Supplement Article

Mother-to-Child Transmission of Human T-Cell Lymphotropic Viruses-1/2: What We Know, and What Are the Gaps in Understanding and Preventing This Route of Infection

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Received March 18, 2014; accepted June 14, 2014.

Although human T-cell lymphotropic viruses (HTLV-1/2) were described over 30 years ago, they are relatively unknown to the public and even to healthcare personnel. Although HTLV-1 is associated with severe illnesses, these occur in only approximately 10% of infected individuals, which may explain the lack of public knowledge about them. However, cohort studies are showing that a myriad of other disease manifestations may trouble infected individuals and cause higher expenditures with healthcare. Testing donated blood for HTLV-1/2 started soon after reliable tests were developed, but unfortunately testing is not available for women during prenatal care. Vertical transmission can occur before or after birth of the child. Before birth, it occurs transplacentally or by transfer of virus during cesarean delivery, but these routes of infection are rare. After childbirth, viral transmission occurs during breastfeeding and increases with longer breastfeeding and high maternal proviral load. Unlike the human immunodeficiency virus types 1 and 2, HTLV is transmitted primarily through breastfeeding and not transplacentally or during delivery. In this study, we review what is currently known about HTLV maternal transmission, its prevention, and the gaps still present in the understanding of this process.

Key words. breastfeeding; HTLV; human T-cell lymphotropic viruses; perinatal transmission; prevention.

Human T-Cell Lymphotropic Viruses

Human T-cell lymphotropic virus types 1 and 2 (HTLV-1 and HTLV-2) were described in 1980 [1, 2], and they were the first human retroviruses described. More recently, 2 other types of HTLV were identified, HTLV-3 and HTLV-4 [3]. Their geographical distribution and a possible association with human disease are currently being investigated, and not much is known about them. In the present text, we will refer to HTLV-1/2, indicating both HTLV-1 and HTLV-2; the type will be specified only in case of particular characteristic of each viral type.

HTLV-1 has a significant pathogenic potential, given that an average of 10% of the carriers may develop serious clinical manifestations. Epidemiologic proof has been obtained for the causative role of HTLV-1 in major disease associations: adult T-cell leukemia/lymphoma (ATL), HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), HTLV-associated uveitis, and infective dermatitis [4]. As part of the disease spectrum of HTLV-1, inflammatory diseases such as polymyositis and acute rheumatic arthritis, as well as infections (tuberculosis, recurrent strongyloidiasis, Hansen's disease, among others), psychiatric, and dermatological conditions require additional and improved studies to evaluate the mechanism of their connection with HTLV-1 [3].

HTLV-2 has a less significant pathogenic potential, although there are reports of possible association with neurological diseases such as HAM/TSP [3]. There is no effective antiviral treatment for HTLV-1/2, and those available nowadays for ATL and HAM/TSP have not presented satisfactory results [4–6].

Journal of the Pediatric Infectious Diseases Society, Vol. 3, Suppl 1, pp. S24–S29, 2014. DOI:10.1093/jpids/piu070

How HTLV Emerged and Dispersed

HTLV-1/2 probably originated in Africa, where a possible ancestor, the T-cell lymphotropic virus of primates (PTLV), originated [7, 8]. HTLV may have emerged by the contact between human and nonhuman primates infected by PTLV either by their cohabitation in the domestic setting or during hunting and preparation as meals [7].

Although the origin of HTLV-1 in the Americas remains controversial, its presence in isolated indigenous populations and detection of HTLV- 1 in pre-Columbian Chilean and Bolivian mummies suggest an ancient introduction [9–11]. On the other hand, phylogenetic analysis of the virus points to a massive and systematic introduction of HTLV in post-Columbian era, during the forced immigration of sub-Saharan African populations through slave trade [12, 13].

Both hypotheses are probably true, because the virus is endemic in some indigenous communities of the American continent [3]. Note that it may serve as a marker of human migration in different times of history, due to its possible long period of adaptation to humans [4].

