

Staging, classification and monitoring of HIV/AIDS

(Adopted from HIV Manual 2007)

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After acute infection, HIV disease enters a chronic life-long state of infection, which is characterised by a complex interplay between the virus and the host. With a variable asymptomatic duration, the final outcome for most, if not all, of the patients is the development of major complications followed by death, in its natural course of progression. Without effective treatment, clinical morbidity and mortality associated with HIV is the biggest medical problem for infected patients. Conceivably the spectrum of clinical presentations varies with the degree of immunodeficiency. Like other chronic disease conditions, such as cancers, different classification systems have been proposed. The purposes of such can be multi-fold, including assessment of prognosis, guidance to treatment initiation and disease surveillance. As such, classification of HIV disease appears to serve the dual role of supporting clinical management and the public health role of determining societal impacts.

Classification and surveillance definitions of HIV/AIDS

In as early as 1982, before the discovery of its causative agent, the US Centers for Disease Control and Prevention (CDC) had developed a case definition for AIDS.¹ The diagnosis was based on the detection of the "presence of diseases moderately indicative of underlying cellular immunodeficiency in a person without recognised cause", the latter referring to such examples as neoplastic disease and immunosuppressive therapy. In 1984, the term AIDS related complex (ARC) was coined to describe the symptoms of immunodeficiency that were being recognised with increased frequency in persons at risk for AIDS. They were unexplained generalised lymphadenopathy, idiopathic thrombocytopaenia, oral candidiasis, herpes zoster infection, and a constitutional wasting syndrome. This term is now obsolete.

In 1984-85, serological testing became available to confidently provide for the diagnosis of HIV in infected persons. In 1986,² CDC defined a classification system to accommodate the increased number of clinical manifestations that had become associated with chronic HIV infection. This new system classified HIV infection into acute infection, asymptomatic infection, persistent generalised lymphadenopathy, and certain other categories. In 1987, CDC expanded its definition of AIDS in order to track more effectively the morbidity associated with HIV infection. This was revised and further expanded in 1993.³ Progression of disease is indicated by the detection of specifically defined opportunistic conditions. The CD4 count provides another marker for characterising the clinical stages. Generically, AIDS has since been defined as the laboratory diagnosis of HIV infection plus either an opportunistic infection or a CD4 count of below 200/ μ L.

Hong Kong has adopted largely the CDC 1993 classification⁴ (Box 4.1), but with the following modifications: (a) disseminated penicilliosis has been added as one AIDS-defining illness (ADI); (b) pulmonary or cervical lymph node tuberculosis is included only if CD4 <200/ μ L; (c) a CD4 <200/ μ L without any ADI is not counted as AIDS. This latter provision of not classifying AIDS based on CD4 count alone is similar to the European approach.⁵ Among the reasons for the deviation, the Hong Kong and European approaches have resulted as, unlike US, access to medical and social care is not conditional upon meeting the AIDS criteria. On the other hand, modification for *Mycobacterium tuberculosis* and inclusion of *Penicillium marneffe* have been made basing on the uniqueness of local disease epidemiology.

Box 4.1 Classification for HIV infection and surveillance case definitions for AIDS in adults and adolescents in Hong Kong (*Scientific Committee on AIDS. Classification system for HIV infection and surveillance case definition for AIDS in adolescents and adults in Hong Kong. 1995, adapted from US CDC. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992;41(RR-17):1-19.*)

