CDHS/CTCA JOINT GUIDELINES
Guidelines for the Treatment of Active Tuberculosis Disease

Table of Contents

Treatment of Tuberculosis Disease

CALIFORNIA DEPARTMENT OF HEALTH SERVICES/ CALIFORNIA TUBERCULOSIS CONTROLLERS ASSOCIATION JOINT GUIDELINES

Guidelines for the Treatment of Active Tuberculosis Disease

The following guidelines have been developed by the California Department of Health Services, Tuberculosis Control Branch, in consultation with the Executive Committee of the California Tuberculosis Controllers Association. These guidelines are official state recommendations and have been endorsed by the California Tuberculosis Controllers Association.

The treatment of active tuberculosis (TB) patients with effective anti-TB chemotherapy is the highest priority in TB control. Successful treatment benefits both the patient and the public at large, as infectious cases are cured and sources of infection are removed from the community. California state health and safety laws (Health and Safety Code Sections 121365-121369) provide the legal framework to support or mandate completion of therapy in order to safeguard the public's health when less restrictive measures have failed. Poor treatment outcomes are often the result of ineffective drug regimens and/or poor patient adherence to medication. Promoting the use of effective chemotherapy, directly observed therapy (DOT), and case management is necessary for treatment to be successful.

The California Tuberculosis Controllers Association (CTCA) and the California Department of Health Services (CDHS), Tuberculosis Control Branch, have jointly developed the following guidelines for the treatment of TB disease. By providing these official state recommendations, we hope to provide a useful tool for those involved in the treatment of TB disease. No set of guidelines can cover all individual treatment situations**.** When questions on individual situations not covered by these guidelines do arise, consult with the Local TB Control Program or the California Department of Health Services, TB Control Branch, for further information.

Note: For a description of American Thoracic Society (ATS) TB Classifications, see page 19, **Suggested Readings 2**.

Treatment of Tuberculosis Disease

I. Basic Principles

A. Organization and Supervision of Treatment

1. With the local health department's legally mandated oversight (California Code of Regulations Title 17, Section 2500), the provider plays a central role in TB control by having the key responsibility of prescribing the appropriate regimen and ensuring completion of therapy.

2. Directly observed therapy (DOT) should be the initial core management strategy for all patients with active TB (see page 18, **Issues in Case Monitoring and Management**).

3. Five day-a-week DOT administration is considered to be equivalent to seven day-a-week DOT administration (based on expert opinion).

B. Treatment

1. The recommended treatment regimens are largely based on evidence from clinical trials and rated using a system delineated in the unpublished 2002 American Thoracic Society TB treatment guidelines (see page 28, **Appendix 1**).

2. Because of the high level of isoniazid (INH) resistance in California (> 4% in most counties), unless otherwise contraindicated, all active TB cases or suspects should be started on a four-drug regimen of INH, rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB), pending susceptibility results (see pages 20-21, **Tables 1 and 2**).

3. Initiation of treatment should be based on clinical suspicion and treatment should be started as soon as TB is suspected, even before laboratory confirmation is available.

4. Never add a single drug to a failing treatment regimen (see page 4, **Section IV**).

5. First line TB medications should be given together as a single daily dose. Split doses should be avoided if possible.

6. Duration of treatment is determined by a number of factors including risk of relapse, microbiologic response to therapy, type of regimen used, site of disease, the host's immune status and interruptions in treatment.

7. Completion of treatment is determined by the total number of doses taken by the patient rather than the duration of treatment (see page 20, **Table 1**).

C. Clinical Management Issues

1. Intermittent therapy should only be given by DOT.

2. Intermittent treatment regimens should not be used in HIV-infected patients (based on expert opinion).

3. Fixed-dose combination drugs (Rifater®, Rifamate®) should be considered for use in patients receiving self-administered therapy (SAT) and DOT to reduce pill burden and improve adherence.

4. Pyridoxine administration (25 mg/day) is indicated for individuals who have a higher risk of peripheral neurotoxicity from INH because of pregnancy or underlying medical conditions (*e.g.*, nutritional deficiency, diabetes, HIV infection, renal failure, alcoholism, illicit drug use).

5. For patients with treatment interruptions, the length of the treatment regimen that is restarted should be determined by the bacillary load of the patient, the point in time of the interruption, and the amount of treatment received prior to the interruption. Interruptions that are long or occur earlier in the course of treatment may require restarting treatment from the beginning.

6. If active TB is suspected, regardless of the primary site of infection, the presence or absence of pulmonary TB should be evaluated with a chest radiograph because TB is generally transmitted through the pulmonary route.

II. Diagnosis

A. Sputa for acid-fast bacilli (AFB) smear and culture should be obtained in all patients in whom laryngeal, pleural, or pulmonary TB is suspected.

1. When TB is included in the differential diagnosis, the initial diagnostic test should be the examination of sputa for AFB smear and culture. If the AFB smear is negative, then bronchoscopy may be used for diagnostic purposes. Sputum smears are necessary to determine the patient's infectiousness (see page17, **Section VI.E**), and sputum cultures, when positive, should be used to monitor clinical response (see page 15, **Section VI.C**).

2. Sputum induction should be performed for all patients unable to spontaneously expectorate sputum specimens adequate for smear and culture.

B. Both AFB smear and culture should be ordered for all specimens collected during the diagnostic evaluation for TB (sputum, tissue, cerebrospinal fluid, urine, other body fluid, *etc.*).

C. Providers should determine whether the laboratory they use automatically performs susceptibility testing on first-line drugs and, if not, susceptibilities should be ordered.

D. An HIV test should be performed, with informed consent, at the time of diagnosis for all patients suspected of having TB, as both treatment and prognosis may be significantly impacted by HIV infection.

III. Recommended Treatment Regimens

A. Standard Initial Treatment Regimens (see page 20, **Table 1**)

1. These regimens for initial treatment are suggested for patients without a prior history of TB in whom susceptibilities are unknown.

2. In most cases, treatment for all adults with previously untreated TB should consist of a two month initial phase of INH, RIF, PZA, and EMB.

3. Rifampin and rifabutin do not necessarily share the same drug interaction profile. In drug-sensitive cases where RIF cannot be used (*e.g.*, due to RIF's stronger induction of cytochrome P450), rifabutin may be considered as an alternative therapy, but may require dose adjustment (see page 22, **Table 3**).

4. The initial phase may be given daily throughout, daily for two weeks, then twice weekly for 6 weeks by DOT, or three times weekly by DOT. Intermittent therapy should not be used for HIV-infected individuals (based on expert opinion) (see page 19, **Suggested Readings 4**).

5. For patients receiving daily or intermittent therapy, EMB can be discontinued as soon as drug susceptibility results demonstrate that the isolate is sensitive to INH and RIF.

B. Continuation Phase of Treatment in Disease with Fully Drug-Sensitive Organisms (see page 20, **Table 1**)

1. The continuation phase of treatment should consist of INH and RIF given for four months. This phase may be given daily, two times weekly by DOT, or three times weekly by DOT.

2. After four-drug therapy is given daily or twice weekly in the initial phase, rifapentine may be used with INH as once weekly therapy by DOT in the continuation phase for treating NONCAVITARY PULMONARY TB among HIV-UNINFECTED patients. The regimen of once-weekly rifapentine and INH is CONTRAINDICATED because of the increased risk of relapse and treatment failure in any one of the following circumstances:
   a. Cavitation is present on the initial chest radiograph
   b. Sputum smears or cultures are positive two months after treatment was begun
   c. The patient is HIV-infected, OR
   d. The patient has extrapulmonary TB.

C. Indications for Longer Treatment in Disease with Fully Drug-Sensitive Organisms for Rifamycin (RIF, rifabutin, rifapentine) Containing Regimens (see page 20, **Table 1**)

1. If PZA cannot be included for the first two months of treatment, the duration of treatment, regardless of whether the regimen is given intermittently, should be a minimum of nine months.

2. Patients at higher risk for relapse or treatment failure (*e.g.,* extensive disease, lack of culture conversion within two months, drug intolerance, cavitary disease, lapses in therapy, *etc*.) should be considered for a minimum of nine months of therapy.

3. In cases of TB meningitis, treatment should be extended to 9-12 months.

D. Alternative Treatment Regimens (see page 25, **Table 5**)

1. The decision to consider an alternative regimen should be based on the drug susceptibility pattern of the organism and host factors such as high bacillary load, underlying medical conditions (*e.g.,* uncontrolled diabetes mellitus, advanced HIV disease), older age, and drug intolerance.

2. When INH cannot be used, RIF, EMB, and PZA should be given for a minimum of six months.

3. When INH and PZA cannot be used, RIF and EMB for 12 months should be used.

4. When RIF cannot be given, INH and EMB should be given for 18 months (preferably with PZA for the first two months).[1]

5. Levofloxacin, and potentially other fluoroquinolones, may be useful in these regimens as an alternative oral agent (especially in multidrug-resistant TB (MDR-TB) or cases of liver toxicity), but the role of fluoroquinolones has not been fully defined.

6. In situations in which both INH and RIF cannot be used because of intolerance or resistance, regimens based on the principles described for treating MDR-TB should be used (see page 25, **Table 5**).

7. Expert consultation should be sought when none of the above regimens can be used for other reasons.

IV. Management of Relapse, Treatment Failure, and Drug-Resistant Disease

A. Relapse

1. Definition/Basic Principles

a. Relapse is defined as the circumstance in which a patient becomes and remains culture-negative throughout the course of therapy, but, at some point after therapy, either becomes culture-positive again or develops signs and symptoms consistent with active TB.

b. Relapse may be secondary to a failure to sterilize host tissues or, less commonly, exogenous re-infection.

c. Risk factors for relapse include advanced HIV disease (based on expert opinion), extensive TB with cavitary disease, and persistent positive sputum cultures two or more months after treatment initiation.

d. In patients previously treated with DOT, relapse generally occurs with organisms having the same susceptibility profile as the pretreatment isolate.

e. In patients previously treated with SAT, the greater likelihood of erratic drug administration leads to an increased risk of drug-resistant disease.

f. It is critical to perform drug susceptibility testing of the *M. tuberculosis* organism responsible for the relapse and adjust the treatment regimen as necessary.

g. DOT (see page 18, **Issues in Case Monitoring and Management**) must be the method of treatment administration.

h. The treating physician should discuss the management of these patients with the local TB control program and possibly with other TB experts.

