Rizkallah G, Mahieux R, Dutartre H. Clinical Approaches of HIV-1/HTLV-1 Co-infection Still Keep their Mysteries. J Infectiology. 2019; 2(4): 25-31

Journal of Infectiology

Journal of Infectiology

Mini Review Open Access

Clinical Approaches of HIV-1/HTLV-1 Co-infection Still Keep their Mysteries

Gerges Rizkallah[1], Renaud Mahieux[2], Hélène Dutartre[2]

[1]Faculty of Public Health, Sagesse University, Beirut, Lebanon

[2]Équipe oncogenèse rétrovirale, équipe labellisée «FRM», CIRI – Centre International de Recherche en Infectiologie, Univ Lyon, Université Claude Bernard Lyon 1, Inserm, U1111, CNRS, UMR, ENS Lyon, Lyon, France

Article Info

Article Notes
Received: July 23, 2019
Accepted: August 30, 2019

***Correspondence:**
Dr. Gerges Rizkallah, Faculty of Public Health, Sagesse University, Beirut, Lebanon;
Email: gerges.rizkallah@hotmail.com.

Keywords:
Rifamycin SV
Pregnane X receptor (PXR)
Cytochrome p540 3A4 isoform (CYP3A4)
P-glycoprotein P (PgP)
Nuclear factor κB (NFκB)
Gastrointestinal (GI) diseases
Chronic inflammatory liver disease
Gut-liver axis

Introduction

Two retroviruses emerged in the 1980s : HTLV-1 and HIV-1[1,2,3]. HTLV-1 infects 5-10 million people worldwide and is detected in highly endemic areas, such as Japan, sub-Saharan Africa, the Caribbean region, South America[4] as well as in Australian indigenous[5]. According to the UNAIDS's 2018 fact sheet, HIV-1 is endemic worldwide, infects 37.9 million people and is particularly prevalent in central and South Africa, the Caribbean region, Latin America, South-East Asia and Eastern Europe[6]. HTLV-1 or HIV-1 infected individuals develop chronic infections. Only in 1-10% of infected carriers, HTLV-1 leads either to the development of Adult T-cell Leukemia/Lymphoma (ATLL), or of Tropical Spastic Paraparesis/HTLV-1 Associated Myelopathy (TSP/HAM)[7]. In most chronically infected people, HIV-1 infection leads to an Acquired Immunodeficiency Syndrome (AIDS), and around 22% of the death causes among HIV-infected patients remains AIDS-related[6]. The aim of this mini-review is to highlight some of the points discussed in the review ''HTLV-1, the Other Pathogenic Yet Neglected Human Retrovirus: From Transmission to Therapeutic Treatment''[8]. First, it will focus on the similarities regarding transmission mechanisms and cellular tropism between these retroviruses. Then, starting from the therapeutic protocols currently used in the treatment of each of these retroviral infections, this mini-review will summarize the therapeutic protocols used for co-infections management.

HIV-1 and HTLV-1 Share Striking Similarities

Although molecular mechanisms are different, HTLV-1 and HIV-1 share striking similarities in their transmission pathways, in their *in vivo* tropism and in their cell-to-cell transmission mechanisms.

HIV-1 and HTLV-1 share common entry routes: a vertical transmission from mother-to-child particularly during prolonged breastfeeding for HTLV-1[9,10], during delivery for HIV[11], a horizontal transmission preferentially from male-to-female during non-protected sexual intercourse[12,13] and contamination with cell containing blood products for HTLV-1[14] and cell-free material for HIV[15].

HIV-1 and HTLV-1 share striking similarities in their *in vivo* tropism, since CD4+ T-cells are the major targets of HIV-1 and HTLV-1 infection. In addition, HTLV-1 proviral DNA is also detected, but to a lesser extent, in other immune cell types, including CD8+ T-cells, B cells, monocytes, or dendritic cells[16], although mechanisms

explaining viral presence in each cell type are not the same. *In vivo*, latent HIV-1 proviruses are found in memory CD4+ T-cells, monocytes and macrophages, thus constituting viral reservoirs[17,18]. Both viruses are able to enter in dendritic cells *in vitro* and alter their function. This interaction, which may occur before T-cell infection *in vivo*, has been suggested as an important step for the subsequent infection of T-cells and further viral spread[19].

In vitro, three non-mutually exclusive cell-to-cell transmission mechanisms have been reported so far for HTLV-1 and HIV-1: the viral synapse, the viral biofilm and the tunneling nanotubes[16,20].

The viral synapse is a virtual space in which viral particles are budding and where they accumulate, close to an uninfected cell's plasma membrane[21]. The viral biofilm refers to HTLV-1 viral particles retained at the infected T-cell surface by extracellular-matrix proteins[22]. Presence of a viral biofilm has not been shown yet for HIV-1, although the virus accumulates near the surface of infected cells[23] in structures that were proposed as budding platforms, and that polarized toward the cell-cell contact[24], thus allowing viral transfer at the viral synapse[25].

