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Human immunodeficiency virus and pregnancy

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Pregnancy in HIV-infected individuals was not initially recognized as an important problem in the United States because of the predominance of the disease in men. The more recent spread of the infection into the heterosexual population in the United States, Europe, and Australia, as well as its earlier heterosexual presence in the developing world, has led to increased scientific and clinical attention to the role of HIV infection in pregnancy. As of 1993, a cumulative total of about 1 million children were infected, of whom most were infected by vertical transmission [1], and as of 2000, an estimated 6 million pregnant women and 5 to 10 million children were infected worldwide [2].

Human immunodeficiency virus infection profoundly affects the medical community and society at large. The burden of providing for such a large population of infected individuals has led to fundamental questions about health care, including the support of basic sciences, timely development and rapid approval of effective therapy, access to medical care, patient confidentiality, and patient discrimination. These questions are most complex during pregnancy, because the interests of both the mother and the child must be considered. These interests can be in conflict: the unborn child has the right to receive specific antiretroviral treatment during gestation to reduce the risk of contracting HIV infection (as discussed later), whereas the mother has a right to refuse treatment and a right of confidentiality that includes a right to refuse HIV testing [3]. This conflict has led to wrenching decisions regarding mandatory testing for HIV infection.

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Prevalence of human immunodeficiency virus infection in women

The increase in infection in children parallels the increase of infection in women of childbearing age in the developed world. In the United States, infections in women have increased from 5% of the total in the 1980s to about 20% now. About half of new infections worldwide occur in women of childbearing age. In the United States, about 0.2% of childbearing women are HIV-seropositive, a three- to-fourfold higher rate than in other Americans. The incidence of HIV-seropositivity in sub-Saharan Africa is much higher, at 6% to 30%. The incidence of seropositivity varies in the United States and is highest in inner cities. Despite widespread knowledge of this problem, many obstetricians do not routinely seek testing for HIV infection, particularly in women who are not members of established risk groups.

Vertical transmission of infection

The risks of vertical transmission vary in different countries, depending on the availability of antiretroviral therapy, as discussed later. Transmission may occur in utero, intrapartum, or postpartum; postpartum transmission most often occurs through breastfeeding. Intrauterine infection is assessed by culture of the virus or detection of retroviral DNA from peripheral blood lymphocytes within 48 hours postpartum. The relative rates of antepartum, intrapartum, and postpartum transmission are uncertain and may vary in different populations. Studies from Africa seem to show that about one third of cases are acquired antepartum and up to one third are acquired postpartum. In developed countries the incidence of postpartum infection is much lower, and intrapartum transmission may cause up to 75% of infections. The higher incidence of postpartum infection in Africa is attributed to breastfeeding, as discussed later. Detection of anti-HIV antibodies in fetal blood is not evidence of active infection, because these antibodies are maternal.

Human immunodeficiency virus-1, however, has been isolated from amniotic fluid and cells [4], as well as from cord blood, indicating intrauterine fetal infection in some cases can occur even relatively early during pregnancy. The prevalence of HIV infection is higher in abortuses than in full-term pregnancies, suggesting that in utero infection may lead to fetal demise [5].

Intrapartum vertical transmission is an important mechanism of disease transmission. The virus is usually isolated from cord blood in HIV-seropositive infants, implying the infection occurred peripartum. Some neonates, however, have negative viral isolation studies at birth followed by viral isolation at 1 to 3 months of life, associated with a decline in CD4+ lymphocyte levels. The exact mechanism of this infection is uncertain. Atraumatic inoculation of the oropharynx or conjunctival sac in newborn monkeys with cell-free simian immunodeficiency virus can transmit the infection, implying the virus can invade through mucous membranes [6]. In vitro, the virus can

invade epithelial cell lines [7]. Other studies have demonstrated that the virus can invade through epithelium through mucosal lymphoid follicles, such as Peyer's patches, to infect subepithelial macrophages [8]. Cell-associated and cell-free virus has been detected in human breast milk; the viral concentration is highest in colostrum. Prospective studies in Africa indicate breastfeeding can cause postnatal transmission, especially during primary maternal infection [9]. In a prospective study, several African women seroconverted postpartum, and most of their infants subsequently developed primary HIV infection [10].

