, 120 and 128.

Indian blood donors (1.0%-1.6%) than among non-Hispanic white donors (0.009%-0.06%)⁶⁵. In the United States, HTLV is endemic among the Navajo and Pueblo people of New Mexico and Seminole people of Florida, with HTLV-2 presenting a higher prevalence^{85,88} (Table 1 and Fig. 2). In Alaska, the prevalence of HTLV among native peoples is 0.5% (two out of 380)³⁴. This was confirmed as HTLV-1 in a subsequent study involving five other native individuals seropositive for HTLV from various geographical areas of Alaska, one being a blood donor with ATL, one with HAM/TSP, one with a neurological disease characterized by gait disturbance and urinary incontinence, and one with Hodgkin disease; all subjects with HTLV-1 had no risk factors for infection⁷⁸.

In Canada, studies in indigenous populations also have been limited. PICARD *et al.* (1995)¹⁰⁸ observed that phylogenetic analysis of HTLV-1 strains recovered from indigenous people living on the coast of British Columbia in western Canada suggested multiple origins for the virus. Subsequently, ANDONOV *et al.* (2012)⁶ performed a phylogenetic analysis on various strains of HTLV-1 from the Nunavut population of Canada, of which 85% are Native Americans of British Columbia's Pacific coast, and Canadian non-indigenous people. The study demonstrated that strains in Nunavut (the cosmopolitan subtype) are related to those from East Asia and consistent with the presence of HTLV-1 in ancient indigenous peoples of the Canadian Arctic, noting the diversity of other strains of HTLV-1 analyzed from other Indians and reinforcing previous evidence of multiple incursions of this virus in indigenous populations of coastal British Columbia.

PETERS *et al.* (2000)¹⁰⁷ found a prevalence of 2.8% for HTLV-1 and 1.6% for HTLV-2 among 494 serum samples from the Nuu-Chah-Nulth tribe of Vancouver Island in British Columbia, which is known for a high incidence of rheumatic disease. Although they found no association between arthropathy and HTLV-1, diseases such as ATL and HAM/TSP have been reported in this region^{36,54,103,107,109}.

In Latin America, there are more than 400 indigenous groups, ranging from 45 million to 48 million individuals⁹⁷. Most live in Bolivia, Guatemala, Peru, Ecuador, and Mexico⁹, comprising the majority of the population in Bolivia (62%) and Guatemala (60%)⁶⁸, and less than 3% live in Paraguay, Venezuela, and Brazil^{29,68,96} (0.4% of the population)²⁹. In South America, only Uruguay has no remaining indigenous population. In Mexico, the only Latin American country in North America, a 0.23% prevalence rate of HTLV-2 was found among 440 native Maya Indians and Mayans living in six communities on the Yucatan Peninsula⁶⁰.

In the seven countries of Central America (Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama), some of which with strong commercial and cultural ties to the Caribbean islands, GESSAIN & CASSAR⁵⁹ reviewed the high endemicity for HTLV-1 infection and associated diseases and demonstrated a very low HTLV-1 seroprevalence, with significant differences observed among the populations tested. In indigenous populations, HTLV-2 was endemic only among Guaymi people, with prevalence rates of 7.9%-8.5% in Panama^{46,81,105,111,132} and 8.0% in Costa Rica¹³¹ (Table 1 and Fig. 2).

In South America, HTLV-2 predominates among indigenous groups (Table 1), with subtype 2b clearly prevailing in Amerindian populations¹²¹, except in Brazil, where it is characterized by subtype 2c^{23,43,69,72,119,126} (Fig. 1). HTLV-1 and HTLV-2 also differ in their

