Vertical Human Immunodeficiency Virus Type 1 - HIV-1 - Transmission – A Review

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Several factors appear to affect vertical HIV-1 transmission, dependent mainly on characteristics of the mother (extent of immunodeficiency, co-infections, risk behaviour, nutritional status, immune response, genetical make-up), but also of the virus (phenotype, tropism) and, possibly, of the child (genetical make-up). This complex situation is compounded by the fact that the virus may have the whole gestation period, apart from variable periods between membrane rupture and birth and the breast-feeding period, to pass from the mother to the infant. It seems probable that an extensive interplay of all factors occurs, and that some factors may be more important during specific periods and other factors in other periods. Factors predominant in protection against in utero transmission may be less important for peri-natal transmission, and probably quite different from those that predominantly affect transmission by mothers milk. For instance, cytotoxic T lymphocytes will probably be unable to exert any effect during breast-feeding, while neutralizing antibodies will be unable to protect transmission by HIV transmitted through infected cells. Furthermore, some responses may be capable of controlling transmission of determined virus types, while being inadequate for controlling others. As occurence of mixed infections and recombination of HIV-1 types is a known fact, it does not appear possible to prevent vertical HIV-1 transmission by reinforcing just one of the factors, and probably a general strategy including all known factors must be used. Recent reports have brought information on vertical HIV-1 transmission in a variety of research fields, which will have to be considered in conjunction as background for specific studies.

Key words: HIV - vertical HIV-1 transmission

Human immunodeficiency virus type 1 (HIV-1) infection in children is generally more serious than in adults, due to different factors with a faster disease progression than observed in adults and a higher mortality (Chu et al. 1991, Shearer et al. 1997a, Krogstad et al. 1999a, Zeichner et al. 1999). Other complications due to HIV-1 infection in children can result from the lower and less sustained response to immunizations (Lecuona et al. 1996, Gibb et al. 1996) or even a higher risk for complications, as has been observed in anti-tuberculosis immunizations of HIV-1 infected children (O'Brien et al. 1995).

Vertical transmission (VT) has been the principal cause (80-90%) of HIV-1 infection in children (Newell 1998). The treatment of pregnant women and their children with zidovudine (better known as azidothymidine or AZT) has reduced transmission by 68% in one trial (Connor et al. 1994). In Africa, Asia and Latin America, this reduction of mother-to-child HIV-1 transmission has not been as extensive, due to the less systematical use of the antiretroviral treatment. In Brazil, the National Coordination for Sexually Transmitted Diseases and AIDS of the Ministry of Health (CNDST/AIDS) has identified a rapid growth of HIV-1 infected fertile women since 1991, with a corresponding increase in numbers of HIV-1 infected children, which has slowly started to diminish from 1996 onwards. In that year, and more intensely in 1997, pregnant women were counseled to make an HIV-1 test as part of prenatal care, and zidovudine was freely administered to all infected women, as well as to the new-born children. Milk-substitutes were offered to reduce postnatal vertical HIV-1 transmission (Boletim Epidemiológico 1999). Actual numbers of vertical HIV-1 transmission are only available for certain cohorts in Brazil, as extreme variations occur between different hospitals, districts and cities. However, 41,052 cases of AIDS have been diagnosed in women, and 5,778 Aids cases in children below 13 years have been reported up to August 1999.

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Even before 1994, when no kind of therapy was available for pregnant HIV-1 infected women, VT varied from 13-48% (Newell 1998), indicating that the majority of children born to HIV-1 infected women did not become infected. This means that something exists that protects the majority of the children born to HIV-1 infected women.

Several factors have shown to affect VT, although controversy exists on most. Table I shows an overview of the different factors that have been associated to VT.

MOTHER'S HEALTH AND GENOTYPE

It appears logical that healthier mothers give birth to healthier children. However, although some authors note that healthier mothers transmit HIV-1 less often than women with advanced immunodeficiency, no statistical significance has been reached (St. Louis et al. 1993, Jansson et al. 1997, Pitt et al. 1997, Tess et al. 1998). It seems probable that the more important factor is the viral load in the mother's blood, normally higher in more advanced disease stages, than the clinical progress of HIV-1 infection. However, some specific factors apparently link VT with the mother's health. For instance, Vitamin A deficiency (Semba et al. 1994, Greenberg et al. 1997, Wabwire-Mangen et al. 1999, disputed by Burger et al. 1997) and infection of pregnant women with other STD (Bulterys et al. 1997) or hepatitis C virus (Hershow et al. 1997) has been linked to a greater risk of VT. Drug use by the mother also increases the risk for mother-to-child transmission (Rodriguez et al. 1996, Bulterys et al. 1997, Greco et al. 1998). The genetical background of HIV-1 infected pregnant women influences the progress of the disease (Kaslow et al. 1996) and, probably, the viral load in any patient's blood. Women with mutations in the main co-receptor used by HIV-1 to infect cells that express the HIV-1 receptor CD4 appear to transmit HIV-1 to their offspring less frequently than do women not presenting such genotype mutations (Shearer et al. 1998). Other authors have not confirmed this observation (Rousseau et al. 1997, Edelstein et al. 1997, Misrahi et al. 1998, Mas et al. 1999). It is known that one specific mutation (CCR5Δ32) is associated to a retardation of disease progression caused by HIV-1 isolates that use the CCR5 co-receptor after binding to CD4, known as macrophage-tropic or R5 isolates (Bratt et al. 1998, Kostrikis et al. 1999). This better clinical evolution of the infection is probably also a consequence to a reduction in viral load due to a slower viral replication resulting from a lower host-cell infection efficacy. Disparity of results presented by different research groups probably derives from the heterogeneity of infecting HIV-1, possibly phenotypic heterogeneity. It has been shown that this specific mutation in the CCR5 co-receptor in HIV-1 infected children is also associated to a slower disease progression (Misrahi et al. 1998).

HIV has been detected in early and late placentas in different cell types (Lewis et al. 1990) at all stages of pregnancy (Newell 1998). However, the placental membrane constitutes an important barrier between mother and fetus (Ortigão 1995). A recent study found that cells from placental membranes of non-transmitters were not infected by HIV-1, although lymphocytes present within the placentas were HIV-1 positive (Tscherning-Casper et al. 1999). However, another study found

TABLE I

Factors that may affect the risk of vertical transmission (VT) of HIV-1

Non HIV related	
Mother's health/risk factors	Other infections (STD, HCV), drug use, malnutrition
Mother's genetic background	Some protection by CCR5Δ32, some HLA types
Child's genetic background	Some protection by CCR5Δ32
Delivery	Longer delivery period = higher risk
Breastfeeding	Increases risk, especially with nipple lesions
HIV related	
Viral load	A high viral load increases the risk of VT
Viral genotype	??? No correlation proven
Viral phenotype	Macrophage-tropism and rapid replication associated to VT
Immune response	Lower antibody response associated to greater risk?
	Low autologous NAb increases VT risk?
	Limited broadness of NAb response increases VT risk?
	Low suppressor cell response increases VT risk?
	Low and narrow CTL response increases VT risk?

NAb: neutralizing antibodies; CTL: cytotoxic T lymphocytes; STD: sexual transmitted disease; HCV: hepatitis C virus; HLA: human leukocyte antigen

HIV-1 in all placentas tested, in free mononuclear and membrane-constituting cells (Menu et al. 1999). As the placental membrane trophoblasts can be infected in vitro (David et al. 1992), both authors may be correct.

Transmission may occur through placental tears or disruptions, as leukocyte traffic through the maternofetal placental interface by continuous low-grade leakage has been demonstrated (Papadogiannakis 1997). Mononuclear cells appear to be able to adhere to placental tissue, and no direct correlation between infected term placentas and vertical HIV-1 transmission has been demonstrated (Schwartz et al. 1995). Inoculation of rabbits with human HIV-infected T lymphocytes has shown that inoculum-cell-specific human leukocyte antigens are transmitted, indicating that infected T cells pass from the mother to her offspring (Simpson et al. 1997). However, cell-free virus has also been shown to be transmitted (De Andreis et al. 1997).

VIRAL LOAD

The concentration of infective HIV-1 in the blood and genital secretions of HIV-1 infected pregnant women appears to be the factor which is best associated with the risk of VT, although it is surely not the only one (Rogers & Shaffer 1999, European Collaborative Study 1999).

A direct correlation between high viral loads in plasma of pregnant women and greater risk of vertical HIV-1 transmission has been shown to exist. This has been evidenced by several studies employing different methodologies, such as: (1) by the more frequent cell-culture isolation of HIV-1; (2) by detection of higher levels of plasmatic p24 in HIV-1 transmitting mothers; and (3) by detection of higher numbers of viral RNA copies in blood, as indicated in Table II. Some authors indicate that a certain threshold of viral load must be reached for vertical HIV-1 transmission (Weiser et al. 1994, Zöllner et al. 1997). However, the majority of the studies published shows an absence of such a threshold but a strong relationship between high viral loads and the risk (or probability), but not the timing, of VT (O'Shea et al. 1998, Garcia et al. 1999). Some studies have found no direct correlation between viral load and HIV-1 transmission (Lathey et al. 1999), but as one study showed a difference in viral load in plasma and in vaginal secretion (Rasheed 1998), it is possible that this lack of correlation could be explained by localized differences in viral load and, as will be discussed later, quality of local immune response.