2. Treatment and Clinical Management

a. Pending drug susceptibility results, the selection of empiric treatment regimens should be based on the prior treatment history.

i. If the patient has a history of drug-sensitive disease with DOT, the standard four-drug treatment regimen can be used.

ii. When clinical manifestations and public health consequences permit, (*e.g.,* smear-negative, noncavitary, low risk of transmission), continue previous treatment regimen until drug susceptibility results are known.

iii. If the patient has a history of drug-resistant disease or irregular drug administration, an expanded regimen (defined below) may be appropriate.

iv. An expanded treatment regimen is indicated in cases in which treatment with an inadequate regimen could have severe consequences (*e.g*., immunocompromised state, central nervous system involvement, limited respiratory reserve).

[1] The INH/EMB regimen has a higher relapse rate than rifampin-based regimes

b. If epidemiological circumstances suggest exogenous re-infection as the cause of apparent relapse,[2] the choice of treatment regimen is influenced by the drug susceptibility pattern of the potential source case.

c. Expanded regimens for treating relapse should generally include INH, RIF, PZA, and EMB plus an additional two drugs never previously used for treatment and against which the organism is likely to demonstrate *in vitro* sensitivity (based on expert opinion). Usual choices include a fluoroquinolone and an injectable agent.

d. Duration of therapy should be at least six months beyond culture conversion and should be tailored to individual clinical circumstances.

B. Treatment Failure

1. Definition/Basic Principles

a. Treatment failure is defined as continued or recurrently positive sputum cultures for ≥ four months after treatment initiation in a patient receiving adequate drug therapy.

b. Patients on treatment for TB whose sputum specimen(s) either remain bacteriologically positive after three months of treatment or become bacteriologically positive after initially converting to negative, with or without ongoing symptoms, should be evaluated for treatment failure. Specimens which are either smear-positive for AFB or culture-positive for *M. tuberculosis* are considered bacteriologically positive.

c. Potential reasons for treatment failure include advanced HIV disease (based on expert opinion), non-adherence to the treatment regimen (usually in patients not receiving DOT or who have cryptic non-adherence while receiving DOT), drug resistance, malabsorption, laboratory error, and an extreme biological variation.

d. Evaluation for possible treatment failure includes symptom review, chest radiography, repeat drug susceptibility testing if sputum specimen is culture-positive, and clinical assessment for malabsorption. When malabsorption is suspected, serum drug levels should be considered. If HIV serology has not been documented, it should be performed after informed consent.

e. If drug resistance is suspected because of lack of clinical improvement, mycobacterial isolates should be sent immediately to a reference lab for susceptibility testing to first- and second-line drugs. As soon as susceptibility results are known, the treatment regimen should be adjusted accordingly.

f. All patients suspected of treatment failure must be treated with DOT (see page, 18, **Issues in Case Monitoring and Management**).

g. The treating physician should discuss management of these patients with the local TB control program and possibly with other TB experts.

2. Treatment and Clinical Management

a. If additional anti-TB drugs are added to the treatment regimen, at least three new drugs never previously used for treatment and against which the organism is likely to demonstrate *in vitro* sensitivity, should be used to decrease the possibility of further acquired resistance.

b. Expanded regimens for treatment failure generally should include a fluoroquinolone, an injectable agent, and an oral drug such as para-amino salicylic acid (PAS) or cycloserine (based on expert opinion).

[2] Documented re-exposure to a smear positive case, previous treatment given adequately by DOT, or recurrent disease ≥ two years following adequate treatment.

c. When clinical manifestations and public health consequences permit, (*e.g.,* smear-negative, noncavitary, low risk of transmission), continue previous treatment regimen until drug susceptibility results are known.

d. Duration of therapy should be at least six months beyond culture conversion and tailored to individual clinical circumstances.

C. Drug-Resistant Disease

1. Background

a. Tubercle bacilli are continuously undergoing spontaneous mutations that confer resistance to individual anti-TB drugs. The frequency of these mutations is sufficiently low that, with appropriate treatment of an initially drug-sensitive isolate, clinically significant drug resistance does not occur.

b. There are two types of drug resistance - acquired and primary.

i. Acquired drug resistance occurs when a patient's isolate develops drug resistance after an unsuccessful course of treatment. Risk factors for acquired drug resistance include a large bacillary load, cavitary disease, advanced HIV disease and inadequate treatment (*i.e*., inadequate regimen, missed doses, malabsorption).

ii. Primary drug resistance occurs when a patient who has no history of treatment for TB is found to have drug-resistant disease. This generally results from transmission from a drug-resistant case.

c. Drug resistance can only be proven by testing performed in a laboratory with expertise in drug susceptibility testing.

d. Risk factors or indicators for development of drug-resistant disease:

i. Acquired drug resistance

- Treatment failure/relapse
- Treatment with SAT or incomplete DOT
- Noncompliance/erratic medication ingestion
- Treatment in areas of the world with inadequate drug supplies or inadequate TB control programs
- Inadequate treatment regimen/errors in therapy
- Advanced HIV disease
- Failure to show at least a partial clinical response after several weeks of standard four-drug therapy
- Failure to show culture conversion within two months
- Worsening radiographic disease on standard four-drug therapy

ii. Primary drug resistance

- Contact with a person with drug-resistant disease
- History of residence in a country with a high incidence of drug-resistant TB
- Residence in institutions where a high level of drug-resistant TB has been documented such as hospitals, skilled nursing facilities, correctional facilities, drug treatment facilities, and homeless shelters

2. Treatment

a. Mono-resistance to INH (at any concentration): the regimens discussed above in Sections III. D2 or III. D3 should be used.

b. Mono-resistance to RIF: the regimen discussed above in Section III, D4 should be used.

c. Mono-resistance to PZA suggests that the etiologic agent may be *M. bovis*, not *M. tuberculosis*. INH, RIF, and EMB may be used and the duration of treatment

should be extended to nine months. EMB may be discontinued after the first two months.

d. Mono-resistance to streptomycin (SM): the standard four-drug regimen should be used.

e. MDR-TB Disease, defined as resistance to at least both INH and RIF: (see page 7, **Multidrug-Resistant Disease**).

3. Multidrug-Resistant Disease (see page 19, **Suggested Readings 7**)

MDR-TB is defined as resistance, at any concentration, to at least INH and RIF. Because of the reduced efficacy and higher toxicity of second-line drugs, the treatment of MDR-TB must be adjusted to the individual case. In order to achieve optimum results one should adhere to the basic principles discussed below:

a. Clinical and Other Management Issues

i. Diagnosis/Evaluation

- An extensive evaluation of patients and their *M. tuberculosis* isolates should be performed prior to initiating treatment including: a review of medical records (medical history, hospitalizations, labs, *etc.*), a detailed history and physical examination, and an evaluation of social/cultural factors which may influence medical care.

ii. Treatment

- When initiating or revising a regimen for MDR-TB, always attempt to employ at least three previously unused drugs to which there is *in vitro* sensitivity. Initially, one drug should be a bactericidal injectable agent.
- An injectable agent is ideally continued for six months after culture conversion. After the injectable agent is stopped, it is preferable to use a minimum of three oral drugs that are continued for the full duration of treatment.
- Never add a single drug to a failing regimen.
- Do not limit the regimen to three drugs. If other, previously unused and potentially viable drugs are available, consider their use. This is especially important if extensively resistant disease is present.
- The type/class of drugs used may be more important than the number of drugs used.
- To minimize toxicity, it is preferable to use drugs with different toxicity profiles and from different drug classes.
- Refer to **Table 4** for dosages of second-line drugs and **Table 5** for treatment regimens suggested for use in patients with various patterns of drug-resistant disease.
- The duration of treatment must be from 18 months to 2 years after culture conversion.[3] The optimum duration of treatment to maximize efficacy depends on many variables. Each case should be assessed on an individual basis with expert consultation.

iii. Clinical Management

- It is strongly recommended that MDR-TB be managed by TB experts familiar with the treatment of MDR-TB, because of the complex treatment issues and the high risk for treatment failure with further acquired resistance. In the event that the treating

[3] Culture conversion is defined as the date of collection of the first negative culture in a series of cultures that remain negative.

physician is not an MDR-TB expert, consultation with an MDR-TB expert must be sought immediately after multidrug resistance is known. It is strongly recommended that written consultation be provided to the treating physician and TB program.