The risks-versus-benefits evaluation of breastfeeding in a population with a high prevalence of HIV infection depends on the available alternatives. Normally breastfeeding would be proscribed because any risk of viral transmission is unacceptable. Thus many published guidelines recommend that women who are HIV-infected refrain from breastfeeding, provided infant formulas and potable water are available. Moreover, breastfeeding is not recommended for women at high risk for HIV infection because of the lack of universal testing and possible transmission, despite an initially negative HIV test, resulting from subsequent maternal postpartum infection. In some developing countries, however, the benefits of breastfeeding outweigh the risks, even in HIV-seropositive patients, and breastfeeding is recommended in these countries.

Determinants of vertical transmission

Many studies have analyzed the factors determining vertical transmission of infection. Initially, fetal infection was thought to be inevitable. The analysis was complicated by difficulty in evaluating the presence of HIV infection in the newborn because of the presence of maternal antibodies in cord blood. Subsequently, cases in which maternal antibodies were lost without replacement by the child's antibodies became apparent.

Factors affecting the probability of vertical transmission include immune status, viral strain virulence [11], viral load, anti-HIV immunity, maternal-fetal nutritional status, placental inflammation, and obstetric factors [12,13]. These factors are often interrelated. Several prospective studies in the United States, Europe, and Africa have confirmed that transmission is more likely in persons with peripheral blood CD4+ lymphocyte depletion, perhaps because plasma viral burden rises with HIV progression. Several studies have associated maternal viral burden, especially at delivery, with the risk of vertical transmission [14]. Sperling et al [15] demonstrated a significant association between viral burden and risk of transmission in placebo-controlled subjects in their definitive study of the effects of zidovudine (azidothymidine, AZT) on transmission, as discussed later. Prospective studies demonstrated a threshold of about 20,000 copies/mL of HIV RNA for transmission [16]. The risk of transmission seems to be very high if seroconversion occurs during pregnancy, probably because the viral load is very

high in primary infection, before the development of anti-HIV immunity. The relationship between anti-HIV immunity and risk of transmission is unclear. One study showed the effects of viral load and CD4+ lymphocyte count on the risk of vertical transmission to be independent [17]. Immune defense most effectively prevented transmission when maternal viral cultures were not persistently positive [18], suggesting that a high viral burden is sufficient for infection, irrespective of other factors.

Placental barriers to retroviral invasion are poorly defined. Evidence of infected placental cells, especially placental macrophages, has been reported [19,20]. Placental inflammation facilitates transmission. There is selectivity to the viral serotypes that cross the placenta, based upon envelope gene sequencing [21]. The fetus can be infected with multiple viral serotypes, however [22].

Obstetric factors may be important in intrapartum vertical transmission [23]. In twins the first-born has a higher likelihood of being infected than the second, presumably because of more prolonged neonatal exposure to maternal mucocutaneous vaginal secretions [24]. Cultures of gastric aspirates in newborns have detected virus [25]. The risk of infection is also related to the duration of ruptured membranes and is particularly increased when this duration is more than 4 hours [23]. A French study, however, failed to detect evidence that obstetric factors affect transmission rates [26].

Nutritional factors may affect viral transmission. In a study from Malawi, maternal vitamin A deficiency promoted disease transmission, increased infant mortality, and impaired infant growth in height and weight during the first year of life [27,28]. Contrariwise, an American study reported that vitamin A levels in the third trimester did not affect the risk of vertical transmission, although no cases of maternal vitamin A deficiency occurred in this study [29]. The effect of vitamin A deficiency on disease transmission is uncertain, and vitamin A deficiency could be a surrogate marker for another nutritional deficiency. Vitamin A affects immune function [30], including epithelial defense mechanisms [31], and could thereby affect viral transmission. Furthermore, maternal vitamin A deficiency was strongly associated with the presence of retroviral DNA in breast milk [32]. Vitamin A supplementation produced better postpartum weight retention, but no difference was found in weight gain during pregnancy, as compared with placebo [33]. Supplementation is not beneficial and not recommended in the United States because of the potential for vitamin A toxicity, including teratogenicity. Cigarette smoking, but not cocaine use, may affect the risk of transmission [34].

