

- I. **TITLE:** Protocol for TB Targeted Testing Activities and Treatment of Latent TB Infection (previously referred to as TB screening and preventive therapy).

**Important Change in Nomenclature:**

- Identification of persons with latent TB infection has previously been accomplished by widespread tuberculin skin testing of individuals or groups at variable risk for TB. In many situations, this screening was done with limited consideration of the risk for TB in the population(s) being tested. To focus on groups at the highest risk for TB, the term “**targeted tuberculin testing**” is used in these guidelines to encourage directed program activities.
- Although the terms “preventive therapy” and “chemoprophylaxis” have been used for decades, they have also been confusing. “Preventive therapy” has referred to the use of a simple regimen (usually isoniazid) to prevent the development of active TB disease in persons known or likely to be infected with *M. tuberculosis*, but it rarely results in true primary prevention (i.e., prevention of infection in persons exposed to persons with infectious TB). To describe the intended intervention more accurately, this guideline uses the terminology “**treatment of latent TB infection (LTBI)**” rather than “preventive therapy” or “chemoprophylaxis”.

- II. **TYPE OF STANDARD:** Service

III. **OUTCOME:**

Prevention of tuberculosis through targeted testing of populations at high risk for TB disease and the appropriate treatment of those persons identified from this testing with latent TB infection (LTBI).

IV. **PERSONNEL:**

Medical Doctor (M.D.), Doctor of Osteopathy (D.O.), Physician Assistant (P.A.), Advanced Registered Nurse Practitioner (A.R.N.P.), Registered Nurse (R.N.), Licensed Practical Nurse (L.P.N.), Health Services Supervisor (H.S.S.), Health Services Representative (H.S.R.).

Each discipline will perform activities within the constraints of their respective practice acts, job descriptions and protocols.

V. **SPECIFIC AREAS OF RESPONSIBILITY**

Florida Statute 392.51 documents the responsibility of the Department of Health and the respective county health departments (CHD) for the control and prevention of TB in the community.

The CHD Director and/or designee are responsible for the implementation of a TB control and prevention program within his/her respective health jurisdiction. In addition to ensuring that the first two priorities of TB control and prevention, (1) treatment until cure of all active cases and (2) contact follow-up and treatment until completion of therapy of latently infected close contacts) are effectively implemented, the CHD Director or his/her designee is responsible for the following:

- Follow Bureau of TB and Refugee Health/Centers for Disease Control and Prevention (CDC) guidelines for utilizing current surveillance information to

determine the community standard for those groups at high risk for TB in the community who should be targeted for tuberculin testing and treatment for latent TB infection.

- Follow Bureau of TB and Refugee Health/CDC guidelines for the treatment of LTBI.

## VI. COMPETENCIES

County Health Department TB care providers listed in section IV must have demonstrated knowledge of the basic principles and concepts related to effective TB targeted testing and the treatment of latent TB infection. Specifically, all of the following:

- The knowledge, ability and resources to epidemiologically identify those groups in their respective geographic areas of responsibility who are at highest risk for TB disease.
- The knowledge, ability, resources, and demonstrated competency to administer and read appropriate tuberculin skin tests (TSTs) for those high risk populations identified for testing.
- The knowledge, ability and resources to provide appropriate chest x-ray and TB diagnostic services for all individuals identified with latent TB infection and/or symptoms of active TB disease.
- The knowledge, ability and resources to ensure effective, medically appropriate treatment and follow-up for individuals at high risk for TB disease identified with latent TB infection.
- The knowledge, ability and resources to appropriately document and evaluate outcomes related to all of the above activities.
- The knowledge and ability to effectively discourage and, if appropriate, eliminate CHD support for tuberculin skin testing of populations at low risk for TB disease in the community.

## VII. RELATIVE PRIORITY OF TARGETED TESTING AND TREATMENT OF LATENT TB INFECTION IN TB CONTROL AND PREVENTION PROGRAMS

Three basic strategies are critical to the control and prevention of TB in Florida. These strategies are listed below, in order of priority, for TB control programs:

- **Priority 1:** Identifying and ensuring the completion of treatment to cure for persons reported and documented to have active TB disease.
- **Priority 2:** Contact investigation to identify, evaluate and treat infectious and/or potentially infectious TB cases. In addition, to identify those contacts infected with TB and initiate and complete therapy for latent TB infection.
- **Priority 3:** Targeted testing (TB skin testing) and treatment to completion of persons with latent TB infection determined to be at high risk for progressing to TB disease.

