

HTLV in South America: Origins of a silent ancient human infection

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Abstract

The description of the first human retrovirus, human T-lymphotropic virus 1 (HTLV-1), was soon associated with an aggressive lymphoma and a chronic inflammatory neurodegenerative disease. Later, other associated clinical manifestations were described, affecting diverse target organs in the human body and showing the enormous burden carried by the virus and the associated diseases. The epidemiology of HTLV-1 and HTLV-2 showed that they were largely distributed around the world, although it is possible to locate geographical areas with pockets of low and very high prevalence and incidence. Aboriginal Australians and indigenous peoples of Brazil are examples of the large spread of HTLV-1 and HTLV-2, respectively. The epidemiological link of both situations is their occurrence among isolated, epidemiologically closed or semi-closed communities. The origin of the viruses in South America shows two different branches with distinct timing of entry. HTLV-1 made its probable entrance in a more recent route through the east coast of Brazil at the beginning of the slave trade from the African continent, starting in the 16th century and lasting for more than 350 years. HTLV-2 followed the ancient route of human migration from the Asian continent, crossing the Behring Strait and then splitting in South America as the population became separated by the Andes Mountains. By that time, HTLV-2c probably arose and became isolated among the indigenous populations in the Brazilian Amazon. The study of epidemiologically closed communities of indigenous populations in Brazil allowed tracing the most likely route of entry, the generation of a new molecular subtype (HTLV-2c), the elucidation of the vertical transmission of HTLV-2, the intrafamilial aggregation of cases and the escape and spread of the virus to other areas in Brazil and abroad. Despite the burden and impact of both viruses, they are maintained as silent infections among human populations because 1, health authorities in most South American countries in which national surveillance is poor have little interest in the disease, 2, the information is commonly lost as indigenous groups do not have specific policies for HTLV and other sexually transmitted infections, and 3, health access is not feasible or properly delivered.

Key words: HTLV-1, HTLV-2, origin, South America, human migration.

1. Introduction

During the 1960s/1970s, there was enormous scientific anxiety about finding a human oncovirus that could act as a counterpart to the known and growing number of animal oncogenic viruses. Animal viruses were sometimes thought to infect humans, but this line of research was quickly abandoned because of the continuous lack of etiological association. In the beginning of the 1980s, two human retroviruses were described, named human T-lymphotropic virus 1 (HTLV-1) and 2 (HTLV-2) (Poiesz et al. 1980, 1981; Kalyanaraman et al. 1982; Gallo 2005) and placed as members of the family *Retroviridae* (ICTV 2017).

HTLV-1 was soon associated with an aggressive lymphoma (adult T-cell leukemia/lymphoma), which can be devastating, leading to a mean survival time of 8–10 months (Katsuya et al. 2015; Taniguchi et al. 2019), and a chronic inflammatory neurodegenerative disease, initially described in the Caribbean area as tropical spastic paraparesis, but soon appropriately renamed HTLV-associated myelopathy, or TSP/HAM (Rodgers-Johnson et al. 1985; Osame et al. 1986; Araujo 2015; Bangham et al. 2015; Nozuma and Jacobson 2019). Later, several other associated clinical manifestations were described, affecting diverse target organs in the human body and showing the enormous burden carried by the virus and its associated diseases (Schierhout et al. 2020). Infection outcomes show the complexity of interactions with the human host, and as of today, clinical manifestations of HTLV-1 have been associated with diseases of the eyes (Chew et al. 2018; Nakao, Abematsu, and Sakamoto 2018; Kamoi et al. 2019; Schierhout et al. 2020), skin (Bimbi, Brzezinski, and Sokolowska-Wojdylo 2019; Schierhout et al. 2020), lungs (Falcão et al. 2017; Dias et al. 2018; Kako et al. 2019; Schierhout et al. 2020), joints (Nishioka et al. 1989; Sato et al. 1991; Dennis and Chitkara 2007), thyroid (Kawai et al. 1992; Matsuda et al. 2005), heart (Abolbashari et al. 2018; Mohammadi et al. 2019; Schierhout et al. 2020), bowels (Oliveira et al. 2019; Schierhout et al. 2020), and bladder (Silva et al. 2009; Nayar et al. 2018; Schierhout et al. 2020), among others (Schierhout et al. 2020; Shimizu et al. 2019). It is commonly asserted that as few as 5 per cent of HTLV-1-infected persons develop any type of disease, but this clinical perspective is under revision as more and new clinical outcomes, previously not associated with the infection, continue to be described, indicating that this figure may be higher and should not be ignored (Araujo 2015). It is worth mentioning that there are no specific antiviral drugs directed to HTLV-1 associated clinical manifestations.

