WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Children Younger than 15 years of Age

World Health Organization
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WHO Case Definition for HIV Infection in Children

Diagnosis of HIV infection is based on laboratory criteria

Children younger than 18 months:

- positive virological test for HIV or its components (HIV-RNA or HIV-DNA or ultrasensitive HIV p24 antigen) confirmed by a second virological test obtained from a separate determination taken more than four weeks after birth.

Positive antibody testing is not recommended for definitive or confirmatory diagnosis of HIV infection in children until 18 months of age.

Children 18 months or older:

- positive HIV antibody testing (rapid or laboratory-based enzyme immunoassay). This is usually confirmed by a second HIV antibody test (rapid or laboratory-based enzyme immunoassay) relying on different antigens or of different operating characteristics

OR

- positive virological test for HIV or its components (HIV-RNA or HIV-DNA or ultrasensitive HIV p24 antigen) confirmed by a second virological test obtained from a separate determination.

HIV cases diagnosed and not previously reported in the country should be reported according to a standard national case definition.

WHO Case Definition for Advanced HIV Infection (including AIDS) in Children

Diagnosis of advanced HIV infection (including AIDS) is based on clinical or immunological criteria in children with confirmed HIV infection

- Confirmed HIV infection AND presumptive or definitive diagnosis of any stage 3 or stage 4 condition

OR

- Confirmed HIV Infection AND
  - %CD4+ <30 among those younger than 12 months
  - %CD4+ <25 among those aged 12-35 months
  - %CD4+ <20 among those aged 36-59 months
  - CD4 count less than 350/ mm^3 among children 5 years or older

Cases diagnosed with advanced HIV infection (including AIDS) not previously reported in the country should be reported according to a standard national case definition.

WHO Case Definition of AIDS in Children

AIDS is defined clinically or immunologically in children with confirmed HIV infection

- Confirmed HIV infection AND clinical diagnosis (presumptive or definitive) of any stage 4 condition

OR

- Confirmed HIV Infection AND first ever documented
  - %CD4+ <25 among infants younger than 12 months of age
  - %CD4+ <20 among children aged 12-35 months
  - %CD4+ <15 among children aged 36-59 months
  - CD4 cell count of less than 200/ mm^3 or % CD4+ <15 among children 5 years or older

AIDS case reporting for surveillance is no longer required if HIV infection or advanced HIV infection is reported.

WHO Clinical Staging of HIV/AIDS for Children with Confirmed HIV Infection

CLINICAL STAGE 1

- Asymptomatic
- Persistent generalized lymphadenopathy

CLINICAL STAGE 2

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Fungal nail infection
- Angular cheilitis
- Lineal gingival Erythema
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Recurrent oral ulceration
- Unexplained persistent parotid enlargement
- Herpes zoster
- Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)

CLINICAL STAGE 3

- Unexplained[i] moderate malnutrition or wasting not adequately responding to standard therapy
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)
- Persistent oral candidiasis (after first 6–8 weeks of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis or periodontitis
- Lymph node tuberculosis
- Pulmonary tuberculosis
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV-associated lung disease including brochiectasis
- Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 10^9 per litre) or chronic thrombocytopaenia (<50 × 10^9 per litre)

CLINICAL STAGE 4[ii]

- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
- Pneumocystis pneumonia
- Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia)
- Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site)
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Extrapulmonary/disseminated tuberculosis
- Kaposi's sarcoma
- Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month
- Extrapulmonary cryptococcosis (including meningitis)
- Central nervous system toxoplasmosis (after one month of life)
- HIV encephalopathy
- Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
- Disseminated non-tuberculous mycobacterial infection
- Chronic cryptosporidiosis (with diarrhoea)
- Chronic isosporiasis
- HIV associated tumours including Cerebral or B-cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy
- Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

[i] Unexplained refers to where the condition is not explained by other causes

[ii] Some additional specific conditions can also be included in regional classifications (such as reactivation of American trypanosomiasis [meningencephalitis and/or mycocarditis] in the WHO region of the Americas penicilliosis in Asia and HIV-associated rectovaginal fistula in Africa).

