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Tuberculosis and Human Immunodeficiency Virus Infection: Recommendations of the Advisory Committee for the Elimination of Tuberculosis (ACET)

INTRODUCTION

Tuberculosis (TB) and other mycobacterioses are well-recognized complications of immunosuppression. In the 1980s, the epidemic of human immunodeficiency virus (HIV) infection and its resulting immunosuppression in large numbers of persons have increased the incidence of mycobacterial diseases (1). Disseminated *Mycobacterium avium* complex (MAC) disease has become an important medical problem; MAC is the most common mycobacterial species isolated from persons with acquired immunodeficiency syndrome (AIDS).

Of particular public health concern, however, is the increasing number of persons with disease caused by *M. tuberculosis* (2-5). HIV infection appears to be an important risk factor for TB. Moreover, TB is one of the few respiratory diseases occurring in HIV-infected persons that is transmissible, curable, and preventable.

The Advisory Committee for Elimination of Tuberculosis (ACET) is concerned that the further spread of HIV infection among populations with a high prevalence of tuberculous infection may result in dramatic increases in TB unless appropriate control measures outlined in this statement are successfully implemented.

EPIDEMIOLOGY

The contribution of HIV-related TB morbidity to total national TB morbidity is not precisely known, but HIV infection appears to have had a substantial impact in some areas (6,7). Matching reported TB cases with the AIDS case registries in 43 states and 11 localities reveals that 4% of AIDS cases appear on the TB registries (CDC, unpublished data).

In Florida, 10% of AIDS patients had histories of TB (8); in New York City, 5% of adult and adolescent AIDS patients (9); in Connecticut, 5% (10); and at a university hospital in New Jersey, 21% (4). In San Juan, Puerto Rico, 11% of autopsied AIDS patients had TB (11), and at a New York City hospital, 4% of autopsied AIDS patients had previously undiagnosed TB (12).

Some data on HIV seroprevalence among TB patients have also been accumulated. In San Francisco, 29% of

non-Asian adult TB patients 18-65 years of age were infected with HIV (13). In Seattle, a combined 23% of black and white adult TB patients 20-50 years of age were HIV-infected (14). Evidence for an association between HIV infection and TB comes from several studies. Of 279 HIV-infected methadone-maintenance patients in New York City, 12 had histories of TB; none of the 240 patients not infected with HIV had histories of TB (15).

In another cohort of methadone-maintenance clients with documented positive tuberculin skin test reactions, 14% of HIV-infected persons and none of the HIV- negative clients developed TB during a 2-year period (16). In Kinshasa, Zaire, a study of 500 decedents who were serologically tested postmortem showed that 16% of HIV-infected persons and 2% of HIV-negative persons had TB diagnosed ante mortem by smear (17).

An association between TB and AIDS is particularly striking among groups with a high prevalence of both tuberculous and HIV infections, e.g., intravenous-drug users (IVDUs) (4,18) and Haitians (2,5). However, HIV-related TB is not restricted to IVDUs and Haitians (2,5,19). It has been reported in homosexual and bisexual men and sexual contacts of bisexual men and in one person with transfusion-associated AIDS (19,20).

Demographically, minority populations in some areas have been at particular risk of HIV-associated TB. Detailed demographic information obtained from registry matching in New York City, Florida, and Newark, New Jersey, revealed that blacks and Hispanics accounted for 80%, 90%, and 100%, respectively, of the TB/AIDS cases (4,8,9).

The finding that TB often precedes other opportunistic diseases constituting the national surveillance definition of AIDS (2,3) was confirmed in two large studies in Florida and New York City (8,9). In Florida, 62 (57%) of the 109 AIDS patients with histories of TB developed TB greater than 1 month before the diagnosis of AIDS (8). In New York City, TB was diagnosed a median of 2 months before the AIDS diagnosis among 258 persons with both diagnoses for whom such information was available (9). These findings suggest that latent, subclinical tuberculous infection may often progress to clinical TB early in the course of HIV-induced immunosuppression and that AIDS patients known to have developed TB may represent only a small proportion of total HIV-associated TB morbidity. Additional evidence for this possibility was gathered in Miami, where 22 (31%) of 71 consecutively tested TB patients had HIV infection, but only two met the pre-1987 case definition for AIDS (21).

Similar serosurveys have not been reported from other areas, but TB clinics are included in HIV serosurveys being implemented in 30 metropolitan areas. This information will help determine the nationwide impact of the HIV epidemic on the incidence of TB.

