Review Article

Current Concepts

Tuberculosis in Patients with Human Immunodeficiency Virus Infection

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TUBERCULOSIS remains an important problem in patients with human immunodeficiency virus (HIV) infection in the United States, with an estimated 6000 to 9000 new cases annually.[1] The case rates are extraordinarily high among indigent patients and substance abusers, and one third of these patients are also infected with HIV.[2] Much has been learned about the pathogenesis, clinical presentation, treatment, and prevention of tuberculosis in HIV-infected persons over the past several years. We summarize recent developments in these areas, as well as the effects of new antiretroviral therapies on antituberculosis regimens.

HIV INFECTION AND SUSCEPTIBILITY TO TUBERCULOSIS

HIV-infected persons are at markedly increased risk for primary or reactivation tuberculosis[3,4] and for second episodes of tuberculosis from exogenous reinfection.[5] Susceptibility to tuberculosis is related to the pattern of cytokines produced by T lymphocytes. T1 lymphocytes, which produce interferon-γ, are central to antimycobacterial immune defenses, and fatal mycobacterial disease develops in children who lack the interferon-γ receptor.[6] In contrast to T1 lymphocytes, T2 lymphocytes, which produce interleukin-4 and interleukin-10, do not contribute to antimycobacterial immunity.[7] When peripheral-blood lymphocytes from HIV-infected patients with tuberculosis are exposed to *Mycobacterium tuberculosis* in vitro, they produce less interferon-γ but similar amounts of interleukin-4 and interleukin-10, as compared with lymphocytes from HIV-negative patients with tuberculosis.[8] These findings suggest that the reduced T1 response in HIV-infected patients contributes to their susceptibility to tuberculosis.

TUBERCULOSIS AND THE COURSE OF HIV INFECTION

Exposure of alveolar macrophages and lymphocytes from HIV-infected patients to *M. tuberculosis* in vitro up-regulates retroviral replication.[9,10] Pleural fluid from patients with tuberculosis increases HIV replication in activated lymphocytes,[11] and in HIV-infected patients with pulmonary tuberculosis, the concentrations of retroviral RNA in bronchoalveolar-lavage fluid are highest in areas of tuberculous involvement.[12] *M. tuberculosis* probably increases HIV replication by inducing macrophages to produce tumor necrosis factor α, interleukin-1, and interleukin-6.[11,12]

Clinical studies have shown the detrimental effects of tuberculosis on the course of HIV infection. The risk of death in HIV-infected patients with tuberculosis was reported to be twice that in HIV-infected patients without tuberculosis, independently of the CD4 cell count.[13] The high mortality rate among patients with tuberculosis appeared to be due to progressive HIV infection rather than tuberculosis. The degree of immunosuppression is the most important predictor of survival in HIV-infected patients with tuberculosis, since negative tuberculin skin tests, prior opportunistic infections, and low CD4 cell counts are associated with increased mortality.[14,15]

TESTING FOR HIV INFECTION IN PATIENTS WITH TUBERCULOSIS

All patients with tuberculosis should be tested for HIV coinfection because of the potential benefits of an early diagnosis of HIV infection.[16] However, in two cities where HIV seroprevalence was high, HIV testing was performed in only 35 to 64 percent of patients with tuberculosis and in only 20 to 57 percent of those without known HIV risk factors.[17,18] Private practitioners performed HIV testing in only 44 percent of patients with tuberculosis, on the basis of their assessment of the risk of HIV infection.[18] Selective HIV testing in patients with tuberculosis is unwise, because health care providers often fail to identify risk factors for HIV related to heterosexual transmission.[19] Even when patients with tuberculosis are questioned about risk factors for HIV infection, up to 5 percent of those who report no risk factors are infected with HIV.[19]

CLINICAL PRESENTATION AND RADIOGRAPHIC FINDINGS

As the level of immunosuppression increases in HIV-infected patients, mycobacteremia and extra-

