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HUMAN T-CELL LYMPHOTROPIC VIRUS-I IN LATIN AMERICA

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EPIDEMIOLOGY

The first human retrovirus, human T-cell lymphotropic virus type I (HTLV-I), was simultaneously discovered in the United States and Japan in 1980 and associated with adult T-cell leukemia/lymphoma (ATLL) patients.[101, 102, 192, 249] Promptly thereafter, seroepidemiologic studies revealed a high HTLV-I seropositive rate (>10%) among healthy adults in southwestern Japan (mainly in Okinawa and Kyushu Island)[28, 131] and moderate rates in the Caribbean, West Africa, and recently in Colombia, Brazil, Peru, Papua New Guinea and Australia.[35, 51, 54, 55, 83, 86, 89, 106, 174, 196, 215, 251]

HTLV-I Transmission

The transmission of HTLV-I involves several cells but mainly CD4 lymphocytes.[5] Although transmission occurs in a manner similar to that described for HIV, there are important differences because of the requirement of infected lymphocytes as the basic underlying mechanism.[7, 149, 160]

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Vertical Transmission

Intrauterine transmission is very rare. Available information suggests that infection occurs through perinatal exposure and breast-feeding, especially when prolonged.[7, 99, 100, 170, 172]

In a retrospective study of 120 HTLV-I–infected Peruvian women and their offspring, infection was not detected in eight newborns that were not breast-fed but was documented in 5 of 36 (13.9%) of those who received maternal milk for less than 6 months, and in 23 of 76 (30.6%) of those breast-fed for more than 6 months ($P<0.05$) (E. Gotuzzo, unpublished data). In Colombia, one of the authors (C. Arango) and his coworkers have found similar rates of vertical transmission. Further evidence of the importance of breast-feeding is provided by studies in hyperendemic areas of Japan, where HTLV-I seropositive pregnant women abstained from breast-feeding, and as a result there was a marked decrease in the number of new infections among their children.[128]

Parenteral Transmission

HTLV-I is transmitted less effectively than HIV in whole blood transfusions, a situation whereby the latter virus infects more than 99% of the recipients. It is calculated that one unit of whole blood serologically positive for HTLV-I can infect 50% to 60% of recipients. The efficacy of transmission is decreased when blood is kept stored for more than 1 week. Transfusion of cryoprecipitate and fresh frozen plasma has not been associated with HTLV-I transmission.[21, 140, 180, 213]

Needle sharing by intravenous drug users (IVDUs) has been shown to be the most common route of HIV transmission in the United States, Italy, Spain, Brazil, and Argentina.[181] HTLV-I can also be transmitted by this route, but the efficacy of transmission is very low. In fact, HTLV-II is currently more prevalent among IVDUs of these countries than HTLV-I.[31, 91, 122, 141, 152, 200]

HTLV-I seropositivity in blood banks of France, the United Kingdom, and the United States has been low, in the range of 0.005% to 0.0046%. In Latin America, studies have shown varied rates of seropositivity. For example, in Buenos Aires, Argentina, 4 of 12,846 donors were confirmed positive (0.032%)[95]; however, eight additional donors were positive by enzyme-linked immunosorbent assay (ELISA) but indeterminate by Western blot (WB). With the recent diagnostic technology advances, these donors would probably have been defined as positive, increasing the seropositivity rate to 0.2%. In Sao Paulo, from a total of 17,063 donors, 0.15% were HTLV-I positive[65]; in Bello Horizonte, of 51,135 blood donors, 689 (1.35%) were repeatedly reactive.[186] The overall seropositivity in all of Brazil in 1995 was around 1%.[72] In Trinidad and Tobago, the overall infection rate in blood donors was 1.6%, but in multiply transfused patients, the rate was as high as 3.7%.[48] In Paraguay, the detected infection rate was 1.1% (7 of 621) in blood donors.[32]

Epidemiologic studies conducted among the general population in Caribbean countries have shown that the prevalence of HTLV-I seropositivity (1) significantly increases with age; (2) is higher in females, specifically in low socioeconomic strata; and (3) correlates with a history of blood transfusion.[164] Other studies performed in Brazil, Chile, Colombia, and Peru[8, 38, 83] on the epidemiology of patients with tropical spastic paraparesis (TSP) have shown that a history of blood transfusion was an important risk factor for infection, ranging from 15% to 40%. In 1997, Fuentes conducted a survey of the National Program of Blood Banks in Peru (PRONAHEBAS). The results indicated that of 142,583 donors tested at 164 different blood banks, 2068 were HTLV-I positive (1.45%) at initial screening, and 1861 (1.2%) were confirmed positive on retesting.[66]

A national survey of HTLV-I seropositivity associated with myelopathy (HAM) in Japan revealed that 20% (26/129) of positive cases had a history of blood transfusion compared with only 3% (41/1290) in a healthy control group (OR=7.7, $P<0.001$). In the subsequent 2 years, screening blood for HTLV-I and discarding of blood from positive donors resulted in a 16% decrease in the number of reported cases of TSP/HAM.[184]

In spite of the above information, recent publications about prevention of bloodborne diseases (such as the article by Schmunis and other communications published in the Pan American Health Organization (PAHO) bulletin that underscore the impact of blood quality in the prevention of HIV, hepatitis, Chagas disease, and other bloodborne infections transmitted through blood transfusion in Latin America)[217] fail to comment about HTLV-I screening as carried out in Europe and the United States. In these countries, the ELISA test is performed in all donors because the procedure is cost-effective. In Latin America and the Caribbean, it is reasonable to conclude that it is especially important to screen for HTLV-I because of the available information and because of the high prevalence of infection among African Americans (3% to 10%), Japanese descendants (4% to 15%),[82, 232] and other ethnic groups (2% to 5%)[256] as well as in blood donors (0.5% to 2.0%) coming from countries with high prevalence and living in the region.[32, 72, 197]

HTLV-I as a Sexually Transmitted Disease (STD)

HTLV-I has been detected in the semen and cervical secretions of infected persons. Sexual intercourse is recognized as an important factor for HTLV-I transmission.[162] Population studies in Japan suggest that male-to-female sexual transmission is more efficient than female-to-male. In one of these studies, after 10 years, 60% of women were infected when a man was the index case; however, only 0.1% to 1.0% of the men were infected when the index case was a woman.[227] In Miyasaki, Japan, the risk factor for transmission within serologically discordant couples included older infected husbands, high antibody titers, and the presence of antitax antibodies.[224] In one family study in Peru, 45% to 55% of stable sexual partners of index cases positive for HTLV-I were infected, but in

women the rate was 60% to 75% when the initial positive index case was the husband ($P<0.001$) (E. Gotuzzo, unpublished data), supporting the concept of high efficacy of male-to-female transmission. In Latin America, there are important gender differences in sexual practices and seroprevalence of STDs that could partially explain these findings.[210]

HTLV-I infection has been frequently recognized in female sex workers (FSW) in the United States.[123] In Peruvian cities, prevalences are as high as 25% in Callao, 13.4% in Cuzco, 4.2% in Iquitos, and 7% in Lima. In all these studies, a critical risk factor was the time working as an FSW (in cases with more than 6 years, 16% were seropositive).[81, 238, 256] In these studies, a positive syphilis serology was a frequently associated risk factor for HTLV-I infection. Other risk factors were a history of any STD ($P<0.001$) in Cusco and infection with *Chlamydia trachomatis* in Lima (OR = 4.5; 95% CI, 1.5–13.4). Other studies have also suggested the association of HLTV-I with syphilis, herpes simplex virus type 2 (HSV-2), and genital ulcers in the Dominican Republic and Colombia. Transmission of HTLV-I was also described in homosexual men in Trinidad, Brazil, and Peru.[20, 34, 45] In studies conducted in Peru in HIV patients, the number of sexual partners was an important associated risk factor.[84, 189]

The use of condoms is accepted as a factor reducing HIV infection in FSWs.[138, 177, 211] The same finding was reported for HTLV-I transmission in two Peruvian studies involving the same risk factor population.[81, 231] In Lima, when condoms were used by more than 50% of the partners of FSWs for more than 3 years, their seropositivity odds ratio was 0.34 (95% CI, 0.13–0.89), in comparison with FSWs that did not use condoms.[81] In another study of clandestine FSW in Lima, when condoms were used by all of the partners, the infection rate of HTLV-I was only 1.7%, but when they did not use condoms or used them only occasionally, the infection rate rose to 10.3% (OR = 0.15; 95% CI, 0.03–0.86).[231]

There is no doubt that HTLV-I is an STD in Latin America. The virus is found in semen and cervical secretions and is more effectively transmitted from males to females than from females to males. Seropositivity is more frequently observed in groups of high sexual risk such as FSWs and promiscuous men who have sex with men (MSM). It is associated with the number of sexual partners, time in prostitution activities, other STDs, and markers of promiscuity, and most importantly, sexual transmission can be significantly reduced by the consistent use of condoms.

DISTRIBUTION OF HTLV-I AND II IN LATIN AMERICAN ETHNIC GROUPS

Evolution of Language and Its Relationship with HTLV-I and II

Genetic evolution is the result of three main forces: mutation, selective pressure, and random genetic drift. The last mentioned refers to

fluctuations of the frequencies of an allele between successive generations. Smaller populations will have relatively high fluctuation of gene frequencies between generations compared with large populations, which can cause an allele to become fixed (frequency = 199%) or extinct (frequency = 0%) in a shorter period of time. Fission refers to excision of a proportion of the population without further contact with the parental individuals. Phylogenetic analysis is usually carried out in genes. Languages and genes are subjected to some common evolutionary forces. With some limitations, the concepts and techniques of phylogenetic analysis can also be applied to languages.[44, 42] A linguistic family is composed of a group of languages with enough similarities to suggest a common phylogenetic origin. There is a remarkable correspondence between genetic clusters and linguistic families.[44, 42] From a linguistic point of view, the pre-Hispanic inhabitants of America can be classified into three families: Amerindians (oldest), Na-Dene, and Eskimo-Aleutian (most recent). The Amerindian family can be subdivided into six subfamilies or primary branches: Northern, Central, Chibchan-Paezian, Andean, Equatorial-Tucanoan, and Ge-pano-Carib.[42, 44, 207]

HTLV-I: Phylogenetic Studies and Relationship with Humans

After HTLV-I and II diverged, an Indonesian simian T-lymphotropic type I strain (STLV-I) and an Australo-Melanesian HTLV-I topotype sequentially appeared. Based on 7 estimated mutation rate of 0.4 to 2.5 $\times$ 10 substitutions per site, per year, this event occurred 140,000 to 850,000 years ago. This would have occurred before or soon after *Homo sapiens* was present on earth. Later, a group called cosmopolitan topotype evolved. This included Zairean and Afro-Indoamerasian geographic phenotypes.[245]

Epidemiology in Pre-Hispanic Inhabitants

HTLV-I has been found in members of at least two of the three families who populated pre-Hispanic America. Some reports indicate that a small proportion of Inuit, who are Eskimos from Alaska and Greenland, are HTLV-I seropositive. HTLV-I has been described in individuals from Nuu-Chaa-Nulth groups, who are northern Amerindians from British Columbia.[52] HTLV-I has also been found in members of the Paez, Embera, Chachi, and Inga tribes from Colombia.[9] The first three belong to the Chibchan-Paezian subfamily.[42, 44, 207] HTLV-I has been reported in Mapuches and Huiliches in Chile and other members of the Andean subfamily.[39] It has also been described in Quechuas from Cuzco[256] and Ayacucho.[5] Its presence has also been noted among Sanapaná from Paraguay and Tobas from Argentina.[24, 29, 33] These two tribes belong to the Ge-Pano-Carib subfamily. We have found HTLV-I seroprev-

alence of 1% and 0.8% among Emberá and Paez tribes. Seroprevalence increased with age in both groups, starting at the second decade. Seroprevalence was higher among females than males.[9] This is consistent with cumulative lifetime infection and supports observations that sexual transmission is more efficient from male to female.[162, 164]

