TREATMENT OF TUBERCULOSIS (TB) DISEASE

I. TITLE: Protocol for the treatment of active tuberculosis (TB) disease.

II. TYPE OF STANDARD: Service

III. OUTCOME: Successful completion of treatment through cure

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

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

V. COMPETENCIES: Health care providers must demonstrate knowledge of the basic principles and treatment regimens for TB, side effects and adverse reactions associated with anti-TB medications, drug interactions, methods of assessing response to treatment and adherence to therapy, and basis for assessing cure. Ongoing training should include didactic, practicum, and clinical training that cover diagnosis, radiologic interpretation, pharmacology and therapeutics, mycobacteriology, case/clinical studies, case management, and potential complications. In addition, health care providers should know how to obtain expert medical consultation for the treatment of TB disease, when necessary.

VI. RECOMMENDED TREATMENT REGIMENS FOR PERSONS WITH SUSPECTED OR CONFIRMED ACTIVE TB DISEASE

Basic TB Treatment Principles

- The ultimate responsibility for assuring the cure of every active TB case in Florida lies with the local county health department.

- TB disease must be treated with a regimen containing at least two drugs to which the organism is susceptible in order to prevent the development of drug resistance. The administration of a single drug can lead to the development of a bacterial population resistant to that drug. Never add a single anti-TB drug to a failing regimen.

- For each person with suspected or confirmed active TB disease, a specific client-centered, case management and treatment plan emphasizing adherence to therapy, should be developed that includes types of drugs to be prescribed, anticipated changes to and duration of therapy, methods of assessing and ensuring adherence (including directly observed therapy (DOT), methods of monitoring for adverse drug reactions, and necessary evaluations with appropriate time frames.

- Each person with suspected or confirmed active TB disease should be educated and counseled about the disease and the importance of anti-TB medications and their potential side effects and adverse reactions. All persons should be educated about the need for client adherence to prescribed anti-TB therapy and medical follow-up.

It is highly recommended that all county health departments initiate an Acknowledgement of Tuberculosis Counseling form, DH 1179 for every client with suspected or confirmed active TB disease in order to document the provision of such counseling.

- All clients in Florida with suspected (Class V) or confirmed (Class III) active TB disease should be started on a four-drug anti-TB regimen that includes isoniazid, rifampin, pyrazinamide, and ethambutol unless there are absolute contraindications. Initial drug resistance should be suspected if the client's history reveals prior treatment for TB, non-adherence with previous treatment, or known exposure to a person with drug resistant TB. For the complete classification system, see "Interjurisdictional Tuberculosis (TB) Notification System", TA-TB 12, p. 2.

- DOT therapy should be considered the community standard for treating clients with active TB disease. All clients with suspected or confirmed active TB disease should be considered for DOT through the county health department. For clients who are not treated via DOT, combination capsules (e.g., Rifamate® or Rifater®) should be prescribed to reduce the potential for non-adherence to therapy and the subsequent development of drug resistance and monitored extremely closely for response to therapy as well as adherence.

- All intermittent therapy, meaning twice or thrice weekly dosing must be given under a program of DOT. When isoniazid, pyrazinamide, or ethambutol is given intermittently, dosages must be increased. Dosages of rifampin remain the same whether the drug is given daily or intermittently. See Table 1 for Dosage Schedules.

- Each person treated for TB disease must be individually managed based on clinical and bacteriological response to therapy. The duration of anti-TB therapy depends on the drugs utilized, susceptibility test results, and response to treatment. Most clients, including those with HIV infection and other immunocompromising conditions, can be treated with a short course six-month treatment regimen. However, clients with certain conditions such as silicosis or TB meningitis and/or those who have exhibited slow response to therapy, e.g. still culture positive after two months of therapy, will require prolonged treatment.

- All six-month regimens must include pyrazinamide for ***at least*** the initial two months of treatment.
  - In clients who can tolerate isoniazid (INH) and are INH susceptible:
    Initial phase: INH, a rifamycin, and pyrazinamide (and ethambutol, if susceptibility results are not known) should be utilized for the initial 2 months;
    Continuation phase: INH and a rifamycin should be utilized for a total of 6 months of treatment including ***at least*** 4 months of treatment **after** culture conversion.
  - In clients who cannot tolerate INH or are INH resistant:
    a rifamycin, ethambutol, and pyrazinamide should be utilized for ***at least*** 6 months of treatment including 4 months of treatment **after** culture conversion.
- Expert clinical consultation and assistance in the diagnosis and treatment of TB may be obtained from the TB Physicians Network by calling 1-800-4TB-INFO (1-800-482-4636) or by contacting local clinicians expert in the care of TB.

