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Molecular and Cellular Interactions of HIV-1/HTLV Coinfection and Impact on AIDS Progression

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Abstract

In the last 10 years HIV-1/human T-cell leukemia virus (HIV-1/HTLV) coinfection has emerged as a worldwide health problem. The numbers of HIV-1/HTLV-1 coinfections in South America and Africa are increasing, as well as HIV-1/HTLV-2 coinfections in the USA and Europe. Coinfections by either HTLV-1 or HTLV-2 and HIV-1 frequently occur in persons with a history of injection drug use. Since HTLV-1 preferentially infects CD4+ T-cells and HTLV-2 has a tropism for CD8+ T-cells, the influence of coinfection on HIV-1 disease progression may be different.

The effect of HIV-1/HTLV-1 coinfection on HIV-1 pathogenesis is controversial as soluble factors produced by HTLV-1 infected cells can either enhance or suppress HIV-1 infection. In HTLV-1/HIV-1 coinfected patients, upregulation of HIV-1 expression was attributed to strong activation of cytokines that promoted HIV infection. The introduction of HAART has dramatically reduced HIV-1 morbidity and mortality, but has given rise to an increased number of inflammatory syndromes. While HAART is successful for controlling HIV disease, it has little impact on HTLV-1/2 genome expression. The consequence of coinfection, even with HAART, may well be the reported increase in neurologic disease.

Several epidemiologic and in vitro ***studies of the influence of HTLV infection on HIV-1 related AIDS progression suggest that HTLV-1 infection can promote HIV-1 replication and accelerate the clinical progression to AIDS. However, other studies have not confirmed these observations. The differences in study outcomes could be related to the occurrence of different HIV-1 phenotypes in clinical disease. In contrast, evidence points to a confirmed protective role of HTLV-2 that is manifested as improved survival and delayed progression to AIDS. The protective effect may be the result of maintaining normal-range levels of CD4 and CD8 counts, lowering HIV replication, and immune activation. As a corollary, the number of long-term nonprogressors for AIDS in the HIV-1/HTLV-2 coinfected group was found to be significantly higher than in HIV-1 monoinfected cases. Investigations of the natural factors induced by HTLV-2 that influence HIV-1 replication show that CCL3L1 (an isoform of CCL3) is preferentially induced in HTLV-2 exposed seronegative HIV individuals and in long-term nonprogressor HTLV-2/HIV-1 coinfected persons. The CCL3L1 inhibits HIV replication and thus acts as a potent effector against both HIV infection and disease progression. As a complement to upregulation of CCL3L1, other chemokines and cytokines induced by HTLV-2 may contribute to induction of the Th1 response against invading pathogens, in contrast to the dominant Th2 response that appears to favor HIV infection.***

The number of individuals with either single HIV-1 or HTLV-2 infection, in a cohort of Italian intravenous drug users monitored for 20 years, decreased significantly over time. However, the magnitude of HTLV-2 decrease was significantly less than that of HIV-1, pointing to the need for increased attention to, and control of, HTLV infection.

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In conclusion, the long-term effects of HIV and HTLV coinfections are poorly understood and the mechanisms of dysregulation of cellular biosynthesis by HTLV that impact HIV disease progression remain elusive. **(AIDS Rev. 2007;9:140-9)**

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Key words

HIV-1. HTLV. HIV-1/HTLV coinfection. Proviral load. Chemokines. AIDS progression.

Introduction

The problem of HIV-1/human T-cell leukemia virus (HIV-1/HTLV) coinfection has emerged as a worldwide health problem in the last 20 years as increasing numbers of HIV-1/HTLV-1 infected individuals in South America and Africa and of HIV-1/HTLV-2 in the USA and Europe have been reported. The coinfection state raises a number of questions that should be carefully considered. Since HTLV-1 preferentially infects CD4+ T-cells and HTLV-2 has a preferential tropism for CD8+ T-cells, their influence on HIV-1 appears to differ substantially. Another issue is whether coinfected patients are more likely to develop further complications, and evidence of an increased incidence of neurologic disorders and liver disease in HIV-1/HTLV-2 has been reported. The introduction of HAART has dramatically reduced HIV-1 morbidity and mortality but, giving rise to inflammatory syndromes, could result in increasing neurologic diseases in coinfected patients. The problem of HIV-1/HTLV-2 coinfection in relation to AIDS progression has recently been the object of several investigations, and evidence was obtained that HTLV-2 may exert a protective role by maintaining CD4 and CD8 counts, lowering HIV replication and immune activation and thus resulting in improved survival and delayed progression to AIDS. In particular, cytokine and chemokine network modulation by HTLV-2 has been proposed as strategic weapon against HIV infection.

