

HIV/AIDS Clinical Staging, HIV/AIDS Case Definitions and Use of HIV Rapid Tests for Diagnosis and Surveillance

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Contents

ACRONYMS AND ABBREVIATIONS	iv
EXECUTIVE SUMMARY	v
1. Introduction	1
2. Opening Session	2
3. WHO Clinical Staging System for HIV/AIDS and HIV/AIDS Case Definitions for Surveillance	3
3.1. WHO Clinical Staging for HIV/AIDS	4
3.2. HIV/AIDS Surveillance Definitions	6
4. Global and Regional HIV Testing Policies and Strategies and the Use of HIV Rapid Tests	9
4.1. Global and Regional Policy and Technical Recommendations on HIV Testing	9
4.2. HIV Testing Strategies and Algorithms	11
4.3. Training and Supervision for use of HIV Rapid Testing	16
4.4. UNAIDS/WHO Statement on HIV Testing and Counselling	17
5. Conclusions and Recommendations	19
5.1. Clinical Staging	19
5.2. Surveillance	20
5.3. HIV Testing for Diagnosis and Surveillance	21
5.4. UNAIDS/WHO Statement on HIV Testing and Counselling	21
5.5. Action Points for WHO	22
Annexes	23
1. List of Participants	23
2. Programme	33
3. Proposed Revisions to WHO clinical staging for HIV/AIDS	37
4. HIV/AIDS Case Surveillance Definitions	67

ACRONYMS AND ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretrovirals
CD4	human T helper cells expressing CD4 antigen (T helper cell)
CDC	Centers for Disease Control and Prevention (USA)
DOTS	directly observed treatment, short-course
EIA	enzyme immuno assay
ELISA	enzyme-linked immunosorbent assay
EQA	external quality assessment
EURO	WHO Regional Office for Europe
HIV	human immunodeficiency virus
IDU	injecting drug user
NARI	National AIDS Research Institute, Pune, India
NRA	national (drug) regulatory authority
NRL	national reference laboratory
NPV	negative predictive value
PEP	post exposure prophylaxis
PLWHA	people living with HIV/AIDS
PMTCT	prevention of mother-to-child transmission
PPV	positive predictive value
QMS	quality management systems
RTI	respiratory tract infection
SEARO	WHO Regional Office for South-East Asia
STI	sexually transmitted infection
T	test
TB	tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
VCT	voluntary counselling and testing
WB	western blot
WHO	World Health Organization
WPRO	WHO Regional Office for the Western Pacific

EXECUTIVE SUMMARY

Considerable advancement in the understanding of the pathogenesis and pattern of HIV/AIDS in Asia and evolution of newer techniques in diagnosis and treatment have occurred since the original WHO HIV/AIDS staging and surveillance definitions were first developed (1985) and revised (1994). Staging and surveillance definitions need to be harmonized for uniform recording and reporting. Moreover, definitions of conditions within clinical staging need to be uniform, so that comparisons across and within countries would be possible. With scaling up of access to antiretroviral treatment (ART), it has become necessary for countries to monitor, track and report on the impact of ART. In response to the need to revise the staging and surveillance definitions the World Health Organization (WHO) organized a bi-regional meeting in Delhi, India in June 2005. The meeting proposed a revised WHO clinical staging system for HIV infection in adults and children, recommended changes in HIV/AIDS case definitions for surveillance purposes, and sought to harmonize HIV clinical staging definitions with that for HIV/AIDS surveillance. The meeting also recommended that the current HIV testing and counselling policies, strategies and HIV testing algorithms be reviewed, and that revisions be made that reflect regional and country concerns.

The following recommendations were made:

Clinical Staging

- There was overall consensus that the proposed revision to the four-stage system was appropriate and useful. No major revisions were suggested. Minor changes/ additions/deletions and modifications were recommended which will be incorporated during the global consultation process;
- For positioning of TB in clinical staging, the recommendations of a bi-regional TB working group that will review existing data on HIV disease progression among TB patients would be considered;
- While it would be useful and desirable to include an immunological classification to accompany clinical staging, the capacity for CD4 testing was limited and would take time to become routine; thus, it was suggested that any immunological classification should remain optional for now;
- The existing data on disease progression and prognosis should be reviewed to assess whether a number of conditions that should be included in clinical staging;
- The use of clinical staging in clinical management and monitoring of HIV care, including ART, should be validated;
- The existing WHO guidelines and tools should be revised to ensure that they reflect the revised clinical staging for adults and children.

Surveillance

- The AIDS case surveillance definitions should be revised and expanded to simplify reporting, surveillance definitions should be harmonized with clinical staging, and information on HIV-infected persons who need ART immediately or in the near future should be captured.
- Reporting of deaths among HIV-infected persons should be strengthened. This should include AIDS-attributed deaths and deaths due to ART complications.
- A case definition of HIV infection based on laboratory criteria for diagnosis and surveillance purposes should be developed.
- Surveillance information on HIV infections should be captured to effectively plan for an appropriate health system response and provide comprehensive prevention, treatment, care and support services for people living with HIV/AIDS (PLWHAs). In order to gain experience in establishing a potential system for routine reporting of HIV infections in the foreseeable future, it would be useful at this stage to:
 - Define minimal useful surveillance data to be collected at the time of diagnosis of HIV-infection, and
 - Test the feasibility of reporting minimal useful data on HIV infections in some areas.
- Effects should be continued to strengthen the existing second-generation surveillance, including HIV sentinel surveillance, and to promote the use of these data for producing HIV estimates and projections through modelling techniques.
- Guidelines and tools, including data collection forms, and training manuals should be developed in order to operationalize the revised advanced HIV infection/AIDS surveillance definitions.

HIV Testing for Diagnosis and Surveillance

- Specifications and the minimum criteria for HIV test kits should be identified, recognizing national requirements and global standards, and it should be ensured that HIV tests used in countries meet the specifications and required standards.
- Countries should be encouraged to review their current testing strategies and algorithms and make revisions in accordance with global strategies that will be revised to account for the new technological developments in HIV testing.
- HIV testing algorithms should be validated for the different testing objectives including PPV, NPV and cost, with an aim to review them on an annual basis.

- Quality management systems should be implemented and strengthened on a continuous basis, including training and supervision.

HIV Testing and Counselling

- HIV testing and counselling should be part of the essential package of HIV prevention, care and treatment, and requires both provider and client-initiated approaches.
- It was recommended that health programmes, such as STI and reproductive health, TB, PMTCT, drug and alcohol, prison health care, overseas workers, community level and focused prevention should offer "by referral" or "on-site" HIV testing and counselling. It was also recommended that blood screening programmes should offer referral to VCT centres.
- Where clinical conditions that suggest HIV infection are being seen and managed, clinicians should refer or offer diagnostic HIV testing to patients. In all situations informed consent should be sought.
- Countries urgently need operational guidelines to expand their ability to offer HIV testing and counselling within other health programmes and settings, e.g. TB clinics, ANC, drug and alcohol/IDU services, prisons, overseas workers programmes and community-level prevention programmes. Such guidelines should be developed based on data generated during programme implementation and through modelling of costs.
- Efforts to decrease HIV-related stigma and discrimination at community and clinic levels in low-prevalence settings are urgently required. For this, HIV testing should be increased through this would clearly be more difficult to achieve in low-prevalence settings.

Action Points for WHO

- The Regional Offices for the South-East Asia (SEARO) and the Western Pacific (WPRO) should organize a review and analysis of existing data from the documentation in selected countries in the regions, for HIV/TB co-infections, disease progression, laboratories and VCT centres.
- WHO should examine the need to incorporate revised clinical staging and surveillance definitions into existing training materials and to identify areas where new training materials may need to be developed. The need for new and additional training activities should be identified.
- Over a longer time-frame (e.g. two years), SEARO and WPRO should identify steps needed to evaluate and validate the staging and surveillance systems and also explore the feasibility for instituting systems for HIV case reporting.

- Organizing multi-country meetings to explore the potential and share experiences, either in SEARO, WPRO or bi-regional sessions, have proved useful, but it is important to group countries in terms of their size (geographical and/or population) and level of institutional capacity and development. Smaller countries and countries with less capacity may need to examine programme considerations with countries in similar situation and/or with comparable capacities, in order to maximize the effectiveness of bi-or inter-regional technical consultation.
- Develop a regional policy statement on HIV testing and counselling.

I. INTRODUCTION

Considerable advancement in the understanding of the pathogenesis and pattern of HIV/AIDS in Asia and evolution of newer techniques in diagnosis and treatment have occurred since the original WHO HIV/AIDS staging and surveillance definitions were first developed (1985) and revised (1994). Staging and surveillance definitions are currently not harmonized, leading to confusion and lack of HIV/AIDS reporting. Moreover, definitions of conditions within clinical staging are also not uniform, meaning that comparisons across and within countries are often not possible. With the scaling-up of access to antiretroviral treatment (ART), it will become necessary for countries to monitor, track and report on the impact of ART.

In response to the need to revise the staging and surveillance definitions, WHO in collaboration with the Centers for Disease Control and Prevention (CDC), Atlanta, USA organized a meeting in Saas Fee, Switzerland in June 2004. The meeting proposed a revised WHO clinical staging system for HIV infection in adults and children, recommended changes in HIV/AIDS case definitions for surveillance purposes, and sought to harmonize HIV clinical staging definitions with those for HIV/AIDS surveillance. It also recommended that regional consultations for the proposed revisions be arranged, to obtain a consensus on the content and format for staging and surveillance, and to capture regional-specific perspectives.

