Patient Safety & Quality Improvement Journal
http://psj.mums.ac.ir
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HIV-1/HTLV Co-Infection: a Survey of Molecular Basis with Clinical Studies

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ARTICLEINFO

Article type:
Review Article

Article history:
Received: 23- Apr-2015
Accepted: 31- May -2016

Keywords:
Co-infection
HIV
HTLV-1

ABSTRACT

Human immunodeficiency virus type-1 (HIV–1) and human T-cell leukemia virus (HIV-1/HTLV) co-infection is a serious health problem worldwide, especially in endemic areas and vulnerable subjects like intravenous drug abusers. This is due to the fact that CD4+ and CD8+ T-cells are the primary targets of HTLV-1 and HTLV-2, respectively. The influence of HTLV-1 and HTLV-2 on CD4+ count can shortened or prolong progression to AIDS and the development of more clinical complications. Opportunistic infections may differ between HIV-1/HTLV-1 and HIV-1/HTLV-2 co-infection subjects. Several epidemiologic studies have discussed molecular bases of HIV-1/HTLV co-infection, including cytokine and chemokine mediated pathways; however, they have yielded discrepant results.

► ***Please cite this paper as*:**
Saberi M, Tavanaii Sani A. HIV-1/HTLV Co-Infection: a Survey of Molecular Basis with Clinical Studies. Patient Saf Qual Improv. 2017; 5(1):497-501.

Introduction

Human Immunodeficiency Virus (HIV), the causative agent of Acquired Immune Deficiency Syndrome (AIDS), has been afflicting humans since 1981.

HIV infection causes both cellular and humoral immune deficiency through invasion to CD4 T-cells.

Co-infection with both types of HTLV-1 and HTLV-2 were reported frequently since HIV discovery.

Co-infection has emerged as a health problem in areas where HIV is prevalent such as South America and Africa with HIV-1 and HTLV-1 co-infection predominance, while HIV-1 and HTLV-2 co-infection is more common in the USA and Europe.

HTLV-1 and HTLV-2 have common modes of transmission, but have different T-cell tropisms because the final targets of HTLV-1 and HTV-2 are CD4+ and CD8+ T-cells, respectively.

How these retroviral agents influence HIV-1 in a co-infected subject was considered an important issue to be investigated.

In many studies, clinical complications and outcomes in co-infected subjects were compared to patients solely infected with HIV-1, however, conflicting results were obtained.

In this review, we investigated the various molecular bases of HIV/HTLV co-infection with consideration of clinical outcomes and viral load in co-infected patients.

Virology

HTLV-1 is responsible for adult T-cell leukemia (1) and is associated with myelopathy/tropical spastic paraparesis (HAM/TSP) (2-4). The former is a malignancy of CD4+ T-lymphocytes that is mediated by abnormal immune response to HTLV-1 early in life and develops to T-cell leukemia in a small proportion of carriers (<5%) over a period of 50-70 years. Adult T-cell leukemia has two different clinical forms of chronic and acute.

A plethora of multistep, pathologic processes are involved in developing adult T-cell leukemia (5).

HAM/TSP is another abnormal immune response related to HTLV-1 and appears late during the third or fourth decades of life. HTLV-1 is associated with other inflammatory disorders like arthropathy, uveitis, infective dermatitis in children, as well as increased frequency of opportunistic infections (6, 7). Subacute myelopathy resembling HAM/TSP was reported in people with HTLV-2 (8).

As recently demonstrated, other neurologic disorders could be a result of HTLV-1 or -2 infection (9). In a prospective cohort study, mortality rate was shown to be higher in carriers of HTLV-2 compared to normal subjects (10). HTLV-1 proviral load levels are directly related to an escalated risk of adult T-cell leukemia and probably HAM/TSP (11, 12).

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However, high tax expression plays a more important role in developing HAM/TSP pathogenesis than proviral load (13). The values of proviral load vary between HTLV-1 and HTLV-2 infections because of their different pathogeneses. HTLV-2 subtypes a and b have the highest and lowest proviral loads, respectively (14, 15).

Various studies suggested contradictory results regarding lower proviral load in HTLV-2 infected females and the correlation between proviral load and age in subjects with HTLV-2 infection (15-18).

Nonetheless, recent studies showed that proviral load of both HTLV-1 and HTVL-2 reach plateau due to immunologic inhibition of clonal expansion (19).

Proviral loads of HTLV-1 and HTVL-2 tend to be high when the kidney or bladder are infected (20), whereas they are at a lower level when infected with a sexual transmitted disease (21). In addition, both HTLV-1 and HTVL-2 are able to modify blood cell count for a lengthy amount of time, resulting in an increase in total lymphocyte count in HTLV-2 carriers (22).

Molecular and cellular bases of HIV/HTLV co-infection

A number of studies proposed that HIV expression can be upregulated by HTLV-1 (23-25) via many modulatory pathways. Tax, which has an essential role in HTLV-1 transcription, activates nuclear factor NF-κB pathway (NF-κB), which in turn, recognizes two binding loci within V3 region of the HTLV-1 long terminal repeat (26), similar to the way tumor necrotizing factor α or interleukin 1-β stimulate the NF-κB related HIV-1 transcription pathway (27).

Modulation of viral RNA by Rev-Rex proteins leading to viral genome transcription and synthesis stimulation of both structural and regulatory proteins is another similar pathway (28). T-cell proliferation is stimulated by HTLV-2 (29-33), while HIV-1 reduces CD4 T-cells in infected subjects. The opposing responses are mediated through various cytokines and chemokines (32, 33).

