Miscellaneous

Carmen de Mendoza, Graham Taylor, Antoine Gessain, Andrea K. Thoma-Kress, Charles Bangham, Jan Vesterbacka, Roberto Accolla, Ali Bazarbachi, Johan van Weyenbergh, Lucy Cook, Jorge Casseb, Juan Carlos Ramos, Carolina Rosadas, Beatrice Macchi, Olivier Cassar and Vicente Soriano*

Virology, pathogenesis, epidemiology and clinical management of HTLV-1 infection. Proceedings of the 30th HTLV European research network (HERN 2023)

https://doi.org/10.1515/nipt-2023-0025
Published online January 11, 2024

Abstract: The 30th workshop of the HTLV European Resea rch Network (HERN) was held in Madrid on September 15–16, 2023. Over fifty researchers from Europe and America convened for a two-day conference to update and discuss basic science, epidemiology, clinical management and therapeutics for patients with HTLV-1 infection. Scientific topics addressed included new estimates for HTLV-1 in Europe; impact of antenatal screening on mother-to-child HTLV-1 infections; new insights into the molecular epidemiology of HTLV-1; reports of elite controllers for HTLV-1 infection; role of antiretrovirals as HTLV-1 pre-exposure prophylaxis; and prospects for a HTLV-1 vaccine. The group agreed to submit a formal request to WHO for increasing the global surveillance and awareness of HTLV-1. This viral infection is a potentially life-threatening, neglected condition with neither treatment nor vaccine. At this time, expanding HTLV-1 screening is the most effective way to reduce viral dissemination.

Keywords: HTLV-1; myelopathy; leukemia; pregnant women; sexual transmission; screening

***Corresponding author: Vicente Soriano**, Health Sciences School, Universidad Internacional de La Rioja (UNIR), Madrid, Spain,
E-mail: vicente.soriano@unir.net
Carmen de Mendoza, Puerta de Hierro University Hospital, Madrid, Spain
Graham Taylor, **Charles Bangham**, **Lucy Cook and Carolina Rosadas**, Imperial College London, London, UK
Antoine Gessain and Olivier Cassar, Institut Pasteur, Université Paris Cité and CNRS, Paris, France
Andrea K. Thoma-Kress, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
Jan Vesterbacka, Karolinska University Hospital, Stockholm, Sweden
Roberto Accolla, University of Insubria, Varese, Italy
Ali Bazarbachi, American University of Beirut, Beirut, Lebanon
Johan van Weyenbergh, Rega Institute for Medical Research, KU Leuven, Leuven, Belgium
Jorge Casseb, University of Sao Paulo Medical School, Sao Paulo, Brazil
Juan Carlos Ramos, University of Miami Miller School of Medicine, Miami, FL, USA
Beatrice Macchi, University of Rome Tor Vergata, Rome, Italy

Introduction

HTLV-1 is one of several retroviruses that infect humans. All produce lifelong infections and at least three cause overt disease. In the absence of antiretroviral therapy, progressive CD4+ T lymphocyte depletion leads to immunodeficiency and AIDS in almost all HIV-1+ individuals. This also occurs albeit more slowly in HIV-2 carriers. In contrast, HTLV-1 causes immortalization of CD4+ T cells, leading to lymphoproliferation and immune dysfunction. Whilst HTLV-1 infection remains asymptomatic in 90 % of carriers, emerging data demonstrate a broader impact on health and life-expectancy [1, 2]. The overt clinical manifestations in HTLV-1 infection are a subacute myelopathy (HAM, HTLV-1-associated myelopathy) which predominantly occurs in women, and an aggressive T-cell malignancy, adult T-cell leukemia/lymphoma (ATLL), which in Europe is equally distributed by sex. In addition, a wide range of immune/inflammatory conditions, including uveitis, thyroiditis, arthritis, and bronchiectasis may develop in HTLV-1 carriers [3].

The HTLV European Research Network (HERN) was originally funded by the European Commission three decades ago. After EU funding expired, most participant researchers continued working together and meeting periodically. On September 15–16, 2023, the 30th HERN conference was held in Madrid, Spain. Over fifty researchers from

Europe and America convened for two days to present and debate updates on basic science, epidemiology, clinical management and therapeutics for patients with HTLV-1 infection. Here we summarise highlights from the six categories of presentations against what was previously known.

Epidemiology & public health

Antoine Gessain, from the Pasteur Institute in Paris, France, addressed the origin of the HTLV-1 retrovirus in humans from natural infection in African primates. HTLV-1 infection is a zoonosis like HIV, Mpox virus and Ebola. There are an estimated 10 million people infected with HTLV-1 worldwide, half of them in equatorial Africa [4]. Gabon and the Democratic Republic of Congo are the countries with the highest infection rate. Nigeria is the country with the largest number of infected individuals worldwide, given its large population of 215 million. Women in these countries exhibit increasing prevalence rates with age, reaching up to 10–25 % in elderly women. Despite Africa being the largest HTLV-1 reservoir worldwide, there is no screening of blood donors in the continent.

Many subjects infected with HTLV-1 are diagnosed late, after developing clinical manifestations. HTLV-1 screening of asymptomatic individuals is rarely performed in populations with high infection risk, including migrants from endemic areas in Western countries [5]. Many physicians and the general population have little knowledge about HTLV-1, in contrast to HIV, for which information is widely available.