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pulmonary tuberculosis become progressively more common.[20] In HIV-infected patients with fever of undetermined cause, diagnostic studies for extrapulmonary tuberculosis should be undertaken. The clinical presentation of abdominal tuberculosis in HIV-infected patients is characterized by visceral lesions and intraabdominal lymphadenopathy with necrosis, which is best visualized by computed tomography. In contrast, ascites and omental thickening are characteristic of abdominal tuberculosis in HIV-negative patients.[21] The clinical presentation of tuberculosis meningitis is similar in HIV-infected patients and in immunocompetent patients, except that intracerebral mass lesions are more common in HIV-infected patients.[22]

In HIV-infected patients with tuberculosis who have CD4 cell counts of 200 or more per cubic millimeter, chest radiographic findings include upper-lobe infiltrates and cavitation, findings similar to those in HIV-negative patients with tuberculosis.[23] In HIV-infected patients with fewer than 200 CD4 cells per cubic millimeter, mediastinal adenopathy is common, a situation similar to that in HIV-negative children with primary tuberculosis.[23] Molecular typing of *M. tuberculosis* isolates to identify patients with primary and reactivation tuberculosis suggested that the presence of mediastinal adenopathy does not indicate primary tuberculosis in HIV-infected patients but probably reflects an ineffective immune response.[24] Approximately 5 percent of HIV-infected patients with pulmonary tuberculosis have positive results on acid-fast staining of sputum, despite normal chest radiographs.[23]

RAPID DIAGNOSTIC TESTS

Two new tests can identify *M. tuberculosis* ribosomal RNA (MTD, Gen-Probe, San Diego, Calif.) or DNA (Amplicor, Roche Molecular Systems, Branchburg, N.J.) in clinical specimens within 24 hours. These tests do not replace acid-fast staining, which provides an index of contagiousness, or mycobacterial cultures, which permit drug-susceptibility testing. Acid-fast staining, mycobacterial cultures, and drug-susceptibility testing are recommended for all patients. Rapid diagnostic tests are costly and should be used primarily when test results will influence the decision whether to institute antituberculosis therapy or perform additional diagnostic procedures.[25] These tests are approved by the Food and Drug Administration for use only in respiratory tract specimens with positive acid-fast staining from patients who have received antituberculosis therapy for less than seven days. In this setting, the tests have sensitivities and specificities of more than 95 percent. In sputum samples with negative acid-fast staining, the test sensitivities range from 40 to 77 percent, but the specificity is more than 95 percent.[25,26]

Rapid diagnostic tests should not be performed for HIV-infected patients with positive smears in whom the clinical suspicion of tuberculosis is high, because positive results merely confirm the clinical impression and negative results do not rule out tuberculosis. An example of such a patient would be a young man with a two-month history of cough and a chest radiograph showing cavitary upper-lobe infiltrates. Because smear-positive tuberculosis is transmissible and potentially fatal, antituberculosis therapy should be given to such patients regardless of the results of rapid diagnostic tests. In contrast, in HIV-infected patients with positive smears for whom the clinical suspicion of tuberculosis is intermediate or low, rapid diagnostic tests can be helpful. For example, in a patient with a positive acid-fast sputum smear and *M. avium* complex bacteremia who is not in a high-risk group for tuberculosis, concomitant tuberculosis is an unlikely but potentially important diagnosis. A positive result on a rapid diagnostic test should prompt antituberculosis therapy, whereas a negative result greatly reduces the likelihood of tuberculosis and permits the use of therapy targeted against nontuberculous mycobacteria. On the basis of the clinical situation, antituberculosis therapy can be withheld and an investigation of the patient's contacts deferred, thus averting adverse drug effects and reducing public health care costs.[25]

