NATAP FORUM

Current Issues in HIV Treatment: NATAP's Fifth Continuing Education Symposium

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Treatment and Prophylaxis for Opportunistic Infections in the New Potent Therapy Era. Can Prophylaxis or Maintenance Therapy Be Discontinued?

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Opportunistic infections (OIs) are the hallmark of the progressive immunodeficiency observed in persons with HIV infection. Natural history studies of persons with HIV infection demonstrate that different pathogens (e.g., MAC, CMV, TB) affect individuals at different levels of immunosuppression. The vast majority of OIs occur in persons with CD4+ lymphocyte counts < 50 cells/mm^3. Since the introduction of highly active antiretroviral therapy (HAART) there has been a dramatic decline in the number of OIs and, as a result, a overall decline in mortality from AIDS. A USPHS/IDSA panel recently released updated guidelines on OI prevention for persons with HIV infection. In this changing era of HIV treatment, it is important for persons with HIV infection and clinicians be familiar with the scientific rationale for the continued use of OI prophylaxis.

OI prophylaxis made a dramatic impact on the natural history of HIV infection. Historically, PCP affected 70% of persons with AIDS and was the leading cause of death. Prophylaxis for PCP is highly effective with rates declining by > 50%. PCP prophylaxis is strongly recommended for persons with CD4+ lymphocyte counts < 200 cells/mm^3 and is associated with prolonged survival. Trimethoprim-sulfamethoxazole (TS) is the prophylactic agent of choice. Unfortunately, as many as 60% of patients cannot tolerate this medication. Starting TS at lower doses and gradually building up to one double strength tablet daily is associated with a significant reduction in the short term rate of intolerance. Alternatives include dapsone, atovaquone and pentamidine. Prophylaxis for MAC (mycobacterium-avium complex) disease has also been shown to confer a survival advantage and is now recommended for all persons with CD4+ lymphocyte counts < 50 cells/mm^3. Azithromycin and clarithromycin should be considered first line agents with rifabutin reserved for those persons who cannot tolerate either of those medications. Chemoprophylaxis for tuberculosis has long been recognized to be an effective strategy and is recommended for HIV infected persons with a PPD of AE5 mm of induration. Prophylaxis for cerebral (brain) toxoplasmosis is also recommended for toxoplasma antibody positive individuals with a CD4+ count of 100 cells/mm^3. PCP prophylaxis with TS is usually adequate for the prevention of cerebral toxoplasmosis. When this cannot be used, the addition of weekly doses of pyrimethamine is adequate. Prophylaxis for CMV disease is controversial. Currently, CMV prophylaxis is not universally recommended but may be considered in some persons with CD4+ lymphocyte counts < 50 cells/mm^3. There are ongoing trials evaluating whether screening a person's blood with a quantitative PCR for CMV can identify those persons who would benefit the most from anti-CMV "preemptive" therapy as opposed to universal prophylaxis. Primary antifungal prophylaxis is not routinely recommended because it is not associated with any survival advantage. Pneumococcal

vaccination, Hepatitis B vaccination and Influenza vaccinations are all recommended though data on efficacy is sparse.

OI prophylaxis has proven to be quite useful. OI prophylaxis is cost effective but adds to the complexity of medical regimens. Side effects are not uncommon and drug interactions do occur. Because of the benefits of HAART, the question has been raised whether individuals who have an adequate antiretroviral response can safely discontinue OI prophylaxis when their CD4+ lymphocyte count rises above the level recommended for specific OI pathogen prophylaxis. This issue is a complex because we are not certain whether the CD4+ lymphocytes regained in response to HAART are as effective in preventing OIs as the ones that were lost during the course of HIV infection. Despite the absence of safety, there are patients who have been stopping their OI prevention drugs. This may be a risky course of action. This issue is currently being studied on several fronts within the AIDS Clinical Trials Group. First, there is a study (ACTG 362) designed to discontinue MAC prophylaxis in persons whose CD4+ lymphocyte counts were < 50 cells/mm^3 and have risen above 100 cells/mm^3 in response to HAART. In addition, there is a study which discontinues PCP prophylaxis in those persons whose CD4+ lymphocyte counts has risen above 200 cells/mm^3 (ACTG 888). Second, there are two other ACTG studies under development which propose to discontinue treatment for persons who had CMV retinitis or MAC disease who are now on HAART and have demonstrated a substantial response to treatment for those diseases and their HIV infection. The purpose of these trials is determine whether the dramatic decline in OIs can be translated into simplification of treatment regimens for those persons who respond to HAART (e.g., HIV viral load < 400 copies/ml and CD4+ lymphocyte count AE 100-200 cells/mm^3). Thus, there should be information available within the next 2-3 years that will help sort out this issue.

It is important to note that although HAART appears to be quite effective in reducing the number of OIs, it is not clear how long these benefits will last in individual patients. In persons whose CD4+ lymphocyte count declines after an initial rise in response to HAART, OI prophylaxis should still be the rule. Until there is data to prove that discontinuation of OI prophylaxis is safe, persons with HIV infection should continue to take OI prevention drugs.

Other speakers at the January 17th Forum included:

Jules Levin, Executive Director of NATAP - Welcoming Address
Dr. Robert Siliciano, MD - HIV in the Lymph Tissue and Latent Long-lasting Virus in T-Cells (CD4s).
Dr. Justin McArthur, MBBS, MPH - The Brain, HIV, and the Effect of New Treatments
Dr. Carl Fichtenbaum, MD - Treatment and Prophylaxis for Opportunistic Infections in the New Potent Therapy Era. Can Prophylaxis or Maintenance Therapy Be Discontinued?
Dr. Louise Markert, Thymus Transplant Research for HIV and Its Potential for Immune Reconstitution