Strategies to prevent vertical transmission

Antiviral therapy with zidovudine (Retrovir, Glaxo Wellcome) markedly diminishes the risk of vertical transmission [35]. Ironically, zidovudine,

which interrupts transcription as a chain terminator and is mutagenic, is the first and only antiretroviral drug recommended during pregnancy. Use of inhibitors of transcription would theoretically be inadvisable during pregnancy for fear of teratogenicity. In practice, zidovudine causes little fetal toxicity, other than reversible anemia, in clinical studies, although potential late toxicity to the child is uncertain. Indeed, reverse transcriptase inhibitors or protease inhibitors may not cross the placenta.

In AIDS Clinical Trials Group protocol 076, pregnant women who were antiretroviral-nave and had CD4+ lymphocyte counts greater than 200/mm^3 randomly received either zidovudine or placebo [35]. Medication was given antenatally during the third trimester, intravenously during parturition, and to the newborn for the first 6 weeks of life. Placebo-treated cases had a rate of transmission of 22.6%, as compared with 7.6% in zidovudine-treated cases, a difference that was highly statistically significant. Other studies corroborated this finding, and showed the effect is similar whether prior zidovudine therapy was administered or not [16,36]. The mechanism for this effect is unclear, because the effect is only partly explained by a decline in maternal HIV RNA plasma levels [15,37]. Whether the critical treatment period is antepartum, intrapartum, or postpartum is also unclear [38].

The combination of lamivudine and zidovudine (Glaxo Smith Kline, Research Triangle Park, NC) [39], as well as nevirapine (Viramune, Boehringer Ingleheim, Ridgefield, VT), the latter administered as a single dose, also reduce vertical transmission. Nevirapine may be moderately more effective than zidovudine, but single-dose nevirapine therapy was associated with both hepatotoxicity and retroviral resistance to non-nucleoside reverse transcriptase inhibitors [40]. Resistance to lamivudine and zidovudine has also been reported. Moreover, the drug-resistant virus may be transmitted from mother to child [41].

Local therapy and obstetric precautions have been applied to prevent intrapartum vertical transmission. Cell-free HIV can be isolated from vaginal secretions in 30% to 40% of infected women [42]. Thus, minimizing fetal exposure to maternal secretions during parturition may be helpful. Delivery by cesarean section decreases the risk of transmission by about 25% [23], but recent studies in the United States showed no benefit beyond those of highly active antiretroviral therapy. Thus, cesarean section should probably be limited to patients with high viral loads caused by viral resistance or refusal to take antiviral medications. In countries where antiviral therapies are unavailable, the benefits versus the risks of cesarean section must be carefully weighed. Artificial rupture of the membranes to facilitate delivery is not recommended. Additional obstetric measures to minimize transmission include protecting the skin integrity of the baby by avoiding the use of forceps and of scalp electrodes during delivery.

Vaginal disinfection with benzalkonium chloride or other virucidal agents before delivery and washing the newborn with benzalkonium chloride may be helpful but are of unproven efficacy [43]. Vertical transmission

might also be reduced by prevention or therapy of maternal venereal infections, maternal nutritional supplementation, and maternal or neonatal immunotherapy. These therapies are of unproven efficacy, however. Vaccination, particularly active-passive vaccination, such as used to prevent vertical transmission of hepatitis B, may be helpful in the future [44]. No vaccination strategies have yet shown sufficient promise to warrant clinical trials, however.

Effect of human immunodeficiency virus infection on perinatal outcome

Early studies suggested that maternal HIV infection adversely affects perinatal outcome [45,46]. Currently, the results are quite variable, depending on the study group. Expectant mothers with advanced HIV disease generally have a poor perinatal outcome, with more prematurity, postpartum endometriosis, and a somewhat higher incidence of still-births [47]. Because abortuses have a higher prevalence of HIV infection than full-term infants, some fetuses may be able to clear the virus. In a recent study, vitamin A supplementation of the newborn decreased the severity of nutritional stunting [48].