In HIV-infected patients for whom acid-fast smears are negative and the clinical suspicion of tuberculosis is high, antituberculosis therapy should be given regardless of the results of rapid diagnostic tests. However, these results can guide further evaluation of patients. For example, in patients with clinical evidence of miliary tuberculosis and negative smears, negative results on a rapid diagnostic test would prompt invasive procedures to establish the diagnosis, whereas positive results might obviate the need for further diagnostic evaluation, reducing morbidity and cost. When acid-fast smears are negative and the clinical suspicion of tuberculosis is intermediate, as in the case of HIV-infected patients with pulmonary symptoms and diffuse interstitial infiltrates, rapid diagnostic tests are also helpful. Positive results should prompt empirical antituberculosis therapy and may eliminate the need for bronchoscopy. Negative results do not rule out tuberculosis. Further diagnostic tests will usually be indicated, and the decision whether to give antituberculosis therapy will depend on clinical circumstances. In HIV-infected patients for whom acid-fast smears are negative and the clinical suspicion of tuberculosis is low, rapid diagnostic tests are not helpful, because a negative result only confirms the clinical impression and a positive result is likely to be falsely positive.

RESTRICTION-FRAGMENT–LENGTH POLYMORPHISM ANALYSIS

The restriction-fragment–length polymorphism (RFLP) analysis of *M. tuberculosis* isolates allows

identification of specific *M. tuberculosis* strains and can document the transmission of disease between patients. Although it was previously thought that 90 percent of cases of tuberculosis in the United States resulted from reactivation of infections acquired in the remote past, RFLP analyses show that recent infection accounts for up to half the cases of tuberculosis among both HIV-infected and HIV-negative patients in urban areas.[27,28]

RFLP analysis is used most frequently to confirm that clusters of cases of tuberculosis are linked by recent transmission. However, RFLP analysis can also be helpful in making clinical decisions about individual HIV-infected patients with tuberculosis.[29] When a single specimen with negative results on acid-fast staining yields *M. tuberculosis* but the clinical findings in the patient are not consistent with the presence of tuberculosis, the possibility of a false positive result from cross-contamination with another patient's sample can be evaluated by comparing the RFLP patterns of the two isolates. Identical RFLP patterns strongly suggest cross-contamination, allowing the discontinuation of potentially toxic antituberculosis medications. RFLP analysis is also useful when two *M. tuberculosis* isolates from a patient differ in drug susceptibility. This situation can arise if the initial isolate develops resistance during therapy, the patient is infected with a second *M. tuberculosis* strain,[5] or the second isolate represents laboratory cross-contamination. RFLP analysis of the patient's isolates, as well as any isolates processed at the same time, can distinguish among these possibilities.

TREATMENT OF TUBERCULOSIS

Current guidelines recommend that HIV-negative patients with tuberculosis receive six-month regimens of treatment for drug-susceptible tuberculosis (Table 1).[30] In HIV-infected patients with drug-susceptible tuberculosis, the standard six-month regimen results in prompt sterilization of sputum and low rates of treatment failure, similar to those in HIV-negative persons.[32,33] However, two studies showed higher rates of relapse in HIV-infected patients who received 6 as compared with 9 to 12 months of antituberculosis chemotherapy.[34,35] The longer regimens may have provided more effective treatment or may have prevented exogenous reinfection.[36] In view of these uncertainties, some authors recommend more prolonged therapy in HIV-infected patients (Table 1).[35,37,38] The most recent guidelines of the Centers for Disease Control and Prevention (CDC) state that the minimal duration of therapy is six months, but that if the clinical or bacteriologic response is slow, treatment should be given for a total period of nine months, or for four months after cultures become negative.[31] Directly observed therapy improves the outcome, is cost effective, and is strongly recommended for HIV-infected patients.[31,36,39,40] Detailed

TABLE 1. TREATMENT REGIMENS FOR PATIENTS WITH TUBERCULOSIS, ACCORDING TO HIV STATUS.*

DRUG RESISTANCE	PATIENTS WITHOUT HIV INFECTION	PATIENTS WITH HIV INFECTION	ANTIRETROVIRAL THERAPY
None	IRPE for 2 mo, IR for 4 mo†	IRPE for 2 mo, IR for 4–7 mo‡	No protease inhibitors or NNRTIs can be used with rifampin§
		or	
		IPE plus rifabutin for 2 mo, I plus rifabutin for 4–7 mo	Rifabutin can be used with indinavir or nelfinavir but not with saquinavir, ritonavir, or NNRTIs
Isoniazid	RPE for 6 mo	RPE for 6–9 mo¶	No protease inhibitors or NNRTIs can be used with rifampin
		or	
		rifabutin plus PE for 6–9 mo	Rifabutin can be used with indinavir or nelfinavir but not with saquinavir, ritonavir, or NNRTIs
Rifampin	IPE for 18–24 mo	IPE for 18–24 mo	All antiretroviral drugs can be used
		or	
		IPSE for 2 mo, IPS for 7–10 mo	All antiretroviral drugs can be used