Although targeted testing of high risk populations for latent TB infection and completion of appropriate treatment have been documented to prevent TB cases and are critical to effective TB programs in many areas, **completion of TB treatment of known TB cases and appropriate contact investigations around infectious cases remain higher priority program activities.**

## VIII. GOALS AND OBJECTIVES

### **TB targeted testing of high risk populations and treatment of latent TB infection**

The goal of TB targeted testing and subsequent treatment of individuals identified with latent TB infection is to reduce the pool of infected individuals who are at high risk of subsequently developing and transmitting TB. Targeted testing of populations documented at high risk for TB disease and **providing and completing** appropriate treatment for persons identified with latent TB infection will be crucial to achieving the ultimate goal of eliminating TB as a public health problem in Florida. A basic premise of these Technical Assistance (TA) guidelines and current CDC guidelines is that **a decision to tuberculin skin test an individual is a decision to treat until completion if that person is found to be tuberculin positive.**

## IX. BASIC PRINCIPLES

### **A. TB Targeted Testing**

Traditional screening of groups for tuberculosis infection consisted of placing purified protein derivative (PPD) often without consideration of the individual client's risk of TB infection. This led to, at times, erroneous assumptions of TB infection in individuals at low risk for TB. The new recommendations now emphasize that TB targeted testing of persons other than members of high risk groups is **not recommended** because testing low risk persons diverts resources from other high priority activities and also because many positive tests in low risk persons do not represent latent TB infection. The goal of TB targeted testing programs must be clearly defined; this testing should be conducted to identify persons with latent TB infection who are at high risk for progression to disease and would benefit from treatment for latent TB infection. Testing programs also may provide epidemiologic data for assessing TB and its trends in a community, data for assessing the value of continued screening, and baseline data to help with assessment if subsequent exposure occurs. **Testing programs should not be undertaken unless necessary facilities for client evaluation and treatment are identified and made available and unless persons found to be positive are likely to complete treatment for latent TB infection.** **Although it is difficult to predict who is "likely to complete treatment", there are options/alternatives available that will increase the likelihood of completion. Utilizing directly observed therapy (DOT), applying case management principles to high-risk persons with LTBI, and using available short-course regimens are examples of specific alternatives that will increase the likelihood of a client completing treatment. However, these options should only be utilized for infected persons at high risk of progressing to disease.**

To the extent possible, members of high risk groups and their non-health department health care providers should be involved with health departments in the design, implementation, and promotion of testing programs. Implementation of such programs will be clearly enhanced by individuals who have linguistic and cultural familiarity with the population at risk.

There is still a role for screening for TB infection in all individuals, but this would involve screening for risk factors for TB infection and/or progression to disease. This can be accomplished with a questionnaire and observation. The PPD should be reserved only for those individuals who fall into high risk groups for progression to active TB if infected and for whom treatment for latent TB infection is to be prescribed as part of a targeted testing program.

As most TB control programs in Florida that report high or moderate TB morbidity do not have adequate resources to screen all persons in high risk groups, involvement of other health care providers in these activities, whenever possible, can be useful. These health care providers may provide tuberculin skin testing, other appropriate screening, and/or treatment for latent TB infection. Such collaborations will inevitably necessitate additional efforts by CHD staff to provide consultation and/or training in appropriate screening procedures, which could include symptom screening and/or the administration, reading, and interpretation of the TST and in recommended treatment protocols for completion of treatment for latent TB infection. Priorities for targeted testing activities should always be determined by assessment of available resources and the probability of infection and disease among groups in the community.

Flexibility is essential in defining high priority groups for testing. The changing epidemiology of TB indicates that the risk for TB among groups currently considered high priority may decrease over time, and groups currently not identified as at risk subsequently may be considered high priority. CHDs should identify community groups among whom TB and transmission of infection occur. Identification of these groups requires collecting and analyzing data on newly reported cases available as part of disease surveillance. For certain groups, the local CHD should conduct targeted testing. This would be particularly true for testing related to reported cases, specific high risk groups or settings related to potential disease outbreak situations.

CHDs must also assume the responsibility to provide appropriate, scientifically based alternatives to community providers when TST, x-ray and treatment for latent TB infection services are no longer recommended for or provided for low risk persons/clients. Although some general recommendations can be made, CHDs will likely need to evaluate situations on an individual basis. **The Bureau of TB and Refugee Health and A.G. Holley State Hospital are available to provide consultation in these efforts.**

**CHDs have the responsibility to set community standards for TB control and prevention, and therefore should take the lead in promoting and disseminating current CDC recommendations which are based on scientific, data driven assessments. Any other approach, however politically or socially expedient, could now be potentially considered as misinforming or, at least, misleading the community. Please consider the following recommendations:**

- Tuberculin testing should not be provided for low risk populations and treatment for latent TB infection should not be provided by CHDs for persons at low risk for disease in the community.
- Targeted tuberculin testing should not be provided for any population (even high risk) for which there is minimal opportunity for completing this treatment. However, alternative methods to improve completion rates (e.g. Short Course DOT (SCDOT), incentives-see below) should be contemplated and/or initiated when appropriate by CHDs for those groups at high risk for progression to TB disease.
- Minimize, with the intent to eliminate, no charge TST, x-ray and treatment for latent TB infection services for low risk individuals in the community.
- Consider Directly Observed Treatment for LTBI (DOT) for individuals at high risk for disease, (e.g., contacts, HIV infected, children, etc.).
- Consider short course (DOT) for selected high risk individuals at high risk for non-compliance. The State TB Physicians Network should be consulted prior to the utilization of this therapy), 1-800-4TB-INFO.
- Ensure appropriate, intensive follow-up for all high risk individuals placed on treatment for latent TB infection.

