State of Alaska Epidemiology **Bulletin** Recommendations and Reports

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Treatment of Tuberculosis Update

with Corrected Errata*

(Prepared by Beth Funk, MD, MPH, Section of Epidemiology.)

*Corrections:
Appendix: 1c. Regimen 1, Drugs – RFT is changed to RPT
Appendix: 2. Rifampin, Adult, Doses, Daily – 5 mg/kg is changed to 10 mg/kg
Appendix: 2. Ethambutol, Children, 2 x wkly (maximum) – 2,000 mg is changed to 2.5 gm

Treatment of Tuberculosis Update

The goals for treatment of tuberculosis (TB) are two-fold: 1) to cure the individual patient and 2) to minimize transmission of TB to others. This is not an easy charge because the treatment course is long, 6 to 9 months, and multiple drugs are required, each with the potential for adverse reactions. This *Bulletin* updates information about TB treatment regimens, drug dosing, and duration of therapy. These recommendations were developed collaboratively by the American Thoracic Society, the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America.[1]

WHAT IS NEW?

- Extended treatment is recommended for patients with cavitary pulmonary TB who have culture positive sputum after 2 months of treatment (Figure 1).
- A regimen is offered for once weekly dosing with rifapentine and isoniazid for selected adult patients (Table 1).
- Treatment completion is defined by the number of doses ingested, as well as the duration of treatment (Appendix 1).
- Simplified dosing recommendations for ethambutol and pyrazinamide are provided (Appendix 2).

THE DECISION TO BEGIN TREATMENT

A person with signs or symptoms of tuberculosis should undergo clinical evaluation as soon as possible. The Alaska Tuberculosis Program provides consultation by telephone at 907-269-8000 or 1-800-478-0084. In addition, providers may wish to submit clinical information and chest radiographs to the Alaska TB Program for review; a consultation report will be dictated for the patient's record.

The Alaska Tuberculosis Program does not directly evaluate patients with suspected tuberculosis or act as their primary health care provider. However, the Program will provide consultation and assistance with selecting the optimal treatment regimen and dosing.

The decision to begin anti-tuberculosis treatment is based on a combination of factors that reflect the risk of disease and the likelihood of infectivity, including:

- Epidemiologic information
- Clinical, pathologic, and radiologic findings
- Acid-fast smears of sputum and other clinical specimens
- Isolation of *Mycobacterium tuberculosis* from clinical specimens

Although there is value in placing a purified protein derivative tuberculin skin test (TST) when evaluating a patient for TB, a negative test does not exclude the diagnosis of active TB. Likewise, a significant TST test result may be indicative of latent TB infection and not active tuberculosis. More detailed information about the diagnosis of tuberculosis can be found in "Tuberculosis Control in Alaska – July 2001." [2]

RESPONSIBILITY FOR SUCCESSFUL TREATMENT

The patient's health care provider is responsible for reporting each suspected or confirmed case of tuberculosis, prescribing appropriate treatment, and following the patient during the course of treatment.

The Alaska Tuberculosis Program is responsible for ensuring that adequate and appropriate diagnostic and treatment services are available, and for monitoring the response to therapy. The Program will provide antituberculosis drugs free of charge.

Public Health Nursing is responsible for health education and all aspects of case management for persons with tuberculosis, including provisions for directly observed therapy (DOT). Nursing is also responsible for investigation of contacts exposed to persons with tuberculosis.

TREATMENT REGIMENS

There are four treatment regimens recommended for drug-susceptible tuberculosis (Table 1). Each regimen has an 8-week initial phase followed by a continuation phase of either 4 or 7 months. Regimens 1, 2, and 4 have several continuation phase options, which are denoted by a lower-case letter. For example, regimen 1 has three options for continuation: 1a, 1b, or 1c.

Table 1: Treatment regimens for drug-susceptible culture-positive pulmonary TB. Patients with cavitation on chest x-ray and positive cultures after 2 months of therapy should receive 31 weeks of treatment during the continuation phase.

Regimen 1:

Initial phase

Isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) daily for 8 weeks.

Continuation phase

Option 1a – INH and RIF daily for 18 or 31 weeks, or;

Option 1b – INH and RIF twice weekly for 18 or 31 weeks, or;

Option 1c – INH and rifapentine (RPT) once weekly for 18 or 31 weeks for HIV-negative patients who have AFB smear negative sputa after 2 months of therapy.