CLINICAL FEATURES

The diagnosis of TB usually precedes or coincides with the diagnosis of AIDS but may follow it (2,3,8-10,18). The clinical presentation of TB in an HIV-infected person may differ from that in persons with relatively normal cellular immunity who develop reactivation TB. Apical pulmonary disease with cavitation, a classic finding in immunologically normal persons, is less common. Patients may present with infiltrates in any lung zone, often associated with mediastinal and/or hilar lymphadenopathy (22).

Extrapulmonary disease occurs in 40%-75% of patients, often in the presence of pulmonary disease (2,4,8,9). Lymphatic and hematogenous TB are especially common among persons with HIV infection (2,4). Central nervous system (CNS) involvement, including brain abscesses, has been reported (23) and may be especially difficult to diagnose when it occurs in conjunction with other opportunistic CNS infections such as toxoplasmosis (24). Other unusual clinical presentations have also been reported (1).

DIAGNOSIS

These unusual clinical features emphasize the importance of considering a diagnosis of TB in persons with known or possible HIV infection and a diagnosis of HIV infection in persons with TB. Persons who provide care to HIV-infected persons must be informed of the frequently uncharacteristic presentation of TB in this group so that the diagnosis is not overlooked. Failure to diagnose and manage TB appropriately can result in the death of

the patient and infection of contacts, including other patients and health-care personnel.

To establish the diagnosis, a variety of specimens, including respiratory secretions, bronchial washings, gastric lavage, lung tissue, pleural fluid, lymph node tissue, bone marrow, blood, urine, stool, brain biopsy, and cerebrospinal fluid, may need to be obtained for mycobacterial culture. Specimens must be examined microscopically, but the inability to demonstrate acid-fast bacilli and the absence of granuloma formation does not exclude the diagnosis of TB (4,19).

A Mantoux tuberculin skin test with 5 tuberculin units (TU) of tuberculin purified protein derivative (PPD) should be administered as a diagnostic aid, although some persons with HIV infection may have falsely negative reactions because of immunosuppression (2,3). The severity of immunosuppression and the development of AIDS is related to the duration of HIV infection. Furthermore, the proportion of HIV-infected persons with TB who have negative tuberculin skin test reactions is related to the length of time between the diagnoses of TB and AIDS.

In Florida, the proportion of TB patients with positive tuberculin skin tests progressively decreased with decreasing time between the two diagnoses. All five patients in whom TB was diagnosed greater than or equal to 2 years before the diagnosis of AIDS had positive reactions when TB was diagnosed, 27 (63%) of 43 who had TB diagnosed 1-24 months before the AIDS diagnosis had positive reactions, and seven (33%) of 21 in whom TB was diagnosed simultaneously with or after AIDS had positive tuberculin reactions (CDC/Florida Department of Health and Rehabilitative Services, unpublished data).

In New York City, of 23 AIDS patients known to have developed TB and for whom information on the size of the tuberculin reaction was available, seven had no induration, one had a 1-4-mm induration, two had a 5-9-mm induration, and 13 had a greater than or equal to 10-mm induration (CDC/ New York City Department of Health, unpublished data). Because HIV infection causes immunosuppression and the risk for TB is high in persons with both tuberculous and HIV infection, as a general guideline, tuberculin reactions of greater than 5-mm induration should be considered indicative of tuberculous infection in an HIV-infected person.

TREATMENT

Anti-TB chemotherapy as described below should be started whenever acid-fast bacilli are seen in a specimen from the respiratory tract of a person with HIV infection or from a person at increased risk for HIV infection whose HIV-antibody status is unknown and who declines to be tested. Because it is impossible to distinguish TB from MAC disease by any criterion other than culture (which often takes several weeks), and because of the individual and public health implications of TB, it is important to treat such patients with a regimen that is effective against *M. tuberculosis*.

As a general rule, persons with TB and HIV infection respond well to standard anti-TB drugs (2,4,19), but data on clinical and bacteriologic response in these patients are limited. Longitudinal studies will help clarify the long-term outcome of these patients.

To achieve cure, the treatment period may need to be longer than the standard regimens used for TB patients without HIV infection. When HIV infection is known or suspected, the recommended drugs and dosages for adults are isoniazid, 300 mg/day, and rifampin, 600 mg/day (or 450 mg for patients weighing less than or equal to 50 kg), and pyrazinamide, 20-30 mg/kg/day, during the first 2 months of therapy. Patients treated with rifampin who are on methadone should have the methadone dosage increased to avoid withdrawal symptoms resulting from the interaction between the two drugs (25). Ethambutol, 25 mg/kg/day, should be added to the initial treatment regimen for patients with CNS or disseminated TB or when isoniazid resistance is suspected.

