The Epidemiology and Disease Outcomes of Human T-Lymphotrophic Virus Type II

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Abstract

Human T-lymphotropic virus type II (HTLV-II) is a human retrovirus which is endemic in Amerindian and pygmy tribes. Molecular subtypes show geographic segregation consistent with an ancient origin of this virus within humans in Africa or South America. More recently, injection drug users in the United States and Europe have become infected with HTLV-II, and secondary sexual transmission has introduced the virus to low levels into the general population and blood donors. HTLV-II has been linked with a spastic paraparesis called HTLV-associated myelopathy / tropical spastic paraparesis (HAM/TSP), and perhaps with other neurological syndromes. It is also associated with an increased incidence of pneumonia and bronchitis, inflammatory conditions such as arthritis, and perhaps with increased mortality. Except for a few cases of cutaneous lymphoma in patients coinfected with HIV, there is no evidence that HTLV-II causes lymphoproliferative disease. HTLV-II and HIV coinfection has not been proven to alter the course of HIV disease, but such patients may have altered levels of CD4+ and CD8+ lymphocytes, and antiretroviral therapy may paradoxically increase HTLV-II proviral load. (AIDS Reviews 2004;6:144-54)

Key words

HTLV-II. Epidemiology. Tropical spastic paraparesis. Pneumonia. Arthritis. HIV.

Introduction

Since its discovery in 1982, human T-lymphotropic virus type II (HTLV-II) has held a controversial role as a pathogen, compared to its less benign predecessor HTLV-I. Perhaps, due to this perception, scientific research on HTLV-II has lagged behind that of HTLV-I, and HTLV-II disease outcomes are still poorly defined. Recently, however, there is increasing evidence of HTLV-II pathogenicity. One group has estimated that there are 197,000 cases of HTLV-II infection in the United States and several million worldwide. In this review, current information on the epidemiology of HTLV-II, modes of transmission, and clinical disease associations are discussed.

Geographic distribution of HTLV-II subtypes

HTLV-II has a remarkable pattern of distribution worldwide and has often been used as a marker of ancient human migration. Through molecular epidemiology and phylogenetics, scientists are beginning to understand the global distribution and potentially the origins of HTLV-II. The rate of genetic variability is quite low, probably because of proviral multiplication by clonal expansion of infected lymphocytes rather than viral replication. Due to differences in population dynamics and transmission behavior, some evidence suggests that the rate of nucleotide substitutions per site per year in the long terminal repeat (LTR) of HTLV-II is significantly higher in injecting drug users than in the general population. (AIDS Reviews 2004;6:144-54)
drug users (IDUs) compared to endemically infected Amerindian tribes\(^2\). The increased evolutionary rate of HTLV-II in IDUs could potentially have important implications on virulence, pathogenesis, and disease outcome.

There are now four recognized molecular subtypes of HTLV-II (a, b, c and d) with different geographic distributions (Fig. 1). Molecular subtypes HTLV-IIa and HTLV-IIb, discovered in 1992\(^3\), are prevalent throughout the Americas and Europe, but can also be found sporadically in Asia and Africa. HTLV-IIb clearly predominates in Amerindian populations\(^4\). In North America, HTLV-IIa seems to predominate within IDU populations\(^5\) while HTLV-IIb is more common among IDUs in Italy and Spain, but HTLV-IIa is more common among IDUs in Ireland and Sweden\(^6\). Over the past decade, however, two new subtypes (HTLV-IIc and HTLV-IId) have been characterized from indigenous populations in the Amazon region of Brazil and Central Africa, respectively.

