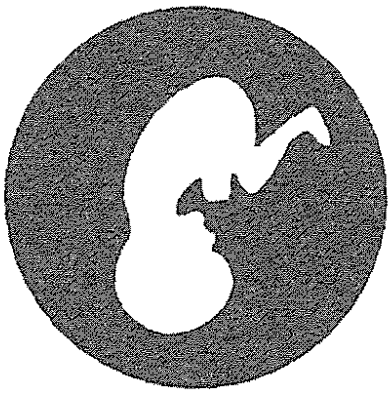
CONGENITAL & PERINATAL INFECTIONS



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10

Human T-cell Lymphotropic Virus

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Human T-cell lymphotropic virus type 1 (HTLV-1), a human retrovirus that infects an estimated 10–20 million people worldwide, has endemic foci in Japan, West and Central Africa, the Caribbean, Central and South America, and Melanesia. It is the etiological agent of a lymphoproliferative malignancy, adult T-cell leukemia/lymphoma (ATLL), as well as chronic inflammatory diseases such as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). HTLV-1 can be transmitted vertically, sexually, or by blood-borne transmission. ATLL occurs in approximately 5% of carriers who are infected during early childhood, and primary prevention is the only strategy likely to reduce this fatal disease. Children born to carrier mothers acquire the virus predominantly from breastfeeding, although there seem to be other minor transmission routes. In endemic areas, the mother-to-child transmission (MTCT) rate can be reduced significantly by screening of pregnant women for HTLV-1 antibody, followed by replacing breastfeeding with exclusive formula feeding. On the other hand, withholding breastfeeding will increase the infant mortality rate in endemic areas in developing countries, and therefore the overall benefit of this approach unclear.

Pathogenesis

HTLV-1 (also known as *human T-cell leukemia virus type 1*) belongs to the genus *Deltaretrovirus* in the Retroviridae family[1, 2]. Human T-cell lymphotropic virus type 2 (HTLV-2) is a closely related human retrovirus that has a distinct geographic distribution and less significant pathogenic potential[3]. Human T-cell lymphotropic virus type 3 (HTLV-3) and human T-cell lymphotropic virus type 4 (HTLV-4), two more related retroviruses that have been recently identified, have not been convincingly associated with any human diseases yet[4]. The main structure of the HTLV-1 virion is similar to those of other animal retroviruses, consisting of a single-stranded RNA genome surrounded by an icosahedral capsid and a double-layered

proteolipid membrane. The single-stranded RNA genome converts to double-stranded DNA and is integrated into the host genome DNA. The HTLV-1 proviral DNA genome has a structural *gag-pol-env* motif with flanking long terminal repeat (LTR) sequences. In addition, HTLV-1 has a unique segment pX region located between *env* and 3'LTR that is responsible for encoding regulatory proteins such as p40tax (Tax), p27rex (Rex), p12, p13, and p30. Moreover, the minus strand of pX encodes the HTLV-1 basic leucine zipper factor, HBZ[5]. All these regulatory proteins play important roles in the infectivity of cells, stimulation of cellular proliferation, and viral escape from the host immune system.

Like human immunodeficiency virus (HIV), another human retrovirus, HTLV-1 targets $CD4^+$ T-cells. However, there are two critical differences in the pathogenesis of these related viruses. First, the replication rate is very high in HIV-1 infection but low in HTLV-1 infection. While HIV-1-infected cells can produce many cell-free virions, HTLV-1-infected cells rarely produce cell-free virions. Spreading of HTLV-1 usually requires direct cell-to-cell contact through formation of a virological synapse. HTLV-1 has a strategy to increase the number of infected cells rather than produce new virions: namely, promoting cellular proliferation under the influence of viral gene products (mainly Tax and HBZ). Accordingly, it is not very surprising that the administration of reverse transcriptase inhibitors (key drugs for the treatment of HIV-1 infection) to HTLV-1-infected individuals has minimal effects on the proviral load[6]. Therefore, HTLV-1 has relatively low viral burden and high genetic stability compared to HIV-1.

Second, while HIV-1 induces the death of $CD4^+$ T-cells, HTLV-1 induces the proliferation (as mentioned previously) and ultimately the transformation of infected $CD4^+$ T-cells. In addition, such a persistent virus infection evokes the host's immune responses to suppress viral replication and kill infected cells, leading to an inflammatory microenvironment. Cellular transformation (leukemogenesis) and immunopathogenesis are the two main mechanisms whereby HTLV-1 causes human diseases such as ATLL and HAM/TSP (Figure 10.1).