As mentioned previously, it is essential for CHDs to provide appropriate TB screening alternatives for those facilities, institutions, agencies and other non-CHD providers for whom CHD TB services are being reduced, changed or eliminated. In low risk settings, facilities could be provided with training in conducting symptom screening. TSTs and x-rays would only be provided when persons were found to have documented TB symptoms and/or medical conditions that increase the risk for progression to active disease. In certain high risk settings, symptom screening should also be utilized instead of TSTs as clients, although high risk, are not likely to complete a recommended course of treatment for LTBI. A good example of this would be homeless shelters where clients are exceedingly transient; TST testing is non-productive as clients would not complete treatment for LTBI. For these individuals symptom screening should be implemented with intensive follow-up of those found to be symptomatic. However, in shelters who provide extended training programs for clients lasting two or more months, targeted TB skin testing could be considered as there would be an enhanced likelihood of completing treatment for LTBI. A somewhat contrasting situation would be correctional employees and healthcare workers. Although these employees may not have conditions that lead to increased progression to disease, the development of disease in these employees found to be infected with TB would lead to significant spread to large number of individuals (including many that are immunosuppressed) which can be prevented by initiation and completion of treatment for LTBI. In addition, monitoring of conversion rates among these employees provides administrative assessment of effectiveness of infection control procedures at these facilities.

Routine TB tuberculin skin testing is not currently recommended for any age level for students in Florida schools/universities. Any such testing in schools/universities should follow the guidelines as previously discussed. Testing should only be conducted for those students documented at high risk for disease and those who are likely to complete a recommended course of treatment for LTBI if found to have TB infection.

Routine TB skin testing is also no longer recommended for pregnant women unless they are considered at high risk for TB disease. In some areas in Florida it has been the practice of hospitals not to permit infants born of TB infected women to return to the home environment unless on-site family members are tuberculin tested by the local CHD. This practice is no longer recommended as these activities have been documented to be unproductive and not cost effective for CHDs. Hospitals may opt to interview these mothers concerning the presence of symptoms in the mother and/or other close family members. If symptoms of active TB disease are suspected in anyone who may have close contact with the infant, referrals to the CHD need to be considered.

**Widespread TB targeted testing is not likely to be a cost effective option in most low morbidity Florida communities.** TB control resources are limited in such communities and should be primarily utilized for active disease surveillance and immediate follow-up, treatment completion until cure and contact investigation for reported TB suspects, cases and contacts. Resources in low morbidity communities should not be utilized for tuberculin testing and treatment for latent TB infection in low risk populations, as such activities would likely inhibit these higher priority activities. Certain population groups may be at high risk in some communities in the state and not in others. Specific populations at high risk are primarily those in which TB cases have been identified locally. Local TB programs should carefully review appropriate data related to TB cases and outcomes of current and previous testing programs and not anecdotal information to determine risk groups. However, TB programs in low morbidity communities should remain vigilant for new occupations, industries or other situations which would result in an influx of persons at high risk for TB. In such situations, targeted testing initiatives may need to be considered.

***Please consult the Bureau of TB and Refugee Health or the TB Hotline (TB Physicians Network) 1-800-4TB-INFO when such a situation is suspected.***

### **Florida Department of Corrections**

The Florida Department of Corrections has an active TB screening and prevention program within their 110 facilities statewide. The Bureau of TB and Refugee Health supports and applauds these efforts to prevent and control TB within their facilities and appreciates that these activities help prevent disease transmission in the community. The DOC program includes TSTs for all new inmates, a retest within 3 months, and annual testing. Contacts to active TB cases, those with known HIV infection, and other immunosuppression (if known), are considered infected if found to have 5 or more mm's of induration, all others are considered infected if found to have 10 mm's of induration. Most medically eligible infected inmates, as well as all HIV infected inmates are placed on 9 months of isoniazid therapy for latent TB infection.

