

HIV Infection in Children

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The human immunodeficiency virus (HIV) is a retrovirus that can be transmitted vertically, sexually or via blood products. Intravenous drug use has been also associated with HIV infection. The main mode of transmission of HIV in children is vertical transmission during pregnancy, delivery or after birth. The estimated risk of perinatal transmission of HIV from the mother to the baby is around 40% if the mother does not receive any treatment. Perinatal transmission is responsible for 80% of pediatric HIV cases. Sexual abuse of children and adolescents is also a risk factor for HIV infection.



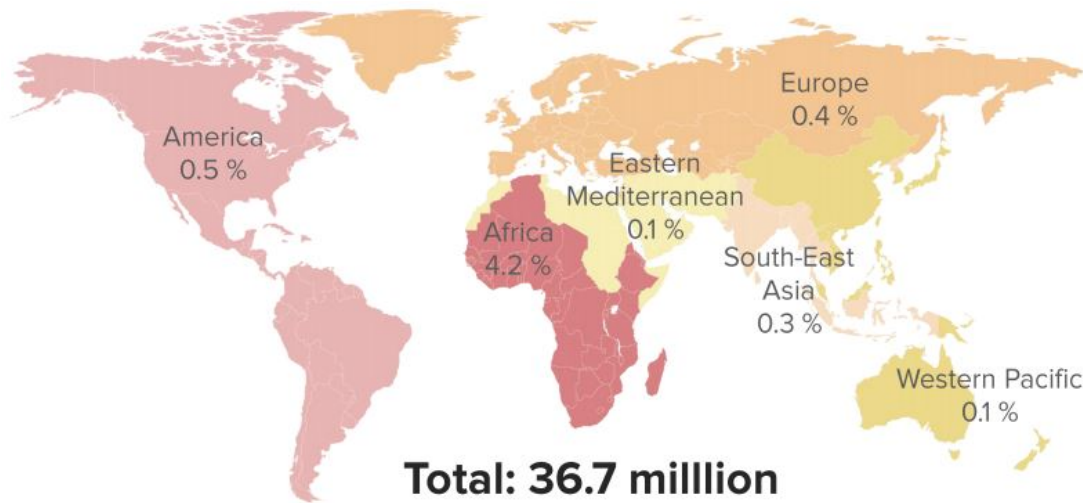
Epidemiology of HIV Infection in Children

Overview

HIV seropositive pregnant women represent 0.3% of the general pregnant women population. Maternal HIV infection is most common in Northeast regions of the United States. **The main risk factor for HIV vertical transmission is not receiving adequate prophylactic treatment.** Screening for HIV seropositivity in pregnant women has become routine in recent years because up to 40% of infected children had a seropositive mother who did not know she was HIV positive. Annually, 131 new cases of vertical transmission of HIV occur in infants in the United States.

Besides vertical transmission other methods of transmission that are evident in

developing countries include blood transfusion, sexual abuse, and high-risk adolescent behavior.



"Estimated Cases of HIV by Region" Image created by Lecturio

Diagnosis

Most cases of pediatric HIV infection are diagnosed in adolescents. A smaller peak is also seen in young children who are younger than 13 years of age. It is hypothesized that this second peak of incidence of pediatric HIV infection is due to the perinatal transmission of the virus.

Note: Acquired immunodeficiency syndrome (AIDS) is a feared complication of the HIV infection that has been also reported in children. Approximately, 13 new cases of pediatric AIDS are diagnosed per year in the United States.

Up to one-quarter of new HIV infections occur in adolescents. This can be explained by the nature of sexual activities that this age-group might participate in. This age group is more likely to partake in high-risk sexual activities. HIV infection is more common in African American adolescents, followed by Latinos and least common in the white population. **Up to 80% of the cases occur in men** and the main risk factor for HIV infection in men was male-to-male sexual contact.

HIV in developing countries

HIV infection in children in developing countries is usually a fatal condition. Aggressive treatment of opportunistic infections, the introduction of new very potent antiretroviral drugs for pediatric use, and the **management of the hematologic complications of HIV in children in the developed world has decreased the mortality of the condition** significantly.

Regardless, few factors have been associated with a grim prognosis regardless of adequate treatment in children. These factors include advanced maternal age, high maternal viral load during pregnancy, premature delivery of the infant, high viral load in the infant for the first two months of life, the presence of p24 antigen, development of AIDS in the infant, early-onset cytomegalovirus infection, and early neurologic disease.

A direct, almost linear, relationship between CD4+ T-lymphocyte percentage and the risk of death in infants with HIV infection was found. As expected, the higher the CD4+ count,

the better the prognosis and the higher the survival rate in the intermediate-term.

Up to 15% of children with vertically transmitted HIV infection develop rapidly progressive disease. Chronic progressive disease and typical HIV disease patterns are seen in the remainder of the patients.

