

# Inflammatory manifestations of HTLV-1 and their therapeutic options

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Human T lymphotropic virus type 1 (HTLV-1) is one of the most intriguing retroviruses infecting humans. Most commonly, infection remains undetected, since it does not cause obvious harm, yet in 4–9% of patients, this infection can be devastating, causing adult T-cell leukemia/lymphoma and/or HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). This review concentrates on all inflammatory aspects of HTLV-1 infection: HAM/TSP, HTLV-1 associated uveitis, HTLV-1 associated conjunctivitis, sicca syndrome and interstitial keratitis, HTLV-1 associated Sjögren's syndrome, Hashimoto's thyroiditis and Graves' disease, HTLV-1 associated pulmonary disease, infective dermatitis associated with HTLV-1, HTLV-1 associated inflammatory myositis and HTLV-1 associated arthritis. With the exception of HAM/TSP treatment, studies of these conditions are sparse and even for HAM/TSP, the level of evidence is limited. While control or elimination of infection remains a goal, most therapy beyond symptomatic management is directed at the immune response to HTLV-1.

**KEYWORDS:** arthritis • Graves' • HAID • HAM/TSP • Hashimoto • HAU • HTLV • infective dermatitis • inflammation • keratitis • polymyositis • Sjögren's • thyroiditis • uveitis

## Aim

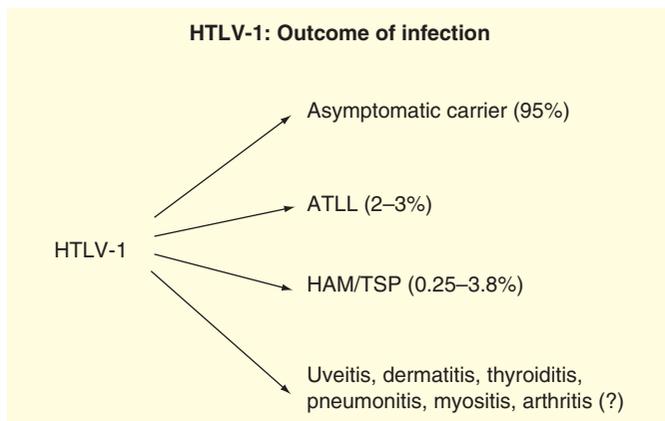
The aim of this review is to summarize knowledge about the inflammatory conditions associated with human T lymphotropic virus type 1 (HTLV-1) infection, collectively referred to as HTLV-1 associated inflammatory disease (HAID). Each HAID, especially HTLV-1 - associated myelopathy/tropical spastic paraparesis (HAM/TSP), will be considered in detail, after the provision of background information on HTLV-1 virology, epidemiology, route of transmission and immunology.

## Structure & transmission of HTLV-1

HTLV-1 is a complex retrovirus in the genus *Deltaretrovirus* of the subfamily *Orthoretrovirinae* of the retroviridae family of viruses [1]. HTLV-1 shares its routes of transmission with other blood-borne infections such as the HIV and hepatitis viruses B and C [2]. The chance of transmission depends on the efficiency of the route of transmission, infectivity of the donor, susceptibility of the recipient and the number of exposures. Transmission risk is therefore highest with non-leukocyte depleted

blood transfusions (8.6–64%) [3], presumed to be high with organ transplantation, sharing needles and syringes based on anecdotal reports, less so with transplacental exposure (~3–5% of all off-spring of infected mothers), breastfeeding (up to 22% if breast-fed to 18 months) and unprotected sexual intercourse (~1% per annum between stable, discordant partners) [4–8]. In endemic areas, transmission peaks at two time points [9], early in life through breastfeeding and after childhood, through unprotected sexual intercourse [10], with some suggestion of increased risk of infection in post-menopausal women. Seropositivity has been associated with older age [9], female gender [11], life-time number of sexual partner [9], commercial sex work [12] and history of genital ulcers [13].

*In vivo* the vast majority of HTLV-1 is found in CD4<sup>+</sup> T lymphocytes [14]. Since *in vitro* cell-free virions have extremely low infectivity [15] and transfusion with cell-free blood products appears to carry a negligible risk of HTLV-1 infection [4], it is assumed that transmission requires virus-containing T lymphocytes and direct cell-to-cell contact [16]. How exactly the



**Figure 1. Outcome of human T lymphotropic virus**

**type 1 infection.** Most patients with HTLV-1 infection remain asymptomatic but about 5% of patients may develop disease. ATLL: Adult T-cell leukemia/lymphoma; HAM/TSP: HTLV-1-associated myelopathy/tropical spastic paraparesis; HTLV-1: Human T lymphotropic virus type 1.

cell-to-cell transmission of HTLV-1 occurs *in vivo* remains unclear, but extracellular viral assemblies in biofilms [17] and formation of a tight virological synapses [18] have been observed *ex vivo*.

### Epidemiology of HTLV-1 infection

It has been estimated that 10–20 million people are infected with HTLV-1 worldwide [19,20]. Prevalence data are mostly based on studies of blood donors, pregnant women, sex workers or injecting drug users (IDU). There is a paucity of data from general population studies [21]. The areas of highest prevalence are in Japan (10–37%) [22,23], Caribbean islands (1.3–8.4%) [24], many African regions (3–5%) [20,25] and South America (1–5.7%) [20,26,27]. Clusters of high endemicity have been detected in Romania, Northern Iran and Melanesia (0.2–5.8%) [28–31]. HTLV-1 seroprevalence is low in Europe and North America (<0.1%) [32,33], but even here there can be significant regional differences [34].

### Diagnosis of HTLV-1 infection

In routine clinical practice, HTLV-1 infection is diagnosed through serological testing of peripheral blood for anti-HTLV antibodies [35]. Screening is most commonly performed through ELISA and HTLV-1 infection is confirmed by detection of antibodies against gag (p19 and p24) and envelope (gp21 and gp46) proteins by western blot or immunoblot. Through the addition of recombinant gp46-1 and gp46-2 to the blots, HTLV-1 and HTLV-2 can usually be discriminated [35]. The immune response to HTLV-1 is strong and the serum antibody titer, which correlates with the HTLV-1 virus load, may be as high as 1:256,000 [36–38]. In most cases, HTLV-1 proviral DNA can be quantified by PCR in peripheral blood mononuclear cells (PBMCs), which is usually reported as HTLV DNA copies per 100 PBMCs (or %) [39]. Since each infected cell usually carries a single provirus [40] (except in some cases of

adult T-cell leukemia/lymphoma [ATLL]), the proviral load (pVL) equates to the percentage of infected cells. In asymptomatic carriers (ACs), the viral load persists at a median low level of 1.55 (0.0003–28) copies/100 PBMCs (1.55%) and in patients with HAM/TSP a median viral load of 14 (0.002–112) copies/100 PBMCs (14%) has been observed [39,41]. HTLV-1 qPCR can be used for rapid confirmation of HTLV-1 associated lymphomas by detecting 100% of more pVL in lymphoma cells or other tissue samples [42].