Detection of human immunodeficiency virus infection in the newborn

The determination of neonatal infection is confounded by the presence of maternal antibodies in cord blood. Many children lose these antibodies over 6 to 18 months and remain seronegative (seroreversion). Thus, serologic testing is inadequate to determine HIV infection in the newborn. Investigators have therefore examined direct tests of viral infection. Viral culture of blood is feasible but is labor-intensive and insensitive. Many investigators use molecular techniques to detect HIV RNA or DNA in the neonate's lymphocytes. Testing for RNA is more sensitive than testing for DNA [49]. Viral isolation, by any means, during the first 48 hours of life is believed to signal antenatal infection and to predict chronic infection. Sometimes, initial studies are negative, but studies become persistently positive after 1 month, a development that is interpreted as evidence of intrapartum infection. In about 5% of cases, HIV culture or polymerase chain reaction (PCR) studies are initially positive but revert to negative [50,51]. The mechanism for this phenomenon is uncertain. It may result from contamination from maternal secretions during sampling. As many as 25% of uninfected children manifest anti-HIV cytotoxicity, suggesting that fetal or neonatal immunity could control or even eradicate the virus [52,53]. Whether the response is alloreactive, rather than virus-specific, is unknown.

Natural history of vertical infection in infants and children

Early studies indicated that infection in infants is often caused by rapidly progressive disease. Several studies showed an increased rate of prematurity and intrauterine growth retardation. Prematurity was associated with shortened survival [54]. Infected children have an increased incidence of failure to thrive, with a decreased rate of linear growth [55], a delay in motor development, and deceleration in mental development [56]. In early studies, about one quarter of infected children developed an AIDS-defining condition by 1 year of age, and more than 80% developed an HIV-related symptom by 2 years of age, with a median age of onset of any symptom before 6 months of age [57]. In contrast, adults have a long clinically latent period that averages from 8 to 12 years. Predictors of rapid disease progression include evidence of in utero infection, high viral load [58], and evidence of thymic dysfunction, as manifested by decreases in both CD4+ and CD8+ lymphocytes [59]. Several recent studies have indicated that the progression rate in children matches that of their mothers around the time of delivery [60,61]. The rate of progression in children is related to the plasma viral load [58,62]. Because of the evident efficacy of antiretroviral therapy in adults, combination therapies have been administered to children, with sustained efficacy in suppressing viral activity [63]. Drug-related toxicity also occurs in children, however [64].

Effect of human immunodeficiency virus infection on the mother

Early studies showed immunosuppression in HIV-infected pregnant women, manifested by a decline in CD4+ lymphocyte counts [65]. Women not infected with HIV also experience a decline in CD4+ lymphocytes during pregnancy, but unlike infected women, their CD4+ lymphocyte levels normalize postpartum [66,67].

Mild to moderate immune suppression may normally occur during late pregnancy, possibly related to tolerance of the fetus, whose genes are half foreign to the mother. Infected women might, therefore, be expected to have an increased risk of opportunistic infections during late pregnancy. This increase in opportunistic infections does not occur: pregnancy does not affect the risk of developing tuberculosis, active herpetic infection, or pneumocystis pneumonia and does not affect the disease course or viral burden [37,68,69]. Pregnant women infected with HIV do not seem to be at higher risk of obstetric problems. Like zidovudine, sulfonamides used to prevent pneumocystis pneumonia, such as trimethoprim-sulfamethoxazole, are safe during pregnancy, without reports of kernicterus of the newborn.

Human immunodeficiency virus and infertility treatment

Improved care of HIV infection has affected the outlook of infected women and their spouses towards childbearing. Most HIV-infected people are in

the active reproductive age. About 20% of HIV-infected people in the United States and about 50% in developing countries are female. In managing an HIV+ woman who is not pregnant, discussion about family planning is important, especially when the partner is HIV-negative [70]. Safe sex practices are important to prevent unplanned pregnancy or other problems. These recommendations are most important in the inner city and the developing world, where most HIV-infected children will be found in coming years.

Infertility treatment in HIV raises ethical questions. In 1994 the Ethics Committee of the American Society of Reproductive Medicine promulgated fairly conservative guidelines for counseling and care. Because of improved recent treatment of HIV infection and the proven safety of semen preparation techniques, the Ethics Committee revised their guidelines in 2002. The Committee analyzed three situations separately: (1) the woman is infected and the man is uninfected, (2) the man is infected and the woman is uninfected, and (3) both the man and the woman are infected.