CD4 categories	(A) Asymptomatic, acute (primary) HIV or PGL	(B) Symptomatic, not (A) or (C) conditions	(C) AIDS-indicator conditions
(1) $\geq 500/\mu\text{L}$	A1	B1	C1
(2) 200-499/ μL	A2	B2	C2
(3) $<200/\mu\text{L}$	A3	B3	C3*
Category A	Asymptomatic HIV infection Persistent generalised lymphadenopathy Acute HIV infection with accompanying illness or history of acute HIV infection		
Category B (includes but not limited to)	Bacillary angiomatosis Candidiasis, oropharyngeal (thrush) Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy Cervical dysplasia (moderate or severe)/cervical carcinoma in situ Constitutional symptoms, such as fever (38.5°C) or diarrhoea lasting >1 month Hairy leukoplakia, oral Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome Idiopathic thrombocytopenia Listeriosis Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess Peripheral neuropathy		
Category C AIDS indicator conditions	Candidiasis of bronchi, trachea, or lungs Candidiasis, oesophageal Cervical cancer, invasive Coccidioidomycosis, disseminated or extrapulmonary Cryptococcosis, extrapulmonary Cryptosporidiosis, chronic intestinal (>1 month's duration) Cytomegalovirus disease (other than liver, spleen or nodes) Cytomegalovirus retinitis (with loss of vision) Encephalopathy, HIV-related Herpes simplex: chronic ulcer(s) (>1 month's duration); or bronchitis, pneumonitis, or oesophagitis Histoplasmosis, disseminated or extrapulmonary Isosporiasis, chronic intestinal (>1 month's duration) Kaposi's sarcoma Lymphoma, Burkitt's (or equivalent term) Lymphoma, primary, of brain ** <i>Mycobacterium tuberculosis</i> ; extrapulmonary or pulmonary/ cervical lymph node (only if CD4 $<200/\mu\text{L}$) Pneumonia, recurrent **Penicilliosis, disseminated <i>Mycobacterium</i> , other species or unidentified species, disseminated or extrapulmonary <i>Pneumocystis carinii</i> pneumonia Progressive multifocal leukoencephalopathy <i>Salmonella</i> septicemia, recurrent Toxoplasmosis of brain Wasting syndrome due to HIV		

*A low CD4 alone is not an AIDS defining condition in Hong Kong for surveillance purpose

**AIDS defining conditions adopted in Hong Kong (see text for explanation)

The classification of a patient as having AIDS serves primarily a public health function. The same classification schema is often used in comparing the clinical characteristics of cohorts. Albeit a useful clinical staging tool, there are a number of limitations. First, the various ADI each carries different prognostic implications. For instance, pulmonary tuberculosis and Kaposi's sarcoma may occur at a relatively high CD4 count with good prognosis, compared to cytomegalovirus diseases and penicilliosis against the background of severe immunodeficiency. Second, while staging is not reversible by definition, the progressively downhill course of AIDS patients can now be completely reversed with HAART.^{6,7} Prior AIDS does not adversely affect new AIDS development or non-accidental death after HAART, an observation that has been confirmed locally.⁸ As a consequence, disease course depends on access to HIV care more than natural progression nowadays.

There are other HIV classification systems. The Walter Reed staging system of HIV infection⁹ classifies patients on the basis of CD4 counts, skin-test responsiveness, lymphadenopathy, oral candidiasis and opportunistic infections. It has limitations with respect to predictive value. The World Health Organization (WHO) has also developed a case definition for AIDS that can be used in developing countries where sophisticated diagnostic technologies are not available.

CD4 count as a surrogate of immunosuppression - a local perspective

Clinical conditions that arise from immune deficiency are highly diversified, depending on which organ/system is involved and the stage of the disease. In general, comparatively minor diseases may precede ADI. Classical examples of pre-AIDS illnesses include mucocutaneous conditions such as herpes zoster, oral thrush and oral hairy leukoplakia, the occurrence of which predict faster disease progression. Opportunistic infection is the commonest cause of ADI, followed by malignancies and HIV specific conditions. Overall, the respiratory system, gastrointestinal system and central nervous systems (Chapters 18, 19 and 20) are common sites of complications in HIV/AIDS.

