Arch Gynecol Obstet (2010) 282:493–501
DOI 10.1007/s00404-010-1559-1

GENERAL GYNECOLOGY

HTLV infection and its implication in gynaecology and obstetrics

Ioannis Mylonas · Ansgar Brüning · Franz Kainer · Klaus Friese

Received: 1 September 2009 / Accepted: 8 June 2010 / Published online: 22 June 2010

Abstract
Introduction Worldwide, 20–30 million people are estimated to be infected with HTLV. HTLV-1 is endemic in Western Africa and Southern Japan, whereas HTLV-2 is considered to be spread among native American people.
Materials and methods The impact of HTLV in gynaecology and obstetrics is being reviewed. Search strategy and selection criteria for identifying relevant data were peformed by searching Medline, Current Contents, Web of Science, Embase and references from relevant articles. English and German gynaecological and infectious diseases textbooks as well as national and international guidelines and recommendations were also reviewed.
Results Transmission may occur by sexual intercourse or cellular blood products. Although materno-fetal transmission is debated, transmission through maternal breast milk has been confirmed. An HTLV-infection can lead to adult T-cell leukaemia (ATL) or cumulative opportunistic and neurological disorders that can occur with varying degrees of severity. Diagnosis can be done by antibody detection via the use of ELISA and western blot analysis as well as PCR diagnosis.
Conclusion Due to inadequate treatment options and the lack of an effective vaccination, prevention is currently only possible by restricting transmission, including the usage of condoms during sexual intercourse or avoiding breastfeeding in HTLV-seropositive mothers. If, due to socio-economic reasons, breastfeeding cannot be avoided, short-term breastfeeding for a maximum of up to 6 months is suggested.

I. Mylonas (✉) · A. Brüning · F. Kainer · K. Friese
First Department of Obstetrics and Gynaecology,
Ludwig-Maximilians-University Munich,
Maistrasse 11, 80337 Munich, Germany
e-mail: ioannis.mylonas@med.uni-muenchen.de

Keywords HTLV infection · Transmission · Breast feeding · Prevention strategies

Introduction

The discovery of the human T lymphotropic virus (HTLV) in 1979 was the first scientific detection of the occurrence of human retroviruses [1]. Although several oncogenic animal retroviruses had already been identified, this was the first human pathogenic retrovirus to be discovered. It is estimated that 20–30 million people worldwide are infected with HTLV and, although the majority of infected people remain asymptomatic, the virus is being implicated with severe diseases [2–5]. An association between adult T cell leukaemia/lymphoma (ATL) and this virus has already been proposed decades earlier [6]. Most mothers of patients with ATL were HTLV-1 carriers and, therefore ATL is believed to develop in HTLV-1 carriers who acquired a perinatal infection [7, 8]. However, the main impact of viruses on cancer development has been recognised only during the last few years [9, 10].

Due to increased human mobility, HTLV infection also occurs "out of Africa", including Europe and North America. Since HTLV is associated with severe diseases, and breast feeding remains one of the major transmission routes, this infection still constitutes a major concern among female patients, gynaecologist and obstetricians.

The impact of HTLV in gynaecology and obstetrics is being reviewed. Search strategy and selection criteria for identifying relevant data were performed by searching Medline, Current Contents, Web of Science, Embase and references from relevant articles. English and German gynaecological and infectious diseases textbooks as well as national and international guidelines and recommendations

were also reviewed. Additionally, numerous articles were identified through searches of the extensive files of the authors. Search terms were: HTLV infection, transmission pregnancy, gestation, breast feeding, prevention and recommendations. English and German language manuscripts were reviewed.

The virus

In 1979, a type C retrovirus was identified in a patient with cutaneous T cell lymphoma, and referred to as the human T cell lymphotropic virus (HTLV) [1]. Although several oncogenic animal retroviruses had already been identified, this was the first human pathogenic retrovirus to be discovered. In 1982, a second form of HTLV (HTLV-2) was isolated [6]. HTLV-1 and -2 have similar genetic regulatory structures, but differ by up to 30% in their amino acid composition.

HTLV belongs to the family of retroviridae and is classified into the genus of deltaretroviruses related to the lentiviruses (which comprise the well-known HIV-1 and -2). The HTLV genome is a positive, single-stranded RNA. After docking of the viral envelope glycoprotein gp46 to the hostal glucose transporter (GLUT1), viral capsid integration and uncoating, the single-stranded RNA is converted to double-stranded DNA by the reverse transcriptase and inserted into human host cells [4, 11, 12]. This inserted form of a retrovirus is referred to as provirus [11]. Like other human retroviruses, HTLV-1 causes a lifelong persistence [4].

HTLV is a spherical virus with a diameter of approximately 100 nm. It consists of an outer proteolipid membrane equipped with membrane proteins (i.e. glycoproteins gp46 and gp41) and an inner envelope containing a matrix layer, which helps to organise the viral components at the inner cell membrane. This icosahedral capsid protects the viral RNA and the functional protease, reverse transcriptase, and integrase, which are organised together with the nucleocapsid in a ribonucleoprotein complex [4, 13, 14]. The function of HTLV is mainly governed by two regulatory genes, the tax and rex genes; the tax product (HTLV-1: p40; HTLV-2: p37) is crucial for the regulation of a wide range of viral and host transcription factors and thus assigned a specific role in the induction of human T cell leukaemia [4].

Pathogenesis

In contrast to HIV, HTLV-1 predominantly exists as a cell-associated provirus [15]. Moreover, HTLV is transmitted in this proviral form [15]. The virus infects primarily CD4+ T cells, although CD8+ T cells are also an important reservoir for the virus [16–18]. Additionally, ubiquitous vertebrate glucose transporter can function as a host-cell receptor for HTLV-1 [12]. Infected T cells do not produce any virus and the viral load is not detectable in human plasma. However, the virus particle-associated RNA can infect new cells through a viral synapse [18, 19]. It is presumed that during early infection, most new HTLV-1-infected cells are produced by cell-to-cell spread, resulting in a polyclonal infection of both CD4+ and CD8+ T cells [4]. In later stages, HTLV-1 mainly multiplies by clonal expansion dependent on mitosis of host cells [4, 16–18].

