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Global epidemiology of HTLV-I infection and associated diseases

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Epidemiologic aspects of human T-lymphotropic virus type I (HTLV-I) infection have been thoroughly studied over the course of approximately 25 years since its first description. The geographic distribution of the virus has been defined, with Japan, Africa, Caribbean islands and South America emerging as the areas of highest prevalence. The reasons for HTLV-I clustering, such as the high ubiquity in southwestern Japan but low prevalence in neighboring regions of Korea, China and eastern Russia are still unknown. The major modes of transmission are well understood, although better quantitative data on the incidence of transmission, and on promoting/inhibiting factors, are needed. Epidemiologic proof has been obtained for HTLV-I's causative role in major disease associations: adult T-cell leukemia (ATL), HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), HTLV-associated uveitis and infective dermatitis. However, more and better studies are needed for other apparent disease outcomes such as rheumatologic, psychiatric and infectious diseases. Since curative treatment of ATL and HAM/TSP is lacking and a vaccine is unavailable, the social and financial cost for the individual, his/her family and the health system is immense. For this reason, public health interventions aimed at counseling and educating high-risk individuals and populations are of paramount importance.
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Introduction

Over the course of nearly 25 years, the epidemiology of human T-lymphotropic virus type I (HTLV-I) has matured. The geographic distribution of the virus has been defined, although some puzzles persist such as the high prevalence in southwestern Japan but low prevalence in neighboring regions of Korea, China and eastern Russia, and seemingly isolated pockets of infection in Iran. The major modes of transmission are well understood, although better quantitative data on the incidence of transmission, and on promoting or inhibiting factors, are needed for some routes of infection. Finally, epidemiologic proof has been obtained for HTLV-I's causative role in major disease associations: adult T-cell leukemia (ATL), HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), and uveitis. However, more and better studies are needed for other apparent disease outcomes such as arthritis, pneumonitis, urinary tract disorders and increased susceptibility to infectious diseases.

This review will discuss the phylogeny and molecular epidemiology of HTLV-I, its worldwide prevalence by geography, and endemic populations, modes of transmission, clinical epidemiology of HTLV-I diseases and public health considerations including preventive measures. The best-published epidemiologic studies have relied upon serological screening for antibodies to HTLV-I using an enzyme-linked immunoassay (EIA), with confirmatory testing by another method such as Western blotting, immunofluorescence (IFA) or radioimmunoprecipitation (RIPA). Polymerase chain reaction (PCR) assays that detect HTLV-I proviral DNA have been used for confirmatory tests, for discriminatory typing of HTLV-I versus HTLV-II, and, when used with proviral DNA sequencing or restriction frangment length polymorphism (RFLP) analysis, for viral subtyping. First, when interpreting and comparing international prevalence studies, caution must be exercised because of differences in the age, gender and risk profile composition of the studied populations. Second, early EIAs were subject to reduced-specificity, especially during the 1980s. Third, until the 1990s, most serologic assays did not discriminate between HTLV-I and crossreacting HTLV-II antibodies; for those studies, others and we use the term HTLV-I/II. Finally, there is a phenomenon of biological false seropositivity, particularly in Africa, with reactive EIAs and indeterminate Western blot patterns, which may be falsely interpreted as positive (Mauclere *et al*., 1997). This phenomenon has been attributed to possible crossreactivity with malaria antigens (Mahieux *et al*., 2000).

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Global epidemiology of HTLV-I

Phylogeny and molecular epidemiology

Despite the frequent error rate of retroviral replication and high levels of provirus in infected lymphocytes, HTLV-I has relatively low intra- and inter-individual sequence variability (Gessain *et al*., 1992). This apparent paradox has been postulated to be due to the clonal expansion of HTLV-I-infected lymphocytes (Wattel *et al*., 1995). After a brief period of reverse transcriptase-mediated replication soon after initial infection, multiplication of provirus occurs mainly via clonal expansion of the infected lymphocyte rather than production of new virions. HTLV-I has been classified into several viral subtypes based upon differences in proviral DNA sequence of the *env* gene and long terminal repeat (LTR) region of human isolates, although the latter classification has taken precedence due to presumed lower selection pressure on the noncoding LTR sequences (Slattery *et al*., 1999).

Published HTLV-I subtypes include subtype A, also known as the cosmopolitan subtype, which includes the prototype HTLV-I sequence from Japan (Seiki *et al*., 1982) and is found in many HTLV-I-endemic areas worldwide; subtypes B, D, and F from Central Africa; subtype E from South and Central Africa (Slattery *et al*., 1999); and subtype C from Melanesia (Gessain *et al*., 1991; Sherman *et al*., 1992). HTLV-I sequences may also be compared to simian T-lymphotropic virus type I (STLV-I) isolates from non-human primate species (Vandamme *et al*., 1994). For most HTLV-I subtypes, STLV-I isolates from the same geographic region cluster closely with the human HTLV-I, suggesting multiple episodes of simian to human transmission and a probable African origin of HTLV-I (Koralnik *et al*., 1994; Vandamme *et al*., 1994). Close sequence similarity between HTLV-Ic and STLV-I isolated from *Macaca arctoides* in Melanesia is an example of this phenomenon (Mahieux *et al*., 1997).

