

Clinical Tract

Module on

An approach to paediatric HIV-infection

LEARNING OUTCOMES FOR DOCTORS AND NURSES

After completion of this module the learner should be able to:

- Describe the modes of transmission of HIV in children
- Describe the natural history of HIV-disease in children
- Diagnose HIV-infection in children of different ages
- Recognize the clinical signs of HIV-disease in children
- Describe how the growth and development of a child is affected by HIV-infection
- Describe the neurological problems encountered in HIV-positive children
- Know how to correctly stage HIV-infection in a child

LEARNING OUTCOMES FOR COUNSELLORS, SOCIAL WORKERS, DIETICIANS, PHARMACISTS, LABORATORY TECHNICIANS AND DATA TYPISTS

After completion of this module the learner should be able to:

- Know how children become infected by HIV
- Know how to explain to a caregiver what will happen to a child if HIV is left untreated
- Have a basic knowledge regarding the tests used to diagnose HIV-infection in children
- Describe what problems children with HIV-infection present with
- Know what the WHO staging of a patient means

1. MODES OF TRANSMISSION OF HIV IN CHILDREN

The vertical route (also called mother-to-child-transmission, MTCT) of HIV transmission is by far the most important route of infection in children. This means that the infant becomes exposed to HIV by contact with the maternal HI-virus before or during birth, or later through breastfeeding. The time span around delivery is the biggest risk period for the baby. This is because the protecting membranes are lost that cover the baby in the uterus, and contact between the mother's and the baby's blood and other secretions is maximal at this stage. MTCT of HIV should in future decline as prevention-of-mother-to-child-transmission (PMTCT) programmes are put into place.

Other less common ways by which children can become infected by HIV are through transfusions of contaminated blood products and through sexual abuse. In a small group of children the HIV infection remains unexplained. Possible reasons would be scarification, nosocomial infection (e.g. by the sharing of needles or blades in a hospital or clinic setting) and surrogate breast-feeding by an HIV-positive caregiver.

2. NATURAL HISTORY OF HIV-DISEASE IN CHILDREN

Untreated HIV-infection is a fatal disease. Knowledge of the natural history of vertically transmitted HIV-1 infection is essential for the planning of appropriate care for infected children as well as for the implementation of suitable health policies. As a general statement, one can say that HIV-disease progresses faster in children than in adults. There are however exceptions, and some children are only diagnosed many years after they have acquired the infection.

HIV-disease in African children progresses even more rapidly than in children living in industrialized countries. The onset of disease is early with most infected infants showing signs of disease by age 3 months. Studies showed that by the age of 6 months, 70% and by 1 year 77% were symptomatic.

It is important to be aware of these statistics, as such information is needed to counsel families adequately on what to expect from the course of their child's illness, and to help plan future resources for these children. It is not only the availability of antiretroviral drugs that determines the survival of an HIV-infected child, but also the quality of supportive care that is given to the child.

It is also extremely important to remember that, even in the absence of any intervention, up to two thirds of children born to HIV-infected women are not infected with HIV. This is proven by the disappearance of maternal antibodies from the infant's blood at 15 to 18 months of age at the latest.

3. DIAGNOSIS OF HIV-INFECTION IN CHILDREN

Usually an HIV-exposed or HIV-infected child enters the health care system because of one of the following:

- The child is identified as being HIV-exposed because the mother is either known to be HIV-positive or was tested HIV-positive during the pregnancy.
- The child presents to the clinic/doctor with a clinical disease suggestive of underlying HIV-infection, an opportunistic infection or failure to thrive and HIV-testing is offered. The IMCI classification gives useful guidelines regarding the need for HIV-testing in symptomatic children (see later).