Finally, the tunneling nanotubes (TNTs) are cellular conduits that interconnect HTLV-1 expressing cells. Intercellular transmission of HTLV-1 through TNTs provides a means of escape from recognition by the immune system[26] and favors HTLV-1 transmission[27]. HIV-1 uses also these long membrane extensions that connect distant cells in order to spread[28,29].

Impact of HIV-1 and HTLV-1 Co-infections on Disease Progression

In 1984, one of the first studies showed that approximately 7% of Haitian AIDS individuals were HTLV-1 infected[30]. Nowadays, HTLV-1 and HIV-1 co-infection is mainly investigated in South America and Africa[31], with prevalence ranging from 0.5 to 10.9%. In addition, *in vitro* studies confirmed that co-infection of HTLV-1-infected cells by HIV-1 is also possible in a T-cell line[32], suggesting the potential presence of both viruses in the same CD4+ T-cells in co-infected individuals.

The mechanisms of HIV-1/HTLV-1 co-infection *in vitro* and their effects on disease progression *in vivo* were evaluated. However, as demonstrated in the table 1, these studies did not allow clear conclusions on a positive or a negative regulatory effect of HTLV-1 on HIV-1 in co-infected individuals.

Current HTLV-1 Associated Diseases Treatments

ATLL Treatment

(See Tables 2 and 3)

TSP/HAM treatment

Management of TSP/HAM mainly consists in treating clinical symptoms. Anti-inflammatory corticosteroids represent a typical treatment due to the inflammation-based manifestations of TSP/HAM. They inhibit inflammatory gene expression and activate anti-inflammatory gene expression[68]. Research is now focusing on drugs that could modulate anti-HTLV-1 immune response and induce a decrease in HTLV-1 proviral load. Valproate, a histone deacetylase inhibitor, induces HTLV-1 proviral gene expression and can therefore expose virus-infected cells to immune response, notably to HTLV-1-specific cytotoxic lysis. However, analysis of valproate efficiency led to conflicting results regarding its efficiency on proviral load decrease[69,70]. Multiple combinations of valproate with prednisolone and IFN-I improve the clinical outcome of TSP/HAM patients, and more importantly, efficiently reduce HTLV-1 proviral load[48]. Another approach

Table 1: Mechanisms of HTLV-1/ HIV-1 co-infections and their effects on disease progression

Mechanisms of HTLV-1 / HIV-1 co-infection of CD4⁺ T-cell	**Mechanisms of co-infections HTLV-1 Tax oncoprotein expression enhances HIV-1 replication**	Tax protein is encoded by HTLV-1[33]. It promotes the activation of P-TEFb, releasing CDK9 and Cyclin T1 from inactive forms in latently infected CD4+ T-cells, promoting transcription elongation and reactivation of latent HIV-1[34].
	Mechanisms of co-infections HTLV-1 Tax oncoprotein expression inhibits HIV-1 replication	Addition to recombinant Tax protein to HIV-1-infected Peripheral Blood Mononuclear Cells *in vitro* leads to inhibition of HIV-1 replication up to 14 days after infection[35].
Effects of HTLV-1 / HIV-1 co-infection on disease progression	HIV-1/HTLV-1 co-infection promotes worsening of symptoms[36]. Compared to HIV-1 mono-infected individuals, most HIV-1/HTLV-1 co-infected individuals are more likely to suffer from myelopathy, thrombocytopenia, bronchitis, urinary tract infection or opportunistic infection, independently of age, ethnicity or CD4+ T-cells count[37]. Compared to HTLV-1 mono-infected individuals, HIV-1/HTLV-1 co-infection has a negative impact on the development of ATLL[38] or of TSP/HAM[39]. These results could be due to the higher production of IL-2 and IFN-Y observed in HIV-1/HTLV-1 co-infected individuals compared to HIV-1 or HTLV-1 mono-infected individuals, together with the up-regulated levels of RANTES in HIV-1/HTLV-1 co-infected cells[40]. This cytokine profile may thus favor a faster onset of myelopathies and neurological disorders in co-infected individuals.	

combining valproate and azidothymidin led to dramatic proviral load decrease in asymptomatic carriers[55].

Mogamulizumab i.e. anti CCR4 treatment (refer to paragraph 3.1) reduced HTLV-1 proviral load, spontaneous proliferation of CCR4-positive CD4+ and CD8+ T-cells, as well as pro-inflammatory cytokines production[56].