The low variability of HTLV-I proviral sequence, together with relatively recent (past several hundred years) migrations of infected humans may together explain the truly cosmopolitan nature of the HTLV-Ia subtype. Its broad geographic diffusion is thought to have occurred over the past several hundred years via European voyages of discovery, the slave trade or other human migrations (Koralnik *et al*., 1994; Yanagihara *et al*., 1995). This situation is quite different from HTLV-II, for which distinct subtypes have been associated with specific populations, such as HTLV-IIc among Brazilian Indians and injection drug users (Eiraku *et al*., 1996), or with specific risk behaviors, such as the HTLV-IIa predominance among older black persons and injection drug users in North America (Murphy *et al*., 1998; Liu *et al*., 2001).

Despite these interesting observations, molecular subtyping of HTLV-I has played a relatively small role in epidemiologic studies of this virus, because the great majority of human infections studied to date are caused by the cosmopolitan subtype A. On the one hand, minor geographic clustering of LTR sequences can be observed within subtype A among isolates from Africa, Brazil and Japan (Slattery *et al*., 1999). On the other hand, isolates from humans in countries as disparate as the Caribbean basin, Japan, Chile, Iran and Kuwait are closely related on phylogenetic trees based upon LTR sequence (Gessain *et al*., 1992). The low variability of HTLV-I proviral sequence limits the use of molecular typing as proof of sexual or vertical transmission between epidemiological linked individuals. Neither is the occurrence of the HTLV-I diseases ATL and HAM/TSP associated with the HTLV-I subtype of the infected human (Ehrlich *et al*., 1992; Gessain *et al*., 1992).

Prevalence by geographic region (Figure 1)

Although the exact number of HTLV-I seropositive individuals in the world is not known, it is estimated that about 15–20 millions persons live with HTLV infection worldwide (de The and Kazanji, 1996). The seroprevalence rates differ, according to geographic area, the socio-demographic composition of the population studied and individual risk behaviors. For example, prevalence rates as high as 37.0% were reported in small, selected populations from some areas in southwestern Japan (Yamaguchi, 1994; Mueller *et al*., 1996) as compared to very low prevalence rates (0.0039%) among French blood donors (Courouce *et al*., 1993). However, information on prevalence rates from representative samples of the general population is rare. Most data on HTLV-I prevalence rates are from studies in generally low-risk blood donors or selected population groups (pregnant women, neurological or hematological patients, relatives of infected individuals, specific native and sometimes isolated population groups, intravenous drug users (IDU) and sex workers) that are certainly not representative of the general population (Mueller, 1991; Ferreira *et al*., 1997; Manns *et al*., 1999).

Overall, relatively high HTLV-I or HTLV-I/II seroprevalence rates in the general population or specific groups of individuals, as pregnant women and/or blood donor candidates, are found in southwestern Japan (up to 10%) (Yamaguchi, 1994; Mueller *et al*., 1996), several countries in the Caribbean basin including Jamaica and Trinidad (up to 6%) (Hanchard *et al*., 1990; Murphy *et al*., 1991) and in several sub-Saharan Africa countries, for example Benin, Cameroon and Guinea-Bissau (up to 5%) (Dumas *et al*., 1991; Gessain and de The, 1996; Andersson *et al*., 1997; Sarkodie *et al*., 2001) and localized areas of Iran and Melanesia (less than 5%) (Mueller, 1991; Manns *et al*., 1999). Somewhat lower seroprevalence rates are found in several countries in South America (Castillo *et al*., 2000; Carneiro-Proietti *et al*., 2002; Kazanji and Gessain, 2003; Catalan-Soares *et al*., 2004; Pouliquen *et al*., 2004), although to our knowledge, no studies from representative samples of the general population have been conducted so far in South America. Data from Argentina, Brazil, Colombia and Peru are for the most part restricted to blood donors (up to 2% of seropositivity to HTLV-I/II) (Galvao-Castro *et al*., 1997; Kazanji and Gessain, 2003;

