WHO/HIV/2005.02

INTERIM WHO CLINICAL STAGING OF HIV/AIDS AND HIV/AIDS CASE DEFINITIONS FOR SURVEILLANCE

AFRICAN REGION

World Health Organization

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Acronyms and Abbreviations

AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral medicine
BAL	bronchoalveolar lavage
CD4	human T helper cells expressing CD4 antigen (T helper cell)
CDC	Centers for Disease Control and Prevention (USA)
CMV	cytomegalovirus
CNS	central nervous system
CRAG	cryptococcal antigen
CSF	cerebrospinal fluid
CT	computed tomography
CXR	chest X-ray
DNA	deoxyribonucleic acid
HIV	human immunodeficiency virus
HSV	herpes simplex virus
IMCI	integrated management of childhood illness
IRS	immune restoration syndrome
JC	Jacob Creutzfeldt (Virus)
LGE	linear gingival erythema
LIP	lymphoid interstitial pneumonitis
LP	lumbar puncture
LRTI	lower respiratory tract infection
LTB	laryngotracheal bronchitis
MOT	mycobacteria other than tuberculosis
MRI	magnetic resonance imaging
NAT	nucleic acid testing
P24	a soluble antigen produced by HIV
PCP	pneumocystis pneumonia
PCR	polymerase chain reaction
PGL	persistent generalized lymphadenopathy
PLWHA	people living with HIV/AIDS
PML	progressive multifocal leukoencephalopathy
RF	rectal fistula
RVF	rectovaginal fistula
RNA	ribonucleic acid
SD	standard deviation
TB	tuberculosis
TLC	total lymphocyte count
URTI	upper respiratory tract infection
WHO	World Health Organization
ZN	Ziehl-Neelsen (staining method)

Executive summary

With a view to facilitating the scale-up of access to antiretroviral therapy (ART) in the African Region the present document outlines recent revisions made by WHO to the clinical staging of HIV/AIDS and to case definitions for HIV/AIDS disease surveillance. These interim guidelines are based on an international drafting meeting held in Saas Fee in June 2004 and on recommendations made by experts from African countries at a meeting held in Nairobi in December of the same year.

The revisions to the clinical staging target professionals ranging from senior consultants in teaching and referral hospitals to surveillance officers and first-level health care providers, all of whom have important roles in caring for people living with HIV and AIDS (PLWHA), including children. It is proposed that countries review, adapt and repackage the guidelines as appropriate for specific tasks at different levels of health service delivery. It is hoped that national HIV/AIDS programmes in African countries will thus be assisted to develop, revise or strengthen their ART guidelines, patient monitoring and surveillance efforts.

The interim clinical staging and revised definitions for surveillance are currently being reviewed in the other WHO regions and will be finalized at a global meeting to be held in September 2005.

Background

HIV/AIDS surveillance is useful for monitoring temporal, geographical and risk-group trends and for estimating the burden of HIV/AIDS-related disease. Surveillance definitions were introduced in 1982, and many different definitions have been used for national and international reporting *(1)*. The clinical case definitions recommended by WHO in 1985 and revised in 1994 are designed for use in resource-limited settings. They require confirmation of HIV infection by means of serological testing. The surveillance definitions were introduced before the widespread use of antiretroviral therapy (ART), which can restore many patients with severe disease to health, and reverse disease progression. Surveillance now needs to capture those patients in need of ART.

The WHO clinical staging system for HIV/AIDS, as developed in 1990, emphasized the use of clinical parameters to guide clinical decision-making for the management of HIV/AIDS patients. It was designed for use in resource-limited settings where there was limited access to laboratory services. The WHO clinical staging system has been widely used in resource-limited countries, particularly in the African Region, and has proved pragmatic and useful in facilities at both the first level and the referral level. It was originally hierarchal in recognition of the relentless progression of HIV infection, with no reversal or improvement allowed. Unfortunately confusion has occurred with clinical case definitions for surveillance being used for clinical purposes. The clinical disease classification system of the Centers for Disease Control and Prevention (CDC) in the USA which is based on immunological parameters (CD4 counts) clinical parameters and virological parameters and requires laboratory confirmation of many clinical events is designed for surveillance purposes, but is frequently used for clinical management purposes.

In response to the changing landscape of HIV/AIDS, particularly in resource-limited settings, and specifically to support scale up of anti-retroviral treatment, revisions and harmonization of the clinical staging and case definitions for surveillance are required. For this reason, WHO in collaboration with CDC, held two expert consultative meetings, in June 2004 in Saas Fe, Switzerland and in December 2004 in Nairobi, Kenya to review and revise the 1994 WHO clinical staging system and AIDS case definitions. The revisions made were based upon the best available evidence or, where evidence was inconclusive or unavailable, on the balance of expert opinion. This present document describes the interim WHO clinical staging system and case definitions as agreed during the second meeting, held in Nairobi.

The revisions are also designed to reflect that with the use of ART HIV is a chronic disease. ART changes the prognosis and can reverse the inevitable progression through the clinical stages.

The revisions were designed to strengthen clinical staging and the AIDS case definitions for both adults and children, and to simplify and standardize definitions for use by a cross-section of health providers, programme managers and surveillance officers. They were also intended to harmonize paediatric and adult clinical staging and AIDS case definitions so as to improve patient management, patient monitoring and surveillance efforts.

The aims of the proposed revisions were to:

- provide greater consistency between the adult and paediatric staging systems;
- harmonize clinical case definitions and surveillance definitions;
- provide clinical and immunological staging for adults and children based upon the degree of immunocompromise and prognosis, but that facilitates follow up care;
- provide guidance on the care of children aged under 18 months, in whom persisting maternal antibodies make it difficult to definitively diagnose HIV infection if virological or P24 antigen testing is not readily available;
- facilitate the use of the clinical staging system and HIV/AIDS case definitions by non-specialist and non-paediatric health care workers at the basic level and in peripheral health care facilities;
- assist with clinical decision-making, including decisions on starting, substituting, switching and stopping ART, and with routine follow up of patients on treatment;
- permit the inclusion of laboratory testing, especially CD4 count, where available, so as to guide prognosis and assist in determining the need for ART and other therapies;
- provide surveillance definitions for advanced stages of HIV infection which reflect disease requiring ART either immediately or in the near future.

The clinical staging is presented in two summary tables (1 and 4). Table 1 is to be is used for those who are 15[a] years and above for whom there is confirmed laboratory evidence of HIV infection. Table 4 concerns infants and children aged under 15 years with confirmed laboratory evidence of HIV infection. An

[a] The cut off age of 15 years is applied as this is the usual cut off for surveillance definitions.

additional classification for presumptive diagnosis of clinical stage 4 (severe HIV infection) in infants under 18 months is also available for use in situations where definitive diagnosis of HIV infection is not readily available.

Clinical events are categorized as those where a **presumptive clinical diagnosis** may be made (conditions that can be diagnosed clinically or with basic laboratory tests) and those where a **definitive diagnosis** may be made (for conditions requiring more complex and sophisticated laboratory investigations). Also given are explanatory notes, proposed immunological staging categories, implications for criteria to initiate ART and proposed harmonized definitions of advanced HIV/AIDS for the purposes of surveillance. Clinical staging needs to be performed at determination or confirmation of HIV infection, and on entry to clinical care (pre-ART) to help guide ART and care related decisions. Assessment of clinical stage at each clinical visit also provides useful information on current clinical status, and can guide clinical decision making. National guidelines for the clinical management of HIV/AIDS can be modified on this basis.