Precautions in the Management of Co-infections

Current guidelines recommend a triple combination of antiretroviral therapies as the first line in treatment of naive people with HIV[71]. According to the Department of Health and Human Services guidelines for the use of antiretroviral therapy (ART) in HIV-1-infected persons, initiation of ART is recommended for all HIV-infected persons regardless of the CD4 count[72]. Thus, in accordance with this guideline, ART is an obligatory part of the treatment of co-infected persons with HIV-1/HTLV-1. Since HTLV-1 and HIV-1 are two strikingly similar retroviruses on multiple levels, it is

Table 2: Directions for the treatment of ATLL

Protocol of treatment	Results
• The first generation of chemotherapy: CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or CHOP-like treatments were used for treating aggressive forms (acute and lymphoma types) of ATLL[41]. • LSG15 (Lymphoma Study Group) based regimens are a combination of eight-drugs consisting of at least VCAP (vincristine, cyclophosphamide, doxorubicin and prednisone), AMP (doxorubicin, ranimustine and prednisone) and VECP (vindesine, etoposide, carboplatin and prednisone). They were used for treating aggressive forms of ATLL[42].	• CHOP and CHOP-like treatments resulted in relatively poor outcomes[41]. • Compared to biweekly CHOP treatment, LSG15-based treatment initially showed better results on the 3-year overall survival (24% vs. 13%) and on complete remission rates (40% vs. 25%)[42]. However, this was not confirmed in a larger longitudinal study that included 1665 Japanese ATLL patients (with lymphoma or acute ATLL) from 2000 to 2009[43,41].
Allogeneic hematopoietic stem cell transplantation following chemotherapy for patients with acute or lymphoma ATLL[44].	It slightly improved the median survival time (14 vs. 6.7 months and 13.9 vs. 9.7 months, respectively) or the 4-year overall survival rates (27.8 vs. 6.8% and 32.3 vs. 13.7 months, respectively)[44].
Antiviral therapies consisting of a combination of zidovudine (ZDV) and IFN-α was investigated in acute, smoldering and ATLL[45,46].	This combination achieved a significantly improved long-term survival in patients with smoldering and chronic ATLL as well as a subset of patients with acute ATLL[45]: on 10 previously untreated patients (8 acute ATLL, 1 smoldering ATLL, and 1 ATLL lymphoma), eight responses were obtained, with two complete remissions, four very good partial remissions with a 95% reduction of the tumor burden, and two partial remissions. Six patients relapsed, with a median event-free survival of 12 months (range, 3-15 months)[45]. Although these results were encouraging, the overall survival of previously untreated ATLL patients was rather short (4.8 months) when compared to those on the LSG15 regimen[46]. Furthermore, the complete remission rate with AZT/IFN in previously untreated ATL patients (25%) was not superior to the complete remission rate in those treated with LSG15. On long-term follow up of 15 ATLL patients treated over a 4-year period, AZT/IFN improved medium survival time (MST) outcome (18 months) possibly due to maintenance treatment with AZT/IFN after achieving a partial remission[47]. Moreover, another prospective phase II clinical trial reported that the use of AZT/IFN as an initial treatment in 19 ATLL patients (15 acute type and four lymphoma type), resulted in a 92% response rate and a MST of 11 months for all patients[48]. These studies confirm the efficacy and safety of AZT/IFN in patients with ATLL[42]. Nowadays, ATLL lymphoma patients still benefit from chemotherapy induction with concurrent or sequential antiretroviral therapy with zidovudine/IFN[49].
Immunotherapies based on monoclonal antibodies targeting specific markers of ATLL cells: CD2[50], CD25[51] or CCR4 chemokine receptor were tested in acute and lymphoma subtypes ATLL[52].	Anti-CD2[50] and anti-CD25[51] showed poor to no effect. In contrast, the CCR4 chemokine receptor seems an interesting target since its expression is high and frequent in ATLL and HTLV-1-immortalized T cells[53]. Thus, a humanized anti-CCR4 monoclonal antibody (Mogamulizumab) has been generated. Mogamulizumab monotherapy showed clinically meaningful antitumor activity, with an acceptable toxicity profile, in patients with aggressive ATLL, who relapsed after at least one chemotherapy regimen. Overall response rate was of 50%. Median progression-free and overall survival were 5.2 and 13.7 months, respectively[53]. These encouraging results fostered the use of mogamulizumab in combination with LSG15-based chemotherapy to treat aggressive ATLL patients[54].
In the last 5 years, several isolated studies have been focusing on additional promising drugs that inhibit ATLL cell proliferation or induce cell death by several mechanisms. Some of them are summarized in table 3:	

