Tuberculosis Manual

State Guidelines for TB Screening, Treatment, Prevention/Control, Reporting & Resources

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Who To Test

In order of priority, the following individuals should be screened for tuberculosis (TB) infection using the intradermal (Mantoux) tuberculin skin test (DO NOT USE multiple puncture tests such as the Tine test). If previous skin test results cannot be provided (measured in mm, not "positive" or "negative"), repeat the test unless there was a severe reaction (e.g. blistering, ulceration, or necrosis) at the site of injection. Mantoux (PPD) retesting should NOT be done if there is appropriate documentation of a previous positive PPD. **Individuals who are not likely to be infected with Mycobacterium tuberculosis (MTB) should generally not be skin tested because the predictive value of a positive skin test in low risk populations is poor.**

Candidates for tuberculin skin testing include those who are/have:

- close contacts to active TB disease
- HIV infection/AIDS
- injection drug users or other high risk substance users, such as crack cocaine users and alcoholics
- medical conditions which increase the risk of TB disease[1]
- abnormal chest radiograph showing fibrotic lesions consistent with old, healed TB
- residents and employees of high-risk congregate settings such as correctional institutions, nursing homes, mental institutions, other long-term residential facilities (all new admissions to a long term care facility as well as current residents who have not had a PPD skin test within one year), and shelters for the homeless.
- health care workers and volunteers who serve high risk clients
- foreign-born persons arrived within 5 years from countries that have a high TB incidence or prevalence (most countries in Africa, Asia, Latin America, Eastern Europe, and Russia)
- some medically underserved, low-income populations as defined locally

[1] diabetes mellitus, silicosis, recent infection with MTB (within the past 2 years), conditions requiring prolonged high-dose corticosteroid therapy and other immunosuppressive therapy (including bone marrow and organ transplantation), end-stage renal disease, some hematological disorders (e.g., leukemias and Hodgkin's disease), other specific malignancies (e.g., carcinoma of the head or neck), chronic malabsorption syndromes, weight of 10% or more below ideal body weight, and intestinal bypass or gastrectomy.

- high-risk racial, ethnic minority, or other populations defined locally as having an increased prevalence of TB (e.g. Asian and Pacific Islanders, Hispanics, African-Americans, Native Americans, migrant farm workers, homeless persons)
- infants, children, and adolescents exposed to adults in high-risk categories
- adult contacts to children with TB infection (see "Contact Investigation")
- persons undergoing employment screening who cannot provide documentation of a previous PPD skin test and who cannot provide information about appropriate follow-up for a "positive" skin test
- persons with a history of inadequately treated TB

NOTE: Colorado Department of Public Health and Environment (CDPHE) TB Program does not provide or pay for skin test products, chest x-rays, or chest x-ray interpretations for jail inmates, persons undergoing immigration examinations, or paid employees/volunteers of health care facilities, long term care facilities, drug treatment centers, correctional facilities, jails, homeless shelters, schools, and child care facilities. **The employer or facility is responsible for these costs and services.**

How to Apply the Tuberculin Skin Test

1. Administer the tuberculin skin test using the Mantoux technique, that is, the intradermal injection of purified protein derivative (PPD).

2. Mantoux test procedure:

Equipment needed[2]:
sharps container
PPD tuberculin (Tubersol or Aplisol)
tuberculin syringe and needle
alcohol pads

- Obtain written consent as per agency requirements (See "Forms - Consent Form(s) – EXAMPLES")
- Follow infection control procedures, including the use of gloves and a sharps container.
- Clean the surface to be injected on the lateral aspect of the left forearm 1-2 inches below the antecubital fossa with an alcohol pad. The left forearm is the standard site for TB skin testing.
- Using a disposable needle and syringe, inject 0.1 ml of PPD tuberculin containing 5 TU between the layers of the skin (intradermally) with the needle bevel facing upward.
- The injection should produce a discrete, pale elevation of the skin (a wheal) 6-10 millimeters (mm) in diameter.
- Repeat the test on the other arm if a 6-10 mm wheal is not produced.

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[2] See Administrative Issues, page 5-1, AHow to Obtain Skin Testing Materials@

How to Read/Measure/Record Test Results

1. Read the tuberculin skin test 48 to 72 hours after the injection.

   - If the individual fails to show up for the scheduled reading, positive reactions may still be measurable up to 1 week after testing.

   - If the results appear negative and more than 72 hours have passed, it is recommended that the test be repeated[3]. It can be repeated immediately, or after 1 week if two-step testing is required (see page 12, "Two Step Tuberculin Skin Testing").

   - PPD test results should be read by designated, trained personnel. Do not accept self-reading of PPD test results.

2. Measure the tuberculin skin test site crosswise to the axis of the forearm.

3. Measure only induration (swelling that can be felt) around the site of the injection. Do NOT measure erythema (redness). A tuberculin skin test with erythema but no induration is non-reactive.

4. Record the test result in mm, not as "positive" or "negative." An exact reading in mm may be necessary to interpret whether conversions occur on a subsequent test. Record a tuberculin skin test with no induration as "0 mm."

5. In addition, all licensed hospitals and nursing home facilities must maintain a register of the TB skin test results of health care workers in their facility, including physicians and physician extenders who are not employees of the facility but provide care to or have face-to-face contact with patients in the facility. The facility must maintain such TB skin test results as confidential.

NOTE: CDPHE TB Program does not provide or pay for skin test products, chest x-rays, or chest x-ray interpretations for jail inmates, persons undergoing immigration medical examinations and paid or volunteer employees of health care facilities, long term care facilities,

[3] There is some evidence to suggest that positive readings may fade beyond 72 hours.

drug treatment centers, correctional facilities, jails, homeless shelters, schools, and child care facilities. **The employer is responsible for these costs and services.** Employers may purchase PPD through Connaught Labs, Inc. at 1-800-822-2463 (Tubersol PPD, 5 TU) or Monarch Pharmacy at 1-800-776-3637 (Aplisol PPD, 5 TU)

How to Interpret Test Results

Use the chart below to interpret tuberculin skin test results:

5 or more mm	10 or more mm	15 or more mm
Induration of 5 or more mm is considered positive for: ▪ People with HIV infection ▪ Close contacts ▪ People who have fibrotic lesions on chest x-ray consistent with healed TB ▪ People with organ transplants and other immunosuppressed persons (receiving the equivalent of ≥ 15mg/day of Prednisone for ≥ 1 month)	Induration of 10 or more mm is considered positive for: ▪ Foreign-born persons from high-prevalence countries ▪ Injection drug users ▪ People who live or work in long-term residential facilities for the elderly (e.g., nursing homes), hospitals and other health care facilities, residential facilities for AIDS patients, prisons and jails and homeless shelters. ▪ Mycobacteriology laboratory personnel ▪ People with certain medical conditions ▪ Children less than 4 years of age, or children and adolescents exposed to adults in high risk categories ▪ Some medically under served, low income populations, high-risk racial or ethnic minority populations, or other populations as defined locally	Induration of 15 or more mm is considered positive for: ▪ People with no risk factors for TB

In addition:

1. For persons previously skin tested, an increase in induration of 10 mm within a 2-year period is classified as a conversion to positive.

2. False negative reactions may be due to:
   - X Anergy (see "Anergy Testing")
   - X Recent TB infection (within the past 10 weeks)
   - X Very young age (< 6 months of age-because their immune systems are not fully developed)
   - X Overwhelming TB disease
   - X Live virus vaccination (see below)
   - X Some viral infections (measles, mumps, chickenpox, and HIV)
   - X Corticosteroids and other immunosuppressive agents at doses of 2 mg/kg/day or greater for 2 or more weeks

3. Vaccination with live viruses (e.g. Measles, Mumps, Rubella, Varicella, Oral Polio, and Yellow Fever) may also interfere with TB skin test reactivity and cause false negative reactions. TB skin testing should be done on either the same day as vaccination with live virus or 5-6 weeks after vaccination.

4. Call the TB Program regarding PPD reactions for which interpretation and medical follow-up is unclear.

NOTE: Physicians, health care providers and health care facilities must report a PPD skin test result of 5 mm or more, if it occurs in a health care worker, correctional facility worker, or detention facility worker who has had close contact to a TB case. This must be reported within 7 days (see "Reporting Procedures").

BCG (Bacillus Calmette-Guerin) Vaccines

BCG vaccines are live vaccines derived from a strain of *Mycobacterium bovis (M. bovis)*. Because their effectiveness in preventing infectious forms of TB is uncertain, they are not recommended as a TB control strategy in the U.S. except under rare circumstances (see below). They are, however, used commonly in other countries.

Tuberculin Skin Testing of an Individual with a History of BCG Vaccination

- A history of BCG vaccination is not a contraindication to tuberculin skin testing if the person is at risk of exposure to TB.

- A false positive reaction may occur in persons vaccinated with BCG. However, tuberculin reactivity caused by BCG vaccination wanes with time and is unlikely to persist > 10 years.

- Consider TB preventive therapy for BCG-vaccinated persons who are infected with HIV and who are at risk for TB infection if they have a skin test reaction of ≥5 mm induration or with a nonreactive skin test if they have a history of contact to infectious TB.

- A diagnosis of TB infection and the use of preventive therapy should be considered for any BCG-vaccinated person who has a PPD skin test reaction of ≥10 mm induration, especially if:

  - X the vaccinated person is exposed continually to populations in which the prevalence of TB is high (e.g., some health care workers, employees and volunteers at homeless shelters, and workers at drug-treatment centers)

  - X the vaccinated person was born or has resided in a country in which the prevalence of TB is high; or

  - X the vaccinated person is a contact of another person who has infectious TB, particularly if the infectious person has transmitted TB to others

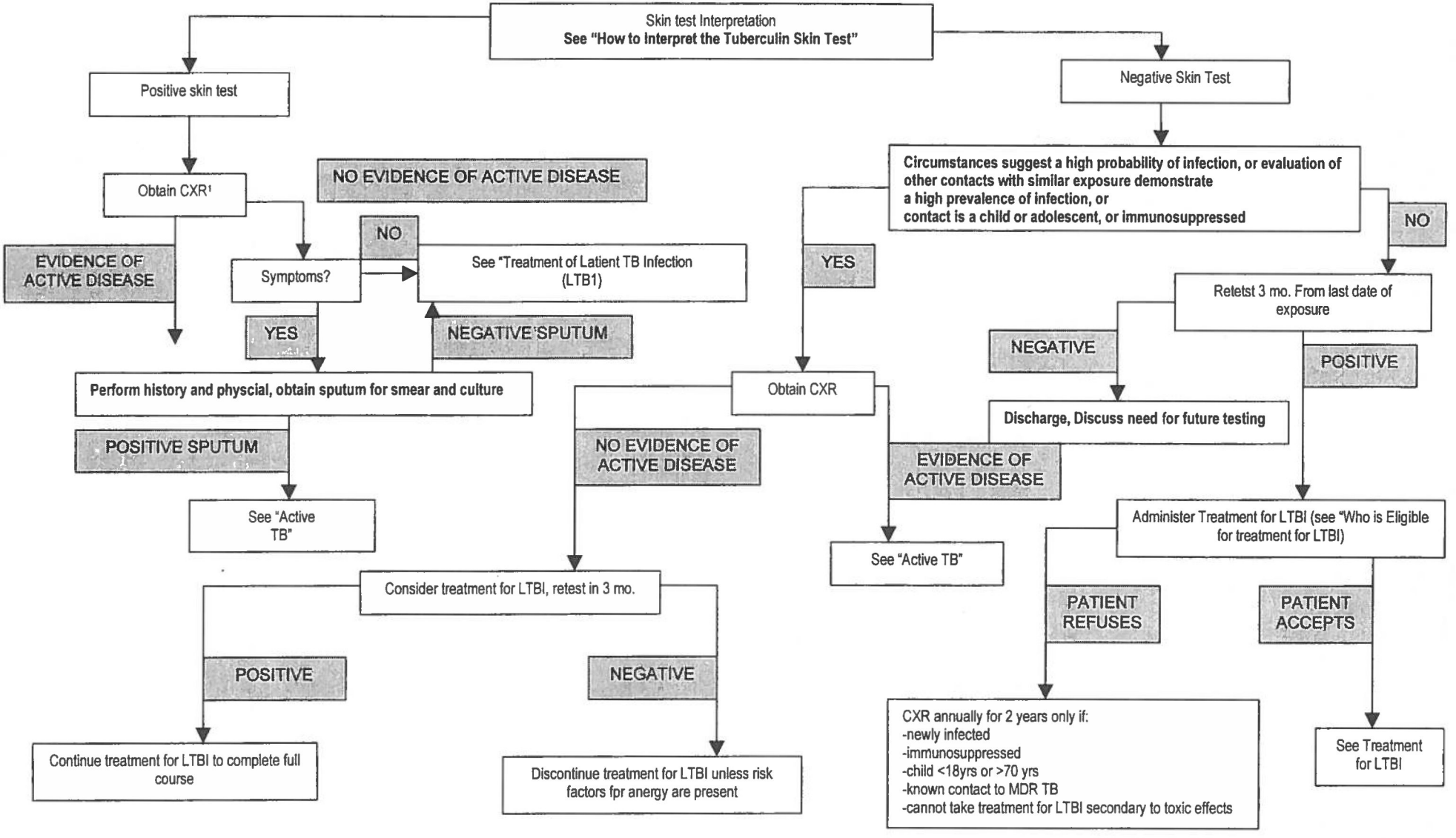
- A PPD of 15 mm or greater in all BCG vaccine recipients should be considered "positive."

Use of BCG in the U.S. should be considered only in rare circumstances. One hypothetical example would be an infant or child who lives in a setting where the likelihood of TB transmission and subsequent infection is high, when no other prevention measures can be implemented (e.g., removing the child from the source of infection). For all practical purposes, BCG should not be used in the United States since resources are available to stop the transmission of TB (e.g. effective therapy, resources for providing direct observed therapy and assistance of Social Services to ensure a safe environment for such a child). BCG vaccine should only be given in consultation with the TB Program at CDPHE.

What to do After Interpreting the Skin Test

The flow chart on the following page details the steps to take after interpreting whether a skin test is positive or negative.

What to Do After Interpreting The TB Skin Test



[1]Pregnant women found to have a positive PPD should receive a chest x-ray after delivery or an immediate shielded chest x-ray if:
-Symptoms of active disease are present
-They are likely to have been recently infected.
-They have high risk medical conditions
(e.g, HIV Infection)

Two-Step Tuberculin Skin Testing (Booster Phenomenon)

Introduction

Delayed type hypersensitivity (a skin test reaction) may wane over the years in some people who are infected with TB. When these people are skin tested many years after infection, they may have a negative reaction. However, this negative skin test may stimulate (boost) their ability to react to tuberculin, causing a positive reaction to subsequent tests. This boosted reaction may be interpreted as new infection. Two-step testing is used to establish a true baseline skin test.

Thus, it is recommended that a baseline two-step tuberculin skin test be performed on workers in health care facilities, correctional institutions and jails, long term care facilities for the elderly, homeless shelters, drug treatment centers, residents of long-term care facilities, and other adults who will be re-tested periodically. Two-step tuberculin skin testing should be performed on these individuals who cannot document a history of a negative tuberculin skin test within the past year.

Protocol:

1. Apply the tuberculin skin test[4].

2. If the initial skin test is positive, consider person infected and refer to "What to do After Interpreting the Skin Test."

3. If the initial tuberculin skin test is negative:

    - It should be repeated within 1-3 weeks using the same dose and strength of tuberculin.

[4]An individual who can provide documentation of a PPD (purified protein derivative) skin test by the Mantoux technique within the preceding year should have an initial skin test performed, and should be managed on the basis of that result. There is no need for a second test because the earlier test is, in effect, the first of a two-step test.

- If the second test is negative, the individual is classified as uninfected and retested at routine intervals (two-step testing is not required for subsequent tests unless one or more years have elapsed since the last test).

4. If the second test is positive, consider person infected and refer to "What to do After Interpreting the Skin Test".

Anergy Testing

Anergy testing is a diagnostic procedure used to obtain information regarding the competence of the cellular immune system. Persons with an impaired cellular immune system (e.g. HIV-infected persons, severe or febrile illness, measles or other viral infections, Hodgkin's Disease, sarcoidosis, live virus vaccination, corticosteroid or immunosuppressive therapy) may have suppressed reactions to PPD skin tests even if infected with TB. However, there are no simple skin testing protocols that can reliably identify persons as either anergic or nonanergic and that have been proven to be feasible for application in public health tuberculosis screening programs. Factors limiting the usefulness of anergy skin testing include:

X problems with standardization and reproducibility
X the low risk for TB associated with a diagnosis of anergy
X the lack of apparent benefit of treatment of LTBI for groups of anergic HIV-infected persons

The results of currently available anergy-testing methods in U.S. populations have not been demonstrated to make a useful contribution to most decisions about treatment of LTBI. **Therefore, the use of anergy testing in conjunction with PPD testing is no longer recommended routinely for screening programs for TB infection conducted among HIV-infected persons in the United States.5**

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5 If a clinician elects to use anergy testing as part of a multifactorial assessment of a person's risk for TB, the two Food and Drug Administration-approved Mantoux-method tests (mumps and Candida), used together, with cut-off diameters of 5 mm of induration, are recommended. Efforts to apply the results of anergy testing to treatment of LTBI decision must be supplemented with information concerning the person's risk for infection with TB. CDPHE TB Program does not provide antigens for anergy testing. These must be obtained through a local pharmacy with a physician's order.

References

1. Centers for Disease Control and Prevention. Essential components of a tuberculosis prevention and control program; and screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis: MMWR 1995;44(RR-11):18-34.

2. Colorado Medical Directors Association and Colorado Department of Public Health and Environment, Division of Disease Control and Environmental Epidemiology. Tuberculosis surveillance and screening for long term care facilities in Colorado. 1997.

3. Updated OSHA Tuberculosis Compliance Directive (CPL 2.106). Feb. 9, 1996.

4. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care facilities, 1994. MMWR 1994;43(No. RR-13)

5. Centers for Disease Control and Prevention. The role of BCG vaccine in the prevention and control of tuberculosis in the United States. MMWR 1996;45(No. RR-4)

6. Centers for Disease Control and Prevention. Core curriculum on tuberculosis. Fourth Edition, 2000.

7. Colorado Rules and Regulations Pertaining to Epidemic and Communicable Disease Control (6 CCR-1009-1).

8. Centers for Disease Control and Prevention. Anergy Skin Testing and Preventive Therapy for HIV-Infected Persons: Revised Recommendations: MMWR September 5, 1997; 46(No. RR-15).

9. 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 October 30, 1998; 47 (No. RR-20).

Resources

For questions regarding tuberculin skin testing, call the TB Program (303) 692-2638.

Who is Eligible for Treatment of Latent TB Infection (LTBI)?

Persons who are **close contacts to active TB** are candidates for treatment of LTBI if their skin test result is **< 5 mm <u>regardless of age</u>**, and they have the following risk factors:

1. Investigation suggests a **high probability of infection**
2. Evaluation of other contacts with a similar degree of exposure demonstrates a **high prevalence of infection**
3. The contact is a **child or adolescent in a very high-risk exposure situation**
4. The contact is **immunosuppressed** (e.g., HIV infected, suspect HIV infected, other immunocompromised persons)

The above persons should be skin tested again in 3 months following cessation of exposure; those with skin test reactions ≥ 5 mm should continue PT, those with reactions < 5 mm may be discharged (except for immunosuppressed persons, who may be anergic).

Persons are candidates for treatment of LTBI if their skin test result is **≥ 5mm, regardless of age**, if they have the following risk factors:

1. **Persons with HIV infection not known to be a close contact**
2. **Recent contacts of persons with newly diagnosed infectious tuberculosis**
3. **Persons with abnormal chest radiographs** that show fibrotic lesions likely to represent old healed tuberculosis
4. **Persons with organ transplants, and other immunosuppressed patients** (receiving the equivalent of ≥ 15 mg/day of prednisone for ≥ 1 month

Persons are candidates for treatment of LTBI if their skin test result is ≥ **10 mm regardless of age**, and they have the following risk factors:

1. Recent arrivals (< 5 years) from high-prevalence countries
2. Substance abuse (especially injection drug users)
3. Residents and employees of high risk congregate settings (e.g. correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)
4. Mycobacteriology laboratory personnel
5. Persons with other clinical conditions that make them high risk (recent converters within 2 years, diabetes mellitus, silicosis, cancer of the head and neck, other immunosuppressive therapy than mentioned above, hematologic and reticuloendothelial diseases such as leukemia and Hodgkin's disease, end stage renal disease, intestinal bypass or gastrectomy, chronic malabsorption syndromes, low body weight of 10% or more below ideal)
6. Children or adolescents exposed to adults in high risk categories

Persons are candidates for treatment of LTBI if their skin test result is ∃**15 mm regardless of age** if they have none of the above risk factors. This group should be given a lower priority for prevention efforts than the groups listed above.

