HIV/Human T-cell Lymphotropic Virus Coinfection Revisited: Impact on AIDS Progression

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Abstract

Human T-cell lymphotropic viruses type 1 and 2 are retroviruses that share the same routes of transmission as HIV-1. Since these agents are prevalent simultaneously in different parts of the world, co-infection is a frequently reported event. However, prevalence rates of co-infection differ for distinct populations and regions of the world or for each virus, with human T-cell lymphotropic virus type 1 being more prevalent among HIV-1-infected individuals in the Southern hemisphere, while type 2 is more frequently found in the Northern hemisphere. In common, they share the tropism for T-lymphocytes, although human T-cell lymphotropic virus type 1 and HIV-1 are predominantly CD4+ T-cell tropic and human T-cell lymphotropic virus type 2 preferentially infects CD8+ cells.

The biological properties of HIV-1 are distinct of those found in human T-cell lymphotropic virus 1/2. This fact makes possible an in vivo interaction between these agents, when co-infecting the same patients, with potentially relevant clinical implications.

The available evidence suggests a protective role for coinfection by human T-cell lymphotropic virus type 2 on AIDS progression. This hypothesis is supported by several laboratory evidences, as well as by a number of clinical studies that found no significant interaction between human T-cell lymphotropic virus type 2 and HIV-1, or even detected a protective effect on HIV-1 disease.

On the other hand, human T-cell lymphotropic virus type 1 seems to be a significant cofactor, with a potentially important role in HIV-1 infection. Although the clinical evidence is still controversial with regard to the real impact that coinfection exerts on clinical evolution, the majority of studies suggest it is associated with a modification of the natural history of HIV-1 infection, with a faster clinical progression and a shorter survival time. The main limitation of the available data is due to methodological problems in the majority of studies, which weaken the validity of their conclusions. A common finding in co-infection by both human T-cell lymphotropic virus type 1 and 2 is the increase in CD4+ cell count, but without any additional immune benefit for patients.

Due to the limited available data, we need more, larger studies, designed to respond to the pending questions on the real significance of coinfection by these retroviruses. (AIDS Rev. 2009;11:8-16)

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Key words

HIV-1, HTLV-1, HTLV-2, Coinfection.
Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) is a human retrovirus that is conclusively associated with adult T-cell leukemia and with a slowly progressive neurologic disorder, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)\textsuperscript{1-7}. In addition, uveitis and a chronic, eczematous skin disease called infective dermatitis are also associated with HTLV-1 infection\textsuperscript{6-12}. Although several clinical manifestations are attributed to this infection, only a minority of HTLV-1-infected individuals develops symptoms of disease. Most infected individuals remain healthy\textsuperscript{13}.

In 1979, HTLV-1 was isolated for the first time from a patient with a T-cell malignancy\textsuperscript{1}. This discovery was the first formal proof that human retroviruses exist and suggested their etiological role in human cancer, a hypothesis that had been proposed decades before\textsuperscript{14}. The second human retrovirus described was HTLV-2, which was isolated by Kalyanaraman, et al. in 1980 from a 37-year-old Caucasian man\textsuperscript{15}.

It is estimated that 10-20 million people worldwide are infected with HTLV-1 or HTLV-2\textsuperscript{13}. The role of HTLV-2 as a causative agent of disease remains undefined, although some reports linked the infection with a higher risk of HAM/TSP, higher mortality, and other inflammatory or bacterial diseases\textsuperscript{16-19}.

Since the initial report on Pneumocystis pneumonia in young male homosexuals in 1981, the AIDS pandemic has spread around the world and has infected over 50 million persons worldwide, including 20 million who have already died\textsuperscript{20,21}. When the causal agent of AIDS was isolated by the same group that discovered HTLV-1 and HTLV-2, they thought it was a third member of the HTLV family\textsuperscript{14,21}. Further studies showed that HIV-1 was a distinct retrovirus from the genus lentivirinae\textsuperscript{22,23}.

The main focus of this review is the interaction of HIV-1 and HTLV-1/2 and its clinical consequences on the natural history of HIV-1 infection. We will emphasize the coinfection by HIV-1/HTLV-1, due to the greater evidence that suggest it is clinically relevant (Table 1).

