

Human T-cell Lymphotropic Virus Infections (HTLV)

Revised 4/29/2013

In 1979, T-cell lymphotropic virus was isolated in a patient with cutaneous T-cell lymphoma. This led to the discovery of the first HTLV and marked the beginning of the human retrovirus era.

Virology

Human T-cell lymphotropic Virus 1 (HTLV)-1 is a human RNA retrovirus. The HTLV-1 genome is diploid, composed of two copies of a single-stranded RNA virus whose genome is copied into a double-stranded DNA form that integrates into the host cell genome, at which point the virus is referred to as a provirus. HTLV-II shares approximately 70% genomic homology (structural similarity) with HTLV-I. On the molecular level, as with all retroviruses, HTLV has a *gag-pol-env* motif with flanking long terminal repeat sequences. Unique to the Deltraviruses, however, it includes a fourth sequence named Px, which participates in open-reading-frame transcription, in turn encoding for regulatory proteins Tax, Rex, p12, p13, and p30. All these proteins are important for the infectivity of cells, as well as in stimulating replication. In ATL, the main pathogenic protein, Tax, leads to leukogenesis and immortalization of T lymphocytes in vitro. Because of the low replicating nature of HTLV, the virus develops little genetic sequence variation.

Six different HTLV-1 subclasses exist; each subtype is endemic to a particular region:

- Subtype A (cosmopolitan subtype) - Japan
- Subtypes B, D, and F - Central Africa
- Subtype C - Melanesia
- Subtype E - South and Central Africa

HTLV-2 is classified into four molecular subtypes; each has a characteristic geographic association:

- Subtypes A and B - present throughout Western Hemisphere and Europe; sporadic distribution in Asia and Africa
- Subtype C - Kayapo indigenous people of the Amazon and urban Brazilian populations
- Subtype D - discovered in an African pygmy tribe

HTLV I and II belong to a group of closely related Primate T Lymphotropic Viruses (PTLVs). Members of this family that infect humans are called Human T-lymphotropic viruses; the ones that infect old world monkeys are called Simian T-lymphotropic viruses.

To date, four types of HTLVs (HTLV-I, HTLV-II, HTLV-III, and HTLV-IV) and four types of STLVs (STLV-I, STLV-II, STLV-III, and STLV-V) have been identified. The HTLVs are believed to originate from intra-species transmission of STLVs.

HTLV III and IV were first isolated in 2005.

HTLV III was initially isolated from a 62-year-old male pygmy in southern Cameroon. Now, with the aid of advancing laboratory technology, new strains are quickly being identified. Individuals infected with HTLV III have all been asymptomatic, with a low pro-viral load.

HTLV-IV has been described in African bush meat hunters.

Neither HTLV-III or HTLV-IV has been associated with specific diseases thus far; further research continues. Given the ongoing discovery of subtypes and strains, it is not surprising that 28% of certain populations in central Africa have been reported to have indeterminate HTLV serology results.

Confused nomenclature: The original name for HIV, the virus that causes AIDS, was HTLV-III; this term is no longer in use. When HIV, the virus that causes AIDS, was characterized in 1984, Robert Gallo in the U.S. named it HTLV-III; Luc Montagnier in France named it Lymphocytic Associated Virus (LAV). Eventually the two viruses proved to be the same (the French isolates had been sent to the U.S. where Gallo thought he had isolated - mistakenly- another virus). HTLV-III is currently the name used to describe another virus related to HTLV-I and HTLV-II. "HTLV-IV" has been used to describe recently characterized viruses. HTLV-IV was sometimes used to name HIV 2.

A closely related virus is the bovine leukemia virus, BLV.

Transmission

- Breast feeding is the most common form of transmission that maintains the HTLVs endemic status in a country. Up to one in four children born to mothers with HTLV-I infection will become infected. However, most infections occur through breast-feeding; if this is avoided, less than one in 20 babies will become infected. The risk of infection through breast-feeding increases with the duration of breast-feeding and may be low during the first three months.

- Sexual transmission: The risk of transmission from an infected man is greater than from an infected woman. The best information indicates that in a steady relationship lasting five years, there is a 7% chance of transmission; this makes the risk of HTLV transmission extremely low (around 0.1% per unprotected sexual contact).

- Intravenous drug use: This mode of transmission is mostly linked to HTLV-2. The prevalence of HTLV-2 infection in North American injection drug users ranges from 8% to 17%.

- Solid organ transplantation (SOT) and transfusion of cell-containing blood products may also result in transmission of infection, if through transfusion of blood from an HTLV-I infected donor. The risk may be as high as 85% depending on how the blood is handled and stored. Persons

with HTLV-I infection should not donate blood, organs or sperm and should not carry an organ donor card.

HTLV viruses are not transmitted person-to-person by coughing, sneezing, kissing or any daily, social contact.