In this review we have taken in consideration the different issues of the molecular features of HIV and HTLV and focused on the consequences of coinfection on clinical diseases and viral load. Particular attention has been given to the understanding of the protective role exerted by HTLV-2 on AIDS progression.

First isolates, classification, and molecular features of HTLV and HIV

In late 1970, as a result of increasing efforts to find human tumor viruses, the first human retroviruses were identified and isolated[1]. First to be characterized was HTLV type 1 (HTLV-1), which was isolated from a patient with cutaneous T-cell lymphoma[2]. The second human retrovirus was HTLV type 2 (HTLV-2) from a patient with a "hairy cell T-cell leukemia"[3]. The understanding of previously isolated HTLV strains facilitated isolation of the third human retrovirus, HIV[4], and its subsequent identification as the causative agent of AIDS[5].

Both HTLV and HIV belong to the Retroviridae family. However, HTLV isolates are delta-retroviruses, while HIV is a lentivirus. The HTLV-1 and HTLV-2, together with their simian counterparts, STLV-1 and STLV-2, are primate T-lymphotropic viruses, which diverged from bovine leukemia virus approximately 60,000 to 100,000 years ago[6]. Phylogenetic analysis of long terminal repeat and *env* sequences shows the existence of seven different HTLV-1 subtypes and four HTLV-2 subtypes[7-10]. Recently, HTLV type 3 (HTLV-3) was discovered in two subjects from south Cameroon[11]. A fourth HTLV type (HTLV-4) was discovered in the same geographic area[12].

The HIV-2 is distinct from HIV-1 and does not contribute to the AIDS pandemic in the same way as HIV-1. Epidemiologically, HIV-2 is largely confined to West Africa. Both HIV-1 and HIV-2 are classified as different groups, also known as clades (M, N and O for HIV-1 and A through H for HIV-2). Additionally there are numerous subtypes, sub-subtypes and circulating recombinant forms[13].

The HTLV-1 and -2 have 65-70% nucleotide similarity and share the same genomic organizational structure. Also, HTLV-1 and -2 subtypes are genetically stable as they have coexisted with humans for thousands of years. Their proviral genome is expanded primarily by clonal proliferation of HTLV-infected cells[14,15]. In contrast to HTLV, the inter- and intra-isolate sequence variation of HIV-1 is high[16].

It is estimated that HTLV-1 has infected 10-20 million individuals worldwide, with a prevalence rate that is greater than 1% in Central Africa, the Caribbean, and southern Japan[17]. In native populations from North and South America, both HTLV-1 and -2 infections are endemic[18]. The HTLV-2 has also been detected among pygmy tribes of Africa[19]. In Europe and the USA, HTLV infections predominantly exist in high-risk groups such as sex workers and intravenous drug users (IDU). Among IDU, the frequency of HTLV-2 is higher than HTLV-1 infection in both Europe and the USA[20], especially when

there is needle sharing. The seroprevalence of HTLV-2 infection in IDU, particularly in urban regions of the USA, is high[21] and subtype 2a is the predominant circulating variant[22]. Subtype HTLV-2a is predominant in northern Europe[23], while HTLV-2b is almost exclusively found in southern Europe, specifically Italy[24] and Spain[25]. In both Italy and Spain, IDU are frequently coinfected by HTLV-2 and HIV-1[26-28]. Coinfection with HIV-1 and HTLV has also been reported in different areas of Brazil[29,30].

Transmission of HTLV-1/2 and HIV-1 is by sexual contact, exchange of contaminated blood products, and from mother-to-child via breast feeding. Both HTLV-1 and -2 can infect several cell types *in vitro*, including T-cells, B-cells, endothelial cells, and monocytes[31,32]. Only T lymphocytes are transformed, as evidenced by interleukin-2 (IL-2)-independent growth *in vitro*[33,34], and studies using recombinant HTLV indicate that *env* is a major viral determinant for HTLV T-cell transformation tropism[35]. *In vivo*, HTLV-1 and -2 have different cellular tropisms. The HTLV-1 preferentially infects CD4+ T lymphocytes in asymptomatic leukemic or HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) patients[36]. However, CD8+ T-cells from HAM/TSP patients were also found to be infected by HTLV-1 and may be an additional *in vivo* viral reservoir[37]. *In vivo*, HTLV-2 shows a preferential tropism for CD8+ T-cells[38], even though some authors have detected HTLV-2 proviral sequences in both CD4+ and CD8+ T-cell subsets[32,39]. The ubiquitous glucose transporter 1 can function as a receptor for HTLV[40]. However, distinct cellular receptors for each type of HTLV have been proposed for binding and entry. For infection of CD8+ T-cells by HTLV-2, glucose transporter 1 appears to be preferred, while heparin sulphate proteoglycan, which is abundantly expressed on CD4+ T-cells, promotes fusion and entry of HTLV-1[41]. The CD4+ cells are the targets for HIV-1 infection via the primary CD4 cellular receptor, which is a member of the immunoglobulin superfamily. However, coreceptors are used by HIV-1 strains to infect specific cell types: for example, CXCR4 for T-cells and CCR5 for macrophages[42,43].