Molecular characterization of samples initially collected from the Kayapo Indians, an indigenous population living in the Amazon, revealed what appeared to be a distinct variant of HTLV-IIa\(^7\). Subsequent studies of this population, as well as of infected individuals from urban areas of Brazil, further clarified the existence of a new molecular subtype phylogenetically related to HTLV-IIa, but with a full tax gene similar to that of HTLV-IIb. This divergent subtype has since been classified as HTLV-IIc\(^8\). Due to the relatively high incidence rate found in Amerindian populations, HTLV-II has long been considered a “New World virus”; however, evidence of HTLV-II found in pygmy tribes living in remote areas of Cameroon and Zaire has since contradicted this notion\(^9\),\(^13\). A new subtype, designated HTLV-IId, was identified within members of an isolated Efe Bambuti pygmy tribe\(^14\). This, along with the discovery of a simian T-lymphotropic virus (STLV-II) isolated from a pygmy chimpanzee (Pan paniscus) in the Democratic Republic of Congo, seems to support an African origin for HTLV-II\(^15\),\(^17\).
Epidemiology

Amerindians

Over the past decade, research has revealed that HTLV-II is endemic and widespread among many Native American Indian populations in South, Central and North America. The Amazon region of Brazil has reported some of the highest HTLV-II seroprevalence rates in the world (Fig. 2A). Until recently, many of these indigenous populations have remained relatively isolated, both geographically as well as culturally, from other tribes and urban areas, suggesting that HTLV-II may be an ancient human pathogen in this region. In addition, prevalence generally increases with age, especially after puberty, and may be higher in men than in women, consistent with ongoing, endemic maternal-child and heterosexual transmission.

Figure 2. Age- and sex-specific seroprevalence of HTLV-II amongst the highly endemic Kayapo Indians (A), and blood donors in the United States with very low HTLV-II seroprevalence (B). The Kayapo data are consistent with ongoing maternal-child and sexual transmission within a closed population, whereas the US data suggest an age-cohort effect due to injection drug use and secondary sexual transmission in the 1960s and 1970s.
South America

HTLV-II seroprevalence in native populations of South America ranges widely from 1 to 58%. HTLV-II is found more often in ethnic tribes living in the lowland regions, whereas HTLV-I tends to be found at a lower prevalence (1-7%) and shows geographic clustering within groups living in the Andes highlands and among persons of African decent in coastal regions. In South America, HTLV-IIb is the predominant molecular subtype within indigenous tribes, except in Brazil where HTLV-IIc is the exclusive subtype. By region, these populations include the Wayu, Guahibo, Orinoco and Tunebo tribes in Colombia; the Yaruto and Guahibo in Venezuela; the Toba, Mataco and Mapuche in Argentina; the Gran Chaco in Paraguay; and the Alacalf and Yahgan in Chile. In Brazil, HTLV-II is highly prevalent within several Indian communities, with a particularly strong focus in the Amazon region. By population and prevalence, this includes the Kayapo (32-58%), Munduruku (8%), Arara do Laranjal (11%), Tyrio (15%) and Kraho (12%) tribes.

Central America

HTLV-II has been reported among the Guaymi Indians of Panama, a tribe that inhabits isolated areas of western Panama and Costa Rica. Several population-based studies in the region have found seroprevalence rates ranging from 8 to 10% with the primary subtype being HTLV-IIb. One large study of 3,686 Guaymi reported a marked increase of infection by age, with the most notable spike occurring at young adulthood. This, combined with a similar distribution of infection in both males and females, suggests that sexual transmission plays a strong role in the spread of infection within these communities.

North America

HTLV-II infection is endemic among several large Native American Indian tribes in North America. By tribe and subtype, this includes the Navajo (IIa/IIb) and Pueblo (IIa/IIb) of New Mexico, the Seminole (IIb) of Florida in the United States; the Nuu-Chah-Nulth (IIa) in Canada; and the Maya (IIb) in Mexico. In the United States, seroprevalence rates of 2-3% and 13.2% have been reported among Pueblo and Seminole Indians, respectively. In addition, serologic screening of blood donors in the Albuquerque, New Mexico, area has revealed unusually high rates of HTLV-II (0.72/1000, most of which was attributed to HTLV-I).

Moreover, HTLV-II seroprevalence was found to be much higher among American Indian blood donors (1.0-1.6%) vs. non-Hispanic white donors (0.009-0.06%) in New Mexico. Studies on Amerindians in Canada have been limited; however, one study of the Nuu-Chah-Nulth tribe in coastal British Columbia found a prevalence of 1.6%. Similarly, HTLV-II prevalence among indigenous Mayans in the Yucatan Peninsula of Mexico has been found to be quite low (<1%).