Vertical HIV-1 transmission appears to be highest during labor and delivery, and risk factors may vary according to time of transmission (Mock et al. 1999). Approximately 25-38% of VT occur *in utero* (Mundy et al. 1987, Dunn et al. 1995, Brossard et al. 1995, Kalish et al. 1997). There are indications that this occurs more probably in the final weeks of gestation (Chouquet et al. 1997). However, the exact timing of transmission is very difficult to define (Rouzioux et al. 1995). Approximately 50% of the children are HIV-1 DNA and RNA negative at birth, confirming the hypothesis that at least 50% of HIV-1 infected children have been infected either peri- or post-natally by infected mother-milk (Kalish et al. 1997). It is known that between 1 and 2 thirds of breast-fed children of HIV-1 infected mothers get infected (Van de Perre 1999a, b). There appears to be a higher risk for infection through breast-feeding early after birth (Dunn et al. 1998), although there is a report of higher risk for VT late in the post-natal period (Leroy et al. 1998). Highest risk for HIV-1 transmission through breast-feeding appears to occur when viral load is highest, as during primary HIV-1 infection (Dunn et al. 1992) and when antiretroviral treatment of the mother is interrupted (Van de Perre 1999a). Colostrum intake has not been related to VT, but nipple bleeding increases the risk (Tess et al. 1998).

CONDITIONS OF DELIVERY

Premature birth, low birth weight, early placental rupture, placental membrane inflammation, long labour, hemorrhage during labour and bloody amniotic fluid are some of the factors associated

TABLE II

Viral load and vertical HIV-1 transmission

A high concentration of infective HIV-1 as indicated by a high efficiency of HIV-1 isolation from peripheral blood of infected pregnant women by cell culture correlates with a higher transmission of HIV-1 from mother to child, in frequencies statistically significant (Fang et al. 1995, Pitt et al. 1997, Bongertz et al. 1999, Rogers & Shaffer 1999)
Higher frequency of HIV-1 core antigen p24 detection in plasma from HIV-1 infected pregnant women (Zöllner et al. 1996, Lathey et al. 1999)
Significantly higher probability of vertical HIV-1 transmission for pregnant infected women with more elevated viral loads during pregnancy and/or at delivery (Borkowsky et al. 1994, Fang et al. 1995, Aleixo et al. 1997, Pitt et al. 1997, Anastos et al. 1999, Phuapradit et al. 1999, Mock et al. 1999)

to an increased risk of VT (Mandelbrot et al. 1996, Wabwire-Mangen et al. 1999, Rogers & Shaffer 1999, Shapiro et al. 1999). Some studies indicate caesarian birth to decrease risk of mother-to-child transmission (Newell 1994), an indication confirmed by studies in twins born to HIV-1 infected mothers, with a higher risk of HIV-1 infection of the first-born twin (Duliege et al. 1995). However, no general consensus on the protective effect of caesarian over natural birth exists up to now, and normally a discussion between doctor and patient decides this issue.

HIV-1 TYPE AND SELECTIVE TRANSMISSION

Studies comparing viral isolates from mother and child have shown that the heterogeneity of the child's isolate can be much more limited than that of the mother's HIV-1 isolate. This indicates that a selection may occur during vertical transmission, and cases where an infrequent variant of the mother's isolate constitutes the dominant variant in the child have been observed (Wolinsky et al. 1992, Wike et al. 1992, Scarlatti et al. 1993a, b, c). Some studies found differences in glycosylation patterns in the viral envelopes (Wolinsky et al. 1992, Wike et al. 1992). The genetical homogeneity of HIV populations in the infant at birth, higher than that found in the mother, indicates that either only a few variants are originally transmitted or are initially replicating in child (Jansson et al. 1997). The detection of only a small number of the mother's HIV-1 variants in placental membrane cells of transmitting mothers (Menu et al. 1999) appears to indicate that selection occurs at least for intra-uterine HIV-1 transmission, although some controversy on this issue exists (Mulder-Kampinga et al. 1995). A recent study indicates that an interindividual variability in HIV co-receptor expression can be observed for trophoblastic cells from early placentas, indicating a possible mechanism for HIV variant selection (Mognetti et al. 2000). However, many variants (Essajee et al. 1996), intrasubtype recombinants (Kampinga et al. 1997) and even genotypes (Lamers et al. 1994, Janini et al. 1998) may be transmitted from the mother to the offspring. No difference in preferential transmission of one genotype above others has been detected (Contag et al. 1997, Campodonico et al. 1998). Some studies found no difference between viral isolates from mother and infant, indicating that selection does not occur in all cases (Lamers et al. 1994). A case of one HIV-1 infected mother transmitting a selected variant to one child and multiple variants to another has been described (Wade et al. 1998), indicating that, if selection occurs, it might be circumstancial or dependent on a variety of factors, of which high numbers of different variants in high concentrations could be one. Some hypotheses on the mechanism of selection have been stipulated, and the variable region V3 of the envelope glycoprotein gp120, as well as the p17 core antigen, appear to be implicated in selection (Lu et al. 1996, Narwa et al. 1996, Leitner & Albert 1999, Hahn et al. 1999). The mechanism of selection is not known as yet, but selection may occur through dilution, through variants escaping from mother's immune response, selective infection, selective amplification or even selective replication in the child.

If selective infection occurs, there should be an association between viral tropism phenotype and HIV-1 transmission. This has been shown to be the case in several studies, indicating that macrophage-tropic, "non-syncytium-inducing", rapidly replicating viral variants are preferentially transmitted from mother to offspring (Ometto et al. 1995, De Rossi et al. 1997, Lathey et al. 1999). However, much controversy still exists on this issue, and even a preferential transmission of "syncytium-inducing" HIV-1 variants has been reported (Scarlatti et al. 1993a, Ayyavoo et al. 1996, Colognesi et al. 1997, Jansson et al. 1997). Our own experience has shown that no statistically significant difference between HIV-1 vertical transmission for mothers harboring macrophage-tropic or T-lymphocyte tropic HIV-1 populations can be observed, although a slight preponderance of the latter phenotype was observed in transmitting mothers (unpublished data). However, no absolute correlation between the children's and mother's HIV-1 phenotype has been found, and all types have been detected in vertically infected children (Scarlatti et al. 1993b). It seems highly probable that viral load and membrane leakage interplay during intrauterine HIV-1 transmission, permitting passage of any phenotype to the fetus. In the absence of membrane leakage, rapidly replicating HIV-1 variants with monocyte-macrophage-tropism appear to be more easily transmitted from mother to child. During delivery, it is probable that no kind of selection occurs, and that the phenotype of the HIV-1 variant(s) transmitted to the child will reflect more closely the predominant phenotype in the mothers blood, although susceptibility of the child's cells to infection by the mother's HIV-1 isolate will also affect the "selection" process.

IMMUNE RESPONSE AND VERTICAL HIV-1 TRANSMISSION

Immune correlates for HIV protection are still not totally defined, although it seems probable that an interaction between several host and viral factors occur (Sheppard et al. 1993). Induction of sup-

pressor and cytotoxic T lymphocytes (CTL) and of neutralizing antibodies (NAbs) is considered fundamental for a protective immune response to anti-HIV/AIDS vaccine candidates (Workshop Report 1997). These immune responses have also been implicated in protection against VT.

T LYMPHOCYTE CYTOTOXICITY AND SUPPRESSION

The CTL response, so effective in primary HIV-1 infection (Autran et al. 1996), has been shown to be stronger in non-transmitting than in HIV-1 transmitting mothers in several studies (Ffrench et al. 1998, Jin et al. 1998, Mac Donald et al. 1998). CTL specific for HIV-1 have been detected more often in exposed-but-uninfected than in infected children of HIV-1 positive mothers (Cheynier et al. 1992). However, the protection against VT due to a strong CTL in HIV-1 infected pregnant women will not be effective for vertical transmission through breastfeeding (Mac Donald 1998). A more recent study indicates that although non-transmitting mothers had a stronger CTL response against autologous variants of HIV-1, this response may not be sufficient to prevent HIV-1 transmission, as the majority of the children's HIV-1 infected cells were susceptible to their mothers CTL response (Wilson et al. 1999). Antibody dependent cellular cytotoxicity levels in pregnant women did not appear to protect their offspring from HIV-1 infection (Jenkins et al. 1994), although some correlation to protection has been reported (Ljunggren et al. 1990, Hutto et al. 1996). However, recent data indicate that the ADCC response in HIV-1 infection may be underestimated up to now (Hildreth et al. 1999).

The importance of suppressor T lymphocytes in VT has been demonstrated, with stronger suppression being associated to non-transmission of HIV-1 (Plaeger et al. 1999). Cytokines have been shown to affect the mothers placental membrane cells (Shearer et al. 1997b, Moussa et al. 1999), to be augmented in non-infected children of HIV-1 infected mothers (Wasik et al. 1999) and associated to levels of viral load in the mothers blood and cervix (Iversen et al. 1998).

