Egypt J Pediatr Allergy Immunol 2004; 2(1): 2-7.

Review article

Pediatric AIDS

Magda A. Khazbak
Professor of Pediatrics, Ain Shams University.

AIDS EPIDEMIOLOGY

HIV infection has been a major cause of morbidity and mortality since the first cases of AIDS among children were reported in 1982 in the United States. In 1997, HIV infection was the 11th leading cause of death among children 1 to 4 years of age. Perinatal transmission of HIV accounts for 90% of pediatirc AIDS cases and almost all new HIV infections in children. An estimated 6000 to 7000 infants were born to HIV-infected women each year from 1989 to 1995, and more than 16,000 perinatally HIV-infected children have been born since the beginning of the epidemic. Considerable advances, especially in the past 5 years, in the understanding of the pathogenesis, diagnosis, treatment, monitoring, and prevention of HIV infection in children have changed the epidemiology of pediatric HIV infection [1].

The Second International Conference on Global Strategies for the Prevention of HIV Transmission from Mothers to Infants held in Montreal Canada, September 1999, focused on those who suffered mainly i.e. women and children. They comprise now almost 50% of those who are infected with HIV. They are more easily infected, have little or no control over the circumstances under which they become infected, progress to disease more rapidly, have poorer health care, benefit from treatment more slowly, and suffer some of the severest consequences of discrimination. A diagnosis of HIV infection often means ostracism, neglect, loss of family, abuse, or orphan status [2].

In spite of the now estimated 40 million persons infected with HIV worldwide, no effective control has been done. There is universal agreement that ultimate control of HIV infection cannot occur until there is an effective preventative vaccine [3].

ETIOLOGY

The HIV-1 virus is an RNA virus related to the group of retroviruses. HIV-2 is another virus that causes a milder form of immunodeficiency in South and West Africa. The individual isolates of HIV from different persons vary a great deal. There is also considerable variation between sequential isolates from the same person. The virus always changes the antigenic structure of its outer coat. It spreads through syncitium formation of an infected cell with uninfected cells in vivo. The human virus is difficult to be cultured in animals except chimpanzee. It differs from the simian virus [4].

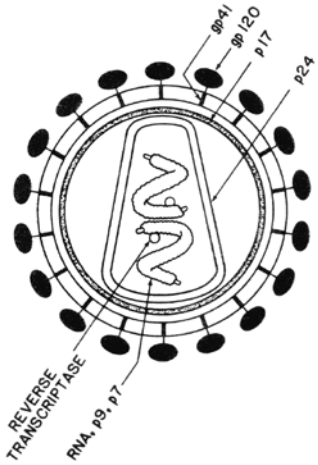

Figure 1: Structure of HIV virus. (Cerveri et al, 1996)[4].

TRANSMISSION OF THE VIRUS

In utero transmission

The mechanism of in utero transmission is most likely through transplacental transmission of HIV, possibly enhanced by placental membrane inflammation that would increase the presence of infected maternal lymphocytes in the placenta and amniotic fluid or through maternofetal transfusion, especially following placental disruption. Direct evidence for in utero transmission comes from the finding that a small proportion of first-trimester and second-trimester abortuses from HIV-infected women have tissues infected with HIV. Several factors provide indirect evidence of in utero infection. The isolation of HIV from amniotic fluid supports the possibility of in utero infection. The consistent finding that a proportion of infected children already have HIV detectable in their peripheral blood at the time of delivery indicates that their infection occurred in utero at least several days before delivery, although mathematic modeling studies suggest that much of this in utero transmission occurs relatively late in gestation. Early, rapid disease progression in some infected children also suggests the possibility of early infection of infants with developing immune systems [5].

Intrapartum transmission

Intrapartum transmission can occur through maternofetal transfusion of blood during labor or contact of infant skin or mucous membranes with the infected blood or other maternal secretions during delivery. Several pieces of evidence support the important role of intrapartum transmission. The small proportion of abortuses with evidence of HIV infection and the relatively small percentage (25%-40%) of infected children with evidence of HIV infection at birth suggest that more infections occur during the intrapartum period than before this time. Also, several of the important risk factors for infection (e.g., increased duration of membrane rupture or vaginal delivery) are specific to the intrapartum period. Finally, the substantial efficacy of some intrapartum interventions (e.g., elective cesarean section) support the importance of intrapartum transmission [6].

