

Current Report—HIV

Mycobacterial Disease In HIV-Infected Persons

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Mycobacterial disease is extremely common among persons infected with the human immunodeficiency virus (HIV). Recent changes in management have been recommended. This Current Report-HIV reviews some of those recommendations, augmenting the recent Current Report-HIV on treatment of HIV disease.¹

Mycobacterium tuberculosis

Diagnosis

Tuberculosis is being diagnosed more frequently in the United States as the HIV epidemic affects increasing numbers of persons previously infected with *Mycobacterium tuberculosis* and as new infections are spread from person-to-person. Previous *M. tuberculosis* infection often can be detected by the intermediate-strength purified protein derivative (PPD) intradermal skin test. In HIV-infected persons, a 5-mm (rather than the usual 10-mm) reaction is considered indicative of tuberculous infection.² A negative PPD skin test, however, cannot be considered an adequate indicator that infection has not occurred. As many as 10 percent of persons—both apparently healthy persons without HIV infection and asymptomatic HIV-infected persons with CD4+ lymphocyte counts greater than 500 cells/mm³—will have no detectable delayed-type hypersensitivity (DTH) response to PPD or any skin test antigen.³ In addition, recent studies have shown that even in early stages of HIV infection, the tuberculosis skin test is often falsely negative, particularly in per-

sons with CD4+ lymphocyte counts less than 400 cells/mm³.

These findings have important implications in the primary health care maintenance of HIV-infected persons. Because the tuberculin skin test cannot reliably exclude coinfection with *M. tuberculosis*, it is essential to attempt to determine whether a patient is at high risk for having latent infection (yet has a negative skin test) and could benefit from preventive therapy with isoniazid. High-risk groups have been defined as intravenous drug users, prisoners, homeless persons, migrant laborers, and persons born in countries of Asia, Africa, and Latin America that have high rates of tuberculosis.³ In these groups the tuberculosis infection rate is greater than 10 percent. Persons using crack cocaine in rooms where ventilation is deliberately limited to minimize detection appear to be at risk for airborne transmission of tuberculosis⁴ and can be added to this list. Similarly, persons with chest roentgenogram findings suggestive of previous tuberculous infection, as well as close contacts of persons with tuberculosis, should be considered at high risk. Not all persons in the above groups have major tuberculosis risk factors, so treatment decisions should be on a case-by-case basis.

The Division of Tuberculosis Elimination (DTBE) of the Centers for Disease Control has recommended evaluating DTH anergy in persons with HIV infection.³ The rationale for this recommendation, however, is not clear. Skin tests for DTH (e.g., using tetanus toxoid or mumps, candidal, or other antigens available either individually or in multiantigen test kits) can be falsely negative. In addition, DTH testing is costly in both patient expense and provider time. The DTBE also suggests that persons with DTH responsiveness (any amount of induration to DTH testing) who have nonreactive PPD tests can, in general, be considered not to be infected with *M. tuberculosis*. This screening ap-

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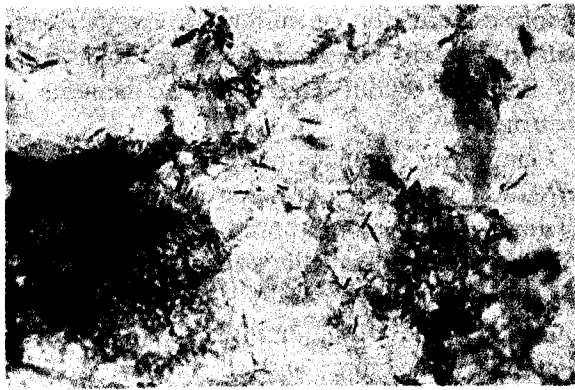


Figure 1. Photomicrograph of *Mycobacterium tuberculosis* organisms in a concentrated sputum specimen (Kinyoun stain). Acid-fast bacilli are usually microscopically indistinguishable, although these organisms demonstrate the longer, narrower, and more beaded morphology more typical of *M. tuberculosis* than of *Mycobacterium avium-intracellulae* organisms.

Photomicrograph, courtesy of Keith Hadley, M.D.

proach can help target certain persons within those high-risk groups for prophylactic antituberculosis treatment. However, even when DTH responsiveness is present, selective anergy to PPD can be present. Therefore, clinical risk assessment, rather than reliance upon DTH testing, seems most appropriate for the primary care provider.

