



## Neurological Manifestations and Risk Factors of HTLV-1 Infection in the Middle East Region and Iran: A Comprehensive Review of 137 Articles of the Last 23 Years

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### Article Info:

#### Article Type:

Review Article

#### Article history:

Received

05 Feb 2024

Received in revised form

21 Apr 2024

Accepted

31 Apr 2024

Published online

05 May 2024

#### Publisher

Fasa University of

Medical Sciences

### Abstract

**Background & Objectives:** The Human T-cell lymphotropic virus type 1 (HTLV-1) retrovirus is prevalent in some regions, such as Iran. This comprehensive literature review explores the symptoms and risk factors associated with HTLV-1 infection Middle East Region and Iran.

**Materials & Methods:** This narrative review used PubMed, Scopus, Embase, ScienceDirect, and Google Scholar as searching engines using terms HTLV-1, neurological disorders, pathogenesis, transmission, diagnosis, treatment, and epidemiology for articles published between 2000 and 2023. In total, 137 articles were eligible.

**Results:** Breastfeeding, unsafe sexual contact, and contaminated blood products are main HTLV-1 transmission routes. Brazil, Ecuador, and the Dominican Republic are countries with a high percentage of HTLV-1 infection, with estimates ranging from 1% to 13.9% in Brazil, up to 57% in Ecuador, and 1% to 5% in the Dominican Republic and it is endemic in Iran, Japan, the Caribbean, South America, and Africa. While numerous patients are asymptomatic, the virus can cause HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and peripheral neuropathy. Tax viral proteins cause nervous system inflammation and HAM/TSP. MRI (magnetic resonance imaging) may decipher spinal cord shrinkage and white matter lesions in affected patients. Immunodeficiency conditions, blood transfusion, and risky sexual behavior increase infection rate. The neurological symptoms are initiated with sensory-motor impairments. The main symptoms are limb weakness, bladder/bowel dysfunction, and cognitive impairment.

**Conclusion:** HTLV-1 infection is highly prevalent in Japan, Africa, the Caribbean, Central and South America, and Iran (especially in northeastern regions like Neyshabur). By understanding the pathogenesis and epidemiology of HTLV-1, proper strategies and targeted treatments can be developed for associated disorders like HAM/TSP. International collaboration is essential in addressing health concerns related to HTLV-1 infection.

**Keywords:** Human T-cell lymphotropic virus type 1, Epidemiology, Pathogenesis, Middle East

**Cite this article:** Rajabpour-Sanati A, Irankhah SH, Rahmani L, Riasi HR. Neurological Manifestations and Risk Factors of HTLV-1 Infection in the Middle East Region and Iran: A Comprehensive Review of 137 Articles of the Last 23 Years. *J Adv Biomed Sci.* 2024; 14(2): 1-17.

**DOI:** 10.18502/jabs.v14i2.15749

### Introduction

Human T-cell Lymphotropic Virus type 1 (HTLV-1) is a retrovirus that infects a significant number of individuals globally.

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Estimates suggest that between 5 to 20 million people worldwide are infected with HTLV-1, with prevalence reaching as high as 30% in certain regions (1–5). Vertical transmission, particularly through





breastfeeding, is a primary mode of spread contributing to clustered infection foci in specific geographical areas like Japan, the Caribbean, sub-Saharan Africa, the Middle East, South America, and indigenous communities in Australia (3). Women predominantly carry the burden of HTLV infection worldwide, often acquiring the virus through condomless sex and unknowingly transmitting it to their offspring (6).

The epidemiology of HTLV-1 is complex, with endemic foci in regions like Japan, the Caribbean, South America, Central Africa, and specific areas in Iran and Melanesia(1,5). Studies have highlighted the need for better understanding and efforts to reduce the prevalence of HTLV-1, given its association with severe diseases and the lack of reliable epidemiological data (2).

Based on the investigations conducted in various texts and articles from 2000 to 2023, it has been evident that the level of HTLV-1 virus contamination in Iran's Northern and Northeastern regions is consistently higher than in other areas. This level is also observed to be significantly elevated in other Middle Eastern countries (7), emphasizing the necessity of better understanding this virus and its transmission methods in this region. In the affected areas, most individuals are asymptomatic, but due to the virus's penetration into the nervous system, the disruption of the cellular defense system, and the release of inflammatory cytokines, individuals can develop neurological diseases, with the most prominent form being HTLV-1-Associated Myelopathy (HAM)/Tropical Spastic Paraparesis (TSP) (HAM/TSP). Half of HAM/TSP receiving follow-up care will become wheelchair-dependent, severely affecting their independence and quality of life (8). These individuals often experience atrophy in the motor nuclei of the brain, as well as disorders in the white matter of the brain and spinal cord (affecting the thoracic and cervical regions (9)), leading to extensive motor and sensory impairments and even autoimmune manifestations. Involvement can occur at the central or peripheral nervous system level,

significantly affecting patients' functional and social aspects. Considering the pathogenesis of the virus, which leads to an abnormal increase in inflammatory cytokines in response to viral proteins, the reduction or elimination of cytokines can assist in alleviating patient symptoms. In this regard, drugs that modulate cytokines quantitatively and qualitatively can be employed.

## Materials and Methods

This review study was conducted using data obtained from databases such as PubMed, Scopus, Embase, Science Direct, and Google Scholar. The retrieved results included those articles published between 2000 and 2023. The study was carried out as a narrative review, and involved no independent data resulting from direct clinical intervention or field collection, thus not requiring written consent forms. Ultimately, 137 articles were utilized in preparing this review study, and through their comparison, an extensive investigation was conducted on the epidemiology, pathogenesis, neurological symptoms, and risk factors associated with HTLV-1 infection.

## Results

### Virology

As a member of the genus *Retroviridae*, HTLV-1 virus (80–100 nm size) has a double-stranded positive sense RNA genome (10) that enters the host DNA and replicates dependently (11) and has envelope, matrix, capsid and nucleocapsid. The virus spreads through cell-to-cell transmission (12) as it enters adjacent cells after infecting a host cell, and thus infects multiple cells. Similar to other retroviruses such as human immunodeficiency virus (HIV), murine leukemia virus (MLV), and avian sarcomaleukosis virus (ASLV) (13), HTLV-1 predominantly infects CD4+ T lymphocytes and develops persistent infections (14). The virus has multiple genotypes, the most common of which is genotype A (15).



## Pathogenesis

In summary, the virus infects astrocytes, which are the interface between the blood vessels and the central nervous system (CNS) neurons. This infection leads to excessive production of the Tax1 viral protein (a critical viral protein involved in virus attachment to host cells) within these cells. Ultimately, an over-secretion of proinflammatory mediators (16,17) occurs, resulting in the manifestation of symptoms in the CNS (18, 19). Based on research findings, the HTLV-1 Tax1 protein, which can be transmitted from cell to cell (20), induces the production of tumor necrosis factor (TNF)- $\alpha$  and reduces glutamate transporters (GLAST and GLT-1) in the CNS glial cells. This leads to decreased glutamate and glucose uptake, increased lactate accumulation in astrocytes, and widespread metabolic disturbances in these cells (21). Further investigations have revealed that HTLV-1-infect T lymphocytes when exposed to glial cells in a laboratory setting, trigger the release of interleukin (IL)-2 and its specific receptor, which promotes proliferation in lymphocytic cells. Additionally, it has been observed that IL-15 can induce a similar effect and cause self-proliferation of these infected cells (22). Patients with HAM/TSP exhibit higher levels of spontaneous proliferation in lymphocytes compared to asymptomatic individuals due to elevated levels of interferon (IFN)- $\gamma$ . This higher level is attributed to the increased production of cytokines by CD8+ T cells in these patients (23). The disease is characterized by a severe and chronic inflammatory response in the CNS, resulting from the interaction between CD8+ T cells and virus-infected cells (24). Cytokines such as IL-8, CXCL9, CXCL10, and CXCL5, being higher in individuals with HAM/TSP, can recruit T cells into the CNS (25). Noticeably, more than half of the infected individuals have a mutation in the 14bp region of the HLA-G gene, which impairs the function of this molecule resulting in an increased viral load in the peripheral blood and a higher susceptibility to the viral infection (26). Further

investigations have shown elevated levels of IL-2 in carriers and IFN- $\gamma$  in individuals with HAM/TSP (27), while cytokines such as IL-4, IL-10, TNF- $\alpha$ , and IL-12 p70 exhibited non-significant changes (28). The Tax viral protein has subgroups A and B (29), which may impact the likelihood of developing HAM/TSP (30). Flow cytometry analysis comparing individuals with HAM/TSP to carriers has demonstrated higher levels of inflammatory cytokines such as IFN- $\gamma$  and TNF- $\alpha$  in individuals with the disease (31).

