

CLINICAL REVIEW

Diagnosing HIV-Related Disease

Using the CD4 Count as a Guide

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OBJECTIVE: To summarize current information on the relation between CD4 counts and the risk of different HIV-related diseases.

MEASUREMENTS AND MAIN RESULTS: MEDLINE search of English language articles between 1985 and 1996 using the medical subject heading (MeSH) term "CD4 lymphocyte count" and searches using key words of multiple HIV-related diseases were conducted. Some HIV-related diseases can be stratified to different CD4 count levels. Regardless of their CD4 count, HIV-infected patients are susceptible to sinusitis, Kaposi's sarcoma, community-acquired pneumonia, and oral hairy leukoplakia. In advanced HIV, when CD4 is below 200/mm³, *Pneumocystis carinii* pneumonia, toxoplasmosis, progressive multifocal leukoencephalopathy, *Mycobacterium avium* complex, molluscum contagiosum, and bacillary angiomatosis all increase in incidence. In very advanced HIV disease, when CD4 counts are below 50/mm³, patients are at risk of pseudomonas pneumonia, cytomegalovirus retinitis, central nervous system lymphoma, aspergillosis, and disseminated histoplasmosis.

KEY WORDS: CD4 count; HIV-related disease; risk stratification. *J GEN INTERN MED* 1998;13:131-136.

Risk of many HIV-related disease varies with the patient's degree of immunosuppression. CD4 count, CD4 percentage, quantitative HIV-1 RNA (viral load), neopterin level, and p-24 antigenemia have all been proposed as surrogate markers of immune function. Among these, CD4 counts and quantitative HIV-1 RNA levels are used most commonly. Quantitative HIV-1 RNA is a more reliable surrogate marker for progression to AIDS and death than CD4 counts.¹ However, HIV-1 RNA levels can vary up to fourfold during acute infections,² and there is no defined relation between HIV-1 RNA levels and risk of opportunistic infections. Consequently, the CD4 count remains the most useful test for estimating risk of many HIV-related diseases.

The advent of combination antiretroviral therapy using protease inhibitors, nucleoside analogues, and non-nucleoside reverse transcriptase inhibitors has led to substantial increases in CD4 counts in some patients. Whether these increased CD4 counts alter patients' risk of opportunistic infections is uncertain. Until studies clarify this issue, it is prudent to base patients' management on their CD4 counts before initiation of antiretroviral therapy.

Technical and physiologic variability contributes to the overall variability of CD4 counts. In one study of clinically stable, HIV-infected patients, CD4 counts varied by 13.7% when measured 4 weeks apart. Laboratory variance accounted for 15% of the overall variance, while physiologic variance accounted for 85%.³ In a different study, CD4 counts varied by 25% when measured 8 weeks apart.⁴ CD4 counts vary throughout the day and in response to acute infections, smoking, exercise, and stress.⁵ One approach to address this variability is to draw specimens at a similar time of the day, use the same laboratory to process the specimens, and use serial tests to guide management decisions.

By appreciating the CD4 counts below which certain HIV-related diseases occur (Table 1) and by appreciating the various ways diseases manifest at different CD4 counts, clinicians can focus their differential diagnoses and improve the efficiency of their diagnostic evaluations. This review examines the relation between CD4 counts and common HIV-related diseases that cause respiratory, central nervous system (CNS), dermatologic, and systemic problems.

METHODS

A MEDLINE search for relevant English language articles between 1985 and 1996 was completed using the MeSH term "CD4 lymphocyte count." We also searched using the terms *Pneumocystis carinii*, tuberculosis, pneumonia, sinusitis, *cryptococcus*, toxoplasmosis, dermatology, *Mycobacterium avium* complex, lymphoma, and CNS. All were combined with the term HIV. Studies were reviewed for information on CD4 count and correlation with specific diseases.