The continuation phase should always include at least isoniazid and rifampin. Drug susceptibility tests should be performed routinely, and the treatment regimen should be revised accordingly if resistance to any of the drugs in the regimen is found. Treatment should be continued for a minimum of 9 months and for at least 6 months beyond documented culture conversion as evidenced by three negative cultures.

In the absence of definitive data on benefits and risks, some experts suggest that, in persons with concomitant tuberculous and HIV infections, isoniazid therapy should be continued for the person's lifetime (26). If either isoniazid or rifampin is not or cannot be included in the regimen, therapy should last a minimum of 18 months and for at least 12 months after culture conversion. After completion of therapy, patients should be followed closely, and bacteriologic examinations should be repeated if signs of TB recur.

Compliance with therapy is sometimes poor. Supervised, directly administered ambulatory therapy is successful in noncompliant patients (27) and should be initiated if noncompliance is anticipated or suspected. Monitoring for symptoms of toxicity to anti-TB drugs may be difficult in persons with AIDS, who frequently have similar symptoms due to HIV infection, other drugs, or other conditions. At least one study has reported a higher incidence of adverse reactions to anti-TB drugs in AIDS patients (28).

CONTACT INVESTIGATION

Persons with pulmonary TB, including those with AIDS or HIV infection, are potentially infectious until a satisfactory clinical and bacteriologic response to therapy is achieved. All cases must be reported immediately to the local health department so that standard procedures for TB contact investigation can be followed (29).

In one investigation carried out by the New York City Department of Health, prevalence of tuberculin positivity (21%) among contacts of pulmonary TB patients who also had, or later developed, AIDS was not substantially different from that among contacts of comparable pulmonary TB patients with no diagnosis of AIDS (30%) (CDC/New York City Department of Health, unpublished data).

It is not known how much of this high cumulative prevalence of infection represents transmission by these index patients and how much represents prior background prevalence, but these data indicate that TB patients with HIV infection must be considered potential transmitters of *M. tuberculosis*.

INFECTION CONTROL

Published recommendations for preventing transmission of HIV infection and tuberculous infection to health-care workers should be followed (30-34). Because health-care workers' risk of exposure to blood during tuberculin skin testing or injecting medication is low, wearing gloves during these procedures to prevent HIV transmission is not routinely recommended. However, used needles should not be recapped and should be disposed of according to published guidelines (31). Recommendations for glove use during drawing of blood (e.g., for liver-function testing) have been published (31); whether to use gloves routinely during phlebotomy requires consideration of several factors.

TB should be considered in the differential diagnosis of persons with HIV infection and unexplained pulmonary symptoms, and appropriate precautions should be followed. These precautions, termed AFB isolation, are most important during and immediately after procedures that may induce coughing, such as bronchoscopy, sputum collection, aerosol induction of sputum, and administration of aerosolized medications, such as pentamidine. In clinical situations where airborne exposure of staff or other patients is likely, such procedures should be carried out in rooms or booths with negative air pressure in relation to adjacent rooms or hallways and with air exhausted directly to the outside and away from intake sources. The number of air exchanges per hour in the room or booth should be sufficient to remove infectious organisms during the time between patients. Ultraviolet lights are also useful in killing airborne tubercle bacilli (33,34).

Special care should be taken to prevent inhalation of tubercle bacilli by HIV-infected persons. Home health-care workers, hospice volunteers, paramedics, and others who care for persons with AIDS in areas where tuberculous infection is also prevalent should be aware of the symptoms of TB, the airborne nature of its transmission, and the appropriate precautions for their particular setting. Workers who have regular contact with TB patients should participate in a TB screening program (29,33). Consultation on methods to reduce transmission of TB is available from state and local health department TB-control programs.

EXAMINING PERSONS WITH TB OR TUBERCULOUS INFECTION FOR HIV INFECTION

All persons with TB or tuberculous infection need to be assessed for HIV infection because the medical management of TB and tuberculous infection must be altered in the presence of HIV infection. TB patients who are infected with HIV may also develop *Pneumocystis carinii* pneumonia, cytomegalovirus pneumonitis, and other pulmonary manifestations of HIV infection as their immunosuppression progresses.