As would be expected a number of inmates receiving this therapy are discharged prior to the completion of therapy. All such inmates will be referred by DOC to their local CHD for completion of therapy. Many of these released inmates are likely at higher risk for TB, but some have also been documented to be non-adherent to treatment subsequent to their discharge. Although the extent of follow-up of these released inmates must be determined by each CHD based on their available resources, the Bureau of TB and Refugee Health recommends the following:

- All released inmates voluntarily reporting to the CHD and remaining compliant should be offered treatment until nine months of therapy is completed
- All released inmates who are HIV positive or are known contacts to active TB, should be actively followed by CHD staff to ensure at least six months of INH therapy is completed, nine months would be desired when possible.
- CHD TB staff should consider at least an initial effort to contact all referred, discharged inmates to convince them to complete at least six months of LTBI therapy, as always nine months would be desirable. Repeated efforts to follow non-compliant HIV negative released inmates would not likely be cost effective.

Prior to release some inmates are placed in work release programs. These inmates are not routinely provided continuing therapy by DOC even though they are still under the jurisdiction of DOC. Such inmates may be brought to the CHD by DOC staff for continued therapy for LTBI. The above recommendations should also be considered for the follow-up of these work release inmates.

***Please call the Bureau of TB and Refugee Health at 850-245-4350 if you have questions or concerns related to this activity***

TB symptom screening is also conducted to identify persons who have clinical disease and need treatment. Such screening is usually limited to populations where significant disease has been reported and/or in populations considered at very high risk for disease. The Mantoux skin test is not a recommended method for the purpose of screening for active TB disease; as an average of 10 - 25% of clients with active disease have a negative reaction to the tuberculin skin test. Chest radiography is the preferred screening method when the objective is to identify persons who have current pulmonary TB and when treatment for latently infected persons is not the primary goal, e.g. high turnover jails and homeless shelters. If chest radiography is not readily available, appropriate symptom screening may be effectively substituted to identify persons for subsequent diagnostic workup.

#### **B. Tuberculin Skin Test**

Although the tuberculin skin test is still the only method for detecting *M. tuberculosis* infection, the test is neither 100% sensitive nor 100% specific. Sensitivity is a test's ability to identify correctly those persons who have a condition (e.g., those infected with TB). Specificity is a test's ability to identify correctly those persons who do not have a condition. Based on the sensitivity and specificity of the purified protein derivative (PPD) tuberculin skin test, and the prevalence of TB in different groups, three cutpoints have been recommended for defining a positive tuberculin reaction:  $\geq 5\text{mm}$ ,  $\geq 10\text{mm}$  and  $\geq 15\text{mm}$  of duration.

Although not frequently documented, a certain percentage of reported tuberculin reactions may be caused by errors in administering the test or in reading results. When unexpected positives occur, it is appropriate to consider this and review testing and procedures involved. In some circumstances, re-testing certain individuals may be considered prior to conducting extensive investigations involving further tuberculin testing and expanded x-ray services. In addition, although also infrequent, there have been clusters of unexpected positive

tuberculin skin tests reported in low risk populations, which repeat testing with a new antigen seemed to indicate that initial reactions were false positive reactions. **The staff of the Bureau of TB and Refugee Health and A.G. Holley is available to provide consultation in any of these situations.**  
**(See TA Guideline, Tuberculin Skin Testing (TST) for guidelines for TST reading/interpretation)**

### **Previous Vaccination with BCG**

Tuberculin skin testing is **not contraindicated** for persons who have been vaccinated with BCG, and the skin-test results of such persons can be used as described to support or exclude the diagnosis of *M. tuberculosis* infection. However, no method can reliably distinguish tuberculin reaction caused by vaccinations with BCG from those caused by natural mycobacterial infections. Therefore, a positive reaction to tuberculin antigen in BCG-vaccinated persons indicates infection with *M. tuberculosis* when the person tested is at increased risk for recent infection or has medical conditions that increase the risk for disease.

### **Energy testing in persons infected with HIV**

Energy testing is **not** recommended for routine use in persons who are infected with HIV or otherwise immunocompromised. However, it may assist in guiding individual treatment decisions in selected situations.

### **Identification of Persons at High Risk for Progression of TB Disease, if Infected**

1. Groups that have the **highest priority** in all areas of the state are persons who are the most likely to progress to disease once infected. These include:
  - Recent contacts of persons who have suspected or confirmed infectious TB,
  - Persons who have human immunodeficiency virus (HIV) infection or risk of HIV infection,
  - Persons who have fibrotic chest radiographs consistent with prior, healed TB, persons who have a positive skin test and parenchymal lung scarring are at high risk for TB if they have not previously received and completed TB treatment for active TB disease or latent TB infection, and
  - Persons with organ transplants and other immunosuppressed clients (e.g., persons receiving the equivalent of  $\geq 15$  mg/d of prednisone for 1 month or more).