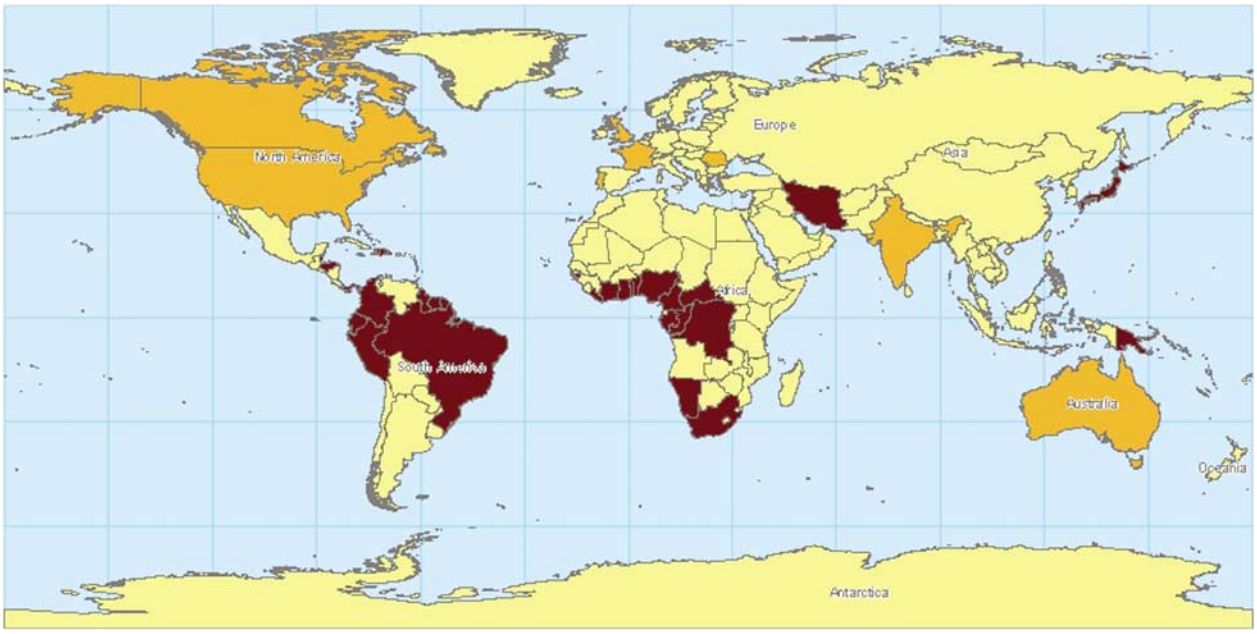

Figure 1 Countries with endemic HTLV-I, defined as prevalence between 1 and 5% in some populations, are shown in dark brown. Countries with reports of low prevalence (less than 1% in some groups), due mainly to immigration from endemic areas, are shown in tan color. It should be noted that HTLV-I endemic areas do not correspond exactly to the country boundaries shown in the map, for example, Brazil, Japan and Iran, where HTLV-I is limited to residents of certain areas of each country

Leon *et al*., 2003; Sanchez-Palacios *et al*., 2003; Gastaldello *et al*., 2004), pregnant women and samples of specific native populations (Ishak *et al*., 2003), as well as IDU from Brazil.

For nonendemic geographic areas such as Europe and North America, HTLV-I infection is mainly found in immigrants from endemic areas, their offspring and sexual contacts, among sex workers and IDU. For blood donors in North America and Europe, seroprevalence is very low, for example, 0.01–0.03% in USA and Canada (Williams *et al*., 1988; Murphy *et al*., 1991; Chiavetta *et al*., 2003), 0.002% in Norway (Stigum *et al*., 2000) and 0.0056% in Greece (Tseliou *et al*., 2003).

Data from studies of pregnant women may better reflect prevalence rates of the general population. Prevalence rates for HTLV-I and II were sixfold higher in pregnant women than in blood donors in the United Kingdom (Taylor *et al*., 2005). A study of 6754 pregnant women in Salvador, Brazil found 0.84% to be seropositive (Bittencourt *et al*., 2001).

Risk factors and routes of transmission – individual and social context

Several individual behaviors and exposures have been associated with HTLV-I seropositivity, corresponding to the known modes of transmission: from mother to child, predominantly through breastfeeding; via sexual intercourse and via parenteral transmission by transfusion of infected cellular blood products or sharing of needles and syringes (Manns *et al*., 1999). Although the biological mechanism of transmission still needs to be clarified, infected cells seem to be essential for transmission, whether the exposure to the virus is through blood, sexual contact or breastfeeding. HTLV-I endemic areas are in the tropics, infection trends to cluster among families and neighbors and a decline in seroprevalence are observed in subsequent generations of people migrating from endemic to nonendemic areas (Miller *et al*., 1994). These observations strongly suggest the presence of biological or social cofactors influencing HTLV-I transmission (Maloney *et al*., 1991).

Mother to child transmission occurs in 20% of offspring from an infected mother, and has been related to mother's proviral load, high antibodies titers and prolonged breastfeeding (Kinoshita *et al*., 1984; Ureta-Vidal *et al*., 1999). Postnatal infection by breastfeeding seems to play the most important role in vertical transmission. Screening for anti-HTLV-I antibodies during prenatal care in Japan followed by counselling of seropositive mothers to avoid breastfeeding their infants led to significant lower rates of infection in bottle versus breastfed infants (Hino *et al*., 1997). Other forms of mother-to-child transmission, such as intrauterine or peri-partum, seem to be less important (Fujino and Nagata, 2000), and may be hindered by HTLV-I-induced apoptosis of placenta cells (Fujino *et al*., 1999). Transmission through saliva is also possible, since the proviral DNA and anti HTLV-I antibodies are detectable in saliva, but currently there is no clear evidence of transmission through this mode (Fujino and Nagata, 2000).