Annex 1 addresses issues related to the recognition and diagnosis of clinical events in adults and adolescents, and key decisions related to clinical events pre-ART and while on ART; Annex 2 does the same for infants and children.

REVISED WHO CLINICAL STAGING OF HIV/AIDS
FOR ADULTS AND ADOLESCENTS

(Interim African Region version for persons aged 15 years or more with positive HIV antibody test or other laboratory evidence of HIV infection)[b]

TABLE 1. REVISED WHO CLINICAL STAGING OF HIV/AIDS FOR ADULTS AND ADOLESCENTS

Primary HIV infection

- Asymptomatic
- Acute retroviral syndrome

Clinical stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy (PGL)

Clinical stage 2

- Moderate unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory tract infections (RTIs, sinusitis, bronchitis, otitis media, pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulcerations
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infections of fingers

Clinical stage 3

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

- Severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhoea for longer than one month
- Unexplained persistent fever (intermittent or constant for longer than one month)
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (TB) diagnosed in last two years
- Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Conditions where confirmatory diagnostic testing is necessary

- Unexplained anaemia (<8 g/dl), and or neutropenia (<500/mm^3) and or thrombocytopenia (<50 000/ mm^3) for more than one month

[b] All clinical events or conditions referred to are described in the Annexes. The UN defines adolescents as persons aged 10–19 years but, in the present document, the category of adults and adolescents comprises people aged 15 years and over for surveillance purposes.

Clinical stage 4

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe or radiological bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)
- Oesophageal candidiasis
- Extrapulmonary TB
- Kaposi's sarcoma
- Central nervous system (CNS) toxoplasmosis
- HIV encephalopathy

Conditions where confirmatory diagnostic testing is necessary:

- Extrapulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacteria infection
- Progressive multifocal leukoencephalopathy (PML)
- Candida of trachea, bronchi or lungs
- Cryptosporidiosis
- Isosporiasis
- Visceral herpes simplex infection
- Cytomegalovirus (CMV) infection (retinitis or of an organ other than liver, spleen or lymph nodes)
- Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, penicilliosis)
- Recurrent non-typhoidal salmonella septicaemia
- Lymphoma (cerebral or B cell non-Hodgkin)
- Invasive cervical carcinoma
- Visceral leishmaniasis

EXPLANATORY NOTES

The 2005 revised clinical staging system for adults and adolescents is designed to:

- be used where HIV infection is confirmed by HIV antibody or virological testing;
- harmonize with newly proposed immunological criteria
- harmonize with revised HIV/AIDS surveillance definitions

For clinical management purposes it is designed to:

- be used for assessment at baseline or entry into HIV care to guide decisions on when to start cotrimoxazole prophylaxis, start ART and other HIV related interventions;
- provide simple guidance to assist clinical care providers on when to start, substitute, switch or stop ART in HIV-infected adults and adolescents, or to trigger referral as outlined in the WHO ART guidelines for a public health approach*(2)*;
- be used to assess current clinical status of individuals in HIV care, either on or off ART;
- encourage clinical care providers to offer diagnostic testing for HIV in adults and adolescents exhibiting the clinical events suggestive of HIV disease;
- prompt urgent offer of HIV diagnostic testing for stage 3 or stage 4 events either on site, or by referral for testing to a site where immediate assessment by HIV care providers able to initiate ART can be performed;
- be used to guide clinicians in assessing the response to ART, particularly where viral load and/or CD4 counts or percentages are not widely or easily available (new or recurrent stage 4 events may suggest failure of response to treatment; new or recurrent stage 2 or stage 3 events may suggest an inadequate response to treatment, potentially because of poor adherence; however further evidence is required in order to determine the significance of staging events once ART has commenced. Clinical events in the first three months after ART has begun may be caused by immune restoration syndrome (IRS) rather than a poor response to ART).

Note: Total lymphocyte count (TLC) is not currently recommended for monitoring therapy.

Annex 1 provides further descriptions of each clinical event and their diagnosis clinically or with basic laboratory or radiological investigations (presumptive diagnosis) and on requirements for more sophisticated investigations (definitive diagnosis).

For surveillance purposes it is designed to:

- classify disease in a progressive sequence from least to most severe and remains hierarchical (with only the first stage 3 or stage 4 clinical event requiring notification);
- be used with reference to current clinical events, meaning those that have been diagnosed or are currently being managed;
- be considered in relation to previous clinical events, such as reported TB, severe pneumonia, PCP or other conditions; this is retrospective clinical staging for surveillance.

Immunological staging of HIV infection

Clinical staging can be used effectively without access to CD4 or other laboratory testing. However, CD4 testing is useful for determining the degree of immunocompromise, and where CD4 facilities are available they should be used to support and reinforce clinical decision-making. Data on CD4 levels are not a prerequisite for starting ART and should only be used in conjunction with consideration of the clinical stage. Table 2 presents CD4 levels in relation to the severity of immunosuppression.

For clinical purposes long term prognosis has been shown to be related to the nadir or lowest-ever value of CD4. It should be noted that the immunological staging of disease reverses with successful ART.

Table 2. CD4 levels in relation to the severity of immunosuppression

Not significant immunosuppression	>500/mm^3
Mild immunosuppression	350 – 499/mm^3
Advanced immunosuppression	200 – 349/mm^3
Severe immunosuppression	<200/mm^3

Implications for clinical and immunological criteria for initiating ART in adults and adolescents

There is strong evidence for the clinical benefit of ART in adults with advanced HIV/AIDS as determined clinically or immunologically. The precise clinical and or immunological criteria for initiating ART is usually outlined in national treatment guidelines. Existing WHO recommendations are provided on a WHO web site *(2)*.

Table 3. Clinical and immunological criteria for initiating ART in adults and adolescents

Clinical stage	ART
4	Treat.
3	Consider treatment: CD4, if available, can guide the urgency with which ART should be started.
1 or 2	Only if CD4 <200/mm^3.

CD4 can be used to monitor responses to treatment, although they are not essential. Absolute CD4 values also fluctuate with intercurrent illness and with physiological and test variability, so the trend over two or three repeated measurements is usually more informative than individual values. Note: that during the course of acute HIV infection the CD4 count may reach very low levels and then recover.

PROPOSED HARMONIZED DEFINITIONS OF ADVANCED HIV/AIDS DISEASE FOR SURVEILLANCE IN ADULTS AND ADOLESCENTS

AIDS case definitions first developed in 1982 were primarily designed as an epidemiological tool for surveillance purposes. Various revisions over the next two decades led to inclusion of clinical and laboratory criteria to the surveillance definitions. WHO introduced a clinical case definition for surveillance in 1985, and revised this in 1986 and 1994 to include serological testing for HIV.

'AIDS' as a term has also been used to describe the various clinical syndromes, specific opportunistic infections or malignancies that occur with HIV infection and signal those in whom advanced HIV infection has occurred. There has been confusion between surveillance definitions and clinical staging definitions. These guidelines seek to harmonize both. In the present context of scaling up ART the purpose of surveillance is to monitor the burden of advanced HIV disease and allow estimates of the number of people who require or may shortly require ART.