After the entry of HTLV into CD4+ lymphocytes, the RNA genome is transcribed into DNA and then integrated in the cellular genome. This can lead to immortalisation of mature T lymphocytes, followed by monoclonal expansion of the host cell, which can result in the clinical appearance of ATL. Interestingly, for isolated lymphocytes in patients with ATL, the proviral DNA form is detected by the PCR method, whereas viral RNA detection is largely negative [20].

Epidemiology

Little is known about the origin of the HTLV. It is assumed that there was a common precursor virus that originated in Africa and infected humans and other primates. This assumption is based on the fact that, although HTLV is currently spread throughout the world, sub-Saharan Africa is the only region where all different primate T lymphotropic viruses [HTLV types 1–4 and simian T lymphotropic viruses (STLV) types 1–3] can been detected [21, 22]. An estimation of the prevalence of HTLV is difficult, since such data are based on serological screening of blood donors, pregnant women or other selected population groups [23]. Data from pregnant women may better reflect the general population, although reports from endemic areas suggest that HTLV seroprevalence increases with age and is higher in women than in men [24]. Moreover, different diagnostic tests and interpretation criteria also make an analysis of prevalence data [25].

The area in the world with the highest HTLV-1 incidence is Southern Japan with more than 10% of the general population being infected [26]. However, HTLV-1 predominantly occurs also in West and Central Africa, the Caribbean, Central and South America, Melanesia and Europe. HTLV-2 is primarily found among Native American of North and South America.

Following the increased human mobility, HTLV infection also occurs in Europe, although it remains still an uncommon infection in the general population in most western European countries. The infection has been reported

in specific population groups, such as immigrants from endemic areas, sex workers, and injecting drug users [27, 28]. A seroprevalence rate of 6.9% has been estimated among drug users in Italy [29]. A prevalence of 0.6% was found among blood donors in Romania and there are several case reports of Romanian patients with HTLV-1-associated ATL [30, 31]. However, HTLV might be more frequent in Eastern Europe, although prevalence data are still missing.

Transmission

Unlike HIV, which can be transmitted by free virions and via infected lymphocytes and macrophages, the transmission of HTLV seems to be linked to the infected host cell. Compared to HIV, HTLV is less contagious. It is believed that it cannot be transmitted through cell-free body fluids. Risk factors associated with a HTLV-1 infection include transfusion history, prolonged breastfeeding, unprotected sex, high number of lifetime sexual partners, presence of other sexually transmitted diseases and history of drug use [32].

Transfusion of contaminated cellular blood components results in seroconversion in more than 40% of recipients [33]. In many countries, candidate blood donors are screened for HTLV-1 antibodies. In Japan, this intervention has decreased the number of new infections in the general population [34]. There is an estimated overall infection risk of 12% upon administering preserved whole blood infected with the HTLV-1 virus [35, 36]. Assuming that there are around 30 million people infected with the virus worldwide, more than 300,000 of those infected with HTLV-1 or -2 are at risk of contracting ATL or HTLV-associated myelopathy (HAM) during their lifetime. For an individual infected with HTLV-1, the cumulative risk of developing an ATL is estimated as 2–4% [37]. A Swedish study found a seroprevalence of two cases of HTLV-1 infections among 100,000 donors and less than 10% showed evidence of a HTLV infection subsequently. The Swedish National Board of Health, therefore, recommended a restriction in testing new blood donors, since death from HTLV-related ATL is only to be anticipated at a rate of one case every 200 years [38].

As expected, there is an increased prevalence of infection for intravenous drug users [35]. Sharing of contaminated needles and syringes by drug users represents another way of parenteral transmission. Interestingly, HTLV-1 is frequent among injecting drug users in Brazil and New York, whereas HTLV-2 is more prevalent in other North American and European injecting drug users [3, 39, 40].

HTLV-1 is present in genital secretions of infected people and can be transmitted through sexual intercourse [41]. In cross-sectional studies, HTLV-1 and -2 infections were transmitted more efficiently from male-to-female than female-to-male [24], with higher transmission rates associated with longer duration of relationship and higher HTLV-2 viral load in the seropositive male [42]. In a cohort of 30 discordant couples, the incidence of a HTLV-1 transmission was estimated to be 0.9 per 100 persons per year [43]. However, prospective studies show that sexual transmission is not as important as previously assumed [43, 44]. Admittedly, the sexual transmission rate of HTLV is lower than for HIV. HTLV-infected lymphocytes in sperm are to be given primary consideration as transmission vectors. However, it is suggested that the concurrence of genital infections and sexually transmitted diseases (STD) can aid the transmission of these viruses, since they expose target cells through genitomucosal lesions.

Clinically significant transmission of HTLV apparently occurs in early childhood, mainly postpartal. HTLV-1 can be transmitted from mother-to-child through breastfeeding. It was proven that the amount of proviral cells in the mother have an influence on transmission [20, 45]. The risk of infection in children of seropositive mothers correlates with the provirus load in breastmilk and the duration of breastfeeding [46, 47]. In several reports from endemic populations, the overall rate of vertical transmission ranged between 15 and 25% [48–52]. In children who received prolonged breastfeeding, these rates were even higher [48–52]. In Japan, screening of pregnant women and avoiding breastfeeding in infected women has reduced the prevalence of HTLV-1 significantly [53, 54].

Peripartal infections can also occur irrespective of an infection through maternal breast milk. However, the transmission route for prenatal and perinatal infections is still largely unknown. Placental transmission is unlikely, given the almost wholly negative proviral HTLV-DNA findings in the umbilical cord lymphocytes of infected mothers [20, 55]. It is debatable whether HTLV is transmitted prenatal or peripartial to any significant degree, as no clear proof has yet been found for the vertical transmission of HTLV-1 and -2 [56]. Intrauterine and peripartum transmission of HTLV-1 is assumed to occur in less than 5% of children of infected mothers [50, 53, 55]. By PCR detection of proviral cells, a transmission rate of 9.7–10% was established without clear determination of the influence of breast feeding [45]. Despite the ambiguity regarding the significance of peripartal transmission, the high rate of infection through breast milk is undisputed [55, 57].