As with other sexually transmitted infections, HTLV-I seropositivity is associated with unprotected sex, many lifetime sexual partners, presence of genital sores or ulcers and paying or receiving money for sex

(Bartholomew *et al*., 1987; Catalan-Soares *et al*., 2003; Belza, 2004). Cross-sectional studies have postulated higher transmission efficiency in the direction male to female than on reverse (Kajiyama *et al*., 1986; Murphy *et al*., 1989a, 1996; Larsen *et al*., 2000). However, prospective studies have been mixed, with one showing higher male–female transmission (Stuver *et al*., 1993) and two others showing no significant difference in male–female versus female–male transmission (Figueroa *et al*., 1997; Roucoux *et al*., 2005).

Intravenous exposure to blood seems to be the most efficient mode of HTLV-I transmission. In the past, this occurred mainly through transfusion of blood not tested for HTLV-I (Okochi *et al*., 1984; Manns *et al*., 1992). Most HTLV-I epidemiologic studies report transfusion in the past as an important risk factor for HTLV-I seropositivity (Murphy *et al*., 1996; Schreiber *et al*., 1997). Higher risk is associated with transfusion of packed red cells, whole blood and platelets compared to plasma products (Manns *et al*., 1992), and cold storage of blood lowers the risk of transmission, presumably due to the death of HTLV-I-infected lymphocytes (Donegan *et al*., 1990). The risk of seroconvertion after transfusion of HTLV-I contaminated blood products ranges from 40 to 60%, with a time interval before seroconvertion between 51 and 65 days after transfusion (Okochi *et al*., 1984; Manns *et al*., 1992). Acquisition of HTLV-I may be associated with the development of HAM/TSP, sometimes after a very short incubation period (Osame *et al*., 1986a; Gout *et al*., 1990).

During the past 20 years, screening for HTLV-I/II antibodies in blood donors was implemented in several countries (Japan, United States, Canada, Brazil and several European countries). This important public health intervention is excluding seropositive individuals from the pool of blood donors and has resulted in fewer HTLV-I infections among transfusion recipients, and a decrease in the number of new infections in the overall population (Osame *et al*., 1986a; Taylor, 1996).

Sharing of contaminated needles and syringes by IDU is another important parenteral mode of HTLV-I and -II transmission (Feigal *et al*., 1991; Khabbaz *et al*., 1992). HTLV-II seems to be much more prevalent than HTLV-I in North American and European IDU, presumably due to a poorly understood epidemic in the 1960s and 1970s (Lee *et al*., 1989, 1990; Murphy *et al*., 1998; Liu *et al*., 2001). However, HTLV-I is prevalent among IDU in Brazil (Etzel *et al*., 2001) and New York (Ehrlich and Poiesz, 1988; Lee *et al*., 1990).

In most HTLV-I endemic and even nonendemic areas, HTLV-I seroprevalence rates are strongly age and sex dependent, increasing with age and are higher in females (Kajiyama *et al*., 1986; Murphy *et al*., 1991; Mueller *et al*., 1996). The higher prevalence with age may have several explanations: the accumulation of seroconversions to new HTLV-I infections over the lifetime of the individuals surveyed; an age-cohort effect due to declining in HTLV-I seroprevalence over the past decades; or delayed seroconversion to infection acquired early in life (Blattner *et al*., 1986; Murphy *et al*., 1991). The latter explanation is not supported by biological data. Higher prevalence in females may be due to a more efficient male-to-female transmission during sexual intercourse; also, hormonal effects may play a role in female susceptibility (Chavance *et al*., 1990; Nakashima *et al*., 1995; Kaplan *et al*., 1996). The dynamics of HTLV-I infection may differ among countries, and variations in sexual behavior (more frequent use of condoms) or breastfeeding practices (duration, use of wet nurses) could contribute to the heterogeneity in prevalence rates. On the other hand, despite dissimilar absolute prevalence rates in Japan, Jamaica and the USA, these countries show the same pattern of age and sex-specific prevalence (Murphy *et al*., 1991, 1999; Mueller *et al*., 1996).

Several studies have reported that indicators of lower socioeconomic status such as education are associated with HTLV-I infection in both endemic and nonendemic areas (Murphy *et al*., 1991; Schreiber *et al*., 1997; Manns *et al*., 1999; Catalan-Soares *et al*., 2003; Sanchez-Palacios *et al*., 2003). These data suggest that social and environmental factors associated with poverty may influence HTLV-I transmission both within endemic countries and across the world (Miller *et al*., 1986; Maloney *et al*., 1991). Similarly, HTLV-I endemic countries (excluding Japan) have low per capita income and have to deal with a higher burden of HTLV-I/II infection and associated diseases with fewer resources than high-income countries.