HTLV-II infection has been demonstrated among several pre-Hispanic tribes, including the following: Navajo Indians, who belong to the Na-Dene family; the Northern branch of the Amerindians, represented by individuals from the Pueblo (Suny) and Seminole (Muskogee) tribes[96]; tribes of the Chibchan-Pezian subfamily, including Guaymi from Panama[236] and Tunebo, and Emberá from Colombia[58]; the Andean subfamily, including members of the Inga tribe from Colombia[52, 250] and Mapuche, Huliches, and Alcalufe from Chile[39]; the Guahibo and Wayu tribes from Colombia[67] as well as Piaroa, Arara do Laranjal, and Muduruku from Brazil of the Equatorial-Tucanoan branch[146]; Ge-Pano-Carib subfamily Indians, represented by Cayapo and Kraho from Brazil[109, 146] and Toba, Mataco, and Pilaga from Argentina[24, 29]; Tume Indians from Venezuela and Yaganes from Chile[59]; and we have found a HTLV-II prevalence of 0.8% among the Emberá tribe in Colombia. There was no significant difference in prevalence by gender. A lifetime increase by age after the third decade was significant. Female preponderance has been reported in one study of Cayapo Indians in Brazil.[146] An age-related increase in seroprevalence rate has also been described among Cayapo and Guaymi Indians.[15, 146] HTLV-I and II coinfection has been reported in different individuals of the following groups: Central African Pygmies from Zaire and Cameroon in Africa,[89] Nuu-Chah-Nult in British Columbia in North America, Emberá and Inga in Colombia, and Tobas in Argentina.[52]

Relationship Between Linguistic Evolution and the Presence of HTLV-I and II

Except for one tribe (Navajo), HTLV-II has been described only and in almost all subfamilies of Amerindian speakers. The genetic variability in America, particularly in South America, is the greatest in the world. This would be consistent with the hypothesis of frequent and sequential population fissions and isolation of small groups. This phenomenon probably occurred in the plains of the South American subcontinent and not in the Andes. Under these circumstances, a strong influence of drift leads to high genetic variability.[42, 44, 207] Isolation and endogamy, practiced by some Amerindian tribes,[42, 44, 108, 207] may also have favored persistence of HTLV-II among them, if the virus was present in their ancestors. The Navajo tribe comes from South Na-Dene speakers. They and the Almosan (Northern Amerindian subfamily), represented, among others, by the Pueblo tribe, are derived from a common linguistic branch. Navajo ancestors probably represent fission from the Northern Na-Dene speakers that occurred more than 1 millennium ago. They likely admixed with neighboring Northern Amerindians, including Almosan.[42, 44, 207] This

could explain the presence of this virus among individuals of the only non-Amerindian tribe, if present originally only in Paleo-Indians, the Amerindian ancestors.

The linguistic branch that gave origin to Almosan and South Na-Dene is also phylogenetically related from a linguistic point of view to the one that originated Ge speakers[42, 207] This could explain the presence of HTLV-II type A among Pueblo, Navajo, and Ge speakers.[103, 104] The latter are represented by Cayapo and Kraho tribes in Brazil.[42, 207]

In summary, HTLV-II has been reported from Pygmies in Africa, Mongolians,[87] and Amerindians. Their common origin, according to a phylogenetic tree, goes back to the initial stock of *Homo sapiens.*[42] It appears that this virus became incorporated into humankind before it diverged into different racial groups. A finding of microgeographic and macrogeographic clustering, as indicated by the absence of the virus in villages and regions adjacent to others with significant seroprevalent rates would establish a parallel between the forces that lead to fixation or extinction of certain genetic elements and these retroviruses. HTLV-I and II would share similar cofactors for transmission. The weight of each one could be different in each one of them.

It is possible that the conditions that lead to perpetuation of HTLV-I and HTLV-II differ in some ways. In the Andes, population density rose to levels higher than the rest of the subcontinent, where fission of small groups at short time intervals probably occurred.[42, 207] HTLV-I is prevalent in the Andes but not HTLV-II. These less stringent conditions would favor persistence of the more worldwide-distributed HTLV-I but not HTLV-II. The higher prevalence of HTLV-I among females may represent not only a predominant unidirectional route of transmission but also a larger reservoir for mother-to-child transmission. We found HTLV-I–positive individuals in both Paeces who live in the Andean highlands and Emberá who live in the lowlands. A report published in Argentina about HTLV-I showed various strains different from the African strains[243]; the strains are more related to other South American[153, 154] countries and Canada[190] with similar anthropological background.

A geographic independence in the distribution of HTLV-I and HTLV-II has been described.[115, 255] Population migration habits rather than altitude may explain these differences.

Afro–Latin American Population

In South America, where there is a strong presence of African Americans in some places, such as Tumaco (Pacific Coast, Colombia), Bahia (Brazil), and Chincha (Peru), the prevalence of HTLV-I ranges from 2% to 5% among healthy adult populations.[8] (C. Sánchez Palacios, personal communication, 1998).

Two hypotheses have been advanced to explain the dissemination of HTLV-I subtype a (HTLV-Ia) in the New World. The first is related to an ancient introduction by Mongoloid migration over the Bering Strait[77]

or a post-Colombian introduction initially from Africa, through the slave trade.[43] Blank in Colombia and Veronesi in Brazil estimated that HTLV-I could be post-Colombian. Recently, Van Dooren[235] reported on the phylogenetic analysis of the *LTR*[223] and *env* sequence of 13 HTLV isolates from four different ethnic Peruvian groups. The results supported the idea of multiple post-Colombian introduction of the African HTLV-Ia strain into the black Latin American population; probably, it spread to Andean groups when living together as occurred in Cuzco during the early seventeenth century.[229]

Japanese Descendants

A serologic survey among Japanese migrants in Bolivia showed that 17% of the older migrants were positive for HTLV-I, especially for adults who came from Okinawa; and 4% to 7% of the next generation were positive.[232] In Peru, a survey of 407 healthy volunteers with Japanese ancestors showed that HTLV-I infection rates were 15.8% for those born in Japan, 4% for the first generation born in Peru, and 0% for the second generation ($P = 0.00001$). Infection rates were higher among males than females (6.8% versus 3.2%), and the frequency was related to the origin of their ancestors (more frequent in Okinawa descendants).[82] Similar observations were reported by Blattner in Hawaii, where the HTLV-I infection rates declined substantially among new generations of Japanese.[27, 230] In the Van Dooren phylogenetic study, the Japanese infection was related to different strains and was not the cause of dissemination of HTLV-I in Latin America[235] as proposed by other investigators.

HTLV-I–ASSOCIATED DISEASES

As documented for all retroviruses, the cell infection is permanent and all patients are carriers and potential sources of infection. Several disease syndromes are associated with HTLV-I, and each syndrome may occur in 1% to 5% of the infected cases. The most common are TSP[118] and ATLL; however, these have been recognized in association with other medical problems such as *Strongyloides stercoralis* infection, Norway scabies, and uveitis.

Tropical Spastic Paraparesis

For many years, neurologists from tropical regions had described cases of a chronic progressive paraparesis of unknown cause. In 1969, Mani et al,[147] recognizing the clinical and histopathologic similarities among these patients, coined the general term *tropical spastic paraparesis* to denominate these syndromes. The precise cause of these myelopathies remained obscure until 1985, when Gessain and coworkers found that

most TSP patients from Martinique had antibodies to HTLV-I in their sera.[75] These initial findings were soon confirmed by Rodgers-Johnson, who detected HTLV-I antibodies in serum and cerebrospinal fluid (CSF) of TSP patients from Jamaica and Colombia.[202] Months later, Osame et al described the same association in patients from Kagoshima in southern Japan.[183] Because these Japanese patients came from a nontropical region, the term TSP seemed inappropriate, and the authors proposed the new designation, *HTLV-I–associated myelopathy.* Soon it became clear that the diseases were the same,[204] and in 1989, a consensus conference sponsored by the World Health Organization suggested the hybrid designation *HTLV-I–associated myelopathy/tropical spastic paraparesis* (HAM/TSP).[241]

HAM/TSP is a disease predominantly found in southern Japan, the Caribbean, and South America. The prevalence of HAM/TSP coincides with the prevalence of HTLV-I in the general population; however, in Papua New Guinea, in spite of an extremely high prevalence of HTLV-I infection among certain groups, there are no reported cases of either ATLL or HAM/TSP.[244] This may be because of a high level of divergence of the prevalent Melanesian strain of the virus.[79]

The first description in Latin America of what was later called HAM/TSP was that of Zaninovic et al, who described spastic paraparesis of unknown cause among patients in Tumaco, Colombia.[253] Four years later, these patients were found to be infected with HTLV-I.[202] Since then, many reports of cases of HAM/TSP from Latin American countries have appeared in the literature. Most of these cases come from Brazil,[10, 13, 41, 57, 70, 142, 150] Colombia,[8, 49, 252, 254] Chile,[37, 38] and Peru.[83, 114] Patients have also been described in Panama,[90] Ecuador,[94] Argentina,[2, 80, 151] the Dominican Republic,[130] Paraguay,[209] Cuba,[62] and Caribbean countries.[20]

HAM/TSP is a myelopathy characterized anatomicopathologically by a chronic, progressive, low-grade inflammatory process heralded by parenchymal infiltration of memory CD4 cells. The inflammation involves both the gray and white matter of the spinal cord and progresses for more than 3 years after the onset of neurologic symptoms, resulting in preferential degeneration of the white matter. In patients with an evolution of more than 9 years, however, the spinal cord lesions appear degenerative rather than inflammatory. Both the inflammation and the white matter degeneration are most conspicuous in the lower thoracic cord. The lateral funiculus is always and most severely affected. Although the parenchymal tissue degeneration is not confined to any particular long tract, symmetric degeneration of the lateral pyramidal tract is evident in all cases. The involvement of the posterior and anterior funiculi is variable, and neurons are relatively well preserved.[110]

The pathogenesis of HAM/TSP is still a matter of debate in the literature. Whereas only a small proportion of HTLV-I–infected individuals develop HAM/TSP (1% to 4%), the mechanisms responsible for the progression of an HTLV-I carrier state to clinical disease are not clear. No specific sequence differences have been found between HTLV-I recovered from HAM patients, patients with ATLL, and HTLV-I–infected carriers. According to Osame's hypothesis, the supply of infected CD4

cells via the blood to the CNS is essential for the development of CNS lesions. Both anatomically determined hemodynamic conditions and adhesion molecule–mediated interactions might contribute to the localization of the lesions. Following an induction of the HTLV-I antigens on the surface of infected T cells in the CNS compartment, expansion of the responses of immunocompetent T cells against the viral protein may result in CNS tissue damage, which may be mediated by released cytokines such as tumor necrosis factor α (TNF-α). CTL-induced apoptosis of T lymphocytes may be one of the possible mechanisms of eliminating HTLV-I–infected cells from the CNS lesions in HAM/TSP. Protection from apoptosis by expression of bcl-2 oncoprotein may explain the long-standing inflammatory process in the CNS of HAM/TSP.[182]

Izumo et al performed a detailed neuropathologic analysis of seven Japanese autopsy patients with HAM/TSP. Inflammatory infiltrates of mononuclear cells and degeneration of myelin and axons were noted in the middle to lower thoracic spinal cords and were continuously extended to the entire spinal cord. Horizontal distribution of inflammatory lesions was symmetric at any spinal level. Immunohistochemical analysis demonstrated T-cell dominance. The numbers of CD4 cells and CD8 cells were equally present in patients with a shorter clinical course. Apoptosis of helper/inducer T cells was observed in the presence of TIA1+ cytotoxic T cells in these active inflammatory lesions. Inflammatory infiltrates were markedly decreased, and CD8+/TIA1− T cells were predominant over CD4 cells in patients with a prolonged clinical course. HTLV-I proviral DNA amounts in the freshly frozen spinal cord measured by quantitative polymerase chain reaction (PCR) were well correlated with the numbers of infiltrated CD4 cells. In situ PCR of HTLV-I proviral DNA demonstrated the presence of HTLV-I–infected cells exclusively in the mononuclear infiltrates of perivascular areas. These findings suggest that the target of the inflammatory process seen in HAM/TSP lesions may be HTLV-I–infected CD4 cells infiltrating the spinal cord.[112]

The diagnosis of HAM/TSP is based on clinical and laboratory data. In summary, the patient should present unequivocal signs and symptoms of a myelopathy along with clear evidences of HTLV-I infection.[11] To try to overcome diagnostic difficulties for epidemiologic studies, Osame et al[184] suggested the following classification:

- Definite HAM
  Slowly progressive paraparesis caused by a symmetrical myelopathy that affects mainly the pyramidal tracts. Antibodies to HTLV-I in serum and CSF.
- Probable HAM
  Slowly progressive paraparesis due to a symmetric myelopathy that affects mainly the pyramidal tracts in a patient with antibodies to HTLV either in serum or in CSF (not in both). Atypical myelopathy in a patient with antibodies to HTLV in both serum and CSF.