Recommended Six Month Short Course Regimens

(The following regimens are for most adults and children, also see sections: TB Treatment in HIV Infected Individuals, p. 4; Recommended Regimens for Pregnant Women, p. 5; Recommended Regimens for Children & Adolescents with TB Disease, p. 5; Recommended Regimens for Persons with Extrapulmonary TB Disease, p. 6; Recommended Regimens for the Treatment of Persons with Drug-Resistant TB Disease, p. 6; Treatment of TB Clients with Chronic Renal Failure, p. 8)

Option 1
Four-drug therapy, administered daily for two weeks then continued for six additional weeks given twice or thrice weekly followed by isoniazid and rifampin twice (not recommended for HIV positive individuals with CD_4 counts <100 cells/ml) or thrice weekly to complete the six-month regimen. Ethambutol may be discontinued once the strain is known to be susceptible to isoniazid and rifampin. It is not necessary to wait two months to discontinue ethambutol if the drug susceptibility results have been received sooner. Pyrazinamide should be discontinued after the initial two months of treatment.

Option 1 is the most widely utilized treatment regimen based on its proven efficacy. It also allows for the efficient use of medical and public health resources. It is highly recommended.

Option 2
Four drug therapy, administered daily for eight weeks followed by isoniazid and rifampin given twice (not recommended for HIV positive individuals with CD_4 counts <100 cells/ml) or thrice weekly to complete the six month regimen. Discontinue ethambutol once the strain is known to be susceptible to isoniazid and rifampin. It is not necessary to wait two months to discontinue ethambutol if the drug susceptibility results have been received sooner. Pyrazinamide may be discontinued after the initial 8 weeks of treatment.

Option 3
Four drug therapy, administered thrice weekly throughout the entire six month regimen.

Option 4
Four drug therapy, self-administered daily for eight weeks followed with isoniazid and rifampin self-administered daily to complete the six-month regimen. For clients for whom DOT is not administered, daily therapy utilizing combination medications should be considered.

Table 1
Dosages for First-Line Anti-TB Medications

Medication	Daily Dose in mg/kg (Maximum Dose)		Intermittent Dose in mg/kg – DOT Only (Maximum Dose)			
			Twice-weekly Dose		Thrice-weekly Dose	
	Children	Adults	Children	Adults	Children	Adults
Isoniazid † ‡ (INH)	10-20 (300 mg)	5 (300 mg)	20-40 (900 mg)	15 (900 mg)	20-40 (900 mg)	15 (900 mg)
Rifampin † ‡ (RIF)	10-20 (600 mg)	10 (600 mg)	10-20 (600 mg)	10 (600 mg)	10-20 (600 mg)	10 (600 mg)
Rifabutin (RBT)**	2.5-10 mg (up to 600mg/day)	2.5-10 mg (up to 600mg/day)	2.5-10 mg (up to 600mg/day)	2.5-10 mg (up to 600mg/day)	2.5-10 mg (up to 600mg/day)	2.5-10 mg (up to 600mg/day)
Pyrazinamide‡ (PZA)	15-30 (2 g)	15-30 (2 g)	50-70 (4 g)	50-70 (4 g)	50-70 (3 g)	50-70 (3 g)
Ethambutol (EMB)	15-25	15-25	50	50	25-30	25-30
Streptomycin* (SM)	20-40 (1 g)	15 (1 g)	25-30 (1.5 g)	25-30 (1.5 g)	25-30 (1.5 g)	25-30 (1.5 g)

Note:
Children refer to those ≤15 years of age.
Adjust weight-based dosages as weight changes.
*Streptomycin is a second-line drug, which can be used in treating drug-resistant tuberculosis.
**Rifabutin - dosage may vary based on use of concomitant medications, e.g. anti-retrovirals (ARVs).
Approval from the TB Physicians Network is necessary before beginning treatment using Rifabutin at 1-800-4TB INFO (1-800-482-4636).

† Isoniazid and rifampin are available as a combination capsule (Rifamate®) containing 150 mg of isoniazid and 300 mg of rifampin.