There are different types of tests used to diagnose HIV-infection. The most commonly used test, which is the gold standard of HIV-testing in adults and children over the age of 18 months, is the HIV-ELISA test. This test detects antibodies against HIV, i.e. the body's reaction to the presence of HIV. The problem with the HIV-ELISA in children under the age of 18 months is, that maternal antibodies (IgG), which cross the placenta from the mother's to the baby's circulation, can still be detected in the infant's blood. This period can be even more prolonged if the mother breastfeeds the baby for a long time. The problem is thus that the baby's HIV-ELISA may give a positive result, although the infant may only be exposed to and not actually infected by HIV. There is thus a need for alternative testing methods in small babies.

Antigen-detection tests fall into the other group of HIV tests that are available. These tests identify the virus itself in the infected person. The p24 antigen test is such a test. Unfortunately the sensitivity of this test is poor, although the specificity is good. In practical terms this means that if the test result comes back as being positive, the baby is by all probability infected by HIV. The problem is that if the test result is negative, it does not exclude HIV-infection in the infant.

Although more expensive, the test of choice for diagnosis of HIV-infection in babies younger than 18 months, is the HIV DNA PCR (polymerase chain reaction) test. This test detects viral DNA, which is incorporated into the human cell genome.

The HIV RNA PCR test, also called the HIV viral load, is a similar test, which detects free virus in the blood. It is however not used as a diagnostic test. Its main use lies in the monitoring of antiretroviral therapy.

Other supportive blood tests in children with HIV infection are:

- 1) The immunological status of the child is evaluated through the CD4+ count and percentage. The normal CD4+ count in children is much higher than that of adults. Adult levels are reached at about six years of age. The percentage of CD4+ cells, though, stays relatively constant over time. Due to this fact the CD4+ percentage, calculated as the percentage of CD4+ cells over the total lymphocytes in the blood, is used as a marker for disease progression in children. A normal CD4+% would be above 25%. A CD4+% of below 15% would indicate severe immune suppression and would correlate with an absolute CD4+ count of below 200 cells/mm³ in an adult.
- 2) Children who are infected by HIV have severe immune stimulation from the first year of life. A marker for this is the globulin level in the blood, which rises to much higher levels in HIV-infection than in other chronic diseases, like in tuberculosis. Although this is not a diagnostic test, a serum globulin level of over 40g/l can be used as a marker indicating an underlying chronic disease process.

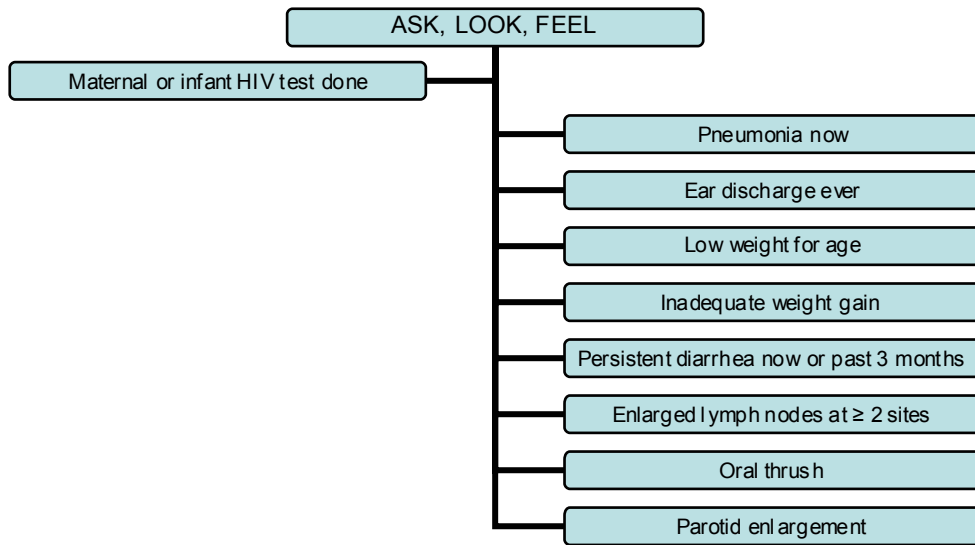
The following guidelines can be used for HIV-testing in children:

- Doing pre-test counselling and obtaining informed consent are prerequisites when doing HIV-testing in children. Testing a child for HIV might change the life of that family forever. If the child is positive, it means that the parents and possibly other children in the family also need to be tested. Counselling is not only a legal obligation, but also a moral one. See also the modules on Counselling in the Social Tract.
- Post-test counselling should be done after the results are available.
- Rapid HIV tests are less reliable in children and should not be performed routinely.
- Maternal HIV antibodies may be present in the infant's blood for up to 18 months after the birth. Children under 18 months of age should not be considered HIV-infected unless they have a positive HIV ELISA test AND have clinical signs of the disease, or if they have a positive HIV DNA PCR test.
- HIV PCR testing is done in a child younger than 18 months if either the mother is known to be HIV positive, or if the child's HIV ELISA is positive. The test is done after the age of 6 weeks, or 6 weeks after stopping of breastfeeding.
- HIV infection should be proven beyond all doubt before starting any child on antiretroviral therapy. Two HIV ELISA tests on two different blood specimens in a child older than 18 months need to give consistent results in order to make the final diagnosis of the disease. If available, children younger than 18 months should have an HIV DNA PCR done to confirm the diagnosis before start of therapy.
- HIV PCR testing may currently not be available at all centres.
- In abandoned infants, an HIV ELISA is done at the age of 6 weeks. If the ELISA is negative, the baby is not infected. If the ELISA is positive, an HIV DNA PCR is done. A repeat HIV DNA PCR is done at age 3 months to confirm the results of the test done at 6 weeks. Both these blood tests should be accompanied by a clinical examination of the infant. Only if the clinical findings and the blood results are consistent is the decision taken regarding the HIV status of the infant.

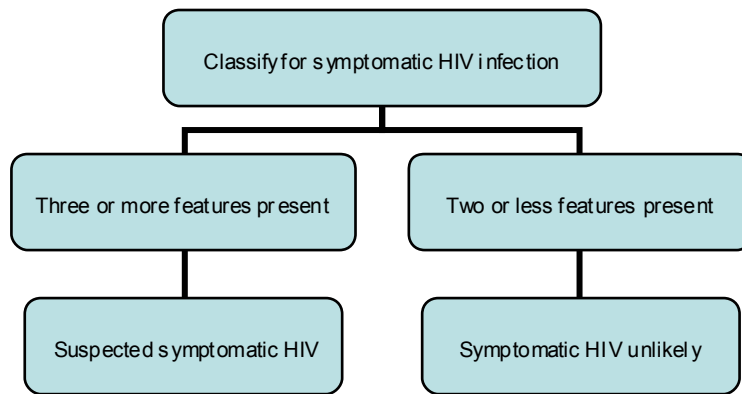
4. CLINICAL PRESENTATION OF HIV-DISEASE IN CHILDREN

The presenting problems in an HIV-infected child can vary greatly, depending on which HIV-related illness the child presents with.

The IMCI guidelines use the following questions to establish the possibility of symptomatic HIV-infection and subsequent need for HIV-testing in an infant or child:



Should any of the above signs and/or symptoms be present?



These IMCI guidelines are very useful as a screening tool, but it should be remembered that the clinical picture of HIV infection in children can be very varied indeed. Any of the following presenting symptoms and signs should alert the clinician to consider the need for an HIV test in the specific child:

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- Weight loss or abnormally slow growth
 - Chronic diarrhoea (>1 month)
 - Prolonged fever (>1 month)

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- Generalised lymph node enlargement
 - Severe oral or pharyngeal thrush
 - Recurrent common infections e.g. ear infections, pharyngitis, etc.
 - Persistent cough (>21 days)
 - Generalised rash