CDC guidelines

The CDC has put some guidelines for antiretroviral treatment of pediatric AIDS in 2010 which considers the clinical symptoms of the patient and the immunologic status. The clinical categories of pediatric AIDS are:

N = not symptomatic

A = mildly symptomatic with lymphadenopathy, splenomegaly, hepatomegaly, recurrent upper respiratory tract infections or dermatitis

B = moderately symptomatic with anemia (Hb below 8 g/dL), neutropenia, thrombocytopenia, bacterial meningitis, sepsis, candidiasis, cardiomyopathy, recurrent or chronic diarrhea, herpes simplex stomatitis, pneumonitis or esophagitis, and disseminated varicella

C = severely symptomatic patients with severe bacterial infections, candidiasis of the esophagus, disseminated coccidioidomycosis, cryptococcosis, Kaposi sarcoma, primary brain lymphoma, disseminated tuberculosis, Pneumocystis jirovecii pneumonia, or recurrent salmonella sepsis. Immunologic staging of the disease is dependent on the absolute CD4+ counts.

Pathophysiology of HIV Infection in Children

Vertical transmission

The most common route of transmission of HIV in young children and infants is the vertical transmission. Vertical transmission **can occur during pregnancy, at the time of delivery, or after delivery**. Breastfeeding plays a role in the post-delivery transmission of HIV to the infant in the developing world.

HIV infection before birth occurs by hematological spread by means of transmission across the placenta or across the amniotic membrane especially if the membranes are inflamed or infected. Most HIV vertical transmissions occur during delivery. Contact with maternal blood and cervicovaginal secretions are the main risk factors for HIV transmission from the mother to the infant during birth with the risk of infection being directly proportional to the duration of exposure.

Moreover, premature and low birth weight neonates appear to be at more risk of infection during delivery due to reduced skin barrier and immunologic defenses.

CD4 and CCR5

HIV is a retrovirus that contains RNA genetic information. **The HI virus attaches to the surface of CD4 positive lymphocytes and macrophages**. This attachment is also dependent on a protein known as CCR5, which belongs to the chemokine co-receptors. The absence of this protein, which is reported in up to 20% of Ashkenazi Jews, has been shown to be protective against HIV infection.

Once acute infection occurs, the viral load is increased rapidly and the infant develops moderate viremia. **The decrease in viral load in infected children is usually slower** than what is seen in adults in the acute stage of infection. HIV viral load in vertically infected children might not reach baseline levels up to 5 years after the acquisition of the virus.

Clinical Presentation of HIV Infection in Children

Symptoms

- Unusual and frequent occurrence of pediatric infections such as otitis media, sinusitis, and diarrheal illnesses
- Recurrent fungal infections such as oral thrush
- Stunted growth and failure to thrive
- Delayed developmental milestones especially language and motor activity

Signs

- Oral thrush and candidiasis
- Parotid gland enlargement
- Lymphadenopathy

Infected children typically have a **reduction in cell-mediated immunity and secondary B-cell dysfunction**. Children who are not treated typically become immunocompromised and can develop opportunistic infections or malignancies.

Note: Hematologic consequences of vertically transmitted HIV are common and they include leukopenia, anemia, and thrombocytopenia. This might be related to impaired bone marrow function which could be a direct effect of the HI virus.

Progressive encephalopathy has been described in HIV infected children. Recent research has shown that the central nervous system microglia may play a critical role in the pathogenesis of encephalopathy in pediatric AIDS.

HIV in infants vs. in adolescent

Infants	Adolescents
Poor weight gain	Asymptomatic until CD4 count falls
Developmental delay	50% with primary infection (flu-like illness)
Severe thrush	Candidal infections
Bacterial infections	Bacterial infections

Perinatal testing

Most cases of HIV infection in children are diagnosed via routine perinatal testing. All pregnant women must **undergo testing to determine the seropositive state for HIV and determine whether any intervention is required** to lower the viral load. Moments of increased maternal-fetal blood exchange or contact, such as during labor, are of critical importance and viral loads should be brought to a minimum during such periods whenever possible.

Half of the cases of pediatric HIV become symptomatic during the first year of life. Symptoms of immunodeficiency might be the presenting feature in untreated children.

Note: Recurrent invasive infections, meningitis, and infections caused by unusual organisms, such as Mycobacterium avium-intracellular complex, should alert the pediatrician towards the possibility of HIV.

Recurrent otitis media, sinusitis, and pneumonia are also common in HIV positive children. Recurrent fungal infections that are caused by the Candida species are reported more frequently in HIV infected children. Additionally, **response to typical antifungals in those children is usually not satisfactory.**

Growth failure and wasting in a child are also suggestive of HIV infection. Children who fail to attain typical milestones, or who have developmental delay, might have HIV encephalopathy.

Physical examination of children should be systemic and complete. There are **many signs suggestive of immunocompromise in children** in general, and of HIV infection in particular. The following table summarizes such findings:

System	Main Findings
Anthropometric	Delayed growth, microcephaly
Head, eyes, ears, nose and throat	Parotitis, tonsillar hypertrophy, oral cavity candidiasis, esophagitis, cytomegalovirus retinitis
Cardiac	Congestive heart failure or cardiomyopathy
Pulmonary	Pneumonia, hypoxemia, fever, chronic lung infections
Abdominal	Hepatomegaly or splenomegaly
Lymphatic system	Generalized lymphadenopathy, lymphoma
Neurologic	HIV encephalopathy, brain abscess, subacute combined degeneration of the spinal cord, ischemic and hemorrhage strokes
Skin	Dermatitis, vesicular lesions because of herpes zoster, candida dermatitis, immune thrombocytopenic purpura

Diagnostic Workup for HIV Infection in Children

American College of Obstetricians and Gynecologists – Guideline

The American college of obstetricians and gynecologists has put a recent guideline that should help in the early detection of children at risk of developing an HIV infection.