African pygmies

HTLV-II has been found to be prevalent in two different pygmy tribes living in remote areas of Cameroon and the Democratic Republic of Congo (formerly Zaire), suggesting that HTLV-II is endemic in Central Africa and has been sustained in isolated communities for a long time. HTLV-II has also been detected sporadically in other populations from several regions of Africa. One study included several HTLV-II infected members of a family in Gabon, where the infection appears to have spanned three generations.

Injecting drug users

Within the United States, HTLV-II appears to be highly focused among African-American IDUs, particularly in New Orleans where a seroprevalence of 19% was reported among black IDUs, an incidence roughly three times that of Hispanic or white IDUs. Similarly, seroprevalence studies of blood donors have shown significantly higher rates of HTLV-II infection in blacks as compared to other racial groups. It is unclear whether the high prevalence of HTLV-II observed among blacks could be attributed to ancestry from endemically infected areas of Africa, or is instead a result of other socio-demographic factors.
of HTLV-II amongst IDUs. Extraordinarily high rates of HTLV-II (>60%) have also been reported in IDUs living in South Vietnam, where the infection was most likely introduced by United States military personnel during the Vietnam War. Finally, given the high seroprevalence of HTLV-II observed in Amerindian populations living in the Amazon, it is not surprising that the virus has also been detected in neighboring urban populations of Brazil, in IDUs and blood donors.

**Blood donors**

Due to the lack of population-based studies of HTLV-II, data from blood donors have been used to approximate population prevalence, although rates in donors are likely to be lower due to selection bias. In 1988, routine serological screening of all blood donations for HTLV-I was implemented in the United States. Cross-reacting antibodies to HTLV-II were also detected through this screening method, although at a slightly lower sensitivity. A study of more than 1.7 million blood donors from five major US cities between 1991 and 1995 detected a seroprevalence of 0.02% for HTLV-II and 0.01% for HTLV-I. HTLV-II prevalence was found to be significantly higher in female donors, black and Hispanic donors, and in those with only a high school or lower education. In contrast to the steadily increasing age-specific HTLV-I seroprevalence, there was a peak of HTLV-II prevalence in middle-aged donors, suggesting an age-cohort effect attributable to an epidemic of IDU and sexually transmitted HTLV-II infection in the 1960s and 1970s. Major risk factors reported among US donors were a history of injecting drug use, sex with an IDU, or a history of blood transfusion. Similar rates of HTLV-II seroprevalence have been reported among blood donors in Brazil and Venezuela, while significantly lower rates of HTLV-II have been found among blood donors in Denmark, Switzerland and France.

**Modes of transmission**

HTLV-II has several well-established modes of transmission, including parenteral exposure by transfusion of infected cellular blood products or intravenous drug use, mother-to-child (primarily through breastfeeding), and between spouses through heterosexual transmission. The predominant routes of transmission vary by population, wherein mother-to-child and sexual transmissions play an important role in Amerindian populations, and parenteral transmission is a clearly significant source of infection in IDUs. However, intravenous drug use has infiltrated many Native American tribes living in North America and there is evidence that sexual transmission may be a strong source of infection among non drug-using sexual partners of IDUs.

In contrast to HTLV-I, sexual transmission of HTLV-II has been less well studied, but cross-sectional studies have identified sexual transmission of HTLV-II as an important route of infection in several populations, including Amerindians, blood donors, patients attending sexually transmitted disease clinics, and prostitutes. Endemic Amerindian tribes offer some of the most compelling evidence of sexual transmission, as prevalence rates are high among both men and women and show a gradual increase with age (Fig. 2). Injecting drug use is also quite rare in these communities, suggesting that sexual transmission is one of the predominant sources of infection. One prospective study of HTLV-II transmission among index seropositive US blood donors and their seronegative sexual partners found an HTLV-II incidence of 0.5 (95% CI, 0.06-1.8) per 100 person-years that was not statistically different from the HTLV-I rate.