Regimen 2:

Initial phase

INH, RIF, PZA, and EMB daily for 2 weeks, and then twice weekly for 6 weeks.

Continuation phase

Option 2a - INH and RIF twice weekly for 18 or 31 weeks, or;

Option 2b - INH and RPT once weekly for 18 or 31 weeks for HIV-negative patients who have AFB smear-negative sputa after 2 months of therapy.

Regimen 3:

Initial phase

INH, RIF, PZA, and EMB three times weekly for 8 weeks.

Continuation phase

INH and RIF three times weeks for 18 or 31 weeks.

Regimen 4:

Initial phase

INH, RIF, and EMB daily for 8 weeks.

Continuation phase

Option 4a – INH and RIF either daily for 31 weeks, or;

Option 4b – INH and RIF twice weekly for 31 weeks.

Each regimen is rated according to the strength of the recommendation (A, B, C, D, or E) and the quality of scientific evidence supporting the recommendation (I, II, or III). These ratings as well as the doses for each drug can be found in Appendix 1.

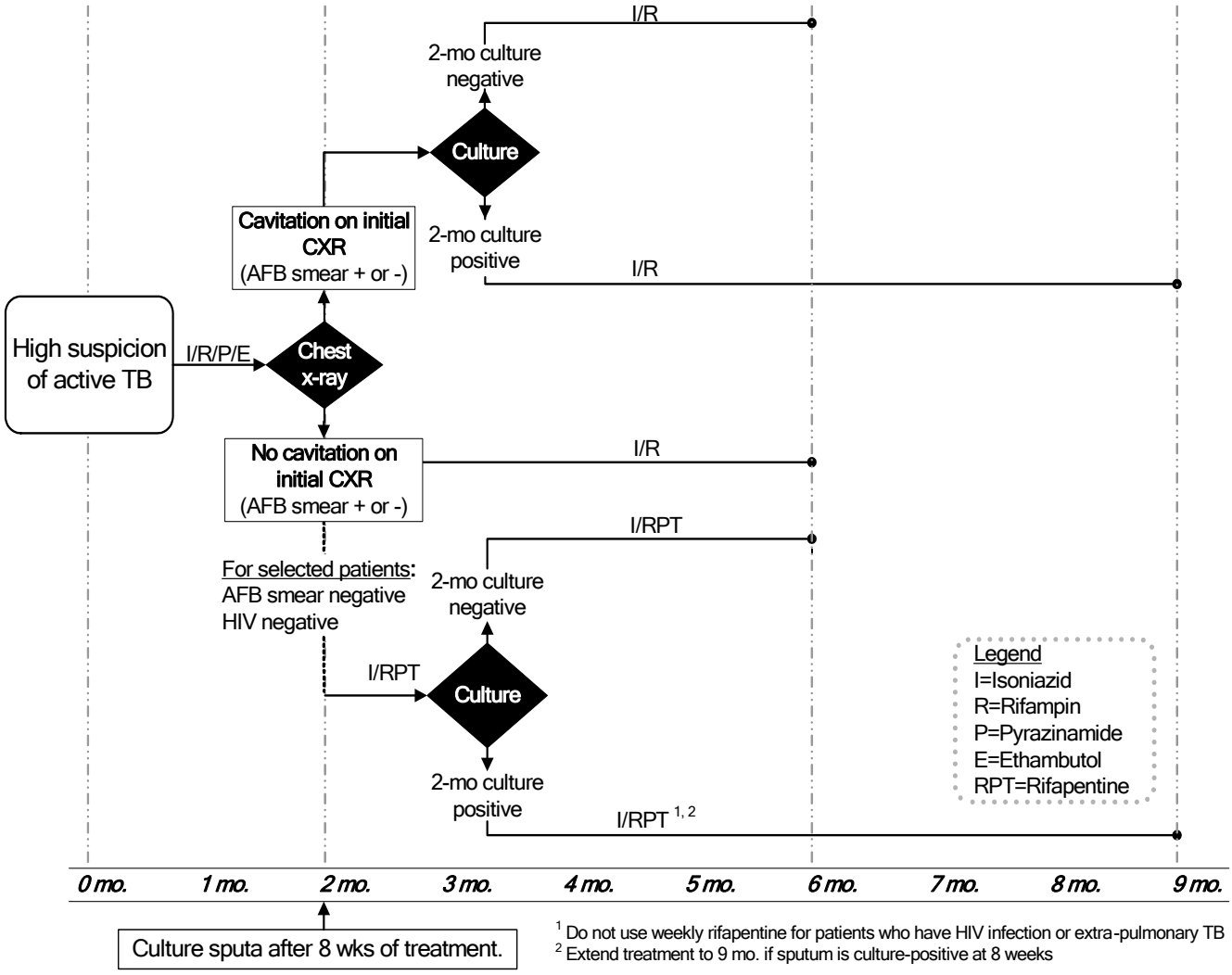
The Alaska TB Program favors Regimen 2 whenever possible, because this regimen minimizes the number of DOT encounters. However, each patient must be considered on a case-by-case basis to select the regimen that will be most effective.