## Diagnosis of the virus in individuals

To diagnose the disease, a novel method called Droplet Digital PCR (ddPCR) can be utilized. In this approach, the sample obtained from peripheral blood or cerebrospinal fluid (CSF) is divided into hundreds of thousands of droplets, and then the number of viruses is determined using PCR and specific algorithms. This method can be used for patients with HAM/TSP, asymptomatic carriers, or for monitoring viral load in treated patients (32). The combination of diagnostic methods such as Western Blot (WB), PCR (tax or pol), and real-time PCR (pol) can lead to the detection of a greater number of carriers. WB was found to be effective in identifying a larger number of infected individuals, while real-time PCR can identify HTLV-1 various types (33). In a study by Nicholas Kwaan et al., it was observed that alcoholics experience long-term increases in HTLV-1 viral load, whereas this effect is reduced in individuals of African descent. This effect on HTLV-2 load is positive in smokers. Furthermore, as the viral load in peripheral blood increases, individuals become more susceptible to kidney infections (34). Considering that the viral load in peripheral blood is an indicator of disease progression (35), the TaqMan PCR technique can be employed to identify the number of tax protein molecules in the virus using highly precise measurement techniques, with a sensitivity of approximately 98% and specificity of 100%, aiding in patient evaluation (36). Based on the conducted studies, CXCL10, derived from Th1 cells and



present at high levels in the CSF of HAM/TSP patients, can be utilized as a marker for disease identification (37). Research has shown that the level of OX40 (a member of the TNF family) in the CSF of HAM/TSP patients is elevated. This response is associated with the interaction between OX40 and the tax protein of the virus in infected cells (38). Investigations have demonstrated that the viral load in peripheral blood and CSF of HAM/TSP patients is higher during symptom exacerbation, indicating increased viral load leading to symptoms exacerbation (39). Studies in Italy have revealed that SYBR Green qPCR Protocol used to measure the viral DNA in the peripheral blood of the examined individuals can serve as an alternative to the enzyme-linked immunosorbent assay (ELISA) or Western Blotting methods (40).

### **Epidemiology**

Over the past 20,000 years, HTLV-1 has circulated among humans (41). This virus was firstly isolated from patients with cutaneous lymphoma in 1979. This virus has affected approximately 20 million individuals worldwide (42–44). Endemic regions of this disease include sub-Saharan Africa, South America, the Caribbean region, southern parts of Japan, and specific areas in the northeastern Middle East, such as Iran (45–47). The prevalence rate in endemic areas ranges from 1% to 6%, reaching 25–40% in individuals over 50 years of age. In 90% of cases, patients asymptomatic throughout their lifetime. However, symptomatic individuals may present with Adult HAM/TSP (48), uveitis (49, 50), and dermatological manifestations (51). Other disease manifestations may include myositis, rheumatoid arthritis (RA), pulmonary disease (52), Hashimoto's thyroiditis, Graves' disease, and Sjögren's syndrome (53).

### **Transmission Routes**

The virus can be transmitted through physiological fluids such as saliva (54), blood products, and sexual contact (55). Despite the unequal prevalence in

contaminated areas, environmental factors and the host genetic factors can influence the rate of viral transmission (56). A retrospective study conducted in England from 1993 to 2007 revealed that 80% of HAM/TSP patients were women, and approximately 80% of cases were attributed to breastfeeding and unprotected sexual contact (53).

### **Risk Factors**

Considering the mode of disease transmission, the following factors can be identified as risk factors:

#### **Immune Deficiency**

Studies conducted on hemodialysis patients with positive HTLV-1 (57) have revealed higher viral load ratios compared to HTLV-1-negative individuals (903 copies per milliliter versus 117 copies per milliliter), which may be attributed to immune system deficiencies in these individuals (58). The results of studies on individuals who tested positive for pulmonary tuberculosis indicate a prevalence rate of 5.8% for HTLV-1 in these patients (59, 60). This rate is higher in older individuals and those with a family history of tuberculosis-related deaths (20, 61). Furthermore, in individuals diagnosed with sarcoidosis and tested for HTLV-1 positivity, it was found that up to 4% of all sarcoidosis patients were HTLV-1 positive (21, 62). Studies have shown that two chromosomal regions, 6q27 and 2p25, due to their involvement in the production of CCR6 (chemokine receptor 6) and ID2 (inhibitor of DNA binding 2), which are functionally impaired in individuals infected with HTLV-1, increase the likelihood of infection (63).

#### **Contact with Blood Products**

It has been unraveled that HTLV-1 positive patients have a close association with hepatitis B and C data. Accordingly, there is a strong association between HTLV-1-positive hemodialysis patients and age (64), marital status, and a history of blood transfusion (65). There was no statistically significant difference in the prevalence of HTLV-1 infection



between the northern areas of Iran and the rest of the country, where 1.4% of thalassemia major patients tested positive for the virus. However, further investigations are necessary to control blood products for these patients (66, 67).

### Sexual Transmission

In investigating the rate of virus transmission through sexual intercourse, it was determined that the prevalence of HTLV-1 infection among individuals who are injection drug users is 2.1%, among men with sex with men is 1.4%, and among non-injecting drug-using heterosexuals is 0.09%. These findings indicate the role of sexual behaviors in the spread of HTLV-1 (68–70). Further studies have revealed the occurrence of HTLV-1 infection among different groups of patients, including 19.1% among injection drug users, 0.4% among men who have sex with men, 2% among female sex workers, 2.1% among individuals with tuberculosis, and 1% among individuals with sexually transmitted infections. Additionally, it has been found that hepatitis B and C viruses have the highest rates of co-infection (71, 72). The occurrence of connective tissue diseases and RA can increase the likelihood of developing HAM/TSP (73), possibly due to a higher viral load in synovial fluid as compared to peripheral blood in these individuals (74).

### Global and Regional Prevalence

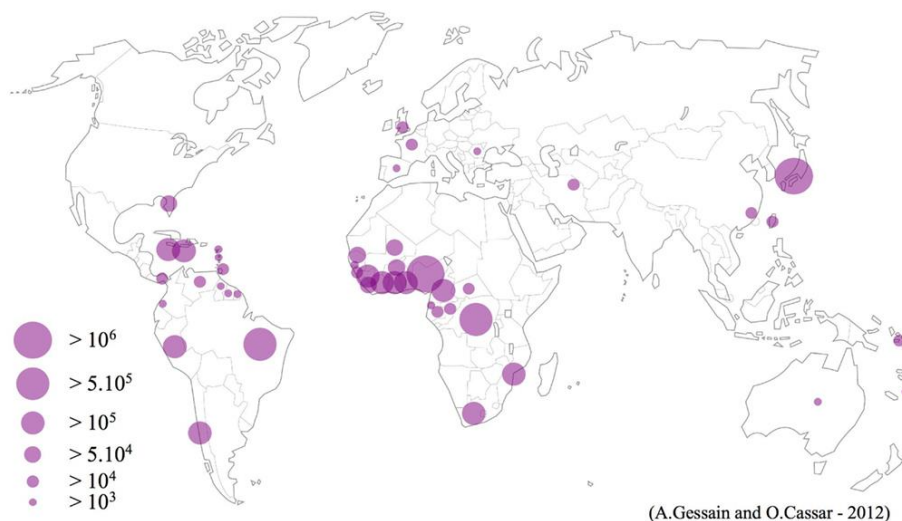
Among 253,855 individuals who donated blood in southeastern China, 43 individuals were found to be HTLV-1 positive, with a higher prevalence observed in the Fujian province compared to other provinces (24). Furthermore, the prevalence of HTLV-1 infection among blood donors in the provinces of Fujian and Guangdong was 2.9 and 9.9 per 10,000 individuals, respectively, which represented the highest rates among all provinces in the country. The predominant viral subtype in these areas has been identified as type A (cosmopolitan subtype) (24). In regional studies conducted in the Middle East, no cases of HTLV-1 positivity were found among

individuals who donated blood in Saudi Arabia (75). Similarly, investigations in Israel focusing on blood donors revealed a prevalence of 5.8 per 100,000 individuals in the overall population. However, this prevalence varied among different ethnic populations immigrating to Israel (e.g., 50.4 among Iranian immigrants, 16 among Turkish immigrants, 10.2 among Iraqi immigrants, and 20 among South American immigrants per 100,000 individuals) (76). Lebanon reported two cases of Adult T-cell leukemia/lymphoma (ATL) that were both HTLV-1 positive, representing the first such cases in the country (77). In the endemic areas of Iran, out of 1,864,489 blood donors between 2009 and 2013, 0.098% (1,840 cases) tested positive for HTLV-1 after accounting for characteristics like age, gender, and previous blood transfusion history (27). In other epidemic areas of Iran, the prevalence of infection varied. Blood donors in the Babol district of Mazandaran province in northern Iran were tested for HTLV-1 using PCR, and the results inferred one positive case (0.2%), outlining extremely low prevalence in this location (78). Another study in Mazandaran on 288 patients with thalassemia, including 151 females and 137 males with a mean age of  $21.5 \pm 6.5$ , showed an HTLV-1 contamination rate of 6.9% (20). Another study in Mashhad, northeastern Iran, examined blood donors from 2011 to 2013, including 174,662 individuals, and confirmed 327 cases. This study also showed that individuals with higher education levels and young blood donors require further investigations (79). In the Neyshabur region of northeastern Iran, out of 8,045 individuals from the accessible population, 6.55% were HTLV-1 and HTLV-2 positive, indicating a high prevalence of infection in this area (80–82). In Sabzevar city, northeastern Iran, among 35,067 blood donors with a mean age of  $38.10 \pm 11.82$  years, the prevalence of HTLV-1 was 0.19%, HTLV-2 was 0.14%, and HTLV-1/2 coinfection was 0.09% per year. Factors such as age, gender, history of blood transfusion, and

education level were found to be important in determining the prevalence (83). Investigations conducted on blood donors in Mashhad from 2011 to 2012 revealed that factors such as low income, being born in a region other than Mashhad, history of blood transfusion, and non-intravenous drug use had an impact on HTLV-1 infection rates (84). Figure 1 from the study by Gessain and O. Cassar (85) shows the geographical distribution of the HTLV-1 infections worldwide.