*Recommendations are based on those of the American Thoracic Society,[30] the Centers for Disease Control and Prevention,[31] and expert opinion. I denotes isoniazid, R rifampin, P pyrazinamide, E ethambutol, NNRTI non-nucleoside reverse-transcriptase inhibitor, and S streptomycin.

†Streptomycin may be substituted for ethambutol. Ethambutol may be omitted only if rates of isoniazid resistance in the community are documented to be less than 4 percent.

‡Therapy should be more prolonged in patients with a slow clinical or bacteriologic response to treatment.[31] A total of 12 months of therapy is recommended for patients who have miliary or skeletal tuberculosis, with or without HIV infection.

§Protease inhibitors and NNRTIs should not be given for at least two weeks after rifampin has been discontinued, because of persistent induction of the cytochrome P-450 CYP3A.

¶The American Thoracic Society recommends six months of therapy; the CDC recommends six to nine months.[31]

dosage schedules for directly observed therapy two or three times weekly have recently been published.[31]

New antiretroviral combination regimens have dramatically improved the prognosis for HIV-infected patients[41,42] but have complicated the management of tuberculosis. Rifampin induces the activity of cytochrome P-450 CYP3A, which lowers the concentrations of HIV-protease inhibitors and non-nucleoside reverse-transcriptase inhibitors to subtherapeutic levels. Low trough plasma levels of these antiretroviral drugs are associated with incomplete viral suppression and the emergence of drug resistance.[43,44] Therefore, concomitant administration of rifampin with these drugs is not recommended.

Because the antituberculosis drug rifabutin is a less potent inducer of CYP3A than rifampin, it can be administered in combination with the protease inhibitor indinavir or nelfinavir. Rifabutin should not be used with the hard-gel formulation of saquinavir, because saquinavir levels are decreased by 45 percent, and we believe that the data are insufficient to recommend the use of soft-gel saquinavir. It may be possible to use rifabutin with amprenavir, which is still under development, because amprenavir concentrations are reduced by only 14 percent. The results of three clinical trials, one of which involved HIV-infected patients, suggest that a regimen of 150 to 300 mg of rifabutin given daily is well tolerated and is at least as effective as rifampin in a standard antituberculosis regimen.[45-47] One trial showed the efficacy of intermittent administration of rifabutin in HIV-negative patients.[47]

To increase the plasma levels of protease-inhibitor drugs and to reduce the likelihood that drug-resistant HIV mutants will emerge, the dose of indinavir should be increased to 1000 mg every eight hours in patients receiving rifabutin. Preliminary data suggest that the dose of nelfinavir may be increased to 1250 mg every 12 hours in this setting, and formal pharmacokinetic studies in HIV-infected patients are in progress. Because protease inhibitors inhibit the metabolism of rifabutin and increase the rate of uveitis associated with the drug,[48,49] a reduced dose of rifabutin (150 mg daily) is recommended.[50] Ritonavir is the most potent inhibitor of the metabolism of rifabutin, and the manufacturer recommends that these drugs not be used in combination.

The use of rifabutin with non-nucleoside inhibitors of reverse transcriptase should be approached with caution. Rifabutin reduces delavirdine levels by 75 percent,[51] and this combination of drugs should not be used. Rifabutin reduces nevirapine and efavirenz levels to a lesser extent,[31] but the resistance of HIV to the latter two drugs is conferred by a single mutation, and lower drug levels may permit the emergence of drug-resistant virus and jeopardize long-term viral suppression. Furthermore, nevirapine and efavirenz may reduce rifabutin levels, and the data are insufficient to recommend dosage adjustments.

