**Human T-Cell Leukemia Lymphoma Virus (HTLV): From Discovery to Oncogenesis**

Eman Al Mussaed

Department of Basic Science, Hematopathology Division, Princess Nourah Bint Abdulrahman University, College of Medicine, Riyadh, Saudi Arabia

[dreman\_almussaed@hotmail.com](mailto:dreman_almussaed@hotmail.com)

**Abstract:** Human T lymphotropic viruses (HTLVs) are complex oncoretrovirus that do not contain a proto-oncogene in their genome; however, they are capable of transforming primary T lymphocytes. There are four known strains of HTLV including HTLV type 1 (HTLV-1), HTLV-2, HTLV-3 and HTLV-4. . HTLV-1 is the etiological agent of adult T-cell leukemia/lymphoma (ATLL) and is also associated with cutaneous T-cell lymphoma (CTCL) and an inflammatory neurodegenerative disease named HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). Epidemiological studies have demonstrated that the relative percentage of malignant lymphoid proliferations varies widely according to geographical location and ethnic populations. Despite similarities with HTLV-1 in its genomic organization, HTLV-2 is only associated with neurological disorders but does not promote leukemia or lymphoma. There have been no diseases associated with HTLV-3 or HTLV-4 to date. In this review, we aim to summarize current information about the HTLVsregarding epidemiology, diagnosis, clinical features of associated diseases, molecular pathogenesis of transformation and Oncogenesis. Also, we highlight the recently advances of management of its associated diseases.

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**Key words:** Human T lymphotropic viruses, leukemia, lymphoma, Oncogenesis**.**

**1. Introduction**

The Human T-lymphotropic viruses (HTLVs) belong to *Retroviridae* family, genus *Deltaretrovirus*. Historically, in 1980, Poiesz *et al.* identified human T-cell leukemia virus (HTLV) in a T-cell line from a patient with cutaneous T-cell lymphoma (CTCL). **[1]** Independently, in 1982, Yoshida *et al.* identified adult T-cell leukemia virus (ATLV). **[2]** Soon, HTLV and ATLV were shown to be identical at the sequence level and were named HTLV type 1 (HTLV-1). **[3]**

HTLV-1 is the etiological agent of adult T-cell leukemia/lymphoma (ATLL) and is also associated with CTCL and an inflammatory neurodegenerative disease named HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). **[1]** HTLV-1 can infect T cells, B cells, monocytes, dendritic cells and endothelial cells with equal efficiency; yet, it can transform only primary T cells. **[4-7]**

After the discovery of HTLV-1, a second human retrovirus, HTLV-2, was identified in a cell line derived from a patient with a variant form of hairy T cell leukemia (HCL). [3, 8-10] Since then, HTLV-2 has not been associated with leukemia/lymphoma; nevertheless, it has been associated with a few sporadic cases of neurological disorders **[11].**

In 2005, two more related viruses, HTLV-3 and HTLV-4, were reported in central Africa **[12].** However, there have been no diseases associated with HTLV-3 or HTLV-4 to date. Approximately15-20 million people worldwide are estimated to be infected with HTLV-1 **[13, 14];** although most of them remain asymptomatic carriers during their lives [21] with 1–5% of infected patients showing developing ATL [14, 15]. HTLV-1 and 2 are transmitted sexually and vertically, firstly by breastfeeding, as well as parenterally, by contaminated blood transfusion, sharing of contaminated needles and syringes, or transplantation of infected organs and tissues [16, 17]

In the recent years, HTLV-1 screening for blood donors has been developed and was slowly implemented worldwide. In 1993, HTLV-1 screening of blood donors was already performed in all developed countries and in many developing countries where HTLV-1 is endemic. **[18- 20]**

In this review, we aim to summarize the data accumulated so far in epidemiology, diagnosis, associated diseases, molecular biology and Oncogenesis. Also, we highlight the recently advances of management of its associated diseases.

