Presumptive and definitive criteria for recognizing HIV-related clinical events in infants and children with established HIV infection

Source: *WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children*. Geneva, World Health Organization, 2007 (http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf, accessed 15 May 2013).

Clinical event	Clinical diagnosis	Definitive diagnosis
Stage 1		
Asymptomatic	No HIV-related symptoms reported and no clinical signs on examination	Not applicable
Persistent generalized lymphadenopathy	Persistent swollen or enlarged lymph nodes >1 cm at two or more non-contiguous sites, excluding inguinal, without known cause	Clinical diagnosis
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 onychomycosis is uncommon without immunodeficiency	Clinical diagnosis
Angular cheilitis	Splits or cracks on the lips at the angle of the mouth with depigmentation, usually responding to antifungal treatment but may recur	Clinical diagnosis
Lineal gingival erythema	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 advanced immunodeficiency	Clinical diagnosis
Recurrent oral ulcerations (two or more in 6 months)	Aphthous ulceration, typically with a halo of inflammation and yellow-grey pseudomembrane	Clinical diagnosis
Unexplained 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, may be haemorrhagic on erythematous background, and may become large and confluent. Does not cross the midline	Clinical diagnosis

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Recurrent upper respiratory tract infection	Current event with at least one episode in the 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 (laryngotracheal bronchitis), persistent or recurrent ear discharge	Clinical diagnosis
Stage 3		
Unexplained moderate malnutrition	For children younger than 5 years, moderate malnutrition is defined as weight-for-height <–2 *z*-score or mid-upper arm circumference <125 mm, not explained by poor or inadequate feeding and/or other infections, and not adequately responding to standard management	Documented loss of body weight of –2 standard deviations, 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 (intermittent or constant for longer than 1 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 >37.5°C with negative blood culture, negative malaria slide and normal or unchanged chest X-ray and no other obvious foci of disease
Oral candidiasis (after the first 6 weeks of life)	Persistent or recurring creamy white, 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 bilateral, which do not scrape off	Clinical diagnosis
Lymph node TB	Non-acute, painless “cold” enlargement of lymph nodes, usually matted, localized in one region. May have draining sinuses. Response to standard anti-TB treatment in 1 month	Histology or isolation of *M. tuberculosis* from fine needle aspirate
Pulmonary TB	Non-specific symptoms, such as chronic cough, fever, night sweats, anorexia and weight loss. In older children, productive cough and haemoptysis as well. Abnormal chest X-ray	Isolation of *M. tuberculosis* on sputum culture
Severe recurrent bacterial pneumonia	Cough with fast breathing, chest indrawing, 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	Isolation of bacteria from appropriate clinical specimens (induced sputum, bronchoalveolar lavage, lung aspirate)
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

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Symptomatic lymphoid interstitial pneumonitis	No presumptive clinical diagnosis	Chest X-ray: bilateral reticulonodular interstitial pulmonary infiltrates present for more than 2 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 with copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis and crepitations and/or wheeze on auscultation	Chest X-ray: 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 (<8 g/dl), neutropaenia (<0.5 × 10^9/l) or chronic thrombocytopaenia (<50 × 10^9/l)	No presumptive clinical diagnosis	Laboratory testing, not explained by other non-HIV conditions, or not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in the IMCI
Stage 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	For children younger than 5 years, moderate malnutrition is defined as length/height for age <–2 *z*-score or mid-upper arm circumference <125 mm For children younger than 5 years of age, severe wasting is defined as weight-for-height <–3 z-score; stunting is defined as length-for-age/height-for-age <–2 *z*-score; and severe acute malnutrition is either weight for height <–3 *z*-score or mid-upper arm circumference >115 mm or the presence of oedema	Confirmed by documented weight loss of >–3 standard deviations and/or oedema
Pneumocystis pneumonia	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 <6 months of age. Response to high-dose co-trimoxazole and/or prednisolone	Confirmed by: chest X-ray, typical bilateral perihilar diffuse infiltrates; microscopy of induced sputum or bronchoalveolar lavage or nasopharyngeal aspirate
Recurrent severe bacterial infection, such as 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	Confirmed by culture of appropriate clinical specimen
Chronic herpes simplex infection; (orolabial or cutaneous of more than 1 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 1 month	Confirmed by culture and/or histology
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)	Chest pain and dysphagia (difficulty in swallowing), odynophagia (pain on swallowing food and fluids) or retrosternal pain worse on swallowing (food and fluids); responds to specific treatment. In young children, suspect particularly if oral	Confirmed by macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology

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	Candida observed and food refusal occurs and/or difficulties or crying when feeding	
Extrapulmonary or disseminated TB	Systemic illness usually with prolonged fever, night sweats and weight loss. Clinical features of organs involved, such as sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis	Positive microscopy showing AFB or culture of *Mycobacterium tuberculosis* from blood or other relevant specimen except sputum or bronchoalveolar lavage. Biopsy and histology
Kaposi 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	Macroscopic appearance or by histology: ▪ Typical red-purple lesions seen on bronchoscopy or endoscopy ▪ Dense masses in lymph nodes, viscera or lungs by palpation or radiology ▪ Histology
Cytomegalovirus retinitis or cytomegalovirus infection affecting another organ, with onset at age >1 month	Retinitis only Cytomegalovirus retinitis may be diagnosed by experienced clinicians: progressive floaters in field of vision, light flashes and scotoma; 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 or cytomegalovirus demonstrated in CSF by culture or DNA-PCR
CNS toxoplasmosis with onset at age >1 month	Fever, headache, focal neurological signs, convulsions. Usually responds within 10 days to specific therapy	Positive serum *Toxoplasma* antibody and, if available, neuroimaging showing single or multiple intracranial mass lesions
Extrapulmonary cryptococcosis, including meningitis	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy	Isolation of *Cryptococcus neoformans* from extrapulmonary site or positive cryptococcal antigen test (CRAG) in CSF or blood