Table 3: Future directions for the treatment of ATLL

Chemotherapeutic molecules such as bortezomib[55];	This study was terminated because bortozomib did not appear to be very promising for the studied cohort of patients[44].
Plant-derived steroids, alkaloids or carotenoids[56];	Six phenanthroindolizidines alkaloids were extracted from aerial parts of *Tylophora tanakae* and their antiproliferative activity examined against chronically-infected HTLV-1 cells. The EC_{50} value of some of the alkaloids was in the low nanomolar range, comparable to that of the clinically used antineoplastic drug doxorubicin[44].
Pro-apoptotic molecules such as Bcl-2 (B-cell Lymphoma 2) inhibitors[57];	ABT-737, a small molecule inhibitor of Bcl-2 significantly induced *in vitro* apoptosis in HTLV-1 infected T-cell lines as well as in fresh ATLL cells. Moreover, ABT-737 significantly inhibited *in vivo* tumor growth of an ATLL mouse model. These results suggest that ABT-737 either alone or in combination with other conventional drugs, represents a novel promising approach for ATLL[45].
CDK9 (Cyclin-dependent Kinase 9) inhibitor[58];	The CDK9 inhibitor BAY 1143572–treated ATLL-bearing mice demonstrated significantly prolonged survival compared with untreated ATLL-bearing mice, showing strong potential as a novel treatment of ATLL[58].
Arsenic in combination with ZDV and IFN-α[59];	The arsenic/interferon combination clears ATLL through degradation of its Tax driver, and this regimen could have broader therapeutic value[59]. Furthermore, Arsenic trioxide (As) dramatically synergizes with IFN to induce growth arrest and apoptosis of ATLL leukemia cells *in vitro*. In a phase II trial of As/IFN combination in seven patients with relapsed/refractory ATLL (four acute and three lymphoma), four patients exhibited a clear initial response. One patient remained alive and disease free at 32 months[60]. In 10 newly diagnosed chronic ATLL patients, an impressive 100% response rate was observed including 7 complete remissions, 2 complete remissions but with more than 5% circulating atypical lymphocytes, and 1 partial response. Responses were rapid and no relapse was noted. Side effects were moderate[61].
Histone deacetylase, such as valproate[62];	Valproate activates viral gene expression to expose virus-positive cells to the host immune response. Based on *in vitro* and *in vivo* data, it was shown that transient activation of the latent viral reservoir causes its collapse, a process that may alleviate the condition of HAM/TSP[62].
Inhibitors of iron uptake such as antibodies directed against the transferrin Receptor 1[63];	High levels of cell surface transferrin receptor 1 (TFR1) expression have been reported in ATLL. The monoclonal antibody JST-TFR09 presents a great affinity to TFR1 on ATLL cells *in vitro* and may consequently become a promising therapeutic antibody for the treatment of ATLL[63].
p53 expression activator such as synthetic retinoid ST1926[64];	Clinically achievable concentrations of ST1926 induced a dramatic inhibition of cell proliferation in malignant T-cell lines and primary ATLL cells with minimal effect on resting or activated normal lymphocytes. ST1926 induced apoptosis, DNA damage, and upregulation of p53 proteins in malignant T cells, whereas it caused an early downregulation of Tax protein in HTLV-1–positive cells. These results highlight the promising use of ST1926 as a targeted therapy for ATLL[64].
An HTLV-1-targeted gene editing zinc-finger nuclease (ZFN)[65].	The ZFN disrupted the promoter function of HTLV-1 LTR and specifically killed HTLV-1-infected cells. The therapeutic effect of ZFN was confirmed in an *in vivo* model of ATLL[65].
BNZ-1, a pegylated peptide designed to specifically bind the γc receptor to selectively block IL-2, IL-15, and to a lesser degree IL-9 signaling (66). It doesn't affect IL-4, IL-7, or IL-21[67].	BNZ-1 drastically reduced leukemic burden in an IL-15-driven human ATLL mouse xenograft model. Thus, BNZ-1 shows great promise as a novel therapy ATLL, and other IL-2 or IL-15 driven hematopoietic malignancies[66].

legitimate to ask whether HTLV-1 infection treatments can interact with antiretroviral therapies used in HIV-1/HTLV-1 co-infections.

The clinical management of HIV-1/HTLV-1 co-infection is delicate[73], and would deserve a specific management, at least in testing combination of available HIV antiviral and HTLV-1 targeted treatments. HIV-1/HTLV-1 co-infected patients usually have significantly higher CD4+ T-cell counts than HIV-1 mono-infected patients. Thus, AIDS diagnosis based on this criteria is impaired, and their survival time is reduced[36]. Indeed, while HTLV-1 stimulates CD4+ T-cells proliferation without cytopathic effects, HIV-1 induces a severe lymphocytic depletion with intensive cytopathic activity. Thus, co-infection may mask HIV-1 induced immunosuppression, and therefore could worsen AIDS progression and might favor subsequent opportunistic infections. Similarly, HIV-1/HTLV-1 co-infection can worsen the clinical outcome of HTLV-1 infection as the lifetime risk of developing TSP/HAM is higher in HIV-1/HTLV-1 co-infected patients than in HTLV-1 mono-infected patients. Furthermore, the lifetime risk is even higher in co-infected patients under ART, which seems responsible for neurological complications[74]. ART composed of zidovudine, lamivudine and abacavir (or

didanosine), initially prescribed to treat HIV-1 infection in HIV-1/HTLV-1 co-infected patients trigger an increase in HTLV-1 proviral load[75].