How to Administer Treatment for Latent TB Infection (LTBI)

Before beginning treatment of LTBI:

- ! rule out the possibility of active tuberculosis
  - by CXR and medical history
  - by physical examination (it is especially important to do a physical exam of infected children because 50% of children with TB present as asymptomatic contacts to an active TB case.)
  - by bacteriology examination (for persons with signs or symptoms consistent with active TB)
- ! ask about previous treatment for LTBI or disease (someone with adequate previous therapy[1] does not require re-treatment)
- ! check for contraindications
  - previous isoniazid-associated hepatic injury
  - history of severe adverse reactions to isoniazid (INH) such as acute or unstable liver disease of any cause
- ! check for adverse reactions to current drugs which have known interactions with drugs used for the treatment of LTBI
- ! recommend HIV testing if risk factors are present
- ! establish rapport with patient and emphasize possible side effects (see AHow to Monitor for Side Effects@), benefits of treatment, importance of adherence to the treatment, and establish an optimal follow-up plan
- ! for patients with HIV, see ATB and HIV@

1. CDPHE TB Program requires the following before treatment of LTBI can be provided:

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[1]Adequate previous therapy is defined as documentation of a minimum of 6 months of INH preventive therapy within 9 months (for adults without HIV infection). Minimum therapy for adults with HIV and children may vary; please consult with CDPHE TB Program for these cases.

- a documented PPD result (exception for patients with a history of a severe reaction to PPD)
- completed ATuberculosis Surveillance and Case Management Report@ form (see AForms@) or information completed in the Colorado Electronic Disease Reporting System (CEDRS)
- CXR report
- appropriate physician prescription(s).

2. Do everything possible to educate, support, influence, and persuade the patient to take the medication as prescribed and to complete treatment. In some cases, direct-observed preventive therapy may be indicated (see next page).

3. Obtain patient consent for treatment.

4. CDPHE will provide up to a 3-month supply of INH for adults and a 1-month supply for children at a time, to the health department or provider. The patient should receive only a 1-month supply of medication at a time.

5. Female patients and their partners should be counseled about the need for effective birth control while on treatment of LTBI to avoid possible adverse affects on the fetus. Because rifamycins (rifampin and rifabutin) may decrease the effectiveness of oral or other systemic hormonal contraceptives, use of treatment regimens containing rifamycins necessitates use of an alternative form of birth control.

6. Special Circumstances:

   a. **Pregnancy.** Although no harmful effects of INH to the fetus have been observed, preventive therapy generally should be delayed until after delivery. A chest x-ray is required before starting treatment. There does not appear to be any substantial increase in tuberculosis risk for women as a result of pregnancy. However, for pregnant women likely to have been recently infected or with high-risk medical condition, especially HIV infection, treatment for LTBI should begin when the infection is documented.

b. **Breast-feeding.** Decisions regarding treatment for LTBI and breast-feeding should be made in conjunction with the patient's private physician.

c. **Children.**

- The only recommended regimen for treatment of LTBI in HIV-uninfected children and the preferred regimen for HIV-infected children is INH at a daily dose of 10-20 mg/kg (maximum 300 mg) or by DOT, twice-weekly at a dose of 20-40 mg/kg (maximum 900 mg) for 9 months.
- When INH cannot be tolerated or the child has had contact with a case patient infected with INH-resistant, but rifamycin-susceptible organism, rifampin alone can be used for the treatment of LTBI at a daily or dose of 10-20 mg/kg (maximum 600 mg) or by DOT, twice-weekly at a dose of 10-20 mg/kg (maximum 600 mg) for 6 months.
- Routine administration of vitamin B6 (pyridoxine) is not recommended for children taking INH, but should be given to breastfeeding infants, children and adolescents with diets likely to be deficient in vitamin B6, HIV-infected children taking INH, and children who experience paresthesias while taking INH.
- Children and adolescents who refuse treatment of LTBI or cannot tolerate treatment are recommended to have chest x-ray annually for 2 years.

d. **Patients on Antabuse**. Although some publications recommend against the use of INH for persons taking Antabuse, there is no strong evidence that Antabuse and INH, when taken together, cause a serious health risk. Therefore, INH should be given when indicated for persons on Antabuse.

e. **Other drug interactions.**

X INH has been **reported to inhibit the metabolism of** the following drugs: anticonvulsants, haldoperidol, ketoconazole, theophylline and warfarin. Thus, INH may need to be introduced slowly and/or the dose of these drugs adjusted to prevent toxicity. The patient=s private physician must

be consulted in these situations.

X Rifamycins are known to induce certain P450 enzymes in the liver (rifampin more than rifabutin), and **may accelerate the metabolism of** certain drugs such as hormonal contraceptives, ketoconazole, fluconazole, itraconazole, beta-blockers, calcium channel blockers, cardiac glycosides, diazepam, hypoglycemic agents (sulfonylureas), some antibiotics, corticosteroids, narcotics (including methadone), anti-coagulants, anti-convulsants, tricyclic antidepressants, theophylline, and AZT.

X Rifampin is **contraindicated** in patients on all protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs). Rifabutin is **contraindicated** with ritonavir (a PI), hard-gel saquinavir (a PI), and delavirdine (a NNRTI).

f. **Heavy alcohol use.** These patients should be followed closely by a physician while on treatment of LTBI because of the increased risk of drug-induced hepatitis. They should be counseled to stop alcohol use and/or be referred for alcohol abuse treatment.

7. Patients (adults and children) failing to complete a 9-month treatment regimen within a 12 month period or a 6-month treatment regimen within a 9 month period of time **must restart** treatment of LTBI. Patients requesting to restart treatment of LTBI for the third time should **only** be allowed to restart therapy if they agree to direct observed preventive therapy (DOPT). Contact the TB Program for recommendations regarding HIV patients who have had a lapse in treatment.

8. For patients exposed to **known drug resistant tuberculosis**, contact the TB Program for treatment of LTBI regimens.

9. Pyridoxine (Vitamin B-6) is recommended for adults taking INH if pregnant, HIV-infected, and adults who experience or are at risk for paresthesias while taking INH. However, because B-6 is a relatively benign medication, many physicians prescribe this drug, in combination with INH, for most patients.

10. Contact the CDPHE TB Program for LTBI treatment recommendations for patients who

have special needs necessitating variation of the common treatment for LTBI as described above (e.g. patients intolerant to INH, patients with silicosis or a chest x-ray demonstrating old fibrotic lesions and no active TB).

RECOMMENDED DRUG REGIMENS FOR TREATMENT OF LATENT TB INFECTION IN ADULTS

Drug	Interval & Duration	Comments	Rating* (evidence)** HIV-	HIV+
Isoniazid	Daily for 9 months§¶	In human immunodeficiency virus (HIV)-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs).	A (II)	A (II)
	Twice weekly for 9 months§¶	Directly observed therapy (DOT) must be used with twice-weekly dosing.	B (II)	B (II)
Isoniazid	Daily for 6 months¶	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children.	B (I)	C (I)
	Twice weekly for 6 months¶	DOT must be used with twice-weekly dosing.	B (II)	C (I)

* Strength of recommendation: A = Preferred, B = Acceptable alternative, C = Offer when A and B cannot be given.

** Quality of evidence: I = Randomized clinical trial data, II = Data from clinical trials that are not randomized or were conducted in other populations, III = Expert opinion.

§ Recommended regimen for children < 18 years of age.

¶ Recommended regimens for pregnant women. Some experts would use rifampin and pyrazinamide for 2 months as an alternative regimen in HIV-infected pregnant women, although pyrazinamide should be avoided during the first trimester.

***Rifabutin should not be used with ritonavir, hard-gel saquinavir, or delavirdine. Caution is also advised with rifabutin if administered with soft-gel saquinavir. When used with other protease inhibitors or NNRTIs, dose adjustment of rifabutin may be required (see table next page).

RECOMMENDED DRUG REGIMENS FOR TREATMENT OF LATENT TB INFECTION IN ADULTS, CONT.

Rifampin plus pyrazinamide	Daily for 2 months	May also be offered to persons who are contacts of patients with isonazid-resistant, rifampin-susceptible TB. In HIV-infected patients, protease inhibitors or NNRTIs should not be administered concurrently with rifampin; based on expert opinion, rifabutin can be used as an alternative for patient treated with indinavir, nelfinavir, soft-gel saquinavir, amprenivir, ritonavir, nevirapine, or efavirenz.***	B (II)	A (I)
	Twice weekly for 2-3 months	DOT must be used with twice-weekly dosing.	C (II)	C (I)
Rifampin	Daily for 4 months	For persons who cannot tolerate pyrazinamide. For persons who are contacts of patient with isoniazid-resistant, rifampin-susceptible TB who cannot tolerate pyrazinamide.	B (II)	B (III)

* Strength of recommendation: A = Preferred, B = Acceptable alternative, C = Offer when A and B cannot be given.

** Quality of evidence: I = Randomized clinical trial data, II = Data from clinical trials that are not randomized or were conducted in other populations, III = Expert opinion.

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***Rifabutin should not be used with ritonavir, hard-gel saquinavir, or delavirdine. Caution is also advised with rifabutin if administered with soft-gel saquinavir. When used with other protease inhibitors or NNRTIs, dose adjustment of rifabutin may be required (see table next page).

MEDICATIONS TO TREAT LATENT TB INFECTION: DOSES, TOXICITIES, AND MONITORING REQUIREMENTS

	Oral Dose in mg/kg (maximum dose)						
	Daily		Twice Weekly*				
Drug	Adults	Children	Adults	Children	Adverse Reaction	Monitoring	Comments
Isoniazid (900mg)	5 (300mg)	10-20 (300mg)	15 (900mg)	20-40	▪ Rash ▪ Hepatic enzyme elevation ▪ Hepatitis ▪ Peripheral neuropathy ▪ Mild central nervous system effects ▪ Drug interactions resulting in increased phenytoin (Dilantin) or Disulfiram (Antabuse) levels	Clinical monitoring monthly Liver function tests** at baseline in selected cases§ and Repeat measurements if ▪ Baseline results are abnormal ▪ Patient is pregnant, in the immediate postpartum period or at high risk for adverse reactions ▪ Patient has symptoms of adverse reactions	Hepatitis risk increases with age and alcohol consumption. Pyridoxine (Vitamin B-6), 10-25 mg/day, might prevent peripheral neuropathy and central nervous system effects.
Rifampin	10 (600mg)	10-20 (600mg)	10 (600mg)	-	▪ Rash ▪ Hepatitis ▪ Fever ▪ Thrombocytopenia ▪ Flu-like symptoms ▪ Orange-colored body fluids (secretions, urine, tears)	Clinical monitoring at weeks 2, 4 and 8 when pyrazinamide given Complete blood count, platelets and liver function tests** at baseline in selected cases§ and Repeat measurement if ▪ Baseline results are abnormal ▪ Patient has symptoms of adverse reactions	Rifampin use contraindicated for human immunodeficiency virus (HIV)-infected patients taking protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs). Decreases levels of many drugs (e.g. methadone, coumadin derivatives, glucocorticoids, hormonal contraceptives, estrogens, oral hypoglycemic agents, digitalis, anticonvulsants, dapsone, ketoconazole, and cyclosporin). Might permanently discolor soft contact lenses.

* All intermittent dosing should be administered by directly observed therapy (DOT).

** Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and serum bilirubin.

§ HIV infection, history of liver disease, alcoholism, and pregnancy.

¶ If nelfinavir, indinavir, amprenavir, or ritonavir is administered with rifabutin, blood concentrations of these protease inhibitors decrease. Thus, the dose of rifabutin is reduced from 300 mg to 150 mg per day when used with nelfinavir, indinavir, or amprenavir; and to 150 mg every other day (or three times a week) when used with ritonavir. If efavirenz is administered with rifabutin, blood concentrations of rifabutin decrease. Thus, when rifabutin is used concurrently with efavirenz, the daily dose of rifabutin should be increased from 300 mg to 450 mg. It is not currently known whether dose adjustment of rifabutin is required when used concurrently with soft-gel saquinavir or nevirapine. For patients receiving multiple PIs or PI in combination with an NNRTI, drug interactions with rifabutin are likely more complex; in such situations, the use of rifabutin is not recommended until additional data are available.

MEDICATIONS TO TREAT LATENT TB INFECTION: DOSES, TOXICITIES, AND MONITORING REQUIREMENTS

	Oral Dose in mg/kg (maximum dose)						
	Daily		Twice Weekly*				
Drug	Adults	Children	Adults	Children	Adverse Reaction	Monitoring	Comments
Rifabutin	5 (300mg)	-	5 (300mg)¶	-	▪ Rash ▪ Hepatitis ▪ Fever ▪ Thrombocyto-penia ▪ Orange-colored body fluids (secretions, urine, tears) With increased levels of rifabutin ▪ Severe arthralgias ▪ Uveitis ▪ Leukopenia	Clinical monitoring at weeks 2,4, and 8 when pyrazinamide given Complete blood count, platelets, and liver function tests at baseline in selected cases§ and Repeat measurement if ▪ Baseline results are abnormal ▪ Patient has symptoms of adverse reactions Use adjusted daily dose of rifabutin and monitor for decreased antiretroviral activity and for rifabutin toxicity if rifabutin taken concurrently with PIs or NNRTIs.¶	Rifabutin is contraindicated for HIV-infected patients taking ritonavir, hard-gel saquinavir (Invirase™), or delavirdine. Caution is also advised if rifabutin is administered with soft-gel saquinavir. Reduces levels of many drugs (e.g. PIs, NNTRIs, methadone, dapsone, ketoconazole, coumadin derivatives, hormonal contraceptives, digitalis, sulfonylureas, diazepam, beta-blockers, anticonvulsants, and theophylline). Might permanently discolor contact lenses.
Pyrazinamide	15-20	-	50	-	▪ Gastrointestinal upset ▪ Hepatitis Rash ▪ Arthralgias ▪ Hyperuricemia ▪ Gout (rare)	Clinical monitoring at weeks 2, 4 and 8 Liver function tests** at baseline in selected cases§ and Repeat measurement if ▪ Baseline results are abnormal ▪ Patient has symptoms of adverse reactions	Treat hyperuricemia only if patient has symptoms. Might make glucose control more difficult in persons with diabetes. Should be avoided in pregnancy but can be given after first trimester.

* All intermittent dosing should be administered by directly observed therapy (DOT).

** AST or ALT and serum bilirubin.

§ HIV infection, history of liver disease, alcoholism, and pregnancy.

¶ If nelfinavir, indinavir, amprenavir, or ritonavir is administered with rifabutin, blood concentrations of these protease inhibitors decrease. Thus, the dose of rifabutin is reduced from 300 mg to 150 mg per day when used with nelfinavir, indinavir, or amprenavir; and to 150 mg every other day (or three times a week) when used with ritonavir. If efavirenz is administered with rifabutin, blood concentrations of rifabutin decrease. Thus, when rifabutin is used concurrently with efavirenz, the daily dose of rifabutin should be increased from 300 mg to 450 mg. It is not currently known whether dose adjustment of rifabutin is required when used concurrently with soft-gel saquinavir or nevirapine. For patients receiving multiple PIs or a PI in combination with an NNRTI, drug interactions with rifabutin are likely more complex; in such situations, the use of rifabutin is not recommended until additional data are available.

How to Monitor for Side Effects

1. Educate patients about possible side effects of treatment before beginning therapy and instruct them to notify the clinic if any occur (see above tables).

2. Active hepatitis and end-stage liver disease are relative contraindications to the use of INH or PZA for treatment of LTBI. Use of these drugs in such patients must be undertaken with caution.

3. Baseline laboratory testing is **NOT** routinely indicated for all patients at the start of treatment for LTBI. Baseline hepatitis measurements of serum AST (SGOT) or ALT (SGPT) and total bilirubin **ARE** indicated for:

   - Patients with an initial evaluation suggesting a liver disorder
   - Patients with HIV infection
   - Women who are pregnant or in the immediate postpartum period (within 3 months of delivery)
   - Patients with a history of chronic liver disease (e.g. hepatitis B or C, alcoholic hepatitis or cirrhosis, persons who use alcohol regularly, and others who are at risk of chronic liver disease).
   - Patients who are taking medications for chronic medical conditions (considered on an individual basis)

   If hepatic measurements are indicated as mentioned above, draw blood for liver function tests before starting therapy and at 1 month. If the tests are normal at 1 month, no further laboratory testing is necessary unless symptoms develop. If the tests are elevated at 1 month, continue monthly testing as long as levels are abnormal. If any one of the liver function tests exceeds 3-5 times the upper limit of normal at any time, consult with the patient=s medical provider and strongly consider stopping therapy.

   Reimbursement for liver function testing is considered automatically approved if initiated through local public health agencies in compliance with TB Program recommendations. Reimbursement for all other liver function or other laboratory testing, requires pre-

authorization from the TB Program. Reimbursement is provided at the Medicaid reimbursement rate if the patient has no other means to pay (see ATB Program Billing and Reimbursement@).

1. If client is taking anti-convulsants (e.g. Dilantin), refer client to PCP for monitoring of anti-convulsant drug levels.

2. At least once a month, clinicians should evaluate patients receiving treatment of LTBI for:

   - Adherence to prescribed regimen
   - Signs and symptoms of active TB disease
   - Signs and symptoms of hepatitis (if receiving INH alone, and at 2, 4, and 8 weeks if receiving RIF and PZA)

   Whenever any of these are present, consult with the patient=s medical provider. Liver function tests may be indicated if signs or symptoms of hepatitis develop. In most cases, therapy should be stopped until laboratory results are reviewed.

6. Other laboratory testing (e.g. uric acid) should be considered for patients on treatment of LTBI and who develop symptoms of acute arthritis.

7. If a patient cannot tolerate treatment of LTBI because of toxic side effects, annual chest x-rays for two years are recommended.

8. Repeat chest x-rays at 6 and 12-month intervals for no more than 2 years may be done for selected high-risk individuals such as HIV-positive persons who cannot or will not take preventive therapy or those believed to be infected with multi-drug resistant strains of TB (recently exposed).

How to Monitor for Compliance With Treatment for LTBI

Health care providers often do not realize that patients are not following recommendations. It is very important for you to determine whether your patients are taking medications as prescribed and to have a high index of suspicion of non-compliance. There are several methods for assessing compliance (see references):

< Ask the patient

< Communicate effectively

< Help the patient to remember

< Listen carefully: ask the patient to report any problem with taking the medications

< Monitor appointment keeping, medication refill, and pick-up

< Monitor pills (perform pill counts)

< Directly observe the patient swallowing each dose of medication - direct observed preventive therapy (DOPT). This is recommended for persons who are at high risk for TB and whose adherence is questionable (e.g., IV drug users, homeless, persons at high risk for progression to disease, children, contacts to drug resistant TB and persons with a history of non-compliance with treatment).

References

American Thoracic Society. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. Am J Respir Crit Care Med 2000;161: S221-S247.

CDC. Core Curriculum on Tuberculosis: What the Clinician Should Know. Fourth Edition, 2000.

CDC. Management of Persons Exposed to Multidrug-Resistant Tuberculosis. MMWR June 19, 1992;41(RR-11).

CDC. Improving Patient Adherence to Tuberculosis Treatment. 1994.

Resources

For questions about treatment for LTBI, call the TB Program (303) 692-2638.

How to Diagnose

A diagnosis of pulmonary tuberculosis (TB) may be considered for any patient who has an abnormal chest x-ray consistent with TB or for any patient who has a persistent cough (i.e., a cough lasting 3 weeks or more) or other signs or symptoms compatible with TB (e.g., bloody sputum, chest pain, night sweats, easy fatigability, weight loss, anorexia or fever). A qualified medical provider should make the diagnosis. The index of suspicion for TB should be very high in areas or among groups of patients in which the prevalence of TB is high.

Approximately 19% of TB cases are exclusively extrapulmonary. The symptoms of extrapulmonary TB depend on the site affected. TB of the spine may cause pain in the back; TB of the kidney may cause blood in the urine. Extrapulmonary TB should be considered in the differential diagnosis of ill persons who have systemic symptoms and who are at high risk for TB.

Persons for whom a diagnosis of TB is being considered should receive:

! **Medical History**

A complete medical history should be obtained and should include questions pertaining to risk factors for TB exposure, infection or disease, symptoms of TB, underlying health conditions, risk factors for human immunodeficiency virus (HIV) infection or HIV antibody status, and information about contacts (especially high risk contacts, where immediate action may be necessary). If the patient received prior treatment for TB and the drug regimen was inadequate or if the patient did not adhere to therapy, TB may recur and may be drug resistant. Patients with an unknown or negative HIV status should be referred for HIV counseling and testing.

! **Physical Examination**

A physical examination is an essential part of the evaluation of any patient. It cannot be used to confirm or rule out TB, but it can provide valuable information about the patient=s overall condition and other factors that may affect how TB is treated.