To inform the revision process and make staging and surveillance universally applicable to a resource-constrained country setting, participants from SEARO and WPRO requested that further regional consultations be undertaken to ensure that expertise, experience and realities from the WHO regions were brought to bear upon the revisions.

Recent efforts to increase access to ART and accelerate prevention have also highlighted problems with regard to HIV testing for clinical care and surveillance. Countries are requesting clarifications on policy and procedural guidance for the use and application of affordable rapid testing technologies within clinical services and surveillance. WHO, Joint United Nations Programme on HIV/AIDS (UNAIDS) and CDC recommend offering HIV testing as a routine part of medical care, particularly where HIV-infected persons are more likely to present to services, such as tuberculosis (TB) clinics, sexually transmitted infection (STI) clinics, injecting drug user (IDU) outreach services and hospital in- and out-patient units. This would increase the number of HIV-infected persons who are aware of their positive serostatus. They also propose that rapid HIV tests can facilitate increased access to HIV testing for national HIV/AIDS surveillance and clinical purposes.

Countries from the WHO SEA and WP regions have been raising questions on whether the proposed quality assurance recommendations as well as serial and parallel strategies are applicable, feasible, reliable and cost-effective for rapid testing in low HIV-prevalence settings. Specific guidance for HIV testing for surveillance purposes is still not clear with regard to which technologies are best suited, which algorithms are most cost-effective, and what quality assurance criteria need to be applied.

To discuss the above issues, a "WHO Consultation on HIV/AIDS Clinical Staging, AIDS Case Definitions and Use of HIV Rapid Tests for Diagnosis and Surveillance" was held from 1-3 June 2005 in New Delhi, India for participants from both SEARO and WPRO.

The objectives of the meeting were to:

- Review the proposed revisions to HIV/AIDS clinical staging and HIV/AIDS case definitions for surveillance for adults and children, and reach a consensus on any additions/modifications for the WHO South-East Asia and Western Pacific regions.
- Discuss the implications of the revised global HIV testing and counselling policies for low HIV prevalence countries and reach a consensus on appropriate testing algorithms and quality control components for use of rapid HIV tests for diagnosis and surveillance in resource-limited countries of the WHO South-East Asia and Western Pacific regions.

A total of 39 participants attended the meeting. They included country representatives from Australia, Bangladesh, Cambodia, China, India, Indonesia, Myanmar, Nepal, Papua New Guinea, Philippines, Sri Lanka, Thailand and Viet Nam; CDC; United Nations Children's Fund (UNICEF); and WHO India country office; SEARO, WPRO and headquarters. [Refer to Annex 1 for the List of Participants and Annex 2 for details on the three-day Programme.]

2. OPENING SESSION

Dr Jai P. Narain, Director, Department of Communicable Diseases, WHO/SEARO opened the bi-regional meeting with greetings from Dr Samlee Plianbangchang, Regional Director, WHO, South-East Asia Region. Through his address, read out by Dr Narain, the Regional Director drew the participants' attention to the HIV situation worldwide—an estimated 39 million people were living with HIV/AIDS and nearly 25 million people had died from it. He further observed that countries in both the WHO SEA and WP regions had been committed to the "3 by 5" initiative, and documented remarkable achievements in scaling up ART in the recent past. Notwithstanding these

advances, however, only about 15% of persons in need of treatment in both regions were currently receiving ART. A major obstacle for access to treatment that Dr Samlee observed was "lack of access to HIV testing and counselling." In addition, the advent and expansion of ART had challenged the public health and clinical staff to simplify staging guidelines to help inform HIV-related care and treatment decisions as well as to strengthen surveillance systems, and to make them more relevant to region-specific planning and management needs. The Regional Director requested the participants "to explore how clinical staging could be used to improve patient management and case reporting, to provide suggestions for additional validation if required, and to identify key steps in the implementation of these revisions."

Dr Siobhan Crowley, Treatment, Prevention and Scale-up Team, Department of HIV/AIDS, WHO/HQ, headquarters, extended greetings and best wishes from the WHO Assistant Director-General, Dr Jack Chow and the HIV department. As an example of intercluster synergy, she was pleased to note that Dr Gaby Vercauteren, Diagnostic Imaging and Laboratory Technology, Department of Essential Health Technology was contributing to this meeting. She stressed that WHO was looking forward to working closely with Member States to understand and best respond to the needs and perspectives in the development of regionally appropriate algorithms for improving the treatment and care of HIV-infected persons in need.

On behalf of WPRO, Dr Michel Tailhades, Medical Officer (Care and Treatment), joined in welcoming the WP country participants to the meeting. He was particularly interested in identifying ways in which WHO could be of even greater assistance to Member States.

Dr R. Paranjape, Director, National AIDS Research Institute (Indian Council of Medical Research), India, and Dr Rosario Tactacan-Abrenica, Medical Specialist, San Lazaro Hospital, STD AIDS Cooperative Central Laboratory, Philippines, were selected as Chair and Co-Chair of the meeting, respectively.

3. WHO CLINICAL STAGING SYSTEM FOR HIV/AIDS AND HIV/AIDS CASE DEFINITIONS FOR SURVEILLANCE

The objectives of this session were to:

- Familiarize the participants with the proposed revisions to the WHO clinical staging system for HIV/AIDS and proposed revisions to HIV/AIDS case definitions for surveillance;

- Develop a consensus on the proposed revisions to the WHO clinical staging system and HIV/AIDS case definitions for surveillance;
- Identify and agree on additions or regional adaptations to the WHO clinical staging system and HIV/AIDS case definitions for surveillance that may reflect the spectrum of HIV in South-East Asia and Western Pacific regions, and
- Make recommendations on how to improve the use of the WHO clinical staging system for HIV/AIDS and strengthen HIV/AIDS case reporting.

3.1 WHO Clinical Staging for HIV/AIDS

The participants were familiarized with the current WHO clinical staging system and its shortcomings, including the lack of standardized definitions of clinical events, lack of staging system for HIV infection in children, limited list of HIV-associated clinical conditions, lack of harmonization of clinical stages with surveillance definitions of HIV and AIDS in use, and lack of flexibility to report "reversal" of the stage of disease on ART, both clinically and immunologically.

Clinical staging is largely useful for clinical management, and is particularly useful where little laboratory diagnostic capacity exists. However, increasing access to CD4 testing is becoming a reality in countries of the SEA and WP regions, and participants were asked to consider how the immunological classification of HIV/AIDS could also be used to facilitate clinical decision making.

Key Issues Considered by Groups

- Are there any clinical conditions included that should be excluded, or conditions that should be included to better reflect the clinical spectrum of HIV in the WHO South-East Asia and the Western Pacific regions?
- Are there particular conditions where further evidence is needed to provide prognostic ranking?
- Is it useful to include descriptions for presumptive and definitive diagnosis?
- Is it necessary to provide immunological criteria?
- How can 'reversing' of clinical stage and immunological category on ART be reflected, and do the conditions retain the same hierarchy and/or prognostic significance once on ART?

Summary of Discussions and Recommendations

The groups were tasked to provide recommendations on regionally appropriate revisions to the proposed clinical staging and recommendations

upon inclusion of immunological criteria. The groups proposed the following recommendations and reflections:

- Clinical staging is used for those who have been diagnosed with HIV infection. It assists the health care provider in recognizing those in need of ART and other HIV-related interventions, including cotrimoxazole prophylaxis, those who need referral to care and ART services, and to guide patients about the likely course of HIV infection with or without HIV care including ART. The participants proposed a few additional conditions and recommended that some conditions should not be considered useful for staging. To support and facilitate greater access to and use of care and treatment, a wider range of health care providers need to be familiar with the clinical staging for adults and children. The revisions proposed are included in Annex 3.
- The ART scale-up will be difficult to achieve without greater use of clinical staging criteria, especially in resource-constrained settings, and will need to be well understood until the CD4 testing technology, becomes widely available. The participants, however, emphasized that relying only on clinical criteria to initiate ART may miss a significant proportion of people who are eligible for treatment based on CD4 criteria alone and have not yet developed stage 3 or 4 conditions. It was therefore recommended that including CD4 immunological criteria and classification should be essential, and advocacy for expanding the use of CD4 testing should be undertaken to support and complement clinical staging in the Asian context.
- Clinical staging criteria should not function as a diagnostic algorithm. They should be designed for use only after HIV infection has been diagnosed. The participants proposed that a case definition for HIV infection would be useful for clinical and surveillance purposes. They felt that the proposed presumptive stage 4 in HIV-exposed children would be useful and necessary to ensure that children gain greater access to ART. The introduction of the four-stage clinical classification for children in the revised definitions was also supported by the participants.
- The proposed clinical staging scheme was reviewed in depth and participants suggested that there would be no need to distinguish between conditions diagnosed presumptively or definitively in the summary tables. However, the more detailed descriptions of this in the annexes were considered and minor modifications and improvements to the proposed annexes were agreed upon. A wider use of this would allow comparison across and within countries.
- The suggested age cut-off for children and adults was 15 years with national programmes adapting this locally to reflect their own age-related definition.