HTLV-2 has never been firmly associated with overt diseases. Although there are few reports of clinical associations (Kalyanaraman et al. 1982; Hjelle et al. 1992; Zucker-Franklin, Hooper, and Evatt 1992; Maytal et al. 1993; Peters et al. 1999; Araujo and Hall 2004), it seems that the virus is an ancient infection already well adapted to the human host. Indeed, it has been commonly used as a marker of human migration since its original infection in humans can be traced from the earliest exploration of the different continents in the search of new and better areas to live (Black 1997; Ishak et al. 2017). HTLV-2 may not be a common etiology of disease, its apparent absence of pathogenesis and virulence may be relevant to study as a potential explanation of the severity exerted by its counterpart, HTLV-1. Two other viruses, HTLV-3 and HTLV-4, were described (Wolfe et al. 2005) as examples of cross-species in a geographically isolated forest area in Cameroon, but so far, neither have been detected elsewhere or have shown further spread (Duong et al. 2008; Perzova et al. 2010).

Understanding the epidemiology of HTLV-1 and HTLV-2 is a key factor in explaining the origin of the viruses worldwide, particularly in South America and Brazil. Unfortunately, epidemiological information is sometimes old, with conflicting results, and consequently, it is not useful for defining appropriate measures for prevention and control and thus needs to be improved (Ishak, Guimarães Ishak, and Vallinoto 2020). This information is useful for detecting the occurrence and frequency of the viruses in order to determine the pathways through which the virus moves and the possible routes for future spread. HTLV-1 and HTLV-2 are largely distributed around the world (Gessain and Cassar 2012; Braço et al. 2019; Li et al. 2019), although it is possible to locate geographical areas with pockets of low and very high prevalence and incidence (Jensen et al. 2019; Pereira et al. 2019; Pham et al. 2019). Areas with high prevalence and incidence seen in some places around the world are indicative of the pathways that brought the viruses to South America and, particularly, to Brazil.

High endemic levels of HTLV-1 infection are common among native aboriginal Australian (Bastian, Hinuma, and Doherty 1993; Einsiedel et al. 2016) and in some areas of southern Japan (Satake et al. 2016; Sagara et al. 2018). HTLV-2 is hyperendemic among the indigenous peoples of the Amazon region of Brazil (Ishak et al. 1995; Vallinoto et al. 2002; Braço et al. 2019). The only epidemiological link that favors both situations is their occurrence among isolated, epidemiologically closed or semi-closed population groups. Japan was a closed community until the beginning of the 20th century, determined by the geographical isolation of its several islands and their closed system of habits and culture (Cullen 2003). Similar situations occurred with the aboriginal population in Australia. The indigenous peoples in the Amazon region of Brazil were geographically isolated by the wild lush rainforest and by different cultural and social behaviors of the large number of linguistic population groups, tribes, and villages that spread over the territory until approximately the 1950s (Instituto Brasileiro de Geografia e Estatística 2005; Santos and Pereira 2005; Santos and Teixeira 2011). The continuous fusion of small groups and the posterior fission of larger groups were determinant factors that spread the virus over the region and maintained either high endemicity (Ishak et al. 1995; Vallinoto et al. 2002; Braço et al. 2019) or contributed to keeping several communities free of the virus until the present day (Vallinoto et al. 2019).

In summary, there is exciting information dealing with phylogenetic analysis on the ancient African origin of PTLV-I that traces back to about 50,000 years ago, and a wide variety of emerging subtypes of HTLV-1 (HTLV-1a, HTLV-1b, HTLV-1d, and HTLV-1e) between 27,300 and 8,200 years ago and inferring that in more recent times (approximately 3,000 years ago), new strains are continuously evolving such HTLV-If subtype (Fig. 1). The most probable route suggested to the virus transfer from simians to humans is interspecies transmission (Van Dooren, Salemi, and Vandamme 2001) and this is still a common event as seen by the rise of new HTLV types with the recently description of the new HTLV-3 and HTLV-4 (Wolfe et al. 2005).

The present paper, brings together the information available from the point of view of human behavior since ancient times to contemporary periods which led humans to move around the different geographical areas of the world and spread infectious agents (HTLV-1 and HTLV-2) and their evolving strains to South America, particularly to Brazil.