‡ Isoniazid, rifampin and pyrazinamide are available as a combination capsule (Rifater®) containing 50 mg of isoniazid, 120 mg of rifampin and 300 mg of pyrazinamide.

TB Treatment in HIV Infected Individuals

It is not uncommon for persons with active TB disease to be HIV co-infected. Clinically, HIV has been shown to exacerbate TB disease. Conversely, TB disease has been shown to significantly increase HIV viral loads and decrease CD_4 counts. As is described above, the treatment of most HIV infected individuals with TB disease can be accomplished through the use of standard, short course anti-TB regimens. However, treatment can be complicated by potentially serious drug interactions between medications used to treat both conditions.

The treatment for HIV is constantly changing. Protease inhibitors, a class of potent antiretroviral agents, are recommended for combination therapy with reverse transcriptase inhibitors in many HIV infected clients. Several Protease inhibitors such as saquinavir (Invirase®), ritonavir (Norvir®), indinavir (Crixivan®), nelfinavir (Viracept®), amprenavir (Agenerase®), lopinavir/ritonavir (Kaletra®), and atazanavir (Reytaz®) are currently approved by the Food and Drug Administration for the treatment of HIV infection. Since the field of HIV therapeutics is changing rapidly, if you have any questions about drug dosing, drug treatment, or drug/drug interactions contact the TB Physicians Network at 1-800-4TB-INFO (1-800-482-4636) for the most current information.

These agents complicate the treatment of TB disease because they interact significantly with rifampin, the most effective anti-TB medication. In general, the concurrent use of protease inhibitors and rifampin significantly reduces the levels of protease inhibitors and significantly increases serum levels of rifampin. As a result, the protease inhibitors may lose their efficacy and the rifampin may have an increased toxic effect. Additionally, lower doses of protease inhibitors are associated with an increased risk for HIV drug resistance and there appears to be cross-resistance between many currently available protease inhibitors. Conversely, other agents, such as efavarenz (Sustiva®) are also inducers of the p450 system of the liver as is rifampin and actually may lower rifampin levels.

The Centers for Disease Control and Prevention (CDC), acknowledges the complexity of treating patients with HIV and TB and recommends consultation with an expert familiar with treating clients concomitantly for HIV and TB. If a decision to treat a client with both anti-TB medications as well as antiretroviral therapy is contemplated, *expert clinical consultation and assistance should be sought from A.G. Holley State TB Hospital at 1-800-4TB-INFO (1-800-482-4636) or by contacting local clinicians expert in the care of TB and HIV.*

Recommended Regimens for Pregnant Women

The treatment of pregnant women with suspected or confirmed active TB disease should not be delayed. Treatment regimens for pregnant women differ from standard treatment regimens because streptomycin is contraindicated and pyrazinamide should be avoided. Streptomycin has been shown to have teratogenic effects on the fetus and the effect of pyrazinamide on the fetus is unknown.

The preferred initial treatment regimen during pregnancy is isoniazid, rifampin, and ethambutol. Ethambutol may be excluded if primary resistance to isoniazid is highly unlikely and the client has no risk factors for multidrug resistant-TB (MDR-TB). If used, ethambutol should be discontinued once the strain is known to be susceptible to isoniazid and rifampin. Therapy should then be continued with isoniazid and rifampin for a minimum of nine months of total therapy. The use of intermittent therapy, meaning twice or thrice weekly, via DOT is recommended. Use Rifamate® (capsules combining isoniazid and rifampin) for patients who are not receiving DOT.

Other TB medications to be avoided during pregnancy include kanamycin, capreomycin, cycloserine, and ethionamide.

Anti-TB medications in breast-feeding women

The small concentrations of anti-TB drugs in breast milk are not toxic to the nursing newborn. Therefore, breast-feeding should not be discouraged for an HIV negative woman who is planning to take or is taking isoniazid or other anti-TB medications.

Conversely, the low concentration of anti-TB medications in breast milk should not be considered effective treatment for disease or as treatment for latent TB infection (LTBI) in a nursing infant. Women who are HIV sero-positive should not breast-feed because of the risk of HIV transmission to the infant.

Isolation of mother with TB disease from infant postpartum

Whether a mother who has TB disease should be separated from her infant at delivery depends on the mother's level of infectiousness, as assessed by the clinician. If the mother is considered infectious, she should be separated from the infant until she becomes non-

infectious. Thereafter, separation of the infant from the mother is not necessary as long as adherence to treatment by the mother is assured.

