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Mother-to-Child Transmission of Human Immunodeficiency Virus Type 1

Grace C. John[1] and **Joan Kreiss**[2]

[1]Department of Medicine, University of Washington, Seattle, WA; and Departments of Medical Microbiology and Paediatrics, University of Nairobi, Nairobi, Kenya

[2]Departments of Epidemiology and Medicine, University of Washington, Seattle, WA

INTRODUCTION

In 1991, a comprehensive review of issues related to vertical transmission of human immunodeficiency virus type 1 (HIV-1) was published in *Epidemiologic Reviews* (1). Over the past 5 years, considerable progress has been made in our understanding of the rates, correlates, and timing of mother-to-child transmission of HIV-1. The objective of this update is to review recent findings and summarize future directions in research related to vertical transmission of HIV-1. This review will include a brief summary of rates and correlates of vertical transmission. We will discuss new areas of interest in HIV-1 vertical transmission, including descriptions of "transiently infected" infants, the role of infant cytotoxic T-lymphocyte activity and viral characteristics in vertical transmission, and late postnatal transmission through breast milk. Finally, we will discuss the rationale and practicability of potential intervention strategies to decrease vertical transmission of HTV-1.

RATES OF VERTICAL TRANSMISSION

Vertical transmission rates range from 14 percent to 48 percent in cohort studies worldwide (table 1) (2–26). Early studies varied in the definition of infant infection status and in the methodology used to estimate vertical transmission rates. A Working Group on Mother-to-Child Transmission of HIV-1, convened in Ghent, Belgium, in 1992, determined guidelines with which to standardize estimates of vertical transmission rates (table 2) (27). Vertical transmission rates from 13 cohorts were recalculated by the Working Group using both the direct and indirect methods (28). Most recalculated vertical transmission rate estimates in cohorts from developing countries were higher (25–30 percent) than those from developed countries (14–25 percent). Differences in maternal disease status, mode of disease acquisition, mode of delivery, viral phenotype, and frequency of breastfeeding all potentially contribute to the observed differences in transmission rates.

TIMING OF VERTICAL TRANSMISSION

While other vertically transmitted organisms typically have a single predominant time and mode of transmission, it has been difficult to determine the most critical time and mode of HIV-1 vertical transmission. This information is crucial to planning of intervention strategies to decrease vertical transmission.

Reprint requests to Dr. Grace C. John, International AIDS Research and Training Program, Box 359909, University of Washington, Seattle, WA 98195.

Vertical transmission of HIV-1 occurs in utero, intrapartum, or postnatally through breastfeeding. The relative contribution of the three modes of transmission is still not well defined. Definitions for time of infant infection based on consecutive blood samples tested for viral markers were proposed by the AIDS Clinical Trials Group and the Working Group on Mother-to-Child Transmission for non-breastfeeding and breastfeeding infants, respectively (table 3) (29, 30).

In non-breastfed infants, the late in utero and intrapartum period appears to be the time during which most vertical transmission occurs (31, 32). Mathematical modeling of sequential data, including viral markers and serologic results, was used to estimate the frequency of in utero and intrapartum transmission in the French Collaborative Study (32). Sixty-five percent of infant infections in this non-breastfed population were estimated to have occurred intrapartum (95 percent confidence interval (CI) 22–92). Ninety-five percent of infant infections occurred later than the last 2 months before delivery.

A meta-analysis of published literature estimated the risk of breastfeeding transmission in prenatally infected women to be 14 percent (33). One study in a breastfed population attempted to determine relative contributions of the three times of transmission using information from serial polymerase chain reaction evaluation of infants born to seropositive mothers (47 infected infants). The estimated rate of in utero transmission was 7.7 percent, that of combined in utero and intrapartum transmission was 17.6 percent, and that of late postnatal transmission was 4.9 percent (34).

Transmission via breastfeeding has been found to be related to the duration of breastfeeding. In the Italian cohort, the odds ratio for infant HIV-1 infection per day of breastfeeding versus exclusive formula feeding was 1.19 (95 percent CI 1.10–1.28) (35). Infants who breastfed for more than 15 months in the Nairobi Mother-to-Child Transmission Study had 1.9-fold odds of infection (95 percent CI 1.1–3.5), and 32 percent of HIV-1 infections were attributable to breastfeeding beyond 15 months (7). Mathematical modeling was used in this cohort to determine the risk: benefit ratio at different infant ages postnatally; the risk of HIV-1 transmission exceeded the potential benefit of breastfeeding at 3–7 months of age (36).