HUMORAL IMMUNE RESPONSE

Antibody specificity of HIV-1 transmitting and non-transmitting mothers has been compared by determining binding of antibodies to synthetic peptides. The peptides are synthesized to correspond to immunologically important epitopes of different HIV-1 genotypes. Some studies report an association between higher levels or higher affinity/avidity of anti-V3 antibodies and non-transmission of HIV-1 (Devash et al. 1990, Markham et al. 1994, Lallemant et al. 1994, Ayyavoo et al. 1996, Jansson et al. 1997). Antibodies specific for peptides in the envelope glycoprotein gp41 have also been reported to be associated to protection against VT (Ugen et al. 1997). However, other studies have found no association with antibody specificity or titer and mother-to-child HIV-1 transmission (Parekh et al. 1991, Robertson et al. 1992, Halsey et al. 1992, Khouri et al. 1995, Louisirirotchanakul et al. 1999). Nevertheless, it must be remembered that HIV-1 specific humoral immune response during pregnancy is known to be reduced (Mikyas et al. 1997, Bongertz et al. 1998). Results obtained by our group indicated that no correlation between specificity, titer or broadness of antibody response with VT could be established. However, differences in peptide choice or manufacturer and in the technique used will affect affinity or titer of the antibodies detected, and may in part explain the controversy of this issue (Halsey et al. 1992, Peckham & Gibb 1995).

Neutralizing antibodies should be expected to be an important factor in protecting the fetus/infant from infection by the mother's HIV-1, as they can pass the placental barrier, have been detected in mothers milk and would also be present during delivery. However, it seems important that these antibodies should be able to neutralize the HIV-1 strain circulating in the mother's blood during pregnancy/delivery, i.e., to be effective against the autologous viral strain. Autologous neutralizing antibodies have been shown to be important for prevention of vertical mother-to-child HIV-1 transmission (Scarlatti et al. 1993a, Hutto et al. 1996, Jansson et al. 1997, Louisirirotchanakul et al. 1999, Lathey et al. 1999), although some reports deny the importance of autologous neutralizing antibodies (Husson et al. 1995, Hengel et al. 1998). In a study carried out by our group no correlation between autologous neutralizing antibodies and VT could be established, although further studies will be necessary to clarify this issue. As selection of HIV-1 transmission occurs, it is possible that neutralizing antibodies would be uneffective if not all variants present in the mother are neutralized, so that non-neutralized variants are transmitted. This hypothesis has been confirmed by results presented by Okamoto et al. (1997). However, there appears to be no major discussion on the finding that broadly neutralizing antibodies present in high titers will be associated to non-transmission of HIV-1 (Sienna Workshop 1992, Scarlatti et al. 1993b, Khouri et al. 1995, Hutto et al. 1996, Jansson et al. 1997, Cologognesi et al. 1997, Bongertz et al. 1999, Louisirotchanakul et al. 1999). Nevertheless, some studies do not detect any protection by neutralizing antibodies in VT (Parekh et al. 1991, Kliks et al. 1994, Gras et al.

1998, Hengel et al. 1998, Mabondzo et al. 1998). A recent study carried out in monkeys indicated that low titer neutralizing antibodies do not protect at all; only partial protection is achieved, even by antibodies able to neutralize up to 90% of HIV-1 infection at low dilutions; and that, in order to be protective, specific neutralization has to be absolute, neutralizing 100% of the present virus (reviewed by Moore & Burton 1999). Our data with neutralization of Brazilian primary HIV-1 isolates support this conclusion (Bongertz et al. 1999, and unpublished data). Moreover, it appears to us that for VT, the timing and mechanism will be important in order to clarify this issue. It seems probable that a strong local neutralizing antibody response, high titered and broad, should be effective in controlling rapidly multiplying viruses present during pregnancy, but will be unable to affect transmission by HIV-1 infected cells.

TRANSIENT HIV-1 INFECTION IN CHILDREN

Reports of spontaneous HIV-1 clearance or transient HIV-1 infections have been published since 1988 (European Collaborative Study 1999). Nowadays, transient infection is defined as cases with one or more positive cultures or polymerase chain reaction assays for HIV-1 followed by subsequent inability to detect the virus in specimens on multiple occasions, or seroreversion, or both (Frenkel et al. 1998). However, only in rare cases will several samples be collected from newborn children, and it is difficult to exhaustively document cases of transient infections. Some recent reports disclose errors responsible for some of the so-called transient infections (Bravo et al. 1996, Kalish et al. 1998, Frenkel et al. 1998). Hypotheses formed to explain HIV-1 "clearance" include infections due to virus with less-pathogenic "attenuated" strains, virus with replicative defects, very effective local mucosal immunity and highly effective natural immunity and even presence of "hidden" HIV-1 (Roques et al. 1995, Jansson et al. 1997). Some reports seem to confirm that transient HIV-1 infection in children of infected mothers exists, but, if so, they must be very rare (Bakshi et al. 1995, Frenkel et al. 1998).

ANTIRETROVIRAL DRUGS

Since viral load appears to be the factor most straightly related to VT, reduction of this load is the first strategy to be adopted. The ACTG 076 study published in 1994 (Connor et al.) indicates that treatment of HIV-1 infected pregnant women is to be strongly recommended.

One of the main problems in drug trials of pregnant women is that conformance with ethical precepts is sometimes difficult, which include not only care of the patients and their offspring during the trial but also possible future complications, and have to consider local health policies and possibilities. It is impossible, for instance, to offer pregnant HIV-1 infected women special benefits during the trial, such as milk substitute, sequential blood examinations, including cell typing/quantification, and viral load determinations, just to abandon these women without these benefits at the end of a trial (Workshop Report 1999).

Indications of collateral effects caused in mother and/or child must be taken seriously. Unacceptable cytotoxicity of AZT has been reported by an Australian group (as reviewed by Cherry 2000). Furthermore, a recent study showing that zidovudine is carcinogenic in newborn mice, and is incorporated into newborn mouse DNA (Olivero et al. 1999a), and that zidovudine crosses the human placenta and becomes rapidly incorporated into DNA of placental tissue in a dose-dependent fashion (Olivero et al. 1999b), caused some countries, notably South Africa, to hesitate before indicating use of this drug in pregnant women. Other collateral effects of reverse transcriptase inhibitors have been reported (Lorenzi et al. 1998). However, the great number of children born to mothers volunteering for the ACTG 076 protocol have been exhaustively examined, and no long-term effects of *in utero* exposure to zidovudine was detected (Culnane et al. 1999, Mc Sherry et al. 1999).

The very high success of the ACTG 076 protocol in preventing VT cannot be explained by reduction in viral load alone. Some indications even suggest that zidovudine reduces pediatric infection independent of the levels of maternal virus (Sperling et al. 1996, Aleixo et al. 1997, Garcia et al. 1999). Also, the European Collaborative Study (1999) indicates that even if the majority of vertical transmissions occurs perinatally, early administration of zidovudine may affect transmission rates through delaying delivery, thereby reducing the odds of low birthweight.

Studies on drug resistance have been carried out for zidovudine, and one study indicated that HIV-1 transmitting mothers had a greater frequency of zidovudine resistance than non-transmitting mothers (Colgrove et al. 1998), while another study, although finding zidovudine resistance in pregnant women, found no association with frequency of VT (Eastman et al. 1998). However, the studies show that zidovudine resistant HIV-1 variants can be transmitted from the infected mother to the child, and, therefore, children will have to be treated with alternative drugs in order to keep viral loads low enough to preclude a fast disease progression.

Many kinds of therapies have now been tested, such as a short-course zidovudine trial, which, although less efficient than the long-term ATCG 076 treatment, still protects approximately 50% of the children of HIV-1 infected mothers (Thaineua et al. 1998, Shaffer et al. 1999, Wiktor et al. 1999). Protease inhibitors such as a single-dose nevirapine treatment (Guay et al. 1999, Musoke et al. 1999) or nelfinavir mesylate (Krogstad et al. 1999b) and several combination therapies (Purswani et al. 1999, Kline et al. 1999) have been tested in pregnant women and children, with acceptable toxicity and high effectiveness. Highly active antiretroviral therapies have shown to reduce VT to zero in small cohorts (Zorilla 2000).

VACCINES

Vaccination or immunotherapy of pregnant HIV-1 infected women is one of the most direct goals in vaccine development. Pregnant women in prenatal care would be an easily accompanied cohort. For trials where protection of the child is the first objective, short term protective immune responses would be administered or induced. However, few trials have been reported. A study of passive administration of HIVIG (a pool of immunoglobulins from infected people, showing potent neutralization of primary HIV-1 isolates) has been carried out, but results were not significant as VT was very low due to zidovudine administration in both treated and placebo groups (Stiehm et al. 1999). Active immunization with DNA plasmids may be promising, as indicated by a trial carried out in pregnant chimpanzees, as cellular immune response and antibodies both at the systemic and mucosal levels were observed (Bagarrazi et al. 1999). Immunization trials of pregnant women with recombinant envelope glycoproteins have been carried out and, although safety and toxicity trials were highly successful, no protection against VT was observed (Lambert et al. 1998, Wright et al. 1999).

CONCLUSION

The strategy used nowadays for diminishing the risk of VT, as reported by Rogers and Shaffer (1999), is indicated in Table III. However, no strategy for increasing the mothers immune response exists, as trials carried out up to now have not been satisfactory. Nevertheless, immune response in association with other factors appear to be able to protect more than half of the children of HIV-1 infected mothers from vertical transmission. The steady fall observed in VT since effective chemotherapy was introduced, indicates that efforts must continue actively in order to eliminate this scourge, affecting approximately one third of the children born to HIV-1 infected mothers in the developing world. For these countries, where HIV-1 incidence in fertile women is high and VT is a real problem, the most effective strategy will probably be a combination of the strategies used today allied to passive immunotherapy or active immunization of pregnant women during gestation and immunization of the infected children.

