Mother-to-child transmission (MTCT) of the human immunodeficiency virus (HIV) continues to be a major global health problem. The pediatric HIV-1 epidemic is fuelled by HIV-1 infection in women of childbearing age. Worldwide every year approximately 750,000 children become infected with HIV. Without specific interventions, the rate of MTCT is approximately 15-20%, with prolonged breastfeeding doubling the rate to 35-40%.

Transmission can occur during pregnancy, labor, or breastfeeding. Intrauterine transmission has been suggested by identification of HIV by culture or polymerase chain reaction in fetal tissue as early as 10 weeks' gestation. It is generally accepted that 30-40% of infected newborns acquire infection in utero because they show laboratory evidence of infection within the 1st week of life. The highest percentage of HIV-infected children acquires the virus intrapartum evidenced by the fact that 60-70% of infected infants do not demonstrate detectable virus before 1 week of age. The mechanism of transmission appears to be exposure to infected blood and cervicovaginal secretions in the birth canal, where HIV is found in high titers during late gestation and delivery. Breast feeding is an important MTCT route in developing countries. Both free and cell-associated viruses have been detected in breast milk from HIV-infected mothers.

The presence of passively transferred maternal antibodies to HIV-1 has not protected infants from HIV-1 infection and there is no clear understanding about the role of antibodies in preventing MTCT. Immune factors, such as leukemia inhibitory factor, CC chemokines, Lewis X component and secretory leukocyte protease inhibitor, appear to be involved in the protection of HIV-exposed, uninfected infants.

Maternal and obstetric risk factors
Worldwide, 60% of HIV-infected individuals are women. The main risk factors for mother-to-child HIV transmission are high maternal viral load and maternal CD4 cell count <700 cells/mm³ and the main protective factor is antiretroviral therapy. Preterm delivery (<34 week gestation), use of illicit drugs during pregnancy, >4 hour duration of ruptured membranes and birth weight <2500 gm are also important risk factors.

Maternal viral load, as quantified by RNA polymerase chain reaction, is associated with increased risk in each mode of vertical transmission. A recent randomized clinical trial in Kenya found that maternal plasma HIV RNA levels higher than 43,000 copies/ml were associated with a fourfold increase in vertical transmission. Infants with rapid disease progression had lower levels of anti-p24 antibodies than did infants whose disease did not rapidly progress, but not independently of HIV-1 RNA levels.

Independent of HIV RNA levels in maternal plasma, additional risk factors include cervical HIV deoxyribonucleic acid (DNA), vaginal HIV DNA, and cervical or vaginal ulcers. Chorioamnionitis has also been documented as a risk factor for MTCT among African mothers. Some investigators reported an association of chorioamnionitis with early in utero transmission of HIV-1. This may help explain the cases of in utero transmission that persist despite antiretroviral prophylaxis, given that therapy is started in the late gestational period.

Exposure to maternal blood during labor and delivery is another major risk factor. For every hour an infant is exposed to ruptured membranes, the risk of transmission increases by 2 percent. Furthermore, the international registry of HIV-exposed twins found that first-born twins were 3 times more likely to be infected, reflecting the longer time that twin A is exposed to the birth canal. Twin pregnancies were considered to be at increased risk of MTCT of HIV-1 in comparison with singletons. However, one should take into account the higher risks of premature rupture of membranes and preterm delivery in multiple pregnancies.

Female infants may be more susceptible to HIV infection before birth and continuing after birth. It is proposed that minor histocompatibility reactions between maternal lymphocytes and infant Y chromosome-derived antigens reduce the risk of HIV transmission in boys. Alternatively, in utero mortality rates of HIV-infected male
infants may be disproportionately higher and thus more HIV-infected female infants are born.\textsuperscript{15}