Healthcare providers should take into account the following points when treating tuberculosis:

- **All patients with pulmonary tuberculosis should be treated using directly observed therapy (DOT).**
  - DOT means that a clinical or public health provider or other designated person observes the patient ingest each dose of medication throughout the course of treatment.
  - Regimens with daily dosing may be given 5 days a week using DOT. DOT dosing over a weekend is not required.
  - Patients with extra-pulmonary TB may also receive DOT but DOT is not required if the respiratory tract is not also involved.
- Ethambutol can be discontinued from a four-drug regimen when the patient's organism is reported to be susceptible to all first line agents.
- The continuation phase for regimens 1, 2 and 3 must be extended from 18 weeks to 31 weeks if cavitation is present on chest radiogram *and* sputum cultures remain positive after 8 weeks of treatment. The one exception to this is for patients with non-cavitary disease and smear-negative, culture-positive sputum collected after 8 weeks of treatment who will be treated with rifapentine – the continuation phase for these patients should also be extended to 31 weeks (Figure 1).
- The once-weekly isoniazid and rifapentine continuation option is contraindicated in patients infected with the human immunodeficiency virus (HIV) because there is a high rate of treatment failure or relapse. This regimen has not been evaluated for the treatment of extrapulmonary TB.
- Twice weekly treatment, either in the initial or the continuation phase, is not recommended for HIV-infected patient with CD4+ cell counts <100 cells/μl. Daily (initial phase) and thrice weekly dosing (continuation phase) may be used for these patients.

A treatment algorithm for drug-susceptible TB is presented in Figure 1. The algorithm demonstrates critical decision points during the course or treatment.

