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# 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 tuberculosis (TB) disease.** Patients infected with the HIV-1 virus are at increased risk for developing TB compared to the general population. In addition, treatment regimens for active TB may differ, depending on the patient's current HIV-related medications.

As discussed below, all patients with HIV should be screened for TB. 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 tuberculin skin tests (TSTs) with HIV risk factors; and
- foreign-born persons from HIV endemic areas (contact the HIV Program at 303-692-2691)

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 who have had their immune function restored because of effective antiretroviral therapy**
- Anergy testing (see page 1-15) is **no longer recommended as a routine component of TB screening among HIV-infected persons.** See section 1, page 15 for special circumstances in which to test for anergy.

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## 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 LTBI patients have a 7-10% **yearly** risk of developing active TB disease. Patients with only LTBI have a 10% **lifetime** risk of developing active TB disease.

Treatment for persons with LTBI 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 TST reaction size of  $\geq 5$  mm who have not previously received treatment for TB, 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 TB.**
- 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 TB (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.

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## Treatment Options for LTBI in Patients With HIV

**OPTION 1:** 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  $\leq$  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  $\leq$  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. 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 2:** Rifampin therapy. An alternative treatment regimen for HIV-positive patients who cannot tolerate INH.

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

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## Special Situations

1. For HIV persons who are contacts of patients with **drug-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. Periodic evaluations are recommended for HIV patients on treatment to look for:
  - a. active disease
  - b. drug interactions
  - c. drug toxicities.
2. Obtain baseline liver function tests (SGOT/AST, SGPT/ALT, and total bilirubin) for **all** patients receiving INH. 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.
3. Obtain baseline complete blood count (CBC), platelets, and liver function tests for patients receiving rifampin. Repeat measurements if baseline results are abnormal or patient has symptoms of adverse reactions.

## Monitoring Compliance With DOPT

Refer to Section 2, page 12, “How to Monitor for Compliance With Treatment for LTBI”.

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## 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 TB 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 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 for rifampin. The use of rifampin is **contraindicated** in patients taking most PIs or delavirdine. 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 is 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, "Reporting 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

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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 TB 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.

**Most of the basic information regarding active TB 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 TB.**

### **Basic Guidelines for Patients With Active TB and HIV**

1. It is recommended that persons with HIV-TB and CD4 cell counts  $< 100/\text{mm}^3$  should not be treated with highly intermittent (i.e., once- or twice-weekly) regimens. These patients should receive daily therapy during the intensive phase, and daily or three doses a week during the continuation phase.
2. DOT is recommended with **all** treatment regimens.
3. Once-weekly administration of INH/rifapentine in the continuation phase should **NOT** be used in any patient with HIV infection.
4. Vitamin B-6 (pyridoxine) is recommended for individuals with HIV who receive INH as part of their treatment regimen.
5. 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 most protease inhibitors (PIs) and delavirdine. Rifampin can be used with efavirenz with two (2) nucleoside analogues or ritonavir (in a dose of at least 400 mg twice-daily) with two (2) nucleoside analogues. If a drug having an unacceptable drug interaction with rifampin is to be started **after** treatment with rifampin, a two-week washout period may be necessary to avoid inadequate drug interactions.
  - Use of treatment regimens for TB that contain rifabutin are **contraindicated** in patients taking hard-gel saquinavir (a PI) or delavirdine (a NNRTI).

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- Use of TB regimens that contain isoniazid, ethambutol, pyrazinamide, or streptomycin can be used with any combination of antiretroviral therapy, but are not recommended except in cases of rifamycin-mono-resistance or occurrence of a severe side effect from rifampin or rifabutin.
6. Assess pregnancy status of female patients. Testing for pregnancy is recommended in potential childbearing females whose menstrual cycle is more than two weeks late.
  7. 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.
  8. Perform baseline and monthly visual acuity tests including test for red-green color perception for patients taking TB regimens that include ethambutol.
  9. Perform baseline audiometry tests for those patients taking TB regimens that include an aminoglycoside (e.g, streptomycin, amikacin, kanamycin) or capreomycin.
  10. 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 TB medications.

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## Dosage and Treatment Schedules for Patients with HIV and Active Tuberculosis

**OPTION 1:** Six-month **rifampin (RIF)-based** therapy. Contraindicated in patients taking most PIs and delvirdine. Rifampin can be used with efavirenz plus two (2) nucleoside analogues; some experts would increase the dose of efavirenz to 800 mg once daily.

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

1. INH/RFB/PZA/EMB daily (5 or 7 days per week) for 8 weeks (40 or 56 doses respectively), then INH/RFB daily (5 or 7 days per week) **or** 2 times/week for 18 weeks (90, 126 or 36 doses, respectively).

(or)

2. INH/RFB/PZA/EMB daily for 2 weeks (14 doses), then INH/RFB/PZA/EMB 2 times/week for 6 weeks (12 doses), then INH/RFB 2 times/week for 18 weeks (36 doses).

Therapy may be prolonged to 9 months depending on response to therapy (e.g, lack of conversion of TB 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.

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

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**OPTION 3:** Should only be used if there is a rifamycin mono-resistance or a severe side effect to rifampin and/or rifabutin. Contraindicated in pregnant women. Can be used with any protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI). A 12-month regimen using this option is recommended.

1. INH/SM/PZA/EMB daily for 8 weeks (56 doses), then  
INH/SM/PZA 2-3 times/week for 10 months (88 or 132 doses).  
(or)
2. INH/SM/PZA/EMB daily for 2 weeks (14 doses), then  
INH/SM/PZA/EMB 2-3 times/week for 6 weeks (12 or 18 doses), then  
INH/SM/PZA 2-3 times/week for 10 months (88 or 132 doses).

Streptomycin should be continued for the duration of therapy. If not possible, ethambutol should be added and continued for the duration of therapy. Consult the TB program for questions concerning substitution for streptomycin.

## 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 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 600 mg.

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#### 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 TB 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 TB 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 TB, contact the TB program for recommendations concerning treatment regimens.
2. Pregnancy: Treatment for pregnant HIV patients with TB should begin without delay. Although regimens that contain pyrazinamide are not recommended for treatment of

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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 nine months.
5. Interrupted therapy: When therapy is interrupted for two months or longer, sputum samples (or other clinical samples) should be obtained 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 TB 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, "Transmission 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.

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## Resources

For questions call the TB Program (303) 692-2638.