Vertical transmission from mother-to-child, mostly through breastfeeding, may also contribute to the high seroprevalence rates observed in these indigenous populations. Few studies have focused on mother-to-child transmission of HTLV-II; however the virus has been isolated from breast milk of infected mothers and children born to infected mothers have a higher seropositivity compared to those born to seronegative mothers. Moreover, high seroprevalence rates have been reported among children younger than 15 years of age in the Guaymi (16.5%), Gran Chaco (14%) and Kayapo (12%) tribes. In the absence of breastfeeding, several studies have indicated that the risk of perinatal transmission of HTLV-II is quite low, suggesting that the predominant source of infection occurs via breastfeeding.

**Cellular tropism and proviral load**

In vitro culture of lymphocytes from persons infected by HTLV-II results in spontaneous proliferation of both CD4+ and CD8+ cells in the absence of any exogenous stimuli, whereas in vivo studies have demonstrated that HTLV-II has a tropism for CD8+ cells. Although the molecular mechanism that determines the cellular tropism of HTLV-II has not yet been precisely determined, recent work suggests that the HTLV receptor may be a T-cell activation marker or a glucose...
transporter GLUT-1. Evidence suggests that cell transformation may involve unique interactions between viral and CD8+ T-cell-specific proteins and that a high HTLV-II proviral load may be associated with clonal expansion. In some cases, particularly those involving patients with a very high proviral load, HTLV-II has been detected in other cell populations, including CD4+ T-cells and CD19+ B-cells.

In contrast to levels of proviral load observed among HTLV-I carriers, HTLV-II carriers have comparatively lower proviral loads overall. A recent cross-sectional analysis of proviral load among a cohort of HTLV-I, HTLV-II, and uninfected blood donors found that on average HTLV-II infected subjects had a five-fold lower proviral load (0.04 copies/100 PBMC) than HTLV-I infected subjects (0.2 copies/100 PBMC), and that subjects with HTLV-IIb had a lower proviral load (0.02 copies/100 PBMC) than subjects with HTLV-IIa (0.07 copies/100 PBMC)77.

In the natural history of HTLV-I infection, higher proviral load has been associated with an increased incidence of disease. For example, HTLV-I proviral load has been found to be significantly higher amongst HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) patients than asymptomatic carriers in our own studies and those of other investigators78-81. Although the number of HAM/TSP patients was small in our recent study, four HTLV-II subjects with HAM/TSP were found to have a mean proviral load (0.003 copies/100 PBMC) that was the same, or possibly lower, than HTLV-II subjects without HAM/TSP81. Furthermore, compared to HTLV-I-associated HAM/TSP subjects in the same study, the lower proviral loads observed in patients with HTLV-II-associated HAM/TSP were consistent with milder signs and symptoms of the disease. More studies are needed to consider what role, if any, HTLV-II proviral load burden plays in HAM/TSP disease progression.

Disease associations

Literature on HTLV-II disease outcomes is limited and often consists of case reports. More substantial etiological links between HTLV-II and disease have been established from the accumulating evidence of neurological disease, and increased incidence of pneumonia, bronchitis and possible autoimmune disease among patients infected with HTLV-II.

Neurological disease

HTLV-II has been most strongly associated with a neurological syndrome known as HTLV-II-associated myelopathy (HAM), also recognized as tropical spastic paraparesis (TSP). HAM/TSP is characterized by spastic weakness of the legs, hyperreflexia, loss of vibration sense, and spastic bladder. Neurological dysfunction is limited to the lower extremities, while upper extremities and cognitive function are conserved. Symptoms of HAM/TSP are similar for both HTLV-I and HTLV-II, but HTLV-II-associated HAM/TSP generally presents with milder and more slowly progressive signs and symptoms.