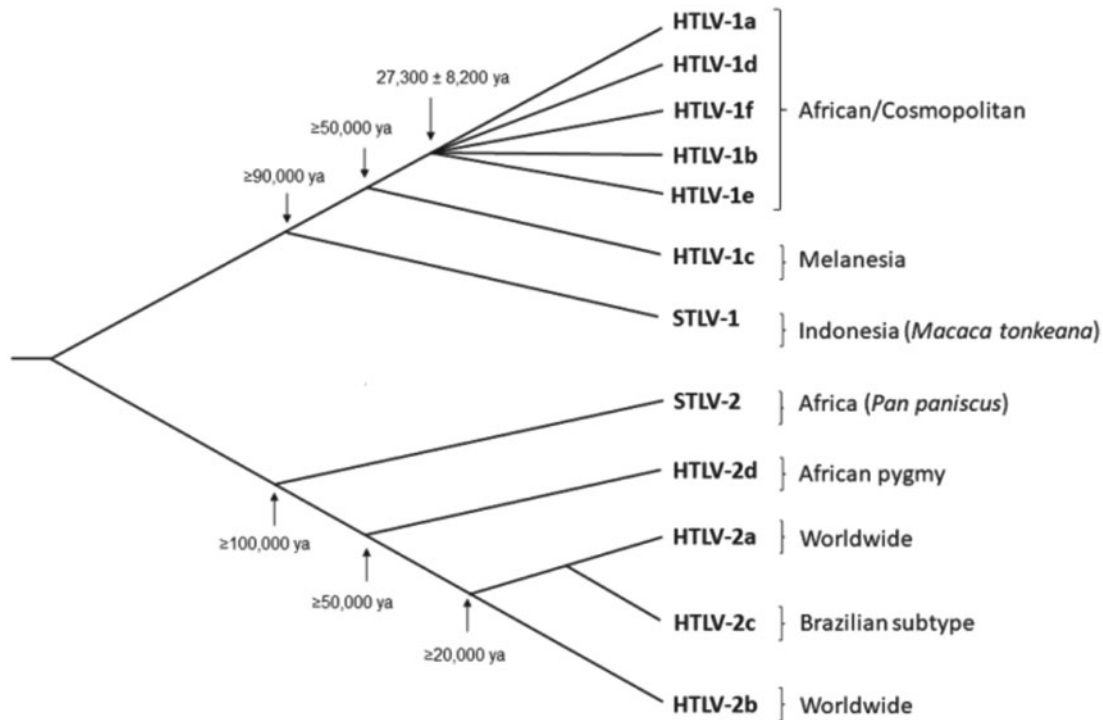


Figure 1. Representation of the phylogenetic relationships of HTLV-1 and HTLV-2 and their molecular subtypes (time scale in years ago, ya). The tree is a schematic representation built by the authors, using CorelDRAW Graphics Suite 2020 software, according to phylogenetic relationships reported by Van Dooren, Salemi, and Vandamme (2001) and Vandamme, Bertazzoni, and Salemi (2000).

2. The origins of HTLV-1 and HTLV-2 infection in South America

2.1 Human T-lymphotropic virus 1

The original routes of HTLV-1 and HTLV-2 infection in South America are apparently distinct from each other and follow two different pathways with different timings and dispersal modes in the process of the colonization of the continent. Following the phylogenetic evidences both human viruses were probably a result of the continuous crossing of the interspecies barrier from non-human primates along the years of multiple close contact (Mahieux et al. 1998; Vandamme et al. 1994). HTLV-1 has not been firmly described in epidemiologically isolated populations in the new continent, which reduces the odds of HTLV-1 as an ancient infection in South America; the description of the virus in an Andean mummy (Li et al. 1999) received severe criticism (Gessain et al. 2000) that weakens the argument of an ancient infection in South America. There is a chance, however, that HTLV-1 infected persons did not survive and did not successfully transmit the virus but the evidence was probably lost along with human migration. The spread of HTLV-1 has been linked with two HLA alleles (HLA*A26 and HLA*A36) originated in Africa and then dispersed to other ethnic groups (Sonoda, Li, and Tajima 2011), but the HLA polymorphisms gene flow does not fully support the ancient spread of virus infection to South America, which may have occurred as separate events. However, a handful of evidence has been shown that HTLV-1 made its massive entrance in the recent past at the east coast of Brazil, brought in with the countless number of entries since the beginning of the slave trade in the 16th century (1535) from

the African continent across the Atlantic Ocean (Aleluia et al. 2015).