Figure 1: Treatment Algorithm for Drug-susceptible Tuberculosis in Adults

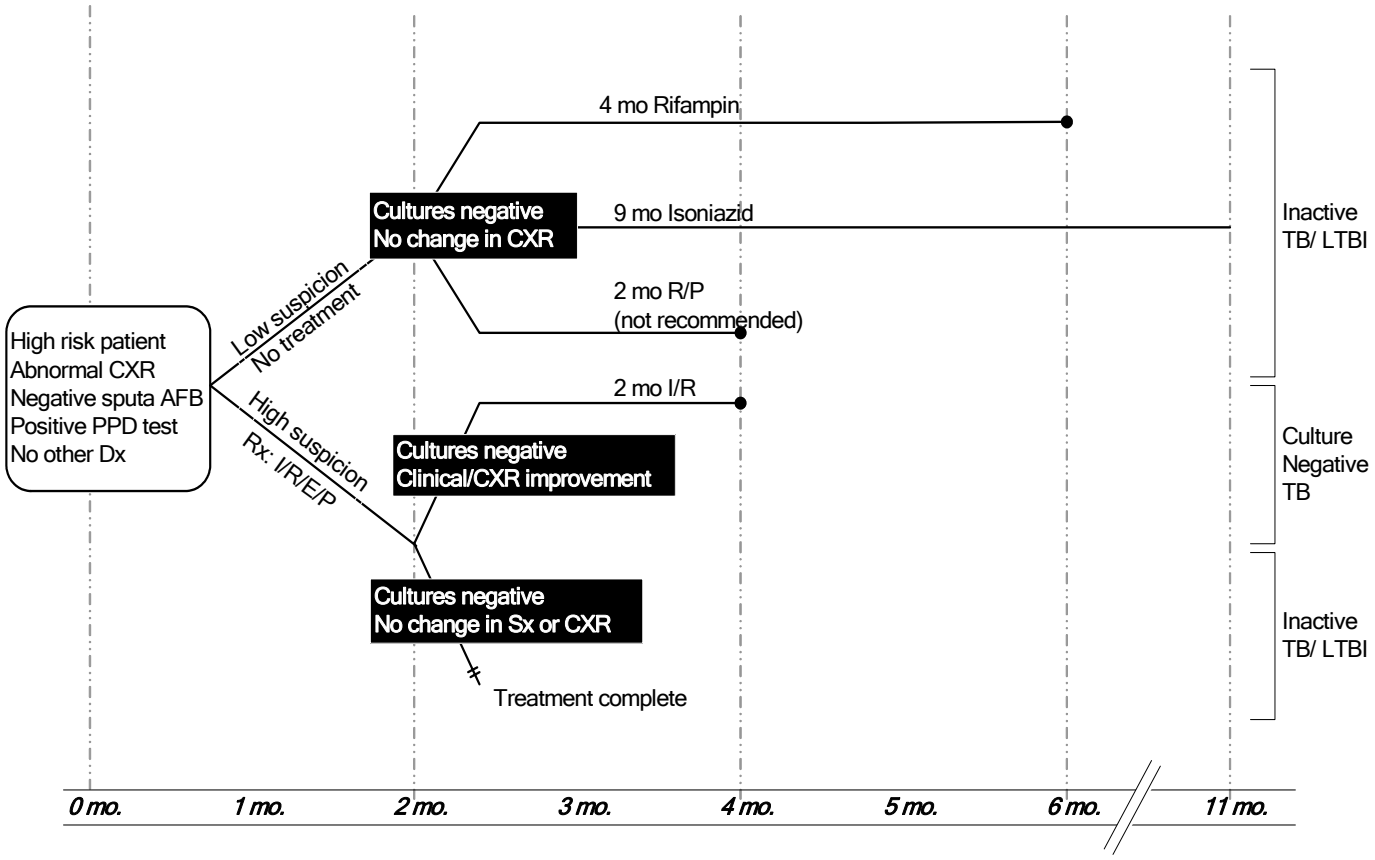


(Adapted from Blomberg, HM, Leonard MK, Jasner RM. Update on the treatment of tuberculosis and latent tuberculosis infection. *JAMA* 2005;293:2776-84.)

CULTURE-NEGATIVE TUBERCULOSIS

TB patients with culture-negative tuberculosis, and persons with inactive tuberculosis, can be treated using a 4-month treatment regimen (Figure 2). The shorter treatment course is feasible because of lower bacillary load in culture-negative TB compared with culture-positive disease. Culture-negative tuberculosis is diagnosed when no other diagnosis is established, the TST is positive, and there is a clinical or radiographic response within 2 months of initiation of therapy; treatment should be continued with an additional 2 months of isoniazid and rifampin.

Figure 2: Treatment Algorithm for Active, Culture-Negative Tuberculosis and Inactive Tuberculosis in Adults



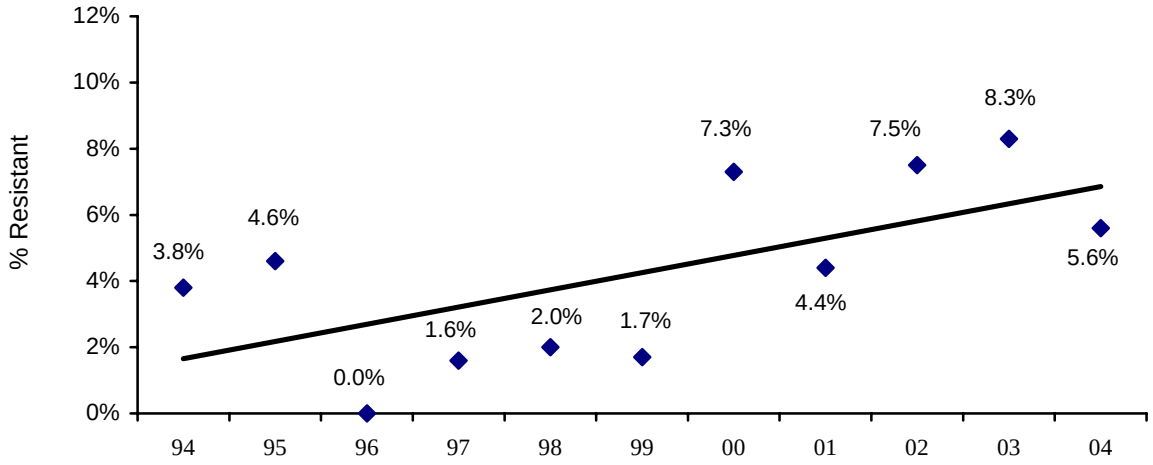
DRUG RESISTANT TB AND RATIONAL FOR FOUR-DRUG TREATMENT