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- Progressive encephalopathy – loss of previously achieved milestones, microcephaly, tone disturbances, convulsions or abnormal behaviour
 - Developmental delay
 - Bilateral parotid enlargement
 - Enlarged spleen
 - Enlarged liver
 - Recurrent abscesses
 - Meningitis
 - Recurrent herpes simplex infections

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- Suppurative otitis media (discharging ear infection): if chronic (>3 weeks), bilateral and resistant to usual therapy
 - Severe pneumonia in a child less than 1 year of age
 - Any child presenting with a lobar pneumonia
 - Recurrent pneumonias or other recurring respiratory tract infections
 - Tuberculosis
 - Clinical and X-ray findings suggestive of Lymphoid Interstitial Pneumonia (LIP) or *Pneumocystis carinii* pneumonia (PCP)
 - Recurrent episodes of diarrhoeal disease
 - Infections with unusual organisms

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- Viral infections: Cytomegalovirus (CMV), herpes simplex virus (HSV)
 - Other opportunistic infections: Cryptosporidium diarrhoea, atypical mycobacterial infection, etc.
 - Haematological abnormalities: Anaemia, lymphopenia, neutropenia and thrombocytopenia
 - Cardiovascular diseases: Cardiomyopathy
 - Renal diseases: HIV-nephropathy
 - Malignancies: T cell lymphomas, leukaemias, Kaposi's sarcoma
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5. GROWTH AND DEVELOPMENT OF HIV-INFECTED CHILDREN

HIV affects the growth of a child

Children with HIV disease are often severely malnourished, with both the weight gain and growth that are compromised. The crossing of percentiles on the Road-to-Health-Chart can be used as an early warning sign that the child needs referral for further medical management.

Factors contributing to malnutrition are multiple. HIV disease itself is known to give abnormalities in growth patterns. Other factors are also abundant though, like, recurrent and chronic infections with resulting increased energy requirements. Gastrointestinal problems e.g. diarrhoea and malabsorption, nausea and vomiting, oral and oesophageal candidiasis, etc. can play an important role. Early cessation of breastfeeding can also have a detrimental effect on the nutritional state of the child. The child may also have developmental problems, with subsequent feeding difficulties. Psychosocial issues regarding both the mother/caregiver and child must not be forgotten either, for instance, limited food supply due to poverty, depression in the mother, etc.

HIV affects the neurodevelopment of a child

HIV-infection leads to neurological deterioration in a large number of infected children. This deterioration is mostly due to the development of HIV encephalopathy, characterised by poor brain growth (acquired microcephaly), developmental delay or regression of milestones and tone disturbances. The treatment of HIV encephalopathy consists of antiretroviral therapy, in conjunction with occupational- and physiotherapy.

Other neurological problems can also occur in these children. Seizures and secondary central nervous system (CNS) infections (such as bacterial-, tuberculous- and cryptococcal meningitis) can also contribute to the poor neurodevelopmental outcome of a child. Toxoplasmosis of the brain can also occur in HIV-infected patients, when the immunosuppression is severe. Seizures and CNS infections should always be diagnosed accurately and treated promptly in order to minimize the damage to the developing brain of the affected child. Please refer to the module on opportunistic infections in adults for further information regarding these conditions.

HIV affects the family of a child

The extent to which HIV-disease affects the whole family structure becomes especially apparent when children are involved. Effects include:

1. The emotional burden of coping with a potentially fatal disease. Both the infected and the uninfected family members share this burden.
2. Guilt, anxiety and depression. This is often seen in affected patients, and needs to be addressed. Mothers who pass on the HIV-infection to their offspring can also suffer from tremendous feelings of guilt.
3. Stigmatization of the patient or the whole family. Fear of stigmatization often leaves patients isolated in their difficult emotional situations.
4. Loss of income to the family due to inability of a breadwinner to go to work due to ill health.
5. The financial demands of a person with chronically ill health on the family budget. This would include the need for chronic medication, repeated clinic

and hospital visits, etc. This burden on the family is increased when more than one family member is affected by the disease.