Hotspots of HTLV-1 endemicity are distributed across all continents. High rates of HTLV-1 infection have been reported among aboriginal people in Australia, Equatorial Africa, Latin America and the Caribbean, northeastern Iran, and southwestern Japan [6, 7]. Romania and neighboring Moldova are the only European countries with a relatively high HTLV-1 seroprevalence. At least 5 new cases of ATLL are reported annually in Romania [8]. Molecular epidemiology studies have found that most infections in Romania were introduced recently and due to a HTLV-1a transcontinental variant most probably originated in South Africa or Mozambique [9].

Using distinct approaches, British and Spanish researchers provided updated estimates of the number of HTLV-1+ individuals in Europe. In England and Wales the estimate of 14,900 in 1991 was revised to 36,300 in 2021, based on the 2021 population census [10]. This doubling of cases of infection parallels the rise in the incidence of ATLL in the UK. Migration from HTLV-1 endemic regions, including Nigeria and Romania, contributed to the increase in the estimate of HTLV-1 in England and Wales during the last 30 years. Based on migrant populations, Spanish investigators updated HTLV-1 prevalence estimates for Italy, France, Spain and UK [11]. The largest HTLV-1 population was estimated in UK, with migrants from the Caribbean and West Africa being the most important contributors. In contrast, Latin American migrants were the most frequent in Spain. In France, persons from French West Indies as well as migrants from West Africa predominated. Finally, Italy had the lowest estimate of HTLV-1 infection among migrants.

HTLV-1 sexual transmission

HTLV-1 is an intracellular virus transmitted through contact with body fluids, including blood, semen and milk. Accordingly, sexual exposure, breastfeeding, transfusions, organ transplantation, and needle-sharing in drug users, etc. pose individuals at high risk of infection. Nowadays sexual transmission may account for most new HTLV-1 infections globally. The virus is more efficiently transmitted from male to female than vice versa. In contrast to HIV-1, men who have sex with men have only slightly higher rates of HTLV-1 infection than heterosexuals. The rate of infection increases with duration of sexual relationships with an infected partner.

Following implementation of HTLV-1 antenatal screening in Japan, new infections in adolescent and adult generations mostly occur through sexual contact. Vertical transmission is no longer the main route for transmission. In Japan, with a population of 125 million, a recent survey estimated that 3,000 new HTLV-1 infections still occur annually, the majority through sexual relationships [12].

Data from sexually transmitted infection (STI) clinics were presented at the meeting. In Spain, a recent study identified 5 subjects infected with HTLV-1 out of 2,000 who attended STI clinics [13]. Three were men who have sex with men from Latin America. These results reinforce the importance of including HTLV-1 screening within the list of STI tests, especially for subjects coming from highly endemic regions.

The HTLV-1 Spanish register

A nationwide register was created in 1989. Main demographics, clinical symptoms/signs and laboratory findings

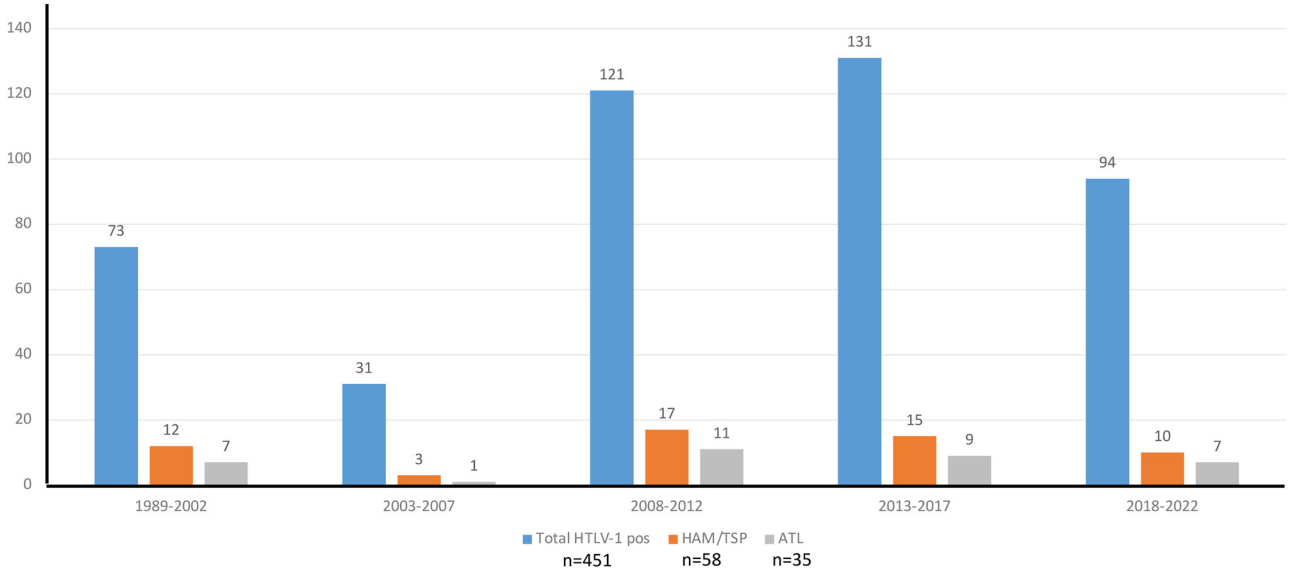

Figure 1: Annual incidence of HAM and ATLL in Spain.

