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# Human T-cell leukemia virus-associated malignancy

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Human T-cell leukemia virus type 1 (HTLV-1) is a tumorigenic delta retrovirus and the causative infectious agent of a non-Hodgkin's peripheral T-cell malignancy called adult T-cell leukemia/lymphoma (ATL). ATL develops in approximately 5% of infected individuals after a significant clinical latency period of several decades. Clinical classifications of ATL include smoldering, chronic, lymphoma, and acute subtypes, with varying median survival ranges of a few months to several years. Depending on the ATL subtype and disease symptoms, treatment options include 'watchful waiting', chemotherapy, antiviral therapy, allogeneic hematopoietic stem cell transplantation (alloHSCT), and targeted therapies. Herein we review the characteristics and development of ATL, as well as current and future treatment options and perspectives.

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## Introduction

HTLV-1 infection is found in most parts of the world with clusters of endemic infection in southwestern Japan, the Caribbean basin, equatorial Africa, parts of South America, the Middle East, and parts of Melanesia [1]. The number of HTLV-1 carriers has been estimated at 10–20 million people worldwide [2,3]. In Japan, seroprevalence rates in HTLV-1 endemic areas can range from roughly 5% to 30–40% [4–6].

## Viral transmission

HTLV-1 infection is heavily dependent upon cell-to-cell transmission [7–10] and new infections require the transfer of virus-infected cells by several routes: mother-to-child, sexual contact, and through infected blood products. Mother-to-child transmission via breastfeeding is a common route of transmission in HTLV-1-endemic areas. Studies show approximately 10–25% of breast-fed infants born to HTLV-1-seropositive mothers seroconvert [3], with seroconversion rates increasing with duration of breastfeeding and high proviral loads in breast milk [11–13]. There is small risk (<3%) of HTLV-1 transmission even without breastfeeding; vertical transmission can occur transplacentally or during delivery [14•]. Importantly, because disease symptoms typically take upwards of four or five decades to present, ATL occurs almost exclusively in individuals who acquire infection during infancy. Since 2010, serological screening for HTLV-1 antibodies has been available for all pregnant women in Japan, especially in endemic areas of the country [15]. However, routine screening in other developed countries has not been commonplace given the low rate of HTLV-1 seroprevalence. While no international guidelines exist on breastfeeding and HTLV-1 prevention, research suggests HTLV-1-positive mothers who avoid breastfeeding have reduced vertical transmission [16]. Unfortunately, this may not always be feasible due to socio-economic circumstances in resource-poor, developing countries. In these cases, short-term breastfeeding for 3 to a maximum of 6 months is recommended [17]. HTLV-1 can also be transmitted during sexual contact via HTLV-1-infected cells in bodily fluids [18–22]. While male-to-female sexual transmission is most efficient, there is a low rate of sexual transmission from female-to-male [22,23]. Finally, another important route of HTLV-1 transmission is through exposure to infected blood products by blood transfusion and sharing of blood-contaminated needles. Prior to routine blood testing, contaminated blood transfusions have been associated with ~20% seroconversion rate in the US [24] and 44–63% seroconversion rate in HTLV-1 endemic regions [25,26]. Routine testing of donor blood products for HTLV-1 has been commonplace in the US since 1988. Occupational exposure to HTLV-1 has not been well documented to date. In one study, no seroconversions were reported over a 10-year period in 53 individuals exposed to HTLV-1-infected blood in a Central Australian hospital [27•]. However, one case was reported involving a healthcare worker in Japan who seroconverted after exposure to blood from an ATL patient [28].

## HTLV-1 genome

As a complex retrovirus, HTLV-1 has a genomic structure similar to, but distinct, from simple retroviruses. In addition to the standard structural and enzymatic genes of all retroviruses, *gag*, *pol*, and *env*, HTLV-1 encodes additional regulatory and accessory genes derived from multiple