The spread of HTLV is by cell-to-cell contact, which is consistent with a low infectious virion release[15,44]. The infectivity ratio for HTLV is lower than that of HIV-1[45,46].

The HIV-1 and HTLV genomes have similar architecture, structurally consisting of long terminal repeats, *gag*, *pol, env,* and regulatory elements. In HTLV-1 the *pX* region includes the trans-regulatory *tax* and *rex* genes, and the accessory genes p12, p13, p30, and p21, which are involved in virus replication and proliferation of infected cells[47]. Of note, in HTLV-1 but not HTLV-2 genome, the HTLV-1b-ZIP gene is in the minus strand of the *pX* region[48]. Rex controls virion production by favoring posttranscriptional expression of the viral mRNA for structural and enzymatic proteins[49,50]. The HTLV-1 and -2 Tax proteins share more than 75% nucleotide similarity. Early in HTLV infection, viral RNA transcription is mediated by Tax. Both proteins have the ability to immortalize lymphocytes and transactivate host genes implicated in cell cycle progression and cell survival[51-53]. However, Tax-1 and Tax-2 are substantially different for inducing the pathologic process. Tax modulates the cell cycle by interacting with several cellular factors[54-57]. In contrast to the suppression of hematopoiesis by Tax-1[58], Tax-2 promotes survival of CD34+ hematopoietic progenitor *in vitro* and increases telomerase activity[59-61]. Recently it has been demonstrated that Tax-1 protein is centrally involved in the malignant transformation occurring in adult T-cell leukemia[62,63]. The HIV-1 genome also includes several genes *(vif, vpr, vpu, tat, rev, nef)*, the products of which are involved in regulation of synthesis, processing viral RNA, and other replicative functions.

The counterpart of Tax in HIV-1 is represented by Tat. Tat is a key viral regulatory protein that is necessary for viral gene expression, cell-to-cell virus transmission and disease progression[64]. Both Tax-2 and Tat interact with the major histocompatibility complex class II transcriptional activator (CIITA), resulting in inhibition of both HTLV-2 and HIV-1 infection[65,66]. *In vitro*, CIITA inhibits Tax-2 transactivation of HTLV-2 long terminal repeats through the binding to the transcription nuclear factor Y[67]. Similarly, CIITA inhibits HIV-1 replication by targeting the viral transactivator Tat[68]. As a consequence, permissive cells do not support either HTLV-2 or HIV-1 replication when CIITA is expressed.

The major differences between HIV and HTLV are related to the cytopathic effects, the time point of interspecies transmission to humans, and genetic variability[45].

Clinical disease, viral load, and rate of HIV/HTLV coinfection

The HTLV-1 is the causative agent of adult T-cell leukemia, a malignancy of CD4+ T lymphocytes[69], as well as a chronic neurologic disorder called HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)[70-72]. Both diseases are linked to immune response abnormalities mediated by the viral infection. The malignant process is initiated by HTLV-1 early in life and gives rise to adult T-cell leukemia in a small fraction of carriers (< 5%) after a latency period of 50-70 years. The pathologic process is the result of a multistep activation of many promoting factors[73]. Adult T-cell leukemia has different clinical outcomes, including indolent (smoldering or chronic) and aggressive (lymphoma or acute) forms of disease. The onset of HAM/TSP generally occurs after the third or fourth decades of life and the risk of development is similar to adult T-cell leukemia. Inflammatory disorders caused by HTLV-1 include ar-

thropathy, uveitis and infective dermatitis in children[74], and HTLV-1 has also been associated with an increased frequency of opportunistic infections[9].