RESPIRATORY DISEASE

HIV-infected individuals frequently present with non-specific respiratory symptoms including cough, dyspnea,

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Table 1. CD4 Counts Below Which Selected Diseases Commonly Occur

Disease Stage	CD4 Count	Respiratory Disease	Dermatologic Disease	CNS Disease	Systemic Disease
Early	>500	Bacterial pneumonia & sinusitis*	Oral hairy leukoplakia Vaginal candidiasis Kaposi's sarcoma	HIV meningitis	
Intermediate	<500	Tuberculosis	Thrush*		
	<400		Herpes zoster*		
	<300		Herpes simplex* Eosinophilic folliculitis		
Advanced	<250	PCP			
	<200			HIV dementia	Non-Hodgkin's lymphoma
	<150	Coccidioidomycosis			
	<100		Bacillary angiomatosis Molluscum contagiosum Esophageal candidiasis	Cryptococcosis Progressive multifocal leukoencephalopathy Toxoplasma encephalitis	
	<75				Disseminated <i>Mycobacterium avium</i> complex
Very advanced	<50	Pseudomonas pneumonia Histoplasmosis Aspergillosis	Large, nonhealing HSV perirectal ulcers	CMV retinitis CNS lymphoma	
	<10		Giant mollusca		

*Diseases increase in incidence and severity as CD4 counts decline.

and chest pain. In patients with CD4 counts above 500/mm³, sinusitis, community-acquired pneumonia, and viral infections commonly account for these symptoms. Tuberculosis can occur at any CD4 count, but it usually occurs when the CD4 count is below 500/mm³. Once the CD4 count drops below 200/mm³, the incidence of *Pneumocystis carinii* pneumonia (PCP), fungal pneumonia, and more severe forms of sinusitis and bacterial pneumonia, including those caused by *Pseudomonas aeruginosa*, rises dramatically.

Sinusitis

The incidence of sinusitis is greater in HIV seropositive individuals than in HIV-seronegative individuals.⁶ Although sinusitis can occur at any CD4 count, it increases in incidence and severity as CD4 counts decline. In patients with CD4 counts less than 200/mm³, sinusitis often involves multiple sinuses, responds incompletely to antibiotic therapy, and becomes chronic.

Patients commonly complain of fever, headache, nasal congestion, and facial tenderness.^{7,8} However, symptoms and signs may be nonspecific or absent, particularly in patients with CD4 counts under 200/mm³. In the review by Godofsky et al. of 72 cases of sinusitis, 10 patients (14%) presented with fever and headache as their only symptoms.⁷ Of the 75 patients with sinusitis that Zurlo et al. studied, 19 patients (25%) with radiographic evidence of active sinusitis were asymptomatic.⁸

When patients do not respond to antibiotics targeted at common pathogens such as *Streptococcus pneumoniae*, *Viridans streptococcus*, and *Haemophilus influenzae*, *Pseudomonas aeruginosa* should be considered. Although *Pseudomonas aeruginosa* rarely causes sinusitis in HIV-seronegative individuals, it may account for 16% to 18% of cases of sinusitis in HIV-infected individuals and is associated with a high rate of recurrent disease.^{9,10} When the CD4 count is below 150/mm³, fungal pathogens such as *Aspergillus* should also be considered.¹¹

Pneumonia

Like sinusitis, bacterial pneumonia occurs with increased incidence in HIV-infected individuals. In the cohort of 1,281 patients studied by Wallace et al., those infected with HIV had an eightfold greater incidence of bacterial pneumonia than the HIV-seronegative control subjects.¹² Although bacterial pneumonia can occur at any CD4 count, its incidence and severity are inversely related to CD4 counts.¹³ In one series, the incidence of bacterial pneumonia in patients with CD4 counts less than 250/mm³ approached the incidence of PCP.¹² Risk factors include CD4 counts less than 200–250/mm³, smoking illicit drugs,^{12,14} and perhaps, intravenous drug use and cigarette smoking.¹³

The most common pathogen is *Streptococcus pneumoniae*. Among patients with pneumococcal pneumonia, HIV-infected individuals are more likely to develop bacteremia

and recurrent disease. However, clinical presentation and response to therapy are similar to those in HIV-seronegative individuals.¹⁵ Other pathogens include *Staphylococcus aureus* and *Haemophilus influenzae*,¹⁶ and in advanced AIDS, *Pseudomonas aeruginosa*. Community-acquired *Pseudomonas aeruginosa* pneumonia occurs at a mean CD4 count of 25/mm³, often in patients who lack traditional risk factors for pseudomonas infection such as neutropenia, indwelling central venous catheters, or chronic steroid use. It can present with cavitary infiltrates on chest radiography, and is associated with a high relapse rate.^{17,18}