are collected for each new case at baseline using one standardized case report form. All positive individuals are followed periodically. Members of the Spanish HTLV Network cover most of the laboratory facilities nationwide where this virus can be diagnosed, including public or private microbiology laboratories or blood banks [14, 15]. The group updates the national figures on a yearly basis and produces recommendations for screening and medical management. Up to the end of 2022, a total of 451 cases of HTLV-1 had been recorded in Spain. HAM had been diagnosed in 58 and ATLL in 35 patients [16]. The current incidence of HAM in Spain is of 2–3 new cases per year whereas it is slightly lower for ATLL (Figure 1). At least 8 individuals had been infected with HTLV-1 in Spain following blood transfusions or solid organ transplantation before screening became mandatory for transplants and targeted for blood donors [17].

Virology

Unlike many other viruses, including HIV-1, cell-free infection by HTLV-1 is rare, and HTLV-1-infected cells release few if any viable virus particles. HTLV-1 infectious spread requires cell-to-cell contact between an infected cell and an uninfected cell. One of the primary mechanisms for HTLV-1 transmission involves the formation of a virological synapse. Once an HTLV-1 virion enters a target cell, its RNA genome is reverse transcribed into dsDNA. During cell division, this dsDNA integrates into the new host genome, at which point it is termed a provirus. Once integrated, this provirus can be transcribed by cellular RNA polymerase II to express viral gene products.

Once HTLV-1 infection is established in a new subject, persistence of infection occurs predominantly without viral replication. After adaptive immunity develops, proliferation of infected lymphocytes occurs with division of cells containing the integrated provirus. This sustained proliferation, and the use of cell-to-cell spread when infection does occur, explains why there is no plasma viraemia, that is, extracellular viral particles in the blood. HTLV-1 primarily infects CD4+ T-cells; due to its widely available target receptors, it has the ability to infect a wide variety of cell types, but efficient propagation of the virus only occurs from infected T cells and (possibly) dendritic cells. The HTLV-1 envelope protein uses neuropilin-1 (NRP1) and heparan sulfate proteoglycan (HSPG) for attachment and binding to target cells. The binding between gp46 and HSPG/NRP1 allows a conformation change in gp46 that exposes a binding domain that interacts with glucose transporter-1 (GLUT-1), followed by viral/cell fusion and the release of HTLV-1 nucleocapsid into the cytoplasm. The chemokine receptor CCR4 and the adhesion molecule LFA-1 also facilitate cell-to-cell transmission of HTLV-1.

Charles Bangham provided new insights into the mechanisms of HTLV-1 persistence. Comparing cells infected *in vivo* with those infected *in vitro*, his team identified selective survival *in vivo* of clones with proviruses located near the nuclear lamina or the nucleolus [18, 19]. The same phenomenon was observed in selective clonal survival in the HIV-1 reservoir.

The HTLV-1 accessory protein p8 induces cellular protrusions through which HTLV-1 passes to newly infect cells. Andrea Thoma-Kress discussed how p8 is transferred to distinct cell types and could hamper immune responses towards HTLV-1-infected CD4+ T cells [20].

Roberto Accolla reported on the role of the viral HBZ protein in the development of leukemic cells. Recent findings from his group pointed to the unprecedented evidence, from nuclear interactome studies, of HBZ interaction with the RNA splicing and non-sense mediated RNA decay (NMD proteins), both basic functions of cell physiology, whose alterations is involved in cancer [21]. Furthermore, Greta Forlani from Accolla's group highlighted that the nuclear localization of HBZ could be a hallmark of neoplastic transformation [22].

HBZ downregulates Tax expression, which activates the NFkB pathway and the release of the cytokine IL-10, both well-accepted primary steps of leukemogenesis. Thereafter, the Tax protein is detected in ATL cells in approximately 50 % of cases. Ali Bazarbachi presented new data demonstrating that primary cells from patients with ATL retain the ability to express very low levels of Tax protein and depend on Tax expression for NFkB activation and survival [23].

Pathogenesis

Most people infected with HTLV-1 remain free of HTLV-1 complications for many years or during their entire lives. Only 10 % develop overt clinical manifestations, typically a subacute myelopathy or a T-cell leukemia. Both conditions are serious and difficult to treat. Most patients with neurological disease end up in a wheelchair and very few patients with leukemia/lymphoma survive longer than one year [3].

HTLV-1 elite controllers

In HIV infection (AIDS), a subgroup of patients with persistently undetectable or very low plasma viral load is well documented. These individuals show little immune damage and their clinical prognosis is good for decades [24]. Many experts consider antiretroviral medication unnecessary for this subset of patients. In an apparent parallel in HTLV-1 infection, an English team described a group of people with western blot seroreactivity to HTLV-1 despite a persistently undetectable proviral load. The longitudinal follow-up of these individuals resulted in occasional HTLV-1 DNA detection, although the proviral load was always very low, near the limit of detection. In a few subjects, the examination of multiple viral genome regions or the use of more sensitive molecular techniques revealed the presence of the provirus. However, no molecular evidence of viral infection was found in other such individuals despite intense efforts [25].