Epidemiology

An estimated 10–20 million people worldwide are infected with HTLV-1, although highly endemic areas are limited to Japan, West and Central Africa, the Caribbean, Central and South America, and Melanesia[7]. This geographical clustering of HTLV-1 carriers may result from the predominance of MTCT in these areas. Unlike HIV, which may be transmitted by free virions or infected cells, the transmission of HTLV-1 is only cell-associated. As a result, HTLV-1 is less contagious than HIV, requiring more intimate and prolonged contact for transmission.

Japan is the only developed country among HTLV-1 endemic areas, with an estimated total of 1.1 million carriers[8]. The prevalence of HTLV-1 infection is especially

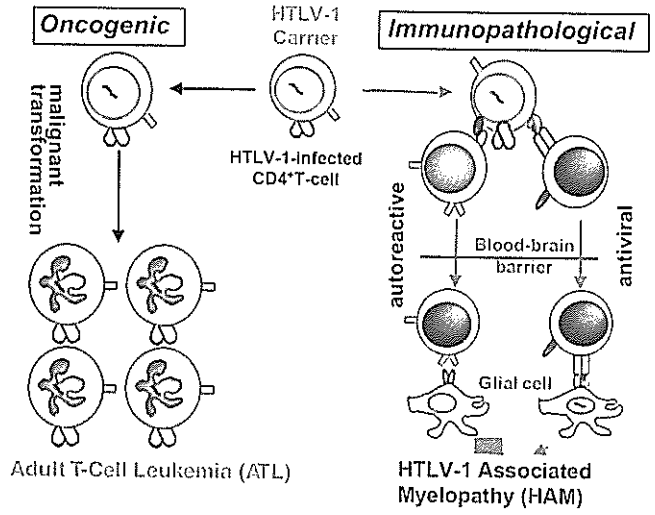

Figure 10.1 **Pathophysiology of HTLV-1-Associated Diseases.** HTLV-1 can cause two important diseases. Adult T-cell leukemia/lymphoma (ATLL) results from malignant transformation of HTLV-1-infected $CD4^+$ T cells. On the other hand, HTLV-1-associated myelopathy (HAM) is an immunopathological disease that affects the spinal cord.

high in the southwestern islands, such as Kyushu and Okinawa, and among Ainu people, aborigines who live on the northernmost Japanese island, Hokkaido. According to the most recent data, the carrier rate among pregnant women is 0.458% in Kyushu and Okinawa and 0.135% in all of Japan. West-Central Africa is another HTLV-1 endemic area[9].

The origin of HTLV-1 in the Americas is considered complex. One source is likely the migration of people from West Africa to the Americas, including the Caribbean, the United States (U.S.), and South America, through the slave trade between the 16th and 19th centuries. The other pathway is believed to involve the migration of people in East Asia to the Americas in two steps. First, prehistoric migration took place of across the Bering Strait into North America, with the spread of viral infection among indigenous North and South Americans, and second, a relatively recent immigration of Japanese (especially people in Okinawa) into South America occurred[10,11].

Accordingly, HTLV-1 infection in the U.S. is linked to a history of immigration from those endemic areas. The prevalence is quite low, estimated to be 0.0051% based on transfusion data, and is associated with female sex, older age, and African and Asian race/ethnicity[12]. Sex workers and injection drug users are also high-risk groups for HTLV-1 infection[13].

As stated previously, HTLV-1 may be transmitted vertically, sexually, or by blood-borne transmission. The increasing HTLV-1 seroprevalence in older women may reflect the relative efficiency of sexual transmission from men to

women compared to the other way around. An *in vitro* study indicated that seminal fluid could enhance replication of HTLV-1[14]. The use of condoms can prevent sexual transmission. Blood-borne transmission requires infected cells; therefore, transfusion of blood products containing a white blood cell fraction, but not those containing only a plasma fraction, may result in HTLV-1 transmission. Routine screening of blood donations has eliminated transfusion-related HTLV-1 transmission in Japan and many other countries. HTLV-1 transmission has also been documented in solid organ transplantation. Transmission of HTLV-1 through injection of drugs is possible, but this mode of transmission is more commonly linked to HTLV-2.