Based on the identified immuno-histochemical findings, the manifestations of the disease in affected individuals in the CNS and peripheral nervous systems are determined by the infiltration of mononuclear cells around the blood vessels and the degeneration of myelin and axons mediated by the secreted cytokines from these cells, which leads to the

destruction of T-helper/inducer cells (86, 87). These manifestations can occur in various forms in the CNS or peripheral nervous system. For example, in a study conducted at Imam Reza Hospital in Mashhad, northeastern Iran, between 1999 and 2004, four patients were examined. These four patients all reported experiencing paresthesia and subsequent muscular weakness. Subsequently, all patients developed arthralgia, and most individuals experienced hypokinesia. The polyneuropathy involved in these patients was mostly of the sensorimotor axonal type, and it was accompanied by an increase in protein in the CSF in only one case (88). In HTLV-1-positive patients without TSP/HAM involvement, the peripheral nerves complications can reflect HTLV-1 infection (89, 90).



**Figure 1.** Geographical distribution of the HTLV-1 infection

However, in patients with HAM/TSP, it was found that 30.1% of them had peripheral involvement, which was of the sensory-motor polyneuropathy type. In the evaluation of patients with urinary problems, it was determined after urodynamic tests

that a significant number of individuals examined had functional disorders characterized by excessive activity in the bladder and dysfunction of the external urinary sphincter, and these types of disorders are more commonly observed in individuals with HAM/TSP



compared to carriers (91). Considering the high prevalence of urinary symptoms in asymptomatic individuals and carriers, including dysuria, frequency, nocturia, and other related symptoms, these symptoms can be considered as the initial neurological signs in asymptomatic carriers (92). Further-more, mention can be made of cognitive impairment, which is closely associated with urinary disorders that significantly affect individuals' functional performance and quality of life (93). Various neurological manifestations and symptoms can be observed among individuals infected with HTLV-1, even without HAM/TSP (94). These symptoms include urinary symptoms, sexual disorders, lower limb weakness, and hyperreflexia in these limbs (95). Further investigations have revealed that individuals with the disease have more viral particles in their peripheral blood than asymptomatic carriers. This study demonstrated that gender and clinical symptoms similarity or age at the onset of symptoms do not impact the number of viral particles in the peripheral blood of affected individuals, but it is higher in severe motor impairment (use of wheelchair vs. walking) (96). Depression is one of the common diseases among HAM/TSP patients (about one-third), and considering the correlation between depression and poor socio-economic and psychological status of individuals and the fact that individuals with this disease are more susceptible to further disruption in socio-economic and psychological functioning, the prevalence of depression is higher in these individuals (97). One of the rare manifestations of the disease, which can occur as unilateral paralysis in the presence of progressive spasticity accompanied by hyperreflexia and is confirmed by the Electroencephalography (EEG) pattern of Guillain-Barré syndrome, can be mentioned (98). Hearing loss and tinnitus can be observed at higher rates in individuals with HAM/TSP compared to carriers or healthy individuals, possibly due to a disorder in the auditory transmission system at the cochlear or auditory nerve level (99). Neurological manifestations in HTLV-

infected carriers, especially in endemic areas, may present as chronic progressive polyneuropathy (slow progressive sensory-motor dysfunction) (100). Studies have shown that most manifestations of HTLV-1 infection in affected children manifest as progressive encephalopathy, microcephaly, myelopathy, peripheral neuropathy, speech disorders, learning disabilities, and motor impairment in the form of developmental delay (101). Furthermore, studies have shown that manifestations in children can include weakness in the lower limbs, back pain, paresthesia, and hyperreflexia, which can also be accompanied by urinary disorders in children with dermatitis (102). Patients with HAM/TSP who have experienced thoracic spinal cord atrophy may exhibit neurological symptoms in the form of orthostatic hypotension resulting from dysfunction in the sympathetic-parasympathetic cardiovascular system (103). Investigations have demonstrated that an important manifestation in individuals infected with HTLV-1 is isolated peripheral neuropathy, which may serve as the sole clinical sign of the infection and should be examined in all individuals with isolated peripheral neuropathy of unknown etiology for HTLV-1 (104). Another neuro-logical sign that may indicate HTLV-1-associated neuropathic symptoms is tinnitus, which can be traced using vestibular-evoked myogenic potential (VEMP), and more than 50% of VEMP tests in individuals with HAM/TSP yield positive results (105). Visual system manifestations may present as uveitis, keratoconjunctivitis sicca, corneal changes, and interstitial keratitis. Younger individuals, those with an earlier onset age, and individuals with more severe motor impairment in HAM/TSP are more susceptible to uveitis (106). Myositis is another symptom observed in HTLV-1-infected individuals, which can result from cytokine reactions to viral products, particularly in response to the viral protein Tax. These findings confirm the pathological findings in patients, which include atrophy in muscle fibers and skeletal muscle dysfunction (107). The study findings have identified that up to 30% of patients with HAM/TSP have peripheral nerve involvement, primarily in the form of axonal neuropathy



accompanied by sensory-motor impairment (108, 109). Regarding other associated diseases, hepatitis C and infective dermatitis can be mentioned. In patients with hepatitis C who are also co-infected with HTLV-1, no significant increase in the likelihood of peripheral neuropathy or HAM/TSP involvement has been observed, but it reduces the risk of liver damage (110). Moreover, the association between infective dermatitis and HAM/TSP has been established, indicating a strong correlation between these two diseases. Therefore, investigating HTLV-1 in children with myelopathy in endemic areas is crucial (111).

### Disease Diagnosis

MRI (magnetic resonance imaging) of the brain and spinal cord is a helpful diagnostic tool as it reveals evidence of spinal parenchymal atrophy in the distal segment of the spinal cord in patients with HAM/TSP (112). In individuals with urinary and sexual disorders, involvement in the central spinal region is more commonly observed, while individuals with cognitive impairments exhibit a combination of involvement in different brain regions (113). Furthermore, individuals with HAM/TSP may have multiple lesions in the brain's white matter (114). These lesions are observed in 85% of affected individuals and 80% of carriers within the white matter (115). A study conducted in Brazil in 2012 on 28 patients demonstrated involvement in the white matter (75-11%) and atrophy in these areas (14-3%), as indicated by MRI findings. It was also identified that major brain lesions exist in the periventricular regions (116). Chronic pain, presenting as either painful points or neuropathy, has been found to have the highest prevalence among individuals with HAM/TSP. This symptom can lead to increased anxiety, depression, and a decreased quality of life in affected individuals (117). Another investigation suggests that the use of MRI and a specific type of PET scan (C-PBR28 PET), employing a specific tracer leads to increased tracer uptake in the brains of patients compared to controls. Regions such as the thalamus, which has more proteins for binding to this

tracer, are more prominently visualized in imaging studies (118). According to studies, the concentration of virus-infected cells in the CSF of individuals with HAM/TSP is 10% higher than that of infected cells in the blood. This percentage can aid in disease diagnosis, as individuals without symptoms have a lower percentage than 10% (119). Monitoring viral load in the peripheral blood of individuals with HAM/TSP provides no prognostic information, and instead, changes in neuro-logical and motor functions need to be assessed (96). The investigations also revealed that individuals with HAM/TSP with higher viral loads and above 50 years of age have a higher likelihood of disease progression. This increase could be attributed to increased viral DNA (deoxyribonucleic acid) production, heightened lymphocyte stimulation, and enhanced cytokine activity (120). Measurement of inflammatory cytokines such as TNF- $\alpha$ ,  $\beta$ , IFN- $\gamma$ , and the occurrence of the rs12979860 polymorphism (a gene associated with disease progression in IL28) in affected individuals shows a close association between TNF- $\alpha$ , IL6 levels, and in carriers, TNF- $\beta$ , IFN- $\gamma$  levels. Moreover, the occurrence of the rs12979860 poly-morphism in affected individuals was not significantly different from carriers (121).

### Treatment

In a group of patients with neurogenic disorders of the bladder, characterized by dysfunction of the lower urinary system due to a neurological impairment following HTLV-1 infection, behavioral therapy, electrical stimulation, and exercise can lead to improvements in symptoms such as nocturia, urinary incontinence, and frequency (122). Studies have shown that a novel combination of marine algae called fucoidan (6 grams per day for 6-13 months), inhibiting the spread of HTLV-1 through cell-to-cell transmission, can reduce viral load in the peripheral blood by up to 50% in patients with HAM/TSP without affecting the immune system cells (123). In patients with lower back pain resulting from HTLV-1 infection and exhibiting motor and postural impairments, specific exercise activities, includ-





ing Pilates exercises, can reduce the intensity of back pain and improve the quality of life for these individuals (124). Additionally, in patients with HAM/TSP, methylprednisolone pulses can be used for pain control. After receiving one gram of intravenous methylprednisolone for three days, patients demonstrated a noticeable reduction in pain and a relative improvement in walking ability (125). Considering the spontaneous proliferation of lymphocytes in HTLV-1 infection and the role of glutathione as a mediator in cellular proliferation, substances such as BSO (dl-buthionine- [S, R]-sulf-oximine) and NAC (N-acetylcysteine), which have inhibitory effects on glutathione function, can be utilized to reduce lymphocyte proliferation in the peripheral blood of carriers, thereby improving symptoms (126). The therapeutic effect of alpha interferon (three million international units for six months) in patients with HAM/TSP has demonstrated temporary effects on the motor and urinary functions of patients. Furthermore, it has been indicated to reduce viral load and levels of inflammatory cytokines such as those from CD4, CD8, CD16, and CD56 cells (127).

