UJMR, Volume 3 Number 2, December, 2018 *ISSN: 2616 - 0668*

Received: 18/10/2018 **Accepted:** 22/11/2018

Human T-Lymphotropic Virus, Associated Myelopathy and Leukemia: A Review

Auwal, I. Kabuga,[1] and Lawal D. Rogo[2*]

[1]Department of Medical Microbiology and Parasitology, Faculty of Clinical Sciences, College of Health Sciences, Bayero University Kano, Nigeria [2]Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, College of Health Sciences, Bayero University Kano, Nigeria

*Correspondence Author: ldrogo.med@buk.edu.ng; lawaldahirurogo@yahoo.com

Tel. +2348039649234, +2348022569132

Abstract

Human T Lymphotronic Virus type 1 was the first retrovirus discovered associated with fatal diseases in humans and said to have emerged following zoonotic transmission from simian populations. Their primary target is adult CD4 T-cells and most infected individuals are asymptomatic. However, a significant number may develop persistent infection and progress to an aggressive lymphoproliferative disease, known as Adult T-cell Leukemia/Lymphoma-ATLL. Some may develop a debilitating neuro-inflammatory disease called Tropical Spastic Paraparesis-TSP, predominantly involving the lower limbs, with or without hyperactive urinary bladder. Unprotected sexual intercourse and breastfeeding account for the highest number of cases and is also transmitted by uncheck blood transfusion or sharing of contaminated sharps. ATLL and TSP are life-threatening diseases initially restricted to Middle East and some parts of Africa, but recently, cases are being reported in many parts of the world. Unfortunately, even though the antiretroviral therapy have greatly improved and significantly reduced HIV progression to AIDS, such great break through is not worthy benefit for HTLV infected individuals. Thus, they are identified as severe human diseases of public health concern. This review is an overview and contains update about the biology of the virus, its interaction with the host, HAM/TSP and ATLL; their epidemiology and clinical presentations.

Key words: CD4 cells, leukaemia, lymphoma, myelopathy, oncogenic viruses, paraparesis, retroviruses, zoonosis.

INTRODUCTION

The first retroviruses discovered to be associated with fatal diseases in the human population were Human- T-cell lymphotropic virus (HTLV) and immunodeficiency virus (HIV). HTLV is an envelope, positive sense, single stranded RNA (ssRNA) virus of the *Oncovirinae* subfamily and *Retroviridae* family, that reverse transcribe their RNA into DNA and integrate into the cellular DNA (Verdonck *et al.*, 2007; Futsch *et al.*, 2018). Five different types (HTLV-1, 2, 3, 4 and 5) have been described in humans but HTLV-1 and 2 have similar genomic structure with almost 70% homology (Fuji and Matsuoka, 2013). They are classified into a complex group of Delta retroviruses, characterized by additional non-structural regulatory *tax* and *rex* genes that play significant role in pathogenesis. They cause infection in humans by integration of proviral DNA into the somatic DNA of the host matured T-lymphocytes. Proliferation of infected lymphocytes has more important role in pathogenesis than production of free viral particles (Murphy and Bruhn, 2015). HTLV-1 and 2 have been recognized as etiologic agents of tropical spastic paraparesis, also known as Human T-lymphotropic virus associated myelopathy (HTLAM/TSP). However, HTLV 1 is implicated only in adult T cell leukemia (ATLL). HTLAM/TSP is a debilitating chronic progressive demyelinating disease that affects the spinal cord and white matter of the central nervous system; cases are mostly reported in the middle-aged men. In contrary, ATLL is a lymphoproliferative disease of matured T-lymphocytes and mostly seen in middle-aged women (Fuji and Matsuoka, 2013).

Vertical transmission from mother to child (breast-feeding and transplacenta) and unprotected sexual intercourse account for the majority of these viral transmissions (Clark *et al.*, 1985; Verdonck *et al.*, 2007). Other means of transmission includes uncheck blood transfusion and sharing of contaminated sharps (Murphy, 2016). The distribution of HTLV is worldwide, but frequent in places like Japan, Taiwan, Southern part of Iran (Mashhad) and East/South African sub-regions (Gonçalves *et al.*, 2010). Infections with HTLVs mostly result in asymptomatic carrier state, but, a significant number (5%) develop either HTLAM/TSP or ATLL (Murphy and Bruhn, 2015).