**The TST cutpoint for persons in these groups is  $\geq 5$ mm.**

2. Another high priority group that has a higher probability of progressing to disease after infection has occurred includes:
  - Persons whose tuberculin skin tests have been **documented** to have converted from negative to positive within a period of 2 years are presumed to have been infected recently and are considered to be at greater risk to develop disease. Trials have documented that persons most frequently develop disease within the first two years subsequent to infection.



**The TST cutpoint for converters is a documented increase of 10mm or more during a two year period.**

3. Other groups at high risk to progress to disease if infected include:
- Recent immigrants (i.e. within the last five years), foreign-born persons who have immigrated from areas of the world with high rates of TB have incidence rates that approach those of their countries of origin for the first several years after arrival in the U.S. and should be considered for targeted testing and treatment for LTBI. These rates decrease as the length of time increases in the U.S. The decision to consider foreign-born for targeted testing subsequent to the first few years should be based on local epidemiology and the ability to complete treatment for latent TB infection.
  - Persons who inject illicit drugs or other locally identified high risk substance users (e.g., crack cocaine users).
  - Persons who have medical risk factors known to increase the risk for disease if infection occurs:
    - ✓ diabetes mellitus,
    - ✓ chronic renal failure,
    - ✓ some hematologic disorders (e.g., leukemias and lymphomas),
    - ✓ other specific malignancies (e.g., carcinoma of the head, neck, or lung),
    - ✓ weight more than 10% below ideal body weight,
    - ✓ silicosis,
    - ✓ gastrectomy,
    - ✓ jejunioileal bypass.
  - Mycobacteriology laboratory personnel.
  - Residents and employees of high risk congregate settings (e.g., correctional facilities, mental institutions, other long-term residential facilities, and shelters for the homeless).
  - Health-care workers who serve high-risk clients.
  - Certain locally identified medically underserved, low income populations.
  - High risk racial or ethnic minority populations, as defined locally.
  - Children younger than 4 yrs of age or infants, children and adolescents exposed to adults at high risk.

**The TST cutpoint for persons in these groups is  $\geq 10$ mm.**

4. **The TST cutpoint is  $\geq 15$  mm for persons with no identified risk factors.** These individuals should not be routinely tested. The decision by CHDs to test and place such individuals on treatment for latent TB infection should be given careful consideration, even if there is a high likelihood that the treatment could be completed.

### **C. Treatment of Latent TB Infection (LTBI)**

The objective of any TB targeted testing initiative is to identify those individuals at increased risk for TB disease for further diagnostic workup and to complete treatment for all high risk persons identified with latent TB infection who are medically appropriate for treatment. Unless this objective is successfully achieved, a targeted screening effort cannot be considered as either cost effective or effective in preventing or controlling disease in the community. Unfortunately, many individuals who currently begin treatment for latent TB

infection in Florida fail to complete this therapy. There are many reasons individuals do not complete this therapy. These include:

- Treatment for latent TB infection is elective for the client,
- Treatment is lengthy ( 6-9 months),
- Medication side effects,
- Preventive health care is not a high priority for the client,
- Lack of effective follow-up by CHDs, often because of resource limitations.

The costs to CHDs for TSTs, x-rays and related staff time for those individuals who do not complete therapy for latent TB infection to minimize their likelihood of developing TB disease are essentially wasted.

### **CDC Drug Therapy Recommendations for LTBI**

**Before beginning treatment of LTBI, active TB must be ruled out by history, physical examination, chest radiography, and, when indicated, bacteriologic studies.**

The Bureau of TB and Refugee Health recommendations are based on current CDC recommendations. CDC's specific treatment recommendations utilize an adaptation of the rating system from recent U.S. Public Health Service documents that grade the strength of the recommendation essentially on the quality of evidence supporting the recommendation.

Four regimens are recommended for the treatment of LTBI in adults. It is important to emphasize that all four regimens have been recommended by CDC, however, the strength of the recommendation is based on the quality of evidence supporting the recommendation. **These regimens are listed from (1) through (4), but this does not indicate that number (1) is necessarily more efficacious than number (4), but that there is more quality, scientific evidence supporting the recommendation.**

<b><u>Drugs</u></b>	<b><u>Duration</u></b>	<b><u>Interval</u></b>
* (1) Isoniazid (INH)	9 months	Daily or Twice weekly
** (2) Isoniazid (INH)	6 months	Daily or Twice weekly
*** (3) Rifampin (RIF)/Pyrazinamide (PZA) (Short Course)	2 months 2-3 months	Daily (DOT) Twice weekly
**** (4) Rifampin (RIF)	4 months	Daily (DOT)

\* The **Isoniazid daily regimen for 9 months** is recommended because prospective randomized trials in HIV-negative persons show that 12 months is more effective than 6 months. However, in subgroup analyses of several trials the beneficial effect of isoniazid appears to be achieved by 9 months, and little additional benefit is gained by extending therapy to 12 months. Both 6-month and 12-month regimens are effective in HIV-positive clients compared to placebo, but have not been compared to each other in randomized trials.