Clinicians are prescribing indinavir and nelfinavir for HIV-infected patients receiving antituberculosis therapy with rifabutin-containing regimens. However, there are no published data on the outcome of tuberculosis or HIV infection in these patients. Despite these uncertainties, recently revised guidelines[31] recommend that all HIV-infected patients with tuberculosis be evaluated to determine whether they would benefit from the initiation or continuation of therapy with protease inhibitors according to published guidelines for HIV therapy.[52,53] In general, protease inhibitors are recommended as part of initial therapy in patients with more than 5000 copies of HIV RNA per milliliter who are willing to adhere to a demanding medical regimen. Patients who have benefited from protease inhibitors before the development of tuberculosis should generally continue to receive them during antituberculosis therapy.

If the decision is made to initiate or continue therapy with a protease inhibitor, indinavir or nelfinavir should be used, and rifabutin should be substituted for rifampin in the antituberculosis regimen (Table 1). To reduce the risk of subtherapeutic levels of protease inhibitors, an alternative is to treat tuberculosis with regimens that do not include a rifamycin. These regimens have demonstrated efficacy only in HIV-negative patients,[54,55] and their utility is limited by toxicity, cost, and inconvenience. The CDC recommends the administration of isoniazid, pyrazinamide, and streptomycin for nine months, with ethambutol for the first two months.[31] However, we believe that the decision should be individualized, since an oral regimen of isoniazid, ethambutol, and pyrazinamide for 18 to 24 months may be preferable in most patients.

For patients who are not currently candidates for therapy with protease inhibitors, standard antituberculosis therapy can be administered, together with antiretroviral therapy that does not include protease inhibitors or non-nucleoside reverse-transcriptase inhibitors (Table 1). In this case, antiretroviral therapy must be carefully selected to minimize the possibility that drug-resistant HIV will develop and to preserve future options for HIV therapy.

PARADOXICAL REACTIONS DURING ANTITUBERCULOSIS THERAPY

Antiretroviral therapy may be initiated early during antituberculosis therapy in HIV-infected patients with tuberculosis. After initial clinical improvement, paradoxical worsening of disease developed in up to 36 percent of these patients, characterized by fever, worsening chest infiltrates on radiography, and peripheral and mediastinal lymphadenopathy.[56] In contrast, only 7 percent of patients who received antituberculosis therapy but not antiretroviral therapy had paradoxical reactions. A substantial reduction in the HIV burden and a marked increase in reactivity on

tuberculin skin testing accompanied these paradoxical reactions, suggesting that they represent inflammation from a stronger immune response to *M. tuberculosis* after antiretroviral therapy. In patients with clinical findings that are compatible with the presence of a paradoxical reaction, other diagnoses must be ruled out. Paradoxical reactions are self-limited and generally last 10 to 40 days. However, some reactions are severe and may require a short course of treatment with a glucocorticoid.[56]

RESISTANCE TO RIFAMPIN

Tuberculosis that is resistant to rifampin but susceptible to isoniazid (rifampin-monoresistant tuberculosis) is more common in HIV-infected patients than in immunocompetent patients,[57] and most cases arise independently from mutations in drug-susceptible strains, not from extensive transmission of a few rifampin-monoresistant strains.[57,58] In one study, the development of rifampin-monoresistant tuberculosis after initial infection with drug-susceptible organisms was independently associated with nonadherence to therapy, severe immunosuppression, and a positive acid-fast sputum smear.[57] A second study suggested that rifampin monoresistance is independently associated with rifabutin use, antifungal therapy, and diarrhea.[59] The mechanism of development of rifampin monoresistance in HIV-infected patients is unclear.