As mentioned above, HTLV-1 infection can be transmitted through blood transfusion, prolonged breastfeeding, unprotected sex or intravenous drug abuse [32]. However, there might be several other, yet unknown, factors influencing HTLV-1 transmission [3], since most HTLV-1-

endemic areas are in the tropical regions with a declining prevalence in subsequent generations migrating from endemic to non-endemic areas [58].

Clinical features

Although HTLV-1, like other human retroviruses, causes a lifelong viral persistence, most infected people remain asymptomatic. The development of associated diseases after HTLV infection depends on several factors like age, comorbidity and the route of infection [4].

HTLV-1

The aetiological role of HTLV-1 in several diseases is being meanwhile established: ATL [59], tropical spastic paraparesis (TSP) [5, 60], HAM [61], B cell leukaemia [62], chronic persisting oligoarthritis [63, 64], lymphocytic uveitis [65–67] and bronchoalveolar lymphocytosis [68, 69] (Table 1). Moreover, HTLV-1 has also been reported in association with infective dermatitis, Sjögren's syndrome, thyroiditis, arthropathy, polymyositis, polyneuropathy, T lymphocyte alveolitis, cutaneous T cell lymphoma and certain infections such as strongyloidiasis, scabies, leprosy and tuberculosis [4, 70–75]. In some cases, a HTLV-1 infection can result in neurological manifestations with mild sensory impairments, erectile dysfunction, or development of a progressive spastic paresis (Table 2). There were similar changes in the nuclear spin, as with multiple sclerosis. Additionally, there is strong evidence that HTLV-1 might be associated with a wide spectrum of predominantly motor abnormalities in patients without an HTLV-associated myelopathy [76].

For HTLV-1-associated diseases (including ATL, HAM/TSP, uveitis, polymyositis, and arthropathy etc.) the lifetime risk was estimated to be almost 10% [77, 78]. Among HTLV-1 carriers, the lifetime risk of developing HAM/TSP ranges between 0.3 and 4% [79] and for ATL approximately 1–5% [77, 78]. Moreover, the outcome of HTLV-1 infection depends on a complex interaction between the virus and host genetic and immunological factors [68, 70, 71, 73, 75, 80].

There is either milder clinical development that can persist over years or fulminate progressions that result in death within a few months. Even prior to clear clinical features of ATL, there can be bacterial and fungal infections of the skin and mucosa. The period leading to the development of ATL can be very long (>20 years). The loss of a coordinated cellular immune defence, due to the massive expansion of functionless and malignant lymphocytes, predisposes a number of opportunistic fungal and protozoal infections along with typical viral diseases, and can lead to infection complications similar to those that occur in an advanced HIV infection, such as aesophagitis caused by *Candida albicans*, pneumonia caused by CMV, and recurrent/generalised infection manifestations caused by HSV and ZV [4].

Table 1 Aetiological relationship between HTLV and diseases [2–4]

HTLV-1	HTLV-2
Adult T cell leukemia (ATL)	Hairy cell leukemia
Tropical spastic paraparesis (TSP)	Tropical spastic paraparesis (TSP) similar disease pattern
HTLV-1 associated myelopathy (HAM)	Mycosis fungoides
B cell leukemia	Cutaneous CD8+ cell lymphoma
Chronic persisting oligoarthritis	
Lymphocytic uveitis	
Bronchoalveolar lymphocytosis	

Table 2 Aetiological relationship between HTLV-1 and diseases

Disease	Pathogenesis/manifestation of the disease
Adult T-cell leukemia (ATL)	Intrauterine infection or infection via breast milk
	Clonal growth of HTLV-1 infected cells
	Dermatological findings similar to mycosis fungoides.
Chronic form	Hepatosplenomegaly
	Lymphadenopathy
	High number of leukemia cells
Acute form	Lytic bone disease
	Increase in LDH
	Hypercalcemia
Tropical spastic paraparesis (TSP) or HTLV-I associated myelopathy (HAM)	Chronic, slowly progressing paraparesis
	Dysesthesia
	Back pain
	Hyperreflexia
	Weakness of the lower limbs
	Incontinence
	Impotence
	Paresthesia

HTLV-2

HTLV-2 has not been aetiologically linked with any disease, although some case reports and cross-sectional studies suggest an association with a tropical spastic paraparesis/HTLV-associated myelopathy (TSP)-like syndrome [60, 81–83]. Additionally, HTLV-2 has been

associated with hairy cell leukaemia [84, 85], cutaneous cell lymphoma [86] or mycosis fungoides [87], although such an association is still controversially discussed. In addition, other manifestations such as pneumonia, bronchitis and urinary tract infection have been described after a HTLV-2 infection [77].

Interestingly, HTLV-2 infection is associated with increased mortality among healthy blood donors [88]. Moreover, an observed association between HTLV-2 with all-cause and cancer mortality might reflect biological effects of HTLV-2 infection, although the precise role of such an infection still remains to be clarified [89].

Diagnostics

For the detection of HTLV antibodies, serological screening can be performed by enzyme immunoassays (EIA), recombinant ELISA or particle agglutination test. Although these EIAs using recombinant proteins and/or synthetic HTLV-1 peptides perform well, confirmatory testing is still recommended to eliminate false-positive reactions and discriminate between the different HTLV types [90]. There are several confirmation tests, including western blot and line immunoassays [91, 92], although cross-reaction or inability to distinguish between HTLV-1 and HTLV-2 should be considered [24].

PCR tests aimed at HTLV-1 and -2 proviruses are also available to further refine the diagnosis. In uncertain serological constellations, PCR analysis can provide the definite diagnosis of infection [93, 94]. The provirus load is expressed as the number of HTLV-1 DNA copies per fixed number of peripheral blood mononuclear cells [95, 96]. It is the most frequently used marker for prognosis and disease progression in infected patients [97, 98]. Recently, in a large prospective study a high proviral load was an independent risk factor for progression of ATL from carrier status [99].