REFERENCES

Aleixo LF, Goodenow MM, Sleasman JW 1997. Zidovudine administered to women infected with human immunodeficiency virus type 1 and to their neonates reduces pediatric infection independent of an effect on levels of maternal virus. *J Pediatr 130*: 906-914.

Anastos K, Kalish LA, Hessol N, Weiser B, Melnick S, Burns D, Delapenha R, DeHovitz J, Cohen M, Meyer W, Bremer J, Kovacs A 1999. The relative value of CD4 cell count and quantitative HIV-1 RNA in predicting survival in HIV-1-infected women: results of the women's interagency HIV study. *AIDS 13*: 1717-1726.

Autran B, Hadida F, Haas G 1996. Evolution and plasticity of CTL responses against HIV. *Curr Opin Immunol 8*: 546-553.

Ayyavoo V, Ugen KE, Fernandes LS, Goedert JJ, Rubinstein A, Williams WV, Weiner DB 1996. Analysis of genetic heterogeneity, antigenicity, and biological characteristics of HIV-1 in a maternal transmitter and nontransmitter patient pair. *DNA Cell Biol 15*: 571-580.

Bagarazzi ML, Boyer JD, Javadn MH, Chattergoon MA, Shah AR, Cohen AD, Bennett MK, Ciccarelli RB, Ugen KE, Weiner DB 1999. Systemic and mucosal immunity elicited after both intramuscular and intra-

TABLE III

Strategies to reduce vertical HIV-1 transmission

Reduce maternal viral load
Reduce exposure of infant to maternal blood and secretions (caesarian)
Treat conditions that might facilitate transmission (e.g. antibiotics against chorioamnionitis)
Reduce viral load in secretions by local agents (e.g. chlorhexidine)
Treat the infant
May also help: prevent premature birth; prevent membrane ruptures more than 4 h before delivery; eliminate unnecessary use of instruments during delivery avoid breastfeeding

(Rogers & Shaffer 1999)

vaginal delivery of HIV-1 DNA plasmid vaccines to pregnant chimpanzees. *J Infect Dis 180*: 1351-1355.

Bakshi SS, Tetali S, Abrams EJ, Paul MO, Pahwa SG 1995. Repeatedly positive human immunodeficiency virus type 1 DNA polymerase chain reaction in human immunodeficiency virus-exposed seroreverting infants. *Pediatr Infect Dis J 14*: 658-662.

Boletim Epidemiológico AIDS 1999. Ministério da Saúde, Secretaria de Políticas de Saúde, Coordenação Nacional de DST e Aids XII(3).

Bongertz V, Costa CI, Guimarães ML, Soares-da-Costa MFG, Grinsztejn B, The HEC/FIOCRUZ AIDS Clinical Research Group, Bastos FI, Pilotto JH, João Filho EC, Loureiro R, Chequer P, Telles PR, Galvão-Castro B, Morgado MG 1998. HIV specific humoral immune response in Rio de Janeiro, Brazil. *Mem Inst Oswaldo Cruz 93*: 391-398.

Bongertz V, Costa CI, Guimarães ML, Grinsztejn B, João Filho EC, Calvet G, Pilotto JH, Morgado MG and The HEC/FIOCRUZ AIDS Clinical Research Group 1999. *Rev Inst Med Trop São Paulo 41*: S-38.

Borkowsky W, Krasinski K, Cao Y, Ho D, Pollack H, Moore T, Chen SH, Allen M, Tao PT 1994. Correlation of perinatal transmission of human immunodeficiency virus type 1 with maternal viremia and lymphocyte phenotypes. *J Pediatr 125*: 345-351.

Bravo R, Gutiérrez M, Soriano V, Mellado MA, Perez-Labad ML, Mas A, Gonzalez-Lahoz J, Martin-Fontelas P 1996. Lack of evidence for viral clearance in children born to HIV-infected mothers. *AIDS 10*: 1744-1745.

Bratt G, Leandersson AC, Albert J, Sandstrom E, Wahren B 1998. MT-2 tropism and CCR-5 genotype strongly influence disease progression in HIV-1-infected individuals. *AIDS 12*: 729-736.

Brossard Y, Aubin JT, Mandelbrot L, Bignozzi C, Brand D, Chaput A, Roume J, Mulliez N, Mallet F, Agut H 1995. Frequency of early in utero HIV-1 infection: a blind DNA polymerase chain reaction study on 100 fetal thymuses. *AIDS 9*: 359-366.

Bulterys M, Landesman S, Burns D, Rubinstein A, Goedert JJ 1997. Sexual behaviour and injecting drug use during pregnancy and vertical transmission of HIV-1. *AIDS 15*: 76.

Burger H, Kovacs A, Weiser B, Grimson R, Nachman S, Tropper P, van Bennekum AM, Elie MC, Blaner WS 1997. Maternal serum vitamin A levels are not associated with mother-to-child transmission of HIV-1 in the United States. *J Aids Hum Retrovirol 14*: 321-326.

Campodonico M, Fay F, Fay D, Hernandez EP, Taborda M 1998. Does a particular HIV-1 subtype strain favor vertical transmission? 12th World AIDS Conf, Geneva, Switzerland, Abstract 23302.

Cherry M 2000. Letter fuels South Africa's AIDS furore. *Nature 404*: 911.

Cheynier R, Langlade-Demoyen P, Marescot MR, Blanche S, Blondin G, Wain-Hobson S, Griscelli C, Vilmer E, Plata F 1992. Cytotoxic T lymphocyte responses in the peripheral blood of children born to human immunodeficiency virus-1-infected mothers. *Eur J Immunol 22*: 2211-2217.

Chouquet C, Burgard M, Richardson S, Rouzioux C, Costagliola D 1997. Timing of mother-to-child HIV-1 transmission and diagnosis of infection based on polymerase chain reaction in the neonatal period by a non-parametric method. *AIDS 11*: 1183-1184.

Chu SY, Oxtoby MJ, Kilbourne BW 1991. The impact of the HIV epidemic on mortality in children, United States. *Pediatrics 87*: 806-810.

Colgrove RC, Pitt J, Chung PH, Welles SL, Japour AJ 1998. Selective vertical transmission of HIV-1 antiretroviral resistance mutations. *AIDS 12*: 2281-2288.

Colognesi C, Halapi E, Jansson M, Hodara V, Steuer G, Tresoldi E, Leitner T, Scarlatti G 1997. The role of virologic and immunologic factors in mother-to-child transmission of HIV-1. *Am J Reprod Immunol 38*: 197-200.

Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, VanDyke R, Bey M, Shearer W, Jacobson RL, Jimenez E, O'Neill E, Bazin B, Delfraissy JF, Culnane M, Coombs R, Elkins M, Moye J, Stratton P, Balsley J 1994. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med 331*: 1173-1180.

Contag CH, Ehrnst A, Duda J, Bohlin AB, Lindgren S, Learn GH, Mullins JI 1997. Mother-to-infant transmission of human immunodeficiency virus type 1 involving five envelope sequence subtypes. *J Virol 71*: 1292-1300.

Culnane M, Fowler M, Lee SS, McSherry G, Brady M, O'Donnell K, Mofenson L, Gortmaker SL, Shapiro DE, Scott G, Jimenez E, Moore EC, Diaz C, Flynn PM, Cunningham B, Oleske J 1999. Lack of long-term effects of *in utero* exposure to zidovudine among uninfected children born to HIV-infected women. Pediatric AIDS Clinical Trials Group Protocol 219/076 Teams. *JAMA 281*: 151-157.

David FJE, Autran B, Tran HC, Menu E, Raphael M, Debre P, Hsi BL, Wegman TG, Barré-Sinoussi F, Chaouat G 1992. Human trophoblast cells express CD4 and are permissive for productive infection with HIV-1. *Clin Exp Immunol 88*: 10-16.

De Andreis C, Simoni G, Castagna C, Sacchi L, Sirchia SM, Garagiola I, Persico T, Serafini P, Pardi G, Semprini AE 1997. Absence of detectable maternal DNA and identification of proviral HIV in the cord blood of two infants who became HIV-infected. *AIDS 11*: 840-841.

De Rossi A, Ometto L, Masiero S, Zanchetta M, Chieco-Bianchi L 1997. Viral phenotype in mother-to-child HIV-1 transmission and disease progression of vertically acquired HIV-1 infection. *Acta Paediatr* Suppl. *421*: 22-28.

Devash Y, Calvelli TA, Wood DG, Reagan KJ, Rubinstein A 1990. Vertical transmission of human immunodeficiency virus is correlated with the absence of high-affinity/avidity maternal antibodies to the gp120 principal neutralizing domain. *Proc Natl Acad Sci USA 87*: 3445-3449. Published erratum appears in *Proc Natl Acad Sci USA 88*: 1084.

Duliege AM, Amos CI, Felton S, Biggar RJ, Goedert JJ 1995. The International Registry of HIV-exposed twins: birth order, delivery route, and concordance in the transmission of HIV-1 from mothers to twins. *J Pediatr 126*: 625-632.

Dunn DT, Brandt CD, Krivine A, Cassol SA, Roques P, Borkowsky W, De Rossi A, Denamur E, Ehrnst A, Loveday C 1995. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intrapartum transmission. *AIDS 9*: F7-11.

Dunn DT, Newell ML, Ades AE, Peckham CS 1992. Risk of human immunodeficiency virus type 1 transmission through breastfeeding. *Lancet 340:* 585-588.

Dunn DT, Tess BH, Rodrigues LC, Ades AE 1998. Mother-to-child transmission of HIV: implications of variation in maternal infectivity. *AIDS 12*: 2211-2216.

