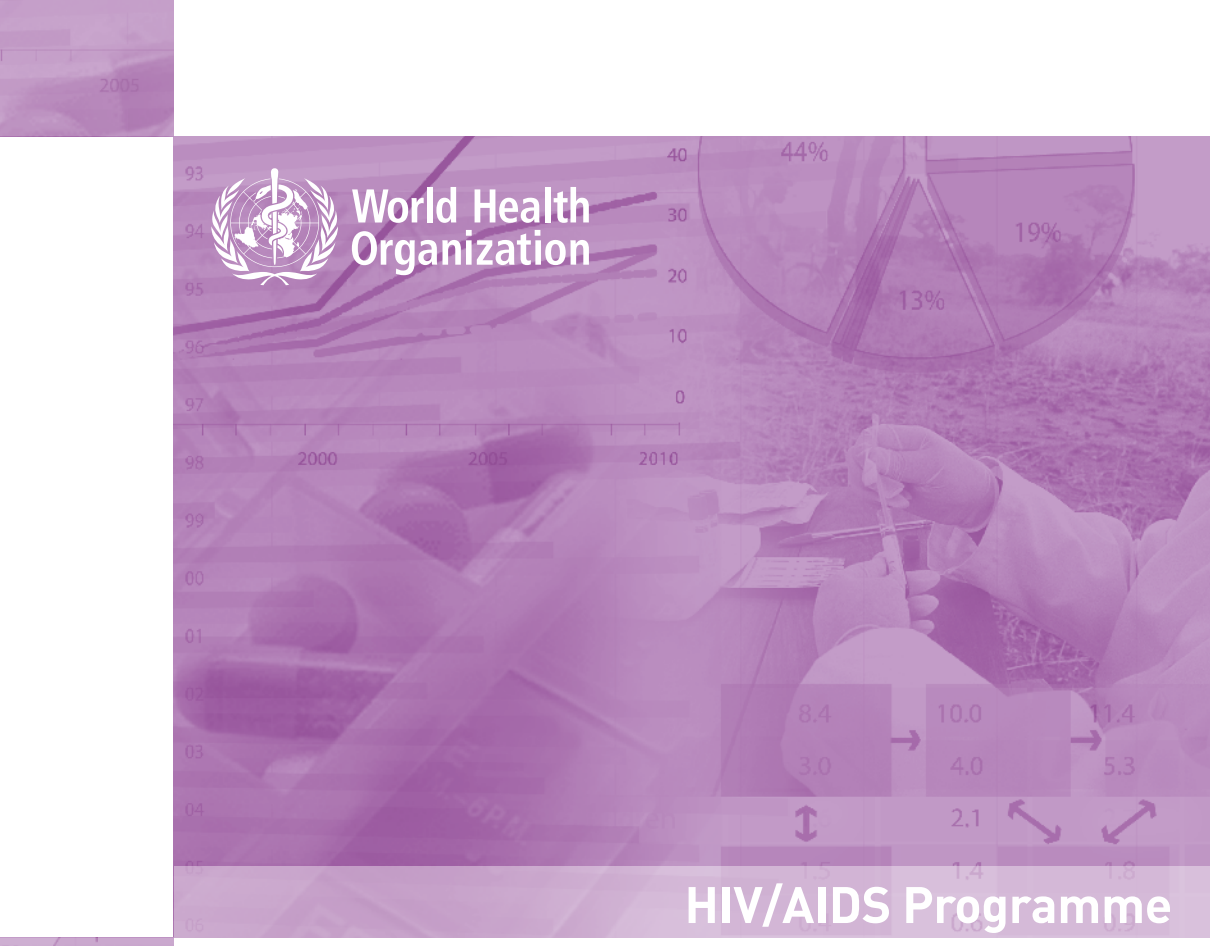

World Health Organization

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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World Health Organization

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

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 clinically managing 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. WHO has not previously defined HIV infection for reporting or for clinical purposes or recommended the universal reporting of HIV.

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* **(in press).**

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, and so the utility of reporting AIDS cases and AIDS mortality is less clear.

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.

WHO CASE DEFINITION FOR HIV INFECTION

To facilitate the reporting of HIV infection, WHO recommends the following:

HIV cases diagnosed and not previously reported in each country should be reported according to a standard national case definition. A case of HIV infection is defined as an individual with HIV infection irrespective of clinical stage (including severe or stage 4 clinical disease, also known as AIDS) confirmed by laboratory criteria according to country definitions and requirements. Countries should develop and regularly review their testing algorithms for diagnostic and surveillance purposes.[i] WHO provides a simplified HIV case definition designed for reporting and surveillance (Box 1).