### HTLV-1 in Iran

Based on studies examining 112 HTLV-1 sequences from Iran, it seems that the virus was most likely introduced into the country several centuries ago. This introduction may have been aided by the routes of the historical Silk Road (128). Molecular clock analyses date the time to the most recent common ancestor of Iranian HTLV-1 sequences to around 1290 AD. Phylogenetic clustering with isolates from the Middle East and Asia supports multiple early introductions, with subsequent viral spread facilitated by the Mongol invasions in the 15th century. Screening of hemodialysis patients in South Khorasan, Iran, detected a low 2.4% hepatitis C virus (HCV) infection rate, but a higher hepatitis B virus (HBV) rate of 9.75% (129). Notably, RT-PCR (Reverse transcription PCR) identified one HCV case, indicating an underestimation of HCV prevalence by serological assays in this population.

A research study conducted in Kuwait examined HTLV-1 isolates from three HAM/TSP patients, confirming the presence of the "Mashhadi" clade and indicating its regional dissemination (128). Lastly, a 36.4% HTLV antibody prevalence was found in HIV-1 infected lymphoma patients compared to 10.3% in controls, suggesting a possible association between HTLV-II and lymphomagenesis (130).

Some studies provide evidence that the prevalence of HTLV-1 infection remains considerable among high-risk populations in Iran, including blood donors, thalassemia patients, and general populations in endemic regions (131–134). Hedayati-Moghaddam et al. and Karimi et al. both noted in their studies a declining trend in HTLV-1 seroprevalence among blood donors over time, from 0.13% in 2009 down to 0.07% in 2013 (131). This trend aligns with the findings of Hezaveh et al. and Habibabadi et al., which reported low pre-valence rates of 0.09% among blood donors in northeastern Iran (133, 134). The declining prevalence could be attributed to ongoing screening of the blood supply coupled with the deferral of seropositive donors (132). However, the 2.5% prevalence detected in thalassemia patients highlights the ongoing risk of transfusion-transmitted HTLV-1 in this population (135).

Phylogenetic analysis of HTLV-1 strains in findings of the studies of Hezave et al. and Habibabadi et al. provide evidence that the virus is spreading from established endemic foci to surrounding regions (133, 134). In both studies, sequences belonged to the cosmopolitan subtype A and clustered with strains from the neighboring province of Khorasan, indicating likely expansion outward from this known endemic focus (133,134). Further genomic analysis of strains from different regions could shed light on the spread of HTLV-1 in Iran. Overall, these findings support continued screening and monitoring of high-risk groups to prevent further viral transmission.

Notably absent from these studies is longitudinal follow-up to document progression to HTLV-1-associated diseases like adult T-cell leukemia-lymphoma (ATLL) and HAM/TSP in infected individuals over time. As discussed



in the studies of Hezave et al. and Hamidi et al., the individuals analyzed were largely asymptomatic carriers (134, 135). Cohort studies monitoring development of HTLV-1 diseases could reveal important insights about viral and host factors influencing disease manifestation. Additional limitations include potential demographic biases and reliance on serological screening alone without confirmatory PCR in some studies (131, 132).

A cross-sectional study by Vahidnia et al. characterized the epidemiology and neuro-logical manifestations of HTLV-1 infection in an endemic region of Iran (136). The study found high rates of HTLV-1 transmission through breastfeeding (95.9%) and infiltrative procedures like dental work, hospitalization, and cupping. In 145 patients with HAM/TSP, common initial symptoms were gait impairment (72.4%), bladder dysfunction (67.8%), and sensory changes, with more severe neurologic deficits in the lower extremities. This first epidemiologic characterization of Iranian HAM/TSP patients provides crucial ground-work for future research collaborations on HTLV-1 pathogenesis and potential treatments (136).

Genetic polymorphisms may also contribute to HAM/TSP development, as demonstrated by a case-control study in Mashhad, Iran (137). Rafatpanah et al. identified associations between HAM/TSP risk and the CXCL10-1447 GG genotype as well as IL-18 -607 CC genotype. No relationships were found for other cytokine gene variants. These results suggest that certain genetic markers may identify Iranian HTLV-1 carriers at elevated risk for myelopathy. Differences compared to other populations could reflect geographic variations in HTLV-1 genetics and Iran's heterogeneous population (137). Overall, the aforementioned findings elucidate the complex interplay between viral, host, and environmental factors underlying HAM/TSP progression. Considering Iran's location and the findings of numerous studies that point to a higher prevalence of HTLV-1 infection in the country's north and northeast, it is essential to conduct more accurate screenings of people living in these parts of the country and in the overall population. In this context, implementing protocols to elevate public awareness regarding the vectors of disease transmission can be of

great benefit. Additionally, due to the virus's initial involvement in the nervous system and the development of symptoms that predominantly cause auto-immune and sensory-motor impairments, all individuals who test positive for viral infection should be monitored and screened for neurological disorders, rather than repeating the reason. Novel and supportive treatments should be considered for individuals who have been diagnosed with HAM/TSP, which is the most common form of these disorders.

## Conclusion

Our comprehensive review highlights the impact and risk factors associated with HTLV-1 infection in Iran and the wider Middle East region. After analyzing 137 articles spanning over two decades, we found that HTLV-1 plays a role in disorders such as HAM/TSP and peripheral neuropathy. The development of these conditions is primarily triggered by the protein Tax, which involves an interaction between viral, host, and environmental factors. Diagnostic methods primarily rely on PCR tests, imaging studies, and analysis of CSF, which have been crucial in identifying HTLV-1 infections and related neurological symptoms. While treatment approaches are still evolving, the focus is currently on managing symptoms through anti-inflammatory therapies, pain management techniques, physiotherapy sessions, and regular monitoring of disease progression. However, there is a need for targeted treatments. Main risk factors associated with HTLV-1 infection include immune deficiencies, exposure to blood products, and sexual transmission. This highlights the importance of raising awareness and implementing measures among high-risk populations. In Iranian regions where HTLV-1 prevalence is significant, continuous screening and monitoring strategies are essential to control the spread of this virus. Based on our review's findings, we strongly advocate for increased collaboration in research efforts, as well as public health initiatives, to gain a better understanding of and effectively combat the neurological consequences



caused by HTLV-1 infection. By gaining an understanding of the epidemiology, of how HTLV-1 develops in the body, and its clinical signs, we can improve the precision of diagnosis, create treatment options, and ultimately enhance the quality of life for individuals impacted by this virus.

### **Conflict of Interests**

This research did not receive any specific grant from any funding agency, commercial or not-for-profit sectors. The authors have no relevant financial or non-financial interests to disclose.

### **Acknowledgments**

We want to extend our thanks to the Library of Birjand University of Medical Sciences for their help, in granting us access to the extensive literature needed for this thorough review. We are truly grateful for their commitment, to supporting research efforts.

### **Author Contributions**

A.R.P.S. contributed substantially to all aspects of this study, including the conception and design of the study, the acquisition, analysis, and interpretation of the data, and the drafting of the article and its revising for critical intellectual content. S.I. and L.R. made minor contributions by reviewing and editing the manuscript. H.R., as the supervisor, made substantial contributions to the conception and design of the study, revising the manuscript for important intellectual content, and gave final approval of the version to be published.

### **Funding**

We would like to emphasize that this article was produced independently, without any financial support or sponsorship from external entities. We conducted this research and wrote this article without the influence of any financial backing or sponsorship.

### **Data Availability Statement**

All data analyzed in this narrative review are available in the cited articles and sources. No new data

was generated or analyzed as part of this review. The search strategies and criteria used to identify and select the relevant literature are described in the Methodology section.