The Committee noted that conception in an HIV-positive woman from an HIV-negative man could be accomplished by artificial insemination. When the man is HIV-positive and the woman is HIV-negative, the mother and the infant are at risk of contracting HIV infection. In one study of timed intercourse (ie, intercourse during ovulation, with barrier protection during intercourse at other times), women had a 4.3% seroconversion rate. Semprini and colleagues [71] and Marina and colleagues [72] reported that infection of mother and child from an HIV-infected father was completely prevented by careful preparation of semen before insemination. When both man and woman are seropositive, conception and delivery of an HIV-uninfected child can occur and is likely if the maternal viral burden is suppressed. Counseling, however, should include the caveats that the long-term outcome of HIV infection is unknown, and that the child might become an orphan.

An ethical dilemma pertains to whether HIV infection confers an unacceptable risk to the unborn child. This situation is similar to that for genetic diseases, such as a man and woman who both carry sickle cell trait, the gene for Wilson's disease, the *BRCA* mutation, or other potentially serious mutations. They all should be counseled similarly. The situation even resembles that of pregnancy late in a woman's reproductive years, when the risk of bearing children with Downs syndrome is increased. In fact, provided maternal infection is well controlled, the risk of transmission of HIV is much lower than that for genetic diseases. The previously mentioned considerations apply to persons who know they have HIV infection, but about 200,000 Americans are unaware of their HIV infection. The Committee evaluated the ethics of counseling HIV testing in patients at high risk for HIV infection who are referred for infertility.

Health care providers are obligated to care for HIV-infected individuals who seek evaluation and treatment of infertility. This requirement is based on the Americans for Disability Act: an HIV-infected patient is considered

to have a disability under this act. Patients are best referred to and treated at centers with special expertise in this field, however. Health care providers should adopt universal precautions to reduce their risk of contracting HIV infection.

Recommendations

In managing a pregnant HIV-positive woman, it is most important to treat the patient as someone who is HIV-positive rather than someone who is pregnant. Withholding antiviral or prophylactic therapies from the mother for fear of harming the child is not justified, because failure to treat the mother increases the fetal risk. The most important parameter to follow is the maternal plasma HIV-RNA level, and the most important treatment issue is to reduce this level because it is directly related to the risk of vertical transmission.

References

[1] Stoneburner R, Sato P, Burton A, et al. The global HIV pandemic. Acta Paediatr Suppl 1994;400:1.
[2] Scarlatti G. Paediatric HIV infection. Lancet 1996;348:863.
[3] Temmerman M, Ndinya-Achola J, Ambani J, et al. The right not to know HIV-test results. Lancet 1995;345:969.
[4] Mundy D, Schinazi RF, Gerver AR, et al. Human immunodeficiency virus isolated from amniotic fluid. Lancet 1987;2:459.
[5] Courgnaud V, Laure F, Broussard A, et al. Frequent and early in utero HIV-1 infection. AIDS Res Hum Retroviruses 1991;7:337.
[6] Baba T, Koch J, Mittler ES, et al. Mucosal infection of neonatal rhesus monkeys with cell-free SIV. AIDS Res Hum Retroviruses 1994;10:351.
[7] Bourinbaiar AS, Phillip DM. Transmission of human immunodeficiency virus from monocytes to epithelia. Journal of Acquired Immune Deficiency Syndromes 1991;4:55.
[8] Amerongen HM, Waltzin R, Farnet CM, et al. Transepithelial transport for HIV-1 by intestinal M cells: a mechanism for transmission of AIDS. Journal of Acquired Immune Deficiency Syndromes 1991;4:760.
[9] Bertolli J, St. Louis ME, Simonds RJ, et al. Estimating the timing of mother-to-child transmission of human immunodeficiency virus in a breast-feeding population in Kinshasa, Zaire. J Infect Dis 1996;174:722.
[10] Van de Perre P, Simonon A, Msellati P, et al. Postnatal transmission of human immunodeficiency virus type 1 from mother to infant: a prospective cohort study in Kigali. Rwanda. N Engl J Med 1991;325:593.
[11] Kliks SC, Wara DW, Landers DV, et al. Features of HIV-1 that could influence maternal-child transmission. JAMA 1994;272:467.
[12] Minkoff H, Bauer TA. Mother-to-infant transmission of HIV. N Engl J Med 1997;336: 1392.
[13] Mwanyumba F, Gaillard P, Inion I, et al. Placental inflammation and perinatal transmission of HIV-1. J Acquir Immun Syndr Hum Retrovirol 2002;29:262.
[14] Mayaux MJ, Dussaix E, Isopet J, et al. Maternal virus load during pregnancy and mother-to-child transmission of immunodeficiency virus type 1: the French perinatal cohort studies–SEROGEST Cohort Group. J Infect Dis 1997;175:172.