The widely accepted diagnostic guidelines for HAM/TSP are summarized in Table 1. According to these guidelines, "the florid clinical picture of chronic spastic paraparesis is not always seen on the patient's first visit. A single symptom or physical sign may be the only evidence of early HAM/TSP."[241]

Besides typical HAM/TSP, other neurologic manifestations, such as polymyositis,[71, 156] motor neuron disease,[2, 97, 136, 221] peripheral neuropathies,[1, 23, 173, 208] encephalomyelitis,[125, 226] spinocerebellar degeneration,[126]

Table 1. GUIDELINES FOR THE DIAGNOSIS OF HAM/TSP

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Modified from WHO Guidelines in HTLV-I Diagnosis.

pandysautonomia or autonomic failure,[6, 248] and hypertrophic pachymeningitis,[121] have been described in association with HTLV-I. These associations suggest that the neurologic spectrum of HTLV-I–induced disease is larger than previously thought.

The risk for development of HAM/TSP among HTLV-I carriers is also a matter of debate in the literature. It has been estimated to vary from 0.25% among Japanese patients[118] to 2.4% among HTLV-I–infected blood donors from the United States.[163] This risk can be higher, as suggested by an ongoing study of blood donors from Brazil, where 5% had HAM/TSP (Ana C. Leite, MD, personal communication, 1999).

Kramer et al sought to quantify the risk of HAM/TSP associated with HTLV-I infection and cofactors associated with this disease among infected individuals in Jamaica. One cofactor associated with the risk of HAM/TSP was young age at initial heterosexual intercourse. Among individuals who reported early age at initial sexual intercourse, an increased risk of HAM/TSP was also associated with having recorded more than five lifetime sexual partners. Neither an early age at initial sexual intercourse nor the number of lifetime sexual partners was a risk factor for ATLL. These data seem to support the notion that HAM/TSP is associated with sexually acquired HTLV-I infection, whereas ATLL is not.[133]

Patients with HAM/TSP have higher antibody titers and virus load compared with asymptomatic HTLV-I carriers.[76, 127] This information has led to the hypothesis that HLA alleles control HTLV-I provirus load and influence susceptibility to HAM/TSP. In fact, it has been recently shown that after infection with HTLV-I, the class I allele HLA-A*02 halves the odds of HAM/TSP, preventing 28% of potential cases of HAM/TSP. HLA-A*02(+) healthy HTLV-I carriers have a proviral load that is one third that of HLA-A*02(−) HTLV-I carriers. An association of HLA-DRB1*0101 with disease susceptibility was also identified, which doubled the odds of HAM/TSP in the absence of the protective effect of HLA-A*02.[113]

HTLV-I leads to systemic manifestations in which the neurologic involvement is only one part. HAM/TSP can be associated with other HTLV-I–related manifestations such as pulmonary alveolitis,[225] uveitis,[171] arthritis,[128] dermatitis,[12, 139] Sjögren syndrome,[148, 168] Behçet's disease,[116] thyroid disease,[119, 155] crusted scabies,[22] cystitis, and prostatitis.[179] In some instances many of these systemic diseases can be observed at the same time.[69] The occurrence of ATLL and HAM/TSP in the same patient is rare.[68, 105, 117, 161, 195, 228, 234, 247]

A variety of systemic laboratory abnormalities can be found in patients with HAM/TSP. These typically include the presence of flower cells in blood smears, hypergammaglobulinemia, increased proportion of CD4 cells, positive VDRL and Lyme serologies, and the presence of autoantibodies such as the rheumatoid factor.[206]

The most common findings in the CSF of HAM/TSP patients are a moderate pleocytosis and elevated protein content.[158, 222] In addition,

oligoclonal IgG bands,[4] increased levels of some cytokines, such as neopterin, TNF-α, interleukin (IL)-6, and interferon (IFN) γ,[135, 169, 178] and increased intrathecal antibody synthesis specific for both HTLV-I core and envelope antigens[129] have also been described. Apparently, the CSF profile changes with time. Although CSF inflammatory alterations can persist over a 10-year period, they tend to become slight or even absent after the second year of the evolution of the disease.[157]

Magnetic resonance (MR) imaging is the study of choice for noninvasive spinal cord and brain evaluation of HAM/TSP patients. Cerebral white matter lesions and spinal cord atrophy have been consistently observed in patients with HAM/TSP,[3] but the exact frequency and clinical relevance of these findings remain to be elucidated. In a recent published series, cerebral white matter lesions occurred in 52% of the patients, and spinal cord atrophy in 74%. There was no significant correlation between these abnormalities and the clinical features studied. These findings suggest that MR imaging is useful for detection of cerebral and spinal cord abnormalities in these patients. The absence of correlation between cerebral white matter lesions and either patient age or risk factors for cardiovascular disease strengthens a possible association between the leukoencephalopathy and neural infection.[64]

Castillo et al examined 22 HAM/TSP patients from Chile and found abnormalities in the somatosensory evoked potentials (SSEPs) in 19 (86.3%), reflecting the involvement of the posterior columns of the spinal cord. Visual evoked potentials (VEPs) and brain stem auditory evoked potentials (BAEPs) were normal in 18 patients. Peripheral nerve conduction was normal in all but one, who showed discrete slowness of the motor conduction velocity in the peroneal nerves. Electromyography was normal in 15 cases in which it was performed.[40] More recently, Moritoyo et al examined lower limb somatosensory evoked potentials (LSEPs) in 96 Japanese HAM/TSP patients. Central sensory conduction time (CSCT) was abnormal in 42 cases. A highly significant correlation was found between CSCT and disability score. Such a correlation was not found between CSCT and other clinical findings, onset of illness, illness duration, and serum and CSF antibody titers to HTLV-I and vibratory sensation. There was no difference in the mean CSCT between the cases with sensory impairment and those without it. Cases with delayed CSCT and normal sensation suggest that LSEPs can be capable of detecting subclinical lesions of the spinal cord in HTLV-I–infected individuals.[159] LSEPs can also be useful in estimating the disability of HAM/TSP patients.

Urodynamic studies and urologic evaluation reveals that both irritative and obstructive symptoms coexisted in HAM/TSP patients. A clear cause of urinary frequency is detrusor hyperreflexia at the filling phase, which is found in more than half of the patients; however, decreased effective bladder capacity resulting from a large amount of residual urine is another possible cause. Detrusor sphincter dyssynergia is the main cause of difficulty of urination, but in some cases, underactive

detrusor activity at voiding is also a factor. Hydronephrosis is observed infrequently. Urinary infection is common, reported in about 35% of patients at first visit.[107]

Differential Diagnosis

The diagnosis of HAM/TSP is based on a compatible clinical presentation of progressive myelopathy, plus the following: a CSF with signs of low-grade inflammation and a characteristic immunoglobulin profile MR image showing spinal cord atrophy or diffuse T2-bright abnormalities, presence of Western blot–confirmed HTLV-I–specific antibodies in the serum and CSF, and exclusion of other causes of progressive myelopathy including compression, B_{12} deficiency, HIV infection, multiple sclerosis, Lyme disease, and genetic myelopathies. Living in an endemic area, transfusion exposure, intravenous drug use, sexual promiscuity, and having other HTLV-I systemic manifestations strengthen the diagnosis.

Treatment Alternatives

Several treatment approaches have been tried for HAM/TSP, but most did not include a proper placebo-controlled, double-blind design. Recently, Nakagawa et al reported the results of therapeutic trials of 200 patients with HAM/TSP from Kagoshima, Japan. Motor disability was improved by more than one grade in 69.5% (91/131) of patients receiving oral prednisolone, 50% (3/6) of those receiving eperisone hydrochloride only, 43.8% (7/16) of those subjected to blood purification—lymphocytapheresis and plasmapheresis—methods, 40.0% (2/5) of those receiving intrathecal injection of hydrocortisone, 30.0% (3/10) of those receiving intravenous injection of high-dose methylprednisolone, 23.3% (10/43) of those receiving α-interferon (αIFN) (intramuscular injection and inhalation), 22.2% (2/9) of those receiving azathioprine, 20.0% (4/20) of those receiving high-dose vitamin C, 16.0% (4/25) of those receiving erythromycin, 12.5% (3/24) of those receiving salazosulfapyridine, 11.8% (2/17) of those receiving mizoribine, 7.1% (1/14) of those receiving fosfomycin, and 6.3% (1/16) of those receiving thyrotropin-releasing hormone. Although the results were a synopsis of different treatments given as an open trial, they considered that immunomodulatory therapies had some beneficial effects for HAM/TSP and that the pharmacologic effects of these agents were related to the improvement of the disease.[167]

To date, the only double-blind, placebo-controlled treatment study in HAM/TSP is the one by Izumo and colleagues, who used αIFN.[111] They concluded that HAM patients may be safely treated with αIFN at daily parenteral doses of 3 million units for 4 weeks. In another study of αIFN in HAM/TSP, the absolute number of peripheral blood lymphocytes harboring the HTLV-I genome decreased significantly during the therapy period (28.6 +/− 16.6% reduction). The autoproliferation of

CD4+ T clone cells from a single cell culture was markedly depressed even after the cessation of αIFN in the responders who completed long-term therapy. In addition, the CD8+DR+ T cells in the peripheral blood and soluble IL-2 receptor levels in the sera increased significantly during the treatment. These results suggest that the reduction of HTLV-I proviral DNA load and immunomodulation by long-term IFN-α therapy contributed to the clinical benefits.[242]

Disease Progression

HAM/TSP is considered a disease with a slow onset and chronic and steady progression.[205] This rule, however, has occasional exceptions, with patients showing either rapid deterioration[124] or spontaneous improvement.[137] Kuroda et al tried to depict factors of relevance to rapid clinical deterioration in HAM/TSP. Only patients who were young at the onset of disease experienced rapid clinical deterioration. Among laboratory parameters, depressed skin reactions to dinitrochlorobenzene and PPD (tuberculin test), depressed lymphoproliferative responses, and increased CSF levels of IgG were associated with rapid clinical deterioration.[134]

Recently, Araujo et al evaluated the progression profile of the neurologic disability of HAM/TSP in a series of 43 patients who had never received any previous immune therapy. The study suggested that the evolution of the neurologic disability in HAM/TSP occurs mainly during the first year of the disease and becomes relatively stable thereafter. They speculated that the variable therapeutic success rates observed in the literature could result from the timing in the beginning of the pharmacologic immunosuppression. It is also speculated that the therapeutic window in HAM/TSP lies within the first year of the disease.[14]

In a study by Nakagawa et al, patients with onset after the age of 15 years and no history of blood transfusion before the onset of the disease showed a shorter interval between the time of disease onset and that of inability to walk. Patients with onset before age 15 and without history of blood transfusion had slower progression of the disease. The interval time and the progression of the disease in patients with history of blood transfusion before onset of disease were in between those of the previous two groups. Patients whose age of onset was greater than 61 years experienced a faster progression than did those with earlier onset, regardless of the mode of HTLV-I transmission. Patients with low anti–HTLV-I antibody titers in the CSF had an older age of onset on average, milder clinical symptoms, and lesser increase of neopterin in the CSF than those in the high-titer subgroup, regardless of the mode of HTLV-I transmission. The clinical course of HAM/TSP may consist of an initial progressive phase, followed by a chronic phase. Some patients show acute/subacute onset and rapid progression.[166]

Adult T-Cell Leukemia/Lymphoma

In the 1970s, an epidemic of ATLL was detected in Japan. In 1980, two groups isolated the oncogenic virus HTLV-I.[102, 192] The typical de-

scription of the clinical pattern involves prolonged fever, lymphadenopathy, hepatosplenomegaly, bone lesions with hypercalcemia, skin lesions, and a rapidly fatal course with poor response to chemotherapy.[233] Early epidemiologic studies and the analysis of HTLV-I provirus integrated into neoplastic cell DNA demonstrated the association between ATLL and HTLV-I[145, 219, 249] and established the relation between HTLV-I and ATLL.[199] This is the description of the most common, acute leukemia form; however, the chronic type and smoldering types are also described with slower courses, more lymphomalike characteristics, and more extensive skin involvement.

