

Congenital Human Immunodeficiency Virus (HIV) Infection

Konjenital İnsan İmmünyetmezlik Virusu (HIV) Enfeksiyonu

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In the developed world, antiretroviral therapy (ART) administered to the mother during pregnancy and intrapartum and to the infant in the neonatal period has resulted in a reduction of the overall risk of vertical transmission of HIV to approximately 8%. In some settings, ART combined with cesarean section and a reduction in duration of ruptured membranes has resulted in a further lessening of risk to levels $\leq 2\%$. The pediatrician has a key role in prevention of mother-to-child transmission of HIV by identifying HIV-exposed infants whose mothers' HIV infection was not diagnosed before delivery, prescribing antiretroviral prophylaxis for these infants to decrease the risk of acquiring HIV infection, and promoting avoidance of HIV transmission through human milk. In addition, the pediatrician can provide care for HIV-exposed infants by monitoring them for early determination of HIV infection status and for possible short and long-term toxicities of antiretroviral exposure, providing chemoprophylaxis for *Pneumocystis pneumonia*, and supporting families living with HIV infection by providing counseling to parents or caregivers.

Key Words: Human immunodeficiency virus, mother-to-child transmission, diagnosis, treatment, follow-up

Gelişen dünyada, antiretroviral terapi'nin (ART) anneye hamilelik süresince ve intrapartum dönemde; yenidoğan bebeğe ise neonatal dönemde uygulanması anneden bebeğe HIV geçiş riskinin yaklaşık % 8' lere kadar düşmesine neden olmuştur. ART ile birlikte sezeryan doğumun tercih edilmesi ve doğumda membran rüptür süresinin kısaltılması gibi bazı uygulamalarla bu risk % 2'lerin altına kadar gerilemiştir. Çocuk hekimleri doğumdan önce HIV enfeksiyonu teşhisi konulmamış annelerin HIV' ne maruz kalmış bebeklerini teşhis ederek, bu bebeklere HIV enfeksiyonu riskini azaltmak için ART profilaksisi uygulayarak ve anne sütü ile HIV geçişinin önlenmesi için anne sütü ile beslenmemelerini sağlamak yolu ile anneden bebeğe HIV virüsü geçişinin önlenmesinde anahtar bir rolü üstlenirler. Ek olarak, çocuk hekimleri HIV'ne maruz kalmış bu bebeklerin ilerde oluşabilecek HIV enfeksiyonu açısından erken tanıya yönelik yakın takiplerini yaparak, ART tedavisi uygulanan çocukların uzun ve kısa dönemde oluşabilecek yan etkiler açısından izlenmesini sağlayarak, gereken durumlarda *Pneumocystis pnömonisi* için profilaksi uygulayarak ve çocuğun ailesine veya bakımını üstlenen kişilere onların HIV enfeksiyonu ile yaşamaları için danışım temin ederek HIV' ne maruz kalmış bu infantların bakımını sağlayabilirler.

Anahtar Sözcükler: İnsan immünyetmezlik virüsü, konjenital enfeksiyon, tanı, tedavi, izlem

VIROLOGY

HIV infection is caused by the human retrovirus HIV type I (HIV-1) and type II (HIV-2). HIV primarily attacks T-lymphocytes and macrophages, and its genomic

structure is more complex than that of many other viruses (1). HIV gains entry to cells when its envelope glycoproteins gp 120 and gp 41 bind with the CD4 receptor and a chemokine co-factor on the target cell surface. M-tro-

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pic strains of HIV-1 require the CC chemokine receptor CCR5, while T-tropic strains require CXCR4, which is a member of the CXC chemokine family (2).

