World Health Organization

HIV/AIDS Programme

Strengthening health services to fight HIV/AIDS

WHO CASE DEFINITIONS OF HIV FOR SURVEILLANCE AND REVISED CLINICAL STAGING AND IMMUNOLOGICAL CLASSIFICATION OF HIV-RELATED DISEASE IN ADULTS AND CHILDREN

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WHO CASE DEFINITIONS OF HIV FOR SURVEILLANCE AND REVISED CLINICAL STAGING AND IMMUNOLOGICAL CLASSIFICATION OF HIV-RELATED DISEASE IN ADULTS AND CHILDREN

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CONTENTS

AbbREVIATIONS

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
CD4+	T-lymphocyte bearing CD4 receptor
CDC	United States Centers for Disease Control and Prevention
DNA	deoxyribonucleic acid
HIV	human immunodeficiency virus
PMTCT	prevention of mother to child transmission (of HIV)
RNA	ribonucleic acid
WHO	World Health Organization
EIA	Enzyme Immunoassay
ELISA	Enzyme-Linked immunosorbent assay
S/R Test	Simple or Rapid HIV antibody test

INTRODUCTION

With a view to facilitating the scaling up of access to antiretroviral therapy, and in line with a public health approach[i], this publication outlines recent revisions WHO has made to case definitions for surveillance of HIV and the clinical and the immunological classification for HIV-related disease. HIV case definitions are defined and harmonized with the clinical staging and immunological classifications to facilitate improved HIV-related surveillance, to better track the incidence, prevalence and treatment burden of HIV infection and to plan appropriate public health responses. The revised clinical staging and immunological classification of HIV are designed to assist in clinical management of HIV, especially where there is limited laboratory capacity. The final revisions outlined here are derived from a series of regional consultations with Member States in all WHO regions held throughout 2004 and 2005, comments from public consultation and the deliberations of a global consensus meeting held in April 2006.

In most countries, reporting of acquired immunodeficiency syndrome (AIDS) cases has been incomplete and children are rarely included. Further, timely and appropriate use of antiretroviral therapy delays and may prevent the development of AIDS as previously defined. The advances in antiretroviral therapy (ART) therefore mean that public health surveillance of AIDS alone does not provide reliable population-based information on the scale and magnitude of the HIV epidemic. Data on adults and children diagnosed with HIV infection are more useful for determining populations needing prevention and treatment services.

Simplified HIV case definitions are provided based on laboratory criteria combined with clinical or immunological criteria. The clinical staging of HIV-related disease for adults and children and the simplified immunological classification are harmonized to a universal four-stage system that includes simplified standardized descriptors of clinical staging events. The revised HIV case definitions and the clinical and immunological classification system proposed are intended for conducting public health surveillance and for use in clinical care services. WHO recommends that national programmes review and standardize their HIV and AIDS case reporting and case definitions in the light of these revisions.

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i The public health approach to antiretroviral therapy is defined in the following article: The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. C Gilks, S Crowley, R Ekpini, et al. Lancet (Vol. 368, August 2006, 505–510).

bACkGROUND

In 1986, WHO developed a provisional clinical AIDS case definition for adults and children (Bangui definition) [1] to report AIDS cases in resource-constrained settings [2, 3]. The definition was formalized in 1986 and modified in 1989 (for adults and adolescents only) to include serological HIV testing and then modified again in 1994 to accommodate 1993 revisions to European and United States Centers for Disease Control and Prevention definitions [3-12]. European and United States Centers for Disease Control and Prevention definitions include specific case definitions for children. Studies in African settings [13-15] suggest that the original WHO clinical case definitions for AIDS in children are not very sensitive or specific. AIDS case reporting in middle- and low-income countries has been incomplete and of variable accuracy, which has hampered its utility. Underreporting and delays in notification are frequent and exacerbated by weak heath information systems and the lack of diagnostic capacity. In high-income countries, AIDS case reporting combined with active AIDS case-finding has allowed AIDS notification and AIDS specific mortality to be monitored. However, the widespread availability of successful antiretroviral therapy means that both new AIDS cases and AIDS mortality have been declining in countries with high coverage of antiretroviral therapy.