CORRELATES OF VERTICAL TRANSMISSION

Viral load to which an infant is exposed

Systemic maternal viral load—The amount of HIV-1 to which an infant is exposed is dependent on maternal viral burden, specifically at sites accessible to the infant. Women with detectable viremia (by p24 antigen or culture) have a two- to three-times higher risk of transmitting HIV-1 to their infants (37, 38). Advanced maternal clinical status is associated with increased vertical transmission (37). In a meta-analysis of breastfeeding transmission, women with primary infection had an estimated breastfeeding transmission rate of 29 percent versus an estimated rate of 14 percent among women with chronic infection. Both advanced clinical disease status and primary infection are associated with increased systemic viral burden. The effectiveness of antiretroviral therapy in decreasing transmission is probably related to a decrease in maternal viral burden (39, 40). Quantitative HIV-1 RNA levels are correlated with transmission. Fifteen (75 percent) of 20 transmitting mothers had HIV-1 RNA levels greater than 50,000 copies per milliliter in the University of California, Los Angeles cohort versus four (5 percent) of 75 nontransmitters ($p < 0.01$) (41).

Maternal local viral load—HIV-1 has been detected in vaginal, cervical, amniotic fluid, and breast milk samples (42–49). HIV-1 detection in cervical, vaginal, and breast milk samples is inversely associated with CD4 count (48, 49). The relation between genital

HIV-1 shedding and infant infection has not been evaluated in the published literature to date. In the Rwandan cohort, the presence of HIV-1-infected cells in breast milk 15 days postpartum was strongly predictive of infant infection (50). Local viral load may be influenced by cofactors such as sexually transmitted diseases which enhance local inflammation and subsequently activate local cellular HIV-1 shedding; cervical inflammation and gonococcal urethritis have been associated with increased detection of HIV-1 infected cells (42–43, 49, 51). The effect of sexually transmitted diseases on perinatal transmission of HIV-1 has been difficult to assess, because antenatally diagnosed sexually transmitted diseases are treated, and diagnosis at the time of delivery is often impractical. In the only study to assess the effect of micro-biologically diagnosed sexually transmitted diseases on vertical transmission, no association was observed (3). While a single case report describes a breastfeeding infant in whom HIV-1 infection appeared to be temporally related to breastfeeding during a time in which the mother had a breast abscess (52), factors such as maternal mastitis, infant stomatitis, and teething have not been systematically evaluated for their effect on vertical transmission.

Maternal immunity—Decreased maternal cell-mediated immunity is correlated with increased vertical transmission (37). Cell-mediated immunity may directly influence transmission or may be a surrogate marker for maternal viral load. The role of specific humoral immunity in vertical transmission is still unclear. The association of prematurity with infant infection suggests a potentially protective effect of maternal humoral immunity, as active transport of antibody occurs late in pregnancy and antibodies have the potential to decrease the viral load to which the infant is exposed. While early studies noted a protective effect of gpl20 antibodies (16), more recent studies have failed to corroborate these observations (53). Recent studies have, in fact, noted higher levels of maternal immunoglobulin G to V3 sequences in transmitting mothers and a broader distribution of antibody classes and subclasses in transmitting mothers suggestive of antibody-mediated *enhancement* of transmission (54–56). Maternal antibodies to p24, a variety of *env, gag,* and *pol* regions, or viral proteins have not been associated with decreased transmission (16, 57). Antibody-dependent cellular cytotoxicity titers were not correlated with infant protection in a multicenter evaluation of 78 neonates (58). Small studies suggest a protective effect of autologous neutralizing antibody on vertical transmission (59, 60). Mucosal secretions contain a population of antibodies which include immunoglobulin A, immunoglobulin G, and immunoglobulin M. The relation between mucosal HIV-1-specific antibodies and viral shedding in the genital tract is not known. Van de Perre et al. (52) observed that infant HIV-1 infection in a breastfed cohort was associated with a lack of persistence of immunoglobulin M and immunoglobulin A in maternal milk.