The significance of HTLV-1 positive serology in the absence of viral genomic detection is uncertain. Hypothetically, it could represent: (1) slow progressors, controlling the infection efficiently; (2) individuals exposed to the virus that completely cleared the infection; and (3) false positive serology. As infection was confirmed by Western blot and proviral DNA was detected at least once during long-term follow-up, false positive serology in the case series presented is unlikely. It is possible that the strong immune responses to HTLV-1 seen in these individuals explains the exceptionally low abundance or complete absence of the virus. It is unlikely to be explained by infection with a low-pathogenicity variant of the virus, because genetic variability in HTLV-1 is very low.

Mother-to-child HTLV-1 transmission

In places with high HTLV-1 endemicity, transmission of the virus to newborns from infected mothers continues to be important. Children may acquire HTLV-1 when breastfeeding extends beyond 3 months. It has been suggested that maternal antibodies passively transmitted protect the baby until then. Researchers from Germany and from the UK presented data showing anti-viral properties of milk, impacting HTLV-1 transmission and replication *in vitro*. Overall, 20 % of infants born to mothers carrying HTLV-1 become infected. Most occur through breastfeeding, although anecdotal cases of intrauterine infection or at the time of vaginal delivery have been demonstrated. If breastfeeding is eliminated and elective cesarean section performed, there is hardly any vertical transmission of HTLV-1 [26].

The results of a Spanish study that examined the presence of antibodies against HTLV-1 in more than 7,000 pregnant women were presented. Four positive cases were identified, all from Latin America. Three were primigravida under the age of 23. They were advised against breastfeeding and to date no children have been infected. On the contrary, several cases of HTLV-1 infected children have already been reported in Spain after late diagnoses of HTLV-1 in their mothers [27].

Considering the large Latin American population residing in Spain and its high birth rate, it has been estimated that around 30 new HTLV-1 infections occur each year by

vertical transmission in Spain. This figure exceeds those of congenital syphilis, HIV or hepatitis B, all diseases for which there is a recommendation for antenatal screening. Given that prenatal screening for Chagas disease is already performed in Spain among pregnant women from Latin America, it would be convenient to add HTLV-1 screening to the same population [27]. An international study has concluded that antenatal HTLV-1 screening would be cost-effective or even cost-saving in many European countries [28], and much more so in HTLV-1 endemic regions [29]. Furthermore, more than 94 % of those living with HTLV-1 in the UK would support HTLV-1 antenatal screening [30].

Clinical manifestations & biomarkers

HTLV-1 associated myelopathy (HAM)

This is a neuroinflammatory disease of the spinal cord. Patients with HAM typically experience chronic lower back pain with early neuropathic urinary bladder symptoms followed by the development of lower-limb spasticity. Proximal weakness of the lower limbs, which eventually spreads distally, is common. Acute and subacute presentations, with progression to severe spastic paraparesis or paraplegia within a few months, can occur. Poorer prognostic indicators in patients with HAM include a high HTLV-1 proviral load, female sex, age at onset of ≥50 years, and early rapid progression.

In patients with HAM, the host's T-cell response appears to drive the tissue damage in the disease. HTLV-1 indirectly damages the CNS through infecting CD4+ T cells, which cross the blood-brain barrier and activated cytotoxic CD8+ T cells which migrate in response to CXCL10 and themselves release more CXCL10; the CD4+ and CD8+ T cells release neurotoxic cytokines IFN-gamma and TNF-alpha, establishing a cycle of neuroinflammation and neuronal death. A high proviral load in the blood is strongly associated with HAM, but alone is not sufficient to cause the disease; a proviral load that is greater in the CSF than in the blood strongly supports the diagnosis of HAM.

Several series of patients with HAM were presented at HERN 2023. Included in the Spanish registry are 58 patients with HAM, of whom 60 % have a Latin American origin and 76 % are women. The prognosis has been poor with 75 % becoming wheelchair-dependent and/or with urinary/fecal sphincter incontinence [31].

In another series of 74 individuals with HTLV-1 followed at the Karolinska Hospital in Stockholm, Sweden, nine had HAM and two ATLL. As previously reported, the HTLV-1 proviral load was relatively stable over several years, and patients with HAM generally had higher proviral load than asymptomatic carriers [32]. Interestingly, many of these patients were originally from Iraq, because of a political migrant agreement that took place after the Gulf War in 1990. HTLV-1 is prevalent in the region, especially in Mashhad, northeast of Iran, but also in Iraq and Kuwait, although less is known about other states in the region.

In a Brazilian cohort, 9 out of 74 initially asymptomatic individuals infected with HTLV-1 developed HAM during 12 years of follow-up. Reduced serum IL-10 concentration at first clinic visit predicted the development of myelopathy [33]. In contrast, high proviral load or older age were not predictors. The predictive value of IL-10 as a biomarker of HAM needs to be further confirmed.

Knowing that HTLV-1 infection per se is associated with a 57 % increase in mortality [1], the mortality rate associated with HAM was examined in the UK cohort, comparing 112 patients with HAM with age, sex and ethnically matched asymptomatic HTLV-1 carriers. The majority of patients were of Caribbean origin and living in London. The mortality rate was 2.4 times higher in patients with HAM compared to the asymptomatic carriers [34]. Furthermore, although HTLV-1 infection was associated with residence in a location with a high deprivation index, a higher mortality rate was observed equally in patients with HAM and asymptomatic carriers, further pointing to HAM as the cause of shortened life expectancy. Similar findings have been reported in Japan [35] and Brazil [36]. The potential role of chronic inflammation and persistent immune activation as a driver of premature death in HTLV carriers has also been suggested by others [2].