PATHOGENESIS

After they gain entry into the target cell, HIV virions are uncoated. Retroviral reverse transcriptase transcribes single-stranded viral RNA into linear double-stranded DNA (3). The viral DNA is then transported into the nucleus, where viral integrase splices the viral DNA into random sites in the host cell genome. Once integrated, the provirus hijacks the host cell's machinery to force the production of its own viral proteins. Unintegrated viral DNA may also accumulate in the cell; inactive provirus has been found in 0.1% to 13.5% of peripheral blood mononuclear cells, compared with viral messenger RNA, which is found in 0.002% to 0.25% of these cells (4). Latent provirus can be activated by the host cell's response to various antigens, mitogens, and cytokines, such as tumor necrosis factor (TNF), and the gene products of other viruses (5).

Both cell-mediated and humoral immunity are devastated by HIV infection. The dysfunction is slow but progressive, resulting in the depletion of CD4+ T-lymphocytes (2). Age-related changes in the number of the different subgroups have been revealed by flow cytometric analysis of lymphocyte subpopulations in healthy children (6). In another study, CD8+ counts did not differ significantly between HIV-infected and noninfected children younger than two years, but HIV-infected infants had depressed le-

vels of CD4+ cells (7). Other immune abnormalities include decreased lymphocyte proliferation in response to an antigen, polyclonal B cell activation resulting in hypergammaglobulinemia, and altered function of monocytes and neutrophils (8).

EPIDEMIOLOGY

Approximately 92% of Acquired Immunodeficiency Syndrome (AIDS) cases in children under 13 years of age in the United States in 2005 were attributed to perinatal transmission (9), but the actual rate of transmission from mother to child is low, under two percent, both in the United States and in other economically-developed countries. Fewer than 400 infants acquire HIV-1 annually from their mothers in the U.S. (10, 11). The reason for this is believed to be the implementation of widespread prenatal testing in wealthy countries. If the mother proves to be infected, measures are recommended to protect the fetus, including antiretroviral prophylaxis, elective cesarean section, and the avoidance of breastfeeding.

In contrast, more than 2000 HIV-infected infants are born annually in the rest of the world. It was estimated that there were approximately 2.3 million children (younger than 14 years) living with HIV-1 by the end of 2005 (12). More than 90 percent of children with HIV/AIDS live outside the U.S., Europe, and other highly developed nations. Clearly, the prevention of mother-child transmission represents a significant public health issue in the developing world (13). There isn't any data about children with HIV/AIDS live in Turkey.

TRANSMISSION

Mother-to-child transmission (MTCT) of HIV has been linked to the high levels of HIV RNA found in the mother; however, in rare instances, transmission can occur at very low viral loads (14-16). The risk of transmission is increased if the clinical stage of the mother's disease is advanced, if she has low CD4 levels, or if her membranes rupture more than 4 hours before delivery. Other risk factors include vaginal delivery, invasive procedures during delivery, and premature birth (9).

In a case-control sub-study evaluating the association between perinatal transmission and genital tract shedding of HIV-1 virus, a significantly higher risk of transmission was found in women receiving antiretroviral therapy (67% Zidovudine [ZDV] alone) for each one-log increase in mean titer of cervicovaginal lavage (CVL) HIV-1 DNA (17).

BREASTFEEDING AND HIV-1 TRANSMISSION

In an attempt to quantify the risks of breastfeeding, the data from nine international trials of mother to child transmission were recently evaluated (18). The risks of transmission associated with breastfeeding seen in this meta-analysis were estimated at 8.9 transmissions per 100 child-years of breastfeeding. Unfortunately, HIV transmission via breastfeeding is not well understood. Risk factors include maternal seroconversion during the lactation period, cracked or bleeding nipples, mastitis, and breast abscesses (9). There are also data suggesting that the risks of transmission increase when detectable levels of HIV-1 virus are found in maternal milk (19).