\*\* While a 9-month regimen of isoniazid is the preferred regimen for the

treatment of LTBI, a 6-month regimen also provides substantial protection and has been shown to be superior to placebo in both HIV-negative and HIV-positive persons. In some situations, treatment for 6 months rather than 9 may provide a more favorable outcome from a cost-effectiveness standpoint. Based on local conditions, CHDs or other health care providers, may conclude that a 6-month rather than 9-month course of isoniazid is preferred.

**Both the 9-month and 6-month isoniazid regimens may be given intermittently, i.e., twice weekly. When isoniazid is given intermittently, it should be administered only as directly observed therapy (DOT).**

\*\*\*The **2-month daily regimen of rifampin and pyrazinamide (Short Course) should be used with caution**, especially in patients concurrently taking other medications associated with liver injury, and those with a history of liver disease or alcoholism, even if alcohol use is discontinued during treatment.<sup>1</sup> It is recommended on the basis of a prospective randomized trial of treatment of LTBI in HIV infected persons that showed the 2-month regimen to be equivalent to a 12 month regimen of isoniazid. Twice weekly rifampin and pyrazinamide for 2 or 3 months may be considered when alternative regimens cannot be given. Both of these 2 drug regimens should be administered as DOT. **In situations where rifampin may not be used, e.g. HIV infected persons receiving protease inhibitors (PI), studies support the use of rifabutin instead of rifampin. When the Short Course regimen is being considered, it should be administered only as directly observed therapy (DOT) and only after initial discussion with the TB Physician's Network (1-800-4TB-INFO) and the Bureau of TB and Refugee Health (1-850-245-4350).**

\*\*\*\* Rifampin given daily for 4 months is recommended on the basis of the efficacy of a similar regimen in a prospective randomized trial of tuberculin-positive persons with silicosis, and in a non-randomized trial in persons exposed to cases of isoniazid-resistant TB. This option may be especially useful for clients who cannot tolerate isoniazid or pyrazinamide. **When rifampin alone is being considered, it should be administered only as directly observed therapy (DOT) and with initial discussion from the TB Physician's Network (1-800-4TB-INFO).**

### 1. **Special considerations for treatment of LTBI**

- ❖ When isoniazid is chosen for treatment of LTBI in persons with HIV infection or those with radiographic evidence of prior tuberculosis, 9 months rather than 6 months is recommended after active TB has been ruled out.
- ❖ For pregnant, HIV-negative women, isoniazid given daily or twice-weekly for 9 or 6 months is recommended. For women at risk for progression from LTBI to TB disease, especially for those who are HIV-infected or who have likely been infected recently, initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. For women whose risk of active TB is lower, some experts recommend waiting until 12 weeks after delivery to treat.
- ❖ For children and adolescents, isoniazid given either daily or twice-weekly for 9 months is the recommended regimen.
- ❖ For persons who are known to be contacts of clients with isoniazid-resistant, rifampin susceptible TB, rifampin and pyrazinamide given daily via DOT for 2 months is recommended.

***Please call the TB Hotline (TB Physicians Network) 1-800-4TB-INFO) for consultation in these situations.***

- ❖ For persons who are likely to be infected with isoniazid and rifampin (multi-drug resistant-TB and at high risk of reactivation, pyrazinamide and ethambutol or pyrazinamide and a quinolone (i.e., levofloxacin, ofloxacin or ciprofloxacin) for 6-12 months are recommended. Immunocompetent contacts may be observed or treated for at least 6 months, and immunocompromised contacts (e.g., HIV-infected persons) should be treated for 12 months.

***Please call the TB Hotline (TB Physicians Network) for consultation in these situations.***

- ❖ For clients with intolerance to pyrazinamide, rifampin give daily for 4 months is recommended. DOT in this regimen is recommended.
- ❖ For clients who are close contacts to a smear-positive index case or are HIV positive or have risk factors for HIV or are otherwise immunocompromised, treatment for LTBI should be started regardless of the initial TST result **after** TB disease is ruled out. Treatment may be discontinued if the post-window period TST is negative. (**See TA Guideline, Tuberculosis (TB) Contact Investigation and Contact Evaluation, for more information on the evaluation and treatment of contacts**)