spliced transcripts. Upon infection, proviral double-stranded DNA is generated from the genomic viral RNA, which is then integrated into the host genome at random chromosomal integration sites [29]. At least two viral gene products, *tax* and *hbz*, are individually linked to oncogenic transformation and play a role in the pathogenesis of ATL [30,31]. Tax is the major driver of viral transcription and transformation [32,33]. Tax also functions at transcriptional and post-transcriptional steps during cellular transformation by upregulating several interleukins and their receptors, cytokines, adhesion molecules, growth promoting factors, and apoptosis inhibiting factors [34•]. However, Tax expression is frequently lost in a significant majority of ATL cases [35•]. Conversely, ATL tumors always express *hbz* [30,36]. Hbz RNA and protein have been shown to support the proliferation of ATL tumor cells *in vivo* and *in vitro* [37,38]. Our current understanding of HTLV-1-mediated tumorigenesis suggests that Tax is responsible for initiating transformation, while HBZ provides maintenance or cell survival signals. There is no evidence to indicate that HTLV-1 causes insertional mutagenesis disrupting tumor suppressor genes or activating proto-oncogenes. Nonetheless, the low incidence and long latency period prior to ATL onset suggests a combination of cellular genetic and epigenetic changes that are required for disease development, in addition to HTLV-1 viral gene effects. Several molecular studies have found a wide spectrum of disrupted/mutated cellular genes and pathways commonly affected in ATL cells [34•,35•].

## Characteristics and development of ATL

HTLV-1 is the causative infectious agent responsible for the development of an aggressive non-Hodgkin's peripheral T-cell malignancy, ATL [6,39,40]. Although most HTLV-1-infected individuals remain asymptomatic, approximately 5% of infected individuals will develop ATL after a long clinical latency period of four to five decades [41•]. Diverse clinical features that include lymphadenopathy, skin lesions, increased abnormal lymphocytes, frequent blood and bone marrow involvement, hypercalcemia, and lytic bone lesions characterize ATL. Although ATL most commonly is a CD4+ T-cell leukemia/lymphoma, occasional examples of CD8+ lymphoma have been described [42].

As a heterogeneous disease, ATL has been divided into four clinical subtypes based on analysis of 854 ATL patients in the 1980s known as Shimoyama classification: acute, lymphoma, smoldering and chronic [43]. Briefly, the smoldering and chronic subtypes, also known as indolent ATL, are characterized by rash and minimal blood involvement. The acute and lymphoma subtypes, also known as aggressive ATL, are characterized by large tumor burden, lymph node and blood involvement, and hypercalcemia. Classification of ATL subtype greatly influences the treatment regimen and prognosis of patients. Patients with aggressive ATL have a dismal prognosis with survival rates of 4–6 months for acute subtype and 9–10 months for lymphoma subtype. Those with indolent ATL have a more encouraging prognosis with survival rates of 17–24 months for the chronic subtype and 34 months to >5 years for the smoldering subtype. Aggressive ATL generally carries a poorer prognosis because of multidrug resistance, a larger tumor burden (compared to indolent forms), multiorgan failure, hypercalcemia, and/or frequent opportunistic infections due to intrinsic T-cell immunodeficiency [43,44]. Otherwise healthy carriers of HTLV-1 with abnormal peripheral blood lymphocytes typical of ATL cells are classified as having a borderline state of disease described as pre-ATL. Patients with pre-ATL can revert spontaneously to an asymptomatic state or progress to ATL malignancy [45].

## Other HTLV-1-associated diseases

In addition to ATL, HTLV-1 infection is associated with several other diseases and conditions including HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), HTLV-1-associated uveitis (HU), and various dermatological conditions. HAM/TSP develops in approximately 3–5% of HTLV-1-infected individuals, commonly women, with an average age of disease onset of 40 years [46]. It is characterized by lower limb spasticity, bowel and bladder disturbances, and slow but steady progression, without remission, over several years [47]. As a neurological condition, HAM/TSP is precipitated by lesions in the central nervous system associated with infiltrates of CD8+ T-cells [48]. HU is most commonly found in middle-aged men and women in areas of Japan with endemic HTLV-1 infection. Characterized by 'floaters' and foggy vision in the eye, this condition is classified as an intermediate uveitis and can be the only symptom of HTLV-1 infection or associated with HAM/TSP [49]. Infective dermatitis associated with HTLV-1 (IDH) is a pediatric form of severe, recurrent eczema commonly associated with endemic HTLV-1 infection [50]. Importantly, IDH has been considered an indicator of future ATL or HAM/TSP development [51]. Research has suggested that many of these HTLV-1-associated diseases are related to high viral load and/or overstimulation of dendritic cells, resulting in chronic production of high levels of type 1 interferons and interferon-stimulated gene expression [52–54]. While these clinical disorders are associated with HTLV-1 infection, this review will focus on ATL, the only known malignancy caused by the retrovirus HTLV-1.

## Diagnosis of ATL

HTLV-1 infection is confirmed through laboratory blood tests that detect antibodies to HTLV-1 infection, such as ELISA and western blotting. Additional diagnostic tests include PCR to confirm the presence of proviral sequences and quantify proviral load. Individuals with HTLV-1 infection in the absence of any known symptoms are known as asymptomatic carriers. There is currently no