Clinical epidemiology of HTLV-I-associated diseases

History of HTLV-I disease association

HTLV-I was the first retrovirus linked to human disease. It has been convincingly associated with adult T-cell leukemia/lymphoma (ATL) (Poiesz *et al*., 1980; Hinuma *et al*., 1981; Miyoshi *et al*., 1981b; Yoshida *et al*., 1984; Takatsuki *et al*., 1985a, b), HAM/TSP (Cruikshank, 1956; Gessain *et al*., 1985; Rodgers-Johnson *et al*., 1985; Osame *et al*., 1986b; Rodgers, 1965), uveitis (Pinheiro, 1990, 1995; Mochizuki *et al*., 1992) and infective dermatitis (LaGrenade *et al*., 1990). HTLV-I has also been linked to cases of polymyositis (Inose *et al*., 1992; Beilke *et al*., 1996), synovitis (Sowa, 1992), thyroiditis (Kawai *et al*., 1992) and bronchio-alveolar pneumonitis (Kimura, 1992), although definitive epidemiologic proof of HTLV-I association is lacking. The two major HTLV-I-associated diseases, ATL and HAM/TSP, are present in all endemic areas, although prevalence and incidence rates show significant geographic heterogeneity.

Interest in the possible association of human retroviruses and tumors led to a concentrated effort to detect the retroviral reverse transcriptase enzyme in the blood and tissues of patients with hematologic malignancies, and resulted in the identification of HTLV-I as the cause of ATL (Gallo, 1973; Poiesz *et al*., 1980; Hinuma *et al*., 1981; Miyoshi *et al*., 1981a). The strength of association of HTLV-I and diseases (Table 1) is based on epidemiologic studies as well as virological and

Table 1 Diseases associated with HTLV-I infection (adapted from Mahieux R and Gessain A, 2003)

Adult disease	*Association*
Adult T-cell leukemia (ATL)	++++
HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP)	++++
Uveitis (frequent in Japan)	++++
Infective dermatitis (rare)	+++
Polymyositis, inclusion body myositis	++
HTLV-I-associated arthritis	++
Pulmonary infiltrative pneumonitis	++
Sjögren's syndrome	+
Childhood disease	*Association*
Infective dermatitis (frequent in Jamaica)	++++
Tropical spastic paraparesis/HTLV-I-associated myelopathy (rare)	++++
Adult T-cell leukemia/lymphoma (very rare)	++++
Persistent lymphadenopathy	+

++++, proven association; +++, probable association; ++, likely association; +, possible association

molecular data, animal models and intervention trials (Mathieux and Gessain, 2003). Ongoing research focuses on the reasons why only a small percentage (up to 5%, depending on the area) of HTLV-I-infected individuals develop disease, while the vast majority of them remain asymptomatic.

Adult T-cell leukemia

ATL was first reported in Kyoto mostly in patients from Southwestern Japan in 1977 (Uchiyama *et al*., 1977) and the largest case series describing the clinical spectrum of ATL come from Japan (Shimamoto and Yamaguchi, 1992; Yamaguchi and Watanabe, 2002). A few years later, it was described in Caribbean immigrants living in United Kingdom (Catovsky *et al*., 1982) and afterwards reported in other endemic areas, including the Caribbean region (Gibbs *et al*., 1987; Hanchard, 1996), Africa (Fouchard *et al*., 1998) and South America (Matutes *et al*., 1994; Gerard *et al*., 1995). Following the initial description of ATL (Takatsuki *et al*., 1977) the epidemiologic clustering of ATL within certain age groups in localized areas of southern Japan instigated the interest by Japanese investigators that the malignancy could be virally induced. T-cell malignancies were recognized to be among the most common lymphoproliferative disorders in certain regions of Japan. Following the discovery of HTLV-I and development of reagents to perform reliable serologic testing, it was shown that both HTLV-I and ATL are endemic in areas of high HTLV-I seroprevalence (Mueller *et al*., 1996; Yamaguchi and Watanabe, 2002). Antibodies against HTLV-I have been found in over one million individuals, and more than 700 cases of ATL have been diagnosed each year in Japan alone (Yamaguchi and Watanabe, 2002).

The association between HTLV-I and ATL was proven by: (1) epidemiologic studies that demonstrated geographic correspondence of ATL and HTLV-I; (2) clonality studies of leukemic cells; (3) demonstration of *in vitro* infection of T lymphocyte by the virus; (4) oncogenic capacity of HTLV-I in animal models; (5) presence of anti-HTLV-I antibodies in 80–90% of ATL cases; (6) ability to cultivate HTLV-I from ATL cells; (7) detection of clonally integrated HTLV-I provirus in leukemic cells (Blattner, 1990).

The risk of HTLV-I-associated diseases among carriers differs substantially across geographic areas and according to other population characteristics. Despite wide geographic distribution, data concerning ATL incidence and prevalence rates are scarce and the reported rates might be an underestimation, especially for lymphomas. The rapid course of the disease, the diagnostic differentiation with similar illnesses and the difficulty of confirming the diagnosis in less developed countries suggest a higher, undetected occurrence of ATL worldwide. The cumulative incidence of ATL among HTLV-I-infected carriers is estimated at 1–5% for both sexes in endemic areas (Murphy *et al*., 1989b).