Postpartum transmission through breast-feeding

Infants born to mothers with HIV infection who escape infection during gestation and delivery may still become infected through breast-feeding. The rate of such infections is estimated at 12% to 14%. Approximately, 29% of breast-fed infants of women who seroconvert following delivery contract HIV.

HIV is commonly contained in the breast milk of HIV infected women. The mechanism of HIV transmission through breast-feeding is most likely the frequent and prolonged exposure of infant's oral and gastrointestinal tracts to breast milk, but the actual unit of infection (i.e., cell free or cell associated) is unknown. Evidence for postpartum transmission from breast-feeding among women with chronic HIV infection comes from several studies in resource-rich and resource-poor settings. In addition, HIV transmission to breast-fed children born to women who became infected after delivery through blood transfusion strongly supports transmission through this route [7].

Risk factors for perinatal transmission of HIV are shown in table 1[8].

Most (91%) of pediatric patients with AIDS acquired their infection through perinatal transmission, whereas 7% acquired HIV infection through receipt of contaminated blood or blood products. Cases of children who acquire HIV infection through sexual abuse have been increasing[9].

PATHOLOGY

I- Immune system:

(1)Thymitis.

(2)Generalized lymphoproliferation with hyper-gammaglobulinemia and B cell activation, decreased T helper cell number and reversed CD4: CD8 ratio.

II-Opportunistic infections: Pneumocystis carinii, Candida, Mycobacterium avium intracellulare, herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus.

Ill-Cardiovascular system: dilated cardiomyopathy, endocardial fibrosis.

IV-Gastro-intestinal tract: enteropathy, malabsorption.

V-Renal disease: Focal segmental glomerulosclerosis, mesangial proliferative glomerulosclerosis.

VI-Central nervous system: Brain atrophy, brain malformation, brain infarction, encephalopathy.

VII-Lungs: lymphocytic interstitial pneumonitis (LIP) (fig. 2).

VIII-Hepatobiliary disease: fatty infiltration, portal inflammation, cholestasis, chronic active hepatitis, and virus C hepatitis.

IX-Neoplastic: lymphoma, Kaposi's sarcoma, leiomyosarcoma.

X-Skin: bacterial, viral and fungal infections, atopy, hypersensitivity, pruritic papular eruption.

(Burns et al, 1997)[9].

Table 1. Risk factors for perinatal transmission of HIV.

Clinical	Advanced maternal HIV disease; illicit drug use during pregnancy; premature delivery <37 wk; breast-feeding
Laboratory	High viral load; low CD4+ count; anemia; low vitamin A levels in international settings
Obstetric	Duration of membrane rupture> 4 h; nonreceipt of C-section before onset of labor; chorioamnionitis; cervicovaginal infection; invasive procedures (e.g., amniocentesis); hemorrhage in labor.

(Burns et al, 1994)[8].

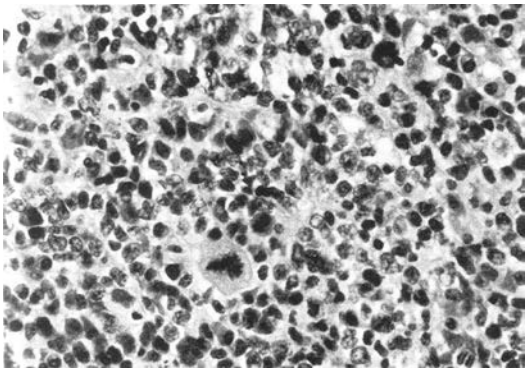

Figure 2. Lung biopsy showing LIP evident as mono-morphic lymphoid infiltrate and an atypical mitotic figure. (Burns et al, 1997)[9].

CLINICAL PICTURE

Incubation period is 10 years in average in adults, less in children, due to immature immune system. The virus is actively destroying the immune system during the incubation period, but with no signs and symptoms.