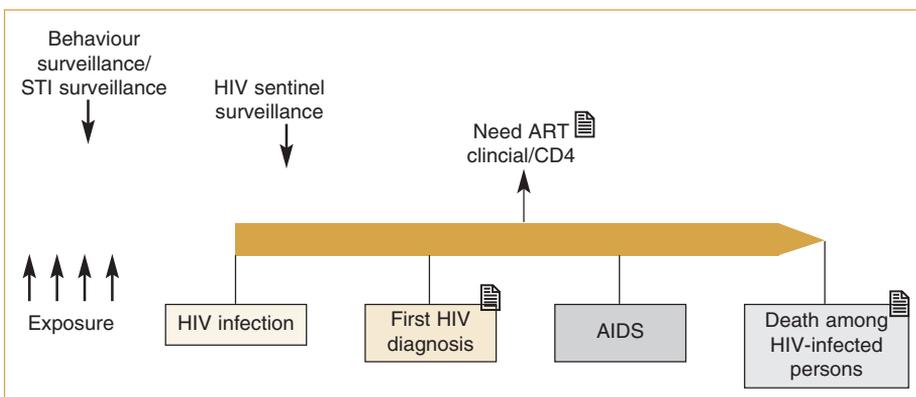
- The participants proposed that an immunological classification, separate and distinct from the clinical stages, be provided. It was suggested that the immunological classification based upon data available from countries of the two regions (Indian and Thai progression data were available for consideration) would be useful; and that distinguishing between those with CD4 of less than 50 might be more useful for clinical care decisions, as the prognosis is worse and clinical management challenges are greater regardless of the presenting of opportunistic infection.
- Lengthy discussions ensued on how best to include TB within the clinical staging system and a variety of suggestions were made as reflected in the annexes. The available data from the regions suggested that many of the TB cases being managed in HIV services had low CD4 counts and were at a late stage of HIV/AIDS. However, the clinicians felt that because TB was so common in many countries of these two regions, many of the TB cases with HIV infection were not yet being recognized, diagnosed or managed. As a consensus could not be reached, it was proposed that the WHO SEARO/WPRO commission should review the TB/HIV co-infection prognosis and disease progression in their respective regions and advise how TB should be reflected within the clinical staging.
- A possible three-stage clinical classification was debated upon. The participants did not recommend that the current four-stage system be changed to a three-stage system since the former had proved to be useful and valid over the last 10 years.
- It was proposed that throughout the revised document, ART as a minimum of triple therapy must be highlighted.
- The participants suggested that using the clinical events as outlined in the clinical staging systems could help to monitor those on ART. However, this would require validation to make sure that stages had the same prognostic hierarchy. It was also proposed that the stage at which ART was started be recorded as it would be very important to know how many months the patient was on ART.

3.2 HIV/AIDS Surveillance Definitions

The participants were presented with an overview of AIDS surveillance in Asia, including the historical background on AIDS case definitions in use to date. In countries of the WHO South-East Asia and Western Pacific regions, the key surveillance events in the course of HIV infection have been at the time of: (i) AIDS diagnosis and (ii) death among reported AIDS patients. Overall, AIDS surveillance is given low priority in countries of the two regions. Reporting of AIDS cases and deaths is grossly incomplete limiting the utility

of these data. In addition, the approaches to AIDS surveillance are inconsistent and non-standardized. Further-more, there is a lack of clarity among clinicians about the use of clinical staging and surveillance definitions.

The availability of ART has led to a decline in deaths among HIV-infected individuals. Widespread provision of ART will decrease the utility of AIDS case reporting as currently defined, because patients should commence on ART prior to developing AIDS. In the context of ART scale-up, a useful and robust surveillance system should attempt to compile information at three main time-points in the natural history of HIV/AIDS: (i) the time of acquisition or diagnosis of HIV infection, (ii) the time HIV-infected persons require ART, and (iii) time of death in an HIV-infected person (HIV/AIDS-related or due to ART or natural causes).



The proposed revision of the AIDS case definition for surveillance aims to simplify and harmonize surveillance definitions with those of clinical staging, and to better capture information on those who are in need of ART. This will be more relevant to the programme and assist in planning, resource allocation and procurement of supplies.

Key Issues Considered by Groups

- What should surveillance systems reveal about HIV-related disease in the era of ART?
- How useful or necessary is it to include immunological criteria for surveillance?
- Would it be useful for countries to report on "advanced HIV infection" (stage 3 and 4 disease and/or any CD4 <350) ?
- Are there additional surveillance data that could usefully guide sub-national and national programmes when they introduce and scale up ART, and if yes, how could this be established or implemented?

Summary of Discussions and Recommendations

The groups were expected to provide regionally appropriate revisions to HIV/AIDS surveillance definitions and recommend next steps in the process of implementing proposed revisions.

- In the era of ART scale-up, there is an undisputed need to have better surveillance regarding the number of people in need of ART to plan for an appropriate health system response. The proposed revisions to the definitions are sound and should be adopted. The proposed reporting of "advanced HIV infection and AIDS" was considered a good concept. The participants recommended, however, that before beginning to recommend this reporting on a widespread scale, report it should be field tested and validated with attention to costs and any logistic problems it might entail.
- Participants agreed that it would be useful to include immunological criteria, but given the expected logistic barriers, namely, high cost of CD4 and its non-availability, they recommended that it should remain optional, and that lack of CD4 information should not negate surveillance efforts.
- In the meantime, existing AIDS case reporting and AIDS-related death reporting should be encouraged to include minimal information on basic demography including age, CD4 where available and exposure to ART.
- Capturing information on new HIV infections as practised in the USA and other developed countries is clearly the ideal. In a recent meeting at the WHO Regional Office for Europe (EURO), expanding the reporting of collected surveillance information on HIV infections was recommended. HIV case reporting should include basic demographic data, date of diagnosis, clinical stage and if available, information on CD4 count and date, any antiretroviral therapy, and date of reporting. While it was deemed desirable to have more information on HIV infections, it was felt that this would be difficult to implement in the WHO South-East Asia and the Western Pacific regions due to lack of operational systems, and due to concerns about double counting of patients, as well as about the ability to ensure confidentiality, and because of the profound prevailing stigma.
- Even if surveillance for HIV infections can be initiated, the completeness of reporting is likely to remain low. The current HIV sentinel surveillance, as part of the second generation surveillance system, should continue to be strengthened and these sentinel surveillance data be used for producing HIV estimates and projections.
- Stigma is an important factor for the poor reporting of deaths among the HIV-infected. There is need to strengthen the reporting of deaths among

the HIV-infected. In addition to death registries, additional mechanisms should be considered to collect information on deaths, e.g. verbal autopsies.

- Routine surveillance and monitoring systems should not be burdened with excessive information needs. It is necessary to carefully distinguish between the kind of information that can be obtained from routine surveillance and monitoring, and information that is better suited to special studies and operational research. Examples of such special studies would be HIV drug resistance surveillance and monitoring, adverse events among those receiving ART, and surveillance for HIV/TB co-infections.

4. GLOBAL AND REGIONAL HIV TESTING POLICIES AND STRATEGIES AND THE USE OF HIV RAPID TESTS

The objectives of this session were to:

- Review international and national HIV testing guidance and the use of HIV rapid tests, including required quality assurance components;
- Review actual implementation of national policies on HIV testing, including barriers to scaling up HIV testing and counselling, and
- Review and discuss appropriate HIV testing strategies and algorithms for surveillance and diagnosis in low-prevalence countries with limited resources.

4.1 Global and Regional Policies and Technical Recommendations on HIV Testing

The participants were familiarized with the objectives of HIV testing, spectrum of HIV diagnostic tests, challenges with HIV testing, HIV test performance, recommended global HIV testing strategies and algorithms, development of national testing strategies and algorithms, and quality management systems.

The main objectives of HIV testing remain the same—screening of all blood donations before use, monitoring the spread of the epidemic by measuring the HIV prevalence in different population groups, diagnostic testing to scale up HIV prevention, and access to HIV care interventions.

Today, a wide variety of HIV tests exist, ranging from enzyme immuno assays (EIA) to very simple rapid HIV tests. Although many HIV rapid tests may look alike their quality and operational characteristics may differ substantially.

Since 1988, WHO has been providing technical advice to its Member States on the quality and operational characteristics of HIV test kits. Results of the most recent HIV test kit assessments were published in Report 14¹ and Report 15² (antigen/antibody EIAs). Evaluations of HIV serological assays conducted by WHO rely on a well-characterized WHO reference panel composed of specimens of different geographical regions, and additional performance panels. Minimal performance criteria have been established in terms of sensitivity (>99% for rapid, 100% for enzyme-linked immuno sorbent assays [ELISA]), specificity (>98%), and inter-reader variability (<4%). Also assessed are the clarity of the test kit instructions, the labelling of components of the kit and the ease of use of the test procedure. The main focus of WHO in recent years has been on HIV rapid tests as they are particularly well suited for scale up of testing and counselling in clinical services including prevention of mother-to-child transmission (PMTCT) services and for surveillance.

Although rapid tests are relatively easy to perform, there is still a debate on who should perform the tests and where these tests can be carried out. It is generally accepted that health care workers with no formal laboratory training can perform HIV rapid tests after training, and after they have shown proficiency in carrying out the tests, and understanding of the quality assurance measures that need to be taken. They should also have learnt to respect confidentiality. Wherever HIV testing is conducted, universal precautions to ensure biosafety need to be adhered to.