ATL occurs mostly in adults, at least 20–30 years after the onset of HTLV-I infection; individuals infected in childhood (vertical transmission) may be at higher risk for developing ATL (Pawson *et al*., 1998). Although ATL is reported to present typically among individuals in their fifth decade of life in Japan (Takatsuki *et al*., 1996), in the Jamaican and Brazilian series, patients tend to present the disease in the fourth decade, which is suggestive of other local cofactors playing a role in the disease occurrence (Gibbs *et al*., 1987; Pombo-de-Oliveira *et al*., 1998). A higher incidence of ATL in blacks has been reported in French Guiana (Gerard *et al*., 1995) and in blacks and mulatos in Bahia and Pernambuco States in Brazil (Pombo-de-Oliveira *et al*., 1998), although the latter finding is complicated by the high miscegenation of the Brazilian population.

Epidemiological risk factors for ATL were studied in the Miyazaki cohort and it was shown that an HTLV-I carrier with a high anti-HTLV-I titer and a low anti-Tax reactivity may be at greater risk of ATL (Hisada *et al*., 1998). ATL is associated with vertical infection mostly through breastfeeding (Wilks *et al*., 1996). Although HTLV-I infection through blood transfusion is considered an important risk for HAM/TSP, cases of post-transfusion ATL are exceptional (Bartholomew *et al*., 1998; Pombo-de-Oliveira *et al*., 2001). Therefore, prevention of vertical transmission could result in significant decrease in HTLV-I-associated malignancies. Several studies showed the presence of infestation by *Strongyloides stercoralis* (SS) in acute ATL or lymphoma; coinfection with SS, by inducing clonal proliferation of HTLV-I-infected lymphocytes and high proviral load, may be a cofactor in the process of HTLV-I-induced leukemogenesis (Gabet *et al*., 2000).

The pathogenesis of ATL and the determinants for disease progression are only partially described and may be related to the virus genetic variants, the host (HLA alleles, major genes) or the environment (mode, dose or age of infection) (Slattery *et al*., 1999; Plancoulaine *et al*., 2000; Yashiki *et al*., 2001; Barmak *et al*., 2003). Host genetic background including human leukocyte

antigen (HLA) genotype, and HTLV-I proviral load are thought to predict the risk of these diseases among HTLV-I carriers (Usuku *et al*., 1988; Bangham, 2003). The genetic background of HTLV-I carriers (South America native Indians and individuals living in Andes highlands and Orinoco lowlands) was investigated, and the results suggested that HLA haplotypes might be ethnically segregated and might be involved in the susceptibility to HTLV-I infection (Fujiyoshi *et al*., 1995).

High levels of HTLV-I proviral load may be associated with HTLV-I diseases; however, risk factors for high proviral load are uncertain (Takenouchi *et al*., 2003; Murphy *et al*., 2004a). Antibody response to HTLV-I may wane with older age while the amount of provirus remains stable, but mean proviral load did not differ by age and was stable within individuals over time (Yashiki *et al*., 2001). Although studies performed in Jamaica confirm that HTLV-I proviral load is strongly correlated with HTLV-I disease status, they did not corroborate a correlation between diseases and presence or absence of HLA-A 02*02 (Li *et al*., 2003).

ATL is a spectrum of diseases that is generally categorized into four forms: acute, chronic, smoldering and lymphoma-type. The acute form of ATL comprises 55–75% of all ATL (Hanchard *et al*., 1990; Yamaguchi *et al*., 1990), with chronic and cutaneous forms comprising the remaining 25%. These variant forms appear to be described more frequently in Japan, and several authors speculate that earlier recognition and diagnosis could account for these differences. Without treatment, acute ATL is invariably and rapidly fatal, with pulmonary complications, opportunistic infections and sepsis emerging as the principal cause of death. Uncontrolled hypercalcemia also contributes to fatality. HTLV-I-associated T-cell lymphoma may present in the absence of blood or bone marrow involvement in approximately 10–15% of cases of ATL.

Conventional chemotherapy, which is active against other lymphoid malignancies, is ineffective for treating aggressive forms of ATL. Therefore, treatment of ATLL has become the target of several clinical studies for the purpose of improving therapeutic outcomes. Patients with smoldering and chronic forms of ATL have a protracted course, often asymptomatic, and there is no evidence that an aggressive treatment is of any benefit (Ishikawa, 2003).

HAM/TSP: neurological manifestations of HTLV-I infection

An interesting sequence of events led to the association of HTLV-I with HAM/TSP. Clinical observation in Martinique and Jamaica revealed unusual prevalence of spastic paraplegia on neurology services. Patients were afflicted with a debilitating process characterized by a slow-onset spastic paraparesis associated with sphincter disturbance and variable degrees of proprioceptive and sensory dysfunction (Cruikshank, 1956; Rodgers, 1965).

Seroprevalence studies first in Martinique, then in Jamaica and Japan, indicated that HTLV-I antibodies were present in a very high proportion of patients with this syndrome (Rodgers, 1965; Gessain *et al*., 1985; Rodgers-Johnson *et al*., 1985; Osame *et al*., 1986a).