Treatment

There is currently no specific and effective treatment available. Although the proliferation of HTLV can be slowed down in vitro by nucleotide analogues, these have only a marginal effect on the virus itself. Antiretroviral agents offer no real alternative in the acute phase of ATL, because the lymphocytes do not contain viral RNA. It should be noted that only a small percentage of infected individuals (approximately 1%) develop clinical symptoms of sub-acute or acute ATL.

Prevention

No vaccines have yet been clinically tested, and thus, general human use cannot be recommended. Likewise, there is no possibility of therapeutic intervention in pregnancy. In view of inadequate treatment options and the lack of an effective vaccination, prevention is only possible by restricting transmission (Table 3). Testing maternal anti-HTLV antibody titre and proviral load before delivery would be an optimal preventive strategy. However, especially with the low incidence rate in Europe and the economic problems regarding such a screening strategy, elective testing for patients coming from endemic regions could be reasonable and feasible. If such a screening test is positive, a reduction or restriction of breastfeeding in HTLV-seropositive mothers should be recommended [53, 54]. If stopping breastfeeding is not possible, for example due to socio-economical circumstances, short-term breastfeeding for 3 to a maximum of 6 months should be advocated. Testing of newborns born to HTLV-seropositive mothers with an adequate close medical follow-up should also be advocated. This might be of extreme importance, since high proviral load is a risk factor for progression from carrier status to ATL. Moreover, educational programmes should be implicated to increase public awareness of

Table 3 Preventive strategies

To prevent transmission through blood transfusion, all blood donors should be examined in high risk regions [38]
Educational programmes should be implicated to increase public awareness of HTLV and the transmission modes, including possible sexual transmission
Additionally, information to health practitioners regarding HTLV transmission and recent developments should be advocated
The use of a condom is advised during sexual intercourse [32, 100]
Testing maternal anti-HTLV antibody titre and proviral load before delivery would be an optimal preventive strategy. However, especially with the low incidence rate in Europe and the economic problems regarding such a screening strategy, elective testing for patients coming from endemic regions could be reasonable and feasible
Testing of newborns born to HTLV-seropositive mothers with an adequate close medical follow up should be advocated
Reduction or restriction of breastfeeding in HTLV-seropositive mothers as demonstrated in large studies from Japan [53, 54]
If stopping breastfeeding is (socio-economically) not possible, advocate short-term breastfeeding for 3 to a maximum of 6 months

HTLV and the transmission modes, including possible sexual transmission. In this context, the use of a condom is advised during sexual intercourse [32, 100]. Additionally, to prevent transmission through blood transfusion, all blood donors should be examined in high risk regions [36].

Although the understanding of the association between viral infection, host response and clinical manifestations has improved markedly during the last few years, there are still no clear and defined prognostic markers as well as sufficient preventive strategies or treatment options.

Conflict of interest statement None.