Factors which influence ease of virus transfer from mother to infant

Placentitis, ascending genital infection during the peripartum period, instrumentation at delivery, and passage through the birth canal are processes which may increase the likelihood of infant exposure to the virus. Chorioamnionitis and prolonged ruptured membranes are associated with infant infection (37, 61). Although the difference in transmission risk between twins is most evident in vaginally delivered twins (50 percent of first-born twins are infected versus 19 percent of second-born twins, $p = 0.006$), first-born twins delivered by cesarean section are also more likely to be infected than second-born twins (62, 63). The first-born with the lower lie may be at increased risk of ascending infection, particularly in the setting of prematurely ruptured membranes. Instrumentation and episiotomy have not been consistently associated with transmission (7, 22). In the University of California, Los Angeles cohort, procedures involving increased infant exposure to maternal blood were associated with increased transmission (odds ratio = 7.7, 95 percent CI 1.5–40.4) (39). Two meta-analyses of several mother-to-child transmission

studies estimate that cesarean delivery may decrease vertical transmission by 25–50 percent (64–66). Cesarean delivery decreases exposure to genital secretions and, if performed electively, may decrease the likelihood of maternal-fetal blood transfusion which occurs late in labor.

Viral infectivity

Biologic differences in retroviruses contribute to differences in transmission. Human immunodeficiency virus type 2 (HIV-2), unlike HIV-1, is rarely transmitted from mother to child, and women who are dually infected with HIV-1 and HIV-2 are more likely to transmit HIV-1 to their infants (5, 67). In one small study, there was increased mother-to-child transmission of HIV-1 in mothers with HIV-1-infected partners; in another study, mothers with more than three sexual partners during pregnancy were more likely to transmit virus than mothers with one partner during pregnancy (68, 69). These observations could be due to a variety of factors, including the likelihood of concomitant sexually transmitted diseases, potentially increased genital viral load, or potential genital acquisition of a fetotropic viral strain. Studies evaluating the influence of viral genotypic or phenotypic properties on vertical transmission are often cumbersome and accordingly limited in size.

Variants—The *env* gene is the most highly variable sequence in the HIV-1 genome. Envelope glycoproteins determine cellular tropism and cytopathicity, as well as serve as epitopes for the host immune response. Selection pressure from this response may contribute to the evolution of increased variability. An individual infected with HIV-1 develops multiple heterogeneous strains which may have divergent cell or tissue tropism and pathogenicity. Because strain isolation requires cell culture, predominantly isolated strains may not reflect the predominantly pathogenic ones; the cytopathic potential of strains may select against their growth. Several small studies have evaluated strain variants in mother-infant pairs with HIV-1 infection. While one study demonstrated a similar degree of variability of VI and V2 sequences in two mother-infant pairs (70), most studies have shown that the infant acquires a subset of the mother's V3 variants (71–74). The observation that the major maternal variant was sometimes transmitted suggests that mechanisms other than variant escape from maternal immune surveillance may be operative in transmission.

Phenotype—Strains differ in terms of in vitro replicative rate, cellular tropism, and syncytium induction. There is evidence to suggest that syncytium-inducing strains have increased virulence (75, 76). While macrophage-specific tropism has been observed in some strains, whether there is site-specific tropism of strains has yet to be established. It is not known, for instance, whether certain strains would be more frequently seen in genital secretions, breast milk, or the placenta. Reinhardt et al. (77) observed that cord blood mononuclear cells were preferentially infected by macrophage-tropic, nonsyncytium-inducing isolates, as opposed to peripheral blood mononuclear cells, which were more likely to be infected by T-lymphotropic syncytium-inducing strains. In a study of 16 HIV-1-infected women, a syncytium-inducing phenotype was associated with a higher HIV-1 RNA copy number in maternal plasma ($p < 0.05$) (60). In another study, nine mother-infant transmitters were compared with nine nontransmitting pairs; two pairs in each group had growth on MT2 and were syncytium-inducing (78). The potential importance of macrophage-tropic virus is suggested by one study in which primary viral isolates from seven of seven transmitting HIV-1-infected mothers were macrophage-tropic versus 14 (50 percent) of 28 nontransmitting mothers (79).