### Inflammatory conditions associated with HTLV-1

Although in the majority of cases HTLV-1 carriers remain asymptomatic (FIGURE 1), 2–6% of infected individuals develop ATLL [43,44] and a further 2–3% develop HAM/TSP [45,46]. HTLV-1 is also associated with uveitis [47,48], dermatitis [49], alveolitis/bronchiectasis [50], arthritis [51], nephritis [52] and myositis (FIGURE 2) [53], but there are few data on prevalence.

### Factors associated with inflammation

HTLV-1 is thought to cause local and systemic inflammatory disease. Two hypotheses for the pathogenesis of HAID have been proposed [54]:

- *Autoimmune antigen mimicry*: host immune system attacks self-cells because of antigen cross-reaction with HTLV-1 antigens;
- *Innocent bystander*: in the course of the response to HTLV-1 infected T cells, HTLV-1 specific cytotoxic cells excrete cytokines that damage surrounding tissue.

As yet, there are no validated surrogate markers that predict the development of HAID. In a Japanese cohort of HAM/TSP, information on gender, age, HTLV-1 pVL, subgroup and genotypes at loci HLA-A, HLA-C, SDF-1 and TNF- $\alpha$  allowed the correct identification in 88% of cases [55]. In another study, only brisk patellar deep tendon reflexes and the poly-lobulated lymphocytes known as ‘flower-cells’ were associated with HAM/TSP [56]. HAM/TSP is the most commonly investigated HTLV-1 associated inflammatory condition since it has the highest reported prevalence. Several factors have been associated with the presence of HAM/TSP:

- Female gender [57–59].
- Ages of 40–50 years [57–59].
- Higher HTLV-1 pVL, particularly when more than 1% PBMCs are infected [38,41,60–62]. Although some ACs have high pVL [63], higher set points are commonly observed in patients with HAM/TSP [60,64]. HTLV-1 pVL has been reported to be higher in those patients with a later age of onset of HAM/TSP, and is associated with higher cerebrospinal fluid (CSF) HTLV-1 antibodies [65]. In HAM/TSP, higher HTLV-1 pVL have also been reported in the CSF of patients compared with the peripheral blood [66].
- High HTLV-1 Tax protein expression and low cytotoxic T lymphocyte (CTL) lysis [67], IL-2-secreting Tax-specific CD8<sup>+</sup> T cells and IFN- $\gamma$ -secreting Tax-specific CD4<sup>+</sup> T cells [68], positive HTLV-1 HBZ protein expression [69] and low HBZ affinity of CD8<sup>+</sup> T-cell response are directly

correlated with presence of HAM/TSP [70]. Elevated levels of local HTLV-1 infected CD4<sup>+</sup> T cells, cytotoxic T cells and chemokines have been found in the aqueous liquid of the eye and CSF in patients with uveitis and HAM/TSP. CXCL10, CXCL9 and increased levels of INF- $\gamma$ , TNF- $\alpha$ , IL-2 and IL-6 have been found in the blood and CSF of patients with HAM/TSP [71–74].

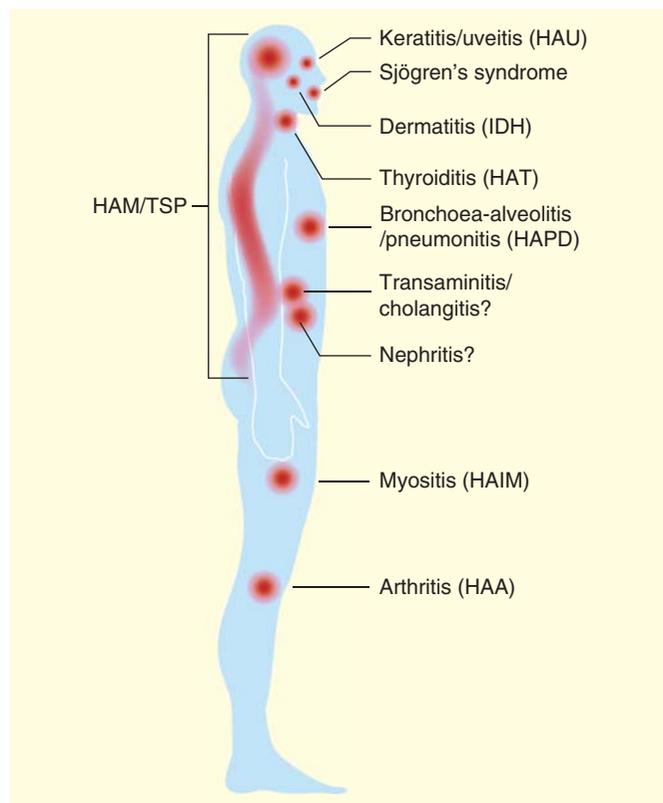
Observations made in the recently published excellent review of the immunopathology of HAM/TSP by Saito and Bangham [75] may also apply to other HTLV-1 associated inflammatory conditions, since HAID coexist commonly in the same patient groups. They give a detailed overview of the currently published data:

