Human T-lymphotropic virus 1: recent knowledge about an ancient infection

Kristien Verdonck, Elsa González, Sonia Van Dooren, Anne-Mieke Vandamme, Guido Vanham, Eduardo Gotuzzo

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Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru (K Verdonck MD, E González MD, Prof E Gotuzzo MD)**; HIV and Retrovirology Research Unit, Department of Microbiology, Institute of Tropical Medicine, Antwerp, Belgium** (K Verdonck, Prof G Vanham PhD)**; REGA Institute for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium** (S Van Dooren PhD, Prof A M Vandamme PhD)**; and Department of Biomedical Sciences, University of Antwerp, Antwerp** (G Vanham)

Correspondence to: Dr Kristien Verdonck, Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Avenida Honorio Delgado 430, Lima 31, Peru.
Tel +51 1 482 39 10; fax +51 1 482 34 04; **tverdonck@itg.be**

Human T-lymphotropic virus 1 (HTLV-1) has infected human beings for thousands of years, but knowledge about the infection and its pathogenesis is only recently emerging. The virus can be transmitted from mother to child, through sexual contact, and through contaminated blood products. There are areas in Japan, sub-Saharan Africa, the Caribbean, and South America where more than 1% of the general population is infected. Although the majority of HTLV-1 carriers remain asymptomatic, the virus is associated with severe diseases that can be subdivided into three categories: neoplastic diseases (adult T-cell leukaemia/lymphoma), inflammatory syndromes (HTLV-1-associated myelopathy/tropical spastic paraparesis and uveitis among others), and opportunistic infections (including *Strongyloides stercoralis* hyperinfection and others). The understanding of the interaction between virus and host response has improved markedly, but there are still no clear surrogate markers for prognosis and there are few treatment options.

Introduction

In 1979, the human T-lymphotropic virus 1 (HTLV-1) was isolated from a patient with a T-cell malignancy.[1] This discovery was the first formal proof that human retroviruses exist and suggested their aetiological role in human cancer, a hypothesis that had been proposed decades before.[2] It is estimated that 10 to 20 million people worldwide are infected with HTLV-1,[3] and although the majority of infected people remain asymptomatic, the virus is associated with exceptionally severe diseases, such as adult T-cell leukaemia/lymphoma (ATL) and an inflammatory disease of the central nervous system called HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP).[4,5] The growing insight into the pathogenesis of these diseases sheds light upon the functioning of human T cells, the major target of HTLV-1. Nonetheless, it is not yet fully understood why some infected individuals develop associated diseases whereas others do not.[6]

HTLV-1 and T cells

HTLV-1 is a type C virus belonging to the family of Retroviridae and classified into the genus of Deltaretrovirus. It is a round-shaped, enveloped virus of approximately 100 nm diameter (figure 1A).[7] The virion is surrounded by a proteolipid envelope bilayer of host cell membrane origin, equipped with viral transmembrane and surface proteins. The inner envelope contains the matrix layer, which helps to organise the viral components at the inner cell membrane. The icosahedral capsid protects the viral RNA and the functional protease, reverse transcriptase, and integrase, which are organised together with the nucleocapsid into a ribonucleoprotein complex.[7]

The genome of HTLV-1 is a positive, single-stranded RNA. During the life cycle of the virus, this single-stranded RNA is converted to double-stranded DNA and inserted into the DNA of a human host cell. This inserted form of a retrovirus is referred to as provirus.[2] Like other human retroviruses, HTLV-1 causes a lifelong infection. The virus preferentially infects CD4+ T cells, but CD8+ T cells are also an important reservoir for the virus.[9] Evidence suggests that the ubiquitous vertebrate glucose transporter could act as a host-cell receptor for HTLV-1.[10]

The HTLV-1 genome encodes typical retroviral structural, functional, and envelope proteins, HTLV-1-specific regulatory proteins, and a minus-strand gene protein designated HTLV-1 bZIP-factor (figure 1B, table 1).[11,12] The virus makes optimum use of its genome by using multiple RNA ribosomal frame shifts and transcript splicing patterns, including differential start sites for protein translation (figure 1C).

By contrast with HIV, HTLV-1 predominantly exists as a cell-associated provirus and is transmitted as such.[6] Naturally infected T cells hardly produce any virus and the plasma viral load is, therefore, undetectable. However, the virus particle-associated RNA can infect new cells through a viral synapse.[13] It is presumed that early during 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. In later stages, when equilibrium between viral replication and immune response is reached, HTLV-1 mainly multiplies by clonal expansion dependent on mitosis of host cells.[14]

An immunological hallmark of HTLV-1-infected individuals is the spontaneous proliferation of peripheral blood mononuclear cells in vitro—ie, without exogenous antigens or stimulants, but driven by the HTLV-1-encoded Tax protein.[15] This mitosis-dependent survival strategy of HTLV-1 contributes to its genomic stability, because it relies on cellular DNA polymerase, which by contrast with viral reverse transcriptase, displays efficient proof reading.[16] Phylogenetic analyses of the proviral DNA contribute to the knowledge about origin and evolution of HTLV-1 and might be useful in anthropological studies.[17]

The predominantly proviral lifestyle of HTLV-1 is an indirect argument for a relatively effective immune response. Class I-restricted CD8+ T cells control the virus by lysis of infected T cells that express viral peptides as a consequence of viral transcription (figure 2).[6] The equilibrium between this cytotoxic T-lymphocyte control

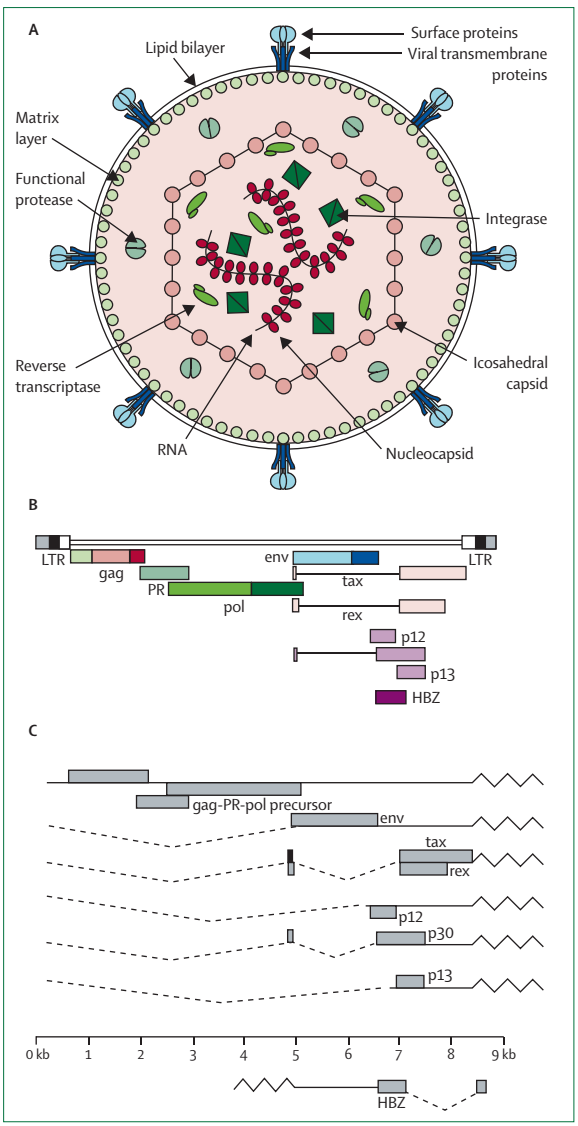

***Figure 1*: HTLV-1 virus structure and genome**
(A) Schematic cross-section through a mature HTLV-1 particle depicting its structure and composition. Reproduced with permission from reference 8 (Van Dooren, 2005). (B) Genomic organisation of HTLV-1. (C) Viral messengers. The primary full-length messenger RNA encodes a large Gag-PR-Pol precursor polyprotein, a singly spliced messenger encodes Env, and doubly spliced messengers encode the regulatory proteins. Viral genes encoded by the plus and minus strand RNA are shown respectively above and below the scale bar of the genomic length. HBZ=HTLV-1 bZIP-factor. LTR=long terminal repeat.

and the proviral replication results in a steady-state provirus load that varies little over time in any given individual.[18,19]

However, there seems to be a trade-off between this beneficial cytotoxic T-lymphocyte response and the simultaneous production of inflammatory cytokines, which can result in inflammatory pathology.[20] Because the virus has a low genetic variability, it can be postulated that the outcome of HTLV-1 infection will depend on intrinsic host factors—ie, the relative efficiency of the purely lytic response, reflected in production of perforin and granzyme, versus the tendency to produce inflammatory cytokines such as interferon-γ and tumour necrosis factor (TNF) α (figure 2).

