Mother-to-Child Transmission of Human T-Cell Lymphotropic Virus Type 1

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Virology and Pathogenesis

Human T-cell lymphotropic virus type 1 (HTLV-1, also known as adult T-cell lymphoma virus type 1) belongs to the oncovirinae subfamily of human retroviruses. Like HIV, it targets $CD4^+$ T cells. However, there are two critical differences in pathogenesis; firstly the replication rate is very high in HIV-1 infection, but low in HTLV-1 infection. Therefore compared to HIV-1, HTLV-1 has relatively low viral burden and high genetic stability. Secondly, while HIV-1 induces death of $CD4^+$ T cells, HTLV-1 induces proliferation, and ultimately, transformation of infected $CD4^+$ T cells. These differences partly explain the distinct spectrum of diseases caused by these two retroviruses.

Disease Association with HTLV-1 Infection

While most infected individuals remain asymptomatic, HTLV-1 may result in two major diseases, adult T-cell leukemia/lymphoma (ATLL) and HTLV-1-associated myelopathy (HAM)/tropical spastic paraparesis (TSP). ATLL results from clonal proliferation of $CD4^+$ T cells, which contain HTLV-1 provirus randomly integrated in to their genome. Four clinical variants of ATLL are described; acute, lymphoma-type, chronic and smoldering, with different clinical manifestations and prognosis. The clinical course of acute and lymphoma-type ATLL is quite aggressive and overall median survival is 7.7 months despite aggressive treatment[1]. In Japan, > 1,000 cases of ATLL are diagnosed annually and the lifetime risk of ATLL in HTLV-1 infected individuals is approximately 5%. ATLL is extremely unusual before 30 years of age. ATLL develops after a long incubation period (a median age of onset is 67 years), and is unlikely to develop if HTLV-1infection acquired in adult life[2]. Risk factors for the development of ATLL include high viral load and family history of ATLL[3].

In contrast HAM/TSP is a slowly progressive disorder characterized by uni- or bilateral lower limb weakness and spasticity, lumbar pain and detrusor instability. The lifetime risk of HAM/TSP is estimated to be 0.25% in Japan[2] and 1.9% in Jamaica and Trinidad[4]. In a US prospective study, 3.7% of HTLV-1 carriers were diagnosed with HAM/TSP[5]. HTLV-1-infected individuals with higher proviral load[6] and/or particular genetic background[7] may be at greater risk of developing HAM/TSP. HAM/TSP may develop after an incubation period of several years to decades.

Epidemiology

An estimated 10-20 million people worldwide are infected with HTLV-1, although highly endemic areas are limited to Southern Japan, West and Central Africa, the Caribbean, Central and South America, and Melanesia[8]. This geographical clustering of HTLV-1 carriers may

result from the predominance of mother-to-child transmission (MTCT). Unlike HIV, which may be transmitted by free virions or via 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. HTLV-1 may be transmitted (i) vertically (from mother to child peri- or postnatally), (ii) sexually or (iii) by blood-borne transmission. The increasing HTLV-1 seroprevalence in women with age may reflect the relative efficiency of sexual transmission from men to women, compared to women to men. Blood-born transmission requires infected cells; therefore, transfusion of blood products containing WBC fraction, but not plasma fraction only, may result in HTLV-1 transmission. Routine screening of blood donations has eliminated transfusion-related HTLV-1 transmission in Japan and many other countries. Transmission through injecting drug use is also possible.

Mother-to-Child Transmission

HTLV-1 is primarily transmitted vertically from mother to child. Data from Nagasaki, an endemic areas in Japan, were the first to demonstrate transmission in breast milk (summarized in ref. 9), a finding subsequently confirmed by other studies. The data supporting the importance of breast-milk transmission included (i) the demonstration of HTLV-1 antigen in breast milk derived from infected mothers; (ii) oral administration of fresh human milk derived from HTLV-1-infected mothers to uninfected marmosets led to HTLV-1 infection; (iii) a significantly increased HTLV-1 infection rate in breast-fed children compared to bottle-fed children; and (iv) long-term prospective data showing that MTCT rates were 20.5% in infants breast-fed for 6 months or more, 8.3% in those breast-fed for less than 6 months, and 2.4% in infants exclusively formula-fed (Supplementary Figure 1)[10]. These data indicate that breastfeeding is the most prevalent, but not the sole route of MTCT of HTLV-1, and that a longer duration of breastfeeding increases the risk of MTCT.