The scale-up of services for ART, preventing mother-to-child transmission of HIV (PMTCT) and HIV counselling and testing has led to an increase in the numbers of adults and children being tested and diagnosed with HIV infection. Accurate data are needed on adults and children diagnosed with HIV infection to facilitate estimation of the treatment and care burden, to plan for effective prevention and care interventions and assess care interventions. WHO therefore recommends that countries consider conducting reporting of newly diagnosed cases of HIV infection in adults and children (Box 1). The requirements for the confidentiality and security of HIV surveillance data are the same as for AIDS-related reporting. Provider-initiated reporting will be required to increase the completeness, timeliness and efficiency of HIV case reporting. Laboratory-initiated reporting alone will be insufficient for reporting HIV, as other surveillance information from the health care provider or medical records will be required.

For the purposes of HIV case definitions for reporting and surveillance, children are defined as younger than 15 years of age and adults as 15 years or older[i].

i For the purposes of the United Nations Convention on the Rights of the Child, a child is a human being younger than 18 years, unless under the law applicable to the child, majority is attained earlier. The United Nations General Assembly defines youth as people 15–24 years old. All United Nations statistics on youth are based on this definition, and children are therefore frequently assumed to be people 14 years old and younger. An infant is a child from birth up to age one year.

There is no standard definition of primary HIV infection. However, reporting primary HIV infection, where recognized and documented, is useful and should be encouraged. The United States Centers for Disease Control and Prevention (CDC) are expected to develop a case definition for reporting primary HIV infection. Primary HIV infection can be recognized in infants, children, adolescents and adults; it can be asymptomatic or be associated with features of an acute retroviral syndrome of variable severity [16-21]. Primary infection usually presents as an acute febrile illness 2–4 weeks postexposure, often with lymphadenopathy, pharyngitis, maculopapular rash, orogenital ulcers and meningoencephalitis. Profound transient lymphopaenia (including low CD4) can develop, and opportunistic infections may occur, but these infections should not be confused with clinical staging events developing in established HIV infection. Primary HIV infection can be identified by recent appearance of HIV antibody or by identifying viral products (HIV-RNA or HIV-DNA and/or ultrasensitive HIV p24 antigen) with negative (or weakly reactive) HIV antibody [16, 22, 23].

Initially in 1990, a four-stage clinical staging system was developed for clinical purposes and only for adults [24]. Subsequently in 2002, a three-stage system for children was proposed to support rolling out ART [25]. This publication revises the 2003 WHO clinical staging of HIV-related disease in infants and children, which is now harmonized with the 1990 classification of disease for adults and adolescents. This is similar to the four-stage clinical classification of the United States CDC revised in 1994 and originally intended for surveillance purposes [26]. Both the United States CDC and WHO clinical classifications recognize primary HIV infection. It is also proposed that the appearance of new or recurrent clinical staging events or immunodeficiency be used to assess individuals once they are receiving ART.

Clinical assessment prior to treatment

Clinical staging is used once HIV infection has been confirmed (serological and/or virological evidence of HIV infection). An additional presumptive clinical diagnosis of severe HIV disease (equivalent to severe immunodeficiency) among infants younger than 18 months is suggested for use in situations in which definitive virological diagnosis of HIV infection is not readily available (Annex 2).

The clinical events used to categorize HIV disease among infants, children, adolescents or adults living with HIV are divided into those for which a presumptive clinical diagnosis may be made (where syndromes or conditions can be diagnosed clinically or with basic ancillary investigations) and those requiring a definitive diagnosis (generally conditions described according to causation requiring more complex or sophisticated laboratory confirmation). Table 1 provides the clinical stage in simplified terms describing the spectrum of HIV related symptomatology, asymptomatic, mild symptoms, advanced symptoms and severe symptoms. Tables 3 and 4 summarize the clinical staging events, and Annex 1 provides further details of the specific events and the criteria for recognizing them.

The clinical stage is useful for assessment at baseline (first diagnosis of HIV infection) or entry into long-term HIV care and in the follow-up of patients in care and treatment programmes. It should be used to guide decisions on when to start co-trimoxazole prophylaxis and other HIV-related interventions, including when to start antiretroviral therapy. The clinical stages have been shown to be related to survival, prognosis and progression of clinical disease without antiretroviral therapy in adults and children [27-38].[i]

i Through the consultation process with WHO Member States, HIV experts have suggested that, if three or more conditions from any one clinical stage are present at the same time, the clinical stage may be considered to be higher. For example, concurrent presence of three or more stage 2 clinical events would suggest clinical stage 3. However, adopting this approach requires further study.