## **2. Clinical and Laboratory Monitoring**

- ❖ Clients being treated for LTBI should receive an initial clinical evaluation. They should also receive follow-up evaluations at least monthly, if receiving isoniazid alone, and at 2, 4, 6 and 8 weeks if receiving rifampin and pyrazinamide. This evaluation should include careful questioning about side effects and a brief physical examination checking for signs of hepatitis. Clients should be educated about the side effects associated with treatment of LTBI and advised to stop treatment and promptly seek medical evaluation if they occur.
- ❖ Baseline laboratory testing is recommended for all clients initially and at 2, 4 and 6 weeks when using the Short Course Rifampin/Pyrazinamide or Rifabutin/Pyrazinamide treatment for LTBI. Baseline laboratory testing is **not** routinely indicated for all clients at the start of other treatments for LTBI. Clients whose initial evaluation suggests a liver disorder should have baseline hepatic measurements of serum AST (SGOT) or ALT (SGPT) and bilirubin. Baseline testing is also indicated for clients with HIV infection, pregnant women and those in the immediate postpartum period (within 3 months of delivery), persons with a history of chronic liver disease, e.g., hepatitis B or C, alcoholic hepatitis or cirrhosis, persons who use alcohol regularly, and other who are at risk for chronic liver disease. Baseline testing is not routinely indicated in older clients who are taking other medications for chronic medical conditions unless known interactions are described. Active hepatitis and end-stage liver disease are relative contraindications to the use of isoniazid or pyrazinamide for treatment of LTBI.
- ❖ Routine laboratory monitoring during treatment of LTBI is indicated for those clients whose baseline liver function tests are abnormal and other persons with a risk of hepatic disease, as well as those receiving the short course (see above). Laboratory testing may also be indicated for the evaluation of possible adverse effects that occur during the course of treatment, e.g., liver function studies for clients with symptoms compatible with hepatotoxicity or a uric acid measurement to evaluate complaints of joint pain. Isoniazid should be withheld if transaminase levels exceed 3 times the upper limit of normal, if



- Mild central nervous system effects,
- Drug interaction resulting in increased phenytoin (Dilantin) or disulfiram (Antabuse) levels.

#### Monitoring

- Clinical monitoring monthly
- Liver function tests (AST or ALT and serum bilirubin) at baseline in selected cases (HIV infection, history of liver disease, alcoholism, pregnancy, post-partum) and repeat measurements if:
  - ✓ Baseline results are abnormal,
  - ✓ Client is pregnant, in the immediate postpartum period or at high risk for adverse reactions,
  - ✓ Client has symptoms of adverse reactions

#### Comments

- Hepatitis risk increases with age and alcohol consumption
- Pyridoxine (Vitamin B6, 10 - 25 mg/day) may prevent peripheral neuropathy and central nervous system effects

## 2. Rifampin (RIF)     Oral dose in mg/kg (maximum dose)

Adults     (Daily dose)     10 mg/kg (maximum 600mg) (DOT)  
                  (Twice-weekly)     10 mg/kg (maximum 600mg)<sup>2</sup>

Children     (Daily dose)     10-20 mg/kg (maximum 600mg)  
                  (Twice-weekly)     **not recommended**

#### Adverse Reactions

- Rash,
- Hepatitis,
- Fever,
- Thrombocytopenia,
- Flu-like symptoms,
- Orange-colored body fluids (secretions, urine, tears).

#### Monitoring

- Clinical monitoring at weeks 2, 4, 6 and 8 when PZA is given
- Complete blood count, platelets and liver function tests (AST or ALT and serum bilirubin) at baseline in selected cases (HIV infection, history of liver disease, alcoholism, pregnancy) and repeat measurements if:
  - ✓ Baseline results are abnormal
  - ✓ Client has symptoms of adverse reaction
  - ✓ When used with PZA as part of the for short course treatment for LTBI
- Baseline LFTs and repeat LFTs at weeks 2, 4 & 6 when using the short course treatment for LTBI

#### Comments

- RIF use relatively contraindicated for HIV-infected client taking protease PIs or non-nucleoside reverse transcriptase inhibitors (NNRTI),
- 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.

3. **Rifabutin (RBU)** Oral dose in mg/kg (maximum dose)

Adults (Daily dose) 5 mg/kg (maximum 600 mg)  
(Twice-weekly) 5 mg/kg (maximum 600 mg)

Children **Not recommended**

Adverse Reactions

- Rash,
- Hepatitis,
- Thrombocytopenia,
- Orange colored body fluids (secretions, urine, tears),
- With increase levels of RBU:
  - ✓ Severe arthralgias
  - ✓ Uveitis
  - ✓ Leukopenia