! **Tuberculin Skin Test** (see ATuberculin Skin Testing@)
! **Chest X-ray**

Patients who have positive skin-test results or symptoms suggestive of TB **(regardless of PPD test results)** should be evaluated with a chest x-ray. Radiographic abnormalities that strongly suggest active TB include upper-lobe infiltration, particularly if cavitation is seen, and patchy or nodular infiltrates in the apical or subapical posterior upper lobes or the superior segment of the lower lobe. If abnormalities are noted, or if the patient has symptoms suggestive of extrapulmonary TB, additional diagnostic tests should be conducted.

Abnormalities on chest x-ray may be suggestive of, but are never diagnostic of, TB. Chest x-rays may be used, however, to rule out the possibility of pulmonary TB in a person who has a positive reaction to the tuberculin skin test and no symptoms of disease.

The radiographic presentation of pulmonary TB in HIV-infected patients may be unusual. Typical apical cavitary disease is less common among such patients. They may have infiltrates in any lung zone, a finding that is often associated with mediastinal and/or hilar adenopathy, pleural effusion or they may have a normal chest radiograph, although this latter finding occurs rarely.

Old healed TB can produce various radiographic findings such as pulmonary nodules, with or without fibrotic scars or visible calcifications. Nodules and fibrotic scars may contain slowly, multiplying tubercle bacilli with the potential for future progression to active TB.

The CDPHE TB Program contracts with expert pulmonologists to provide chest x-ray interpretations for suspected/known active TB cases. Chest x-rays on these patients should be submitted to the TB Program rather that to a private radiologist for interpretation (CDPHE does not reimburse private radiologists for chest x-ray interpretations without prior approval). The program will reimburse for a posterior-anterior (PA) chest x-ray view in adults and a PA and lateral (LAT) x-ray view in children 13 years of age or younger (see ATB Program Billing and Reimbursement@). Exceptions to this policy may apply in certain circumstances; please call the TB Program for details.

! **Bacteriologic Examination**

Three major bacteriologic tests are performed on specimens for TB diagnostic purposes:

< Smear examination - the specimen is concentrated, placed on a slide, and stained with a solution that detects acid-fast bacilli (AFB). Many TB patients have negative AFB smears.

< Culture of the specimen for AFB - the specimen is placed in special media that allows mycobacterial growth. Further biochemical tests are used to identify the type of AFB if growth occurs. Positive cultures for *Mycobacterium tuberculosis complex* (MTB) confirm the diagnosis of TB; however, TB may also be diagnosed on the basis of signs and symptoms in the absence of a positive culture.

< Susceptibility testing from cultures positive for MTB complex – the organism is tested for resistance to any drugs commonly used to treat TB (isoniazid, rifampin, ethambutol, streptomycin and pyrazinamide).

Sputum samples should be obtained for smear and culture examination when pulmonary or laryngeal TB is suspected. Because TB can also occur in almost any anatomical site, a variety of other clinical specimens (e.g. urine, cerebrospinal fluid, pleural fluid, pus, or biopsy specimens) should be submitted for examination when extrapulmonary TB is suspected.

If a diagnosis of pulmonary TB cannot be established from sputum, other procedures may be necessary, including bronchoscopy and gastric aspiration. TB Program approval is required before reimbursement for other procedures can be considered (see, AHow to Obtain@ and ATB Program Billing and Reimbursement@).

We encourage providers to submit all specimens to the CDPHE laboratory for free bacteriological examination (see, AHow to Obtain CDPHE Laboratory Services@). CDPHE Laboratory provides a smear result in 1-2 working days and a culture result as soon as 1 week

using the "MB Alert" system (an enriched liquid media culturing method). Specimens with no growth or slow growth may require as long as 8 weeks of incubation time. Costs for bacteriologic laboratory services provided by private laboratories without prior approval will not be reimbursed.

The following is a guide to specimen smear and culture results (continues on next page):

IF AFB SMEAR IS:	IF CULTURE IS:	INTERPRETATION AND ACTIONS
POSITIVE	POSITIVE for AFB, further identification pending	Assume MTB until proven otherwise; may be later identified as non-tuberculous mycobacteria (NTM). Positive sputum smears are reportable within 24 hours (see, AReporting Procedures@)
POSITIVE	POSITIVE for MTB	Diagnostic of active infection with MTB (see ATransmission prevention precautions@ and AHow to treat@). Reportable within 24 hours (see, AReporting Procedures@)
NEGATIVE	POSITIVE for MTB	Same interpretation and actions as above.
POSITIVE	POSITIVE for NTM	Not infected with MTB, not contagious. Refer to primary care provider for treatment.
NEGATIVE	POSITIVE for NTM	No bacteriological evidence for MTB; not considered contagious. In many such cases the NTM is a contaminant or colonizer (see below).
NEGATIVE	NEGATIVE for MTB and NTM	No bacteriologic evidence for MTB. If patient has clinical symptoms not explained by another diagnosis and the suspicion for MTB is high, may still have active infection with MTB. Consult with TB Program.

A culture result of MTB or *M. tuberculosis complex* provides a definitive diagnosis of TB. Other mycobacteria (*M. avium complex* (MAC), *M. kansasii*, *M. chelonae*) may cause pulmonary disease usually with a positive smear and culture for acid-fast bacilli (AFB) but are not contagious (see "Non-Tuberculous Mycobacteria," page 56). These organisms will be identified on final culture. Additionally, these organisms may also be present intermittently in small numbers and may not be pathogenic. Although uncommon, a person may be infected with more than one type of mycobacteria at any given time.

When a laboratory performs a culture that is positive for MTB, the laboratory must save the isolate until it receives notification from the state or local health department that the patient has completed a full and appropriate course of treatment for active TB. In lieu of such storage, the laboratory may fulfill this requirement by submitting the isolate to either the state public health laboratory or for facilities located in Denver, Douglas, Adams, Arapahoe, and Jefferson counties, to the Denver Public Health Mycobacteriology Laboratory at 605 Bannock St, Denver CO 80204, (303) 436-7366.

When is an Active Case Contagious?

The factors that correlate with the contagiousness of an active case are:

1. Pulmonary or laryngeal TB
2. Presence of cough or cough-inducing procedures
3. Failure of patient to cover his/her mouth and nose when coughing
4. Positive sputum AFB smear
5. Cavitation on chest radiograph
6. Inappropriate or short duration of treatment adequacy
7. Poor clinical response to treatment

Patients are not considered infectious if they meet **all** the following criteria:

1. They have received effective therapy for 2-3 weeks (e.g. when drug susceptibilities are known)
2. They have significant **clinical response to therapy** (i.e., reduction in cough, resolution of fever)
3. They have three consecutive negative sputum smear results from sputa collected on different days

See "Transmission Prevention Precautions@ for more information regarding patient placement issues.

Patients with extra-pulmonary TB usually are not infectious unless they:

- have pulmonary or laryngeal TB in addition to their extra pulmonary disease
- have an abscess or open lesion requiring treatment that may lead to aerosolization of wound drainage

In general, children who have pulmonary TB are less likely to spread TB than adults because children do not usually develop a cough (so they cannot aerosolize TB organisms). However,

transmission from children can occur in certain situations. Therefore, children with TB should be evaluated for infectiousness using the same factors as above for adults.

Quarantine

State and local health departments have primary responsibility for preventing and controlling TB. To meet this challenge successfully, the Colorado Revised Statutes (25-4-503, 506 and 507) allow for the quarantine of patients with infectious TB who pose a risk to public health (see "Appendices"). The following is a brief summary of the statutes:

- Chief Medical Health Officer is directed to use every available means to investigate immediately and ascertain sources of known or suspected cases of TB in the infectious stage within his/her jurisdiction.
- Chief Medical Health Officer may issue an order requiring the medical examination of known or suspected cases of TB, regardless of the person=s religious denomination or beliefs, by a licensed physician of the examinees choice under such terms and conditions as the health officer shall specify.
- Chief Medical Health Officer determines when a quarantine or isolation order is necessary and shall make a quarantine or isolation order in writing which includes: name of patient to be isolated, initial period of time for isolation (not to exceed six months), place of isolation or quarantine, and other such terms and conditions that may be necessary to protect the public health.
- The patient under a quarantine or isolation order shall be examined at the time the order expires or at any other time the patient so requests, to ascertain whether or not the individual continues to be infectious.
- When it has been medically determined that the patient=s disease is no longer infectious or communicable, the patient shall be relieved from all further liability or duty imposed by this statute.

State **and** local medical health officers who are licensed physicians have authority to enact the activities described above. For counties with a County Nursing Service, the County Medical Advisor should contact the State Chief Medical Health Officer (Dr. Richard Hoffman, 303-692-2700) for quarantine orders.

Local efforts should be made to provide for adequate isolation of all persons with known/suspected infectious TB. Examples include, but are not limited to, restricting the patient to; a) a private, in-patient isolation room within a health facility where there is documented, adequate ventilation systems in place, b) home while wearing a mask when around other household members or staying in their room with the door closed and windows open, c) isolation outside of the home/health care facility in consultation with the TB Program. Isolation must be maintained until confirmation of non-contagiousness. If a patient has been or is at risk of being non-compliant with isolation, a state quarantine order or civil warrant procedure may be undertaken to protect the public.

Quarantine and Health Order Procedures

1. There are three different health orders available to enforce the statutes that are summarized above (see, AForms@). These include:

   - Order for Patient to Submit to Medical Examination
   - Isolation/Quarantine Order
   - Order to Discontinue Isolation/Quarantine

2. When it is determined necessary or appropriate to serve one or more of the above orders, the Chief Medical Health Officer (local or state) is required to initiate and sign the appropriate form. The CDPHE TB Program must also be notified.

3. A health department representative, sheriff, or deputy sheriff must serve the form to the patient, and must explain the requirements of the order in the patient=s native language.

4. After serving the form, explaining the order, and answering all of the patient=s questions, the order server requests that the patient sign the form. The patient has the right to refuse to sign the form, however, the order is still implemented.

5. The health department representative, sheriff, or deputy sheriff then signs the form and provides a copy of the order to the patient, the patient=s medical record (if available), and CDPHE. The original form is maintained by the order server. If the order server is a CDPHE representative, the local health agency will be provided with a copy of the order.

6. The local health agency is responsible for fulfilling the requirements of the order. If the patient violates requirements specified in the order, the CDPHE Chief Medical Health Officer must be notified immediately. The Chief Medical Health Officer will then initiate appropriate civil warrant procedures.

7. The TB Program may provide reimbursement for quarantine services. Each request for reimbursement is reviewed on a case-by-case basis. Prior to authorization for reimbursement consideration, a written financial statement of need completed by a licensed social worker is required, indicating whether the client has other financial means to cover the costs of quarantine.

Transmission Prevention Precautions

TB transmission prevention precautions **must** be followed for patients who are known or suspected of having active infectious TB. Patients may be identified as having infectious TB based on the patient=s signs or symptoms of TB, a history of incomplete TB therapy, sputum smear and culture results, chest x-ray results, and/or the primary care provider=s clinical opinion.

An effective TB infection control program requires the early detection, isolation and treatment of persons with known or suspect infectious TB. TB precautions should be based on a careful assessment of risk for transmission of TB in the facility or setting. The primary emphasis of the infection control plan should be on achieving these three goals through a hierarchy of control measures, including:

- Performing the **assessment of the risk** for transmission of TB in the particular setting or area, and for a specific occupational group which should be based on:

  1) The profile of TB in the community
  2) The number of infectious TB patients admitted to the area or ward or the estimated number of infectious TB patients to whom health care workers (HCWs) in an occupational group may be exposed
  3) The results of analysis of HCW skin test conversions (where applicable) and possible person-to-person transmission of MTB;

- Use of **administrative controls** to reduce the risk of exposure to persons with infectious TB:

  1) Developing and implementing effective written policies and work practices to ensure the rapid identification, isolation, diagnostic evaluation, and treatment of persons likely to have TB. Protocols should include at least the following TB prevention precautions:

     a. Use triage to promptly identify patients who may have TB;
     b. Promptly evaluate patients who have TB symptoms;

c. Place patient in a separate area apart from other patients and not in open waiting areas (ideally in a room or enclosure with special ventilation maintained under negative pressure);
d. Give patient a surgical mask to wear until he/she can be transported to an appropriate isolation room or until he/she leaves the building;
e. Give the patient a tissue and instruct them to cover their mouth and nose when coughing or sneezing;
f. Schedule appointments to avoid exposing other patients, especially HIV infected or immunocompromised persons;
g. Avoid performing a cough-inducing procedure (e.g. sputum inductions) on patients who may be infectious unless the procedure is absolutely necessary and performed using local exhaust ventilation devices such as booths or special enclosures or in a room that meets ventilation requirements for TB isolation;
h. Allow enough time to pass before placing another patient in a room or area previously occupied by an infectious patient (requires airflow analysis by a qualified engineer to define the length of time needed to remove at least 99% of airborne contaminants);
i. If the patient is placed in TB isolation and is not wearing a mask, all persons entering the room must wear special respiratory protection which meets minimum requirements for TB transmission prevention;
j. TB transmission prevention precautions can be discontinued if the diagnosis of TB is ruled out or if contagiousness is ruled out (see section 3, page 6);

2) Educating training, and counseling HCWs about TB;
This includes basic education regarding MTB transmission, pathogenesis, diagnosis, difference between and therapy for latent TB infection and disease, signs and symptoms of TB, higher risks of disease associated with immunocompromised persons, prevalence of TB in the community and facility, transmission prevention precautions, situations that increase risk for exposure, purpose of PPD skin testing, significance of a positive PPD test result and recommended follow-up, disease reporting procedures (including symptoms in health care workers), confidentiality, information regarding BCG vaccine associated with principles of PPD skin testing, and options for work reassignments for immunocompromised HCWs;

3) Screening HCWs for TB infection and disease;
This includes developing and implementing a TB skin-testing program for persons in the facility with the potential for exposure to TB. Health care workers, including home health nurses, clinic workers and emergency medical technicians, should be included in a TB testing and prevention program if the risk assessment indicates that they are at risk for exposure. This means TB skin testing upon employment and at repeated intervals determined by their risk of exposure thereafter. Any worker who develops symptoms of TB disease or whose TB skin test result converts to positive should be evaluated promptly.

- Use of **engineering controls** to prevent the spread and reduce the concentration of infectious droplet nuclei in the air (adequate ventilation);

- Use of **personal (particulate) respiratory protection** which has been certified by the National Institute for Occupational Safety and Health (NIOSH), including a respiratory protection program that teaches HCWs how and when to use the respirators.

TB Precautions in Hospitals and Other Inpatient Facilities

Hospitals and other inpatient facilities must initiate isolation in a private isolation room with special ventilation maintained under negative pressure relative to other parts of the facility (air flow from the corridors into the isolation room). The room must be monitored daily while in use to assure that appropriate ventilation is maintained, the door must remain closed, and the patient should only leave the room for medically essential purposes.

For the safety of all workers, the isolation room must be clearly identified as housing a potentially infectious patient. When the patient must leave the room, the patient should wear a surgical mask that covers the nose and mouth at all times.

Patients who are placed in isolation rooms should be educated about the transmission of TB, the reasons for isolation, and the importance of staying in their rooms. The patient should also be instructed to cover their nose and mouth when coughing or sneezing.

The number of persons entering the room should be limited and those entering the room must wear appropriate respiratory protective devices. These devices must adequately fit the worker or visitor and be fit checked before its use.

Patients evaluated at or admitted to an inpatient facility and determined to have suspected or known infectious TB cannot be released until the state or local public health agency has made arrangements for appropriate isolation/quarantine post discharge. Proper isolation procedures must be maintained while at the facility.

Isolation should only be discontinued when it is determined that the patient is no longer contagious (see, AWhen is an active case contagious?@)

TB Precautions in Ambulatory-Care Settings and Emergency Departments

Some patients with suspected or known active TB may be evaluated or treated in an outpatient setting under the supervision of or directly provided by the local public health agency. All ambulatory-care settings and emergency departments must develop, implement and update a TB infection control plan in accordance with federal and state rules and/or recommendations (see above recommendations).

Home and Other Health Care Settings

Contact the TB Program for consultation regarding the appropriateness of home placement for individual patients. Patients who are placed at home should be instructed to cover their nose and mouth when coughing or sneezing and be instructed on the importance of taking prescribed therapy and administering DOT. Healthcare workers or visitors must wear appropriate respiratory protection when visiting patients with confirmed or suspect TB. Avoid performing

cough-inducing procedures on patients who are infectious or use appropriate respiratory protection and perform in a well-ventilated area.

For further detail about transmission prevention, see AGuidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health Care Facilities@, 1994, MMWR vol 43, No RR-13).

How to Treat Active Tuberculosis - Basic Guidelines

1. Patients who have confirmed active TB (e.g. patients with positive cultures for MTB or clinical diagnosis by a qualified health care provider) or patients who are considered highly likely to have active TB should be started promptly on appropriate treatment. It is not necessary to wait for laboratory confirmation of TB before starting treatment for patients highly likely to have TB. Patients with confirmed or suspect active TB must be under the medical supervision of a qualified health care provider.

2. Treatment regimens must contain multiple drugs to which the organism is susceptible. The administration of a single drug or the addition of a single drug to a failing regimen can lead to the development of a strain of TB resistant to that drug. Because the drug-resistance rate for TB is higher than 4% in Colorado, all patients should be started on a four-drug regimen containing isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB). See #8 on the following page for specific treatment regimens and first-line TB drug dosages. Adjust weight-based dosages as weight changes.

3. Pyridoxine (Vitamin B-6) is recommended for some individuals receiving INH as part of their treatment regimen to prevent peripheral neuropathy. It should be used in persons at risk for neuropathy (diabetes, uremia, alcoholism, and malnutrition), plus pregnant women and those with a seizure disorder.

4. Research has shown that non-compliance with patient-administered treatment for active TB leads to high failure rates (e.g., failure to cure the TB and the development of multiple-drug-resistant TB). **Therefore, Colorado regulations require that directly observed therapy (DOT) be provided to all patients with active pulmonary TB and is strongly recommended for active extra-pulmonary disease (due to risk of progression to pulmonary disease).** Exceptions for a particular patient from this DOT requirement must be per approval of the TB Program. Public health agencies are

responsible for making arrangements to assure that DOT is provided.

DOT means observation of the patient by a health care provider or other responsible person as the patient ingests antituberculosis medications (the observer should generally not be a family member). DOT may be administered to patients in the office or clinical setting, but can also be given by a health department worker or another responsible community member (i.e., home health care worker, minister, school nurse, or migrant health worker) at the patient=s home, place of employment, school, or other mutually agreed-upon place.

5. Patients should be monitored bacteriologically (e.g., sputum smear and culture) at least every 4 weeks until cultures convert to negative or if new symptoms develop during therapy.

6. Consult the TB program for information regarding the treatment of patients with drug-resistant TB.

7. Consult the TB Program if the patient is symptomatic or smear/culture positive after 3 months of appropriate treatment.

8. Children with TB are treated the same way as adults with TB, except that dosages should be adjusted according to the table on the following page. Caution should be used when considering the use of ethambutol in children. Inability to adequately assess potential vision changes may be a contraindication for its use. Consult the TB Program for further recommendations.

9. Extra-pulmonary TB should be treated the same as pulmonary TB, except for cases of miliary TB, bone/joint TB, or TB meningitis. Those cases should receive a minimum of 12 months of therapy.

10. Careful attention should be given to measures that foster adherence to therapy (e.g incentives). See AHow to Motivate People to Comply With Therapy.@

11. Because rifampin may decrease the effectiveness of oral contraceptives (the "pill"), an alternate method should be used.

12. All patients with active TB should be offered HIV testing. In the presence of HIV infection, it is critically important to assess the clinical and bacteriological response. If there is evidence of a slow or suboptimal response, therapy should be prolonged as judged on a case-by-case basis.

13. It is important to assess whether HIV infected patients who have TB are receiving or plan to receive therapy with protease inhibitors. Protease inhibitors are used to interfere with human immunodeficiency viral maturation and replication and are known to interact with rifamycin derivatives, such as rifampin and rifabutin. Rifamycins (rifampin more so than rifabutin) accelerate the metabolism of protease inhibitors resulting in subtherapeutic levels of the protease inhibitors. In addition, protease inhibitors retard the metabolism of rifampin/rifabutin, resulting in increased serum levels of these drugs and the likelihood of increased drug toxicity. **Therefore, the TB management of these patients is complex and requires an individualized approach, only in consultation with the TB Program (see Section 6, ATB and HIV@).**

Treatment Regimens

OPTION 1 - Daily therapy for duration of treatment

Isoniazid (INH)/rifampin (RIF)/pyrazinamide (PZA)/ethambutol (EMB) daily for 8 weeks.
Continue INH/RIF/EMB (discontinue PZA) daily until:

- drug susceptibility testing shows that the TB organism is susceptible to all four drugs and
- the patient=s sputum smears and/or cultures are negative or are showing decreasing numbers of organisms (sputum conversion) and
- the patient is clinically responding to treatment.

When all of the above criteria are met, EMB can be discontinued and INH/RIF continued daily for an additional 16 weeks. See also, section 5-2, AHow to Obtain Anti-Tuberculosis Medications@. Consult the TB Program if the patient is symptomatic or smear or culture positive after 3 months.