geographical distribution among the various indigenous groups (Fig. 3). FUJIYOSHI *et al.* (1999)⁵¹ conducted a seroepidemiological study on indigenous peoples of the Andes of Colombia, Peru, Bolivia, Argentina, and Chile; Chiloé Island (Chilean coast); Easter Island (Chilean province of Polynesia); and the plains along the Atlantic coast from Colombia to the Orinoco, Amazon, and Patagonia, demonstrating an ethnic and geographically independent distribution between HTLV-1 and HTLV-2, with foci of HTLV-1 prevalent mainly in the Andean highlands and that of HTLV-2 in the coastal plains. FUJIYOSHI *et al.* (1995)⁵⁰ also observed that HLA haplotypes in indigenous Andean groups with HTLV-1 and indigenous groups with HTLV-2 of the lower Orinoco (Venezuelan Amazon) were mutually exclusive. HLA haplotypes associated with HTLV-1 are commonly found in the known HTLV-1 endemic Indian and Japanese populations, whereas the haplotypes associated with HTLV-2 are specifically found among indigenous Orinoco and North American groups, suggesting that ethnic HLA haplotypes are separate from those native to South America and may be involved in the susceptibility to infection by HTLV-1 or HTLV-2. In southern Colombia, for example, HTLV-1 was first detected among natives belonging to the Paez people of the Andes¹³⁶. Subsequently, HTLV-2 has been identified among the Wayuu, Guahibo, and Tunebo groups in the Guajira Peninsula in extreme northeastern Colombia (Caribbean Sea), with prevalence rates between 4.1% and 31.5%^{39,50,121,136}. Other foci of HTLV-1 are found in various isolated indigenous populations (Wayuu, Waunana/Noanama, Inga, Kamsa, Embera), with prevalence rates from 1.0% to 8.5%^{7,39,40,137}. Both viruses have been detected within some of these groups^{7,39}, although in most, HTLV-1 and HTLV-2 appear to be mutually exclusive^{40,41,49,136,137}, including a 31.5% HTLV-2 rate among Guahibo natives⁴⁹ (Table 1). These observations suggest that the natives of South America could be divided into two major ethnic groups by an HTLV-1 and HTLV-2 carrier state that evolved among mongoloid populations and transmitted independently as two different strains among the indigenous peoples of the Andes highlands and coastal Atlantic plains^{41,50,51,137}.

In Venezuela, a high prevalence was found for HTLV-2, reaching 61% among Guahibo and Yaruro^{83,84,106}, whereas in central and southern Bolivia, only HTLV-1 was detected among the Quechua and Aymara indigenous peoples, with a prevalence of 6.8% and 5.3%, respectively⁵¹. In the Peruvian Andes, Quechua and Aymara, the most populous indigenous groups in the region, also present solely HTLV-1, with prevalence rates from 1.6% to 2.82%^{51,73,92,117}, whereas in the Amazon, the Peruvian Shipibo-Konibo notably carry both viruses, with high prevalence rates ranging from 1.43% to 5.9%^{4,15,92} and 2.1% to 3.8%^{4,15} for HTLV-1 and HTLV-2, respectively. A few cases of only HTLV-2 have also been reported in two other indigenous groups of the Peruvian Amazon⁹² (Table 1).

In Chile, where HTLV-1 seems to be endemic among groups of isolated indigenous peoples living in the Andes or in the southernmost region of the country⁵⁹, prevalence ranges from 0.5% to 0.8% among the Mapuche and Rapa Nui^{24,51,67} and up to 4.1% among the Atacama were found⁵¹. Foci of HTLV-2 were reported among the Alacalf (34.8%)⁵¹, Yaghan (9.1%)⁵¹, and Huilliches/Mapuche (1.0%) peoples²⁴.

In Argentina, ethnic and geographic restriction are also seen for both viruses¹³, with HTLV-1 prevalent among the Qulla and Puná of northwestern Argentina^{38,44,51} and HTLV-2 variably, but generally more prevalent among the Chorote, Wichí, Chulupí, and Toba peoples of

Table 1
Prevalence of positivity for HTLV in indigenous groups of other countries of the Americas