- Among different HTLV-1 Tax protein subgroups, HTLV-1 Tax subgroup A was more frequently observed in HAM/TSP patients [55].
- The integration of HTLV-1 into transcriptionally active sites and near to genes correlates with high *ex vivo* Tax expression and the presence of HAM/TSP and infective dermatitis associated with HTLV-1 (IDH) [76–78].
- In HAM/TSP and IDH, the most abundant clone tends to proliferate, potentially allowing other HTLV-1 associated disease to develop [77,78].
- HTLV-1 pVL is under polymorphic control. Three host genetic factors: the promoter TNF- $\alpha$ -863A allele and longer CA repeat alleles of MMP-9 predisposes to disease and IL-10–592A, SDF-1 +801A 3'UTR and IL-15 +191C alleles confer protection from HAM/TSP and have been found to influence viral load [55].
- The class I gene HLA A\*02 is associated with twofold reduction in viral load and three- to fourfold reduction in the risk of HAM/TSP [79,80]. HLA A\*02 restricted CTL are very efficient at eliminating HTLV-1 infected lymphocytes, especially in HTLV-1 tax subgroup B [81] in the Japanese population. However, this protection was not seen in the Iranian population [82].
- Cw\*08 has protective effects similar to and independent from HLA-A02 [79,80].
- HLA-B54 is associated with increased pVL and occurrence of disease [79,80].
- HLA-DRB1-0101 is also associated with increased pVL and higher risk of HAM/TSP but only in the absence of HLA-A02 [79,80].
- Higher levels of gene expression of granzyme A, granzyme B, granulysin and perforin were associated with lower pVL [83].

### HTLV-1 associated myelopathy/tropical spastic paraparesis

#### History

A slow-onset spastic paraparesis in adults was first described by Cruikshank in 1956 [84], but Strachan may have included HAM/TSP in his Jamaican Neuropathies in 1888 [85]. An association between myelopathy and HTLV-1 seropositivity in serum and CSF was reported in 1985 as TSP in



**Figure 2. Distribution of human T lymphotropic virus 1-associated inflammatory diseases by body sites.**

Hotspots indicate different organs, which may be affected by HTLV-1: CNS, eye, skin, mucosa, thyroid, lungs, liver, kidneys, muscle and joints.

HAM/TSP: HTLV-1-associated myelopathy/tropical spastic paraparesis; HAU: HTLV-1-associated uveitis; IDH: Infective dermatitis associated with HTLV-1; HAT: HTLV-1-associated thyroiditis; HAPD: HTLV-1-associated pulmonary disease; HAIM: HTLV-1-associated inflammatory myositis; HAA: HTLV-1-associated arthritis.

Jamaica [86] and in 1986 as HAM in Japan [87]. A study comparing the Miyazaki cohort in Japan with the Food Handler cohort in Jamaica gave some insight into the regional differences of HAM/TSP [57,88]. Although the mean HTLV-1 viral load was similarly high ( $p = 0.26$ ), female carriers were more commonly affected in the Jamaican cohort with higher mean HTLV-1 antibody titers ( $p = 0.03$ ) and higher mean anti-Tax antibodies ( $p = 0.002$ ). Most strikingly, the difference lay in the incidence of HAM/TSP, which was 1/100,000 in the Japanese compared with 20/100,000 in the Jamaican population.

#### Clinical course

Patients with HAM/TSP may present with backache or falls. Patients typically complain of stiff legs, weakness and heaviness of the thighs, the inability to rise from a chair or to climb stairs, lower backache and a wide range of sensory disturbances of lower limbs. Constipation is common as are urinary frequency, urgency and incontinence, while a significant minority are unable to fully empty the bladder.

Clinically, there is evidence of lower limb proximal muscle weakness. Typically, cranial nerves and upper limbs are not affected. Initially, there is generalized hyperreflexia and upgoing plantar (Babinski's sign) responses and later diminished or loss of ankle reflexes. Tone is commonly increased and clonus of one or both ankles may be present. Neuropathic pain is a major feature, which may be localized in the lower back or radiate down one or both legs [89–92].

The natural history of HAM/TSP is chronic and a slow deterioration is seen in most patients. Studies of HAM/TSP prior to 1996 described progression of the myelopathy during the first year followed by a plateau phase [65,93]. However, studies since 1996 describe a more insidious onset with delayed diagnosis and continuous progression in both Japanese and Afro-Caribbean cohorts [91,94]. Sub-groups of patients, who progress rapidly or are non-progressors, have been identified [41]. A much more rapid onset and progression of HAM/TSP has been reported in patients transfused with HTLV-1 infected blood [90].

A Japanese study of 64 patients with HAM/TSP followed-up for 10 years, showed deterioration of gait, muscle power and bladder function in 56%; 41% remained unchanged and 3% improved clinically. The rate of disease progression was associated with higher HTLV-1 viral load and older age of onset (>65 years) as well as a history of blood transfusions [94].

In 2006, a study group in Martinique published longitudinal data on 123 Afro-Caribbean patients with HAM/TSP followed-up for a median of 9 years. Of these patients, 81.3, 56.9 and 36.6% patients needed one walking stick, two walking sticks or a wheelchair, respectively, with a median time from onset of HAM/TSP to the use these aids of 6, 13 and 21 years. The time from onset to wheelchair dependence was significantly shorter in patients who developed HAM/TSP at an older age (>50 years) and who had a high HTLV-1 viral load; 15.4% of patients with HAM/TSP died of complications directly attributed to myelopathy [91].

A UK-based 15-year natural history study of HAM/TSP of 48 patients reported a mean age of onset at 46 years, and the most common first recalled symptom was unilateral leg weakness. The median times from onset to unilateral, bilateral walking aid, frame or a wheelchair were 11, 11.2, 11.3 and 18 years. The overall average deterioration in timed walk in patients whose need for aid did not change was 2 s/10 m/year. Three patients progressed rapidly and were unable to walk within 2 years. Six patients were non-progressors. The median HTLV-1 viral load was high and remained unchanged at 14%. The mortality was 2.4/100 person-year follow-up [41].

Histopathology of new lesions in the CNS showed perivascular infiltration with CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes [95]. Inflammatory infiltration was seen in the brain and the spinal cord with the same composition of cell subsets [96]. In old lesions, CD8<sup>+</sup> cells predominate but lesions become atrophic and acellular with disease progression [65,95,97]. These changes have been described as active, chronic meningomyelitis mostly involving the spinal cord [65].

MRI studies have indicated sites of predilection. In HAM/TSP patients, atrophy of cervical and thoracic cord as well as atrophy and white matter brain lesions which were asymmetrical and mostly periventricular and subcortical have been documented [66,98,99]. The 3D MR Images reveal the spinal cord atrophy to be more extensive and marked than previously realized [100]. Lesions seen on MRI in patients with multiple sclerosis are different from those seen in patients with HAM/TSP [101].