The two clinical conditions are now categorized as severe human diseases of public health importance because of their associated severe immunosuppression and resistance to chemotherapy (Jamilii *et al.*, 2015), and until now there is no known cure or protective vaccine available. In an effort to contain the situation, the Global Virus Network in 2014, launched a taskforce to promote basic research, develop new methods of prevention and treatment modalities including new public health preventive measures. Members of the taskforce were recruited from various locations across the globe as shown in figure 1(Willems *et al.*, 2017).

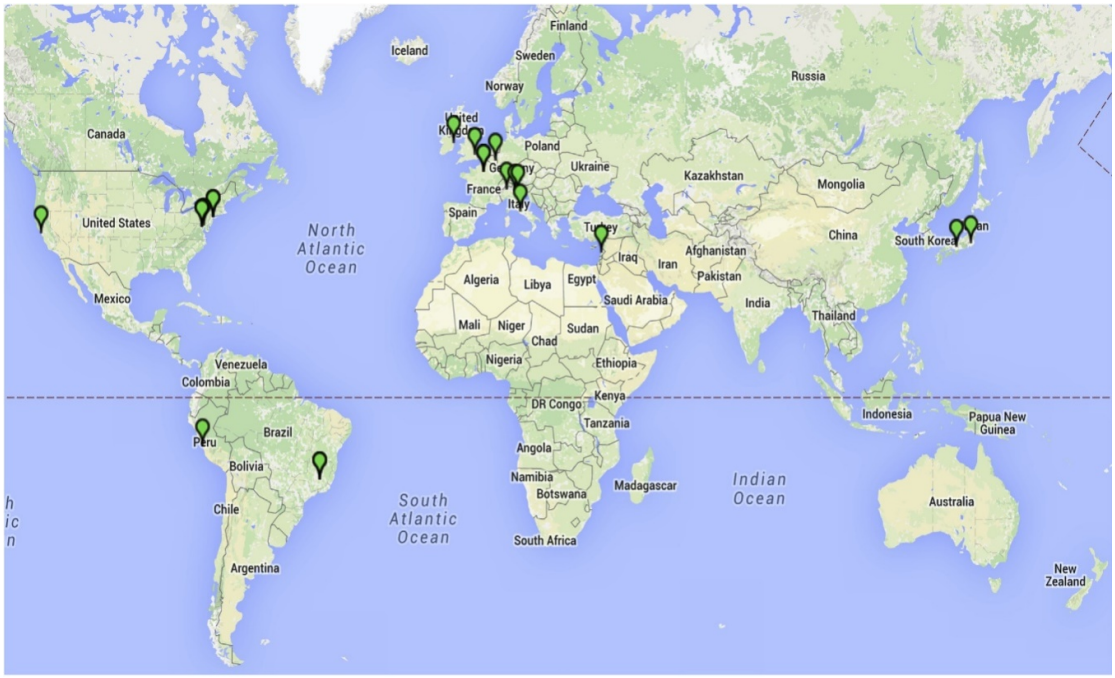

Figure 1. The global reach of the HTLV taskforce (Willems *et al.*, 2017)

HTLV origin and basic virology

HTLV is an envelope single stranded RNA (ssRNA) virus of positive sense polarity of the *Retroviridae* family, *Oncovirinae* subfamily, genus Deltaretrovirus and Human T-cell Lymphotropic virus type specie. Seven genotypes of HTLV-1 were recognized that is HTLV-1a to g (Verdonck *et al.*, 2007). Genotype A is the most common type. Genotypes B, D, E, F and G have merely been isolated from Central Africa while Genotype C is only present in Asia. HTLV-1 simian genotypes are interspersed in-between the human genotypes, indicating frequent zoonotic and anthroponotic transmission (Verdonck *et al.*, 2007). Genotype A is the only known human genotype that does not have a simian relation. It is thought that genotypes B, D, E, F and G originated in Africa from intimately linked STLV about 30,000 years ago, while the Asian genotype C is considered to have originated separately in simians from Indonesia. Two subtypes, transcontinental and Japanese subgroups are found in Japan (Otani *et al.*, 2012). HTLV-I possesses a distinctive 1.6 kb region, termed pX, which is positioned between env and the 3'LTR (Scadden *et al.*, 2018). This area encodes a number of regulatory proteins: p40 (Tax), p27 (Rex), p21, p12, p13 and p30. The HTLV-I basic leucine zipper factor (HBZ) is encoded by the minus (complementary) strand of pX region. Of these viral proteins, Tax and HBZ are strongly implicated in pathogenesis (Scadden *et al.*, 2018).