### **List of Abbreviations**

- DNA: Deoxyribonucleic Acid
- RNA: Ribonucleic Acid
- ASLV: Avian Sarcoma-Leukosis Virus
- HIV: Human Immunodeficiency Virus
- MLV: Murine Leukemia Viru
- CD4<sup>+</sup>: Cluster of Differentiation 4 Positive
- CD8<sup>+</sup>: Cluster of Differentiation 8 Positive
- GLAST: Glutamate Aspartate Transporter
- GLT1: Glutamate Transporter 1
- TNF: Tumor Necrosis Factor
- IL: Interleukin
- IFN: Interferon
- CXCL: Chemokine (C-X-C motif) Ligand
- HLA: Human Leukocyte Antigen
- WB: Western Blot
- OX40: A tumor necrosis factor receptor superfamily, member 4 (TNFRSF4)
- SYBR: SYBR Green (a dye used in molecular biology for DNA staining)
- ELISA: Enzyme-Linked Immuno-sorbent Assay
- ATL: Adult T-cell Leukemia/ Lymphoma
- EEG: Electroencephalogram
- VEMP: Vestibular Evoked Myogenic Potential
- PET: Positron Emission Tomography
- HTLV-1: Human T-cell lymphotropic virus type 1
- HAM/TSP: HTLV-1-associated myelo-pathy/tropical spastic paraparesis
- CNS: Central nervous system
- CSF: Cerebrospinal fluid
- MRI: Magnetic resonance imaging
- PCR: Polymerase chain reaction
- ddPCR: Droplet Digital PCR



- BSO: Buthionine sulfoximine (DL-Buthionine-S R-sulfoximin)
- NAC: N-acetylcysteine

## References

- Morais MPE, Gato CM, Maciel LA, Lalwani P, Costa CA d., Lalwani JDB. Prevalence of Human T-Lymphotropic Virus Type 1 and 2 Among Blood Donors in Manaus, Amazonas State, Brazil. *Rev Inst Med Trop São Paulo*. 2017;59(0). DOI: 10.1590/s1678-9946201759080.
- Willems L, Hasegawa H, Accolla RS, Bangham CRM, Bazarbachi A, Bertazzoni U, et al. Reducing the Global Burden of HTLV-1 Infection: An Agenda for Research and Action. *Antiviral Res*. 2017;137:41–8. DOI: 10.1016/j.antiviral.2016.10.015.
- Mohanty S, Harhaj EW. Mechanisms of Innate Immune Sensing of HTLV-1 and Viral Immune Evasion. *Pathogens*. 2023;12(5):735. DOI: 10.3390/pathogens12050735.
- Percher F, Jeannin P, Martin-Latil S, Gessain A, Afonso PV, Vidy-Roche A, et al. Mother-to-Child Transmission of HTLV-1 Epidemiological Aspects, Mechanisms and Determinants of Mother-to-Child Transmission. *Viruses*. 2016;8(2):40. DOI: 10.3390/v8020040.
- Aldemir Branco de Oliveira Filho, Ana Paula Serra de Araújo, Souza APC, Gomes CB, Silva-Oliveira GC, Martins LC, et al. Human T-Lymphotropic Virus 1 and 2 Among People Who Used Illicit Drugs in the State of Pará, Northern Brazil. *Sci Rep*. 2019;9(1). DOI: 10.1038/s41598-019-51383-7.
- Martin F, Gilks CF, Gibb R, Jenkins A, Protani MM, Francis F, et al. Human T-Cell Leukaemia Virus Type 1 and Adult T-Cell Leukaemia/Lymphoma in Queensland, Australia: A Retrospective Cross-Sectional Study. *Sex Transm Infect*. 2022;99(1):50–2. DOI: 10.1136/sextans-2021-055241.
- Santana CS, Andrade F d. O, da Silva GCS, Nascimento JO d. S, Campos RF, Giovanetti M, et al. Advances in preventive vaccine development against HTLV-1 infection: A systematic review of the last 35 years. *Front Immunol*. 2023;14:1073779.
- Rosadas C, Menezes MLB, Galvão-Castro B, Assone T, Miranda AE, Aragón MG, et al. Blocking HTLV-1/2 silent transmission in Brazil: Current public health policies and proposal for additional strategies. *PLoS Negl Trop Dis*. 2021;15(9):e0009717.
- Bastos Ferreira AP, do Nascimento ADFS, Sampaio Rocha-Filho PA. Cerebral and spinal cord changes observed through magnetic resonance imaging in patients with HTLV-1-associated myelopathy/ tropical spastic paraparesis: a systematic review. *J Neurovirol*. 2022;28(1):1–16.
- Berkhout B, Grigoriev A, Bakker M, Lukashov VV. Codon and amino acid usage in retroviral genomes is consistent with virus-specific nucleotide pressure. *AIDS Res Hum Retroviruses*. 2002;18(2):133–41.
- Matsuo M, Ueno T, Monde K, Sugata K, Tan BJY, Rahman A, et al. Identification and characterization of a novel enhancer in the HTLV-1 proviral genome. *Nat Commun*. 2022;13(1):2405.
- Eusebio-Ponce E, Anguita E, Paulino-Ramirez R, Candel FJ. HTLV-1 infection: An emerging risk. Pathogenesis, epidemiology, diagnosis and associated diseases. *Rev Esp Quimioter*. 2019;32(6): 485.
- Derse D, Crise B, Li Y, Princler G, Lum N, Stewart C, et al. Human T-cell leukemia virus type 1 integration target sites in the human genome: comparison with those of other retroviruses. *J Virol*. 2007;81(12):6731–41.
- Rosadas C, Taylor GP. HTLV-1 and co-infections. *Front Med*. 2022;9:145.
- Verdonck K, González E, Van Dooren S, Vandamme AM, Vanham G, Gotuzzo E. Human T-lymphotropic virus 1: recent knowledge about an ancient infection. *Lancet Infect Dis*. 2007;7(4):266–81.
- Grassmann R, Aboud M, Jeang KT. Molecular mechanisms of cellular transformation by HTLV-1 Tax. *Oncogene*. 2005;24(39):5976.
- Zhao T, Wang Z, Fang J, Cheng W, Zhang Y, Huang J, et al. HTLV-1 activates YAP via NF- $\kappa$ B/p65 to promote oncogenesis. *Proc Natl Acad Sci*. 2022;119 (9):e2115316119.
- Szymocha R, Brisson C, Bernard A, Akaoka H, Belin MF, Giraudon PJ. Long-term effects of HTLV-1 on brain astrocytes: sustained expression of Tax-1 associated with synthesis of inflammatory mediators. *J Neurovirol*. 2000;6(4):350–7.
- Fuzii HT, da Silva Dias GA, de Barros RJS, Falcão LFM, Quaresma JAS. Immunopathogenesis of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). *Life Sci*. 2014;104(1):9–14.
- Lairmore MD, Haines R, Anupam R. Mechanisms of human T-lymphotropic virus type 1 transmission and disease. *Curr Opin Virol*. 2012;2(4):474–81.
- Akaoka H, Szymocha R, Beurton-Marduel P, Bernard A, Belin MF, Giraudon P. Functional changes in astrocytes by human T-lymphotropic virus type-1 T-lymphocytes. *Virus Res*. 2001;78(1):57–66.
- Azimi N, Mariner J, Jacobson S, Waldmann TA. How Does Interleukin 15 Contribute to the Pathogenesis of HTLV Type 1-Associated Myelopathy/Tropical Spastic Paraparesis? *AIDS Res Hum Retroviruses*. 2000;16(16):1717–22.
- Carvalho EM, Da Fonseca Porto A. Epidemiological and clinical interaction between HTLV-1 and *Strongyloides stercoralis*. *Parasite Immunol*. 2004;26(11–12):487–97.
- Lepoutre V, Jain P, Quann K, Wigdahl B, Khan Z. Role of resident CNS cell populations in HTLV-1-associated