In contrast with HAM/TSP, this disease occurs in older patients. The group more frequently affected is 50 to 60 years of age, with males predominating over females.[120, 246] In Japan, where HTLV-I is hyperendemic, studies have suggested a lifetime risk for ATLL of 2% to 4%. In Jamaica, Murphy estimated that lifetime risk of ATLL could be 4.0% for those infected before age 20.[164] In other Caribbean countries, HTLV-I has also been associated with ATLL.[26] Newly diagnosed ATLL cases are estimated at 500 per year in Japan, whereas in the United States and Europe, only a few cases are seen.

In Latin America, this association between HTLV-I and ATLL was recognized by Pombo in Brazil,[193] Blank in Colombia,[25] and in Argentina. At the National Institute of Cancer in Lima, Peru, 300 new cases of non-Hodgkin's lymphoma are detected each year, and at least 30 (10%) of these 300 new cases are associated with HTLV-I. The disease is usually seen in adults older than 50 years.[203] In Jamaica, 55% of non-Hodgkin's lymphoma have HTLV-I infection versus 5.4% in the general population. Surprisingly, HTLV-I infection acquired through blood transfusion has not been associated with the development of ATLL, but this may reflect short follow-up periods rather than nonassociation.

Strongyloides stercoralis Infection

Strongyloides stercoralis is a soil-transmitted intestinal nematode that has been estimated to infect at least 60 million people worldwide. The uncomplicated intestinal form of the disease produces nonspecific abdominal symptoms with or without mild sporadic diarrhea; however, an autoinfective cycle may develop in a proportion of untreated cases. The autoinfective cycle usually results in low-grade, chronic infection in immunocompetent hosts.[73, 74, 92, 93]

In contrast to autoinfection, *S. stercoralis* may produce a life-threatening disseminated infection in immunocompromised hosts who are incapable of mounting an appropriate immune response against the parasite.[175, 218] An association of disseminated *S. stercoralis* infection with malignant tumors, severe malnutrition, acquired immunodeficiency syndrome (AIDS), corticosteroid therapy and renal transplantation has been well documented.[46, 63, 144, 194, 198]

The results of previous studies carried out mostly in Japan and

Jamaica showed a significant association between HTLV-I infection and *S. stercoralis* infection.[165, 201] None of these earlier studies contain sufficient clinical data to determine whether the high rate of parasite carriage had any influence on the clinical manifestations of HTLV-I–infected individuals; however, an association between disseminated *S. stercoralis* infection syndrome and concomitant HTLV-I infection has been suggested by several isolated case reports.[56, 176, 188]

In recent publications, our group has described that 85.7% (18 of 21) of our patients with *S. stercoralis* hyperinfection have HTLV-I in the absence of other immunosuppressive diseases such as AIDS and cancer. The difference is statistically significant in comparison with a carefully matched control group (4.7%, 1/21) and a group with intestinal strongyloidiasis (10%, 6 of 62) ($P<0.001$).[85] On the basis of these findings, we now recommend testing for HTLV-I infection in apparently immunocompetent patients who present with the syndrome of *S. stercoralis* hyperinfection.

There is report of a diminution of the therapeutic efficacy of thiabendazole among patients in Okinawa with concomitant *S. stercoralis*–HTLV-I infection.[214] Recently, Terashima (submitted for publication) showed that the failure of the standard treatment against intestinal strongyloides with thiabendazole or ivermectin is an important marker for HTLV-I infection. The above information suggests the usefulness of the performance of HTLV-I serology in patients failing standard therapy for *S. stercoralis* infection.

Norwegian Scabies

A rare clinical pattern of crusted scabies with generalized itching was observed among patients with various immunosuppressive diseases, Down syndrome, cancer, AIDS, and those undergoing chemotherapy.[61, 187] Because of the massive numbers of mites present and delay in making an appropriate diagnosis, the disease has been nosocomially transmitted to healthy health care workers.[220]

The association of Norwegian scabies with HTLV-I has been well documented.[48, 53, 60] A selective immunosuppression against *Sarcoptes scabiei* has been described in patients with HTLV-I, ATLL, and TSP, and in asymptomatic seropositive patients in different locations. At Cayetano Heredia Hospital, in Lima, Peru, we have studied 10 patients with Norwegian scabies. Six had coinfection of HTLV-I (two had TSP).

Coinfection with HIV

Dual infection with HIV and HTLV-I was observed in Trinidad,[18] Brazil,[45] Peru,[189] and the United States.[191] In 552 Peruvian HIV-infected patients in 1989, 18.6% of the males and 5.3% of the females were HTLV-I coinfected. Coinfected males reported a significantly higher number of

new different sexual partners during the month prior to serum sample collection than those infected only with HIV ($P = 0.002$). The effect of HTLV-I in the evolution of HIV infection is still largely unknown; two recent studies have suggested that patients with dual infections have a higher risk of developing AIDS.[18, 31] In a prospective study of HIV-positive male IVDUs, those patients infected with both viruses were three times more likely to die from AIDS during the follow-up than those infected with HIV-I alone.[185] In a Peruvian study conducted by the author (E. Gotuzzo), the mortality was 63.3% (38/60) in patients with HIV and 80% (12/1) in dually infected patients. Of 50 patients who died without receiving any antiretroviral treatment, the natural history of the disease produced a survival time of only 5.02 ± 3.27 months in patients with dual infection, shorter than that of patients with HIV alone (10.07 ± 4.42 months).[84] In IVDUs with HIV infection, the cofactor of HTLV-I/II infection may adversely affect the clinical outcome of HIV infection. Similar data have been obtained in MSMs in Trinidad[18]; however, they are in conflict with Schatcher in Brazil, who has presented information in which dual HIV–HTLV-I infection was not associated with worse prognosis or deeper immunodepression in comparison with HIV infection alone.[191]

Recently in Bahia, Brazil, patients with tuberculosis and HTLV-I exhibited a worse clinical course and carried a poorer prognosis than tuberculosis patients without HTLV-I coinfection. Other diseases that are probably associated with HTLV-I include arthritis, Sjögren syndrome, polymyositis, and uveitis with or without thyroiditis.

HTLV-I is endemic in several Latin American countries and is becoming an emerging disease. Breast-feeding is an important risk factor for neonatal acquisition of HTLV-I. In the region, HTLV-I infection is considered a preventable STD. Unique and disseminated ethnic groups, mainly Quechua origin, African–Latin Americans, and Japanese descendants are more commonly infected. HAM/TSP, ATLL, and *Strongyloides stercoralis* hyperinfection are enhanced by concomitant HTLV-I infection. We recommend HTLV-I blood screening for blood donors in the region and family studies when one HTLV-I index case is detected.

References

1. Akamatsu MM, Mitsui Y, Kihara M, et al: A case of polyneuropathy with B-CLL and HTLV-I associated myelopathy (HAM). Rinsho Shinkeigaku 37:701, 1997
2. Alarcón TA, Hidalgo C, Santibañez R, et al: Paraparesia espástica tropical en el Ecuador: Comunicación preliminar. Revista Ecuatoriano de Neurologia 1:54, 1992
3. Alcindor F, Valderrama R, Canavaggio M, et al: Imaging of human T-lymphotropic virus type I-associated chronic progressive myeloneuropathies. Neuroradiology 35:69, 1992
4. Ali A, Rudge P, Dalgleish AG: Neopterin concentrations in serum and cerebrospinal fluid in HTLV-I infected individuals. J Neurol 239:270, 1992
5. Anderson S, Bankier AT, Barrell B, et al: Sequence organisation of the human mitochondrial genome. Nature 290:457–465, 1981
6. Ando Y, Ando E, Vchino M, et al: HTLV-I associated pandysautonomia with adrenal dysfunction [letter]. Muscle Nerve 18:928, 1995

7. Ando Y, Nakano S, Saito K, et al: Transmission of adult T-cell leukemia retrovirus (HTLV-I) from mother to child: Comparison of bottle-fed with breast-fed babies. Jpn J Cancer Res 78:322–324, 1987
8. Arango C, Concha M, Zaninovic V, et al: Epidemiology of tropical spastic paraparesis in Colombia and associated HTLV-I infections. Ann Neurol 238:161–165, 1988
9. Arango C, Maloney E, Bernal E, et al: HTLV-I and HTLV-II coexist among the Embers and Inga Amerindians of Colombia. J Acquir Immune Defic Syndr Hum Retrovirol 20:102–103, 1999
10. Araujo AQC, Afonso CR, Schor D, et al: Spastic paraparesis of obscure origin. A case-control study of HTLV-I positive and negative patients from Rio de Janeiro, Brazil. J Neurol Sci 116:165, 1993
11. Araujo AQC, Alfonso CR, Schor D, et al: Clinical and demographic features of HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) in Rio de Janeiro, Brazil. Acta Neurol Scand 88:59, 1993
12. Araujo AQC, Andrada-Serpa MJ, Paulo-Filho TA, et al: Folliculitis decalvans and human T cell lymphotropic virus type I-associated myelopathy/tropical spastic paraparesis. Clin Infect Dis 20:696, 1995
13. Araujo AQC, de Andrada-Serpa MJ: Tropical spastic paraparesis/HTLV-I–associated myelopathy in Brazil. J Acquir Immune Defic Syndr Hum Retrovirol 13:S33, 1996
14. Araujo AQC, Leite AC, Dultra SV, et al: Progression of neurological disability in HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP). J Neurol Sci 129:147, 1995
15. Armien B, Maloney B, Castillo L, et al: Sexual risk factors associated with HTLV-II seropositivity among Guaymi Indians, Panama [abstract]. Presented at the Eighth International Conference of Human Retrovirology: HTLV. Rio de Janeiro, Brazil, June 9–13, 1997
16. Barnard M, McKeganey N, Leyland A: Risk behaviours among male clients of female prostitutes. Br Med J 307(7):359–361, 1993
17. Barreto P: El origen de los negros en Colombia. *In* Zaninovic V, Galindo, Blank A: HTLV-I. Edited Fundación MXXX, Cali 1992
18. Bartholomew C, Blattner W, Cleghorn F: Progression to AIDS in homosexual men co-infected with HIV and HTLV-I in Trinidad. Lancet 2:1469, 1987
19. Bartholomew C, Cleghorn F, Charles W, et al: HTLV-I and tropical spastic paraparesis. Lancet 2:99–100, 1986
20. Bartholomew C, Saxinger C, Clark JW, et al: Transmission of HTLV-I and HIV among homosexual men in Trinidad. JAMA 257:2604–2608, 1987
21. Bazarbachi A, Huang M, Gessain A, et al: Human T-cell-leukemia virus type I in post-transfusional spastic paraparesis: Complete proviral sequence from uncultured blood cells. Int J Cancer 63:494–499, 1995
22. Bergman JN, Dodd WA, Trotter MJ, et al: Crusted scabies in association with human T-cell lymphotropic virus 1. J Cutan Med Surg 3:148, 1999
23. Bhigjee AI, Bill PL, Wiley CA, et al: Peripheral nerve lesions in HTLV-I associated myelopathy (HAM/TSP). Muscle Nerve 16:21, 1993
24. Biglione M, Vidan O, Colombo M, et al: Seroepidemiological studies and molecular characterization of HTLV-II subtype b in isolated groups of Toba and Mataco Amerindians in North Argentina [abstract]. J Acquir Immune Defic Syndr Hum Retrovirol 10:186, 1995
25. Blank A, Zaninovic V: Leucemia/Linfoma de Células T del Adulto. Hospital Universitario del Valle, Cali, Colombia. Rev VIS 18:85–90, 1990
26. Blattner WA, Kaynaraman VS, Robert-Guroff M, et al: The human type-C retrovirus HTLV in blacks from the Caribbean region and relationship in adult T-cells leukemia/lymphoma. Int J Cancer 30:257–264, 1982
27. Blattner WA, Nomura A, Clark JW, et al: Modes of transmission and evidence for viral latency from studies of human T-cell lymphotropic virus type I in Japanese migrant populations in Hawaii. Proc Natl Acad Sci U S A 83:4895–4898, 1986
28. Blattner WA: Epidemiology of HTLV-I and associated diseases. *In* Blattner WA (ed): Human Retrovirology: HTLV. New York, Raven Press, 1990,
29. Bouzas MB, Zapiola I, Quiruelas S, et al: HTLV Type I and HTLV Type II infection