HTLV-1 is primarily transmitted vertically from mother to child. Data from Nagasaki, an endemic area in Japan, were the first to demonstrate transmission in breast milk[15], a finding subsequently confirmed by other studies[16]. The data supporting the importance of breast-milk transmission included (a) the demonstration of HTLV-1 in breast milk derived from infected mothers[17, 18]; (b) the finding that oral administration of fresh human milk derived from HTLV-1-infected mothers to uninfected marmosets led to HTLV-1 infection[19]; (c) observations of a significantly increased HTLV-1 infection rate in breastfed children compared to bottle-fed children[20, 21]; and (d) long-term prospective data showing that MTCT rates were 20.5% in infants breastfed for 6 months or more, 8.3% in those breastfed for less than 6 months, and 2.4% in infants exclusively formula-fed (Figure 10.2)[22]. These data indicate that breastfeeding is the most prevalent, but not the sole route of MTCT of HTLV-1, and also that longer duration of breastfeeding increases the risk of MTCT.

While the aforementioned studies clearly indicate that breastfeeding is a major route for MTCT of HTLV-1, the mechanisms whereby HTLV-1 is transmitted through the infantile digestive tract remain largely unknown. The source of the virus is thought to be infected lymphocytes in breast milk, and proviral load in breast milk[23] and maternal blood[24] appears to contribute to milk-borne transmission. Moreover, it has been demonstrated that mammary epithelial cells can be productively infected with HTLV-1, transferring infection to lymphocytes[25, 26]. It has been postulated that components in the milk whey may also help to facilitate HTLV-1 infection. Previous studies demonstrated that lactoferrin and transforming growth factor-beta, which are rich in breast milk whey, were able to enhance HTLV-1 replication *in vitro*[27, 28, 29].

The anatomical sites of HTLV-1 entry also remain unknown. Since the digestive tract possesses the largest mass of lymphoid tissue in the human body, including Waldeyer's ring and gut-associated lymphoid tissue, the virus presumably has ready access to its target cells via this mechanism. Although it is unlikely that HTLV-1 disrupts the epithelial barrier integrity or infects enterocytes, it has been shown that either M-cell-mediated transepithelial transport, paracellular passage,

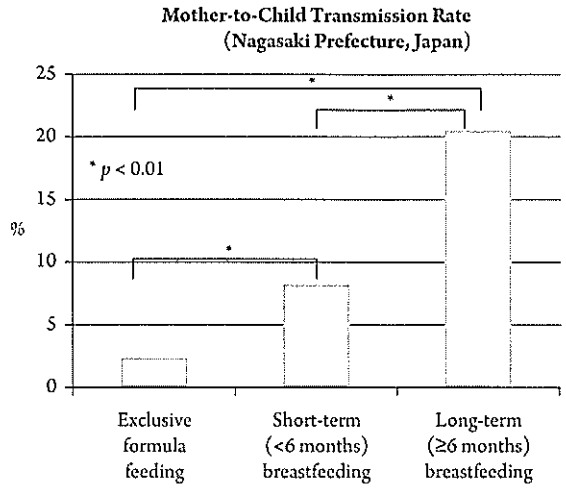

Figure 10.2 **Mother-to-Child Transmission Rates.** MTCT rates by feeding methods in Nagasaki Prefecture, Japan between 1987 and 2007 are shown (modified from Moriuchi *et al.*, 2013). There are statistically significant differences between the three groups.

or transcytosis may allow virions to cross the epithelial barrier and reach the lamina propria, which harbors T-cells and dendritic cells that can be productively infected with HTLV-1[30,31].

The observation of transmission of HTLV-1 infection to exclusively formula-fed infants indicates that other routes of MTCT must be tenable. Transplacental infection or placental microtransfusion are considered as possible routes. The presence of proviral HTLV-1 DNA in cord blood of infected mothers suggested that intrauterine infection might be feasible[32]. However, none of 7 children with HTLV-1 proviral DNA positive cord blood had seroconverted by 24–48 months of age, and none of the cord blood samples of 9 formula-fed children later confirmed to be infected was positive for HTLV-1, indicating that intrauterine infection was not likely to represent an alternative infection pathway[32]. Exposure to maternal blood and vaginal secretions during delivery is another possible source of infection, although there is no evidence that elective cesarean deliveries can reduce the risk of MTCT. Maternal saliva has been found to contain proviral HTLV-1 DNA; however, natural antiviral activity and neutralizing antibody present in saliva appear to inhibit HTLV-1 transmission by this mechanism[33].