There are currently about a dozen known cases of typical HTLV-II-associated HAM/TSP. Most cases have been diagnosed in middle-aged women, as is true for HTLV-I-associated HAM/TSP. The cases include four from a well-defined prospective cohort of 405 HTLV-II infected blood donors (cumulative prevalence = 1.0%; 95% CI, 0.3-2.5) followed for more than ten years81. In this same study, six cases of HAM were detected among 160 donors (cumulative prevalence = 3.7%; 95% CI, 1.4-8.0), suggesting that the risk of acquiring HAM may be lower in HTLV-II carriers. Lehky, et al. reported another four cases of HAM/TSP in patients with HTLV-II, including four African-American patients, of whom three were also of Amerindian decent. Magnetic resonance imaging (MRI) from three of these patients showed white-matter disease and HTLV-II antibodies in the cerebrospinal fluid and serum. HTLV-II RNA was also detected from a spinal cord biopsy in one patient83. These clinical findings, along with other case reports of typical HAM/TSP, support a neuropathogenic role for HTLV-II84-86.

In addition to HAM/TSP, HTLV-II has been suggested to be the causative agent of several other neurological disorders, including an ataxic variant of HAM, peripheral neuropathy and spinocerebellar syndrome. Ataxic HAM shares many of the same signs and symptoms of classic HAM, namely paraparesis and spasticity, but is distinguished by prominent ataxia, neuropathy and mental changes. Several cases of ataxic HAM have been reported30,87,88. In addition, studies on IDUs have found an increased incidence of sensory neuropathy in persons infected with HTLV-II89. The association between HTLV-II and neuropathy may be even more pronounced in patients coinfected with HIV-1, where the risk of developing peripheral neuropathy was shown to be three-times higher in patients infected with HIV-1 alone90. A recent comprehensive review supported an HTLV-II association with HAM/TSP, but criticized associations with these other neurological syndromes as potentially spurious or complicated by concurrent HIV infection92.
Pneumonia, bronchitis & other bacterial infections

HTLV-II has been associated with an increased incidence of pneumonia, bronchitis, tuberculosis, bladder or kidney infection and abscess. While several studies have found that respiratory disorders were significantly higher among persons infected with HTLV-II (particularly pneumonia and bronchitis\(^91\)), the pathological mechanism has yet to be determined. HTLV-II has also been associated with increased incidence of tuberculosis (TB) in studies involving IDUs\(^95\) and blood donors\(^91\). Moreover, a serologic survey in Nigeria found a 3% seroprevalence of HTLV-II among TB patients compared to 0.9% among blood donors, although rates were not adjusted for age, a possible confounding variable with TB infection\(^96\).

A recent study on pulmonary function found no significant differences in pulmonary function and diffusing capacity in asymptomatic HTLV-I and HTLV-II carriers as compared to uninfected controls\(^97\). Due to the cross-sectional design of the study, however, progressive loss of pulmonary function over time and clinical or subclinical pulmonary inflammation may have been difficult to capture in HTLV-II subjects during this short-term observation. Another recent study found normal production and function of antipneumococcal antibody in response to pneumococcal vaccination in HTLV-II seropositives\(^98\). However, baseline levels of antipneumococcal antibody were increased in HTLV-II compared to seronegative subjects.

Murphy, et al. hypothesizes that increased incidence of pneumonia and acute bronchitis may be the result of transient inflammatory or autoimmune reaction within the bronchoalveolar regions of the lungs, with or without concomitant respiratory infections\(^99\). A similar effect has been demonstrated in HTLV-I patients, in which bronchoalveolar lavage cells and fluid has been found to exhibit a host of biological changes\(^99\)-\(^103\). The notion that HTLV-II may induce an autoimmune response within the host is further supported by a recent report that found an increased incidence of arthritis and asthma in a prospective cohort of HTLV-II\(^104\). Compared to seronegative controls, individuals with HTLV-II were more than twice as likely to have arthritis (OR, 2.66; 95% CI, 1.58-4.45) and more than three times as likely to have asthma (OR, 3.28; 95% CI, 1.57-6.84).