Although HTLV-2 has an imprecise etiologic role in human disease, cases of subacute myelopathy resembling HAM/TSP have been reported[75-77]. Recently, HTLV-1 and -2 infections have been associated with a spectrum of neurologic abnormalities other than classical HAM/TSP[78]. In a prospective cohort study, HTLV-2 infection in blood donors was associated with increased mortality[79]. High levels of HTLV-1 proviral load are a recognized risk factor for developing adult T-cell leukemia and possibly HAM/TSP[80,81]. High Tax expression, rather than high proviral load, has been proposed as the cause of the association with HAM/TSP pathogenesis[82].

The difference in pathogenesis caused by HTLV-1 and HTLV-2 is supported by the differences in proviral load values, which are significantly higher in HTLV-1 than in HTLV-2 carriers[83]. Higher proviral load is found in persons infected with HTLV-2 subtype a than in persons infected with HTLV-2 subtype b[84]. In HTLV-2 patients with high proviral load, a clonal expansion of infected cells is observed[85]. The observations that i) there is an inverse correlation between age and proviral load in HTLV-2 carriers and ii) proviral load is lower in female HTLV-2 infected subjects[83,86] remain controversial. In recent reports, HTLV-1 and -2 proviral load values were found to be stable over time, suggesting that clonal expansion is counterbalanced by immunologic control of infection[87]. Both HTLV-1 and -2 infected subjects with bladder or kidney infection tended to present with increasing proviral loads[87]. Also, HTLV-1 and -2 are associated with long-term modification of blood cell counts, leading to an elevation of total lymphocyte counts in HTLV-2 subjects[88]. The HTLV-1 and -2 proviral load may be lower in sexually acquired infection[86].

The consequences of coinfection with HIV-1 and HTLV have been reviewed[89]. In a long-term observational study of HIV/HTLV-1 and HIV/HTLV-2 coinfections of more than 3500 patients in New Orleans (USA), coinfected patients were more likely to have neurologic complications, thrombocytopenia, respiratory and urinary tract infections, and hepatitis C[90]. In a retrospective case-control study conducted in Bahia (Brazil), coinfection with HTLV-1 is associated with a shorter survival time for HIV-1 infected patients[91]. Because a significant proportion of IDU are infected with HIV-1, most HTLV-2 positive cases reported in Europe show evidence of dual HIV-1/HTLV-2 infection. We have recently observed an increased incidence of liver disease and hepatitis C virus (HCV) positivity among HIV-1/HTLV-2 coinfected subjects, but without an increase in incidence of myelopathy, peripheral neuropathy, bronchitis and urinary tract infection[28]. However, the introduction of HAART has dramatically reduced both morbidity and mortality in HIV-1 infected persons. The type of disorders affecting this population has changed from opportunistic pathogens to a rising incidence of inflammatory syndromes[92] that could precipitate neurologic disease in HIV-1/HTLV coinfected patients. Both sporadic cases of neurologic disease and increased risk of developing peripheral neuropathy have been reported in IDU who are coinfected with HIV-1/HTLV-2[93,94]. In addition, an increase in HTLV-2 proviral load after beginning HAART has been observed[95,96]. Data from our laboratory confirm that antiretrovirals enhance HTLV-2 proviral load, suggesting an expansion of infected cells[28]. When HTLV proviral load is higher in patients with HIV/HTLV-1 coinfection than in patients with HIV/HTLV-2 coinfection, HAART is of limited value in controlling HTLV expression[97].

A single case of myelopathy resembling HAM/TSP in a patient coinfected by HIV-1 and HTLV-2 and belonging to an IDU cohort has been reported[98]. The disease developed after HAART initiation and other viral infections as causes could be ruled out. The investigators also observed that, of a total 677 HTLV-2 infections reported in Spain, four cases presented neuromuscular abnormalities possibly associated with HTLV-2 infection, but only one case presented with HAM/TSP-like disease.

Our laboratory has a long-standing history of investigation of HIV-1/HTLV coinfection and AIDS, using virologic, clinical, and immunologic parameters for studies of AIDS progression in HIV-1/HTLV-2 coinfected and HIV-1 monoinfected subjects[28]. Our most recent serologic data for HIV and HTLV are summarized in table 1. A cohort of 2427 HIV-1 positive IDU was identified in a total population of 4292 individuals. The average HIV-1/HTLV-2 coinfection rate was 6.8% (165/2427). Considerable variation in HTLV-2 positivity was observed among the different cohorts of Italian HIV-1 positive IDU, with the highest percentage found in large metropolitan areas and lower percentages in small centers. There were 20 HTLV-2 monoinfected cases in 1865 HIV-1 negative subjects (1.1%). It is noteworthy that HTLV-2 seropositivity was significantly higher in HIV-1 positive (6.8%) than in HIV-1 negative (1.1%) subjects. Only a single individual of Asian origin was positive for HTLV-1 and this subject was HIV-1 negative.