Although the widespread use of prophylactic antibiotics has lowered the incidence of PCP, it remains a common complication of HIV infection. PCP often presents with gradually progressive dyspnea, fever, and cough. It rarely occurs when the CD4 count is greater than 250/mm³. In one series, Jensen et al. found that only 3 (5%) of 61 cases of PCP occurred with a CD4 count above 250/mm³.¹⁹ Wallace et al. found that only 4 (9%) of 43 patients with PCP had CD4 counts greater than 250/mm³, and 3 of these 4, had CD4 counts less than 333/mm³.¹² In another series, Masur et al. found that only 3 (6%) of 49 patients with PCP had CD4 counts greater than 200/mm³.²⁰ Risk factors for PCP include CD4 less than 200/mm³, prior PCP, and oral thrush. These, as well as unexplained fevers for longer than 2 weeks, are indications for instituting PCP prophylaxis.

Fungal pneumonia occurs in advanced AIDS. Patients usually have indolent, nonspecific symptoms including fever, fatigue, weight loss, cough, and dyspnea lasting weeks to months. Coccidioidomycosis occurs most commonly in the Southwestern states and in patients with CD4 counts below 150/mm³.²¹ Disseminated histoplasmosis occurs in the Mississippi and Ohio River valleys and in patients with CD4 counts below 50/mm³. In a series of 980 patients with AIDS studied by Nightingale et al., those with disseminated histoplasmosis had a median CD4 count of 33/mm³.²² Aspergillosis is rare and occurs in patients with CD4 counts below 50/mm³.²³ Risk factors for aspergillosis include neutropenia, corticosteroid use, and underlying lung disease. *Cryptococcus neoformans* can cause pulmonary disease, but more commonly causes meningitis (see Central Nervous System Disease section).

Tuberculosis

Tuberculosis tends to occur at CD4 counts below 500/mm³. In a series of 193 HIV-infected patients with tuberculosis, only 4 (2.1%) had CD4 counts above 500/mm³.²⁴ Whether the incidence of tuberculosis increases as the CD4 count declines is unclear.^{12,21}

Compared with HIV-seronegative patients, HIV-seropositive patients have a greater risk of developing disseminated primary tuberculosis, reactivation of latent tuberculosis, extrapulmonary disease, and adverse reactions

to antituberculosis medications.²⁵ Patients infected with HIV and tuberculosis, particularly those with CD4 counts less than 200/mm³, are also more likely to be anergic.

Patients with advanced immunosuppression may have atypical chest radiographs. Rather than the typical cavitary, upper lobe lesions seen in immunocompetent patients, individuals with AIDS often have lower lobe parenchymal infiltrates, pleural effusions, or mediastinal adenopathy. In Long and colleagues' series of 67 HIV-infected patients with tuberculosis, 80% of those with AIDS had atypical chest radiographs.²⁶ In a study by Keiper et al., 21 (81%) of 26 patients with tuberculosis who had CD4 counts below 200/mm³ presented with atypical chest radiographs, compared with only 1 (11%) of 9 subjects with CD4 counts above 200/mm³.²⁷

DERMATOLOGIC DISEASE

HIV-infected individuals are susceptible to a wide range of dermatologic disease. Candidiasis, seborrheic dermatitis, oral hairy leukoplakia, herpes simplex lesions of the mouth and anus, varicella zoster, anal warts, and skin cancers are all more prevalent in HIV-infected individuals.⁶

Candida

Candida can cause oropharyngeal, vaginal, cutaneous, and esophageal disease. Oropharyngeal candidiasis, often the first sign of HIV infection, is the most prevalent oral lesion in HIV-infected individuals,²⁸ and it tends to occur at CD4 counts less than 500/mm³.²⁹ Esophageal candidiasis occurs at CD4 counts below 100/mm³ and is usually accompanied by odynophagia. In a study by Imam et al., vaginal candidiasis occurred at a mean CD4 count of 506/mm³, oropharyngeal candidiasis occurred at a mean CD4 count of 230/mm³, and esophageal candidiasis occurred at a mean CD4 count of 30/mm³.³⁰