Adult T-cell leukemia/lymphoma (ATLL)

There are 4 clinical forms of ATLL. The acute and lymphomatous forms are aggressive and the prognosis is very poor. Several chemotherapy modalities have been used with poor results. The other two forms (chronic and 'smoldering') are more indolent and have a better prognosis, although most eventually transform and the overall 5-year survival is poor.

The Spanish register has recorded to date 35 cases of ATLL [16]. Survival was shorter than one year in almost all cases. More than half were women, mostly from Latin America or sub-Saharan Africa. The median age at diagnosis was 47 years.

Juan Carlos Ramos, from the University of Miami, reported on the combination of interferon, AZT and

belinostat in a case series with encouraging results [37]. The latter is a histone deacetylase inhibitor, which is an anti-neoplastic drug that re-activates HTLV-1, thus possibly increasing the immune response against infected tumor cells with interferon. A clinical trial has begun in the United States to examine the combination treatment. It is administered intravenously and is relatively well tolerated, although cytopenias are commonly seen. So far, data show this combination regimen can result in deep molecular remission in some patients.

Ambroise Marçais, of the Necker Hospital in Paris, France, described the efficacy of allogeneic bone marrow transplantation in 23 patients with ATL after a course of chemotherapy with complete response [38]. In some patients, the monoclonal antibody mogamulizumab (anti-CCR4) was used after the first two months of transplantation [39]. At two years, 75 % were free of oncological disease. In addition, the HTLV-1 provirus was no longer detected in peripheral blood mononuclear cells and all patients had developed specific immune responses [40]. Resembling the so-called 'Berlin patient', originally infected with HIV and then cured after a bone marrow transplant [41], in the patients with ATL described here who underwent bone marrow transplantation, had not only cured their leukemia but also eradicated HTLV-1 infection.

HTLV-1 prevention: prophylaxis & vaccines

Since HTLV-1 is a retrovirus like HIV, and many proteins are similar in both viruses, including reverse transcriptase, integrase, and protease, the possible efficacy of antiretrovirals in established HTLV-1 infection has been investigated. Overall, the results to date have been negative [42].

Once HTLV-1 infection is established in a new host, persistence of infection mostly occurs by proliferation of infected cells, although viral replication persists at a low level. This proliferation of infected lymphocytes by cell division explains why antiretrovirals do not reduce HTLV-1 proviral load *in vivo*. However, they do block infection in *in vitro* models, with inhibitory concentrations similar to those observed against HIV-1. The integrase inhibitors bictegravir, cabotegravir and dolutegravir are the most potent inhibitors of HTLV-1 transmission [43].

British and Italian researchers discussed the evidence supporting the use of antiretrovirals to prevent and manage HTLV-1 infection. Sexual contact being the predominant transmission route for HTLV-1, is there room to consider pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP), resembling HIV-1 prevention strategies? The time window for PEP to have any expected potential inhibitory effect on HTLV-1 infection would be very early in the acute infection period, before clonal proliferation of infected cells replaces viral replication as the driver of proviral load. This is before 2–4 weeks after initial HTLV-1 exposure and based on HIV infection likely to be less than 72 h. Thus, only during the early phase, when transfer of virions throughout cell-to-cell contact via the virological synapsis occurs, antiretrovirals that block the full viral replication cycle might be effective (Figure 2). Based on *in vitro* data, PrEP with integrase inhibitors will provide susceptible cells the chances to block the HTLV-1 life cycle before proviral integration.

Could antiretrovirals used as HIV PrEP or PEP work in uninfected persons at risk for HTLV-1 exposure? There are at least three target populations: (i) individuals having multiple sex partners, especially when they are from highly endemic regions; (ii) babies of infected mothers; and (iii) transplant recipients of HTLV-1+ donors. Advocates of PrEP

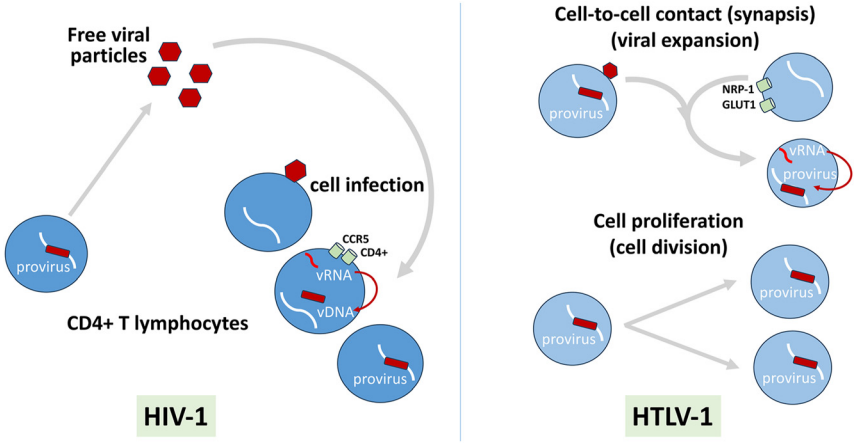

Figure 2: Difference in the life cycle of human retroviruses.

for HTLV-1 consider that tenofovir would be the most convenient agent and that recruitment should be done in highly endemic regions. These researchers have estimated for the size of study populations but the difficulties in the design of trials to prove the benefit of antiretrovirals in these populations are acknowledged. An alternative to prospective, randomized trials would be to examine the HTLV-1 incidence in individuals on in HIV-1 PrEP programmes, including bimonthly cabotegravir, in regions with significant HTLV-1 prevalence [44, 45].