The relationship between coinfection and AIDS progression was monitored in two study groups of IDU patients for an average of 15 years[28]. The study groups were HIV-1 monoinfected and HIV-1/HTLV-2 coinfected subjects. The individuals in the group coinfected with HTLV-2 were significantly older, and both CD4+ and CD8+ cell counts were significantly higher than in the HIV-1 monoinfected IDU group of individuals. Neither HIV viral loads nor average duration of HIV infection were significantly different between the two groups. Within the coinfected group we identified a subgroup of patients with the typical features that define the long-term

Table 1. Serologic screening for HIV-1 and HTLV-2* infection in Italian intravenous drug users

Serostatus	Tested	HTLV-2 (+)†	
		Number	%
HIV-1 (+)‡	2427	165	6.8
HIV-1 (–)§	1865	20	1.1
Total	4292	185	4.3

*Sera were screened according to HERN algorithm.
†HTLV infection confirmed by PCR/SB and allowed differentiation between types 1 and 2.
‡HIV-1 (+) = HIV-1 seropositive.
§HIV-1 (–) = HIV-1 seronegative.

nonprogressors for AIDS[99]. This long-term nonprogressor subgroup of patients with CD4 counts > 500 cells/µl and a stable HIV viremia between 1000-1500 copies/ml did not develop opportunistic infections and did not require treatment with antiretrovirals during a follow-up period of at least 12 years. The number of long-term nonprogressors in the coinfected group (13.5%) is significantly higher than in the HIV-1 monoinfected cases (1.1%) followed for the same period of time. It is noteworthy that the mean HTLV-2 proviral load in the group of coinfected individuals not undergoing treatment (primarily the long-term nonprogressor subgroup) was not significantly different from that of the HTLV-2 monoinfected cases. This observation suggests that HIV-1 infection has no influence on HTLV-2 proviral load. The variability in the quantitation of HTLV-2 proviral loads in subjects infected by HTLV-2 alone was high, with about 40% of the cases having less than 1000 copies per 10^6 cells[28]. Recently it has been confirmed that HTLV-2 coinfection may exert a protective role on HIV disease progression by lowering HIV replication and immune activation[100].

Our Italian IDU cohort of 2500 patients has also been monitored for 20 years for infection by HIV-1 and HTLV-2. We have observed that HTLV-2 infection is not decreasing as rapidly as HIV-1. The data (unpublished) are shown in figure 1. The rate of HIV-1 infection among IDU, which was about 40% in 1988, has decreased to 8% in 2005. The rate of HTLV-2 infection of the population of this cohort was about 4% in 1988 and has also decreased to 2% in 2005. However, the magnitude of HTLV-2 decrease was less than that of HIV-1, so that the 1:10 proportion of HTLV-2 to HIV-1 in 1988 is now 1:4, showing that HTLV-2 infection is decreasing less rapidly than that of HIV-1. An explanation for these results may relate to the fact that HTLV detection and control is given less attention in Italy than HIV-1, resulting in the observed slower decrease among IDU as compared to HIV-1.

Molecular and cellular interactions between HIV and HTLV

In addition to its role in HTLV-1 transcription, Tax has been shown to upregulate HIV expression via activation of nuclear factor kappa B (NFκB), the cellular transcription factor that recognizes two binding sites in the U3 region of the HIV-1 long terminal repeat[101]. The mechanism of upregulation is similar to that used by cytokines, such as tumor necrosis factor-α or interleukin-1β, which act on NFκB-dependent triggering of potentiation of HIV-1 transcription[102]. A similar pathway also exists for Rex/Rev proteins, which bind to viral RNA regions, named Rex-RRE, and allow the export of both partly spliced and unspliced viral transcripts to the cytoplasm where translation for both structural and regulatory proteins occurs[103]. Thus, both retroviral infection and/or the expression of retroviral proteins can modulate the expression and secretion of some cytokines and chemokines.

Infection by HTLV-2 results in activation and spontaneous proliferation of T-cells, as well as cellular events such as increased production of various cytokines and chemokines[59,60,100,104,105]. In contrast, HIV-1 infection induces a strong cytopathic effect on CD4+ T-cells that leads to the progressive loss of this subset in infected individuals. The enhanced HIV-1 replication observed in certain strains can gain an advantage as a result of cytokine- and chemokine-mediated immune reactions[106,107]. However, different viruses have specific cytokine and chemokine requirements for maintenance *in vivo*. What appears to be optimal for one strain may be detrimental for another[108].