The expansion of European colonies (particularly those from England, Spain, Portugal, and the Netherlands) in Africa, Asia, and the Americas led to the sharp resurgence of the old practice of slavery perpetrated by the African people against other communities within the continent, by making prisoners and keeping them as slaves. The enhanced demand for a cheap labor force in the Americas generated one of the major and shameful sins of humanity against other human beings, the most severe cause of human mortality (from capture to travel to the ports, the period of waiting to travel, travel across the ocean and inland travel to the final properties) and the tremendous expansion of human slavery on Earth so far. For at least 350 years, 23–24 million persons were captured in the African continent. Approximately 12.5 million persons were taken by force to the Americas, and approximately 9 million persons survived after 3 years in their new hostile work environments; it is worth mentioning that Brazil received more than 5 million persons (Miller 1996; Gomes 2019; Slave Voyages 2019).

The slave trade was intense on the Atlantic coast but was less evident on the Pacific. Cartagena, Colombia, was another major ports of entry in South America, but the transport of slaves into Pacific countries was not an easy task. Contrary to the Portuguese colonies, the Spanish colonies frequently used indigenous peoples as slaves more commonly than the African populations. This is markedly evident when comparing the high proportion of African ancestry in Brazil with the lower proportion in the Pacific coast populations (Santos and Guerreiro 1995; Pena et al. 2011; Salzano and Sans 2014), except in Colombia,

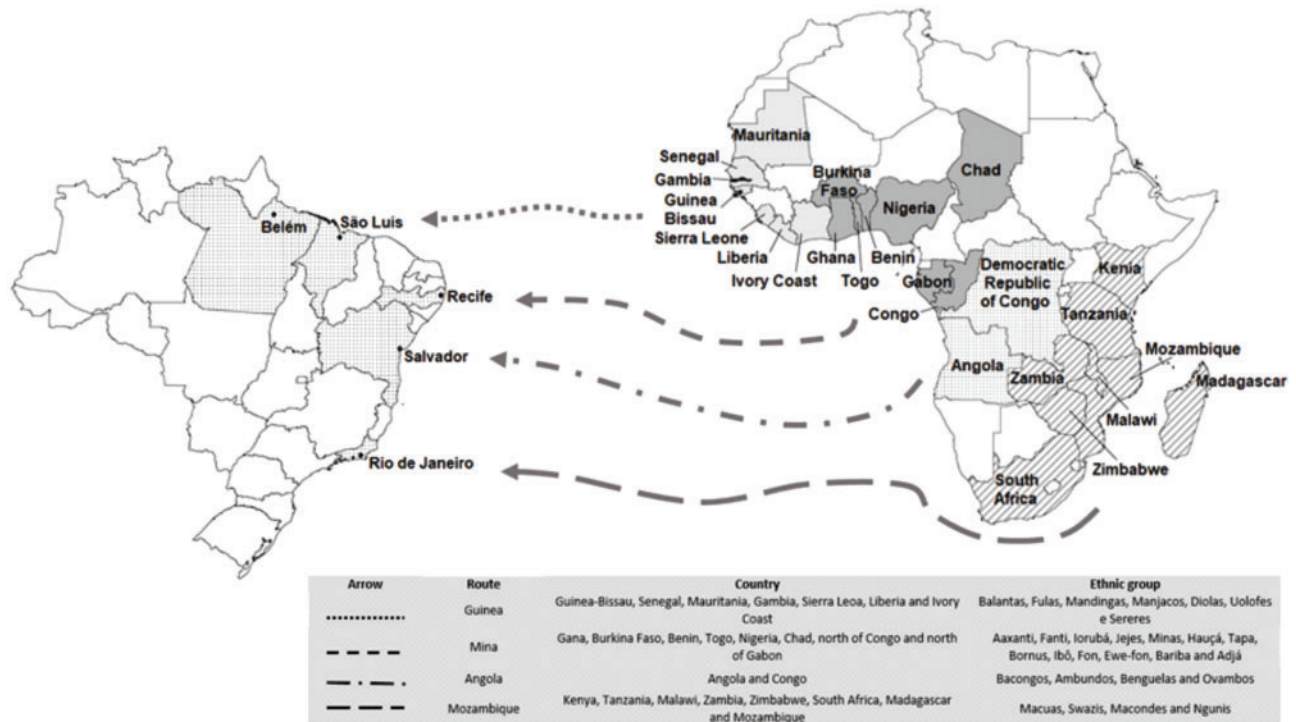


Figure 2. Routes of forced migration from different regions in the African continent, showing the present-day countries, the ethnic groups introduced and the major ports of entry in Brazil from 1535 to 1888.

where at least 10.5 per cent of the population identifies themselves as Afro Colombian, living predominantly on the Caribbean and Pacific coasts and islands and constituting the second largest population of African descent in Latin America after Brazil (Rojas et al. 2010).