- It is legally mandated (California Code of Regulations Title 17, Section 2500) that the treating physician notify the local TB Control Program as soon as possible to discuss management, follow up and public health aspects of the case.
- Treatment must be given with daily DOT throughout the entire course of therapy (see page 18, **Issues in Case Monitoring and Management)**.
- A case management tool such as a drug-o-gram should be used to show serial changes in medications, bacteriology, radiographic findings and toxicities throughout treatment (see **Appendix 2**).
- It is important to optimize the management of underlying medical conditions and nutritional status during treatment.
- The role of resectional surgery in the management of patients with extensive pulmonary MDR-TB has not been established by randomized controlled studies. In patients with extensive drug resistance, however, resection of cavitary or badly damaged lung tissue appears to be of benefit. An MDR-TB expert should be involved in the decision-making process prior to surgical intervention.

b. Drug Susceptibility Issues

i. As soon as the isolate is known to be resistant to at least INH and RIF, second-line drug susceptibility testing must be ordered. The local laboratory is required to send the isolate to the state laboratory (Title 17, California Code of Regulations, Section 2505).

ii. Susceptibility testing should be repeated on cultures that remain positive after two to three months on an appropriate treatment regimen to detect any evidence of additional resistance.

iii. While there is generally complete cross resistance between RIF and rifapentine, cross resistance between RIF and rifabutin is not always complete. In cases of MDR-TB, rifabutin susceptibility testing is recommended.

iv. Cross resistance between amikacin and kanamycin is universal, but there is no cross resistance between streptomycin (SM) and amikacin, kanamycin or capreomycin.

v. There is complete cross resistance between levofloxacin and ofloxacin because levofloxacin is the L-isomer of ofloxacin. Cross resistance among other fluoroquinolones may be incomplete.

c. Infection Control Issues

i. Patients with pulmonary disease should be in respiratory isolation either at home or in a hospital until three consecutive sputa AFB smears are negative and cultures are consistently negative.

ii. Hospitalization is strongly recommended for initiation of MDR-TB treatment to simplify evaluation, control infectiousness/transmission to the community, facilitate early management of adverse reactions, detect and lessen toxicity, facilitate laboratory monitoring, assess nutritional needs, and manage co-existing medical problems.

iii. If isolated in a hospital, the patient should not share a room with a patient with drug-sensitive TB disease.

iv. Health care providers interacting with infectious patients (see page 17, **Section VI.E**) must follow the TB exposure control plan of their facility and TB program which should include the use of fit-tested N95 respirators approved by the National Institute for Occupational Safety and Health (NIOSH).

d. Monitoring and Toxicity

i. Staff administering DOT should perform a symptom screen on a regular basis during treatment and alert licensed personnel if there is any indication that the patient is not tolerating the treatment regimen. The frequency of screening will be determined by the toxicity profile of the individual drug, but should generally be performed at least monthly.

ii. Sputum smears and cultures should be collected at least monthly throughout the treatment course and an end-of-treatment culture should be obtained.

iii. Chest radiographs should be performed every three to six months during treatment and at the end of treatment.

iv. When confronted with adverse side effects, an effort to identify potentially toxic drug levels, offer symptomatic treatment, or change dosing schedules should be attempted before discontinuing a medication.

v. Toxicity monitoring should be individualized and be based on the medication regimen of the patient (see page 24, **Table 4**).

vi. Patients with pulmonary disease should be followed with symptom review, medical evaluation, sputum collection and chest radiograph for a minimum of two years following treatment; quarterly for the first year after completion of therapy and every six months for the second year.

vii. Female patients should be counseled regarding the risks of pregnancy during treatment because of the teratogenic potential of some drugs necessary for the treatment of MDR-TB.

V. Treatment in Special Situations

A. Smear- and Culture-Negative TB

1. Definition/Diagnosis

a. Smear- and culture-negative TB is defined as clinical and radiographic improvement attributed to anti-TB therapy WHEN:

i. No other etiology is found despite thorough evaluation, AND

ii. There is no laboratory confirmation of *M. tuberculosis.*

b. Failure to isolate *M. tuberculosis* from appropriately collected specimens in persons thought to have TB on the basis of clinical or radiographic findings does not exclude a diagnosis of active TB.

c. Low bacillary populations, temporal variations in the number of bacilli produced, poor specimen quality (*e.g.*, expectorated versus induced sputum) and laboratory error may result in failure to isolate organisms from a person with active TB.

d. Depending on the clinical features, alternative diagnoses and other diagnostic testing, such as bronchoalveolar lavage and biopsy, should be considered before a presumptive diagnosis of culture-negative TB is made.

2. Treatment and Clinical Management

a. Persons who are thought to have drug-sensitive pulmonary TB based on clinical and radiographic evaluation should have treatment initiated with INH, RIF, PZA, and EMB even when initial sputum smears are negative.

b. A thorough follow-up clinical and radiographic evaluation should be performed after two months of therapy to determine if there has been a response attributable to the anti-TB treatment.

c. Because of the high level of INH resistance in California, adults with smear- and culture-negative TB should be treated with a six month regimen of INH, RIF, PZA, and EMB. As an alternative, PZA may be stopped after two months.

B. Extrapulmonary TB (see page 26, **Table 6**)

1. Diagnosis

a. To establish the diagnosis of extrapulmonary TB, appropriate fluid and/or tissue specimens should be collected for AFB staining, mycobacterial culture and pathology (when appropriate).

b. Tissue specimens should be examined microscopically, in conjunction with AFB staining, but the absence of AFB and granulomas or the failure to culture *M. tuberculosis* does not exclude the diagnosis of TB.

c. A positive AFB smear should be considered *M. tuberculosis* until proven otherwise.

2. Treatment and Clinical Management

a. Extrapulmonary TB can generally be managed in the same way as pulmonary TB. A six month regimen (two months on INH, RIF, PZA and EMB followed by four months of INH and RIF) is recommended unless the organisms are known or suspected of being resistant to first-line drugs.

b. The exception to this recommendation is TB involving the central nervous system (CNS), where 9-12 months of therapy is recommended.

c. Expert opinion suggests that all of the intermittent regimens, EXCEPT the INH/rifapentine once weekly continuation phase, can be used in the treatment of extrapulmonary TB.

d. Adjunctive corticosteroid use is strongly recommended when treating pericardial and CNS TB.

e. Response to treatment often must be measured by clinical and radiographic findings rather than by culture because of the relative inaccessibility of the sites of disease.

C. Treatment of TB in HIV-Infected Individuals (see page 19, **Suggested Readings 4**)

Because the optimal strategy for treating TB in HIV-infected persons is evolving at this time, the following section can only outline some of the current issues. The local TB Controller or experts in the treatment of TB in HIV-infected patients should be consulted for the most recent recommendations.

1. Basic Principles/Presentation

a. The index of suspicion for TB must be high in HIV-infected individuals because of the frequently atypical presentations of TB disease including:

i. Negative tuberculin skin test
ii. Normal chest radiograph
iii. Intrathoracic lymphadenopathy
iv. Lower lobe infiltrates
v. Miliary or disseminated disease
vi. Paucity of symptoms despite advanced TB disease

b. In HIV-infected persons, a more careful evaluation for nonpulmonary sites of involvement with TB should be undertaken.

c. Treatment of TB in HIV-infected individuals follows the same principles as treatment in patients without HIV infection, however, there are several important differences:
   i. Paradoxical reactions (see page 11, **Section V.C.3.a),** which may be misinterpreted as clinical worsening, are more common.
   ii. Concomitant illnesses or infections may complicate treatment.
   iii. The potential for drug interactions is greater.
   iv. Acquired drug resistance is more likely.
   v. Intermittent regimens are not recommended.
   vi. Malabsorption of drugs is more common.
   vii. There is less room for error.

2. Treatment
   a. For patients with TB due to a fully drug-sensitive organism, six months of treatment (using the standard initial regimen) is effective.
   b. A more conservative but well-accepted approach is to prolong the treatment to nine months or until six months beyond the last positive sputum culture, especially if there is CNS involvement, disseminated or extensive disease or a slow response to therapy such as positive cultures after two months of treatment.
   c. Intermittent treatment regimens should not be used in HIV-infected patients (based on expert opinion).
   d. When susceptibility results support its use, a rifamycin should not be excluded from the TB treatment regimen unless absolutely necessary. The exclusion of a rifamycin from the treatment regimen is likely to delay sputum conversion, prolong the duration of therapy, and may result in a poorer outcome.

3. Clinical Management
   a. Occasionally, after beginning anti-TB therapy, a paradoxical reaction, due to a heightened immunologic response, presents as a temporary worsening of symptoms, signs or radiographic manifestations of TB. This reaction is more common in HIV-infected patients, especially after starting antiretroviral therapy, but may also occur in patients who are not HIV-infected. Treatment failure must be excluded as a cause of the worsening clinical presentation before findings are attributed to a paradoxical reaction.
   b. Concurrent administration of antiretroviral agents and rifamycins: (see page 19, **Suggested Readings 5**)
      i. The use of effective antiretroviral agents during the treatment of TB in HIV-infected persons improves outcomes. Antiretroviral therapy, if indicated, should not be withheld simply because the patient is being treated for TB. This is especially critical given that mortality during treatment among HIV-infected persons with TB has been associated with advanced HIV disease.
      ii. Antiretroviral therapy and treatment for TB should not be started at the same time because of the increased risk of drug interactions and toxicities. It is preferable to start antiretroviral therapy after the TB regimen is proven safe and well tolerated, and the burden of organisms is significantly diminished.
      iii. RIF can be used in combination with certain antiretroviral drugs for the treatment of TB (www.cdc.gov/nchstb/tb).
      iv. When RIF cannot be used, rifabutin should be considered as an alternate for RIF because it is less likely to interact with other drugs (due to RIF's stronger induction of the cytochrome P450 system). Expert opinion suggests that both TB and HIV can be treated successfully with

concurrent use of a rifabutin-based regimen and combinations of antiretroviral drugs. However, the rifabutin dose and the doses of protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) may require adjustment. When starting NNRTIs or PIs, a two week "wash out" period is recommended between the last dose of RIF and the first dose of NNRTIs or PIs to allow for reduction in the enzyme-inducing activity of RIF.

v. The best approach to managing TB in a patient using a protease inhibitor has not been determined. The CDC has outlined the problem in detail and provided some preliminary suggestions (see page 19, **Suggested Readings 5**).

c. Experts in the management of TB in HIV-infected persons should be consulted when managing a TB patient using or planning to use a protease inhibitor.

4. Case Management Issues

a. All patients with HIV should receive TB treatment by daily DOT because taking every dose is extremely important in the immunocompromised patient. Even minor lapses in therapy may lead to relapse, treatment failure and/or emergence of drug-resistance (see page 18, **Issues in Case Monitoring and Management)**.

b. Coordination between clinicians managing TB and HIV disease is essential.