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- neuroinflammatory disease. *Front Biosci Landmark Ed.* 2009;14:1152–68.
25. Chaves D, Sales C, de Cássia Gonçalves P, da Silva-Malta M, Romanelli L, Ribas J, et al. Plasmatic proinflammatory chemokines levels are tricky markers to monitoring HTLV-1 carriers. *J Med Virol.* 2016;88(8):1438–47.
  26. Haddad R, Alves D, Rocha-Junior M, Azevedo R, Pombo-de-Oliveira M, Takayanagui O, et al. HLA-G 14-bp Insertion/Deletion Polymorphism Is a Risk Factor for HTLV-1 Infection. *AIDS Res Hum Retroviruses.* 2011;27(3):283–8.
  27. Massoud R, Enose-Akahata Y, Tagaya Y, Azimi N, Basheer A, Jacobson S. Common  $\gamma$ -chain blocking peptide reduces in vitro immune activation markers in HTLV-1-associated myelopathy/tropical spastic paraparesis. *PNAS.* 2015;112(35):11030–5.
  28. Montanheiro P, Penalva de Oliveira A, Smid J, Fukumori L, Olah I, Duarte A, et al. The elevated interferon gamma production is an important immunological marker in HAM/TSP pathogenesis. *Scand J Immunol.* 2009;70(4):403–7.
  29. Kress A, Grassmann R, Fleckenstein B. Cell surface markers in HTLV-1 pathogenesis. *Viruses.* 2011;3(8): 1439–59.
  30. Saito M. Association Between HTLV-1 Genotypes and Risk of HAM/TSP. *Front Microbiol.* 2019;10(1101).
  31. Santos S, Porto A, Muniz A, De Jesus A, Magalhães E, Melo A, et al. Exacerbated inflammatory cellular immune response characteristics of HAM/TSP is observed in a large proportion of HTLV-I asymptomatic carriers. *BMC Infect Dis.* 2004;4(1):7.
  32. Brunetto G, Massoud R, Leibovitch E, Caruso B, Johnson K, Ohayon J, et al. Digital droplet PCR (ddPCR) for the precise quantification of human T-lymphotropic virus 1 proviral loads in peripheral blood and cerebrospinal fluid of HAM/TSP patients and identification of viral mutations. *J Neurovirol.* 2014;20(4):341–51.
  33. Costa E, Magri M, Caterino-de-Araújo A. The best algorithm to confirm the diagnosis of HTLV-1 and HTLV-2 in at-risk individuals from São Paulo, Brazil. *J Virol Methods.* 2011;173(2):280–6.
  34. Kwaan N, Lee TH, Chafets D, Nass C, Newman B, Smith J, et al. Long-Term Variations in Human T Lymphotropic Virus (HTLV)–I and HTLV-II Proviral Loads and Association with Clinical Data. *J Infect Dis.* 2006;194(11):1557–64.
  35. Olindo S, Lézin A, Cabre P, Merle H, Saint-Vil M, Edimonana Kaptue M, et al. HTLV-1 proviral load in peripheral blood mononuclear cells quantified in 100 HAM/TSP patients: A marker of disease progression. *J Neurol Sci.* 2005;237(1):53–9.
  36. Naderi M, Paryan M, Azadmanesh K, Rafátpanah H, Rezvan H, Mirab Samiee S. Design and development of a quantitative real time PCR assay for monitoring of HTLV-1 provirus in whole blood. *J Clin Virol.* 2012;53(4):302–7.
  37. Narikawa K, Fujihara K, Misu T, Feng J, Fujimori J, Nakashima I, et al. CSF-chemokines in HTLV-I-associated myelopathy: CXCL10 up-regulation and therapeutic effect of interferon- $\alpha$ . *J Neuroimmunol.* 2005;159(1):177–82.
  38. Saito M, Tanaka R, Arishima S, Matsuzaki T, Ishihara S, Tokashiki T, et al. Increased expression of OX40 is associated with progressive disease in patients with HTLV-1-associated myelopathy/tropical spastic paraparesis. *Retrovirology.* 2013;10(1):51.
  39. Takenouchi N, Yamano Y, Usuku K, Osame M, Izumo S. Usefulness of proviral load measurement for monitoring of disease activity in individual patients with human T-lymphotropic virus type I-associated myelopathy/tropical spastic paraparesis. *J Neurovirol.* 2003;9(1):29–35.
  40. Vitone F, Gibellini D, Schiavone P, D’Antuono A, Gianni L, Bon I, et al. Human T-lymphotropic virus type 1 (HTLV-1) prevalence and quantitative detection of DNA proviral load in individuals with indeterminate/positive serological results. *BMC Infect Dis.* 2006;6(1):41.
  41. Bangham CR. HTLV-1 persistence and the oncogenesis of adult T-cell leukemia/lymphoma. *Blood J Am Soc Hematol.* 2023;141(19):2299–306.
  42. Cook LB, Elemans M, Rowan AG, Asquith B. HTLV-1: persistence and pathogenesis. *Virol J.* 2013;435(1):131–40.
  43. Pinto DO, DeMarino C, Pleet ML, Cowen M, Branscome H, Al Sharif S, et al. HTLV-1 extracellular vesicles promote cell-to-cell contact. *Front Microbiol.* 2019;10:2147.
  44. Legrand N, McGregor S, Bull R, Bajis S, Valencia BM, Ronnachit A, et al. Clinical and public health implications of human T-lymphotropic virus type 1 infection. *Clin Microbiol Rev.* 2022;35(2):e00078-21.
  45. Abbaszadegan MR, Gholamin M, Tabatabaee A, Farid R, Houshmand M, Abbaszadegan M. Prevalence of human T-lymphotropic virus type 1 among blood donors from Mashhad, Iran. *J Clin Microbiol.* 2003;41(6):2593–5.
  46. Gessain A, Cassar O. Epidemiological aspects and world distribution of HTLV-1 infection. *Front Microbiol.* 2012;3:388.
  47. Iwanaga M. Epidemiology of HTLV-1 infection and ATL in Japan: an update. *Front Microbiol.* 2020;11:1124.
  48. Nozuma S, Matsuura E, Tanaka M, Kodama D, Matsuzaki T, Yoshimura A, et al. Identification and tracking of HTLV-1–infected T cell clones in virus-associated neurologic disease. *JCI Insight.* 2023;8(7):e167422.
  49. Koseki A, Araya N, Yamagishi M, Yamauchi J, Yagishita N, Takao N, et al. EZH1/2 dual inhibitors suppress HTLV-1-infected cell proliferation and hyperimmune response in HTLV-1-associated myelopathy. *Front Microbiol.* 2023;14:1175762.
  50. Schor D, Porto LC, Roma EH, Castro-Alves J, Villela AP, Araújo AQ, et al. Putative role of HLA polymorphism among a



- Brazilian HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) population. *Sci Rep.* 2023;13(1):7659.
51. Yasunaga J, Matsuoka M. Molecular mechanisms of HTLV-1 infection and pathogenesis. *Int J Hematol.* 2011;94(5):435–42.
52. Gabet AS, Mortreux F, Talarmin A, Plumelle Y, Leclercq I, Leroy A, et al. High circulating proviral load with oligoclonal expansion of HTLV-1 bearing T cells in HTLV-1 carriers with stronglyloidiasis. *Oncogene.* 2000;19(43):4954–60.
53. Martin F, Fedina A, Youshya S, Taylor GP. A 15-year prospective longitudinal study of disease progression in patients with HTLV-1 associated myelopathy in the UK. *J Neurol Neurosurg Psychiatry.* 2010;81(12):1336–40.
54. Hino S. Establishment of the milk-borne transmission as a key factor for the peculiar endemicity of human T-lymphotropic virus type 1 (HTLV-1): the ATL Prevention Program Nagasaki. *Proc Jpn Acad Ser B.* 2011;87(4):152–66.
55. Gonçalves DU, Proietti FA, Ribas JGR, Araújo MG, Pinheiro SR, Guedes AC, et al. Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. *Clin Microbiol Rev.* 2010;23(3):577–89.
56. Kanzaki Ljj. HTLV-1: A real pathogen or a runaway guest of a diseased cell? *J Biol Res.* 2018;43(4):785–95.
57. Khameneh Z, Baradaran M, Sepehrvand Njsj Transplantation. Survey of the seroprevalence of HTLV I/II in hemodialysis patients and blood donors in Urmia. *Saudi J Kidney Dis Transplant.* 2008; 19(5):838.
58. Hekmat R, Gholami F, Ahmadnia H, Ahmadi M, Hassannia T. Serum human T-lymphotropic virus 1 proviral load in patients on hemodialysis. *Iran J Kidney Dis.* 2013;7(2):124.
59. Marinho J, Galvao-Castro B, Rodrigues L, Barreto M. Increased risk of tuberculosis with human T-lymphotropic virus-1 infection: a case-control study. *AIDS J Acquir Immune Defic Syndr.* 2005;40(5): 625–8.
60. de Lourdes Bastos M, Osterbauer B, Mesquita D, Carrera C, Albuquerque M, Silva L, et al. Prevalence of human T-cell lymphotropic virus type 1 infection in hospitalized patients with tuberculosis. *BMC Infect Dis Int J Tuberc Lung Dis.* 2009;13(12):1519–23.
61. Norrgren H, Bamba S, Da Silva Z, Koivula T, Andersson S. Higher mortality in HIV-2/HTLV-1 co-infected patients with pulmonary tuberculosis in Guinea-Bissau, West Africa, compared to HIV-2-positive HTLV-1-negative patients. *Int J Infect Dis.* 2010;14:e142–7.
62. McKee D, Young A, Haeney M. Sarcoidosis and HTLV-1 infection. *J Clin Pathol.* 2005;58(9):996–7.
63. Plancoulaine S, Gessain A, Tortevoeye P, Boland-Auge A, Vasilescu A, Matsuda F, et al. A major susceptibility locus for HTLV-1 infection in childhood maps to chromosome 6q27. *Hum Mol Genet.* 2006;15(22):3306–12.
64. Anaraki Mohammadi G, Sadeghipour A, Vossough P, Nour Mohammadi I, Mirnateghi A. Assessment of the prevalence of human T-lymphotropic virus type 1 among thalassemic patients with frequent blood transfusion in Tehran in 2003. *Razi J Med Sci.* 2005;12(47):19–24.
65. Santos R, Conceição G, Martins M, Kraychete A, Penalva M, Carvalho E, et al. Prevalence and risk factors for Human T-Lymphotropic Virus Type 1 (HTLV-1) among maintenance hemodialysis patients. *BMC Nephrol.* 2017;18(1):64.
66. Moradi A, Mansurian A, Ahmadi A, Ghaemi E, Kalavi K, Marjani A, et al. Prevalence of HTLV-1 antibody among major thalassemic patients in Gorgan (South East of Caspian Sea). *Appl Sci.* 2008;8(2):391.3.
67. Ghaffari J, Kowsarian M, Mahdavi M, Shahi K, Rafatpanah H, Tafreshian A. Prevalence of HTLV-I infection in patients with thalassemia major in Mazandaran, North of Iran. *Jundishapur J Microbiol.* 2012;6(1):57–60.
68. Giuliani M, Rezza G, Lepri A, Di Carlo A, Maini A, Crescimbeni E, et al. Risk factors for HTLV-I and II in individuals attending a clinic for sexually transmitted diseases. *Sex Transm Dis.* 2000;27(2):87–92.
69. Bautista C, Pando M, Reynaga E, Marone R, Saterén W, Montano S, et al. Sexual practices, drug use behaviors, and prevalence of HIV, syphilis, hepatitis B and C, and HTLV-1/2 in immigrant and non-immigrant female sex workers in Argentina. *J Immigr Minor Health.* 2009;11(2):99–104.
70. Nunes D, Boa-Sorte N, Grassi M, Taylor G, Teixeira M, Barreto M, et al. HTLV-1 is predominantly sexually transmitted in Salvador, the city with the highest HTLV-1 prevalence in Brazil. *PLoS One.* 2017;12(2):e0171303.
71. Berini C, Pando M, Bautista C, Eirin M, Peralta L, Weissenbacher M. HTLV-1/2 among high-risk groups in Argentina: Molecular diagnosis and prevalence of different sexual transmitted infections. *J Med Virol.* 2007;79(12):1914–20.
72. Moreira M, Ramos A, Netto E, Brites C. Characteristics of coinfections by HCV and HBV among Brazilian patients infected by HIV-1 and/or HTLV-1. *Braz J Infect Dis.* 2013;17(6):661–6.
73. Murphy E, Wang B, Sacher R, Friley J, Smith J, Nass C. Respiratory and urinary tract infections, arthritis, and asthma associated with HTLV-I and HTLV-II infection. *Emerg Infect Dis.* 2004;10(1):109.
74. Yakova M, Lézin A, Dantin F, Lagathu G, Olindo S, Jean-Baptiste G. Increased proviral load in HTLV-1-infected patients with rheumatoid arthritis or connective tissue disease. *Retrovirology.* 2005;2(1):4.
75. Hindawi S, Badawi M, Fouda F, Mallah B, Mallah B, Rajab H. Testing for HTLV 1 and HTLV 2 among blood donors in