HIV infection is diagnosed based on laboratory criteria. Clinically diagnosing suspected or probable HIV infection by diagnosing an AIDS-defining condition or HIV at any clinical or immunological stage in an adult or child requires confirmation of HIV infection by the best age-appropriate test. Further, as maternal HIV antibody transferred passively during pregnancy can persist for as long as 18 months among children born to mothers living with HIV, positive HIV antibody test results are difficult to interpret in younger children, and alternative methods of diagnosis are recommended.

Box 1. WHO case definition for HIV infection

- **Adults and children 18 months or older:**

HIV infection is diagnosed based on:

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.

and /or;

a 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.

- **Children younger than 18 months:**

HIV infection is diagnosed based on:

a 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[1].

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

i Further technical information on algorithms for HIV testing by WHO can be found at http://webitpreview.who.int/entity/diagnostics_laboratory/evaluations/hiv/en.

WHO CASE DEFINITION OF ADVANCED HIV (INFECTION OR DISEASE) (INCLUDING AIDS) FOR REPORTING:

Cases diagnosed with advanced HIV infection (including AIDS) not previously reported should be reported according to a standard case definition. Advanced HIV infection is diagnosed based on clinical or immunological (CD4) criteria among people with confirmed HIV infection (Box 2).

Box 2. Criteria for diagnosis of advanced HIV (including AIDS[a]) for reporting for adults and children:

- **Clinical criteria for diagnosis of advanced HIV in adults and children with confirmed HIV infection**

Presumptive or definitive diagnosis of any stage 3 or stage 4 condition[b]

- **Immunological criteria for diagnosing advanced HIV in adults and children five years or older with confirmed HIV infection**

CD4 count less than 350 per mm^3 of blood in an HIV-infected adult or child

- **Immunological criteria for diagnosing advanced HIV in a child younger than five years of age with confirmed HIV infection:**

%CD4+ <30 among those younger than 12 months

%CD4+ <25 among those aged 12–35 months

%CD4+ <20 among those aged 36–59 months

[a] AIDS in adults and children is defined as: clinical diagnosis (presumptive or definitive) of any stage 4 condition (as defined in Annex 1) with confirmed HIV infection; OR immunological criteria in adults and children with confirmed HIV infection and ≥5 years of age; first-ever documented %CD4 count less than 200 per mm^3 or %CD4+ <15; or, among children aged 12–35 months first-ever documented CD4 of +<20; or among infants less than 12 months of age first-ever documented %CD4+ <25.

[b] Annex 1 provides criteria for presumptive or definitive diagnosis of all conditions.

WHO CASE DEFINITION OF AIDS

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

PRIMARY HIV INFECTION

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]*.

CLINICAL AND IMMUNOLOGICAL CLASSIFICATION OF HIV AND RELATED DISEASE

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 developed to support rolling out antiretroviral therapy *[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 Centers for Disease Control and Prevention revised in 1994 and originally intended for surveillance purposes *[26]*. Both the United States Centers for Disease Control and Prevention and WHO clinical classifications recognize primary HIV infection. It is also proposed that the appearance of new or recurrent clinical staging events and immunological classification 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 or severe clinical disease) 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 with their relation in simplified terms to describe 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] Recurrence of HIV-related opportunistic infections or HIV-related clinical events once people are receiving antiretroviral therapy has already been used as a clinical guide to recognizing antiretroviral therapy failure and the need to switch therapy.

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 classification 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 about when to switch antiretroviral therapy among children and adults living with HIV, particularly when the CD4 count is not available. It is assumed that the clinical staging events have the same prognostic significance among people receiving antiretroviral therapy as they do 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 define 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 Centers for Disease Control and Prevention 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.

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+ or >30 among children younger than

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.

12 months, >25 among children 12–35 months or >20 in children over 36 months, or >350 per mm^3 in adults and older children), and the individual is asymptomatic or only has mild symptoms.

Table 2. WHO-proposed 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

CLINICAL STAGE 1
Asymptomatic Persistent generalized lymphadenopathy
CLINICAL STAGE 2
Unexplained moderate 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.**

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 37.5°C intermittent or constant, for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis
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) and/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
Chronic isosporiasis
Disseminated mycosis (extrapulmonary histoplasmosis or coccidiomycosis)
Recurrent septicaemia (including non-typhoidal *Salmonella*)
Lymphoma (cerebral or B-cell non-Hodgkin)
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 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
Extensive wart virus infection
Extensive molluscum contagiosum
Fungal nail infections
Recurrent oral ulcerations
Unexplained persistent parotid enlargement
Lineal gingival erythema
Herpes zoster
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis)
CLINICAL STAGE 3
Unexplained[i] moderate malnutrition 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 ($<0.5 \times 10^9$ per litre) and or chronic thrombocytopaenia ($<50 \times 10^9$ per litre)

