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Opportunistic Infections: Still a Problem, Even in the Era of HAART

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Trends in Morbidity and Mortality

Virtually every clinician and every medical facility have witnessed the decreased rate of AIDS-defining opportunistic infections that has resulted from the introduction of highly active antiretroviral therapy (HAART) and from the widespread use of opportunistic infection prophylaxis. AIDS-defining opportunistic infections continue to occur, both in individuals under intense medical supervision and in individuals not under care. However, over the past few years, newly appreciated processes have been supplanting AIDS-defining opportunistic infections as the major causes of morbidity and mortality. This development has been recognized by the inclusion of hepatitis C and hepatitis B among the diseases covered by the [1999 US Public Health Service \(USPHS\) and Infectious Diseases Society of America \(IDSA\) Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus](#). Several studies presented at the 8th Conference on Retroviruses and Opportunistic Infections looked at these recent trends.

Bauer and associates^[1] at the University of California at San Diego analyzed trends in their hospitalization rates between 1993 and 1999. All individuals with at least 1 visit to the outpatient clinic were evaluated: there were 4252 individuals in their database (1337 patients were hospitalized 3452 times). From 1993-1997, hospitalization rates fell, but from 1997-1999, they rose, often due to events that were considered non-HIV-related. Hospitalization rates rose after 1997 despite the fact that hospitalized individuals had higher CD4+ T-lymphocyte counts and lower viral loads than individuals in the earlier time period, as might be expected if the hospitalizations were often related to events other than infectious complications. Bauer and colleagues did not provide data about the specific causes of hospitalization.

From a European perspective, in an analysis of 1670 deaths occurring in the EuroSIDA cohort of HIV-infected individuals (1994-2000), Mocroft and colleagues^[2] found that the ratio of AIDS-related to AIDS-unrelated deaths declined from 17 in 1996 to 5-6 during 1997-2000. This suggests that the causes of death were not the traditional AIDS-defining opportunistic infections. When Mocroft and colleagues assessed the causes of death, many of the deaths that occurred since 1997 were due to non-Hodgkin's lymphoma and hepatitis C- or hepatitis B-related liver disease.

In contrast, Ahmad and coworkers^[3] assessed a very different patient population — individuals from Cook County Hospital in Chicago, Illinois. At this inner-city facility, a considerable proportion of patients continued to die due to advanced HIV disease and opportunistic infections. However, even at Cook County Hospital, 38% of deaths were due to bacterial infections, hepatic disease, or renal disorders.

Thus, morbidity and mortality trends in the United States and Western Europe document that opportunistic infections continue to cause serious or lethal complications in individuals with advanced disease, especially those who are not receiving care. However, renal disease, liver disease, and complications of therapy are becoming more important causes of serious morbidity — as 1 segment of the HIV-infected patient population shifts to include more intravenous drug users, and as

another group of patients survives for longer periods because of better HIV disease management.

Another potential change in morbidity and mortality to watch for is an upswing in cardiovascular disease. As discussed in more detail in [Graeme Moyle's report on adverse effects of therapy](#), several abstracts assessed the frequency of cardiac risk factors, such as hypertension, diabetes, or cholesterol/triglyceride abnormalities, and suggested the obvious potential for HIV-infected individuals to develop premature atherosclerosis over time. There was no consistent relationship found between risk factors and protease inhibitor use or other specific drug regimens.

A variety of investigations have suggested that cytomegalovirus (CMV) is somehow linked to the pathogenesis of premature atherosclerosis in this population: Indeed, the ARIC study^[4] demonstrated a correlation between carotid intimal thickness (a presumptive surrogate for atherosclerosis) and CMV antibody titer. However, Thiebaut and colleagues^[5] presented data from the French SUPRA study that found no relationship between CMV serology or clinical CMV disease and carotid intimal thickening. Although HIV-infected individuals appear to have risk factors for developing premature atherosclerosis, and it is logical to predict that such disease will occur, there have been no longitudinal studies showing that clinical events related to atherosclerosis will occur disproportionately in this population, nor is there evidence that an infectious agent is related to atherosclerosis. More sensitive techniques to assess microbial signals in atherosclerotic plaque need to be assessed more carefully before a pathogenic role for CMV or some other microbial process is excluded. Until such time, prophylaxis to prevent atherosclerosis with drugs active against CMV seems to be unwarranted.