Assessing these patients' responses to anti-TB therapy and evaluating new infiltrates may be especially difficult. Because the differential diagnosis and medical management of pulmonary infiltrates varies greatly between normal and immunosuppressed persons, knowledge of patients' HIV status is crucial for appropriate medical management. Providing these persons with the benefits of HIV education and counseling and providing the opportunity for HIV testing may enhance HIV prevention and control efforts. All persons with TB or tuberculous infection can benefit from receiving information about reducing their risk of acquiring or transmitting HIV infection. TB patients who are infected with HIV will also benefit by being monitored for early diagnosis of opportunistic infections and other manifestations of HIV infection. Previously published guidelines for counseling and testing and notification of sex partners and those who share needles with HIV-infected persons should be followed (35).

All patients diagnosed with TB should be offered counseling and HIV-antibody testing. Particular emphasis should be placed on offering counseling and HIV- antibody testing to persons with extrapulmonary TB and persons with TB in the age groups in which most HIV infections have been found. Although there are probably some geographic areas and population groups in which most persons with TB are not likely to have HIV infection, data on the prevalence of HIV infection among TB patients in the United States are too limited to be useful in defining such populations. Furthermore, even if such data were available, there is no assurance that these populations will remain free of HIV infection in the future. Monitoring the prevalence of HIV infection among persons with TB is one method for detecting the spread of HIV infection into new areas and population groups and of assuring the appropriate management of TB in the HIV-infected patient.

While the occurrence of clinical TB may be an indication of immunosuppression related to HIV infection, the presence of a positive tuberculin skin test in a person without clinical manifestations of disease does not imply a higher likelihood of HIV infection. Nevertheless, behaviors* that are associated with an increased risk or prevalence of HIV infection should be routinely sought in persons with positive tuberculin skin test reactions.

If HIV infection is considered a possibility, counseling and HIV-antibody testing should be strongly encouraged. Because HIV infection is one of the strongest known risk factors for the progression of latent tuberculous infection to TB, the presence of HIV infection in a person with a positive tuberculin skin test is an indication for preventive therapy regardless of that person's age. Preventive therapy should be started only after excluding active pulmonary or extrapulmonary TB.

Persons with positive skin test reactions and factors that put them at high risk for HIV infection who decline to be tested for HIV antibody should also be considered at increased risk for developing TB. At this time, isoniazid preventive therapy should be considered for such persons on an individual basis. However, as more data become available on the prevalence of HIV infection among various population groups in different geographic areas, more definitive recommendations may be issued.

Such persons should be followed closely; the patients' ability and willingness to participate in the follow-up are factors that influence the decision to provide isoniazid preventive therapy. Some HIV-infected persons and persons who decline testing but are at high risk for HIV infection might be considered at increased risk of developing TB even if their tuberculin skin tests are negative. Thus, preventive therapy might be considered for those persons with clinical or laboratory evidence of severe immunosuppression who are from developing countries where the prevalence of tuberculous infection is very high, who have a history of close contact with an infected person, who previously have had a positive tuberculin skin test reaction, or who have a radiographic abnormality consistent with past TB.

EXAMINING HIV-INFECTED PERSONS (AND PERSONS AT RISK FOR HIV INFECTION) FOR THE PRESENCE OF TB AND TUBERCULOUS INFECTION

HIV-infected persons, with or without AIDS or other HIV-related disease, should be given a Mantoux skin test with 5 TU tuberculin, PPD. Although false-negative results may occur in these persons because of HIV-induced immunosuppression, positive tuberculin reactions are clinically meaningful. If the skin test reaction shows greater than or equal to 5-mm induration, a chest radiograph should be obtained, and the patient should be examined for evidence of extrapulmonary TB. If abnormalities are noted, additional diagnostic studies for TB should be undertaken.

Persons with clinical AIDS or other HIV-related disease should receive a chest radiograph and be examined for evidence of extrapulmonary TB, regardless of the skin test reaction. Some population groups may have a substantially higher prevalence of HIV infection than the total population (e.g., clients in drug-treatment programs and inmates of correctional institutions). Health-care providers should routinely provide tuberculin skin testing for persons in these settings even if counseling and HIV- antibody testing are not routinely offered or such testing is refused.

PREVENTIVE THERAPY FOR TUBERCULOUS INFECTION

Because preventive therapy with isoniazid reduces the incidence of TB in a variety of populations with tuberculous infection, any person, regardless of age, who is HIV-infected and who has a positive tuberculin skin test reaction (greater than or equal to 5-mm induration) should be offered isoniazid preventive therapy unless it is medically contraindicated. The recommended duration is a minimum of 12 months, but, analogous to considerations for the treatment of TB in AIDS patients (26), some experts have suggested prolongation of isoniazid preventive therapy beyond 12 months. Although it is not known whether isoniazid prevents TB in HIV-infected persons as effectively as in other groups, the usually positive response to standard chemotherapy in HIV-infected persons with TB suggests that isoniazid preventive therapy would also be effective.