OPTION 2 - Daily therapy for 2 weeks followed by twice weekly treatment for duration of therapy.

INH/RIF/PZA/EMB (or Streptomycin) daily, for 2 weeks.
Continue INH/RIF/PZA/EMB (or Streptomycin) for 6 more weeks, given twice weekly.
Continue INH/RIF/EMB (discontinue PZA) twice weekly until:

- drug susceptibility testing shows that the TB organism is susceptible to all four drugs and
- the patient=s sputum smears and/or cultures are negative or are showing decreasing numbers of organisms (sputum conversion) and
- the patient is clinically responding to treatment

When all of the above criteria are met, then PZA & EMB (or Streptomycin) can be discontinued and INH/RIF continued twice weekly for an additional 16 weeks. See also AHow to Obtain@. Consult the TB Program if the patient is symptomatic or smear or culture positive after 3 months.

OPTION 3 - 3 times weekly treatment for duration of therapy.
INH/RIF/PZA/EMB 3 times weekly for 24 weeks. Consult the TB Program if the patient is symptomatic or smear or culture positive after 3 months.

NOTE: CDPHE will provide a one-month supply of medication for adults and children at a time, to the health department or provider treating active/suspect active TB.

First-Line TB Drugs - Dosages

Drug	Daily		2 Times/Week (DOT)	
	Children ≤ 12 yr old	Adults	Children ≤ 12 yr old	Adults
Isoniazid	10-20 mg/kg (300 mg max dose)	5 mg/kg (300 mg max dose)	20-40 mg/kg (900 mg max dose)	15 mg/kg (900 mg max dose)
Rifampin	10-20 mg/kg (600 mg max dose)	10 mg/kg (600 mg max dose)	10-20 mg/kg (600 mg max dose)	10 mg/kg (600 mg max dose)
Pyrazinamide	15-30 mg/kg (2 g max dose)	15-30 mg/kg (2 g max dose)	50-70 mg/kg (4 g max dose)	50-70 mg/kg (4 g max dose)
Ethambutol	15-25 mg/kg	15-25 mg/kg	50 mg/kg	50 mg/kg
Streptomycin	20-40 mg/kg (1 g max dose)	15 mg/kg (1 g max dose)	25-30 mg/kg (1.5 g max dose)	25-30mg/kg (1.5g max)
Vitamin B-6	25 mg	50 mg	25 mg	100 mg

Drug	3 Times/Week (DOT)	
	Children ≤ 12 yr old	Adults
Isoniazid	20-40 mg/kg (900 mg max dose)	15 mg/kg (900 mg max dose)
Rifampin	10-20 mg/kg (600 mg max dose)	10 mg/kg (600 mg max dose)
Pyrazinamide	50-70 mg/kg (3 g max dose)	50-70 mg/kg (3 g max dose)
Ethambutol	25-30 mg/kg	25-30 mg/kg
Streptomycin	25-30 mg/kg	25-30 mg/kg

	(1.5 g max dose)	(1.5 g max dose)
Vitamin B-6	25 mg	50 mg

Tuberculosis Medications--Available Forms

Isoniazid	100 mg, 300 mg tablets	Various strength suspension.
Rifampin	150 mg, 300 mg capsules	Various strength suspension.
Vitamin B6 (Pyridoxine)	25 mg, 50 mg tablets	Various strength suspension.
Pyrazinamide	500 mg tablet	100 mg/ml, 300 mg/ml, and various strength suspension.
Ethambutol (Myambutol)	100 mg, 400 mg tablets	Liquids not recommended; may crush tablet and give with other suspensions.
Levoquin (Levofloxacin)	250 mg, 500 mg tablets	------
Streptomycin	400 mg/ml, 2.5 ml ampule for intramuscular (IM) injection use	------
Seromycin	250 mg capsule	------

First-Line TB Drugs - Adverse Reactions and Monitoring

Drug	Adverse Reactions	Monitoring*	Comments
Isoniazid	Hepatic enzyme elevation Hepatitis Peripheral neuropathy Mild effects on central nervous system Drug interactions	Baseline and monthly hepatic enzymes for adults Repeat measurements if baseline abnormal, if high risk for adverse reactions, if symptoms of adverse reactions	Hepatitis risk increases with age and alcohol consumption Pyridoxine can prevent peripheral neuropathy
Rifampin	GI upset Drug interactions Hepatitis Bleeding problems Flu-like symptoms Rash	Baseline CBC, platelets, and hepatic enzymes for adults Repeat if baseline abnormal or if symptoms of adverse reactions	Significant interactions with methadone, birth control pills, and other drugs Colors body fluids orange May permanently discolor soft contact lenses
Pyrazinamide	Hepatitis Rash GI upset Joint aches Hyperuricemia Gout (rare)	Baseline uric acid and hepatic enzymes for adults Repeat if baseline abnormal or if symptoms of adverse reactions	Treat hyperuricemia only if patient has symptoms
Ethambutol	Optic neuritis	Baseline and monthly tests of visual acuity and color vision	Not recommended for children too young to be monitored for changes in vision unless TB is drug resistant
Streptomycin	Ototoxicity (hearing loss or vestibular dysfunction) Renal toxicity	Baseline and repeat tests for hearing and kidney function as needed	Avoid or reduce dose in adults >60 yrs

* Most third party payers will cover monitoring costs. However, costs for monitoring as described above are reimbursable through the TB Program for patients with no other means to pay (see, ATB Program Billing and

Reimbursement@).

Management of Cases With Adverse Reactions to First-Line Anti-Tuberculosis Medications

The following protocol applies to:
Individuals on therapy with isoniazid, rifampin, pyrazinamide, streptomycin and ethambutol who develop clinical or biochemical evidence of an adverse reaction.

Adverse Reactions Most Commonly Encountered

Nature	Symptoms and Signs	Usual Causes
Dermatologic	Itching, rash, hives, fever, etc.	Pyrazinamide (most commonly), rifampin, rarely ethambutol, isoniazid, streptomycin
Hepatitis	Anorexia, nausea, vomiting, jaundice	Isoniazid, rifampin, pyrazinamide
Gastrointestinal complaints	Anorexia, nausea, vomiting, epigastric pain	Rifampin, pyrazinamide
Peripheral neuritis	Numbness or paresthesia of feet or hands	Isoniazid
Joint abnormalities	Gout-like	Pyrazinamide, rarely isoniazid
Renal	Azotemia	Streptomycin, rarely rifampin
Hematologic	Leukopenia, other Thrombocytopenia	Rifampin, pyrazinamide
Eye	Loss of vision and color blindness	Ethambutol
Flu like illness	Fever, myalgias, malaise	Rifampin. isoniazid, pyrazinamide

8th nerve damage	Hearing loss, ataxia	Streptomycin

Dermatologic Reactions

History and Examination:

1. The individual should be questioned about exposure to other medications or skin preparations, environmental contact, etc., that may be responsible.

2. HIV-seropositive individuals are subject to a variety of dermatologic diseases either directly or indirectly related to HIV infection, or to other medications used for therapy or prophylaxis. Consultation with an appropriate infectious disease service or dermatology clinic is recommended.

3. There should be a careful examination to detect evidence of unrelated skin disease (scabies, contact dermatitis, childhood exanthem, acne, etc.).

4. Rash, particularly with other systemic symptoms, may be associated with hepatitis; measurement of AST (SGOT) should be considered.

Follow up:

1. Unless an explanation is found for skin reaction unrelated to anti-TB medications, all anti-TB medications should be discontinued promptly and the individual examined each week until the skin reaction disappears.

2. CBC with platelet count may be indicated if there is evidence of petechiae.

3. Cases of severe dermatologic reactions, such as exfoliative dermatitis, and other cases of dermatitis associated with severe systemic reactions should be referred for hospital admission and for establishing a new anti-tuberculosis regimen or for rechallenge with the current medications while the patient is under daily surveillance as an inpatient.

4. Transient rashes that occur within 30-60 minutes of pyrazinamide administration and that last only 1-2 hours are usually due to pyrazinamide and are usually not treatment-limiting. If not severe and not associated with clinical or chemical hepatitis, treatment can be cautiously continued (preferably by direct observed therapy--DOT) and antihistamines used to reduce systems.

Restarting Anti-TB Medications:

1. In cases managed in a clinic with a mild dermatological reaction, it is appropriate to rechallenge after the skin reaction clears or subsides. It may not be possible to identify the specific causative agent by the characteristics of the skin reaction. Thus, it is appropriate to restart the most important member or members of the regimen (isoniazid or rifampin) immediately, before trying pyrazinamide and/or ethambutol.

    - Single daily doses of isoniazid or rifampin should be given alone for three days with instruction to discontinue them promptly if the reaction recurs. The individual should be examined in three (3) to four (4) days.

    - If there is no reaction, the alternate drug, rifampin or isoniazid, should be given with similar instructions. The individual should be reexamined in three (3) to four (4) days.

    - Ethambutol or streptomycin should be given next, as these are unlikely to cause a rash.

    - If there is no recurrence of the skin reaction, pyrazinamide should be given, if this was in the initial regimen. If rash occurs with pyrazinamide but is not severe or associate with systemic symptoms, symptomatic management with the patient with the use with pyrazinamide with allow a 3-month shorter course of therapy.

2. If one of the initial drugs cannot be restarted because of an adverse reaction, treatment

should be continued with the original regimen without the causative agent, with consideration about adding a new alternative drug (quinolone or aminoglycoside). If isoniazid, rifampin or pyrazinamide must be discontinued during the initial 2-months of treatment, a longer period of treatment is required. If treatment must be continued with a regimen that contains isoniazid or rifampin but not both, a 3-drug regimen may be needed for the remaining course. In such instances, the addition of a single agent to a successful regimen does not violate the rule of "do not add a single drug to a failing regimen."

3. The same principles of management apply to cases with dermatologic reactions while on "retreatment" regimens for multi-drug resistant TB.

Drug-Related Hepatitis

History and Examination:

1. Individuals taking anti-TB medication(s) and who develop symptoms consistent with hepatitis (anorexia, nausea, vomiting, abdominal pain, jaundice) should be instructed to discontinue all medications promptly, be examined by their care provider, and have liver function tests (LFTs).

Laboratory Evaluation:

1. If symptoms disappear quickly and LFTs are normal, anti-TB drug-induced hepatitis is unlikely. Another cause for symptoms should be suspected, and depending upon the nature, duration and severity of symptoms, a decision made regarding further diagnostic investigation. If evidence is secure that symptoms are unrelated to anti-TB medication(s), the entire regimen should be reinstituted promptly and the individual followed closely for recurrence of symptoms.

2. If the LFTs are abnormal (SGOT/AST or SGPT/ALT is >3-5 times the upper limit of normal) with or without symptoms, drug-related hepatitis should be strongly suspected and all anti-TB medication(s) discontinued. Isolated mild bilirubin elevations without

elevated AST (SGOT) may occur with rifampin and resolve with continued therapy; in most instances, treatment should be interrupted. Physicians/care providers should be strongly encouraged to consider cautiously continuing treatment for patients with known, pre-existing liver disease (e.g. chronic hepatitis or alcohol abuse).

3. The individual should be examined, and have LFTs repeated at least weekly. If symptoms persist for more than two (2) weeks without anti-TB medication(s), or if LFTs continue to worsen, either an unrelated cause for hepatitis, or progressive drug-related hepatitis should be suspected. Depending upon the severity of the hepatitis, judged by clinical findings and LFTs, hospitalization for closer observation and therapy may be indicated.

Restarting Anti-TB Medications:

1. If the individual has severe pulmonary, or disseminated TB, or is HIV-seropositive, institution of a new regimen with lesser potential for hepatotoxicity (e.g. streptomycin, ethambutol, fluoroquinolone) may be indicated even before liver enzymes normalize, while sorting out the cause of toxicity.

2. Except for cases of liver toxicity unrelated to anti-TB therapy, and those included in item #1 immediately above, treatment should be withheld until symptoms resolve and the LFTs are normal, or have "plateaued" at a stable but elevated level. During this time, the individual should be followed closely with weekly examinations and test of liver functions. It is then appropriate to rechallenge with a single daily dose of one of the drugs in the prior regimen.

   If AST (SGOT) elevation is greater than 500 IU/L and no other likely cause for elevation is present, INH hepatotoxicity should be strongly considered. Some experts would avoid a rechallenge with INH. If AST elevations are smaller and minimal symptoms are present, a rechallenge with INH should be considered. Consult with the TB Program for further information regarding drug rechallenge.

2. Individuals who cannot take either isoniazid nor rifampin should be treated with a "retreatment regimen", usually streptomycin for four months after culture conversion,

   combined with pyrazinamide, ethambutol and a fluoroquinolone, and treated for a period of 12-18 months.

4. Although the specific cause for hepatitis cannot be identified by the pattern of LFT abnormality, in general, rifampin is implicated if the pattern is cholestatic (elevated bilirubin and alkaline phosphatase out of proportion to other enzyme elevations).

5. If the pattern is "hepatocellular" (AST and ALT enzymes elevated out of proportion to bilirubin or alkaline phosphatase), isoniazid, rifampin, or pyrazinamide may be the cause. Ethambutol, which very rarely causes hepatitis, can produce a hepatocellular pattern.

6. In some individuals, rifampin may cause gastritis with symptoms similar to those of hepatitis. In these, the LFTs remain normal or stable despite symptoms. Refer to: "Gastrointestinal Reactions" below.

7. Similar principles of management apply to cases of hepatitis induced by second-line drugs (e.g., ethionamide, PAS, rifabutin, and rarely fluoroquinolones).

Gastrointestinal Reactions

Principles:

1. Almost any medication can cause gastrointestinal symptoms in susceptible individuals. Among first-line anti-tuberculosis medications, pyrazinamide is most often the cause for gastrointestinal symptoms, although rifampin may also be responsible.

   Because rifampin is the most important member of combined chemotherapy, every effort should be made to reintroduce this drug without recurrence of gastrointestinal symptoms.

2. Because the gastrointestinal symptoms (anorexia, nausea, vomiting, epigastric distress) may be due to drug-related hepatitis, LFTs must be done on all individuals who present such symptoms.
3. Anti-TB medications should be discontinued in such symptomatic individuals both to ameliorate symptoms, and pending the results of liver function tests - if LFTs are normal, or unchanged from baseline, and symptoms persist for 4-5 days without medication, unrelated GI disease (e.g. peptic ulcer disease, gastritis due to another cause, etc.) should be suspected and appropriate referral made for diagnostic investigation.

Restarting Anti-TB Medications:

1. If the individual is on isoniazid, rifampin, pyrazinamide, and ethambutol, pyrazinamide is the most likely the cause for gastrointestinal symptoms. After symptoms subside, it is appropriate to restart treatment with isoniazid, rifampin, and ethambutol. If gastric symptoms return, rifampin should be suspected as the cause and treatment should be attempted with isoniazid, pyrazinamide, and ethambutol.

2. If symptoms do not recur, it is usually possible to reintroduce pyrazinamide without recurrence of gastric symptoms by modifying the pattern of administration, such as giving all of the medication before bedtime, preceding the medication with a small meal, restarting pyrazinamide with a smaller dose and increasing it over a period of one to two weeks.

3. An H-2 blocker (e.g. Cimetidine) may be useful to help alleviate gastrointestinal symptoms. Antacids may also be useful. They may, however, interfere with the absorption of isoniazid and rifampin. When employed, antacids should be given one to two hours after isoniazid has been taken, and preferably, not used for prolonged periods.

4. When gastritis is caused by pyrazinamide, this drug can be omitted from the regimen with less risk than is the case with rifampin. If the individual has tuberculosis susceptible to isoniazid and rifampin, he/she can be treated with these two medications for a total of nine to twelve months.

Peripheral Neuritis

Predisposing Factors:
Isoniazid may cause peripheral neuropathy, especially in individuals with a predisposing cause such as alcoholism, diabetes, HIV infection, malnutrition, etc.

Role of Pyridoxine (Vitamin B6):

Pyridoxine (Vitamin B6) usually, but not invariably, prevents the emergence of isoniazid-induced peripheral neuropathy. Isoniazid should be assumed to be the primary cause for paresthesia and numbness of the feet and hands, with or without peripheral motor weakness, in isoniazid-treated subjects even if other predisposing causes are present. This drug should be discontinued, and large doses of pyridoxine given.

Follow up:

Although the neuropathy usually subsides when the diagnosis is made early and isoniazid discontinued, neurologic injury may be irreversible if the diagnosis is delayed and the manifestations become severe. Neurologic consultation should be obtained if the diagnosis is not clear.

Joint Manifestations

Isoniazid:

Isoniazid can rarely induce active systemic lupus erythematosus (SLE) –like syndrome especially in subjects who have this disease in a subclinical stage. The individual may have only arthralgias or may present a full-blown pattern of SLE with arthritis and other systemic manifestations. The diagnosis requires clinical suspicion and positive antinuclear antibodies (ANA) markers of SLE.

Isoniazid must be discontinued, and such individuals referred to an appropriate medical or rheumatology clinic. Usually the symptoms resolve with cessation of therapy.

Pyrazinamide:

1. Pyrazinamide may leads to increased levels of serum uric acid by impairment of renal excretion of uric acid.

2. Hyperuricemia without symptoms of gout usually does not provide a basis for discontinuing pyrazinamide.

3. Arthralgias and myalgias occasionally occur with pyrazinamide that are not due to gout or increased uric acid levels and need not prevent continuation of therapy.

Renal Manifestations

Rifampin

1. Rifampin can cause acute or chronic nephritis, with or without symptoms, and evidenced by proteinuria, hematuria, and urinary WBCs. Acute or chronic renal failure has occurred.

2. Urinalysis, BUN, and creatinine should be monitored serially in individuals with underlying renal disease given rifampin, and similar studies obtained promptly in any individual who evidences symptoms consistent with acute or chronic nephritis (e.g. systemic symptoms, low back pain, or red/dark urine).

Aminoglycosides and Capreomycin

Aminoglycosides or capreomycin are a frequent cause of renal injury in individuals treated with these drugs.

Other Anti-TB Medications

Isoniazid, pyrazinamide and ethambutol are not known to cause renal disease, although the blood levels of ethambutol (and cycloserine, aminoglycosides and capreomycin) may become markedly elevated in individuals with renal function impairment and may require additional monitoring.

Hematologic Manifestations

1. All first-line anti-TB agents rarely can lead to hematologic abnormalities. Thrombocytopenia is more often due to rifampin; although the other first-line drugs may depress platelets as well. A "flu-like syndrome" has been reported with rifampin, especially when it is used intermittently and is manifested by an acute episode with fever, chills, and muscle pain that may be associated with renal failure, severe anemia, thrombocytopenia and leukopenia.

2. Leukopenia has been caused by rifampin, isoniazid and pyrazinamide, and rarely, ethambutol. Hemolytic syndromes and other types of anemia have been encountered rarely.

3. If an individual on anti-TB drugs develops symptoms, signs or laboratory evidence of significant anemia, leukopenia, or thrombocytopenia that cannot otherwise be explained, it is prudent to discontinue all anti-TB drugs and refer the individual promptly for hematologic consultation.

Visual Manifestations

1. Ethambutol-induced optic neuritis occurs only rarely, and usually regresses completely when ethambutol is discontinued. It may progress, however, to severe visual loss if diagnosed late. In general, optic neuritis most commonly occurs in patients receiving higher doses of ethambutol (doses of ethambutol greater than 15 mg/kg body weight), longer duration of treatment, or in individuals with impaired renal functions since the drug is cleared largely by renal excretion.

2. The usual symptoms are loss of visual acuity for small objects (newsprint, sewing, etc.) and/or impairment of red-green color discrimination.

3. Ethambutol should be avoided, or used with caution and with frequent monitoring of vision and renal function, in subjects know to have, or are at risk of renal function abnormality, such as the elderly, diabetics, hypertensives, etc., and those with preexisting non-correctable visual loss. Serum BUN and creatinine should be obtained before ethambutol treatment on all that are at risk of renal disease. Serial tests of visual acuity and color vision are indicated for early detection of signs of optic neuritis; in addition, the patient should be asked about visual changes on each follow-up visit.

4. Ethambutol should be discontinued immediately if optic neuritis is suspected, and the patient referred for ophthalmology consultation if the visual impairment does not reverse promptly.

TB and HIV

Please see section 6, ATB and HIV@ for complete information regarding persons with TB and HIV.

Active TB in Pregnant or Lactating Women

Pregnant and lactating women with TB must be given adequate therapy as soon as TB is suspected. The preferred treatment regimen is isoniazid, rifampin, and ethambutol for 9 months (see, AFirst-line TB Drugs Dosages@ and ATreatment Regimens@. A minimum of 9 months of therapy should be given since pyrazinamide cannot be used in pregnant patients. Pyridoxine (vitamin B-6) should also be given to prevent peripheral neuropathy. The following drugs should not be used because they have either been shown to have harmful effects on the fetus or because the effects on the fetus are unknown: pyrazinamide, streptomycin, capreomycin, ethionamide, cycloserine, ciprofloxacin, ofloxacin, amikacin, clofazimine.