Subtype—HIV-1 has been classified genotypically into several subtypes (clade groups) on the basis of genotypic variation in the *env* region. Variation of *env* amino acid composition within each subtype is less than 10 percent, while intersubtype variation is over 20 percent

(80). There is typically a predominant subtype within a geographic region, although a few populations have more than one major subtype. It is not yet known whether genotypic subtype reflects either pathogenicity or infectivity. Small studies suggest a relation between subtype and phenotype, although important potential confounders of the relation, such as disease stage or duration, were not considered (81, 82). Subtype-related cell tropism has been observed in isolates obtained from Thailand (83). Epithelial cells from vaginal, cervical, breast, and penile foreskin tissue were more easily infected with subtype E virus than with subtype B virus. It is possible that subtype influences transmissibility and, hence, influences the epidemiologic patterns of HIV-1 subtype distribution (84, 85). If subtype influences cell tropism, it may affect the rate and timing of vertical transmission. Thus, subtypes with breast milk lymphocyte tropism would more frequently be transmitted postnatally, while genital-tropic subtypes would likely be transmitted intrapartum. An understanding of the relation between HIV-1 subtype and vertical transmission will be important in determining whether interventions need to be subtype-specific.

Infant susceptibility

Prematurity and low birth weight—Infants born prematurely have an immature immune system, and prematurity is associated with increased transmission of HIV-1 (37). Low birth weight has not been consistently associated with vertical transmission (37). Both prematurity and low birth weight may be caused by in utero infection with HIV-1. Determining whether these characteristics are the result of infection rather than predisposing factors for infection is difficult.

Transient infection—Transient detectable viremia was observed at day 19 and day 51 in a child who has had no subsequent evidence of infection (86). Laboratory contamination is difficult to completely exclude as an explanation for observed transient viremia. In this case, the two viral cultures were genetically identical, and genotypic analysis of the peripheral blood lymphocytes indicated that it was unlikely that the samples originated from different individuals. In the European Collaborative Study, nine of 264 HIV-1 seronegative infants had detectable viral markers (culture or polymerase chain reaction) on at least one occasion (87). Six (2.7 percent) of 219 infants had detectable viral markers on at least two occasions. None of the infants were breastfed and none had clinical or immunologic abnormalities. Further immunologic evaluation of transiently viremic children will be useful in determining whether there is the possibility of an effective immune response to this infection.

Cellular immunity—Host defenses are the final barrier to infection. Infant cell-mediated immunity may be an important correlate of protection from perinatal infection. HIV-1-specific cytotoxic T-cell activity has been detected in uninfected infants of seropositive mothers (88, 89). Clerici et al. (90) observed that 35 percent of 23 infants had in vitro env-specific T-helper cell immunity detectable in cord blood. None of the eight infants with evidence of in utero immunity developed infection, while three of 15 infants without immunity were infected.

Other correlates

Vitamin A deficiency was associated with a highly significant increase in vertical transmission in a mother-to-child transmission cohort in Malawi (11). Women with low vitamin A levels (<0.7 μmol/liter) had a 4.4-fold increased risk of transmission compared with women with high vitamin A levels (> 1.4 μmol/liter) (95 percent CI 1.6–11.9). The effect of vitamin A on transmission was still seen after adjustment for CD4 count in a multivariate logistic regression model. Vitamin A levels may be a surrogate marker for general nutritional status or disease status rather than a direct correlate of transmission. However, vitamin A is an immune modulator which might affect maternal viral burden.

Alternatively, because vitamin A is important in the maintenance of mucosal integrity, it could affect either maternal mucosal viral shedding or infant mucosal susceptibility to infection, and thus influence vertical transmission.