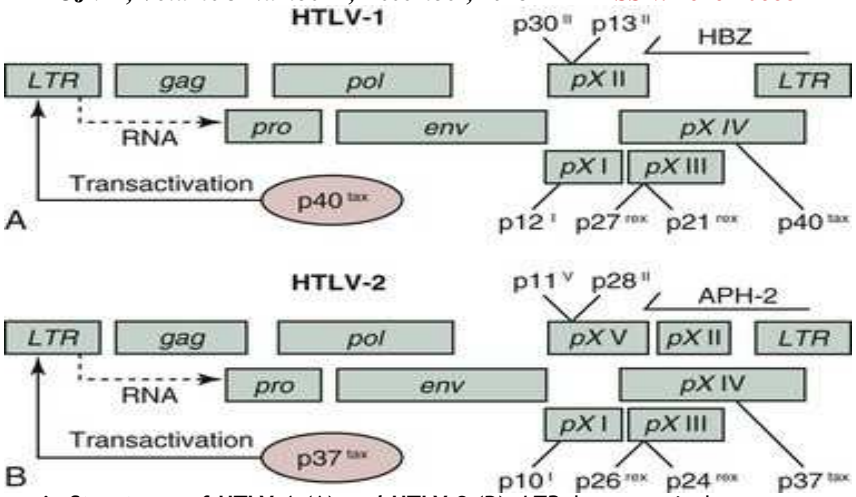

Figure 1. Genomic Structures of HTLV-1 (A) and HTLV-2 (B). *LTR,* long terminal repeat; *gag,* group-specific antigen whose products form the skeleton of the virion (matrix, capsid, nucleocapsid, nucleic acid–binding protein); *pro,* gene for protease; *pol,* gene for reverse transcriptase and integrase; *env,* envelope gene; *rex,* viral regulatory gene involved in promoting genomic RNA production; *tax,* transactivator gene; HBZ, antisense transcribed HTLV-1 basic zipper protein involved in cell proliferation; and APH-2, antisense transcribed antisense protein of HTLV-2 gene involved in transcription regulation (Murphy and Bruhn, 2018).

Pathogenesis

HTLV-1 is a provirus that passes through formation of a "virological synapse", allowing the viral genome to be passed from one cell to another. GLUT-1, a ubiquitous glucose transporter, has been recognized as a receptor for HTLV-1 (Manel *et al.*, 2003); this may elucidate on its capability to infect different cell types. It preferentially infects CD4+ lymphocytes *in vivo*. It causes hematological malignancy known as adult T-cell leukemia, and an inflammatory disease in the central nervous system (CNS) called HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). HAM/TSP patients exhibit spastic paraparesis and sphincter dysfunction, as well as sensory uproar of the lower extremities, which corresponds to pathological lesions in the spinal cord. It was proposed that HTLV-1-specific inflammation induction through interaction of HTLV-1-infected CD4+ T cells and HTLV-1-specific CD8+ CTL causes bystander injury to the CNS (Kubota, 2017).