Country	Author *	Population	N	HTLV-1 (%)		HTLV-2 (%)	
United States	Levine <i>et al.</i> 1993 ⁸⁵	Seminole	106			14	13.2
	Lowis <i>et al.</i> 1999 ⁸⁸	Seminole	46	1	2.17	11	23.9
	Davidson <i>et al.</i> 1990 ³⁴	Alaska Natives	380	2	0.5		
Canada	Peters <i>et al.</i> 2000 ¹⁰⁷	Nuu-Chah-Nulth	494	14	2.8	8	1.6
Mexico	Gongora-Bianchi <i>et al.</i> 1997 ⁶⁰	Maya	440			1	0.23
	Lairmore <i>et al.</i> 1990 ⁸¹	Guaymi	8			1	12.5
Panama	Reeves <i>et al.</i> 1988 ¹¹¹	Guaymi	317			25	7.9
	Pardi <i>et al.</i> 1993 ¹⁰⁵	Guaymi	317			25	7.9
	Feigenbaum <i>et al.</i> 1994 ⁴⁶	Guaymi	109			9	8.3
	Vitek <i>et al.</i> 1995 ¹³²	Guaymi	3686			352	9.5
Costa Rica	Visoná <i>et al.</i> 1997 ¹³¹	Guaymi					8.0
	Inostroza <i>et al.</i> 1991 ⁶⁷	Mapuche	405	3	0.7		
	Cartier <i>et al.</i> 1993 ²⁴	Huilliches/Mapuche	199	1	0.5	2	1.0
Chile		Atacama	217	9	4.1		
	Fujiyoshi <i>et al.</i> 1999 ⁵¹	Alacalf	23			8	34.8
		Yahgan	22			2	9.1
		Rapa Nui	132	1	0.8		
Bolivia	Fujiyoshi <i>et al.</i> 1999 ⁵¹	Aymara	151	8	5.3		
		Quechua	96	6	6.2		
	Zamora <i>et al.</i> 1990 ¹³⁶	Paez	32	2	6.3		
	Dueñas-Barajas <i>et al.</i> 1992 ³⁹	Wayuu	523	1	1.6	3	4.8
	Fujiyama <i>et al.</i> 1993 ⁴⁹	Guahibo	92			29	31.5
Colombia	Duenas-Barajas <i>et al.</i> 1993 ⁴⁰	Waunana/Noanama	143	3	2.1		
		Tunebo	40			2	5.0
	Zaninovic <i>et al.</i> 1994 ¹³⁷	Inga	62	1	1.6		
		Kamsa	59	5	8.5		
		Wayuu	123			5	4.1
	Arango <i>et al.</i> 1999 ⁷	Embera	1014	10	1.0	7	0.7
		Inga	155	2	1.2	1	0.7
	Egea ⁴¹	Wayuu	157			11	7.0
	Ferrer <i>et al.</i> 1994 ⁴⁷	Toba and Wichi	175			24	13.7
	Bouzas <i>et al.</i> 1994 ¹⁶	Toba	222	1	0.45	22	9.91
Biglione <i>et al.</i> 1999 ¹²	Wichi	205	1		62	3.0	
	Toba	105			23	21.9	
Medeot <i>et al.</i> 1999 ⁹²	Toba	72	2	2.78	2	2.78	
Dipierre <i>et al.</i> ³⁸	Indians in Puna Jujeña	86	2	2.32			
Argentina		Mapuche	94			2	2.1
		Chorote	171			61	35.6
	Ferrer <i>et al.</i> 1996 ⁴⁸	Toba	21			5	23.8
		Wichi	204			26	12.7
		Chorote/Wichi	14			4	28.5
		Chorote/Chulupi	10			8	80
	Eirin <i>et al.</i> 2010 ⁴⁴	Kolla	112	11	9.8		
	Fujiyoshi <i>et al.</i> 1999 ⁵¹	Puna	88	2	2.3		

Table 1
Prevalence of positivity for HTLV in indigenous groups of other countries of the Americas (cont.)