D. Treatment of TB Disease in Pregnancy and Breastfeeding

1. Basic Principles

a. Treatment of TB should be initiated when the likelihood of disease is moderate to high. Untreated TB generally represents a greater risk to a pregnant woman and her fetus than does treatment of the disease.

b. Breastfeeding should not be discouraged in women being treated with first-line drugs as there is no known harm to breast-fed infants in mothers taking these drugs.

c. Because of the unknown risk of second-line drugs to the fetus, pregnant women being treated for MDR-TB should be counseled accordingly and expert consultation should be sought.

2. Treatment and Clinical Management

a. The three drug, nine month regimen with INH, RIF, and EMB can be used in pregnant women. While PZA has not been approved for use in pregnancy in the U.S. due to inadequate data on teratogenicity, it has been used safely throughout the world and recommendations for its use should be individualized**:**

i. <u>If PZA is not used, the minimum duration of therapy is nine months</u>.

ii. The CDC recommends the use of PZA in HIV-infected pregnant women.

iii. PZA should be used when there is suspected or known drug-resistant disease.

b. Streptomycin or other aminoglycosides should not be used because of the high incidence of 8th nerve toxicity in the fetus.

c. The fluoroquinolones should be avoided, if possible, in pregnant women as they have been associated with arthropathies in young animals.

d. There is insufficient data to accurately determine the risk of cycloserine or ethionamide in pregnant women. Ethionamide, however, has been associated with nonspecific teratogenic effects.

e. Vitamin B6 (25 mg/day) should be administered with anti-TB drugs during pregnancy and breastfeeding in order to minimize the potential toxicity of INH.

E. Treatment of TB Disease in Children and Adolescents

The basic principles of treatment of TB in children and adolescents are essentially the same as for adults. These guidelines apply to children and adolescents up to the age of 16 - 18. The following information is provided to highlight selected issues in this population.

1. Basic Principles/Presentation
   a. Children most commonly develop TB as a complication of the initial infection with *M. tuberculosis.* The presentation of TB disease in young children is different than that in adults in the following ways:
      i. Clinical symptoms are frequently more modest and are often absent.
      ii. Intrathoracic hilar adenopathy may be the sole abnormality on the chest radiograph.
      iii. Pulmonary infiltrates may involve any lung field.
      iv. Cavitation is rare before adolescence.
      v. Extrapulmonary and disseminated disease are more common than in adults.
   b. Expert consultation with a pediatrician familiar with the treatment of active TB in children and adolescents is strongly recommended.
   c. Cases of MDR-TB should be managed by, or in consultation with, an expert who is familiar with the treatment of MDR-TB in children.
2. Diagnosis
   a. Clinical and radiographic evaluation are key to the diagnosis and monitoring of children with active TB. Microbiologic confirmation and documentation of culture conversion are frequently not possible, because sputum specimens are seldom available and other specimens have sub-optimal sensitivity.
   b. Early morning gastric aspirates, bronchoalveolar lavage or tissue biopsy specimens should be obtained, especially in children for whom a definitive source case is not identified or in whom drug resistance is suspected.
   c. In infants and children under the age of four, treatment should be initiated as soon as the diagnosis is suspected (while specimen collection is underway) because of greater likelihood of disseminated disease.
   d. When culture and susceptibility results are not available for a child's *M. tuberculosis* isolate, results from the isolate of the presumed source case should be used to guide the choice of anti-TB therapy.
3. Treatment and Clinical Management
   a. Treatment of active TB follows the principles outlined below:
      i. Because of the high level of INH-resistant disease in California, all children should receive standard four-drug therapy with INH, RIF, EMB, and PZA.
      ii. Treatment of pulmonary TB with INH and RIF for six months with PZA and EMB in the initial two months is almost always adequate. When drug resistance is likely and no susceptibility results are available from the patient or source case isolate, some clinicians treat children with six months of all four drugs (based on expert opinion).
      iii. Extrapulmonary TB can be managed the same way as in adults, with prolonged treatment (9-12 months) when disease involves the central nervous system.
   b. Ethambutol can likely be used safely in older children but should be used with caution in children under five years old in whom visual acuity is difficult to monitor.

c. Tablets should be crushed and capsules opened into a semi-solid vehicle (*e.g.,* applesauce) rather than informally compounded into liquid preparations (see page 14, **Section VI.A .5**).

4. Case Management Issues

a. DOT must be used for all children and adolescents with TB. Parents should not be relied upon to supervise therapy.

F. Hepatic Disease

1. The treatment of TB in persons with advanced liver disease is problematic for all of the following reasons:

a. The likelihood of drug-induced hepatitis may be greater.

b. The implications of drug-induced hepatitis are potentially serious and life threatening.

c. Toxicity monitoring may be confounded by fluctuations in the indicators of liver function based on the preexisting liver disease.

2. Expert consultation should be sought from a gastroenterologist or other expert who is familiar with the treatment of active TB in cases of TB complicated by underlying advanced liver disease.

G. Renal Insufficiency and End Stage Renal Disease (ESRD)

1. Alteration of doses and/or of frequency of administration of anti-TB drugs is often necessary with renal insufficiency and ESRD. Some of these drugs are cleared by the kidney and removed by hemodialysis (see page 27, **Table 7**).

2. Administration of all drugs immediately after hemodialysis will facilitate DOT and avoid premature removal of drugs by hemodialysis.

VI. Practical Aspects of Treatment

A. Drug Administration

1. First-line anti-TB drugs should be administered together as a single dose to optimize peak serum concentrations and facilitate DOT.

2. While some TB drugs are better absorbed on an empty stomach, first-line drugs may be given with food if GI intolerance occurs.

3. Levofloxacin, ofloxacin, and other fluoroquinolones should not be administered within two hours of ingestion of antacids, dairy products, or other medications containing divalent cations (didanosine, sucralfate, iron, magnesium, calcium, zinc, or vitamins).[4]

4. Administration of therapy on an intermittent basis, as opposed to daily dosing, facilitates supervision of therapy and promotes adherence to the anti-TB treatment regimen. Based on expert opinion, intermittent drug administration is not advised in HIV-infected individuals, however, because of the increased likelihood of treatment failure, relapse, and emergence of drug resistance.

5. Patients who cannot swallow tablets whole (*e.g.*, children) should have drugs administered using the following principles:

a. Tablets should be crushed and capsules opened into a semi-solid vehicle (*e.g.*, applesauce) rather than informally compounded into liquid preparations.

b. If it is impossible to dose the patient without a liquid vehicle, tablets should be crushed (or capsules opened) and mixed into the liquid immediately prior to administration to ensure accurate dosing and to avoid drug degradation.

[4] Ciprofloxacin should not be administered ≤ two hours before or < six hours after ingestion of these substances

c. To ensure adequate dosing, the entire portion of the substance into which the drug has been crushed or mixed must be ingested.

B. Use of Fixed-Dose Combination Drugs

1. The theoretical advantages of fixed-dose preparations include reducing the risk of inadvertent monotherapy, improving the ease of administration, reducing the potential for medication errors, and, often, reducing the cost to the patient.

2. Fixed-dose preparations are recommended for persons on either daily SAT or daily DOT. Fixed-dose drug preparations are not recommended for persons on intermittent therapy because it is difficult to adjust the number of pills to achieve proper dosages.

3. Two tablets of Rifamate® (INH 150 mg + RIF 300 mg/capsule) are used daily for persons weighing $\geq$ 50 kg. The number of Rifater® tablets (INH 50 mg + RIF 120 mg + PZA 300 mg/tablet) used per day should be adjusted by weight according to the manufacturer's recommendations.

C. Monitoring During Treatment of Pulmonary TB

1. Patients with smear-positive pulmonary TB should have sputa collected at least every two weeks until three consecutive negative sputum smears have been documented. Once sputum smears become negative, or for those patients with smear-negative but culture-positive pulmonary TB, a minimum of one to two adequate sputum specimens should be collected monthly for smears and cultures until persistently negative cultures have been documented. Sputum induction should be employed, if necessary, to collect adequate specimens.

2. Collection of one to two sputum specimens for smear and culture at the completion of therapy, when possible, is highly recommended, especially for patients with a delay in response to therapy or a high risk of relapse (*i.e.,* cavitary/extensive disease, lack of culture conversion for $\geq$ two months, or advanced HIV disease).

3. Patients with MDR-TB should have sputa collected for smear and culture monthly throughout the entire course of treatment and one to two specimens at the completion of therapy.

4. Chest radiographs should be performed every three to six months during treatment and an end-of-treatment chest radiograph should be obtained to provide a new baseline for comparison with follow-up films.

5. Baseline medical evaluation, physical exam, symptom review and laboratory testing (*i.e.*, CBC, electrolytes, BUN, creatinine, liver function tests (LFTs) and uric acid) should be performed. Subsequent monitoring should include face-to-face monthly medical evaluation, symptom review and, if clinically indicated, additional laboratory testing. Additional laboratory tests are ordered as indicated by the patient's underlying medical history and treatment regimen.

6. If the patient is on EMB, visual acuity and color discrimination should be performed at baseline and monthly while the patient remains on EMB.

7. Patients with drug-sensitive pulmonary disease should be followed with symptom review and medical evaluation for a minimum of six months after completion of treatment.

8. If there is a history of MDR-TB, recurrent TB, extensive disease or poor adherence to treatment, more intensive end-of-treatment and post-treatment monitoring is recommended.