### Pathogenesis

For the CNS to be affected, HTLV-1 and anti-HTLV-1 cytotoxic cells need to be able to overcome the blood–brain barrier. The HTLV-1 receptors, glucose transporter 1, neuropilin-1 and heparan sulfate proteoglycans, have been shown to be present in spinal cord autopsies of patients with HAM/TSP and uninfected subjects. Endothelial cells could be productively infected with HTLV-1 *in vitro* altering the expression of the tight-junction proteins. This increased the permeability of the junction allowing the passage of lymphocytes [102].

### Diagnosis

In order to make the diagnosis of HAM/TSP, the patient must be anti-HTLV-1 antibody positive. High HTLV-1 pVL in the blood and analysis of CSF for signs of inflammation will aid the diagnosis. A 2006 revision of the original WHO diagnostic criteria of HAM/TSP, referred to as Belem Criteria, defines three levels of ascertainment for HAM/TSP diagnosis: definite, probable and possible after excluding all conditions that could mimic HAM/TSP [103]. Division of HAM/TSP into subgroups has been proposed recently: rapid, slow and non-progressing disease [41,74]. The majority of patients are slow progressors.

### Complications of HAM/TSP

Most patients will need walking aids within a decade and become wheelchair or bed bound after another decade [41]. Due to the inability to control the bladder sphincter, patients may suffer from urinary retention, recurrent and chronic urinary infections and hydronephrosis with renal failure [104]. Poor immobility puts patients at risk of lower respiratory tract abnormalities, which is also a complication associated with death from rapidly progressing HAM/TSP [105,106].

Patients with HAM/TSP may also be affected by one or more of the additional HAIDs described below. Patients co-infected with HTLV-1 and *Strongyloides stercoralis* have been reported to suffer from hyperinfection, which has a high morbidity and mortality rate [107].

### Treatment

Despite various reports on therapy since 1990, there is no internationally agreed treatment for HAM/TSP [108]. Study outcomes, cohorts and investigational products vary, the studies are usually small and include HAM/TSP patients at different stages of disease. The most common outcome measures are clinical improvement and a reduction of HTLV-1 pVL, but

inhibition of lymphocyte migration and CTL activity has been examined. Most studies are open label and of small size, which inevitably introduces bias. Unfortunately, there is a lack of subsequent or comparative data to support the findings of proof-of-concept studies [108]. So far, only two randomized controlled trials, one of which was placebo controlled, have been conducted in HAM/TSP. Preventing HAM/TSP from developing in ACs at risk, namely in those with high titer of antibodies to HTLV-1, high HTLV-1 pVL and specifically high levels of *ex vivo* Tax expression has not been studied.

To date, therapeutics in HAM/TSP include: antiretrovirals [109], corticosteroids [110,111], steroid-sparing immunosuppressive drugs such as azathioprine [110], methotrexate [112], ciclosporin-A [113], monoclonal antibodies [114], interferons [110,115] and histone de-acetylase inhibitors [116,117]. Currently, three proof-of-concept studies are being conducted: testing monoclonal antibodies against IL-15 (humanized Mik- $\beta$ -1, in the USA), anti-CCR4 antibodies (mogamulizumab, in Japan) and the integrase inhibitor raltegravir in patients with HAM/TSP (in the USA). Nucleoside analog reverse transcriptase inhibitors (NRTI) have been of great interest with the aim to reduce the HTLV-1 pVL as one of the main biological markers associated with HAM/TSP. High-dose zidovudine, a NRTI, tested in patients with HAM/TSP was associated with 50% improvement of time required to walk 50 feet and an improvement of mean Expanded Disability Status Scale from 5.5 to 4.0 in seven ambulant patients with HAM/TSP in 1993 [118].

The only randomized, double-blind, placebo-controlled trial of 16 patients with HAM/TSP did not detect clinical, viral or immunological response to the combination of zidovudine 300 mg and lamivudine 150 mg twice daily after 24–48 weeks therapy. This lack of response was attributed to the long duration of HAM/TSP, potentially inadequate intracellular concentrations of active triphosphate NRTI metabolites and/or the possibility that HTLV-1 reverse transcriptase does not play a major role in maintaining pVL [119]. Subsequent *ex vivo* analysis showed pre-treatment sensitivity of HTLV-1 reverse transcriptase to zidovudine but resistance to lamivudine, which remained unchanged during 48 weeks of treatment [120]. This means that the patients were effectively receiving zidovudine monotherapy but this still does not account for the lack of effect as the virus remained fully sensitive to zidovudine.

Lamivudine, tenofovir and raltegravir have been shown to be potent HTLV-1 reverse transcriptase and integrase inhibitors when tested *in vitro* but have not been successful in reducing pVL in HAM/TSP patients [121–124]. Raltegravir is currently being tested in ACs with the aim to reduce pVL (ClinicalTrial.gov) and in HAM/TSP to assess immunologic and virological outcome measures (NIH protocol # 13-N-0135).

IFN- $\alpha$  was reported to influence the clinical outcome of HAM/TSP in an open study [110]. This was followed by a randomized, double-blind, dose-finding trial where daily subcutaneous 3.0 MU IFN- $\alpha$  for 4 weeks was found to be more

effective compared with 0.3 and 1.0 MU doses. The total follow-up was 8 weeks. The downside of this treatment is that it is parenteral and may be poorly tolerated [115]. INF- $\beta$ 1 was tested in 12 HAM/TSP patients in an uncontrolled proof-of-concept study. Although some viral and immunological markers changed, significant and long-lasting clinical benefits were not detected [125]. However, it is not clear if this intervention prevented disease progressions.

Oral corticosteroids have been reported to be of short-term benefit in observational studies [110,126]. Methylprednisolone, 1 g/day for 3 days, every 3–4 months seemed to improve the Incapacity Status Scale by 25% but not Disability Status Scale or Osame's Motor Disability Scales after 2.2 years mean follow-up. Patients who benefited most also received physiotherapy and the significance of the improvement was lost by the third round of infusion. This study does not comment on the patients' experience of life quality or pain score.

However, high-dose corticosteroid treatment is known to cause early and late side effects and is therefore not recommended long term [127]. Moreover, patients continue to progress once treatment is stopped [111].