HIV-Related Opportunistic Infections

Pneumocystis carinii Pneumonia

An abstract by Larsen and associates^[6] at the National Institutes of Health, Bethesda, Maryland, described a quantitative method for diagnosing *Pneumocystis carinii* pneumonia (PCP) by using a quantitative polymerase chain reaction (PCR) test on oral gargles. Oral washes, in which saline is gargled and then spat into a cup, have been reported to contain *P carinii* in individuals with PCP if the saline is analyzed by a very sensitive PCR technique. However, qualitative (as opposed to quantitative) PCR techniques are often too sensitive — ie, they detect signal from individuals who have small amounts of organisms, but no clinically important disease. In this study, Larsen developed a quantitative technique that showed promise for distinguishing individuals who are merely colonized (low quantity of organisms) from those who have disease due to *P carinii* (high quantity). If this quantitative technique can be commercialized, the diagnosis of PCP will be much easier to establish because expertise will not be needed to coax an adequate sputum sample from a individual, and the expense and discomfort associated with a bronchoalveolar lavage will not be necessary for many individuals.

In a report from Kazanjian from the University of Michigan, Ann Arbor, and colleagues,^[7] mutations in cytochrome b — the target site for atovaquone — were identified in 33% of *P carinii* samples obtained from individuals who had been receiving atovaquone prophylaxis vs 0% in samples from individuals who had not been exposed to atovaquone. This suggests that atovaquone resistance is developing, although it does not yet prove that such resistance is at a high enough level to be clinically significant (ie, the decreased atovaquone susceptibility may be small scale). Recent reports^[8] have shown for the first time that *P carinii* organisms can contain genetic sequences that are likely to confer sulfonamide resistance, and that individuals with such isolates are less likely to respond to

sulfa therapy (eg, sulfamethoxazole/trimethoprim) than individuals without such mutations. Thus, the report from Kazanjian and colleagues suggests that exposure to atovaquone can be associated with reduced atovaquone susceptibility, and that clinically important atovaquone resistance could become an issue.

Progressive Multifocal Leukoencephalopathy

Clinicians continue to see occasional cases of progressive multifocal leukoencephalopathy (PML), a white matter lesion caused by JC virus. Although some cases improve after initiation of HAART, some individuals do not improve despite responding immunologically and virologically to HAART, and some individuals worsen. There is no specific chemotherapy available that is effective.

Marra and colleagues^[9] on behalf of the AIDS Clinical Trials Group (ACTG) Protocol 363 investigators reported a prospective pilot study of zidovudine for individuals with recently recognized PML, diagnosed within the last 90 days. Individuals were given 2 doses of zidovudine at weekly intervals and then given doses every 2 weeks and evaluated after 24 weeks. Zidovudine did not appear to improve individual survival compared with no therapy. Thus, there was no evidence suggesting efficacy for zidovudine — nor was there any encouraging evidence in another study that assessed the efficacy of topotecan.^[10]

In a large study from Spain, Miralles and coworkers^[11] reported that they had observed 66 individuals with PML between 1994 and 2000, 30 of whom had biopsy confirmation of their diagnosis. They reported on 28 of these individuals. Only 17 of the 28 stabilized or improved after initiation of HAART. Baseline CD4+ cell count at the time of diagnosis was the only variable that predicted prognosis: those who stabilized or improved had a median count of 144 cells/mm³ compared with 78 cells/mm³ for those who deteriorated. Of interest, 3 individuals deteriorated soon after starting HAART. All showed increased number or size of lesions typical for PML on their MRI scans. All 3 had brain biopsies which confirmed that the process was PML and showed perivascular inflammation. Clinicians need to be aware that the manifestations of PML may worsen after initiation of HAART. Presumably conservative care is appropriate rather than intervening with anti-inflammatory therapy.

Stopping Secondary Prophylaxis: Cryptococcosis and Disseminated MAC

A major issue in managing individuals who have had an opportunistic infection and then had a good virologic and immunologic response to HAART is whether life-long maintenance therapy for the prior opportunistic infection can safely be stopped. In 1999, the USPHS/IDSA guidelines recommended that secondary prophylaxis need not be life-long for individuals with a history of treated CMV retinitis and a stable CD4+ cell count greater than 100 cells/mm³ as a consequence of HAART. The guideline committee was reluctant to recommend stopping secondary prophylaxis for pneumocystosis, toxoplasmosis, cryptococcosis, or disseminated *Mycobacterium avium* complex (MAC) because of a paucity of clinical data demonstrating the safety of such a practice.

In January 2001, *The New England Journal of Medicine* published reports on 2 investigations^[12,13] which demonstrated that stopping secondary prophylaxis for PCP is associated with very little risk for relapse if individuals have a CD4+ cell count greater than 200 cells/mm³ for at least 3 months. However, the question remains: Is it safe to stop secondary prophylaxis following successful therapy of other HIV-associated opportunistic infections?

Two studies provided helpful data regarding the safety of stopping secondary prophylaxis for disseminated MAC and for cryptococcosis.^[14,15] Shafran and colleagues^[14] from 12 Canadian clinics performed a retrospective evaluation of 35 individuals with disseminated MAC who opted to discontinue therapy for MAC after completing what the patients and their healthcare providers considered to be a successful course, and after responding “adequately” to HAART. Individuals who were assessed in this study had completed a median of 29 months of therapy for MAC and were followed for a median of 17 months after stopping MAC therapy. Only 1 of the 35 individuals relapsed. At the time of last follow-up, the median CD4+ cell count was 239 cells/mm³ for the 34 individuals who were free of disease; more than 70% also had undetectable plasma HIV-1 RNA levels. The 1 individual who relapsed had stopped his HAART.

