

# What are the clinical indicators of HIV infection in children?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at [http://www.who.int/child-adolescent-health/publications/CHILD\\_HEALTH/PB.htm](http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm)

**This review addresses the question:** *What are the Clinical Indicators of HIV Infection in Children*

The WHO Pocketbook of Hospital Care for Children states: The clinical expression of HIV infection in children is highly variable. Some HIV-positive children develop severe HIV-related signs and symptoms in the first year of life. Other HIV-positive children may remain asymptomatic or mildly symptomatic for more than a year and may survive for several years. (Pocketbook chapter 8.1.1, page 200).

From WHO Pocketbook, page 200:

## Signs that may indicate possible HIV infection:

- *Recurrent infection:* three or more severe episodes of a bacterial infection (such as pneumonia, meningitis, sepsis, cellulitis) in the past 12 months.
- *Oral thrush:* Erythema and white-beige pseudomembranous plaques on the palate, gums and buccal mucosa. After the neonatal period, the presence of oral thrush - without antibiotic treatment, or lasting over 30 days despite treatment, or recurring, or extending beyond the tongue - is highly suggestive of HIV infection. Also typical is extension to the back of the throat which indicates oesophageal candidiasis.
- *Chronic parotitis:* the presence of unilateral or bilateral parotid swelling (just in front of the ear) for >14 days, with or without associated pain or fever.
- *Generalized lymphadenopathy:* the presence of enlarged lymph nodes in two or more extra-inguinal regions without any apparent underlying cause.
- *Hepatomegaly with no apparent cause:* in the absence of concurrent viral infections such as cytomegalovirus (CMV).
- *Persistent and/or recurrent fever:* fever (>38 C) lasting >7 days, or occurring more than once over a period of 7 days.
- *Neurological dysfunction:* progressive neurological impairment, microcephaly, delay in achieving developmental milestones, hypertonia, or mental confusion.
- *Herpes zoster (shingles):* painful rash with blisters confined to one dermatome on one side.
- *HIV dermatitis:* erythematous papular rash. Typical skin rashes include extensive fungal infections of the skin, nails and scalp, and extensive molluscum contagiosum.

- *Chronic suppurative lung disease.*

## Signs common in HIV-infected children, but also common in ill non-HIV infected children:

- *Chronic otitis media:* ear discharge lasting >14 days.
- *Persistent diarrhoea:* diarrhoea lasting > 14 days.
- *Moderate or severe malnutrition:* weight loss or a gradual but steady deterioration in weight gain from the expected growth, as indicated in the child's growth card. Suspect HIV particularly in breastfed infants <6 months old who fail to thrive.

## Signs or conditions very specific to HIV-infected children:

*Strongly suspect HIV infection if the following are present:*

- *Pneumocystis pneumonia (PCP)*
- *Oesophageal candidiasis*
- *Lymphoid interstitial pneumonia (LIP) or*
- *Kaposi's sarcoma.*

*These conditions are very specific to HIV-infected children.*

- *Acquired recto-vaginal fistula in girls is also very specific but rare.*

## INTRODUCTION

Of the estimated 40 million people living with Human Immunodeficiency Virus (HIV) infection, 2.3 million are children. [1] The majority of cases are in resource poor settings where diagnostic tools and facilities may not be afforded, or qualified staff not available. HIV positive children born to infected mothers require Polymerase Chain Reaction (PCR) testing to confirm infection prior to 18 months of age. The age at which diagnosis may be made is highly dependent upon whether the infant is breast fed. General recommendations suggest a diagnosis may be made 4 – 6 weeks after cessation of breast feeding. If replacement fed, it may be as early as 6 weeks of age, but if breast feeding continues then 18 months is a realistic age for diagnosis.

Enzyme-Linked Immunosorbent Assay (ELISA) is more economical than PCR, however should be used in conjunction with clinical indicators to suggest exposure rather than diagnose HIV infection. Maternal antibodies persist in the infant up to 18 months of age, and the inability of ELISA to distinguish them from the infant's immune system mean that it should not be used for diagnosis. As such, clinical indicators have an important role to play in the diagnosis of HIV infection in resource poor settings, particularly in infants.

90% of the 2.3 million children living with HIV are in sub-Saharan Africa. South-east Asia represents a low prevalence

area, and the recommendations of this report are aimed at high prevalence settings. The relative burdens of disease in the south-east Asia region significantly impact on the sensitivity and specificity of the indicators included in the report.

This review intends to answer the question, 'what are the clinical indicators of HIV infection in children?' By seeking a clinical diagnosis, the aim is to confirm it by laboratory testing and commence antiretroviral therapy.