D. Management of Common Side-Effects

1. Hepatitis

a. An asymptomatic increase in aspartate transaminase (AST) or alanine transaminase (ALT) occurs in nearly 20% of patients treated with the standard four-drug regimen. In most patients, asymptomatic aminotransferase elevations resolve spontaneously.

b. Drug-induced hepatitis is defined as an increase in AST or ALT ≥ 3 times the upper limit of normal in the presence of symptoms or > 5 times the upper limit of normal in the absence of symptoms.

c. INH, PZA and less commonly, RIF can cause drug-induced hepatitis.

d. In the absence of symptoms, therapy should NOT be altered because of asymptomatic elevations of AST and ALT < 5 times the upper limit of normal. If such elevations are detected, the frequency of clinical and laboratory monitoring may be increased.

e. If AST levels are > 5 times the upper limit of normal (with or without symptoms) or ≥ 3 times the upper limit of normal in the presence of symptoms:

i. Consultation with an expert who is familiar with the management of hepatotoxicity in the setting of treatment for TB disease should immediately be sought.

ii. Anti-TB drugs should be stopped immediately and the patient evaluated carefully.

iii. Serologic tests for Hepatitis A, B and C should be performed, and the patient should be questioned regarding the ingestion of other hepatotoxins (alcohol and other medications).

iv. If the patient is smear-positive or acutely ill, three non-hepatotoxic anti-TB drugs (*e.g.*, levofloxacin, EMB, SM) should be started until the specific cause of hepatotoxicity can be determined.

v. For re-challenge, hepatotoxic anti-TB drugs should be started one by one at weekly intervals after the AST returns to < 2 times the upper limit of normal. RIF should be started first because of its efficacy and because it is least likely to cause hepatotoxicity. If there is no worsening in liver function, INH, and then PZA may be restarted at weekly intervals. If an increase in liver function tests recurs the last drug added is the likely cause and should be stopped. Non-hepatotoxic drugs (*e.g.,* EMB) should be continued while re-challenging with RIF, INH and PZA.

2. Gastrointestinal Symptoms (nausea, vomiting, poor appetite, abdominal pain)

a. Gastrointestinal (GI) symptoms are common, may be transient, and are caused by many of the anti-TB drugs, particularly in the first few weeks of therapy.

b. In the setting of GI symptoms, hepatitis must first be excluded by obtaining AST and ALT values as described in the above section. The approach to GI symptoms not associated with hepatotoxicity includes:

i. Changing the hour of drug administration.

ii. Administering drugs with food.

iii. Taking drugs at bedtime (if not on DOT).

3. Rash

a. All anti-TB drugs can cause rash. The management of a patient with rash depends on the severity:

i. If the rash is minor and causes only itching, antihistamines may be prescribed and anti-TB drugs continued.

ii. A petechial rash suggests thrombocytopenia and a platelet count should be ordered. If the platelet count is low and the patient is on RIF, hypersensitivity to RIF should be the presumed cause. RIF should be

stopped immediately, and the patient followed with platelet counts/clinical evaluation.

iii. If a generalized, erythematous rash is noted, especially with mucous membrane involvement and fever, the following principles apply:

- All drugs should be stopped immediately.
- If the patient is acutely ill and may decompensate without treatment, three new drugs, of different classes, may be started.
- When the rash has improved significantly, the medications may be restarted one by one, at intervals of 2-3 days. RIF should be started first (because of its efficacy and decreased likelihood of causing rash), followed by INH, then EMB, and then PZA.
- If the rash recurs, the last drug added is the likely cause and should be stopped.

E. Infectiousness of TB Patients[5]

1. Patients with smear-positive, drug-sensitive pulmonary TB should be considered infectious until all of the following criteria are met:
   a. Completion of adequate therapy for two weeks AND
   b. A favorable clinical response to therapy AND
   c. Three consecutive negative sputum smears from sputa collected on different days.
2. Patients with pulmonary MDR-TB, regardless of smear status, should be considered infectious until all of the following criteria are met:
   a. Completion of adequate therapy for two weeks AND
   b. A favorable clinical response to therapy AND
   c. Three consecutive negative sputum smears from sputa collected on different days AND
   d. Consistent negative AFB cultures.
3. All people required to interact with an infectious patient should wear NIOSH approved fit-tested N95 respirators (consult the Occupational Safety and Health Administration).

F. Use of Serum Drug Concentration Measurements

1. Therapeutic drug monitoring may be helpful in the following situations:
   a. Patients with treatment failure that is not explained by nonadherence or drug resistance.
   b. Patients with medical conditions that may result in abnormal pharmacokinetics of first- or second-line drugs (*e.g.,* significant gastroparesis, other forms of malabsorption, underlying renal or hepatic disease, potential for drug interactions), and
   c. Management of MDR-TB using second-line drugs.
2. The disadvantages of therapeutic drug monitoring include:
   a. The time and cost of measuring serum drug concentrations, and
   b. The lack of sufficient data to formulate clinically validated therapeutic ranges for anti-TB drugs.
3. Until more data are available, restrict therapeutic drug monitoring for the first-line drugs to patients who have an inadequate response to therapy with DOT and those who have evidence of severe gastrointestinal or metabolic abnormalities.

[5] CDHS/CTCA **"Guidelines for the Placement or Return of TB Patients to High Risk Housing, Work, Correctional, or In-Patient Settings",** (4/97)

Issues in Case Monitoring and Management

I. Directly Observed Therapy (DOT)

A. Directly Observed Therapy (DOT), the process by which a health care worker observes the patient swallowing anti-TB medications, is being used extensively throughout the States and the world. Because adherence to therapy cannot be accurately predicted for any patient, DOT should be considered as the initial core management strategy for all patients with active TB. If for some reason resources do not allow DOT for all patients, the decision to order DOT should be considered based on the potential for non-adherence of the patient and the consequence to the individual, or the public at large, of not adequately treating disease. Fixed-dose drug combination may be used when administering drugs through DOT to reduce pill burden and improve adherence. Providers should contact their local health department to coordinate DOT for patients. Because the local health department is responsible for ensuring completion of therapy for all patients, the ultimate decision regarding DOT resides with the health department.

B. DOT is indicated for patients with the following characteristics: [6]

1. Risk of significant consequence to the public
    a. Pulmonary TB with positive sputum smears
    b. Current or recent (within past year) history of residing in a correctional facility
    c. Slow sputum conversion (>2 months) or slow clinical improvement
    d. Organisms resistant to INH, RIF or both
    e. Hemodialysis patients
    f. Persons with relapse of TB disease
    g. Homeless/shelter resident, or unstably housed persons
    h. Persons residing in congregate medical settings (assisted living facilities, skilled nursing facilities, hospitals)
    i. Persons with a history of previous TB treatment
2. Potential for non-adherence
    a. Demonstrated non-adherence with TB medications, present or past
    b. Major psychiatric disorder/memory or cognitive disorder
    c. Persons under 18 years old
    d. Poor or non-acceptance of TB diagnosis
    e. Poor compliance during initial medication management
    f. Adverse reaction to TB medications
    g. Current or recent (within past year) history of alcohol or drug abuse
    h. Frequent interruption of treatment
    i. Too ill to self manage
3. Risk of significant consequence to the individual
    a. HIV disease or AIDS
    b. Children
    c. Clinical deterioration while on TB therapy

C. Before weekends or holidays, patients receiving daily therapy in a DOT program may be given a dose appropriate for twice weekly treatment regimen, or provided with drugs for self-administration over the weekend or holiday.

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[6] CDHS/CTCA **"Directly Observed Therapy Program Guidelines"**, (4/97)

D. DOT should be used with incentives and enablers to encourage compliance and remove barriers to completion of therapy.

Suggested Readings

1. American Thoracic Society / Centers for Disease Control and Prevention. Treatment of tuberculosis and tuberculosis infection in adults and children. Am J Respir Critical Med 1994; 149: 1359-1374.
2. American Thoracic Society / Centers for Disease Control and Prevention. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000; 161: 1376 - 1395.
3. American Thoracic Society / Centers for Disease Control and Prevention. Control of tuberculosis in the United States. Am Rev Respir Dis 1992; 146: 1623 - 1633.
4. Centers for Disease Control and Prevention. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. MMWR 1998; 47 (No. RR-20)
5. Centers for Disease Control and Prevention. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnuceoside reverse transcriptase inhibitors. MMWR 2000; 49 (No. 9)
6. Centers for Disease Control and Prevention Division of Tuberculosis Elimination website http://www.cdc.gov/nchstp/tb
7. Seaworth, Barbara; Multidrug-resistant Tuberculosis. Infectious Disease Clinics of North America 2002; 16: 73-107.

Table 1. Drug Regimens for Culture-positive Pulmonary Tuberculosis

INITIAL PHASE		**CONTINUATION PHASE**		**Total Duration and Doses[1]**
Drugs	***Interval and Doses Minimum Duration***	***Drugs***	***Interval and Doses Minimum Duration***	***(minimum duration)***
Regimen 1 Isoniazid Rifampin Pyrazinamide Ethambutol	7 days/week[2] 56 doses (8 weeks)	Isoniazid/Rifampin	7 days/week[2] 126 doses (18 weeks)	182 (26 weeks)
		Isoniazid/Rifampin	2 days/week 36 doses (18 weeks)	92 (26 weeks)
		Isoniazid/Rifapentine[3]	1 day/week 18 doses (18 weeks)	74 (26 weeks)
Regimen 2 Isoniazid Rifampin Pyrazinamide Ethambutol	7 days/week 14 doses[2] (2 weeks) THEN 2 days/week 12 doses (6 weeks)	Isoniazid/Rifampin	2 days/week 36 doses (18 weeks)	62 (26 weeks)
		Isoniazid/Rifapentine[3]	1 day/week 18 doses (18 weeks)	44 (26 weeks)
Regimen 3 Isoniazid Rifampin Pyrazinamide Ethambutol	3 days/week 24 doses (8 weeks)	Isoniazid/Rifampin	3 days/week 54 doses (18 weeks)	78 (26 weeks)
Regimen 4 Isoniazid Rifampin Ethambutol	7 days/week[2] 56 doses (8 weeks)	Isoniazid/Rifampin	7 days/week[2] 196 doses (28 weeks)	252 (36 weeks)
		Isoniazid/Rifampin	2 days/week 56 doses (28 weeks)	112 (36 weeks)

[1] Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (28 week; either 196 doses[daily] or 56 doses [twice-weekly] continuation phase (total nine month regimen).