Diagnosis of HTLV-1 infection

Serological screening for the presence of HTLV antibodies can either be done by an enzyme immunoassay (EIA) or by a particle agglutination test. The first generation EIAs were based on viral lysate and frequently resulted in false-positive reactions.[21] Second generation EIAs using recombinant proteins and/or synthetic HTLV-1 peptides perform better, but confirmatory testing is still recommended to eliminate false-positive reactions and to discriminate between the different HTLV types.[22]

There are several serology-based confirmation tests, including homebrew indirect immunofluorescence assays (IFA), and commercially available western blot and line immunoassays.[23,24] One problem with these tests is the occurrence of indeterminate results, when samples react to one or more of the antigens incorporated in the test but lack the typical HTLV profile—ie, reactivity to at least Gag and Env.[25] Another problem is that the confirmatory tests cannot always distinguish between HTLV-1 and HTLV-2.[26]

In these indeterminate or untypable cases, PCR can provide the definite diagnosis of infection.[27,28] Several generic and/or type-specific HTLV PCRs have been developed; they are often based on the most conserved region of the genome, *tax*. In PCR and real-time PCR assays, proviral HTLV-1 DNA is amplified to a detectable level. Real-time PCR has the advantage that the provirus can be quantified. The provirus load is expressed as the number of HTLV-1 DNA copies per fixed number of peripheral blood mononuclear cells.[29,30] It is the most frequently used marker for prognosis and disease progression in infected patients.[19,31,32]

Transmission

HTLV-1 can be transmitted from mother to child through breastfeeding. The risk of infection in children of seropositive mothers correlates with the provirus load in breastmilk, the concordance of HLA class I type between mother and child, and the duration of breastfeeding.[33,34] In several reports from endemic populations, the overall rate of vertical transmission ranged between 15% and 25%, and in subgroups of children who received prolonged breastfeeding, these rates were even higher.[35–39] In Japan, screening of pregnant women and avoiding breastfeeding in those infected has reduced the prevalence of HTLV-1.[40,41] Intrauterine and peripartum transmission of HTLV-1 occurs in less than 5% of children of infected mothers.[37,40,42]

HTLV-1 is present in genital secretions of infected people and can be transmitted through sexual intercourse.[43] In a cohort of 30 discordant couples

HTLV-1 proteins and glycoproteins	Functions
Envelope proteins (encoded by *env*)	
Surface glycoprotein (gp46)	Binds to host cell receptor
Transmembrane protein (gp21)	Anchors surface glycoproteins to virus
Structural proteins (encoded by *gag*)	
Matrix layer (p19)	Organises viral components at the inner cell membrane
Capsid (p24)	Protects viral RNA and proteins (core shell)
Nucleocapsid (p15)	Nucleic acid-binding protein
Functional proteins (encoded by *pol*)	
Protease (p14)	Cleaves polyproteins into functional components
Reverse transcriptase (p95)	Converts single-stranded RNA to double-stranded DNA
Integrase	Facilitates insertion of provirus into host cell DNA
Regulatory proteins	
Tax	Activates transcription provirus Activates transcription host genes
Rex	Modulates transport of viral RNA
p12^{I}	Role in viral replication and T-cell activation
p30^{II}	Modulates transcription
p13^{II}	Targets mitochondria
HTLV-1 bZIP-factor	Downregulates viral transcription

Table 1: **Functions of HTLV-1 proteins and glycoproteins**

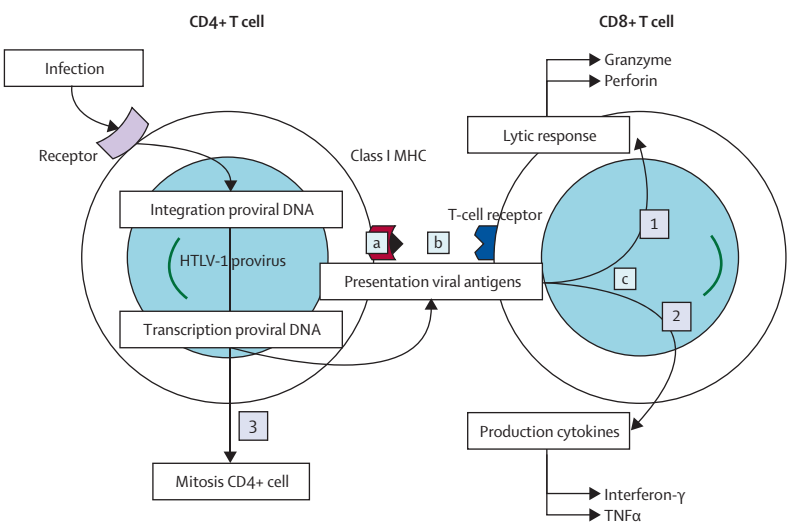

Figure 2: **The interaction between an infected CD4+ T cell and a CD8+ T cell indicating how HTLV-1 infection can lead to different outcomes**

(1) An efficient lytic response controls the provirus load and protects people from disease. (2) The production of inflammatory factors can eventually lead to HTLV-1-associated myelopathy/tropical spastic paraparesis and other inflammatory diseases, and (3) the proliferation of infected cells can result in adult T-cell leukaemia/lymphoma. The relative efficiency of (1) versus (2) may depend on (a) the relative affinity of different human leucocyte antigen molecules for crucial HTLV-1 peptides; (b) the efficiency of their interaction with the T-cell receptor; and (c) a genetic tendency to produce more inflammatory than lytic factors. TNF=tumour necrosis factor.

followed for 10 years, the incidence of HTLV-1 infection in the previously uninfected partner was estimated to be 0·9 per 100 person-years (95% CI 0·1–3·3).[44] Cross-sectional studies have suggested higher transmission efficiency from men to women than from women to men.[26,45] However, prospective studies show that this difference is less important than previously thought.[44,46] Condom use was shown to protect against infection among Peruvian sex workers.[47,48]

Transfusion of contaminated cellular blood components results in seroconversion in more than 40% of recipients.[49] 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.[50] Sharing of contaminated needles and syringes by injecting drug users is another way of parenteral transmission. HTLV-1 is frequent among injecting drug users in Brazil and in New York, whereas HTLV-2 is more prevalent in other North American and European injecting drug users.[51–53]

Origin, spread, and prevalence

To estimate the global prevalence of HTLV-1 on the basis of published reports is difficult because there are few population-based studies. HTLV-1 prevalence estimates are usually based on serological screening of blood donors, pregnant women, and other selected population groups. Studying the prevalence in healthy donors might underestimate the population prevalence.[54] Data from pregnant women may better reflect the general population, although reports from endemic areas suggest that HTLV-1 seroprevalence increases with age and is higher in women than in men.[26,55,56] A second obstacle for the comparison of prevalence studies is that different diagnostic tests and criteria for interpretation have been used. In a US study, a change in diagnostic strategy led to a false impression of increase in HTLV prevalence in blood donors.[57]