Eastman PS, Shapiro DE, Coombs RW, Frenkel LM, McSherry GD, Britto P, Herman SA, Sperling RS 1998. Maternal viral genotypic zidovudine resistance and infrequent failure of zidovudine therapy to prevent perinatal transmission of human immunodeficiency virus type 1 in pediatric AIDS Clinical Trials Group Protocol 076. *J Infect Dis 177*: 557-564.

Edelstein RE, Arcuino LA, Hughes JP, Melvin AJ, Mohan KM, King PD, McLellan CL, Murante BL, Kassman BP, Frenkel LM 1997. Risk of mother-to-infant transmission of HIV-1 is not reduced in CCR5/delta32ccr5 heterozygotes. *J Aids Hum Retrovirol 16*: 243-246.

Essajee S, Pollak H, Rochford G, Oeansky I, Krasinski K, Borkowsky W 1996. Characterization of the relationship between quasispecies repertoire in HIV-1 infected mothers and their infants using heteroduplex analysis. 36th ICAAC Conference, Abstract 1071.

European Collaborative Study 1999. Maternal viral load and vertical transmission of HIV-1: an important factor but not the only one. *AIDS 13*: 1377-1385.

Fang G, Burger H, Grimson R, Tropper P, Nachman S, Mayers D, Weislow O, Moore R, Reyelt C, Hutcheon N, Baker D, Weiser B 1995. Maternal plasma human immunodeficiency virus type 1 RNA level: a determinant and projected threshold for mother-to-child transmission. *Proc Natl Acad Sci USA 92*: 12100-12104.

Ffrench R, Maplestone MA, Goode M, Hughes C, Stewart GJ, Benson EM, Ziegler JB 1998. Strong cytotoxic T cell responses detected in the majority of uninfected infants born to HIV-positive mothers. 12th World AIDS Conf Geneva, Switzerland, Abstract 31157.

Frenkel LM, Mullins JI, Learn GH, Manns-Arcuino L, Herring BL, Kalish ML, Steketee RW, Thea DM, Nichols JE, Liu SL, Harmache A, He X, Muthui D, Madan A, Hood L, Haase AT, Zupancic M, Staskus K, Wolinsky S, Krogstad P, Zhao J, Chen I, Koup R, Ho D, Korber B, Apple R, Coombs RW, Pahwa S, Roberts Jr NJ 1998. Genetic evaluation of suspected cases of transient HIV-1 infection of infants. *Science 280*: 1073-1077.

Garcia PM, Kalish LA, Pitt J, Minkoff H, Quinn TC, Burchett SK, Kornegay J, Jackson B, Moye J, Hanson C, Zorrilla C, Lew JF 1999. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. *N Engl J Med 341*: 394-402.

Gibb D, Giacomelli A, Masters J, Spoulou V, Ruga E, Griffiths H, Kroll S, Giaquinto C, Goldblatt D 1996. Persistence of antibody responses to Haemophilus influenzae type b polysaccharide conjugate vaccine in children with vertically acquired human immunodeficiency virus infection. *Pediatr Infect Dis J 15*: 1097.

Gras G, Beyssen V, Tranchot-Diallo J, Parnet-Mathieu F, Lasfargues G, Courpotin C, Dormont D 1998. Neutralizing antibodies and complement-mediated, antibody-dependent enhancement (C'-ADE) of human immunodeficiency virus infection in its vertical transmission. *Am J Reprod Immunol 39*: 381-386.

Greco P, Vimercati A, Fiore JR, Kardashi A, Lotesoriere V, Loverro G, Milillo F, Selvaggi L 1998. Maternal viral and gestational risk factors in vertical transmission of HIV-1 infection. *Minerva Ginecol 50*: 449-454.

Greenberg BL, Semba RD, Vink PE, Farley JJ, Sivapalasingam M, Steketee RW, Thea DM, Schoenbaum EE 1997. Vitamin A deficiency and maternal-infant transmissions of HIV in two metropolitan areas in the United States. *AIDS 11*: 325-332.

Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Ducar C, Deseyve M, Emel L, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Dransfield K, Bray D, Mmiro F, Jackson JB 1999. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet 354*: 795-802.

Hahn T, Matala E, Chappey C, Ahmad N 1999. Characterization of mother-infant HIV type 1 gag p17 sequences associated with perinatal transmission. *AIDS Res Hum Retroviruses 15*: 875-888.

Halsey NA, Markham R, Wahren B, Boulos R, Rossi P, Wigzell H 1992. Lack of association between maternal antibodies to V3 loop peptides and HIV-1 transmission. *AIDS 5:* 153-157.

Hengel RL, Kennedy MS, Steketee RW, Thea DM, Abrams EJ, Lambert G, McDougal JS 1998. Neutralizing antibody and perinatal transmission of human immunodeficiency virus type 1. New York City Perinatal HIV Transmission Collaborative Study Group. *AIDS Res Hum Retroviruses 14*: 475-481.

Hershow RC, Riester KA, Lew J, Quinn TC, Mofenson LM, Davenny K, Landesman S, Cotton D, Hanson IC, Hillyer GV, Tang HB, Thomas DL 1997. Increased vertical transmission of human immunodeficiency virus from hepatitis C virus-coinfected mothers. Women and Infants Transmission Study. *J Infect Dis 176*: 414-420.

Hildreth JEK, Hampton R, Halsey NA 1999. Antibody dependent cell mediated cytotoxicity can protect PBMC from infection by cell-associated HIV-1. *Clin Immunol 90*: 203-212.

Husson RN, Lan Y, Kojima E, Venzon D, Mitsuya H, McIntosh K 1995. Vertical transmission of human immunodeficiency virus type 1: autologous neutralizing antibody, virus load, and virus phenotype. *J Pediatr 126*: 865-871.

Hutto C, Zhou Y, He J, Geffin R, Hill M, Scott W, Wood C 1996. Longitudinal studies of viral sequence, viral phenotype, and immunologic parameters of human immunodeficiency virus type 1 infection in perinatally infected twins with discordant disease courses. *J Virol 70*: 3589-3598.

Iversen AK, Fugger L, Eugen-Olsen J, Balslev U, Jensen T, Wahl S, Gerstoft J, Mullins JI, Skinhoj P 1998. Cervical human immunodeficiency virus type 1 shedding is associated with genital beta-chemokine secretion. *J Infect Dis 178*: 1334-1342.

Janini LM, Tanuri A, Schechter M, Peralta JM, Vicente AC, Dela Torre N, Pieniazek NJ, Luo CC, Ramos A, Soriano V, Schochetman G, Rayfield MA, Pieniazek D 1998. Horizontal and vertical transmission of human immunodeficiency virus type 1 dual infections caused by viruses of subtypes B and C. *J Infect Dis 177*: 227-231.

Jansson M, Orlandi P, Scarlatti G, Moschese V, Romiti ML, Cancrini C, Mancia L, Livadiotti S, Castelli-Gattinara G, Rossi P, Halapi E 1997. Role of immunity in maternal-infant HIV-1 transmission. *Acta Paediatr* Suppl. *421*: 39-45.

Jenkins M, Landers D, Williams-Herman D, Wara D, Viscarello RR, Hammill HA, Kline MW, Shearer WT, Charlebois ED, Kohl S 1994. Association between anti-human immunodeficiency virus type 1 (HIV-1) antibody-dependent cellular cytotoxicity antibody titers at birth and vertical transmission of HIV-1. *J Infect Dis 170*: 308-312.

Jin X, Roberts CG, Nixon DF, Cao Y, Ho DD, Walker BD, Muldoon M, Korber BT, Koup RA 1998. Longitudinal and cross-sectional analysis of cytotoxic T lymphocyte responses and their relationship to vertical human immunodeficiency virus transmission. ARIEL Project Investigators. *J Infect Dis 178:* 1317-1326 Published erratum appears in *J Infect Dis 179*: 1593.

Kalish LA, Pitt J, Lew J, Landesman S, Diaz C, Hershow R, Hollinger FB, Pagano M, Smeriglio V, Moye J 1997. Defining the time of fetal or perinatal acquisition of human immunodeficiency virus type 1 infection on the basis of age at first positive culture. Women and Infants Transmission Study (WITS). *J Infect Dis 175*: 712-715.

Kalish M, Brown TM, Schoenbaum E, Abrams EJ, Lambert G, Steketee RW, Robbins KE, Thea DM 1998. Viral and host genetic characterization of possible transient infections in perinatally exposed infants. 12th World AIDS Conf., Geneva, Switzerland, Abstract 23312.

Kampinga GA, Simonon A, Van de Perre P, Karita E, Msellati P, Goudsmit J 1997. Primary infections with HIV-1 of women and their offspring in Rwanda: findings of heterogeneity at seroconversion, coinfection, and recombinants of HIV-1 subtypes A and C. *Virology 227*: 63-76.

Kaslow RA, Carrington M, Apple R, Park L, Munoz A, Saah AJ, Goedert JJ, Winkler C, O'Brien SJ, Rinaldo C, Detels R, Blattner W, Phair J, Erlich H, Mann DL 1996. Influence of combinations of human major histocompatibility complex genes on the course of HIV-1 infection. *Nat Med 2*: 405-411.

Khouri YF, McIntosh K, Cavacini L, Posner M, Pagano M, Tuomala R, Marasco WA 1995. Vertical transmission of HIV-1. Correlation with maternal viral load and plasma levels of CD4 binding site anti-gp120 antibodies. *J Clin Invest 95*: 732-737.