HTLV-2 infection appears to be present among American Indians for a long time, and the transmission maintained mainly through sexual intercourse and breastfeeding. More recently, it has been introduced in urban America, Europe, and Asia, especially among intravenous drug users (IDUs), with transmission by contact with infected blood through needle sharing [14].

Geographical Distribution

HTLV-1 and HTLV-2 have a worldwide distribution, with prevalence rates quite variable depending on the region, reaching 5%–30% of the population in endemic areas. It is estimated that approximately 20 million people worldwide are infected with HTLV-1/2 [3, 15].

The geographic distribution of HTLV-1 has been well defined, with Japan, Africa, Caribbean islands, and South America emerging as the areas of highest prevalence. The reasons for HTLV-1 clustering, such as the high ubiquity in southwestern Japan but low prevalence in neighboring regions of Korea, China, and eastern Russia, are still unknown [3].

Data from retrospective studies in Japan, an area with a high prevalence rate, highlight the effect of improving the socioeconomic and human development in general on the transmission: the prevalence of HTLV-1 in the Japanese population began to decline in the 1950s, long before the discovery of HTLV-1 [16].

Transmission of HTLV

The major modes of transmission of HTLV-1/2 are well understood, although better quantitative data on the incidence of transmission, and on promoting or inhibiting factors, are still needed [3]. Viral transmission requires the transfer of live infected T lymphocytes, that is, T cells in breast milk, in semen, and in the blood of HTLV-1 carriers of proviruses. To facilitate its transmission, HTLV-1 increases clonally the population of infected cells by the pleiotropic actions of viral proteins, especially Tax [17].

HTLV-1 transmission routes are related to individual behaviors and exposures: from mother to child (MTC), sexually, and parenterally [3, 18]. In studies conducted in French Guiana, observing naturally breastfed infants and those born to HTLV-1-seropositive mothers, the rate of vertical transmission was 10.6% and 9.7%, respectively [71, 72].

Like other sexually transmitted infections, seropositivity for HTLV-1 is associated with unprotected sex, multiple sexual partners, paid sex, and presence of genital ulceration [19–21]. Cross-sectional studies have postulated greater rates of sexual transmission from men to women [22]. Transmission rate of men to women was calculated as being 60.8%, and from women to men the rate was just 0.4% [69]. However, prospective studies have shown conflicting results, one confirming greater rates in male-female transmission [3, 23] and 2 others showing no difference in effectiveness of transmission based on direction (man-woman or woman-man) [3, 24, 25].

Intravenous exposure to contaminated blood seems to be the most effective route of transmission of HTLV-1 [20, 26, 27]. Increased risk is associated with the transfusion of red blood cells, platelets, and whole blood. Fresh red blood cells that were less than 6 days old had a transmission efficiency of 80% [27] compared with plasma alone [28]. Cold storage decreased the risk of transmission, possibly due to destruction of infected lymphocytes [29]. However, these procedures were done primarily before the HTLV-1/2 testing of donated blood [28, 30].

Sharing needles and syringes by IDUs is another important source of parenteral transmission of HTLV-1/2 [31, 32]. HTLV-2 appears to be much more prevalent than HTLV-1 in this population in North America and Europe, presumably because of an epidemic in the 1960s and 1970s [33–35]. However, HTLV-1 is also more prevalent in IDUs from Brazil and New York [3].

Mother-to-Child Transmission

Data from studies in pregnant women can better reflect the prevalence rates of the general population than blood donors, which generally have low vulnerability. Yet, in data analysis and inferences, it is important to consider that women of reproductive age are usually younger. The seroprevalence of HTLV-1 among pregnant women ranges from 400 to 500 for 10 000 in highly endemic areas of