As a rule CD4 count is the single most important tell-tale laboratory marker, the level of which correlates with the occurrence of the spectrum of opportunistic complications. The US CDC reported that over 80% of patients with ADIs (including *Pneumocystis carinii* pneumonia, oesophageal candidiasis, immunoblastic lymphoma and HIV encephalopathy) occur at a CD4 count $<200/\mu\text{L}$; and conditions like CMV retinitis, cerebral toxoplasmosis, disseminated *Mycobacterium avium intracellulare* and extrapulmonary cryptococcosis do not usually manifest until CD4 is below 50-100/ μL .¹⁰ Nevertheless, the CD4 cell level of healthy Chinese adults appears to be lower than that of Caucasians, which could have bearing in disease staging, monitoring and even treatment. In a local study to establish lymphocyte subpopulations reference ranges in healthy Chinese adults, the mean were 725 cells/ μL and 589 cells/ μL , with a 95% reference range of 292-1366 cells/ μL and 240-1028 cells/ μL , for CD4 and CD8 T lymphocytes respectively.¹¹ The mean CD4 and CD8 percentages were low when compared with healthy Caucasian persons.¹² In a separate study that looked at natural immunologic and clinical disease progression before the HAART era, it also appeared that major opportunistic complications occurred at somewhat lower CD4 levels in Chinese patients.¹³ From a study on the clinical course of events and CD4 changes in a cohort of local patients again in the pre-HAART era, a different set of CD4 criteria was considered to stage HIV disease in Chinese.¹⁴ The study suggested that a CD4 of $<100/\mu\text{L}$ (6%) and 100-220/ μL (6-12%) corresponded to $<200/\mu\text{L}$ ($<14\%$) and 200-500/ μL (14-28%) respectively according to US CDC staging.

Assessment and monitoring of a newly diagnosed HIV positive individual

Thorough assessment of a newly diagnosed HIV positive patient is essential, which serves the following purposes:

- (a). Determination of disease stage and treatment strategy - this is done by history, physical and laboratory tests (Boxes 4.2 and 4.3)
- (b). Education about risk reduction and lifestyle management - this involves the consideration of pregnancy, condom use, accommodation at work, disclosure (or not) of HIV status.
- (c). Addressing issues unique to special groups - the needs of, for example, women, haemophiliacs, drug users and other marginalised communities should be noted.

Box 4.2 The essentials of history-taking and physical examination in a newly diagnosed HIV-infected individual

HISTORY

- ♦ **Past conditions** indicative of symptomatic HIV infection, e.g. zoster, thrush, vaginal candidiasis, oral hairy leukoplakia, etc
- ♦ **Past opportunistic and associated conditions** like *Pneumocystis carinii* pneumonia, cryptococcal meningitis, TB, other STDs, etc
- ♦ **Current conditions and symptoms** – fever, night sweats, weight loss, oral discomfort, visual changes, headaches, diarrhoea, lymphadenopathy, dermatologic conditions, respiratory symptoms, neurologic symptoms, etc
- ♦ **Social history** – past and present drug use, needle-sharing, practice of safer sex, current and past sex partners, diet, household pets, employment, current living situation, family history of cardiovascular diseases etc
- ♦ **Previous immunisations**

PHYSICAL EXAMINATION

- ♦ Weight, temperature, skin, oropharynx, fundi, lymph nodes, lungs, abdominal organs, genitalia, and the nervous system
- ♦ Tuberculin test (to test for exposure to TB) for indicated persons
- ♦ Pap smear for women (to rule out cervical dysplasia)
- ♦ STD screening

HIV disease progresses to AIDS after a median of 11 years. However, the rate of progression is very variable. There are long term survivors who are free of clinical AIDS after 20 years.¹⁵ On the other end of the spectrum, there are those who manifest AIDS and die within 2 to 3 years. Researches have been conducted to determine factors that influence the rate of disease progression. Both viral and immune factors are important (refer to Chapter 1) in this regard. Nevertheless, the two most commonly used parameters for disease prognosis and monitoring in day-to-day patient management are the CD4 lymphocyte count and viral load.

Box 4.3 Baseline investigations of a newly diagnosed HIV-seropositive individual

Investigation	Clinical reason
Immunology	
T-lymphocyte subsets	Prognostic marker; initiation of antiretroviral or prophylaxis
HIV virology	
HIV antibody test	Confirmation of HIV infection
Plasma viral load	Disease prognosis
Resistance testing	Guide antiretroviral therapy
Microbiology	
Syphilis serology (VDRL/TPHA/FTA)	Latent disease
Toxoplasma serology	Previous exposure; risk of future disease
Hepatitis B and C serology	Considerations in treatment of HIV and hepatitis co-infections
Biochemistry	
RFT (renal function test)	Baseline; drug therapy
LFT (liver function test)	Subclinical liver disease; drug therapy
Fasting sugar, cholesterol, triglyceride	Baseline; drug therapy
Haematology	
Full blood count & differentials	HIV-related haematologic abnormalities/ drug therapy
G6PD level	Drugs for treatment and prophylaxis of opportunistic infections
Radiology	
Chest	Occult disease/baseline