Africa

HTLV-1 infection is now present in the whole world but Africa is the only continent where all different primate T-lymphotropic viruses (PTLV) have been found: HTLV types 1 to 4 and their simian counterparts simian T-lymphotropic viruses (STLV) types 1 to 3. Therefore, it is assumed that the common ancestor of all PTLV originated in Africa. Phylogenetic studies also point to central Africa as the cradle of PTLV.[58,59]

The African/cosmopolitan part of the PTLV-1 phylogenetic tree is characterised by short branches and a star-like topology (figure 3A). This suggests an explosive spread of the virus on the African continent, giving rise to all African PTLV-1 clusters. It is estimated that the spread of PTLV-1 in Africa occurred 27 300 years ago (95% CI 19 100–35 500).[60] STLV-1 strains are interspersed within and between the five central African human subtypes (HTLV-1b, HTLV-1d, HTLV-1e, HTLV-1f, and HTLV-1g), suggesting frequently occurring interspecies transmissions between primates and human beings.[58] Only HTLV-1 subtype a, the subtype that became cosmopolitan, has no simian strains clustering within the clade (figure 3B). These HTLV-1 subtypes appear to have diverged between 21 100 and 5300 years ago.[60]

In most African countries, the actual HTLV-1 prevalence cannot be estimated because of lack of information. However, data from Guinea-Bissau, Togo, and south Cameroon suggest that at least in these countries, more than 1% of the general population is infected (figure 4).[61–63]

Asia

In southern Japan, the area in the world with the highest HTLV-1 prevalence, more than 10% of the general population is infected.[55,56,64] Several research groups have postulated the presence of HTLV-1a in Japan since ancient times, a view supported by the detection of HTLV-1 infection in the Japanese Ainu and Ryukyuans, both considered to be direct descendants of the oldest migrating Mongoloid populations.[65] However, an early report on the origin of HTLV-1, together with phylogenetic analyses and molecular clock studies suggest that HTLV-1a has been introduced into Japan much more recently as a result of Portuguese navigation adventures and the African slave trade.[17,66–68]

In Taiwan, in Iran, and in Fujian, a Chinese province near Taiwan, there are regions with a seroprevalence of 0·1–1%.[69–71] The infection is probably rare in the rest of Asia, although there are vast areas from where information is lacking (figure 4).

Oceania

HTLV-1 is endemic in Papua New Guinea, the Solomon Islands, and Vanuatu: more than 1% of the aboriginal population is infected with HTLV-1 subtype c.[72–74] The Asian/Oceanian part of the PTLV-1 phylogenetic tree presents deeply branching monophyletic host-specific clades, suggesting a long, host species-specific evolution (figure 3A).[75] The only human strains in this part of the tree belong to the HTLV-1 subtype c.[72] It has been suggested that HTLV-1c arose through the first settlers of Melanesia and Australia who probably acquired the virus from STLV-1-infected simians in Indonesia along their migratory pathway (figure 4).[76,77]

America

The presence of HTLV-1 in aboriginal populations from Kamchatka at one side of the Bering Strait and in native Eskimos and Amerindians on the other side suggests an

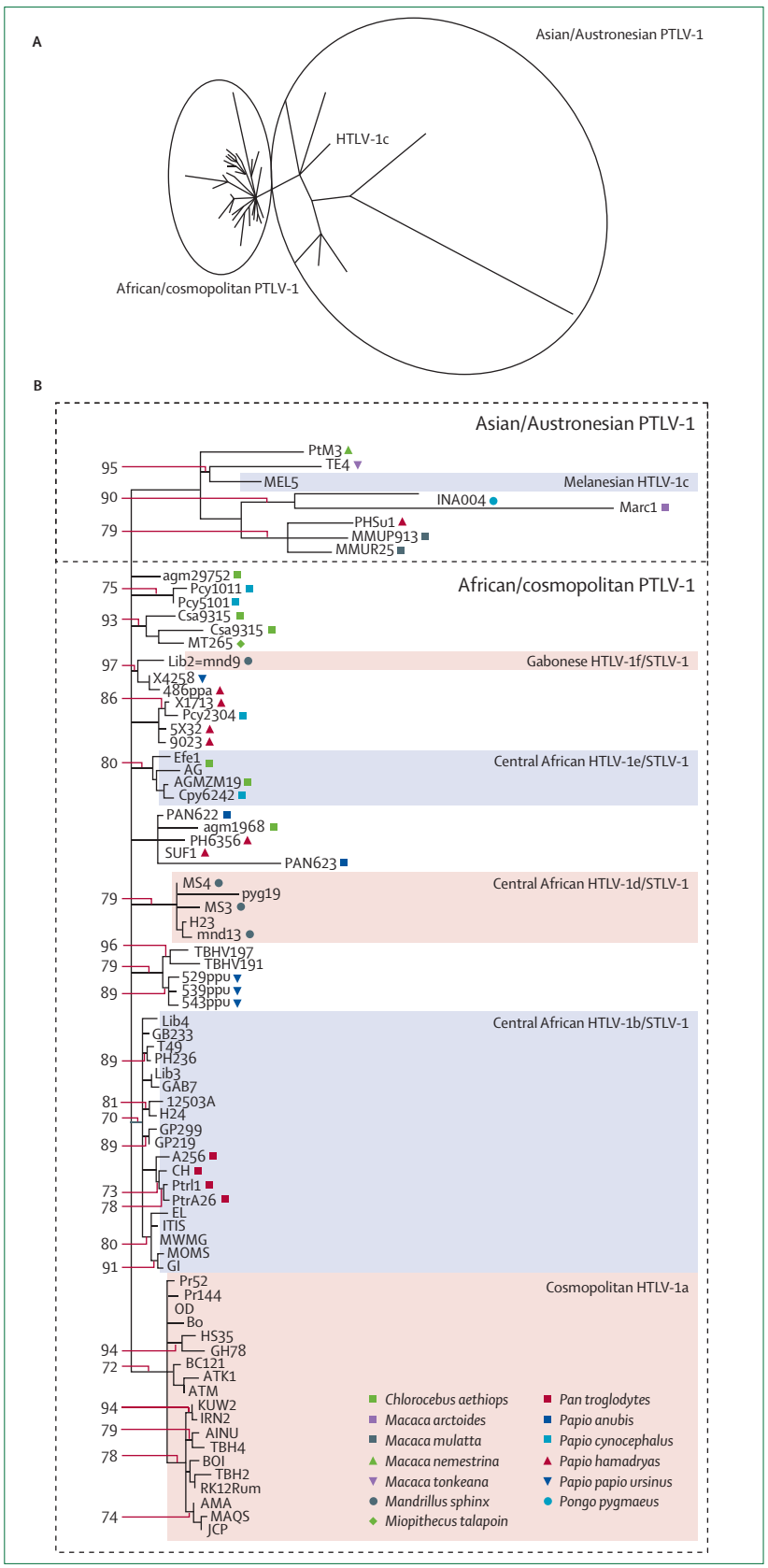

***Figure 3*: Puzzle maximum likelihood tree of the long terminal repeat region of 79 representative PTLV-1 strains**

(A) Unrooted version of the tree to demonstrate short branches and star-like topology in the African/cosmopolitan part versus deeply branching host-specific clades in the Asian/Austronesian part of the tree. (B) PTLV-1 long terminal repeat phylogram. The STLV-1 host species are represented by a symbol after the viral strain name. Strains with no symbols are HTLV-1 strains. The values on the left side of the nodes represent puzzling support values of 70% or more. The clear separation between Asian/Austronesian and African/cosmopolitan strains is demonstrated. The cosmopolitan HTLV-1a subtype and Melanesian HTLV-1c subtype are indicated together with the central African HTLV-1b, HTLV-1d, HTLV-1e, and HTLV-1f subtype clades, interspersed with STLV-1 strains. Reproduced with permission from reference 8 (Van Dooren, 2005).