Certain circumstances place an individual at higher risk for acquiring drug-resistant tuberculosis:

- Exposure to a person with drug-resistant TB.
- Exposure to a person who has either relapsed TB or has failed treatment, where susceptibility results are not known.
- Exposure to tuberculosis in areas where there is a high rate of drug resistance.
- Exposure to a person with TB who has positive sputum smears after 2 months of treatment.

In 2003, 7.9 % of TB patients nationally had an isonizid-resistant stain of *M. tuberculosis*. In Alaska, the mean isoniazid resistance rate from 1994 through 2003 was 4.0 % (Figure 3). That rate has shown an upward trend over the past several years. For that reason four drugs are recommended for initial treatment of all TB patients to ensure that the regimen contains at least two active drugs.

Figure 3: Annual Proportion of *M. tuberculosis* Isolates Resistant to Isoniazid--Alaska, 1994-2004*



*The equation for the linear trend is y=00.005x +0.011 (r2+0.4, P=0.04).

USE OF PYRIDOXINE

Pyridoxine supplementation (25 mg/day) can reduce the risk of isoniazid-induced peripheral neuropathy, but it is only recommended for those taking isoniazid who are at increased risk for neuropathy:

- Women who are pregnant or breastfeeding
- Infants who are breastfed
- Children and adolescents on meat- and milk-deficient diets [3]
- Persons with nutritional deficiency
- Persons with diabetes
- Persons with HIV infection
- Persons with renal failure
- Persons with alcoholism

BASELINE LABORATORY EVALUATION

All adult patients beginning anti-tuberculosis therapy should have the following baseline blood tests:

- HIV serology (if HIV positive, obtain a CD4+ count)
- Baseline serum amino transferases (AST, ALT)
- Bilirubin
- Alkaline phosphatase
- Serum creatinine
- Platelet count

In addition, persons with risk factors for hepatitis B or C viruses should have serologic tests for these viruses. Risk factors include history of injection drug use, foreign birth in Asia or Africa, and HIV infection.

Visual acuity (Snelling chart) and red-green color discrimination (Ishihara test) should be tested when ethambutol is used.

EVALUATION DURING TREATMENT

During treatment, patients with pulmonary tuberculosis should receive the following:

- Monthly sputum laboratory testing until three consecutive specimens are culture negative.
  - For AFB smear-positive cases, more frequent examinations may be used to document treatment response and need for respiratory isolation.
  - A patient may be released from respiratory isolation when three consecutive sputa collected 8-24 hours apart are AFB smear negative. At least one specimen should be collected in the early morning.

- Culture results from sputa specimens after 8 weeks of treatment are used to determine treatment duration.

- Monthly clinical evaluation to assess resolution of symptoms and to detect adverse reactions to treatment.
- While on ethambutol:
  - Monthly evaluations for visual problems, including blurred vision or scotomata, and
  - Monthly visual acuity and color discrimination testing.

Routine laboratory testing is not necessary during treatment unless patients have baseline abnormalities or have an increased risk of hepatotoxicity.

Patients with extra-pulmonary tuberculosis should have follow-up evaluations that are appropriate for the site of infection.

DURATION OF TREATMENT

Six months: The shortest acceptable duration of treatment for all children and adults with culture-positive TB is 6 months (26 weeks). This regimen must contain isoniazid, rifampin, and pyrazinamide for the first 8 weeks of treatment (Appendix 1).