## Other HTLV-1 associated inflammatory diseases

### HTLV-1 associated uveitis

An association between idiopathic uveitis and HTLV-1 infection was first made in Kyushu, an HTLV-1 endemic region of Japan [128,129]. HTLV-1 associated uveitis (HAU) has since been reported in Brazil and Martinique [59,130]. HAU occurs in patients with other HTLV-1 associated inflammatory conditions such as HAM/TSP [131] and Graves' disease/autoimmune thyroiditis [132–134]. Two cases of HAU have been reported in association with tubulointerstitial nephritis [52].

HAU is mostly unilateral (60%) more common in women (60%) below the age of 50 years, but children can also be affected [135]. Patients present with sudden onset of a painful and red eye with floaters obscuring vision and are diagnosed with intermediate uveitis [59,87,131,136]. HTLV-1 antibodies were detected in the vitreous fluid of all patients with HAU [137]. The HTLV-1 viral load is increased in patients with HAU (3.84 copies per 100 PBMCs [%]) compared with asymptomatic carriers (<1%) [61]. The pVL in the inflamed eye was significantly higher compared with peripheral blood [49].

The majority of aqueous humor infiltrating cells were CD3<sup>+</sup>CD4<sup>+</sup>CD8<sup>-</sup> T cells positive for HTLV-1 DNA [73,138]. Inflammatory cells expressing viral mRNA as well as virus particles were seen in T-cell clones derived from the ocular fluid. These cells produced IL-1 $\alpha$ , IL-2, IL-3, IL-6, IL-8, IL-10, TNF- $\alpha$ , IFN- $\gamma$  and GM-CSF, which are highly associated with intraocular inflammation [73,138]. Similar to HAM/TSP, the CD4<sup>+</sup>CD25<sup>+</sup> T-cell fraction of PBMCs and serum levels of soluble IL-2 receptors (sIL2R or sCD25) were also significantly higher in patients with HAU than in seronegative healthy controls [136].

Topical or systemic corticosteroids and mydriatics usually improve the symptoms rapidly but relapse is common [59].

### **HTLV-1 associated conjunctivitis sicca syndrome & interstitial keratitis**

The most comprehensive report on ocular disease is a prospective case series of 200 HTLV-1 infected patients (39% ACs and 62% HAM/TSP patients) in Martinique. Apart from uveitis, keratoconjunctivitis sicca was found in 74 patients (37%), accompanied by lympho-plasmocytoid infiltration of the secondary salivary glands rated 3 or 4 on the Chisholm scale in nearly 50% of cases. Ocular pruritus was the most commonly reported complaint. No filamentous keratitis, ulceration or corneal neo-vascularization was observed. Interstitial keratitis was observed in 10% of patients. The essential characteristics were rounded, cloudy, anterior stromal opacities that were whitish, bilateral, painless and without ulceration or neo-vascularization, which did not respond to local corticosteroid therapy. Both keratoconjunctivitis sicca (46 vs 23%) and interstitial keratitis (15 vs 3%) were more common in patients with HAM/TSP than in ACs [131].

The sicca syndrome related to HTLV-1 differs from primary or secondary Sjögren's syndrome (SS), in that auto-antibodies cannot be demonstrated [139]. It is similar to the sicca syndromes seen in infection with HIV or hepatitis C virus [140].

### **HTLV-1 associated Sjögren's Syndrome**

SS is an autoimmune exocrinopathy causing keratoconjunctivitis sicca and/or xerostomia [141]. Characteristic histological findings are sialadenitis with lymphocytic infiltration of the salivary and lacrimal glands and proliferating nests of epithelial cells. Both lacrimal and salivary glands may be enlarged. Rheumatoid factor is commonly positive, antinuclear antibodies (ANA) and anti-Ro are positive in 60–70% of cases [142]. Retroviruses have been implicated in the etiology of SS [143], and in 1989 an exocrinopathy resembling SS was reported in HTLV-1 tax transgenic mice [144]. In Nagasaki, a HTLV endemic region, 13 (36%) of, mostly female, patients with primary SS tested positive for HTLV-1 antibody. Some patients also had extraglandular manifestations including recurrent uveitis, arthropathy, interstitial pneumonitis, Raynaud's phenomenon and inflammatory bowel disease, but none had rheumatoid arthritis (RA) or mixed connective tissue disease [145]. Another study from the Nagasaki Prefecture reported a 23% seroprevalence of HTLV-1 in patients with primary SS compared with blood donors (3%). Salivary IgA class antibodies to HTLV-1 were common among HTLV-1 seropositive patients with SS (5/7), but not in HAM/TSP patients or healthy carriers. Ocular and oral manifestations of SS were more frequently detected in HAM/TSP patients compared with ACs and healthy carriers. Low volume of saliva and frequency of ANA correlated with the density of mononuclear cell infiltration in labial salivary glands, which itself was higher in HTLV-1 seropositive than in seronegative patients with SS [146].

The HTLV-1 seroprevalence in 135 patients with primary SS and 97 patients with secondary SS was 25% and 29.2%, respectively. There was no significant demographic or immunological implication, such as the prevalence of other auto-antibodies (rheumatoid factor, ANA, anti-SS-A [Ro], anti-SS-B [La]), detected between the infected and uninfected SS patients,

apart from a significantly higher anti-centromere antibody prevalence in HTLV-1 negative SS patients [147]. Treatment options are artificial tears and saliva replacement solutions as well as systemic pharmacotherapy with pilocarpine hydrochloride.