among Indians and Natives from Argentina. AIDS Res Hum Retroviruses 10:1567–1571, 1994
30. Britten RJ: Rates of DNA sequence evolution differ between taxonomic groups. Science 231:1393–1398, 1986
31. Brown L, Lee S, Cerney H, et al: HTLV-I and HIV-1 infection in intravenous drug abusers (IVDAs). *In* Program and abstracts of the IV International Conference on AIDS. Stockholm, Sweden, June 12–16, 1988
32. Cabral MB, Vera ME, Bouzas B, et al: Riesgo de adquirir HTLV-I/II en la transfusión de hemoderivados. IV Congreso Paraguayo de Medicina Interna. Nov, 1997
33. Cabral MB, Vera ME, Samudio M, et al: HTLV-I/II antibodies among three different Indian groups from Paraguay [abstract]. J Acquir Immune Defic Syndr Hum Retrovirol 10:199, 1995
34. Cáceres C, Gotuzzo E, Wignall S, et al: Comportamiento sexual y seroprevalencia del Virus de la Inmunodeficiencia Humana tipo I en varones homosexuales peruanos. Boletin de la Oficina Panamericana de la Salud 111(3):218–230, 1991
35. Caribbean Epidemiology Center: Public health implications of HTLV-I in the Caribbean. Wkly Epidemiol Rec 65:63–65, 1990
36. Cartier L, Araya F, Castillo JL, et al: HTLV-I retrovirus in Chile: Study on 140 neurological patients. Rev Med Chil 118:622, 1990
37. Cartier L, Mora C, Araya F, et al: HTLV-I positive spastic paraparesis in a temperate zone. Lancet 1:556, 1989
38. Cartier L, Araya F, Castillo JL, et al: Progressive spastic paraparesis associated with human T-cell leukemia virus type I (HTLV-I). Intern Med 31:1257–1261, 1992
39. Cartier L, Cartier E: HTLV-I/II in Chile. *In* Zaninovic V (ed): HTLV, Truths and Questions. Cali, Colombia, Fundación MAR, 1996, pp 150–158
40. Castillo JL, Cartier L, Araya F, et al: Evoked potential abnormalities in progressive spastic paraparesis associated to HTLV-1. Acta Neurol Scand 83:151, 1991
41. Castro LH, Chaves CJ, Callegaro D, et al: HTLV-I associated myelopathy in Brazil: A preliminary report. Arq Neuropsiquiatr 47:501, 1989
42. Cavalli-Sforza LL, Menozzi P, Piazza A: The history and geography of human genes. Princeton, NJ, Princeton University Press, 1994, pp 340–342
43. Chandler A: Negro slavery in Colombia. Cali, Colombia, International Center for Medical Research and Training. Progress Report, 1969
44. Concepts, data and methods. Princeton, NJ, Princeton University Press, 1994, pp 1–59
45. Cortes E, Deterls R, Aboulafia D, et al: HIV-1, HIV-2 and HTLV-I infection in high risk groups in Brazil. N Engl J Med 320:953–958, 1989
46. Cruz T, Reboucas G, Rocha H: Fatal strongyloidiasis in patients receiving corticosteroids. N Engl J Med 275:1093–1096, 1966
47. Dailey H, Charles W, Landeau P, et al: HTLV-I in multiply transfused patients in Trinidad and Tobago, West Indies. Vox Sang 64:189–190, 1993
48. Daisley H, Charles W, Suite M: Crusted (Norwegian) scabies as a prediagnostic indicator for HTLV-I infection. Trans R Soc Trop Med Hyg 87:295, 1993
49. Dangond F, Daza JS, Rosania A, et al: Tropical spastic paraparesis on the Caribbean coast of Colombia. Am J Trop Med Hyg 52:155, 1995
50. De Thé G, Bomford R: An HTLV-I vaccine: Why, how, for whom? AIDS Res Hum Retroviruses 9:381–386, 1993
51. De Thé JG, Gessain A, Gazzolo L, et al: Comparative seroepidemiology of HTLV-I and HTLV-II in the French West Indies and some African countries. Cancer Res 45(suppl):4633s–4636s, 1985
52. Debakan GA, Ward R, Waters, et al: Low level endemic infection of HTLV-I and HTLV-II in an Amerindian tribe of Vancouver Island, British Columbia, Canada [abstract]. J Acquir Immune Defic Syndr Hum Retrovirol 10(2):216, 1995
53. Del Guidice P: HTLV-I and scabies [letter]. J Am Acad Dermatol 36:134–135, 1997
54. Delaponte E, Peters M, Durand JP, et al: Seroepidemiological survey of HTLV-I infection among randomized populations of Western Central African countries. Journal of AIDS 2:410–413, 1989
55. Delaponte E, Monplaisir N, Louwagie J, et al: Prevalence of HTLV-I and HTLV-II

infection in Gabon, Africa: Comparison of the serological and PCR results. Int J Cancer 49:373–376, 1991
56. Dixon AC, Yanagihara ET, Kwock DW, et al: Strongyloidiasis associated with human T-cell lymphotropic virus type I infection in a nonendemic area. West J Med 151:411–413, 1989
57. Domingues RB, Muniz MR, Pinho JR, et al: Human T lymphotropic virus type I–associated myelopathy/tropical spastic paraparesis in Sao Paulo, Brazil. Clin Infect Dis 20:1540, 1995
58. Duenas-Barajas E, Bernal J, Vaught D, et al: Human retroviruses in Amerindians of Colombia: High prevalence of human T-cell lymphotropic virus type II infection among the Tunebo Indians. Am J Trop Med Hyg 49:657–663, 1993
59. Echevarria de Pérez G, León Ponte M, Noya O, et al: First description of endemic HTLV-II infection among Venezuelan Amerindians. J Acquir Immune Defic Syndr Hum Retrovirol 6:1368–1371, 1993
60. Egawa K, Johno M, Hayashibara T, et al: Familial occurrence of crusted (Norwegian) scabies with adult T-cell leukaemia. Br J Dermatol 127:57–59, 1992
61. Espy PD, Jolly HW Jr: Norwegian scabies. Arch Dermatol 112:193–196, 1976
62. Estrada RA, Luis S, Mustelier R, et al: Absence of human retroviral antibodies in epidemic neuropathy in Cuba: Report of the first two cases of HTLV-I-associated tropical spastic paraparesis observed in Cuba. La Habana s.n.: 2p., 1995
63. Fagundes LA, Busato O, Brentano L: Strongyloidiasis: A fatal complication of renal transplantation. Lancet ii:439–440, 1971
64. Ferraz AC, Gabbai AA, Abdala N, et al: Magnetic resonance in HTLV-I associated myelopathy, leukoencephalopathy and spinal cord atrophy. Arq Neuropsiquiatr 55:728, 1997
65. Ferreira OC Jr, Vaz RS, Valvalho MB, et al: HTLV-I and type II infections and correlation with risk factors vs blood donors from Sao Paulo. Revista Transfusion 35:258–263, 1995
66. Fuentes J, Roca O: Seroprevalencia de enfermedades transmisibles en los Bancos de Sangre del Perú. XII Congreso LA de Patologia Clinica, Abstract 87, Lima, Peru, Noviembre, 1998
67. Fujiyama C, Fujiyoshi T, Miura, et al: A new endemic focus of HTLV-II carriers among Orinoco natives in Colombia. J Infect Dis 168:1075–1077, 1993
68. Furukawa Y, Okadome T, Tara M, et al: Human T-cell lymphotropic virus type-I (HTLV-I)-associated myelopathy/tropical spastic paraparesis with acute type of adult T-cell leukemia. Intern Med 34:1130, 1995
69. Furuya T, Nakamura T, Goto H, et al: HTLV-I-associated myelopathy associated with multi-organ inflammatory disease: A case report. J Neurol Sci 157:109, 1998
70. Gabbai AA, Bordin JO, Vieira-Filho JP, et al: Selectivity of human T lymphotropic virus type-1 (HTLV-1) and HTLV-2 infection among different populations in Brazil. Am J Trop Med Hyg 49:664, 1993
71. Gabbai AA, Wiley CA, Oliveira AS, et al: Skeletal muscle involvement in tropical spastic paraparesis/HTLV-1-associated myelopathy. Muscle Nerve 17:923, 1994
72. Galvao B, Proietti F, Rodrigues L, et al: HTLV-I/II differential geographic distribution in Brazil. *In* 10th International Conference on AIDS. Yokohama Japan, p 304
73. Genta RM, Schad GA, Hellman ME: *Strongyloides stercoralis:* parasitological, immunological and pathological observations in immunosuppressed dogs. Trans R Soc Trop Med Hyg 80:34–41, 1986
74. Genta RM: Strongyloidiasis. Baillieres Clin Trop Med Commun Dis 2:645–665, 1987
75. Gessain A, Barin F, Vernant JC, et al: Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. Lancet 2:407, 1985
76. Gessain A: Virological aspects of tropical spastic paraparesis/HTLV-I associated myelopathy and HTLV-I infection. J Neurovirol 2:299, 1996
77. Gessain A, Boeri E, Yanagihara R, et al: Complete nucleotide sequence of a highly divergent human T-cell leukemia (lymphotropic) virus type I (HTLV-I) variant from Melanesia: Genetic and phylogenetic relationship to HTLV-I strains from other geographical regions. J Virol 67:1015–1023, 1993
78. Gessain A, Mauclere P, Froment, et al: Isolation and molecular characterization of a human T-cell lymphotropic virus type II (HTLV-II) subtype B from a healthy Pygmy