Gene therapy and gene editing

It is estimated that HTLV-1 persists in approximately 10^3–10^6 infected T-cell clones within any infected host [46]. After initial viral infection, the virus is thought to become transcriptionally silent (latent) in each cell at a given time, as it is difficult to detect sense viral transcripts or proteins in infected individuals. However, the presence of activated cytotoxic T lymphocytes (CTLs) directed against sense-strand-encoded viral antigens suggests that constant, low-level viral transcription occurs. Indeed, recent studies found that Tax is transcribed in intense, intermittent bursts within infected cells [47].

The genetic sequence stability of the virus and the fact that proviral sequences integrate into the genome of infected cells make HTLV-1 a suitable candidate for treatment with gene editing tools [48]. Indeed, recombinase-mediated excision of the HTLV-1 provirus represents a promising approach to reduce proviral load in HTLV-1-infected individuals, potentially reducing the risk of developing HTLV-1-associated diseases. However, the great clonal diversity of infected cells in each host presents a formidable obstacle to control or eradicate the infection.

Conclusions

HTLV-1 is the second most prevalent human retroviral infection globally after HIV-1. Current estimates are of at least 10 million people living with HTLV-1 worldwide. The majority are asymptomatic, unaware of their infection and inadvertently able to transmit due to the paucity of testing. Once HTLV-1 is acquired, either sexually, vertically or parenterally, infection is lifelong. In contrast with HIV-1 infection, which causes a depletion of CD4+ T lymphocytes, HTLV-1 immortalizes infected CD4+ T-cells.

Nearly 10 % of HTLV-1 carriers develop overt clinical manifestations related to inflammation, such as, but not restricted to HAM, and malignancy in the form of ATLL. Worsened outcomes are also recognized with a range of co-infections [49] and associated to persistent immune activation and inflammation [1, 2]. Typically, HAM affects more frequently middle-aged women whereas ATLL occurs about a decade later, and in both sexes. A wide range of inflammatory conditions, including uveitis, thyroiditis and arthritis appear more frequently in individuals living with HTLV-1 than in the general population.

Although antiretrovirals are ineffective in established HTLV-1 infection, *in vitro* data support their potential as prophylaxis. Conversely, mogamulizumab, an anti-CCR4 monoclonal antibody, reduces HTLV-1 proviral load through semi-selective depletion of HTLV-1 infected cells, the majority of which express CCR4. Treatment with mogamulizumab infusion has shown efficacy in patients with HAM, with recent disease onset being a predictor of response.

The advent of new gene therapies and CRISPR editing has opened ways for targeting HTLV-1 proviral DNA. If not eradicative, these new treatment approaches could reduce proviral load, which ultimately predicts the risk of overt clinical disease [50]. Finally, the unique low genetic variability of HTLV-1 compared to many other RNA viruses, has encouraged the search for protective HTLV-1 vaccines [51]. However, the recognition that HTLV-1 spreads almost wholly by cell-to-cell contact through a virological synapse has diminished the initial enthusiasm for producing antibody-mediated vaccines [52].

Research ethics: According to Helsinki declaration.
Informed consent: Not applicable.
Author contributions: CdM, GT and VS wrote the first draft. All authors were oral presenters at HERN 2023 and checked the whole text and provided comments. All checked and approved the final version.
Competing interests: The authors state no conflict of interest.
Research funding: Grant UNIR-itei 005/23.
Data availability: All abstracts are freely available at www.aidsreviews.com.

References

1. Schierhout G, McGregor S, Gessain A, Einsiedel L, Martinello M, Kaldor J. Association between HTLV-1 infection and adverse health outcomes: a systematic review and meta-analysis of epidemiological studies. Lancet Infect Dis 2020;20:133—43.
2. Ramos JM, de Mendoza C, Soriano V, Spanish HTLV Network. HTLV-1 infection and health outcomes. Lancet Infect Dis 2020;20:407—8.
3. Legrand N, McGregor S, Bull R, Bajis S, Valencia BM, Ronnachit A, et al. Clinical and public health implications of HTLV-1 infection. Clin Microbiol Rev 2022;35:e0007821.