Finally, HTLV-1 serological status should be checked in all HIV-1 patients from HTLV-1 endemic areas. However, as ART seems to worsen HTLV-1 infection, combined therapies should be considered. However, no study has documented the use of the drugs cited in paragraphs 3.1 and 3.2 in the case of HIV-1/HTLV-1 co-infection.

Conclusion

HIV-1 and HTLV-1 share striking similarities in their cellular tropism and their cell-to-cell transmission mechanisms. Co-infection with these two viruses is possible, observed in up to 10% of infected individuals from endemic areas and is associated to a poor prognosis. Nowadays, even if protocols for treating HIV-1 and HTLV-1 mono-infected patients are well established, therapeutic options for co-infected patients are still poorly documented, may not be appropriate and may even worsen disease occurrence and evolution in case of unidentified co-infection. That's why it is necessary to search for both retroviruses at the time of diagnosis of HIV-1 or HTLV-1 infection to formally exclude the risk of HIV-1/HTLV-1 co-infection, and to propose appropriated management. Likewise, treatment protocols specifically designed for those co-infections need to be set, in order to fight the high morbidity associated with the co-infection.

Acknowledgments

Gerges Rizkallah is supported by Sagesse University, Beirut. Hélène Dutartre is supported by INSERM. Renaud Mahieux is supported by Ecole Normale Supérieure de Lyon. The authors acknowledge the financial support from La Fondation pour la Recherche Médicale (équipe Labellisée).

References

1. Poiesz BJ, Ruscetti FW, Reitz MS, et al. Isolation of a new type C retrovirus (HTLV) in primary uncultured cells of a patient with Sézary T-cell leukaemia. Nature. 1981 Nov 19; 294(5838): 268–71.
2. Gallo RC, Sliski A, Wong-Staal F. Origin of human T-cell leukaemia-lymphoma virus. Lancet. 1983 Oct 22; 2(8356): 962–3.
3. Barré-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS) 1983. Rev Invest Clin. 2004 Apr; 56(2):126–9.
4. Gessain A, Cassar O. Epidemiological Aspects and World Distribution of HTLV-1 Infection. Front Microbiol. 2012; 3: 388.
5. Vandamme AM, Salemi M, Desmyter J. The simian origins of the pathogenic human T-cell lymphotropic virus type I. Trends Microbiol. 1998 Dec; 6(12): 477–83.
6. Mahy M, Marsh K, Sabin K, et al. HIV estimates through 2018: data for decision making. AIDS. 2019 Jul 22.
7. Yamano Y, Sato T. Clinical pathophysiology of human T-lymphotropic virus-type 1-associated myelopathy/tropical spastic paraparesis. Front Microbiol. 2012; 3: 389.
8. Futsch N, Mahieux R, Dutartre H. HTLV-1, the Other Pathogenic Yet Neglected Human Retrovirus: From Transmission to Therapeutic Treatment. Viruses. 2017; 21: 10(1).
9. Hino S. Establishment of the milk-borne transmission as a key factor for the peculiar endemicity of human T-lymphotropic virus type 1 (HTLV-1): the ATL Prevention Program Nagasaki. Proc Jpn Acad. Ser B Phys Biol Sci. 2011; 87(4): 152–66.
10. Potty RS, Sinha A, Sethumadhavan R, et al. Incidence, prevalence and associated factors of mother-to-child transmission of HIV, among children exposed to maternal HIV, in Belgaum district, Karnataka, India. BMC Public Health. 2019 Apr 6; 19(1): 386.
11. Liu JF, Liu G, Li ZG. Factors responsible for mother to child transmission (MTCT) of HIV-1 - a review. Eur Rev Med Pharmacol Sci. 2017 Oct; 21(4 Suppl): 74–8.
12. Kaplan JE, Khabbaz RF, Murphy EL, et al. Male-to-female transmission of human T-cell lymphotropic virus types I and II: association with viral load. The Retrovirus Epidemiology Donor Study Group. J Acquir Immune Defic Syndr Hum Retrovirol. 1996 Jun 1; 12(2): 193–201.
13. Gonçalves de Melo M, Sprinz E, Gorbach PM, et al. HIV-1 heterosexual transmission and association with STIs in the era of treatment as prevention. Int J Infect Dis. 2019 Aug 9.
14. Okochi K, Sato H. Transmission of ATLV (HTLV-I) through blood transfusion. Int Symp Princess Takamatsu Cancer Res Fund. 1984; 15: 129–35.
15. Williams-Wietzikoski CA, Campbell MS, Payant R, et al. Comparisons of Human Immunodeficiency Virus Type 1 Envelope Variants in Blood and Genital Fluids near the Time of Male-to-Female Transmission. J Virol. 2019 Jul 1; 93(13).
16. Rizkallah G, Mahieux R, Dutartre H. [Intercellular transmission of HTLV-1: not all mechanisms have been revealed]. Med Sci (Paris). 2015 Jul; 31(6-7): 629–37.
17. Kandathil AJ, Sugawara S, Balagopal A. Are T cells the only HIV-1 reservoir? Retrovirology. 2016 Dec 20; 13(1): 86.
18. Carvalho Barros LR, Linhares-Lacerda L, Moreira-Ramos K, et al. HTLV-1-infected thymic epithelial cells convey the virus to CD4+ T lymphocytes. Immunobiology. 2017; 222(12): 1053–63.
19. Rizkallah G, Alais S, Futsch N, et al. Dendritic cell maturation, but not type I interferon exposure, restricts infection by HTLV-1, and viral transmission to T-cells. PLoS Pathog. 2017 Apr; 13(4): e1006353.
20. Bracq L, Xie M, Benichou S, et al. Mechanisms for Cell-to-Cell Transmission of HIV-1. Front Immunol. 2018; 9: 260.
21. Igakura T, Stinchcombe JC, Goon PKC, et al. Spread of HTLV-I between lymphocytes by virus-induced polarization of the cytoskeleton. Science. 2003 Mar 14; 299(5613): 1713–6.
22. Pais-Correia AM, Sachse M, Guadagnini S, et al. Biofilm-like extracellular viral assemblies mediate HTLV-1 cell-to-cell transmission at virological synapses. Nat Med. 2010 Jan; 16(1): 83–9.
23. Rudnicka D, Feldmann J, Porrot F, et al. Simultaneous cell-to-cell transmission of human immunodeficiency virus to multiple targets through polysynapses. J Virol. 2009 Jun; 83(12): 6234–46.
24. Ivanchenko S, Godinez WJ, Lampe M, et al. Dynamics of HIV-1 assembly and release. PLoS Pathog. 2009 Nov; 5(11): e1000652.
25. Hübner W, McNerney GP, Chen P, et al. Quantitative 3D video microscopy of HIV transfer across T cell virological synapses. Science. 2009 Mar 27; 323(5922): 1743–7.
26. Omsland M, Pise-Masison C, Fujikawa D, et al. Inhibition of Tunneling Nanotube (TNT) Formation and Human T-cell Leukemia Virus Type 1 (HTLV-1) Transmission by Cytarabine. Sci Rep. 2018 Jul 24; 8(1): 11118.