Table (1) Risk factors for mother-to-child transmission of HIV

<table>
<thead>
<tr>
<th>Maternal risk factors:</th>
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<tbody>
<tr>
<td>• High maternal viral load</td>
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<tr>
<td>• Low CD4 count</td>
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<tr>
<td>• Low p24 antibody level</td>
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<tr>
<td>• Use of illicit drugs during pregnancy</td>
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<tr>
<td>• Sexual activity during pregnancy</td>
</tr>
<tr>
<td>• Lack of antenatal care and access to antiretroviral therapy</td>
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<tr>
<td>• Fetal gender: girls are more likely to become infected than boys (? Y chromosome derived factors or higher in utero male mortality)</td>
</tr>
<tr>
<td>• Polymorphisms in maternal chemokine receptor genes may increase infectivity e.g. CCR2 &amp; CCR5 (controversial)</td>
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</tbody>
</table>

<table>
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<tr>
<th>Obstetric risk factors:</th>
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</thead>
<tbody>
<tr>
<td>• Mode of delivery: elective CS versus vaginal</td>
</tr>
<tr>
<td>• Premature rupture of membranes &gt; 4 hr</td>
</tr>
<tr>
<td>• Birth weight &lt; 2500 gm</td>
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<tr>
<td>• Preterm delivery</td>
</tr>
<tr>
<td>• Chorioamnionitis</td>
</tr>
<tr>
<td>• Prolonged second stage of vaginal delivery due to longer exposure to cervicovaginal secretions</td>
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<tr>
<th>Viral risk factors:</th>
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<tr>
<td>• Rapidly replicating virus</td>
</tr>
<tr>
<td>• Macrophage-tropic virus</td>
</tr>
<tr>
<td>• Preferentially using the CCR5 co-receptor (controversial)</td>
</tr>
<tr>
<td>• Multiple HIV variant transmission during peripartum infection.</td>
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<tr>
<th>Risk factors for transmission from human milk:</th>
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<tbody>
<tr>
<td>• Longer duration of breast feeding</td>
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<tr>
<td>• Young age and high parity of the mother</td>
</tr>
<tr>
<td>• Lower CD4 count and higher viral load in the mother</td>
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<tr>
<td>• Postnatal acquisition of HIV</td>
</tr>
<tr>
<td>• Breast abnormalities: abscess, mastitis or nipple fissuring</td>
</tr>
<tr>
<td>• Oral candidiasis in the infant</td>
</tr>
<tr>
<td>• Milk content:</td>
</tr>
<tr>
<td>- High viral load</td>
</tr>
<tr>
<td>- Lower virus-specific cytotoxic T cells</td>
</tr>
<tr>
<td>- Lower secretory IgA and IgM (doubtful)</td>
</tr>
<tr>
<td>• Mixed feeding:</td>
</tr>
<tr>
<td>- Higher risk than exclusive breast feeding and early weaning</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>State of knowledge as a risk factor:</th>
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<tr>
<td>• Poor maternal and paternal knowledge about screening and prophylaxis</td>
</tr>
<tr>
<td>• Missed prevention opportunities due to lack of screening by obstetricians</td>
</tr>
<tr>
<td>• Poor awareness of the pediatricians to postpartum means of transmission</td>
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Viral risk factors

In order to infect a target cell, the HIV envelope glycoprotein gp120 has to interact with the cellular receptor CD-4 and co-receptor, usually the chemokine receptor 5 (CCR5) or CXCR4. These interactions trigger fusion of viral and cellular membranes and aid viral entry into cells. The HIV-1 isolates that predominantly use CCR5 as a coreceptor are frequently described as macrophage tropic.\textsuperscript{16,17} Genetic studies have yielded major insights into the in vivo roles of individual co-receptors and their ligands in providing resistance to HIV infection. Mutations in chemokine receptor genes may be associated with protection against HIV infections and are also involved in delayed progression to AIDS in infected individuals.\textsuperscript{18}

The viral determinants that underlie HIV-1 neurotropism are unknown, due in part to limited studies on viruses isolated from the brain. Previous studies suggest that brain-derived viruses are macrophage tropic (M-tropic) and principally use CCR5 for virus entry. HIV-1 tropism for macrophages and microglia is restricted at the entry level by a mechanism independent of coreceptor specificity. These findings may provide evidence that M-tropism rather than CCR5 usage predicts HIV-1 neurotropism.\textsuperscript{19}