living in a remote area of Cameroon: An ancient origin for HTLV-II in Africa. Proc Nat Acad Sci U S A 92:4041–4045, 1995
79. Gessian A, Yanagihara R, Franchini G, et al: Highly divergent molecular variants of human T-lymphotropic virus type I from isolated populations in Papua New Guinea and the Solomon Islands. Proc Natl Acad Sci U S A 88:7694, 1991
80. Gonzalez LA, Villa AM, Kohler G, et al: Further studies on HTLV-I associated myelopathy in Argentina. Medicina 58:411, 1998
81. Gotuzzo E, Sánchez J, Escamilla J, et al: Human T cell lymphotropic virus type I infection among female sex workers in Peru. J Infect Dis 169:754–759, 1994
82. Gotuzzo E, Yamamoto V, Kanna M, et al: Human T lymphotropic virus type I infection among Japanese immigrants in Peru. Int J Infect Dis 1:75–77, 1996
83. Gotuzzo E, De las Casas C, Deza L, et al: Tropical spastic paraparesis and HTLV-I infection: Clinical and epidemiological study in Lima, Peru. J Neurol Sci 143:114–117, 1996
84. Gotuzzo E, Escamilla J, Phillips I, et al: The impact of human T lymphotropic virus type I/II infection on the prognosis of sexually acquired cases of acquired immunodeficiency syndrome. Arch Intern Med 152:1429–1432, 1992
85. Gotuzzo E, Terashima A, Alvarez H, et al: *Strongyloides stercoralis* hyperinfection associated with human T cell lymphotropic virus type-I infection in Peru. Am J Trop Med Hyg 60(1):146–149, 1999
86. Goubau P, Desmyter J, Ghesquiere J: HTLV-II among pygmies [letter]. Nature 35:201, 1992
87. Goubau P, Liu HF, DeLange GG, et al: HTLV-II seroprevalence in pygmies across Africa since 1970. AIDS Res Hum Retroviruses 9:709–713, 1993
88. Goubau P, Van Brussel M, Vandamme AM, et al: A primate T-lymphotropic virus, PTLV-L, different from human T-lymphotropic viruses types I and II, in a wild-caught baboon (Papio hamagyas). Proc Nat Acad Sci U S A 91:2848–2852, 1994
89. Goubau P, Vandame AM, Beuselink K, et al: Proviral HTLV-I and HTLV-II in the Efe Pygmies of Northeastern Zaire. J Acquir Immune Defic Syndr Hum Retrovirol 12:208–210, 1996
90. Gracia F, Castillo LC, Larreategui M, et al: Relation between human T-lymphotropic virus type I and neurologic diseases in Panama: 1985–1990. J Acquir Immune Defic Syndr Hum Retrovirol 10:192, 1995
91. Grandilone A, Zani M, Barillari G, et al: HTLV-I and HIV infection in drug addicts in Italy. Lancet 2:753–754, 1986
92. Grove DI, Warren KD, Mahmoud AAF: Algorithms in the diagnosis and management of exotic diseases, III. Strongyloidiasis. J Infect Dis 131:755–758, 1975
93. Grove DI: Historical introduction. *In* Grove DI (ed): Strongyloidiasis: A Major Roundworm Infection of Man. London, Taylor & Francis, 1989, pp 1–11
94. Guderian R, Guevara A, Cooper P, et al: HTLV-1 infection and tropical spastic paraparesis in Esmeraldas Province of Ecuador. Trans R Soc Trop Med Hyg 88:399, 1994
95. Guifraind Z, Blejer JL, Saquier MC, et al: Seroprevalence of HTLV-I/II in blood donors in Buenos Aires, Argentina. Vox Sang 67:408–409, 1994
96. Hall WW, Ishak R, Zhu SW, et al: HTLV-II: Epidemiology, molecular properties, and clinical features of infection. J Acquir Immune Defic Syndr Hum Retrovirol 13:S204–214, 1996
97. Hanakawa T, Nakamura M, Suenaga T, et al: Response to corticosteroid therapy in a patient with HTLV-I-associated motor neuron disease. Neurology 50:1188, 1998
98. Hattori T, Koito A, Takatsuki K, et al: Frequent infection with human T-cell lymphotropic virus type I in patients with AIDS but not in carriers of human immunodeficiency virus type I. J Acquir Immune Defic Syndr Hum Retrovirol 2:272–276, 1989
99. Hino S, Yamaguchi K, Katamine S, et al: Mother to child transmission of human T-cell leukemia virus type-1. Jpn J Cancer Res 76:474–480, 1985
100. Hino S, Sugiyama H, Doi H, et al: Breaking the cycle of HTLV-I transmission via carrier mothers' milk. Lancet 2:158–159, 1987
101. Hinuma Y, Komoda H, Chosa T, et al: Antibodies to adult T-cell leukemia-virus–

associated antigen (ATLA) in sera from patients with ATL and controls in Japan: A nation-wide sero-epidemiology study in Japan. Int J Cancer 29:631–635, 1982
102. Hinuma Y, Nagata K, Hanaoka M, et al: Adult T cell leukemia antigen in an ATL cell line and detection of antibodies to the antigen in human sera. Proc Natl Acad Sci U S A 78:6476–6480, 1981
103. Hjelle B, Zhu SW, Takahashi H, et al: Endemic human T cell leukemia virus type II infection in southwestern US Indians involves two prototype variants of virus. J Infect Dis 168:737–740, 1993
104. Hjelle B, Mills R, Swenson S, et al: Incidence of hairy cell leukemia, mycosis fungoides, and chronic lymphocytic leukemia in first known HTLV-II endemic population. J Infect Dis 163:435–440, 1991
105. Honma S, Yamada K, Moriwaka F, et al: A case of HTLV-1 associated myelopathy and adult T-cell leukemia, presenting unique muscle pathology including rimmed vacuole. Rinsho Shinkeigaku 31:1129, 1991
106. Hunsnann G, Scheiner J, Wendler L, et al: HTLV positivity in Africans. Lancet 2:952–953, 1985
107. Imamura A: Studies on neurogenic bladder due to human T-lymphotropic virus type-I associated myelopathy (HAM). Nippon Hinyokika Gakkai Zasshi 85:1106, 1994
108. Instituto Colombiano de antropologia. Introducción a la Colombia Amerindian 1987
109. Ishak R, Harrington WJ, Azevedo VN, et al: Identification of human T-cell lymphotropic virus type IIa infection in the Kayapo, an indigenous population of Brazil. AIDS Res Hum Retroviruses 7:813–821, 1995
110. Iwasaki Y: Human T cell leukemia virus type I infection and chronic myelopathy. Brain Pathol 3:1, 1993
111. Izumo S, Goto I, Itoyama Y, et al: Interferon-alpha is effective in HTLV-I-associated myelopathy: A multicenter, randomized, double-blind, controlled trial. Neurology 46:1016, 1996
112. Izumo S, Umehara F, Kashio N, et al: Neuropathology of HTLV-1-associated myelopathy (HAM/TSP). Leukemia 11(suppl 3):82, 1997
113. Jeffery KJ, Usuku K, Hall SE, et al: HLA alleles determine human T-lymphotropic virus-I (HTLV-I) proviral load and the risk of HTLV-I-associated myelopathy. Proc Natl Acad Sci U S A 96:3848, 1999
114. Johnson RT, Griffin DE, Arregui A, et al: Spastic paraparesis and HTLV-I infection in Peru. Ann Neurol 23:S151, 1988
115. Kalyanaraman VS, Sarngadharan MG, Robert-Guroff M, et al: A new subtype of human T-cell leukemia virus (HTLV-II), associated with a T-cell variant of hairy cell leukemia. Science 218:571–573, 1982
116. Kanazawa H, Ijichi S, Eiraku N, et al: Behçet's disease and Sjögren syndrome in a patient with HTLV-I-associated myelopathy [letter]. J Neurol Sci 119:121, 1993
117. Kanno M, Nakamura S, Matsuda T: Adult T-cell leukemia with HTLV-I-associated myelopathy after complete remission of acute myelogenous leukemia [letter]. N Engl J Med 338:333, 1998
118. Kaplan JE, Osame M, Kubota H, et al: The risk of development of HTLV-I associated myelopathy/tropical spastic paraparesis among persons infected with HTLV-I. AIDS 3:1096–1101, 1990
119. Kawai H, Kashiwagi S, Inui T, et al: HTLV-I-associated myelopathy (HAM/TSP) with Hashimoto's thyroiditis. Tokushima J Exp Med 38:99, 1991
120. Kawano F, Yamaguchi K, Nishimura H, et al: Variate in the clinical cases of adult T-cell leukemia. Cancer 55:851–856, 1985
121. Kawano Y, Kira J: Chronic hypertrophic cranial pachymeningitis associated with HTLV-I infection. J Neurol Neurosurg Psychiatry 59:435, 1995
122. Keller GC, DiGiovanna TA, Lofy L, et al: HLTV-I/II infection among patients in an inner city. Emergence Department. Ann Intern Med 113:368–372, 1990
123. Khabbaz R, Darrow W, Hartley MT, et al: Seroprevalence and risk factors for HTLV-I infection among female prostitutes in the United States. JAMA 263:60–64, 1990
124. Kida H, Nakagawa M, Iwasaki H, et al: A case of rapidly progressive HTLV-I–associated myelopathy (HAM). Rinsho Shinkeigaku 37:802, 1997
125. Kira J, Fujihara K, Itoyama Y, et al: Leukoencephalopathy in HTLV-I-associated

myelopathy/tropical spastic paraparesis: MRI analysis and a two year follow-up study after corticosteroid therapy. J Neurol Sci 106:41, 1991
126. Kira J, Goto I, Otsuka M, et al: Chronic progressive spinocerebellar syndrome associated with antibodies to human T-lymphotropic virus type I: Clinico-virological and magnetic resonance imaging studies. J Neurol Sci 115:111, 1993
127. Kira J, Koyanagi Y, Yamada T, et al: Increased HTLV-I proviral DNA in HTLV-I–associated myelopathy: A quantitative polymerase chain reaction study. Ann Neurol 29:194, 1991
128. Kitajima I, Maruyama I, Maruyama Y, et al: Polyarthritis in human T lymphotropic virus type I-associated myelopathy [letter]. Arthritis Rheum 32:1342, 1989
129. Kitze B, Puccioni-Sohler M, Schaffner J, et al: Specificity of intrathecal IgG synthesis for HTLV-1 core and envelope proteins in HAM/TSP. Acta Neurol Scand 92:213, 1995
130. Koenig RE, Tolentino M, Taveras L, et al: Prevalence of HTLV infection in the Dominican Republic: Association with neurological disease. AIDS Res Hum Retroviruses 8:221, 1992
131. Kohakura M, Nakada K, Yonahara M, et al: Seroepidemiology of the human retrovirus (HTLV/ATLV) in Okinawa where adult T-cell leukemia is highly endemic. Jpn J Cancer Res 77:21–23, 1986
132. Koralnik I, Boeri E, Saxinger WC, et al: Phylogenetic associations of human and simian T-cell leukemia/lymphotropic virus type I strains: evidence for interspecies transmission. J Virol 68:2693–2707, 1994
133. Kramer A, Maloney EM, Morgan OS, et al: Risk factors and cofactors for human T-cell lymphotropic virus type I (HTLV-I)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in Jamaica. Am J Epidemiol 142:1212, 1995
134. Kuroda Y, Fujiyama F, Nagumo F: Analysis of factors of relevance to rapid clinical progression in HTLV-I-associated myelopathy. J Neurol Sci 105:61, 1991
135. Kuroda Y, Matsui M: Cerebrospinal fluid interferon-gamma is increased in HTLV-I–associated myelopathy. J Neuroimmunol 42:223, 1993
136. Kuroda Y, Sugihara H: Autopsy report of HTLV-I-associated myelopathy presenting with ALS-like manifestations. J Neurol Sci 106:199, 1991
137. Kuroda Y, Yukitake M, Kurohara K, et al: A follow-up study on spastic paraparesis in Japanese HAM/TSP. J Neurol Sci 132:174, 1995
138. Laga M, Alary M, Nzila N, et al: Condom promotion, sexually transmitted diseases treatment, and declining incidence of HIV-I infection in female Zairian sex workers. Lancet 344:246–248, 1994
139. LaGrenade L, Morgan C, Carberry C, et al: Tropical spastic paraparesis occurring in HTLV-1 associated infective dermatitis. Report of two cases. West Indian Med J 44:34, 1995
140. Larson C, Taswell H: Human T-cell leukemia virus (HTLV-I and blood transfusion. Mayo Clin Proc 63:860–875, 1988
141. Lee H, Swanson P, Shorty VS, et al: High rate of HTLV-II infection in seropositive IV drug abusers in New Orleans. Science 244:471–475, 1989
142. Lessa I, Moraes D, Moura L, et al: HTLV-1 and myelopathy in Salvador (northeastern Brazil): A case control study. Arq Neuropsiquiatr 51:447, 1993
143. Link H, Cruz M, Gessain A, et al: Chronic progressive myelopathy associated with HTLV-I: Oligoclonal IgG and anti-HTLV-I IgG antibodies in cerebrospinal fluid and serum. Neurology 39:1566, 1989
144. Maayan S, Wormser GP, Widerhorn J, et al: *Strongyloides stercoralis* hyperinfection in a patient with the acquired immune deficiency syndrome. Am J Med 83:945–948, 1987
145. Malik KTA, Even J, Karpas A: Molecular cloning and complete nucleotide sequence of an adult T cell leukemia virus/human T-cell leukemia virus type I (ATLV/HTLV-I) isolate of Caribbean origin: Relationship to the members of the ATLV/HTLV-I subgroup. J Gen Virol 69:1695–1710, 1988
146. Maloney EM, Biggar RJ, Neel JV, et al: Endemic human T-cell lymphotropic virus type II infection among isolated Brazilian Amerindians. J Infect Dis 166:100–107, 1992
147. Mani KS, Mani AJ, Montgomery RD: A spastic paraplegic syndrome in South India. J Neurol Sci 9:179, 1969