Presumptive and Definitive Criteria for Recognizing HIV Related Clinical Events in HIV Infected Children

(Children younger than 15 years with confirmed HIV infection)

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
CLINICAL STAGE 1		
Asymptomatic	No HIV related symptoms reported and no signs on examination.	Clinical diagnosis
Persistent generalized lymphadenopathy (PGL)	Swollen or enlarged lymph nodes >1 cm at two or more non-contiguous sites, without known cause.	Clinical diagnosis
CLINICAL STAGE 2		
Unexplained persistent hepatosplenomegaly	Enlarged liver and spleen without obvious cause.	Clinical diagnosis
Papular pruritic eruptions	Papular pruritic vesicular lesions.	Clinical diagnosis
Fungal nail infections	Fungal paronychia (painful, red and swollen nail bed) or onycholysis (painless separation of the nail from the nail bed). Proximal white subungual onchomycosis is uncommon without immunodeficiency.	Clinical diagnosis
Angular cheilitis	Splits or cracks at the angle of the mouth not attributable to iron deficiency, and usually responding to anti fungal treatment.	Clinical diagnosis
Lineal gingival Erythema (LGE)	Erythematous band that follows the contour of the free gingival line; may be associated with spontaneous bleeding.	Clinical diagnosis
Extensive wart virus infection	Characteristic warty skin lesions; small fleshy grainy bumps, often rough, flat on sole of feet (plantar warts); facial, more than 5% of body area or disfiguring.	Clinical diagnosis
Extensive molluscum contagiosum infection	Characteristic skin lesions: small flesh-coloured, pearly or pink, dome-shaped or umbilicated growths may be inflamed or red; facial, more than 5% of body area or disfiguring. Giant molluscum may indicate more advanced immunodeficiency.	Clinical diagnosis
Recurrent oral ulcerations (two or more in six months)	Aphthous ulceration, typically with a halo of inflammation & yellow-grey pseudomembrane.	Clinical diagnosis
Unexplained persistent parotid enlargement	Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause, usually painless	Clinical diagnosis
Herpes zoster	Painful rash with fluid-filled blisters, dermatomal distribution, can be haemorrhagic on erythematous background, and can become large and confluent. Does not cross the midlines.	Clinical diagnosis
Recurrent or chronic upper respiratory tract infection (URTI)	Current event with at least one episode in past 6 months. Symptom complex; fever with unilateral face pain and nasal discharge (sinusitis) or painful swollen eardrum (otitis media), sore throat with productive cough (bronchitis), sore throat (pharyngitis) and barking croup-like cough (LTB). Persistent or recurrent ear discharge.	Clinical diagnosis
CLINICAL STAGE 3		
Unexplained moderate malnutrition	Failure to gain weight: low weight-for-age, up to 2 standard deviations (SDs), not explained by poor or inadequate feeding and or other infections, and not adequately responding to standard management.	Documented failure to gain weight or weight loss: body weight of –2SD, failure to gain weight on standard management and no other cause identified during investigation.
Unexplained persistent diarrhoea	Unexplained persistent (14 days or more) diarrhoea (loose or watery stool, three or more times daily), not responding to standard treatment.	Stools observed and documented as unformed. Culture and microscopy reveal no pathogens.
Unexplained persistent fever (>37.5 °C intermittent or constant, for longer than one month)	Reports of fever or night sweats for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or antimalarials. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Documented fever of >37.5 °C with negative blood culture, negative malaria slide and normal or unchanged CXR, and no other obvious foci of disease.
Persistent oral candidiasis (after first 8 weeks of life)	Persistent or recurring creamy white to yellow soft small plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form).	Microscopy or culture.
Oral hairy leukoplakia	Fine small linear patches on lateral borders of tongue, generally bilaterally, which do not scrape off.	Clinical diagnosis
Acute necrotizing ulcerative gingivitis or stomatitis, or acute necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and/or soft tissue.	Clinical diagnosis
Lymph node TB	Non acute, painless "cold" enlargement of peripheral lymph nodes, localized to one region. Response to standard anti-TB treatment in one month.	Histology or fine needle aspirate for ZN stain. Culture.
Pulmonary TB	Nonspecific symptoms, e.g. chronic cough, fever, night sweats, anorexia and weight loss. In the older child also productive cough and haemoptysis. Abnormal CXR. History of contact with adult with smear positive PTB. No response to standard broad spectrum antibiotic treatment	Isolation of *M. tuberculosis* on sputum culture.
Severe recurrent bacterial pneumonia	Cough with fast breathing, chest in drawing, nasal flaring, wheezing, and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous 6 months	Confirmed by isolation of bacteria from appropriate clinical specimens (induced sputum, BAL, lung aspirate).
Symptomatic lymphoid interstitial pneumonitis (LIP)	No presumptive clinical diagnosis.	CXR: bilateral reticulonodular interstitial pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Oxygen saturation persistently <90%. May present with cor pulmonale and may have increased exercise-induced fatigue. Characteristic histology.
