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

Vera Bongertz

Laboratório de Aids e Imunologia Molecular, Departamento de Imunologia, Instituto Oswaldo Cruz, Av. Brasil 4365, 21045-900 Rio de Janeiro, RJ, Brasil

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 occurrence 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 (CN-DST/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.
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 placenta 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 placenta 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

<table>
<thead>
<tr>
<th>Non HIV related</th>
<th>HIV related</th>
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<tbody>
<tr>
<td>Mother’s health/risk factors</td>
<td>Viral load</td>
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<tr>
<td>Mother’s genetic background</td>
<td>A high viral load increases the risk of VT</td>
</tr>
<tr>
<td>Child’s genetic background</td>
<td>Viral genotype</td>
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<tr>
<td></td>
<td>??? No correlation proven</td>
</tr>
<tr>
<td>Delivery</td>
<td>Viral phenotype</td>
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<td></td>
<td>Macrophage-tropism and rapid replication</td>
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<tr>
<td>Breastfeeding</td>
<td>associated to VT</td>
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<td></td>
<td>Lower antibody response associated to</td>
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<td></td>
<td>greater risk?</td>
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<td></td>
<td>Low autologous NAb increases VT risk?</td>
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<td></td>
<td>Limited broadness of NAb response increases VT risk?</td>
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<td></td>
<td>Low suppressor cell response increases VT risk?</td>
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<tr>
<td></td>
<td>Low and narrow CTL response increases VT risk?</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Viral load and vertical HIV-1 transmission</th>
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<tr>
<td>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 &amp; Shaffer 1999)</td>
</tr>
<tr>
<td>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)</td>
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</table>
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, Campodomico 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 circumsocial 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 (NAb) 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, Lallemand 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 ineffective 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, Colognonesi et al. 1997, Bongertz et al. 1999, Louisirirotchanakul 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. 1995).
One of the main problems in drug trials of pregnant women 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). Hypoth-eses 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 (Bagarazzi 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.

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| 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)


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