**2.Epidemiology**

HTLVs are complex deltaretroviruses; currently they are classified into four types: 1, 2, 3 and 4. The geographic distribution of the virus has been studied in since its initial description, with Japan, Africa, the Caribbean islands, and Central and South America emerging as the areas of highest prevalence in the world. **[21]** Over 20 million persons are infected with HTLV-1/2 in the world. [13]

HTLV-I infection is geographically confined in specific areas such as Japan, the Caribbean basin, South America, Sub-Saharian Africa, Melanesia, Eastern Europe and the Middle East. The current estimations indicate 15-20 million people worldwide are infected with HTLV-I. While most HTLV-I-infected individuals remain asymptomatic carriers, 1–5% will develop ATLL; **(Figure 1)** **[13, 22]** the estimation of the global prevalence of HTLV-1 is based mainly on the serological screening of healthy blood donors, which might underestimate the prevalence in the population. The HTLV-1 prevalence rates have been stratified into high (more than 5% of the population tested), middle (5% to 1%), and low (less than 1%) prevalences. [**21]**The seroprevalence rates increase with age and are higher in females than males.

Japan is the most important area where HTLV-1 is endemic. The estimated prevalence in the general population varies from areas in which the virus is not found to selected areas with seroprevalences of up to 37%. [**2]** High rates of HTLV-1 infection have been reported for some Caribbean islands instudies of blood donors as in Jamaica, the prevalence is around 5% **[23].** In Africa, the seroprevalence increases from the north to the south, varyingfrom 0.6% in Morocco to greater than 5% in several sub- Saharan African countries **[24].** In Europe and North America, the prevalence is low and limited to groups that emigrated from areas of endemicity **[23].**For blood donors, very low rates were found in France (0.0039%), **[25]** and the United States (0.025%) **[23].** In South America, the virus was found in all countries, medium prevalence was found in blood donors from Chile (0.73%) and Argentina (0.07%) **[26].** In Brazil, Colombia, and Peru, the prevalences vary considerably according to the area. In Brazil, the highest prevalence was described for the central area and the coast (1.35%), with low prevalences in the north and south (0.08%) **[27].** In Australia, even though the prevalence in blood donors is low, a cluster among Aborigines in the Northern Territory was described, with a prevalence of 14% (4).

Since HTLV-2 was described in 1982, it has a more restricted distribution than HTLV-1. HTLV-2 infects 2 to 5 million people and more prevalent among some native Americans and some Central African tribes, but is relatively common among intravenous drug users (IDUs) and their sex partners in Europe, North America, and other regions of the world.[21, 29]. Areas and populations with high prevalence of HTLV-2 include Central and South America **[30],** the United States **[31],** Europe [32], and Southeast Asia **[33],** mainly among IDUs.

HTLV-3 and 4 were first isolated in 2005. HTLV-3 was initially isolated from a 62-year-old male pygmy in southern Cameroon. [34] HTLV-4 has been described in African bush meat hunters. In 2010, no evidence of HTLV-3 and HTLV-4 infection was found in a sample of 1200 New York State subjects (human and simian subject types) at risk for retroviral infection**. [35]**

**3.HTLV transmission and** [**Prevention**](http://virology-online.com/viruses/HTLV6.htm)

HTLV-1/2 transmission between humans is very similar that of human immunodeficiency virus (HIV), and differs only in that HTLV is less infective. Transmission between humans primarily occurs through sexual contact, vertical contact (prolonged breastfeeding and through the placenta during delivery), and blood contact through cellular blood components (whole blood, red blood cells, and platelets but not with the plasma fraction or plasma derivatives from HTLV-I-infected blood) or the sharing of contaminated needles or syringes. [16, 17, 36, 37] The intravenous route of infection, mainly by blood transfusion, appears to be the most efficient mode for HTLV-1 transmission [38]. Approximately 12% of HTLV infections occur by blood transfusion. Unlike HIV-1, whole cell transfusion is required for transmission of the virus [39, 40], with a seroconversion rate of approximately 50% [39, 41]; however, the risk of transmission decreases markedly if the blood units are stored for more than six days before transfusion [40, 42]. The development of HAM/TSP has been noted as early as six months after transfusion of an individual with infected blood [43]. To avoid HTLV-1 transmission by transfusion, screening of blood donors for HTLV-1/2 infection has been mandatory in Japan since 1986; the United States since 1989; Canada since 1990; the French Caribbean since 1989 and the entire French territory since 1991; the Netherlands since 1993; Sweden, Denmark, Iran since 1994; and Saudi Arabia included tests for HTLV-1 since 1995 and added tests for HTLV-2 since 1997 and more recently in Portugal and Greece**.[20]** Implementing such screening as mandatory is still under debate in other countries [20, 44, 45].