Table 1. WHO clinical staging of established HIV infection

HIV-associated symptoms	WHO clinical stage
Asymptomatic	1
Mild symptoms	2
Advanced symptoms	3
Severe symptoms	4

Clinical assessment of people receiving antiretroviral therapy

Treatment with potent and effective antiretroviral therapy regimens can reverse and improve clinical status in keeping with immune recovery and suppression of viral load [37, 39-41]. New or recurrent clinical staging events once people are receiving antiretroviral therapy for more than 24 weeks may be used to guide decision-making, particularly when the CD4 count is not available. It is assumed that the clinical staging events remain significant among people receiving antiretroviral therapy as they are among children and adults before the start of antiretroviral therapy. In the first 24 weeks of starting an antiretroviral therapy regimen, clinical events appear largely due to immune reconstitution [42-46] (or the toxicity of antiretroviral therapy); after 24 weeks, clinical events usually reflect immune deterioration. However, the monitoring of disease progression and response to therapy using clinical staging events urgently needs to be validated.

Immunological assessment

The pathogenesis of HIV infection is largely attributable to the decrease in the number of T cells (a specific type of lymphocyte) that bear the CD4 receptor (CD4+). The immune status of a child or adult living with HIV can be assessed by measuring the absolute number (per mm^3) or percentage of CD4+ cells, and this is regarded as the standard way to assess and characterize the severity of HIV-related immunodeficiency. Progressive depletion of $CD4^+$ T cells is associated with progression of HIV disease and an increased likelihood of opportunistic infections and other clinical events associated with HIV, including wasting and death [47-52].

Immune status in children

The absolute CD4 cell count and the %CD4+ in healthy infants who are not infected with HIV are considerably higher than those observed in uninfected adults and slowly decline to adult values by the age of about six years. Age must therefore be taken into account as a variable in considering absolute CD4 counts or %CD4+ [50, 53-59]. Among children younger than five years of age, the absolute CD4 count tends to vary within an individual child more than the %CD4+. Currently, therefore, the measurement of the %CD4+ is thought to be more valuable in younger children[i]. Absolute CD4 counts (and less so %CD4+) fluctuate within an individual and depend on intercurrent illness, physiological changes or test variability. Measuring the trend over two or three repeated measurements is therefore more informative than an individual value. Not all the equipment in use in resource-constrained settings can accurately estimate the %CD4+. The dedicated cytometers are designed to exclusively perform absolute CD4 measurements without the need for a haematology analyser and therefore do not provide %CD4+[ii].

Any classification of immune status has to consider age. The 1994 immunological classification of the United States CDC has previously been used [60]. WHO has proposed a modified immunological classification based on more recent analysis of the prognosis. Analysis of prognosis from 17 studies of children including 3941 children living with HIV from United States and European settings provide estimations of CD4 and age-related risk of progression to AIDS or death [50]. A %CD4+ of 35 is associated with a 15% risk of progression to AIDS in the next 12 months among children aged three months and an 11% risk among those six months old. The revised WHO classification attempts to better reflect this increased risk in these younger children. Based on reanalysis of the data, the thresholds for severe immunodeficiency in children have been revised [30]. For children in the WHO classification, age-related severe HIV-related immunodeficiency is defined as values at or below age-related CD4 thresholds below which children have a greater than 5% chance of disease progression to severe clinical events (AIDS) or death in the next 12 months. Further research is urgently required to assess the prognostic significance and to ascertain normal and disease-associated CD4 levels among African and Asian children [61]. Note that, among children younger than one year, the immunological categories do not reflect the same level of risk at any given age; thus, a child six months old has a higher risk of progression for any given CD4 count than a child 11 months old. However, to facilitate the scaling up of access to antiretroviral therapy, WHO proposes this simplified harmonized immunological classification system for adults and children. The immune parameters and therefore classification improve with successful antiretroviral therapy (Table 2) [30, 62-67]. Immune parameters can be used to monitor the response to antiretroviral therapy, and it is hoped that the immunological classification will facilitate this.

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i To calculate the %CD4+, use the following formula: %CD4+ = (absolute count CD4 (mm^3) times 100)/ absolute total lymphoctye count (mm^3).

ii WHO guidance on CD4 technology is available at: http://www.who.int/diagnostics_laboratory/CD4_Technical_Advice_ENG.pdf.