The majority of infected children are asymptomatic during the first 6 months of life. Common signs are failure to thrive, lymphadenopathy, splenomegaly, hepatomegaly and encephalopathy [10,11] (Table 2, fig. 3,4).

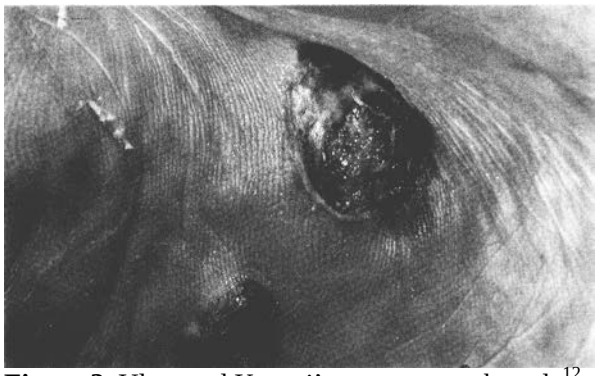

Figure 3. Ulcerated Kaposi's sarcoma on the sole[12].

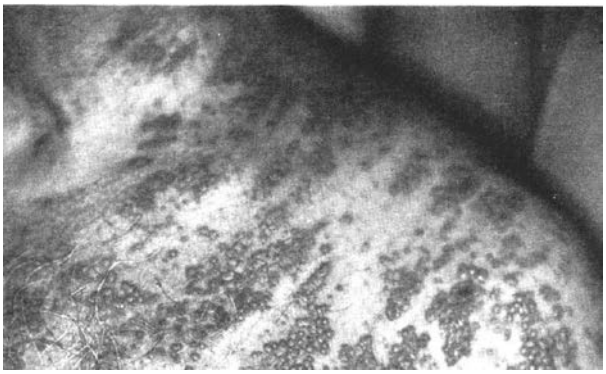

Figure 4. Extensive eruption of herpes zoster on chest and shoulder[12].

Table(2). 1994 revised HIV pediatric classification system: clinical categories[13].

Category N: not symptomatic

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A

Category A: mildly symptomatic

Children with two or more of the conditions listed below but none of the conditions listed in categories Band C

- Lymphadenopathy (> 0.5 cm at more than two sites; bilateral = one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis or otitis media

Category B: moderately symptomatic

Children who have symptomatic conditions other than those listed for category A or C to HIV infection. Examples of conditions in clinical category B include but are not limited to:

- Anemia (<8 gm/dl), neutropenia (<1000/mm3) or thrombocytopenia (<100 000/mm3).
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (thrush) persisting (>2 months) in children > 6 months old
- Cardiomyopathy
- Cytomegalovirus infection, with onset before 1 month of age
- Diarrhea, recurrent or chronic
- Hepatitis
- Herpes simplex virus stomatitis, recurrent (more than two episodes within 1 year)
- Herpes simplex virus bronchitis, pneumonitis, or esophagitis with onset before 1 month of age
- Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonitis (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Persistent fever (lasting > 1 month)
- Toxoplasmosis, onset before 1 month of age
- Varicella, disseminated (complicated chickenpox)

Category C: severely symptomatic

Children who have any condition listed in the 1987 surveillance case definition for AIDS, with the exception of LIP (which is a category B condition)

- Serious bacterial infections, multiple or recurrent (i.e. any combination of at least two culture-confirmed infections within a 2-year period) of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and in-dwelling catheter-related infections)
- Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph node)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhea persisting >1 month
- Cytomegalovirus disease with onset of symptoms at age >1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): 1) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; 2) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy

demonstrated by CT or MRI (serial imaging is required for children <2 years of age); 3) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance

Herpes simplex virus infection causing a mucocutaneous ulcer that persists for >1 month, or bronchitis, pneumonitis, or esophagitis for any duration affecting a child >1 month of age

Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)

Kaposi's sarcoma

Lymphoma, primary in brain

Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic abnormality

DIAGNOSIS [14-17]