[2] When DOT is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses, there is no reason to believe this would not be an effective practice.

[3] Should only be used in HIV-negative patients who have negative sputum cultures at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph (see text).

Table 2. First-Line Drugs for TB Disease

Drug	Supplied	Daily	Intermittent	Side Effects	Monitoring	Comments
Isoniazid:	Tabs: 300mg 100mg 50mg Susp: 50mg/5ml Inj: 100mg/ml (IM or IV)	Adults: 300mg Children: 10–15mg/kg (>20kg receives 300mg)	Adults 2 or 3X weekly: 15mg/kg up to 900mg Children 2X weekly: 20–30 mg/kg up to 900 mg	Hepatitis; peripheral neuropathy; mild CNS effects; skin rash; increased Dilantin levels.	LFTs (not routine) unless known or suspected liver disease or other hepatotoxic drugs used concurrently.	Give pyridoxine 25mg/day to prevent neuropathy in elderly, D.M., nutritionally deficient, renal disease, pregnancy, HIV, alcoholics.
Rifampin:	Caps: 300mg 150mg Inj: 600mg vial (IM or IV)	Adults: 10mg/kg up to 600mg Children: 10–20 mg/kg up to 600mg	Adults 2 or 3X weekly 10mg/kg up to 600mg Children 2X weekly: 10–20 mg/kg up to 600 mg	Orange discoloration of secretions; cholestatic or hepatocellular hepatitis; febrile (flu-like) reaction; thrombocytopenia; drug interactions; skin rash.	LFTs (not routine) unless known or suspected liver disease or other hepatotoxic drugs used concurrently. Baseline CBC.	Warn patient about orange discoloration of urine and other body secretions. Discoloration of contact lens. Induces hepatitis microsomal enzymes.
Ethambutol:	Tabs: 400mg 100mg	Adults: 15–25mg/kg Children: 15–25mg/kg up to 2.5gm	Adults 2X weekly: 50mg/kg Adults 3X weekly: 30mg/kg Children 2Xweekly: 50 mg/kg	Optic neuritis (reversible with discontinuation of drug; very rare at 15mg/kg if renal function is normal); skin rash.	Red-green color discrimination and visual acuity done at baseline and monthly.	Dose adjustment needed for renal disease; use with caution if eye testing is not feasible.
Pyrazinamide:	Tabs: 500mg scored	Adults: 20–25mg/kg up to 2 gm Children: 15–30mg/kg up to 2000mg	Adults 2X weekly: 50mg/kg up to 3gm Adults 3X weekly: 40mg/kg up to 4gm Children 2 or 3X weeky: 50 mg/kg	Hepatitis; GI upset; hyperuricemia; arthralgis; photosensitive dermatitis.	LFTs at start of therapy and monthly. Uric acid (not routine).	Dose adjustment needed for renal disease. Safety not established in pregnancy.
Rifabutin:	Caps: 150mg	Adults: 5 mg/kg up to 300mg Children: Unknown	Adults 2 or 3X weekly: 5mg/kg up to 300mg Children: Unknown	As for rifampin and risk of uveitis when used with macrolides, PI's and azole antifungal agents.	As for rifampin.	As for rifampin.
Rifapentine:	Film-Coated Tabs: 150mg	Not given daily	Adults once weekly: 10mg/kg up to 600mg Children: not studied	As for rifampin.	As for rifampin.	As for rifampin.

Table 3. Clinically-significant Drug- Drug Interactions Involving the Rifamycins*

Drug class	Drugs whose concentrations are substantially decreased by the rifamycins	Comments
Anti-infectives	HIV-1 protease inhibitors (saquinavir, indinavir, nelfinavir, amprenavir, ritonavir, lopinavir/ritonavir)	Can be used with rifabutin (may need dose adjustment). Ritonavir, alone (400-600mg twice daily) or in combination with Saquinovir, can probably be used with rifampin.
	NNRTIs Delavirdine Nevirapine Efavirenz	Delavirdine should not be used with any rifamycin. Doses of nevirapine and efavirenz may need to be increased if given with rifampin, no dose-increase needed if given with rifabutin.
	Macrolide antibiotics (clarithromycin, erythromycin)	Azithromycin has no significant interaction with rifamycins.
	Doxycycline	May require use of an alternate drug or drug combination.
	Azole antifungal agents (ketoconazole, itraconazole)	Itraconazole and ketoconazole concentrations may be sub-therapeutic with any of the rifamycins. Fluconazole can be used with rifamycins, but the dose may have to be increased.
	Atovaquone	Consider alternate form of *Pneumocystis carinii* treatment or prophylaxis.
	Chloramphenicol	Consider an alternative antibiotic.
	Mefloquine	Consider alternate form of malaria prophylaxis.
Hormone therapy	Ethinylestradiol, norethindrone	Women of reproductive potential on oral contraceptives should be advised to add a barrier method of contraception when on a rifamycin.
	Tamoxifen	May require alternate therapy.
	Levothyroxine	Monitoring of serum TSH recommended, may require increased dose of levothyroxine
Narcotics	Methadone	Rifampin use may require methadone dose increase. Rifabutin infrequently causes methadone withdrawal.
Anticoagulants	Warfarin	Monitor prothrombin time; may require 2-3 fold dose increase.
Immunosuppres -sive agents	Cyclosporine, tacrolimus	Rifabutin may allow concomitant use of cyclosporine and a rifamycin.
	Corticosteroids	Monitor clinically, may require 2-3 fold dose increase.
Anticonvulsants	Phenytoin, lamotrigine	Therapeutic drug monitoring recommended; may require dose increase.

Cardiovascular agents	Verapamil, nifedipine, diltiazem**	Clinical monitoring recommended, may require change to an alternate drug.
	Propranolol, metoporol	Clinical monitoring recommended; may require dose increase or change to an alternate drug.
	Enalapril, losartan	Monitor clinically; may require a dose increase or use of an alternate drug.
	Digoxin (among patients with renal insufficiency), digitoxin	Therapeutic drug monitoring recommended; may require dose increase.
	Quinidine	Therapeutic drug monitoring recommended; may require dose increase.
	Mexilitine, tocainide, propafenone	Clinical monitoring recommended; may require change to an alternate drug.
Theophylline	Theophylline	Therapeutic drug monitoring recommended; may require dose increase.
Sulfonylurea hypoglycemics	Tolbutamide, chlorpropamide, glyburide, glimepiride, repaglinide	Monitor blood glucose; may require dose increase or change to an alternate drug.
Hypolipidemics	Simvastatin, fluvastatin	Monitor hypolipidemic effect; may require use of an alternate drug
Psychotropic drugs	Nortriptyline	Therapeutic drug monitoring recommended; may require dose increase or change to alternate drug.
	Haloperidol, quetiapine	Monitor clinically; may require a dose increase or use of an alternate drug.
	Benzodiazepines (e.g., diazepam, triazolam), zolpidem, buspirone	Monitor clinically; may require a dose increase or use of an alternate drug.

* Adapted from the unpublished 2002 American Thoracic Society TB treatment guidelines
** A similar interaction is also predicted for felodipine and nisoldipin

Table 4. Second Line Drugs for TB Disease

Drug	Supplied	Daily	Intermittent	Side Effects	Monitoring	Comments
Streptomycin*:	Aqueous solution: 1gm vial (IM or IV)	Adults: 15mg/kg up to 1gm > 60 yrs. old 10mg/kg up to 750mg Children: 20-40mg/kg up to one gram	Adults and Children 2 or 3 X weekly: same as daily dose	8th nerve damage (primarily vestibular); nephrotoxicity; circumoral paresthesias.	Baseline audiogram, vestibular testing, Cr, BUN at baseline. Monthly Cr and vestibular/hearing symptom review. Repeat audiogram as needed.	Should not be used in pregnancy. Adjust dose for renal disease. Use with caution in elderly. Ototoxicity increases with use of loop inhibiting diuretics.
Capreomycin*:	Aqueous solution: 1gm vial (IM or IV)	Adults: 15mg/kg up to 1gm > 60 yrs. old 10mg/kg up to 750mg Children: 15-30mg/kg up to 1 gram	Adults and Children 2 or 3 X weekly: same as daily dose	8th nerve damage (primarily auditory, vestibular rare); nephrotoxicity common; low K+, low Mg.	As for streptomycin. In addition, Mg & K+ at baseline and monthly. Calculate Cr clearance: $\text{CrCl} = \frac{(140 - age) \times wt}{72 \times Creat}$	As for streptomycin.
Amikacin/ Kanamycin*:	Aqueous solution: 500mg and 1gm vials (IM or IV)	Adults: 15mg/kg up to 1gm Over 60 yrs. old 10mg/kg up to 750mg Children: 15-30mg/kg up to 1 gram	Adults and Children 2 or 3 X weekly: same as daily dose	As for Capreomycin.	As for streptomycin and capreomycin.	As for streptomycin. Also, increased risk of nephrotoxicity in severe hepatic disease.
Levofloxacin:	Tabs: 250mg 500mg 750mg Inj: 500mg vial 750mg vial	Adults: 500 – 1000mg Children: Safety not yet established (orthropathy/ osteochondrosis in juvenile animal studies)	Not established	G.I. intolerance; dizziness; rash; pruritis; photosensitivity.	No specific monitoring recommended.	Dose adjustment needed for renal disease. Safety not yet established in pregnant women & children.
Para-amino-salicylic Acid (PAS)	Granules (4gm packets) can be mixed with food or drink [Paser®]	Adults: 8 to 12gm per day in 2–3 divided doses. Children: 200–300mg/kg up to 10gm in 2–4 divided doses	Not established	G.I. intolerance; hepatotoxicity; hypersensitivity; hypothyroidism (especially if used with ethionamide); Coagulopathy.	LFTs, coagulation tests (PT, PTT) and TSH at baseline and every 3 months.	Do not use in severe renal disease. Dividing doses may help G.I. side effects.
Ethionamide:	Tabs: 250mg	Adults: 15–20mg/kg up to 1gm usually 500-750mg per day in 2 divided doses Children: 15–20mg/kg up to 1 gm in 2-3 divided doses	Not established	G.I. intolerance; metallic taste; hepatotoxicity; hypothyroidism & psychosis.	LFTs and TSH at baseline.	Dividing doses may help G.I. side effects. Predosing with an antiemetic may be necessary. Should not be used in pregnancy. Use with high dose pyidoxine.
Cycloserine:	Caps: 250mg	Adults: 10-15mg/kg up to 1gm. Usually 500–750mg per day in two divided doses Children: 10– 20 mg/kg up to 1gm usually in 2 divided doses	Not established	CNS effects; head-aches; restlessness; personality changes; psychosis; can exacerbate seizure disorders or mental illness.	Monitor drug levels. Review for mood changes, depression, memory, concentration.	Increase dose by 250mg every 5 – 7 days. Give pyridoxine 50mg/250CS daily to prevent CNS toxicity. Use with extreme caution in renal disease.