Biological characteristics of HIV-1 and human T-cell lymphotropic virus type 1

Human T-cell lymphotropic virus type 1

The virus HTLV-1 is a type C virus belonging to the genus of deltaretroviruses, family of Retroviridae. It is a round-shaped, enveloped virus of approximately 100 nm in diameter. The virion envelop displays a proteolipid envelope bilayer of host cell membrane origin, which has viral transmembrane and surface proteins. The icosahedral capsid enables protection of the viral RNA and the viral enzymes (functional protease, reverse transcriptase, and integrase), while the inner envelope contains the matrix layer\textsuperscript{24}. The genome of HTLV-1 is a positive, single-stranded RNA. Glucose transporter 1 (GLUT-1) is the likely host-cell receptor for the virus, although the virus is able to infect cells without expression of GLUT-1, which suggests that other mechanisms are involved in the cell entry process\textsuperscript{25-28}. After entering a cell, this single-stranded RNA is converted to double-stranded DNA and inserted into the DNA of a human host cell, originating the provirus, a process mediated by the viral enzyme integrase. The HTLV-1 is tropic for CD4\textsuperscript{+} T-cells, although other lymphocytes can also be infected by the virus, while HTLV-2 is predominantly tropic for CD8\textsuperscript{+} T-cells\textsuperscript{29-32}.

One of the main differences between HTLV-1/2 and HIV-1 is that HTLV exists as cell-associated provirus, with minimal active replication, once the infection is established. In contrast, HIV is characterized by extremely active replication, which results in high levels of detectable viremia for HIV-1-infected individuals, while it is usually not detected in HTLV infection\textsuperscript{33,34}. Although, during the early phase of infection, HTLV can spread through cell-to-cell contact, resulting in a polyclonal infection of CD4 and CD8\textsuperscript{+} cells, after the initial phase the main mechanism of viral multiplication is dependent on cell division during the host cells’ mitosis process\textsuperscript{35,36}. This mechanism contributes to HTLV genomic stability, once the cellular DNA polymerase is less error prone than the viral reverse transcriptase\textsuperscript{37}. Six proteins are encoded by the pX region of the genome, including the Tax protein, which is critical to viral replication and induction of cellular activation and transformation\textsuperscript{38,39}. It increases the expression and production of cytokines and receptors involved in T-cell growth and transformation, such as monokines IL-15 and IL-2\textsuperscript{39,40}. The activity of Tax protein is an important mechanism to maintain viral multiplication through this process\textsuperscript{38}. These characteristics of the viral life cycle explain why HTLV infection is not cytopathic, in sharp contrast to infection by HIV.

Infection by HTLV-1 elicits a cell-mediated immune response. Class I-restricted CD8\textsuperscript{+} T-cells promote a lytic attack against infected T-cells displaying viral
peptides in their surface as a result of viral transcrip-
tion\textsuperscript{41-43}. On the other hand, this immune response
may be responsible for the onset of HAM/TSP, the
neurologic disease associated with HTLV-1 infec-
tion\textsuperscript{44}. The cytotoxic attack against infected cells in
the central nervous system may cause severe dam-
age, destroying neuronal cells and leading to an
inflammatory disease, which ultimately results in
myelopathy\textsuperscript{45,46}. Molecular mimicry is also considered
a mechanism of autoimmunity involved in neurologic
disease\textsuperscript{47,48}.

In addition, the modulation of immune response
caused by HTLV-1 infection may cause other immune
disturbances, which may contribute to an increased
risk for parasitic diseases, tuberculosis, and other clin-
ical manifestations\textsuperscript{49-51}.

Infection by HTLV-2 is not associated with any spe-
cific disease. Although there are some anecdotal re-
ports on neurologic disease associated with infection
by HTLV-2, as well as on increased risk for bacterial
infections, no conclusive evidence of its causal role in
a specific disease is available\textsuperscript{16-19}.