Country	Author *	Population	N	HTLV-1 (%)		HTLV-2 (%)	
Paraguay	Ferrer <i>et al.</i> 1996 ⁴⁸	Chulupi	94			32	34
		Ayoreo	51			2	3.9
		Lengua	49			5	10.2
	Cabral <i>et al.</i> 1998 ¹⁸	Sanapaná	30	2	6.7		
		Angaité	21			1	4.8
	Fujiyoshi <i>et al.</i> 1999 ⁵¹	Chaco	146			24	16.4
Peru	Medeot <i>et al.</i> 1999 ⁹²	Quechua	40	1	2.5		
		Shipibo-Konibo	70	1	1.43		
		Harakmbet	22			1	4.54
		Huambisa	42			1	2.38
	Fujiyoshi <i>et al.</i> 1999 ⁵¹	Aymara	62	1	1.6		
	Sanchez-Palacios <i>et al.</i> 2003 ¹¹⁷	Quechua women	198	5	2.5		
Venezuela	Alva <i>et al.</i> 2010 ⁴	Shipibo-Konibo	290	12	4.1	6	2.1
	Ita <i>et al.</i> 2013 ⁷³	Quechua	389	11	2.82		
	Blas <i>et al.</i> 2013 ¹⁵	Shipibo-Konibo women	1253	74	5.9	47	3.8
	Perez <i>et al.</i> 1993 ¹⁰⁶	Pume (Yaruro)	210			12	5.7
	Leon-Ponte <i>et al.</i> 1996 ⁸³	Guahibo	166			41	24.7
	Leon-Ponte <i>et al.</i> 1998 ⁸⁴	Yaruro/Guahibo	41			25	61
French Guiana	Talarmin <i>et al.</i> 1999 ¹²²	Arawack	54	1	1.8		
		Palikur	78	2	2.6		
		Wayampi	138	2	1.4		

* Numbering as given in the references.

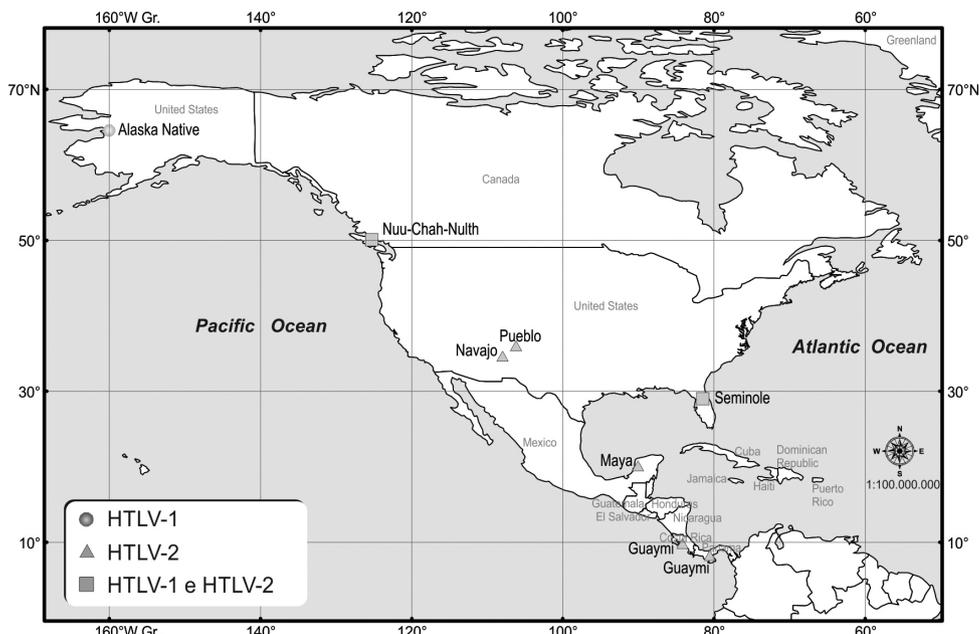


Fig. 2 - HTLV-1 and HTLV-2 among indigenous populations of North America and Central America. Based on the references from Table 1.

the Chaco region, covering parts of Bolivia, Argentina, Brazil, and Paraguay^{12,13,16,47,48,51,92} (Table 1).