27. Van Prooyen N, Gold H, Andresen V, et al. Human T-cell leukemia virus type 1 p8 protein increases cellular conduits and virus transmission. Proc Natl Acad Sci USA. 2010 Nov 30; 107(48): 20738–43.

28. Sowinski S, Jolly C, Berninghausen O, et al. Membrane nanotubes physically connect T cells over long distances presenting a novel route for HIV-1 transmission. Nat Cell Biol. 2008 Feb; 10(2): 211–9.

29. Hashimoto M, Bhuyan F, Hiyoshi M, et al. Potential Role of the Formation of Tunneling Nanotubes in HIV-1 Spread in Macrophages. J Immunol. 2016 Feb 15; 196(4): 1832–41.

30. Robert-Guroff M, Blayney DW, Safai B, et al. HTLV-I-specific antibody in AIDS patients and others at risk. Lancet. 1984 Jul 21; 2(8395): 128–31.

31. Silva MTT, Neves ES, Grinsztejn B, et al. Neurological manifestations of coinfection with HIV and human T-lymphotropic virus type 1. AIDS. 2012 Feb 20; 26(4): 521–3.

32. Spear GT, Jiang HX, Sullivan BL, et al. Direct binding of complement component C1q to human immunodeficiency virus (HIV) and human T lymphotrophic virus-I (HTLV-I) coinfected cells. AIDS Res Hum Retroviruses. 1991 Jul; 7(7): 579–85.

33. Giam CZ, Semmes OJ. HTLV-1 Infection and Adult T-Cell Leukemia/Lymphoma-A Tale of Two Proteins: Tax and HBZ. Viruses. 2016; 16: 8(6).

34. Geddes VEV, José DP, Leal FE, et al. HTLV-1 Tax activates HIV-1 transcription in latency models. Virology. 2017; 504: 45–51.

35. Barrios CS, Castillo L, Giam CZ, et al. Inhibition of HIV type 1 replication by human T lymphotropic virus types 1 and 2 Tax proteins in vitro. AIDS Res Hum Retroviruses. 2013 Jul; 29(7): 1061–7.

36. Pedroso C, Netto EM, Weyll N, et al. Coinfection by HIV-1 and human lymphotropic virus type 1 in Brazilian children is strongly associated with a shorter survival time. J Acquir Immune Defic Syndr. 2011 Aug; 57 Suppl 3: S208–211.