HTLV-2 is primarily found in intravenous drug users and sexual contacts of infected persons.

HTLV-3 and HTLV-4 seem to be transmitted through direct human contact with primates (e.g., through hunting, butchering, keeping them as pets), but data are lacking.

Epidemiology

- In endemic areas, HTLV-1 seropositivity is clustered in families, especially among women, suggesting that transmission occurs more easily from men to women than from women to children - determining the sexual predominance of HTLV-2.

- The prevalence of HTLV-1 and HTLV-2 infections increases with advancing age. The onset of ATL or HAM/TSP is often delayed until later in life because of the prolonged latency state; vertical transmission is associated with an elevated risk of ATL or HAM/TSP.

Geographical Distribution

HTLV-I is a very old virus, which appears to have infected and moved with mankind for hundreds, perhaps thousands of years. It is thought to have migrated during ancient times with Native American Indians in North and South America, with Australian aborigines and the Melanesian people of the South West Pacific, and to Japan. During the last few centuries it has migrated from Africa to the Caribbean and again to North and South America. In some areas, more than 1% of the population carries the virus. The same rates of infection are seen in populations wherever they migrate. In Europe, HTLV-I is mainly found among people who have originated from these endemic areas.

HTLV-1 is endemic in the Caribbean, parts of South America, West Africa, Asia and Oceania. In the Caribbean, 2% to 5% of adults are infected. In the U.S., 0.04% to 0.05% of blood donors are infected with HTLV-1 or HTLV-2

HTLV-2 is endemic in American Indian populations, and in West and Central Africa.

HTLV-III and IV viruses were discovered in 2005 in rural Cameroon, and were, it is presumed, transmitted from monkeys to hunters of monkeys through bites and scratches.

Patho-physiology

Once infection has occurred, little replication takes place. Infection affects the expression of T-lymphocyte gene expression, leading to increased proliferation of affected T-lymphocytes. HTLV primarily affects T-lymphocytes: specifically, HTLV-1 predominantly affects CD4 lymphocytes, while HTLV-2 predominantly affects CD8 lymphocytes.

Clinical

Most infections are completely asymptomatic. The virus appears to remain in the body throughout life without causing any harm at all.

HTLV-1 is associated with development of:

- Acute T-cell leukemia/lymphoma (ATL) in 2% to 5% of infected individuals. ATL is unlikely to develop, following infection acquired in adult-life. This means that avoiding infection of infants by avoidance of breast-feeding is very important for the prevention of ATL in the next generation.
- The acute form comprises 55% to 75% of all ATL cases. It is characterized by a significantly increased white blood cell count that is mostly made up of leukemic T-cells. It also features generalized lymphadenopathy.
- The chronic form is characterized by absolute lymphocytosis ($4 \times 10^9/L$ or more), with T-lymphocytosis comprising more than $3.5 \times 10^9/L$. These laboratory findings persist for months to years in most patients with chronic ATL. The lymphatic system may become involved.
- The latency period for ATL is typically 30 to 50 years. ATL is usually rapidly progressive and fatal, with a median survival time of two years.
- Smoldering ATL is characterized by 5% or more abnormal T-lymphocytes in peripheral blood, with a normal total lymphocyte count.
- The lymphoma type involves generalized lymphadenopathy and an absence of peripheral blood involvement.

HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), is a demyelinating disease in a smaller percentage.

- The pathophysiology of HAM/TSP remains unclear, but, clinically, it can be defined as a slowly progressive degenerative disease that primarily affects the corticospinal tracts of the thoracic cord.
- Major pathologic findings of HAM/TSP may include inflammatory perivascular and parenchymal infiltration by T-lymphocyte cells, leading to degeneration and fibrosis in the spinal cord. The degree of infiltration is less than in other retroviral infections (e.g., HIV infection), perhaps because of the slow pathogenesis of the virus.
- Immunologic mechanisms may be involved in the development of HAM/TSP. This is likely mediated through autoimmune processes or cytotoxic attack on the HTLV-1-infected cells.
- A higher provirus load increases not only the overall risk of HAM/TSP but also the likelihood that the disease will progress more quickly.
- HTLV-1 is also associated with a broader spectrum of neurologic abnormalities that are not as severe as HAM/TSP. It is not clearly established if individuals with the other neurologic abnormalities will eventually develop HAM/TSP or will remain stable.

- HAM/TSP can occur as early as three months after blood transfusion–related HTLV-1 infection. Three years of latency is more typical, and a latency of 20 to 30 years is possible.