### Decreased Immunity

Declining immune status is believed to be central to the propagation of HIV-related illnesses, and recognition of clinical presentation may improve early diagnosis. The sensitivity and predictive value of these indicators is dependent upon the burden of HIV in the population, and the prevalence of other infectious diseases. A deterioration in immunity (decline in CD4 count) leads to opportunistic infections such as tuberculosis, *Pneumocystis carinii* pneumonia and diarrhoea, or other complications such as HIV - related cancers. A decline in CD4 count has been associated with disease progression in children ( $P = 0.001$ ), [2] leading to the development of an AIDS defining illness, such as *Pneumocystis carinii* pneumonia. [3]

A decreased CD4 count was found to be significantly associated with TB, parotiditis and acute otitis media in a study in Kenya.[4] Systemic signs of infection may be predictive of HIV infection and generalised lymphadenopathy was found to be more likely in HIV infected children (OR 2.77; 95% CI 1.16-6.64). [5] A decline in immunological function may lead to an inability to prevent and clear infection, and when present for 14 days or more, fever, cough, diarrhoea, ear discharge, oral ulcers and skin rash were all significantly more common in HIV-1-infected than in HIV-uninfected children ( $P < 0.001$ ). [6]

### METHODOLOGY

Articles were identified via the PubMed Clinical Queries Framework. The search strategy used was (indicators OR features) AND (HIV) AND (child\* OR pedia\* OR paedi\*), and was put through the filters 'diagnosis' and 'broad, sensitive.' The strategy produced 470 articles and citations listed were also searched. Indicators were weighted according to their sensitivity and specificity. The majority of articles used are from African populations and are representative of the region where the indicators are most sensitive and specific.

### RESULTS

#### Failure to Thrive

Failure to thrive is a common presentation in resource poor countries and it may be difficult to determine whether it is caused by malnutrition or HIV infection. As an indicator for HIV infection, it may be only applicable where there is a high prevalence of HIV and low rates of background malnutrition (eg. South Africa). In countries such as Malawi and Ethiopia this may not be the case.

When multiple clinical symptoms or signs of HIV infection are present, the probability of HIV infection is increased. There is an increased incidence of low birth weight in infants born to HIV positive mothers compared to those who are not infected ( $P = 0.001$ ). [7] Neonates presenting with signs of a perinatally acquired infection (lymphadenopathy, hepatosplenomegaly or persistent pneumonia) were more likely to have HIV if they had

a birth weight of less than 1.6kg (RR = 1.7; 95% CI 1.1 to 2.8;  $P = 0.02$ ). [8]

Failure to thrive occurs in HIV infected children in Africa more commonly than those who are uninfected (RR = 2.4; 2.1 - 2.8). [9] On a background of malnutrition, growth faltering may commonly occur earlier in Africa, however may not manifest in North America. Loss of weight in children with HIV infection may be due to opportunistic infections, or be caused by anorexia due to HIV infection itself.

Poor weight gain during childhood is an independent risk factor for mortality. Children with poor weight gain have been shown to have an increase in mortality prior to commencing antiretroviral therapy, [10] while those receiving it but with poor weight gain also have a worse mortality outcome. [11] The difficulty in clinical practice is that HIV - related wasting cannot be distinguished from that of malnutrition, most commonly due to marasmus.

Perhaps as an associate of failure to thrive, HIV infection has been coupled with the delayed eruption of teeth. At 3 years of age, children with an average CD4 count of 200 cells mm<sup>3</sup> had 3 teeth fewer than those with a count of 800 cells mm<sup>3</sup> ( $P = 0.036$ ). [12]

A large study reported that mean head circumference was below the third centile in 40% of HIV-infected children compared with 22% of those who were uninfected ( $P < .001$ ).<sup>13</sup> Furthermore, marasmus was a significant finding ( $P < 0.01$ ) in those with HIV infection, whereas kwashiorkor was not predictive of HIV infection. [13]

### Respiratory Infections

#### URTI

Upper respiratory tract infections may complicate paediatric HIV infection and were recognised as a significant indicator in a community - based study in Kenya.<sup>4</sup> All children were born to HIV infected mothers, and the study compared infected and uninfected children. Availability of microbial culture in resource poor countries may benefit identification of HIV indicative infections in the paediatric population.

#### LRTI

In a study in South Africa identifying children with pneumococcal isolates from serogroups 6, 9, 14, 19 or 23 (paediatric serogroups) were more common in HIV-infected children compared to those uninfected (68 of 115 vs. 18 of 44 cases respectively;  $P = 0.03$ );<sup>[14]</sup> similarly concurrent meningitis was also more common (17 of 115 vs. 0 of 44 cases;  $P = 0.003$ ), whereas concurrent septic shock occurred more often in HIV-uninfected children (6 of 44 vs. 0 of 115 cases respectively;  $P = 0.0003$ ). [14]

#### Pneumocystis Jiroveci Pneumonia

In children with radiologically confirmed pneumonia, the establishment of *Pneumocystis jiroveci* as the causative organism is highly suggestive of HIV infection. [15] 16 cases of *Pneumocystis jiroveci* pneumonia were identified among 150 children with radiologically confirmed severe pneumonia. All were HIV-positive and younger than 6 months.