CLINICAL MANIFESTATIONS

When an infant presents with HIV/AIDS, it is vital to review the mother's medical history to determine whether the child has also been exposed to tuberculosis, syphilis, toxoplasmosis, hepatitis B or C, cytomegalovirus, or herpes simplex virus (20). Immunocompromised pregnant women may be susceptible to co-infections with such agents, or to the reactivation of latent infections (21). There is a need for comparative studies to determine transmission rates for these pathogens in infants whose mothers who are HIV-infected versus infants with mothers who are not HIV-infected.

DIAGNOSIS

Infants who may have been infected with HIV should be screened as early as possible to allow early initiation of antiretroviral therapy and adjunctive therapies (2). There are several methods of detecting the virus:

- **HIV-1 DNA polymerase chain reaction (PCR):** These assays detect HIV-1 DNA in peripheral blood mononuclear cells. A single DNA PCR assay has a sensitivity of 95% and specificity of 97% on samples collected from infants 1 to 36 months of age (1). For HIV-1 subtype B, which is the most common subtype in North America, the sensitivity of DNA PCR at 28 days of age is 96% and the specificity is approximately 99% (22). False negative DNA PCR assay results have been reported for infants infected with non-B subtype virus (23-25).
- **HIV-1 RNA assays (viral load):** There are several methods of de-

tecting viral RNA in the plasma. These include PCR, in vitro signal amplification nucleic probes (branched DNA, known as bDNA), and nucleic acid sequence-based amplification (NASBA). RNA assays tend to be at least as sensitive, or even more sensitive, than HIV-1 DNA PCR assays. They are also as specific (26, 27). The use of single-drug therapy with ZDV has not been shown to affect the sensitivity of HIV-1 RNA (27), but it is not known whether the use of other antiretroviral agents would alter the sensitivity of these tests. This assay may be used to diagnose HIV infection if the result is positive (10,000 copies/mL or greater) (1).

- **HIV-1 peripheral blood cell culture:** Virus isolation by culture is expensive, is available only in a few laboratories, requires up to 28 days for positive results. This test essentially has been replaced by DNA PCR assay (1).
- **HIV-1 immune complex-dissociated p24 antigen:** Because of its low sensitivity, HIV-1 p24 antigen is not recommended for diagnosis in infants (21).

After 12 months of age, serologic testing should be done to determine whether the child still retains the maternal HIV-1 antibodies that were transferred in *utero*. Children who remain antibody positive at 12 months of age should be tested again at 18 months. Loss of HIV-1 antibodies in a child whose HIV-1 DNA PCR test was previously negative confirms that the child is HIV-1 free. On the other hand, if the child has positive HIV-1 antibodies at 18 months of age or above, this indicates HIV-1 infection (28, 29).

TREATMENT

Once infection has been confirmed, a specialist in HIV/AIDS should be consulted to determine options for antiretroviral therapy (30, 31). The current recommendation is that infected children younger than 12 months who have immunologic abnormalities should be treated even if their HIV-1 RNA levels are low. Indeed, because of the risk of rapid disease progression, treatment with antiretrovirals should be considered even for infants who are asymptomatic and have no immunological abnormalities (32). It is currently impossible to predict which children will progress and which ones will not (30, 31).

Current recommendations for treatment of HIV infection are continuously updated by the Panel on Clinical Practices for Treatment of HIV Infection and reflect the opinions of the Panel. For information on a diversity of recommendations from other experts and for the most up-to-date recommendations, the Panel summary statements can be viewed at <http://aidsinfo.nih.gov/guidelines>.

PREVENTION

Despite dramatic declines, MTCT of HIV-1 continues to occur in the U.S. The Centers for Disease Control and Prevention estimated that 145 infected babies were born in 2004 (33). The reason for the continued infections is believed to be the lack of HIV testing due to inadequate pre-natal care in certain populations (9). Both the American College of Obstetricians and Gynecologists and CDC recommend that a second HIV test be repeated in the third tri-

mester for women who are known to have elevated risk for HIV infection (e.g., illicit drug use or a history of sexually transmitted disease). This recommendation also applies to women living in populations that have an elevated HIV prevalence among females of childbearing age (29, 34).

