

Perspective

The Changing Nature of the Prevention and Management of Opportunistic Infections

As related by Henry Masur, MD, at the International AIDS Society-USA CME course in Washington, DC, in May 2002, opportunistic infection rates have declined since the advent of potent antiretroviral therapy. However, there is evidence to indicate that these declines have stalled and perhaps reversed in some populations in association with long-term antiretroviral failure and inadequate access to care.

The use of chemoprophylaxis for opportunistic infections and the advent and widespread use of potent antiretroviral therapy were associated with a marked decline in rates of most opportunistic infections in HIV-infected individuals from the early 1990s through 1997. However, a recent report from the Adult/Adolescent Spectrum of Disease Project indicates that additional reductions in rates for many opportunistic infections were not observed between 1997 and 1999 (McNaghten et al, 39th IDSA, 2001). One explanation for these observations is that more patients are experiencing immunologic decline in association with long-term virologic failure of antiretroviral therapy. An optimal virologic response (ie, viral suppression to below limits of assay detection) is not achieved in many patients with initial or subsequent treatment. Continued virologic failure places such patients at increased risk of disease progression. For example, a 2000 review of 20 potent therapy arms in antiretroviral treatment studies (Bartlett et al, AIDS, 2001) indicated that, on intent-to-treat analysis in the majority of the study arms, 50% or less of patients achieved plasma HIV-1 RNA levels less than 50 copies/mL at 48 weeks. An increased incidence of opportunistic infections during virologic failure is not currently supported in the published literature, however.

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A second explanation for the absence of continued decline in opportunistic infection rates is the continued spread and progression of HIV disease in patient groups that are not receiving adequate medical care. In some sites in Washington, DC, for example, many patients are now presenting with opportunistic infections as the initial manifestation of HIV disease. Adult/Adolescent Spectrum of HIV Disease Project data on 2365 patients developing *Pneumocystis carinii* pneumonia (PCP) from 1996 through 1999 indicate that 45% were not in care at the time they developed PCP, compared with 41% of 3863 patients who developed PCP from 1993 through 1996. The proportion of patients developing PCP who were in care and met the criteria for PCP prophylaxis but received no prophylaxis was 6% in the period from 1993 to 1996, and increased to 14% in 1996 to 1999. A large proportion of patients developing PCP were in care and met criteria for and received PCP prophylaxis, but developed PCP because of nonadherence or resistance to prophylactic regimens. A smaller proportion of patients continue to develop PCP at CD4+ cell counts higher than the level established as the criterion for institution of primary PCP prophylaxis, which is 200/ μ L or less.

Opportunistic Infection Risk and Prophylaxis

CD4+ cell count still appears to be a reliable predictor of risk for opportunistic infections in the potent antiretroviral therapy era. In terms of heightening diagnostic vigilance for opportunistic infections, however, it has long been recognized that risk extends to patients with CD4+ cell counts above the levels established as threshold levels for initiation of prophylactic therapy. For example, data from the Multicenter AIDS Cohort study (Phair et al, *N Engl J Med*, 1990) prior to the advent of potent therapy showed that among patients devel-

oping PCP within 6 months of a medical visit, one quarter had a CD4+ cell count greater than 200/ μ L. Thus clinicians should keep in mind that the "thresholds" published for opportunistic infections are general guidelines, not absolute boundaries of susceptibility. Both prior to the era of potent antiretroviral therapy and currently, opportunistic infections will occasionally occur at unusually high CD4+ cell counts.

There are data to indicate that the CD4+ cell count nadir reached prior to restoration of CD4+ counts to greater than 200 cells/ μ L is not predictive of increased risk for opportunistic infections. As shown in a study by Miller and

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colleagues (*Ann Intern Med*, 1999), opportunistic infection incidence rates and 95% confidence intervals in patients with CD4+ count nadirs of less than 200, 150, 100, or 50 cells/ μ L did not differ substantially (incidence rates of 3.7-8.1 per 100 patient-years) when cell counts increased to greater than 200/ μ L on potent therapy. However, the incidence rate was dramatically elevated to 72.9 per 100 patient-years in patients with persistently low CD4+ cell counts (Figure 1).

These and other data indicating that CD4+ cell count increases on potent antiretroviral therapy are associated with reduced risk for opportunistic infec-

tions have led to recommendations for discontinuation of prophylaxis based on CD4+ cell count and adequate control of plasma HIV-1 RNA level. Currently, there are specific CD4+ cell count-based guidelines for discontinuation of primary prophylaxis for PCP, toxoplasmosis, and *Mycobacterium avium* complex (MAC) infection and secondary prophylaxis for these infections and for cytomegalovirus (CMV) disease and cryptococcosis (USPHS/IDSA, 2001). Data are currently insufficient to recommend discontinuation of secondary prophylaxis for histoplasmosis or coccidioidomycosis based on CD4+ cell count. However, many practitioners with considerable experience with these latter types of infections are of the opinion that discontinuation of prophylaxis is safe with sufficient CD4+ cell count increase on potent antiretroviral therapy.