Other HTLV-I-associated diseases - HTLV-I can also cause inflammation of the:

- Eye (uveitis) - These conditions are even less common than ATL and HAM. This skin condition is usually only seen in tropical climates. Most individuals have no clinical sequelae of HTLV-1 infection.
- Skin: HTLV-1–associated infective dermatitis (IDH) is a chronic and severe dermatitis that mainly affects children who have been infected with HTLV via vertical transmission.
- Joints (arthritis), muscles (myositis) and lung (alveolitis).
- Strongyloidiasis: This worm infection usually acquired in the tropics can, after lying dormant for years, cause a serious illness in HTLV-I carriers

Unlike HTLV-1, the link between HTLV-2 and human disease is uncertain, although there have been occasional case reports of neurological disease, inflammatory disorders and leukemia in infected patients.

The HTLV-1 virus displays relatively low antibody production variability, natural immunity does occur in humans, and experimental vaccination using envelope antigens has been shown to be successful in animal models.

Novel HTLV-3 and HTLV-4 have been isolated only in a few cases; no specific illnesses have yet been associated with these viruses.

Laboratory Tests

An enzyme-linked immunosorbent assay (EIA) is currently used to screen organ donors for HTLV-1 and HTLV-2. These tests do not distinguish between HTLV-1 or HTLV-2. This test is sensitive but lacks significant specificity and therefore the positive predictive value is low when applied to low seroprevalence populations.

A positive EIA result can be confirmed by a Western blot or specific line immunoassay, although this is not standard practice for organ donation. In many cases these confirmatory assays distinguish between HTLV-1 and HTLV-2 but none are FDA-licensed or approved for this purpose.

Polymerase chain reaction (PCR) tests may also be useful to confirm infection and can distinguish between infection with HTLV-1 and HTLV-2 (HTLV-1/2). At present, no Food and Drug Administration (FDA) - licensed, commercially available nucleic acid test (NAT) with a turn-around time appropriate for donor screening is available.

Organ Transplantation

Currently, Organ Procurement and Transplant Network (OPTN) policy requires that all potential solid organ donors are tested for HTLV-1/2 using an FDA-licensed screening test. There are presently three FDA-licensed tests for this purpose:

1. Abbott HTLV-I/HTLV-II Enzyme Immunoassay (EIA)
2. Abbott PRISM HTLV-I/HTLV-II
3. BioMerieux-Vironostika HTLV-I/II Microelisa System.

The Abbott PRISM HTLV I-II assay is the only commercially available licensed test after December 31, 2009. It is designed to test large numbers of samples in a high-throughput setting and is not optimized to the time constraints associated with organ donation. The Abbott PRISM HTLV-I/II assay is a chemiluminescence immunoassay for HTLV-1/2 screening and is part of an automated testing system designed for high throughput labs. In volunteer blood donors, the specificity of the assay was 99.93%. Sensitivity of the assay is estimated to approach 100%. Several case reports described likely donor-derived transmission of HTLV-1 after organ transplant; in some of these reports, recipients developed HTLV-1-associated disease. The most definitive case occurred in Spain; three seronegative recipients of an HTLV-1/2 seropositive donor developed myelopathy within two years of transplantation. There were a few less definitive reports.

Retrospective reviews of the OPTN database have assessed the outcome of elective transplantation of HTLV-1/2 seropositive organs. The Organ Procurement and Transplantation Network (OPTN) database was queried and identified 162 recipients of 134 donors testing positive for HTLV-1/2 from 1999 to 2008: ten developed post-transplant malignancies, but these were skin cancers (except for one case of recurrent liver cancer), and no cases of ATL or post-transplant lympho-proliferative disease were reported.

Prevalence of HTLV-1/2 in Organ Donors

While HTLV-1/2 donor antibody testing is required and performed by all Organ Procurement Organizations (OPO) on all prospective donors, only data on donors whose organs are procured, are collected in the OPTN database. Some European countries have surveyed all potential organ donors; in France 0.05% to 0.067% were found to be HTLV-1/2-positive. A similar survey was conducted in Spain; over 1,000 potential organ donors were tested - none was positive for HTLV-1 and one was positive for HTLV-2.

Based on higher rates of immigration from high prevalence countries, HTLV-1/2 rates would be expected to be higher in the United States than in Europe. In one study of 1,408 potential donors, 1.6% were positive on repeated EIA testing with only one patient (0.07%) confirmed positive for HTLV-1. Similar low rates of HTLV-1 infection among screened positive donors in Wisconsin were reported. A survey of several OPOs regarding their rates of positive HTLV-1/2 showed that overall 1.04% of donors screened positive for HTLV-1/2; in the three labs in which a confirmatory assay was performed, 0.5% of donors were confirmed positive for HTLV-1/2. Only one lab attempted to distinguish HTLV-1 from HTLV-2 and documented a HTLV-1 positive rate of 0.03%. While the overall rate of HTLV-1 infection in the donor population is likely very low, it should be noted that local areas of higher prevalence, likely based on immigration patterns from high incidence countries, have been described.