References

1. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC (1980) Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci USA 77:7415–7419
2. Proietti FA, Carneiro-Proietti AB (2006) HTLV in the Americas. Rev Panam Salud Publica 19:7–8
3. Proietti FA, Carneiro-Proietti AB, Catalan-Soares BC, Murphy EL (2005) Global epidemiology of HTLV-I infection and associated diseases. Oncogene 24:6058–6068
4. Verdonck K, Gonzalez E, Van Dooren S, Vandamme AM, Vanham G, Gotuzzo E (2007) Human T-lymphotropic virus 1: recent knowledge about an ancient infection. Lancet Infect Dis 7:266–281
5. Gessain A, Barin F, Vernant JC, Gout O, Maurs L, Calender A, de The G (1985) Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. Lancet 2:407–410
6. Gallo RC (1985) The human T-cell leukemia/lymphotropic retroviruses (HTLV) family: past, present, and future. Cancer Res 45:4524s–4533s
7. Bartholomew C, Jack N, Edwards J, Charles W, Corbin D, Cleghorn FR, Blattner WA (1998) HTLV-I serostatus of mothers of patients with adult T-cell leukemia and HTLV-I-associated myelopathy/tropical spastic paraparesis. J Hum Virol 1:302–305
8. Wilks R, Hanchard B, Morgan O, Williams E, Cranston B, Smith ML, Rodgers-Johnson P, Manns A (1996) Patterns of HTLV-I infection among family members of patients with adult T-cell leukemia/lymphoma and HTLV-I associated myelopathy/tropical spastic paraparesis. Int J Cancer 65:272–273
9. Gallo RC (2005) History of the discoveries of the first human retroviruses: HTLV-1 and HTLV-2. Oncogene 24:5926–5930
10. zur Hausen H (2009) Papillomaviruses in the causation of human cancers—a brief historical account. Virology 384:260–265
11. Jeang KT (2005) Retrovirology highlights a quarter century of HTLV-I research. Retrovirology 2:15
12. Manel N, Kim FJ, Kinet S, Taylor N, Sitbon M, Battini JL (2003) The ubiquitous glucose transporter GLUT-1 is a receptor for HTLV. Cell 115:449–459
13. Gaudray G, Gachon F, Basbous J, Biard-Piechaczyk M, Devaux C, Mesnard JM (2002) The complementary strand of the human T-cell leukemia virus type 1 RNA genome encodes a bZIP transcription factor that down-regulates viral transcription. J Virol 76:12813–12822
14. Albrecht B, Lairmore MD (2002) Critical role of human T-lymphotropic virus type 1 accessory proteins in viral replication and pathogenesis. Microbiol Mol Biol Rev 66:396–406 (Table of contents)
15. Bangham CR (2003) Human T-lymphotropic virus type 1 (HTLV-1): persistence and immune control. Int J Hematol 78:297–303
16. Zane L, Sibon D, Mortreux F, Wattel E (2009) Clonal expansion of HTLV-1 infected cells depends on the CD4 versus CD8 phenotype. Front Biosci 14:3935–3941
17. Umeki K, Hisada M, Maloney EM, Hanchard B, Okayama A (2009) Proviral loads and clonal expansion of HTLV-1-infected cells following vertical transmission: a 10-year follow-up of children in Jamaica. Intervirology 52:115–122
18. Tanaka G, Okayama A, Watanabe T, Aizawa S, Stuver S, Mueller N, Hsieh CC, Tsubouchi H (2005) The clonal expansion of human T lymphotropic virus type 1-infected T cells: a comparison between seroconverters and long-term carriers. J Infect Dis 191:1140–1147
19. Igakura T, Stinchcombe JC, Goon PK, Taylor GP, Weber JN, Griffiths GM, Tanaka Y, Osame M, Bangham CR (2003) Spread of HTLV-I between lymphocytes by virus-induced polarization of the cytoskeleton. Science 299:1713–1716
20. Saji F, Tokugawa Y, Kamiura S, Samejima Y, Ohashi K, Azuma C, Tanizawa O (1989) Vertical transmission of human T-cell leukemia virus type I (HTLV-I): detection of proviral DNA in HTLV-I carrier gravida. J Clin Immunol 9:409–414
21. Vandamme AM, Salemi M, Van Brussel M, Liu HF, Van Laethem K, Van Ranst M, Michels L, Desmyter J, Goubau P (1998) African origin of human T-lymphotropic virus type 2 (HTLV-2) supported by a potential new HTLV-2d subtype in Congolese Bambuti Efe Pygmies. J Virol 72:4327–4340
22. Lemey P, Pybus OG, Van Dooren S, Vandamme AM (2005) A Bayesian statistical analysis of human T-cell lymphotropic virus evolutionary rates. Infect Genet Evol 5:291–298
23. Taylor GP, Bodeus M, Courtois F, Pauli G, Del Mistro A, Machuca A, Padua E, Andersson S, Goubau P, Chieco-Bianchi L, Soriano V, Coste J, Ades AE, Weber JN (2005) The seroepidemiology of human T-lymphotropic viruses: types I and II in Europe: a prospective study of pregnant women. J Acquir Immune Defic Syndr 38:104–109
24. Larsen O, Andersson S, da Silva Z, Hedegaard K, Sandstrom A, Naucler A, Dias F, Melbye M, Aaby P (2000) Prevalences of HTLV-1 infection and associated risk determinants in an urban population in Guinea-Bissau, West Africa. J Acquir Immune Defic Syndr 25:157–163
25. Glynn SA, Kleinman SH, Schreiber GB, Busch MP, Wright DJ, Smith JW, Nass CC, Williams AE (2000) Trends in incidence and prevalence of major transfusion-transmissible viral infections in US blood donors, 1991 to 1996. Retrovirus Epidemiology Donor Study (REDS). JAMA 284:229–235
26. Kishihara Y, Furusyo N, Kashiwagi K, Mitsutake A, Kashiwagi S, Hayashi J (2001) Human T lymphotropic virus type 1 infection influences hepatitis C virus clearance. J Infect Dis 184:1114–1119
27. Price J, Cant BA, Barbara JA, Tedder RS (2001) Human T-cell leukaemia/lymphoma virus risk may be enhanced in some selected donor populations. Vox Sang 80:148–150
28. Zehender G, Colasante C, De Maddalena C, Bernini F, Savasi V, Persico T, Merli S, Ridolfo A, Santambrogio S, Moroni M, Galli M (2004) High prevalence of human T-lymphotropic virus type 1 (HTLV-1) in immigrant male-to-female transsexual sex workers with HIV-1 infection. J Med Virol 74:207–215
29. Lillo FB, Capiluppi B, Chiarolini A, McDermott JL, Varnier OE (1999) First report of the presence of human T-cell lymphotropic virus I infection in Italian drug addicts. Eur J Clin Microbiol Infect Dis 18:671–672
30. Paun L, Ispas O, Del Mistro A, Chieco-Bianchi L (1994) HTLV-I in Romania. Eur J Haematol 52:117–118