Three efficacious interventions to prevent MTCT of HIV exist: antiretroviral prophylaxis, cesarean section before labor and before ruptured membranes, and complete avoidance of breastfeeding (1).

Antiretroviral prophylaxis has been shown in multiple studies to be effective at preventing perinatal mother to child transmission of HIV-1, including those with low viral loads (i.e., less than 1,000 copies/mL) (14). ZDV alone administered to HIV-infected women with viral loads of fewer than 1,000 copies/mL has been shown to reduce perinatal HIV transmission to 1% (35). Therefore, it is recommended that all HIV-infected women receive prophylaxis during pregnancy with the Pediatric AIDS Clinical Trials Group (PACTG) 076 Study ZDV regimen alone, or, if maternal viral load is 1,000 copies/mL or greater, with combination therapy, followed by oral ZDV for 6 weeks to the infant. In addition, elective cesarean delivery is recommended if the maternal viral load is 1,000 copies/mL or greater near delivery. No long-term effects on women's health have been noted among U.S. women enrolled in the PACTG 076 trial in terms of disease progression, mortality, viral load, or ZDV resistance between randomized treatment and placebo groups (36). In some cases, a woman's HIV infection status will not be known

until labor and delivery. In that event, there are several measures that may be initiated to prevent perinatal transmission. Recent clinical trials suggest several efficacious intrapartum/postpartum regimens that include ZDV, lamivudine, and nevirapine alone or combination in short courses for the children of women who received no antiretroviral therapy during pregnancy (Table 2) (35, 37-39). In addition, ZDV should be prescribed to the neonate as soon as possible after delivery and then continued for 6 weeks. In such instances, other antiretroviral agents could be added to the postnatal ZDV regimen (10).

It should be noted that the mechanism of ZDV action is not fully understood. In the PACTG 076 study, transmission was reduced at all levels of maternal HIV-1 RNA, but only 17% of the reported effectiveness of the drug could be attributed to a ZDV-associated drop in viral load (40). Since ZDV was effective at reducing transmission even in mothers whose viral loads were low, these results suggest that both pre- and post-exposure prophylaxis of the infant during labor and delivery may confer protection (10). Several studies from the U.S. and Europe have shown that ZDV prophylaxis helps prevent perinatal transmission of HIV-1, regardless of the woman's viral load. A meta-analysis of the mother-to-child transmission risk factor data from seven of these found that transmission was significantly lower among 1,202 HIV-infected mothers with RNA viral loads of less than 1000 copies/mL at delivery among subjects who had been treated with ZDV (1% vs. 9.8% among untreated women) (14). Multivariate analysis also showed that transmission was lower with ZDV, independent

of cesarean delivery, birth weight, and CD4+ count. Therefore, ZDV prophylaxis should be given even to women with very low or undetectable viral load levels.

The goal should be to diagnose HIV infection early in pregnancy to allow interventions to prevent transmission. In the United States, antiretroviral drugs should be administered to HIV-infected women during pregnancy, labor, and delivery. Zidovudine should be given to all newborn infants as soon as possible after birth to decrease the likelihood of mother-to-child transmission of HIV, even if their mothers did not receive ZDV. The first-line regimen recommended in resource-limited settings is to administer ZDV as early as possible in the third trimester, plus one dose of NVP to the mother and to the infant (1).