**HIV-1**

HIV-1 is a lentivirus, family \textit{Retroviridae}, with many
structural similarities to HTLV-1/2. It is a spherical
viral particle, composed of an outer lipoprotein mem-
brane and a nucleocapsid with an internal core. The
viral envelope is composed by the protein gp120 and a transmembrane portion, gp41. In addition, the
viral envelope displays cellular proteins, like beta-2
microglobulin, and human leukocyte antigens HLA-DR
and HLA class I\textsuperscript{52}. One of the most impressive char-
acteristic of HIV is its extreme genetic variability. The
viral reverse transcriptase has one of the highest
error rates described\textsuperscript{53}. The virus enters the cell fol-
lowing attachment to the CD4 molecule and further
interaction with chemokine coreceptors CCR5 or
CXCR4\textsuperscript{54,55}. In the next step, the viral envelope fuses
to the cell membrane and the viral genetic material
is inserted into the cytoplasm. This initiates the re-
verse transcription of viral RNA into a double-strand-
ed molecule of DNA, which is transported to the cell
nucleus where it is inserted into the cell DNA. This
last step is mediated by the integrase, another viral
enzyme. The viral cycle includes, in addition, the
production of viral proteins and viral RNA by the cell
machinery, which are assembled and exported to the
outer membrane where the viral particles are
released\textsuperscript{56}.

Another major consequence of infection by HIV-1 is
dependent on the virus’ ability to cause direct infection
of the cells of the immune system. It leads to a pro-
gressive loss of CD4\textsuperscript{+} cells, as well as an impairment
of the function of remaining cells, which may be already
present at early stages of infection\textsuperscript{57,58}. In contrast to
HTLV-1 infection, HIV-infected individuals have been
shown to have impaired cytotoxic T-lymphocyte (CTL)
responses\textsuperscript{57,58}. A misbalanced production of cytokines
and other factors, as well as host genetic factors, are
believed to contribute to this incapacity to elicit a proper
immune response\textsuperscript{59-63}.

In summary, infection by HIV-1 is characterized by
latency, persistent viremia, infection of the nervous sys-
tem, and a weak host immune response, leading to a
progressive depletion in CD4 count, which initiates
early in the course of the infection. Almost all individu-
als infected by HIV-1 develop AIDS after a variable period
of time. The onset of opportunistic infections and ma-
lignancies characterizes the late stage of disease. The
minority of patients that can achieve control of HIV-1
infection (‘elite controllers’) seem to have a specific
genetic background, which is involved in a strong im-
une response that enables them to control HIV-1
viremia\textsuperscript{63-65}.

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**Table 1. Characteristics of infection by HIV-1 and human T-cell lymphotropic virus type 1/2**

<table>
<thead>
<tr>
<th>Human T-cell lymphotropic virus</th>
<th>HIV</th>
</tr>
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| Stimulates lymphocyte prolifera-
tion | Severe lymphocyte depletion |
| No cytopathic effect | Intense cytopathic activity |
| T lymphocyte tropism | T lymphocyte tropism |
| Clonal replication | Active replication |
| Clinical disease in only a minor-
ity of infected patients | Clinical disease in most of infected patients |
Epidemiology of HIV/human T-cell lymphotropic virus coinfection

More than 33 million people worldwide are infected with HIV-1. It is estimated that 10-20 million people are infected by HTLV-1/2, which are endemic to southern Japan, Africa, the Caribbean, and eastern parts of South America. Furthermore, HTLV shares with HIV the same routes of transmission; it can be acquired through unprotected sexual relations, or by exposure to contaminated blood/blood products, or breast milk. As a consequence of these epidemiologic similarities, coinfection by HIV and HTLV-1/2 is a quite frequent event.

Coinfection by HIV/HTLV-2 predominates in the USA and Europe, whereas HIV/HTLV-1 coinfection is more frequently reported in South America, the Caribbean, and Africa. This pattern follows the distinct distribution of prevalence rates for HTLV-1/2 infections in different regions.

In Brazil, there is a wide geographic diversity in the prevalence of HTLV infection.

Bahia, a northeastern state of Brazil, is considered the epicenter of HTLV-1 infection in the country, probably because it was the main destination of the slave traffic during the colonial era. A recent study showed that HTLV-1 was likely introduced into Brazil in the late 19th century through the slave traffic from South Africa to Bahia.

Regarding HTLV-2, it is much more prevalent among Amerindians in the northern region than in other populations and areas of the country.

The rates of HIV/HTLV coinfection also vary with the geographic location, and follow a similar distribution to HTLV-1, reaching 16% of HIV-1-infected patients in Bahia.