Including a CD4 threshold in surveillance definitions specifies the level at which advanced HIV related immunosuppression is deemed to have occurred and from which intervention with ART is immediately or soon needed to offset disease progression. For surveillance purposes once the clinical OR immunological trigger event has occurred the patient should be captured only once in surveillance data, regardless of ART or other treatment interventions or outcomes.

BOX 1. ADVANCED HIV/AIDS DISEASE DEFINITIONS FOR SURVEILLANCE

Any clinical stage 3 or stage 4 disease
or,
where CD4 is available[c], any clinical stage and CD4 <350/mm^3.

[c] CD4 based reporting remains optional

REVISED WHO CLINICAL STAGING OF HIV/AIDS FOR INFANTS AND CHILDREN

(INTERIM AFRICAN REGION VERSION FOR PERSONS AGED UNDER 15 YEARS WITH CONFIRMED LABORATORY EVIDENCE OF HIV INFECTION: HIV ANTIBODY IF AGED 18 MONTHS AND ABOVE; VIROLOGICAL OR P24 ANTIGEN TESTING IF AGED UNDER 18 MONTHS)[D]

TABLE 4. REVISED WHO CLINICAL STAGING OF HIV/AIDS FOR INFANTS AND CHILDREN

Clinical Stage 1

Asymptomatic
PGL

Clinical Stage 2

Hepatosplenomegaly
Papular pruritic eruptions
Seborrhoeic dermatitis
Extensive human papilloma virus infection
Extensive molluscum contagiosum
Fungal nail infections
Recurrent oral ulcerations
Lineal gingival erythema (LGE)
Angular cheilitis
Parotid enlargement
Herpes zoster
Recurrent or chronic RTIs (otitis media, otorrhoea, sinusitis)

Clinical Stage 3

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

Moderate unexplained malnutrition not adequately responding to standard therapy
Unexplained persistent diarrhoea (14 days or more)
Unexplained persistent fever (intermittent or constant, for longer than one month)
Oral candidiasis (outside neonatal period)
Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis/periodontitis
Pulmonary TB
Severe recurrent presumed bacterial pneumonia

[d] All clinical events or conditions referred to are described in the Annexes.

Conditions where confirmatory diagnostic testing is necessary

Chronic HIV-associated lung disease including brochiectasis

Lymphoid interstitial pneumonitis (LIP)

Unexplained anaemia (<8g/dl), and or neutropenia (<1000/mm^3) and or thrombocytopenia (<50 000/ mm^3) for more than one month

Clinical Stage 4

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

Unexplained severe wasting or severe malnutrition not adequately responding to standard therapy

Pneumocystis pneumonia

Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)

Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration)

Extrapulmonary TB

Kaposi's sarcoma

Oesophageal candidiasis

CNS toxoplasmosis (outside the neonatal period)

HIV encephalopathy

Conditions where confirmatory diagnostic testing is necessary

CMV infection (CMV retinitis or infection of organs other than liver, spleen or lymph nodes; onset at age one month or more)

Extrapulmonary cryptococcosis including meningitis

Any disseminated endemic mycosis (e.g. extrapulmonary histoplasmosis, coccidiomycosis, penicilliosis)

Cryptosporidiosis

Isosporiasis

Disseminated non-tuberculous mycobacteria infection

Candida of trachea, bronchi or lungs

Visceral herpes simplex infection

Acquired HIV associated rectal fistula

Cerebral or B cell non-Hodgkin lymphoma

Progressive multifocal leukoencephalopathy (PML)

HIV-associated cardiomyopathy or HIV-associated nephropathy

Presumptive diagnosis of clinical stage 4 HIV in children aged under 18 months

The presumptive diagnosis is designed for use where access to confirmatory diagnostic testing for HIV infection by means of virological testing (usually nucleic acid testing, NAT) or P24 antigen testing for infants and children aged under 18 months is not readily available. **It is not recommended for use by clinical care providers who are not trained in ART or experienced in HIV care.** It should be accompanied by immediate efforts to confirm the HIV diagnosis with the best nationally or locally available test for age. Presumptive diagnosis of clinical stage 4 disease suggests severe immunosuppression, and ART is indicated.

Box 2. Presumptive clinical stage 4 in infants and children aged under 18 months where virological confirmation of HIV infection is not available

A presumptive diagnosis of stage 4 clinical disease should be made if:

An infant is HIV-antibody positive (ELISA or rapid test), aged under 18 months and symptomatic with two or more of the following:

+/– oral thrush;
+/– severe pneumonia[e]
+/– severe wasting/malnutrition
+/– severe sepsis[f]

CD4 values, where available, may be used to guide decision-making; CD4 percentages below 25% require ART

Other factors that support the diagnosis of clinical stage 4 HIV infection in an HIV-seropositive infant are:

- recent HIV related maternal death
- advanced HIV disease in the mother.

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

Explanatory notes

The 2005 revised clinical staging system for infants and children is designed to:

- be used where HIV infection is confirmed by HIV antibody or virological testing;
- harmonize with newly proposed immunological criteria
- harmonize with revised HIV/AIDS surveillance definitions

[e] Pneumonia requiring oxygen.

[f] Requiring intravenous therapy.

For clinical management purposes it is designed to:

- be used for assessment at baseline or entry into HIV care to guide decisions on when to start cotrimoxazole prophylaxis, start ART and other HIV related interventions;
- provide simple guidance to assist clinical care providers on when to start, substitute, switch or stop ART in HIV-infected children, or to trigger referral as outlined in the WHO ART guidelines for a public health approach*(2)*;
- be used to assess current clinical status of children in HIV care, either on or off ART;
- encourage clinical care providers to offer HIV diagnostic testing in infants and children exhibiting clinical events suggestive of HIV disease;
- prompt urgent referral for diagnostic HIV testing and assessment for all Stage 3 or stage 4 events in children where HIV status is unknown or a child is known to be HIV exposed;
- be used to guide clinicians in assessing the response to ART, particularly where viral load and/or CD4 counts or percentages are not widely or easily available (however, further evidence is required in order to determine the significance of staging events once ART has been started; new or recurrent stage 4 events may suggest a failure of response to treatment; new or recurrent stage 2 or stage 3 events may suggest an inadequate response to treatment, potentially attributable to poor adherence); note that clinical events in the first three months after starting ART may be attributable to IRS rather than a poor response to ART; this is reported less commonly in children;

Note: Total lymphocyte count (TLC) is not currently recommended for monitoring therapy.

Annex 2 provides further descriptions of each clinical event and their diagnosis clinically or with basic laboratory or radiological investigations (presumptive diagnosis) and on requirements for more sophisticated investigations (definitive diagnosis).

For surveillance purposes it is designed to;

- classify disease in a progressive sequence from least to most severe and remains hierarchical (with only the first stage 3 or stage 4 clinical event requiring notification);
- be used with reference to current clinical events, meaning those that have been diagnosed or are currently being managed;

- be considered in relation to previous clinical events, such as reported TB, severe pneumonia, PCP or other conditions; this is retrospective clinical staging for surveillance.