* Usual adult dose 750-1000mg IM or IV typically given as a single dose 5-7 days a week and reduced to 2-3X a week after first 2-4 months or after culture conversion, depending on the efficacy of other drugs in the regimen.

Table 5. Potential Regimens for the Management of Patients with Drug-Resistant Pulmonary Tuberculosis

Pattern of Drug Resistance	Suggested Regimen	Duration of Rx	Comments
INH (± SM)	RIF, PZA, EMB **or** RIF, PZA, I.A.± FQN	6 months	In BMRC trials, 6-month intermittent regimens have yielded ≥ 95% success rates despite resistance to INH (4) (5). Injectable agents (IA), such as streptomycin, were slightly more active than EMB in these trials. In cases of SM resistance, amikacin, kanamycin, or capreomycin may be employed. Fluoroquinolones (FQNs) were not employed in BMRC studies, but should strengthen the regimen for patients with more extensive disease. To provide a sufficient margin of safety, the oral agents (in addition to RIF) should be continued beyond the first 2 months with RIF and at least one additional active agent being given throughout the 6 months. INH should be stopped in cases of INH mono-resistance (see text for additional discussion).
INH and PZA	RIF, EMB	12 months	RIF and EMB for 12 months may be used.
INH and RIF (± SM)	FQN, PZA, EMB, I.A., ± alternative agent	18 to 24 months (from culture conversion)	In such cases, extended treatment is needed to lessen the risk of relapse. In cases with extensive disease, the use of an additional agent ("alternative agents") may be prudent to lessen the risk of failure and additional acquired drug resistance. Resectional surgery may be appropriate (see text).
INH, RIF, (± SM) and EMB or PZA	FQN (EMB or PZA if active) I.A. and two alternative agents	24 months	Use the first-line agents to which there is susceptibility. Add two or more alternative agents in case of extensive disease. Surgery should be considered (see text).
RIF	INH, PZA, EMB, FQN, ± I.A.	9 to 12 months	A thrice-weekly regimen of INH, PZA, and SM was effective in a BMRC trial. However, extended use of an injectable agent may not be feasible. An all oral regimen for 12 months should be effective. But for more extensive disease and/or to shorten duration, an injectable agent may be added in the initial two-months of therapy.
RIF	INH, PZA (for 2 months), EMB	18 months	INH and EMB can be given for 18 months with PZA included for the first two months

Legend

FQN = fluoroquinolone; most experience involves ofloxacin, levofloxacin, or ciprofloxacin.
I.A. = Injectable agent; may include aminoglycosides (streptomycin, amikacin, or kanamycin) or the polypeptide, capreomycin.
Alternative agents = Ethionamide, cycloserine, para-aminosalicylic acid, clarithromycin, amoxicillin/clavulanate, linezolid.

Table 6. Evidenced-based Guidelines for the Treatment of Drug Susceptible Extrapulmonary Tuberculosis and Adjunctive Use of Corticosteriods

Site of tuberculosis	Length of Therapy	Rating/Evidence	Adjunctive Corticosteroid Therapy	Rating for use of corticosteroids
Lymph Node	6 months	A I	Not recommended	D III
Bone and Joint	6 months	A I	Not recommended	D III
Pleural disease	6 months	A II	Not recommended	D I
Pericarditis	6 months	A II	Strongly recommended	A I
CNS Tuberculosis including Meningitis	9 to 12 months	B II	Strongly recommended	A I
Disseminated Disease	6 months	A II	Not recommended	D III
Genitourinary	6 months	A II	Not recommended	D III
Peritoneal	6 months	A II	Not recommended	D III

Table 7. Dosing Frequency Recommendations for Adult Patients Receiving Hemodialysis or with Reduced Renal Function

Drug	Change in frequency of administration?	Recommended dose and frequency for patients receiving hemodialysis or for patients with creatinine clearance < 30 ml / min
Isoniazid	No change	300 mg once daily, or 900 mg three times/week
Rifampin	No change	600 mg once daily, or 600 mg three times/week
Pyrazinamide	Yes	25-35 mg/kg/dose three times/week (not daily)
Ethambutol	Yes	15-25 mg/kg/dose three times/week (not daily)
Levofloxacin	Yes	750-1000 mg/dose three times/week (not daily)
Cycloserine	Yes	250 mg once daily, or 500 mg/dose three times/week* (not daily)
Ethionamide	No change	250-500 mg/dose daily
PAS	No change	4 gm/dose twice daily
Streptomycin	Yes	12-15 mg/kg/dose two-three times/week (not daily)
Capreomycin	Yes	12-15 mg/kg/dose two-three times/week (not daily)
Kanamycin	Yes	12-15 mg/kg/dose two-three times/week (not daily)
Amikacin	Yes	12-15 mg/kg/dose two-three times/week (not daily)

- Standard doses are given unless the patient shows that he or she cannot tolerate the standard doses.
- The medications should be given after hemodialysis on the day of hemodialysis.
- Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption without excessive drug accumulation, and to assist in avoiding certain dose-related drug toxicities.
- Data are not currently available for patients receiving peritoneal dialysis. Until data become available, begin with hemodialysis patient doses and verify adequacy of dosing using serum drug concentration monitoring.

* The appropriateness of 250 mg daily doses in selected patients requires further study. Monitor for CNS effects.

Appendix 1.

Adapted Public Health Service Rating System for the Strength of Treatment Recommendations Based on Quality of Evidence

- **Strength of the recommendation**

  A. Preferred; should generally be offered

  B. Alternative; acceptable to offer

  C. Offer when preferred or alternative regimens cannot be given

  D. Should generally not be offered

  E. Should never be offered

- **Quality of evidence supporting the recommendation**

  I. At least one properly randomized trial with clinical endpoints

  II. Clinical trials that are either not randomized or were conducted in other populations.

  III. Expert opinion

Appendix 2. Sample Drug-O-Gram (LA County TB Control Program)

DRUG-O-GRAM

NAME:	DATE OF BIRTH:	HEALTH CENTER:	PATIENT FILE NUMBER:

TREATMENT														BACTERIOLOGY				COMMENTS
DATE	INH	RIF	R/I	PZA	EMB	SM	ETA	CS	PAS	CM	KM	LEV	OFL	CF	DATE	SPEC	SMEAR	CULT.	COMMENTS

SUSCEPTIBILITY RESULTS																
DATE	INH	RIF	SM	EMB	PZA	ETA	KM	CM	OFL	CS	PAS	CIP	CF	AK	RFB	OTHER

CODE: Ž = Directly Observed Therapy / • = Self-Administered Therapy

Appendix 2. Sample Drug-O-Gram 2

DRUG-O-GRAM

NAME:	DATE OF BIRTH:	HEALTH CENTER:	PATIENT FILE NUMBER:

DATE	INH	RIF	R/I	PZA	EMB	SM	ETA	CS	PAS	CM	KM	LEV	OFL	CF	DATE	SPEC	SMEAR	CULT.	COMMENTS

SUSCEPTIBILITY RESULTS

DATE	INH	RIF	SM	EMB	PZA	ETA	KM	CM	OFL	CS	PAS	CIP	CF	AK	RFB	OTHER

CODE: Ž = Directly Observed Therapy / • = Self-Administered Therapy

Appendix 2. Sample Drug-O-Gram 3

DRUG-O-GRAM

NAME:	DATE OF BIRTH:	HEALTH CENTER:	PATIENT FILE NUMBER:
Sample, Patient	1/1/89		

TREATMENT															Bacteriology				Comments
DATE	INH	RIF	Rifamate	PZA	EMB	SM	ETA	CS	PAS	CM	KM	CIP	OFL	CF	DATE	TYPE	SMEAR	CULT	
5/22/91			?Ž II	?Ž1500											5/22/91	SP	N	N	
6/14/91			?	?											6/14/91	SP	RARE	2 COL MTB	
8/91			?	?											8/21/91				
12/91			?	?											--	--	--	--	
3/92			?	?											--	--	--	--	
5/28/92			?	?	?										5/29/92	SP	MANY	4+MTB	
6/26/92			?	?	?										6/26/92	SP	RARE	MTB	
12/10/92					Ž1600		Ž500			Ž1GM		Ž1500			--	--	--	--	
2/21/93					Ž		Ž			HELD		Ž			2/12/93	SP	N	10 COL MTB	
3/16/93					Ž		Ž			HELD		Ž			--	--	--	--	
4/14/93					Ž		Ž			Ž		Ž			4/14-4/16/93	SPX3	NX3	NX3	
5/26/93					Ž		Ž			Ž		Ž			5/26/93	SP	N	N	
6/16/93					Ž		Ž			Ž		Ž			6/16/93	SP	N	N	WT. 149 LBS. ON 6/10/93
7/1/93															7/1/93				LOST
1994																			
11/17/95															11/17/95	--	--	--	Admitted to DF Hospital
11/18/95			Ž II	Ž1500	Ž1200										11/18/95	SPX2	3+X2	2+MTB	TRANSFERRED TO Hospital X