HTLV-1 screening tests are usually an enzyme-linked immunoassay (EIA) or particle agglutination (PA) assays. EIAs combine testing for HTLV-1 and HTLV-2, while PA assays test only for HTLV-1. Therefore, the chosen technique takes into account the type of retrovirus found in the geographic area. The confirmation is done by testing of the blood with another method that also discriminates between HTLV-1 and HTLV-2. The most commonly used tests are Western blotting (WB), immunofluorescence assay (IFA), or radioimmunoprecipitation assay (RIPA). Indeterminate results of the confirmatory test may occur. **[46, 47]** Polymerase chain reaction (PCR), which detects HTLV-1 proviral DNA, has been used for clarifying indeterminate results and also as a confirmatory test.

**Molecular Biology and Oncogenesis**

HTLVs are complex delta retroviruses that do not contain a proto-oncogene in their genomes and are yet capable of transforming primary T lymphocytes *in vitro* and *in vivo* (48). A complete understanding of the functions of the viral genes would give insights into the pathogenic mechanisms by which HTLV-1 induces oncogenesis.

HTLV is a C-type an enveloped retrovirus, with a central, electron dense nuclear core **[49, 50]** Genetic material is in the form of two positively charged single stranded RNA fragments. A reverse transcriptase is contained within the virion. Virions are round with a diameter of approximately 100 nm. **[50, 51, 52]** The inner membrane of the virion envelope is lined by the viral matrix protein (MA) which encloses the viral capsid (CA). Inside the capsid is found the viral genome, constituted by two copies of single-stranded RNA, besides viral proteins, such as reverse transcriptase and integrase, essential in the process of transcription of viral RNA into complementary DNA and integration of proviral DNA in the host cell genome. **(Figure 2) [21, 48, 50]**

On the molecular level, as with all retroviruses, HTLV has a gag-pol-env motif with flanking long terminal repeat sequences. Unique to the Deltraviruses, however, it includes a fourth sequence named Px, which participates in open-reading–frame transcription, in turn encoding for regulatory proteins Tax, Rex, p12, p13, and p30. All these proteins are important for the infectivity of cells, as well as in stimulating replication. **[53]** The structure of the viral genome is a linear, dimeric, single-stranded positive RNA (ssRNA) with a 5'-cap and a 3'poly-A tail. There are two long terminal repeats (LTRs) at the 5' and 3' ends of about 550-750 nucleotides long containing U3, R, and U5 regions. Primer binding site (PBS) is present at the 5'end and a polypurine tract (PPT) at the 3'end. The lengths of the HTLV-1 and HTLV-2 proviral genomes are about 9.0 and 8.9 kilobases, respectively. **Figure 3** **[53]**

HTLV-1 employs several means for inducing tumors. The viral oncoprotein Tax plays a major role in the process of initiation and development of cancer. It binds to host cell proteins and inhibits the transcription of genes which regulate cell proliferation, programmed cell death, and DNA repair. By inactivating these important mechanisms, Tax protein stimulates the infected T-cells to proliferate uncontrollably which results in cancer. Subsequently, HBZ suppresses Tax expression to evade immune elimination by Tax specific CTLs, and also complements for Tax to support proliferation; it provides a second oncogenic signal required for the maintenance of the leukemic cell. **[48]**

In adult T-cell leukemia (ATL), the main pathogenic protein, Tax, leads to leukogenesis and immortalization of T lymphocytes *in vitro*. [**[54]**](javascript:showrefcontent('refrenceslayer');)This is achieved by stimulation of interleukin-15 (IL-15) and interleukin-2 (IL-2), in turn leading to T-cell growth and transformation. Furthermore, Tax is inherent to both HTLV-1 and HTLV-2, although HTLV-1 is more pathogenic.[**[55, 56]**](javascript:showrefcontent('refrenceslayer');) The HTLV-1 basic zipper factor gene (HBZ) has been found to be consistently expressed in ATL cells, suggesting a role in cellular transformation and leukemogenesis. This might correlate with the increased pathogenesis of HTLV-1.[**[57]**](javascript:showrefcontent('refrenceslayer');)The expression of the HBZ gene also correlates with the provirus load of HTLV-1.