HTLV-2 is found almost exclusively among the indigenous population of Paraguay, who mostly live in the Gran Chaco region in the northwest, with a prevalence ranging from 3.9% to 34%^{18,48,51} (Table 1). In French Guiana (not included in Latin America), TALARMIN *et al.* (1993)¹²² did not detect HTLV-2 among the 847 indigenous peoples of the Arawak, Palikur, Wayampi, Galibi, Emerillon, and Wayana, but HTLV-1 was detected in 1.81% (5 out of 270) of the Arawak, Palikur, and Wayampi, with prevalence ranging from 1.4% to 2.6% (Table 1), with the virus probably acquired through contact with people of African descent during slave trade, according to phylogenetic analyses¹²⁸.

HTLV IN INDIGENOUS POPULATIONS OF BRAZIL

The first description of HTLV infection among indigenous people in Brazil dates back to 1990 when, while assessing the prevalence of the virus in some human populations at risk, NAKAUCHI *et al.*⁹⁹ reported a 39% positivity for HTLV-1 in the serum of 82 Mekranoit subjects and 20% in 55 Tiriyo subjects from Pará. Confirmatory tests of the final results of this study were positive in 3.63% (two out of 55), 12.19% (10 out of 82), and 13.88% (10 out of 72) for HTLV-1 among Tiriyo, Mekranoit, and Xicrin subjects, respectively^{99,100}.

Subsequent studies showed that HTLV-2 is predominant among Brazilian indigenous groups^{14,51,52,69,91,93,102,119,126}, with an area of high endemicity in the Amazon region. HTLV-1, on the other hand, is present in isolated clusters^{69,119} (Table 2 and Fig. 3).

ISHAK *et al.* (1995)⁶⁹ investigated sera collected from 1,382 individuals belonging to 26 indigenous communities within endemic



Fig. 3 - HTLV-1 and HTLV-2 among indigenous populations of South America. Based on the references from Table 2.

regions of HTLV-2. These communities are distributed through the states of Maranhão (Urubu-Kaapor), Amapá (Galibi, Palikur, Wayampi), Amazonas (Yamamadi), Roraima (Yanomami), Rondônia (Cinta Larga, Surui, Karitiana), and Pará (Wayana-Apalai, Tiriyo, Assurini Kuañinemo, Assurini Trocará, Zoé, Arara Laranjal, Arara Kurambê, Arara, Iriri, Araweté, Parakanã, Munduruku, and six different Kayapo tribes). The authors found HTLV-2 to be present in 17 of the 26 communities, providing evidence that the Amazon region of Brazil is the most endemic area in the world for HTLV-2^{69,72}. This study also found the presence of antibodies to HTLV-1 limited to five individuals: one Galibi (Amapá), three Yanomami (Roraima), and one Kayapo from the village of Aukre (Pará) (Table 2). The highest prevalence for HTLV-2 was observed among the Kayapo (32.2%), followed by Tiriyo (15.4%), Munduruku (8.1%), and Arara Laranjal (11.4%) peoples⁶⁹. Several other studies have also shown a very high prevalence of HTLV-2 among the Kayapo, at rates ranging from 28% to 57.9%^{14,51,91,102,126}. Moreover, MALONEY *et al.* (1992)⁹¹ reported the presence of HTLV-2 in 12.2% (21 out of 172) of Krahos people in Tocantins.

Tiriyo and Wayampi indigenous peoples live at the border between Brazil, Suriname and French Guiana, respectively (approximately 1,700 Tiriyo, 750 of whom live in Brazil and are spread over 15 villages, and 1,200 Wayampis, 450 of whom live in Brazil in the state of Amapá)¹¹⁹. The presence of both HTLV-1^{100,119} and HTLV-2^{69,119,126} was confirmed among Wayampi and Tiriyo from Brazil in whom HTLV-2 was predominant^{69,119,126}, in contrast to what is observed among the indigenous population of the Amazon region of French Guiana, where only HTLV-1 is present and probably brought from Africa during the post-Columbian slave trading period^{74,122}.