The diagnosis of active tuberculosis usually precedes or coincides with the diagnosis of the acquired immunodeficiency syndrome (AIDS).⁵ Tuberculosis can also be found with advanced AIDS as one of the late opportunistic infections. The most common clinical presentations of active tuberculosis in HIV-infected persons include pulmonary infiltrates, lymphadenopathy, and disseminated (extrapulmonary) disease. The central nervous system, liver, genitourinary tract, bone marrow, blood, and numerous other sites can be involved. Apical pulmonary disease with cavitation is a less common presentation among HIV-infected persons than in persons with lesser degrees of immunosuppression. The presence of acid-fast bacilli in sputum usually signifies infection with *M. tuberculosis* (Figure 1). Acid-fast bacilli noted on biopsy specimens (with or without granuloma formation) or in other bodily fluids usually justify treatment for *M. tuberculosis* infection, although the *Mycobacterium avium-*

intracellulae complex bacillus is at times the more likely pathogen.

Treatment

Treatment of *M. tuberculosis* infection is essential for both personal and public health reasons. Preventive therapy with isoniazid (INH) is recommended for HIV-infected persons who have no evidence of active tuberculosis but have positive tuberculin skin tests and for high-risk persons listed above. Prophylaxis with oral isoniazid, 300 mg daily, should be administered for a minimum of 1 year, unless drug toxicity is a problem. Although there are no controlled studies evaluating preventive treatment with isoniazid in HIV-infected persons, its efficacy has been shown in other populations, and isoniazid appears to be well tolerated in HIV-infected persons.

Evaluation for active tuberculosis must precede the decision to offer preventive therapy. Although acid-fast bacilli seen on microscopic examination of specimens can be *M. tuberculosis*, *M. intracellulae*, *M. kansasii*,⁶ or other atypical mycobacteria, recommendations have been made to treat for *M. tuberculosis* upon finding them.² Patients with active tuberculosis (with or without coinfection with HIV) can be treated successfully.⁷ Initial treatment with isoniazid 300 mg/d orally, rifampin 600 mg/d orally, and pyrazinamide 20 to 30 mg/kg/d orally is recommended. Ethambutol 25 mg/kg/d orally should be added for patients with central nervous system involvement or disseminated tuberculosis or when isoniazid resistance is suspected. Long-term drug selection, including at least isoniazid and rifampin, should be based on studies of drug sensitivities (usually reported by 2 months). Treatment should continue for at least 9 months; isoniazid should probably be continued indefinitely in HIV-infected persons. Because many persons coinfect with HIV and *M. tuberculosis* have received previous treatment against tuberculosis or have contracted tuberculosis from persons with drug resistance, multi-drug resistant tuberculosis must be considered.⁸ These patients will require initial treatment with isoniazid, rifampin, and pyrazinamide, plus two other drugs to which the *M. tuberculosis* strain is likely to be susceptible. Toxicity from antituberculosis

medications occurs more frequently among HIV-infected persons, but usually does not necessitate drug discontinuation.^{5,7} Rash and hepatitis, often from rifampin, are most common. Ketoconazole and fluconazole concentrations can be reduced by isoniazid and rifampin, resulting in inadequate antifungal treatment. Similarly, the clinical effectiveness of rifampin is reduced by concurrent ketoconazole. By administering these drugs 12 hours apart, rifampin levels can be maintained.

***Mycobacterium avium-intracellulae* Complex**

Diagnosis

Disseminated *Mycobacterium avium-intracellulae* complex (MAC) disease is the most common mycobacterial disease in persons with HIV disease.^{9,10} It usually occurs late in the course of AIDS when CD4+ lymphocyte counts fall below 60 cells/mm³. Investigation for MAC is appropriate when persistent fevers, weight loss, or otherwise undiagnosed problems, such as diarrhea, abdominal pain, symptomatic intrahepatic obstruction, or mass lesions, are present.

Because dissemination is common, MAC can be found in examination or culture of the blood, lymph nodes, bone marrow, stool, liver, and many other specimens. Stool cultures are almost always positive because the gastrointestinal tract is the principal site of initial infection. With the advanced laboratory methods now available, blood cultures are positive in more than 85 percent of patients with disseminated disease. Unless risk factors for tuberculosis are present, the finding of acid-fast bacilli in blood can be presumed to indicate disseminated MAC disease. In addition, the presence of acid-fast bacilli in specimens from persons with far advanced HIV disease at low risk for *M. tuberculosis* infection most often indicates MAC infection rather than tuberculosis. Under these circumstances treatment for MAC (pending culture results) seems most appropriate.