### **HTLV-1 associated Hashimoto's thyroiditis & Graves' disease**

In the Tokushima and Kochi prefectures in Japan, 6.3% of patients with HTLV-1 associated thyroiditis (HAT) were reported to be HTLV-1 infected. This is significantly higher than the prevalence of HTLV-1 infection in the general population of this region (2.2%,  $p = 0.01$ ) [148]. A similar association was also observed in the Fukuoka prefecture [149]. In blood donors, 7.9% of patients infected with HTLV-1 also had anti-thyroid antibodies [150]. Hashimoto's thyroiditis has been associated with HAM/TSP [148] and Graves' disease with uveitis [71,151]. The clinical picture ranges from no symptoms and only a positive thyroid auto-antibody screen and/or an abnormal thyroid on ultrasound to full-blown hyperthyroidism. The titers of anti-microsomal antibodies may be elevated and anti-T4, anti-T3 and anti-thyroglobulin antibodies can be found. Ultrasonography of the thyroid can show enlargement and decreased echogenicity. Thyroid scintigram may show non-homogeneous uptake of labeled iodine with more discreet areas of decreased uptake. Histological examination of the thyroid may demonstrate lymphocytic infiltration, germinal centers, hypertrophy of follicular epithelium and interstitial fibrosis [152]. HTLV-1 envelope protein and mRNA but no viral particles were found in follicular epithelial cells of the thyroid of patients with HAT and HTLV-1 DNA was found in thyroid tissue of patients with HAT and Graves' disease [151,153]. In patients with HAT and Graves' disease, the HTLV-1 pVLs were five-times higher than in ACs but did not correlate with the thyroid peroxidase antibody or thyroglobulin antibody titers in the peripheral blood [154]. Patients may be treated with partial or complete thyroidectomy and hormone replacement therapy.

### **HTLV-1 associated pulmonary disease**

A broad spectrum of pulmonary involvement of HTLV-1 carriers has been described. This includes alveolitis [50], bulla formation, diffuse panbronchiolitis, lymphocytic interstitial pneumonia and bronchiectasis [105,155,156]. Bronchiectasis seems to be highly prevalent in HTLV-1 positive indigenous people from central Australia [157], and associated with a high mortality rate at a young age [158]. A retrospective review of high resolution computed tomography of the chest in 320 HTLV-1 infected Japanese patients showed abnormal findings in 30% patients with a peripheral parenchymal predominance in 71% of these. The abnormalities comprised centrilobular nodules (97%), thickening of bronchovascular bundles (56%), ground-glass opacity (52%), bronchiectasis (51%), interlobular septal thickening (29%) and consolidation (5%). The histology of those patients, who underwent lung biopsies, showed lymphocytic infiltration along respiratory bronchioles and bronchovascular bundles [105]. Children can be affected [159].

Bronchoalveolar lavage shows T lymphocytosis, high HTLV-1 pVL [160], increased IL-2 receptor  $\alpha$ /CD25<sup>+</sup> T lymphocytes and marked elevation of soluble IL-2 receptor  $\alpha$  [161] together with an increase in chemokines such as macrophage inflammatory peptide-1 $\alpha$  and macrophage chemoattractant protein-1 [162,163]. HTLV-1 Tax protein is known to induce the expression of IL-2 [164,165]. A correlation between lymphocytosis, increased CD4<sup>+</sup>CD25<sup>+</sup> cells with tax mRNA [166], Foxp3 and HBZ mRNA expression [167] and CD8<sup>+</sup> T cells in bronchoalveolar fluid was demonstrated in HTLV-1 carriers and HAM/TSP patients [168]. The presence of HTLV-1 infected cells in the alveoli seems to induce T-lymphocyte migration and clonal expansion leading to inflammation of pulmonary tissue through secretion of cytokines and chemokines [163].

In most cases, patients remain asymptomatic, but can present with chronic and productive cough unresponsive to long-term corticosteroid therapy [169].

#### **Infective dermatitis associated with HTLV-1**

Infective dermatitis, a unique clinical entity described in HTLV-1 infected children, was most probably observed in Jamaican children as early as 1966 by Sweet [170]. However, the first formal description of IDH was by Legrande in Trinidad [49]. Girls (60%) are more commonly affected, with the mean age of onset at 2 years of age and the condition becomes less severe as the children grow older. Familial clustering has been observed in a Jamaican family, who shared MHC class II haplotype, DRB1\*DQB1\*, the same haplotype associated with HAM/TSP in Japanese patients [171]. Reports outside of the tropics are rare but Hlela *et al.* have observed IDH in Cape Town with some differences in presentation [172]. ATLL and HAM/TSP have been described in children who had IDH [173]. The patients present with severe exudative dermatitis of the scalp, ears, eyelids, nose, axillae and groins accompanied by chronic watery nasal discharge and crusting of the para-nasal skin. Skin super-infection with *Staphylococcus aureus* and/or  $\beta$ -hemolytic *Streptococcus* is commonly present. CD4<sup>+</sup> and CD8<sup>+</sup> T-lymphocyte counts and the CD4<sup>+</sup>/CD8<sup>+</sup> T-cell ratio are raised. Histologically, IDH may represent a benign form of mycosis fungoides with a predominance of CD8<sup>+</sup> T-lymphocytes and a low percentage of cells with cytotoxic granules, indicating that most CD8<sup>+</sup> T lymphocytes are not activated [174]. Patient with IDH have significantly higher pVLs than ACs. This was mainly attributed to an increased abundance of existing HTLV-1 positive CD4<sup>+</sup> T-cell clones [78]. Treatment consists of antibiotics and corticosteroids, but relapse is common when treatment is stopped.

#### **HTLV-1 associated inflammatory myositis**

HTLV-1 has been found to be myotoxic *in vitro* [175]. Polymyositis, dermatomyositis and sporadic inclusion body myositis are uncommon but have been reported in HTLV-1 infected adults and children [53,176,177]. The first case was reported in 1989 in a Haitian woman with myelopathy, myositis and SS

living in Clichy, France [178]. In a small Jamaican cohort, 85% (11/13) of patients with polymyositis were found to be HTLV-1 seropositive [179]. Patients with polymyositis did clinically worse if infected with HTLV-1 [180]. In a Brazilian cohort, 36% (4/11) of patients with HAM/TSP were found to have evidence of polymyositis on muscle biopsy [181]. In Martinique, 50% (7/14) of patients diagnosed with polymyositis (five cases) or dermatomyositis (two cases) were HTLV-1 positive [53]. These patients were followed-up for 8 years. Initially, patients report proximal upper and lower limb weakness and muscle tenderness. Muscle bulk and reflexes are preserved. Creatine kinase is markedly raised, but auto-antibody screening is often negative and electromyography may be normal. Over the ensuing decade, there is severe loss of muscle bulk, reduction in creatine kinase levels and the electromyography shows myopathic and neurogenic changes. At this stage, there might be evidence of type II (hypercapnic) respiratory failure with reduced vital capacity and evidence of global respiratory muscle weakness [106]. In the muscle biopsies of three patients with HAM/TSP, CD8<sup>+</sup> and CD4<sup>+</sup> T cells and macrophages were the predominant cells surrounding healthy muscle fibers. HTLV-1 sequences were amplified from the whole muscle biopsy specimens but the cells harboring viral antigens were rare endomysial macrophages and not myocytes. Although HTLV-1 DNA was amplified from all patients' PBMCs, these cells did not exert myotoxicity and viral replication could not be detected in co-cultures with their homologous myotubules [182]. Another study showed predominantly HTLV-1 infected CD8<sup>+</sup> T cells in the muscle biopsies of HTLV-1 positive patients with polymyositis [183]. The muscle biopsies of HTLV-1 positive West African and West Indian patients with myopathy showed mainly idiopathic myositis and rarely HTLV-1 infected infiltrating cells. HTLV antibody titers but not pVL were significantly higher than ACs [184].