Quality management systems (QMS) are designed to ensure that the testing site issues reliable test results in a consistent and timely manner. The 12 elements of the QMS include: organization; personnel; equipment; purchasing and inventory; process/quality control and specimen management; information management; documents and records; occurrence management; assessment; process improvement; customer service, and facilities and safety.

To ensure the quality of HIV testing at any testing site, standard operating procedures need to be in place and adhered to. Irrespective of where and by whom HIV testing is performed, the quality of the HIV test should be

¹ *HIV Assays: Operational Characteristics (Phase 1), Report 14. Simple/Rapid tests.* Geneva, World Health Organization, 2004.

² *HIV Assays: Operational Characteristics (Phase 1), Report 15. Antigen/Antibody EIAs.* Geneva, World Health Organization, 2004.

validated by internal controls and by independent quality control samples. The performance of the staff carrying out the testing needs to be monitored and supervised on a regular basis.

4.2 HIV Testing Strategies and Algorithms

There is an important distinction between a "testing strategy" and a "testing algorithm". The "testing strategy" provides guidance on, for example, the number of tests to be used in combination according to the purpose of testing and HIV prevalence, whereas a "testing algorithm" refers to the specific combination of tests and defines the specific test kits and sequence of use in a given testing strategy.

Establishing national HIV testing strategies and algorithms is very important. WHO recommends three basic testing strategies³ for national programmes to develop testing algorithms. The purpose of testing blood donation/transplant screening, diagnostics, or surveillance is to determine which strategy and algorithm is used. The selection of test kits to be used in any testing algorithm is not a mechanical calculation based upon published sensitivity and specificity data, but should be based on the actual performance in the environment where the HIV test kits will be used. Obviously, the appropriateness of the selected HIV test kits and the exact order in which they will be used in the algorithm will determine the reliability of the final results.

Selecting the test kits to be used involves decisions about the quality of the tests (e.g. sensitivity, specificity, lot-to-lot variation), interaction between the kits (shared false-positive and false-negatives) and the testing environment (ease of use, skill of staff, training, equipment and evaluation processes). Preferably these decisions need to be based on national data. The selection of the two or three HIV tests that will be used in combination is crucial for the outcome of the testing algorithm. Test kit combinations can include both EIA and rapid tests. Reference laboratories will usually have to provide confirmatory testing to resolve indeterminate test results. Western Blot is not used much now in industrialized countries as it can give a relative high rate of indeterminate results, particularly in low-prevalence situations.

When selecting HIV test kits that will be used in combination it is crucial that they do not share the same false-negative or false-positive results, as this will

³ For details on WHO HIV testing strategies refer to the original document *HIV Assays: Operational Characteristics (Phase 1), Report 14. Simple/Rapid tests*. Geneva, World Health Organization, 2004. website: http://www.who.int/diagnostics_laboratory/publications/hiv_assays_rep_14.pdf

reduce the reliability of the final result. A simple rule to minimize such undesired events may be selecting kits that use different antigen preparations, a different test format or a different detection technology. However, it is important to also consider that false-positive reactions with rapid HIV testing occur due to the appropriate reading time not being respected.

There is a consensus that the positive predictive value (PPV), which is the probability that when the final result is positive the person is indeed infected with HIV, of an algorithm should be at least 99%.

The PPV of testing algorithms is highly related to the underlying prevalence of HIV in the test population. Even when selecting high quality tests with sensitivities of 99%-100% and specificities of 98%-99%, the PPV will vary considerably with the prevalence in the population to be tested (Table 1).

Table 1: Predictive values for a range of prevalence using serial testing with all assays sensitivity 99% and specificity 98%

Prevalence %	PPV % : 1 test	PPV % : 2 tests	PPV % : 3 tests	NPV* %
0.05	2.4	55.1	98.4	100.00
0.5	19.9	92.5	99.8	100.00
2.0	50.3	98.0	99.96	99.98
5.0	72.3	99.0	99.98	99.95
10.0	91.9	99.7	99.99	99.89
30.0	95.5	99.9	100	99.57

*NPV: negative predictive value

Overall, the use of only one test (usually only in the context of Strategy I⁴) is reserved for special circumstances of urgency (labour and delivery, trauma) or blood safety.

The use of two tests (Strategy II) is generally sufficient for testing in populations with HIV prevalence greater than 5%. For diagnostic purposes in low-prevalence countries, Strategy III, which requires up to three tests should be used for diagnostic testing in populations where HIV prevalence is less than 5%. Three tests are necessary for obtaining a PPV of 99%. Countries

⁴ For details on WHO HIV testing strategies refer to *HIV Assays: Operational Characteristics (Phase 1), Report 14. Simple/Rapid tests*. Geneva, World Health Organization, 2004.

would have to decide how reliable their HIV surveillance data need to be. However, for most settings (except for the perhaps extremely low-prevalence countries) a two-test strategy may be sufficient for unlinked anonymous surveillance testing.

Two types of testing algorithms have been advocated so far—"parallel" and "serial" testing. In the parallel testing strategy all specimens are tested simultaneously with two different HIV tests (T1 and T2; T=Test). Specimens with discordant results are further tested with a third assay (called tie breaker, T3) to arrive at a consensus. In a serial testing strategy all specimens are tested with one test (T1), and only those specimens that have reactive test results (T1+) are further tested with a second different HIV test (T2). A third serial test (T3) is performed on those specimens that are reactive in both the previous tests (T1 and T2).

Examples of Country Implementation

- Participants from China, India, Sri Lanka and Thailand made presentations on their national experience with HIV testing. Issues covered in these presentations included the following.
- All countries have established a network of laboratories linking peripheral laboratories with centralized reference laboratories. The level of quality management systems provided by these reference laboratories varies from country to country. Thailand has a particularly extensive network of laboratories and a well-developed system of HIV test kit evaluations and licensing programme, and is operating a national and regional external quality assessment (EQA) scheme that monitors laboratory performance.
- Most of the countries are using three or more tests in a serial HIV testing algorithm, either using multiple EIAs, EIAs-Western Blot or EIAs-Rapid Test combinations. However, overall, the use of rapid tests is lower than the use of multiple EIAs and HIV testing is still mainly performed in laboratory settings. With the roll out of voluntary counselling and testing services (VCT), this may change in the near future. China evaluated a range of rapid tests and due to cost and concerns about sensitivity have opted to continue to rely more on locally produced EIA tests.
- India's National AIDS Research Institute (NARI) in Pune conducted an evaluation of five rapid tests in both serial and parallel algorithms. The tests produced an acceptable level of PPV following both algorithms and found that the serial testing algorithm was more economical.
- Sri Lanka evaluated the potential for use of rapid testing and, while they were seen useful in special circumstances, they also presented problems

for health staff that might not be adequately equipped or skilled to deal with reactive test results. Another problem in Sri Lanka is that of the economics of extensive screening because of the low population prevalence of HIV (for example, the screening of 30 000 patients attending antenatal clinics in 1998 identified only three cases of HIV infection).

Key Issues Considered by Groups

- What are the minimum criteria for HIV test kits?
- In which situations would rapid tests be more suitable?
- What would be the appropriate HIV testing algorithm in low-prevalence countries for each of the test objectives mentioned below?
 - Surveillance, and
 - Diagnosis and prevention: HIV in PMTCT, STI clinics, TB clinics, in-patient settings, emergency situations and in VCT sites (such as blood safety of the patient and for untested women in labour)

Summary of Discussion and Recommendations

- Technical information provided in WHO reports and other published data on sensitivity and specificity and operational aspects of HIV test kits can be used as a guide when selecting potential candidate test kits for inclusion in the national testing strategies and algorithms. National HIV testing algorithms should be validated before nationwide implementation. The performance as well as the quality of HIV tests and of the respective algorithms need to be monitored, because of batch-to-batch variations in the quality of HIV tests and other factors, such as transport and storage conditions.
- Any laboratory test being considered within national programmes needs to balance sensitivity and specificity. Neither the Western Blot nor any other laboratory test is a true "gold standard" or 100% sensitive and specific.
- One of the most frequently asked questions regarding quality assurance is "what does it cost?" The more relevant and important question should be "How much does the lack of quality assurance cost?" The key message is that "Quality costs, but bad quality costs more".
- Concerns related to quality assurance of rapid testing are exactly the same as those needed for EIA-testing or any laboratory testing programme.
- "Rapid tests" should be considered as reliable and sensitive and will, with time play a more central role in testing strategies in most countries of the SEA and WPR regions. The HIV testing method of choice will depend on the environmental setting, e.g. it may be more feasible and appropriate to use EIA in a centralized laboratory test setting.

I. Minimum criteria for HIV test kits should include:

- A shelf-life of one year;
- Checking of expiry dates;
- Examining and monitoring storage and transport conditions;
- Verifying test kit sensitivity (should be at least 99%) and specificity (at least 98%), and
- Preferring tests of maximum quality (both sensitivity and specificity are important) as performance under field conditions may be less than that in optimal conditions.