The source of the virus is thought to be infected lymphocytes in breast milk, and proviral load in breast milk[11] or maternal blood[12] appears to contribute to milk-born transmission. A 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[11].

Transmission of HTLV-1 infection to exclusively formula-fed infants indicates that other largely unknown routes of MTCT. Transplacental infection or placental microtransfusion is less likely, as proviral HTLV-1 DNA in cord blood of infected mothers is not indicative of intrauterine infection, and none of the cord blood samples derived from exclusive formula-fed HTLV-1 infected Japanese children contained HTLV-1 DNA[13]. Maternal saliva also contains proviral HTLV-1 DNA; however, natural activity and neutralizing antibody present in saliva

appear to inhibit HTLV-1 transmission[14].

Prevention of MTCT of HTLV-1

It is not possible 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 only achievable by restricting transmission. As the majority of HTLV-1 infection follows MTCT and ATLL develops only after MTCT, prevention of milk-born transmission is the most efficient and feasible way to reduce the disease burden.

Exclusive formula-feeding is the most reliable and easiest method to prevent milk-born 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%. Since lifetime risk of ATLL is approximately 5%, exclusive formula-feeding will reduce incidence of ATLL patients among individuals born from HTLV-1 carrier mothers from 0.75-1% to 0.1-0.15%. In contrast, breastfeeding can reduce infantile mortality rates for more than 20% in some developing countries[15]. Therefore, this preventive strategy may only be justified in developed country like Japan and even so is likely to be controversial.

There are two alternative methods to reduce breast milk HTLV-1 transmission – freeze-thawing and reducing the duration of breast-feeding. Freeze-thawing effectively destroys HTLV-1-infected cells in breast milk *in vitro* and small-scale field studies demonstrated significant reduction of MTCT,[16] although it is laborious and may be impractical for many mothers. Expressed breast milk should be frozen at -20^{o}C or below for >12 h. MTCT can be reduced by limiting the duration of breastfeeding[10]. In Japan, seroconversion after 2 years of age is infrequent and most infected infants became seropositive by 12 months[9 17]. A prospective study in Jamaica showed that 32% of children breastfed for >12 months were infected, compared to 9% of those breastfed for <12 months (relative risk 3.4; 95% CI 1.7-6.9)[18]. An estimated median time of HTLV-1 infection in those children was 11.9 months[19]. A number of small Japanese studies in Japan suggest that short-term breastfeeding (<3 months) was as effective as exclusive bottle-feeding in reducing MTCT of HTLV-1.

Current strategy in Japan to prevent MTCT of HTLV-1

Since 2011, it is recommended that all pregnant women in Japan are screened for HTLV-1 antibody by particle agglutination (PA) or chemiluminescent enzyme immunoassay (CLEIA), with Western blotting and/or PCR for confirmation[20]. PA and CLEIA have high sensitivity and specificity, but still give a substantial number of false positive results, especially in

non-endemic areas. Western blotting is also sometimes inconclusive. PCR is both sensitive and specific. Pregnant women with HTLV-1 infection receive detailed information about HTLV-1, MTCT and infant 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 the offspring at three years of age[20].

Perspectives in other endemic countries

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 will increase infantile mortality rate in developing countries and therefore the overall benefit is unclear. Long-term results from the current nationwide MTCT prevention program in Japan will be important in informing preventative strategies in other settings.

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Figure legends

Figure 1. Mother-to-child transmission rates

MCTC rates by feeding methods in Nagasaki Prefecture, Japan between 1987 and 2007 are shown (modified from reference 10). There are statistically significant differences between the three groups.

Figure 2. A flow chart showing a national program for prevention of mother-to-child transmission of HTLV-1.

The details are described in the text. (Modified from reference 20)

Figure 1.