Viral Infections

Recurrent varicella-zoster virus infection is an early opportunistic infection that occurs more frequently in HIV-infected individuals than in HIV-seronegative individuals and tends to occur at CD4 counts less than 400/mm³.³¹

Incidence and recurrence of oral and genital herpes simplex virus (HSV) infections may increase as immunosuppression increases.³² In a study by Crowe et al., all nine cases of anogenital HSV infection occurred at CD4 counts less than 300/mm³.²⁹ In advanced AIDS, perirectal HSV may present as large, confluent, nonhealing, ulcerations reminiscent of decubitus ulcers.

Molluscum contagiosum is a cutaneous poxvirus infection that leads to formation of characteristic, umbilicated skin lesions. In HIV-seronegative adults, lesions arise in genital regions, whereas in HIV-seropositive adults, lesions more commonly involve the face and trunk. In a series of 10 patients with mollusca, Koopman et al. found that all

had CD4 counts below 100/mm³.³³ In a review of 27 patients with mollusca, Schwartz et al. found a mean CD4 count of 85.7/mm³, and there was an inverse relation between CD4 count and number of lesions. Giant mollusca developed in three patients, all of whom had profound immunosuppression and CD4 counts under 10/mm³.³⁴

The occurrence of oral hairy leukoplakia is not clearly related to CD4 count, but it is a marker for progression to AIDS.³⁵ In a retrospective and prospective cohort study of 434 HIV-infected men, Holmberg et al. found that those with oral hairy leukoplakia had a mean CD4 count of 340/mm³.⁶

Folliculitis

Folliculitis occurs frequently in HIV-infected individuals. It can occur at any CD4 count and is usually caused by *Staphylococcus aureus*. At CD4 counts below 300/mm³, patients can develop eosinophilic folliculitis, a clinical entity unique to HIV-infected individuals³⁶ that is characterized by discrete, pruritic, erythematous, follicular papules on the trunk or face and is associated with eosinophilia and increased serum IgE levels.³⁷

Kaposi's Sarcoma

Kaposi's sarcoma is the most common tumor and the fourth most common dermatologic condition (after candidiasis, seborrheic dermatitis, and folliculitis) seen in HIV-infected individuals. The suspected etiologic agent is Kaposi's sarcoma-associated herpes virus (human herpes virus 8).³⁸ An infectious etiology may explain why Kaposi's sarcoma is most common in homosexual and bisexual men, especially those with a history of oral or anal sexual contacts. In a series of 130 cases, 75% had CD4 counts less than 200/mm³. However, low CD4 counts were not a prerequisite for the development of Kaposi's sarcoma, as 10% of the patients in this series had CD4 counts greater than 500/mm³.³⁹ Painless, violaceous skin lesions are typical, but they may progress to painful, indurated lesions. In advanced HIV disease, they may also involve the oral mucosa, gastrointestinal tract, and lungs.

Bacillary Angiomatosis

Bacillary angiomatosis causes angiomatous skin lesions that may mimic Kaposi's sarcoma. It occurs at CD4 counts less than 100/mm³ and is caused by *Bartonella henselae* and *B. quintana*. In a review of patients with bacillary angiomatosis, Koehler and Tappero found the average CD4 count was 57/mm³.⁴⁰

CENTRAL NERVOUS SYSTEM DISEASE

HIV-infected individuals are susceptible to the same viral and bacterial CNS infections as immunocompetent hosts. In addition, HIV-infected individuals may develop HIV meningitis at any CD4 count. Classically, this occurs at

the time of seroconversion. In contrast, most HIV-related diseases that affect the CNS occur in advanced stages of AIDS. AIDS dementia occurs when the CD4 count is below 200/mm³.⁴¹ Cryptococcal meningitis, toxoplasmosis, and progressive multifocal leukoencephalopathy occur when the CD4 count is below 100/mm³. Central nervous system lymphoma occurs even later when the CD4 count is below 50/mm³.

