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

Gerges Rizkallah¹, Renaud Mahieux², Hélène Dutartre²

¹Faculty of Public Health, Sagesse University, Beirut, Lebanon
²Équipe oncogénèse 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

Introduction

Two retroviruses emerged in the 1980s: HTLV-1 and HIV-1. 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 as well as in Australian indigenous. 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. 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). 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. 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”. 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, during delivery for HIV, a horizontal transmission preferentially from male-to-female during non-protected sexual intercourse and contamination with cell containing blood products for HTLV-1 and cell-free material for HIV.

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, 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\(^{38}\). 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>
<thead>
<tr>
<th>Table 1: Mechanisms of HTLV-1/ HIV-1 co-infections and their effects on disease progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanisms of HTLV-1 / HIV-1 co-infections of CD4+ T-cell</strong></td>
</tr>
<tr>
<td>Mechanisms of co-infections HTLV-1 Tax oncogene expression enhances HIV-1 replication</td>
</tr>
<tr>
<td>Tax protein is encoded by HTLV-1(^{35}). 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}).</td>
</tr>
<tr>
<td>Mechanisms of co-infections HTLV-1 Tax oncogene expression inhibits HIV-1 replication</td>
</tr>
<tr>
<td>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(^{39}).</td>
</tr>
<tr>
<td><strong>Effects of HTLV-1 / HIV-1 co-infection on disease progression</strong></td>
</tr>
<tr>
<td>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}).</td>
</tr>
<tr>
<td>Compared to HTLV-1 mono-infected individuals, HIV-1/HTLV-1 co-infection has a negative impact on the development of ATL(^{38}) or of TSP/HAM(^{39}). These results could be due to the higher production of IL-2 and IFN-γ 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 myelopathy and neurological disorders in co-infected individuals.</td>
</tr>
</tbody>
</table>
combining valproate and azidothymidine led to dramatic proviral load decrease in asymptomatic carriers55.

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 production56.

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 HIV71. 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 count72. 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>
<thead>
<tr>
<th>Protocol of treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 ATLL41, 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 (vindeze, etoposide, carboplatin and prednisone). They were used for treating aggressive forms of ATLL42.</td>
<td>CHOP and CHOP-like treatments resulted in relatively poor outcomes41.</td>
</tr>
<tr>
<td>Allogeneic hematopoietic stem cell transplantation following chemotherapy for patients with acute or lymphoma ATLL44.</td>
<td>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.</td>
</tr>
<tr>
<td>Antiviral therapies consisting of a combination of zidovudine (ZDV) and IFN-α was investigated in acute, smoldering and ATLL45,46.</td>
<td>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 ATLL46: 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 regimen46. Furthermore, the complete remission rate with AZT/IFN in previously untreated ATLL 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 remission47. 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 patients48. These studies confirm the efficacy and safety of AZT/IFN in patients with ATLL42. Nowadays, ATLL lymphoma patients still benefit from chemotherapy induction with concurrent or sequential antiretroviral therapy with zidovudine/IFN49.</td>
</tr>
<tr>
<td>Immunotherapies based on monoclonal antibodies targeting specific markers of ATLL cells: CD25, CD25+ or CCR4 chemokine receptor were tested in acute and lymphoma subtypes ATLL52.</td>
<td>Anti-CD25 and anti-CD25 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 cells53. 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, respectively53. These encouraging results fostered the use of mogamulizumab in combination with LSG15-based chemotherapy to treat aggressive ATLL patients54.</td>
</tr>
</tbody>
</table>

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:
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, 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. 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. ART composed of zidovudine, lamivudine and abacavir (or

### Table 3: Future directions for the treatment of ATLL

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapeutic molecules such as bortezomib</td>
<td>This study was terminated because bortezomib did not appear to be very promising for the studied cohort of patients.</td>
</tr>
<tr>
<td>Plant-derived steroids, alkaloids or carotenoids</td>
<td>Six phenanthroindolizidine alkaloids were extracted from aerial parts of Tylophora tanakae and their antiproliferative activity examined against chronically-infected HTLV-1 cells. The EC50 value of some of the alkaloids was in the low nanomolar range, comparable to that of the clinically used antineoplastic drug doxorubicin.</td>
</tr>
<tr>
<td>Pro-apoptotic molecules such as Bcl-2 (B-cell Lymphoma 2) inhibitors</td>
<td>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.</td>
</tr>
<tr>
<td>CDK9 (Cyclin-dependent Kinase 9) inhibitor</td>
<td>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.</td>
</tr>
<tr>
<td>Arsenic in combination with ZDV and IFN-α</td>
<td>The arsenic/interferon combination clears ATLL through degradation of its Tax driver, and this regimen could have broader therapeutic value. 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. 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.</td>
</tr>
<tr>
<td>Histone deacetylase, such as valproate</td>
<td>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.</td>
</tr>
<tr>
<td>Inhibitors of iron uptake such as antibodies directed against the transferrin Receptor</td>
<td>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.</td>
</tr>
<tr>
<td>p53 expression activator such as synthetic retinoid</td>
<td>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.</td>
</tr>
<tr>
<td>An HTLV-1-targeted gene editing zinc-finger nuclease (ZFN)</td>
<td>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.</td>
</tr>
<tr>
<td>BNZ-1, a pegylated peptide designed to specifically bind the yc 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</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

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 École Normale Supérieure de Lyon. The authors acknowledge the financial support from La Fondation pour la Recherche Médicale (équipe Labellisée).

References