Nine months: A 9-month regimen (39 weeks) is necessary when pyrazinamide cannot be used, or when a patient with cavitary pulmonary disease is culture positive after taking 8 weeks of a pyrazinamide-containing regimen.

Extended regimens: A longer course of treatment may be necessary when:

- A patient has an adverse reaction to one or more first-line antituberculosis drugs, necessitating interruption of therapy with first-line agents;
- The organism demonstrates drug resistance to one or more antituberculosis drugs;
- A patient has meningeal, bone or joint, or disseminated (miliary) tuberculosis;
- Treatment is interrupted due to noncompliance.

In each of these situations, the duration of treatment must be decided on a case-by-case basis.

FOLLOW-UP AFTER TREATMENT COMPLETION

Patients do not usually require routine follow-up after completion of therapy (e.g., end of treatment chest x-rays and sputa examinations are not necessary when DOT treatment is completed). However, patients should be advised to seek medical care immediately if symptoms of tuberculosis recur.

PEDIATRIC TUBERCULOSIS

Children, especially young children, are likely to develop disease quickly after their initial infection with *M. tuberculosis*. This form of tuberculosis, known as primary tuberculosis, is characterized by intrathoracic adenopathy, middle and lower lung infiltrates, and the absence of cavitation.

For children who are suspected or known to have fully susceptible tuberculosis, the initial phase should consist of three drugs: isoniazid, rifampin and pyrazinamide. Drug susceptibility may be inferred from susceptibility tests of specimens from the adult presumed to be the source of infection for the child, when this information is available.

If susceptibility of the presumed infecting strain is not known, four drug therapy using isoniazid, rifampin, pyrazinamide and ethambutol is recommended. Ethambutol can be used safely in a dose of 15-20 mg/kg per day, even in children too young for routine eye testing. However, because bacillary load is low in primary tuberculosis and the risk of treatment failure is low, some experts feel it is acceptable to exclude ethambutol if the child is too young to participate in vision testing.

Some children and adolescents present with adult-type pulmonary TB, also known as reactivation tuberculosis. Signs include upper lobe infiltration and cavitation associated with sputum production. When children present with adult-type TB, a four-drug regimen should be used, unless the organism is known to be susceptible to the first generation anti-tuberculosis drugs.

All children with tuberculosis should be treated using DOT. The doses for daily and twice weekly treatment for children are listed in Appendix 2. Three times weekly therapy is not recommended for children, however, twice weekly dosing is acceptable. The duration of therapy is the same as for adults.

EXTRAPULMONARY TUBERCULOSIS

The basic principles of treatment of pulmonary tuberculosis also apply to extrapulmonary forms of the disease. Evidence suggests that 6- to 9-month regimens that include isoniazid and rifampin are effective for most forms of extrapulmonary disease. If pyrazinamide cannot be used in the initial phase, the continuation phase must be 7 months (31 weeks), as is recommended for pulmonary tuberculosis.

There are a few exceptions to this rule.

- Tuberculous meningitis requires a longer course of treatment, and although the optimal duration has not been established, some experts recommend 9-12 months.
- Bone and joint tuberculosis is often treated for a 9-month duration due to the difficulty in assessing response to treatment.
- Disseminated (miliary) tuberculosis in children should be treated using a 9-month regimen. In adults, a 6-month regimen is recommended.

PREGNANCY AND BREAST FEEDING

Pregnant women with suspected or confirmed tuberculosis should be started on treatment immediately. Although the first line anti-tuberculosis agents cross the placenta, the risk of tuberculosis to the woman and her fetus far outweigh the risk of treatment. The initial regimen should consist of isoniazid, rifampin, and ethambutol, but not pyrazinamide. Isoniazid, rifampin, and ethambutol have not been shown to have teratogenic effects. There are insufficient data to determine the safety of pyrazinamide in pregnancy.

Ethambutol should be discontinued if susceptibility results demonstrate sensitivity to isoniazid and rifampin. Pyridoxine, 25 mg/day, should be given during the course of treatment. The minimum duration of therapy is 9 months.