Sporadic inclusion body myositis has been reported in HTLV-1 positive patients [185,186]. Muscle biopsies show primary endomysial inflammation, red-rimmed vacuoles, amyloid deposits, eosinophilic inclusions and small round fibers in groups, without direct viral infiltration of the muscle [185,187]. HTLV-1 infected CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells specific for HTLV-1 tax antigen were isolated from muscle cell cultures of patients with HAM/TSP and sporadic inclusion body myositis [186], confirming the inflammatory nature of this condition. Myositis is resistant to corticosteroids and immunomodulatory therapies such as ciclosporin-A, showing only mild improvement of symptoms and no delay in progression [106,176].

#### **HTLV-1 associated arthritis**

An association between arthritis/polyarthritis and HTLV-1 infection has been observed in patients with ATLL [188,189], and HAM/TSP [190] as well as in ACs [191]. The prevalence of RA was significantly higher in HTLV-1 carriers (0.56%) compared with seronegative (0.31%) patients in Tsushima, Japan ( $p < 0.05$ ) [192]. A study from Nagasaki suggested that 13% of cases of RA were associated with HTLV-1 infection [193]. An increased incidence of arthritis was

found in HTLV-1 (incidence ratio 2.84) and HTLV-2 (incidence ratio 2.66) infected people in a prospective blood donor study in the USA [194]. However, an association between HTLV-1 seropositivity and RA could not be established in a South African study [195]. The clinical picture of HTLV-1 positive patients with polyarthritis does not differ from HTLV-1 negative patients with RA matched by gender, ethnic origin and disease duration [51,196]. Patients display symptoms and signs of RA indistinguishable from idiopathic RA with or without neurological signs [197]. In a retrospective study in Martinique, out of 17 HTLV-1 positive patients with polyarthritis 5 (29%) also had HAM/TSP and 1 (6%) had ATLL. Fever, myalgia and/or skin lesions were present at onset of the polyarthritis in 7 (41%) cases and all 17 patients had peripheral, bilateral, symmetric polyarthritis. The most commonly involved sites were the hands (17/17) and knees (14/17). Three patients had a positive rheumatoid factor result (18%) and five (29%) had ANA [51]. The synovial fluid and tissue of HTLV-1 positive patients with arthritis have been shown to contain atypical T lymphocytes [196,198,199], high titers of anti-HTLV-1 IgM antibodies, integrated HTLV-1 viral DNA [198] and tax mRNA and protein [200]. Higher HTLV-1 pVL has been detected in patients with RA and connective tissue disease compared with ACs. These levels were as high as pVL in HAM/TSP patients. High pVL was also detected in the synovial fluid of a HTLV-1 positive patient with RA [201]. Possibly, the migration of T lymphocytes into the articular space [202,203], attracted by viral antigens such as HTLV-1, which is synovial cell tropic [204], leads to the development and progression of arthritis and arthropathy. Transfection of a tax-expressing plasmid into synovial cell clones resulted in the same phenotype of increased proliferation and cytokine expression as exhibited by HTLV-1 provirus carrying and tax expressing synovial cell clones [200]. Finally, HTLV-1 transgenic mice developed a chronic arthritis at 2–3 months of age, resembling RA. Synovial and peri-articular inflammation with articular erosion caused by invasion of granulation tissues was also observed [205,206].

Very little is known about an ideal treatment of HTLV-1 associated arthritis. Corticosteroids are often used. There is always the worry of ATLL development if immune-modulatory drugs, such as TNF- $\alpha$ , which are standard treatment for RA, are used. There are reassuring reports on TNF- $\alpha$  blockers, although it seems to be less effective in HTLV-1 positive patients [207,208]. Rituximab and etanercept have been used [209], but need to be verified in clinical trials.

#### **Inflammatory conditions less commonly associated with HTLV-1**

As mentioned above, tubulointerstitial nephritis has been reported in patients with HAID [52], however, this has not been reported in isolation. Mixed connective tissue disease [210] but not systemic lupus erythematosus (SLE) [211] have been associated with HTLV carrier status. However, a publication in 2007 suggests that SLE in HTLV-1 positive patients might

behave differently than in seronegative patients [212]. Seropositive patients had a later age of onset of SLE (median 45.5 vs 30 years;  $p < 0.0005$ ) and the required maintenance dose of prednisolone was significantly lower than in seronegative patients (median 5 vs 9 mg/day;  $p = 0.012$ ). A case of primary biliary cirrhosis has been described [213]. Currently, a HTLV-1 positive patient with advanced idiopathic autoimmune hepatitis is attending our services. Our in-house observational study of liver disease in HTLV-positive patients showed a 3.6% ( $n = 5$ ) prevalence of idiopathic hepatitis in 140 patients [MARTIN F, TAYLOR GP, UNPUBLISHED DATA]. Two patients were asymptomatic carriers and two patients had other HAID. All five patients had increased level of alanine transaminase and four patients also had increased level of  $\gamma$ -glutamyl transferase. Four patients underwent liver ultrasounds, one patient had fatty liver disease and one liver cirrhosis. Liver biopsy was not performed. Diabetes mellitus type 1 and endogenous asthma, both idiopathic conditions with a high prevalence in general population, have not been associated with HTLV-1 infection.