1. All women should be offered the option to get an HIV detection test during their prenatal testing.
2. Women who have multiple sex partners during pregnancy, or who use intravenous drugs during pregnancy, should be offered a repeat HIV test in the third trimester of pregnancy.
3. Women who have not been tested before should receive a rapid detection test during delivery. When the rapid detection test is reactive during labor, prophylactic antiretroviral therapy is indicated while waiting for confirmatory tests.
4. Finally, if the diagnosis of HIV infection in the mother is confirmed, she should be referred for specialist care as soon as possible.

DNA/RNA polymerase chain reaction test

The diagnosis of HIV infection in an infant is always done by an HIV culture or by a DNA/RNA polymerase chain reaction test. A positive test should be repeated for the

confirmation of the diagnosis. HIV testing **should be performed within the first 48 hours of life, at the age of 1 to 2 months, and again at the age of 3 to 6 months.**

The sensitivity and specificity of polymerase chain reaction testing for HIV in infants who are one month, or older, are 96% and 99% respectively. The main screening tests for HIV in the United States are the Oraquick, Reveal G3 Rapid HIV Antibody Test, Uni-Gold Recombigen HIV, and Multispot HIV-1/HIV-2 Rapid test. These tests are dependent on the detection of certain viral antigens. They have 100% sensitivity, hence are good for screening, but a low specificity; therefore, a positive rapid test should always be followed by a more specific confirmatory test.

Antibody detection tests are not used for diagnosis in infants younger than 18 months, this is due to the persistence of the maternal antibodies in circulation that would be a confounding factor in the interpretation of the results.

Staging process

Once the diagnosis of HIV infection is confirmed, CD4+ levels should be monitored for adequate staging. **A complete blood count, a urine analysis, and cultures for cytomegalovirus are indicated** in children with HIV infection. HIV RNA viral load should be assessed twice at the baseline and then once every 3 to 4 months.

Other necessary screenings

Infants of HIV positive mothers **should be also screened for hepatitis B, hepatitis C, syphilis, and toxoplasmosis.** Chest x-rays and computed tomography scans are indicated to evaluate the status of the lungs and exclude chronic lung disease. Brain imaging with magnetic resonance imaging is indicated in children with HIV encephalopathy. The main findings on brain imaging in a child with HIV encephalopathy include white matter degeneration, brain atrophy, and calcifications of the basal ganglia.

Management of HIV Infection in Children

Appropriate antiretroviral therapy and the treatment of opportunistic infections or malignancies are the mainstay treatments for HIV infection in children. Combination appropriate antiretroviral therapy (ART) is recommended for all infants, children, and adolescents.

Note: The main goals of treatment of HIV in children are to reduce HIV-related mortality and morbidity, restore immune function, suppress viral replication, achieve these results with minimum toxicity, maintain normal physical and neurological development, and improve the quality of life of the child.

Combination therapy

Initial ART should consist of 3 drugs from two different classes of antiretroviral agents.

Lopinavir/ritonavir and nevirapine therapy is the preferred combination therapy for HIV in children younger than 3 years of age. Children who are 12 years or older might receive the combination product known as Genvoya (elvitegravir, cobicistat, emtricitabine, and tenofovir AF). Complera regimen which consists of emtricitabine, rilpivirine, and tenofovir DF has been used in children older than 12 years of age who have a viral load of more

than 100,000 copies per mL.

The following table summarizes the recommended regimens of antiretroviral therapy for HIV infection in children based on age:

Age	Antiretroviral therapy
Birth to 3 months	Zidovudine plus emtricitabine
14 days to 3 years	2 Nucleoside reverse transcriptase inhibitors (NRTIs) plus lopinavir/ritonavir
3 years to 6 years	2 NRTIs plus efavirenz or 2 NRTIs plus lopinavir/ritonavir
More than 6 years	2 NRTIs plus atazanavir plus ritonavir

Breastfeeding by HIV-infected women is not recommended. **The use of nevirapine for prophylaxis during breastfeeding has been proven to be effective** in seronegative infants of seropositive HIV mothers; therefore, the use of nevirapine is recommended if breastfeeding is preferred by the mother.

Adequate monitoring of viremia and CD4+ counts is required to assess response to treatment. Children who do not have a decrease in their HIV RNA copy number from the baseline that is above 1010, and those who have more than 400 copies per microliter after 6 months, or those with detectable HIV RNA levels 12 months' post-treatment are considered as having an incomplete virologic response to therapy. Changing to another antiretroviral regimen might be warranted.

References

[Pediatric HIV Infection](#) via emedicine.medscape.com

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