Expression of chemokine receptors may be required for fusion and entry of HIV-1 into CD4+ cells. The CCR5, a cell surface receptor for the CC-chemokines CCL3, CCL4, and CCL5, acts as a coreceptor for non-syncytium-inducing, macrophage-tropic strains of HIV-1, which predominate in the initial transmission and early phases of the disease. In addition, CXCR4, which binds stromal cell-derived factor-1 or CXCL12, is the coreceptor for syncytium-inducing HIV-1 strains[109], which emerge with disease progression in approximately 50% of infected individuals[110]. The acquisition of CXCR4 usage as a coreceptor corresponds to the switch from non-syncytium-inducing to a syncytium-inducing phenotype and leads both to a loss of sensitivity to the suppressive effect of CC-chemokines and a steep decrease in $CD4^+$ T-cell counts[110,111].

Three CCR5 binding chemokines (CCL3, CCL4, and CCL5) act as major HIV-1 suppressive factors and are released by both cultured T-cells and primary CD8+ T-cells in response to HTLV infection[112], pointing to a possible role in HIV suppression. In addition, HTLV-1 specific CD8+ cytotoxic T lymphocyte clones derived

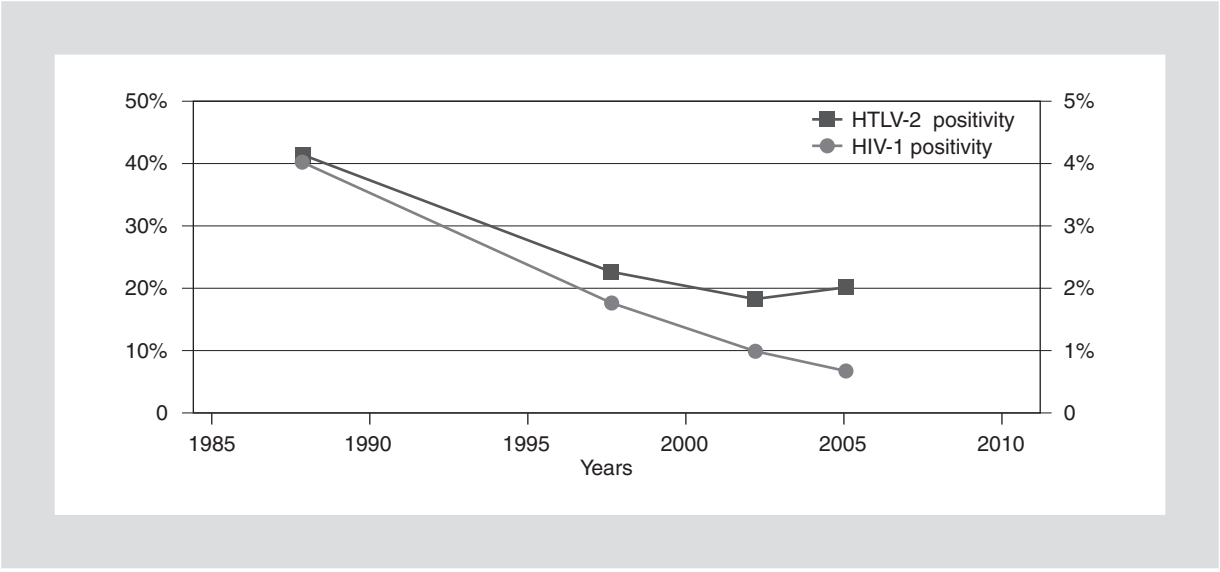

Figure 1. *Monitoring of an Italian intravenous drug user cohort of 2500 subjects for a period of 20 years. The percentage of infected HIV-1 subjects is represented by the light gray and that of HTLV-2 subjects by the dark gray. The monitoring was performed according to the usual serological screening for HIV-1 and to HERN algorithm for HTLV-2.*

from patients with HAM/TSP are actively producing CCL3 and CCL4 chemokines[113], suggesting that HTLV can influence HIV replication via chemokine expression and release. Thus, human retroviruses can interact not only at the molecular level, but also by producing extracellular cytokines or chemokines, to modulate their replicative and cytopathic functions.