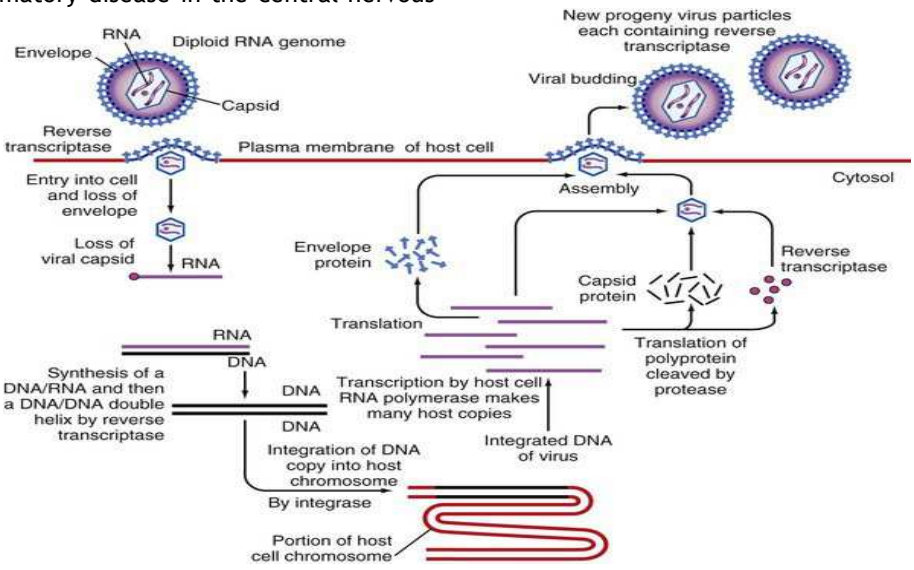

Figure 2. Life cycle of HTLV-1. Virus infection involves initial binding to cell surface of target CD4 cell, uncoating, and release of viral genetic material. Virally encoded reverse transcriptase creates a DNA copy (provirus) that is integrated into the host genome under the influence of viral integrase. Viral replication involves production of both genomic RNA and polyproteins that are cleaved by the viral protease, resulting in virion assembly at the cell surface (Murphy and Bruhn, 2018).

Epidemiology

There is no concrete data yet to represent the global prevalence of ATLL or HTLAM/TSP. Most studies carried out were centered on the epidemiology of HTLV-1 and 2. The geographical distribution of the virus has been studied for almost 35 years, since the description of HTLV-1. Estimation of global prevalence of HTLVs is based mainly on serologic screening of healthy blood donors, pregnant women and hospital patients, which might under estimate the prevalence (Mahzounieh *et al.*, 2015). In few instances, there have been population-based studies done in villages, towns or regions in a given country with varying demographic and epidemiological characteristics.

HTLV has global distribution, with more than 20 million people carrying the infection (Willems *et al.*, 2017); endemic areas include Central Africa, South America, the Caribbean Basin, Southern part of Iran, South Western Japan and Melanesia (Goncalves *et al.*, 2010; Gessain and Cassar, 2012; Utsunomiya *et al.*, 2015; Willems *et al.*, 2017). However, , only a small proportion (5-10%) of individuals carrying the virus develop clinical disease (Achiron *et al.*, 1993; Vallinoto *et al.*, 2015). In Asia, endemic clusters are present in Southern Japan, the Islands of Ryukyu including Okinawa, while inhabitants of People's Republic of China and Vietnam were found free of the infection (Murphy and Bruhn, 2015). In the Americas, major endemic foci occur in the Caribbean's and cases in South America were attributed to persons of African ancestry. In Europe, occasional infections were reported among emigrants from endemic areas. In middle East, Iranian Jews from North-Eastern Iran, Mashhad, the capital city of the province of Khorasan were among those with the highest prevalence (Tabei, 2011)., Southern indies and Indonesia reported some non-endemic foci of infection (Murphy and Bruhn, 2015). In African sub-region, Central Africa was tagged with the highest prevalence of 5%.

Phylogenetic studies have gone further to classify HTLV-1 into 5 major molecular and geographic sub-types. They are; (1) a cosmopolitan (C) subtype isolated all over the world (endemic to the Caribbean, South America), (2) a Japanese (J) subtype, (3) a West African (WA) subtype, (4) a Central African (CA) subtype and (5) a Melanesian (M) subtype found in Papua New Guinea, Melanesia, and Australian Aboriginals (Murphy and Bruhn, 2018). Studies of the long terminal repeat (LTR) by restriction fragment length polymorphism covering the major endemic areas demonstrated strong connection with the geographic origin of the infected individuals in comparison to the patients' clinical status (Murphy and Bruhn, 2015). The geographic origin of HTLV-2 is less certain. It was first demonstrated in and is highly prevalent among intravenous (IV) drug users in urban North American Amerindians, Indian groups of Panama and Argentina, likewise among Bakola pygmies in Cameroon and Europe. Prevalence studies have provided basis for classifying the infection into high prevalence (more than 5%), middle (1-5%) and low (less than 1%) prevalence (Karimi *et al.*, 2017; Santos *et al.*, 2017; Murphy and Bruhn, 2018).