Immune status in adults

The normal absolute CD4 count in adolescents and adults ranges from 500 to 1500 cells per mm^3 of blood. In general, the CD4 (%CD4+ or absolute count) progressively decreases as HIV disease advances. As in children, individual counts may vary within an individual adult or adolescent and assessing the CD4 count over time is more useful [68-73]. The CD4 count usually increases in response to effective combination antiretroviral therapy, although this may take many months [74-78]. The proposed immunological classification outlines four bands of HIV-related immunodeficiency (Table 2): no significant immunodeficiency, mild immunodeficiency, advanced immunodeficiency and severe immunodeficiency. The likelihood of disease progression to AIDS or death without ART increases with increasing immunodeficiency (decreasing CD4) [79], opportunistic infections and other HIV related conditions are increasingly likely with CD4 counts below 200 per mm^3 [29, 80, 81]. Response to ART is affected by the immune stage at which it is started, people commencing ART with advanced immunodeficiency (CD4 >200–350 per mm^3) appear to have better virological outcomes than those who commence with more severe immunodeficiency. Adults starting ART with CD4 <50 per mm^3 have a much greater risk of death [37, 40, 41, 76]. Adults who commence ART with only mild immunodeficiency do not appear to obtain any additional benefits [41]. Revised antiretroviral therapy recommendations reflect this.[i] Pregnancy does affect the CD4 count although the significance of these changes is not clearly understood [58, 82], and for practical purposes the immunological classification remains the same.

Clinical decision-making

Regardless of age or clinical stage CD4 testing is very valuable and should be encouraged. It is useful to guide the decision on initiation of co-trimoxazole and when to start first-line ART or to identify treatment failure and the need to switch to a second-line regimen of ART. Measurement of CD4 can also be used to assess and monitor response to ART.

Where clinical and immunological classifications are both available, immune status, reflected by CD4 (%CD4+ or absolute count) is usually more informative. This is reflected in the most up-to-date WHO recommendations on ART for infants, children and adults.[ii] In younger children %CD4+ should be used, and from five years of age the absolute count is preferred.

Severe HIV-related disease always requires ART irrespective of whether defined by clinical condition or immune status. Advanced HIV disease based on immune status requires considering ART, especially when disease is advanced as defined clinically. Starting antiretroviral therapy can usually be delayed if the immune status suggests that there is only mild or insignificant immunodeficiency (%CD4+ >30 among children younger than 12 months, >25 among children 12–35 months or >20 in children over 36 months, or CD4 count >350 per mm^3 in adults and older children), and the individual is asymptomatic or only has mild symptoms.

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i WHO recommendations for antiretroviral therapy for adults and children and antiretroviral drugs for preventing mother-to-child transmission have been revised in 2006. Details are available on the WHO web site at:

ii Available at http://www.who.int/hiv/pub/guidelines/arv/en/index.html.

Table 2. WHO immunological classification for established HIV infection

HIV-associated immunodeficiency	Age-related CD4 values			
	<11 months (%CD4+)	12–35 months (%CD4+)	36–59 months (%CD4+)	>5 years (absolute number per mm^3 or %CD4+)
None or not significant	>35	>30	>25	> 500
Mild	30–35	25–30	20–25	350 – 499
Advanced	25–29	20–24	15 – 19	200 – 349
Severe	<25	<20	<15	<200 or <15%

Table 3. WHO clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV infection[i]

Clinical stage 1
Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight)[i] Recurrent respiratory tract infections sinusitis, tonsillitis, otitis media and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections

i Assessment of body weight in pregnant woman needs to consider the expected weight gain of pregnancy.

Adults and adolescents

Clinical stage 3

Unexplained[i] severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhoea for longer than one month
Unexplained persistent fever (above 37.6°C intermittent or constant, for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis (current)
Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained anaemia (<8 g/dl), neutropaenia ($<0.5 \times 10^9$ per litre) or chronic thrombocytopaenia ($<50 \times 10^9$ per litre)

Clinical stage 4[ii]

HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi's sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis (with diarrhoed)
Chronic isosporiasis
Disseminated mycosis (coccidiomycosis or histoplasmosis)
Recurrent non-typhoidal Salmonella bacteraemia
Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

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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 [meningoencephalitis and/or myocarditis]) in the WHO Region of the Americas and disseminated penicilliosis in Asia).

