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

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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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{21}. The viral biofilm refers to HTLV-1 viral particles retained at the infected T-cell surface by extracellular-matrix proteins\textsuperscript{22}. Presence of a viral biofilm has not been shown yet for HIV-1, although the virus accumulates near the surface of infected cells\textsuperscript{23} in structures that were proposed as budding platforms, and that polarized toward the cell-cell contact\textsuperscript{24}, thus allowing viral transfer at the viral synapse\textsuperscript{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\textsuperscript{26} and favors HTLV-1 transmission\textsuperscript{27}. HIV-1 uses also these long membrane extensions that connect distant cells in order to spread\textsuperscript{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\textsuperscript{30}. Nowadays, HTLV-1 and HIV-1 co-infection is mainly investigated in South America and Africa\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{39,40}. 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\textsuperscript{41}. Another approach

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**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 | Mechanisms of HTLV-1 Tax oncoprotein expression enhances HIV-1 replication |
|-----------------|-----------------------------|-----------------------------------------------------------------------|
|                 | Tax protein is encoded by HTLV-1\textsuperscript{35}. It promotes the activation of \textsuperscript{R}-TEFb, releasing CDK9 and Cyclin T1 from inactive forms in latently infected CD4+ T-cells, promoting transcription elongation and reactivation of latent HIV-1\textsuperscript{14}. |

| Mechanisms of co-infections | Mechanisms of 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\textsuperscript{35}. |

| Effects of HTLV-1 / HIV-1 co-infection on disease progression | HIV-1/HTLV-1 co-infection promotes worsening of symptoms\textsuperscript{46}. 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\textsuperscript{47}. |

| Compared to HTLV-1 mono-infected individuals, 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\textsuperscript{48}. This cytokine profile may thus favor a faster onset of myelopathies and neurological disorders in co-infected individuals. |

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combining valproate and azidothymidine led to dramatic proviral load decrease in asymptomatic carriers\textsuperscript{55}.

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

| 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\textsuperscript{41}. | • CHOP and CHOP-like treatments resulted in relatively poor outcomes\textsuperscript{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\textsuperscript{42}. | • 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%)\textsuperscript{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\textsuperscript{43,44}. |
| **Allogeneic hematopoietic stem cell transplantation following chemotherapy for patients with acute or lymphoma ATLL\textsuperscript{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)\textsuperscript{44}. |
| **Antiviral therapies consisting of a combination of zidovudine (ZDV) and IFN-α was investigated in acute, smoldering and ATLL\textsuperscript{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\textsuperscript{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)\textsuperscript{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\textsuperscript{46}. 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 remission\textsuperscript{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\textsuperscript{48}. These studies confirm the efficacy and safety of AZT/IFN in patients with ATLL\textsuperscript{49}. Nowadays, ATLL lymphoma patients still benefit from chemotherapy induction with concurrent or sequential antiretroviral therapy with zidovudine/IFN\textsuperscript{49}. |
| **Immunotherapies based on monoclonal antibodies targeting specific markers of ATLL cells:** CD25\textsuperscript{50}, CD25\textsuperscript{51} or CCR4 chemokine receptor were tested in acute and lymphoma subtypes ATLL\textsuperscript{52}. | Anti-CD25\textsuperscript{52} and anti-CD25\textsuperscript{53} 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\textsuperscript{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\textsuperscript{53}. These encouraging results fostered the use of mogamulizumab in combination with LSG15-based chemotherapy to treat aggressive ATLL patients\textsuperscript{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:
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 \(^{27}\), 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 \(^{65}\). 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 \(^{25,27}\). 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.

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.

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