37. Regis C, Oliveira A, Brites C. Onset of opportunistic infections in patients co-infected by HTLV-1 and HIV-1, with high CD4+ cells count. Braz J Infect Dis. 2009 Aug; 13(4): 311–3.

38. Shibata D, Brynes RK, Rabinowitz A, et al. Human T-cell lymphotropic virus type I (HTLV-I)-associated adult T-cell leukemia-lymphoma in a patient infected with human immunodeficiency virus type 1 (HIV-1). Ann Intern Med. 1989 Dec 1; 111(11): 871–5.

39. Casseb J, De Oliveira ACP, Vergara MPP, et al. Presence of tropical spastic paraparesis/human T-cell lymphotropic virus type 1-associated myelopathy (TSP/HAM)-like among HIV-1-infected patients. J Med Virol. 2008 Mar; 80(3): 392–8.

40. Oo Z, Barrios CS, Castillo L, et al. High levels of CC-chemokine expression and downregulated levels of CCR5 during HIV-1/HTLV-1 and HIV-1/HTLV-2 coinfections. J Med Virol. 2015 May; 87(5): 790–7.

41. Katsuya H, Ishitsuka K, Utsunomiya A, et al. Treatment and survival among 1594 patients with ATL. Blood. 2015 Dec 10; 126(24): 2570–7.

42. Uozumi K. Treatment of adult T-cell leukemia. J Clin Exp Hematop. 2010; 50(1): 9–25.

43. Tsukasaki K, Hermine O, Bazarbachi A, et al. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: a proposal from an international consensus meeting. J Clin Oncol. 2009 Jan 20; 27(3): 453–9.

44. Ishida T, Hishizawa M, Kato K, et al. Allogeneic hematopoietic stem cell transplantation for adult T-cell leukemia-lymphoma with special emphasis on preconditioning regimen: a nationwide retrospective study. Blood. 2012 Aug 23; 120(8): 1734–41.

45. Bazarbachi A, Hermine O. Treatment with a combination of zidovudine and alpha-interferon in naive and pretreated adult T-cell leukemia/lymphoma patients. J Acquir Immune Defic Syndr Hum Retrovirol. 1996; 13 Suppl 1: S186–190.

46. Tobinai K, Kobayashi Y, Shimoyama M. Interferon alfa and zidovudine in adult T-cell leukemia-lymphoma. Lymphoma Study Group of the Japan Clinical Oncology Group. N Engl J Med. 1995 Nov 9; 333(19): 1285; author reply 1286.

47. Matutes E, Taylor GP, Cavenagh J, et al. Interferon alpha and zidovudine therapy in adult T-cell leukaemia lymphoma: response and outcome in 15 patients. Br J Haematol. 2001 Jun; 113(3): 779–84.

48. Hermine O, Allard I, Lévy V, et al. A prospective phase II clinical trial with the use of zidovudine and interferon-alpha in the acute and lymphoma forms of adult T-cell leukemia/lymphoma. Hematol J. 2002; 3(6): 276–82.

49. Bazarbachi A, Suarez F, Fields P, et al. How I treat adult T-cell leukemia/lymphoma. Blood. 2011 Aug 18; 118(7): 1736–45.

50. O'Mahony D, Morris JC, Stetler-Stevenson M, et al. EBV-related lymphoproliferative disease complicating therapy with the anti-CD2 monoclonal antibody, siplizumab, in patients with T-cell malignancies. Clin Cancer Res. 2009 Apr 1; 15(7): 2514–22.

51. Ceesay MM, Matutes E, Taylor GP, et al. Phase II study on combination therapy with CHOP-Zenapax for HTLV-I associated adult T-cell leukaemia/lymphoma (ATLL). Leuk Res. 2012 Jul; 36(7): 857–61.

52. Ishida T, Joh T, Uike N, et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. J Clin Oncol. 2012 Mar 10; 30(8): 837–42.

53. Yoshie O, Fujisawa R, Nakayama T, et al. Frequent expression of CCR4 in adult T-cell leukemia and human T-cell leukemia virus type 1-transformed T cells. Blood. 2002 Mar 1; 99(5): 1505–11.

54. Ishida T, Jo T, Takemoto S, et al. Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive adult T-cell leukaemia-lymphoma: a randomized phase II study. Br J Haematol. 2015 Jun; 169(5): 672–82.

55. Ishitsuka K, Utsunomiya A, Katsuya H, et al. A phase II study of bortezomib in patients with relapsed or refractory aggressive adult T-cell leukemia/lymphoma. Cancer Sci. 2015 Sep; 106(9): 1219–23.

56. Nakano D, Ishitsuka K, Ikeda M, et al. Screening of promising chemotherapeutic candidates from plants against human adult T-cell leukemia/lymphoma (IV): phenanthroindolizidine alkaloids from Tylophora tanakae leaves. J Nat Med. 2015 Jul; 69(3): 397–401.