Table 4. 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 ulcerations
Unexplained persistent parotid enlargement
Herpes zoster
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or 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) and or chronic thrombocytopaenia (<50 × 10^9 per litre)

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

Children

Clinical stage 4[i]
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 tuberculosis
Kaposi sarcoma
Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month
Central nervous system toxoplasmosis (after one month of life)
Extrapulmonary cryptococcosis (including meningitis)
HIV encephalopathy
Disseminated endemic mycosis (coccidiomycosis or histoplasmosis)
Disseminated non-tuberculous mycobacterial infection
Chronic cryptosporidiosis (with diarrhoed)
Chronic isosporiasis
Cerebral or B-cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

i Some additional specific conditions can also be included in regional classifications (such as reactivation of American trypanosomiasis [meningoencephalitis and/or myocarditis] in the WHO Region of the Americas, disseminated penicilliosis in Asia and HIV-associated rectovaginal fistula in Africa).

CRITERIA FOR HIV STAGING EVENTS
Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Clinical stage 1		
Asymptomatic.	No HIV-related symptoms reported and no signs on examination.	Not applicable.
Persistent generalized lymphadenopathy.	Painless enlarged lymph nodes >1 cm in two or more non-contiguous sites (excluding inguinal) in the absence of known cause and persisting for three months or more.	Histology.
Clinical stage 2		
Unexplained moderate weight loss (<10% of body weight).	Reported unexplained involuntary weight loss in pregnancy failure to gain weight.	Documented weight loss <10% of body weight.
Recurrent upper respiratory tract infections (current event plus one or more in last six-month period).	Symptom complex, such as unilateral face pain with nasal discharge (sinusitis), painful inflamed eardrum (otitis media) or tonsillopharyngitis without features of viral infection (such as coryza or cough).	Laboratory studies where available, such as culture of suitable body fluid.
Herpes zoster.	Painful vesicular rash in dermatomal distribution of a nerve supply, does not cross the midline.	Clinical diagnosis.
Angular cheilitis.	Splits or cracks at the angle of the mouth not due to iron or vitamin deficiency, usually respond to antifungal treatment.	Clinical diagnosis.

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Recurrent oral ulceration (two or more episodes in last six months).	Aphthous ulceration, typically painful with a halo of inflammation and a yellow-grey pseudomembrane.	Clinical diagnosis.
Papular pruritic eruption.	Papular pruritic lesions, often with marked post-inflammatory pigmentation.	Clinical diagnosis.
Seborrhoeic dermatitis.	Itchy scaly skin condition, particularly affecting hairy areas (scalp, axillae, upper trunk and groin).	Clinical diagnosis.
Fungal nail infection.	Paronychia (painful red and swollen nail bed) or onycholysis (separation of the nail from the nail bed) of the fingernails (white discoloration – especially involving proximal part of nail plate – with thickening and separation of the nail from the nail bed).	Fungal culture of the nail or nail plate material.
Clinical stage 3		
Unexplained severe weight loss (more than 10% of body weight).	Reported unexplained involuntary weight loss (>10% of body weight) and visible thinning of face, waist and extremities with obvious wasting or body mass index <18.5 kg/m2; in pregnancy, the weight loss may be masked.	Documented loss of more than 10% of body weight.

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Unexplained chronic diarrhoea for longer than one month.	Chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month.	Three or more stools observed and documented as unformed, and two or more stool tests reveal no pathogens.
Unexplained persistent fever (intermittent or constant and lasting for longer than one month).	Fever or night sweats for more than one month, either intermittent or constant with reported lack of response to antibiotics or antimalarial agents, without 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 Ziehl-Nielsen stain, negative malaria slide, normal or unchanged chest X-ray and no other obvious focus of infection.
Persistant oral candidiasis.	Persistent or recurring creamy white curd-like plaques that can be scraped off (pseudomembranous) or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form).	Clinical diagnosis.
Oral hairy leukoplakia.	Fine white small linear or corrugated lesions on lateral borders of the tongue that do not scrape off.	Clinical diagnosis.