Monitoring with CD4 lymphocyte and HIV-1 viral load

The search for a marker of disease progression began with the identification of β 2-microglobulin, p24 and CD4 as prognostic markers in the early days. Then in the landmark study of Multicenter AIDS Cohort Study (MACS), a low baseline CD4 count and high viral load were found to predict time to AIDS.¹⁶

Measurement of CD4 - CD4 count is commonly measured by flow cytometry which uses specific monoclonal antibodies to determine the percentage of lymphocytes bearing the CD4 glycoprotein. The

absolute CD4 count is calculated by multiplying this percentage and the total lymphocyte count. The CD4 count is widely variable, depending also on factors other than HIV (Box 4.4). To a certain extent, this variability may be countered by using the CD4 percentage instead; thus both values are useful. A significant change usually refers to that of more than 30% for absolute count, or 3% for CD4 percentage. Comparison is preferably made between CD4 counts obtained from blood drawn at the same time of the day.

Box 4.4 Factors known to influence CD4 lymphocyte count*

Factor	Effect on CD4 count
Diurnal variation	Lower in AM; higher in PM
Splenectomy	Increased absolute CD4 count; does not imply improved immune function
Age	Decreased absolute CD4 count with age
Acute infections (tuberculosis, herpesvirus infections, bacterial sepsis, respiratory infections, others)	Most studies reported a decreased CD4 lymphocyte count, percent, or CD4/CD8 ratio
Other factors (major surgery, exercise, malnutrition, smoking)	Most have been associated with a decreased CD4 count or percent
Ethnicity	Chinese may have a lower normal range of CD4 count

*Adapted from: Johnson SC, Kuritzkes DR. Monitoring therapy with plasma HIV RNA and CD4 counts. HIV Advances in Research and Therapy 1997;7:13-8.

Measurement of viral load - Cell free HIV-RNA in plasma is best measured by the branched DNA technique - bDNA (Chiron) or reverse transcription polymerase chain reaction - RT-PCR (Roche). Nucleic acid sequence based amplification - NASBA (Organon) is not available in Hong Kong. At this stage of development, viral load testing is not an exact test yet, having a significant intratest variability of up to 0.3-0.5 log. Furthermore viral load results obtained by bDNA and PCR may not correlate with each other. Neither do results obtained with less and more sensitive (<50 copies/mL) versions of the same testing method. Factors affecting viral load measurements are in Box 4.5. To minimise the intrinsic variability of viral load tests, repeat measurement is indicated when the decision to initiate or change treatment is to be based on the results. Serial measurements are best made with the same methodology and with the same version of test. A rise or reduction in viral load is deemed significant only if it is more than 0.5 log. In practice, the most sensitive assay available is recommended, in recognition of the fact that the nadir of viral load suppression correlates with the durability of response. This is particularly important in managing patients on antiretroviral therapy.

Box 4.5 Factors known to influence viral load measurements

Factor	Effect on viral load measurement
Selected aspects of specimen handling (delay in processing, freeze/thaw, etc)	Variable effects, but handling of specimens should be consistent
Intrinsic variability of assays	0.1 -0.2 log standard deviation
Immunisations, including influenza vaccine, pneumococcal vaccine, hepatitis B vaccine, and presumably other vaccines	Viral load may increase for 2 to 4 weeks after immunisation
Tuberculosis, herpesvirus infections, and presumably many other infections	Increased viral load for 2 to 4 weeks after infection
Sex	Women may have lower viral load; Viral load may decrease during ovulation