II. For evaluations of HIV test kits

- The role of the National Regulatory Authority (NRA) needs to be defined and strengthened.
- The capacity to perform HIV test kit evaluations at national level needs to be strengthened. Alternatively, countries lacking this capacity may rely on independent regional and/or international data.
- Information on the manufacturer of HIV test kits and the origin of the kit components is required and important.
- Evaluations need to be carried out on a large enough scale to provide meaningful statistical power.
- Low titre specimens should be included in the evaluation portion, but not diluted specimens.

The other issues discussed included problems with HIV test kits donated by donor agencies. This occurs because test kits may have passed the batch release criteria for the donor country, but still be in date for a short period and therefore may be donated to countries with limited resources and less stringent NRA or regulatory requirements for test kit distribution. These kits may not fit into the national algorithms or have a short shelf-life and therefore may not get used before their expiry date.

III. Use of rapid HIV tests

- In low-volume HIV testing sites, rapid tests are more cost-effective and provide a better turnaround time in reporting of results. It was noted that to ensure proficiency, test sites need to have a minimum workload of at least 15-20 tests a week.
- Where HIV test results are required immediately to inform clinical interventions (e.g. labour and delivery, and emergency screening of blood donors) rapid HIV tests are the method of choice. They also offer

significant advantages in settings where rapid results facilitate service delivery, such as ANC, STI or TB clinics.

- Rapid tests may also offer advantages over EIA as the second or third test in the traditional HIV testing algorithm, where EIA is the first test, as it allows for greater flexibility. In general, lateral flow rapid tests have a high specificity if the test procedure is strictly followed.

IV. HIV testing strategies and algorithms

- HIV testing strategies should be designed around the different HIV testing objectives, i.e. blood and transplant safety, surveillance, and diagnosis and prevention.
- *Blood safety:* HIV testing strategy; it may be sufficient to use only one test to screen all blood donations in certain countries, however, levels of blood wastage may be unacceptably high due to false-positive reactions in low-prevalence countries. Approaches to reduce wastage without jeopardizing blood safety may need to be investigated. Donors who would like to know their HIV test results should be referred to VCT sites for confirmatory testing.
- *Emergencies:* no consensus was arrived at regarding the testing strategy to use for women in labour in low-prevalence settings. Depending on the prevalence in this population group it was felt that either no test should be performed, or one test should be carried out, or two HIV tests in parallel.
- *Surveillance:* The choice of using two or three HIV tests for HIV serosurveillance depends on the HIV prevalence in the population group surveyed and the desired accuracy of surveillance data.
- *Diagnosis:* A consensus was reached that the decision on using either two or three tests would depend on the PPV; and hence will be related to the HIV prevalence in the country. It was acknowledged that the prevalence within the country may vary; however, to harmonize the approach the lowest prevalence should be used to decide on the national HIV testing strategy for diagnosis. It was agreed that >5% would be considered as high prevalence.
- It was agreed that for TB patients in the WHO SEA and WP regions, the same testing algorithm should be applied as for diagnosis of HIV infection in the general population.

4.3 Training and Supervision for use of HIV Rapid Testing (CDC/WHO)

The joint CDC/WHO training package on "Providing Training and Supervision for HIV Rapid Testing" is a comprehensive five-day "workshop in a box" that

contains all materials necessary to conduct a training programme, including didactic materials as well as guides for instructors.

The package comprises different modules and places HIV rapid testing in the overall context, covering the technical and quality assurance aspects of performing HIV rapid testing, besides detailing the potential applications of rapid testing in PMTCT and VCT services.

The package is aimed at three target audiences, laboratory workers, health care workers (nurses) and counsellors. It is universally applicable and is designed to be customized to country-specifics. The training is highly interactive and engaging with emphasis on performance assessment, both at the end of the training and for follow-up monitoring.

The key messages in the training programme are:

- Attention must be paid to the organization and quality of the entire testing process;
- The usefulness of testing depends on its quality and reliability;
- Training is both on how to perform a test and to understand what the test is achieving;
- Ongoing supervision is important, and
- Monitoring and evaluation of training is important.

4.4 UNAIDS/WHO Statement on HIV Testing and Counselling

As access to care and treatment increases, there is a need to simultaneously expand access to free, quality HIV testing and counselling. It is estimated that globally only 10% of people who are HIV infected know their HIV status and can access care and treatment services. In June 2004, UNAIDS and WHO released a Statement on HIV Testing and Counselling that aimed to encourage countries to review their policies and practices in order to increase the access to HIV testing. The statement reemphasizes the need for HIV testing to always be confidential, accompanied by counselling, and to be conducted only with voluntary informed consent. The statement also urges countries and programmes to expand the routine offer of testing and counselling in a selected range of service delivery settings. Increasingly in many countries, models used for HIV testing include client-initiated HIV testing (VCT services) and provider-initiated testing (diagnostic testing, routine offer in public health programmes such as PMTCT, STI and TB and inpatient hospital settings). The routine offer of HIV testing and counselling in antenatal clinics is a key pillar of PMTCT programmes as implemented in a number of Member

States in the WHO SEA and WP Regions. The routine offer of HIV testing/referral to VCT in/from TB treatment (DOTS) centres has started in north-east Thailand and selected states in India. However, concerns related to whether the consent for HIV testing is actually sought, as well as provision of HIV testing on site or "by referral" from TB centres remain low.

Key Issues Considered by the Group

- Are there settings in your countries where HIV testing and counselling should be offered to all clients?
- Are there clinical conditions that prompt clinicians to refer patients for HIV testing to improve clinical care?
- What are the major barriers to delivering HIV test considering the three C's (confidentiality, counselling, consent) in clinical care settings?
- What are the recommendations to WHO/partners and countries on how best to address these barriers?

Summary of Discussion and Recommendations

- Increasing the access to HIV testing and counselling requires further decentralization of services to the sub-district level and reinforcing the referral linkages to HIV prevention, care and treatment services as well as to other health care programmes.
- A phased approach is required for the expansion of HIV testing and counseling. It should be based on HIV prevalence and health system capacity [including access, and availability of prevention, treatment (ART), care and support programmes], and the strength of linkage and referral systems.
- Health programmes, such as STI and reproductive health, TB, PMTCT, drug and alcohol, prison health care, overseas workers, community level and focused prevention should offer "by referral" or on-site HIV testing and counselling. It was also proposed that blood screening programmes should offer referral to VCT centres.
- Where clinical conditions that suggest HIV infection are being seen and managed, clinicians should directly refer or offer diagnostic HIV testing for HIV to patients. In all situations consent needs to be sought. Currently the coverage of HIV testing is very low in clinical care settings informed consent of the patient. However in many countries of the regions this does not happen, for example in TB services.
- In many countries there is major concern that offering HIV testing may undermine or threaten existing services, especially in respect of TB cases because of the prevailing stigma and discrimination.

- There is a need for a refined Policy Statement that reflects the realities of the regions, and which would allow flexibility at the programme level (based on epidemiological data), to expand to include equal emphasis on prevention, and to reflect issues around consent for adolescents and children, and the essential packages of programmes needed for provider-initiated and client-initiated TC. This should also include statements on post-exposure prophylaxis (PEP) for health care workers and the broader community.
- HIV testing and counselling should be part of the essential package of HIV prevention, care and treatment, and requires both provider- and client-initiated approaches.
- Countries urgently need operational guidelines to expand their ability to offer HIV testing and counselling within other health programmes, (eg TB clinics, ANC, drug and alcohol/IDU services, prisons, oversees worker programmes and community-level prevention programmes). These need to be developed based on data generated during programme implementation and through modelling of costs. Efforts to decrease HIV-related stigma and discrimination at community and clinic levels in low-prevalence settings are urgently required. For this, HIV testing should be increased though this would clearly be more difficult to achieve in low-prevalence settings.
- In some countries HIV testing is required in situations related to migration and travel for employment or study. HIV prevention, treatment, care and support programmes urgently need to be linked to HIV testing in these situations.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Clinical Staging

The following were the conclusions and recommendations:

- There was overall consensus that the proposed revision to the four-stage system was appropriate and useful. No major revisions were suggested. Minor changes/additions/deletions and modifications were recommended which will be incorporated during the global consultation process;
- For positioning of TB in clinical staging, the recommendations of a bi-regional TB working group that will review existing data on HIV disease progression among TB patients would be considered;
- While it would be useful and desirable to include an immunological classification to accompany clinical staging, the capacity for CD4 testing is limited and would take time to become routine; thus, it was

suggested that any immunological classification should remain optional for now;

- The existing data on disease progression and prognosis should be considered to identify additional conditions that should be included in clinical staging;
- The use of clinical staging in clinical management and monitoring of HIV care, including ART should be validated;
- The existing WHO guidelines and tools should be revised to ensure that they reflect the revised clinical staging for adults and children.

5.2 Surveillance

The following were the recommendations:

- The AIDS case surveillance definitions should be revised and expanded to simplify reporting, surveillance definitions should be harmonized with clinical staging, and information on HIV-infected persons who need ART immediately or in the near future should be captured (Annex 4).
- Reporting of deaths among HIV-infected persons should be strengthened. This should include AIDS-attributed deaths and deaths due to ART complications.
- A case definition of HIV infection based on laboratory criteria for diagnosis and surveillance purposes should be developed.
- Surveillance information on HIV infections should be captured to effectively plan for an appropriate health system response and provide comprehensive prevention, treatment, care and support services for people living with HIV/AIDS (PLWHA). In order to gain experience in establishing a potential system for routine reporting of HIV infections in the foreseeable future, it would be useful at this stage to:
 - Define minimal useful surveillance data to be collected at the time of diagnosis of HIV-infection, and
 - Test the feasibility of reporting minimal useful data on HIV infections in some areas.
- Efforts should be continued to strengthen the existing second-generation surveillance, including HIV sentinel surveillance, and to promote the use of these data for producing HIV estimates and projections through modelling techniques.
- Guidelines and tools, including data collection forms, and training manuals should be developed in order to operationalize the revised advanced HIV infection/AIDS surveillance definitions.