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

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)
Extrapulmonary tuberculosis
Kaposi sarcoma
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Central nervous system toxoplasmosis (after one month of life)
HIV encephalopathy
Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month
Extrapulmonary cryptococcosis (including meningitis)
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated non-tuberculous mycobacterial infection
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, penicilliosis in Asia and HIV-associated rectovaginal fistula in Africa).**

ANNEX 1. PRESUMPTIVE AND DEFINITIVE CRITERIA FOR RECOGNIZING HIV-RELATED CLINICAL EVENTS IN ADULTS (15 YEARS OR OLDER) AND CHILDREN (YOUNGER THAN 15 YEARS) WITH CONFIRMED HIV INFECTION

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		
Moderate unexplained 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

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE 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
Recurrent oral ulcerations (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 infections	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 EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
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/m^2; in pregnancy, the weight loss may be masked	Documented loss of more than 10% of body weight
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
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

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Oral hairy leukoplakia	Fine white small linear or corrugated lesions on lateral borders of the tongue that do not scrape off	Clinical diagnosis
Pulmonary tuberculosis (current)	Chronic symptoms: (lasting more than 2–3 weeks) cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats, and no clinical evidence of extrapulmonary disease Discrete peripheral lymph node *M. tuberculosis* infection (especially cervical) is considered a less severe form of extrapulmonary tuberculosis	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 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

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 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 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

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 severe bacterial pneumonia	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

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Oesophageal candidiasis	Recent onset of retrosternal pain or difficulty on swallowing (food and fluids) together with oral *Candida*	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, such as pleura, pericardia, meninges, mediastinum or abdominal 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 TB (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

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)

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
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
Disseminated non-tuberculous mycobacterial 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 (such as coccidiomycosis, histoplasmosis or penicilliosis)	No presumptive clinical diagnosis	Histology, antigen detection or culture from clinical specimen or blood culture

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
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
Visceral leishmaniasis	No presumptive clinical diagnosis	Diagnosed by histology (amastigotes visualized) or culture from any appropriate clinical specimen
HIV-associated nephropathy	No presumptive clinical diagnosis	Renal biopsy
HIV-associated cardiomyopathy	No presumptive clinical diagnosis	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography

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 swollen or 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
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

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE 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
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
Lineal gingival erythema	Erythematous band that follows the contour of the free gingival line; may be associated with spontaneous bleeding	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

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Recurrent 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	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

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

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE 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
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)

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
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
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 EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
CLINICAL STAGE 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	Persistent weight loss 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 loss of more than –3 standard deviations from the mean with or without oedema
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

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
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
Extrapulmonary or disseminated 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 or 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

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
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	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; and • 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. Cerebrospinal fluid 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
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

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
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, histoplasmosis or 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 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

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Chronic cryptosporidiosis	No presumptive clinical diagnosis	Cysts identified on modified Ziehl-Nielsen microscopic examination of unformed stool
Chronic *Isospora*	No presumptive clinical diagnosis	Identification of *Isospora* spp.
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 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

ANNEX 2. PRESUMPTIVE DIAGNOSIS OF SEVERE HIV DISEASE AMONG HIV-SEROPOSITIVE HIV-EXPOSED CHILDREN

Clinical criteria for presumptive diagnosis of severe HIV disease among infants and children aged under 18 months in situations where virological testing is not available

A presumptive diagnosis of severe HIV disease should be made if:

- the infant is confirmed as being HIV antibody-positive

  and

- diagnosis of any AIDS-indicator condition(s)a can be made

  or

- the infant is symptomatic with two or more of the following:
  - oral thrush[b]
  - severe pneumonia[b]
  - severe sepsis.[b]

Other factors that support the diagnosis of severe HIV disease in an HIV-seropositive infant include:

- recent HIV-related maternal death or advanced HIV disease in the mother;
- CD4 <20%.[c]

Confirmation of the diagnosis of HIV infection should be sought as soon as possible.

a AIDS indicator conditions include some but not all HIV clinical stage 4 conditions in children such as Pneumocystis pneumonia, oesophageal candidiasis, cryptococcal meningitis, cerebral toxoplasmosis, HIV wasting and Kaposi sarcoma.

b Defined in accordance with WHO Integrated Management of Childhood Illness guidelines:

- Oral thrush: Creamy white soft small plaques on red or normally coloured mucosa which can often be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender.
- Severe pneumonia: Cough or difficult breathing in a child with chest indrawing, stridor or any of the general danger signs outlined in the WHO Integrated Management of Childhood Illness guidelines: that is lethargic or unconscious, not able to drink or breastfeed, vomiting and presence or history of convulsions during current illness,.
- Severe sepsis: Fever or low body temperature in a young infant with any severe sign, such as rapid breathing, chest indrawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast-milk, convulsions, stiff neck.

c It is unclear how often the CD4 count is lowered in these conditions in HIV-uninfected children.

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