The most important routes of HTLV transmission were found to be vertical and predominantly through breast-feeding and sexual intercourse (Clark *et al.*, 1985; Verdonck *et al.*, 2007); uncheck blood transfusion and sharing of contaminated sharp objects such as needles and syringes are among other means (Willems *et al.*, 2017). Intrauterine transmissions are among the newly documented routes. Sexual transmission of the virus is associated with unprotected sexual activity, multiple sexual partners, lifetime contact with infected partner and genital sores or ulcers (Goncalves *et al.*, 2010). Other risk factors include low socioeconomic status and low literacy level. In addition, environmental factors may influence the transmission as people born in endemic areas in Iran reported a higher prevalence (Hedayati-Moghaddam *et al.*, 2015).

Besides ATLL and HAM/TSP, infection with HTLV is associated with several other diseases of high morbidity and mortality. These include polymyositis, uveitis, infective dermatitis, crusted scabies, rheumatoid arthritis and Sjogren's syndrome (Gonçalves *et al.*, 2010), but the mechanisms leading to these conditions are currently unknown (Willems *et al.*, 2017). Although the incidence of ATLL in HTLV-1 endemic areas is known to be high (5%) (Goncalves *et al.*, 2010), population-based evidence concerning the incidence in non-endemic areas is scarce. In Japan, approximately 1.1 million individuals are infected with HTLV-1 and almost 1000 develop ATLL each year (Utsunomiya *et al.*, 2015), mostly males between the ages of 24-94 years (mean age =63 years)(Fuji and Matsuoka, 2013), 20-30 years following infection, but commoner among people infected in childhood (Goncalves *et al.*, 2010). In Iran, the average age of ATLL was 52±8 years (Akbarin *et al.*, 2013).

HAM/TSP predominates in HTLV-1 endemic areas and in some places poor hygiene and endogamic sexual activities facilitate disease development (Safabakksh *et al.*, 2014).

The rate at which carriers can express the neurologic disease was evaluated and approximated to 1 in 400 in elderly population of Iranian Jewish descent from Israel. This suggests that aging favors expression of the disease (Achiron *et al.*, 1993). A prospective study at blood centers in San Francisco reveals that the incidence of HAM/TSP among healthy carriers was higher than anticipated (6 cases among 160 HTLV-1 over 10 years) (Orland *et al.*, 2003). A long-term prospective study on a cohort of initially asymptomatic individuals in Brazil found that the incidence density of HAM/TSP was 5.3 cases per 1000 HTLV-1 seropositive cases per year (95% CI=2.6-10.9) (Romanelli *et al.*, 2013). A cohort study in Brazil revealed that 75 out of 414 HTLV-1 positive patients had HAM/TSP (Tanajura *et al.*, 2015). Among the 251 non-TSP patients followed, five developed HAM, 187 feet numbness, 130 nocturia, 127 urgency, 76 leg hyperreflexia, 53 leg weaknesses and 37 Babinski sign. Females and individuals with viral load 50,000/1,000,000 PBMC had higher risk of progression towards HAM/TSP (Tanajura *et al.*, 2015). Among Japanese couples, only 10% of men became positive after 10 years of common life with infected woman, whereas 80% of women will develop the disease if the male partner is positive. Also, children of infected mothers, females are more often and sooner seropositive (Carles *et al.*, 2004). Co-infection with HIV seems to increase the risk of developing HAM/TSP in HTLV-1 infected patients, younger age at presentation and a more rapid disease progression (Schutte *et al.*, 2012). The average age of occurrence among Iranian population was 45.52±15.17 years (Akbarin *et al.*, 2013).

Clinical presentations

Following infection with HTLV-1 or/and 2 most patients remain asymptomatic, only a small fraction develop disease(s), which result from the virus or host immune response. ATLL and HAM/TSP among others are now considered severe diseases, making HTLV 1 and 2 of global public health importance. In addition, HTLV causes severe subclinical immune suppression that can result in high rate of opportunistic infections such as tuberculosis and Strongyloidiasis (Goncalves *et al.*, 2010).