5.3 HIV Testing for Diagnosis and Surveillance

The following recommendations were made:

- Specifications and the minimum criteria for HIV test kits should be identified, recognizing national requirements and global standards, and it should be ensured that HIV tests used in countries meet the specifications and required standards.
- Countries should be encouraged to review their current testing strategies and algorithms and make revisions in accordance with global strategies that will be revised to account for the new technological developments in HIV testing.
- HIV testing algorithms should be validated for the different testing objectives including PPV, NPV and cost, with an aim to review them on an annual basis.
- Quality management systems should be implemented and strengthened on a continuous basis, including training and supervision.
- Technical assistance should continue to be provided to countries in implementing these recommendations.

5.4 UNAIDS/WHO Statement on HIV Testing and Counselling

The following were the recommendations:

- HIV testing and counselling should be part of the essential package of HIV prevention, care and treatment, and requires both provider- and client-initiated approaches.
- It was recommended that health programmes, such as STI and reproductive health, TB, PMTCT, drug and alcohol, prison health care, overseas workers, community level and focused prevention should offer "by referral" or "on-site" HIV testing and counselling. It was also recommended that blood screening programmes should offer referral to VCT centres.
- Where clinical conditions that suggest HIV infection are being seen and managed, clinicians should refer or offer diagnostic HIV testing to patients. In all situations informed consent should be sought.
- Countries urgently need operational guidelines to expand their ability to offer HIV testing and counselling within other health programmes and settings, e.g. TB clinics, ANC, drug and alcohol/IDU services, prisons, overseas worker programmes and community-level prevention programmes. Such guidelines should be developed based on data generated during programme implementation and through modelling of costs.

- Efforts to decrease HIV-related stigma and discrimination at community and clinic levels in low-prevalence settings are urgently required. For this, HIV testing should be increased though this would clearly be more difficult to achieve in low-prevalence settings.

5.5 Action Points for WHO

It was recommended that:

- SEARO and WPRO should organize a review and analysis of existing data from the documentation in selected countries in the regions, for HIV/TB co-infections, disease progression, laboratories and VCT centres.
- WHO should examine the need to incorporate revised clinical staging and surveillance definitions into existing training materials and to identify areas where new training materials may need to be developed. The need for new and additional training activities should be identified.
- Over a longer time-frame (e.g. two years), SEARO and WPRO should identify steps needed to evaluate and validate the staging and surveillance systems and also explore the feasibility for instituting systems for HIV case reporting.
- Organizing multi-country meetings to explore the potential and share experiences, either in SEARO, WPRO or bi-regional sessions, have proved useful, but it is important to group countries in terms of their size (geographical and/or population) and level of institutional capacity and development. Smaller countries and countries with less capacity may need to examine programme considerations with countries in similar situation and/or with comparable capacities, in order to maximize the effectiveness of bi- or inter-regional technical consultation.
- A regional policy statement on HIV testing and counseling should be developed.

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Annex 2

Programme

Wednesday, 1 June 2005

08.00 - 09.00

Registration

09.00 - 10.00

Opening Ceremony

- RD's inaugural speech (read out by Dr Jai P. Narain, CDS)
- Welcome remarks by *Dr Siobhan Crowley, WHO/HQ*
- Introduction of participants
- Objectives and expected outcomes, review of the meeting agenda
administrative announcements by *Dr Ying-Ru Lo, WHO/SEARO*
- Group photograph

10.30 - 17.30

Session 1: WHO clinical staging system for HIV/AIDS and AIDS case definitions

Specific Objectives:

- To familiarize the participants with the proposed revision of the WHO clinical staging system for HIV/AIDS and AIDS case definitions for surveillance, and
- To develop consensus on the proposed revisions of WHO clinical staging system for HIV/AIDS and AIDS case definitions for surveillance.
- To identify and agree on additions or regional adaptations to the WHO clinical staging system for HIV/AIDS and AIDS case definitions for surveillance that may reflect the spectrum of HIV in South-East Asia and Western Pacific regions.
- To make recommendations on how to improve the use of the WHO clinical staging system for HIV/AIDS and on AIDS case definitions for reporting.

10.30 - 11.15

Proposed revision to the WHO clinical staging system for HIV/AIDS in adults and adolescents, and children

Dr Siobhan Crowley, HQ

11.15 - 11.45

Overview of the proposed AIDS case definitions for surveillance in adults and children and their relevance to WHO clinical staging

Dr Renu Garg, SEARO

11.45 - 12.30

Plenary discussion on WHO clinical staging system for HIV/AIDS and AIDS case definitions

13.30 - 16.30

Group work review of proposed revisions to clinical staging and AIDS case definitions for surveillance (*with tea/coffee served at 15.30 hours*)

16.30 - 17.30

Finalize key recommendations to WHO on revisions to clinical staging and AIDS case definitions for reporting

17.30 - 18.00

Secretariat meeting

Thursday, 2 June 2005**08.30 - 09.00**

Admin. and feedback from day 1 — *Dr Ying-Ru Lo, SEARO*

09.00 - 10.30

Presentations: Final recommendations on revisions to WHO clinical staging system for HIV/AIDS in adults and adolescents and children, and AIDS case definitions

- ♦ Rapporteurs from groups
- ♦ Discussion

11.00 - 12.30

Practical next steps in implementation and early use

Dr Ying-Ru Lo, SEARO and Dr Michel Tailhades, WPRO

13.30 - 17.45

Session 2: Global and regional HIV testing policies and strategies and recommendations on use of HIV rapid tests

Specific Objectives:

- ♦ To review international and national HIV testing policies and guidance on use of rapid testing technologies, and
- ♦ To review actual implementation of national policies for HIV testing including rapid testing and barriers to scaling up access to HIV testing and counselling.

13.30 - 14.00

Global and regional policy and technical recommendations on HIV testing

Dr Gaby Vercauteren, HQ

- ♦ Technical aspects- sensitivity, specificity
- ♦ Operational aspects; who, where and laboratory requirements

- Algorithms
- Quality assurance

14.00 - 14.30

Proposed HIV testing algorithms for surveillance and diagnosis in low-prevalence countries with limited resources

Dr John Parry, UK

14.30 - 15.30

Country examples of implementation

(Four countries present experiences, highlighting specific obstacles of concern):

- HIV testing policies and strategies — *Dr Jiang Yan, China*
- Serial vs. parallel algorithms — *Dr R. Paranjape, India*
- Rapid testing for HIV testing and HIV surveillance — *Dr Sujatha Samarakoon, Sri Lanka*
- Quality control — *Mrs Wilai Chalermchan, Thailand*

16.00 - 17.45

Country presentations (continued) followed by Plenary discussion

17.45 - 18.15

Secretariat meeting

Friday, 3 June 2005

Specific Objective:

- To agree on essential testing algorithms and quality control components for use in rapid HIV testing services for diagnosis and surveillance in low-prevalence countries with limited resources.

08.30 - 08.45

Admin. and feedback from day 2 — *Dr Ying-Ru Lo, SEARO*

08.45 - 09.15

Joint CDC-WHO training package on "Provision of training and supervision for use of HIV rapid testing"

Dr John Ridderhoff, CDC

- Training for use of HIV rapid tests in T and C services
- Quality management
- Supervision

09.15 - 09.30

UNAIDS/WHO Policy Statement on HIV Testing

Dr Ying-Ru Lo, SEARO

09.30 - 12.30

Group Work:

1. Testing essential algorithms and quality control components for use in rapid HIV testing services
2. UNAIDS/WHO Policy Statement on HIV Testing

13.30 - 14.00

Group Work 1 and 2 (continued)

14.00 - 14.30

Practical next steps in implementation and early use

Dr Ying-Ru Lo, SEARO and Dr Michel Tailhades, WPRO

14.30 - 16.00

Conclusions and recommendations followed by closure of the meeting

16.00 - 17.00

Secretariat meeting

Annex 3

PROPOSED REVISIONS TO WHO CLINICAL STAGING FOR HIV/AIDS

[A]

SEARO/WPRO comments on WHO clinical staging of HIV/AIDS for adults and adolescents. *Revisions are in italics*

Table 1. 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, *tonsillitis*, bronchitis, otitis media, pharyngitis)
Herpes zoster (*single episode-complicated, severe or frequent recurrences may be a higher stage*)
Angular cheilitis - Remove
Recurrent oral ulcerations
Papular pruritic eruptions (*severe PPE may be stage 3*)
Seborrhoeic dermatitis - Remove
Fungal nail infections of fingers (*questioned should this be stage 3*)
Suggest to add cervical lymphnode TB

Clinical stage 3

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)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis (*needs review of national data on TB/HIV to determine if it should be positioned as stage 3 or 4 - where CD4 is available, use it to determine if ART is urgently required*)
Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)

Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Unexplained anaemia (<8 g/dl *check the haemoglobin grading cut-off*), and or neutropenia (<500/mm³) and or thrombocytopenia (<50 000/ mm³) for more than one month

Consider adding:

Anal intraepithelial neoplasia (AIN)

Cervical intraepithelial neoplasia (CIN)

Extensive multiple wart virus infection

Recurrent vulvo vaginal candida

Clinical stage 4

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 *or visceral at any site*)

Oesophageal candidiasis

Extrapulmonary/disseminated TB (*Severe forms*)

Kaposi's sarcoma

Central nervous system (CNS) toxoplasmosis

HIV encephalopathy

Cryptococcosis

Disseminated non-tuberculous mycobacteria infection

Progressive multifocal leukoencephalopathy (PML)

(Candida of trachea, bronchi or lungs - Remove)

Cryptosporidiosis

Isosporiasis

Cytomegalovirus (CMV) infection

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

Consider additions:

Microsporidiosis

Myelitis

Norwegian scabies

Amoebic abscess

Nocardiosis

AIN - Anal intraepithelial neoplasia

CIN - Cervical intraepithelial neoplasia

SEARO/WPRO comments on WHO clinical staging of HIV/AIDS for children
Revisions are in italics

Table 2. Children

Clinical Stage 1

Asymptomatic

PGL

Clinical Stage 2

Hepatosplenomegaly

Papular pruritic eruptions

(Seborrhoeic dermatitis - Remove)

Extensive wart virus infection

Extensive molluscum contagiosum

Fungal nail infections

Recurrent oral ulcerations

Lineal gingival erythema (LGE)

(Angular cheilitis - Remove)

Parotid enlargement

Herpes zoster *(single uncomplicated - severe disseminated primary should be higher stage)*

Recurrent or chronic RTIs (otitis media, otorrhoea, sinusitis, tonsillitis)

Respiratory tract infections (RTIs)

Suggest add: Cervical lymphnode tuberculosis

Clinical Stage 3

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 and recurrent presumed bacterial pneumonia

Symptomatic lymphoid interstitial pneumonitis (LIP)

Chronic HIV-associated lung disease including bronchiectasis

Unexplained anaemia (<8g/dl *check the grading*), and or neutropenia (<500/mm³) and or thrombocytopenia (<50 000/mm³) for more than one month

Clinical Stage 4

Unexplained severe wasting, *stunting* or severe malnutrition not adequately responding to standard therapy

Pneumocystis pneumonia

Recurrent and 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 (severe or disseminated)

Kaposi's sarcoma

Oesophageal candidiasis

CNS toxoplasmosis (outside the neonatal period)

HIV encephalopathy

CMV infection (CMV retinitis or infection of organs other than liver, spleen or lymph nodes; onset at the 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 - Remove

Cerebral or B cell non-Hodgkin lymphoma

Progressive multifocal leukoencephalopathy (PML)

HIV-associated cardiomyopathy or HIV-associated nephropathy (? consider for stage 3)

[B]**SEAROW/PRO Comments on 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.). *Revisions are in italics.*

Clinical event	Presumptive diagnosis	Definitive diagnosis
Primary HIV infection		
Asymptomatic infection <i>(was unrecognized)</i>		Detectable core P24 antigen and high blood HIV RNA, profound temporary lymphopenia and other transient blood abnormalities may occur. Not usually HIV Ab-positive until after symptoms.
Acute retroviral syndrome	Acute febrile illness 2-4 weeks post-exposure, often with lymphadenopathy, pharyngitis and <i>skin rashes</i>	Seroconversion from HIV Ab-negative to Ab-positive.
Clinical Stage 1		
Asymptomatic	No symptoms reported and no signs on examination.	Not required.
Persistent generalized lymphadenopathy (PGL)	<i>Painless enlarged lymph nodes >1 cm, in two or more non-contiguous sites, excluding inguinal nodes, in absence of known cause.</i>	Not required but can be confirmed by histology (germinal centre hyperplasia, lymph node structure preserved).
Clinical Stage 2		
Moderate unexplained weight loss (of measured body weight)	Reported weight loss but no visible thinning of face or body.	Confirmed by documented <i>less than 10% weight loss.</i>

Clinical event	Presumptive diagnosis	Definitive diagnosis
Recurrent presumed bacterial RTI <i>(was upper only two or more in any six-month period)</i>	Symptoms complex, e.g. unilateral face pain with nasal discharge (sinusitis) or painful swollen eardrum (otitis media), cough with purulent sputum (bronchitis), sore throat (pharyngitis), tonsillitis Two or more documented occurrences of antibiotic- responsive RTI.	Not required but may be confirmed by laboratory studies where available, e.g. culture of suitable body fluid.
<i>Single episode of Herpes zoster</i>	Painful rash of small fluid-filled blisters in distribution of a nerve supply, can be haemorrhagic on erythematous background, and does not cross midline. <i>Severe or frequently recurrent herpes zoster is usually associated with more advanced HIV disease.</i>	Not required.
<i>Angular cheilitis - Remove</i>	<i>Splits or cracks on lips at the angle of the mouth with depigmentation, usually respond to antifungal treatment but may recur. Also common in nutritional deficiency, e.g. of B vitamins.</i>	<i>Not required.</i>
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	Not required.

Clinical event	Presumptive diagnosis	Definitive diagnosis
	bites should be excluded. <i>Severe PPE should be considered a stage 3 condition</i>	
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 onychomycosis is uncommon without immunodeficiency.	Not required but confirmed by culture of nail scrapings.

Clinical Stage 3

Severe unexplained weight loss (<i>more than 10% of body weight</i>)	Reported weight loss without trying, and <i>visible</i> 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	Reports of fever or night sweats for more than one	Not required but confirmed if documented fever $>37.5^{\circ}\text{C}$

Clinical event	Presumptive diagnosis	Definitive diagnosis
(intermittent or constant and for longer than one month)	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.	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	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), persistent or recurring.	Not required.
Oral hairy leukoplakia	Fine small linear patches on lateral borders of the tongue, generally bilaterally, which do not scrape off.	Not required.
Pulmonary TB (<i>current</i>)	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.	Not required but confirmed by positive sputum culture.

Clinical event	Presumptive diagnosis	Definitive diagnosis
	<p>Note: TB diagnosis and treatment should follow national or international guidelines.</p> <p>CD4 should be used where possible to guide therapy; <i>very low CD4 should be considered stage 4 and require urgent ART.</i></p>	
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 respond 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 <i>check the grading level for this</i>), neutropenia (<500/mm ³) or thrombocytopenia (<50 000/ 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.
<i>Add frequent or severe recurrences of herpes zoster</i>	<i>Need to check and review cohort data from India and Thailand and then define.</i>	

Clinical event	Presumptive diagnosis	Definitive diagnosis
Clinical Stage 4		
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 oC 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 usually shows 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.

Clinical event	Presumptive diagnosis	Definitive diagnosis
Chronic herpes simplex virus (HSV) infection (orolabial, genital or anorectal of more than one month, or visceral of any duration)	Severe and progressively 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 mucocutaneous HSV but required for visceral HSV. Suggestive symptoms of organ damage, e.g. bronchitis, pneumonitis, oesophagitis, colitis, encephalitis, supported by histology or culture.
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 <i>Candida</i> . Responds to antifungal treatment.	Not required but confirmed by macroscopic appearance at endoscopy or bronchoscopy, microscopy or histology.
Extrapulmonary/ disseminated TB (<i>severe forms</i>)	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. <i>Mycobacterium tuberculosis</i> isolated from blood culture or any appropriate specimen except sputum or bronchoalveolar lavage (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).

Clinical event	Presumptive diagnosis	Definitive diagnosis
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 : <ul style="list-style-type: none"> - typical red-purple lesions seen on bronchoscopy or endoscopy; - dense masses in lymph nodes, viscera or lungs by palpation or radiology; - histology.
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 non-specific or normal. Resolution of findings after treatment if patient survives.

Clinical event	Presumptive diagnosis	Definitive diagnosis
Cryptococcal meningitis or other extrapulmonary <i>Cryptococcus</i> infection	Meningitis: usually sub-acute, fever with increasingly 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.
Disseminated non-tuberculous mycobacteria infection	No presumptive diagnosis.	Non-specific 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.

Clinical event	Presumptive diagnosis	Definitive diagnosis
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. Isosporiasis responds to high-dose cotrimoxazole.
Any disseminated mycosis (e.g. coccidiomycosis, histoplasmosis, penicilliosis)	No presumptive diagnosis.	Clinical symptoms non-specific, e.g. skin rash, cough, shortness of breath, fever, anaemia, weight loss.

Clinical event	Presumptive diagnosis	Definitive diagnosis
		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.	Non-specific 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, post-coital or intermenstrual bleeding unresponsive to appropriate antibacterial or antifungal treatment; cervical lesions visualized. Histology. Cytology, but not carcinoma <i>in situ</i> .
Visceral leishmaniasis	No presumptive diagnosis.	Suggestive symptoms: malaise, chronic fever,

Clinical event	Presumptive diagnosis	Definitive diagnosis
<p><i>Proposed to consider adding :</i></p> <ul style="list-style-type: none"> <i>Microsporidiosis</i> <i>Myelitis?</i> <i>Norwegian scabies</i> <i>Amoebic abscess</i> <i>Nocardiosis</i> 		<p>hepatosplenomegaly, pancytopenia. Amastigotes visualized or cultured from any appropriate clinical specimen.</p>

- Ab - Antibody
- PGL - Persistent generalized lymphadenopathy
- PML - Progressive multifocal leukoencephalopathy

[C]**Clinical Staging Events as Tools 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	May consider interruption of cotrimoxazole if stable on ART for longer than six months
New or recurrent : Stage 2	Check adherence Treat and manage condition Restart cotrimoxazole Should alert the provider to the possibility of poor adherence or failure of response to treatment.