#### Chronic Lung Disease

Persistent lung disease can be defined as the presence of clinical and radiological changes persisting for greater than one month in spite of treatment. Chronic lung disease can be defined as the presence of clinical and radiological changes persisting for

greater than 3 months. A study in South Africa compared persistent lung disease between HIV infected and uninfected children. More than half (57%) of cases in the HIV cohort were due to lymphoid interstitial pneumonitis (LIP), while none in the uninfected population were caused by it ( $p < 0.01$ ). [16]

### TB

TB in HIV infected children is associated with worse short-term survival. [17], [18] The clinical signs, symptoms and chest radiography of children with TB who were HIV positive and negative were looked at in a study in Ethiopia. [17] Children were treated with a TB regimen, and prolonged cough (54 of 58 vs. 318 of 459 cases;  $P = 0.001$ ), decreased reactivity to a Tuberculin test (12 of 58 vs. 354 of 438 cases;  $P < 0.001$ ) and abnormal radiological findings (57 of 58 vs. 409 of 459 cases;  $P < 0.01$ ) were indicative of co-existent HIV infection.

### Gastrointestinal Symptoms:

Acute diarrhoea affects up to 90% of children infected with HIV and is generally caused by the same infective organisms as those who are uninfected. The gastrointestinal symptoms that accompany malnutrition may also be present in HIV infection. In Uganda, a study investigated severe malnutrition using standard WHO guidelines; namely a very low weight for height (below -3z scores of the median WHO growth standards), by visible severe wasting, or by the presence of nutritional oedema. It determined that persistent diarrhoea was significantly associated with HIV infection (OR 2.0; 95% CI 1.2 – 3.6) in children with severe malnutrition. [19] In addition, children presenting with diarrhoea were more likely to be HIV infected (31.9% versus 22.5%;  $P < 0.03$ ). [19]

Progression from acute to chronic diarrhoea is six times more likely to develop in HIV infected babies compared to those who are uninfected. [20] Evidence from Zaire demonstrates that infants are at an 11-fold increased risk of death from persistent diarrhoea. [21] Dysentery, especially non-typhi salmonella, is highly suggestive of HIV, in particular in those less than 6 months of age. The mean growth for HIV-infected infants with >1 episodes of diarrhoea / yr was 1.4 cm/yr less than infants with <1 episode. [22]

### Ear, nose and throat:

Oral lesions are common presentations in HIV infected adults and have been associated with a decreased CD4 count in children. [23],[24] Oropharyngeal candidiasis acts as an indicator in discriminating between hospitalised HIV infected children and the general population (OR 7.6; 95% CI 4.9 – 11.8;  $P < 0.001$ ), [13] and is associated with a low CD4 count and advanced disease progression. [25] In these studies, oropharyngeal thrush is commonly associated with other symptoms and it should be noted that it is a common symptom in all children, especially those who are bottle fed. Discriminating whether or not the child is bottle fed may help in determining the likelihood of HIV infection in oropharyngeal candidiasis. In children older than 1 year, it is more highly suggestive of HIV.

In a retrospective study, HIV-infected children were significantly more likely to present with parotid enlargement (4% vs 0%; OR 19; 95% CI 1 – 358) and orofacial herpes simplex infection (mouth ulcers) (3% vs. 0%; OR 15; 95% CI 1 – 287). [25] Furthermore, ear discharge is very common in HIV infection (OR 15.1; 95% CI 5.7 – 46.4;  $P = 0.001$ ). [13]

### Neurological Impact:

HIV may have a devastating impact upon the neurological development of a child and their ability to function. In conjunction with failure to thrive, neurological function may be affected. A prospective cohort study from birth to two years of age assessed neurological function in 32 HIV-infected children at 6, 12 and 18 months. Statistical analysis revealed an association with worsening function in a number of domains: fine motor ( $P = 0.03$ ), gross motor ( $P < 0.001$ ), primitive reflexes ( $P = 0.38$ ) and language ( $P = 0.24$ ). Children were at an increased likelihood of being classified as abnormal for cerebellar ( $P < 0.001$ ) and cranial nerve ( $P = 0.18$ ) symptoms if they were infected with HIV. [26] Delayed achievement of developmental milestones was observed in a large prospective study in Malawi. [27]

### Drug Susceptibility:

Monitoring of antimicrobial treatment and its efficacy may provide clues to the immune status of the child. HIV infected children with invasive pneumococcal disease had reduced susceptibility to penicillin (45.9% vs. 27.9%;  $P = 0.009$ ), trimethoprim-sulfamethoxazole (44.5% vs. 19.0%;  $P = 0.0002$ ) when compared to HIV-uninfected children. In addition, multiple drug resistance was more common in the HIV infected group (24.0% vs. 6.4%;  $P = 0.01$ ). [14]

### SUMMARY

In summary in high HIV prevalent areas:

- Any child who is younger than 6 months of age and has Pneumocystis Carinii pneumonia (PCP) should be suspected to have HIV infection
- Presence of persistent (> 14 days) fever, cough, diarrhoea, ear discharge, oral ulcers and skin rashes should be considered as possible indicators of HIV infection
- Oropharyngeal candidiasis should be considered as an indicator of HIV infection
- Delayed development and impaired neurological function at 2 years of age suggest HIV infection
- HIV infection should be considered in children with faltering growth

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