The small concentrations of TB drugs in breast milk do not have a toxic effect on nursing newborns, and breast-feeding should not be discouraged. Conversely, drugs in breast milk should not be considered effective treatment for disease or infection in a nursing infant.

Because rifampin may decrease the effectiveness of hormonal birth control methods, an alternate method should be used.

Drug Resistant TB

When an initial culture is identified as positive for MTB, a drug susceptibility test is performed. In this test the organism is incubated in the presence of a panel of anti-tuberculosis drugs. If the organism grows, then it is considered to be resistant to that drug. The test may take up to two weeks after the identification of MTB. It is crucial to identify drug resistance as early as possible to ensure appropriate treatment.

A person can either acquire a drug resistant strain of TB from another person (primary resistance) or can develop resistance as a result of inadequate treatment (secondary resistance). Non-compliance with drug treatment plays a major role in the development of drug-resistant TB.

Drug resistance presents difficult treatment problems. Treatment must be individualized and based on the patient=s medication history and susceptibility studies. Clinicians who are unfamiliar with the treatment of drug-resistant TB should consult with the CDPHE TB Program or with a TB expert.

Isoniazid-Resistant TB

In general, when isolated resistance to isoniazid is documented during the initial 4-drug regimen, the treatment regimen should be adjusted by discontinuing isoniazid and continuing the other 3 drugs for a total of 9 months. An alternate regimen is to treat with rifampin and ethambutol for 12 months.

Multi-drug resistant TB

Multi-drug resistant TB is TB that is resistant to at least isoniazid and rifampin. Unfortunately, adequate data are not available on the effectiveness of various regimens and the necessary duration of treatment for patients with organisms resistant to both isoniazid and rifampin. Moreover, many of these patients also have resistance to other first-line drugs (ethambutol, streptomycin, or pyrazinamide). Because of the poor outcome in such cases, it is preferable to

give at least 3 new drugs to which the organism is susceptible. **Clinicians should never add a single drug to a failing regimen**. Commonly, these patients will require a total of 2 years of therapy.

Information about second line drugs (i.e., drugs other than isoniazid, rifampin, pyrazinamide, ethambutol or streptomycin) and dosages may be obtained from the CDPHE TB Program.

How to Motivate People to Comply with Therapy

Poor adherence to TB medication regimens is a common problem and leads to inadequate treatment. The consequences of inadequate and incomplete TB treatment are serious:

- Prolonged illness and disability for the patient
- Infectiousness of the patient, causing continued transmission of TB in the community
- Development of drug-resistant TB
- Death

Many health care providers believe they can predict whether a particular patient will take medication as prescribed. However, research data indicate that providers, on the average, are correct only 50% of the time. Directly observed therapy (DOT) is therefore the standard method of providing treatment to all persons with active TB. In addition, DOT allows for the immediate detection of non-compliance so that actions can be taken to avoid treatment failure.

Health care providers must recognize that even with DOT, additional strategies and efforts are necessary for treatment success. It is important to use any tool available in order to promote adherence to therapy.

- Learn as much as possible about your patient's health history, beliefs and attitudes about TB, sources of social support, and barriers to treatment
- Work with an interpreter or a person of the same cultural background as the patient, if possible

- Look for early warning signs of future adherence problems (e.g., patient feels medicine is no longer needed because they are feeling well, difficulty in accessing health care)
- Designate a person to do DOT who does not have a strong emotional tie with the patient Suitable designees might include school nurse/staff, employee health, public health, or visiting nurse, work supervisor, clergy, or other responsible person)
- Provide effective education to patients and key individuals in the patient=s social environment
- Provide patient with needed health or social services or make referral to other health or social service agencies
- Use a team of personnel whose members work together to assist each patient in completing treatment
- Establish an efficient, patient-friendly clinic system for scheduling appointments, keeping records, and monitoring adherence
- Mutually agree on a time and location for DOT (be creative and flexible)
- Be aware of patients who may require techniques to assess for ingestion of medication (e.g., hiding pills in mouth, vomiting after pills swallowed)
- Encourage a social support system that enhances the patient=s adherence to treatment.
- Use incentives and enablers (see examples next page)

In summary, use all available strategies for maintaining adherence to DOT.
If, despite your best efforts, the patient does not adhere to DOT voluntarily, Colorado State statutes allow a public health official to require court-ordered DOT, involuntary quarantine, or isolation for treatment of TB (see, AQuarantine@).

Incentives and Enablers

Food	**Clothing**	**Services**	**Children**
Applesauce (in which to mix medicine)	Socks	Helping obtain birth certificate	Reading stories
Fruit	Gloves	Washing patient=s clothing	Painting child=s nails
Chewing gum	Stockings	Arranging building of wheelchair ramps	Tea party with child
Homemade cakes/cookies	Sweaters	Installing wood stove	Playing games
Milk	Coats	Helping obtain driver=s license	Chewing gum
Big Macs		Repairing bicycle	Charts with stars and stickers
French fries	**Personal Care**		Stuffed animals
Chicken snacks and dinners	Contraceptives (e.g., condoms)	**Automotive**	Grab bag with assorted treats
Whole, uncooked chickens	Razor blades	Battery	School supplies
Bread	Shaving cream	Gasoline	Storybooks
Eggs	Face cream	Motor oil	Basketball
Pickles	Powder		Crossword puzzle books
Vienna sausages	Makeup	**Seasonal**	
Ice cream	Nail polish	Homemade Valentine cookies	**Transportation**
Blow-Pops	Obtaining non-TB medicines	Easter baskets	Bus fare
Shrimp		Christmas baskets (food)	Bicycle
Canned food	**Household**	Birthday cakes	Paying a friend for transportation
Oatmeal cakes	Wood stove	Thanksgiving hams	Staff transporting patient to doctor
Pudding (in which to mix medicine)	Kerosene	Nurses dressed in Halloween costumes	
Steak dinner	Fuel oil for heat	Birthday cards	**Garden**
Sausage biscuits	Smoke alarm		Flowers
Beverages, soft drinks, juices	Cooking utensils		Flower bulbs
Coffee/Tea	Furniture		
Nutritional supplements (e.g., Ensure)	**Fishing Supplies**		**Money**
	Fishing pole		
	Crickets		
	Worms		

Source: Using incentives and enablers in the tuberculosis control program. Columbia: American Lung Association of South Carolina and South Carolina Department of Health and Environmental Control, Division of Tuberculosis Control, 1989.

Contact Investigation

Introduction

Contact investigation is an integral part of any TB program and one of the best ways to find people who have TB disease. According to the Centers for Disease Control and Prevention, 7-8 cases of disease are found for every 1000 contacts that are evaluated. Finding infected contacts that do not yet have disease and offering treatment for latent tuberculosis infection (LTBI) is important as well. On average, about 20% of contacts are found to have TB infection, but in some contact investigations as many as 80-100% of the close contacts may be infected. Successful contact investigation requires skills in patient assessment, counseling, interviewing, and evaluation. **Results of all TB contact investigation activities should be documented on the "TB Contact Investigation Record" (see "Forms") and submitted to the TB Program upon completion (including names and locating information for any out-of-state contacts identified). The information will be compiled and evaluated by TB Program management staff as part of ongoing program evaluation activities. This information is reported to the Centers for Disease Control and Prevention on an annual basis.**

Purpose

The purposes of contact investigation include:

- To identify persons who have TB disease so that they can be given treatment to stop further transmission
- To identify persons who have LBTI and offer treatment to prevent progression to disease
- To identify persons who are at high risk of developing TB disease and need treatment for LTBI until it becomes clear whether they have TB infection
- To identify the source of TB disease transmission
- To identify environmental factors that may contribute to the transmission of TB

Who is a Contact?

Contacts are persons exposed to someone with infectious TB disease. Exposure to TB is time spent with or near such a person and is determined by the duration, proximity, and intensity of the shared time. Contacts generally include family members, roommates or housemates, close friends, coworkers, classmates, and others. Public health agency staff usually identifies contacts by interviewing the person with TB and by visiting the places where that person spends time regularly.

When Is A Contact Investigation Done?

A contact investigation is a systematic procedure for tracing, testing, and evaluating persons who have been exposed to someone with infectious TB. **In general, a contact investigation should be done whenever a patient is found to have or is suspected of having infectious TB disease (e.g. symptoms and chest x-ray consistent with TB disease).** Infectiousness depends on a variety of factors, but is more likely when patients have:

- Cough
- Hoarseness
- Other symptoms of pulmonary or laryngeal TB
- Positive AFB smear or culture results for MTB (recent evidence suggests that transmission can occur in AFB sputum smear-negative cases as well)
- Cavity on chest x-ray
- Inadequate or no treatment

Young children with pulmonary TB disease are rarely infectious, so a contact investigation is generally not conducted for them. However, young children with pulmonary TB disease should be evaluated for infectiousness and contact investigation may be warranted in some circumstances.

In addition, a **source case investigation** (looking for the source of exposure) should be conducted to find the source of TB transmission when recent transmission is likely. This is

usually done when:

- A young child is found to have TB infection or disease
- A severely immunocompromised person who does not have a known history of TB infection is found to have TB disease
- A cluster of TB skin test conversions is found in a high-risk institution (e.g. health care or correctional facility)

A source case investigation is conducted to determine who transmitted TB to the child, index patient or persons in the cluster of skin test conversions, whether this person is still infectious, whether this person was reported to the health department or if others were infected by the same source patient.

Supervisory clinical and management staff should make decisions regarding prioritization of contact investigations. Setting priorities between two or more contact investigations is a decision that should be made based on the likelihood of infectiousness of the index case. If program resources are limited, priority should be given to contacts that were exposed to the most infectious TB patients or to those who are at highest risk for progressing to disease, if infected. CDPHE TB Program DOES NOT PAY for testing or follow-up for non-contacts (persons who have not shared time or were near a person with infectious TB).

Steps in a Contact Investigation

A successful contact investigation requires careful gathering and evaluation of detailed information, often involving many people. In general, contact investigations follow a process that includes these 9 basic steps:

1. Medical Record Review

   Review of the TB patient's medical record/information and information from the clinician to determine whether the patient has been infectious and, if so, when. Knowing when the patient was infectious helps to determine which contacts are at risk.

Information that should be collected includes site of disease, symptoms, approximate date of onset of symptoms, sputum smear and culture or other mycobacterial laboratory results (including dates of specimens and drug susceptibility results), chest x-ray results, TB treatment information (medications, dosages, and dates of treatment), and method of treatment (e.g. DOT vs. self-administered). Clinical and supervisory staff should determine the period of infectiousness after a complete assessment of the information is available.

2. Patient Interview (TB Case Interview)

The patient interview is one of the most critical parts of the contact investigation. If the interviewer does not communicate well enough with the patient to get accurate information about symptoms, places where patient spent time, and contacts, people who need evaluation and treatment may be missed. The interviewer should keep in mind that the patient first learns of their new TB diagnosis during the initial interview. The patient may be overwhelmed, fearful of their diagnosis, or still very ill and unable or unwilling to participate fully in an interview. Thus, follow-up interviews should be scheduled to educate patients and to complete a thorough contact investigation. Good communication (ask open-ended questions), good listening skills, patient education, and establishing and maintaining a trusting relationship are essential during all interviews.

The initial interview should occur **no more that 3 working days** after the case is reported. During the interview, the TB patient should be asked more about:

- Symptoms—type and onset; especially cough and sputum production
- Places where the patient spent time while he/she were infectious (e.g. household—including guests and visitors, work, school, leisure, recreation, transportation, incarceration, travel, medical/dental or beauty appointments)
- Any contacts
- How often and how long the contacts were exposed
- Locating information for the contacts

In addition, the patient should be asked about the characteristics of each place (room size, windows open or closed, time spent in each place, etc.) to help determine the risk that MTB was transmitted in each place. Written educational materials regarding TB should also be provided to the patient.

Some patients may be reluctant to identify some or all of their contacts. For example, a patient may not want to identify people who use illegal drugs with him/her. The interviewer should be sensitive to the patient's fears, explain the importance of testing the contacts, and **assure the patient that all information will be kept confidential (including the patient's name)**. A patient interview checklist can assist the interviewer obtain the correct information (see Appendix 5).

3. Field investigation

A field investigation means visiting the TB patient's home or shelter, workplace (if any), and other places where the patient said he/she spent time while infectious to identify contacts and evaluate the environmental characteristics of the places where exposure occurred. The public health worker should assess for:

- room size
- crowding
- ventilation
- contacts (especially children) and their locating information
- evidence of other contacts who may not be present (e.g. pictures of others who may live in the place, shoes left by others who may live in the house, maintenance/cleaning workers in the home, toys left by children)

Close contacts that are present should 1) receive a TB skin test and arrange for reading of the results; 2) be educated about the purpose of the investigation, basic TB transmission, risk of transmitting TB to others, and importance of testing, treatment, and follow-up for

latent TB infection and disease; and 3) be referred for medial evaluation, including chest x-ray and sputum collection if they have symptoms of TB.

4. Risk Assessment for MTB Transmission

The infectiousness of the TB patient is dependent upon the duration of time when the patient was infectious and estimated degree of infectiousness. The degree of infectiousness is estimated from information regarding the patient's symptoms, sputum smear results, and other conditions identified during the medical record review and patient interview. The greater degree of infectiousness, the more likely transmission will occur.

The risk of transmission in a particular space depends on the concentration of infectious droplet nuclei in the air. Small room size, crowding conditions, poor ventilation (no or little fresh air to dilute the droplet nuclei in a room), and lack of air cleaning systems increase the risk of transmission of MTB.

The length and closeness of exposure between the TB patient and a particular contact are key factors in assessing the contact's risk. Persons who frequently spend a lot of time with the TB patient or have been physically close to the patient are at higher risk of becoming infected.

5. Prioritization of contacts

To use time and resources wisely, the contact investigation should be focused on the high-priority contacts (contacts who are at greatest risk for developing TB infection or disease). These high-priority contacts include:

- **Close Contacts**--most likely to be infected based on risk assessment information (close, regular, prolonged contact with the TB patient while he/she was infectious, especially in small, poorly ventilated places)

- **High Risk Contacts**--contacts who are at high risk of developing TB, once infected (e.g. children less than 4 years of age, HIV-infected or other immunocompromised persons, and persons with certain medical conditions (see Chapter 1, page 1 footnote).

Contacts with less intense, less frequent or shorter durations of contact to the TB patient are classified as **other-than-close contacts** and should be given lower priority for testing.

6. Evaluation of Contacts

Evaluation of TB contacts includes at least a medical history and TB skin test. **Close contacts and high-risk contacts should be examined within 7 working days after the index case has been diagnosed.** Contacts should be asked about their history or treatment of previous TB infection or disease, documented previous TB skin test results, previous exposure to TB, risk factors for developing TB disease, and current symptoms of TB. All high-priority contacts should be given a TB skin test. **A reaction of 5 mm or greater is considered positive for contacts**. Contacts with a positive reaction should be further evaluated for TB disease (see "Contact Investigation Guideline" next page). In some cases, sputum inductions are necessary to obtain an appropriate specimen.

Contacts who have a previously documented positive TB skin test should not receive another test, but should be evaluated for symptoms of TB disease. Depending on the results of the evaluation, some of these contacts may be candidates for treatment of LTBI or disease. A recent chest x-ray should be obtained and interpreted before initiating any treatment.

Because it takes 2-12 weeks after TB infection for the body's immune system to react to tuberculin (window period), contacts who had a negative reaction on the initial TB skin test should be retested 12 weeks after their last exposure to the infectious TB patient.

Infants under 6 months of age may have a false-negative TB skin test reaction because their immune systems are not yet able to react to tuberculin. Thus, infants need careful clinical evaluation.

Contacts who have TB symptoms, are HIV-infected, have other immunosuppressive conditions, or are under 4 years of age should have a chest x-ray at the same time as the initial skin test to evaluate him/her for TB disease. This is because of their high risk of quickly developing TB disease. In addition, these close contacts should be considered for treatment of LTBI even if the initial skin test reaction is negative during the window period. Treatment may be discontinued if the 12-week follow-up skin test is still negative and the contact is not at continued risk for exposure to infectious TB.

Contacts who have an abnormal chest x-ray or symptoms of TB disease should have three early-morning sputum specimens, collected on three different days, for smear and culture examination, regardless of his/her TB skin test reaction.

7. Treatment and follow-up for contacts

The following contacts should be offered treatment for LTBI:

- Contacts with a positive TB skin test reaction and no evidence of TB disease
- High-risk contacts who have a negative TB skin test reaction who may develop TB disease quickly after infection (e.g. children under 4 years of age, HIV-infected people, other high-risk contacts)

Contacts recently infected with MTB are a high-priority for treatment for LTBI because they are at high-risk of developing TB disease (highest risk of developing TB disease is in the first 2 years after infection). HIV-infected contacts or other immunosuppressed contacts may be given a full course of treatment for LTBI, regardless of their skin test results, because of the possibility of a false-negative skin test result (inability to react to tuberculin due to a compromised immune system).

Contacts who have a positive sputum smear or chest x-ray result suggestive of current TB disease should begin treatment for TB disease.

Contacts who have started treatment for LTBI or TB disease should be monitored to ensure compliance and completion of treatment. Contacts with LTBI and at high-risk for progressing to TB disease should be considered for directly observed preventive treatment (e.g. children, HIV positive or immunosuppressed patients).

8. Decision About Whether to Expand Testing

After the highest-priority contact group has been evaluated for LTBI and TB disease, the contact investigation staff should evaluate the results of testing for evidence of recent transmission. Evidence of recent transmission is indicated by any of the following factors:

- High infection rate among contacts as compared to the local community positivity rate
- Infection in a young child
- A skin test conversion in a contact
- A secondary case of TB disease

To calculate the infection rate among a given group of contacts

1. Determine the number of contacts with newly-identified positive skin tests.

2. Determine the total number of contacts without a documented previous positive skin test. Subtract the number of contacts with a documented previous positive skin test from the total number of contacts.

3. Determine the infection rate. Divide the number of contacts with a new positive skin test by the total number of contacts without a documented previous positive skin test. Multiply by 100; the resulting percentage is the infection rate for the group of contacts.

4. Compare the level of skin test positivity rate in the local community (based on TB

Program estimates) to the infection rate for the group of contacts.

When there is evidence of recent transmission of TB in the first group of close contacts tested, the likelihood that MTB has also been transmitted to contacts with less exposure, increases. The testing should, therefore, be expanded to these contacts ("concentric circle approach"--see References, "Contact Investigations for Tuberculosis. Self Study Module 6, October 1999"). This should be done as soon as it becomes clear that transmission may have occurred. The decision about expanding contact investigation to the next group of contacts should be made by clinical and supervisory staff, based on an assessment of all available information.

On the other hand, if there is NO evidence of recent MTB transmission among close contacts, testing should not be expanded to the next group of contacts (e.g. new positive skin test rate among contacts is lower than or similar to the level of infection in the community, no young children have a positive skin test reaction, no contact skin test conversions have occurred, no contacts have TB disease). Once the infection rate among the group being tested is the same as the infection rate in the local community and there are no other factors indicating recent transmission, testing can be stopped.