Immunological categories for paediatric HIV infection

Immunological staging for children is also possible. The absolute CD4 count and the percentage values 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 6 years. In considering absolute counts or percentages, therefore, age must be taken into account as a variable. The absolute CD4 count associated with a specific level of immunosuppression tend to change with age, whereas the CD4 percentage related to immunological damage does not vary as much. Currently, therefore, the measurement of the CD4 percentage is recommended in younger children. CD4 testing is not essential for the initiation of ART, and should only be used in conjunction with the clinical stage. As for adults, immunological staging assists clinical decision-making and provides a link with monitoring and surveillance definitions. It is usually reversed by successful ART.

Table 5. CD4 levels in relation to the severity of immunosuppression

Immune status	Age		
	Up to 12 months	**13-59 months**	**5 years or over**
Not significant immunosuppression	>35%	>25%	>500/mm^3
Mild immunosuppression	25–34%	20–24%	350–499/mm^3
Advanced immunosuppression	20–24%	15–19%	200–349/mm^3
Severe immunosuppression	<20%	<15%	<200/mm^3

Implications for clinical and immunological criteria for initiating ART

Although there are concerns about the early use of ART in asymptomatic infants, all children with stage 3 or stage 4 disease (advanced HIV defined clinically) should start ART following discussion with their families. There is very strong evidence for the clinical benefit of ART in children with advanced HIV/AIDS. For older children some clinical conditions, e.g. LIP, appear to have a more stable clinical course, although there are few data on cohorts from African settings. Because of the revisions in clinical staging these recommendations should replace those provided in the 2003 WHO reference guide *(2)*.

Table 6. Clinical and immunological criteria for initiating ART in infants and children

Clinical stages	ART
4	Treat.
Presumptive stage 4	Treat.
3	Consider treatment for all ages. Children aged under 2 years usually require ART. CD4 %, if available should be used to guide decisions on ART.
1 and 2	Usually only where CD4 available. Under 12 months: CD4 % < 20 13-59 months : CD4 % < 15 5 years or over CD4 < 200/mm^3
Note: co-trimoxazole prophylaxis should be given to all HIV-exposed infants and children until HIV infection is excluded and to all HIV-infected infants and children	

CD4 can be used to monitor responses to treatment, although it is not essential. Absolute CD4 values also fluctuate with intercurrent illness and with physiological and test variability, so the trend over two or three repeated measurements is usually more informative than individual values.

PROPOSED HARMONIZED DEFINITIONS OF ADVANCED HIV/AIDS DISEASE FOR SURVEILLANCE IN CHILDREN AGED UNDER 15 YEARS

The surveillance of paediatric HIV/AIDS can provide estimates of the number of infants and children who require or may shortly require ART. AIDS case definitions for surveillance have until recently only been provided by CDC and include laboratory criteria. There has been confusion between surveillance definitions and clinical staging definitions.

These guidelines propose age-related clinical and immunological case definitions of advanced HIV/AIDS disease in infants and children for surveillance purposes. Age-related definitions are required because of the age-related changes in immunological markers. Advanced HIV disease for surveillance purposes should be reported only once for each individual.

BOX 3. ADVANCED HIV/AIDS DISEASE DEFINITIONS FOR SURVEILLANCE FOR INFANTS AND CHILDREN

Clinical stage 3 or stage 4 disease at any age
or
where CD4 is available[g], any clinical stage with

- **CD4 % <25% in children aged under 12 months**
- **CD4 % <20% in children aged 12 -59 months**
- **CD4 <350/mm^3 in children aged 5 years and above**

[g] CD4 based reporting remains optional

Recommendations for implementation

The following recommendations concern the use of the revised clinical staging and HIV/AIDS case definitions for clinical management and case-reporting.

- The revised clinical staging should be used to update and strengthen national guidelines so as to ensure that they provide clear guidance on which clinical and immunological stages require or are eligible for co-trimoxazole prophylaxis and ART treatment and support patient follow up.
- All infants, children, adolescents and adults with clinical stage 3 or stage 4 disease should be reported as having advanced HIV/AIDS disease. Such case reports can be used to calculate the burden of HIV/AIDS which immediately requires or will soon require ART. HIV/AIDS reporting for surveillance should preserve patient confidentiality in accordance with existing national or international recommendations.
- National HIV/AIDS programmes should be encouraged to support CD4-based HIV/AIDS case-reporting for surveillance.

The following additional recommendations concern actions facilitating the use of the interim clinical staging system and HIV/AIDS case definitions for surveillance.

Actions at the global and regional level:

- At the global level, WHO should publish details of the new HIV/AIDS clinical staging.
- At the global level, WHO should develop and disseminate guidelines on the use of the revised HIV clinical staging system and of the revised case definitions.
- At the regional level, WHO should organize intercountry meetings in order to introduce the revisions and to encourage rapid implementation in countries.
- WHO and CDC should incorporate the proposed revisions to surveillance definitions into surveillance training materials that are under development.
- WHO and CDC should provide technical support for the adoption and scaling-up for implementation of these revisions in countries.
- WHO and CDC should provide technical support for the development of systems for reporting AIDS-related deaths.
- WHO and CDC will hold a meeting during the fourth quarter of 2006 in order to review and update the clinical staging system and case definitions.

Actions at the national level

- Ministries of health and their partners should organize national consensus meetings on the proposed revisions, and should adapt and repackage the regional guidelines in accordance with existing national specifications in a way that is appropriate for use at different levels of health service delivery.
- Ministries of health should integrate the proposed revisions into existing guidelines and procedures for HIV/AIDS clinical management and HIV/AIDS case-reporting.
- Ministries of health should organize in-country training in order to build capacity for the implementation of the revisions, including integration into the curricula of relevant professional and non-professional training institutions.
- Ministries of health should produce simplified wall charts, laminated desk-top guides, pocket guides and other materials facilitating the use of the recommended revisions.
- Ministries of health should establish systems for HIV/AIDS reporting in children at a few sentinel sites where children are seen to improve and strengthen the provision of information on children with HIV/AIDS.
- Ministries of health should ensure that reliable systems are in place for reporting AIDS-related deaths.

Annex 1.

WHO clinical staging for adults and adolescents: presumptive and definitive criteria for recognizing HIV/AIDS-related clinical events

(For use in adults and adolescents aged 15 years and above with laboratory evidence of HIV infection.)

Clinical event	Presumptive diagnosis	Definitive diagnosis
Primary HIV infection		
Asymptomatic		Detectable core P24 antigen and high blood HIV RNA, profound temporary lymphopenia and other transient blood abnormalities may occur. Not usually HIV antibody-positive until after symptoms. Seroconversion from HIV Ab-negative to Ab-positive.
Acute retroviral syndrome	Acute febrile illness 2–4 weeks post-exposure, often with lymphadenopathy, pharyngitis and skin manifestations.	
Clinical Stage 1		
Asymptomatic	No symptoms reported and no signs on examination.	Not required.
Persistent generalized lymphadenopathy (PGL)	Swollen or enlarged lymph nodes >1 cm, in two or more non-contiguous sites, excluding inguinal nodes, in absence of known cause.	Not required but can be confirmed by histology (germinal centre hyperplasia, lymph node structure preserved).
Clinical Stage 2		
Moderate unexplained weight loss (<10% of presumed or measured body weight)	Reported weight loss but no obvious thinning of face or body.	Confirmed by documented weight loss.
Recurrent presumed bacterial RTI (two or more in any six-month period)	Symptom complex, e.g. unilateral face pain with nasal discharge (sinusitis) or painful swollen eardrum (otitis media), cough with purulent sputum (bronchitis), sore throat (pharyngitis). Two or more documented occurrences of antibiotic- responsive URTI.	Not required but may be confirmed by laboratory studies where available, e.g. culture of suitable body fluid.