ATLL is a rare and often aggressive lymphoproliferative disease of matured T-lymphocytes that can be found in the blood (Leukemia), lymph nodes (Lymphoma), skin or and multiple areas of the body, with varying clinical features and prognosis. It is categorized into four groups based on lactate dehydrogenase, organ involvement and serum calcium, which includes acute ATLL, lymphomatous ATLL, chronic ATLL and smoldering type (Tsukasaki and Tobinai, 2014). Clinically the first two variants are classified as aggressive while the other two are indolent (Qayyum and Choi, 2014). Generally, patients with ATLL present with anaemia, peripheral lymphadenopathy, hepato-splenomegaly and skin lesions. There could be systemic manifestations involving the bone, lungs, skin, gastrointestinal tract and central nervous system. Bone involvement could be associated with hypocalcaemia as was reported in over 70% of some patients (Takatsuki *et al.*, 1994).

HAM/TSP is a slow progressive inflammatory disease that affects nerves and the spinal cord, resulting in demyelination of white and grey matter. Initial presentations include stiffness and weakness of the lower limb and lumbar pain with or without sensory presentations like tingling, burning or pinprick sensations. There may be dizziness in the early phase of the disease while urinary and sexual problems could be the presentations in some group of individuals. Autonomic dysfunction of the urinary bladder and bowel may result in frequency, urgency, urge-incontinence, post void residual urine and constipation. Urinary tract infections are common and in most cases associated with complications such as urolithiasis, vesico-ureteric reflux, hydronephrosis, pyelonephritis and chronic renal failure (Gonçalves *et al.*, 2010).

CONCLUSION

Adult T-lymphotropic leukemia (ATLL) and Human T-lymphotropic virus associated myelopathy (HAM/TSP) are two severe clinical conditions associated with long-term infection with Human T-lymphotropic virus I & II which are transmitted through breast feeding, sexual intercourse and blood transfusion. ATLL is a lymphotropic disease in middle-aged males associated with anemia, lymphatic enlargement and hepato-splenomegaly. HAM/TSP is a neurodegenerative inflammatory disorder that is mostly seen in middle-aged women and results in upper motor neuron disease. Despite effort to achieve cure or develop a reliable vaccine, ATLL and HAM/TSP continue to be associated with severe immunosuppression and remain chemoresistant. Until now, there is no specific cure or reliable vaccine; thus, most treatments are based on immune response suppression, which do not significantly improve disease process or quality of life.

Recommendations:

Going by the current trend of HTLV infection and sequel, there is urgent need for public health measures to fast tract the spread of the infection and minimize complications.

Emphasis should be given on public enlightenment about modes of transmission and the health consequences, especially the long term complications. There is the need to address issues regarding reckless sexual activities, illicit use of syringes and needles, especially among intravenous drug users, unchecked blood transfusion and use of protective gadgets among health care workers and other related personnel. Furthermore, a proper global epidemiological survey, not only among blood donors but in the general population should be carried out so as to have a good picture of the problem. This will facilitate the development of reliable vaccine, antiviral agent(s) and other prevention/control measures.

REFERENCES

Achiron, A., Pinhas-Hamiel, O., Doll, L., Djaldetti, R., Chen, A., Ziv, I., Avni, A., Frankel, G., Melamed, E. and Shohat, B. (1993). Spastic paraparesis associated with human T-lymphotropic virus type I: a clinical, serological, and genomic study in Iranian-born Mashhad Jews. *Annals of Neurology*, 34 (5):670-675.

Akbarin, M. M., Rahimi, H., HassanNia, T., Razavi, G. S., Sabet, F. and Shirdel, A. (2013). Comparison of HTLV-I proviral load in Adult T cell leukemia/lymphoma (ATL), HTLV-I-associated myelopathy (HAM-TSP) and healthy carriers. *Iranian Journal of Basic Medical Sciences*, 16 (3):208-212.

Carles, G., Tortevoye, P., Tuppin, P., Ureta-Vidal, A., Peneau, C., El Guindi, W. and Gessain, A. (2004). HTLV-I infection and pregnancy. *Journal Gynecology Obstetrics Biology and Reproduction*, (Paris) 33:14-20.

Clark, J., Saxinger, C., Gibbs, W. N., Lofters, W., Lagranade, L., Deceulaer, K., Ensroth, A., Robert-Guroff, M., Gallo, R. C. and Blattner, W. A. (1985). Seroepidemiologic studies of human T-cell leukemia/lymphoma virus type I in Jamaica. *International Journal of Cancer*, 36 (1):37-41.