[15] Sperling RS, Shapiro DE, Coombs RW. 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 1996;335:1621.
[16] Dickover RE, Garraty EM, Herman SA, et al. Identification of levels of maternal HIV-1 RNA associated with risk of perinatal transmission: effect of maternal zidovudine treatment on viral load. JAMA 1996;275:599.
[17] Khouri YF, McIntosh K, Cavacini L, et al. Vertical transmission of HIV-1: correlation with maternal viral load and plasma levels of CD4 binding site anti-gp 120 antibodies. J Clin Invest 1995;95:732.
[18] Pitt J, Brambilla D, Reichelderfer P, et al. 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 1997;175:567.
[19] Kesson AM, Fear WR, Kazazi F, et al. Human immunodeficiency virus type-1 infection of human placental macrophages in vitro. J Infect Dis 1993;168:571.
[20] McGann KA, Collman R, Kolson DL, et al. Human immunodeficiency virus type 1 causes productive infection of macrophages in primary placental cell cultures. J Infect Dis 1994; 169:746.
[21] Wolinsky SM, Wike CM, Korber BTM. Selective transmission of human immunodeficiency virus type-1 variants from mothers to infants. Science 1992;225:1134.
[22] Lamers SL, Sleasman JW, She JX, et al. Persistence of multiple maternal genotypes of human immunodeficiency virus type 1 in infants infected by vertical transmission. J Clin Invest 1994;93:380.
[23] Landesman SH, Kalish LA, Burns DN, et al. Obstetrical factors and the transmission of human immunodeficiency virus type 1 from mother to child: the Women and Infants Transmission Study. N Engl J Med 1996;334:1617.
[24] Duliege AM, Amos CI, Felton S, et al. Birth order, delivery route, and concordance in the transmission of human immunodeficiency virus type 1 from mothers to twins: International Registry of Exposed Twins. J Pediatr 1995;126:625.
[25] Nielsen K, Boyer P, Dillon M, et al. Presence of human immunodeficiency virus (HIV) type 1 and HIV-1-specific antibodies in cervicovaginal secretions of infected mothers and in the gastric aspirates of their infants. J Infect Dis 1996;173:1001.
[26] Mandelbrot L, Mayaux MJ, Bongain A, et al. Obstetric factors and mother-to-child transmission of human immunodeficiency virus type 1: the French perinatal cohorts–SEROGEST French Pediatric HIV Infection Study Group. Am J Obstet Gynecol 1996; 175:661.
[27] Semba RD, Miotti PG, Chiphangwi JD, et al. Maternal vitamin A deficiency and mother-to-child transmission of HIV-1. Lancet 1994;343:1593.
[28] Semba RD, Miotti P, Chiphangwi JD. Maternal vitamin A deficiency and child growth failure during human immunodeficiency virus infection. J Acquir Immunodefic Syndr 1997; 14:219.
[29] Burger H, Kovacs A, Weiser B. Maternal serum vitamin A levels are not associated with mother-to-child transmission of HIV-1 in the United States. Journal of Acquired Immune Deficiency Syndromes 1997;14:321.
[30] Ross AC. Vitamin A status: relationship to immunity and the antibody response. Proc Soc Exp Biol Med 1992;200:303.
[31] Sommer AI, Tarvotio G, Hussaini G, et al. Increased mortality in children with mild vitamin A deficiency. Lancet 1983;2:585.
[32] Nduati RW, John GC, Richardson BA. Human immunodeficiency virus type 1-infected cells in breast milk: association with immunosuppression and vitamin A deficiency. J Infect Dis 1995;172:1461.
[33] Kennedy-Oji C, Coutsoudis A, Kuhn L, et al. Effects of vitamin A supplementation during pregnancy and early lactation on body weight of South African HIV-infected women. J Health Popul Nutr 2001;19:167.