Women can safely breastfeed while being treated with first-line anti-tuberculosis agents. The small amounts of these drugs in breast milk do not cause adverse effects in the nursing infant. However, the amounts of these drugs in breast milk are not sufficient to effectively treat active or latent tuberculosis in a nursing infant. Pyridoxine (25 mg/day) is recommended for nursing mothers receiving isoniazid, but their breastfed infants do not require pyridoxine unless they are also receiving isoniazid therapy.

HIV/AIDS

Persons who are co-infected with tuberculosis and HIV can, for the most part, be treated for TB using the same guidelines that are recommended for HIV-uninfected persons. The exceptions are listed below:

- The isoniazid-rifapentine once weekly continuation phase (regimens 1c and 2b) is contraindicated for individuals infected with HIV, because of a high relapse rate.
- Patients with CD4+ cell counts <100/µl should receive daily or three times weekly treatment (regimens 1/1a, 3/3a or 4/4a). Twice weekly regimens have an unacceptable relapse rate.

Patients with HIV-related TB may have a transient exacerbation of tuberculosis symptoms (e.g., fever lymphadenopathy) or radiographic findings when TB anti-retroviral therapy is initiated. This paradoxical reaction is probably the result of improved immunological response from effective antiretroviral therapy. Some experts recommend delaying initiation of antiretroviral therapy until 4-8 weeks after starting antituberculosis medications to reduce the chance of paradoxical reactions. For patients already receiving antiretroviral therapy, treatment should be continued, although the regimen may require adjustment to reduce the risk of drug interactions.

HIV-infected patients often take medications that may interact with antituberculosis drugs. The rifamycins (rifampin, rifabutin, and rifapentine) are potent inducers of hepatic enzymes required for drug metabolism. Interaction between rifamycins and certain antiretroviral agents is a particular concern. The rifamycins differ substantially in their potency as enzyme inducers; rifampin is most potent, rifapentine is intermediate, and rifabutin is least potent. Rifabutin is highly active against *M. tuberculosis*, and may be preferable to rifampin when certain antiretroviral drugs are used concurrently.[3]

Nucleoside and nucleotide reverse transcriptase inhibitors do not have significant drug interactions with antituberculosis medications, and drugs in these categories can be used concurrently with rifamycins without dose adjustment. Nonnucleoside reverse transcriptase inhibitors and protease inhibitors, depending on the specific drug, may either inhibit or induce hepatic metabolic enzymes. Thus, dose adjustment of the antiretroviral and the rifamycin may be necessary. *The nonnucleoside reverse transcriptase*

inhibitor delavirdine should not be used with any rifamycin. Recommendations for use of rifamycins will change as new drugs and regimens for HIV and AIDS are developed. Updated information is available at http://www.cdc.gov/nchstp/tb.

Management of HIV-related tuberculosis is complex and requires expertise about both tuberculosis and HIV treatment. Current recommendations for treatment of patients coinfected with TB and HIV can be found at the CDC TB Elimination Internet site.[4] Consultations can also be obtained through the Alaska TB Program (907-269-8000) and the Francis J. Curry National Tuberculosis Center in San Francisco, California (415-502-4700).

SUMMARY

1. Health care providers and laboratories should report all suspected or confirmed tuberculosis disease to the Section of Epidemiology (7 AAC 27.005).
2. Successful treatment of TB is the combined responsibility of the public health program and the clinical health care provider.
3. Regimen 2, defined in Table 1, is the preferred treatment regimen in Alaska. Other regimens may be considered on a case-by-case basis.
4. In Alaska, pulmonary TB is treated using directly observed therapy (DOT), which may also be used to treat persons with extra-pulmonary TB.
5. The Alaska TB Program provides TB drugs free of charge for the treatment of tuberculosis and latent TB infection.