Kline MW, Van Dyke RB, Lindsey JC, Gwynne M, Culnane M, Diaz C, Yogev R, McKinney Jr RE, Abrams EJ, Mofenson LM 1999. Combination therapy with stavudine (d4T) plus didanosine (ddI) in children with human immunodeficiency virus infection. The Pediatric AIDS Clinical Trials Group 327 Team. *Pediatrics 103*: e62.

Kliks SC, Wara DW, Landers DV, Levy JÁ 1994. Features of HIV-1 that could influence maternal-child transmission. *JAMA 272*: 467-474.

Kostrikis LG, Neumann AU, Thomson B, Korber BT, McHardy P, Karanicolas R, Deutsch L, Huang Y, Lew JF, McIntosh K, Pollack H, Borkowski W, Spiegel HM, Palumbo P, Oleske J,Bardeguez A, Luzuriaga K, Sullivan J, Wolinsky SM, Koup RA, Ho DD, Moore JP 1999. A polymorphism in the regulatory region of the CC-chemokine receptor 5 gene influences perinatal transmission of HIV-1 to African-American infants. *J Virol 73*: 10264-10271.

Krogstad P, Uittenbogaart CH, Dickover R, Bryson YJ, Plaeger S, Garfinkel A 1999a. Primary HIV infection of infants: the effects of somatic growth on lymphocyte and virus dynamics. *Clin Immunol 92*: 25-33.

Krogstad P, Wiznia A, Luzuriaga K, Dankner W, Nielsen K, Gersten M, Kerr B, Hendricks A, Boczany B, Rosenberg M, Jung D, Spector SA, Bryson Y 1999b. Treatment of human immunodeficiency virus 1-infected infants and children with the protease inhibitor nelfinavir mesylate. *Clin Infect Dis 28*: 1109-1118.

Lallemant M, Baillou A, Lallemant-Le Coeur S, Nzingoula S, Mampaka M, M'Pele P, Barin F, Essex M 1994. Maternal antibody response at delivery and perinatal transmission of human immunodeficiency virus type 1 in African women. *Lancet 343*: 1001-1005.

Lambert JS, McNamara J, Katz SL, Fenton T, Kang M, Van Cott TC, Livingston R, Hawkins E, Moye J Jr, Borkowsky W, Johnson D, Yogev R, Duliege AM, Francis D, Gershon A, Wara D, Martin N, Levin M, McSherry G, Smith G 1998. Safety and immunogenicity of HIV recombinant envelope vaccines in HIV-infected infants and children. National Institutes of Health-sponsored Pediatric AIDS Clinical Trial Group (ATCG -218). *J Aids Hum Retrovirol 19*: 451-461.

Lamers SL, Sleasman JW, She JX, Barrie KA, Pomeroy SM, Barrett DJ, Goodenow MM 1994. Persistence of multiple maternal genotypes of human immunodeficiency virus type I in infants infected by vertical transmission. *J Clin Invest 93*: 380-390.

Lathey JL, Tsou J, Brinker K, Hsia K, Meyer WA 3rd, Spector AS 1999. Lack of autologous neutralizing antibody to human immunodeficiency virus type 1 (HIV-1) and macrophage tropism are associated with mother-to-infant transmission. *J Infect Dis 180*: 344-350.

Lecuona JE, Aldamiz-Echevarria Azuara L, Eguiluz G C, Trallero EP 1996. Responses to triple viral and tetanus vaccination in HIV-infected children. *An Esp Pediatr 44*: 317-320.

Leitner T, Albert J 1999. The molecular clock of HIV-1 unveiled through analysis of a known transmission history. *Proc Natl Acad Sci USA 96*: 10752-10757.

Leroy V, Newell ML, Dabis F, Peckham C, Van de Perre P, Bulterys M, Kind C, Simonds RJ, Wiktor S, Msellati P 1998. International multicentre pooled analysis of late postnatal mother-to-child transmission of HIV-1 infection. Ghent International Working Group on Mother-to-Child Transmission of HIV. *Lancet 352*: 597-600. Published erratum appears in *Lancet 352*: 1154.

Lewis SH, Reynolds-Kohler C, Fox HE, Nelson JA 1990. HIV-1 in trophoblastic and villous Hofbauer cells, and haematological precursors in 8-week fetuses. *Lancet 335*: 565-568.

Ljunggren K, Moschese V, Broliden PA, Giaquinto C, Quinti I, Fenyö EM, Wahren B, Rossi P, Jondal M 1990. Antibodies mediating cellular cytotoxicity and neutralization correlate with a better clinical stage in children born to HIV-infected mothers. *J Infec Dis 161*: 198-202.

Lorenzi P, Spicher VM, Laubereau B, Hirschel B, Kind C, Rudin C, Irion O, Kaiser L 1998. Antiretroviral therapies in pregnancy: maternal, fetal and neonatal effects. Swiss HIV Cohort Study, the Swiss Collaborative HIV and Pregnancy Study, and the Swiss Neonatal HIV Study. *AIDS 12*: F241-F247.

Louisirirotchanakul S, Beddows S, Cheingsong R, Shaffer N, Mastro TD, Likanonsakul S, Wasi C, Taylor GP, Weber JN 1999. Role of maternal humoral immunity in vertical transmission of HIV-1 subtype E in Thailand. *AIDS 21*: 259-265.

Lu Y, Brosio P, Lafaile M, Li J, Collman RG, Sodroski J, Miller CJ 1996. Vaginal transmission of chimeric simian/human immunodeficiency viruses in rhesus macaques. *J Virol 70*: 3045-3050.

Mabondzo A, Narwa R, Roques P, Gras GS, Herve F, Parnet-Mathieu F, Lasfargues G, Courpotin C, Dormont D 1998. Lack of correlation between vertical transmission of HIV-1 and maternal antibody titers against autologous virus in human monocyte-derived macrophages. *J Aids Hum Retrovirol 17*: 92-94.

Mac Donald KS, J Castillo, Embree J, Njenga S, Nagelkerke Nicolas JD, Ngatia I, Mohammed Z 1998. Class I MHC polymorphism and mother to child HIV-1 transmission in Kenya. 12th World AIDS Conf., Geneva, Switzerland, Abstract 31131.

Mandelbrot L, Mayaux MJ, Bongain A, Berrebi A, Moudoub-Jeanpetit Y, Benifla JL, Ciraru-Vigneron N, Le Chenadec J, Blanche S, Delfraissy JF 1996. Obstetric factors and mother-to-child transmission of HIV-1: the french perinatal cohorts. *Am J Obstetric Gynecol 175*: 661.

Markham RB, Coberly J, Ruff AJ, Hoover D, Gomez J, Holt E, Desormeaux J, Boulos R, Quinn TC, Halsey NA 1994. Maternal IgG1 and IgA antibody to V3 loop consensus sequence and maternal-infant HIV-1 transmission. *Lancet 343*: 390-391.

Mas A, Espanol T, Heredia A, Pedraza MA, Hernandez M, Caragol I, Fernando M, Bertran JM, Alcami J, Soriano V 1999. CCR5 genotype and HIV-1 infection in perinatally-exposed infants. *J Infect Dis* 38: 9-11.

McSherry GD, Shapiro DE, Coombs RW, McGrath N, Frenkel LM, Britto P, Culnane M, Sperling RS 1999. The effects of zidovudine in the subset of infants infected with human immunodeficiency virus type-1 (Pediatric AIDS Clinical Trials Group Protocol 076). *J Pediatr 134*: 717-724.

Menu E, Mbopi-Keou FX, Lagaye S, Pissard S, Mauclere P, Scarlatti G, Martin J, Goossens M, Chaouat G, Barre-Sinoussi F 1999. Selection of maternal human immunodeficiency virus type 1 variants in human placenta. European Network for In Utero Transmission of HIV-1. *J Infect Dis 179*: 44-51. Published erratum appears in *J Infect Dis 179*: 1053.

Mikyas Y, Aziz N, Harawa N, Gorre M, Neagos N, Nogueira M, Wafer D, Dillon M, Boyer PJ, Bryson YJ, Plaeger S 1997. Immunologic activation during pregnancy: serial measurements of lymphocytic phenotype and serum activation molecules in HIV-1 infected and uninfected women. *J Reprod Immunol 33*: 157-170.

Misrahi M, Teglas JP, N'Go N, Burgard M, Mayaux MJ, Rouzioux C, Delfraissy JF, Blanche S 1998. CCR5 chemokine receptor variant in HIV-1 mother-to-child transmission and disease progression in children. French Pediatric HIV Infection Study Group. *JAMA 279*: 277-280.

Mock PA, Shaffer N, Bhadrakom C, Siriwasin W, Chotpitayasunondh T, Chearskul S, Young NL, Roongpisuthipong A, Chinayon P, Kalish ML, Parekh B, Mastro TD 1999. Maternal viral load and timing of mother-to-child HIV transmission, Bangkok, Thailand. Bangkok Collaborative Perinatal HIV Transmission Study Group. *AIDS 13*: 407-414.

Mognetti B, Moussa M, Croitoru J, Menu E, Dormont D, Roques P, Chaouat G 2000. HIV-1 co-receptor expression on trophoblastic cells from early placentas and permissivity to infection by several HIV-1 primary isolates. *Clin Exp Immunol 119*: 486-492.