INTERVENTIONS TO DECREASE VERTICAL TRANSMISSION

Antiviral therapy

In the AIDS Clinical Trial Group 076 trial, a multicenter, randomized, double-blind, placebo-controlled study, women in the zidovudine (AZT) treatment arm had a transmission rate of 8.3 percent, while women receiving placebo had a transmission rate of 25.5 percent. The 67.5 percent reduction in risk was highly significant ($p = 0.00006$) (40). Women received AZT antepartum and during delivery, and infants received AZT for the first 6 weeks of life. Boyer et al. (39) also noted a protective effect of AZT in a nonrandomized prospective cohort. One (4 percent) of 26 mothers who received AZT transmitted virus versus 12 (29 percent) of 42 untreated mothers ($p = 0.01$) (39). The findings of the AIDS Clinical Trial Group 076 trial were important in establishing that most HIV-1 transmission from mother to child can be prevented. These findings are now the basis for the standard of care in the management of HIV-1-infected pregnant women in developed countries. Extrapolation of the AIDS Clinical Trial Group 076 trial findings to other populations is difficult. The comprehensive treatment course used in the AIDS Clinical Trial Group 076 trial was chosen in order to optimize the likelihood of detecting an effect on transmission, but it leaves uncertainty regarding the point at which the drug exerted its effect. AZT could affect vertical transmission via a reduction in maternal viremia or genital viral shedding, or via prophylactic protection of the infant postnatally (table 4). The full AIDS Clinical Trial Group 076 trial regimen is expensive and logistically difficult to administer in developing-country settings. A variety of clinical trials are planned or ongoing to determine the effectiveness of various regimens of antiviral therapy in Africa and Thailand. It will be particularly important to determine the effect of AZT on vertical transmission in the breastfeeding cohorts of Africa.

Topical antiseptic

A large randomized trial of intrapartum vaginal chlorhexidine washes failed to demonstrate a protective effect against vertical transmission (91). Although there was no protection in the group overall, chlorhexidine was associated with a significantly lower rate of infection in a subgroup of women with prolonged ruptured membranes. Several observations, including the differential infection rate of vaginally delivered first-born twins, the protective effect of cesarean delivery, and the association of prolonged ruptured membranes with vertical transmission, suggest that infant exposure to HIV-1 in the genital tract during delivery is an important determinant of transmission. Compared with other intervention strategies, topical microbicides have the advantage of being safe and inexpensive and can be used without HIV-1 screening of pregnant women. Another trial of chlorhexidine is currently under way.

Cesarean section

Although cesarean delivery may be associated with decreased transmission, this intervention is not one that can be easily implemented in resource-poor settings. The long-term effects of operative delivery on disease progression in HIV-1-infected mothers also need to be considered. A randomized clinical trial of cesarean versus vaginal delivery is ongoing. As a randomized trial, the study will be able to evaluate the unconfounded risk of vaginal delivery for vertical transmission. In the future, a decision algorithm which identifies high risk transmitters, comparable to the one used for herpes simplex virus, may be useful in determining which women should undergo operative delivery.

Immunoglobulin

Immunoglobulin administration in combination with vaccination has been an effective intervention in the prevention of vertical transmission of hepatitis B. An ongoing trial is evaluating the effectiveness of postpartum administration of HIV-1-specific immunoglobulin to infants. In hepatitis B infection, the presence of specific immunoglobulin G in the absence of antigenemia indicates clearance of infection secondary to an effective host immune response. The presence of HIV-1-specific antibody, however, is not associated with clearance of HIV-1 infection. Thus, passive protection of the infant by HIV-1 -specific immunoglobulin may be a less promising intervention.

Avoidance of breastfeeding

While it is clear that breastfeeding transmission of HIV-1 occurs, there are limited alternatives to breast-feeding in settings where HIV-1 is most prevalent. A randomized clinical trial of breast and formula feeding is ongoing. Determination of the amount and timing of breastfeeding transmission will be useful in determining safe recommendations for the feeding of HIV-1-exposed infants. If there is a substantial amount of late breastfeeding transmission, early weaning might be a practical intervention.

Vitamin A

A trial of antenatal maternal vitamin A administration is ongoing. Vitamin A is inexpensive and could probably be safely administered to all expectant mothers in populations with high prevalences of HIV-1 infection, without the need for HIV-1 screening. Although vitamin A has been associated with teratogenicity when administered in large doses during pregnancy, supplementation with lower doses during pregnancy has not been associated with toxicity (92). Vitamin A has the additional benefit of decreasing childhood morbidity in infants exposed to HIV-1 (93).