Monitoring

- Clinical monitoring at weeks 2, 4, 6 and 8 when PZA is given (as above)
- Complete blood count, platelets and liver function tests (AST or ALT and serum bilirubin) at baseline in selected cases (HIV infection, history of liver disease, alcoholism, pregnancy) and repeat measurements if:
  - ✓ Baseline results are abnormal
  - ✓ Patient has symptoms of adverse reactions
  - ✓ When used with PZA as part of the for short course treatment for LTBI
- Baseline LFTs and repeat LFTs at weeks 2, 4 & 6 when using the short course treatment for LTBI
- Use adjusted daily dose of rifabutin and monitor for decreased antiretroviral activity and for rifabutin toxicity if rifabutin taken concurrently with PIs or NNRTIs.
- If nelfinavir, indinavir, amprenavir, or ritonavir is administered with RBU, blood concentrations of these protease inhibitors decrease. Thus, when RBU is used concurrently with any of these-drugs, the daily dose of RBU is reduced from 300mg to 150 mg per day (ritonavir is decreased to 150 mg 2 to 3 times per week). If efavirenz is administered with RBU, blood concentration of RBU decreases. Thus, when RBU is used concurrently with efavirenz, the daily dose of RBU should be increased from 300 mg to 450 mg or 600 mg. It is not currently known whether dose adjustment of RBU is required when used concurrently with soft-gel saquinavir or nevirapine.

Comments

- Rifabutin should be used in those individuals on regimens containing PIs other than ritonavir. Rifampin may be used when clients are taking HIV regimens which include ritonavir, but adjusted dosages are necessary.

Increased dosages of rifabutin is necessary when efavirenz is utilized. Delavirdine should not be used with rifampin or rifabutin. Consultation with a medical expert strongly recommended.

- Rifabutin reduces levels of many drugs (e.g., PIs, NNTRIs, methadone, dapson, ketoconazole, coumadin derivatives, hormonal contraceptives, digitalis, sulfonyleureas, diazepam, beta-blockers, anticonvulsants, and theophylline)
  - Might permanently discolor contact lenses
- Please call the TB Hotline (TB Physicians Network) 1-800-4TB-INFO) for consultation in these situations.***

**4. Pyrazinamide (PZA) Oral dose in mg/kg (maximum dose)**

<u>Adults</u>	(Daily dose)	25 15-20 mg/kg (maximum 2 gm)
	Twice weekly)	70 50 mg/kg (maximum 4 gm)

Children **Not recommended**

Adverse Reactions

- Gastrointestinal upset
- Hepatitis
- Rash
- Arthralgias
- Hyperuricemia
- Gout (rare)

Monitoring

- Clinical monitoring at weeks 2, 4, 6 and 8
- Liver function tests (AST or ALT and serum bilirubin) at baseline in selected cases (HIV infection, history of liver disease, alcoholism, pregnancy) and repeat measurements if:
  - ✓ Baseline results are abnormal
  - ✓ Client has symptoms of adverse reactions
  - ✓ When used with RIF/RBT as part of the short course treatment for LTBI
- Baseline LFTs and repeat LFTs at weeks 2, 4 & 6 when using the short course treatment for LTBI

Comments

- 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 the first trimester.

**F. SPECIFIC FLORIDA DEPARTMENT OF HEALTH, BUREAU OF TB AND REFUGEE HEALTH DRUG THERAPY RECOMMENDATIONS FOR THE TREATMENT OF LATENT TB INFECTION**

The Bureau of TB and Refugee Health agrees that, depending upon client specific circumstances, all four of the CDC recommendations for treatment of LTBI options would be



acceptable. We would also recommend that when there is a good likelihood that a client would complete 9 months of self-administered INH, this would be the most acceptable option. Six months of INH would also be considered complete therapy when CHDs and other providers feel resources are not available for follow-up subsequent to the documented 6 months of therapy. However, for individuals at high risk for disease and at high risk for non-adherence to medication regimens (e.g., HIV infected, close contacts, jail inmates in high risk geographic areas and certain others), the short course treatment should be considered with caution<sup>1</sup>. The decision to provide daily or bi-weekly short-course therapy would also depend on resources available and potential client adherence. Jails should routinely utilize daily regimens, but for county health department clients, bi-weekly is a reasonable option, depending on available resources and client circumstances.

***Please remember the staff of the Bureau of TB and Refugee Health or the A.G. Holley hotline 1-800-4TB-INFO is available for consultation in any or all circumstances.***

<sup>1</sup> Per revised recommendations by the Bureau of TB and Refugee Health/A.G. Holley State TB Hospital for the Utilization of Rifampin/Rifabutin and Pyrazinamide for the treatment of Latent TB Infection in Florida (September 2001)

<sup>2</sup> Only when used with the Short Course Rifampin/Rifabutin/Pyrazinamide treatment for LTBI

## References

Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection, Official Statement of the American Thoracic Society (ATS), Adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS), and The Centers For Disease Control and Prevention (CDC). It first appeared in the American Journal of Respiratory and Critical Care Medicine, Vol. 161 S221-S247, 2000.

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Centers for Disease Control and Prevention. June 9, 2000. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. *M.M.W.R.* 40 (No. RR-6).

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