9. Evaluation of Contact Investigation Activities

An evaluation of the contact investigation activities should be conducted with or by a supervisor to determine such things as:

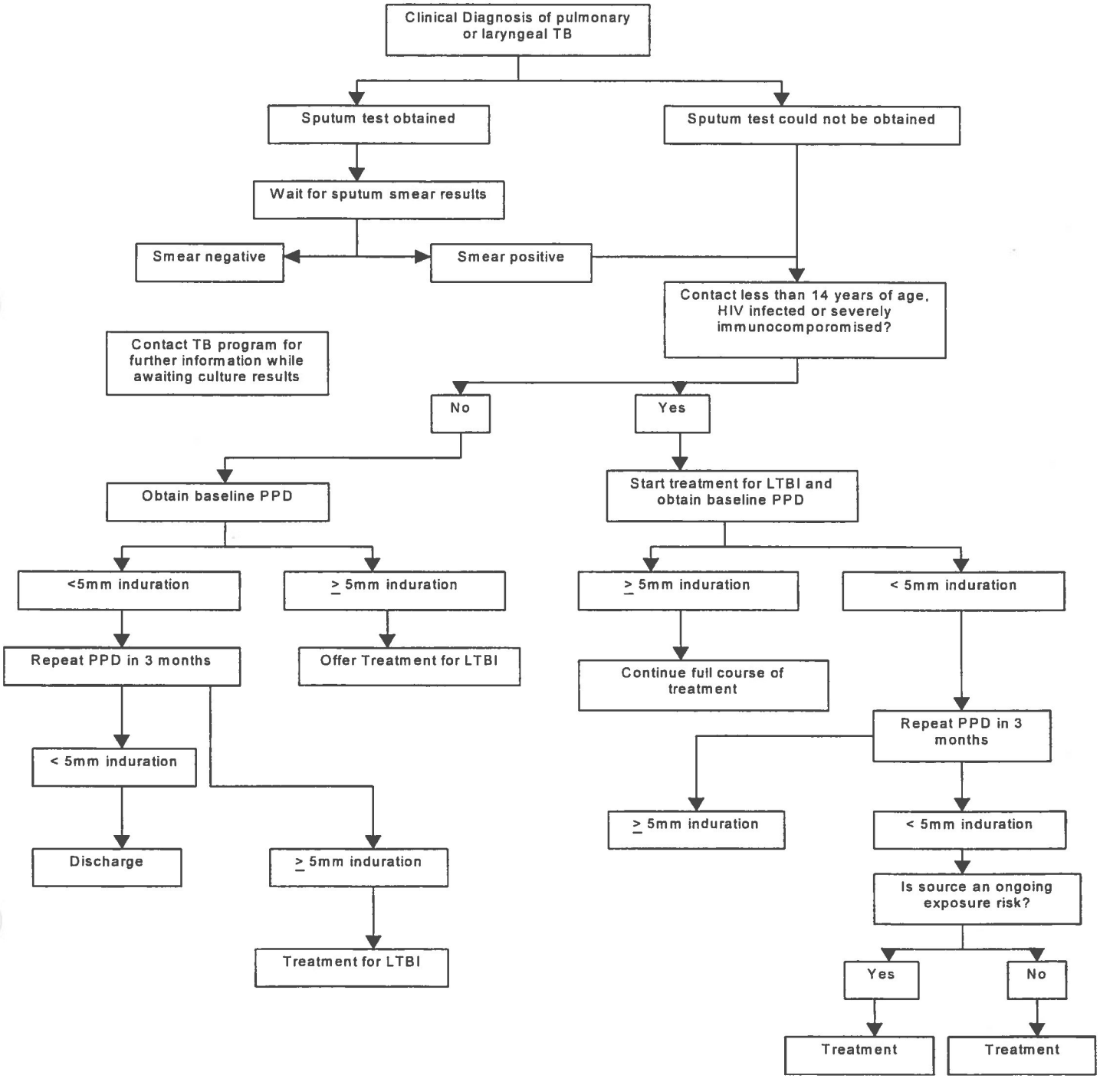
- Were an appropriate number of contacts identified?
- Were the highest-priority contacts located and tested?
- Was the contact investigation performed in all settings: household or residence, work or school, and leisure or recreational environments?
- Was the contact investigation expanded appropriately? Were contacts completely evaluated (including second skin test if needed) and given appropriate therapy if they had TB infection or disease?

- How many infected contacts completed a regimen of treatment for LTBI?
- Did all identified cases complete and adequate treatment regimen?

The answer to these questions will help determine how successful the contact investigation has been.

Results of all TB contact investigation activities should be documented on the "TB Contact Investigation Record" and submitted to the TB Program upon completion (including names and locating information for any out-of-state contacts identified). The information will be compiled and evaluated by TB Program management staff as part of ongoing program evaluation activities.

CONTACT INVESTIGATION GUIDELINE



Post-treatment Evaluation and Follow-up

All individuals should be evaluated after completion of anti-TB treatment. At this evaluation:

- X perform symptom review,
- X obtain PA and lateral chest x-ray and;
- X instruct patients to promptly report any new or recurring symptoms of TB post-treatment

After the follow-up evaluation, contact the CDPHE TB Program to obtain further follow-up recommendations (e.g. frequency of repeat chest x-rays) in collaboration with the patient=s primary care provider.

Non-Tuberculous Mycobacteria

Mycobacteria other than tuberculosis (non-tuberculous mycobacteria-NTM) are bacteria widely distributed in nature, primarily found in soil, water, and domestic and wild animals. These bacteria may be found as contaminants, colonizers, or may cause human disease. Most human infections with NTM appear to be acquired by aspiration or inoculation of the organisms from a environmental reservoir. There is little evidence to support person-to-person transmission, if it occurs at all. These bacteria have also been referred to as atypical mycobacteria or mycobacteria other than tuberculosis (MOTT). Drug resistance is commonly found in NTM organisms.

Clinicians and patients have also often used the term ATB@ to describe these infections, although ATB@ should only be used to refer to *Mycobacterium tuberculosis* (MTB). Therefore it is important to confirm the species of mycobacteria involved in a clinical situation. The TB Program provides services related only to MTB treatment, prevention and control. All clinical treatment and follow-up of NTM infections should be referred back to the patient=s primary care provider. Consultation by an expert in the treatment of NTM infections is recommended because of the complexity and length of treatment required for these infections (call the TB Program for references). The cost of care for NTM infections, including antituberculous drugs, is the responsibility of the patient.

NTM can cause serious infections in immunocompromised individuals, particularly those with AIDS or other types of impaired cellular immunity, or in individuals with underlying lung disease. More than 95 percent of NTM infections in AIDS patients are caused by one species of NTM, *M. avium* complex (MAC). MAC organisms may also be referred to as *M. avium-intracellulare* (MAI). Other NTM infections may be caused by species such as *M. kansasii, M. chelonae, M. fortuitum*, etc. The table, next page, summarizes important features of NTM.

Non-tuberculous Mycobateria and Human Disease (Continued on Next Page)			
Mycobacterium	**Environmental Source**	**Causes Human Disease?**	**Usual Site of Disease**
M. asiaticum	Animals	Yes	Lung
M. avium complex	Soil, water, swine, cattle, birds, fowl	Yes	Disseminated, lungs, lymph nodes
M. bovis	Humans, cattle (unpasteurized milk), other mammals	Yes	Lung, abscess, disseminated
M. gastri	Soil, water	Very rarely	-
M. flavescens	Soil, water	Very rarely	-
M. fortuitum/M. chelonae	Soil, water, animals, marine life	Yes	Skin, lungs
M. gordonae	Water	Very rarely	-
M. haemophilum	Unknown source	Yes	Skin
M. kansasii	Water, cattle, swine (rarely)	Yes	Lungs
M. malmoense	Unknown	Yes	Lungs
M. marinum	Fish, water	Yes	Skin
M. scrofulaceum	Soil, water, moist or liquid food stuffs	Yes	Lymph nodes
M. shimoidei	Unknown	Yes	Lungs

Non-tuberculous Mycobateria and Human Disease			
Mycobacterium	**Environmental Source**	**Causes Human Disease?**	**Usual Site of Disease**
M. simiae	Water, primate	Yes	Lungs
M. szulgai	?Fish	Yes	Lungs
M. terrae	Soil, water	Very rarely	-
M. triviale	Soil, water	No	-
M. ulcerans	Tropical grasses	Yes	Skin
M. xenopi	Water	Yes	Lungs

For additional questions about NTM, call the TB Program (303) 692-2638.

Specimen Collection and Transport

Many different types of specimens may be submitted for mycobacterial culture. The majority of the specimens submitted are from the respiratory tract. Tissue, normally sterile body fluids, urine, and gastric aspirates are other commonly submitted specimens. Blood and stool specimens may also be submitted for mycobacterial culture. The quality of specimens collected and the proper transport of those specimens to the laboratory are critical to the successful isolation of AFB (acid-fast bacilli).

Specimen Collection

Specimens should be collected and submitted in sterile, leak proof, disposable, appropriately labeled, laboratory-approved containers. All specimens can be collected in the sterile collection tubes supplied by the CDPHE Laboratory. Do not use waxed containers, as they may provide false-positive smear results.

Initial specimens should ideally be collected prior to the initiation of antimycobacterial chemotherapy. Specimens should be collected aseptically, or the collection method should bypass areas of contamination as much as possible in order to minimize contamination with indigenous flora. Avoid contamination with tap water or other fluids that may contain either viable or nonviable environmental mycobacteria, since saprophytic mycobacteria may produce false-positive culture and/or smear results.

Sputum: Sputum, both expectorated and induced, is the principal specimen obtained for the diagnosis of pulmonary tuberculosis. Collect an early-morning specimen, preferably 5-10 ml, from a deep, productive cough on at least 3, but usually not more than 5 or 6 consecutive days (24 or more hours apart). Processing of additional specimens does not seem to improve recovery. For expectorated sputum, patients should be instructed to cough deeply to produce specimens distinct from saliva or nasopharyngeal discharge. The patient should also be instructed to press the rim of the container under the lower lip at the time of expectoration to minimize the chance of contaminating the outside of the container. For induced sputum, use sterile hypertonic saline, and avoid sputum

contamination with nebulizer reservoir water to avoid possible false-positive culture or smear results due to saprophytic mycobacteria. Indicate on the requisition whether the specimen is induced or expectorated to ensure proper handling, as induced sputa appear watery and much like saliva. Pooled sputum specimens are unacceptable specimens for mycobacterial culture because of increased risk of contamination.

Bronchoalveolar Lavage Fluids and Bronchial Washings: Bronchial washings, bronchoalveolar lavage fluid, transbronchial biopsy specimens, and brush biopsy specimens may all be collected during bronchoscopy. Collect at least 5 ml of bronchial washing or bronchoalveolar lavage fluid in a sterile container. Avoid contaminating the bronchoscope with tap water. Frequently, bronchoscopy causes the patient to produce sputum spontaneously for several days after the procedure, and specimens collected a day or two after bronchoscopy enhance detection of mycobacteria.

Gastric Lavage Fluids: Aspiration of swallowed sputum from the stomach by gastric lavage may be necessary for infants, young children, and the obtunded. On each of 3 consecutive days, collect 5-10 ml of fluid in a sterile container without a preservative. Fasting, early-morning specimens are recommended in order to obtain sputum swallowed during sleep. Gastric contents are initially collected with a sterile suction syringe connected to a tube inserted in the stomach. Sterile saline (20-30 ml) may then be introduced into the stomach and aspirated as lavage fluid. The gastric contents and lavage fluid may be pooled in a sterile container. These specimens should be processed within 4 hours. If the specimens cannot be processed with 4 hours, adjust fluid to neutral pH with 100 mg of sodium carbonate immediately following collection. Unneutralized specimens are not acceptable, as acid is detrimental to the mycobacteria.

Blood: Cultures for the isolation of mycobacteria from blood are usually reserved for immunocompromised patients. The BACTEC 13A bottle is specifically designed for the recovery of mycobacteria from blood (contains a lysing agent). The 13A medium can be directly inoculated with 5 ml of blood. If blood needs to be transported before inoculation of BACTEC medium, use sodium polyanetholsulfonate (SPS) or heparin as an anticoagulant. Blood collected in EDTA or blood that is coagulated is **NOT** acceptable.

Urine: Collect the first morning specimens, either by catheterization or midstream clean catch, into a sterile container on 3 consecutive days. Appropriate cleaning of genitalia should precede collection. Organisms accumulate in the bladder overnight, and the first morning void provides best results. Specimens collected at other time are dilute and thus not optimal. A minimum of 40 ml of urine is usually required for culture.

Stools: Stool specimens (>1 g) should be collected in sterile, wax-free, disposable clean containers or transferred from a bedpan or from plastic wrap stretched over the toilet bowl and sent directly to the laboratory.

Body Fluids: Body fluids (cerebrospinal--CSF, pleural, peritoneal, pericardial, etc.) are aseptically collected by aspiration or surgical procedures. Collect as much as possible (10-15 ml minimum) in a sterile container or syringe with a luer tip cap. CSF culture requires at least 2 ml.

Tissues (Lymph Node, Skin, Other Biopsy Material): Aseptically collect at least 1g of tissue, if possible, into a sterile container without fixative or preservative. Do not immerse in saline or other fluid or wrap in gauze. For cutaneous ulcers, collect biopsy material from the periphery of the lesion. Specimens submitted in formalin are unacceptable.

Specimen Transport

All specimens should be refrigerated (except blood) prior to transport to the laboratory unless transport to the laboratory is anticipated within 1 hour of specimen collection. When shipping specimens:

1. Make sure that the specimen is in the appropriate sterile specimen collection container.
2. Seal the container and label appropriately.

3. Place the sealed specimen container and an appropriate laboratory requisition form into a second shipping container with ice packs (except blood).

3. Send specimens to:

CDPHE
Laboratory and Radiation Services
For US Mail: PO Box 17123
Denver, CO 80217
For Courier: 8100 Lowry Boulevard
Denver, CO 80220-6928

References

CDC. Core Curriculum on Tuberculosis: What the Clinician Should Know. Fourth Edition, 2000.

Colorado Revised Statutes, Part 5; 25-4-501 through 25-4-513.

Colorado Rules and Regulations Pertaining to Epidemic and Communicable Disease Control (6 CCR-1009-1).

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CDC. The use of preventive therapy for tuberculous infection in the United States. Recommendations of the Advisory Committee for Elimination of Tuberculosis. MMWR 1990; 39(RR-8):9-12.

CDC. Improving patient adherence to tuberculosis treatment. 1994.

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American Academy of Pediatrics, Report of the Committee on Infectious Diseases. 23rd ed. Elk Grove, IL: American Academy of Pediatrics, 1997.

Reves and Burman. Denver TB Clinic Medical Protocol.

Manual of Clinical Microbiology. 7th Edition, ASM, Washington D.C.

CDC. Contact Investigations for Tuberculosis. Self Study Module 6, October 1999.

Resources

For questions about active TB, call the TB Program (303) 692-2638, Denver/Metro TB Clinic (303) 436-7286, Francis J. Curry National TB Center in San Francisco (415) 502-4600, or the National Jewish Center Consultation Line (303) 398-1279.

What to Report

The following is a summary of reportable conditions related to tuberculosis in the state of Colorado:

CONDITION/TEST RESULT:	REPORTABLE BY WHOM:
Confirmed or suspected cases of active tuberculosis disease, regardless of whether confirmed by laboratory tests.	Physicians, health care providers, hospitals, other similar private or public institutions, or any other person providing treatment to the confirmed or suspected case must report **within 24 hours**. A report of test results by a laboratory does not relieve the attending physician of his/her reporting obligation.
Sputum smears positive for acid-fast bacilli (AFB) and cultures positive for *Mycobacterium tuberculosis* (MTB).	All laboratories that perform TB testing and in-state laboratories that send specimens for out-of state testing must report **within 24 hours**. The requirement to report specimen results are fulfilled if the specimens or isolates are sent to the State public health laboratory no more than two days after specimen collection or identification of MTB. A report by the physician does not relieve the laboratory of its reporting obligation.
Persons who are infected with TB (without active disease) and who are requesting treatment or chest x-ray interpretations through the TB Program (see "Treatment for LTBI").	Physicians, public health agencies, other health care providers requesting treatment or chest x-ray interpretations for a client through the TB Program.
A PPD skin test result of 5 mm induration or more, if it occurs in a health care worker, correctional facility worker, or detention facility worker who has had close contact to a known TB case.	Physicians, health care providers and health care facilities must report **within 7 days.**
Any patient on directly observed therapy that has missed one dose.	Medical providers and health care organizations must report **within 7 days**.

The TB Program or the local health agency will need the following information regarding a reported confirmed/suspect TB case or latent TB infection case for whom services/medications are requested (see ATB Surveillance and Case Management Report,@ section 5, AForms@):

Name
Date of birth
Address
Sex
Race/ethnic origin
Marital status
Site of disease
Symptoms/onset
Hospital admission information
Bacteriology results, date(s), and name of laboratory performing test(s)
X-ray results (if applicable)
HIV testing information
TB skin test results (in mm) and date of test
Drug therapy (medications used, dates given, mode of treatment)
Type of isolation/quarantine arrangements
Other pertinent medical & epidemiological information
Provider names/addresses/telephone numbers

Who to Notify Regarding Active/Suspect TB

All cases, suspect cases and positive laboratory results (see, AWhat to Report@) must be reported within 24 hours to the local health agency or the TB Program. Options for reporting a case include:

Telephone report to: (303) 692-2638 or after hours and on weekends at (303-370-9395).

Fax report to (303) 691-7749 **(Mon-Fri only)**

Via computer modem reporting system (CEDRS)[1] **(Mon-Fri only)**

1 Colorado Electronic Disease Reporting System (CEDRS) is available via the Internet by approved, trained users. Contact the TB Program for further information or requests for training/approved use.

References

Colorado Revised Statutes, Part 5; 25-4-501 through 25-4-513.

Colorado Rules and Regulations Pertaining to Epidemic and Communicable Disease Control (6 CCR-1009-1).

Resources

For questions about reporting procedures, call the TB Program (303) 692-2638.

How to Obtain...

Skin Testing Materials

The TB Program provides free PPD 5 tuberculin units (TU) for TB skin testing to county public health agencies, some federally funded clinics and migrant health TB screening programs in Colorado (Aplisol from Monarch Pharmaceuticals). Aplisol can be ordered from the TB Program by submitting an order form (see, "Forms"). **All other private providers, health care facilities and employers may purchase Aplisol from Monarch Pharmaceuticals at 1-800-776-3637 or Tubersol from Aventis Pasteur, Inc. at 1-800-822-2463.** The TB Program does not provide medical supplies for administering the PPD skin test.

Bacteriology Services

The CDPHE Lab provides testing for TB acid-fast bacilli (AFB) smears and cultures for any resident of Colorado suspected or known to have *Mycobacterium tuberculosis* complex (MTB) and identification for MTB and *M. avium* complex (MAC) only. Drug susceptibility testing is available only for MTB against INH, rifampin, ethambutol, pyrazinamide, and streptomycin. Further identification and drug susceptibility testing is provided by the Centers for Disease Control and Prevention (CDC) laboratory free of charge, or, as a fee-for-service by the National Jewish Center Laboratory. The provider will be given the option of further testing when final culture results are available.

Specimen containers can be ordered from the CDPHE Lab (303) 692-3074. Mailing and packaging instructions are included.

All specimens should be submitted with a microbiology laboratory form #102 (see, "Forms") and sent to:

CDPHE
Laboratory and Radiation Services
For US Mail: PO Box 17123
Denver, CO 80217
For Courier: 8100 Lowry Boulevard
Denver, CO 80220-6928

AFB smear results are available 1-2 working days after the specimen has been received at the CDPHE Lab. Final culture results are available in 1-8 weeks. All results are reported to the requesting provider and the TB Program.

Other Laboratory Services

Other laboratory services (e.g., blood chemistries, and complete blood counts) are provided for persons who meet pre-authorization requirements (see, "Billing and Reimbursement"). These laboratory services are obtained either through the local public health agency or the patient's private provider. Reimbursement requests for these pre-authorized laboratory services should be submitted to the TB Program.

Anti-tuberculosis Medications

All first-line anti-tuberculosis medications are provided to all persons with latent TB infection (LTBI) and suspected/known active disease, as state resources allow. These medications include: isoniazid, rifampin, ethambutol, pyrazinamide, streptomycin and pyridoxine (vitamin B-6). Second-line anti-tuberculosis medications, however, require pre-authorization (see, "Billing and Reimbursement"). No medications are provided for mycobacterial infections other than MTB.

Medications can be obtained through the TB Program or the local public health agency. A completed "Tuberculosis Surveillance and Case Management Report" form, chest x-ray result, physician prescriptions, and an "Anti-tuberculosis Medication Order" form is required before medications can be provided (see "Forms"). Please allow 10 days for processing of medication reorders or non-urgent, initial orders.

Chest X-rays

Persons with a positive skin test result or with suspect/known active TB can obtain chest x-rays through the local public health agency free of charge. **Exceptions to this policy: Employers are responsible for providing initial chest x-ray and interpretation services for employees who are tested through employment screening programs. Persons seeking permanent residency status through INS are responsible for the costs of their chest x-rays.** A patient's

private provider may also obtain chest x-rays if the patient meets pre-authorization requirements (see, "Billing and Reimbursement").

Pre-approved chest x-rays (see above) are read and interpreted by the State Medical TB Consultant and thus are not generally a reimbursable service. When immediate interpretations are needed (e.g., initial chest x-rays in-patients with suspected active TB) an outside interpretation may be obtained with pre-authorization from the TB Program.

A completed "Tuberculosis Surveillance and Case Management Report" form (see, "Forms") and the chest x-ray(s) must be submitted to the TB Program to obtain approved chest x-ray interpretations and follow-up recommendations. If available, old chest x-rays should also be submitted for comparison. Chest x-ray readings and follow-up recommendations will be printed on the "Tuberculosis Surveillance and Case Management Report" form and returned to the submitter.

Effective Language Interpreters

Language interpretation services may be obtained fee-for-service through the interpreter banks at:

1) Asian Pacific Center for Human Development (303)-393-0304
2) Justice Information Center (303)-623-5950
3) AT&T Language Line 1-(800)-528-5888
4) All Language Services (303)-758-2202

Refugee interpretation services are available free of charge through the Colorado Refugee Services Program (303)-863-8211.

Local community organizations may also be able to provide information regarding other available interpreter services.

Patient Education Materials

The TB Program provides some free patient education materials and can provide samples of other materials that may be purchased (see, "Patient Support").

TB Program Billing and Reimbursement

The TB Program provides reimbursement for specific medical procedures, chest x-rays, laboratory testing, other diagnostic/medical monitoring procedures, TB medications, and quarantine services related to the diagnosis, treatment, and control of TB. The following outlines the pre-authorization requirements, reimbursable procedures and tests, current reimbursement rates, and billing procedures.