Clinical event	Presumptive diagnosis	Definitive diagnosis
Herpes zoster	Painful rash of small fluid-filled blisters in distribution of a nerve supply, can be haemorrhagic on erythematous background, and does not cross midline. Current or in the last two years. Severe or frequently recurrent herpes zoster is usually associated with more advanced HIV disease.	Not required.
Angular cheilitis	Splits or cracks on lips at the angle of the mouth with depigmentation, usually responds to antifungal treatment but may recur. Also common in nutritional deficiency, e.g. of B vitamins.	Not required.
Recurrent oral ulcerations occurring twice or more in six months	Aphthous ulceration, typically with a halo of inflammation and a yellow-grey pseudomembrane.	Not required.
Papular pruritic eruptions	Papular pruritic vesicular lesions. Also common in uninfected adults. Note: scabies and obvious insect bites should be excluded.	Not required.
Seborrhoeic dermatitis	Itchy scaly skin condition, particularly affecting scalp, face, upper trunk and perineum. Also common in uninfected adults.	Not required.
Fungal nail infections of fingers	Fungal paronychia (painful red and swollen nail bed) or onycholysis (separation of the nail from the nail bed) of the fingernails. Also common in uninfected adults. Proximal white subungual onchomycosis is uncommon without immunodeficiency.	Not required but confirmed by culture of nail scrapings.

Clinical Stage 3		
Clinical event	**Presumptive diagnosis**	**Definitive diagnosis**
Severe unexplained weight loss (more than 10% of presumed or measured body weight)	Reported weight loss without trying, and noticeable thinning of face, waist and extremities.	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.	Not required but confirmed if three or more stools observed and documented as unformed, and two or more stool tests reveal no pathogens on microscopy and culture and no faecal leukocytes.
Unexplained persistent fever (intermittent or constant and for longer than one month)	Reports of fever or night sweats for more than one month, either intermittent or constant with reported lack of response to antibiotics or antimalarials. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Not required but confirmed if documented fever >37.5 °C with negative blood culture, negative Ziehl-Nielsen (ZN) stain, negative malaria slide, normal or unchanged chest X-ray (CXR) and no other obvious foci of disease.
Oral candidiasis	Persistant creamy white to yellow 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 (erythematous form), not responding to local antifungal treatment.	Not required.
Oral hairy leukoplakia	Fine small linear patches on lateral borders of the tongue, generally bilaterally, which do not scrape off.	Not required.

Clinical event	Presumptive diagnosis	Definitive diagnosis
Pulmonary TB (current or in last two years)	Chronic (symptoms lasting three or more weeks) productive cough, haemoptysis, shortness of breath, weight loss, fever, night sweats and fatigue, no resolution of symptoms with standard broad-spectrum antibiotics, positive ZN stain. Response to standard anti-TB treatment in one month. Note: TB diagnosis and treatment should follow national or international guidelines. CD4 should be used where possible to guide therapy; very low CD4 may require urgent ART.	Not required but confirmed by positive sputum culture.
Severe presumed bacterial infection (e.g. pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia)	Fever accompanied by specific symptoms or signs that localize infection, and response to antibiotic.	Not required but confirmed by bacteria isolated from appropriate clinical specimens.
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.	Not required.
Unexplained anaemia (<8g/dl), neutropenia (<1000/mm^3) or thrombocytopenia(<50000/mm^3) for more than one month	No presumptive clinical diagnosis.	Diagnosed on laboratory testing and not explained by other non-HIV conditions. Not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in relevant national treatment guidelines, WHO guidelines or other relevant guidelines.

Clinical Stage 4

Clinical event	Presumptive diagnosis	Definitive diagnosis
HIV wasting syndrome	Unexplained weight loss greater than 10% of body weight and visible thinning of face, waist and extremities; plus either unexplained chronic diarrhoea (lasting more than one month) or unexplained prolonged or intermittent fever for one month or more.	Confirmed by documented weight loss without trying; plus documented unformed stools negative for pathogens; negative for modified ZN; or Documented temperature of 37.5 °C or more on occasions with no obvious foci of disease, negative blood culture, negative malaria slide and normal or unchanged CXR.
Pneumocystis pneumonia	Dry cough, progressive shortness of breath, especially on exertion, with cyanosis, tachypnoea and fever, response to high-dose co-trimoxazole +/– prednisolone. Bilateral crepitations on auscultation with or without reduced air entry. CXR may show typical bilateral interstitial infiltrate with bat wing appearance.	Not required but confirmed by: microscopy of induced sputum or bronchoalveolar lavage (BAL), or histology of lung tissue.
Recurrent severe or radiological bacterial pneumonia (two or more episodes within one year)	Two episodes of fever, wet cough, fast and difficult breathing and chest pain. Consolidation on clinical examination and CXR. Response to antibiotics.	Not required but confirmed by culture or antigen test from appropriate specimen.
Chronic herpes simplex virus (HSV) infection (orolabial, genital or anorectal of more than one month, or visceral of any duration)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by recurrent HSV infection reported for more than one month. History of previous episodes. Scarring from previous episodes may be evident.	Not required for mucocutanoues HSV but required for visceral HSV. Suggestive symptoms of organ damage, e.g. bronchitis, pneumonitis, oesophagitis, colitis, encephalitis, supported by histology or culture.

Clinical event	Presumptive diagnosis	Definitive diagnosis
Oesophageal candidiasis	Chest pain and dysphagia (difficulty in swallowing), odynophagia (pain on swallowing food and fluids), or retrosternal pain worse on swallowing (food and fluids) +/– oral *Candida*. Responds to antifungal treatment.	Not required but confirmed by macroscopic appearance at endoscopy or bronchoscopy, microscopy or histology.
Extrapulmonary/disseminated TB	Systemic illness usually with prolonged fever, night sweats, weakness and weight loss. Clinical features of organs involved, e.g. focal lymphadenopathy, cold abscess, sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis, lupus vulgaris. CXR may reveal diffuse uniformly distributed small miliary shadows Response to standard anti-TB treatment in one month.	Not required but confirmed by acid-fast bacilli (AFBs) seen in microscopy of cerebrospinal fluid (CSF), effusion, lymph node aspirate, urine, etc. Mycobacteria TB isolated from blood culture or any appropriate specimen except sputum or BAL. Histology (e.g. pleural or pericardial biopsy). CXR may show interstitial infiltrates. Lymphocytic CSF with typical abnormalities, no bacterial growth and negative cryptococcal antigen (CRAG).
Kaposi's sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise colour, skin lesions that usually develop into nodules. Can be confused clinically with bacillary angiomatosis, non-Hodgkin lymphoma and cutaneous fungal or bacterial infections.	Not required but may be confirmed by : • typical red-purple lesions seen on bronchoscopy or endoscopy; • dense masses in lymph nodes, viscera or lungs by palpation or radiology; • histology.