Chronic HIV-associated lung disease (including bronchiectasis)	History of cough productive of copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and/or wheezes on auscultation;	CXR may show honeycomb appearance (small cysts) and/or persistent areas of opacification and/or widespread lung destruction, with fibrosis and loss of volume.
Unexplained anaemia (<8g/dl), neutropenia (<0.5X 10 ^{9}/L^3) or chronic thrombocytopenia (<50 X 10 ^{9}/L^3)	No presumptive clinical diagnosis.	Laboratory testing, not explained by other non-HIV conditions, not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in IMCI.
CLINICAL STAGE 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	Persistent failure to gain weight or weight loss not explained by poor or inadequate feeding, other infections and not adequately responding in two weeks to standard therapy. Characterized by: visible severe wasting of muscles, with or without oedema of both feet, and/or weight-for-height of –3 SDs, as defined by WHO IMCI guidelines.	Documented weight loss of at least -3 SD +/- oedema
Pneumocystis pneumonia (PCP)	Dry cough, progressive difficulty in breathing, cyanosis, tachypnoea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in IMCI). Usually of rapid onset especially in infants under six months of age. Response to high-dose co-trimoxazole +/- prednisolone. CXR typical bilateral perihilar diffuse infiltrates	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage (BAL), or histology of lung tissue.
Recurrent bacterial infection, e.g. empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus one or more in previous 6 months	Culture of appropriate clinical specimen.
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by HSV infection present for more than one month.	Culture and/or histology
Oesophageal candidiasis (or candida of trachea, bronchi or lungs).	Difficulty in swallowing, or pain on swallowing (food and fluids). In young children, suspect particularly if oral candida observed and food refusal occurs and/or difficulties/crying when feeding.	Macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology.
Extrapulmonary TB	Systemic illness usually with prolonged fever, night sweats, weight loss. Clinical features depend on organs involved.	*M. tuberculosis* isolation or compatible histology from appropriate site, together with compatible symptoms/signs
Kaposi's sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise colour, skin lesions that usually develop into nodules.	Not required but may be confirmed by : ● typical red-purple lesions seen on bronchoscopy or endoscopy; ●dense masses in lymph nodes, viscera or lungs by palpation or radiology; ● histology.
CMV retinitis or CMV infection affecting another organ, with onset at age over 1 month.	Retinitis only. CMV retinitis may be diagnosed by experienced clinicians: typical eye lesions on serial fundoscopic examination; discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Definitive diagnosis required for other sites. Histology. CSF polymerase chain reaction (PCR).
CNS toxoplasmosis onset after age 1 month.	Fever, headache, focal neurological signs, convulsions. Usually responds within 10 days to specific therapy.	Computed tomography (CT) scan (or other neuroimaging) showing single/multiple lesions with mass effect/enhancing with contrast.
HIV encephalopathy	At least one of the following, progressing over at least two months in the absence of another illness: ● failure to attain, or loss of, developmental milestones, loss of intellectual ability; **OR** - progressive impaired brain growth demonstrated by stagnation of head circumference; **OR** - acquired symmetric motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia, gait disturbances.	Neuroimaging demonstrating atrophy and basal ganglia calcification and excluding other causes.
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually sub acute, fever with increasing severe headache, meningism, confusion, behavioural changes that responds to cryptococcal therapy.	CSF microscopy (India ink or Gram stain), serum or CSF CRAG or culture.
Disseminated mycosis (coccidiomycosis, histoplasmosis, penicilliosis)	No presumptive clinical diagnosis.	Histology: usually granuloma formation. Isolation: antigen detection from affected tissue; culture or microscopy from clinical specimen or blood culture.
Disseminated non tuberculous mycobacteria infection.	No presumptive clinical diagnosis.	Nonspecific clinical symptoms including progressive weight loss, fever, anaemia, night sweats, fatigue or diarrhoea; plus culture of atypical mycobacteria species from stool, blood, body fluid or other body tissue, excluding lung.
Chronic cryptosporidiosis	No presumptive clinical diagnosis.	Cysts identified on modified ZN microscopic examination of unformed stool.
Chronic Isospora	No presumptive clinical diagnosis.	Identification of Isospora
Cerebral or B cell non-Hodgkin lymphoma	No presumptive clinical diagnosis.	Diagnosed by CNS neuroimaging:; histology of relevant specimen
Progressive multi focal leukoencephalopathy (PML)	No presumptive clinical diagnosis.	Progressive neurological disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuro-imaging or positive polyomavirus JC (JCV) PCR on CSF.
Symptomatic HIV-associated nephropathy	No presumptive clinical diagnosis	Renal biopsy
Symptomatic HIV-associated cardiomyopathy	No presumptive clinical diagnosis	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography

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