Maternal Highly Active Antiretroviral Therapy (HAART) During the Antenatal Period

Because the level of HIV-1 RNA in the mother is strongly associated with the risk of perinatal HIV-1 transmission (15), the effects of maternal HAART have been investigated in several studies. For example, in a study performed in the United States, HIV-1 transmission was 20.0% (95% CI, 16.1% to 23.9%) for 396 women out of 1542 infected mothers who received no prenatal antiretroviral treatment (16). For those subjects who received ZDV alone, transmission was 10.4% (95% CI, 8.2% to 12.6%) for 710 women and 3.8% (95% CI, 1.1% to 6.5%) for 186 women who were given combination antiretroviral therapy without protease inhibitors. The transmission rate dropped to 1.2% (95% CI, 0 to 2.5%) for the 250 women who received combi-

nation antiretroviral therapy with protease inhibitors. Another variable investigated in this study was HIV-1 RNA level at delivery: the data showed that the transmission rate was 1.0% for less than 400 copies/mL; 5.3% for 400 to 3,499 copies/mL; 9.3% for 3,500 to 9,999 copies/mL; 14.7% for 10,000 to 29,999 copies/mL; and 23.4% for more than 30,000 copies/mL. The odds of transmission increased 2.4-fold (95% CI, 1.7 to 3.5) for every log₁₀ increase in viral load at the time of delivery. In multivariate analyses adjusting for maternal viral load, duration of therapy, and other factors, the OR for transmission for women who received combination therapy with or without protease inhibitors was 0.30 (95% CI, 0.09 to 1.02), and the OR for transmission for women who received monotherapy with ZDV was 0.27 (95% CI, 0.08 to 0.94). The levels of HIV-1 RNA at delivery and prenatal antiretroviral therapy were independently associated with transmission. The protective effect of therapy increased with the complexity and duration of the regimen, and maternal HAART was associated with the lowest rates of transmission.

Resistance Due to Antiretroviral Prophylaxis

An important area of concern is that the widespread use of antiretroviral prophylaxis to prevent perinatal HIV-1 could cause the spread of antiretroviral drug resistance, especially in the developing world. It only takes a single gene mutation to cause viral resistance to commonly used antiretroviral agents such as 3TC and NVP (41).

In a French study, 39% of women receiving ZDV/3TC for more than 4 weeks had genetic mutations

associated with 3TC resistance (the M184V mutation) at the time of labor and delivery (42). In the HIVNET 012 study, 19% of women receiving the single-dose NVP therapy at beginning of labor were found to have NVP-resistant mutations (the K103N mutation), but these mutations were no longer detectable 12 to 24 months after delivery (43). NVP resistance was seen in 46% of NVP-treated infants who later became infected, but the mutations disappeared by the age of 12 months. Since the mutations identified in the mother were different from those identified in the infant, no resistant strains were actually transmitted from mother to child. These data suggest that mutations may fade as drug pressure lessens, which would make the widespread transmission of NVP-resistant virus less likely. In a later study, mutations indicating resistance were detected 10 days after delivery in 32% of women who had received intrapartum NVP, and women who continued on NVP regimens after delivery were less likely to show evidence of suppression of the virus six months postpartum (44).

Non-antiretroviral interventions

Some investigations have been done of possible HIV/AIDS therapies that do not include antiretroviral regimens. The results have not been encouraging. For example, several trials conducted in sub-Saharan Africa established that washing of cervicovaginal mucosa with chlorhexidine and the use of 1% benzalkonium chloride vaginal suppositories does not result in a reduction of perinatal HIV-1 transmission (45-47). Because severe maternal vitamin A deficiency has been iden-

tified as a contributory factor to perinatal transmission in Africa (48), three randomized, controlled trials of vitamin A or other multivitamin administration were conducted in South Africa, Malawi, and Tanzania (49-51). However, they failed to show any reduction in perinatal HIV-1 transmission.

The prevention of new HIV infections in women of childbearing age remains a challenge in many areas of the world. The difficulty is often increased among adolescent girls who are members of minority races and/or ethnic groups. Prevention of unplanned pregnancy in adolescent women is a vital component of any plan to reduce perinatal HIV-1 transmission (52).