[34] Turner BJ, Hauck WW, Fanning TR. Cigarette smoking and maternal-child HIV transmission. 1997;14:327.
[35] Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type I with zidovudine treatment: Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med 1994;331:1173.
[36] Matheson PB, Abrams EJ, Thomas PA, et al. Efficacy of antenatal zidovudine in reducing perinatal transmission of human immunodeficiency virus type-1: the New York City Perinatal HIV Transmission Collaborative Study Group. J Infect Dis 1995;172:353.
[37] Melvin AJ, Burchett SK, Watts DH, et al. Effect of pregnancy and zidovudine therapy on viral load in HIV-1 infected women. Journal of Acquired Immune Deficiency Syndromes 1997;14:232.
[38] Frenkel LM, Cowles MK, Shapiro DE, et al. Analysis of the maternal components of the AIDS clinical trial group 076 zidovudine regimen in the prevention of mother-to-infant transmission of human immunodeficiency virus type-1. J Infect Dis 1997;175:971.
[39] Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-zidovudine combination for prevention of maternal infant transmission of HIV-1. JAMA 2001;285: 2083.
[40] Eshelman SH, Mracna M, Guay LA, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET-012). AIDS 15:1951, 2001.
[41] De Jose MI, Ramos JT, Alvarez S, et al. Vertical transmission of HIV-1 variants resistant to reverse transcriptase and protease inhibitors. Arch Intern Med 2001;161:2738.
[42] John GC, Nduati RW, Mbori-Ngacha D, et al. Genital shedding of human immunodeficiency virus type-1 DNA during pregnancy: association with immunosuppression, abnormal cervical or vaginal discharge, and severe vitamin A deficiency. J Infect Dis 1997; 175:57.
[43] Biggar RJ, Miotti PG, Taha TE, et al. Perinatal intervention trial in Africa: effect of a birth canal cleansing intervention to prevent HIV transmission. Lancet 1996;347:1647.
[44] Van Rompay KK, Otsyula MG, Tarara RP, et al. Vaccination of pregnant macaques protects newborns against mucosal simian immunodeficiency virus infection. J Infect Dis 1996;173:1327.
[45] Temmerman M, Plummer FA, Mirza NB. Infection with HIV as a risk factor for adverse obstetrical outcome. AIDS 1990;4:1087.
[46] Braddick MR, Kreiss JK, Embree JE. Impact of maternal HIV on obstetrical and early neonatal outcome. AIDS 1990;4:1001.
[47] Temmerman M, Chomba EN, Ndinya-Achola J, et al. Maternal human immunodeficiency virus type-1 infection and pregnancy outcome. Obstet Gynecol 1994;83:495.
[48] Villamor E, Mbise R, Spiegelman D, et al. Vitamin A supplements ameliorate the adverse effects of HIV-1, malaria, and diarrheal infections on child growth. Pediatrics 2002; 109:E6.
[49] Steketee RW, Abrams EJ, Thea DM, et al. Early detection of perinatal human immunodeficiency virus (HIV) type-1 infection using HIV RNA amplification and detection. New York City Perinatal HIV Transmission Collaborative Study. J Infect Dis 1997;175:707.
[50] Bryson YJ, Pang S, Wei LS, et al. Clearance of HIV infection in a perinatally infected infant. N Engl J Med 1995;332:833.
[51] Newell ML, Dunn D, De Maria A, et al. Detection of virus in vertically exposed HIV-antibody-negative children. Lancet 1996;347:213.
[52] De Maria A, Cirillo C, Moretta L. Occurrence of human immunodeficiency virus type 1 (HIV-1)-specific cytolytic T cell activity in apparently uninfected children born to HIV-1-infected mothers. J Infect Dis 1994;170:1296.
[53] Rowland-Jones SL, Nixon DF, Aldhous MC, et al. HIV-specific cytotoxic T-cell activity in an HIV-exposed but uninfected infant. Lancet 1993;341:860.