6. The early death of one or both parents can be devastating for children – both in emotional and financial terms.

6. STAGING OF HIV-DISEASE IN CHILDREN

Staging systems for HIV disease in children:

There are two staging systems for HIV-disease in children.

- 1) The CDC (Centres for Disease Control in the USA) classification:
This classification uses a combination of clinical features and the CD4+-count / percentage. It is used extensively in first world countries, but its use is more problematic in resource-poor countries due to need for specialized laboratory facilities to diagnose certain of the conditions used in the staging system.
- 2) The modified WHO (World Health Organization) classification:
This is a clinical staging system, focussing more on the clinical presentation of the patient than on the laboratory results. Its implementation into areas with insufficient back up of laboratory services is therefore easier, and it was thus chosen for the Comprehensive Plan for Management, Care and Treatment of HIV and AIDS in South Africa.

<u>The Modified WHO classification for HIV infection in children</u>	
<u>Stage I</u>	<ul style="list-style-type: none"> • Asymptomatic • Generalized lymphadenopathy • Hepatomegaly • Splenomegaly • Parotomegaly • Chronic suppurative otitis media • Eczema/ seborrhoeic dermatitis
<u>Stage II</u>	<ul style="list-style-type: none"> • Unexplained chronic diarrhoea (> 2 weeks) • Failure to thrive (60-80% expected body weight for age, not responding to nutritional intervention, or TB treatment (if indicated)) • Recurrent or severe bacterial infections (≥ 2 pneumonias, ≥ 1 meningitis) • Severe persistent / recurrent oral candidiasis, beyond the neonatal period, not responding to topical treatment • Thrombocytopenia (< 40 000 x 10⁹/l, not responding to prednisone 2mg/kg/d for 2 weeks), neutropenia (< 500 x 10⁹/l, not responding to a switch of co-trimoxazole to dapsone) • Severe LIP (Lymphocytic interstitial pneumonia): persistent hypoxia with saturations <90%, persistent tachypnoea, easy fatigability on exertion, bronchiectasis, cor pulmonale • ≥ 2 episodes of herpes zoster or severe herpetic disease
<u>Stage III</u>	<ul style="list-style-type: none"> • Severe failure to thrive (<60% weight for age, not responding to nutritional intervention, or TB treatment (if indicated)) • Encephalopathy • Recurrent septicaemia (≥ 2 episodes) • Bronchiectasis • Cardiomyopathy • Progressive nephropathy • Candidiasis (oesophageal or pulmonary) • Disseminated fungal infection • Disseminated mycobacterial infection (M. tuberculosis, BCG, avium-intracellulare, kansasii)

	<ul style="list-style-type: none"> • CMV disease, non-neonatal (sites other than lymph nodes, spleen, liver) • HSV mucocutaneous ulcer persisting >1month, or disseminated disease (non-neonate) • PCP (<i>Pneumocystis jiroveci</i> (<i>carinii</i>) pneumonia) • Progressive multifocal leukoencephalopathy • Cerebral toxoplasmosis (non-neonatal) • Recurrent/persistent salmonella infections • Malignancy
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7. FURTHER READING

- Bobat R, Moodley D, Coutsooudis A, Coovadia H, Gouws E. The early natural history of vertically transmitted HIV-1 infection in African children from Durban, South Africa. *Annals of Tropical Paediatrics*. 1998; 18: 187-196.
- Integrated management of childhood illness. South Africa (Department of Health), World Health Organization (Division of Child Health), Unicef. Jan 2003: 7.
- Coovadia HM, Wittenberg DF. *Paediatrics & Child Health*. 5th Edition. Oxford University Press Southern Africa 2004; 343-356.
- L. Levin. Antiretroviral therapy in children. Clinical guidelines of the Southern African HIV Clinicians Society. *The Southern African Journal of HIV medicine*, Oct. 2002, p23 – 33.
- National Department of Health, South Africa, 2004: National Antiretroviral Treatment Guideline.