Moore JP, Burton DR 1999. HIV-1 neutralizing antibodies: how full is the bottle? *Nat Med 5*: 142-144.

Moussa M, Mognetti B, Dubanchet S, Menu E, Roques P, Gras G, Dormont D, Barre-Sinoussi F, Chaouat G 1999. Vertical transmission of HIV: parameters which might affect infection of placental trophoblasts

by HIV-1: a review. Biomed Group on the Study of in Utero Transmission of HIV 1. *Am J Reprod Immunol 41*: 312-319.

Mulder-Kampinga GA, Simonon A, Kuiken CL, Dekker J, Scherpbier HJ, van de Perre P, Boer K, Goudsmit J 1995. Similarity in env and gag genes between genomic RNAs of human immunodeficiency virus type 1 (HIV-1) from mother and infant is unrelated to time of HIV-1 RNA positivity in the child. *J Virol 69*: 2285-2296.

Mundy DC, Schinazi RE, Gerber AR, Nahmias AJ, Randall HW 1987. HIV isolated from amniotic fluid. *Lancet 2*: 459.

Musoke P, Guay LA, Bagenda D, Mirochnick M, Nakabiito C, Fleming T, Elliott T, Horton S, Dransfield K, Pav JW, Murarka A, Allen M, Fowler MG, Mofenson L, Hom D, Mmiro F, Jackson JB 1999. A phase I/II study of the safety and pharmacokinetics of nevirapine in HIV-1-infected pregnant Ugandan women and their neonates (HIVNET 006). *AIDS 13*: 479-486.

Narwa R, Roques P, Courpotin C, Parnet-Mathieu F, Boussin F, Roane A, Marce D, Lasfargues G, Dormont D 1996. Characterization of human immunodeficiency virus type 1 p17 matrix protein motifs associated with mother-to-child transmission. *J Virol 70*: 4474-4483.

Newell ML 1994. Caesarean delivery cuts HIV infection. *Nurs Stand 8*: 16.

Newell ML 1998. Mechanisms and timing of mother-to-child transmission of HIV-1. *AIDS 12*: 831-837.

O'Brien KL, Ruff AJ, Louis MA, Desormeaux J, Joseph DJ, McBrien M, Coberly J, Boulos R, Halsey NA 1995. Bacillus Calmette-Guerin complications in children born to HIV-1-infected women with a review of the literature. *Pediatrics 95*: 414-418.

Okamoto Y, Shiosaki K, Eda Y, Tokiyoshi S, Yamaguchi Y, Gojobori T, Hachimori T, Yamazaki S, Hondo M 1997. Father-to-mother-to-infant transmission of HIV-1: clonally transmitted isolate of infant mutates more rapidly than that of the mother and rapidly loses reactivity with neutralizing antibody. *Microbiol Immunol 41*: 131-138.

Olivero OA, Parikka R, Poirier MC, Vahakangas K 1999a. 3'-azido-3'-deoxythymidine (AZT) transplacental perfusion kinetics and DNA incorporation in normal human placentas perfused with AZT. *Mutat Res 428*: 41-47.

Olivero OA, Shearer GM, Chougnet CA, Kovacs AA, Landay AL, Baker R, Stek AM, Khoury MM, Proia LA, Kessler HA, Sha BE, Tarone RE, Poirier MC 1999b. Incorporation of zidovudine into leukocyte DNA from HIV-1-positive adults and pregnant women, and cord blood from infants exposed *in utero*. *AIDS 13*: 919-925.

Ometto L, Zanotto C, Maccabruni A, Caselli D, Truscia D, Giaquinto C, Ruga E, Chieco-Bianchi L, De Rossi A 1995. Viral phenotype and host-cell susceptibility to HIV-1 infection as risk factors for mother-to-child HIV-1 transmission. *AIDS 9*: 427-434.

Ortigão MB 1995. AIDS em crianças: considerações sobre a transmissão vertical. *Cad Saúde Públ RJ 11:* 142-148.

O'Shea S, Newell ML, Dunn DT, Garcia-Rodriguez MC, Bates I, Mullen J, Rostron T, Corbett K, Aiyer S, Butler K, Smith R, Banatvala JE 1998. Maternal viral load, CD4 cell count and vertical transmission of HIV-1. *J Med Virol 54*: 113-117.

Papadogiannakis N 1997. Traffic of leukocytes through the maternofetal placental interface and its possible consequences. *Curr Top Microbiol Immunol 222*: 141-157.

Parekh BS, Shaffer N, Pau CP, Abrams E, Thomas P, Pollack H, Bamji M, Kaul A, Schochetman G, Rogers M 1991. Lack of correlation between maternal antibodies to V3 loop peptides of gp120 and perinatal HIV-1 transmission. The NYC Perinatal HIV Transmission Collaborative Study. *AIDS 5*: 1179-1184.

Peckham C, Gibb D 1995. Mother-to-child transmission of the human immunodeficiency virus. *N Engl J Med 333*: 298-302.

Phuapradit W, Panburana P, Jaovisidha A, Vichitphun N, Kongsin P, Chantratita W, Bhodhiphala P, Pairoj W 1999. Maternal viral load and vertical transmission of HIV-1 in mid-trimester gestation. *AIDS 13*: 1927-1931.

Pitt J, Brambilla D, Reichelderfer P, Landay A, McIntosh K, Burns D, Hillyer GV, Mendez H, Fowler MG 1997. Maternal immunologic and virologic risk factors for infant human immunodeficiency virus type 1 infection: findings from the Women and Infants Transmission Study. *J Infect Dis 175*: 567-575.

Plaeger S, Bermudez S, Mikyas Y, Harawa N, Dickover R, Mark D, Dillon M, Bryson YJ, Boyer PJ, Sinsheimer JS 1999. Decreased CD8 cell-mediated viral suppression and other immunologic characteristics of women who transmit human immunodeficiency virus to their infants. *J Infect Dis 179*: 1388-1394.

Purswani M, Johann-Liang R, Cervia J, Noel GJ 1999. Effect of changing antiretroviral therapy on human immunodeficiency virus viral load: experience with fifty-four perinatally infected children. *Pediatr Infect Dis J 18*: 512-516.

Rasheed S 1998. Infectivity and dynamics of HIV type 1 replication in the blood and reproductive tract of HIV type 1-infected women. *AIDS Res Hum Retroviruses Suppl 1*: S105-S118.

Robertson CA, Mok JY, Froebel KS, Simmonds P, Burns SM, Marsden HS, Graham S 1992. Maternal antibodies to gp120 V3 sequence do not correlate with protection against vertical transmission of human immunodeficiency virus. *J Infect Dis 166*: 704-709.

Rodriguez EM, Mofenson LM, Chang BH, Rich KC, Fowler MG, Smeriglio V, Landesman S, Fox HE, Diaz C, Green K, Hanson IC 1996. Association of maternal drug use during pregnancy with maternal HIV culture positivity and perinatal HIV transmission. *AIDS 10*: 273-282.

Rogers MF, Shaffer N 1999. Reducing the risk of maternal-infant transmission of HIV by attacking the virus. *N Engl J Med 341*: 441-442.

Roques PA, Gras G, Parnet-Mathieu F, Mabondzo AM,

Dollfus C, Narwa R, Marce D, Tranchot-Diallo J, Herve F, Lasfargues G, Courpotin C, Dormont D 1995. Clearance of HIV infection in 12 perinatally infected children: clinical, virological and immunological data. *AIDS 9*: F19-F26.

Rousseau CM, Just JJ, Abrams EJ, Casabona J, Stein Z, King MC 1997. CCR5del32 in perinatal HIV-1 infection. *J Aids Hum Retrovirol* 16: 239-242.

Rouzioux C, Costagliola D, Burgard M, Blanche S, Mayaux MJ, Griscelli C, Valleron AJ 1995. Estimated timing of mother-to-child HIV-1 transmission by use of a Markov model. *Am J Epidemiol 142*: 1330-1337.

Scarlatti G, Hodara V, Rossi P, Muggiasca L, Bucceri A, Albert J, Fenyö EM 1993a. Transmission of human immunodeficiency virus type 1 (HIV-1) from mother to child correlates with viral phenotype. *Virology 197*: 624-629.

Scarlatti G, Leitner T, Hodara V, Halapi E, Rossi P, Albert J, Fenyö EM 1993b. Neutralizing antibodies and viral characteristics in mother-to-child transmission of HIV-1. *AIDS* (Suppl.) *2*: S45-S48.

Scarlatti G, Albert J, Rossi P, Hodara V, Biraghi P, Muggiasca L, Fenyö EM 1993c. Mother-to-child transmission of human immunodeficiency virus type 1: correlation with neutralizing antibodies against primary isolates. *J Infect Dis 168*: 207-210.

Schwartz DH, Sharma UK, Perlman EJ, Blakemore K 1995. Adherence of human immunodeficiency virus-infected lymphocytes to fetal placental cells: a model of maternal —> fetal transmission. *Proc Natl Acad Sci USA 92*: 978-982.

Semba RD, Miotti PG, Chiphangwi JD, Saah AJ, Canner JK, Dallabetta GA, Hoover DR 1994. Maternal vitamin A deficiency and mother-to-child transmission of HIV-1. *Lancet 343*: 1593-1597.

Shaffer N, Chuachoowong R, Mock PA, Bhadrakom C, Siriwasin W, Young NL, Chotpitayasunondh T, Chearskul S, Roongpisuthipong A, Chinayon P, Karon J, Mastro TD, Simonds RJ 1999. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet 353*: 773-880.