The forced migration from the African continent followed specific pathways, and they can quite explicitly explain the introduction of HTLV-1 in the Brazilian territory (Fig. 2). The Guinea, Mina, Angola, and Mozambique routes were the major ports of exit from Africa: 1, the Guinea route (contributed with approximately 3% of the total slaves entering in Brazil), from West Central Africa, which included areas that today comprise Guinea-Bissau, Senegal, Mauritania, Gambia, Sierra Leone, Liberia, and the Ivory Coast, took persons to the North and Northeast of Brazil; 2, the Mina route (approximately 20% of the total), from West Central Africa, which included areas that now comprise the territories of Ghana, Burkina Faso, Benin, Togo, Nigeria, Chad, the north part of the Congo and the north part of Gabon, took persons to the ports of Belem, Sao Luis, Recife, Salvador, and Rio de Janeiro; 3, the Angola route (the major route, with approximately 70% of the human trafficking to Brazil), from West Central and South of Africa, included the trafficking of people from present-day Angola and the Congo to the ports of Recife, Salvador, and Rio de Janeiro; and 4, the Mozambique route (the last area involved, in a final attempt to maintain the slave trade hidden from the British Navy, which by the time, was fighting against slavery and sinking the ships carrying slaves; this area contributed with approximately 7% of the total entering in Brazil), from the east coast of Africa, trafficked people from areas that now comprise Kenya, Tanzania, Malawi, Zambia, Zimbabwe, South Africa, Madagascar, and Mozambique mainly to Rio de Janeiro (Gomes 2019; Slave Voyages 2019).

It is relevant to mention that although entry into Brazil commonly occurred from the southern to the northern ports, including the major ports Rio de Janeiro, Salvador, Recife, Sao Luis, and Belem, the slave trade occurred without any geographical restrictions within the country, and different groups were commonly found in different areas from those where they originally made their entry (Gomes 2019). The distribution of haplotypes of the HBB**S* gene in Belem in northern Brazil (60% Bantu, 27% Benin, 12% Senegal, and 1% Cameroon) illustrates this scenario. The observed high frequency of the Benin haplotype and the presence of the Cameroon haplotype is most likely due to the domestic slave trade and internal migrations, particularly from the Northeast (Bahia, Pernambuco, and Maranhao), a region heavily supplied with slaves from West Central Africa. In this area, the Benin haplotype is common; and the Cameroon haplotype has been found mainly in Nigeria, and there are no historical records of the direct trafficking of slaves from West Central Africa to northern Brazil (Cardoso and Guerreiro 2006). In Bahia, the HTLV-1 infection was associated with an ancient post-Columbian introduction as a consequence of the slave trade, with a massive predominance of Benin and Bantu haplotypes of the β -globin gene and mtDNA (Aleluia et al. 2015).

In addition to the introduction of HTLV-1 in Brazil by the slave trade, the virus certainly had its dissemination amplified due to the common practice of breastfeeding white children by female African slaves, the 'amas de leite' (a special slave nanny who would breastfeed the white children, for many different reasons and for very long periods in the first years of life).

In the most recent past, HTLV-1 made a second large-scale entry in Brazil with the massive Japanese migration that occurred in the 20th century into the northern and southern areas of the country. Japanese migration to other countries was a consequence of internal conflicts in Japan, the migration from rural