Prevention of Human Milk HIV-1 Transmission

Ever since 1985, when HIV was isolated from breast milk (53) and breastfeeding was associated with mother-to-child transmission of HIV (54), the CDC has recommended that women infected with the virus refrain from breastfeeding their infants (55). In the United States and other highly developed countries where safe alternatives to breast-feeding exist, this policy is easily implemented and economically feasible (1). In other parts of the world, however, studies have estimated that one third to one half of mother to child transmission of HIV is due to breastfeeding (56).

Antiretroviral prophylaxis with NVP for the breast-feeding infant offers protection against postnatal transmission. NVP has several properties that make it a powerful preventative measure during breastfeeding. It is highly lipop-

hilic, rapidly crosses the placenta, and easily enters human milk. It has a relatively long half-life, excellent bioavailability, and is generally well-tolerated (21). In a phase I/II trial (HIVNET 023) in South Africa and Zimbabwe, data have demonstrated that extended therapy with NVP is safe and effective. High plasma concentrations were obtained in children who received the drug daily or twice-weekly for the first 6 months after birth (57).

Scheduled cesarean delivery

Mother to child transmission can also be reduced by planned cesarean delivery. Several studies have shown that cesarean delivery before the onset of labor reduces HIV transmission to infants whose mothers received no ARV therapy during pregnancy or received only ZDV (58, 59). After these results were presented in 1998, rates of cesarean delivery among HIV-infected pregnant women in one large cohort study increased from 20 percent to 44 percent (60). However, it is not known whether cesarean delivery is associated with a significant reduction in transmission rates among women who have low HIV RNA levels (<1,000 copies/mL). The potential risks of surgery for such women may be greater than the uncertain benefit to their infants, particularly since the risk for HIV transmission during routine labor and delivery is less than two percent. The U.S. Public Health Service Task Force (USPHSTF) recommends that scheduled cesarean delivery be offered to women whose HIV RNA levels are greater than 1,000 copies/mL near the time of delivery (61).

FOLLOW-UP

Monitoring for Toxicity from Exposure to Antiretroviral Drugs in Utero and During Infancy

There is not a great deal of information available regarding adverse effects for infants exposed in *utero* to antiretroviral agents, and the data that do exist are conflicting (62, 63). Some studies suggest that combination antiretroviral therapy increases the risk of preterm birth problems during pregnancy (64). On the other hand, a review of pregnancy outcomes in seven studies of a total of 3266 HIV-1-infected women suggests that combination therapy is not associated with increased rates of preterm birth, low birth weight, low Apgar scores, or stillbirth (65).

Since anemia is the most common short-term adverse consequence associated with ZDV (62, 63), infants on ZDV regimens should receive a complete blood cell count at birth, at one month of age, and again at two months of age. Transient lactatemia also has been observed, but its significance is not well understood (66, 67). Mitochondrial dysfunction was described in 8 of 1754 (0.46%) uninfected infants in a French cohort who had been exposed in *utero* to ZDV with 3TC or to ZDV alone (68). Two of the children who were exposed to ZDV with 3TC developed severe neurological disease and died; 3 had mild-to-moderate symptoms (including a transient cardiomyopathy); and 3 were asymptomatic with transient abnormal laboratory findings, including high lactate concentration.

Because drug exposure can cause long-term adverse effects, infants should be examined at birth for

congenital anomalies and carefully assessed both at 6 months of age and at annual visits (69). In particular, follow-up assessments should include evaluation for the symptoms of mitochondrial toxicity. These indications tend to be varied and/or nonspecific, but serious signs of mitochondrial toxicity include encephalopathy, afebrile seizures or developmental delay, cardiac irregularities consistent with cardiomyopathy, and gastrointestinal symptoms attributable to hepatitis. Physicians should also perform a developmental assessment of infants who have been exposed to these drugs. If abnormalities suggestive of mitochondrial toxicity are observed, consultation with a specialist in this field should immediately be sought (21).

Immunizations

Infants who have been exposed to HIV-1 should receive all routine immunizations. If HIV-1 infection is confirmed, immunization guidelines for the HIV-1-infected child should be observed (1).

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