148. Matsumoto Y, Katada E, Uemura A, et al: A case of HTLV-I associated myelopathy (HAM) with Sjögren's syndrome. Nippon Naika Gakkai Zasshi 78:1352, 1989
149. McDougal JS, Mawle A, Cort SP, et al: Cellular tropism of the human retrovirus and depression of the T-4 antigen. J Immunol 135:3151–3162, 1985
150. Meireles A, Moreira Junior ED, Moreno-Carvalho OA, et al: HTLV-I associated myelopathy in Salvador (northeastern Brazil). Arq Neuropsiquiatr 50:189, 1992
151. Micheli F, Diaz S, Besasso O, et al: Mielopatia asociada al HTLV-1: Presentación de 2 casos en Argentina. Revised Neurológia Argentina 20:153, 1995
152. Mildvan D, Des Jarlais D, Sotheran J, et al: Prevalence and significance of HTLV-I in a cohort of IV drug abusers in New York. *In* Program and Abstracts of the IV International Conference on AIDS. Stockholm, Sweden, June 12–16, 1988
153. Miura T, Fukunaga T, Igarashi T, et al: Phylogenetic subtypes of human T-lymphotropic virus type I and their relations to the anthropological background. Proc Nat Acad Sci U S A 91:1124–1127, 1994
154. Miura T, Yamashita M, Zaninovic V, et al: Molecular phylogeny of human T-cell leukemia virus type I and II of Amerindians in Colombia and Chile. J Mol Evol 44:S76–S82, 1997
155. Mizokami T, Okamura K, Ikenoue H, et al: A high prevalence of human T-lymphotropic virus type I carriers in patients with antithyroid antibodies. Thyroid 4:415, 1994
156. Mora CA, Garruto RM, Brown P, et al: Seroprevalence of antibodies to HTLV-I in patients with chronic neurological disorders other than tropical spastic paraparesis. Ann Neurol 23:S192, 1988
157. Moreno-Carvalho OA, Nascimento-Carvalho CM, Galvao-Castro B: HTLV-I associated tropical spastic paraparesis. Cerebral spinal fluid evolutive aspects in 128 cases. Arq Neuropsiquiatr 53:604, 1995
158. Moreno-Carvalho OA, Santos JI, Di Credico G, et al: Evidence of preferential female prevalence of HTLV-I associated tropical spastic paraparesis in Bahia-Brazil. Arq Neuropsiquiatr 50:183, 1992
159. Moritoyo H, Arimura K, Arimura Y, et al: Study of lower limb somatosensory evoked potentials in 96 cases of HTLV-I-associated myelopathy/tropical spastic paraparesis. J Neurol Sci 138:78, 1996
160. Mueller N, Tachibana N, Stuver SO, et al: Epidemiologic perspectives of HTLV-I. *In* Blattner WA (ed): Human Retrovirology: HTLV. New York, Raven Press, 1999, pp 281–293
161. Murata M, Mizusawa H, Kanazawa I, et al: An autopsy case of HTLV-I associated myelopathy (HAM) with adult T-cell leukemia (ATL). Rinsho Shinkeigaku 30:754, 1990
162. Murphy E, Figueroa O, Gibbs W, et al: Sexual transmission of human T-lymphocyte virus type I (HTLV-I). Ann Intern Med 111:555–560, 1995
163. Murphy EL, Fridey J, Smith JW, et al: HTLV-associated myelopathy in a cohort of HTLV-I and HTLV-II-infected blood donors. The REDS investigators. Neurology 48:315, 1997
164. Murphy EL, Wilks K, Hanchard B, et al: A case-control study of risk factor for seropositivity to HTLV-I in Jamaica. Int J Epidemiol 25:1083–1089, 1996
165. Nakada K, Kohakura M, Komoda H, et al: High incidence of HTLV antibody in carriers of *Strongyloides stercoralis* [letter]. Lancet 1:633, 1984
166. Nakagawa M, Izumo S, Ijichi S, et al: HTLV-I-associated myelopathy: Analysis of 213 patients based on clinical features and laboratory findings. J Neurovirol 1:50, 1995
167. Nakagawa M, Nakahara K, Maruyama Y, et al: Therapeutic trials in 200 patients with HTLV-I-associated myelopathy/tropical spastic paraparesis. J Neurovirol 2:345, 1996
168. Nakamura H, Eguchi K, Nakamura T, et al: High prevalence of Sjögren's syndrome in patients with HTLV-I associated myelopathy. Ann Rheum Dis 56:167, 1997
169. Nakamura S, Nagano I, Yoshioka M, et al: Detection of tumor necrosis factor-alpha-positive cells in cerebrospinal fluid of patients with HTLV-I-associated myelopathy. J Neuroimmunol 42:127, 1993
170. Nakano S, Ando Y, Saito S, et al: Primary infection of Japanese infant with adult T-cell leukemia associated retrovirus (ATLV) for viral transmission from mother to children. J Infect 12:203–212, 1986

171. Nakao K, Ohba N, Matsumoto M: Noninfectious anterior uveitis in patients infected with human T-lymphotropic virus type I. Jpn J Ophthalmol 33:472, 1989
172. Narita M, Shibata M, Togashi T, et al: Vertical transmission of human T-cell leukemia virus type I [letter]. J Infect Dis 163:204, 1991
173. Nascimento OJM, Araujo AQC, Freitas MRG, et al: Peripheral nerve involvement in HTLV-I-associated myelopathy. J Acquir Immune Defic Syndr Hum Retrovirol 10:230, 1995
174. Nerurkar VR, Song KJ, Saitou B, et al: Interfamilial and intrafamilial genomic diversity and molecular phylogeny of human T-cell lymphotropic virus type I from Papua New Guinea and the Solomon Islands. Virology 196:506–513, 1993
175. Neva FA: Biology and immunology of human strongyloidiasis. J Infect Dis 153:397–406, 1986
176. Newton RC, Limpuangthip P, Greenberg S, et al: *Strongyloides stercoralis* hyperinfection in a carrier of HTLV-I virus with evidence of selective immunosuppression. Am J Med 92:202–208, 1992
177. Ngugi EN, Plummer FA, Simonsen JN, et al: Prevention of transmission of human immunodeficiency virus in Africa. Effectiveness of condom promotion and health education among prostitutes. Lancet 2:887–890, 1988
178. Nishimoto N, Yoshizaki K, Eiraku N, et al: Elevated levels of interleukin-6 in serum and cerebrospinal fluid of HTLV-I-associated myelopathy/tropical spastic paraparesis. J Neurol Sci 97:183, 1990
179. Nomata K, Nakamura T, Suzu H, et al: Novel complications with HTLV-I–associated myelopathy/tropical spastic paraparesis: Interstitial cystitis and persistent prostatitis. Jpn J Cancer Res 83:601, 1992
180. Okochi K, Sata H, Hinuma Y: A retrospective study on transmission of adult T-cell leukemia virus via blood transfusion: Seroconversion in recipients. Vox Sang 46:245–253, 1984
181. Organización Panamericana de la Salud: Vigilancia Epidemiológica del SIDA en las Américas. Informe Trimestral, Diciembre, 1994
182. Osame M, Nakagawa M, Umehara F, et al: Recent studies on the epidemiology, clinical features and pathogenic mechanisms of HTLV-I associated myelopathy (HAM/TSP) and other diseases associated to HTLV. J Neurovirol 3(suppl 1):S50, 1997
183. Osame M, Usuku K, Izumo S, et al: HTLV-I associated myelopathy, a new clinical entity. Lancet 1:1031, 1986
184. Osame M, Janssen R, Kubota H, et al: Nationwide survey of HTLV-I associated myelopathy in Japan: Association with blood transfusion. Ann Neurol 28:50–56, 1990
185. Page JB, Shengham L, Chitwood DD, et al: HTLV-I/II seropositivity and death from AIDS among HIV-1 seropositive intravenous drug users. Lancet 335:1439–1441, 1990
186. Passos VM, Calazans FF, Carneiro-Peoeitti AB: Counseling blood donors seropositive for HTLV-I and II in a developing country. Ed Saude Public Rio de Janeiro 14:417–420, 1998
187. Paterson WD, Allen BR, Beveridge GW: Norwegian scabies during immunosuppressive therapy. Br Med J 4:211–212, 1973
188. Patey O, Gessain A, Breuil J, et al: Seven years of recurrent severe strongyloidiasis in an HTLV-I infected man who developed adult T-cell leukemia. AIDS 6:575–579, 1992
189. Phillips I, Hyams KC, Yuen A, et al: HTLV-I co-infection in a HIV-I infected Peruvian population. J Acquir Immune Defic Syndr Hum Retrovirol 4:301–302, 1991
190. Picard FJ, Coulthart MB, Oger J, et al: Human T-lymphotropic virus type I in coastal natives of British Columbia: Phylogenetic affinities and possible origins. J Virol 69:7248–7256, 1995
191. Pierik LT, Murphy EL: The Clinical Significance of HTLV-I and HTLV-II Infection in the AIDS Epidemic. *In* Volberding P, Jacobson MA (eds): AIDS Clinical Review 1991. New York, Marcel Dekker, 1991, pp 41–57
192. Poiesz BJ, Ruscetti WF, Gadzar AF, et al: Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T cell lymphoma. Proc Natl Acad Sci U S A 77:7415–7419, 1990
193. Pombo de Oiveira MS, Matutes E, Famadas LC, et al: Adult T-cell leukemia/lymphoma in Brazil and its relation to HTLV-I. Lancet 336:987–990, 1990