The south of Brazil, on the other hand, is directly related both geographically and ethnically to northern Argentina and southern Paraguay, areas known to be endemic for HTLV-2^{12,16,18,47,48,51,92}. A study of the Guaraní Indians in southern Brazil reported a prevalence of 5.76% for HTLV-2 among 52 individuals examined, suggesting that the Guaraní is another endemic indigenous group for this retrovirus and the need for molecular and phylogenetic studies with larger numbers of samples⁹³.

The prevalence of infection reported in Brazil for the various ethnic groups ranges from 0.48% to 13.9% for HTLV-1 (Xicrin, Mekranoit, Tiriyo, Yanomami, Galibi, Wayampi, and Kayapo)^{69,100,119} and 0.44% to 57.9% for HTLV-2 (Kayapo, Tiriyo, Xicrin, Kraho, Arara Laranjal, Munduruku, Guaraní, Yamamadi, Karitiana, Yanomami, Parakanã, Galibi, Wayana-Apalai, Cinta Larga, and Wayampi)^{14,51,52,69,91,93,102,119,126} (Table 2).

In addition to approximately two dozen cases initially reported in 1992 by NAKAUCHI *et al.*¹⁰⁰ among the Xicrin, Mekranoit, and Tiriyo peoples of Brazil, only seven cases were confirmed as HTLV-1 infection among Brazilian indigenous^{69,119} (Table 2). The possibility of post-transfusion infection cannot be ruled out as a means of introduction of the virus to these ethnic groups with a low prevalence for retrovirus and in whom malaria is frequent⁷⁶. These data support the African origin of HTLV-1 in Brazil introduced in the post-Columbian period through slave trade, similar to what would have occurred in French Guiana and the Caribbean basin^{2,37,53,57,74,122}.

The importance of maintaining the endemicity of HTLV in these epidemiologically closed populations by transmission through sexual

Table 2
Prevalence of positivity for HTLV in indigenous populations of Brazil

State	Tribe/Nation	Author *	N	HTLV-1 (%)		HTLV-2 (%)	
Amazonas	Yamamadi	Ishak <i>et al.</i> 1995 ⁶⁹	36			2	5.6
	Galibi	Ishak <i>et al.</i> 1995 ⁶⁹	148	1	0.67	3	2.0
Amapá	Wayampi	Ishak <i>et al.</i> 1995 ⁶⁹	71			1	1.4
		Shindo <i>et al.</i> 2002 ¹¹⁹	321	2	0.62		
Pará	Kayapo	Maloney <i>et al.</i> 1992 ⁹¹	264			88	33.3
		Black <i>et al.</i> 1994 ¹⁴	703				28.0
		Ishak <i>et al.</i> 1995 ⁶⁹	207	1	0.48	67	32.2
		Fujiyoshi <i>et al.</i> 1999 ⁵¹	19			11	57.9
		Vallinoto <i>et al.</i> 2002 ¹²⁶	27			6	22.2
	Kayapo **	Novoa <i>et al.</i> 1997 ¹⁰²	141			59	41.8
	Tiriyo	Nakauchi <i>et al.</i> 1992 ¹⁰⁰	55	2	3.6		
		Ishak <i>et al.</i> 1995 ⁶⁹	26			4	15.4
		Vallinoto <i>et al.</i> 2002 ¹²⁶	150			3	2.0
	Xicrin	Shindo <i>et al.</i> 2002 ¹¹⁹	683			3	0.44
Nakauchi <i>et al.</i> 1992 ¹⁰⁰		72	10	13.9			
Mekranóiti	Gabbai <i>et al.</i> 1993 ⁵²	206			31	15.0	
	Nakauchi <i>et al.</i> 1992 ¹⁰⁰	82	10	12.2			
Parakanã	Gabbai <i>et al.</i> 1993 ⁵²	89			2	2.25	
	Ishak <i>et al.</i> 1995 ⁶⁹	52			1	1.92	
Arara Laranjal	Ishak <i>et al.</i> 1995 ⁶⁹	44			5	11.4	
Munduruku	Ishak <i>et al.</i> 1995 ⁶⁹	161			13	8.1	
Wayana-Apalaf	Ishak <i>et al.</i> 1995 ⁶⁹	50			1	2.0	
Roraima	Yanomami	Ishak <i>et al.</i> 1995 ⁶⁹	102	3	2.94	4	3.9
Rondônia	Karitiana	Ishak <i>et al.</i> 1995 ⁶⁹	50			2	4.0
	Cinta-Larga	Ishak <i>et al.</i> 1995 ⁶⁹	50			1	2.0
Tocantins	Kraho	Maloney <i>et al.</i> 1992 ⁹¹	172			21	12.2
Paraná	Guarani	Menna-Barreto <i>et al.</i> 2005 ⁹³	52			3	5.8