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Pulmonary tuberculosis (current).	Chronic symptoms: (lasting at least 2–3 weeks) cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats; PLUS EITHER positive sputum smear; OR negative sputum smear; AND compatible chest radiograph (including but not restricted to upper lobe infiltrates, caritation, pulmonary fibrosist shrinkage. No evidence of extrapulmonary diseas.	Isolation of M. Tuberculosis on sputum culture or histology of lung biopsy (with compatible symptoms).
Severe bacterial infection (such as pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia and severe pelvic inflammatory disease).	Fever accompanied by specific symptoms or signs that localize infection and response to appropriate antibiotic.	Isolation of bacteria from appropriate clinical specimens (usually sterile sites).
Acute necrotizing ulcerative gingivitis or 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.

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 10^9 per litre) or chronic (more than one month) thrombocytopaenia (<50 × 10^9 per litre).	Not presumptive clinical diagnosis.	Diagnosed on laboratory testing and not explained by other non-HIV conditions; not responding to standard therapy with haematinics, antimalarial agents or anthelmintic agents as outlined in relevant national treatment guidelines, WHO Integrated Management of Childhood Illness guidelines or other relevant guidelines.
Clinical stage 4		
HIV wasting syndrome.	Unexplained involuntary weight loss (>10% baseline body weight), with obvious wasting or body mass index <18.5; PLUS EITHER unexplained chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month; OR reports of fever or night sweats for more than one month without other cause and lack of response to antibiotics or antimalarial agents; malaria must be excluded in malarious areas.	Documented weight loss (>10% of body weight); PLUS EITHER two or more unformed stools negative for pathogens; OR documented temperature of >37.5°C with no other cause of disease, negative blood culture, negative malaria slide and normal or unchanged chest X-ray.

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Pneumocystis pneumonia.	Dyspnoea on exertion or nonproductive cough of recent onset (within the past three months), tachypnoea and fever; AND Chest X-ray evidence of diffuse bilateral interstitial infiltrates; AND No evidence of bacterial pneumonia; bilateral crepitations on auscultation with or without reduced air entry.	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage or histology of lung tissue.
Recurrent bacterial pneumonia; (this episode plus one or more episodes in last six months).	Current episode plus one or more previous episodes in the past six months; acute onset (< 2 weeks) of severe symptoms (such as fever, cough, dyspnoea, and chest pain) PLUS new consolidation on clinical examination or chest X-ray; response to antibiotics.	Positive culture or antigen test of a compatible organism.
Chronic herpes simplex virus infection (orolabial, genital or anorectal) of more than one month or visceral infection of any duration.	Painful, progressive anogenital or orolabial ulceration; lesions caused by recurrence of herpes simplex virus infection and reported for more than one month. History of previous episodes. Visceral herpes simplex virus requires definitive diagnosis.	Positive culture or DNA (by polymerase chain reaction) of herpes simplex virus or compatible cytology or histology.

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Oesophageal candidiasis.	Recent onset of retrosternal pain or difficulty on swallowing (food and fluids) together with oral candidasis.	Macroscopic appearance at endoscopy or bronchoscopy, or by microscopy or histology.
Extrapulmonary tuberculosis.	Systemic illness (such as fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated tuberculosis varies by site: Pleural, pericardia, peritoneal involvement, meningitis, mediastinal or abdominal lymphadenopathy or ostetis. Discrete peripheral lymph node Mycobacterium tuberculosis infection (especially cervical) is considered a less severe form of extrapulmonary tuberculosis.	M. tuberculosis isolation or compatible histology from appropriate site or radiological evidence of miliary tuberculosis; (diffuse uniformly distributed small miliary shadows or micronodules on chest X-ray).
Kaposi sarcoma.	Typical gross appearance in skin or oropharynx of persistent, initially flat, patches with a pink or violaceous colour, skin lesions that usually develop into plaques or nodules.	Macroscopic appearance at endoscopy or bronchoscopy, or by histology.

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Cytomegalovirus disease (other than liver, spleen or lymph node).	Retinitis only: may be diagnosed by experienced clinicians. Typical eye lesions on fundoscopic examination: discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Compatible histology or cytomegalovirus demonstrated in cerebrospinal fluid by culture or DNA (by polymerase chain reaction).
Central nervous system toxoplasmosis.	Recent onset of a focal nervous system abnormality consistent with intracranial disease or reduced level of consciousness AND response within 10 days to specific therapy.	Positive serum toxoplasma antibody AND (if available) single or multiple intracranial mass lesion on neuroimaging (computed tomography or magnetic resonance imaging).
HIV encephalopathy.	Disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or condition other than HIV infection that might explain the findings.	Diagnosis of exclusion: and (if available) neuroimaging (computed tomography or magnetic resonance imaging).
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 on cerebrospinal fluid or blood.