Regarding cryptococcosis, Mussini and associates^[15] reported an observational study from 5 centers in Italy, in which they compared the characteristics of 24 individuals who chose to stop cryptococcal maintenance therapy after a median duration of 24.9 months (group A), and 22 individuals who chose to continue maintenance (group B). The median CD4+ cell count was 326 cells/mm³ at the time that group A stopped their maintenance therapy. No individual in either group was documented to have a relapse. It is important to point out, however, that this was not a randomized study.

These 2 studies support the concept that it is safe to stop secondary prophylaxis for cryptococcosis or MAC in some individuals who have had a good immunologic response to HAART. However, clinicians in these cited studies may have consciously or unconsciously chosen which individuals they thought were particularly good candidates to stop prophylaxis. Further studies may show populations in whom stopping secondary prophylaxis is not prudent.

At this point, it is probably reasonable to consider stopping prophylaxis in individuals who have completed a course of therapy for MAC (probably 12 months) or cryptococcosis (probably 12 weeks); are asymptomatic with regard to the opportunistic pathogen; and have had a CD4+ cell count of at least 100 cells/mm³ for at least 3 months.

The USPHS/IDSA guidelines are currently in the process of being revised. Watch for recommendations regarding the safety of stopping secondary prophylaxis for these pathogens in selected individuals who have had an “adequate” response to HAART.

Hepatitis B and Hepatitis C

The natural history and management of hepatitis, especially hepatitis C virus (HCV), received considerable attention at the annual meeting. Kenneth Sherman^[16] from the University of Cincinnati provided an overview of HIV/HCV coinfection. He emphasized the importance of screening all HIV-infected patients for HCV because approximately 30% are coinfecting. He indicated that screening is important since therapy can be effective in some individuals with HCV in terms of preventing long-term morbidity and mortality, although we have unfortunately little information as to which individuals are most likely to progress to clinically important fibrotic liver disease. He also emphasized the importance of knowing the HCV status so that liver function test abnormalities could be appropriately evaluated — ie, are transaminase elevations due to HCV, to protease inhibitor therapy, or to some other drug or disease process?

Numerous investigators documented that the sequelae of hepatitis C are responsible for an increasing proportion of serious complications and deaths in individuals with HIV infection. Torriani and colleagues^[17] from the University of California at San Diego and Oviedo Medical School in Spain

looked retrospectively at 94 individuals coinfecting with HIV and HCV, and compared their course with 94 matched individuals who were HIV-infected but not infected with HCV. They noted that the coinfecting individuals had poorer responses to HAART in terms of CD4+ cell count increase or viral load reduction compared with HIV-positive matched controls. This could have been due to an effect of HCV on immune response or to poorer adherence to or tolerance of HAART regimens.

Bochet and associates⁽¹⁸⁾ at l'Hôpital Pitié-Salpêtrière in Paris described their experience using interferon-alfa plus ribavirin in 56 HIV/HCV coinfecting individuals, 46% of whom had previously failed monotherapy with interferon-alfa. They reported an impressive level of toxicity: 33 patients developed asthenia and 10 patients reported psychiatric disturbances. Overall, 15 individuals discontinued therapy due to toxicity. At the end of therapy, only 20% of HCV-treatment-naïve individuals and 19.2% of interferon-alfa-experienced individuals had undetectable HCV viral loads, a disappointing result. All but 1 of the successfully treated individuals had a sustained response 6 months after termination of therapy.

Thus, more effective and better-tolerated therapeutic options are needed. Although pegylated interferon-alfa, which was recently approved by the US Food and Drug Administration, will be easier to administer because it has a longer half-life than non-pegylated interferon-alfa, there are few drugs that will likely be available soon which will have a different mechanism of action and thus are likely to be more effective or better tolerated.

Sessions on HCV/HIV coinfection were some of the most heavily attended at the conference. Audience interest was fueled by great uncertainty about when to treat hepatitis C, what therapeutic regimen to use, and how long to treat. Given the number of individuals who are coinfecting, and the long overdue interest in studying this disease, one can anticipate an explosion of information in this area. More information is welcome and new drugs are needed, and although there are some promising compounds being investigated, clinical development unfortunately is still in very early stages.