Lymphoproliferative disease

Despite the hematologic abnormalities and case reports of cutaneous lymphoma observed in carriers, HTLV-II has not been proven to cause human leukemia or lymphoma. A number of initial case reports linking HTLV-II to various forms of leukemia, including hairy cell leukemia, large granular lymphocytic leukemia, T-prolymphocytic leukemia and mycosis fungoides, have since been contradicted by larger studies showing no association\(^105\)-\(^109\). In addition, HTLV-II integration could not be demonstrated in tumor specimens from these diseases\(^109\). Kaplan and Hall published two case reports of HIV-1/HTLV-II coinfected patients with severe T-lymphocytic infiltration of skin, eosinophilia, and dermatopathic lymphadenopathy\(^110\). A more recent case report involving HTLV-II cutaneous T-cell lymphoma has surfaced in one patient coinfected with HIV-1\(^111\); however no such cases have been found in patients infected with HTLV-II alone. If the host immune system plays a role in controlling the expansion of lymphocytes transformed by HTLV-II, patients coinfected with HIV-1 may be at unusually high risk for HTLV-II-associated T-cell leukemia/lymphoma than asymptomatic HTLV-II carriers.

Other laboratory abnormalities observed among asymptomatic HTLV-II carriers include small, but significant, increases in absolute lymphocyte and platelet counts, and decreased creatine kinase and serum calcium levels, as compared to age-, sex-, and race-matched seronegative controls\(^112\).

Skin & soft-tissue infections

Skin and soft-tissue infections are common among IDUs, a population in which HTLV-II is prevalent. The incidence of abscess and the risk factors associated with its occurrence amongst IDUs has received limited investigation. A cross-sectional study found that HTLV-II-seropositive IDUs were more vulnerable to skin and soft-tissue abscess than were seronegative IDUs\(^84\). However, the findings of this study may have been confounded by factors related to both abscess and HTLV-II seropositivity such as sex, race and frequency of drug injection. Subsequent studies, including one nested case-control study within an ongoing cohort that did not control for such variables, found no significant association between abscess and HTLV-II infection\(^113\),\(^114\).

Mortality

There have been few studies on HTLV-II-associated mortality and two recent analyses have found conflicting results. One study of 6,570 IDUs who were tested for antibodies to HIV and HTLV-II and then matched by age, sex, race, and year to the National Death Index,
found that for HTLV-II infection alone, all-cause mortality was reduced (RR, 0.8; 95% CI, 0.7-0.9), with no statistically significant reduction or elevation in cause-specific mortality. There was a non-significant excess of tuberculosis deaths with HTLV-II (RR, 4.6; 95% CI, 0.8-25.2), but no association was seen between mortality and any other HTLV-II related disorder. In contrast, a prospective survival analysis on 1,340 blood donors (138 HTLV-I, 358 HTLV-II and 759 seronegative controls) found that HTLV-II was associated with an overall increased risk of mortality when compared to uninfected controls (HR, 2.3; 95% CI, 1.1-4.9), but no single cause of death appeared to be responsible for the increased mortality. More mortality studies will be needed to further clarify whether or not HTLV-II infection has an adverse effect on survival.

**HIV-1/HTLV-II coinfection**

Since HTLV-II is prevalent among IDUs in the United States and Europe, coinfection with HIV-1 is common and therefore research on HIV-1/HTLV-II coinfection is particularly relevant. Coinfection has been reviewed in detail in a recent book chapter. Investigation has focused on HTLV-II as a potential modifier of HIV disease progression. Earlier studies on HIV-1/HTLV coinfection did not differentiate between HTLV-I and HTLV-II. More recent findings have been contradictory, with some studies suggesting HTLV-II coinfection accelerates HIV disease progression while other studies have shown no significant effect, and one showed possibly slower progression of HIV disease. Many of the studies had limitations, however, including cross-sectional design and small numbers of coinfected patients. Thus, controlling for potentially confounding variables such as age, gender and duration of HIV infection (seroconversion date) may have been difficult.