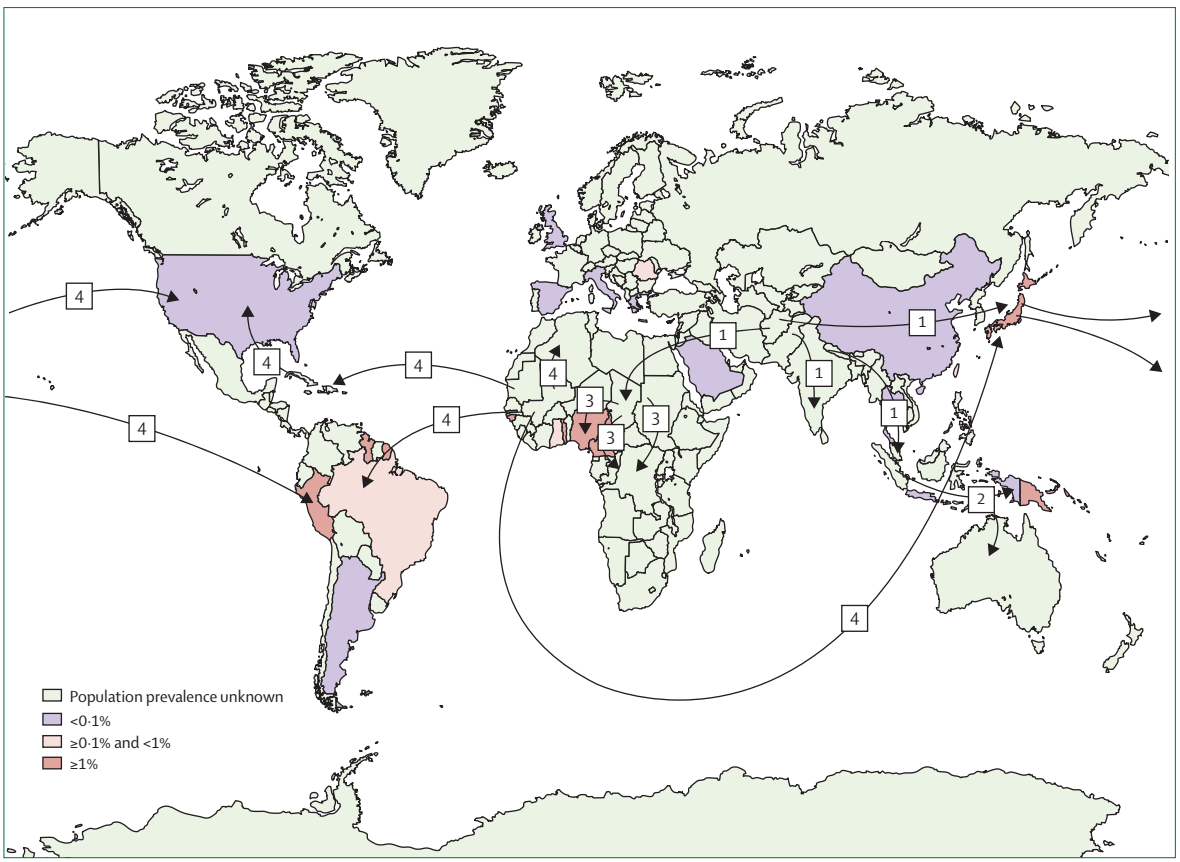

***Figure 4*: Origin, spread, and prevalence of HTLV-1**
Origin and spread hypothesis based on phylogenetic and anthropological data. PTLV originated in African primates and migrated to Asia where it evolved into STLV-1. This early STLV-1 lineage spread to India, Japan, Indonesia, and back to Africa (arrows 1). It crossed the simian–human barrier in Indonesian human beings who migrated to Melanesia, resulting in the HTLV-1c subtype (arrows 2). In Africa, STLV-1 evolved through several interspecies transmissions into HTLV-1a, HTLV-1b, and HTLV-1d, HTLV-1e, and HTLV-1f (arrows 3). Because of the slave trade and increased mobility, HTLV-1a was introduced in the New World, Japan, the middle east, and north Africa (arrows 4). Colours indicate current prevalence estimates based on population surveys and on studies in pregnant women and blood donors. In some countries, HTLV-1 infection is limited to certain population groups or areas. Adapted from reference 68 (Van Dooren et al, 1998).

ancient introduction of HTLV-1a into the New World through Mongoloid migrations.[78–81] However, the HTLV-1a phylogeny demonstrates dispersal of African strains all over and clustering of Amerindian strains within and not at the origin of the cosmopolitan HTLV-1a subgroup clusters. Together with molecular clock estimates, these observations are consistent with the dissemination of HTLV-1 to the New World through the African slave trade.[68] The report of the presence of HTLV-1 DNA in an Andean mummy and its subsequent statistical parsimony phylogeny reopened the debate on a possible ancient dissemination.[82–84] However, the sequence data remain controversial, as argued by several research groups, as well as the unmatched and ambiguous mutation-order dependent positioning of the clonal HTLV-1 mummy sequences.[84–86]

Introduced in ancient or post-Colombian times, the infection is now endemic in several population groups. In Jamaica, Martinique, Guyana, French Guyana, Colombia, and the north of Brazil, HTLV-1 is particularly frequent among descendants of African slaves, whereas in other areas such as Peru and the north of Argentina it is the indigenous people who present the highest prevalences.[87–93] Except for some foci among native Americans, HTLV-1 is rare in the rest of Central and North America (figure 4).[57,92]

Europe

Following the increased human mobility in the past five centuries, HTLV-1a infection has also reached Europe. In most western European countries, HTLV-1 is still uncommon in the general population.[54] The infection has been reported in specific population groups, such as immigrants from endemic areas, sex workers, and injecting drug users.[94,95] HTLV-1 could be more frequent in eastern Europe. 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.[96,97]

It is not clear why after spreading over the whole world, HTLV-1 became and remained highly prevalent

in some populations and not in others. Many factors associated with HTLV-1 infection in prevalence studies such as prolonged breastfeeding, transfusion history, unprotected sex, many lifetime sexual partners, presence of other sexually transmitted diseases, and history of drug use correspond to the known modes of HTLV-1 transmission.[93] Other observations, however, suggest the presence of yet unknown biological or social cofactors influencing HTLV-1 transmission.[53] The most important arguments in favour of this hypothesis are that most HTLV-1-endemic areas are in the tropics, the virus clusters among neighbours, and the prevalence declines in subsequent generations migrating from endemic to non-endemic areas.[98] Moreover, although HTLV-1 and HIV-1 have similar modes of transmission, the viruses do not necessarily spread in the same way. In some areas, HTLV-1 prevalence tends to decrease over time while HIV-1 can be on the rise in the same population.[89]

HTLV-1-associated diseases

Most people infected with HTLV-1 remain asymptomatic throughout life. How many people eventually develop any of the associated diseases depends on several factors, including age and the route of infection.[99] Additionally, the incidence of HTLV-1-associated diseases is not uniform across geographical areas.[100]

Among HTLV-1 carriers, the lifetime risk of developing HAM/TSP ranges from between 0·3% and 4%.[101] For ATL, this risk is calculated as 1% to 5% and for HTLV-1-associated diseases in general, including ATL, HAM/TSP, uveitis, polymyositis, and arthropathy, the lifetime risk may be close to 10%.[102–104]

The aetiological role of HTLV-1 in ATL, HAM/TSP, and uveitis is well established.[53] 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. For some of these diseases, the association with HTLV-1 is proposed on the basis of epidemiological data, whereas in others there are also biological arguments (table 2 and webappendix). Even if the underlying physiopathological mechanisms are not yet fully understood, we propose to group the associated diseases into three categories: malignant diseases, inflammatory diseases, and infectious complications (table 2 and webappendix). We have classified infective dermatitis as an infectious complication, although an inflammatory component also appears to be involved in this syndrome.