areas and the modernization of the country after the Industrial Revolution (Handa 1987). By the end of the slave period in Brazil, there was an intense migration from some European countries, but in 1908, the Japanese started their migration through the port of Santos (Sao Paulo), and up to 1962 circa 229,000 Japanese immigrants from different areas of the country, including Kyushu in the south (particularly from Kumamoto and Fukuoka), Chugoku in central Japan (particularly from Hiroshima), Tohoku in the north, and in the archipelago of Okinawa (Okinawa, Kagoshima, Fukushima, Hiroshima, Kumamoto, Ehime, Yamaguchi, Miyagi, Niigata, and Tokio), were distributed throughout Brazil (Comissão de Recenseamento da Colonia Japonesa 1964; Emmi 2013). The largest number of Japanese descendants outside Japan is located in Brazil, and in northern Brazil (1929), they were located mainly in the states of Para (in the city of Tome Açu) and Amazonas (in the cities of Parintins and Maues) (Homma 2009). For many years, they comprised a small, epidemiologically closed community and maintained their original social, cultural and behavioral practices. It is worth mentioning that during the Second World War, Tome Açu was one of the locations in Brazil where Japanese immigrants were forcefully kept in complete segregation from other parts of the state as a consequence of the war in Europe and the Pacific (Tafner and da Silva 2015).

The introduction of HTLV-1 in Brazil successfully occurred along these two waves of migration and helped to spread the virus throughout all geographical areas of the country (Amoussa et al. 2017). The distribution of the virus is almost uniform in the major cities, where the Cosmopolitan subtype is the predominant strain, with subgroups A (Transcontinental) and B (Japanese) being the most commonly found, according to the phylogenetic analysis (Vallinoto et al. 2004, 2006; Mota-Miranda et al. 2008; Vicente et al. 2011; Pessôa et al. 2014; Amoussa et al. 2017; Nobre et al. 2018; Oliveira-Filho et al. 2019). The phylogenetic variability of HTLV-1 was reported in eighty-six samples from Brazil, confirming the Cosmopolitan Transcontinental subgroup as the most prevalent strain overall and the Cosmopolitan Japanese subgroup among the Japanese immigrants (Pessôa et al. 2014). Brazilian HTLV-1 nucleic acid sequences grouped into different subclusters served as strong evidence for multiple introductions of the virus, as the sequences were interspersed with strains from South America, Europe, Asia, and Africa (particularly Algeria, Morocco, Mauritania, Senegal, Cameroon, Gabon, Central Africa, and Mozambique, which clearly represent the four main slavery trafficking routes).

The Japanese migration brought the HTLV-1 Cosmopolitan Japanese subgroup, but not the high prevalence of infection found in some areas of Japan, to the eventual immigrant communities now residing in Brazil (Song et al. 1995; Yamashita et al. 1999; Bandeira et al. 2015). In the state of Para, the Japanese subgroup was indeed present among women from the Kyushu region, which comprises the southern part of Honshu Island, Japan (Vallinoto et al. 2004), and was further spread outside the communities among drug users (Oliveira-Filho et al. 2019) along with the Transcontinental subgroup.

2.2 Human T-lymphotropic virus 2

HTLV-2 entry in the Amazon region of Brazil is a well-studied piece of information in the field of paleomicrobiology. This field shows evidence of the most likely routes through which viral and bacterial infectious agents entered into various regions during ancient and, sometimes, more recent times along with the

human beings that entered the Amazon environment (Ishak et al. 2017).

Infection with HTLV-2 among indigenous American communities was shown to be largely distributed in more than twenty villages from six states in the Amazon region of Brazil (Maloney et al. 1992; Ishak et al. 1995; Eiraku et al. 1996). A unique molecular subtype (HTLV-2c; Fig. 1) is endemically distributed in an area of more than 5 million km², maintained under continuous transmission (horizontal and vertical) among epidemiologically isolated human communities as a consequence of their physical, cultural, and linguistic barriers; this large distribution among different indigenous populations is the primary evidence for virus introduction and spread via ancient populations (Ishak et al. 1995; Vallinoto et al. 2002; Braço et al. 2019).

HTLV-2 apparently emerged in the African continent and was brought to the Americas with the human migratory movements crossing the Behring Strait to Alaska 30,000 – 15,000 years ago (Switzer et al. 1996; Vallinoto et al. 2002). Approximately 16,000 years ago, there was a split in the Ancient North Siberian migratory group that inhabited North America and headed south; by 15,000 years ago, the remaining population reached South America (Fagundes et al. 2008; Goebel, Waters, and O'Rourke 2008; Stone 2019).

HTLV-2 is present in North, Central, and South America and persists in North America mostly as the molecular subtype HTLV-2a (found predominantly in urban areas); HTLV-2b originated with the southern migration, predominantly among native groups from North, Central, and South America (Heneine et al. 1991; Biglione et al. 1993; Ferrer et al. 1993; Levine et al. 1993; Switzer et al. 1996). HTLV-2 seems to be more stable in some specific situations, for instances, molecular clock analysis suggests that HTLV-2 presents different evolutionary rates, being 150 – 350 times faster among intravenous drug users when compared with isolates from endemically infected tribes (Vandamme, Bertazzonib and Salemi 2000).