Toxoplasmosis

Toxoplasmosis is the most common opportunistic infection of the CNS in patients with AIDS. It occurs when the CD4 count is below 100/mm³ and frequently presents with subacute onset of focal neurologic deficits with or without evidence of generalized cerebral dysfunction.⁴²

Cryptococcal Meningitis

Cryptococcal meningitis is caused by *Cryptococcus neoformans*, an encapsulated yeast found worldwide, and is most likely to occur at CD4 counts less than 100/mm³. Symptoms are often indolent and nonspecific. Fever is the most common symptom and occurs in 62% to 88% of patients. The most common nonmeningeal site of involvement is the lung. However, dissemination often occurs by the time pulmonary disease is diagnosed, and meningitis is found in 60% to 70% of patients with primary pulmonary symptoms.⁴³

Cytomegalovirus Retinitis

Cytomegalovirus (CMV) retinitis develops in 7.5% to 30% of AIDS patients during the course of their illness. It usually occurs at CD4 counts less than 50/mm³. In one series of 26 patients with CMV retinitis, the mean CD4 count was 15.6/mm³.⁴⁴ Patients present with painless visual disturbances including floaters, blurred vision, decreased visual acuity, and visual field deficits. Visual loss progresses rapidly over days to weeks, and retinal detachment may occur as a late complication.⁴⁵

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy occurs at CD4 counts less than 100/mm³. In a review of 15 cases, the mean CD4 count was 84/mm³. This disease is caused by a ubiquitous papovavirus, the JC virus, which infects myelin-producing oligodendrocytes and causes cell lysis and demyelination. Patients can present with focal neurologic deficits or with a rapid decline in mental status.⁴⁶

Central Nervous System Lymphoma

After toxoplasmosis, CNS lymphoma⁴⁷ is the second leading cause of intracerebral masses in HIV-infected patients and usually occurs when the CD4 count is below

50/mm³. Patients present with headaches, seizures, and cranial neuropathies. Diagnosis is by computed tomography or magnetic resonance imaging and biopsy, since malignant cells are found in the cerebrospinal fluid in only 15% to 25% of patients.

SYSTEMIC DISEASES

HIV-infected individuals often develop nonspecific symptoms and signs such as fatigue, malaise, anorexia, weight loss, and night sweats. In later stages of immunosuppression, these are frequently caused by opportunistic infections and malignancies.

Non-Hodgkin's Lymphoma

HIV-infected individuals have a 60-fold greater risk of developing non-Hodgkin's lymphoma than the general population. Non-Hodgkin's lymphoma²⁹ usually occurs at CD4 counts under 200/mm³ and can present with fevers, weight loss, and night sweats. Compared with non-HIV-infected individuals, those with HIV tend to have more extranodal disease, higher-stage and higher-grade disease, and a poorer response to chemotherapy.

Mycobacterium avium Complex

Mycobacterium avium complex is now one of the most common opportunistic infections associated with AIDS. The incidence of the disseminated complex as the first opportunistic infection has increased from 5.7% of patients from 1985 to 1988 to 23.3% of patients from 1989 to 1990. *Mycobacterium avium* complex usually occurs in those with CD4 counts below 75/mm³ and rarely in those with CD4 counts above 100/mm³. It commonly presents with persistent fever, weight loss, night sweats, and diarrhea.⁴⁸

SUMMARY

Regardless of their CD4 count, HIV-infected patients are susceptible to sinusitis, community-acquired pneumonia, oral hairy leukoplakia, Kaposi's sarcoma, and HIV meningitis. Once their CD4 counts drop below 500/mm³, they are at risk of developing tuberculosis, thrush, herpes simplex, and herpes zoster. In advanced HIV, when their CD4 counts are below 200/mm³, PCP, coccidioidomycosis, bacillary angiomatosis, molluscum contagiosum, cryptococcal meningitis, toxoplasmosis, progressive multifocal leukoencephalopathy, *Mycobacterium avium* complex, and non-Hodgkin's lymphoma all increase in incidence. In very advanced HIV, when their CD4 counts are below 50/mm³, they are at risk of pseudomonas pneumonia, CMV retinitis, CNS lymphoma, aspergillosis, and histoplasmosis. By appreciating these characteristic changes in disease incidence, and by knowing a patient's CD4 count, clinicians

should be better able to develop differential diagnoses and plans for diagnostic evaluation.

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