HIV-Associated Pulmonary Disease

Pulmonary disease remains one of the most common infectious complications encountered in patients with HIV disease. PCP, tuberculosis, and pneumococcal and *Haemophilus* infections remain common among pulmonary infections, as does infection due to atypical and viral pathogens. Less common causes of disease include histoplasmosis and coccidioidomycosis, toxoplasmosis, and Kaposi's sarcoma. Among the relatively less common pulmonary complications, cases of disease caused by *Aspergillus*, *Staphylococcus*, and lymphoma are increasing in frequency. Pathogens that may cause pulmonary disease in other immunosuppressed populations and that cause other types of disease in HIV-infected patients, but that remain rare causes of pulmonary disease in the latter, include CMV, MAC, herpes simplex virus, and *Rhodococcus*.

Changes in the spectrum of HIV-related pulmonary disease have been observed during the potent antiretroviral therapy era. Data from 204 patients seen at a Georgetown consult service from 1993 to 1995 indicate that pulmonary manifestations were due to PCP in 74 patients (36%), other bacterial infection in 59 (29%), CMV in 14 (7%), and lymphoma in 7 (3%). By comparison, data from 51 patients seen in the

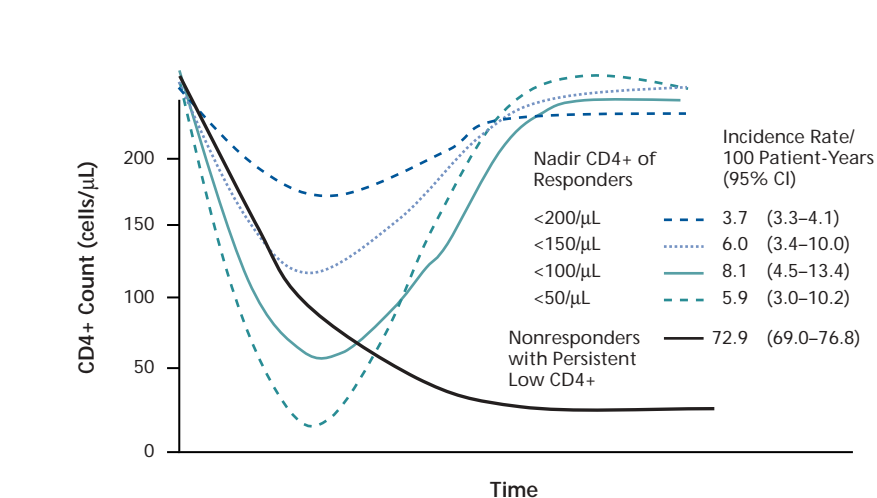


Figure 1. Effect of pretreatment nadir CD4+ cell count on incidence of opportunistic infections in patients whose CD4+ cell count increased to greater than 200/μL on potent antiretroviral therapy (responders) and incidence in patients with persistently low cell count (nonresponders). Adapted with permission from Miller et al, *Ann Intern Med*, 1999.

same consult service from 1997 to 2000 indicate that manifestations were due to PCP in 9 (18%), other bacterial infection in 24 (47%), CMV in 2 (4%), and lymphoma in 8 (16%; Wolff and O'Donnell, *Chest*, 2001). However, the types of opportunistic infections observed may depend on the patient populations studied. As noted, experience at some centers indicates that many HIV-infected individuals without adequate connections to health care are now presenting with opportunistic infections as initial manifestations of HIV disease, and the frequency with which PCP is encountered is greater among such individuals.

Current Status of PCP Diagnosis and Management

PCP should be considered in any HIV-infected individual with pulmonary disease. Although suspicion should be heightened in patients with lower CD4+ cell counts, it should be remembered that PCP occurs at counts greater than 200/μL in a sizable proportion of patients. PCP has a variety of radiologic presentations. Although symmetrical diffuse interstitial infiltrates are most common, the presentation can include asymmetrical infiltrates, nodules, lobar disease, and cavitation. Specific diagnosis can be made in a very high percentage of cases using bronchoalveolar

lavage and immunofluorescence staining. In practiced hands, diagnosis can be made in a high percentage of cases using induced sputum and immunofluorescence. There is considerable interest in polymerase chain reaction (PCR)-based diagnostic techniques for PCP. One recent study showed that PCR analysis of simple oral washes was associated with 91% sensitivity, 94% specificity, 76% positive predictive value, and 98% negative predictive value (Fischer et al, *J Infect Dis*, 2001). Quantitative PCR techniques for PCP diagnosis currently are being developed, and may be commercially available in the relatively near future.