- CBC: thrombocytopenia, neutropenia, anemia.
- Coagulation abnormalities with tendency to thrombosis.
- Hypergammaglobulinemia.
- Anti-HIV IgA: detected at 3-6 months of age.
- Anti-HIV IgM: insensitive and nonspecific.
- Anti-HIV IgG: passive maternal transfer, remains till 18 months of age.
- Reversed CD4:CD8 ratio.
- Culture, PCR →if repeatedly negative till 6 months of age then → do ELISA test: if positive → confirm by → Western blot test. [Early diagnosis is important for early initiation of therapy].
- Detection of $P_{24,}$ the major internal core protein of the virus.
- Infants are considered to have in utero infection if virologic test results (HIV DNA or RNA or culture) are positive within 48 hours of life and subsequent results are also positive; because of the risk for contamination with maternal blood, cord blood samples typically are not recommended for diagnostic evaluations.
- Infants are considered to have intrapartum HIV infection if diagnostic test results within the first 48 hours of life are negative but additional virologic testing after 1 week of life is positive in the absence of breast-feeding.

PREVENTION

Based on the current knowledge of the pathogenesis of perinatal HIV transmission, prevention can be focused in four areas: (1) reducing viral load, (2) reducing exposure to HIV during delivery, (3) preventing infection during or after exposure, and (4) reducing exposure to HIV during breast-feeding [18-20].

Reducing Viral Load

Viral load seems to be a predictor of in utero and intrapartum transmission. Moreover, decreasing viral load by antiretroviral therapy is effective in reducing the risk for transmission.

Reducing Exposure of Fetus at Delivery

During labor, infants are intensively exposed to HIV-infected blood and cervicovaginal secretions of their mothers. Reducing the concentration of virus in blood and secretions and minimizing their contact with the skin and mucous membranes of the fetus is expected to reduce transmission risk. A short antenatal course of zidovudin (ZDV) begun at 36 weeks' gestation has been shown to reduce transmission risk by 50% in Thailand in a non-breast-feeding group of HIV-infected women. The efficacy of this regimen was only 29% (95% confidence interval, 63-69%) for preventing in utero transmission but was 61% (95% confidence interval, 19-82%) for preventing intrapartum transmission. Elective C-section has also been shown to significantly reduce transmission, but other intrapartum interventions alone have not shown efficacy. In two studies, in Malawi and Kenya, vaginal disinfection during labor and cleansing of neonates did not demonstrate an overall reduction in the risk for HIV transmission.

Reducing the Risk for Infection If Exposed

Evidence suggests that, when an infant has been exposed to HIV during labor and delivery, antiretroviral therapy given during or following exposure probably blocks infection in some cases. In animal models, postexposure prophylaxis has blocked retroviral infections. The use of ZDV as postexposure prophylaxis is thought to protect from infection following occupational exposure to HIV. Likewise, two clinical perinatal trials in Africa in which infants received prophylactic antiretrovirals (either ZDV-3TC or nevirapine) during labor and delivery and during the first week of life demonstrated the effectiveness of neonatal antiretroviral prophylaxis.

Reducing Postpartum Exposure to HIV

Infants born to HIV-infected mothers and who escape infection at birth are still at risk for infection if breast-fed by their mothers. A meta-analysis suggests that the incidence of infection in these children is approximately 3.2 infections per 100 child/year of breast-feeding among children more than 2.5 months old. A report by Miotti el al suggests a higher risk for transmission in the first 6 months of life compared with during the second year of life. The factors associated with HIV transmission by breast milk are

just beginning to be understood and include the presence or absence of detectable proviral HIV and RNA viral load in breast milk and immunologic factors, such as IgM levels in breast milk and secretory leukocyte protease inhibitor. Still unknown is whether cell-free or cell-associated virus is the infectious unit of infection and whether colostrum or mature milk is more infectious. Also, infant-host factors, such as immunologic maturity, local mucosal factors in the mouth and gut that may affect transmission risk, and immunogenetic factors could affect the risk for infection of perinatally exposed children.

TREATMENT [21-23]

(1) Antiviral drugs:

a- Reverse transcriptase inhibitors

- nucleoside e.g. azidothymidine (zidovudine) 60-180 mg/m^2/6 hr IV, didanosine.
- non-nucleoside e.g. niverapine

b- Protease inhibitors e.g. ritanovir.