31. Shtalrid M, Shvidel L, Korenfeld R, Duek A, Landau Z, Berrebi A (2005) HTLV-1 associated adult T-cell leukemia/lymphoma in Israel: report of two patients of Romanian origin. Haematologica 90:ECR13
32. Gotuzzo E, Sanchez J, Escamilla J, Carrillo C, Phillips IA, Moreyra L, Stamm W, Ashley R, Roggen EL, Kreiss J et al (1994) Human T cell lymphotropic virus type I infection among female sex workers in Peru. J Infect Dis 169:754–759
33. Manns A, Wilks RJ, Murphy EL, Haynes G, Figueroa JP, Barnett M, Hanchard B, Blattner WA (1992) A prospective study of transmission by transfusion of HTLV-I and risk factors associated with seroconversion. Int J Cancer 51:886–891
34. Osame M, Izumo S, Igata A, Matsumoto M, Matsumoto T, Sonoda S, Tara M, Shibata Y (1986) Blood transfusion and HTLV-I associated myelopathy. Lancet 2:104–105
35. Jason JM, McDougal JS, Cabradilla C, Kalyanaraman VS, Evatt BL (1985) Human T-cell leukemia virus (HTLV-I) p24 antibody in New York City blood product recipients. Am J Hematol 20:129–137
36. Sato H, Okochi K (1986) Transmission of human T-cell leukemia virus (HTLV-I) by blood transfusion: demonstration of proviral DNA in recipients' blood lymphocytes. Int J Cancer 37:395–400
37. Siegel R, Gartenhaus R, Kuzel T (2001) HTLV-I associated leukemia/lymphoma: epidemiology, biology, and treatment. Cancer Treat Res 104:75–88
38. Tynell E, Andersson S, Lithander E, Arneborn M, Blomberg J, Hansson HB, Krook A, Nomberg M, Ramstedt K, Shanwell A, Bjorkman A (1998) Screening for human T cell leukaemia/lymphoma virus among blood donors in Sweden: cost effectiveness analysis. BMJ 316:1417–1422
39. Lee HH, Weiss SH, Brown LS, Mildvan D, Shorty V, Saravolatz L, Chu A, Ginzburg HM, Markowitz N, Des Jarlais DC et al (1990) Patterns of HIV-1 and HTLV-I/II in intravenous drug abusers from the middle Atlantic and central regions of the USA. J Infect Dis 162:347–352
40. Bassani S, Toro C, de la Fuente L, Brugal MT, Jimenez V, Soriano V (2004) Rate of infection by blood-borne viruses in active heroin users in 3 Spanish cities. Med Clin (Barc) 122:570–572
41. Zunt JR, Dezzutti CS, Montano SM, Thomas KK, Alarcon JO, Quijano E, Courtois BN, Sanchez JL, Campos P, Gotuzzo E, Guenthner PC, Lal RB, Holmes KK (2002) Cervical shedding of human T cell lymphotropic virus type I is associated with cervicitis. J Infect Dis 186:1669–1672
42. Kaplan JE, Khabbaz RF, Murphy EL, Hermansen S, Roberts C, Lal R, Heneine W, Wright D, Matijas L, Thomson R, Rudolph D, Switzer WM, Kleinman S, Busch M, Schreiber GB (1996) Male-to-female transmission of human T-cell lymphotropic virus types I and II: association with viral load. The Retrovirus epidemiology donor study group. J Acquir Immune Defic Syndr Hum Retrovirol 12:193–201
43. Roucoux DF, Wang B, Smith D, Nass CC, Smith J, Hutching ST, Newman B, Lee TH, Chafets DM, Murphy EL, Investigators HOS (2005) A prospective study of sexual transmission of human T lymphotropic virus (HTLV)-I and HTLV-II. J Infect Dis 191:1490–1497
44. Figueroa JP, Ward E, Morris J, Brathwaite AR, Peruga A, Blattner W, Vermund SH, Hayes R (1997) Incidence of HIV and HTLV-1 infection among sexually transmitted disease clinic attenders in Jamaica. J Acquir Immune Defic Syndr Hum Retrovirol 15:232–237
45. Ureta-Vidal A, Angelin-Duclos C, Tortevoye P, Murphy E, Lepere JF, Buigues RP, Jolly N, Joubert M, Carles G, Pouliquen JF, de The G, Moreau JP, Gessain A (1999) Mother-to-child transmission of human T-cell-leukemia/lymphoma virus type I: implication of high antiviral antibody titer and high proviral load in carrier mothers. Int J Cancer 82:832–836
46. Li HC, Biggar RJ, Miley WJ, Maloney EM, Cranston B, Hanchard B, Hisada M (2004) Provirus load in breast milk and risk of mother-to-child transmission of human T lymphotropic virus type I. J Infect Dis 190:1275–1278
47. Biggar RJ, Ng J, Kim N, Hisada M, Li HC, Cranston B, Hanchard B, Maloney EM (2006) Human leukocyte antigen concordance and the transmission risk via breast-feeding of human T cell lymphotropic virus type I. J Infect Dis 193:277–282
48. Tsuji Y, Doi H, Yamabe T, Ishimaru T, Miyamoto T, Hino S (1990) Prevention of mother-to-child transmission of human T-lymphotropic virus type-I. Pediatrics 86:11–17
49. Hirata M, Hayashi J, Noguchi A, Nakashima K, Kajiyama W, Kashiwagi S, Sawada T (1992) The effects of breastfeeding and presence of antibody to p40tax protein of human T cell lymphotropic virus type-I on mother to child transmission. Int J Epidemiol 21:989–994
50. Nyambi PN, Ville Y, Louwagie J, Bedjabaga I, Glowaczower E, Peeters M, Kerouedan D, Dazza M, Larouze B, van der Groen G, Delaporte E (1996) Mother-to-child transmission of human T-cell lymphotropic virus types I and II (HTLV-I/II) in Gabon: a prospective follow-up of 4 years. J Acquir Immune Defic Syndr Hum Retrovirol 12:187–192
51. Takezaki T, Tajima K, Ito M, Ito S, Kinoshita K, Tachibana K, Matsushita Y (1997) Short-term breast-feeding may reduce the risk of vertical transmission of HTLV-I. The Tsushima ATL study group. Leukemia 11(Suppl 3):60–62
52. Wiktor SZ, Pate EJ, Rosenberg PS, Barnett M, Palmer P, Medeiros D, Maloney EM, Blattner WA (1997) Mother-to-child transmission of human T-cell lymphotropic virus type I associated with prolonged breast-feeding. J Hum Virol 1:37–44
53. Hino S, Katamine S, Kawase K, Miyamoto T, Doi H, Tsuji Y, Yamabe T (1994) Intervention of maternal transmission of HTLV-1 in Nagasaki, Japan. Leukemia 8(Suppl 1):S68–S70
54. Kashiwagi K, Furusyo N, Nakashima H, Kubo N, Kinukawa N, Kashiwagi S, Hayashi J (2004) A decrease in mother-to-child transmission of human T lymphotropic virus type I (HTLV-I) in Okinawa, Japan. Am J Trop Med Hyg 70:158–163
55. Bittencourt AL, Dourado I, Filho PB, Santos M, Valadao E, Alcantara LC, Galvao-Castro B (2001) Human T-cell lymphotropic virus type 1 infection among pregnant women in northeastern Brazil. J Acquir Immune Defic Syndr 26:490–494
56. Caterino-de-Araujo A, de los Santos-Fortuna E (1999) No evidence of vertical transmission of HTLV-I and HTLV-II in children at high risk for HIV-1 infection from Sao Paulo, Brazil. J Trop Pediatr 45:42–47
57. Kinoshita K, Yamanouchi K, Ikeda S, Momita S, Amagasaki T, Soda H, Ichimaru M, Moriuchi R, Katamine S, Miyamoto T et al (1985) Oral infection of a common marmoset with human T-cell leukemia virus type-I (HTLV-I) by inoculating fresh human milk of HTLV-I carrier mothers. Jpn J Cancer Res 76:1147–1153
58. Miller GJ, Lewis LL, Colman SM, Cooper JA, Lloyd G, Scollen N, Jones N, Tedder RS, Greaves MF (1994) Clustering of human T lymphotropic virus type I seropositive in Montserrat, West Indies: evidence for an environmental factor in transmission of the virus. J Infect Dis 170:44–50
59. Yoshida M, Miyoshi I, Hinuma Y (1982) Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. Proc Natl Acad Sci USA 76:2031–2035
60. Rodgers-Johnson P, Gajdusek DC, Morgan OS, Zaninovic V, Sarin PS, Graham DS (1985) HTLV-I and HTLV-III antibodies and tropical spastic paraparesis. Lancet 2:1247–1248