Different viruses target specific cytokines and chemokine pathways. One pathway that is necessary for maintaining a virus may be fatal to other strains (34). HIV-1 may need chemokine receptor expression to bind to CD4 cells (35-37).

CD8+ in vitro, CD8+ cytotoxic T- cells in in HAM/TSP cases infected with HTLV-1 are capable of producing some CC chemokine binding including CC13, CC14, and CC15, which are inhibitory factors for HIV-1 (38-40). Therefore, HIV replication can be modulated through cytokine-mediated pathways induced by HTLV.

Another chemokine pathway, named Janus kinase (JAK)/signal transducer/activator of transcription (STAT) signaling pathway, is activated only in HIV-1/HTLV-1 and not in HIV-1/HTLV-2 co-infected patients (41-43), suggesting the various consequences of HIV-1 co-infection with HTLV-1 and/or HTLV-2 (38). This finding also indicated that the ability of HIV for JAL/STAT induction is suppressed by either HTLV-2 proteins or by HTLV-2 induced host factors (38).

The factors released by HTLV-1 have a dual influence on HIV-1 infection. They play both stimulatory and inhibitory roles in HIV-1 and HIV-1/HTLV-1 co-infection (44). These converse effects were noted in various studies. Many investigations indicated the shorter course of progression to AIDS in HIV-1/HTLV-1 co-infection subjects (45-49), while other studies failed to demonstrate cytopathic effects of HTLV-1 on HIV-1 in HIV-1/HTLV-1 co-infection (50). One explanation for this discrepancy could be the various phenotypes of HIV-1 in clinical disorders.

Various authors reported contradictory results about the influence of HTLV-2 on HIV-1 in HIV-1/HTLV-2 co-infection. Some of them confirmed accelerated progression to AIDS in HIV-1/HTLV-2 co-infection.

Conversely, others suggested no effects or even protective role of HTLV-2 in co-infected patients. HTLV disease development is directly related to the viral burden of HTLV-1/2 in HIV-1/HTLV-1 co-infection as demonstrated in two investigations.

A brief review of HIV-1/HTLV co-infection

Both types of HTLV are retroviruses and spread by the same means of transmission as HIV-1. Co-infection of HIV with both types of HTLV is a frequent event and is commonly reported in all parts of the world. HIV-1/HTLV-1 is more common in the southern hemisphere, while HIV-1/HTLV-II co-infection is more prevalent in the northern hemisphere.

They all have a special tropism for T-lymphocytes, however, CD4 T-cells have a preference for HIV-1 and HTLV-1, whereas HTLV-2 has a predominant tendency toward CD8+ T-cells. The biological consequences and clinical implications of HIV-1 and HTLV-1/2 co-infection were noted in many studies.

Researchers assessed clinical outcomes such as protective role of HTLV against HIV-1 or faster progression to AIDS in co-infected patients as compared to mono-infected HIV-1 cases. Paraclinical parameters, such as proviral burden of viruses and CD4+ count, are compared in co-infected patients with mono-infected subjects. Furthermore, frequency of other associated clinical complications and response to antiretroviral treatments are investigated among co-infected patients. The above-mentioned outcomes were reviewed in former articles.

In a large-sized study conducted in New Orleans, USA, it was demonstrated that HIV-1 co-infection with HTLV-1 or HTLV-2 is associated with a higher probability of having neurologic complications, urinary and respiratory tract infections, thrombocytopenia, and hepatitis C.

Shorter survival and rapid progression to AIDS among HIV-1/HTLV co-infected patients were

demonstrated in a retrospective, case-control study performed in Bahia, Brazil. Co-infection with HTLV-2, especially among intravenous drug abusers is associated with liver disease and seropositivity of hepatitis C, but not an increase in myelopathy, peripheral neuropathy, bronchitis, and urinary tract infections after successful introduction of HAART for HIV-1 patients (43). Clinical outcomes have changed in this group, for instance, opportunistic pathogens are replaced with inflammatory syndromes resulting in neurologic diseases. This includes peripheral neuropathy and sporadic neurologic symptoms, which are developed more rapidly in HIV-1/HTLV co-infected patients (51). Furthermore, HTLV proviral load increased after the initiation of HAART, which indicates lack of efficacy of HAART in limiting HTLV-1 and -2 in HIV-1/HTLV co-infected patients. HTLV seropositivity is presented more commonly as co-infection with HIV-1 rather than mono-infection (6.8% vs 1.1%).

HIV-1 and HTLV-2 co-infection provides a protective role for patients against progression to AIDS in two study groups during a period of 15 years (43). In this study, HIV-1 mono-infected subjects were compared with HIV-1/HTLV-2 group for clinical outcomes and paraclinical parameters for an average of 15 years. The co-infected group had a higher mean age, as well as CD4+ and CD8+ T-cell counts, but the two groups were not different in viral load and mean duration of HIV infection.

A well-defined subgroup of patients with features such as an average of 12 years of non-progression to AIDS, CD4 count > 500 cell/µl, a stable HIV viremia between lovo-1500 copies/ml without developing opportunistic infection, and forgoing the need of antiretroviral treatment for a long period of time were more commonly found in the co-infected group (13.5%) than in the mono-infected HIV-1 group (1.1%). This finding supports the protective role of HTLV-2 infection in HIV-1 infected subjects. By lowering HIV replication and immune activation, it was observed that HTLV-2 proviral load was not different between co-infected group and HTLV-2 mono-infected subjects, suggesting that HIV-1 infection has little or no influence on HTLV-2 proviral load.

Conclusion

Our findings were confirmed by other studies, in which a delay in progression to AIDS was observed in HIV-1 co-infection with HTLV-1 or -2.

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