- Better use a combination e.g. HAART. (highly active anti-retroviral therapy) or pentatherapy.
- Regimens should include zidovudine (the best one proved to prevent vertical transmission).
- Early institution of therapy gives better results.

(2) Opportunistic infections:

-Pneumocystis carinii pneumonia

Prevention oral 150 mg trimethoprim (TMP), 750 mg sulfamethoxazole (SMZ)/m2/24h, as 2 daily doses for 3 consecutive days each week.

→ oral daily dapsone

→ monthly aerosolized or IV pentamidine

Treatment→IV TMP/SMZ/6h with methyl-prednisolone/6h for 5-7d, then orally for a total of 21d.

→ IV pentamidine

→ TMP + dapsone orally

→ Respiratory support.

-Antifungals for Candida or cryptococcal pneumonia.

-Antimicrobials for mycobacteria, STD.

-Prevention of atypical mycobacteria is through use of azithromycin 20 mg/kg orally once a week.

-Prevention of TB is through regular tuberculin testing using 5IU of PPD every 2 year and every I year if there is contact with a case.

-Antivirals of VZV, HSV, RSV and CMV.

(3) Immunotherapy using IVIGs if there is hypo-gammaglobulinemia (in 10% of cases) or history of recurrent bacterial infections.

(4) Cytokine therapy :

- Cytokines as hematological growth factors, e.g. erythropoietin, thrombopoietin, G-CSF, GM-CSF, IL-2, IL-3.
- Interferons e.g. INF alpha as antibacterial INF gamma as antiviral
- TNF inhibitors.

(5) Immunizations:

- Live attenuated virus vaccines are contraindicated, also for household contacts.
- Live bacterial vaccines e.g. BCG are contraindicated except in a country with widespread TB infection, it can be given early before overt immunosuppression takes place.
- Hib is given at 2, 4, 6 and 15 months of age.
- Rotavirus vaccine: (controversy but some advise giving it at 2, 4, 6 months if no severe immunosuppression).
- MMR and varicella vaccines: can be given at younger age before severe immnosuppression takes over, and be repeated after 3 months.
- Pneumococcal vaccine is given at 2 years of age.
- Influenza vaccine is to be given at 6 months and repeated yearly.
- Vaccines given before HIV-related disease are no more effective and have to be repeated.

The immunization schedule is shown in table 3.

(6) General nutrition: failure to thrive is due to low birth weight together with poor intake due to anorexia. Enteropathy leads to chronic diarrhea and malabsorption. So, give high protein, micronutrient and calory nutrition through TPN or tube feeding. Breast-feeding is recommended in low socioeconomic classes to avoid gastroenteritis.

(7) Others:

- Treatment of other STD.
- Treatment of the mother for HIV-infection.
- Psychological and social support especially for orphans after death of one or both parents.
- Pain relief and terminal care.
- Ensure normal day care or school attendance.
- Family health education.

Table 3. Immunization of HIV-infected children.

Immunization	Schedule
Poliomyelitis	IPV: 2, 4, and 6-8 mo of age; booster 4-6 y of age OPV contraindicated
Diphtheria	2, 4, 6, and 15-18 mo; booster 4-6 y of age
Pertussis	2, 4, 6 and 15-18 mo; booster 4-6 y of age; whole cellular or acellular vaccine
Tetanus	2, 4, 6, and 15-18 mo, booster 4-6 y of age; then age 10 y and every 10 y thereafter
H. influenzae B	1, 4, 6, and 15-18 mo of age
Hepatitis B	0, 1, and 6 mo of age if at risk for hepatitis B at birth; otherwise give at 6, 7, and 12 mo of age
MMR	12-15 mo, booster 4-6 y; contraindicated in immune category 3

Influenza	Yearly, starting at 6 mo of age; first dose is followed by another dose 1 mo later; split vaccine is preferred
Pneumococcal	Polyvalent: 2 y of age; 1 booster 5 y later; heptavalent; not established yet
Varicella	Considered only for children in category N1 or Al with an age-specific CD4 % equal to or greater than 25%
BCC	Contraindicated except in developing countries

(Laufer and Scott, 2000)[10].

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