[**Disease Associations**](http://virology-online.com/viruses/HTLV3.htm)

Among HTLVs, HTLV-1 is the more clinically significant, as it has been proven to be the etiologic agent of multiple disorders; ATLL which is a cancerous growth of HTLV-1-infected T-cells with severe organ infiltration and HAM/TSP. The evidence implicating HTLV-I as the aetiological agent of ATL includes the association of ATL with HTLV-I antibodies, the isolation of the virus, the finding of monoclonal integrated proviral sequences in leukaemic cells of patients with ATL, and epidemiological data. ATL, in the majority of cases, is a rapidly progressive fatal disease, occurs in 1-2% of those infected. Symptoms present 20-30 years after infection **[38, 49]** of those who develop ATLL, more than two thirds develop leukemia while the remainder develop lymphoma **[58].** Prognosis is approximately 1 year after development of ATLL **[59]** ATLL is characterized by diffuse lymph node infiltration, hypercalcaemia, leukaemia, skin infiltrates, and a positive HTLV-I antibody test. The early stage of ATLL is characterized by general malaise, fever, abnormal lymph nodes, enlarged liver, jaundice, drowsiness, weight loss, and infections. Skin rash, papules, nodules and bone lesions are commonly seen. As the disease progresses, affected individuals may experience extreme weakness, back pain, and incontinence**. [49, 60, 61]**

HTLV-1 also causes HAM/TSP, a nonmalignant demyelinating neurologic disorder. The viral load of HTLV-1 is higher in patients with HAM/TSP than in HTLV-1 infected patients who do not have clinical signs. **[62]** The association of HTLV-I with TSP was discovered in 1985 while screening blood donors for HTLV-I antibodies in Martinique, West Indies. More than 75% of patients with TSP were found to have antibodies against HTLV-I and the association is further supported by the isolation of HTLV-I from the blood and CSF of patients with TSP. Clinically, it resembles multiple sclerosis (MS), but lacks the intracranial nerve signs and remissions characteristic of MS. Initial symptoms are bilateral weakness and stiffness of the lower extremities. The course is slowly progressive, usually with bladder involvement, but shows considerable variations. **[23]** HTLV-1 has also shown to be associated with several inflammatory diseases, such as alveolitis, polymyositis, arthritis, HTLV-1–associated uveitis/ocular manifestations, Sjorgen's syndrome and HTLV-1–associated infective dermatitis **[62-69]** It is likely that the spectrum of disease associations with increase with time.

To date, no conclusive evidence has proven that HTLV-2 is an etiologic agent in any specific disease. HTLV-2 infection may result in neurologic manifestations similar to the non-HAM complications of HTLV-1 infection. Recent data suggest that HTLV-1 and HTLV-2 carry similar risks in terms of resulting in non-HAM neurological illness. **[64, 70]** Also, case reports have linked HTLV-2 infection with pneumonia, bronchitis, arthritis, asthma, and dermatitis. **[71]**

HTLV-3 and HTLV-4 were first isolated in 2005. HTLV-3 was initially isolated from a 62-year-old male pygmy in southern Cameroon **[72]** Individuals infected with HTLV-3 have all been asymptomatic, with a low proviral load. HTLV-4 has been described in African bush meat hunters. In 2010, no evidence of HTLV-3 and HTLV-4 infection was found in a sample of 1200 New York State subjects (human and simian subject types) at risk for retroviral infection **[34]**Neither HTLV-3 nor HTLV-4 has been associated with specific diseases thus far, and further research is ongoing. Given the ongoing discovery of subtypes and strains, it is not surprising that 28% of certain populations in central Africa have been reported to have indeterminate HTLV serology results. **[35]**

[**Laboratory Diagnosis**](http://virology-online.com/viruses/HTLV4.htm)

Laboratory testing for HTLV-1/2 infections has become routine for blood transfusion and organ transplantation in many countries worldwide. The serological tests for anti-HTLV-1/2 antibodies are divided in two major groups: the screening serological assays and the confirmatory tests. The most used tests for the diagnosis of HTLV-1/2 are enzyme immunoassays (ELISA), IFA, WB and PCR assays. ELISA is a screening assay and the others are considered confirmatory tests. HTLV-1/2 infections which are detected with ELISA, must be confirmed IFA, WB and PCR) assays.