Shapiro DE, Sperling RS, Mandelbrot L, Britto P, Cunningham BE 1999. Risk factors for perinatal human immunodeficiency virus transmission in patients receiving zidovudine prophylaxis. Pediatric AIDS Clinical Trials Group protocol 076 Study Group. *Obstet Gynecol 94*: 897-908.

Shearer WT, Langston C, Lewis DE, Pham EL, Hammill HH, Kozinetz CA, Kline MW, Hanson IC, Popek EJ 1997a. Early spontaneous abortions and fetal thymic abnormalities in maternal-to-fetal HIV infection. *Acta Paediatr* (Suppl.) *421*: 60-64.

Shearer WT, Reuben J, Lee BM, Popek EJ, Lewis DE, Hammil HH, Hanson IC, Kline MW, Langston C 1997b. Role of placental cytokines and inflammation in vertical transmission of HIV infection. *Acta Paediatr* (Suppl.) *421*: 33-38.

Shearer WT, Kalish LA, Zimmerman PA 1998. CCR5 HIV-1 vertical transmission. Women and Infants Transmission Study Group. *J Aids Hum Retrovirol 17*: 180-181.

Sheppard HW, Lang W, Ascher MS, Vittinghoff E, Winkelstein W 1993. The characterization of nonprogressors: long-term HIV-1 infection with stable CD4+ T-cell levels. *AIDS 7*: 1159-1166.

Sienna Workshop: report of a consensus workshop, Siena, Italy, Jan 17-18, 1992. Maternal factors involved in mother-to-child transmission of HIV-1. *AIDS 5*: 1019-1025.

Simpson RM, Hubbard BS, Zhao TM, Kindt TJ 1997. Experimental perinatal transmission of human immunodeficiency virus type 1 by passage of infected T cells. *J Infect Dis 175*: 1337-1343.

Sperling RS, Shapiro DE, Coombs RW, Todd JA, Herman SA, McSherry GD, O'Sullivan MJ, Van Dyke RB, Jimenez E, Rouzioux C, Flynn PM, Sullivan JL 1996. Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med 335*: 1621-1629.

Stiehm ER, Lambert JS, Mofenson LM, Bethel J, Whitehouse J, Nugent R, Moye Jr J, Glenn Fowler M, Mathieson BJ, Reichelderfer P, Nemo GJ, Korelitz J, Meyer WA 3rd, Sapan CV, Jimenez E, Gandia J, Scott G, O'Sullivan MJ, Kovacs A, Stek A, Shearer WT, Hammill H 1999. Efficacy of zidovudine and human immunodeficiency virus (HIV) hyperimmune immunoglobulin for reducing perinatal HIV transmission from HIV-infected women with advanced disease: results of Pediatric AIDS Clinical Trials Group Protocol 185. *J Infect Dis 179*: 567-575.

St. Louis E, Kamenga M, Brown C 1993. Risk for perinatal HIV-1 transmission according to maternal immunologic, virologic and placental factors. *JAMA 269*: 2853.

Tess BH, Rodrigues LC, Newell ML, Dunn DT, Lago TD 1998. Infant feeding and risk of mother-to-child transmission of HIV-1 in São Paulo State, Brazil. São Paulo Collaborative Study for Vertical Transmission of HIV-1. *J Aids Hum Retrovirol 19*: 189-194. Published erratum appears in *J Aids Hum Retrovirol 19*: 550.

Thaineua V, Sirinirund P, Tanbanjong A, Lallemant M, Soucat A, Lamboray JL 1998. From research to practice: use of short course zidovudine to prevent mother-to-child HIV transmission in the context of routine health care in Northern Thailand. *Southeast Asian J Trop Med Public Health 29*: 429-442.

Thea DM, Steketee RW, Pliner V, Bornschlegel K, Brown T, Orloff S, Matheson PB, Abrams EJ, Bamji M, Lambert G, Schoenbaum EA, Thomas PA, Heagarty M, Kalish ML and the New York City Perinatal HIV Transmission Collaborative Study Group 1997. The effect of maternal viral load on the risk of perinatal transmission of HIV-1. *AIDS 11*: 437-444.

Tscherning-Casper C, Papadogiannakis N, Anvret M, Stolpe L, Lindgren S, Bohlin AB, Albert J, Fenyö EM 1999. The trophoblastic epithelial barrier is not

infected in full-term placentae of human immunodeficiency virus-seropositive mothers undergoing antiretroviral therapy. *J Virol 73*: 9673-9678.

Ugen KE, Srikantan V, Goedert JJ, Nelson Jr RP, Williams WV, Weiner DB 1997. Vertical transmission of human immunodeficiency virus type 1: seroreactivity by maternal antibodies to the carboxy region of the gp41 envelope glycoprotein. *J Infect Dis 175*: 63-69.

Van de Perre P 1999a. Mother-to-child transmission of HIV-1: the 'all mucosal' hypothesis as a predominant mechanism of transmission. *AIDS 13*: 1133-1138.

Van de Perre P 1999b. Transmission of human immunodeficiency virus type 1 through breast-feeding: how can it be prevented? *J Infect Dis 179* (Suppl. 3): S405-S407.

Wabwire-Mangen F, Gray RH, Miro FA, Ndugwa C, Abramowsky C, Wabinga H, Whalen C, Li C, Saah AJ 1999. Placental membrane inflammation and risks of maternal-to-child transmission of HIV-1 in Uganda. *AIDS 22*: 379-385.

Wade CM, Lobdiel D, Brown AJ 1998. Analysis of HIV-1 env and gag sequence variants derived from a mother and two vertically infected children provides evidence for the transmission of multiple sequence variants. *J Gen Virol 79*: 1055-1068.

Wasik TJ, Bratosiewicz J, Wierzbicki A, Whiteman VE, Rutstein RR, Starr SE, Douglas SD, Kaufman D, Sison AV, Polansky M, Lischner HW, Kozbor D 1999. Protective role of beta-chemokines associated with HIV-specific Th responses against perinatal HIV transmission. *J Immunol 162*: 4355-4364.

Weiser B, Nachman S, Tropper P 1994. Quantitation of HIV-1 during pregnancy: relationship of viral titer to mother-to-child transmission and stability of viral load. *Proc Natl Acad Sci USA 91*: 8037.

Wike CM, Korber BT, Daniels MR, Hutto C, Munoz J, Furtado M, Parks W, Saah A, Bulterys M, Kurawige JB, Wolinsky SM 1992. HIV-1 sequence variation between isolates from mother-infant transmission pairs. *Aids Res Hum Retroviruses 8*: 1297-1300.

Wiktor SZ, Ekpini E, Karon JM, Nkengasong J, Maurice C, Severin ST, Roels TH, Kouassi MK, Lackritz EM, Coulibaly IM, Greenberg AE 1999. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomised trial. *Lancet 353*: 781-785.

Wilson CC, Brown RC, Korber BT, Wilkes BM, Ruhl DJ, Sakamoto D, Kunstman K, Luzuriaga K, Hanson IC, Widmayer SM, Wiznia A, Clapp S, Ammann AJ, Koup RA, Wolinsky SM, Walker BD 1999. Frequent detection of escape from cytotoxic T-lymphocyte recognition in perinatal human immunodeficiency virus (HIV) type 1 transmission: the ariel project for the prevention of transmission of HIV from mother to infant. *J Virol 73*: 3975-3985.

Wolinsky SM, Wike CM, Korber BT, Hutto C, Parks WP, Rosenblum LL, Kunstman KJ, Furtado MR, Munoz JL 1992. Selective transmission of human immunodeficiency virus type-1 variants from mothers to infants. *Science 255*: 1134-1137.

Workshop Report from the European Commission (DG XII, INCO-DC) and Joint United Nations Programme on HIV/AIDS 1997: HIV-1 subtypes: implications for epidemiology, pathogenicity, vaccines and diagnostics. *AIDS 11*: UNAIDS17-UNAIDS36.

Wright PF, Lambert JS, Gorse GJ, Hsieh RH, McElrath MJ, Weinhold C, Wara DW, Anderson EL, Keefer MC, Jackson S, Wagner LJ, Francis DP, Fast PE, McNamara J 1999. Immunization with envelope MN gp120 vaccine in human immunodeficiency virus-infected pregnant women. *J Infect Dis 180*: 1080-1088.

Zeichner SL, Palumbo P, Feng Y, Xiao X, Gee D, Sleasman J, Goodenow M, Biggar R, Dimitrov D 1999. Rapid telomere shortening in children. *Blood 93*: 2824-2830.

Zöllner B, Feucht HH, Mattner UM, Helling-Giese G, Baumgartner EM, Laufs R 1996. Better prediction of vertical HIV-1 transmission from maternal blood at delivery compared with cord blood samples. *AIDS 10*: 1600-1601.

Zöllner B, Feucht HH, Helling-Giese G, Mattner UM, Schartl W, Polywka S, Laufs R 1997. Threshold of HIV-1 copy numbers for vertical transmission. *AIDS 11*: 542-543.

Zöllner B, Feucht HH, Mattner UM, Helling-Giese G, Baumgartner EM, Laufs R 1996. Better prediction of vertical HIV-1 transmission from maternal blood at delivery compared with cord blood samples. *AIDS 10*: 1600-1601.

Zorilla CD 2000. Mother-to-child HIV-1 transmission: state of art and implications for public policy. *PR Health Sci J 19*: 29-34.