61. Osame M, Usuku K, Izumo S, Ijichi N, Amitani H, Igata A, Matsumoto M, Tara M (1986) HTLV-I associated myelopathy, a new clinical entity. Lancet 1:1031–1032
62. Verastegui E, Ortega V, Soler C, Lazo de la Vega S, Ocadiz R, Meneses A, Reynoso E, Alfaro G (1992) Primary B cell lymphoma of the rectum in a patient coinfected with HIV-1 and HTLV-I. Rev Invest Clin 44:387–392
63. Eguchi K, Nakamura T, Mine M, Ida H, Kawakami A, Migita K, Nagasato K, Kurata A, Fukuda T, Nagataki S (1992) HTLV-I associated arthritis: characteristics of an HTLV-I virus infected T cell line from synovial fluid. Ann Rheum Dis 51:673–677
64. Eguchi K, Origuchi T, Takashima H, Iwata K, Katamine S, Nagataki S (1996) High seroprevalence of anti-HTLV-I antibody in rheumatoid arthritis. Arthritis Rheum 39:463–466
65. Mochizuki M, Yamaguchi K, Takatsuki K, Watanabe T, Mori S, Tajima K (1992) HTLV-I and uveitis. Lancet 339:1110
66. Nakao K, Ohba N (1993) Clinical features of HTLV-I associated uveitis. Br J Ophthalmol 77:274–279
67. Nakao K, Ohba N, Nakagawa M, Osame M (1999) Clinical course of HTLV-I-associated uveitis. Jpn J Ophthalmol 43:404–409
68. Sugimoto M, Nakashima H, Kawano O, Ando M, Araki S (1989) Bronchoalveolar T-lymphocytosis in HTLV-1-associated myelopathy. Chest 95:708
69. Couderc LJ, Caubarrere I, Venet A, Magdeleine J, Jouanelle A, Danon F, Buisson G, Vernant JC (1988) Bronchoalveolar lymphocytosis in patients with tropical spastic paraparesis associated with human T-cell lymphotropic virus type 1 (HTLV-1): clinical, immunologic, and cytologic studies. Ann Intern Med 109:625–628
70. Nakada K, Yamaguchi K, Furugen S, Nakasone T, Nakasone K, Oshiro Y, Kohakura M, Hinuma Y, Seiki M, Yoshida M et al (1987) Monoclonal integration of HTLV-I proviral DNA in patients with strongyloidiasis. Int J Cancer 40:145–148
71. Primo JR, Brites C, Oliveira Mde F, Moreno-Carvalho O, Machado M, Bittencourt AL (2005) Infective dermatitis and human T cell lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis in childhood and adolescence. Clin Infect Dis 41:535–541
72. Bittencourt AL, Oliveira Mde F, Brites C, Van Weyenbergh J, da Silva Vieira MG, Araujo I (2005) Histopathological and immunohistochemical studies of infective dermatitis associated with HTLV-I. Eur J Dermatol 15:26–30
73. Matsuda T, Tomita M, Uchihara JN, Okudaira T, Ohshiro K, Tomoyose T, Ikema T, Masuda M, Saito M, Osame M, Takasu N, Ohta T, Mori N (2005) Human T cell leukemia virus type I-infected patients with Hashimoto's thyroiditis and Graves' disease. J Clin Endocrinol Metab 90:5704–5710
74. Sugimoto M, Nakashima H, Watanabe S, Uyama E, Tanaka F, Ando M, Araki S, Kawasaki S (1987) T-lymphocyte alveolitis in HTLV-I-associated myelopathy. Lancet 2:1220
75. Sabouri AH, Saito M, Usuku K, Bajestan SN, Mahmoudi M, Forughipour M, Sabouri Z, Abbaspour Z, Goharjoo ME, Khayami E, Hasani A, Izumo S, Arimura K, Farid R, Osame M (2005) Differences in viral and host genetic risk factors for development of human T-cell lymphotropic virus type 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis between Iranian and Japanese HTLV-1-infected individuals. J Gen Virol 86:773–781
76. Biswas HH, Engstrom JW, Kaidarova Z, Garratty G, Gibble JW, Newman BH, Smith JW, Ziman A, Fridey JL, Sacher RA, Murphy EL (2009) Neurologic abnormalities in HTLV-I- and HTLV-II-infected individuals without overt myelopathy. Neurology 73:781–789
77. Murphy EL, Wang B, Sacher RA, Fridey J, Smith JW, Nass CC, Newman B, Ownby HE, Garratty G, Hutching ST, Schreiber GB (2004) Respiratory and urinary tract infections, arthritis, and asthma associated with HTLV-I and HTLV-II infection. Emerg Infect Dis 10:109–116
78. Maloney EM, Cleghorn FR, Morgan OS, Rodgers-Johnson P, Cranston B, Jack N, Blattner WA, Bartholomew C, Manns A (1998) Incidence of HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in Jamaica and Trinidad. J Acquir Immune Defic Syndr Hum Retrovirol 17:167–170
79. Kaplan JE, Osame M, Kubota H, Igata A, Nishitani H, Maeda Y, Khabbaz RF, Janssen RS (1990) The risk of development of HTLV-I-associated myelopathy/tropical spastic paraparesis among persons infected with HTLV-I. J Acquir Immune Defic Syndr 3:1096–1101
80. Bittencourt AL, Sabino EC, Costa MC, Pedroso C, Moreira L (2002) No evidence of vertical transmission of HTLV-I in bottle-fed children. Rev Inst Med Trop Sao Paulo 44:63–65
81. Berger JR, Svenningsson A, Raffanti S, Resnick L (1991) Tropical spastic paraparesis-like illness occurring in a patient dually infected with HIV-1 and HTLV-II. Neurology 41:85–87
82. Jacobson S, Lehky T, Nishimura M, Robinson S, McFarlin DE, Dhib-Jalbut S (1993) Isolation of HTLV-II from a patient with chronic, progressive neurological disease clinically indistinguishable from HTLV-I-associated myelopathy/tropical spastic paraparesis. Ann Neurol 33:392–396
83. Orland JR, Engstrom J, Fridey J, Sacher RA, Smith JW, Nass C, Garratty G, Newman B, Smith D, Wang B, Loughlin K, Murphy EL, Study HO (2003) Prevalence and clinical features of HTLV neurologic disease in the HTLV outcomes study. Neurology 61:1588–1594
84. Hjelle B, Mills R, Swenson S, Mertz G, Key C, Allen S (1991) Incidence of hairy cell leukemia, mycosis fungoides, and chronic lymphocytic leukemia in first known HTLV-II-endemic population. J Infect Dis 163:435–440
85. Kalyanaraman VS, Sarngadharan MG, Robert-Guroff M, Miyoshi I, Golde D, Gallo RC (1982) A new subtype of human T-cell leukemia virus (HTLV-II) associated with a T-cell variant of hairy cell leukemia. Science 218:571–573
86. Poiesz B, Dube D, Dube S, Love J, Papsidero L, Uner A, Hutchinson R (2000) HTLV-II-associated cutaneous T-cell lymphoma in a patient with HIV-1 infection. N Engl J Med 342:930–936
87. Zucker-Franklin D, Hooper WC, Evatt BL (1992) Human lymphotropic retroviruses associated with mycosis fungoides: evidence that human T-cell lymphotropic virus type II (HTLV-II) as well as HTLV-I may play a role in the disease. Blood 80:1537–1545
88. Orland JR, Wang B, Wright DJ, Nass CC, Garratty G, Smith JW, Newman B, Smith DM, Murphy EL, Investigators H (2004) Increased mortality associated with HTLV-II infection in blood donors: a prospective cohort study. Retrovirology 1:4
89. Biswas HH, Kaidarova Z, Garratty G, Gibble JW, Newman BH, Smith JW, Ziman A, Fridey JL, Sacher RA, Murphy EL, for the HOS (2010) Increased All-Cause and Cancer Mortality in HTLV-II Infection. J Acquir Immune Defic Syndr (In press)
90. Thorstensson R, Albert J, Andersson S (2002) Strategies for diagnosis of HTLV-I and -II. Transfusion 42:780–791
91. Gallo D, Hoffman MN, Cossen CK, Diggs JL, Hurst JW, Penning LM (1988) Comparison of immunofluorescence, enzyme immunoassay, and western blot (immunoblot) methods for detection of antibody to human T-cell leukemia virus type I. J Clin Microbiol 26:1487–1491
92. Sabino EC, Zrein M, Taborda CP, Otani MM, Ribeiro-Dos-Santos G, Saez-Alquezar A (1999) Evaluation of the INNO-LIA HTLV I/II assay for confirmation of human T-cell leukemia virus-reactive sera in blood bank donations. J Clin Microbiol 37:1324–1328