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Disseminated non-tuberculous mycobacteria infection.	No presumptive clinical diagnosis.	Diagnosed by finding atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding the lungs.
Progressive multifocal leukoencephalopathy.	No presumptive clinical diagnosis.	Progressive nervous system 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 polymerase chain reaction on cerebrospinal fluid.
Chronic cryptosporidiosis (with diarrhoea lasting more than one month).	No presumptive clinical diagnosis.	Cysts identified on modified Ziehl-Nielsen stain microscopic examination of unformed stool.
Chronic isosporiasis.	No presumptive clinical diagnosis.	Identification of Isospora.
Disseminated mycosis (coccidiomycosis or histoplasmosis).	No presumptive clinical diagnosis.	Histology, antigen detection or culture from clinical specimen or blood culture.
Recurrent non-typhoid Salmonella bacteraemia.	No presumptive clinical diagnosis.	Blood culture.
Lymphoma (cerebral or B-cell non-Hodgkin).	No presumptive clinical diagnosis.	Histology of relevant specimen or, for central nervous system tumours, neuroimaging techniques.
Invasive cervical carcinoma.	No presumptive clinical diagnosis.	Histology or cytology.

Adults (15 years or older)

Clinical event	Clinical diagnosis	Definitive diagnosis
Atypical disseminated leishmaniasis.	No presumptive clinical diagnosis.	Diagnosed by histology (amastigotes visualized) or culture from any appropriate clinical specimen.
Symptometic HIV-associated nephropathy.	No presumptive clinical diagnosis.	Renal biopsy.
Symptometic HIV-associated cardiomyopathy.	No presumptive clinical diagnosis.	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography.

CRITERIA FOR WHO CLINICAL STAGING EVENTS
Children (younger than 15 years)

Clinical event	Clinical diagnosis	Definitive diagnosis
Clinical stage 1		
Asymptomatic.	No HIV-related symptoms reported and no clinical signs on examination.	Not applicable.
Persistent generalized lymphadenopathy.	Persistent enlarged lymph nodes >1 cm at two or more non-contiguous sites (excluding inguinal) 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 or vitamin deficiency, and usually responding to antifungal treatment.	Clinical diagnosis.
Lineal gingival erythema.	Erythematous band that follows the contour of the free gingival line; may be associated with spontaneous bleeding.	Clinical diagnosis.

Children (younger than 15 years)

Clinical event	Clinical diagnosis	Definitive 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 ulceration.	Current event plus at least one previous episode in past six months. Aphthous ulceration, typically with a halo of inflammation and 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 midline.	Clinical diagnosis.

Children (younger than 15 years)

Clinical event	Clinical diagnosis	Definitive diagnosis
Recurrent or chronic upper respiratory tract infection.	Current event with at least one episode in the past six 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.
Clinical stage 3		
Unexplained moderate malnutrition or wasting.	Weight loss: low weight-for-age, up to −2 standard deviations from the mean, 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 from the mean, 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.

Children (younger than 15 years)

Clinical event	Clinical diagnosis	Definitive diagnosis
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 antimalarial agents. 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 chest X-ray and no other obvious foci of disease.
Oral candidiasis; (after the first 6–8 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, that 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 tuberculosis.	Non-acute, painless “cold” enlargement of peripheral lymph nodes, localized to one region. Response to standard antituberculosis treatment in one month.	Histology or fine needle aspirate positive for Ziehl-Nielsen stain or culture.

Children (younger than 15 years)

Clinical event	Clinical diagnosis	Definitive diagnosis
Pulmonary tuberculosis.	Nonspecific symptoms, such as chronic cough, fever, night sweats, anorexia and weight loss. In the older child also productive cough and haemoptysis. History of contact with adults with smear-positive pulmonary tuberculosis. No response to standard broad-spectrum antibiotic treatment.	One or more sputum smear positive for acid-fast bacilli and/or radiographic abnormalities consistent with active tuberculosis and/or culture-positive for Mycobacterium.
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 six months.	Isolation of bacteria from appropriate clinical specimens (induced sputum, bronchoalveolar lavage and lung aspirate).
Symptomatic lymphocytic interstitial pneumonia.	No presumptive clinical diagnosis.	Chest X-ray: 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%. Cor pulmonale and 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.	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.