The wave of migration into South America split at the Andean region, sending one group along the Pacific Ocean and the other group to the Amazon; evidence for this is shown in archaeological, anthropological and genetic studies (Greenberg et al. 1986; Rothhammer and Silva 1989; Fagundes et al. 2008; Goebel, Waters, and O'Rourke 2008; Stone 2019). HTLV-2c probably originated at this time and was introduced into the region as a new independent evolutionary pathway, a different molecular subtype that spread largely among the Amerindians in the Amazon region of Brazil (Fig. 3) (Vallinoto et al. 2002). It is worth mentioning that there are anthropological evidence of human migration from Polynesia to South America (Goebel, Waters, and O'Rourke 2008) in addition to the controversial ancient HTLV-1 infection in Chilean mummy (Li et al. 1999; Gessain et al. 2000). However, there are no consistent scientific evidence supporting pre-Columbian introduction of HTLV-1 and HTLV-2 in South America through this specific pathway, but it is highly probable that HTLV-1 accompanied human migration through the Pacific and found a population already infected by HTLV-2. Virus spread was successful for both agents as their presence is not restricted to geographical compartments and occur (with variable prevalences) in both urban and indigenous populations (Gotuzzo et al. 1994; Alva et al. 2012).

Evolutionary fission and fusion processes in large and small indigenous communities were responsible for the initial distribution of the virus in the Amazon (Ishak et al. 1995; Vallinoto et al. 2002) and reached the indigenous populations such as the Guarani at the southern border of the country (Menna-Barreto et al. 2005). Investigations of epidemiologically closed

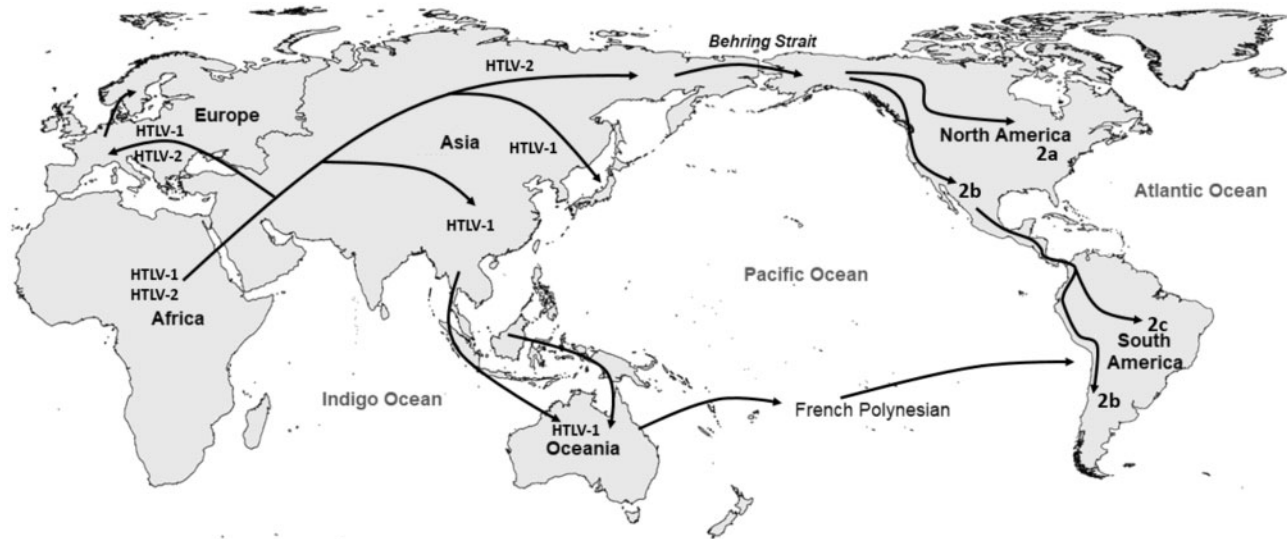


Figure 3. Routes of the HTLV-1 and HTLV-2 pathways from the African to other continents.

indigenous communities in Brazil aided in expanding previous knowledge defined for HTLV-1. These studies allowed us to trace the most likely route of entry of the viruses, the generation of a new molecular subtype (HTLV-2c), the elucidation of the vertical transmission of HTLV-2 and the intrafamilial aggregation of cases (Ishak et al. 1995, 2001; Vallinoto et al. 2002).