SUMMARY

A great deal of progress has been made in our understanding of mother-to-child transmission of HIV-1. Standardization of case definitions and transmission rate calculation methodologies, and a broader array of diagnostic options for detection of infant HIV-1 infection, will enhance our ability to evaluate and compare cohorts worldwide. In the next decade, several intervention studies should be completed. Carefully designed intervention studies have the potential both to determine which interventions are effective as well as to add to our understanding of vertical transmission of HIV-1. Regional differences in vertical transmission rates reflect a variety of viral, host, and obstetric factors. Intervention strategies will probably need to be regionally designed, taking into consideration these factors. Further research on timing and correlates of vertical transmission is necessary to determine the extent to which specific clinical trials can be extrapolated to public health policy.

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Abbreviations

AIDS acquired immunodeficiency syndrome

AZT	zidovudine
Cl	confidence interval
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2

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TABLE 1

Vertical transmission rates

Location	Vertical transmission rate (%)	Reference(s)
Africa	22–43	
Zaire		2,3
Zambia		4
Ivory Coast		5
Rwanda		6
Kenya		7,8
Congo		9
Uganda		10
Malawi		11
Tanzania		12
Asia	48	
India		13
Caribbean	24	
Haiti		14
United States	17–30	
Miami, FL		15
Brooklyn, NY		16
New York, NY		17, 18
Baltimore, MO		19
Atlanta, GA		20
Europe	14–27	
European Collaborative Study		21,22
Italian Multicenter Study		23
French Collaborative Study		24, 25

TABLE 2

Ghent (Belgium) 1992 recommendations for estimation of mother-to-child transmission rates

Clinical and laboratory procedures
• Identification of women during pregnancy
• Comparison group of HIV* -seronegative mother-child pairs to calculate excess mortality among HIV-seropositive mother-child pairs
• Regular collection of infant blood samples until at least 15 months of age
• Verbal autopsy of children who died at home
Diagnostic criteria and case definitions
• World Health Organization clinical criteria for pediatric AIDS*
• Ghent 1992 definitions for “HIV-related signs and symptoms”
• Ghent 1992 definitions for “probable HIV-related death”, “probable non-HIV related death”, and “indeterminate”
• Western blot positive determination using World Health Organization criteria (at least gp 41 and gp 120/160 positive) and negative if complete absence of any band, all others indeterminate
• 15-month cut-off point for estimating mother-to-child transmission rates using antibody test for definition of infant infection status
Transmission rate calculations (four methods)
• Use of antibody test only
• Use of antibody test added to estimated excess mortality in infants of HIV-seropositive mothers (when compared with HIV-seronegative comparison group) (indirect method)
• Use of antibody test combined with clinical assessment of HIV infection status of children with indeterminate serostatus due to death or loss to follow-up (direct method)
• Use of other virologic and immunologic methods to define infant infection

* HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

TABLE 3

Definitions for timing of human immunodeficiency virus type 1 vertical transmission

AIDS Clinical Trial Group recommendations 1992, non-breast-feeding infants
In utero—Viral marker (polymerase chain reaction or culture) positive in first 48 hours (cord blood sample ideally confirmed with peripheral blood sample)
Intrapartum—Viral marker negative in blood samples obtained in the first week of life; first positive viral marker detected from day 7 to day 90
Ghent (Belgium) recommendations 1994, breast-feeding infants
In utero—First positive viral marker detected in first 2 days of life (cord blood uninterpretable)
In utero plus intrapartum— First positive viral marker obtained between 30 and 60 days of life
In utero plus intrapartum plus early postnatal—First positive viral marker obtained between 90 and 180 days of life

TABLE 4

Intervention strategies to prevent mother-to-child transmission of human immunodeficiency virus type 1

Correlate	Model	Intervention
Maternal viral load	Antenatal treatment of syphilis, gonorrhea, chlamydia	Antiviral therapy (i.e., zidovudine)
Infant viral exposure	Postnatal antibiotic treatment of infants at risk for bacterial infections acquired intrapartum (i.e., after prolonged ruptured membranes/maternal fever)	Antiviral therapy (i.e., zidovudine)
Maternal genital viral load	Group B streptococcus	Topical antiseptic (i.e., chlorhexidine)
	Primary active herpes simplex virus (HSV)	Cesarean section
Maternal immunocompromise	Hepatitis B	Passive immunotherapy of infant
Breast feeding	Human T-cell lymphotropic virus type 1	Breast milk alternatives
Vitamin A deficiency	None	Vitamin A