There has been evidence of multiple virus variant transmission during peripartum MTCT. Viral escape from cytotoxic T-lymphocyte (CTL) recognition was repeatedly detected in transmitting mothers. The hypothesis on the mechanisms of selection during MTCT are still an open question, and include possibly that the transmitted variant is derived from a variant in the mother that escaped immune response, or that transmission is a stochastic event with the random transmission of a limited number of viral variants, or otherwise that selection occurs in the infant through a replication advantage of some transmitted viral variants.\textsuperscript{20}

Risk of transmission through breastfeeding

Transmission through breastfeeding is likely associated with an elevated viral load in the breast milk, which in turn is associated with maternal plasma viral load and CD4 lymphocyte counts. Mastitis has also been associated with increased risk of transmission.\textsuperscript{21} Prolonged breast feeding doubles the likelihood of MTCT.\textsuperscript{22} Moreover, humoral mucosal immunity including secretory IgA to HIV does not appear to protect against viral transmission through breast milk.\textsuperscript{23,24}
A meta-analysis of prospective studies found that the additional risk of transmission through breast feeding in women with HIV infection before pregnancy was 14% compared with a 29% increase in breast-feeding women who acquired HIV postnatally. This suggests that the viremia experienced by the mother during primary infection doubles the risk of transmission.4

Several studies revealed that breast fed infants receiving other supplementary foods were twice as likely to be infected at age 6 months compared to infants fed exclusively on breast milk or on formula.25, 26 The hypothesis is that antigens and bacterial contaminants present in supplemental fluids and foods may cause inflammation and microtrauma to the infant's intestinal gut, thereby facilitating viral transmission. Another hypothesis is that mixed feeding increases the risk of subclinical or clinical mastitis in the mother, which could increase milk viral load.27

Lack of awareness of HIV serostatus as a transmission risk factor
The main risk factor, which is also a barrier to the prevention of MTCT of HIV, is lack of awareness of HIV serostatus. Because approximately 25% of all people infected with HIV do not know their HIV status, many women may not know that they are infected. Without antiretroviral therapy (ART), approximately 25% of HIV-infected pregnant women will transmit the virus to their children.28 More disturbingly, most HIV-infected women live in developing countries where many pregnant women even when tested do not return for their HIV results for a variety of reasons including stigma, and where most, if not all, strategies for prevention of MTCT have been of limited accessibility and/or feasibility.29

Clinical picture of perinatal AIDS
In most infants, physical examination at birth is normal. Initial symptoms may be subtle, such as lymphadenopathy and hepatosplenomegaly, or nonspecific, such as failure to thrive, chronic or recurrent diarrhea, interstitial pneumonia, or oral thrush, and may be distinguishable only by their persistence. Symptoms found more commonly in children than adults include recurrent bacterial infections, chronic parotid swelling, lymphocyte interstitial pneumonitis (LIP), and early onset of progressive neurological deterioration.4

HIV-1 encephalopathy among perinatally infected children in the United States was initially defined by a classic triad of findings that included: 1) developmental delay, 2) secondary or acquired microcephaly, and 3) pyramidal tract neuromotor deficits. The most severe form of this disorder typically occurred among young children who developed rapidly progressive disease in concert with profound immunosuppression, and Pneumocystis carinii (jiroveci) pneumonia. It subsequently leads to neuronal injury secondary to apoptosis, necrosis and astrocytosis, as well as dendritic and synaptic damage.30

Nonimmune hydrops fetalis and hepatitis shortly after birth were found to be due to perinatal AIDS. Maternal HIV infection was discovered after delivery. After beginning highly active antiretroviral therapy, hepatitis resolved and the HIV viral load became undetectable.31