The outcome of HTLV-1 infection depends on a complex interaction between the virus and host genetic and immunological factors.[127] In this context, it is worth mentioning that certain HTLV-1 complications seem to affect the same patients, suggesting that these diseases have common pathogenic mechanisms. Examples of complications occurring together are: HAM/TSP with other inflammatory diseases (including Sjögren's syndrome, arthritis, alveolitis, and uveitis), uveitis with thyroiditis, strongyloidiasis with ATL, and infective dermatitis with ATL and with HAM/TSP.[106,111–113,128–130]

	Epidemiological evidence			Biological evidence	
	Case reports or series	Case control studies	Cohort studies	HTLV-1 in lesions	Animal model
Inflammatory syndromes					
HAM/TSP	Yes	Yes	Yes	Yes	Yes
Uveitis	Yes	Yes	..	Yes	Yes
Arthropathy	Yes	Yes	..	Yes	Yes
Sjögren's syndrome	Yes	..	..	Yes	Yes
Polymyositis	Yes	..	..	Yes	Yes
Thyroiditis	Yes	..	..	Yes	..
Pneumopathy	Yes	..	..	..	..
T lymphocyte alveolitis	Yes	..	..	..	..
Malignant diseases					
ATL	Yes	Yes	Yes	Yes	Yes
Cutaneous T-cell lymphoma	Yes	..	..	Yes	..
Infectious complications					
Strongyloides stercoralis	Yes	Yes	Yes	..	..
Crusted scabies	Yes	..	..	..	..
Infective dermatitis	Yes	..	..	..	..
Tuberculosis	Yes	Yes	..	..	..
Leprosy	Yes	Yes	..	..	..

HAM/TSP=HTLV-1-associated myelopathy/tropical spastic paraparesis. ATL=adult T-cell leukaemia/lymphoma. ..=unknown. References 1, 5, 55, 103, 105–126. See webappendix for supplemental list of references, and an indication of which studies relate to each association and basis for association.

Table 2: **Diseases reported in association with HTLV-1 and basis for this association**

Adult T-cell leukaemia/lymphoma

History

In the 1970s, clinicians in Japan felt that the haematological malignancies they observed did not fit the pattern described in the literature of that time.[4] They diagnosed, for instance, few cases of chronic lymphocytic leukaemia on one hand and many acute, aggressive T-cell malignancies on the other, particularly among patients from southwestern Japan. The impression of an autochthonous pathology led to the description of a clinical entity: adult T-cell leukaemia/lymphoma.[4,115]

See **Online** for webappendix

Pathogenesis

ATL is a malignancy of CD4+ post-thymic T cells in which the HTLV-1 provirus is integrated. Unlike animal retroviruses causing neoplasm, HTLV-1 does not contain a transforming oncogene. In the case of HTLV-1, it is the regulatory protein Tax that induces abnormal growth of infected T cells through several pathways.[15] By binding to certain transcription factors and transcriptional cofactors, Tax promotes the transcription of its own proviral genome, but it also promotes transcription of

	Acute	Lymphomatous	Chronic	Smouldering
General characteristics				
Proportion of ATL cases	55%	20%	20%	5%
Median survival time	6 months	10 months	24 months	..
4-year survival	5%	6%	27%	66%
Diagnostic criteria				
Anti-HTLV antibody	Yes	Yes	Yes	Yes
Lymphocyte count	ND	<4000 per mL	>4000 per mL	<4000 per mL
Lactate dehydrogenase	ND	ND	<2xNUL	<1·5xNUL
Calcium, corrected	ND	ND	<5·5 mEq/L	<5·5 mEq/L
Abnormal T lymphocytes	≥5%*	<1%	≥5%*	≥5%*
Flower cells	Yes	No	Occasionally	Occasionally
Tumour lesion				
Skin and/or lung	ND	ND	ND	If abnormal lymphocyte <5%*
Lymph node	ND	Yes	ND	No
Liver or spleen	ND	ND	ND	No
CNS	ND	ND	No	No
Bone	ND	ND	No	No
Ascites	ND	ND	No	No
Pleural effusion	ND	ND	No	No
Gastrointestinal tract	ND	ND	No	No

ND=not definitory. NUL=normal upper limit. CNS=central nervous system. ..=not reported. *If abnormal T lymphocytes less than 5%, histologically proven tumour lesion required for diagnosis. Adapted from reference 135 (Shimoyama, 1991).

Table 3: **Comparison of adult T-cell leukaemia/lymphoma (ATL) subtypes**

cellular genes, including cytokine (eg, interleukin-2), cytokine receptor (interleukin-2Rα), and anti-apoptotic genes. By binding to other protein complexes, Tax represses the transcription of genes that are important in negative control of the cell cycle, in activation of apoptosis, and in DNA repair. Tax also binds and inhibits proteins directly involved in tumour suppression and DNA repair. Finally, Tax causes cells to bypass normal cell-cycle checkpoints.[15]

The net effect of all these activities of Tax is that T cells are rushed into and through the mitotic phase without checking for chromosomal abnormalities. Genetic damage that would normally be repaired accumulates and apoptotic cell death does not occur even in cells with severely damaged DNA. In these circumstances, T cells can accumulate DNA mutations, resulting in transformation and monoclonal outgrowth of a truly malignant cell. In addition to these genetic changes, epigenetic changes such as DNA methylation may have an important role in leukaemogenesis.[131]

Despite the fact that these phenomena occur in all infected people, only a minority develop ATL. It is possible that the development of ATL is determined mainly by chance, particularly in view of the finding that HTLV infection results in chromosomal instability.[132] However, as yet unknown factors could be involved in the pathogenesis. This view is supported by the finding that the occurrence of ATL appears to vary according to geographical location.

Epidemiology

Although ATL has been described in all HTLV-1-endemic areas, there are intriguing disparities. First, ATL seems to be more common in southwestern Japan than anywhere else.[133] It is not clear whether this corresponds to an actual difference in incidence or whether it only reflects access to health care and consistency of registration. Second, there is a difference in the mean age at diagnosis of ATL: 40 to 50 years in Central and South America, and 60 years in Japan.[103,116,133,134]

Several studies suggest that ATL develops mostly in individuals infected early in life through breastfeeding. Infection of immature thymocytes at young age might increase the risk of later transformation into malignant cells.[99]

Clinical characteristics and diagnosis

There are several types of HTLV-1-induced ATL: acute, lymphomatous, chronic, and smouldering (table 3).[135] A fifth category, primary cutaneous tumoral ATL, has been proposed recently.[134] Chronic ATL has a relatively good prognosis, even without treatment. Chronic and smouldering forms can, however, evolve to acute ATL, which has a poor prognosis: the median survival time after diagnosis is only 6 months.[133]

Almost all patients with ATL present with lymphadenopathy and 50% have hepatosplenomegaly. Skin lesions are also common; they can precede or coincide with the lymphadenopathy and/or splenomegaly. ATL can also affect the lungs, gastrointestinal tract, and central nervous system; involvement of other organs is uncommon.[135]

Hypercalcaemia is an important complication: it occurs in up to 70% of patients and is often accompanied by lytic bone lesions. A possible explanation is that ATL cells induce the differentiation of haematopoetic precursor cells into osteoclasts. These osteoclasts accelerate bone resorption, resulting in hypercalcaemia.[131] A parathyroid hormone-related peptide is frequently increased in ATL patients and could be involved.[131,136] ATL patients are immunosuppressed and opportunistic infections, such as *Pneumocystis jirovecii* pneumonia, cryptococcus meningitis, and disseminated herpes zoster are, therefore, frequent.[137] Liver dysfunction is another complication.