- Western Saudi Arabia: prevalence and cost considerations. *Transfus Med.* 2018;28(1):60–4.
76. Stienlauf S, Yahalom V, Schwartz E, Shinar E, Segal G, Sidi Y. Epidemiology of human T-cell lymphotropic virus type 1 infection in blood donors, Israel. *Emerg Infect Dis.* 2009;15(7):1116–8.
77. Bitar N, Hajj H, Houmani Z, Sabbah A, Otrock Z, Mahfouz R. Adult T-cell leukemia/lymphoma in the Middle East: first report of two cases from Lebanon. *Am Assoc Blood Banks.* 2009;49(9):1859–64.
78. Yahyapour Y, Aghajani K, Mir S, Khademian A, Sadeghi F. Human T-Lymphotropic Virus Type 1 in Blood Donors from Babol County Blood Transfusion Center: A Pilot Study From Northern Iran. *Jundishapur J Microbiol.* 2017;10(9):e13757.
79. Safabakhsh H, Jalalian M, Karimi G. Seroepidemiology of human T-cell lymphotropic virus type-1 (HTLV-1) in Mashhad. *Glob J Health Sci.* 2014;6(5):99.
80. Rafatpanah H, Hedayati-Moghaddam M, Fathimoghaddam F, Bidkhorji H, Shamsian S, Ahmadi S. High prevalence of HTLV-I infection in Mashhad, Northeast Iran: a population-based seroepidemiology survey. *J Clin Virol.* 2011;52(3):172–6.
81. Rafatpanah H, Torkamani M, Valizadeh N, Vakili R, Meshkani B, Khademi H. Prevalence and phylogenetic analysis of HTLV-1 in a segregated population in Iran. *J Med Virol.* 2016;88(7):1247–53.
82. Salehi M, Mostafavi S, Ghasemian A, Gholami M, Kazemi-Vardanjani A, Rahimi M. Seroepidemiology of HTLV-1 and HTLV-2 infection in Neyshabur city, North-Eastern Iran, during 2010-2014. *Iran Biomed J.* 2017;21(1):57.
83. Maghsudlu M, Safabakhsh H, Jamili P. Seroepidemiology of human T-cell lymphotropic virus type-I in blood donors of Northeastern Iran, Sabzevar. *Asian J Transfus Sci.* 2015;9(2):203.
84. Hedayati-Moghaddam M, Tehranian F, Bayati M. Human T-Lymphotropic virus type I (HTLV-1) infection among Iranian blood donors: First case-control study on the risk factors. *Viruses.* 2015;7(11):5736–45.
85. Gessain A, Cassar O. Epidemiological Aspects and World Distribution of HTLV-1 Infection. *Front Microbiol* [Internet]. 2012 Nov 15 [cited 2024 Jul 14];3. Available from: <https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2012.00388/full> DOI: 10.3389/fmicb.2012.00388.
86. Jernigan M, Morcos Y, Lee S, Dohan F, Raine C, Levin M. IgG in brain correlates with clinicopathological damage in HTLV-1 associated neurologic disease. 2003;60(8):1320–7.
87. Izumo S. Neuropathology of HTLV-1-associated myelopathy (HAM/TSP). *Jpn Soc Neuropathol.* 2010;30(5):480–5.
88. Habiballah N, Hassanabady H, Rafatpanah H. Four cases of polyneuropathy due to HTLV-1 infection in Imam Reza Hospital: North East of Iran. *Pak J Med Sci.* 2007;23(2):283.
89. Cavrois M, Gessain A, Gout O, Wain-Hobson S, Wattel E. Common Human T Cell Leukemia Virus Type 1 (HTLV-1) Integration Sites in Cerebrospinal Fluid and Blood Lymphocytes of Patients with HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis Indicate that HTLV-1 Crosses the Blood-Brain Barrier via Clonal HTLV-1-Infected Cells. *J Infect Dis.* 2000;182(4):1044–50.
90. Zehender G, Colasante C, Santambrogio S, De Maddalena C, Masetto B, Cavalli B, et al. Increased risk of developing peripheral neuropathy in patients coinfected with HIV-1 and HTLV-2. *J Acquir Immune Defic Syndr.* 2002;31(4):440–7.
91. Castro NM, Freitas DM, Rodrigues Jr. W, Muniz A, Oliveira P, Carvalho EM. Urodynamic features of the voiding dysfunction in HTLV-1 infected individuals. *Int Braz J Urol.* 2007;33:238–45.
92. Castro NM, Rodrigues Jr. W, Freitas DM, Muniz A, Oliveira P, Carvalho EM. Urinary symptoms associated with human T-cell lymphotropic virus type I infection: evidence of urinary manifestations in large group of HTLV-I carriers. *BMC Infect Dis Urol.* 2007;69(5):813–8.
93. Castro N, Oliveira P, Freitas D, Rodrigues W, Muniz A, Carvalho E. Erectile dysfunction and HTLV-I infection: a silent problem. *Int J Impot Res.* 2005;17(4):364–9.
94. Biswas H, Engstrom J, Kaidarova Z, Garratty G, Gibble J, Newman B, et al. Neurologic abnormalities in HTLV-I and HTLV-II-infected individuals without overt myelopathy. *Neurology.* 2009;73(10):781–9.
95. Tanajura D, Castro N, Oliveira P, Neto A, Muniz A, Carvalho NB, et al. Neurological manifestations in human T-cell lymphotropic virus type 1 (HTLV-1)-infected individuals without HTLV-1-associated myelopathy/tropical spastic paraparesis: a longitudinal cohort study. *BMC Clin Infect Dis.* 2015;61(1):49–56.
96. Furtado M d. SBS, Andrade RG, Romanelli LCF, Ribeiro MA, Ribas JG, Torres EB, et al. Monitoring the HTLV-1 proviral load in the peripheral blood of asymptomatic carriers and patients with HTLV-associated myelopathy/tropical spastic paraparesis from a Brazilian cohort: ROC curve analysis to establish the threshold for risk disease. *J Med Virol.* 2012;84(4):664–71.
97. Galvão-Castro AV, Boa-Sorte N, Kruschewsky RA, Grassi MFR, Galvão-Castro B. Impact of depression on quality of life in people living with human T cell lymphotropic virus type 1 (HTLV-1) in Salvador, Brazil. *PLoS One Qual Life Res.* 2012;21(9):1545–50.
98. Sasannejad P, Azarpazhooh MR, Rahimi H, Ahmadi AM, Ardakani AM, Saber HR. Guillain-Barré-like Syndrome, as a rare presentation of adult T-cell leukemia-lymphoma (ATLL): A case report. *Iran Red Crescent Med J.* 2012;14(8):497.