93. Mangano AM, Remesar M, del Pozo A, Sen L (2004) Human T lymphotropic virus types I and II proviral sequences in Argentinian blood donors with indeterminate western blot patterns. J Med Virol 74:323–327
94. Vandamme AM, Van Laethem K, Liu HF, Van Brussel M, Delaporte E, de Castro Costa CM, Fleischer C, Taylor G, Bertazzoni U, Desmyter J, Goubau P (1997) Use of a generic polymerase chain reaction assay detecting human T-lymphotropic virus (HTLV) types I, II and divergent simian strains in the evaluation of individuals with indeterminate HTLV serology. J Med Virol 52:1–7
95. Dehee A, Cesaire R, Desire N, Lezin A, Bourdonne O, Bera O, Plumelle Y, Smadja D, Nicolas JC (2002) Quantitation of HTLV-I proviral load by a TaqMan real-time PCR assay. J Virol Methods 102:37–51
96. Lee TH, Chafets DM, Busch MP, Murphy EL (2004) Quantitation of HTLV-I and II proviral load using real-time quantitative PCR with SYBR green chemistry. J Clin Virol 31:275–282
97. Kamihira S, Dateki N, Sugahara K, Hayashi T, Harasawa H, Minami S, Hirakata Y, Yamada Y (2003) Significance of HTLV-1 proviral load quantification by real-time PCR as a surrogate marker for HTLV-1-infected cell count. Clin Lab Haematol 25:111–117
98. Olindo S, Lezin A, Cabre P, Merle H, Saint-Vil M, Edimonana Kaptue M, Signate A, Cesaire R, Smadja D (2005) HTLV-1 proviral load in peripheral blood mononuclear cells quantified in 100 HAM/TSP patients: a marker of disease progression. J Neurol Sci 237:53–59
99. Iwanaga M, Watanabe T, Utsunomiya A, Okayama A, Uchimaru K, Koh KR, Ogata M, Kikuchi H, Sagara Y, Uozumi K, Mochizuki M, Tsukasaki K, Saburi Y, Yamamura M, Tanaka J, Moriuchi Y, Hino S, Kamihira S, Yamaguchi K (2010) Human T-cell leukemia virus type I (HTLV-1) proviral load and disease progression in asymptomatic HTLV-1 carriers: a nationwide prospective study in Japan. Blood (In press)
100. Trujillo L, Munoz D, Gotuzzo E, Yi A, Watts DM (1999) Sexual practices, prevalence of HIV, HTLV-I/II, and Treponema pallidum among clandestine female sex workers in Lima, Peru. Sex Transm Dis 26:115–118