Pre-Authorization Requirements

Some services related to the diagnosis and treatment of TB are subject to pre-authorization prior to reimbursement by the TB Program. The same services do not require pre-authorization if provided through a local public health agency (see AReimbursement for Chest X-rays and Chest X-ray Interpretations@ and AReimbursement for Laboratory Testing@ below). Authorization for reimbursement of services may depend on the client=s health insurance status, income, and the TB Program funding resources.

The TB Program reserves the right to deny any and all costs for services without appropriate approval. Immigration and Naturalization Services (INS) physical examinations are not an approved service for reimbursement. The TB Program, however, currently allows for chest x-ray interpretations and other public health follow-up related to TB.

To obtain pre-authorization for services, contact the TB Program at (303)-692-2638. A TB Program representative will review the request and provide verbal authorization. Billings for pre-authorized service(s) should be done according to the procedures outlined in the ABilling Procedures@ section below.

Reimbursement for Medical Procedures

Reimbursement for all medical procedures related to the treatment for TB requires pre-authorization from the TB Program. Medical procedures currently subject to reimbursement include:

- Physical examinations prior to initiation treatment of active TB disease or latent TB infection (LTBI)
- Medical monitoring for active TB patients
- Examinations for patients experiencing potential adverse effects related to TB medication
- Medical procedures required for the diagnosis of active TB (sputum inductions, bronchoscopies, gastric washings, or other invasive specimen collection procedures)
- Directly observed therapy (DOT) visits in the office or in the field

Reimbursement for Chest X-rays and Chest X-ray Interpretations

Reimbursement for chest x-rays are considered automatically approved for persons with a positive TB skin test or with suspected active TB when the request is initiated through a local public health agency and is in compliance with state TB follow-up recommendations (see "TB Skin Testing" and "Active TB"). Otherwise, reimbursement for all chest x-rays require pre-authorization from the TB program.

Chest x-ray interpretations are provided by the State Medical TB Consultant and thus are not generally a reimbursable service. Under special circumstances, when an outside interpretation is necessary, pre-authorization by the TB Program is required.

Chest x-ray views that are reimbursable include:

X Posterior-anterior (PA) and lateral (LAT) views on children less than 13 years of age

X PA on persons 13 years of age or older

All other views require pre-authorization by the TB Program.

Reimbursement for Laboratory Testing

Reimbursement for specific laboratory testing is considered automatically approved if initiated through a local public health agency in compliance with state recommendations. These tests include:

X Hepatic enzymes or up to 8 clinical multichannel chem panel (includes AST, ALT, LDH, total & direct bilirubin, alkaline phos, uric acid, and calcium)--baseline and repeat testing for all persons on treatment for active TB and for persons with LTBI who have specific risk factors (see "Treatment for LTBI: How to Monitor for Side Effects")

X CBC and Platelets -- baseline and repeats for symptoms of adverse reactions if taking rifampin

X Uric acid (included in chem panel)-- baseline and repeat for symptoms of hyperuricemia/gout if taking PZA

X Kidney function (BUN, creatinine clearance)-- baseline and monthly for all persons taking Streptomycin

X AFB smears, cultures, and susceptibilities -- Baseline and repeat (no more frequent than every two weeks) are available free of charge if tested by CDPHE Laboratory for persons with suspected/known active pulmonary TB. The State Lab only provides susceptibility testing for MTB. If the organisms identified are not MTB and the clinician requests susceptibility testing, the specimen can be forwarded to CDC (free of charge) or to National Jewish Laboratory as fee for service.

Reimbursement for all other laboratory testing or AFB smear/cultures performed by any other laboratory requires pre-authorization from the TB program.

Reimbursement for Other Diagnostic/Medical Monitoring Procedures

Reimbursement for all other diagnostic/medical monitoring procedures (e.g. CT scans) require pre-authorization by the TB Program. Exceptions include:

- Visual acuity and color vision testing -- automatically approved baseline and monthly for persons treated with EMB

- Hearing tests -- automatically approved baseline and monthly for persons treated with streptomycin

Reimbursement for TB Medications

All first-line TB medications are provided to all persons with LTBI and suspected/known active disease, as state resources allow. Second-line TB drugs, however, require pre-authorization from the TB Program. No medications are provided for mycobacterial infections other than MTB.

Reimbursement for Quarantine Services

Reimbursement for all quarantine services for TB require pre-authorization from the TB Program. Reimbursable services for quarantine may include security guard services and temporary detainment of an infectious person in order to protect the public.

Current Reimbursement Rates

The table on the following 3 pages outlines the current reimbursement rates for all services as described in this section. Most rates are based on the current Medicaid reimbursement rates and are subject to change.

Billing Procedures

All services that have been pre-authorized by the TB Program may be billed to:

Colorado Department of Public Health and Environment
TB Program
4300 South Cherry Creek Drive South, A-3
Denver, CO 80246

All bills must be submitted using an appropriate billing form (preferably vendor letterhead). The bill must include the patient's name, birth date, date of service, service provided, service charge, Current Procedural Terminology (CPT) code, and the vendor name and address. A W-9 form must also be provided for service reimbursement requests from new vendors. TB Program contract reimbursement forms are required for local health agencies submitting bills for TB Control personnel, laboratory tests, chest x-rays, medical consultation, and/or DOT visits. Contact the TB Program at (303)-692-2638 for further questions regarding billing of services.

TB PROGRAM REIMBURSEMENT RATES FOR SPECIFIC DIAGNOSTIC/MEDICAL MONITORING SERVICES

PROCEDURE	CODE	MEDICAID PAYS
Endoscopy-bronchoscopy diagnostic (flexible or rigid), with or without cell washing or brushing	31622	$167.15
Broncho-endoscopy with transbronchial lung biopsy, with or without fluoroscopic guidance	31628	113.66
Endoscopy- with transbronchial needle aspiration biopsy	31629	236.35
Endoscopy-with therapeutic aspiration of tracheobronchial tree, initial (e.g. drainage or lung abscess)	31645	167.15
Draw-venipuncture routine venipuncture of finger, heel, ear stick for collection of specimen(s)	36415	3.00
Radiology-chest; single view frontal	71010	14.14
Radiology-chest PA LAT (must be under 14 years of age, suspect or active TB case, or recommended by the TB Program to be eligible for reimbursement for this type of x-ray)	71020	 35.00 21.00
Radiology-apical lordotic procedure	71021	14.14
Radiology Diagnostic-fluoroscopy (separate procedure), up to one hour physician time, other than 71023 or 71034	76000	35.35

Fluoroscopy, physicians time more than one hour, assisting a non-radiologic physician (e.g., nephrostolithotomy, ERCP, bronchoscopy transbronchial biopsy)	76001	21.21
8 clinical chem tests multichannel (e.g. liver profile): Calcium, uric acid, total and direct bili, alkaline phos, LDH, AST, ALT	80008	12.02
Urine analysis	81003	3.18
Blood Count; manual differential WBC count includes RBC morphology & platelet est.	85007	4.89
Blood Count; automated differential WBC count includes RBC morphology & platelet est.	85023 85024 85025	9.77
Urine culture	87086	11.46
Culture, tubercle or other acid-fast bacilli, (e.g. TB, AFB, mycobacteria); any source, isolation only	87116	15.34
Lab, concentration plus isolation	87117	16.42
Culture, mycobacteria, definitive identification of each organism	87118	15.53
Tubercle bacillus (TB, AFB), sensitivity each drug	87190	5.87
Lab, fluorescent and/or acid fast stain for bacteria, fungi or cell types	87206	7.62
Audiogram-Comprehensive audiometry threshold eval & speech recognition	92557 92256 92553	28.00 14.00 14.00

Pulmonary function tests- out patient **office** second & third tests Pulmonary function test - out patient **hospital**	94664 94665	23.80 19.60 73% of billed charges
Office Visits- Initial	99201 99202 99203 99204 99205	22.34 35.58 49.22 73.31 92.10
Office Visits- Established	99211 99212 99213 99214 99215	11.82 21.56 31.50 46.00 73.44
DOT Visit (Directly Observed Therapy)	99211 99352	12.50 12.50

Forms

The following is a description of TB Program forms and instructions for completing them. Completed forms must be submitted to the TB Program at:

Colorado Department of Public Health and Environment
TB Program
4300 Cherry Creek Drive South, A-3
Denver, CO 80246-1530

Please note special instructions and contact the TB Program with additional questions. **All forms are available free of charge by calling the TB Program at (303) 692-2704.** Examples of all forms follow this table.

Name of Form	When is the Form Required?	Special Instructions
Anti-tuberculosis Medication Order Form (TB-61)	Required when ordering anti-tuberculosis medications.	1. Original physician prescriptions must accompany the form for all new drug orders or changes in treatment regimens. 2. A TB Surveillance and Case Management Report (or verbal case report) must be completed before medications for treatment of active disease or LTBI can be released. 3. Provide updated patient status information with each reorder. Dates that medications were given to patients must be completed on all reorders (bottom of TB-61—table)

Chest X-ray Request (TBC-50)	Required when referring a client for a x-ray that is to be billed to the TB Program	1. See "Billing and Reimbursement" to determine whether pre-authorization is necessary. 2. A representative of the public health agency must sign the form. 3. Indicate views authorized for reimbursement (CDPHE will not pay for extra views taken). 4. Send form with patient to radiology service provider and a copy to the TB Program.
Consent Form(s) – EXAMPLES	Examples of consent forms for TB skin testing and treatment for LTBI/disease are provided at the end of this section. These examples should be customized by local health agencies if they choose to use them. CDPHE does not provide standard consent forms.	Instructions for use are determined by each local health agency.
Consent to Release Confidential Information (TBC-25)	Required to release all confidential medical information related to LTBI and disease to the patient or a third party.	1. Patient must authorize the release of information.

Contract Reimbursement Statement	Used by local health agencies to request reimbursement for services outlined in the contract (e.g. TB Control personnel costs, chest x-rays, laboratory testing, other diagnostic or medical monitoring procedures--e.g. hearing/vision exams, TB Clinic physician fees, and directly observed therapy--DOT visits for suspect/confirmed active TB and pre-approved directly observed visits for treatment of LTBI.	1. Refer to your contract for specific billing instructions. All statements must include, at a minimum, the name of agency (payee), contract number, date(s) of service, description of service(s), reimbursement amount requested, local agency match, total expenditures incurred by agency (sum of local agency match and amount requested for reimbursement), and authorized signature. 2. Attach a report of the detailed DOT activity during the invoice period including patient name, number and date(s) of visits. 3. See "Billing and Reimbursement" section to determine whether pre-authorization is necessary.
Laboratory Request (LAB MICRO 102)	Required when submitting specimens for TB testing by CDPHE Laboratory.	1. Check both "CULTURE" and "MICROSCOPIC" if an AFB smear and culture are being requested.
Mantoux Skin Test & Preventive Treatment Record (Blue Cards)	If the client requires documentation of their TB skin test and/or treatment history.	1. Complete the card and give to the client. Counsel the client to keep this record for future reference.
Order for Medical Evaluation for Tuberculosis (TBC-21)	Required for mandated medical evaluations to rule out infectious TB.	1. See "Quarantine Procedures".

Order Form for TB Program Supplies (TB-1)	May be used to order forms, videos, audiotapes, posters, statistical reports, and written educational materials.	1. These supplies may also be obtained by calling the TB Program (see "How to Obtain").
Patient Follow-up Information and Transfer Form (TB-10)	Required when patient refuses therapy, completes therapy, stops therapy, is lost to follow-up or moves from county/state.	1. Fill out form **completely** and include patient's forwarding address/locating information, if known. 2. Attach/include information regarding recent diagnostic test results. 3. Include dates of therapy, drugs used and dosages given.
Quarantine or Isolation Order (TBC-22)	Required mandated quarantine or isolation.	1. See "Quarantine Procedures".
TB Contact Investigation Record (TB-3)	Used to document information regarding follow-up of contacts to an infectious TB case.	1. Must be submitted to the TB Program upon completion of contact investigation and follow-up.
TB Surveillance and Case Management Report Form* *This form is available in electronic format via the TB Colorado Electronic Disease Reporting System (CEDRS-internet access). Use of this electronic reporting system requires special training before use. Contact the TB Program with training requests.	Used to report a known or suspected case of TB. Also required when chest x-ray interpretations or treatment for LTBI are requested from CDPHE. A new form must be completed with each chest x-ray interpretation request. Can be used to report changes in a patient's status.	1. Fill out form **completely** (see form and completion instructions at the end of this section). Form can be completed using a pen or pencil. 2. Attach any pertinent copies of previous x-ray readings (reports), laboratory data, and other diagnostic test results. 3. Alternately, this information may be provided via phone report to the TB Program.

Tuberculin Skin Testing Material (PPD) Order Form (TB-2)	Used to order PPD for pre-approved, TB skin testing purposes.	1. Must be an agency pre-approved to receive PPD free of charge. 2. PPD provided by the TB Program cannot be used for testing of jail inmates, persons undergoing immigration examinations, or paid employees/volunteers of health care facilities, long term care facilities, drug treatment centers, correctional facilities, jails, homeless shelters, schools, and child care facilities. **The employer or facility is responsible for the cost of PPD for these groups.**

Record Retention

The CDPHE TB Program will maintain all state TB public health records for 25 years. Public health records will be available at the TB Program offices for 2 years beyond completion of case follow-up. All other records will be stored off-site and will require a minimum of 48 hours for retrieval.

Local TB records should be maintained at the local site according to current applicable record retention rules and regulations.

Technical Assistance

The public health entities (i.e., Organized Health Departments and County Nursing Services) are responsible for assisting the Colorado Department of Public Health and Environment (CDPHE) in preventing and controlling tuberculosis (CRS 25-4-501 to 25-4-513). Consultation regarding active tuberculosis management and treatment will involve the local patient's physician, the local medical advisor of the county nursing services, the local medical health officer of the organized health departments, and the Medical Advisor for the CDPHE TB Program (Dr. Ellen Mangione, 303-692-2613).

Nursing consultation[1] may be obtained from the following:

CDPHE TB Nursing Consultant - Gayle Schack - 692-2635

CDPHE TB Nursing Consultant – Barbara Hummel – 692-2647

CDPHE Community Nursing Section - 692-2356

Medical and technical consultation may be obtained from the following:

National Jewish Medical and Research Center
Lung Line - 1-800-222-LUNG or 303-355-LUNG

Denver TB Clinic, Denver Health - 303-436-7260 for menu
(ask to speak to RN Supervisor or RN)

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1 Some Public Health Nurses have minimal experience in TB case management due to low incidence of TB in specific areas of Colorado. Therefore, questions regarding nursing role, contact investigation, screening, treatment, tuberculosis management, etc. should first be referred to CDPHE TB Program Consultant. The other resources are listed for those RNs who have general questions regarding tuberculosis.

National TB Centers

Charles P. Felton National TB Center at Harlem Hospital (212)-939-8403
Francis J. Curry National TB Center, San Francisco (415)-502-4600
New Jersey Medical School National TB Center (973)-972-3270

Educational Materials

The following agencies provide tuberculosis education materials that can be reproduced locally.

PATIENT EDUCATION MATERIALS

1. **The Colorado Department of Public Health & Environment (CDPHE)**
   TB Section
   4300 Cherry Creek Drive South
   Denver, CO 80246
   Telephone: (303) 692-2638 FAX: (303) 691-7749

   One-page, multilingual fact sheets/brochures:

   "Tuberculosis Facts - You Can Prevent TB" (English & Spanish)
   "Tuberculosis Facts - TB & HIV (The Aids Virus)" (English & Spanish)
   "Tuberculosis Facts - The TB Skin Test" (English & Spanish)
   "Tuberculosis Facts - Exposure to TB" (English & Spanish)
   "Tuberculosis Facts - TB Can Be Cured" (Spanish only)
   "Mantoux Skin Test for Tuberculosis" (English, Spanish, Cambodian, Hmong, Laotian, Russian, Serbo-Croatian, Somalian, Tibetan, and Vietnamese)
   "Medicine for Tuberculosis Infection" (English, Spanish, Cambodian, Hmong, Laotian, Russian, Serbo-Croatian, Somalian, Tibetan, Vietnamese)
   "Tuberculosis Disease" (English, Spanish, Cambodian, Hmong, Laotian, Russian, Serbo-Croatian, Somalian, Tibetan, Vietnamese)

   Pamphlets:

   "Tuberculosis - A Handbook for TB Patients"
   "This Is Mr. TB Germ"
   "Tuberculosis - Get the Facts" (English & Spanish)
   "The Connection between TB and HIV" (English & Spanish)
   "TB/HIV: The Connection, What Health Care Workers Should Know"
   "Questions and Answers About TB"

PATIENT EDUCATION MATERIALS, CONT.

Videotapes:

"You Can Prevent TB" (available in Cantonese, English, Haitian Creole, Mandarin Chinese, and Russian)

Four-part video: 1. "You Can Beat TB," 2. "The Facts About TB," 3. "TB and HIV: The Connection," 4. "Think TB" (English only)

"The Facts About TB" (available in Cantonese and Haitian Creole, only)

2. **The American Lung Association of Colorado**
1600 Race Street
Denver, CO 80206
Telephone: 303-388-4327

There is a charge for ALA materials and an order form listing the prices is enclosed in the Appendix.

3. **Centers for Disease Control and Prevention, U.S. Public Health Service, Atlanta, Georgia**

A website is available for on-line ordering of patient educational materials at http://www.cdc.gov/nchstp/tb.

or

Copies of patient educational materials may be ordered by telephone 404-639-1819, FAX 404-639-8628 or by writing:

Information & Technology Services
National Center for HIV, STD & TB Prevention
Mailstop E-06
Center for Disease Control and Prevention
1600 Clifton Road N.E.
Atlanta, Georgia 30333

An order form listing available materials is enclosed in the Appendix.

HEALTH CARE PROVIDER MATERIALS

Publications:

1. Morbidity & Mortality Weekly Reports (MMWR)
   CDC publication with recent epidemiological information regarding communicable diseases

2. Controlling TB in Correctional Facilities

3. Core Curriculum on Tuberculosis: What the Clinician Should Know, Fourth Edition, 2000

4. "Diagnostic Standards and Classification of Tuberculosis in Adults and Children" (The official statement of the American Thoracic Society and CDC, July 1999)

5. "Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection" (The official statement of the American Thoracic Society and CDC, July 1999)

6. Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Facilities, 1994

All above publications can be obtained through the TB program or directly from the Centers for Disease Control and Prevention, U.S. Public Health Service, Atlanta, Georgia. A website is available for on-line ordering of health care provider educational materials at http://www.cdc.gov/nchstp/tb. Copies of health care provider educational materials may be ordered by telephone 404-639-1819, FAX 404-639-8628 or by writing:

Information & Technology Services
National Center for HIV, STD & TB Prevention
Mailstop E-06
Center for Disease Control and Prevention
1600 Clifton Road N.E.
Atlanta, Georgia 30333

An order form listing available materials is enclosed in the Appendix.

HEALTH CARE PROVIDER MATERIALS, CONT.

Audiotapes:

1. "Pediatric TB" (2000)

   Can be checked out by the TB Program at CDPHE

Video Tapes:

The TB Program at CDPHE can check out all the following videotapes:

1. "A Satellite Primer on Tuberculosis" (Five Part Set - June 1995)

   Can be checked out through the TB Program OR purchased for $25 per video or $125 for complete set:

   Video Communications Division
   Bureau of Health Promotion and Information
   Alabama Department of Public Health
   434 Monroe Street
   Montgomery, Alabama 36130-3017
   FAX: 334-240-3045 Telephone: 334-613-5300

2. "Droplets of Death: TB in the Workplace"

3. "Introduction to Interpreting" (two-part Set)

4. "Tuberculosis Skin Testing"

5. "Tuberculosis 2000: Fundamentals of Clinical Tuberculosis and Tuberculosis Control" (Three Part Set - February 1997)

7. Four-part video: 1. "You Can Beat TB," 2. "The Facts About TB," 3. "TB and HIV: The Connection," 4. "Think TB" (English version, for primary care physicians)

8. "How You Can Assess Engineering Controls for Tuberculosis In Your Health Care Facility"

9. "Satellite Primer Continued: Modules 6-9; "Contact Investigations for Tuberculosis," "Confidentiality in Tuberculosis and Tuberculosis Surveillance and Case Management in Hospitals and Institutions," and "Patient Adherence to Tuberculosis Treatment" (December 1999-February 2000)

10. "The Patient Guide to TB"

11. "Tuberculosis Protection for Healthcare Workers"

Statistical Reports (see sample in the Appendix):

1. **"Tuberculosis in Colorado"** (analysis through most current calendar year; available on CDPHE website, http://www.cdphe.state.co.us/dc/TB/Tbsummary98-99.PDF)

OTHER RESOURCES

Two regulatory agencies in Colorado with regard to tuberculosis control include:

1. **Health Facilities Division of CDPHE**
   Contacts: Jane Hermanson or Shelley Hitt
   Telephone: 303-692-2832 303-692-2840

2. **Occupational Safety & Health Administration (OSHA)**
   1999 Broadway, Suite 1690
   Denver, CO 80202-5716
   Telephone: 303-391-5858
   FAX: 303-391-5850
   Contact: Terry M. Terry, TB Coordinator, Region VIII

Note: A booklet entitled **"Protect Yourself Against Tuberculosis - A Respiratory Guide for Health Care Workers,"** Publication No. 96-102 may be obtained at the above address or call 1-800-35N-IOSH.