MULTIDRUG-RESISTANT TUBERCULOSIS

Explosive outbreaks of nosocomial multidrug-resistant tuberculosis presented a serious public health threat in New York City and Miami in the early 1990s, with unprecedented case fatality rates of 80 percent in HIV-infected patients.[60] Stringent infection-control policies curtailed these outbreaks, and a strengthened public health infrastructure and widespread use of directly observed therapy limited the spread of the disease, resulting in a 44 percent decrease in multidrug-resistant tuberculosis in New York City between 1991 and 1994.[61] Because multidrug-resistant tuberculosis initially arises in patients who do not adhere to antituberculosis therapy, the continued decline in the rates of multidrug-resistant tuberculosis hinges on the allocation of adequate public health resources to ensure that patients complete their antituberculosis therapy.

Prompt treatment with two or more effective antituberculosis drugs increased the median survival from 2 to 14 months in HIV-infected patients with multidrug-resistant tuberculosis.[62,63] Most deaths among patients who receive effective therapy are due to complications of HIV infection rather than to tuberculosis. In cases in which multidrug-resistant tuberculosis is strongly suspected, empirical therapy for this disease should be initiated according to the available guidelines.[64]

MALABSORPTION OF ANTITUBERCULOSIS MEDICATIONS

Reports of malabsorption of antituberculosis medications in HIV-infected patients, associated with treatment failure and acquired drug resistance,[65] have prompted pharmacokinetic studies of antituberculosis drugs in these patients. Two studies of HIV-infected patients with tuberculosis have yielded conflicting results. One study found that the plasma levels of rifampin and ethambutol were lower in HIV-infected patients with tuberculosis than in historical HIV-negative control patients with tuberculosis,[66] whereas another study found no differences between HIV-positive and HIV-negative patients with tuberculosis, in terms of the peak level or total absorption of isoniazid, rifampin, or pyrazinamide.[67] Thus, the prevalence and clinical significance of malabsorption of antituberculosis medications in HIV-infected patients with tuberculosis remain controversial, and routine monitoring of plasma drug levels is unwarranted. However, in patients who adhere to but have no response to antituberculosis therapy, clinicians should strongly consider measuring drug levels to evaluate the possibility of malabsorption.

CHEMOPROPHYLAXIS AND ANERGY TESTING

HIV-infected patients with recent or remote *M. tuberculosis* infection are at extremely high risk for the development of tuberculosis,[3,4] and the importance of chemoprophylaxis cannot be overestimated. Once active tuberculosis has been ruled out, chemoprophylaxis is recommended for all HIV-infected persons with a positive tuberculin skin test (induration of 5 mm or more in diameter), a previous positive tuberculin skin test without prior chemoprophylaxis against tuberculosis, or recent close contact with potentially infectious patients with tuberculosis.[16,30,31] Isoniazid chemoprophylaxis for six months reduced the risk of tuberculosis by approximately 70 percent in HIV-infected patients with positive tuberculin skin tests.[68] Rifampin and pyrazinamide administered twice weekly for 2 months and isoniazid administered twice weekly for 6 months were equally effective,[69] and preliminary data suggest that the efficacy of daily rifampin and pyrazinamide for 2 months is similar to that of 12 months of isoniazid in tuberculin-positive, HIV-infected patients.[70] Currently recommended preventive-therapy regimens for HIV-infected patients are nine months of daily or twice-weekly isoniazid, or two months of daily pyrazinamide and either rifampin or rifabutin.[31] Chemoprophylaxis for an HIV-infected person exposed to a patient with multidrug-resistant tuberculosis should include at least two drugs with activity against the drug-resistant isolate.[71]

Because HIV-infected patients have defective cell-mediated immunity, false negative tuberculin skin tests

are common. It has therefore been recommended that skin testing be performed with tuberculin and other antigens and that chemoprophylaxis be considered for anergic patients in whom the risk of tuberculosis infection is 10 percent or more.[72] However, recent studies have shown that the results of anergy testing are not reproducible in HIV-infected patients[73] and that isoniazid chemoprophylaxis does not reduce the incidence of tuberculosis in HIV-infected patients with anergy.[68,74] Given these findings, anergy testing is no longer recommended to assess the risk of tuberculosis infection.[75]

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