Japan, whereas in nonendemic areas of this country it varies from 10 to 100 for 10 000 [36]. In a study of samples from 7 Western European countries, seropositivity for HTLV-1/2 was 4.4 for 10 000, ranging from 0.7 in Germany to 11.5 for 10 000 in France [17]. Research from various countries have shown the following seroprevalence for HTLV-1/2, for 10 000 pregnant women: 2 in Spain [37], 19 in Argentina [38], 193 in Martinique [39], 170 in Peru [40], 200 Jamaica [41], 210 in Gabon [42], 250 in Ghana [43], 344 in French Guiana [44], 370 in Zaire [45], and 1670 in Nigeria [46]. Studies on the prevalence of HTLV-1/2 conducted in Brazil among pregnant women showed rates that varied from 0.0% to 1.0% [3, 47–53]. These data demonstrate the heterogeneity in the prevalence of HTLV-1/2 between the various geographical regions (Table 1).

The rate of vertical transmission ranges from 3.9% to 22% in endemic areas and may reach 31% in mothers coinfected with *Strongyloides stercoralis* [54]. Studies show that the frequency of transmission in a population of African descent in Guyana (South America) was 10% [55].

Risk factors of HTLV-1 vertical transmission are mainly associated with breastfeeding (duration of breastfeeding and proviral load in breast milk), maternal infection (clinical status, proviral load in peripheral blood) and with additional factors such as low level of education and vulnerable socioeconomic position, among others [3, 54, 69, 70].

Strategies to Prevent MTC Transmission of HTLV-1/2

Vertical transmission of HTLV-1/2 could theoretically occur during the intrauterine period or during delivery, but it is has been shown that it is through breastfeeding that the majority of its transmission occurs, with HTLV-infected cells entering the infant's body by the oral route. An exposure period of higher than 6 months (long-term breast-feeding) and high proviral load in breast milk are usually considered risk factors for HTLV infection transmission [49, 56, 69, 70].

Table 1. HTLV-1/2 Prevalence in Pregnant Women in Diverse Geographical Areas

Area	Prevalence (n/10 000)	References
Nigeria	1670	[46]
Japan		
Endemic areas	400–500	[36]
Nonendemic areas	10–100	
Germany	0.7	[17]
France	11.5	
Spain	2	[37]
Argentina	19	[38]
Martinique	193	[39]
Peru	170	[40]
Jamaica	200	[41]
Gabon	210	[42]
Ghana	250	[43]
French Guiana	344	[44]
Zaire	370	[45]
Brazil	0–100	[47–53]

Cessation of breast milk feeding or its treatment by freeze-thawing has been applied with success to prevent HTLV-1 infection from an infected mother to her child [3, 57]. In Japanese endemic areas, pregnant mothers are routinely examined for HTLV-1 antibodies, and once the mother is identified to be infected, bottle feeding is strongly recommended. These measures were rather successful in preventing HTLV-1 infection in Japan, where it revealed a marked reduction of HTLV-1 vertical transmission from 20.3% to 2.5%. A significantly higher risk of short-term breast feeding (<6 months) versus bottle feeding (7.4% vs 2.5%; $P < .001$) was also demonstrated [3, 58].

However, there is a concern whether this strategy of avoiding natural feeding of infants would be the best choice in developing regions, where breast milk is valuable for nourishing as well as in transferring mother's immunity to her children to protect against various infectious agents [15, 59]. An alternative would be treating the mother's milk, because if living cells can be eliminated by freeze and thawing or pasteurizing the milk, viral transmission could be avoided [15, 61]. Nevertheless, extracting the maternal milk and applying physical treatment to it could be a time-consuming and tiresome process, which could be prone to contamination if the hygienic conditions are not ideal [59].

Because there is a minor possibility of HTLV transmission even without breastfeeding (<3%), one should also consider avoiding direct transfer of body fluids, including blood, during child delivery, but studies are still necessary to establish whether cesarean deliveries are safer and whether the use of antiretroviral drugs during and after delivery could be useful, as is the case with human immunodeficiency virus (HIV) protocols. There have been no studies of either antiretroviral therapy or mode of delivery to address the potential for further reducing MTC transmission.