With respect to laboratory tests, peripheral blood smears show flower cells—ie, pleomorphic, atypical lymphoid cells with basophilic cytoplasm and convoluted nuclei (figure 5), in which the integrated HTLV-1 provirus can be detected.[138] During the leukaemic phase, the white blood cell count may increase to hundreds of thousands.

The diagnosis of ATL is usually based on morphological analysis. Flower cells are indicators of acute or lymphoma-type ATL. This must be confirmed by clonal integration of HTLV-1 provirus in the host genome. The predominant immunological phenotype of neoplastic cells is helper

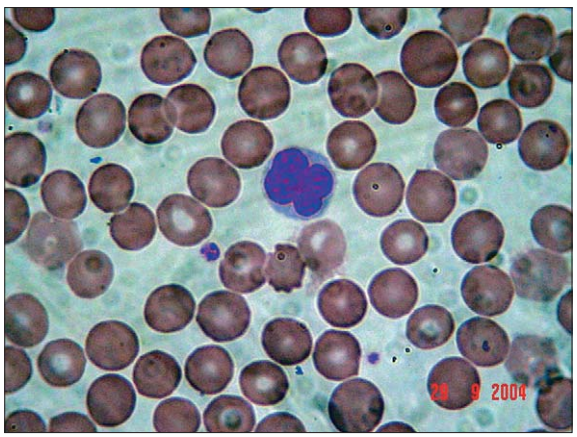

***Figure 5*: Image of a flower cell**
Flower cells are atypical lymphoid cells with basophilic cytoplasm and convoluted nuclei, commonly seen in the blood smears of HTLV-1-infected people.

T cell, CD3+, CD4+, L-selectin+, CD25+, CD45RA+, HLA-DR+, CD29–, and CD45RO– in peripheral blood, or CD3+, CD4+, L-selectin+, CD29+, CD45RO+, HLA-DR+, and CD45RA– in the skin and lymph nodes.[138]

Factors associated with a poor prognosis include high expression of the Ki67 antigen, and high serum levels of calcium, parathyroid hormone-related protein, lactate dehydrogenase, thymidine kinase, soluble interleukin-2 receptor, β2-microglobulin, and neuron-specific enolase.[138]

Treatment

Many strategies have been evaluated for the treatment of ATL, and the following therapies appear to improve the prognosis compared with conventional chemotherapy: interferon-α with zidovudine, intensive chemotherapy (as in LSG-15 with granulocyte colony-stimulating factor support), and allogenic haematopoietic stem cell transplantation.[131,138] Nevertheless, the median survival of patients with acute, lymphomatous, and progressing chronic ATL remained low: less than 1 year in most reports.[131,133] Novel approaches include histone deacetylation inhibitors, monoclonal antibodies, and proteasome inhibitors, but their added value remains to be established.[131]

Inflammatory syndromes

HTLV-1-associated myelopathy/tropical spastic paraparesis

History

Long before HTLV-1 was discovered, neurologists had reported the frequent occurrence of a myelopathy of unknown origin in tropical areas. The first descriptions of this syndrome go back to the 19th century.[139] The association with HTLV-1 was recognised independently in the Caribbean and in Japan in 1985–1986.[5,140] Soon thereafter, it was agreed to refer to this disease as HTLV-1-associated myelopathy/tropical spastic paraparesis.

Pathogenesis

The main pathological feature of HAM/TSP is a chronic inflammation of the white and grey matter of the spinal cord. Mononuclear cells, mainly T cells, cause perivascular cuffing and infiltrate the parenchyma. Later in the disease, the pattern becomes less cellular and more atrophic. The damage occurs mostly in the white matter of the lower thoracic spinal cord, which is consistent with the spastic paraparesis in the lower limbs.[141]

The lesions in the central nervous system could be a consequence of a genuine anti-HTLV-1 reaction. By comparison with asymptomatic carriers, HAM/TSP patients have a higher provirus load, a higher production of proinflammatory cytokines such as interferon-γ and TNFα, and a higher frequency of HTLV-1-specific CD8+ T cells.[32,142–144] Additionally, in a Japanese population, polymorphism in the TNFα promoter and the chemokine gene SDF-1α influenced the risk of HAM/TSP.[145] Altogether, these findings indicate that a high HTLV-1 burden and an exaggerated proinflammatory cellular immune response, partly based on the host genetic constitution, are involved in the pathogenesis of HAM/TSP.

More direct evidence of an immunopathological reaction in the central nervous system itself includes the observation of infected T cells within the spinal cord lesions and the accumulation of Tax-specific CD8+ T cells in the cerebrospinal fluid.[146,147] There is no evidence that HTLV-1 directly infects neuronal cells, astrocytes, or microglia. Therefore, the damage to these cells could be interpreted as a bystander effect. Nevertheless, the question remains why HTLV-1-infected and anti-HTLV-1 T cells accumulate at these sites.

There is some evidence that autoimmunity—ie, cross-reactivity between HTLV-1 antigens and tissue antigens—could be involved in the pathogenesis. Patients with HAM/TSP appear to develop antibodies to human neurons but not to systemic organs, although this finding is contentious.[148] Moreover, monoclonal and patients' polyclonal antibodies show cross-reactivity between an epitope of Tax and neuronal heterogeneous ribonucleoprotein A1, a phenomenon that has been associated with genuine autoimmune diseases such as systemic lupus erythematosus.[149] Additionally, autoantibodies against other nuclear and perinuclear human brain proteins cross-reacting with different HTLV-1 epitopes have been found in the serum of HAM/TSP patients.[150] It seems unlikely, however, that these autoantibodies play a primary role in tissue damage, because of the intracellular localisation of their targets. Since inflammatory T cells, rather than antibodies, seem to be involved in the tissue damage, the question is whether autoreactivity at the level of the T-cell receptor is present.

Epidemiology

More women than men develop HAM/TSP and this difference is not entirely attributable to the higher prevalence of HTLV-1 among women in endemic

areas.[101,151,152] Therefore, it has been suggested that the risk of HAM/TSP could be higher if HTLV-1 infection is acquired during adulthood, and more specifically through sexual transmission.[105] HAM/TSP is considered uncommon in children, although case reports have increased in recent years.[130,153] In a report of seven children with infective dermatitis and HAM/TSP, the progression of neurological symptoms was remarkably rapid.[130]

Clinical characteristics and diagnosis

In most cases, HAM/TSP presents as a gradually appearing, symmetrical paraparesis of the lower limbs with signs of pyramidal tract involvement, which progresses slowly and without remissions (figure 6).[5,130,151,154] Bladder disorders are very common and represent an important cause of functional impairment among HAM/TSP patients.[130,151,155,156] Dyssynergy of the detrusor sphincter during micturition leads to disorders in bladder emptying and results in repeated urinary infections.[157] In many patients, urinary and sexual problems are the first symptoms of the disease. Back pain, constipation, and sensory symptoms and signs are also frequent.[151,152,154]