The disorder, subsequently designated HAM/TSP by a WHO working group, is characterized by a slowly progressive spastic paraparesis. The occasional presentation of ATL in HAM/TSP patients (and *vice versa*) was also reported (Kawai *et al*., 1989; Freitas *et al*., 1997; Goncalves *et al*., 1999; Kasahata *et al*., 2000). HTLV-I has been implicated as the cause of HAM/TSP through several lines of evidence: (1) HTLV-I has been isolated from the cerebrospinal fluid (CSF) of HAM/TSP patients (Bhagavati *et al*., 1988); (2) intrathecal synthesis of HTLV-I antibodies within the CSF can be detected in some patients (Gessain *et al*., 1988); (3) viral genome can be detected within involved tissues by polymerase chain reaction (PCR) and by *in situ* hybridization (Iannone *et al*., 1992; Lehky *et al*., 1995); and (4) HAM/TSP has been shown to develop following blood transfusion to an HTLV-I seronegative recipient from an HTLV-I-infected donor (Gout *et al*., 1990).

HAM/TSP typically develops in up to 4% of HTLV-I-infected persons, and more frequently in women than in men (Orland *et al*., 2003). Some of the youngest patients reported were still in their first decade of life (McKhann *et al*., 1989; Quintas *et al*., 2004); however, the majority of individuals are diagnosed in their fourth or fifth decade. Epidemiologic evidence suggests that sexual transmission of HTLV-I is the predominant mode of transmission leading to the later development of HAM/TSP. This contention is supported by the female predominance of HAM/TSP (Maloney *et al*., 1998) and by sexual activity at an earlier age and in higher frequency in HAM/TSP patients compared to matched HTLV-I carriers without HAM/TSP (Kramer *et al*., 1995). Rare cases, often with a short incubation period, have been reported after HTLV-I infection by blood transfusion (Osame *et al*., 1986a; Gout *et al*., 1990).

HAM/TSP is characterized pathologically by parenchymal infiltration of mononuclear cells into the gray and white matter of the thoracic spinal cord, resulting in severe white matter degeneration and fibrosis (Iwasaki, 1990). It is thought to be caused by an immunological response to HTLV-I infection in a subset of those chronically infected with the retrovirus. A number of studies suggest that HTLV-I-specific immune responses play a critical role in the pathogenesis of HAM/TSP (Sonoda, 1990; Jeffery *et al*., 1999). Influence of MHC class I/II alleles on immune response and the possibility of a HLA profile that could be protective or conversely, enhance HTLV-I-associated diseases risk has been evaluated in some studies (Sonoda, 1990; Nakane *et al*., 2000; Yashiki *et al*., 2001). Additionally, a study examining fresh, uncultured peripheral blood mononuclear cells for the presence of HTLV-I *tax*/*rex* mRNA by *in situ* hybridization in HAM/TSP patients and their spouses revealed higher numbers of HTLV-I mRNA-positive cells in the female spouses of male HAM/TSP patients (Beilke *et al*., 1991). The risk of developing

HAM/TSP is at least in part related to HTLV-I proviral load (Takenouchi *et al*., 2003).

Treatment of HAM/TSP has included corticosteroids, other immunosuppressive medications, trials of high-dose vitamin C and interferons, and supportive care with antispasmodics and physical therapy. However, none of these treatments is satisfactory, and clinical trials of new approaches are needed.

Uveitis, arthritis and other autoimmune diseases

Beyond the confirmed associations between HTLV-I and ATL and HAM/TSP, a spectrum of HTLV-I-associated rheumatologic conditions have been described in which viral genome and/or viral proteins were detected in target tissues. These include uveitis, polymyositis, bronchioalveolar pneumonitis, autoimmune thyroiditis and arthritis (Ijichi *et al*., 1990; Iwakura *et al*., 1991; Eguchi *et al*., 1992, 1996; Inose *et al*., 1992; Kawai *et al*., 1992; Kimura, 1992; Mochizuki *et al*., 1992; Sowa, 1992; Pinheiro *et al*., 1995; Beilke *et al*., 1996). However, with the exception of HTLV-I-associated uveitis, epidemiologic association between HTLV-I and autoimmune diseases still needs more evidence.

In cases of HTLV-associated-uveitis (Mochizuki *et al*., 1992), HTLV viral sequences could be detected in vitreous fluid in conjunction with higher numbers of HTLV-infected T lymphocytes compared with the peripheral blood compartment (Ono A *et al*., 1998). HTLV-I seroprevalences of 35.4–44.8% were found in patients with uveitis of unknown etiology in Southwestern Japan, much higher than HTLV-I prevalence in the local population (Mochizuki *et al*., 1992). In studies of other areas lower seropositivity was found (Goto *et al*., 1994; Pinheiro *et al*., 1996; Yamamoto *et al*., 1999).

