Profilaxis de Infecciones Oportunistas en Pacientes Bajo Terapia Antirretroviral
Opportunist Infection Prophylaxis for Patients Receiving HAART

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The advent of HAART dramatically changed the course and manifestations of HIV disease in the United States. Whereas previously, the management consisted largely of diagnosing and treating opportunistic infections, today most treaters are occupied with selecting antiretrovirals, educating patients and monitoring HIV RNA plasma levels. One small but striking change can be seen in the program of the annual Conference on Retroviruses and Opportunistic Infection. Although this conference initially gave equal billing to opportunistic infections, in the most recent one held in January-February of this year, only 6% (51 of 876) of the presentations dealt with opportunistic infections. Opportunistic infections, however, have not disappeared. Prevention and prophylaxis are key components of the management of HIV disease, especially so for those with clinical AIDS. The important issues in a discussion of prophylaxis include, what are the targets for prevention? which preventative interventions are necessary – and effective? and how long must prophylaxis be maintained when patients respond to HAART?

Opportunistic Infections Amenable to Prophylaxis

The targets for prophylaxis and the degree of immunodeficiency at which prophylaxis is initiated remain essentially the same as over the past several years. *Pneumocystis carinii* pneumonia, toxoplasmic encephalitis, disseminated *Mycobacterium avium*-complex, Candidiasis, and Tuberculosis are the most important opportunists for which we have effective preventive therapy. Cytomegalovirus and some mycoses may be considered for prophylaxis in selected circumstances. Cytomegalovirus prophylaxis is marginally effective for persons with less than 50 CD4 cells/ml, but the drug is expensive. Monitoring patients with > 50 CD4 cells/ml with CMV positive serology clinically and initiating treatment at the earliest possible point is the recommendation of the latest USPH/IDSA guidelines. Cryptococcosis can be prevented with fluconazole prophylaxis, but the risk for any one patient is so low, the potential for selecting azole-resistant Candida species a genuine concern or provoking an adverse reaction and the cost so high that prophylaxis is not recommended.

Chronic suppressive therapy, frequently mis-named secondary prophylaxis, for Cytomegalovirus disease, Cryptococcosis, Histoplasmosis, among others, is not, strictly speaking, prophylaxis.

In the absence of an overt episode of disease, only tuberculosis is a target for prophylaxis treatment when cellular immunity is intact. PCP prophylaxis is initiated when CD4 cells

fall below 200 cells/ml (<14%) or the patient develops symptomatic disease, whereas toxoplasmosis prophylaxis is initiated with a fall in CD4 cells below 100 cells/ml. Cytomegalovirus (with positive CMV serology) and disseminated MAC become an issue with drops below 50 CD4 cells/ml, whereas mucosal Candidiasis prophylaxis is started only for patients with recurrent episodes, regardless of their immune status.

Vaccination , while not quite the same as prophylaxis, must be mentioned as an integral component of prophylaxis in the full sense of the term. Unfortunately, for adults, the vaccines are not as effective as one would hope. Multivalent pneumococcal vaccine is arguably the most important vaccine, and it should be offered to all HIV patients at the time of their initial evaluation. Unfortunately, it does not elicit a robust antibody response in the immunosuppressed, especially for those with less than 200 CD4 cells. Nor is the durability of the antibody response known (re-vaccination is recommended every 5 years). A recent study by Fleming and co-workers of re-vaccination after immune reconstitution with HAART found that even with a rise in the CD4 count most patients responded poorly. It is possible that the new conjugate vaccines will elicit stronger responses. Hepatitis B infection is very common in men who have sex with men and intravenous drug users, but for the patient in one of these groups who is not antibody positive, hepatitis B vaccine should be given. Again, in the immunosuppressed patient, the vaccine is not reliably immunogenic and is not worth the expense. Hepatitis A is recommended for patients with Hepatitis C because of the severity of disease should Hepatitis A infection occur. Influenza vaccination is routinely given to patients in my clinic, although the protective effect has not been proven and there is not much response in the severely immunosuppressed patient. Varicella vaccine, a live vaccine, is recommended, but only for the nonimmunosuppressed patient who is antibody negative. Live measles vaccine is also recommended, but only for the nonimmunosuppressed; live polio and typhoid vaccines are not recommended.