***Figure 6*: Husband and wife, both with HAM/TSP, stand in their shop on the outskirts of Lima, Peru**

Cerebrospinal fluid examination may show mild lymphocytic pleocytosis and a mild-to-moderate increase of protein. Antibodies against HTLV-1 are present and the cerebrospinal fluid/serum antibody index is elevated.[152] The HTLV-1 provirus can be demonstrated in cerebrospinal fluid cells of HAM/TSP patients.[158]

The definite diagnosis of HAM/TSP requires the demonstration of HTLV-1 infection and the exclusion of other causes of myelopathy, such as spinal cord compression, paraneoplastic syndromes, parasitic myelopathy, B12 and folate deficiency, multiple sclerosis, and amyotrophic lateral sclerosis, among others. A WHO working group established diagnostic guidelines (panel) in 1989; an actualisation of these guidelines is in preparation.[152] Repeatedly reported atypical clinical presentations of HAM/TSP include syndromes with cerebellar, encephalitis-like, lateral amyotrophic-like, and Parkinson-like features. It is, therefore, justified to consider HAM/TSP in the differential diagnosis of atypical neurological conditions of unknown origin, especially in areas where HTLV-1 infection is frequent. Obviously, HAM/TSP in HTLV-1-infected patients should be carefully distinguished from other neurological disorders where the HTLV-1 infection is just incidental.

The HTLV-1 provirus load in peripheral blood mononuclear cells has been proposed as a marker of HAM/TSP risk and progression. It is estimated that the risk of disease increases exponentially with the logarithm of the provirus load once the provirus load exceeds 1 per 100 peripheral blood mononuclear cells.[159] Additionally, patients with rapidly progressive HAM/TSP appear to have a higher provirus load than those with slowly progressive disease.[32] The provirus load in cerebrospinal fluid cells is also associated with HAM/TSP.[158] The HTLV-1 mRNA load is another marker associated with disease severity in HAM/TSP patients.[160]

Treatment

Therapies directed at modulating the immune response have been considered for the treatment of HAM/TSP. Other therapies aim at decreasing the HTLV-1 viral antigen burden, which in turn should lead to a reduction in HTLV-1-specific cytotoxic lymphocyte activity.

There are conflicting reports on the effect of corticosteroids.[161] Interferon-α has shown to be of short-term benefit to some patients in a randomised study.[162] Interferon-β1a, evaluated in an open trial, reduced the HTLV-1 mRNA load; but the HTLV-1 provirus load remained unchanged and there was only a slight improvement in motor function.[163]

The combination of two nucleoside analogues (zidovudine and lamivudine) has been evaluated in a randomised, double-blind, placebo-controlled study including 16 HAM/TSP patients. After up to 12 months of follow-up, there were no significant changes in provirus load and no clinical improvement was observed.[164]

Most of the treatments for HAM/TSP proposed to date have been evaluated in small and/or uncontrolled studies, and among patients with rather long disease duration and varying disease severity. There is an urgent need for new, controlled studies of both anti-inflammatory and antiviral agents.[164]

Arthropathy

An association between HTLV-1 and arthropathy was first proposed in 1989.[107] Since then, reports have been contradictory. In some series, the majority of rheumatoid

arthritis cases were found to be HTLV-1 negative.[165,166] By contrast, in a Japanese cross-sectional study and a US cohort study, the prevalence and the incidence of arthritis were found to be higher among HTLV-1-infected patients than among uninfected individuals.[108,109] Another argument in favour of an association is that Tax transgenic mice develop an arthritis that is pathologically similar to human rheumatoid arthritis.[110,167] Tax has been shown to stimulate the proliferation of synovial cells in vitro.[168] Hence, Tax, released by HTLV-1-infected cells in vivo, could have a part in the pathogenesis of arthropathy.

HTLV-1-associated arthropathy resembles rheumatoid arthritis, with synovial proliferation and a positive rheumatoid factor.[169] Conversely, in ATL patients, polyarthritis with a negative rheumatoid factor has been described.[170] The treatment of HTLV-1-associated arthropathy is empiric and symptomatic; usually, a combination of anti-inflammatory and analgesic drugs is used.

Uveitis

Reports from Japan have shown that HTLV-1 infection is more frequent in patients with uveitis of unknown origin than in the general population.[114] HTLV-1-associated uveitis is twice as frequent in women as in men and although the syndrome mostly affects adults, it has been described in children too.

At onset, patients generally complain of blurred vision with floaters. Iritis and vitreous opacities of variable size and shape are almost always present, often in association with retinal vasculitis and, occasionally, with retinal exudates and haemorrhages. In more than half of cases, HTLV-1-associated uveitis is an intermediate uveitis. Bilateral is as frequent as unilateral inflammation.[171,172] The prognosis of HTLV-1-associated uveitis is good: spontaneously, the disease resolves within weeks and recovery is even faster with topical or systemic corticosteroid treatment. However, sight-threatening complications can occur, including retinochoroidal degeneration, glaucoma, and corticosteroid-induced cataracts. Unfortunately, more than 90% of cases recur within 3 years; the mean interval between episodes is 16 months.[173]

Infectious complications

Strongyloidiasis

Strongyloides stercoralis is an intestinal nematode of tropical regions that can replicate within the human host, an unusual characteristic among helminths. In the normal strongyloides cycle, filariform larvae from the soil penetrate the human skin and migrate to the lungs. The larvae ascend the bronchi and are swallowed. Adult females stay and lay eggs in the intestinal mucosa. Rhabditiform larvae hatch, migrate to the intestinal lumen and pass with the faeces into soil. An autoinfection cycle starts when rhabditiform larvae develop into infectious filariform larvae within the intestine instead of in soil. These filariform larvae penetrate the colon or the anal skin and then continue their cycle within the same host.

Most people with strongyloidiasis have mild diarrhoea or vague abdominal complaints, or remain asymptomatic. In immunocompromised hosts, *S stercoralis* may produce a disseminated infection, in which invasive, filariform larvae move to the lung, liver, kidney, and central nervous system. The larvae can carry bacteria from the colon and cause sepsis and meningitis. This disseminated form of strongyloidiasis, also referred to as hyperinfection, has been described in patients with malignant tumours, severe malnutrition, corticosteroid or cytotoxic therapy, renal transplantation, and HTLV-1 infection.[119,120]

By contrast with patients infected with *S stercoralis* alone, those with HTLV-1 and strongyloidiasis have a

***Panel:* Guidelines for the diagnosis of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)**

Age and sex
Mostly sporadic, sometimes familial. Adult females predominate, occasionally in childhood

Onset
Usually insidious

Main neurological manifestations
Chronic spastic paraparesis, which usually progresses slowly, but may remain static after initial progression
Weakness of lower limbs, more marked proximally
Bladder disturbance usually an early feature; constipation usually occurs later; impotence and decreased libido are common
Sensory symptoms are more prominent than objective physical signs
Low lumbar pain with radiation to the legs is common
Vibration sense is frequently impaired
Hyperreflexia of lower limbs, often with clonus and Babinski's sign
Hyperreflexia of upper limbs; positive Hoffman's and Tromner's signs are frequent; weakness may be absent
Exaggerated jaw jerk in some patients

Less frequent neurological findings
Cerebellar signs, optic atrophy, deafness, nystagmus, other cranial nerve deficits, hand tremor, absent or depressed ankle jerk

Other neurological manifestations that may be associated with HAM/TSP
Muscular atrophy, fasciculations, polymyositis, peripheral neuropathy, polyradiculopathy, cranial neuropathy, meningitis, encephalopathy

Systemic non-neurologic manifestations that may be associated with HAM/TSP
Pulmonary alveolitis, uveitis, Sjögren's syndrome, arthropathy, vasculitis, ichthyosis, cryoglobulinaemia, monoclonal gammopathy, adult T-cell leukaemia/lymphoma

Laboratory criteria
Presence of HTLV-1 antibodies or antigens in blood and cerebrospinal fluid
Cerebrospinal fluid may show mild lymphocytic pleocytosis
Lobulated lymphocytes may be present in blood or cerebrospinal fluid, or both
Mild to moderate increase of protein may be present in cerebrospinal fluid
Viral isolation from blood and/or cerebrospinal fluid when possible

Adapted from reference 152 (WHO, 1989).