4. Gessain A, Ramassamy JL, Afonso P, Cassar O. Geographic distribution, clinical epidemiology and genetic diversity of the human oncogenic retrovirus HTLV-1 in Africa, the world's largest endemic area. Front Immunol 2023;14:1043600.
5. de Mendoza C, Pérez L, Fernández-Ruiz M, Pena MJ, Ramos JM, Richart A, et al. Late presentation of HTLV-1 infection in Spain reflects suboptimal testing strategies. Int J Infect Dis 2022;122:970—5.
6. Gessain A, Cassar O. Epidemiological aspects and world distribution of HTLV-1 infection. Front Microbiol 2012;3:388.
7. Talukder M, Woodman R, Pham H, Wilson K, Gessain A, Kaldor J, et al. High HTLV-1c proviral loads are associated with diabetes and chronic kidney disease: results of a cross-sectional community survey in Central Australia. Clin Infect Dis 2023;76:e820—6.
8. Tanase A, Colita A, Craciun O, Lipan L, Varady Z, Stefan L, et al. Allogeneic Stem Cell Transplantation for Adult **T**-Cell Leukemia/Lymphoma - Romanian Experience. J Clin Med. 2020;9:2417.
9. Cassar O, Marçais A, Hermione O, Begliomini G, Afonso P, Gessain A. Genetic variability and molecular epidemiology of HTLV-1 in Romania. AIDS Rev 2023;25(1 Suppl):5.
10. Mughal S, Rosadas C, Taylor G, Bradshaw D. Updating the estimated prevalence of HTLV-1 in England and Wales, and worldwide. AIDS Rev 2023;25(1 Suppl):9.
11. De Mendoza C, Pozuelo MJ, Blanco M, Aguilera A, Eiros JM, Benito R, et al. HTLV-1 estimates for Europe based on migration flows from endemic countries. AIDS Rev 2023;25(1 Suppl):10.
12. Sagara Y, Nakamura H, Satake M, Watanabe T, Hamaguchi I. Increasing horizontal transmission of HTLV-1 in adolescents and young adults in Japan. J Clin Virol 2022;157:105324.
13. Ayerdi O, Benito R, Ortega D, Aguilera A, Montiel N, Pintos I, et al. HTLV infection in persons with sexually transmitted diseases in Spain. AIDS Rev 2023;25(1 Suppl):6.
14. De Mendoza C, Caballero E, Aguilera A, Requena S, de Lejarazu RO, Pirón M, et al. HTLV-1 infection and disease in Spain. AIDS 2017;31:1653—63.
15. de Mendoza C, Carrizo P, Sauleda S, Richart A, Rando A, Miró E, et al. The slowdown of new infections by human retroviruses has reached a plateau in Spain. J Med Virol 2023;95:e28779.
16. de Mendoza C, Rando A, Miró E, Pena MJ, Rodríguez-Avial I, Ortega D, et al, Spanish HTLV Network. Adult T-cell leukemia/ lymphoma in HTLV-1 non-endemic regions. J Clin Virol 2023;167:105578.
17. de Mendoza C, Roc L, Benito R, Reina G, Ramos JM, Gómez C, et al. HTLV-1 infection in solid organ transplant donors and recipients in Spain. BMC Infect Dis 2019;19:706.
18. Melamed A, Tomas W, Fitzgerald W, Ma J, Birney E, Bangham CRM. Selective clonal persistence of human retroviruses in vivo: radial chromatin organization, integration site and host transcription. Sci Adv 2022;8:eabm6210.
19. Melamed A, Yaguchi H, Aristodemou A, Kiik H, Fitzgerald T, Wang Y, et al. HTLV-1 integration site: impact on viral persistence and host chromatin structure and expression. AIDS Rev 2023;25(1 Suppl):17.
20. Simon F, Donhauser N, Raasch N, Heym S, Eichler J, Thoma-Kress A. Characterizing the transfer of the mobile HTLV-1 accesory protein p8. AIDS Rev 2023;25(1 Suppl):11.
21. Shallak M, Alberio T, Fasano M, Monti M, Iacobucci I, Ladet J, et al. The endogenous HBZ interactome in ATL leukemic cells reveals an unprecedented complexity of host interacting partners involved in RNA splicing. AIDS Rev 2023;25(1 Suppl):12.
22. Forlani G, Shallak M, Tedeschi A, Cavallari I, Marçais A, Hermine O, et al. Dual cytoplasmic and nuclear localization of HTLV-1-encoded HBZ protein is a unique feature of ATL. AIDS Rev 2023;25(1 Suppl):18.
23. Hleihel R, Skayneh H, de The H, Hermine O, Bazarbachi A. Primary cells from patients with ATL depend on HTLV-1 tax expression for NF-kB activation and survival. AIDS Rev 2023;25(1 Suppl):18.
24. Jiang C, Lian X, Gao C, Sun X, Einkauf KB, Chevalier JM, et al. Distinct viral reservoirs in individuals with spontaneous control of HIV-1. Nature 2020;585:261—7.
25. Sotomi M, Greiller C, Haddow J, Cockbain B, Maher AK, Dhasmana D, et al. Characterizing HTLV-1 elite controllers using a range of molecular techniques. AIDS Rev 2023;25(1 Suppl):34.
26. Vieira B, Bidinotto A, Darotra W, Pedrotti LG, de Oliveira VM, Wendland EM. Prevalence of HTLV-1 and HTLV-2 infection in pregnant women in Brazil: a systematic review and meta-analysis. Sci Rep 2021;11:15367.
27. Encinas B, Benito R, Rojo S, Reina G, Montiel N, Aguilera A, et al. High rate of HTLV-1 infection among Latin American pregnant women living in Spain. AIDS Rev 2023;25(1 Suppl):7.
28. Rosadas C, Senna K, da Costa M, Assone T, Casseb J, Nukui Y, et al. Women living with HTLV-1 should have the opportunity to make informed decisions on prevention of mother-to-child transmission. Lancet Global Health 2023;11:E781—90.
29. Kowada A. Cost-effectiveness of HTLV-1 antenatal screening for prevention of mother-to-child transmission. PLoS Neglected Trop Dis 2023;17:e0011129.
30. Wilkie R, Davison K, Brailsford S, Taylor G. Perceived importance and likelihood of anxiety caused by antenatal screening among HTLV national register survey respondents in the UK. AIDS Rev 2023;25(1 Suppl):28.
31. Perez L, de Mendoza C, Rando A, Reina G, Aguilera A, Benito R, et al. HTLV-1 associated myelopathy in Spain, a non-endemic region. AIDS Rev 2023;25(1 Suppl):32.
32. Svensson A, Vesterbacka J, Gredmark-Russ S, Paucar M, Lidman C, Nowak P. Characteristics of the HTLV patient cohort followed at Karolinska University Hospital, Stockholm, Sweden. AIDS Rev 2023;25(1 Suppl):4.
33. Assone T, Menezes S, Gonçalves F, Folgosi VA, Habito ME, Marcus RNM, et al. Identification of immune predictors of incident HAM/TSP in a large cohort of people living with HTLV-1. AIDS Rev 2023;25(1 Suppl):30.
34. Biswas A, Taylor G. Investigating survival of patients with HTLV-associated myelopathy in the UK, compared with asymptomatic HTLV-1 carriers: a quantitative, retrospective cohort study. AIDS Rev 2023;25(1 Suppl):31.
35. Nagasaka M, Yamagishi M, Yagishita N, Araya N, Kobayashi S, Makiyama J, et al. Mortality and risk of progression to adult T cell leukemia/lymphoma in HTLV-1-associated myelopathy/ tropical spastic paraparesis. Proc Natl Acad Sci USA 2020;117:11685—91.
36. Marcusso R, Van Weyenbergh J, de Moura J, Dahy FE, de Moura Brasil Matos A, Haziot MEJ, et al. Dichotomy in fatal outcomes in a large cohort of people living with HTLV-1 in São Paulo, Brazil. Pathogens 2019;9:25.
37. Ramos JC, Toomey N, Barber G. Preliminary safety and efficacy of belinostat with zidovudine plus interferon for adult T-cell leukemia/lymphoma. AIDS Rev 2023;25(1 Suppl):38.