Children (younger than 15 years)

Clinical event	Clinical diagnosis	Definitive diagnosis
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 10^9 per litre) and or chronic thrombocytopaenia (<50 × 10^9 per litre).	No presumptive clinical diagnosis.	Laboratory testing, not explained by other non-HIV conditions, not responding to standard therapy with haematinics, antimalarial agents or anthelmintic agents as outlined in WHO Integrated Management of Childhood Illness guidelines.
Clinical stage 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy.	Persistent weight loss stunting wasting or malnutrition not explained by poor or inadequate feeding, other infections and not adequately responding in two weeks to standard therapy. Visible severe wasting of muscles, with or without oedema of both feet, and/or weight-for-height of –3 standard deviations from the mean, as defined by WHO Integrated Management of Childhood Illness guidelines.	Documented weight for height or weight for age of more than –3 standard deviations from the mean with or without oedema.

Children (younger than 15 years)

Clinical event	Clinical diagnosis	Definitive diagnosis
Pneumocystis pneumonia.	Dry cough, progressive difficulty in breathing, cyanosis, tachypnoea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in WHO Integrated Management of Childhood Illness guidelines.) Rapid onset especially in infants younger than six months of age. Response to high-dose co-trimoxazole with or without prednisolone. Chest X-ray shows typical bilateral perihilar diffuse infiltrates.	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage or histology of lung tissue.
Recurrent severe bacterial infection, such as empyema, pyomyositis, bone or joint infection or 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 six 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 herpes simplex virus infection present for more than one month.	Culture and/or histology.
Oesophageal candidiasis; (or candidiasis 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 difficulty or crying when feeding.	Macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology.

Children (younger than 15 years)

Clinical event	Clinical diagnosis	Definitive diagnosis
Extrapulmonary tuberculosis.	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, pericardial or abdominal.	Positive microscopy showing acid-fast bacilli 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.	Macroscopie appearence or by histology.
Cytomegalovirus retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month.	Retinitis only. Cytomegalovirus 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 or cytomegalovirus demonstrated in cerebrospinal fluid by polymerase chain reaction.
Central nervous system toxoplasmosis onset after age one month.	Fever, headache, focal nervous system signs and convulsions. Usually responds within 10 days to specific therapy.	Computed tomography scan (or other neuroimaging) showing single or multiple lesions with mass effect or enhancing with contrast.

Children (younger than 15 years)

Clinical event	Clinical diagnosis	Definitive diagnosis
Extrapulmonary cryptococcosis (including meningitis).	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion and behavioural changes that respond to cryptococcal therapy.	Cerebrospinal fluid microscopy (India ink or Gram stain), serum or cerebrospinal fluid cryptococcal antigen test or culture.
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 or loss of intellectual ability; OR progressive impaired brain growth demonstrated by stagnation of head circumference; OR acquired symmetrical motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia and gait disturbances.	Neuroimaging demonstrating atrophy and basal ganglia calcification and excluding other causes.
Disseminated mycosis (coccidiomycosis or histoplasmosis).	No presumptive clinical diagnosis.	Histology: usually granuloma formation. Isolation: antigen detection from affected tissue; culture or microscopy from clinical specimen or blood culture.

Children (younger than 15 years)

Clinical event	Clinical diagnosis	Definitive diagnosis
Disseminated mycobacteriosis, other than tuberculosis.	No presumptive clinical diagnosis.	Nonspecific clinical symptoms including progressive weight loss, fever, anaemia, night sweats, fatigue or diarrhoea; plus culture of atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding the lung.
Chronic cryptosporidiosis; (with diarrhoea).	No presumptive clinical diagnosis.	Cysts identified on modified Ziehl-Nielsen microscopic examination of unformed stool.
Chronic Isosporiasis.	No presumptive clinical diagnosis.	Identification of Isospora.
Cerebral or B-cell non-Hodgkin lymphoma.	No presumptive clinical diagnosis.	Diagnosed by central nervous system neuroimaging; histology of relevant specimen.
Progressive multifocal leukoencephalopathy.	No presumptive clinical diagnosis.	Progressive nervous system disorder (cognitive dysfunction, gait or speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuroimaging or positive polyomavirus JC (JCV) polymerase chain reaction on cerebrospinal fluid.
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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NOTES

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