Coinfection by HTLV-1 or HTLV-2 and HIV-1 occurs in a substantial number of persons with a history of injection drug use. However, experimental evidence suggests notable differences between consequences of HIV-1/HTLV-1 and HIV-1/HTLV-2 coinfection. *In vivo* and *in vitro* infections by both HTLV-1 and HIV-1 but not HTLV-2[114-116] result in the constitutive activation of Janus kinase (JAK)/signal transducer/activator of transcription (STAT) signaling pathway. The JAK/STAT pathway is needed for activity by some cytokines, including interferons (IFN)[117]. *In vitro* HTLV-1 infection of either PBMC or cord blood lymphocytes induces the transition from IL-2 dependent to IL-2 independent growth. The transition correlates with the constitutive activation of kinases JAK-1 and JAK-3 and of transcription factors STAT-3 and STAT-5[114]. Furthermore, the majority of leukemic cells from adult T-cell leukemia/lymphoma patients displayed constitutive activation of JAK-3 and DNA-binding activity of STAT-1, STAT-3 and STAT-5[118]. No constitutive activation of either the JAK or STAT proteins was detected in six HTLV-2 transformed T-cell lines[115]. Up to 80% of randomly selected HIV-1 infected individuals showed a constitutive activation of STAT-1 and of a truncated STAT-5 form in their PBMC[116]. The HTLV-2 monoinfected and, interestingly, HIV-1/HTLV-2 dually infected individuals belonging to the same cohort of IDU usually do not show a constitutive activation of their PBMC-associated STAT. Therefore either HTLV-2 proteins or HTLV-2 induced host factors may overcome the capacity of HIV to activate the JAK/STAT pathway[59].

The effect of HIV-1/HTLV-1 coinfection on HIV-1 pathogenesis is still controversial. Soluble factors produced by HTLV-1 infected cells are capable of either enhancing or suppressing HIV-1 infection. A pivotal role is played by CC chemokines CCL3, CCL4, and CCL5, which can both suppress M-tropic HIV-1 infection or enhance T- and dual-tropic HIV-1 infection[119]. These CC chemokines are the major suppressive factors for M-tropic HIV-1 as well as positive regulating factors for T-tropic HIV-1. This study suggests that in HIV-1 infected individuals, HTLV-1 may precipitate the transition from M- to the T-tropic phenotype that is associated with HIV disease progression[110]. In addition, HTLV-1 Tax protein upregulates HIV-1 expression[120], as well as expression of various cytokines and cytokine receptors involved in T-cell activation[121], thereby providing a favorable condition for HIV-1 infection. This mechanism of influence does not necessarily require coinfection of the same cell. Several epidemiologic studies have indicated that HTLV-1 infection exacerbates the cytopathic effects of HIV-1 and accelerates clinical progression to AIDS in coinfected individuals[122-127]. However, other studies have not confirmed these observations[90,97,128]. The differences could be related to the occurrence of different HIV-1 phenotypes in clinical disease.

The influence of HTLV-2 on HIV-1 infection is also debatable. Some authors claim an acceleration to AIDS

with coinfection[28,123], while others show a delay or no influence[129,130].

This issue of whether there is a protective role for HTLV-2 infection against AIDS progression has been studied extensively by our research group, with special attention paid to the role of HTLV-2 infection in AIDS progression. Coinfection with HTLV-2/HIV-1 is frequently found in long-term nonprogressors. Our recent work points to the maintenance of elevated CD4 counts in a significant proportion of coinfected individuals[28]. We have previously reported that upregulation of CCR5-binding chemokine expression occurs in *ex vivo* cultivated PBMC of HTLV-2/HIV-1 coinfected individuals as compared to individuals infected with only HIV-1[104]. More specifically, CCL3 secretion from PBMC was found to be responsible for anti-HIV-1 activity in cell cultures derived from dually infected subjects. Spontaneous production of CCR5-binding chemokines was confirmed by Lewis, et al.[105], who linked the spontaneous production to transactivation of *CCL4* and *CCL5* gene promoters by HTLV-2 regulatory proteins. Independent studies have demonstrated that an increased copy number of *CCL3L1* gene results in enhancing the secretion of the corresponding protein CCL3L1. The CCL3L1 is an isoform of CCL3 with potent inhibitory activity for R5 HIV-1 strains[131] that are replicating in activated leukocytes[132,133]. The inverse association between *CCL3L1* copy number and CCR5 expression on T-cell membranes suggested that either chemokine binding or CCR5 signaling in the presence of an elevated *CCL3L1* copy number is causing receptor internalization[132]. Recent data from our group shows that the cell activation state induced by HTLV-2 infection drives *CCL3L1* expression that results in CCR5 downregulation without interfering with gene copy number[134]. In addition, PBMC from HTLV-2 infected individuals upregulate granulocyte-macrophage colony-stimulating factor (GM-CSF) and IFNγ secretion[134], which can also inhibit CCR5 expression[135]. These findings lend further support to the hypothesis that a Tax-2 specific/preferential induction of CCL3L1 chemokine promoter is occurring in HIV-1/HTLV-2 coinfected individuals[105]. As a complement to this upregulation of CCL3L1, the pattern of chemokines and cytokines induced by HTLV-2 infection (i.e. GM-CSF and IFNγ) may indeed contribute to induce a "protective" Th1 response against invading pathogens[136] since a dominant Th2 response appears to be involved in the progression of HIV infection[137]. The relevance of CCR5-binding chemokines as correlates of protective innate immunity against R5 HIV-1 infection has been analyzed in the context of HTLV-2 infection or coinfection in experimental infection of macaques[138,139]. Two recent studies[90,97] suggest that higher levels of HTLV-1/2 viral burden correlate with a higher risk for HTLV disease development in HIV-1 coinfected subjects, since HAART therapy is not effective against HTLV-1 or HTLV-2 infection.