Clinical event	Presumptive diagnosis	Definitive diagnosis
CMV (retinitis or CMV infection of an organ other than liver, spleen or lymph nodes)	Retinitis only. CMV retinitis may be diagnosed by experienced clinicians. Progressive floaters in field of vision, light flashes and scotoma. Typical eye lesions on serial fundoscopic examination; discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Definitive diagnosis required for other sites. Symptoms and signs of other organ involvement, e.g. pneumonitis, pancreatitis, colitis, cholecystitis, not responding to co-trimoxazole or antibiotics. Histology. CSF polymerase chain reaction (PCR).
CNS toxoplasmosis	Fever, headache, focal neurological signs, convulsions. Rapid response (within 10 days) to high-dose co-trimoxazole, or pyrimethamine and sulphadiazine or clindamycin.	Not required but confirmed by computed tomography (CT) scan showing single/multiple lesions with mass effect/ enhancing with contrast. If lumbar puncture (LP) performed, CSF nonspecific or normal. Resolution of findings after treatment if patient survives.
Cryptococcal meningitis or other extrapulmonary *Cryptococcus* infection	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion, behavioural changes. Responds to antifungal therapy.	Confirmed by CSF microscopy (India ink or Gram stain). Serum or CSF CRAG-positive or culture-positive.
HIV encephalopathy	Clinical finding of 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 which might explain the findings. LP should be conducted to exclude other infectious causes.	Recommended to confirm clinical features and exclude other causes including neurosyphilis: • brain scan by means of CT or magnetic resonance imaging (MRI) with • LP.

Clinical event	Presumptive diagnosis	Definitive diagnosis
Disseminated non-tuberculous mycobacteria infection	No presumptive diagnosis.	Nonspecific clinical symptoms including progressive weight loss, fever, anaemia, night sweats, fatigue or diarrhoea. Severe anaemia and/or elevated alkaline phosphatase and/or (in case of diarrhoea) persisting AFB in the stool in spite of TB therapy. Plus: Culture of atypical mycobacteria species from stool, blood, body fluid or other body tissue, excluding lung.
PML	No presumptive diagnosis.	Progressive focal neurological signs without headache or fever, cortical blindness, cerebellar signs, dementia. Confirmed by consistent MRI or CT scan, and biopsy. Viral PCR for Jacob Creutzfeldt virus.
Candidiasis of trachea, bronchi, lungs	No presumptive diagnosis.	Confirmed by symptoms, clinical signs suggestive of organ involvement and/or macroscopic appearance at bronchoscopy. Histology or cytology, or microscopy of specimen from tissue.
Cryptosporidiosis (with diarrhoea lasting more than one month)	No presumptive diagnosis.	Chronic diarrhoea, often profuse and watery, with weight loss, ± abdominal pain, nausea, vomiting; confirmed by modified ZN microscopic examination of stool. Stools observed to be unformed with organism visualized in stool sample.
Isosporiasis	No presumptive diagnosis.	Watery diarrhoea, cramps and weight loss. Symptoms usually indistinguishable from those of cryptosporidiosis. Isosporiaisis responds to high-dose cotrimoxazole.

Clinical event	Presumptive diagnosis	Definitive diagnosis
Any disseminated mycosis (e.g. coccidiomycosis, histoplasmosis, penicilliosis)	No presumptive diagnosis.	Clinical symptoms nonspecific, e.g. skin rash, cough, shortness of breath, fever, anaemia, weight loss. CXR: infiltrates or nodules. Confirmed by direct microscopy. Histology: usually granuloma formation. Isolation: antigen detection from affected tissue. Skin lesion culture or microscopy positive.
Recurrent non-typhoidal salmonella septicaemia (two or more episodes in last year)	No presumptive diagnosis.	Nonspecific symptoms: fever, sweats, headaches, weight loss, diarrhoea and anorexia. Confirmed by blood culture.
Lymphoma (cerebral or B cell non-Hodgkin)	No presumptive diagnosis.	Symptoms consistent with lymphoma: lymphadenopathy, splenomegaly, pancytopenia, testicular or lung mass lesions; no response clinically to antitoxoplasma or anti-TB treatment. CNS imaging: at least one lesion with mass effect on brain scan; histology.
Invasive cervical carcinoma	No presumptive diagnosis.	Persistent vaginal discharge, postcoital or intermenstrual bleeding unresponsive to appropriate antibacterial or antifungal treatment; cervical lesions visualized. Histology. Cytology, but not carcinoma in situ.
Visceral leishmaniasis	No presumptive diagnosis.	Suggestive symptoms: malaise, chronic fever, hepatosplenomegaly, pancytopenia . Amastigotes visualized or cultured from any appropriate clinical specimen.

Clinical staging events as a tool to guide clinical management in adults and adolescents (pre-ART and ART follow-up care)

The same criteria for presumptive and definitive diagnosis apply

Clinical events pre-ART	Action
Stage 1	No action required
Stage 2	Requires cotrimoxazole
Stage 3 Or Stage 4	Requires cotrimoxazole if not already started Consider ART First ever occurrence of a stage 3 or 4 event requires notification for surveillance purposes
Clinical events on ART	**Action**
Stage 1	Consider interruption of cotrimoxazole if stable on ART for 6 months or more.
New or recurrent : Stage 2 or stage 3	Check adherence Treat and manage condition Restart cotrimoxazole Should alert the provider to the possibility of poor adherence or failing response to treatment.
New or recurrent Stage 4	Check adherence Treat and manage condition Restart cotrimoxazole Consider regimen switch Suggest failure to respond to ART, possibly because of true failure of the regimen and/or poor adherence.

Annex 2.

WHO clinical staging for infants and children: presumptive and definitive criteria for recognizing HIV/AIDS-related clinical events

(For use in infants and children aged under 15 years with laboratory evidence of HIV infection: HIV antibody in those aged 18 months and above, DNA or RNA virological testing or P24 antigen testing for those aged under 18 months.)

Highlighted events are still awaiting further data for clarification of definitions

Clinical event	Clinical diagnosis	Definitive diagnosis
Clinical Stage 1		
Asymptomatic	No symptoms reported and no signs on examination.	Not required.
PGL	Swollen or enlarged lymph nodes >1 cm at two or more non-contiguous sites, without known cause.	Not required. (Histology; germinal centre hyperplasia, lymph node structure preserved.)
Clinical Stage 2		
Hepatosplenomegaly	Unexplained enlarged liver or spleen.	Not required.
Papular pruritic eruptions	Persistent papular pruritic vesicular lesions; scabies should be excluded.	Not required.
Seborrhoeic dermatitis	Itchy scaly skin condition particularly affecting scalp, face, upper trunk and perineum. Also common in uninfected children and in babies.	Not required.
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.	Culture of nail scrape.