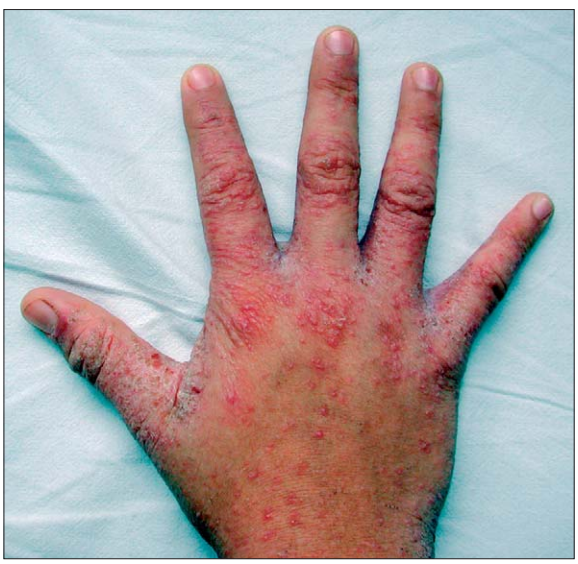

Figure 7: **HTLV-1-infected patient with scabies**
Papules and vesicles in the interdigital spaces extend toward the dorsum of the hand

stronger Th1 response (high levels of interferon-γ) and a weaker Th2 response (low levels of interleukin-4, interleukin-5, interleukin-13, IgE, and eosinophils). The decrease in interleukin-4 and IgE reduces the efficacy of mast cell degranulation and the lowered interleukin-5 impairs eosinophil recruitment and killing activity against the parasite. As a result, the rate of parasite killing decreases and the rate of autoinfection increases.[174]

There is now epidemiological evidence that HTLV-1 is not only associated with *S stercoralis* hyperinfection but also with strongyloidiasis in general and with relapse after treatment with ivermectin, tiabendazole, and albendazole.[117,120,175] On the basis of a Japanese cohort, it is estimated that the risk to develop strongyloidiasis is twice as high among HTLV-1-infected people as among healthy controls.[120]

Tuberculosis

Several cross-sectional studies have found a high prevalence of HTLV-1 among tuberculosis patients and a high prevalence of tuberculosis among HTLV-1-infected people.[55,118] Additionally, HTLV-1 carriers have a reduced delayed type hypersensitivity response to *Mycobacterium tuberculosis* purified protein derivative, suggesting that HTLV-1, like HIV, could increase the risk of developing tuberculosis.[176] A strong argument in favour of this hypothesis comes from a Brazilian case-control study in which HTLV-1 was three times more frequent among tuberculosis patients than among hospital controls.[124] Furthermore, the finding of an association between HTLV-1 infection and mortality among tuberculosis patients suggests that HTLV-1 infection might increase the severity of the tuberculosis.[123]

Whereas the suppression of protective Th2 responses by HTLV-1 is an acceptable explanation for its association with strongyloidiasis, this cannot be extrapolated to tuberculosis, where Th1 responses are protective. A generalised immune suppression is a tentative, but probably incomplete explanation—ie, it remains puzzling why some, but not all infections known to be prevalent in otherwise immunosuppressed individuals are associated with HTLV-1.

Crusted scabies

In immunosuppressed patients, *Sarcoptes scabiei* can produce massive infections, causing extensive, crusted lesions, located mainly in pressure areas (figure 7). This phenomenon has been described in relation to corticosteroid therapy, malignancies, Down's syndrome, diabetes, HIV, and HTLV-1 infection, among others. In a Peruvian study 16 out of 23 patients with crusted scabies were HTLV-1 positive and none had HIV.[122] In a Brazilian study including 91 cases of scabies, crusted or severe forms were strongly associated with HTLV-1 and, to a lesser degree, with HIV infection.[121]

Infective dermatitis

Infective dermatitis was described in Jamaica long before the discovery of HTLV-1.[177] There are markedly less reports of this disease from Japan than from other HTLV-1-endemic regions. Infective dermatitis is a chronic, relapsing syndrome that usually affects young children. It presents as a generalised papular rash, with exudates and crusting on the scalp, ear, eyelid margins, paranasal skin, neck, axilla, and groin (figure 8). Watery nasal discharge, lymphadenopathy, and colonisation with β-haemolytic streptococci or *Staphylococcus aureus,* or both, are frequent.[126,178] The histological characteristics of infective dermatitis are not distinctive and therefore the differential diagnosis with other types of eczema and with seborrhoeic and atopic dermatitis is based on clinical criteria.[129,178] Response to treatment with antibiotics and mild topical steroids is usually good and immediate, but symptoms tend to recur rapidly after suspension of the antibiotics.[125]

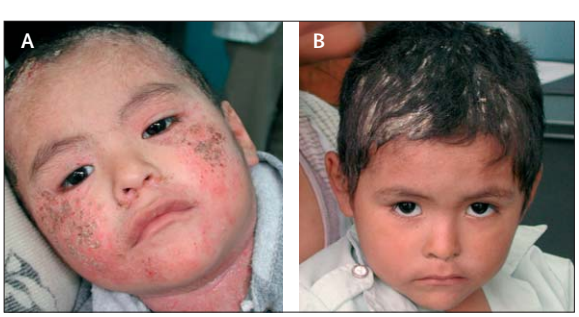

Figure 8: **Boy with infective dermatitis**
(A) At a moment of exacerbation of the disease. The patient has a generalised rash with exudates in the face and neck and lesions on the ears, eyelid margins, and paranasal skin. There is crusting on the scalp and the boy has a watery nasal discharge. (B) At a moment when the disease is better under control with antibiotics.

Search strategy and selection criteria

We used "human T-lymphotropic virus 1" (MeSH major topic) as the search term in PubMed and considered journal articles in English, Spanish, Portuguese, French, and Dutch. Reference lists of these articles were also reviewed and many articles were identified through searches of the files of the authors. We selected clinical and basic science articles related to prevalence, pathogenesis, diagnosis, clinical management, and prevention of HTLV-1 infection and associated diseases. For the selection of articles included in the reference list, priority was given to publications in high impact factor journals within the last 5 years.

Up to one-third of patients with infective dermatitis present complications and comorbidities, such as severe bacterial superinfection, corneal opacities, glomerulonephritis, chronic bronchiectasis, lymphocytic interstitial pneumonitis, scabies and helminthiasis, anaemia, and elevated white blood cell counts with lymphocytosis and atypical lymphocytes.[129,178,179]

Conclusion

A quarter of a century after its first description, HTLV-1 is still a poorly recognised infection. Many carriers remain asymptomatic, which contributes to the silent transmission of the virus. Since several associated diseases can also occur in uninfected people, the role of underlying HTLV-1 often passes unnoticed. Even though important knowledge about the pathogenesis is emerging, there are no clear surrogate markers for follow-up and the proviral lifestyle of HTLV-1 complicates the development of antiretroviral drugs. The treatment of associated diseases is mostly restricted to symptomatic relief. Prevention of transmission remains fundamental in HTLV-1 control, but safe alternatives to breastfeeding, the major route of transmission worldwide, are difficult to provide in many resource-limited endemic areas.

Conflicts of interest

We declare that we have no conflicts of interest.

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