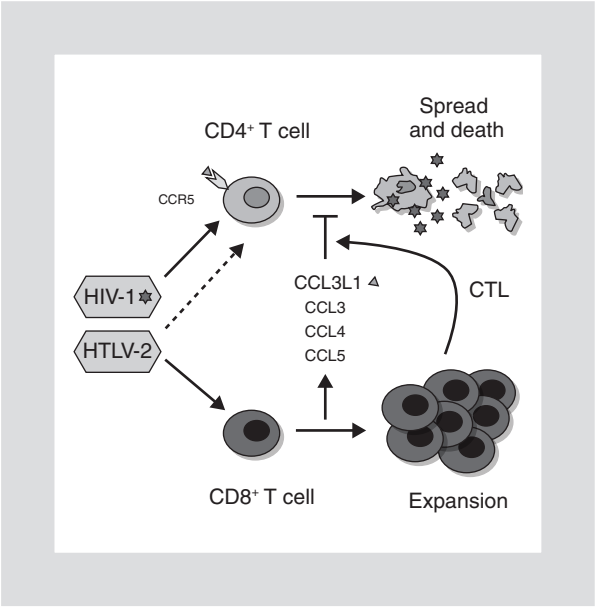

Figure 2. *Mechanism of HTLV-2 interference with HIV-1 infection process. The function and regulation of CC-chemokines by HTLV-2 expression and of cytotoxic T lymphocyte (CTL) clones are explained in the main text.*

We have previously observed that a significant correlation exists between CCL3 anti-HIV activity and HTLV proviral load in HIV-1/HTLV-2 coinfected subjects[104]. The mechanism by which HTLV-2 interferes with the HIV-1 infection process is illustrated schematically in figure 2. The HTLV-2 infection of CD8+ cells and their expansion induces the secretion of CC chemokines, which can reinforce the cytotoxic T lymphocyte response against CD4+ HIV-1 infected cells.

Other HIV-1 coinfections

A protective effect against HIV-1 disease progression by other viral coinfections has recently been described. Induction of HIV-inhibitory chemokines and reduction of CCR5 and/or CD4 expression, possibly leading to a protection against HIV-1 disease progression, has been reported after *in vitro* infection of PBMC with hepatitis GB virus C[140,141]. Other systems in which protection was observed with coinfections include human lymphoid tissue infected with HIV-1 and human herpesvirus 7 (HHV-7)[142]. *In vivo,* HIV-1 infected individuals who are also positive for HIV-2 tend to have less symptomatic HIV associated disease[143]. Similarly, HIV replication is suppressed during active measles virus infection in humans[144,145]. However, other viruses, such as cytomegalovirus[146] and herpes simplex virus (HSV)[147] have an accelerating effect on HIV disease progression. Human herpes 6 (HHV-6) can exert both a protective and accelerating effect, depending upon the

experimental conditions[148]. Recent clinical and experimental evidence show that HHV-6 variant A (HHSV-6A) may promote AIDS progression in macaques[149].

Hepatitis C virus (HCV) infection in HIV-1/HTLV coinfected IDU is widespread. Its influence on HIV-1, HTLV-1, or HTLV-2 disease progression should be carefully evaluated, particularly since HCV load is significantly higher in those coinfected with HTLV-2 and HCV[28].

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