Choice of Prophylaxis

There have been several advances in our knowledge of the relative merits of prophylactic regimens in the past few years. For PCP, trimethoprim-sulfamethoxazole (Tmx-Sulfa), one double strength tablet a day is unsurpassed in effectiveness, although a single strength tablet daily, or a double strength tablet three days a week is a popular regimen with nearly equal efficacy. Dapsone, 100 mg per day in a single or divided dose plus pyrimethamine 50 mg (with leucovorin 25mg) once weekly, aerosolized pentamidine 300 mg once monthly; and atovaquone, 1500 mg daily, are alternatives for persons who do not tolerate Tmx-Sulfa. None of the alternative regimens are as effective as the Tmx-Sulfa regimen. The Tmx-Sulfa once daily double strength regimen is also effective against toxoplasmosis. There is less data about alternative regimens such as atovaquone with pyrimethamine with leucovorin, but they likely provide some efficacy. For the patient who has had toxoplasmosis and is receiving suppressive treatment with pyrimethamine and sulfadiazine or clindamycin, there is often a question about what to do for PCP prophylaxis. There is not much data, but the toxoplasmosis therapy is probably adequate to prevent PCP. For tuberculosis, isoniazid, 300 mg (plus pyridoxine 50 mg) daily for nine months is currently

the regimen of choice. Two alternatives involve more intense regimens given intermittantly or for shorter periods of time: isoniazid 900 mg with 100 mg pyridoxine twice weekly, or rifampin 600 mg plus pyrazinamide 20 mg/kg daily for two months, respectively, allow for directly observed preventive therapy. This is of interest because of the uncertainty of self-administered prophylaxis. For isoniazid resistance, the two month rifampin-pyrazinamide regimen is recommended. Rifabutin, 300 mg plus pyrazinamide daily for two months may be an alternative. Rifabutin has less interaction with protease inhibitors and non-nucleoside reverse transcriptase inhibitors; although the dose of rifabutin should be reduced to 150 mg per day (there is little data, to my knowledge, about this regimen in preventive therapy). If multi-drug resistant tuberculosis is suspected, the alternatives will depend on the susceptibility patterns and drug availability. Cytomegalovirus currently is not considered a target for prophylaxis, although oral ganciclovir has some efficacy. Acyclovir is without benefit, and valcyclovir is not recommended because of a study which suggested increase mortality with this drug.

Discontinuation of Prophylaxis

At what point prophylaxis can be safely stopped has not yet been fully defined, although there is increasing data confirming that immune reconstitution does restore natural immunity and that prophylaxis can be discontinued. Several studies have confirmed that primary PCP prophylaxis can be stopped once CD4 counts rise above 200 cells/ml for more than three months. Additional reports have shown the same for toxoplasmosis, Mycobacterium avium complex, and Cytomegalovirus. What is particularly interesting are the accumulating data that secondary prophylaxis (including chronic suppressive therapy) can be stopped for patients with cytomegalovirus, disseminated MAC and toxoplasmosis. In a presentation at the 7th Conference on Retroviruses and OIs, there was a report of discontinuation of maintenance therapy of cryptococcal meningitis in 6 patients with non-detectable HIV on HAART treated for more than 12 months with fluconazole. These patients had been followed only for several months but there were no relapses.

Unfortunately, the immune reconstitution is not a uniform process. There have also been anecdotal reports of opportunistic infections occurring in patients on HAART with good CD4 cell counts (see Johnson et al). These observations imply that if patients lose CD4 clones specific for certain pathogens, the patient remains at risk even with apparent immune restoration.