A distinct feature of coinfection in Brazil is as regards to the main risk for acquisition of HTLV-1 among coinfected patients; most of the studies in Brazil showed an association between HTLV-1 coinfection and intravenous drug users, in contrast to studies in the Northern hemisphere that have detected such an association mainly for HTLV-2. This difference is a likely consequence of the distinct prevalence of HTLV-1 infection in the general population of these regions.

Another frequent finding is that coinfection is the higher proportion of coinfected women compared to monoinfected subjects. There is no consistent explanation for this feature, but it could be a consequence of a greater exposure due to cumulative risks. Some studies have shown a more efficient male-to-female sexual transmission of HTLV-1, which could lead to a potential risk increase for female intravenous drug users.

Laboratory evidence of significant interaction between HIV-1 and human T-cell lymphotropic virus type 1/2

Since HTLV-1 is tropic for CD4+ lymphocytes, and HTLV-2 infects preferentially CD8+ T-cells, their interactions resulting from coinfection by HIV-1 are likely to be different. Although there is a body of evidence suggesting that HTLV-2 infection is a protective factor against AIDS progression, coinfected patients, the situation is quite different for HTLV-1 coinfection. Some reports support the hypothesis that HTLV-1 coinfection accelerates the progression of AIDS, but there are other results suggesting that it causes no deleterious effect on HIV-1 disease. Several in vitro studies have focused on the potential consequences of the interaction of these agents.

In 1998 Moriuchi, et al. demonstrated that primary CD4+ cells treated with a cell-free supernatant from HTLV-1-infected cell culture became resistant to M-tropic strains of HIV-1, but highly susceptible to T-tropic HIV-1 strains. This finding indicated that coinfection could favor the transition from M- to T-tropic virus, which is associated with an increased risk of disease progression. The authors also identified the CC chemokines RANTES, and the macrophage inflammatory protein (MIP)-1 alpha, and MIP-1 beta in the cell culture supernatants as the major suppressive factors for M-tropic HIV-1, but highly susceptible to T-tropic HIV-1 infection, while soluble Tax protein increased susceptibility to both M- and T-tropic HIV-1. They concluded that the net effect of coinfection, as suggested by these in vitro data, would be a potential acceleration of HIV-1 disease.

The same author showed in a further study that co-infection with HTLV-1 induced viral replication in the latent viral reservoirs, but co-culture of resting CD4+ T-cells with autologous CD8+ T-cells markedly inhibited the HTLV-1-induced virus replication, suggesting that CD8+ T-cells may play an important role in controlling the spread of virus upon microbial stimulation (in vitro induction of HIV-1 replication in resting CD4+ T-cells derived from individuals with undetectable plasma viremia upon stimulation with HTLV-1).

Another potential mechanism of viral interaction was demonstrated by Leung, et al. They reported that activated nuclear factor kappa B (NFkB) can functionally interact with the Tax-derived protein (through HTLV-1
Tax protein) and the long terminal repeat fragment of HIV genome, which would result in stimulation of viral replication. In an experimental model, Lawson, et al. showed that HTLV-1-transformed cells, after coinfection by HIV-1, produced HIV-1 copies presenting with envelopes containing HTLV-1 proteins, which could potentially explain why these viral strains have an expanded tropism and can infect cells with distinct phenotypes, even including B-cells.

In contrast with coinfection by HTLV-1, the available laboratory data suggest no effect or a protective effect of HTLV-2 on AIDS evolution. Several studies focusing on immune function, coreceptor usage, viral load, and production found no significant impact of HTLV-2 co-infection on HIV disease.

Recently, an extensive review on the molecular interactions of HIV and HTLV coinfections was published, which summarizes the current knowledge on that issue.

**Clinical impact of human T-cell lymphotropic virus coinfection on HIV-1 disease progression**

The real impact of HTLV-1 coinfection on HIV disease is still an unsolved question. Several reports published in the last two decades provided contradictory results. One of the first reports on the potential impact of coinfection on AIDS progression was published in 1989, and suggested that it could be linked to an adverse clinical outcome. However, the small sample size and the cross-sectional design did not allow any conclusive association. In 1994, Schechter, et al. evaluated 27 coinfected patients, in a nested case-control study, and detected that coinfection was associated with higher CD4+ lymphocyte counts, more advanced clinical disease, and higher beta 2-microglobulin levels than HIV infection alone. An 82% excess in CD4+ cell count was estimated for coinfected patients, without any detectable immunological benefit. Other reports have detected the same profile, with coinfected patients presenting higher CD4+ cell counts when compared to HIV-1 monoinfected patients. In contrast, Bessinger, et al. did not find an association between HIV/HTLV-1 coinfection and high CD4+ cell counts.