Clinical event	Clinical diagnosis	Definitive diagnosis
Angular cheilitis	Splits or cracks on lips at the angle of the mouth with depigmentation, usually responding to antifungal treatment but may recur. Also common in nutritional deficiency, e.g. of B vitamins.	Not required.
LGE	Erythematous band that follows the contour of the free gingival line; may be associated with spontaneous bleeding. Uncommon in HIV-uninfected children.	Not required.
Human papilloma virus infection (extensive facial, more than 5% of body area or disfiguring)	Characteristic skin lesions; warts; small fleshy grainy bumps, often rough, on sole of feet are flat (plantar warts). Also common in uninfected children.	Not required.
Molluscum contagiosum infection (extensive facial, more than 5% of body area or disfiguring)	Characteristic skin lesions: small flesh-coloured, pearly or pink, dome-shaped or umbilicated growths, may be inflamed or red. Also common in uninfected children.	Not required.
Recurrent oral ulcerations (two or more in six months)	Aphthous ulceration, typically with a halo of inflammation and a yellow-grey pseudomembrane.	Not required.
Parotid enlargement	Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause, usually painless. Uncommon in HIV-uninfected children.	Not required.

Clinical event	Clinical diagnosis	Definitive diagnosis
Herpes zoster	Painful rash with fluid-filled blisters, dermatomal distribution, can be haemorrhagic on erythematous background, and can become large and confluent. Does not cross the midlines. Note: severe persistent herpes zoster may have worse prognosis.	Viral culture, histology, EM of lesion fluid.
Recurrent RTI (twice or more in any six-month period)	Symptom complex, e.g. fever with unilateral face pain and nasal discharge (sinusitis) or painful swollen eardrum (otitis media), sore throat with productive cough (bronchitis), sore throat (pharyngitis) and barking croup-like cough (LTB). Persistent or recurrent ear discharge.	Not required but may be confirmed by laboratory or X-ray studies where available, especially for sinus, and culture or appropriate specimens.
Clinical Stage 3		
Unexplained moderate malnutrition (very low weight-for-age: up to –2 standard deviations (SDs) *(3, 4)*; not responding adequately to standard therapy,	Unexplained weight loss or failure to gain weight not explained by poor or inadequate feeding or other infections , and not adequately responding within two weeks to standard management ,	Documented loss of body weight, failure to gain weight on standard management and no other cause identified during investigation.
Unexplained persistent diarrhoea (14 days and above)	Unexplained persistent diarrhoea (loose or watery stool, three or more times daily), not responding to standard treatment.	Not required, but confirmed if stools observed and documented as unformed. Culture and microscopy reveal no pathogens.
Unexplained persistent fever (intermittent or constant and for longer than one month)	Reports of fever or night sweats for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or antimalarials. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Not required but confirmed if documented fever of >37.5 °C with negative blood culture, negative malaria slide and normal or unchanged CXR, and no other obvious foci of disease.

Clinical event	Clinical diagnosis	Definitive diagnosis
Oral candidiasis (outside first 6 weeks of live)	Persistent creamy white to yellow soft small plaques on red or normally coloured mucosa, easily scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender, responding to antifungal treatment.	Microscopy or culture.
Oral hairy leukoplakia	Fine small linear patches on lateral borders of tongue, generally bilaterally, which do not scrape off.	Not required.
Pulmonary TB	Nonspecific symptoms, e.g. chronic cough, fever, night sweats, anorexia and weight loss. In the older child also productive cough and haemoptysis. Response to standard anti-TB treatment in one month. Note: diagnosis should be made in accordance with national guidelines.	Abnormal CXR plus positive sputum smear, or culture.
Severe recurrent presumed bacterial pneumonia	Cough with fast breathing, chest indrawing, nasal flaring, wheezing, and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics.	Not required but confirmed by isolation of bacteria from appropriate clinical specimens.
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.	Not required.

Clinical event	Clinical diagnosis	Definitive diagnosis
Symptomatic LIP	No presumptive clinical diagnosis.	CXR: bilateral reticulonodular interstitial pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Oxygen saturation persistently <90%. May present with cor pulmonale and may have increased exercise-induced fatigue. Frequently confused with miliary TB.
Chronic HIV-associated lung disease (including brochiectasis)	No presumptive clinical diagnosis.	History of cough productive of copious amounts of purulent sputum, with or without clubbing, halitosis, and crepitations and/or wheezes on auscultation; CXR may show honeycomb appearance (small cysts) and/or persistent areas of opacification and/or widespread lung destruction, with fibrosis and loss of volume. CT scan of chest may be used to confirm.
Unexplained anaemia (<8g/dl), and or neutropenia (<500/ mm^3) and or thrombocytopenia (<50 000/ mm^3) for longer than one month	No presumptive clinical diagnosis.	Diagnosed on laboratory testing, not explained by other non-HIV conditions, or not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in IMCI.

Clinical Stage 4		
Clinical event	**Clinical diagnosis**	**Definitive diagnosis**
Unexplained severe wasting 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. Characterized by: visible severe wasting of muscles, with or without oedema of both feet, and/or weight-for-height of –3 SDs, as defined by WHO IMCI guidelines.	Documented loss of weight or failure to gain weight.
Pneumocystis pneumonia (PCP)	Dry cough, progressive shortness of breath, cyanosis, tachypnoea and fever; chest indrawing or stridor. Response to high-dose co-trimoxazole +/– prednisolone. (Severe or very severe pneumonia as in IMCI). Usually of sudden onset and very severe in infants under six months of age .	Microscopy of induced sputum or BAL, or histology of lung tissue. CXR shows typical bilateral perihilar diffuse infiltrates.
Recurrent severe presumed bacterial infection (two or more episodes in one year), e.g. meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics.	Not required but confirmed by bacteria isolated from appropriate clinical specimens and includes recurrent non-typhoidal salmonella septicaemia.
Chronic herpes simplex virus infection (chronic orolabial or intraoral lesions of more than one month or visceral of any duration)	Severe and progressive painful orolabial or skin lesions attributable to recurrent HSV reported for more than one month. History of previous episodes. Scarring from previous episodes may be evident.	Visceral HSV requires confirmation. Suggestive symptoms of organ damage, e.g. bronchitis, pneumonitis, oesophagitis, colitis, encephalitis, supported by histology or culture.

Clinical event	Clinical diagnosis	Definitive diagnosis
Oesophageal candidiasis	Chest pain and dysphagia (difficulty in swallowing), odynophagia (pain on swallowing food and fluids), or retrosternal pain worse on swallowing (food and fluids) +/– oral Candida. Responds to antifungal treatment. May be difficult to detect in young children. Suspect if oral Candida observed and if refusal occurs or if there are difficulties or crying when feeding.	Not required but confirmed by macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology.
Extrapulmonary TB	TB not limited to lungs. Systemic illness usually with prolonged fever, night sweats, weight loss. Clinical features of organs involved, e.g. focal lymphadenopathy, cold abscess, sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis, lupus vulgaris. Responds to standard anti-TB therapy. Note: simple lymph gland extrapulmonary TB may have a better prognosis.	Mycobacterium TB isolated form blood culture or other specimen except sputum or BAL. Positive AFB on microscopy or culture on relevant specimens. Biopsy and histology. X-ray.
Kaposi's sarcoma	Typical appearance in skin or oropharynx, initially flat patches with a pink or blood-bruise colour, usually developing into nodules.	Typical red-purple lesions seen on bronchoscopy or endoscopy. Biopsy.