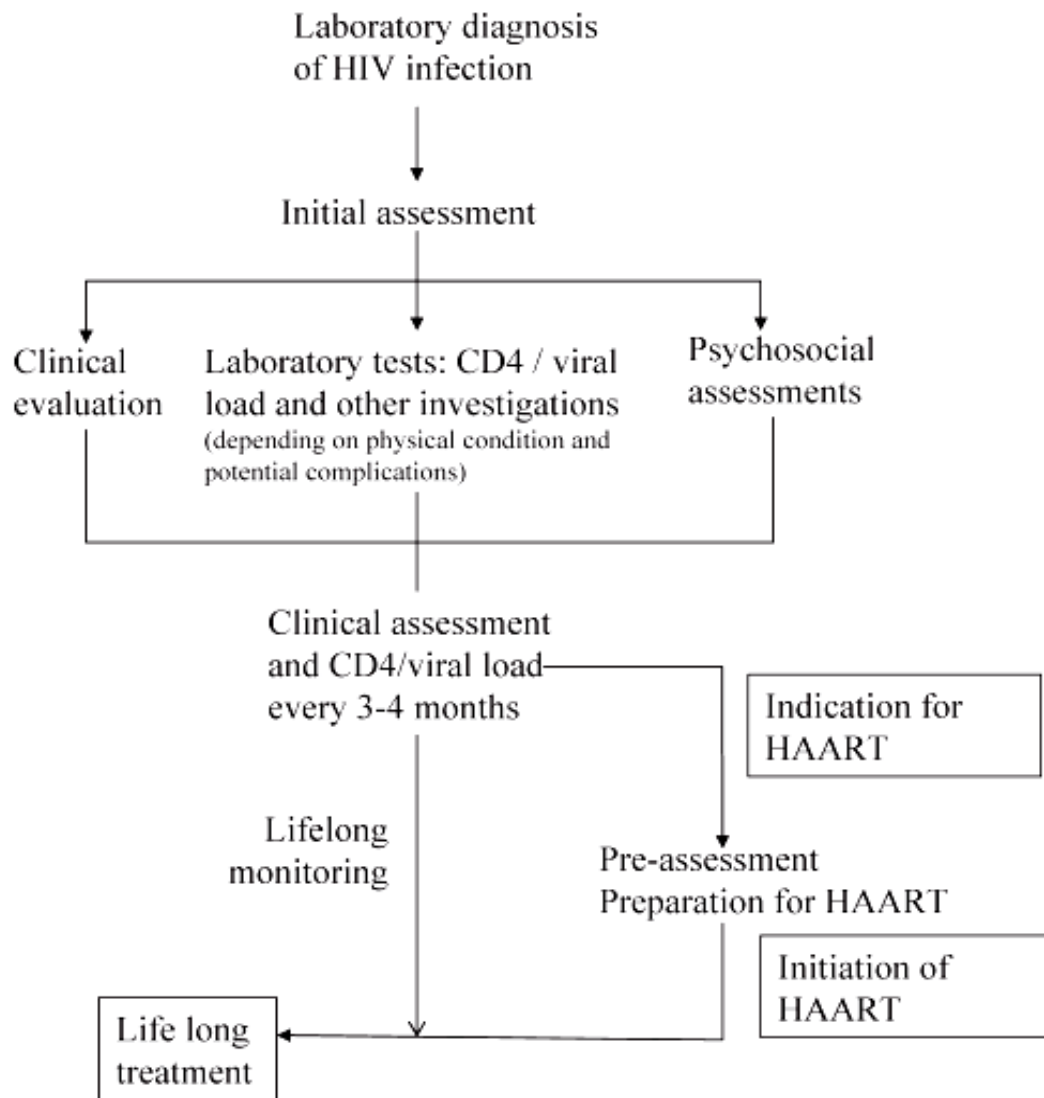
Adapted from: Johnson SC, Kuritzikes DR. Monitoring therapy with plasma HIV RNA and CD4 counts. HIV Advances in Research and Therapy 1997;7:13-8.

Viral load as tested by other techniques such as quantitative cell culture or plasma culture is also useful but expensive. Ultrasensitive cell culture techniques that stimulate CD4 lymphocytes into production of HIV allow the virus to be isolated even in those individuals with undetectable viral load in clinical practice. Their clinical utility is however uncertain, and is currently a research tool.