Fuji, M. and Matsuoka, M. (2013). Human T-cell leukemia virus types 1 and 2. In: Knipe DM, Hawley PM, eds. Fields Virology. New York, Wolters Kluwer, Lippincott, Williams and Wilkins; pp 1474-501.

Futsch, N., Mahieux, R. and Dutartre, H. (2018). HTLV-1: The other pathogenic yet neglected human retrovirus: From transmission to therapeutic treatment. *Viruses*, 10:1.

Gessain, A. and Cassar, O. (2012). Epidemiological aspects and world distribution of HTLV-1 infection. *Frontiers in Microbiology*, 3:1e23.

Gonçalves, D. U., Proietti, F. A., Ribas, J. G., Araújo, M. G., Pinheiro, S. R., Guedes, A. C. and Carneiro-Proietti, A. B. (2010). Epidemiology, Treatment, and Prevention of Human T-cell leukemia virus type 1-associated diseases. *Clinical Microbiology Review*, 23:577-589.

Hedayati-Moghaddam, M., Tehranian, F. and Bayati, M. (2015). Human T-Lymphotropic Virus Type I (HTLV-1) Infection among Iranian Blood Donors: First Case-Control Study on the Risk Factors. *Viruses*, 7(11):5736-5745.

Jamilii, P., Maghsudlu, M. and Safabakhsh, H. (2015). Seroepidemiology of Human T-Cell lymphotropic virus type-1 in blood donors of north-eastern Iran, Sabzevar. *Asian Journal of Transfusion Science*, 9:203-206.

Karimi, G., Zadsar, M. and Pourfathollah, A. A. (2017). Seroprevalence and geographical distribution of human T-lymphotropic virus type 1 among volunteer blood donors in endemic areas of Iran. *Virology Journal*, 14:14.

Kubota, R. (2017). Pathogenesis of human T-lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis. *Clinical Experimental Neuroimmunology*, 8(2):117-128.

Mahzounieh M., Ghorani M., Karimi A., Pourgheysari, B. and Nikoozad, R. (2015). Prevalence of Human T-Lymphotropic Virus Types I and II in Patients with Hematological Disorders in Isfahan, Iran. *Jundishapur Journal Microbiology*, 8:e17201.

Manel, N., Kim, F. J., Kinet, S., Taylor, N., Sitbon, M. and Battini, J. L. (2003). The ubiquitous glucose transporter GLUT-1 is a receptor for HTLV. *Cell*, 115(4):449-459.

Murphy, E. L. (2016). Infection with human T-lymphotropic virus types-1 and -2 (HTLV-1 and -2): Implications for blood transfusion safety. *Transfusion in Clinical Biology*, 23:13-19.

Murphy, E. L. and Bruhn, R. L. (2015). Human T-lymphotropic virus (HTLV). In: Bennett JE, Dolin R, Blaser MJ, eds. Mendell, Douglas and Bennett's Principles and Practice of Infectious Diseases. Philadelphia, Elsevier; pp 2038-53.

Murphy, E. L. and Bruhn, R. L. (2018). Human T-Lymphotropic Virus. https://oncohemakey.com/human-t-lymphotropic-virus-htlv/. 2018 [Accessed 4 March 2018].

Orland, J. R., Engstrom, J., Fridey, J., Sacher, R. A., Smith, J. W., Nass, C., Garratty, G., Newman, B., Smith, D., Wang, B., Loughlin, K. and Murphy, E. L. (2003). Prevalence and clinical features of HTLV neurologic disease in the HTLV Outcomes Study. *Neurology*, 61:1588-1594.

Otani, M., Honda, N., Xia, P. C., Eguchi, K., Ichikawa, T., Watanabe, T., Yamaguchi, K., Nakao, K. and Yamamoto, T. (2012)."Distribution of Two Subgroups of Human T-Lymphotropic Virus Type 1 (HTLV-1) in Endemic Japan". *Tropical Medicine and Health*, 40(2):55-58.

Qayyum, S. and Choi, J. K. (2014). Adult T-Cell Leukemia/Lymphoma. *Achieve of Pathology and Laboratory Medicine*, 138:282-286.