Because of the particularly high risk for TB in persons with both HIV and tuberculous infection, ensuring completion of at least 12 months of preventive therapy is crucial.

PREVENTION AND CONTROL OF TB IN DRUG-TREATMENT PROGRAMS FOR IVDUS

IVDUs require special consideration because they are at high risk for tuberculous as well as HIV infection. Tuberculin skin test surveys among heroin addicts in New York City showed that the prevalence of tuberculous infection in this population was considerably higher than in the city-wide population, even after adjustment for age, race, and economic status (36). Even before the HIV epidemic, opiate-dependent patients in New York City had a higher prevalence of TB than did nondependent patients (37).

HIV infection among IVDUs is responsible for much of the HIV-associated increase in TB in New York City and New Jersey (4,9). Matching TB and AIDS registries in New York City revealed that 57% of the patients with both TB and AIDS were IVDUs (9).

Isoniazid preventive therapy for tuberculin-positive IVDUs provides an opportunity to prevent many TB cases, especially in the setting of drug-treatment programs, where compliance issues can be addressed. Federal regulations require tuberculin skin testing of IVDUs before admission to a treatment program (38). The recommended technique is the intradermal (Mantoux) test with 5 TU tuberculin PPD. Given the substantial risk for TB in this group and the potential for its prevention, drug-treatment programs should perform a skin test and record the diameter of induration on each new enrollee and on others already enrolled who have not been previously tested.

Persons with a tuberculin skin test of greater than or equal to 5-mm induration should be further evaluated for clinical TB and, if disease is present, treated according to current guidelines. Counseling and HIV-antibody testing should be carried out for all consenting persons with greater than or equal to 5-mm induration on their tuberculin skin test, all persons with a past or present history of IV-drug use, and their sex partners (35).

If there is no clinical, radiographic, or laboratory evidence of TB, isoniazid preventive therapy should be

recommended for all HIV-infected persons regardless of age with a tuberculin reaction of greater than or equal to 5-mm induration. Isoniazid preventive therapy should also be recommended for all other IVDUs with a tuberculin reaction of greater than 10-mm induration regardless of age. The rationale for this recommendation is based on epidemiologic studies of HIV seroprevalence among IVDUs.

Although in some geographic areas the seroprevalence of HIV is still low in IVDUs, this should not be considered a stable situation. Studies of previously collected blood samples from IVDUs indicate the potential for very rapid spread of the virus within the group.

The prevalence of HIV infection among IVDUs in Manhattan, Edinburgh (Scotland), and Italy had increased to 40% 3-4 years after the virus was first introduced into the group (39). Consequently, TB and HIV prevention programs are urgently needed for IVDUs, even in areas where the current HIV seroprevalence is very low.

To ensure compliance, isoniazid therapy should preferably be fully supervised and administered (daily or on a twice-weekly basis) by the drug-treatment program staff, if possible at the same time the person is seen for treatment of IV-drug abuse. Patients who discontinue treatment before completing at least 6 months of uninterrupted preventive therapy should be restarted on preventive therapy after reenrollment into the treatment program. Drug-treatment programs should work closely with health department TB programs in their jurisdictions for assistance in carrying out these screening and prevention recommendations.

BCG VACCINATION OF HIV-INFECTED PERSONS

The benefits and risks of BCG vaccination of HIV-infected persons remain largely undocumented. However, disseminated *M. bovis* (BCG) disease was reported in one person with AIDS and Kaposi's sarcoma who was given a BCG vaccination, presumably to "stimulate" his immune system (40). The ACET agrees with the recommendation of the World Health Organization that BCG should not be administered to persons with HIV infection in countries where the risk of infection is low, such as in the United States (41).

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*Based on seroprevalence studies, behaviors that place a person at risk for HIV infection include IV-drug use and male homosexual contact. Other factors that increase the risk for HIV infection in adults include having received blood or clotting factor concentrate between 1978 and 1985 and having had sexual relations at any time since 1978 with 1) a person known to be infected with HIV or to have AIDS, 2) a man who has had sexual contact with another man, 3) prostitutes, 4) IVDUs, or 5) persons born in countries where most transmission of HIV is thought to occur through heterosexual sexual contact. Risk factors for HIV infection in infants and children include 1) parents, especially the mother, with HIV infection or any of the adult risk factors, and 2) receipt of blood or clotting factor concentrates between 1978 and 1985.

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