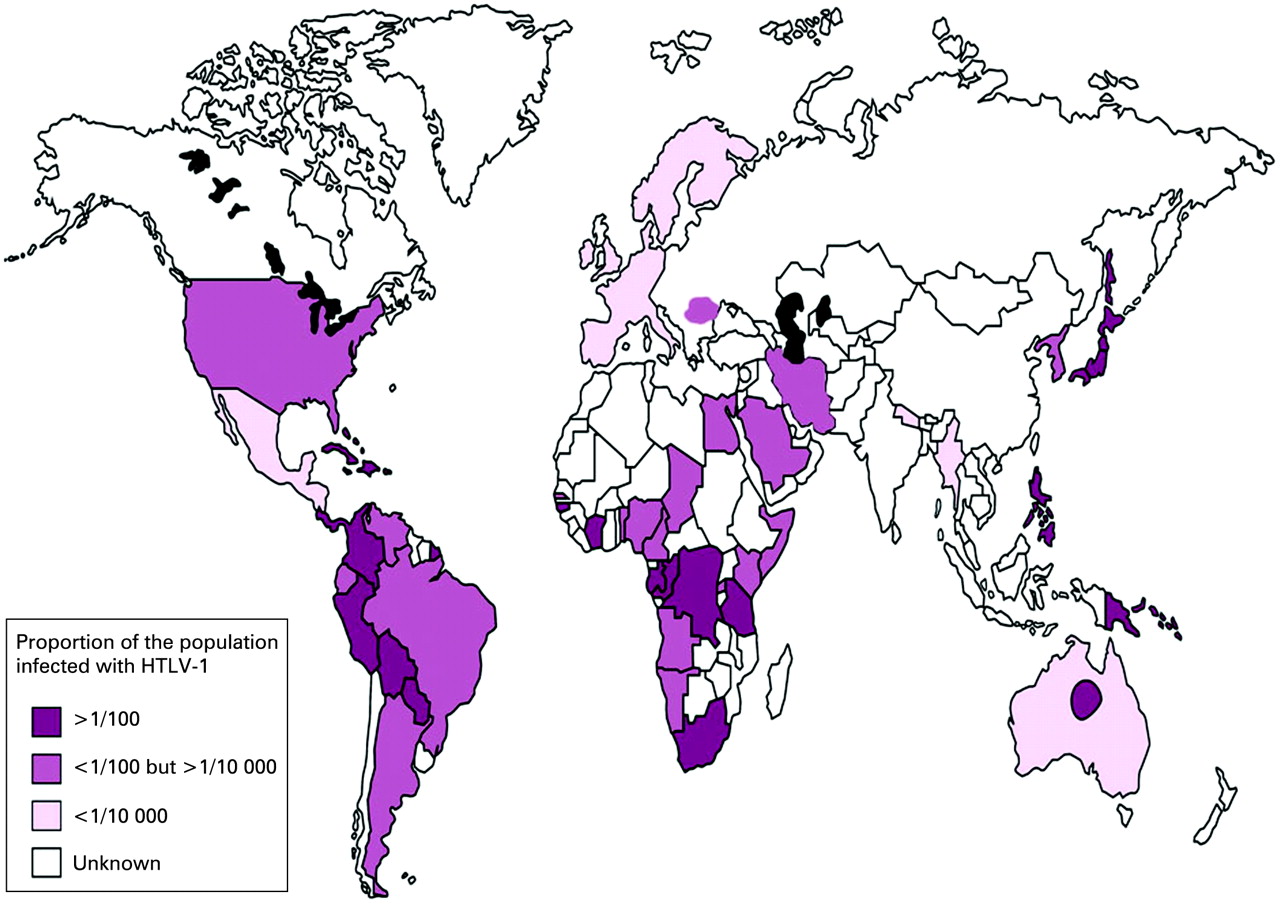
HTLV ELISA yields very high false-positive rates in areas of low prevalence. For example, confirmatory testing rules out HTLV infection in 60%-80% of blood donors in whom ELISA is initially positive in nonendemic areas. A passive PA assay is also available and is widely used in Japan for the screening of blood donations. **[73]** Current EIAs cannot distinguish between HTLV-I and HTLV-II. However, commercial WB using recombinant HTLV antigens are available which can distinguish between HTLV-I and HTLV-II. PCR can also be used to detect proviral DNA from peripheral blood mononuclear cells and can distinguish between HTLV-1 and HTLV-2. PCR is also necessary in infants who may have false-positive results because of circulating maternal anti-HTLV antibodies. **[73]** There is also interest in quantitative PCR assays to quantify viral load since, as in the case of antibody titer, there appears to be correlation of high viral loads with the likelihood of developing ATL and TSP in HTLV-I carrier.