SUSCEPTIBILITY TESTS																
Date	INH	RIF	SM	EMB	PZA	ETA	KM	CM	OFL	CS	PAS	CIP	CF	AMIK	RFB	
6/14/91	S.1	S2	S2	S5	S100											PH LAB
5/29/92	R5	R10	S2	S5	S100	S5		S10								PH LAB #
2/12/93	R5	R10	S2	S5	S100	S5		S10								
11/18/95	R5	R5	S2	S5												
12/4/95	R5	R10	S2	S2.5	S100	S5	S2.5	S2.5	S1.25	S30	S2					PH LAB #

CODES: **!** = DOT/> = Self-Administered

Appendix 2. Sample Drug-O-Gram 4

DRUG-O-GRAM

NAME:	DATE OF BIRTH:	HEALTH CENTER:	PATIENT FILE NUMBER:
Sample, Patient	1/1/89		

TREATMENT															Bacteriology				Comments
DATE	INH	RIF	Rifamate	PZA	EMB	SM	ETA	CS	PAS	CM	KM	CIP	OFL	CF	DATE	TYPE	SMEAR	CULT	
11/21/95			Ž	Ž2000	Ž1700	Ž1GM		Ž500					Ž800		11/23/95	SP	2+	3+MTB	
11/22/95			Ž	Ž	Ž	Ž		Ž750					D/C		--	--	--	--	
11/28/95			Ž	Ž1500	Ž1800	Ž		Ž	Ž12GM						11/27/95	SP	3+	3+MTB	TRANSFERRED TO Hospital Y
11/30/95			D/C	Ž	Ž1600	Ž		Ž	Ž				Ž800		11/30-12/1/95	SPX2	MANYX2	MTB	
12/5/95				Ž	Ž	Ž		Ž	Ž				Ž		12/4/95	SP	MANY	MTB	
12/29/95				Ž	Ž	Ž850		Ž	Ž				Ž		12/27/95	SP	MOD	MTB	
1/4/96				Ž	Ž	Ž		Ž	Ž				Ž		1/4/96	SP	MANY	MTB	
1/9/96				Ž	Ž	Ž		Ž	Ž				Ž		1/9/96	SP	FEW	3COL MTB	
1/19/96				Ž	Ž	Ž750		Ž	Ž				Ž		1/177/96	SP	FEW	3COL MTB	
1/23/96				Ž	Ž	Ž		Ž	Ž				Ž		1/23/96	SP	N	MTB	
1/23/96				Ž	Ž	Ž		Ž	Ž				Ž		1/23/96	URINE	N	N	
2/5/96				Ž	Ž	Ž		Ž	Ž12GM				Ž800		2/5/96	SPX2	FEW/MOD	NX2	WT. 127 LBS.
2/21/96				Ž	Ž	Ž		Ž	Ž				Ž		2/21/96	SP	N	N	
3/7/96				Ž	Ž1200	Ž		Ž	Ž				Ž		3/7/96	SP	N	N	WT. 131 LBS.
4/4/96				Ž	Ž	Ž		Ž	Ž				Ž		4/5-4/8/96	SPX2	NX2	NX2	WT. 126 LBS.
4/26/96				Ž1500	Ž1200	Ž750		Ž250	Ž12g				Ž800		4/16/96	SP	N	N	WT. 127 LBS.
5/2/96				Ž	Ž	Ž		Ž	Ž				Ž		5/2/96	SP	N	N	

SUSCEPTIBILITY TESTS																
Date	INH	RIF	SM	EMB	PZA	ETA	KM	CM	OFL	CS	PAS	CIP	CF	AMIK	RFB	
6/14/91	S.1	S2	S2	S5	S100											PH LAB
5/29/92	R5	R10	S2	S5	S100	S5		S10								PH LAB #
2/12/93	R5	R10	S2	S5	S100	S5		S10								
11/18/95	R5	R5	S2	S5												
12/4/95	R5	R10	S2	S2.5	S100	S5	S2.5	S2.5	S1.25	S30	S2					PH LAB #

CODES: **!** = DOT/**>** = Self-Administered

DRUG-O-GRAM

NAME:	DATE OF BIRTH:	HEALTH CENTER:	PATIENT FILE NUMBER:
Sample, Patient	1/1/89		

TREATMENT														Bacteriology				Comments
DATE	INH	RIF	Rifamate	PZA	EMB	SM	ETA	CS	PAS	CM	KM	CIP	OFL	CF	DATE	TYPE	SMEAR	CULT	
5/7/96				Ž	Ž	Ž		Ž	Ž				Ž		5/7/96	SP	N	N	
5/15/96				Ž	Ž	Ž		Ž	Ž				Ž		5/15/96	SP	RARE	N	
6/13/96				Ž	Ž	Ž		Ž	Ž				Ž		6/12/96	SP	N	N	WT. 129 LBS.
6/18/96				Ž	Ž	Ž		Ž	Ž				Ž		6/18/96	SP	N	N	D/C TO TBC HOUSING
6/19/96				Ž	Ž900	Ž		Ž	Ž				Ž		6/19/96	SP	N	N	DOT STARTED @ CLINIC
7/3/96				Ž	Ž	Ž		Ž	Ž				Ž		7/3/96	SP	N	N	
7/17/96				Ž	Ž	Ž		Ž	Ž8 • 4				Ž		7/17/96	SP	N	N	PAS SPLIT 2E TO 9 APPETITE/NAUSEA
8/2/96				--	--			--	--				--		--	--	--	--	INCARCERATED
8/5/96				Ž	Ž	NOT AVAILABLE		Ž750	NOT AVAILABLE				Ž800		--	--	--	--	
8/12/96				Ž	Ž	Ž		Ž	Ž				Ž		8/12/96	SP	N	N	DOT RESUMED @ CLINIC
9/9/96				Ž	Ž	D/C		Ž	Ž				Ž		9/9/96	SP	N	N	WT. 124 LBS.
10/17/96				Ž	Ž800			Ž	Ž				Ž		10/17/96	SP	N	N	WT. 126 ½ LBS.
11/14/96				Ž	Ž			Ž	Ž				Ž		11/14/96	SP	N	N	
12/18/96				Ž	Ž			Ž	Ž				Ž		12/18/96	SP	N	N	WT. 127 ½ LBS.
1/30/97				Ž1500	Ž800			Ž750	Ž12g				Ž800		1/30/97	SP	N	N	WT. 128 LBS.
2/13/97				Ž	Ž			Ž	Ž				Ž		2/13/97	SP	N	N	
4/9/97				Ž	Ž			Ž	Ž				Ž		4/9/97	SP	N	N	WT. 127 LBS.

SUSCEPTIBILITY TESTS																
Date	INH	RIF	SM	EMB	PZA	ETA	KM	CM	OFL	CS	PAS	CIP	CF	AMIK	RFB	
6/14/91	S.1	S2	S2	S5	S100											PH LAB
5/29/92	R5	R10	S2	S5	S100	S5		S10								PH LAB #
2/12/93	R5	R10	S2	S5	S100	S5		S10								
11/18/95	R5	R5	S2	S5												
12/4/95	R5	R10	S2	S2.5	S100	S5	S2.5	S2.5	S1.25	S30	S2					PH LAB #

CODES: **!** = DOT/**>** = Self-Administered

DRUG-O-GRAM

NAME:	DATE OF BIRTH:	HEALTH CENTER:	PATIENT FILE NUMBER:
Sample, Patient	1/1/89		

TREATMENT															Bacteriology				Comments
DATE	INH	RIF	Rifamate	PZA	EMB	SM	ETA	CS	PAS	CM	KM	CIP	OFL	CF	DATE	TYPE	SMEAR	CULT	
5/7/97				Ž	Ž			Ž	Ž				Ž		5/7/97	SP	N	N	WT. 125 LBS.
6/18/97				Ž	Ž			Ž	Ž				Ž		6/4/97	SP	N	N	
7/16/97				Ž	Ž			Ž	Ž				Ž		7/16/97	SP	N	N	
8/14/97				Ž	Ž			Ž	Ž				Ž		8/14/97	SP	N	N	WT. 128 LBS.
9/11/97				Ž	Ž			Ž	Ž				Ž		9/11/97	SP	N	N	WT. 127 LBS.
10/9/97				Ž	Ž			Ž	Ž				Ž		10/9/97	SP	N	N	
11/3/97				Ž	Ž			Ž	Ž				Ž		11/3/97	SP	N	N	WT. 128 LBS.
12/8/97				Ž	Ž			Ž	Ž				Ž		12/8/97	SP	N	N	WT. 130 LBS.
1/29/98				Ž	Ž			Ž	Ž				Ž		1/15/98	SP	N	N	WT. 130 LBS.
2/2/98				D/C	D/C			D/C	D/C				D/C		--	--	--	--	COMPLETED TX.
															4/23/98	SP	N	M. GORDONAE	WT. 128 LBS.
															8/10/98	SP	N	N	CXR no change
															11/98	----	----	----	Broken appt x3
															12/11/98	SP	N	N	CXR stable - Wt. 128 lbs.
															3/8/99	SP	N	N	

SUSCEPTIBILITY TESTS

Date	INH	RIF	SM	EMB	PZA	ETA	KM	CM	OFL	CS	PAS	CIP	CF	AMIK	RFB	
6/14/91	S.1	S2	S2	S5	S100											PH LAB
5/29/92	R5	R10	S2	S5	S100	S5		S10								PH LAB #
2/12/93	R5	R10	S2	S5	S100	S5		S10								
11/18/95	R5	R5	S2	S5												
12/4/95	R5	R10	S2	S2.5	S100	S5	S2.5	S2.5	S1.25	S30	S2					PH LAB #

CODES: **!** = DOT/**>** = Self-Administered