HIV-infected children grow considerably slower. Infected children, who were born before availability of ART, were more likely to reach a weight below the third centile for age than children who were born after 1994, when effective HIV treatment was widely available. Severely ill children grow poorly at all ages and were found to benefit from antiretroviral (ARV) combination therapy in terms of weight and, to a smaller extent, in height. Growth faltering, particularly stunting, may adversely affect children’s quality of life, especially once they reach adolescence, and this should be taken into account when making decisions about starting and changing ART.32

Investigations
– Many perinatally infected infants have a negative viral culture or PCR in the 1st week of life and are therefore considered to be infected intrapartum. In a typical patient, the viral load rapidly increases by 2-3 months of age (median is 100,000 copies/ml) and slowly declines over a period of 24 months. The slow decline in viral load is in sharp contrast to the rapid decline after primary infection seen in adults. This observation can be explained partially by the immaturity of the immune system in newborns and infants. HIV infection is reasonably excluded if an infant has had at least 2 negative virologic tests at age ≥2 months with at least one test performed ≥4 months of age.
– Because infants normally have relative lymphocytosis, a value of 1,500 CD4 cells/mm³ in children <1 year of age is indicative of severe CD4 depletion and is comparable to <200 CD4 cells/mm³ in adults. CD4 and CD8 lymphocyte counts should be assessed every 3 months in infected infants and the frequency of testing
should be increased if the CD4 count declines rapidly.

- All infants born to HIV infected mothers test antibody-positive (HIV IgG) at birth due to passive transfer across the placenta during gestation. Most uninfected infants (seroconvertors) lose maternal antibody between 6-12 months of age. Because a small proportion of uninfected infants continue to test positive for up to 18 months of age, positive IgG tests cannot be used to make a definitive diagnosis in infants <18 months. In any child >18 months of age, demonstration of IgG antibody to HIV by EIA and confirmatory test (e.g. Western blot or immunofluorescence assay) establishes the diagnosis.

- The presence of IgA or IgM anti-HIV in the infant's circulation can indicate infection because these antibody classes do not cross the placenta. However, detectable IgA levels are not generally produced until 3-6 months of age, limiting its utility in young infants.

- Cutaneous anergy is frequent in healthy children <1 year of age and thus its interpretation is difficult in infected infants.

- A complete blood count with differential leukocyte and platelet counts should be performed at 4 weeks of age. If the infant is proved to be HIV-infected, these tests should be repeated every 1-3 months to assess the hematological effect of the disease and its treatment (e.g. prophylactic cotrimoxazole and antiretroviral therapy).

**Prevention of mother-to-child transmission of HIV**

MTCT rates of less than 2% are now reported from countries where antiretroviral prophylaxis, elective Caesarean section (ECS) and refraining from breastfeeding can be applied, whilst in settings where refraining from breastfeeding is not feasible or safe and where ECS is also not a safe option, peripartum ART can halve the risk to levels of approximately 10%, although further acquisition of infection through breastfeeding substantially increases the overall rate to 20% or more. The Centers for Disease Control and Prevention (CDC) perinatal HIV-prevention programs currently focus on five key areas: 1) implementation of rapid HIV testing in labor and delivery for women with undocumented HIV status; 2) social marketing efforts to increase awareness of the need for HIV testing among pregnant women; 3) outreach efforts to promote receipt of prenatal care by pregnant women; 4) case management services to promote receipt of prenatal care and receipt of appropriate medication and interventions among HIV-infected pregnant women; and 5) provider training to increase availability of rapid testing services. The World Health Organization (WHO) promotes a comprehensive strategic approach consisting of 4 components: 1) primary prevention of HIV infection, 2) prevention of unintended pregnancies among women living with HIV, 3) prevention of HIV transmission from mothers to their children, and 4) care, treatment and support for mothers living with HIV, their children and families. Most commonly applied preventive measures include:

**Avoidance of unwanted pregnancies among infected mothers**

One of the most effective strategies to reduce HIV among infants is to provide better contraception services. Use of antiretroviral therapy Evidence indicates that the provision of ARV drugs to infected mothers significantly reduces vertical transmission. ARV drugs reduce viral replication and can reduce MTCT of HIV either by lowering the plasma viral load in pregnant women or through post-exposure prophylaxis in their newborns. Interruption of perinatal transmission has been achieved by administering zidovudine (ZDV) chemo-prophylaxis to the pregnant woman (100 mg five times/24 hr PO, started as early as 4 wk of gestation) and continued during delivery (2 mg/kg loading dose IV followed by 1 mg/hr IV) and in the newborn for the first 6 wk of life (2 mg/kg every 6 hr PO). Current guidelines recommend the use of highly active antiretroviral therapy (HAART) including ZDV whenever possible for women who require it for their own health and for all women whose plasma HIV RNA levels are ≥1,000 copies/ml. In a recent study, the overall transmission rate for women who had combination treatment with nevirapine, stavudine and lamivudine was 9.1% which was lowered to zero level among those who had elective caesarean section and infant formula in addition to the drugs. Some evidence from in vitro and in vivo models has suggested the potential for teratogenic or carcinogenic effects from some ARV agents in pregnancy. However, analysis of all prospective cases reported to the Antiretroviral...
Pregnancy Registry from January 1989 to July 2005 identified no detectable increase in overall risk of birth defects or of specific birth defects in humans.38

Feeding substitution
CDC recommends that women with HIV infection avoid breastfeeding in areas, including the United States, where safe alternatives are reliably accessible and affordable.39 In developing countries, the feasibility of this approach is often limited by such factors as cost, sustainability, lack of safe water, and by sociocultural factors.40 The WHO recommends that in developing countries where other diseases (e.g. diarrhea, pneumonia and malnutrition) substantially contribute to a high infant mortality rate, the benefit of breast feeding outweighs the risk of HIV transmission, and HIV-infected women should breast-feed their infants.4

Evidence indicates that mixed feeding (breast milk and formula or other substance) has a higher risk of transmission than exclusive breastfeeding.26,41 The WHO recommends exclusive breast feeding during the first months of life and should then be discontinued as soon as feasible. Women receiving ART who are breast feeding should continue their ARV regimen but the use of ARV drugs in the mother and/or baby solely to prevent transmission through breast feeding is currently not recommended.42

Elective cesarean section (ECS)
ECS before labor and before rupture of membranes has been introduced as an intervention for the prevention of MTCT. However, the efficacy of cesarean delivery in women who have received potent combination therapy and have low HIV RNA levels (<1,000 copies/ml) remains unclear.35 The uncertain benefit for prevention of perinatal HIV transmission is likely outweighed by the potential risks of operative delivery in such women, given that the risk for HIV transmission is less than 2%.3 Therefore, the role of mode of delivery in the management of HIV-1-infected women should be assessed in light of risks as well as benefits.43 The previous notion that ECS decreases transmission predated the advent of HAART. The additional benefit of cesarean section might be negligible if the mother's viral load is <500 copies/ml.4

Social factors
The benefit of therapy, both for the mother's health and to prevent transmission to the infant cannot be overemphasized.4 Attention to potent social and institutional barriers that impair the ability of the most marginalized women to disclose their HIV status and accept care is essential to achieve eradication of perinatal transmission.44 Successful prevention of MTCT requires improved uptake of antenatal HIV antibody testing and better access to antiretroviral medications.45

Treatment of infected infants
Anti-retroviral therapy
Although early treatment trials consisted of single or dual drug therapy, more recent trials have uniformly confirmed the superiority of three or more drug combination therapy. Children <1 yr of age are at a high risk for disease progression and should be treated with ARVs as soon as the diagnosis of HIV infection is confirmed, regardless of clinical or immunologic status, or viral load. Data suggest that infants who are treated before the age of 3 months control their HIV infection better. Combinations of three drugs such as a thymidine analog reverse transcriptase inhibitor (NRTI), a non-thymidine analog NRTI (to suppress replication in both active and resting cells), and a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) have been shown to produce prolonged viral suppression. Additional regimens such as triple NRTIs (i.e. abacavir, zidovudine, and lamivudine) or lopinavir/ritonavir in combination with two NRTIs or one NRTI and an NNRTI are also recommended 4 (Table 2).