It was also shown that the virus soon escaped its geographical isolation as a consequence of the increasing incursions of man by the 1950s into areas of North and Central Brazil previously inhabited solely by indigenous populations. In contemporary times, the initial contact involved sexual relations between Brazilian male and indigenous females, a practice that changed considerably. Recently, small villages that were maintained by agriculture, mining, and minor industries were commonly visited by indigenous male from neighboring villages to have sexual relations with Brazilian women. Both practices were common since colonial times and resulted in an interethnic admixture of the urban Amazon populations that consisted of up to 40 per cent indigenous ancestry (Santos and Guerreiro 1995).

HTLV-2 infection has been largely identified in the indigenous communities of several countries from North, Central, and South America. In Brazil, HTLV-2c is present among indigenous people and, in a more recent move, the populations of urban communities as a direct result of the mixing of indigenous and neo Brazilian populations; the strain has been detected in Belem (Ishak et al. 1995, 1998), Sao Paulo (Eiraku et al. 1996), Rio de Janeiro (Silva et al. 2002), Belo Horizonte (Catalan-Soares et al. 2005), Porto Alegre (Renner et al. 2006), and Salvador (Barreto et al. 2014) (Fig. 4). It is worth mentioning that the virus has been described in Senegal, showing the great capacity of infectious agents to spread (Diop et al. 2006). The presence of HTLV-2c in Senegal may be a result of the return of quilombos refugees that occurred soon after the abolition of slavery, to their motherland in Africa following an intense interaction with local indigenous peoples.

3. Concluding remarks

Political instability, war, famine, and disasters in several countries throughout the world is, again, causing a massive movement of humans from one place to another. A great difference

from the migrations of early man and those of the Columbian era is that, today, migrations occur at a faster speed, which favors the transmission of infectious agents practically overnight (Lewis 2020). Viruses that infect and establish persistent infections are of major importance to trace and follow-up on the present waves of world migration. The emergence of new infectious agents into different geographical areas is expected to be seen continuously in the future. In addition to ancient and past introduction of HTLV-1/2, other infectious agents have their past introduction satisfactorily documented in the Amazon region of Brazil, and their presence is revealed when used as a biomarker associated with anthropological and other relevant information to trace ancient, past, and contemporary human migration into this geographical area (Ishak et al. 2017).

It is a difficult task to map the most likely pathways of the dispersal of ancient infectious agents alongside the initial human migrations from the African continent to the rest of the world, including the routes of HTLV-1 and HTLV-2. Although there is more evidence for HTLV-2 crossing the Behring Strait, it is almost impossible to rule out the same pathway for HTLV-1.

The possible impact of HTLV-1 and HTLV-2 during the movement and settlement of the respective populations remains a major and nearly insurmountable challenge to discern. However, the almost complete absence of disease resulting from HTLV-2 infection apparently indicates the better adaptation of the virus to its human host as a primary ancient human infection and that it may be older than HTLV-1.

There is no serious doubt that HTLV is a good marker of human migration. Unfortunately, despite the burden and impact of infection by either virus, they are silently spreading among human populations. Although the viruses are ancient, health authorities in most South American countries in which national surveillance is poor have little interest in the diseases, information about the diseases is commonly lost as indigenous groups do not have specific policies for HTLV and other sexually transmitted infections, and health access is not feasible or properly delivered for the unfortunate population infected by these viruses.

The combined approach for detecting infectious agents involves anthropological, archeological, genetics, historical, and social information and improves the understanding of the



Figure 4. Distribution of HTLV-2 among the different indigenous peoples of the Americas and its presence in major cities of Brazil.

origin, emergence, evolution and dynamics of infectious agent transmission. The detection of different strains of HTLV as well as other viruses (JCV, HHV-8) and *Chlamydia trachomatis* in the Amazon region of Brazil, which infect different population groups, has demonstrated the association of these agents with their ethnic origins in Europe, Asia, and the African continent (Ishak et al. 2017). Massive migrations or the movement of small groups was effective in contributing to the formation of the human Amazonian population. HTLV is a fairly good companion to and marker of human migration, and it certainly took part in human history as well.

Data Availability

Not applicable.

Authors' Contributions

All authors contributed to the writing and approved the manuscript.

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