With respect to milk-borne transmission, the duration of breastfeeding and the magnitude of proviral loads in breast milk contribute to the risk of MTCT. In addition to the aforementioned study in Japan, a prospective study in Jamaica

demonstrated that MTCT rates were 32% and 9% among infants breastfed for more than 12 months and those breastfed for shorter periods, respectively[34]. Another Jamaican study showed that MTCT occurred at 4.7 and 28.7 per 1,000 person-months at low and high proviral loads in breast milk, respectively[23]. In the case of milk-borne HIV-1 infection, exclusive breastfeeding has been found to be associated with a significantly lower risk of transmission than mixed feeding[35,36]. However, whether mixed feeding carries a higher risk of milk-borne HTLV-1 infection has not yet been comprehensively investigated.

Other factors associated with high MTCT rate include a high maternal anti-HTLV-1 antibody titer, a high maternal HTLV-1 proviral load, a child's gender (girls being more frequently infected with HTLV-1 than boys), and HLA class I type concordance[24,37]. While it appears clear that mothers with a higher proviral load transmit the virus to their children more readily, those with recent HTLV-1 infection may also be efficient transmitters, even though their proviral load is quite low (unpublished data).

Certain HLA types have been shown to influence the susceptibility of HTLV-1 carriers to progress to HAM/TSP or ATLL[38,39,40]. Several host genetic factors have also been shown to determine susceptibility to HTLV-1 infection during childhood, including a HLA-G 14-bp insertion/deletion polymorphism[41], variations in the mannose binding lectin-associated serine protease-2 gene[42], and a major susceptibility locus mapping to chromosome 6q27[43].

Diagnosis

Serological diagnosis of HTLV-1-infected children is complicated by transplacental passage of maternal antibodies. Maternally transferred antibodies can be detected even beyond 18 months of age. Seroconversion may occur at any time during and after prolonged breastfeeding. Therefore, the proper timing for serological diagnosis is around 24 months of age for children with exclusive formula feeding, and 36 months of age for children with a history of long-term breastfeeding. Positive results with PA, CLEIA, or CLIA are confirmed by Western blotting or line immunoassay.

Polymerase chain reaction (PCR) is another tool of diagnosis of HTLV-1 MTCT; however, there are several drawbacks to consider. Because of lack of cell-free virions in plasma, DNA must be extracted from peripheral blood mononuclear cells for amplification of proviral DNA. In a previous study, the detection of HTLV-1 proviral DNA in cord blood samples by PCR did not predict serologically confirmed MTCT[32]. On the other hand, extremely low proviral loads during early childhood may yield pseudonegative results, even with real-time PCR (unpublished data). Therefore, at present, PCR is not suitable for the confirmatory diagnosis of HTLV-1 MTCT.

Prevention

At present, it is impossible to prevent the development of ATLL or other HTLV-1-associated disorders in HTLV-1 carriers, and primary prevention is the only strategy likely to reduce disease. No HTLV-1 vaccine has reached clinical trials, and therefore prevention is achievable only by restricting transmission. Insofar as the majority of HTLV-1 infections follow MTCT, and ATLL develops almost exclusively after MTCT, prevention of milk-borne transmission is the most efficient and feasible way to reduce the disease burden conferred by this virus.

Exclusive formula feeding is the most reliable and easiest method to prevent milk-borne infection, although the manifold advantages of breastfeeding would also be lost. An expected outcome of withholding breastfeeding is reduction of MTCT rate from 15%–20% to 2%–3% in seropositive women. Since the lifetime risk of ATLL is approximately 5%, exclusive formula feeding will reduce incidence of ATLL among individuals born from HTLV-1 carrier mothers from 0.75%–1% to 0.1%–0.15%. This reduction must be juxtaposed against the survival benefit of breastfeeding in the developing world, which can reduce infantile mortality rates by more than 20% in some populations[44]. Therefore, this preventive strategy may only be justified in developed country like Japan, and even so, it is likely to be controversial.

There are two alternative methods to reduce breast milk HTLV-1 transmission—freeze-thawing and reducing the duration of breastfeeding. Freeze-thawing effectively destroys HTLV-1-infected cells in breast milk *in vitro* and small-scale field studies demonstrated significant reduction of MTCT[45], although it is laborious and may be impractical for many mothers. Expressed breast milk should be frozen at −20°C or below for more than12 h. MTCT can be reduced by limiting the duration of breastfeeding[22]. In Japan, seroconversion after 2 years of age is infrequent and most infected infants became seropositive by 12 months[21, 46]. A prospective study in Jamaica showed that 32% of children breastfed for more than 12 months were infected, compared to 9% of those breastfed for less than 12 months (relative risk 3.4; 95% CI 1.7–6.9)[34]. An estimated median time of HTLV-1 infection in those children was 11.9 months[47]. A small number of Japanese studies suggest that short-term breastfeeding (less than 3 months) is as effective as exclusive bottle feeding in reducing MTCT of HTLV-1, but these data have not been confirmed and several methodological issues remain to be clarified (unpublished data).