Screening for HTLV-1 in pregnancy has been introduced in some endemic areas, including Japan, Martinique, and Brazil [59, 60–62], but it is not yet ideal, and it is much less widespread than screening of blood donors, as shown by Mello et al [70].

The route of infection has been shown to be related to the development of specific diseases associated with HTLV-1. HTLV-associated myelopathy/TSP was related with blood transfusion [63] and ATL has been associated with breastfeeding [15]. Approximately 1%–5% of children infected through vertical transmission will develop ATL [3, 15, 36]. Whether HTLV-1 infection acquired in utero or during delivery carries the same risk of ATL as breast milk-associated transmission is unknown. The

development of ATL after blood transfusion acquisition of HTLV-1 has rarely been reported [3, 15].

Preventing MTC transmission would unquestionably have the most significant impact on the occurrence of HTLV-1-associated diseases. Prenatal screening for HTLV-1 should be implemented in specific geographical areas, combined with counseling of seropositive mothers regarding transmission through breastfeeding [3, 64]. However, in many HTLV-1 endemic areas, the interruption of breastfeeding could have individual and public health impact, such as malnutrition and increased infant mortality. Public health policies should consider this adverse effect in less developed countries and recommend alternative feeding formula for children in risk of HTLV-1 infection through mother's milk [3, 59].

Psychosocial problems such as fear or guilt about pregnancy, as well as depression and increased anxiety, may well be associated with HTLV-1 infection diagnosed during pregnancy [59, 60], similarly to HIV, especially due to the confusion in lay people and even health professionals about those viruses, which are popularly called "cousins." The stigma tends to be the same, unless information to the community and education of health-related workers are provided.

Therefore, access to adequate counseling and correct information about HTLV, like that given to HIV patients, is of fundamental importance if adequate preventive measures are to take place. As shown by Piwoz et al [73] in their studies on postnatal HIV-1 transmission in Zimbabwe, the postnatal counseling during a medical interview to infected mothers with HIV-1 was associated with 38% reduction on the viral vertical transmission, and those mothers that were exposed to both print and video materials were 79% less likely to infect their infants, compared with mothers who had no exposure. Since both viruses could be transmitted by breastfeeding, the counseling could be applied with a similar approach.

Obstetric Care of Pregnant Women With MTC-Transmittable Viral Infections

Several studies have been conducted to determine the best management in the care of pregnant women infected with MTC-transmittable diseases. For HIV, it is already known that elective caesarean section in positive pregnant women reduces the risk of MTC transmission [64]. However, the relative risks, according to the mode of delivery in pregnant women infected with low viral load, using or not using antiretroviral therapy, remains uncertain [64–66].

Other points that still need clarification in relation to obstetric management in HIV-positive pregnant women, which could be extrapolated to HTLV prevention, are the effectiveness of avoiding fetal invasive monitoring and iatrogenic rupture of membranes, the influence of maternal viral load [65], and what would be the best gestational age for elective termination of pregnancy [66]. In pregnant women with hepatitis B, elective cesarean section is not currently indicated because there is insufficient evidence that this measure protects the infant [67]. Likewise, there is insufficient evidence for its efficacy in preventing maternal-fetal transmission of hepatitis C virus (HCV). However, if the coinfection of HCV and HIV exists, elective cesarean section has been advocated to reduce vertical transmission of both viruses [68].

The high incidence of unnecessary cesarean delivery is a matter of global concern, and thus the decision to perform it should be judicious and based on evidence. Therefore, studies with pregnant women infected with HTLV are needed to help in clarifying its usefulness to decrease MTC transmission.

Gaps in the Knowledge of HTLV Vertical Transmission

As seen above, there are many gaps in our knowledge on the multiple factors involved in HTLV transmission from the infected mother to the child (Table 2). Further studies are necessary to understand how the vertical transmission not ascribed to breast milk use occurs, which could be intrauterine through maternal blood passage in placenta bleeding or during the delivery process. Increasing our knowledge in this area would be useful to devise appropriate strategies, for example, recommending cesarean delivery.