[D]**SEARO/WPRO Comments on 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.). *Revisions are in italics.*

Clinical event	Clinical diagnosis	Definitive diagnosis
Clinical Stage 1		
Asymptomatic	No symptoms reported and no signs on examination.	Not required.
PGL	<i>Painless</i> 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	Enlarged liver or spleen: Unexplained	Not required.
Papular pruritic eruptions	Persistent papular pruritic vesicular lesions; scabies should be excluded.	Not required.
<i>Seborrhoeic dermatitis - Remove</i>	<i>Itchy scaly skin condition particularly affecting scalp, face, upper trunk and perineum. Also common in uninfected children and in babies.</i>	<i>Not required.</i>
Fungal nail infections	Fungal paronychia (painful, red and swollen nail bed) or onycholysis (painless)	<i>Not required. Culture of nail scrape - Remove</i>

Clinical event	Clinical diagnosis	Definitive diagnosis
	separation of the nail from the nail bed). Proximal white subungual onychomycosis is uncommon without immunodeficiency.	
<i>Angular cheilitis - Remove</i>	<i>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.</i>	<i>Not required.</i>
Lineal Gingival Erythema	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 wart virus infection <i>(extensive remove facial, more than 5% of body area or disfiguring)</i>	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 <i>(extensive facial, remove more than 5% of body area or disfiguring)</i>	Characteristic skin lesions: small flesh-coloured, pearly or pink, dome-shaped or umbilicated growths, may be inflamed or red. Also common in uninfected children. <i>Giant molluscum is stage 3</i>	Not required.

Clinical event	Clinical diagnosis	Definitive diagnosis
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.
Herpes zoster (<i>Note: severe or frequent persistent herpes zoster may have worse prognosis</i>)	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.	<i>Not required</i> <i>Viral culture, histology, EM of lesion fluid - Remove.</i>
Recurrent RTI (otitis media, otorrhoea or sinusitis) 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 (<i>tonsillitis</i>), 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	<i>Unexplained weight loss or failure to gain weight, not explained by poor or</i>	<i>Not required</i> <i>Documented loss of body</i>
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Clinical event	Clinical diagnosis	Definitive diagnosis
standard deviations (SDs) (3, 4); not responding adequately to standard therapy,	inadequate feeding or other infections (<i>including TB</i>), and not adequately responding within two weeks to standard management.	<i>weight, failure to gain weight on standard management and no other cause identified during investigation.</i>
Unexplained persistent diarrhoea (14 days or more)	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 $>37.5^{\circ}\text{C}$ with negative blood culture, negative malaria slide and normal or unchanged CXR, and no other obvious foci of disease.
Oral candidiasis (outside neonatal period)	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.	<i>Not required Microscopy or culture - Remove</i>
Oral hairy leukoplakia	Fine, small linear patches on lateral borders of tongue, generally bilaterally, which do not scrape off.	Not required.

Clinical event	Clinical diagnosis	Definitive diagnosis
Pulmonary TB	Non-specific 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 and presumed bacterial pneumonia	Cough with fast breathing, chest indrawing, nasal flaring, wheezing, and grunting. Crackles or consolidation on auscultation. Responds to a 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.
LIP	<i>Chronic cough, fever, and clubbing and radiologically bilateral reticulonodular interstitial pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Frequently confused with miliary TB. May present with cor pulmonale and may have</i>	Oxygen saturation persistently <90%.

Clinical event	Clinical diagnosis	Definitive diagnosis
	<i>increased exercise-induced fatigue.</i>	
Chronic HIV-associated lung disease (including bronchiectasis)	<i>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 not explained by other conditions.</i>	<i>CT scan of chest may be used to confirm the diagnosis.</i>
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

Unexplained severe wasting, or severe malnutrition or <i>stunting</i> not adequately responding to standard therapy	Persistent weight loss, <i>stunting or developmental delay including pubertal delay</i> 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	<i>Not required</i> <i>Documented weight loss without trying - Remove.</i>
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Clinical event	Clinical diagnosis	Definitive diagnosis
	oedema of both feet, and/or weight-for-height of -3 SDs, as defined by WHO IMCI guidelines.	
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 a 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 and 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 progressively 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.
Oesophageal candidiasis	Chest pain and dysphagia (difficulty in swallowing), odynophagia (pain on	Not required.

Clinical event	Clinical diagnosis	Definitive diagnosis
	<p>swallowing food and fluids), or retrosternal pain worse on swallowing (food and fluids) +/- oral <i>Candidiasis</i>. Responds to antifungal treatment. May be difficult to detect in young children. Suspect if oral <i>Candida</i> observed and if refusal occurs or if there are difficulties or crying when feeding.</p>	
Extrapulmonary TB	<p><i>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 cervical lymph gland extrapulmonary TB has a better prognosis.</i></p>	<p><i>Definite diagnosis not required but confirmed by Mycobacterium tuberculosis isolated from blood culture or other specimen except sputum or BAL. Positive AFB on microscopy or culture on relevant specimens. Biopsy and histology. X-ray.</i></p>
Kaposi's sarcoma	<p><i>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.</i></p>	<p><i>Not required but may be confirmed by :</i></p> <ul style="list-style-type: none"> - <i>typical red-purple lesions seen on bronchoscopy or endoscopy;</i> - <i>dense masses in lymph nodes, viscera or lungs by palpation or radiology;</i> - <i>histology.</i>

Clinical event	Clinical diagnosis	Definitive diagnosis
<p>CMV retinitis and CMV infection of organs other than liver, spleen or lymph nodes.</p>	<p>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.</p>	<p>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.</p>
<p><i>CMV (retinitis or CMV infection of an organ other than liver, spleen or lymph nodes) onset at age over one month</i></p>	<p><i>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.</i></p>	<p><i>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).</i></p>
<p>CNS toxoplasmosis (outside the neonatal period)</p>	<p><i>Fever, headache, focal neurological signs, convulsions. Usually responds to high-dose co-trimoxazole or pyrimethamine and sulphadiazine or clindamycin.</i></p>	<p><i>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 non-specific or normal. Resolution of findings after treatment if child survives.</i></p>

Clinical event	Clinical diagnosis	Definitive diagnosis
Cryptococcal meningitis	Meningitis: usually sub-acute fever with increasingly 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: <ul style="list-style-type: none"> - failure to attain, or loss of, developmental milestones, loss of intellectual ability; or - progressively 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. 	<i>Not required</i>
PML	<i>Progressively focal neurological signs without headache or fever. Cortical blindness and cerebellar signs. Convulsions are rare.</i>	<i>Confirmed by MRI or CT scan</i>
Any disseminated mycosis (e.g.	No presumptive clinical diagnosis.	Organ-specific and non-specific symptoms, e.g. may

Clinical event	Clinical diagnosis	Definitive diagnosis
histoplasmosis, coccidiomycosis, penicilliosis)		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 <i>bronchoscopy</i> . Microscopy and culture of specimen from endoscopic tissue.
Disseminated mycobacteriosis, other than TB	No presumptive clinical diagnosis.	Non-specific 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 lungs.
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.

Clinical event	Clinical diagnosis	Definitive diagnosis
		Isosporiasis responds to high-dose co-trimoxazole.
Cerebral or B cell non-Hodgkin lymphoma	No presumptive clinical diagnosis.	Symptoms consistent with lymphoma: lymphadenopathy, hepatosplenomegaly, pancytopenia, besides other non-specific 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.
<i>Acquired HIV-associated rectal fistula, including rectovaginal fistula - Remove</i>		<i>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.</i>
<i>HIV-associated nephropathy</i>	No presumptive clinical diagnosis.	Symptoms and signs suggestive of renal disease,

Clinical event	Clinical diagnosis	Definitive diagnosis
<p><i>Should this be stage 3?</i> Further information and evidence relating to this condition and its definition are being sought.</p>		<p>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.</p>
<p><i>HIV-associated cardiomyopathy</i> <i>Should this be stage 3?</i> Further information and evidence relating to this condition and its definition are being sought.</p>	<p>No presumptive clinical diagnosis.</p>	<p>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.</p>

Annex 4

HIV/AIDS Case Surveillance Definitions

Definition of advanced HIV/AIDS infection for adults:

- Any clinical stage 3 or stage 4 disease

OR

- Where CD4 is available, $CD4 < 350/mm^3$ at any clinical stage

Definition of advanced HIV infection for children:

- Clinical stage 3 or stage 4 disease at any age

OR

Where CD4 available, any clinical stage with

- $CD4 < 25\%$ for under 12 months
- $CD4 < 20\%$ for 12-59 months
- $CD4 < 350/mm^3$ for 5 years and above

Note: The immunological criteria to define advanced HIV infection/AIDS should be optional.