In addition, case reports or small case series have described an accelerated progression to AIDS, or the development of AIDS, for coinfected patients presenting with this immunological profile. In Bahia, in a cross-sectional study we found that coinfected women...
were more likely to have an AIDS diagnosis when compared with those HIV-1 monoinfected.

On the other hand, a recent large, longitudinal study showed that there were no significant differences regarding the presence of opportunistic infections, progression to AIDS, or death between HIV/HTLV-1 coinfected and HIV-monoinfected patients. However, some methodological issues may have influenced the results obtained by the study.

Another important (and controversial) point to consider is the impact of coinfection on mortality. A study published by Solbesky, et al. in 2002 showed an increased risk of death (RR: 2.2; 95% CI: 1.1-4.5) for coinfected patients in Martinica. Again, the small sample size (18 coinfected patients) limited the power of their conclusion. In Bahia, we conducted a retrospective study involving 63 coinfected individuals, which detected a significantly shorter survival time for coinfected patients (median: 2,349 days vs. 3,000 days for coinfected and monoinfected patients, respectively; p = 0.001). In the same study, intravenous drug use and female gender were the main risk factors for coinfection. However, Beilke, et al. did not find any association between coinfection and survival in a similar cohort in New Orleans, although they detected again a significantly higher proportion of severe forms of scabies and coinfection by Strongyloides stercoralis for coinfected patients, which seems to exceed that expected for single infection. In addition, we observed a strong association between severe forms of scabies and coinfection by HIV-1 and HTLV-1. These findings were already reported for HTLV-1-monoinfected patients, but the risk for development of such conditions seems to be increased for coinfected individuals.

Taken together, these studies do not allow us to define the real impact of coinfection by HTLV-1 on HIV-associated disease. In common, most of the available studies have methodologic weakness: they usually are limited by the small sample size, the cross-sectional or retrospective design, and absence of data on the moment of infection by each agent. Another frequent problem is the absence of discrimination between HTLV-1 and HTLV-2, which can mislead the conclusions. There is an urgent need for prospective studies, involving larger cohorts of coinfected patients, in order to define the role of coinfection on AIDS progression.

In contrast, when we look at the coinfection by HTLV-2, the results are quite consistent in showing no effect on disease progression, as summarized in table 2. Several clinical studies (four longitudinal, two cross-sectional, one case-control, and one case report) detected no effect, or a protective one, on AIDS progression. Although these studies largely differ in terms of the methodology used to evaluate the impact of coinfection, taken together they provided an impressive sample of 375 coinfected patients.

The distinct biological properties of this agent favor the hypothesis that it has no important pathogenic role for humans, even for those infected by HIV-1. However, some reports on a potential effect of coinfection by HTLV-2 as a risk for neurologic disease highlight the need for a better evaluation of this specific point in order to discard HTLV-2 as the cause of these disturbances. A careful evaluation of these patients must be conducted before concluding for a causal role of HTLV-2, since many other factors are potentially capable of inducing neuropathy in HIV-1-infected patients.

Conclusions

Coinfection by HIV-1 and HTLV-1/2 is a frequent finding in different parts of the world. Due to the distinct biological characteristics of these agents, and the fact that they are tropic for the same cells, a potentially significant interaction is expected, especially when HTLV-1 is the coinfection virus. Most of the consequences of HIV-1 infection are linked to its tropism for CD4+ cells, which has an essential role in immune defenses and immune regulation. Since HTLV-1 infects preferentially the same cells, but has a distinct biological behavior, the interaction of these agents has the potential to cause changes in the natural history of both infections. The available laboratory evidence corroborates this contention: However, the published clinical studies are contradictory on the impact of HTLV-1 on AIDS evolution. The main problems with these studies are the methodologic limitations presented by most of them. There is a clear need for larger, better-designed...
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