Japanese investigators first reported cases of arthritis occurring in HTLV-I-infected patients, sometimes with concurrent HAM/TSP; and an epidemiologic study in the USA has reported an excess of arthritis among HTLV-I seropositives compared to seronegative controls (Murphy *et al*., 2004b). A transgenic mice model has supported a role for HTLV-I in chronic arthritis (Yakova *et al*., 2005). Also, high proviral load is present in the peripheral blood and synovial compartments of HTLV-I-infected patients with rheumatoid arthritis (Yakova *et al*., 2005).

Concurrent autoimmune-mediated disorders, including polymyositis, Grave's disease, arthritis and HAM/TSP, have been described in several case series. Indeed, HTLV-I has been associated with conjunctivitis sicca syndrome and has also been detected in biopsies from polymyositis, in bronchoalveolar fluids from alveolitis and in synovial fluids from arthritis cases. In most of these reports, HTLV-I-proviral sequences can be readily detected while viral antigen expression is low or absent in areas with extensive lymphocytic infiltration. Existing evidence suggests that restricted viral gene expression by antigen-presenting cells in the affected tissues triggers an vigorous CD4+ and CD8+ immune response directed towards HTLV-Tax or some other gene product (McCallum *et al*., 1997; Sugaya *et al*., 2002).

Infectious diseases

Several opportunistic infections have been documented to occur in cases of acute ATL. These include *Pneumocystis carinii* infection, pulmonary aspergillosis, cytomegalovirus (CMV) pneumonitis, disseminated herpes zoster, *Crypococcus neoformans*, *Mycobacterium avium-intracellulare*, and hyperinfection syndrome with *Strongyloides stercoralis* (Takatsuki *et al*., 1985a, b). Some HTLV-I-infected carriers without ATL also appear to have immune deficiency associated with an increased risk for certain infectious disease complications, including strongyloidiasis (Marsh, 1996; Hayashi *et al*., 1997; Satoh *et al*., 2002). HTLV-I-infected individuals in areas of high endemicity for *S. stercoralis* should probably undergo examination for stool ova and parasites, although there is no formal recommendation in this regard. Other infections associated with HTLV-I (single case reports) include Norwegian scabies, disseminated molluscum contagiosum, and extrapulmonary histoplasmosis (Marsh, 1996). Finally, staphylococcal and streptococcal skin infections are common in the infective dermatitis syndrome (La Grenade, 1996) described in Jamaica in association with HTLV-I infection in childhood. This syndrome was the first pediatric manifestation associated with HTLV-I (LaGrenade *et al*., 1990). Socioeconomic or genetic factors may contribute to the development of infective dermatitis, since the disease has not been reported in HTLV-I epidemic Japan.

Prevention: individual and public health interventions

The impact of HTLV-I-associated diseases on the individual and his/her community is often devastating. No preventive vaccine exists; and the prognosis of ATL and HAM/TSP is poor, in terms of both survival and quality of life. For HAM/TSP, a long lasting, progressive disease, the financial cost for the individual, his/her family and the health system may be immense. In this sense, public health interventions such as counseling and education of high-risk individuals and populations are of paramount importance.

Screening of blood donor candidates has been shown to be an effective strategy in preventing HTLV-I transmission. Many countries in endemic areas have implemented systematic and permanent screening of all blood donors. For nonendemic areas, reports showed that the risk of HTLV-I infection might be enhanced in some selected donor population, recommending the implementation of policies for selective donor recruitment (Price *et al*., 2001). However, given the high cost of imported test kits, more cost-effective strategies for blood donation screening need to be designed and evaluated for developing countries. Blood transfusion still represents a risk of HTLV-I infection for recipients in most African countries, as well as for other less developed areas that

lack appropriate public policies and infrastructure of transfusion services (Mbanya *et al*., 2003).

Preventing mother to child transmission would probably have the most significant impact on the occurrence of HTLV-I-associated diseases. Prenatal screening for HTLV-I should be implemented in specific geographical areas, combined with counseling of seropositive mothers regarding transmission through breastfeeding (Hino *et al*., 1997). However, in many HTLV-I endemic areas the interruption of breastfeeding could have individual and public health impact, such as malnutrition and increased infant mortality. Public health policies should consider this adverse effect in less developed countries and recommend alternative feeding formula for children in risk of HTLV-I infection through mother's milk (Manns and Blattner, 1991; Passos, 1998; Poiesz *et al*., 2003). Recommendations to prevent sexually transmitted infections should be emphasized, including condom use, avoiding multiple and unknown sexual partners and paying or receiving money for sex. Finally, counseling and education of IDU to implement harm reduction practices may be effective in preventing HTLV-I infection in this population group.

Finally, psychosocial problems such as depression, increased anxiety, difficulty in establishing or maintaining relationships, fear or guilt about pregnancy may well be the most common adverse effects associated with HTLV-I infection (Guiltinan *et al*., 1998; DeVita *et al*., 2003). Access to adequate counseling and correct information about HTLV is of fundamental importance for HTLV-I seropositive individuals (Passos, 1998).

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