

# Virtual Mentor

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## CLINICAL PEARL

### The WHO Clinical Staging System for HIV/AIDS

Jennifer L. Weinberg and Carrie L. Kovarik, MD

For over twenty years, human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) have been significant public health concerns, and the epidemic continues to challenge humanity. The majority of the world's new HIV infections occur in low- and middle-income countries, with two-thirds of the world's HIV-infected population living in Africa [1]. Many complex factors contribute to the disproportionate impact of HIV in resource-poor settings: poverty, disease stigma, cultural and social barriers to testing and treatment, insufficient health care infrastructure to support the large patient pool, lack of health literacy, limited provider training, inadequate medical equipment, scarce manpower to distribute health care throughout the region, and few qualified laboratory facilities [2].

In areas with adequate resources, laboratory measurements of CD4+ T cells and plasma HIV viral load are commonly used to establish a patient's degree of immunosuppression and the rate of destruction of the immune system [3]. These tools are used to ascertain a patient's eligibility for treatment and to monitor disease progression. With insufficient resources to test CD4+ T-cell counts and plasma HIV viral load in many resource-limited settings, including many of the regions hardest hit by the HIV/AIDS epidemic, clinicians must rely on clinical parameters when assessing a patient's disease status. The World Health Organization (WHO) has developed case definitions for HIV surveillance and clinical staging and immunological classification of HIV-related disease in adults and children. This system uses standardized clinical parameters to direct medical decision making for patients with HIV/AIDS and can be used based solely on patient clinical features, thus accommodating facilities with no or limited access to laboratory testing [4]. The WHO Clinical Staging system has been shown to be a practical and accurate way to manage HIV-infected patients, with international studies showing agreement between clinical manifestations included in the WHO staging system and laboratory markers including CD4 cell count and total lymphocyte count [5-8].

With the progression of the HIV/AIDS epidemic, consideration of the entire spectrum of infection is necessary. Several discrete clinical phases can be recognized along the continuum, and they correlate with the degree of immunodeficiency that arises with progression of HIV infection. Early identification and treatment is crucial to reduce transmission of the virus, but many people remain unaware of their HIV status during the crucial early months of infection when transmission risk is high, secondary to elevated levels of viremia [3]. Monitoring systems that do not rely on

laboratory techniques are also needed in resource-limited settings to monitor the increasing numbers of patients on antiretroviral medications [9]. The Revised WHO HIV/AIDS Clinical Staging System is intended for baseline assessment of patients and for use in provision of ongoing care. The revised system:

- Provides guidance including when to start, switch, or stop prophylactic medications, antiretrovirals, and other interventions;
- Assists clinicians in the assessment of a patient's current clinical status;
- Encourages clinical providers to offer diagnostic HIV testing to patients who exhibit clinical signs suggestive of HIV infection;
- Classifies disease in a progressive sequence from least to most severe;
- Is designed to be used with reference to current and previous clinical events, making it useful for surveillance purposes [4].

### **Four Clinical Stages**

The WHO system for adults sorts patients into one of four hierarchical clinical stages ranging from stage 1 (asymptomatic) to stage 4 (AIDS). Patients are assigned to a particular stage when they demonstrate at least one clinical condition in that stage's criteria. Patients remain at a higher stage after they recover from the clinical condition which placed them in that stage [5].

*Stage 1.* Patients who are asymptomatic or have persistent generalized lymphadenopathy (lymphadenopathy of at least two sites [not including inguinal] for longer than 6 months) are categorized as being in stage 1, where they may remain for several years [10].

*Stage 2.* Even in early HIV infection, patients may demonstrate several clinical manifestations. Clinical findings included in stage 2 (mildly symptomatic stage) are unexplained weight loss of less than 10 percent of total body weight and recurrent respiratory infections (such as sinusitis, bronchitis, otitis media, and pharyngitis), as well as a range of dermatological conditions including herpes zoster flares, angular cheilitis, recurrent oral ulcerations, papular pruritic eruptions, seborrhoeic dermatitis, and fungal nail infections [4].

*Stage 3.* As disease progresses, additional clinical manifestations may appear. Those encompassed by the WHO clinical stage 3 (the moderately symptomatic stage) category are weight loss of greater than 10 percent of total body weight, prolonged (more than 1 month) unexplained diarrhea, pulmonary tuberculosis, and severe systemic bacterial infections including pneumonia, pyelonephritis, empyema, pyomyositis, meningitis, bone and joint infections, and bacteremia. Mucocutaneous conditions, including recurrent oral candidiasis, oral hairy leukoplakia, and acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis, may also occur at this stage [4].