References

1. Bauer JA, Matthews WC, Barber RE. Trends in HIV/AIDS hospitalization: rates of hospitalization and an examination of discharge diagnoses of a cohort of HIV/AIDS individuals at UCSD Medical Center 1993-1999. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago, Illinois. Abstract 294. Available at: <http://www.retroconference.org/2001/abstracts/abstracts/abstracts/294.htm>
2. Mocroft A, Brette R, Kirk O et al. Changes in cause of death across Europe. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago, Illinois. Abstract 298. Available at: <http://www.retroconference.org/2001/abstracts/abstracts/abstracts/298.htm>
3. Ahmad S, Pulvirenti J, Shastri P et al. Death in HIV-infected inpatients in the HAART era: an evaluation of mortality in an inner-city hospital. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago, Illinois. Abstract 300. Available at: <http://www.retroconference.org/2001/abstracts/abstracts/abstracts/300.htm>
4. Nieto FJ, Adam E, Sorlie P, et al. Cohort study of cytomegalovirus infection as a risk factor for carotid intimal-medial thickening, a measure of subclinical atherosclerosis. *Circulation*. 1996;94:922-927.
5. Thiebaut R, Fabre I, Mercie P et al. Is CMV a cardiovascular risk factor in HIV-1 infected

- patients? Supra Study, Bordeaux, France 1999. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago, Illinois. Abstract 296. Available at: <http://www.retroconference.org/2001/abstracts/abstracts/abstracts/296.htm>
6. Larsen HH, Masur H, Kovacs JA et al. Clinical utility of a quantitative real-time light cyclor PCR assay for *Pneumocystis carinii*. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago, Illinois. Abstract 238. Available at: <http://www.retroconference.org/2001/abstracts/abstracts/abstracts/238.htm>
 7. Kazanjian P, Armstrong W, Hossler P et al. *Pneumocystis carinii* cytochrome b mutations are associated with atovaquone exposure in AIDS patients. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago, Illinois. Abstract 543. Available at: <http://www.retroconference.org/2001/abstracts/abstracts/abstracts/543.htm>
 8. Mei Q, Gurunathan S, Masur H, Kovacs JA. Failure of co-trimoxazole in *Pneumocystis carinii* infection and mutations in dihydropteroate synthase gene. *Lancet*. 1998;351(9116):1631-1632.
 9. Marra CM, Rajcic N, Barker DE, et al. Prospective pilot study of zidovudine for HIV-associated progressive multifocal leukoencephalopathy. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago, Illinois. Abstract 596. Available at: <http://www.retroconference.org/2001/abstracts/abstracts/abstracts/596.htm>
 10. Dupont B, Fish D, McGuire D, et al. 21-day continuous infusion of zalcitabine in AIDS-associated progressive multifocal leukoencephalopathy (PML). Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago, Illinois. Abstract 597. Available at: <http://www.retroconference.org/2001/abstracts/abstracts/abstracts/597.htm>
 11. Miralles P, Berenguer J, Lacruz C et al. Paradoxical worsening of AIDS associated progressive multifocal leukoencephalopathy following HAART. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago, Illinois. Abstract 598. Available at: <http://www.retroconference.org/2001/abstracts/abstracts/abstracts/598.htm>
 12. Lopez BQ, Miro JM, Pena JM et al. A randomized trial of the discontinuation of primary and secondary prophylaxis against *Pneumocystis carinii* pneumonia after highly active antiretroviral therapy in patients with HIV infection. *N Engl J Med*. 2001;344:159-167.
 13. Lederberger B, Mocroft A, Reiss P et al. Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy. *N Engl J Med*. 2001;344:168-174.
 14. Shafran SD, Gill MJ, Lajonde RG et al. Successful discontinuation of MAC therapy following effective HAART. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago, Illinois. Abstract 547. Available at: <http://www.retroconference.org/2001/abstracts/abstracts/abstracts/547.htm>
 15. Mussini C, Cossarizza A, Pezzotti P et al. Discontinuation or Continuation of maintenance therapy for cryptococcal meningitis in patients with AIDS treated with HAART. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago, Illinois. Abstract 546. Available at: <http://www.retroconference.org/2001/abstracts/abstracts/abstracts/546.htm>

16. Sherman KE. Hepatitis C coinfection. Presented at the 8th Conference on Retroviruses and Opportunistic Infections; February 4-8, 2001; Chicago, Illinois. Session 9.
17. Torriani FJ, Byrnes C, Asensi V, et al. A comparison of hepatotoxicity and response to potent antiretroviral therapy in HIV/HCV infected and matched HIV-infected patients. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago, Illinois. Abstract 575. Available at: <http://www.retroconference.org/2001/abstracts/abstracts/abstracts/575.htm>
18. Bochet M, De Torres M, Valantin MA, et al. Efficacy and tolerance of IFN alfa plus ribavirin for chronic hepatitis C in HIV-infected patients. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago, Illinois. Abstract 574. Available at: <http://www.retroconference.org/2001/abstracts/abstracts/abstracts/574.htm>