Treatment

Multiple processes occur simultaneously in late-stage HIV infection, so the diagnosis of symptomatic MAC disease, as opposed to incidental MAC infection, is difficult. Symptomatic MAC complex disease can respond to treatment.^{10,11} MAC found incidentally on micro-

scopic examination or culture in asymptomatic patients should not be treated, as drug toxicity is likely to outweigh potential benefits of treatment.

Many drug regimens have been used against MAC. The following regimen is recommended: rifampin 600 mg orally once daily, clofazimine 100 mg orally once daily, ethambutol 15 mg/kg (usually 800 mg) orally once daily, and ciprofloxacin 500 mg orally twice daily. The rifampin, clofazimine, and ethambutol are best given at bedtime to minimize gastrointestinal side effects. Amikacin 10 to 15 mg/kg/d intravenously in two divided doses can be given for seriously ill, hospitalized patients. Isoniazid 300 mg/d orally should be added if there is a reasonable chance the infection is caused by *M. tuberculosis*. Long-term drug selection depends upon identification of the organism and in vitro sensitivity studies. Other drugs with activity against MAC that are expected to be approved by the Food and Drug Administration are azithromycin¹² and clarithromycin. Azithromycin 600 mg orally once daily and clarithromycin 500 mg orally 4 times daily are being used in Europe and are now available through "buyers clubs" in the United States. When these agents are used, one of the other four drugs can be omitted. Usually, the ciprofloxacin is omitted; alternatively, another drug that might be causing toxicity (most commonly rifampin) can be omitted.

Response to treatment is usually evident within 1 month. When a definite response occurs (e.g., complete or partial resolution of fever or pain, reduction of elevated hepatic enzyme levels) treatment should continue indefinitely. The lack of a clear response justifies discontinuing anti-MAC medications to avoid drug toxicity. Frequently, however, there is uncertainty whether new manifestations (such as the development of abnormal liver function tests, rashes, and gastrointestinal disturbances) are caused by underlying disease processes or by medications. A trial of drug discontinuation is required in these instances.

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(PCP) further advance treatment of human immunodeficiency virus (HIV) disease and associated opportunistic infections.

Didanosine (ddI), an Alternative Antiretroviral Agent

Didanosine (ddI, 2',3'-dideoxyinosine, [Videx™]), like zidovudine (AZT, [Retrovir™]), inhibits the replication of HIV. Didanosine is the second antiretroviral drug to be approved for use against HIV. Results of Phase I studies, as well as information from expanded access and open label programs in the United States, France, and Britain, suggest that didanosine might be effective in slowing the progression of HIV disease. These studies, however, use surrogate laboratory markers of HIV disease (CD4+ lymphocyte counts and p24 antigen levels) rather than clinical endpoints (opportunistic infections, hospitalizations, mortality) as measures of possible therapeutic benefit. Clinical efficacy, therefore, is not yet established. Nevertheless, based on modest improvements in key laboratory values, the United States Food and Drug Administration (FDA) has approved didanosine for use by prescription on a noninvestigational basis (9 October 1991).

Toxicities of didanosine include painful peripheral neuropathy, severe pancreatitis, hepatitis, abdominal cramps, and diarrhea. Because the drug is prepared with a buffer to facilitate absorption, it should be administered 2 hours apart from other drugs (such as ketoconazole, dapsone, tetracyclines, and quinolone antibiotics) whose absorption is impaired by buffered products.

Didanosine can be used in patients who do not tolerate zidovudine or who have failed treatment with zidovudine. Because didanosine has minimal hematologic toxicity, it is a logical alternative for those patients who develop anemia or other hematologic toxicity while receiving zidovudine. The clinical and laboratory parameters indicating "failed therapy" with zidovudine are less clear. Persistently falling CD4+ lymphocyte counts, new or progressive opportunistic infections and malignancies or persistent generalized symptoms and signs, such as fevers, weight loss, and inanition, can be interpreted as "failed therapy." Another indication for didanosine usage (although not

Updates

New Developments In Treatment: Didanosine (ddI), Foscarnet, And Trimethoprim-Sulfamethoxazole

Studies of two previously investigational drugs, didanosine and foscarnet, and new data on prophylaxis against *Pneumocystis carinii* pneumonia