At the present time, the data seem to support discontinuation of primary OI prophylaxis with a high probability that secondary prophylaxis can also be discontinued if CD4 counts rise and remain well above the level associated with increased risk for OIs. Hopefully, further understanding of specific protective immune mechanisms will enable us to know who remains at risk and a candidate for continued prophylaxis. And lastly, it is obvious that the protective effect of the restored immune function is dependent upon the patient remaining adherent with his or her HAART regimen.

Immune Reconstitution Syndrome (Paradoxical Reaction)

Although not, strictly speaking, a complication of prophylaxis, the so called paradoxical reaction should be mentioned. There have been multiple reports of the immune reconstitution – inflammatory reaction with a variety of opportunistic infections – Cytomegalovirus, Mycobacterium tuberculosis, Mycobacterium avium-complex, Hepatitis B, to name a few of the most prominent. The presumed pathogenesis is an incipient, asymptomatic opportunistic infection or a controlled but not yet eradicated infection is met with a newly rejuvenated immune system one to two months after initiation of HAART. The manifestations may be very dramatic and depending upon the opportunistic pathogen, may include fever, lymphadenitis, pulmonary infiltrates, hepatitis, uveitis, etc. They must be distinguished from new infections, drug reactions and unrelated pathology, and often give rise to considerable confusion.

Suggested Readings

1. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with Human Immunodeficiency Virus. MMWR 1999;48:RR-10

2. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with Human Immunodeficiency Virus. At ATIS website: www.hivatis.org.

3. Aberg JA, Price RW, Heeren DM, Bredt B. Discontinuation of antifungal therapy for cryptococcosis after immunologic response to antiretroviral therapy. Abst #250. 7th Conference on Retroviruses and Opportunistic Infections, Jan 30-Feb 2, 2000, San Francisco.

4. Fleming C, Cilento J, Steger K, McNamara E, Pelton S, Craven D. Immunogenicity of revaccination with pneumococcal vaccine in HIV-infected patients on combination antiretroviral therapy, Abst #249. 7th Conference on Retroviruses and Opportunistic Infections, Jan 30-Feb 2, 2000, San Francisco.

5. Furrer H, Egger M, Opravil M, et al. Discontinuation of primary prophylaxis against Pneumocystis carinii pneumonia in HIV-1-infected adults treated with combination antiretrovriral therapy. N Engl J Med. 1999;340:1301-6.

6. Furrer H, et al. The Swiss StopCox Study: Is it safe to discontinue PCP prophylaxis in patients with detectable viremia, low nadir CD4 count, or T. gondii seropositivity? Abst #244. 7th Conference on Retroviruses and Opportunistic Infections, Jan 30-Feb 2, 2000, San Francisco.

7. Furrer H et al. Discontinuing or withholding primary prophylaxis against M. avium inpatients on successful antiretroviral combination therapy: the Swiss HIV Cohort

experience. Abst #246. 7th Conference on Retroviruses and Opportunistic Infections, Jan 30-Feb 2, 2000, San Francisco.

8. Johnson S, Benson C, Johnson D, Weinberg. Recurrent Cytomegalovirus retinitis in a patient on highly active antiretroviral therapy despite apparent immune reconstitution. Abst #272. 7th Conference on Retroviruses and Opportunistic Infections, Jan 30-Feb 2, 2000, San Francisco.

9. Miro JM, Lopez JC, Podzamczer D, et al. Discontinuation of toxoplasmic encephalitis prophylaxis is safe in HIV-1 and T. gondii-co-infected patients after immunological recovery with HAART. Preliminary results of the GESIDA 04/98-B study. Abs # 230). 7th Conference on Retroviruses and Opportunistic Infections, Jan 30-Feb 2, 2000, San Francisco.

10. Tural C, Rmeu J, Sicrera G, et al. Long-lasting remission of cytomegalovirus retinitis without maintenance therapy in human immunodeficiency virus-infected patients. J Infect Dis. 1998;177:1080-3.