References

Colorado Revised Statutes, Part 5; 25-4-501 through 25-4-513.

State of Colorado Procurement Rules.

State of Colorado Fiscal Rules.

American Medical Association. Physicians' Current Procedural Terminology: CPT 1996.

American Medical Association. International Classification of Diseases. Ninth Revision, Clinical Modification: ICD-9-CM 1997.

Resources

For questions regarding Administrative Issues, call the TB Program (303) 692-2638.

General Comments on TB & HIV

When to Test for HIV Infection

It is considered standard of practice to determine HIV status of all persons diagnosed with active TB disease. Patients infected with the HIV-1 virus are at increased risk for developing tuberculosis compared to the general population. In addition, treatment regimens for active TB may differ, depending on the patient=s current HIV-related medications. In some instances, TB medications, which are provided by the TB Program, **may be withheld** if HIV testing is not offered within one month of initiation of TB treatment.

As is discussed below, all patients with HIV should be screened for tuberculosis. In addition, HIV testing and counseling should be offered to the following persons:

- all persons diagnosed with TB disease, regardless of age or apparent risk factors for HIV infection.
- all persons with positive TB skin tests (PPD) with HIV risk factors; and
- foreign-born persons from HIV endemic areas.

As much as possible, there should be coordinated activities between the HIV and TB sections of public health.

Tuberculin Skin Testing in HIV Infected Individuals

Tuberculin skin testing is outlined in Section 1 of this manual and describes how to administer, read, and interpret skin tests. This information applies to HIV positive as well as HIV negative individuals. Some general comments about tuberculin skin testing (TST) in HIV patients are listed below.

- As soon as possible after HIV infection is diagnosed, these clients should receive a TST unless previously tested and found to be TST-positive; those who are negative should be retested periodically, **especially those who belong to populations at high risk of exposure and those that have had their immune function restored because of effective antiretroviral therapy**
- Anergy testing (see page 1-14) is **no longer recommended as a routine component of TB screening among HIV-infected persons.** See section 1, page 14 for special circumstances in which to test for anergy
-

HIV Patients with Latent TB Infection (LTBI)

HIV infection is the strongest known risk factor for progression of latent TB infection (LTBI) to active TB disease. HIV persons with latent TB are 100 times more likely to progress to active disease than are those patients without HIV. Co-infected HIV and latent TB patients have a 7-10% **yearly** risk of developing active TB disease. Patients with only latent TB have a 10% **lifetime** risk of developing active TB disease.

Treatment for persons with latent TB infection is covered extensively in Section 2, "Treatment of Latent TB Infection," of this manual. There have been changes in relation to LTBI therapy in those infected with HIV. Directly observed preventive therapy (DOPT) should be used whenever possible. Preventive therapy taken correctly can reduce the risk of progression of LTBI to active TB disease in HIV individuals by 90%, just as is seen in patients without HIV infection.

Who is Eligible for Treatment of LTBI?

- HIV persons with tuberculin skin test reaction size of **≥5 mm** who have not previously received treatment for tuberculosis, regardless of age, and do not have active disease.
- HIV persons who are **close contacts** to active TB patients and who do not have active disease themselves, **regardless of age, TST results, or history of previous treatment for tuberculosis**.
- HIV persons with prior untreated or inadequately treated TB, regardless of age or TST results and who do not have active disease.
- In **some** situations, HIV persons with TST reaction size **<5 mm** may be **considered** to receive primary prophylaxis if they have ongoing and unavoidable risk of exposure to MTB (e.g. residents of prisons, jails, or homeless shelters).

Treatment of LTBI in Patients With HIV

Administering treatment for LTBI to patients with HIV is similar to administering LTBI treatment to patients without HIV, and the general comments beginning on page 2-4 apply. Some special considerations are listed in the following tables.

Treatment Options for Latent TB Infection Therapy in Patients With HIV

OPTION 1: Rifamycin (rifampin or rifabutin) plus pyrazinamide (PZA) therapy (**adults, only**). **Contraindicated** in pregnant patients. Approval of the state health department is necessary prior to beginning preventive therapy with a rifamycin-based regimens.

1. Rifampin 10 mg/kg (maximum 600 mg) and PZA 15-20 mg/kg (maximum 2 g) administered daily for 2 months for patients not receiving protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs). Rifampin is **contraindicated** with all PIs and NNRTIs

   or

2. Rifabutin 5 mg/kg (maximum 300 mg) and PZA 15-20 mg/kg (maximum 2 g) administered daily for 2 months. Rifabutin is **contraindicated** with ritonavir, hard-gel saquinavir, and delavirdine. An **alternative** is the use of rifabutin with indinavir, nelfinavir, amprenavir, efavirenz, soft-gel saquinavir and nevirapine. If nelfinavir, indinavir, or amprenavir is administered with rifabutin, the daily dose is reduced to 150 mg. If efavirenz is administered with rifabutin, the daily dose of is increased to 450 mg or 600 mg daily (see Section 2, "Treatment of Latent TB Infection," of this manual).

NOTE:

- Two-month regimens for treatment of LTBI that include rifampin or rifabutin are appropriate for HIV-positive adults who are likely to be infected with TB organisms susceptible to rifamycins.
- DOT is recommended when feasible for these 2-month therapy regimens.
- All patients should receive monthly evaluations while on therapy.
- Consider potential drug interactions when prescribing rifamycins to patients receiving HIV therapy with PIs and NNRTIs.
- Daily regimens of a rifamycin (rifampin or rifabutin) and PZA should consist of at least 60 doses to be administered for 2 months or up to 3 months.
- This regimen may also be given two times weekly. DOT must be used with twice-weekly dosing.
- Treatment regimens containing rifampin or rifabutin may decrease the effectiveness of hormonal contraceptives and therefore alternative forms of birth control are recommended.

OPTION 2: Isoniazid (INH) therapy. These regimens are safe to use with **all** antiretrovirals. This is the preferred therapy for children and pregnant women, with or without HIV infection.

1. INH (adults--5 mg/kg, maximum 300 mg; children ≤ 12 years--10-20 mg/kg, maximum 300 mg) **daily** for 9 months. INH should be administered with 25-50 mg Vitamin B-6 daily for persons with HIV infection, pregnant women, those with a seizure disorder risk factors or others at risk for peripheral neuropathy (diabetes, uremia, alcoholism, and malnutrition).

   or

2. INH (adults--15 mg/kg, maximum 900 mg; children ≤ 12 years—20-40 mg/kg, maximum 900 mg) **twice weekly** for 9 months (with 50-100 mg B6 twice weekly).

NOTE:

- DOPT should **always** be used with intermittent dosing regimens and is recommended when feasible for daily dosing.
- These regimens are safe to use with **all** antiretrovirals.
- This is the preferred treatment of LTBI for HIV-positive pregnant women, administered either daily or twice weekly. Such women taking INH should also take Vitamin B6 (pyridoxine) supplementation. Initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester, since HIV-positive women are at high risk for progression to active TB.
- All patients should receive monthly evaluations while on preventive therapy.

OPTION 3: Rifampin therapy. An alternative treatment regimen for HIV-positive patients who cannot tolerate INH or PZA.

1. Rifampin (adults--10 mg/kg, maximum 600 mg; children ≤ 12 years--10-20 mg/kg, maximum 600 mg) administered daily for 4 months (minimum of 120 doses administered within 6 months).

Special Situations

1. For HIV persons who are contacts of patients with **resistant** TB, contact the health department for recommendations.

2. After completing treatment for LTBI, follow-up (including chest x-rays) is not necessary, unless the patient develops symptoms of active TB or is re-exposed as a close contact to someone with active TB.

Monitoring Patients With HIV on Treatment for LTBI.

1. Clinical monitoring is required monthly for patients receiving INH and rifampin, alone. Clinical monitoring is required at weeks 2, 4 and 8 for patients receiving rifamycin (rifampin or rifabutin) and PZA. Monthly evaluations are recommended for HIV patients on treatment to look for:
    a. active disease
    b. drug interactions
    c. drug toxicities.

3. Obtain baseline liver function tests (SGOT/AST, SGPT/ALT, and total bilirubin) for **all** patients receiving INH or PZA. Repeat measurements if baseline is abnormal, patient is pregnant, patient is in the immediate postpartum period, patient is at high risk for adverse reactions, or patient has symptoms of adverse reactions.

4. Obtain baseline complete blood count (CBC), platelets, and liver function tests for patients receiving a rifamycin (rifabutin or rifampin). Repeat measurements if baseline results are abnormal or patient has symptoms of adverse reactions.

5. Obtain a uric acid for patients on PZA who develop acute arthritis.

Monitoring Compliance With DOPT

Refer to Section 2, page 13, "How to Monitor for Compliance With Treatment for LTBI".

HIV Patients With Active TB

Persons infected with HIV can rapidly develop TB disease because of a weakened immune system. Additionally, HIV co-infection is associated with a higher mortality rate due to tuberculosis when effective treatment is delayed and if directly observed therapy (DOT) is not used.

There have been new developments over the past few years in the realm of HIV disease, which have impacted on the treatment of TB. In particular, the previously recommended practice of stopping protease inhibitors while patients received rifampin based TB treatment, is **no longer recommended.** Stopping therapy for HIV leads to increasing viral loads and simply dropping protease inhibitor (PI) therapy while continuing other antiretroviral therapy frequently will lead to drug resistance. If PI therapy is dropped without adding other antiretrovirals, the remaining therapy for HIV will, in most cases, be inadequate. Therefore, since alternatives are available, most patients with HIV and TB are candidates for full **concurrent** administration of antituberculosis and antiretroviral therapies. In many cases, this will mean substituting rifabutin or streptomycin for rifampin. The use of rifampin is **contraindicated** in patients taking PIs or non-nucleoside reverse transcriptase inhibitors (NNRTIs). There are reasons to treat TB and HIV concurrently. HIV-1 clearly has a negative impact on natural progression of TB. Recent studies also seem to indicate that TB enhances HIV replication and accelerates the natural progression of HIV.

TB disease in patients with HIV can present in unusual ways. For instance, almost any abnormality seen on chest x-ray may represent TB in patients infected with HIV, and patients with normal chest x-rays may have culture positive sputum results. Lymphatic and miliary TB are also more commonly found in patients with HIV. Lastly, extrapulmonary TB is frequently accompanied by pulmonary TB, and clinicians should have a high index of suspicion and obtain sputum tests on patients with HIV who present with extrapulmonary TB.

Pulmonary and extrapulmonary TB are among the conditions included in the 1993 AIDS Surveillance Case Definition. Any HIV-infected person with a diagnosis of TB disease should be reported as having TB and AIDS, (see, AReporting Procedures@).

In most cases of concurrent HIV and TB disease, six month therapy regimens are appropriate. When using a regimen that includes streptomycin, however, the recommended treatment length is extended to nine months. There are some situations in which prolonged therapy is recommended which may extend six month therapies to nine months, and may extend nine month streptomycin based therapy to twelve months. Lack of adherence to TB therapy, delayed

conversion of sputum cultures from positive to negative, and delayed clinical response may be indications to extend therapy. Decisions to extend therapy should be made on a case-by-case basis, and consultation with the TB program may be appropriate. Because of the complexities of treating both HIV and TB, it is recommended that treatment of these patients be directed by, or conducted in consultation with, a physician with extensive experience in the treatment of these diseases. Patients suspected of having active tuberculosis should be placed on appropriate medications as soon as possible, and infection control measures, such as isolation of the patient, should be followed as is appropriate. Ideally, patients should be given directly observed therapy (DOT).

Most of the basic information regarding active tuberculosis is covered in Section 3, "Active Tuberculosis," of this manual. Please refer to that section which will in most cases apply to HIV positive as well as HIV negative individuals. The following is additional information that pertains to HIV infected (and in some cases HIV noninfected) individuals with concurrent active tuberculosis.

Basic Guidelines for Patients With Active TB and HIV

1. Vitamin B-6 (pyridoxine) is recommended for individuals with HIV who receive INH as part of their treatment regimen.

2. On initial evaluation, obtain information regarding current, past, and future use of antiretroviral therapy as the following information applies:
   - Use of treatment regimens for TB that contain rifampin are **contraindicated** in patients taking protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs). If either a PI or an NNRTI is to be started **after** treatment with rifampin, a two week washout period may be necessary to avoid toxic drug interactions.
   - Use of treatment regimens for TB that contain rifabutin are **contraindicated** in patients taking ritonavir (a PI), hard-gel saquinavir (a PI), or delavirdine (a NNRTI).
   - Use of TB regimens that contain isoniazid, ethambutol, pyrazinamide, or streptomycin are acceptable to use with any combination of antiretroviral therapy.

3. Assess pregnancy status of female patients. Testing for pregnancy is recommended in potential childbearing females whose menstrual cycle is more than two weeks late.

4. DOT is recommended with **all** treatment regimens.

5. On initial evaluation, the following baseline laboratory readings should be obtained:
   - Complete blood count (including platelets),
   - Liver function tests (including SGOT/AST, SGPT/ALT, total bilirubin),
   - Uric acid level,
   - Blood urea nitrogen and creatinine.

6. Perform baseline and monthly visual acuity tests including test for red-green color perception for patients taking TB regimens that include ethambutol.

7. Perform baseline audiometry tests for those patients taking TB regimens that include an aminoglycoside (e.g, streptomycin, amikacin, kanamycin) or capreomycin.

8. Patients should be evaluated monthly for symptoms and signs of TB, response to therapy, and paradoxical reactions (see below). Patients should be educated and evaluated monthly on the adverse side effects of tuberculosis medications.

Dosage and Treatment Schedules for Patients with HIV and Active Tuberculosis

OPTION 1: six month **rifampin (RIF)-based** therapy. Contraindicated in patients taking PIs or NNRTIs.

INH/RIF/PZA/EMB daily for 8 weeks, then:
INH/RIF daily **or** 2-3 times/week for 4 months (18 weeks).
(or)
INH/RIF/PZA/EMB daily for 2 weeks and then 2-3 times/week for 6 weeks, then:
INH/RIF 2-3 times/week for 4 months (18 weeks).
(or)
INH/RIF/PZA/EMB 3 times/week for 8 weeks, then:
INH/RIF/PZA/EMB 3 times/week for 4 months (18 weeks).

Therapy may be prolonged to 9 months depending on the response to therapy (e.g, lack of conversion of cultures from positive to negative, or continued or worsening signs or symptoms of TB). Consult the TB program for questions concerning prolongation of therapy. Ethambutol (EMB) may be discontinued when susceptibility tests indicate susceptibility to INH and RIF. Streptomycin (**contraindicated** in pregnant women) may be substituted for EMB in all of the above regimens.

OPTION 2: Six month **rifabutin-based** therapy. Contraindicated in patients taking ritonavir, hard-gel saquinavir, or delavirdine.

INH/RFB/PZA/EMB daily for 8 weeks, then:
INH/RFB daily **or** 2 times/week for 4 months (18 weeks).
(or)
INH/RFB/PZA/EMB daily for 2 weeks, then 2 times/week for 6 weeks, then:
INH/RFB 2 times/week for 4 months (18 weeks).

Therapy may be prolonged to 9 months depending on response to therapy (e.g, lack of conversion of MTB cultures from positive to negative, or continued or worsening signs or symptoms of TB). Consult the TB program for questions concerning prolongation of therapy. If the patient is also taking indinavir, nelfinavir, or amprenavir, the daily dose of **rifabutin** is decreased from 300 mg to 150 mg, but the twice weekly dose of 300 mg stays the same. If the patient is taking efavirenz, the daily and twice weekly dose of **rifabutin** is increased from 300 mg to 450 mg.

OPTION 3: Nine-month **streptomycin-based** therapy. Contraindicated in pregnant women. Can be used with any protease inhibitor (PI) or nonnucleoside reverse transcriptase inhibitor (NNRTI). INH/SM/PZA/EMB daily for 8 weeks, then:
INH/SM/PZA 2-3 times/week for 7 months (30 weeks).
(or)
INH/SM/PZA/EMB daily for 2 weeks, then 2-3 times/week for 6 weeks, then
INH/SM/PZA 2-3 times/week for 7 months (30 weeks).

Therapy may be prolonged to 12 months depending on response to therapy. Consult the TB program with questions concerning prolongation of therapy. Streptomycin should be continued for the duration of therapy. If not possible, ethambutol should be added and the duration of therapy should be extended to 12 months (52 weeks). Consult the TB program for questions concerning substitution for streptomycin.

** For **drug-resistant** or **multi-drug-resistant** tuberculosis, contact the TB program for recommendations on treatment regimens.**

Dosages and Adverse Reactions to Tuberculosis Medications

Please see discussion and tables starting on page 3-18 of this manual for INH/RIF/EMB/SM and vitamin B-6 (pyridoxine) dosages and adverse reactions.

RIFABUTIN

Dosages:

- Adults 5 mg/kg (300 mg max dose) for daily or twice weekly administration.
- Children 10-20 mg/kg (300 mg max dose) for daily or twice weekly administration.

If patients are taking indinavir, nelfinavir, or amprenavir, the **daily** dose of rifabutin is reduced to 150 mg (in adults and children), but the **twice weekly** dose remains at 300 mg. (Even with the reduction in rifabutin, serum concentrations of indinavir and nelfinavir may be lowered and dosing of these two medications may need to be increased). If patients are taking efavirenz, the **daily and twice weekly** dose of rifabutin is increased to 450 mg.

Adverse Reactions:

- Rash
- Hepatitis
- Fever
- Thrombocytopenia
- Orange-colored body fluids
- Arthralgias
- Uveitis
- Leukopenia

Monitoring:

- Baseline CBC (including platelets), and liver function tests (SGOT/AST, SGPT/ALT, and total bilirubin).
- Repeat measurements if abnormal or if symptoms of adverse reactions occur.

  (Please see general section on managing adverse reactions starting on page 3-20 for more information.)

Paradoxical Reactions

Paradoxical reactions are temporary exacerbations of symptoms, signs, or even radiographic manifestations of tuberculosis that can occur among patients who have had their immune system restored by successful antiretroviral therapy. Despite enlarging lymph nodes, or worsening of chest x-rays or cutaneous lesions, the patients generally feel well. In addition, these reactions are **not** associated with bacteriological changes such as changing from negative to positive smears or cultures. All patients suspected of having paradoxical reactions should be evaluated to rule out other possible causes of treatment failure. Managing patients with mild paradoxical reactions may consist of symptomatic treatment without changing medical management of tuberculosis or HIV infection. There are cases of severe paradoxical reactions, however, that may require hospitalization and use of steroids.

Special Situations

1. Drug resistance: For drug-resistant or multi-drug resistant tuberculosis, contact the TB program for recommendations concerning treatment regimens.

2. Pregnancy: Treatment for pregnant HIV patients with tuberculosis should begin without delay. Although regimens that contain pyrazinamide are not recommended for treatment of latent TB infection, the benefits of TB treatment regimens containing pyrazinamide outweigh the risks, and therefore can be used in pregnant patients with active disease. Aminoglycosides (including streptomycin) and capreomycin are **contraindicated** in pregnancy.

3. Children: Treatment of HIV-infected children with TB should begin without delay, and ethambutol should generally be included in the initial treatment regimen.

4. Extrapulmonary TB: Most cases of extrapulmonary TB can be treated with the regimens as listed above, with durations as listed above. Certain extrapulmonary TB cases such as meningioma, bone, and joint TB, should be treated with a rifamycin-based regimen for at least 9 months.

5. Interrupted therapy: When therapy is interrupted for $\geq$2 months, sputum samples (or other clinical samples) should be taken for smear, culture, and drug-susceptibility testing.

6. Drug levels: Obtaining drug levels are not recommended, but in rare instances they may be helpful in management of treatment of tuberculosis in HIV infected individuals.

Infection Control

Infection control measures for persons who are infected with both HIV and TB are the same as for persons infected with only TB. All persons with HIV infection and undiagnosed pulmonary disease should be suspected as having TB. Appropriate precautions to prevent airborne transmission should be taken until TB is diagnosed and treated or ruled out. See, ATransmission Prevention Precautions@. These precautions are most important during and immediately after procedures that may induce coughing, such as bronchoscopy, sputum collection, aerosol induction of sputum and administration of aerosolized medications such as pentamidine.

Health care workers who have regular contact with persons with TB or HIV infection should participate in an ongoing TB screening program.

References

1. 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(RR-20):1-58.

2. Colorado Department of Public Health and Environment. Tuberculosis Surveillance and Screening for Long Term Care Facilities in Colorado. August 1997.

Resources

For questions regarding tuberculin skin testing, call the TB Program (303) 692-2638.