Romanelli L. C., Caramelli P., Martins M. L., Gonçalves, D. U., Proietti, F. A., Ribas, J. G., Araújo, M. G. and Carneiro-Proietti, A. B. (2013). Incidence of human T cell lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis in a long-term prospective cohort study of initially asymptomatic individuals in Brazil. *AIDS Research in Human Retroviruses*, 29:1199-202.

Safabakksh, H., Jalalian, M. and Karimi, G. (2014). Seroepidemiology of human T-cell lymphotropic virus type-1 (HTLV1) in Mashhad. *Global Health and Science*, 6:99-104.

Santos, R. F. S., Conceição, G. C., Martins, M. S., Kraychete, A., Penalva, M. A., Carvalho, E. M., Lopes, A. A. and Rocha, P. N. (2017). Prevalence and risk factors for Human T-Lymphotropic Virus Type 1 (HTLV-1) among maintenance hemodialysis patients. BMC *Nephrology*, 18:64.

Scadden, D. T., Freedman, A. R. and Robertson, P. (2018) Human T-lymphotropic virus type I: Virology, pathogenesis, and epidemiology. https://www.uptodate.com/contents/human-t-lymphotropic-virus-type-i-virology-pathogenesis-and-epidemiology. [Accessed 16 May 2018].

Schutte, C., Townsend, T., Van Coller, R. and Olorunju, S. (2012). Comparison of HTLV-associated myelopathy (HAM) in HIV-positive and HIV-negative patients at a tertiary South African hospital. *South Africa Medical Journal*, 103:43-46.

Tabei, S. Z. (2011). Human T lympmphotrophic virus (HTLV1) related diseases. *Iran Red Crescent Medical Journal*, 13:374-376.

Takatsuki, K., Yamaguchi, K. and Matsouka, M. (1994). ATL and HTLV-1 related diseases. In: Takatsuki K, ed. Adult-Cell leukemia. New York: Oxford University Press; 1994. pp1-27.

Tanajura, D., Castro, N., Oliveira, P., Neto, A., Muniz, A., Carvalho, N. B., Orge, G., Santos, S. and Glesby, M. J. Carvalho E. M. (2015). Neurological manifestations in human T-cell lymphotropic virus type 1 (HTLV-1)-infected individuals without HTLV-1-associated myelopathy/tropical spastic paraparesis: A longitudinal cohort study. *Clinical Infectious Diseases*, 2015;61:49-56.

Tsukasaki, K. and Tobinai, K. (2014). Human T-cell Lymphotropic Virus Type I–Associated Adult T-cell Leukemia-Lymphoma: New Directions in Clinical Research. *Clinical Cancer Research*, 20:5217-5225.

Utsunomiya, A., Choi, I., Chihara, D. and Seto, M. (2015). Recent advances in the treatment of adult T-cell leukemia-lymphomas. *Cancer Science*, 2015;344-51.

Vallinoto, A. C. R., Santana, B. B., Sá, K. S. G., Ferreira, T. C. S., Sousa, R. C. M., Azevedo, V. N., Feitosa, R. N. M., Machado, L. F. A., Ishak, M. O. G. and Ishak, R. (2015). HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis Is Not Associated with SNP rs12979860 of the IL-28B Gene. *Mediators in Inflammation*, 1-7.

Verdonck K, González E, Van Dooren S. Vandamme, A. M., Vanham, G. and Gotuzzo, E. (2007). Human T-lymphotropic virus 1: Recent knowledge about an ancient infection. *Lancet Infectious Disease*, 7:266-281.

Willems L, Hasegawa H, Accolla R. Bangham, C., Bazarbachi, A., Bertazzoni,U., Carneiro-Proietti, A. B. de-F., Cheng, H., Chieco-Bianchi,L., Ciminale,V., Coelho-dos-Reis, J., Esparza,J., Gallo,R. C., Gessain, A., Gotuzzo, E., Hall, W., Harford, J., Hermine,O., Jacobson,S., Macchi,B., Macpherson, C., Mahieux, R., Matsuoka,M., Murphy, E., Peloponese,J-M., Simon,V., Tagaya, Y., Taylor,G. P., Watanabe, T. and Yamano, Y. (2017). Reducing the global burden of HTLV-1 infection: An agenda for research and action. *Antiviral Research*, 137:41e48.