[54] Abrams EJ, Matheson PB, Thomas PA, et al. Neonatal predictors of infection status and early death among 332 infants at risk of HIV-1 infection monitored prospectively from birth. New York City Perinatal HIV Transmission Collaborative Study Group. Pediatrics 1995;96:451.
[55] Moye Jr. J, Rich KC, Kalish LA. Natural history of somatic growth in infants born to women infected by human immunodeficiency virus: Women and Infants Transmission Study Group. J Pediatr 1996;128:58.
[56] Chase C, Vibbert M, Pelton SI, et al. Early neurodevelopmental growth in children with vertically transmitted immunodeficiency virus infection. Arch Pediatr Adolesc Med 1995; 149:850.
[57] Scott GB, Hutto C, Makuch RW. Survival in children with perinatally acquired human immunodeficiency virus type-1. N Engl J Med 1989;321:1791.
[58] Mayaux MJ, Burgard M, Teglas JP, et al. Neonatal characteristics in rapidly progressive perinatally acquired HIV-1 disease: the French Pediatric HIV Infection Study Croup. JAMA 1996;275:606.
[59] Kourtis AP, Ibegbu C, Nahmias AJ. Early progression of disease in HIV-infected infants with thymus dysfunction. N Engl J Med 1996;335:1431.
[60] Blanche S, Mayaux MJ, Rouzioux C, et al. Relation of the course of HIV infection in children to the severity of the disease in their mothers at delivery. N Engl J Med 1994; 330:308.
[61] Tovo PA, de Martino M, Gabiano C, et al. AIDS appearance in children is associated with the velocity of disease progression in their mothers. J Infect Dis 1994;170:1000.
[62] Shearer WT, Quinn TC, LaRussa P. Viral load and disease progression in infants infected with human immunodeficiency virus type-1. N Engl J Med 1997;336: 1337.
[63] Luzuriaga K, Bryson Y, Krogstad P. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type-1 infection. N Engl J Med 1997;336:1343.
[64] Arpadi SM, Cuff PA, Horlick M, et al. Lipodystrophy in HIV-infected children is associated with high viral load and low CD4+ lymphocyte count and CD4+ lymphocyte percentage at baseline and use of protease inhibitors and stavudine. J Acquir Immune Defici Syndr Hum Retrovirol 2001;27:30.
[65] Biggar RJ, Pahwa S, Minkoff H. Immunosuppression in pregnant women infected with human immunodeficiency virus. Am J Obstet Gynecol 1989;161:1239.
[66] Johnstone FD, Thong KJ, Bird AG, et al. Lymphocyte subpopulations in early human pregnancy. Obstet Gynecol 1994;83:941.
[67] Rich KC, Siegel JN, Jennings C, et al. CD4+ lymphocytes in perinatal human immunodeficiency virus (HIV) infection: evidence for pregnancy-induced immune depression in uninfected and HIV-infected women. J Infect Dis 1995;172:1221.
[68] Espinal MA, Reingold AL, Lavandera M. Effect of pregnancy on the risk of developing active tuberculosis. J Infect Dis 1996;173:488.
[69] Hocke C, Morlat P, Chene G, et al. Prospective cohort study of the effect of pregnancy on the progression of human immunodeficiency virus infection: the Groupe d'Epidemiologie Clinique Du SIDA en Aquitaine. Obstet Gynecol 1995;86:886.
[70] Gupta GK. Human immunodeficiency virus testing and counseling: nuts and bolts. Am J Obstet Gynecol 1996;175:1502.
[71] Semprini AF, Levi-Setti P, Ravizza M, et al. Assisted conception to reduce the risk of male-to-female sexual transfer of HIV in serodiscordant couples: an update [abstract]. Presented at the 1998 Symposium on AIDS in Women. Sao Paolo, Brazil, September 14–15, 1998.
[72] Marina S, Marina F, Alcolea R, et al. Human immunodeficiency virus type-1 serodiscordant couples can bear healthy children after undergoing intrauterine insemination. Fertil Steril 1998;70:35.