The HTLV serological window period is not clearly known. The period of seroconvertion is related to the route of transmission and with the level of infected cells received in this event. The virus transmission through blood transfusion is considered the most efficient route and the seroconvertion of the recipients is around two months while for the other routes of transmission the seroconvertion can reach six months or more**. [42]** The results of ELISA test can be: reactive, non-reactive or indeterminate, the sample is usually tested in triplicate, and if two or three replicates are reactive, a new blood collection should be realized and the new sample tested by ELISA. The reactivity in two or three replicates implicates in the use of a confirmatory test, such as WB which is a confirmatory assay used to test samples that were repeatedly reactives in screening tests. Commercial tests normally use as antigens viral lysate of HTLV-1, besides HTLV-1 and HTLV-2 recombinant envelope proteins. The sample will be considered seronegative if no reactivity to viral antigens is observed; indeterminate if are specific reactivity for HTLV antigens but do not fulfill the criterion of seropositivity; and seropositive if presents reactivity to all antigens defined by the manufacturer as positive pattern. **[73]** The high proportion of indeterminate results in the screening tests for HTLV infection has been a challenge worldwide and has been an important problem faced by blood banks. The improvement in the diagnosis for HTLV has been necessary to reduce inconclusive results and to avoid unnecessary follow-up to define the status of infection. **[74, 75]** In endemic areas, indeterminate WB results can range from 0.02% to 50%. The causes of indeterminate WB tests and what is the medical importance of this status is still not clear. Molecular tests based primarily on the detection of viral nucleic acid in the form of proviral DNA by PCR can be useful to solve the majority of these inconclusive cases, as well as to discriminate between HTLV-1 or HTLV-2 infection **[76]** Indeterminate results of the confirmatory test may occur. The most commonly reported reasons for indeterminate results are the window period, the presence of a viral variant, and an unspecific reaction of the patient’s serum to viral antigens. **[46, 47]**

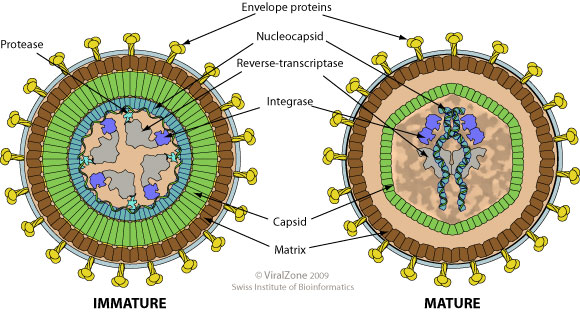
[**Management**](http://virology-online.com/viruses/HTLV5.htm)

Limited therapy is available for HTLV infections. [49] There is a possibility that some of the agents currently in use against HIV, especially the nucleoside analogue inhibitors, may work against HTLV-1. However, since ATL and TSP present years following infection, there appears little justification in using antiviral therapy in healthy carriers. A combination of interferon-alpha and zidovudine had been reported to be effective in treating ATL patients. Other treatments are currently under investigation including arsenic, trioxide, proteasome inhibitors, retenoids, angiogenesis inhibitors and cellular immunotherapy. Mogamulizumab, a defucosylated humanized anti-CCR4 IgG1 monoclonal antibody, was approved in Japan as a new therapy for ATL. ATL cells usually express chemokine receptor CCR4. [77] It is important to monitor for opportunistic infections in patients with ATL,including cytomegalovirus infection, Pneumocystis carinii infection, S stercoralis infection, Norwegian scabies, disseminated molluscum contagiosum, extrapulmonary histoplasmosis, and complications of staphylococcal and streptococcal skin infections.