38. De Masson A, Beylot-Barry M, Ram-Wolff C, Mear JB, Dalle S, d'Incan M, et al. Allogeneic transplantation in advanced cutaneous T-cell lymphomas (CUTALLO): a prospective score matched controlled prospective study. Lancet 2023;401:1941—50.
39. Cook L, Phillips A. How I should treat adult T-cell leukemia/lymphoma. Blood 2021;137:459—70.
40. Marçais A, Loiseau C, Gilbert A, Belhadj M, Cazelles C, Deruelle E, et al. Allogenic hematopoietic stem cell transplantation is effective for patients with adult T-cell leukemia/lymphoma and can eradicate HTLV-1 infection. AIDS Rev 2023;25(1 Suppl):39.
41. Hutter G, Nowak D, Mossner M, Ganepola S, Müßig A, Allers K, et al. Long-tern control of HIV by CCR5 delta32/delta32 stem-cell transplantation. N Engl J Med 2009;360:692—8.
42. Macchi B, Stefanizzi V, Mateucci C, Balestrieri E, Minutolo A, Marino-Merlo F, et al. Antiretrovirals for HTLV-1 treatment and prevention. AIDS Rev 2023;25(1 Suppl):37.
43. Maertens G, Kalemera M, Barski M, Vanzo T, Schneiderman B. Cell culture evaluation hints first-line HIV medicines are primed for success if repurposed for HTLV-1 prevention. AIDS Rev 2023;25 (1 Suppl):36.
44. Bradshaw D, Khawar A, Patel P, Tosswill J, Brown C, Ogaz D, et al. HTLV seroprevalence in people using HIV pre-exposure prophylaxis in England. J Infect 2023;86:245—7.
45. Soriano V, Edagwa B, Mendoza C, Barreiro P, Corral O, Treviño A, et al. Ultra-long-acting antivirals as chemical vaccines to prevent viral diseases. Future Microbiol 2022;17:887—97.
46. Bangham CRM, Miura M, Kulkarni A, Matsuoka M. Regulation of latency in the human T cell leukemia virus, HTLV-1. Annu Rev Virol 2019;6:365—85.
47. Bangham CRM. HTLV-1 persistence and the oncogenesis of adult T-cell leukemia/lymphoma. Blood 2023;141: 2299—306.
48. Rojo-Romanos T, Karpinski J, Millen S, Beschorner N, Simon F, Paszkowski-Rogacz M, et al. Precise excision of HTLV-1 provirus with a designer-recombinase. Mol Ther 2023;31:2266—85.
49. Rosadas C, Taylor G. HTLV-1 and co-infections. Front Med 2022;9:812016.
50. Kalil R, Vasconcellos I, Rosadas C, Cony A, Lima DP, Gonçalves CCA, et al. Association between high proviral load, cognitive impairment, and white matter brain lesions in HTLV-1-infected individuals. J Neurovirol 2021;27:810—9.
51. Tu J, Maksimova V, Ratner L, Panfil A. The past, present, and future of a HTLV-1 vaccine. Front Microbiol 2022;13:897346.
52. Tu J, King E, Maksimova V, Smith S, Cheng X, Ratner L, et al. Development of a HTLV-1 mRNA vaccine. AIDS Rev 2023; 25(1 Suppl):41.