The importance of specific HTLV-1 transmission routes (breastfeeding versus sexual versus parenteral) in the future development of diseases associated with this virus also deserves more studies. Regarding the host's immune system, it is still not clear how an effective T-cell response against HTLV-1 could be defined, which viral antigens could generate protector immunity, and what is the function of the mucosa immunity in preventing transmission. It has been shown that the effect of the protective human leukocyte antigen alleles in Japan is exerted mainly through a reduction in proviral load [3]. Additional statistically significant protective effect of each of these alleles, even after the proviral load has been taken into account, has an unknown mechanism.

There are no reports of effective vaccines against HTLV-1 and no curative drugs against HTLV-1 have been described. Adult T-cell leukemia/lymphoma and HAM/TSP, the main diseases associated with this virus, carry a poor prognosis, despite all therapeutic efforts.

Table 2. Questions and Gaps in the Knowledge of MTC Transmission of HTLV

- What are the promoting or inhibiting factors of MTC transmission of HTLV (viral factors, host factors)?
- Viral pathogenesis, host's immune system responses need more clarification.
- MTC transmission not attributed to breast milk use: how does it occur?
- What is the value of cesarean section in lowering HTLV transmission to newborn?
- Are antiretroviral drugs effective in lowering HTLV transmission in the perinatal period?
- What is the efficiency of freeze and thawing in interrupting HTLV transmission in maternal milk?
- Lack of effective treatment of the infection and associated diseases.
- Lack of vaccines against HTLV.
- Lack of testing women for HTLV in prenatal care settings in endemic areas.

Abbreviations: HTLV, human T-cell lymphotropic virus; MTC, mother-to-child.

New drugs and multicentric studies are needed to face this reality. For this purpose, many aspects of HTLV-1 mechanisms of pathogenicity need clarification. For instance, it remains unknown whether the nonproductive engulfing or transport of virions, described for HIV and other retroviral as well as non-retroviral pathogens, play a role in HTLV infection [3].

HTLV-1 shares features with other so-called "tropical diseases," which mainly affect poor and marginalized communities of the world, and it is virtually nonexistent in other places. The Japanese experience demonstrates that is possible to reduce prevalence of HTLV-1 infection in populations without vaccines or anti-HTLV-1 drugs through general prevention measures, such as HTLV-1 trials in blood banks, testing pregnant women, and suppression of breastfeeding by infected mothers.

CONCLUSIONS

Because curative treatment of ATL and HAM/TSP is lacking and a vaccine is unavailable, the social and financial cost for the individual, his/her family, and the health system is immense. For this reason, public health interventions aimed at counseling and educating high-risk individuals and populations are of paramount importance. The knowledge of HTLV-1/2 infection prevalence in female population in reproductive age or in pregnant women, allows public health action aiming to avoid viral transmission, which includes ensuring access to appropriate prenatal care.

The results of different studies and interventions indicated that avoidance of breastfeeding was an effective measure to block the transmission of the virus. In our view, after basic calculations (data not published), it is possibly cost-effective in endemic countries to test all pregnant women in the prenatal care setting or the newborn through neonatal screening, pasteurizing the maternal milk or providing baby formula to newborns of seropositive mothers, to reduce vertical transmission and to prevent future development of illnesses related to HTLV.

In many areas of the world, the screening for HTLV in the prenatal care setting is established, which is the first step towards control of the transmission from mother to child. Unfortunately, this procedure is not the scenario in the majority of endemic regions, where the highest rates of seropositivity coincide with the worst social and economic indicators.

Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Acknowledgments

We thank the Interdisciplinary HTLV Research Group staff for assistance with the elaboration of the manuscript and references.

Financial support. This work was supported by FAPEMIG and Fundação Hemominas. F. A. P. received award from Conselho Nacional de Pesquisa (CNPq), Brazil. This work was also supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development—National Institutes of Health.

Potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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*Please see references 41–73 as supplementary data online at http://jpids.oxfordjournals.org.