Clinical event	Clinical diagnosis	Definitive diagnosis
CMV retinitis and CMV infection of organs other than liver, spleen or lymph nodes, with onset at age over 1 month	No presumptive clinical diagnosis. Clinically, disease suspected if there are 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.	Symptoms and signs of organ involvement, e.g. typical eye lesions on fundoscopy or pneumonitis not responding to co-trimoxazole or antibiotics. Histology or detection of antigen from affected tissue.
CNS toxoplasmosis (outside the neonatal period)	Fever, headache, focal neurological signs, convulsions. Response to high-dose co-trimoxazole or pyrimethamine and sulphadiazine or clindamycin.	CT scan showing single/ multiple lesions with mass effect/enhancing with contrast. CSF results normal or nonspecific. Resolution of findings after treatment if patient survives.
Cryptococcal meningitis	Meningitis: usually subacute, fever with increasing severe headache, irritability, meningism, confusion, behavioural changes. Responds to antifungal therapy	CSF: microscopy (India ink or Gram stain) Positive serum CRAG test.
HIV encephalopathy	At least one of the following, progressing over at least two months in the absence of another illness: • gross discrepancy between the actual and developmental age, failure to attain, or loss of, developmental milestones, loss of intellectual ability; or • progressive impaired brain growth demonstrated by stagnation of head circumference; or • acquired symmetric motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia, gait disturbances.	Brain CT scan or MRI to exclude other causes.

Clinical event	Clinical diagnosis	Definitive diagnosis
Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, penicilliosis)	No presumptive clinical diagnosis.	Organ-specific and nonspecific symptoms, e.g. may cause skin rash, or cough, shortness of breath, fever, anaemia, weight loss. Diagnosis confirmed by direct microscopy, histology or antigen detection in relevant specimens. CXR may show infiltrates or nodules.
Candidiasis of the trachea, bronchi or lungs	No presumptive clinical diagnosis.	Macroscopic appearance at endoscopy. Microscopy and culture of specimen from endoscopic tissue.
Disseminated mycobacteriosis, other than TB	No presumptive clinical diagnosis.	Nonspecific clinical symptoms including progressive weight loss, fever, anaemia, night sweats, fatigue or diarrhoea; plus culture of atypical mycobacteria species from stool, blood, body fluid or other body tissue, excluding lung.
Cryptosporidiosis (with diarrhoea lasting more than one month)	No presumptive clinical diagnosis.	Chronic diarrhoea, often profuse and watery, with weight loss, ± abdominal pain, nausea, vomiting, but usually mild or no fever. Confirmed by microscopic examination on modified ZN stain.
Isosporiasis	No presumptive clinical diagnosis.	Chronic diarrhoea, often profuse and watery, with weight loss, ± abdominal pain, nausea, vomiting. Isosporiasis responds to high-dose co-trimoxazole.

Clinical event	Clinical diagnosis	Definitive diagnosis
Cerebral or B cell non-Hodgkin lymphoma	No presumptive clinical diagnosis.	Symptoms consistent with lymphoma: lymphadenopathy, hepatosplenomegaly, pancytopenia, besides other nonspecific or organ-specific symptoms. No response clinically to antitoxoplasma or anti-TB treatment. CNS imaging: at least one lesion with mass effect on brain scan, and no response to antitoxoplasma and anti-TB treatment. Cytology. Histology. Response to chemotherapy.
PML	No presumptive clinical diagnosis.	Progressive focal neurological signs without headache or fever. Cortical blindness and cerebellar signs. Convulsions are rare. MRI or CT scan
Acquired HIV-associated rectal fistula, including rectovaginal fistula		Further information and evidence relating to this condition and its definition are being sought. Case reports from African countries suggest that it is highly specific to HIV and that the prognosis is poor. Clinical features suggestive, exclusion of other causes, faecal discharge through the vagina or urethra, or urine discharge through the rectum in an HIV-infected child usually following an episode of diarrhoea.

Clinical event	Clinical diagnosis	Definitive diagnosis
HIV-associated nephropathy	No presumptive clinical diagnosis.	Further information and evidence relating to this condition and its definition are being sought. Symptoms and signs suggestive of renal disease, with no other obvious cause identified. Early morning urine protein/creatinine ratio of >200mg/mmol in absence of a urinary tract infection and absence of an axillary temperature of 38.0 °C. Renal biopsy and histology.
HIV-associated cardiomyopathy	No presumptive clinical diagnosis.	Further information and evidence relating to this condition and its definition are being sought. Exclusion of other causes of congestive cardiac failure. The left ventricle and right ventricle are enlarged. The end-diastolic and end-systolic dimensions of the left or right ventricle are increased (2 SDs from the mean for body surface area), with a reduced fractional shortening and ejection fraction (2 SDs from the mean). Echocardiography check.

Clinical staging events as a tool to guide clinical management for infants and children (pre-ART and ART follow-up care)

The same criteria for presumptive and definitive diagnosis apply

Clinical events pre-ART	Action
Stage 1	May require cotrimoxazole
Stage 2	Requires cotrimoxazole
Stage 3 Or stage 4	Requires cotrimoxazole if not already started Consider ART Notification for surveillance purposes of first ever occurrence of a stage 3 or 4 event.
Clinical events on ART	**Action**
Stage 1	Currently not advised to discontinue cotrimoxazole in children under 5 years.
New or recurrent : Stage 2 or stage 3	Check adherence, provide support Treat and manage condition Should alert the provider to the possibility of poor adherence or failing response to treatment.
New or recurrent Stage 4	Check adherence, provide support Treat and manage condition Consider ART regimen switch Suggests failure to respond to ART, possibly because of true failure of the regimen and/or poor adherence.

Key References

1. http://www.who.int/hiv/strategic/surveillance/definitions/en/

2. http://www.who.int/3by5/publications/documents/arv_guidelines/en/

3. http://www.who.int/child-adolescent-health/publications/child_health/who_fch_cah_00.1.htm

4. http://www.who.int/nut/documents/manage_severe_malnutrition_eng.pdf

5. Oral Manifestations of HIV in the Developing and Developed World. Proceedings and abstracts of the 4th International Workshop on Oral Manifestations of HIV Infection. Oral Dis. 2002; 8 Suppl 2:6-8.

6. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. The Lancet 2004; 364:1236-1243. Marie Louise Newell, Hoosen Coovadia, Marjo Cortina-Borja, Nigel Rollins, Philippe Gaillard & Francois Dabis. Available at :
http://www.thelancet.com/journals/lancet/article/PIIS0140673604171407/fulltext

7. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomized placebo-controlled trial C Chintu b, GJ Bhat b, AS Walker a, V Mulenga b, F Sinyinza b, K Lishimpi b, L Farrelly , N Kaganson , A Zumla , SH Gillespie , AJ Nunn and DM Gibb on behalf of the CHAP trial team. Available at:
http://www.thelancet.com/journals/lancet/article/PIIS0140673604174424/fulltext

8. PENTA guidelines for the use of antiretroviral therapy, 2004 M Sharland, S Blanche, G Castelli, J Ramos and DM Gibb on behalf of the PENTA Steering Committee. Available at http://www.ctu.mrc.ac.uk/penta/guidelin.pdf

9. US The Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children.Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection .March 24, 2005. Available at: http://aidsinfo.nih.gov/guidelines/default_db2.asp?id=51

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