Trimethoprim/sulfamethoxazole (TMP-SMX) remains the drug therapy of choice for PCP, with adjunctive corticosteroids being used in patients with severe disease. Pentamidine is also an effective therapy, but is associated with adverse effects. Other treatment options, including atovaquone and clindamycin-primaquine, have not provided sufficient efficacy to be considered as first-line treatment. There is some evidence that *P carinii* can become resistant to TMP-SMX, which may explain some proportion of the disease incidence in patients receiving TMP-SMX prophylaxis. Since attempts to culture *P carinii* have met with failure, conventional resistance testing of the organism has not been performed. However, within the past several years,

the target enzyme of TMP-SMX, dihydropteroate synthase (DHPS), has been sequenced, and it has been found that mutations in the enzyme are associated with sulfa drug resistance in pneumococci and other organisms. A study performed by Danish investigators indicates that mortality due to PCP is greater in patients exhibiting the DHPS mutations (Helweg-Larsen et al, *Lancet*, 1999). Mutations appear to be more common in patients with prior exposure to sulfa drugs, and have been found in stored samples from patients treated in the 1990s and 1980s. There is thus some concern that *P carinii* resistance to TMP-SMX, although not a problem currently, could become a problem in the future.

Immune Reconstitution Syndromes

Immune reconstitution syndromes in patients initiating potent antiretroviral therapy have been described in the settings of PCP and a variety of other pathogens, including CMV, MAC, tuberculosis, herpes simplex virus, varicella-zoster virus, hepatitis C virus, and oral human papilloma virus. There are not yet good guidelines for distinguishing between reactivation syndromes and acute infections. The potential for immune reconstitution syndromes in patients initiating potent antiretroviral therapy should be taken into account in those cases in which HIV-infected patients not receiving antiretroviral treatment present with an acute opportunistic infection. Delay of antiretroviral treatment until the acute infection has completely resolved should be considered in these cases. Randomized clinical trials of immediate versus deferred antiretroviral therapy in acutely ill patients are needed.

In an illustrative case (Wislez et al, *Am J Respir Crit Care Med*, 2001), a patient presenting with PCP and a PO_2 of 59 was started on TMP-SMX and showed normal PO_2 and considerably improved radiologic findings on day 15. After initiation of potent antiretroviral therapy, the patient returned on day 26 in respiratory failure; PO_2 was 69 and an infiltrate was observed on x-ray. Biopsy showed the presence of very few *P carinii* organisms and an intense inflammatory response, indicating that the respiratory syndrome

was due to provocation of the immune response to PCP despite relative absence of the organisms.

Similar cases have been described in both patients with prior opportunistic infections and those in whom presence of an opportunistic pathogen was previously unrecognized. For example, it appears that nearly every patient with a history of CMV retinitis in whom potent antiretroviral therapy is initiated will develop some degree of retinal inflammation due to immune reactivation syndrome, with deterioration of vision occurring in some. Other cases have described reactivation syndromes involving, for example, cryptococcal pulmonary infection and MAC infection of mediastinal lymph nodes in patients with no history of acute opportunistic infection. In some cases, resolution of the syndrome occurs without specific treatment and with continuation of potent antiretroviral therapy.

Conclusion

Opportunistic infections are still occurring in HIV-infected individuals. In some settings, many of the patients with opportunistic infections are patients who are not receiving adequate medical care for HIV disease, including an increasing number who present with opportunistic infections as the initial manifestation of HIV disease. The recent leveling off, and perhaps increase, of opportunistic infection rates is also likely attributable in part to immunologic decline in the large number of patients maintained on virologically failing antiretroviral regimens for prolonged periods. Renewed attention to guidelines for prophylaxis and treatment for opportunistic infections is warranted. Additional work is needed in providing information on distinguishing between acute opportunistic infections and immune reactivation syndromes and defining optimal management of the latter. For the future, it is hoped that better antiretroviral regimens and the addition of immunotherapy to antiretroviral treatment will permit more patients to achieve viral control adequate to prevent immunologic deterioration. For example, novel approaches to raising CD4+ cell counts such as interleukin-2 have considerable promise. It is also

hoped that advances can be made in identifying and providing quality treatment to the large number of HIV-infected individuals who currently are at increased risk of disease progression because of lack of medical care.

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Suggested Reading

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