The current strategy in Japan to prevent MTCT of HTLV-1 is summarized in Figure 10.3. Since 2011, it is recommended that all pregnant women in Japan be screened for HTLV-1 antibodies by particle agglutination (PA), chemiluminescent enzyme immunoassay (CLEIA), or chemiluminescence immunoassay (CLIA), with Western blotting and/or PCR for confirmation[48]. Any of the aforementioned screening methods has high sensitivity and specificity but still gives a substantial number of inconclusive and/or false positive results, especially in nonendemic areas. Pregnant women with HTLV-1 infection receive detailed information about HTLV-1, MTCT, and infant

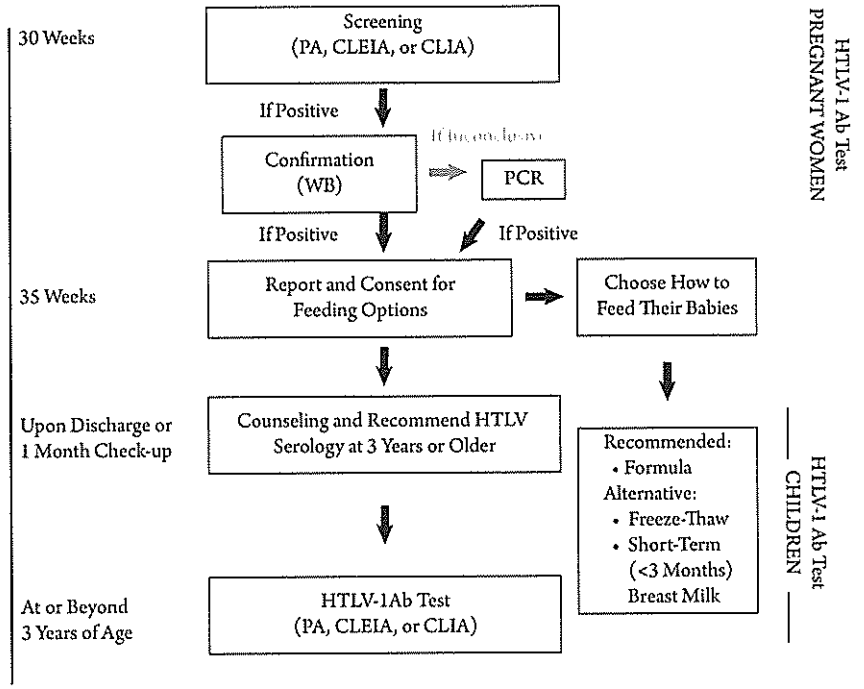

Figure 10.3 **National Program for Prevention of Mother-to-Child Transmission of HTLV-1.** Flow chart demonstrates algorithm for prevention transmission with key decision steps as outlined. The details are described in the text (modified from Moriuchi, 2011).

feeding strategies. Unless they give birth to high-risk infants (e.g., premature babies), they are advised to undertake either exclusive formula feeding, freeze-thawing of expressed breast milk, or breastfeeding for a maximum of 3 months. Ongoing support is critical, especially for those who have chosen the latter two options. We recommend anti-HTLV-1 antibody testing of offspring at 3 years of age[48].

HTLV-1 causes ATLL or HAM/TSP in only a minority of carriers after a long incubation period. Withholding breastfeeding significantly reduces MTCT of HTLV-1, but it will increase infantile mortality rates in developing countries, and therefore, the overall benefit is unclear. In this setting, short-term breastfeeding may be more beneficial than exclusive formula feeding. Long-term results from a nationwide MTCT prevention program currently ongoing in Japan will be important in informing preventative strategies in other settings.

Clinical Manifestations

While most infected individuals remain lifelong asymptomatic carriers, only a minority of carriers develop HTLV-1-associated diseases that typically occur after

decades of latency. ATLL, HAM/ TSP, and HTLV-1-associated uveitis (HAU) have been convincingly associated with HTLV-1 infection. There are some other clinical conditions more frequently found in HTLV-1-infected individuals, including opportunistic coinfections, autoimmune disorders, and some dermatological problems.