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4. CDC. Updated Guidelines for the Use of Rifamycins for the Treatment of Tuberculosis Among HIV-Infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors. Updated January 2004. (http://www.cdc.gov/nchstp/tb/TB_HIV_Drugs/TOC.htm)

Appendix 1: Four treatment regimens for drug-susceptible tuberculosis

Initiation Phase			Continuation Phase			Total Doses	Rating❶	
Regimen	**Drugs**	**Interval & Duration**	**Regimen**	**Drugs**	**Interval & Duration❷**	**Minimum duration❷**	**HIV-**	**HIV+**
1	I, R, P, E	Daily for 8 wks❸	1a 1b 1c❹	I, R I, R I, RPT	Daily for 18 wks Twice wkly for 18 wks Once wkly for 18 wks.	182 –130 (26 wks) 92-76 (26 wks) 74-58 (26 wks)	A (I) A (I) B (I)	A (II) A (II) E (I)
2	I, R, P, E	Daily x 2 wks❸, then twice wkly x 6 wks	2a 2b❹	I, R I, RPT	Twice wkly for 18 wks Once wkly for 18 wks	62-58 (26 wks) 44-40 (26 wks)	A (II) B (I)	B (II) E (I)
3❺	I, R, P, E	Three times wkly x 8 wks	3a	I, R	Three times wkly for 18 wks	78 (26 wks)	B (I)	B (II)
4	I, R, E	Daily for 8 wks❸	4a 4b	I, R I, R	Daily for 31 wks Twice wkly for 31 wks	273-195 (39 wks) 118-102 (39 wks)	C (I) C (I)	C (II) C (II)

Definition of abbreviations: I=isoniazid, R=rifampin, RPT=rifapentine, P=pyrazinamide, E=ethambutol

❶ Definitions of ratings:

Strength of 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 recommendation

I. At least one properly randomized trial with clinical end points
II. Clinical trials that either were not randomized or were conducted in other populations
III. Expert opinion

❷ ***Patients with cavitation on initial CXR and positive cultures at completion of 2 mo. of therapy should receive a 7-month (31 weeks) continuation phase for a total of 9 months (39 wks) of treatment.***

❸ When DOT is used, daily dosing may be given 5 days a week (rating A III). DOT is the standard of care for all persons with pulmonary tuberculosis in Alaska.

❹ Options 1c and 2b should only be used in HIV-negative patients who have negative sputum smears after 2 mo. of therapy and who do not have cavitation on initial CXR; however, if these patients have positive cultures after 2 months of therapy, the continuation phase should be extended to 31 weeks.

❺ Regimen 3 is not approved for children.

Appendix 2: First-line anti-tuberculosis drugs and dosing for adults and children

			Doses (maximum)			
Drug	**Preparation**	**Adult/Child**	**Daily**	**1 x wkly**	**2 x wkly**	**3 x wkly**
Isoniazid	Tablets (50, 100, 300 mg); Elixir (50 mg/5 ml); Aqueous IV/IM solution (100 mg/ml)	Adults	5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)
		Children	10-15 mg/kg (300 mg)	----	20-30 mg/kg (900 mg)	----
Rifampin	Capsule (150, 300 mg); suspend powder for PO; Aqueous IV solution	Adults❶	10 mg/kg (600 mg)	----	10 mg/kg (600 mg)	10 mg/kg (600 mg)
		Children	10-20 mg/kg (600 mg)	----	10-20 mg/kg (600 mg)	----
Rifapentine	Tablet (150 mg)	Adults	----	10 mg/kg (600 mg); continuation phase only	---	---
		Children	Not approved	Not approved	Not approved	Not approved
Pyrazinamide	Tablet (500 mg)	Adults	40-55 kg → 1,000 mg 56-75 kg → 1,500 mg 76-90 kg → 2,000 mg	----	40-55 kg → 2,000 mg 56-75 kg → 3,000 mg 76-90 kg → 4,000 mg	40-55 kg → 1,500 mg 56-75 kg → 2,500 mg 76-90 kg → 3,000 mg
		Children	15-30 mg/kg (2,000 mg)	----	50 mg/kg (2,000 mg)	----
Ethambutol	Tablet (100 and 400 mg)	Adults	40-55 kg → 800 mg 56-75 kg → 1,200 mg 76-90 kg → 1,600 mg	----	40-55 kg → 2000 mg 56-75 kg → 2,800 mg 76-90 kg → 4,000 mg	40-55 kg → 1,200 mg 56-75 kg → 2,000 mg 76-90 kg → 2,400 mg
		Children	15-20 mg/kg (1000 mg)	----	50 mg/kg (2.5 gm)	----

❶ Dose may need to be adjusted when there is concomitant treatment for HIV/AIDS.

State of Alaska
Epidemiology

Bulletin

Recommendations and Reports

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