194. Purtilo DT, Wayne MM, Connor DH: Fatal strongyloidiasis in immunosuppressed patients. Am J Med 56:488–493, 1974
195. Rajamani K, Rugman FP, Savant CS, et al: HTLV 1 associated myelopathy and adult T cell leukaemia-lymphoma in the same patient: Report of a case [letter]. J Neurol Neurosurg Psychiatry 59:560, 1995
196. Reidel DA, Evans AS, Saxinger C, et al: A historical study of human T lymphotropic virus type I transmission in Barbados. J Infect Dis 159:603–609, 1989
197. Remondegui C: Screening of blood donors in Jujuy, Argentina. Presented at the 8th International Conference of Human Retrovirology: HTLV. Rio de Janeiro, 1997
198. Rivera E, Maldonado N, Garcia EV, et al: Hyperinfection syndrome with *Strongyloides stercoralis*. Ann Intern Med 72:199, 1979
199. Robert-Guroff M, Gallo RC: Establishment of an etiologic relationship between the human T-cell leukemia/lymphoma virus (HTLV) and adult T-cell leukemia. Blut 47:1–12, 1983
200. Robert-Guroff M, Wiess SH, Gironja, et al: Prevalence of antibodies to HTLV-I, II, III, IV intravenous drug abusers from an AIDS endemic region. JAMA 255:3133–3137, 1986
201. Robinson RD, Lindo JF, Neva FA, et al: Immunoepidemiologic studies of *Strongyloides stercoralis* and human T lymphotropic virus type I infections in Jamaica. J Infect Dis 169:692–696, 1994
202. Rodgers-Johnson P, Gajdusek DC, Morgan OS, et al: HTLV-I and HTLV-III antibodies and tropical spastic paraparesis [letter]. Lancet 2:1247, 1985
203. Rodriguez W, Misad O, Garcia Madrid J, et al: Sindrome Leucemia: Linfomas a células T del adulto (ATL) en el Peru. Acta Cancerologia Peru 3:7–19, 1994
204. Roman G, Osame M: Identity of HTLV-I associated tropical spastic paraparesis and HTLV-I associated myelopathy. Lancet 1:651, 1988
205. Roman GC, Roman LN: Tropical spastic paraparesis. A clinical study of 50 patients from Tumaco (Colombia) and review of the worldwide features of the syndrome. J Neurol Sci 87:121, 1988
206. Roman GC, Vernant J-C, Osame M, et al: HTLV-I and the nervous system: Proceedings of an international meeting organized by the Departments of Neurology of Texas Tech University and La Meynard Hospital, held in Fort-de-France, Martinique, French Antilles, April 15–16, 1988. New York, Alan R Liss, 1989, p xliii
207. Ruhlen M: A Guide to the World's Languages, vol 1: Classification of the World Languages. Stanford, CA, Stanford University Press, 1987, pp 290–378
208. Said G, Goulon-Goeau C, Lacroix C, et al: Inflammatory lesions of peripheral nerve in a patient with human T-lymphotropic virus type I-associated myelopathy. Ann Neurol 24:275, 1988
209. Salazar-Grueso EF, Holzer TJ, Gutierrez RA, et al: Familial spastic paraparesis syndrome associated with HTLV-I infection. N Engl J Med 323:732, 1990
210. Sánchez J, Gotuzzo E, Escamilla J, et al: Gender differences in sexual practices and seroprevalence of sexually transmitted infections. Am J Public Health 856:1098–1107, 1996
211. Sanchez J, Gotuzzo E, Escamilla J, et al: Sexually transmitted infections in female sex workers. Sex Transm Dis 25(2):82–89, 1998
212. Santos I, Dos Santos IB, Dos Santos P, et al: Sarna crostosa em paciente portador do retrovirus HTLV-I. Analos Brasileiros de Dermatologie 70:49–51, 1995
213. Sato H, Okochi K: Transmission of human T-cell leukemia virus (HTLV-I) by blood transfusion: Demonstration of proviral DNA in recipients' blood lymphocytes. Int J Cancer 37:395–400, 1986
214. Sato Y, Shiroma Y, Kiyuna S, et al: Reduced efficacy of chemotherapy might accumulate concurrent HTLV-I infection among strongyloidiasis patients in Okinawa, Japan. Trans R Soc Trop Med Hyg 88:59, 1994
215. Sazinger W, Blattner WA, Levine P, et al: Human T-cell leukemia virus (HTLV-I) antibodies in Africa. Science 225:1473–1476, 1984
216. Schechter M, Harrison LH, Neal AH, et al: Coinfection with human T-cell lymphotropic virus type I and HIV in Brazil. JAMA 271(5):353, 1994

217. Schmunis G, Zicker F, Pinhar F, et al: Risk for transfusions-transmitted infections diseases in Central and South America. Emerg Infect Dis 4(1):5–11, 1998
218. Scowden EB, Schaffner W, Stone WJ: Overwhelming strongyloidiasis: An unappreciated opportunistic infection. Medicine (Baltimore) 57:527–544, 1978
219. Seiki M, Hattori S, Hirayama Y, et al: Human adult T-cell leukemia virus: Completed nucleotide sequence of the provirus genome integrated in leukemia cell DNA. Proc Nat Acad Sci U S A 80:3618–3622, 1983
220. Sirera G, Romeu J, Ribera M, et al: Hospital outbreak of scabies stemming from two AIDS patients with Norwegian scabies. Lancet 335:1227, 1990
221. Smadja D, Cabre P, Bellance R, et al: Paraplegia associated with HTLV 1 in Martinique. Study of 271 cases including 70 with neuromuscular involvement. Bull Soc Pathol Exot 86:433, 1993
222. Spina-Franca A, Livramento JA, Machado LR, et al: HTLV-1 antibodies in serum and cerebrospinal fluid in tropical spastic paraparesis in Brazil. Arq Neuropsiquiatr 48:441, 1990
223. Strimmer K, von Haeseler A: Likelihood-mapping: a simple method to visualize phylogenetic content of a sequence alignment. Proc Nat Acad Sci U S A 94:6815–6819, 1997
224. Stuver SO, Tachibara N, Okayama A, et al: Heterosexual transmission of human T-cell leukemia/lymphoma virus type I among married couples in southwestern Japan. Am Intl Report from the Miyazaki Cohort Study. J Infect Dis 167:57–68, 1993
225. Sugimoto M, Nakashima H, Watanabe S, et al: T-lymphocyte alveolitis in HTLV-I–associated myelopathy [letter]. Lancet 2:1220, 1987
226. Tachi N, Watanabe T, Wakai S, et al: Acute disseminated encephalomyelitis following HTLV-I associated myelopathy [letter]. J Neurol Sci 110:234, 1992
227. Tajima K, Tominaga S, Suchi, et al: Epidemiological analysis of the distribution of antibody to adult T-cell leukemia-virus–associated antigen: Possible horizontal transmission of adult T-cell leukemia virus. Gann 73:893–901, 1982
228. Tamiya S, Matsuoka M, Takemoto S, et al: Adult T cell leukemia following HTLV-I–associated myelopathy/tropical spastic paraparesis: Case reports and implication to the natural course of ATL. Leukemia 9:1768, 1995
229. Tardieu JP: El Negro en el Cuzco. Editorial Pontificia Universidad Católica del Perú, Lima, 1998
230. Trelles L: Tropical Spastic Paraparesis in Peru in HTLV-I and the Nervous System. New York, Alan R Liss, 1989, pp 157–165
231. Trujillo L, Muñoz D, Gotuzzo E, et al: Sexual practices and prevalence of HIV, HTLV-I/II and *Treponema pallidum* among clandestine female sex workers in Lima, Peru. Sex Transm Dis 26:115–118, 1999
232. Tsugane S, Watanabe S, Sugimura H, et al: Infectious status of human T lymphotropic virus type I and hepatitis B virus among Japanese immigrants in the Republic of Bolivia. Am J Epidemiol 128(5):1153–1161, 1988
233. Uchiyama T, Yodoi J, Sagawa K, et al: Adult T-cell leukemia: Clinical and haematological features of 16 cases. Blood 50:481–492, 1977
234. Uozumi K, Iwahashi M, Ueda H, et al: Adult T-cell leukaemia and HTLV-I–associated myelopathy in a family [letter]. Lancet 338:572, 1991
235. Van Dooren S, Gotuzzo E, Salemi M, et al: Evidence for a post-Columbian introduction of HTLV-I in Latin America. J Gen Virol 79:2695–2708, 1998
236. Vitek CR, Gracia FI, Giusti R, et al: Evidence for sexual and mother-to-child transmission on HTLV-II among the Guaymi Indians in Panama. J Infect Dis 171:1022–1026, 1995
237. Ward R, Waters, et al: Low level endemic infection of HTLV-I and HTLV-II in an Amerindian tribe of Vancouver Island, British Columbia, Canada [abstract]. J Acquir Immune Defic Syndr Hum Retrovirol 10(2):216, 1995
238. Wignall FS, Hyams KC, Phillips IA, et al: Sexual transmission of human T-lymphotropic virus type I in Peruvian prostitutes. J Med Virol 38:44–48, 1992
239. Williams AE, Fang CT, Sullivan MT, et al: Human T-lymphotropic virus type I screening in volunteer blood donors—United States. MMWR Morb Mortal Wkly Rep 39:915, 921–923, 1989

240. World Health Organization: Proposed WHO criteria for interpreting results from Western blot assays for HIV-1, HIV-2 and HTLV-I/HTLV-2. Wkly Epidemiol Rec 65:281–288, 1990
241. World Health Organization: Scientific Group on HTLV-I Infections and Associated Diseases. Scientific Group on HTLV-I Infections and Associated Diseases: Report. Manila, Philippines, The Office, 1989, pp 17–18
242. Yamasaki K, Kira J, Koyanagi Y, et al: Long-term, high dose interferon-alpha treatment in HTLV-I-associated myelopathy/tropical spastic paraparesis: A combined clinical, virological and immunological study. J Neurol Sci 147:135, 1997
243. Yamashita M, Picchio G, Veronesi R, et al: HTLV-Is in Argentina are phylogenetically similar to those of other South American countries but different from HTLV-Is in Africa. J Med Virol 55:152–160, 1998
244. Yanagihara R, Nerukar VR, Ajdukiewicz AB: Comparison between strains of human T lymphotropic virus type I isolated from inhabitants of the Solomon Islands and Papua New Guinea. J Infect Dis 164:443, 1991
245. Yanagihara R, Saitou N, Nerurkar VR, et al: Molecular phylogeny and dissemination of human T-cell lymphotropic virus type I viewed within the context of primate evolution and human migration. Cell Mol Biol (Noisy-le-grand) 41(Suppl):S145–161, 1995
246. Yanaguchi K, Nishimura H, Jono M, et al: A project for smolding adult T-cell leukemia. A clinical pathologic study of five cases. Blood 62:758–766, 1983
247. Yasui C, Fukaya T, Koizumi H, et al: HTLV-I-associated myelopathy in a patient with adult T-cell leukemia. J Am Acad Dermatol 24:633, 1991
248. Yokota T, Miura Y, Yamada M, et al: Multiple system atrophy with autonomic failure and human T-lymphotrophic virus type I infection [letter]. Ann Neurol 35:244, 1994
249. Yoshida B, Miyoshi I, Hinuma Y: Isolation and characterization of retrovirus from cell lines of human adult T cell leukemia and its implication in the disease. Proc Natl Acad Sci U S A 79:2031–2035, 1982
250. Zamora T, Zaninovic V, Kajiwara M, et al: Antibody to HTLV-I in indigenous habitants of the Andes and Amazon regions in Colombia. Jpn J Cancer Res 81:715–719, 1990
251. Zaninovic M, Zamora T, Tajima K: Origins of T-cell leukemia virus. Nature 344:299, 1990
252. Zaninovic V, Arango C, Biojó R, et al: Tropical spastic paraparesis in Colombia. Ann Neurol 23:S127, 1988
253. Zaninovic V, Biojó R, Barreto P: Paraparesia espástica del Pacifico. Colombia Medica 12:111, 1981
254. Zaninovic V, Leon FE: Fifteen years of follow-up on HTLV-I positive and HTLV-I negative spastic paraparesis patients in southwestern Colombia, South America [letter]. J Neurovirol 2:357, 1996
255. Zaninovic V, Sanzon F, Lopez F, et al: Geographic independence of HTLV-I and HTLV-II foci in the Andes highland, the Atlantic coast, and the Orinoco of Colombia. AIDS Res Hum Retroviruses 10:97–101, 1994
256. Zurita S, Costa C, Gotuzzo E, et al: Prevalence of human retroviral infection in Quillabamba and Cuzco, Peru: A new endemic area for human T-cell lymphotropic virus type 1. Am J Trop Med Hyg 56(5):561–565, 1997

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