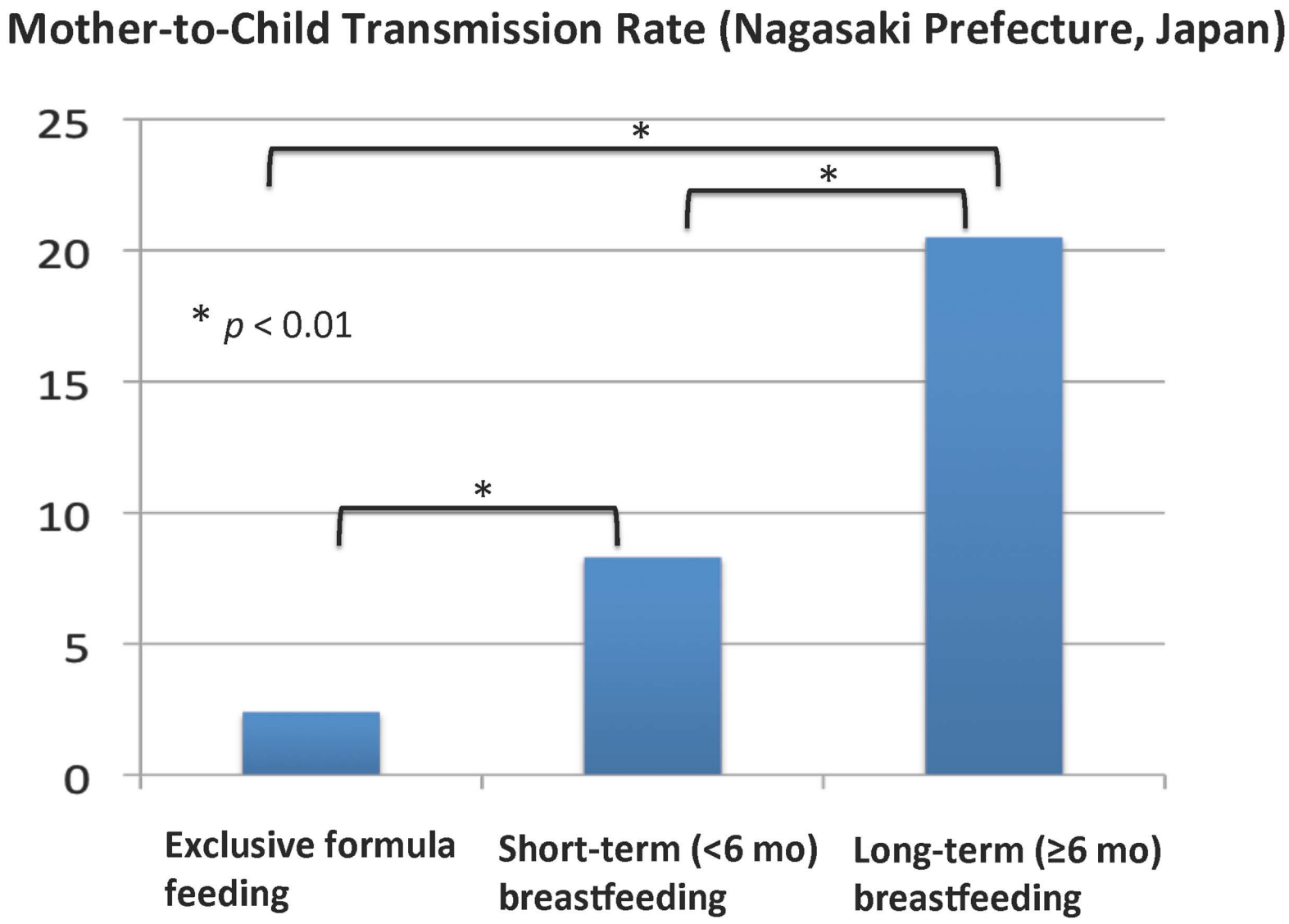
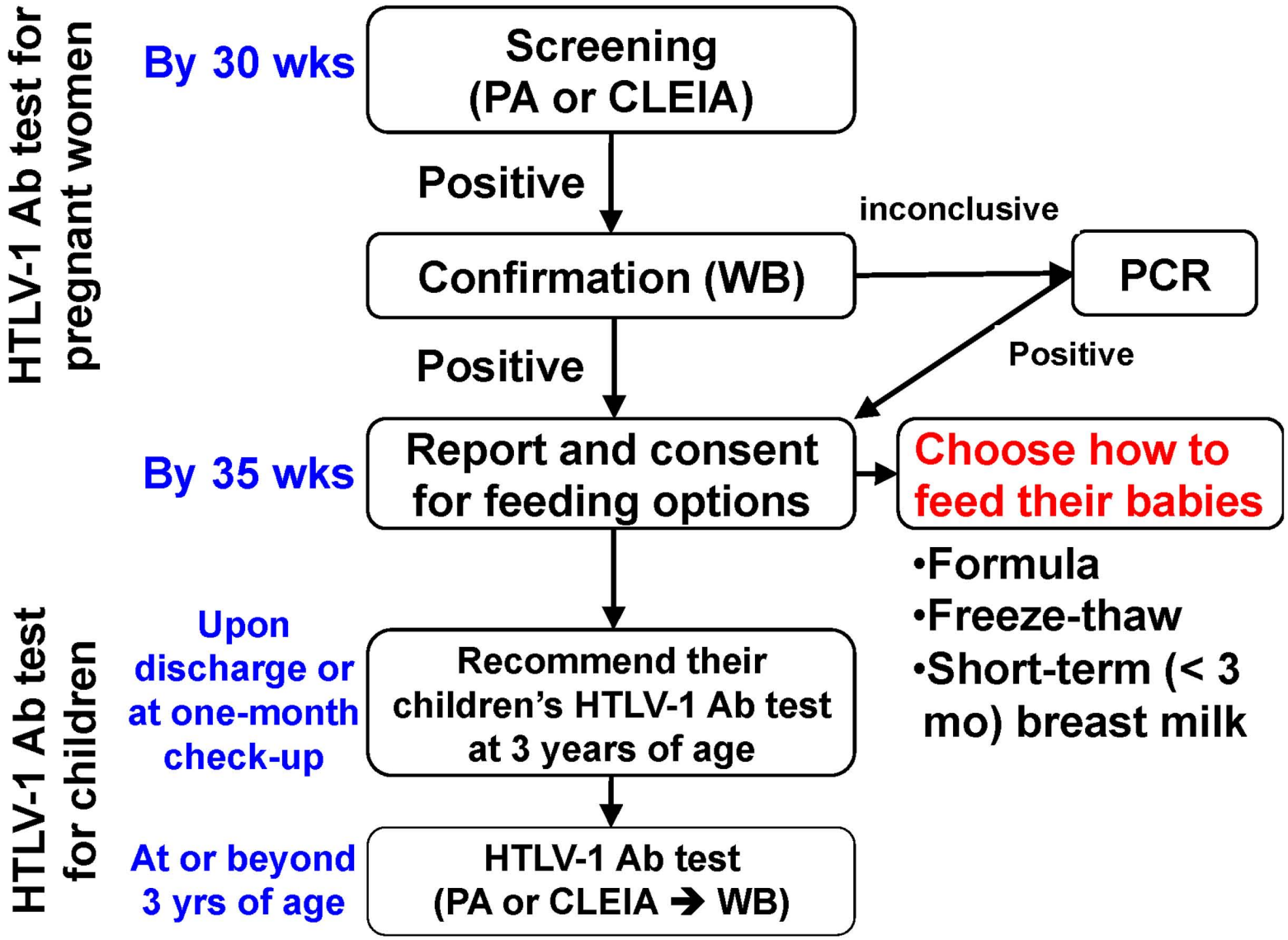

Mother-to-Child Transmission Rate (Nagasaki Prefecture, Japan)
25
20
15
10
5
0
* p < 0.01
*
*
*
Exclusive formula feeding
Short-term (<6 mo) breastfeeding
Long-term (≥6 mo) breastfeeding

Figure 2.


HTLV-1 Ab test for pregnant women
By 30 wks
Screening (PA or CLEIA)
Positive
inconclusive
Confirmation (WB)
PCR
Positive
Positive
By 35 wks
Report and consent for feeding options
Choose how to feed their babies
•Formula
•Freeze-thaw
•Short-term (< 3 mo) breast milk
HTLV-1 Ab test for children
Upon discharge or at one-month check-up
Recommend their children's HTLV-1 Ab test at 3 years of age
At or beyond 3 yrs of age
HTLV-1 Ab test (PA or CLEIA → WB)