



# TUBERCULOSIS INFORMATION

## -Treatment of Drug-Resistant Tuberculosis

### **Summary**

Multidrug-resistant TB (MDR TB), particularly among HIV-infected persons, contributed to the resurgence of TB in the late 1980s and early 1990s. Resistance to anti-TB drugs among reported TB cases in the United States remains a serious public health concern. Since CDC began monitoring anti-TB drug resistance through the national TB surveillance system in 1993, levels of isoniazid resistance have been relatively stable. Overall, the number and proportion of MDR TB cases has decreased. Nevertheless, during 1993-1998, 45 states and the District of Columbia reported cases of multidrug-resistant TB. The extent of drug resistance confirms the importance of initial treatment regimens of four first-line drugs for most TB patients and the use of drug susceptibility testing to guide optimal treatment of patients with culture-positive disease. All health departments must be prepared to deal with the challenge of MDR TB, which includes the capacity to ensure that clinicians with expertise in the management of MDR TB are always involved in the care of these patients.

### **Treatment of latent TB infection**

*Contacts of isoniazid-resistant TB.* For persons who are known to be contacts of patients with isoniazid-resistant, rifampin-susceptible TB, a 4-month regimen of daily rifampin is recommended. In situations where rifampin cannot be used, rifabutin may be substituted.

*Contacts of multidrug-resistant TB.* For persons likely to have been infected with a strain of *M. tuberculosis* resistant to both isoniazid and rifampin, alternative regimens should be considered. Alternative regimens should consist of two drugs to which the infecting organism has demonstrated susceptibility. Potential alternative regimens include either 6-12 months of daily ethambutol and pyrazinamide or 6-12 months of pyrazinamide and a quinolone (i.e., levofloxacin, ofloxacin, or ciprofloxacin). Immunocompetent contacts may be treated for 6 months or observed without treatment. Immunocompromised contacts (e.g., HIV-positive persons) should be treated for 12 months. Persons receiving pyrazinamide and a quinolone antibiotic should be monitored closely for adverse effects. Some evidence suggests that the combination of pyrazinamide and ofloxacin may be poorly tolerated. All persons with suspected multidrug-resistant LTBI should be followed for 2 years regardless of the treatment regimen.

Ethambutol at the usual dose is safe for children. The regimen of pyrazinamide and ethambutol for 9-12 months is recommended for children if the infecting organism has demonstrated susceptibility. When pyrazinamide and/or ethambutol cannot be used, a combination of two other drugs to which the infecting organism is likely susceptible is recommended.

### **Treatment of drug-resistant TB disease**

Clinicians who are unfamiliar with the treatment of drug-resistant TB should seek expert consultation. Because second-line drugs can cause serious adverse reactions, patients taking these drugs should be monitored closely throughout the course of treatment. The role of agents such as the quinolone derivatives and amikacin in the treatment of multidrug-resistant disease is not well characterized, although these drugs are commonly being used in such cases. Surgery seems to offer considerable benefit and a significantly improved cure rate for patients who have multidrug-resistant TB if the bulk of disease can be resected. However, drug therapy is usually required to sterilize the remaining disease.

*TB disease resistant to isoniazid only.* A 6-month regimen of isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin has been demonstrated to be effective for the treatment of TB resistant only to isoniazid. When resistance to isoniazid is documented during the recommended initial four-drug therapy, the

regimen should be adjusted by discontinuing isoniazid and continuing the other three drugs for the entire 6 months of therapy. TB resistant only to isoniazid may also be treated with rifampin and ethambutol for 12 months.

When isoniazid resistance is documented in the 9-month regimen without pyrazinamide, isoniazid should be discontinued. If ethambutol was included in the initial regimen, treatment with rifampin and ethambutol should be continued for a minimum of 12 months. If ethambutol was not included initially, susceptibility tests should be repeated, isoniazid should be discontinued, and two drugs (e.g., ethambutol and streptomycin) should be added. The regimen can be adjusted when the results of the susceptibility tests become available.

*Multidrug-resistant TB (resistant to both isoniazid and rifampin).* Multidrug-resistant TB (i.e., TB resistant to at least isoniazid and rifampin) presents difficult treatment problems. Treatment must be individualized and based on the patient's medication history and susceptibility studies.

Unfortunately, adequate data are not available on the effectiveness of various regimens and the necessary duration of treatment for patients with organisms resistant to both isoniazid and rifampin. Moreover, many of these patients also have resistance to other first-line drugs (e.g., ethambutol and streptomycin) when drug resistance is discovered. Because of the poor outcome in such cases, it is preferable to give at least three new drugs to which the organism is susceptible. This regimen should be continued until culture conversion is documented, followed by at least 12 months of two-drug therapy. Often, a total of 24 months of therapy is given empirically. Some experts recommend that at least 18-24 months of three-drug therapy be given after culture conversion.

### **TB Treatment for HIV-Infected Patients with Drug-Resistant TB Disease**

*TB disease resistant to isoniazid only.* The treatment regimen should generally consist of a rifamycin (rifampin or rifabutin), pyrazinamide, and ethambutol for the duration of treatment. Because the development of acquired rifamycin resistance would result in MDR TB, clinicians should carefully supervise and manage TB treatment for these patients.

*TB disease resistant to rifampin only.* The 9-month treatment regimen should generally consist of an initial 2-month phase of isoniazid, streptomycin, pyrazinamide, and ethambutol. The second phase of treatment should consist of isoniazid, streptomycin, and pyrazinamide administered for 7 months. Because the development of acquired isoniazid resistance would result in MDR TB, clinicians should carefully supervise and manage TB treatment for these patients.

*Multidrug-resistant TB (resistant to both isoniazid and rifampin).* These patients should be managed by or in consultation with physicians experienced in the management of MDR TB. Most drug regimens currently used to treat MDR TB include an aminoglycoside (e.g., streptomycin, kanamycin, amikacin) or capreomycin, and a fluoroquinolone. The recommended duration of treatment for MDR TB in HIV-seropositive patients is 24 months after culture conversion, and posttreatment follow-up visits to monitor for TB relapse should be conducted every 4 months for 24 months. Because of the serious personal and public health concerns associated with MDR TB, health departments should always use directly observed therapy (DOT) for these patients and take whatever steps are needed to ensure their adherence to the treatment regimen.

#### For More Information

For information about implementing CDC guidelines, call your state health department.

ATS/CDC. Targeted Tuberculin Testing and Treatment of Latent TB Infection. *Am J Respir Crit Care Med* 2000;161: S221-S247.

Publication # 99-6422. ATS/CDC. Targeted tuberculin testing and treatment of latent TB infection. *MMWR* 2000;49(No. RR- 6).

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also visit the Division of TB Elimination's Web site at [www.cdc.gov/nchstp/tb](http://www.cdc.gov/nchstp/tb).

Publication # 99-6422. ATS/CDC. Targeted tuberculin testing and treatment of latent TB infection. *MMWR* 2000;49(No. RR- 6).

Publication # 99-5879. CDC. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. *MMWR* 1998;47(No. RR- 20).

Publication #00-6453. ATS/CDC. Treatment of tuberculosis and tuberculosis infection. *Am J Respir Crit Care Med* 1994;149.