Addressing many of the limitations of prior studies, the best analysis on HIV-1/HTLV-II coinfection included pooled longitudinal data on 370 HIV-infected IDUs from four cohort studies. The investigators took into account possible confounding variables such as age and sex. More importantly, the dates of HIV seroconversion for each subject were clearly defined, thereby allowing for the prospective monitoring of clinical AIDS development or AIDS-related mortality in IDUs with and without HTLV-II coinfection. The rates of decline in CD4+ cell percentages were similar in singly infected HIV-1 and coinfected HIV-1/HTLV-II injection drug users, and the study concluded that overall, HTLV-II coinfection did not independently affect HIV disease progression.

Data concerning the effect of HIV-1 coinfection on HTLV-II proviral load have been limited. One study found no significant difference in proviral load between HTLV-II infected and HIV-1/HTLV-II coinfected individuals and, similarly, no correlation was seen between HTLV-II proviral load and CD4+ or CD8+ counts in HIV-1 coinfected individuals. Another study, examining HIV-1/HTLV-II coinfection and sensory neuropathy, found that patients affected by neuropathy had higher mean HTLV-II proviral loads than patients without the disorder. Interestingly, the patients with neuropathy and the highest proviral loads also exhibited the broadest tropism of HTLV-II for different cell subpopulations, including PBMCs, CD3+, CD8+, CD14+ and CD19+ cells.

Another focus of current research has been on the effects of highly active antiretroviral therapy (HAART) on HIV-1/HTLV-II coinfection. Preliminary data suggest that HAART may have the paradoxical affect of raising HTLV-II proviral load. Two separate case series found a similar and marked increase in HTLV-II proviral load after initiating treatment, which was then followed by a decrease in proviral load over time; however, the degree of decline in HTLV-II proviral load differed between the two studies. A study of one HIV-1/HTLV-II coinfected patient demonstrated a 1-log peak in proviral load after initiating HAART, followed by a 1-log decrease thereafter. In contrast, another study of two coinfected patients observed a greater (2-log) increase, followed by a gradual decline in HTLV-II viral expansion, although proviral load remained well above baseline after 15 months of treatment. The CD4+ lymphocyte count of these two patients also increased in concert with HTLV-II proviral load, suggesting that integrated HTLV-II provirus was amplified in expanding T-cell clones during HAART.

An increased HTLV-II proviral load following HAART may predispose HIV-coinfected patients to HTLV-II-related pathology. This may include conditions such as HTLV myelopathy, cutaneous lymphoma or peripheral neuropathy. Another study reported a high frequency of peripheral neuropathy in IDUs who were both HTLV-seronegative (15%) and HIV seropositive (32%). Since IDUs are at high risk for HIV-1/HTLV-II coinfection, the effect of HAART therapy on HTLV-II proviral load has important implications for this subpopulation. However, it would be premature to draw conclusions about HAART based solely on these few case reports, and further studies are needed to better understand the impact of HAART on HTLV-II coinfection.
nderstand the outcomes of antiretroviral therapy in patients with HIV-1/HTLV-II coinfection.

Conclusion & directions for future research

Despite mounting case reports, data on HTLV-II disease associations remain limited. Nevertheless, HTLV-II has been linked to HAM/TSP, and recent findings have suggested a connection to other neurological and pulmonary disorders. Additional studies are needed to investigate whether or not the increased incidence of pneumonia and bronchitis, as well as arthritis and asthma, are the result of inflammatory or autoimmune reactions in HTLV-II carriers, or instead are due to other pathological factors. Larger studies are also needed to better understand the consequences of antiretroviral therapy on HTLV-II proviral load in HIV-1 coinfected patients and to further clarify what role, if any, HTLV-II has on mortality or HIV-1 disease progression.

In addition, many questions still surround the origins of HTLV-II, with molecular and phylogenetic evidence pointing towards two separate endemic foci – South America and Central Africa. Are there still other endemic populations that have not been uncovered? And how and from which of these existing endemic foci did HTLV-II shift into the IDU population? More long-term follow-up studies will be needed of endemic populations so as to better understand the epidemiological and clinical outcomes of HTLV-II. Finally, little research has been directed at HTLV-II vaccine development. Given the potentially large numbers of endemically infected persons worldwide, as well as the impending disease burden, a vaccine may merit further exploration.

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