* Numbering as given in the references. ** Children born to HTLV-2-positive mothers.

relations and vertical pathways is supported by evidence from the Kayapo Indians, who are experiencing a gradual increase in antibody prevalence with age and constant and continuous transmission between couples^{14,72}. Molecular biology has confirmed a high prevalence (42%) of HTLV-2 among children born to HTLV-2-positive mothers^{71,102}. Breastfeeding (and cross-feeding) is a primary source of nutrition for indigenous children, which increases the spread of the virus⁷². If transmission is not stopped, HTLV-2 will become hyperendemic^{14,69}, and transmission to non-indigenous populations is increasingly possible despite the relative geographical isolation of the Kayapo. For example, some villages of Kayapo (Kubenkore, Kokraimoro, Aukre, Kararaô, Gorotire, and Kikretum) are located near small towns maintained by commercial industries, agriculture, and mining, and it is common practice of indigenous Brazilian men to visit these towns to have sexual relations with non-indigenous women⁷².

Ignorance about the virus greatly increases the risk of transmission; thus, preventive measures to reduce the spread and transmission of retroviruses in indigenous populations initially depend on the identification of cases and educational programs^{17,23,32,139,140}. The

indigenous community should be adequately informed about the modes of HTLV transmission and the risks associated with prolonged breastfeeding and cross-feeding. Pregnant women should be routinely screened for HTLV infection and, if positive, should be given access to other alternatives to breast milk, such as formulas^{17,23,32,64}. Women who are likely to breast feed other children should be also screened for HTLV.

Regarding the prevention of sexual transmission of HTLV, programs should emphasize the importance of condom use, systematic screening for infection, and individual counseling^{17,23,32,139,140}. Screening should also include the parents of the infected individual and siblings if the mother tests positive; children born to mothers with the virus should receive appropriate follow-up^{17,32,64}.

In Brazil, HTLV is not considered a public health problem and, thus, has been widely neglected^{25,32,139}. Like disease, injury, and public health events, cases of HTLV should be reportable to better approximate its incidence among indigenous peoples and to track its spread to the general population.

RESUMO

Origem e prevalência do vírus linfotrófico de células T humanas em populações indígenas das Américas

O vírus linfotrófico de células T humanas do tipo 1 (HTLV-1) é encontrado em populações indígenas de países do Pacífico e Américas enquanto o tipo 2 (HTLV-2) é amplamente distribuído entre as populações indígenas das Américas, nas quais aparenta ser mais prevalente que o HTLV-1, e em algumas tribos da África Central, sendo considerado ancestral nas Américas e transmitido à população geral e de usuários de drogas injetáveis a partir da população indígena. No continente americano o HTLV-1 teria mais de uma origem, sendo trazido na era paleolítica pelos imigrantes através do estreito de Bering, através do tráfico de escravos no período colonial e com a imigração japonesa a partir do início do século XX, enquanto para o HTLV-2 teria sido trazido pelos imigrantes através do estreito de Bering. A endemicidade do HTLV-2 entre os indígenas do Brasil tornam a região amazônica brasileira a maior área endêmica do mundo para sua ocorrência e a revisão da infecção pelo HTLV-1 em todas as tribos brasileiras apoiam a origem africana do HTLV-1 no Brasil. O risco de hiperendemicidade nestas populações epidemiologicamente fechadas e de transmissão a outras populações reforçam a importância de medidas no âmbito da saúde pública para seu controle, incluindo o reconhecimento da infecção entre os agravos e eventos de notificação compulsória.

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