*Stage 4.* The WHO clinical stage 4 (the severely symptomatic stage) designation includes all of the AIDS-defining illnesses. Clinical manifestations for stage 4 disease that allow presumptive diagnosis of AIDS to be made based on clinical

findings alone are HIV wasting syndrome, *Pneumocystis pneumonia* (PCP), recurrent severe or radiological bacterial pneumonia, extrapulmonary tuberculosis, HIV encephalopathy, CNS toxoplasmosis, chronic (more than 1 month) or orolabial herpes simplex infection, esophageal candidiasis, and Kaposi's sarcoma [4]. Other conditions that should arouse suspicion that a patient is in clinical stage include cytomegaloviral (CMV) infections (CMV retinitis or infection of organs other than the liver, spleen or lymph nodes), extrapulmonary cryptococcosis, disseminated endemic mycoses (e.g., coccidiomycosis, penicilliosis, histoplasmosis), cryptosporidiosis, isosporiasis, disseminated non-tuberculous mycobacteria infection, tracheal, bronchial or pulmonary candida infection, visceral herpes simplex infection, acquired HIV-associated rectal fistula, cerebral or B cell non-Hodgkin lymphoma, progressive multifocal leukoencephalopathy (PML), and HIV-associated cardiomyopathy or nephropathy [4]. Presence of these conditions unaccompanied by the AIDS-defining illnesses, however, should prompt confirmatory testing.

These categories apply to adults and adolescents 15 years-of-age and older. A modified version of the WHO Clinical Staging System is available for infants and children under 15 [4].

Like CD4 counts and viral load testing, recognition of these clinical findings included in the WHO system is an important method for identifying HIV-infected individuals at high risk for morbidity and mortality. Remaining aware of the natural course of HIV infection allows one to base management decisions on the patient's clinical presentation. According to the WHO, advanced HIV/AIDS disease is defined for surveillance purposes as any clinical stage-3 or stage-4 disease or any clinical stage with a CD4 count greater than 350 per cubic mm, and this information can be used to calculate the burden of disease and the demand for antiretroviral therapy [4]. Strong evidence supports the clinical benefit of antiretroviral medications for adults with advanced HIV/AIDS as determined clinically or immunologically, with the WHO recommending definitive initiation of antiretroviral therapy in adults and adolescents in clinical stage 4, consideration of therapy initiation for those in clinical stage 3, and antiretroviral use for those in clinical stage 1 or 2 only if the CD4 count is greater than 200 per cubic mm [4]. For patients taking antiretroviral therapy for more than 24 weeks, new or recurrent clinical staging events can be a guide to decision-making. Prior to 24 weeks of antiretroviral treatment, clinical events are largely influenced by immune reconstitution or treatment toxicity and may not accurately reflect immune deterioration [11]. WHO guidelines report that the appearance of new or recurrent WHO clinical stage 3 and 4 conditions beyond 24 weeks after initiation of therapy suggests treatment failure [9].

The HIV/AIDS epidemic clearly has broad and significant implications for individuals living around the globe. Populations in developing nations are especially hard-hit by HIV infection and, at the same time, frequently lack access to technological advances and other resources for diagnosing and managing care. Screening strategies, such as the WHO Clinical Staging System, allow for efficient

identification of early infection and aggressive management when clinicians are equipped with the knowledge to apply them, and can therefore be useful tools for improving access to and implementation of care.

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Jennifer L. Weinberg is an MD/master of bioethics dual-degree candidate at the University of Pennsylvania in Philadelphia and will complete both degrees by May 2010. She has traveled to Botswana, Thailand, the Czech Republic, Slovakia, Turkey, and Croatia to participate in international health outreach efforts and community service projects. She has also dedicated time to studying and improving the reach of tele dermatology for resource-limited settings. Weinberg hopes to

integrate her interests in international health, bioethics, and public health in her career.

Carrie L. Kovarik, MD, is an assistant professor of dermatology, dermatopathology, and infectious diseases at the University of Pennsylvania in Philadelphia. Dr. Kovarik has a special interest in tropical, infectious, and HIV-related dermatology. She is head of dermatology for the Botswana-UPenn Partnership and is the primary dermatology consultant for the Baylor International Pediatric AIDS Initiative (BIPAI) in Africa. Dr. Kovarik has created an African teledermatology consult service ([africa.telederm.org](http://africa.telederm.org)) that is a collaborative effort between BIPAI, the American Academy of Dermatology, 12 African countries, and several other institutions. Dr. Kovarik has started an initiative in global health at the University of Pennsylvania, and she is the director of the Penn Dermatology Global Health program.

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