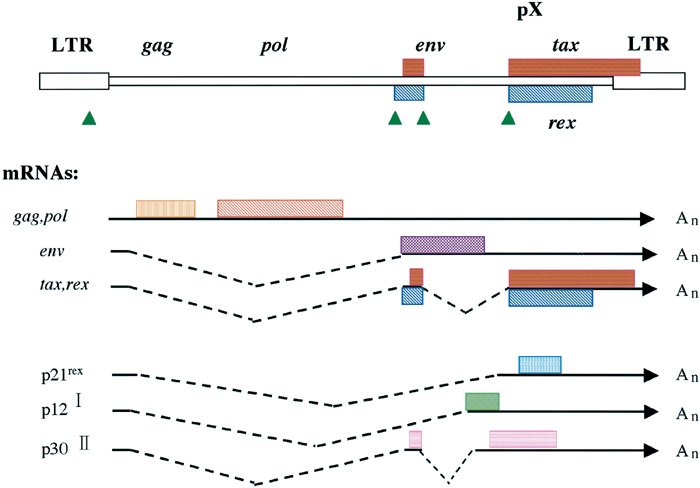
HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP) treatment options are even more limited and focus on symptomatic therapy. Antiretroviral treatments using lamivudine and high dose interferon alpha and interferon beta is used for HAM/TSP. Studied therapies have included corticosteroids, plasmapheresis, cyclophosphamide, and interferon, which may produce temporary improvement in signs and symptoms associated with HAM/TSP. Mogamulizumab, is also under study for treatment of HAM/TSP. This antibody effectively reduced HTLV-1 proviral load (56.4%), spontaneous proliferation, and production of proinflammatory cytokines. Further studies are needed if this treatment will translate into clinical treatment of HAM/TSP. **[78]** Also, a combination of zidovudine, danazol, and Vitamin C in providing temporary relief for TSP patients. Uveitis is treated with topical and systemic corticoids to improve sight. Infective dermatitis is treated with antibiotics. **[79]** All patients with HTLV-1 or HTLV-2 infection should be counseled extensively on the lifelong implications of their infection. [80]



**Figure 1:** Countries with endemic HTLV-I. . Cooper SA, et al. The neurology of HTLV-1 infection. Pract Neurol. 2009 Feb; 9(1):16-26. **[22]**



**Figure 1: HTLV Viral Structure**



## Figure 3: HTLV-1 genomic regions, virus mRNAs and proteins. The HTLV-I provirus genome is shown at the top of the figure. The structure of mRNAs and locations of proteins encoded by the provirus are shown underneath. MatsuokaM. Human T-cell leukemia virus type I and adult T-cell leukemia. *Oncogene* (2003) 22, 5131–5140. [53]

**Conclusion**

HTLVs are complex deltaretroviruses that do not contain a proto-oncogene in their genome, yet are capable of transforming primary T lymphocytes both *in vitro* and *in vivo.*HTLV-1/2 transmission between humans is very similar that of HIV. To avoid HTLV-1 transmission by transfusion, screening of blood donors for HTLV-1/2 infection has been mandatory in many countries.

Like simple retroviruses, HTLV-1 expresses structural and enzymatic proteins for its assembly and maturation, and for entry into new target cells. HTLV-1 also expresses regulatory and accessory proteins that are essential for viral persistence, immune evasion and ultimately, leukemogenesis. Among HTLVs, HTLV-1 is the more clinically significant, as it has been proven to be the etiologic agent of multiple disorders.

HTLV-1 is primarily associated with adult T cell leukemia (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Despite similarities between HTLV-1 and HTLV-2 in genomic organization, HTLV-2 is only associated with rare cases of HAM/TSP-like diseases but does not promote leukemia or lymphoma. The exact mechanisms and pathways have not been fully elucidated, however, multiple reports already pointed out the key roles played both by Tax and HTLV-1 antisense-encoded protein in cell transformation. There have been no diseases associated with HTLV-3 or HTLV-4 to date. Limited therapy is available for HTLV infections.

# Competing interests

# The author declares that he has no competing interests.

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