Overall, regular viral load monitoring provides useful information on the rate of disease progression. This, together with CD4 enumeration every three to four months is recommended for assessing individual patient. CD4 monitoring is more useful than viral load in untreated patients whereas the reverse holds for patients on antiretroviral therapy and should be closely followed. Overall, the indications for viral load testing are:¹⁷

- (a). Use in conjunction with CD4 for decision to start or defer HAART
- (b). Determining the virologic effectiveness of HAART and as a regular monitoring tool after initiation of treatment in chronic infection
- (c). Supporting the presumptive diagnosis of acute HIV infection

Algorithm 4(A) Assessment and monitoring of chronic HIV infection



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Test paper - Staging, classification and monitoring of HIV/AIDS

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1. Which of the following is not true about the purposes of devising classification/staging system for disease conditions?
 - (a) To assess public health impact
 - (b) To shed light on prognosis
 - (c) To guide treatment
 - (d) To monitor disease burden and epidemiology
 - (e) None of the above

2. Which of the following is not true regarding the evolution of HIV/AIDS classification by US CDC (Centers for Disease Control and Prevention)?
 - (a) Case definition was developed for AIDS before discovery of its causative agent
 - (b) AIDS related complex (ARC) is commonly used nowadays
 - (c) The 1986 system classified HIV infection into acute infection, asymptomatic infection, persistent generalized lymphadenopathy and other categories
 - (d) In 1993, the system is substantially revised and with AIDS conditions expanded
 - (e) None of the above

3. What is the pitfall of HIV/AIDS classification/staging system?
 - (a) Not all AIDS-defining illnesses carry equal prognostic significance
 - (b) The irreversible worst stage of a patient may not tally with improved health condition from effective treatment
 - (c) AIDS does not necessarily predict poor prognosis in future
 - (d) One system will not fit all places
 - (e) All of the above

4. Which of the following is not true about the HIV/AIDS classification system in Hong Kong?
 - (a) A low CD4 alone is an AIDS criteria
 - (b) It is based on the US CDC 1993 classification system
 - (c) Pulmonary tuberculosis is considered AIDS only if CD4<200/uI
 - (d) Penicilliosis is included as an AIDS indicator disease unlike western countries
 - (e) Local disease epidemiology is factored in for its development

5. Which of the following is not true regarding the disease conditions under the local classification system?
 - (a) Acute infection is classified as category A condition
 - (b) Recurrent salmonella septicaemia is a category C condition
 - (c) Stage C3 represents a worst disease stage
 - (d) Oral thrush is a common occurring category C condition
 - (e) Oral hairy leucoplakia predicts faster disease progression

6. Which of the following is recommended in baseline investigations of HIV infected patients?
 - (a) T lymphocyte subsets
 - (b) HIV-1 viral load
 - (c) Chest X ray
 - (d) Hepatitis B and C serology
 - (e) All of the above

7. Which of the following is not true regarding CD4 count monitoring?
 - (a) Age and splenectomy can affect absolute CD4 count
 - (b) It should be performed no more frequent than every six months
 - (c) CD4 percentage adds information to the absolute count
 - (d) Flow cytometry is the commonest method used to discern CD4 level
 - (e) Healthy Chinese may have a lower CD4 range than Caucasian counterparts
8. Which of the following is not true concerning HIV viral load?
 - (a) Polymerase chain reaction and branched chain DNA are the most commonly used methods
 - (b) A less than 0.3 log change is not significant
 - (c) HIV-2 viral load measurement is not available for clinical management
 - (d) Men may have a lower viral load than women
 - (e) The nadir of viral load suppression can correlate with durability of treatment response
9. Which of the following should be included in clerking a new HIV patient?
 - (a) Pap smear for female
 - (b) History of sexually transmitted diseases
 - (c) Current HIV-related conditions/symptoms
 - (d) Counseling on prevention of onward HIV transmission
 - (e) All of the above
10. Which of the following is not true about CD4 in relation to HIV disease progression?
 - (a) It is the single most important marker of immune function in infected patients
 - (b) Major opportunistic infections usually occur only when CD4 drops below 200/ μ l
 - (c) A study before HAART era in Hong Kong found major complications occurred at lower CD4 levels than Caucasians
 - (d) CMV retinitis and Mycobacterium avium intracellulare usually occur at a CD4 $>100/\mu$ l
 - (e) None of the above