99. Bakhshae M, Sorouri A, Shoeibi A, Boustani R, Golhasani-Keshtan F, Amali A, et al. Is human T-lymphotropic virus type 1 infection associated with hearing loss? *The Laryngoscope*. 2015;125(4):956–60.
100. Ali A, Char G, Hanchard B. Chronic inflammatory demyelinating polyneuropathy in a patient infected with human T lymphotropic virus type I. *BMJ Case Rep*. 2009;2009:bcr0320091680.
101. Montano SM, Zunt JR, Rodriguez L, Quispe I, Rodriguez C, Altamirano J, et al. Human T Cell Lymphotropic Virus Type 1 Infection and Early Neurologic Development: A Pilot Study of 48 Children. *Clin Infect Dis*. 2004;39(7):1079–82.
102. Kendall EA, González E, Espinoza I, Tipismana M, Verdonck K, Clark D, et al. Early neurologic abnormalities associated with human T-cell lymphotropic virus type 1 infection in a cohort of Peruvian children. *J Pediatr*. 2009;155(5):700–6.
103. Kuriyama N, Niwa F, Watanabe Y, Yamada K, Tokuda T, Mizuno T, et al. Evaluation of autonomic malfunction in HTLV-1 associated myelopathy (HAM). *Auton Neurosci*. 2009;150(1):131–5.
104. Leite AC, Silva MTT, Alamy AH, Afonso CR, Lima MA, Andrada-Serpa MJ, et al. Peripheral neuropathy in HTLV-I infected individuals without tropical spastic paraparesis/HTLV-I-associated myelopathy. *J Neurol Neurosurg*. 2004;251(7):877–81.
105. Ludimila L, Borges SAL, Roberto d. SPS, Ferreira RLC, Bárbara d. FCPA, Novaes CL, et al. Electrophysiological Analysis Shows Dizziness as the First Symptom in Human T Cell Lymphotropic Virus Type-Associated Myelopathy/Tropical Spastic Paraparesis. *AIDS Res Hum Retroviruses*. 2015;31(6):649–54.
106. Merle H, Cabre P, Olindo S, Merle S, Smadja D. Ocular lesions in 200 patients infected by the human T-cell lymphotropic virus type 1 in martinique (French West Indies). *Am J Ophthalmol*. 2002;134(2):190–5.
107. Ozden S, Mouly V, Prevost MC, Gessain A, Butler-Browne G, Ceccaldi PE. Muscle Wasting Induced by HTLV-1 Tax-1 Protein: An in Vitro and in Vivo Study. *Am J Pathol*. 2005;167(6):1609–19.
108. Saeidi M, Sasannejad P, Foroughipour M, Shahami S, Shoeibi A. Prevalence of peripheral neuropathy in patients with HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). *Acta Neurol Belg*. 2011;111(1):41–4.
109. Kiwaki T, Umehara F, Arimura Y, Izumo S, Arimura K, Itoh K, et al. The clinical and pathological features of peripheral neuropathy accompanied with HTLV-I associated myelopathy. *J Neurol Sci*. 2003;206(1):17–21.
110. Espindola OM, Vizzoni AG, Lampe E, Andrada-Serpa MJ, Araújo AQ, Leite ACC. Hepatitis C virus and human T-cell lymphotropic virus type 1 co-infection: impact on liver disease, virological markers, and neurological outcomes. *Int J Infect Dis*. 2017;57:116–22.
111. Primo JRL, Brites C, de Oliveira M d. FS, Moreno-Carvalho O, Machado M, Bittencourt AL. Infective dermatitis and human T cell lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis in childhood and adolescence. *Clin Infect Dis*. 2005;41(4): 535–41.
112. Carod-Artal F, Mesquita HM, Ribeiro SL. Neurological symptoms and disability in HTLV-1 associated myelopathy. *Neurologia*. 2008;23(2):78–84.
113. Cervilla J, Cartier L, García L. Brain and spinal cord magnetic resonance imaging in spastic paraparesis associated to human T-lymphotropic virus. *Rev Med Chil*. 2006;134(8):1010–8.
114. Milagres AC, Jorge MLS, Marchiori PE, Segurado AA. Human T cell lymphotropic virus type 1-associated myelopathy in São Paulo, Brazil. *Neuroepidemiology*. 2002;21(3):153–8.
115. Morgan DJ, Caskey MF, Abbehusen C, Oliveira-Filho J, Araújo C, Porto AF, et al. Brain Magnetic Resonance Imaging White Matter Lesions Are Frequent in HTLV-I Carriers and Do Not Discriminate from HAM/TSP. *AIDS Res Hum Retroviruses*. 2007;23(12):1499–504.
116. Puccioni-Sohler M, Gasparetto E, Cabral-Castro MJ, Slatter C, Vidal CM, Cortes RD, et al. HAM/TSP: association between white matter lesions on magnetic resonance imaging, clinical and cerebrospinal fluid findings. *Arq Neuropsiquiatr*. 2012;70(4):246–51.
117. Netto EC, Brites C. Characteristics of Chronic Pain and Its Impact on Quality of Life of Patients With HTLV-1-associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP). *Clin J Pain*. 2011;27(2):131–5.
118. Dimber R, Guo Q, Bishop C, Adonis A, Buckley A, Kocsis A, et al. Evidence of Brain Inflammation in Patients with Human T-Lymphotropic Virus Type 1-Associated Myelopathy (HAM): A Pilot, Multimodal Imaging Study Using 11C-PBR28 PET, MR T1-Weighted, and Diffusion-Weighted Imaging. *J Nucl Med*. 2016;57(12):1905–12.
119. Lezin A, Olindo S, Olié S, Varrin-Doyer M, Marlin R, Cabre P, et al. Human T lymphotropic virus type I (HTLV-I) proviral load in cerebrospinal fluid: a new criterion for the diagnosis of HTLV-I-associated myelopathy/tropical spastic paraparesis? *J Infect Dis*. 2005;191(11):1830–4.
120. Carod-Artal F. Immunopathogenesis and treatment of the myelopathy associated to the HTLV-I virus. *Rev Neurol*. 2009;48(3):147–55.
121. Vallinoto ACR, Santana B, et al. HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis Is Not Associated with SNP rs12979860 of the IL-28B Gene. *Mediators Inflamm*. 2015;2015:7.
122. Andrade RCP, Neto JA, Andrade L, Oliveira TS, Santos DN, Oliveira CJV, et al. Effects of Physiotherapy in the Treatment





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- of Neurogenic Bladder in Patients Infected With Human T-Lymphotropic Virus 1. *Urology*. 2016;89:33–9.
123. Araya N, Takahashi K, Sato T, Nakamura T, Sawa C, Hasegawa D, et al. Fucoidan therapy decreases the proviral load in patients with human T-lymphotropic virus type-1-associated neurological disease. *Antivir Ther*. 2011;16(1):89–97.
124. Borges J, Baptista AF, Santana N, Souza I, Kruschewsky RA, Galvão-Castro B, et al. Pilates exercises improve low back pain and quality of life in patients with HTLV-1 virus: A randomized crossover clinical trial. *J Bodyw Mov Ther*. 2014;18(1):68–74.
125. Buell KG, Puri A, Demontis MA, Short CL, Adonis A, Haddow J, et al. Effect of Pulsed Methylprednisolone on Pain, in Patients with HTLV-1-Associated Myelopathy. *PLOS ONE*. 2016;11(4):e0152557.
126. Novaes R, Freire-de-Lima CG, de Albuquerque RC, Affonso-Mitidieri OR, Espindola O, Lima MA, et al. Modulation of glutathione intracellular levels alters the spontaneous proliferation of lymphocyte from HTLV-1 infected patients. *Immunobiol*. 2013;218(9):1166–74.
127. Rafatpanah H, Rezaee A, Etemadi MM, Hosseini RF, Khorram B, Afsahr L, et al. The impact of interferon-alpha treatment on clinical and immunovirological aspects of HTLV-1-associated myelopathy in northeast of Iran. *J Neuroimmunol*. 2012;250(1–2):87–93.
128. Pashabayg CR, Momenifar N, Malekpour SA, Sadeghi M, Froushani AR, Rafatpanah H, et al. Phylogenetic and phylodynamic study of Human T-cell lymphotropic virus Type 1 (HTLV-1) in Iran. *Infect Genet Evol*. 2020;85:104426.
129. Ziaee M, Azizee R, Namaei MH. Prevalence of HCV infection in hemodialysis patients of South Khorasan in comparison With HBV, HDV, HTLV I/II, And HIV infection. *Bangladesh J Med Sci*. 2014;13(1):36.
130. Bitar N, Hajj EH, Houmani Z, Sabbah A, Otrrock ZK, Mahfouz R, et al. Adult T-cell leukemia/ lymphoma in the Middle East: first report of two cases from Lebanon. *Transfusion (Paris)*. 2009;49(9):1859–64.
131. Hedayati-Moghaddam MR, Tehranian F, Bayati M. Human T-Lymphotropic virus type I (HTLV-1) infection among Iranian blood donors: First case-control study on the risk factors. *Viruses*. 2015;7(11):5736–45.
132. Karimi G, Zadsar M, Pourfathollah AA. Seroprevalence and geographical distribution of human T-lymphotropic virus type 1 among volunteer blood donors in endemic areas of Iran. *Virol J*. 2017;14:1–9.
133. Habibabadi HM, Parsania M, Pourfathollah AA, Bahrami A, Sharifi Z. Prevalence and phylogenetic analysis of HTLV-1 in blood donors in Golestan Province, in the Northeast of Iran. *J Virol Methods*. 2021;290:114073.
134. Hezave YA, Sharifi Z, Kermani FR, Shahabi M. Association of the rs4143815 polymorphism of PDL1 gene with HTLV-1 infection and proviral load in asymptomatic blood donors in northeast Iran. *Microbiol Immunol*. 2022;66(6):324–9.
135. Hamidi S, Bashizadeh-Fakhar H, Nazemi A. Identification of Human T-Cell Lymphotropic Virus Type 1 Pro-Invasion in Patients with  $\beta$ -Thalassemia Major Using TaqMan Real-Time PCR in Tonekabon, Iran. *Zahedan J Res Med Sci*. 2018;20(5):e59961.
136. Shoebibi A, Rafatpanah H, Azarpazhooh A, Mokhber N, Hedayati-Moghaddam MR, Amiri A, et al. Clinical features of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in northeast Iran. *Acta Neurol Belg*. 2013;113:427–33.
137. Rafatpanah H, Poursina Z, Boostani R, Marzouni HZ, Atabaki M, Hosseini RF, et al. A significant association between CXCL10-1447 A> G and IL18-607 C> A gene polymorphism with human T-cell lymphotropic virus type 1 associated myelopathy/tropical spastic paraparesis (HAM-TSP), a case-control report from city of Mashhad, Iran. *J Neurovirol*. 2021;27:249–59.