57. Ishitsuka K, Kunami N, Katsuya H, et al. Targeting Bcl-2 family proteins in adult T-cell leukemia/lymphoma: in vitro and in vivo effects of the novel Bcl-2 family inhibitor ABT-737. Cancer Lett. 2012 Apr 28; 317(2): 218–25.

58. Narita T, Ishida T, Ito A, et al. Cyclin-dependent kinase 9 is a novel specific molecular target in adult T-cell leukemia/lymphoma. Blood. 2017 31; 130(9): 1114–24.

59. Dassouki Z, Sahin U, El Hajj H, et al. ATL response to arsenic/interferon therapy is triggered by SUMO/PML/RNF4-dependent Tax degradation. Blood. 2015 Jan 15; 125(3): 474–82.

60. Hermine O, Dombret H, Poupon J, et al. Phase II trial of arsenic trioxide and alpha interferon in patients with relapsed/refractory adult T-cell leukemia/lymphoma. Hematol J. 2004; 5(2): 130–4.

61. Kchour G, Tarhini M, Kooshyar MM, et al. Phase 2 study of the efficacy and safety of the combination of arsenic trioxide, interferon alpha, and zidovudine in newly diagnosed chronic adult T-cell leukemia/lymphoma (ATL). Blood. 2009 Jun 25; 113(26): 6528–32.

62. Boostani R, Vakili R, Hosseiny SS, et al. Triple Therapy with Prednisolone, Pegylated Interferon and Sodium Valproate Improves Clinical Outcome and Reduces Human T-Cell Leukemia Virus Type 1 (HTLV-1) Proviral Load, Tax and HBZ mRNA Expression in Patients with HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis. Neurotherapeutics. 2015 Oct; 12(4): 887–95.

63. Shimosaki S, Nakahata S, Ichikawa T, et al. Development of a complete

human IgG monoclonal antibody to transferrin receptor 1 targeted for adult T-cell leukemia/lymphoma. Biochem Biophys Res Commun. 2017 25; 485(1): 144–51.

64. El Hajj H, Khalil B, Ghandour B, et al. Preclinical efficacy of the synthetic retinoid ST1926 for treating adult T-cell leukemia/lymphoma. Blood. 2014 Sep 25; 124(13): 2072–80.

65. Tanaka A, Takeda S, Kariya R, et al. A novel therapeutic molecule against HTLV-1 infection targeting provirus. Leukemia. 2013 Aug; 27(8): 1621–7.

66. Wang TT, Yang J, Zhang Y, et al. IL-2 and IL-15 blockade by BNZ-1, an inhibitor of selective γ-chain cytokines, decreases leukemic T-cell viability. Leukemia. 2019; 33(5): 1243–55.

67. Wang TT, Yang J, Zhang Y, et al. Blockade of IL-2 and IL-15 Gamma Chain Receptor Signaling Decreases Leukemic Cell Viability in T-Cell Large Granular Lymphocyte Leukemia and Adult T-Cell Leukemia. Blood. 2017 Dec 7; 130(Suppl 1): 3585.

68. Osame M, Usuku K, Izumo S, et al. HTLV-I associated myelopathy, a new clinical entity. Lancet. 1986 May 3; 1(8488): 1031–2.

69. Lezin A, Gillet N, Olindo S, et al. Histone deacetylase mediated transcriptional activation reduces proviral loads in HTLV-1 associated myelopathy/tropical spastic paraparesis patients. Blood. 2007 Nov 15; 110(10): 3722–8.

70. Olindo S, Belrose G, Gillet N, et al. Safety of long-term treatment of HAM/TSP patients with valproic acid. Blood. 2011 Dec 8; 118(24): 6306–9.

71. Feng Q, Zhou A, Zou H, et al. Quadruple versus triple combination antiretroviral therapies for treatment naive people with HIV: systematic review and meta-analysis of randomised controlled trials. BMJ. 2019 Jul 8; 366: l4179.

72. Ticona E, Huaman MA, Yanque O, et al. HIV and HTLV-1 coinfection: the need to initiate antiretroviral therapy. J Int Assoc Provid AIDS Care. 2013 Dec; 12(6): 373–4.

73. Costin JM. Cytopathic mechanisms of HIV-1. Virol J. 2007 Oct 18; 4: 100.

74. Beilke MA, Japa S, Moeller-Hadi C, et al. Tropical spastic paraparesis/human T leukemia virus type 1-associated myelopathy in HIV type 1-coinfected patients. Clin Infect Dis. 2005 Sep 15; 41(6): e57–63.

75. Pomier C, Rabaaoui S, Pouliquen JF, et al. Antiretroviral therapy promotes an inflammatory-like pattern of human T-cell lymphotropic virus type 1 (HTLV-1) replication in human immunodeficiency virus type 1/HTLV-1 co-infected individuals. J Gen Virol. 2013 Apr; 94(Pt 4): 753–7.