Other investigational lines of therapy
Survival by HIV-1 infected children requires a competent immune response early in infection to counter the rapidly replicating virus and this correlates significantly with the percentage of CD4+ T-lymphocytes. Interventions aimed at boosting the naive immune system may prolong survival in such children.46

As resistance and long-term metabolic abnormalities hamper the efficacy of drugs against HIV-1, targeting of HIV co-receptors represents an exciting new frontier for antiretroviral therapeutics. CCR5 inhibitors are most likely to be the new available drugs within the class of entry inhibitors.47 The current leading CCR5 antagonists in clinical development include maraviroc, aplaviroc and vicriviroc.48 The development of effective CXCR4 antagonists for dual treatment would be beneficial; however, whether long-term treatment with antagonists of

Social factors
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the widely expressed CXCR4 receptor is feasible without toxicity is unknown.49

**Table (2) Antiretroviral Drugs**

**Reverse transcriptase inhibitors (NRTI)**
- Abacavir (ABC)
- Didanosine (ddI)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TNF)
- Zalcitabine (ddC)
- Zidovudine (ZDV)

**Non-nucleoside reverse transcriptase inhibitors (NNRTI)**
- Delavirdine (DLV)
- Efavirenz (EFV)
- Nevirapine (NVP)

**Protease inhibitors (PI)**
- Amprenavir (APV)
- Indinavir (IDV)
- Lopinavir (LPV)
- Nelfinavir (NFV)
- Ritonavir (RTV)
- Saquinavir (SQV)

*Adapted from Yogev, Chadwick, 2004*

**Supportive care**

- Close attention should be paid to nutritional status, which is often delicately balanced and may require aggressive preemptive intervention (e.g. nasogastric or gastric feeding or parenteral nutrition).
- Routine dental evaluation and attention to oral hygiene is needed.
- Pharmacologic and non-pharmacologic protocols for pain management should be instituted.
- Developmental evaluation and provision of necessary physical and/or speech therapy is necessary.
- HIV-exposed and infected children should receive immunization. Live oral polio and BCG vaccines should not be given. Varicella and MMR vaccines should not be given to severely immunocompromised infants.
- Prophylactic regimens are integral for the care of HIV infected infants. The best regimen is 150/750 mg/m2/24 hr of trimethoprim-sulfamethoxazole (TMP-SMZ) given as one or two daily doses 3 days per week. For severe adverse reactions, alternative therapies include dapsone, atovaquone or aerosolized or IV pentamidine.
- Prophylaxis against Mycobacterium avium-intracellulare complex (MAC) should be offered to infants with advanced immunosuppression (i.e. CD4 count <500 cells/mm³ in children <1 year and <75 cells/mm³ in children 1-6 years of age). The drugs of choice are clarithromycin (7.5 mg/kg twice daily PO) or azithromycin (20 mg/kg once a week PO or 5 mg/kg once daily PO).
- Intravenous immunoglobulin (IVIG) therapy is sometimes recommended to prevent recurrent bacterial infections for children who 1) have suffered from at least two documented bacterial infections within one year, 2) have laboratory-documented inability to make antigen-specific antibodies, or 3) are hypogammaglobulinemic. The dose is 400 mg/kg every 4 weeks.
- Skin testing for TB should be performed at 1 year of age and repeated every two years.
- Parents should be counselled about 1) the importance of good hand washing, 2) avoiding raw or undercooked food (Salmonella), 3) avoiding drinking or swimming in lake, river or canal water or being in contact with young farm animals (Cryptosporidium), and 4) the risk of playing with pets (e.g. Toxoplasma and Bartonella from cats and Salmonella from reptiles).

**REFERENCES**