ATLL is an extremely aggressive lymphoproliferative malignancy of mature $CD4^+$ T-cells, resulting from clonal proliferation of HTLV-1-infected cells carrying the provirus randomly integrated into their genome. Previous studies indicate that clonal proliferation is driven by the function of proviral gene products (mainly Tax and HBZ), counterbalanced by the HTLV-1-specific host immune response against Tax-expressing cells. Many experts now believe that Tax plays a role in the initiation of ATLL and HBZ in the maintenance of a transformed phenotype[49, 50]. Four clinical variants of ATLL are described: acute, chronic, smoldering, and lymphoma-type, with different clinical manifestations and prognosis. The acute type is the most common and aggressive, characterized by adynamia; generalized lymphadenopathy; hepatosplenomegaly; skin, bone, and multiple visceral lesions or pulmonary infiltration; and hypercalcemia. The lymphoma type involves generalized lymphadenopathy but lacks peripheral blood involvement. The clinical course of acute and lymphoma-type ATLL is quite aggressive and overall median survival is 7.7 months, even with aggressive treatment[51]. The smoldering or chronic type is indolent and their symptoms are nonspecific. In Japan, more than 1,000 cases of ATLL are diagnosed annually and the lifetime risk of ATLL in HTLV-1 infected individuals is approximately 5%. ATLL develops after a long incubation period and is unusual before 30 years of age. A median age of onset is 67 years in Japan[52], but the occurrence of ATLL in the fourth decade predominates in the Caribbean and South America[13], suggesting that some local factors play a role in the disease's pathogenesis. ATLL is unlikely to develop if HTLV-1 infection acquired in adult life[8]. Risk factors for the development of ATLL include high viral load and family history of ATLL[53].

HAM/TSP is a chronic meningomyelitis of the gray and white matter in the spinal cord, predominantly at the lower thoracic level, with perivascular demyelination and axonal degeneration. It is usually a slowly progressive disorder characterized by unilateral or bilateral lower limb weakness and spasticity, lumbar pain, and detrusor instability. Subacute (relatively rapid) progression occurs in approximately 20% of the patients, who need early therapeutic intervention. The lifetime risk of HAM/TSP is estimated to be 0.25% in Japan[8] and 1.9% in Jamaica and Trinidad[54]. In a U.S. prospective study, 3.7% of HTLV-1 carriers were diagnosed with HAM/TSP[55]. Such differences in occurrence may suggest the presence of local factors involving the pathogenesis. In previous studies, HTLV-1-infected individuals with higher proviral load[56], particular genetic background, or both[57] may be at greater risk of developing HAM/TSP. HAM/TSP may develop after an incubation period of

several years to decades, and an average age of onset is around 40 years[54]. Pediatric cases have been rarely reported. Women are affected more frequently than men; the male-to-female ratio is 1:2.5.

Infective dermatitis (ID) is a dermatological condition associated with HTLV-1 infection and is commonly seen in pediatric populations in tropical regions, but it is very rare in Japan. It is characterized by intractable eczematous skin lesions involving the scalp, neck, external ears, axillae, and groin; nasal discharge and crust formation in the nostrils; and blepharoconjunctivitis[58]. Previous studies revealed that patients with ID have a higher proviral load than asymptomatic carriers and that approximately 30% of Brazilian children with ID developed HAM in adolescence[59]. Cultures from the affected lesions usually yield *Staphylococcus aureus* and *Streptococcus pyogenes*. Although patients with ID usually respond to systemic antibiotics and topical steroids, they frequently relapse.

Future Directions

Much remains to be learned about the pathogenesis and prevention of perinatal HTLV-1 infection. The mechanism by which this virus induces leukemogenesis remains incompletely understood. Elucidating the pathogenesis of malignancies induced by HTLV-1 would have a major global effect, and could lead to vaccines and/or novel antivirals. In addition to understanding the pathogenesis of virus-induced cancers, an issue of particular interest to the problem of perinatally acquired infections is the question of the mechanism of MTCT by breast milk. How HTLV-1 is transmitted through the infantile digestive tract remain largely unknown. Although the source of the virus is thought to be infected lymphocytes in breast milk, mammary gland epithelial cells can be productively infected with HTLV-1, suggesting alternative routes for viral transmission to the infant in addition to leukocytes. Understanding how breast milk leads to infection of the infant could lead to potential vaccines inducing those correlates of protection that might block transmission by this route. Moreover, identification of novel strategies that could inactivate HTLV-1 in breast milk, without destroying the salutary components of milk, would be of enormous public health importance in areas of the world where HTLV-1 is endemic, and further research on this topic is of great value. Such interventions would have to be practical and easily applicable in the developing world, where HTLV-1 is common.

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