#### **Expert commentary**

Based on published data, approximately 10 million people are infected with HTLV-1 but such data cover only one-sixth of the global population. Furthermore, with 4–9% of those infected developing one or more of the known related diseases the impact on health is greater than commonly cited. HTLV-1 is not classified as a neglected tropical disease, and although most cases occur in the tropics, HTLV-1 infections are common in some non-tropical regions such as Japan, Iran and Romania. On the other hand, HTLV-1 associated diseases while rare in most industrialized countries, struggle to compete for funding for rare diseases, which is predominantly directed at inherited conditions. Consequently, since 1983, the importance of this human retroviral infection has generally been overlooked. While the majority of infections are believed to be asymptomatic (FIGURE 1), the true impact of HTLV-1 on carriers is not known. The extent to which HTLV-1 is directly associated with 'auto-immune disorders' is not fully appreciated, nor have the consequence of chronic viral carriage on common inflammatory conditions been assessed. Finally, the impact of HTLV-1 perturbations of immune surveillance on malignancy has not been measured, although there are early signals [214–216] that this may be important.

This review focuses on specific inflammatory conditions with which HTLV-1 has been associated. It is clear from the diversity of clinical manifestations that HTLV-1 associated inflammation can present in many tissue types, and although most data available are from HAM/TSP studies, they suggest a common pathogenesis with high HTLV pVL and chronic immune activation key factors. The observation that 50% of ACs have HTLV-1 pVLs  $>1\%$  [217] and thus within the range for HTLV-1 associated disease suggests that while an essential prerequisite high pVL alone is insufficient to trigger these diseases. Various genetic associations with disease risk have been identified, some of which relate to the control of infection. In the absence of a suitable alternative model of disease detailed, long-

term, prospective studies of carriers with high pVL are needed to identify the triggers that result in overt clinical inflammatory disease and the patients at highest risk. In the absence of effective antiretroviral therapy for HTLV-1, current treatments target the by-stander inflammatory damage of the ineffective immune response to HTLV-1. Although short-term (up to 12 months) treatment with HTLV-1 reverse transcriptase inhibitors did not reduce pVL, the identification of CCR4 expression as a marker of infected cells [218,219] offers new hope for a treatment to reduce the viral burden and thus the inflammatory response. Since HTLV-1 infected lymphocytes and anti-HTLV-1 CTL are likely to migrate through most tissues, it is probable that the spectrum of disease is broader than currently described. Furthermore, there is evidence of subclinical disease. The range of disease associated with HTLV-1 has yet to be fully described and the reported prevalence of a specific inflammatory condition from one region cannot be assumed to apply globally.

As there is considerable knowledge of the molecular biology of and immunological response to HTLV-1 in patients with HAM/TSP, the neurological consequences of HTLV-1 infection have been highlighted in this report. This in-depth characterization of both the virological and immunological consequences of an HTLV-1 infection coupled with detailed clinical and para-clinical observations have led to models of disease pathogenesis that are becoming more amenable to interventional clinical strategies. Worldwide, there are few if any centers with sufficient patients with HAID to run appropriately powered and designed treatment trials. Therefore, international cooperation to compile sufficient patients within multicenter trial designs is essential. In this manner, the international community can amass databases with sufficient patients and detailed virologic, immunologic and clinical data to better inform patients, basic scientists and clinical investigators about this disease with the goal of translating information into effective treatments (bench-to bedside). In addition, such trials must bank clinical samples paired with clinical metrics data, as an invaluable resource for mechanistic and biomarker studies (bedside-to-bench).

### Five-year view

There is global appreciation that now is the time to study rare infectious diseases, such as HTLV-1. There are over 7000 rare diseases with many affecting developing nations. A goal of many institutions is to provide care for patients affected by rare diseases, while conducting studies in order to gain a deeper understanding of these conditions with the aim to find effective treatments (NIH, Office of Rare Diseases, Rare Disease Clinical Research Network, NIHR, Rare Disease UK, European Organisation for Rare Diseases). Studies of rare

diseases like HAM/TSP lead not only to clinical benefits for patients affected with an HTLV-1 associated disorder, but in a way to a short cut to understanding other rare or common inflammatory and malignant conditions. An example of this is multiple sclerosis (MS). Similar to HAM/TSP, some patients with MS have a chronic and progressive form of myelopathy. Because of this similarity, HAM/TSP patients are often misdiagnosed as MS. However, this has also been exploited since clinical trials in HAM/TSP have revealed mechanistic information that has been used in the treatment of MS. The first successful use of anti-IL-2 receptor therapy (anti-Tac or Xenapax) [114] was in patients with HAM/TSP and is now in Phase III trials in MS (daclizumab) [220]. Conversely, successful therapies in MS, such as INF- $\beta$ , did not show long-lasting clinical improvements in HAM/TSP patients [125]. However, only a double-blind controlled trial may detect a potential halt in disease progression with this therapy.

Another example of the relevance of HTLV studies for other diseases are the use of non-invasive technological advancements, such as brain and spinal cord MRI high-field imaging and the use of novel PET ligands to image inflammatory responses in the CNS. This will lead to a greater understanding of HTLV-1 associated inflammatory disease in real time, which will be highly relevant to other, more common metabolically active diseases. This review is a timely work on an important and clinically relevant pathogen. Clearly, we are at a time and place where we must expand our studies into rare disease with the aim to discover new treatment options. Specifically, a better understanding of HTLV-1 associated disorders will lead to a better mapping of disease pathogenesis, which will have applications for more common diseases. In the next 5 years, we will see more international cooperation between nations that have high rates of HTLV-1 infection. Industry will undoubtedly play a more important role as there will be greater appreciation of new and repurposed drug discoveries for rare infectious diseases applicable to other rare but also more common diseases that share similar clinical and mechanistic pathways.

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## Key issues

- Human T lymphotropic virus type 1 (HTLV-1) causes chronic inflammation in many different types of human tissue.
- Local and systemic host versus pathogen interaction drive inflammation.
- HTLV-1 associated myelopathy/tropical spastic paraparesis is the most commonly reported HTLV-1 associated inflammatory disease (HAID), affecting disproportionately women of older age.
- HTLV-1 proviral DNA level, HBZ protein expression and its low antigenicity play a role in driving inflammation.
- There is currently no evidence-based treatment to prevent HAID from developing or progressing.
- Worldwide, corticosteroids are most commonly prescribed in HAID, although no randomized controlled trial to date has shown its efficacy.
- International collaborations and large enough state-of-the-art randomized controlled trials are needed to discover efficient novel and/or repurposed treatment for HAID.

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