Recommended Regimens for Children and Adolescents with TB Disease

The short course regimens recommended for adults are also the regimens of choice for children and adolescents with pulmonary TB, with appropriately adjusted weight-based dosages.

Young children who cannot be evaluated for visual acuity or color vision should not routinely be treated with ethambutol, although some anecdotal reports indicate its safe use in younger children. If ethambutol must be used to treat TB in a young child, such as in drug-resistant TB, the minimum daily and/or intermittent dosages should be used. Streptomycin, while considered to be safe and well tolerated in children, should only be used when necessary for children who have been exposed to drug-resistant TB and with caution due to its potential for ototoxicity and parenteral administration.

In general, extrapulmonary TB in children can be treated with the same 6-month short course regimens as pulmonary TB, with the exception of bone and joint disease, disseminated (miliary) TB, and TB meningitis, for which a minimum of 12 months of therapy is recommended.

For younger children, isoniazid or pyrazinamide tablets can be divided, crushed, or added to food or liquids such as fruit juice or jello or applesauce. Also, rifampin may be emptied from the capsule and added to food or liquids.

Children with suspected or confirmed TB disease should be treated under a program of DOT through the county health department. After the initial phase of daily therapy, children receiving DOT should be switched to an intermittent regimen.

Recommended Regimens for Persons with Extrapulmonary TB Disease

The basic principles that underlie the treatment of pulmonary TB also apply to extrapulmonary forms of the disease. As a general rule, regimens that are adequate for treating pulmonary TB in adults and children are also effective for treating extrapulmonary disease, because in most cases the mycobacterial burden is considerably smaller in the latter.

However, for certain forms of extrapulmonary disease, such as TB of the bone and joint, miliary TB, and TB meningitis, treatment must be prolonged to at least 9-12 months in adults and 12 months in children.

Use of corticosteroids has been shown to be beneficial in extrapulmonary forms of TB where there are accompanying inflammatory reactions, such as in constrictive pericarditis, endobronchial disease, massive or painful pleural effusion, Pott's disease with nerve compression, meningeal disease, severe TB adenitis in children where there is compression of the tracheobronchial tree causing respiratory distress, and severe miliary disease. It has also been useful in paradoxical reactions in clients with extrapulmonary TB where manifestations such as adenopathy and fevers may worsen despite signs of clinical improvement.

Recommended Regimens for the Treatment of Persons with Drug-Resistant TB Disease

The following suggested regimens should be considered guidelines only. The treatment of persons with drug-resistant TB disease must be individualized, especially for clients with drug resistance to several medications. Unlike the treatment of drug-susceptible TB disease, it is not possible to develop standardized protocols for the treatment of known or suspected drug resistant TB. Several issues are involved: first, any treatment recommendation must take into account the drug susceptibility results of the individual isolate; second, good data are lacking on the efficacy of non-standard drug regimens; and third, side effects to second line medications,

often serious and intolerable, may preclude the use of these drugs for the recommended period of time.

It should be emphasized that the presence of resistance to rifampin should be confirmed with the Bureau of Laboratories (904-791-1571) and another culture be tested to confirm the resistance. However, appropriate treatment should not be withheld while awaiting such confirmation.

DOT should be strongly considered for all clients with suspected or confirmed drug resistance to any first-line medication.

Expert clinical consultation and assistance in the diagnosis and treatment of drug resistant TB may be obtained from the TB Physicians Network by calling 1-800-4TB-INFO (1-800-482-4636) or by calling local clinicians expert in the care of drug resistant TB.

Resistance to Isoniazid Alone
When primary resistance to isoniazid alone is known at the initiation of therapy, rifampin, pyrazinamide, and ethambutol should be prescribed for the duration of a six-month short course treatment regimen. This regimen may be prescribed on an intermittent schedule.

When partial resistance to isoniazid alone is demonstrated during the recommended initial four-drug therapy, the regimen may be adjusted by increasing the isoniazid to 900 mg in addition to continuing the rifampin, ethambutol and pyrazinamide for the entire 6 months either daily, twice or thrice weekly. When full resistance to isoniazid alone is demonstrated during the initial four-drug therapy, the isoniazid should be discontinued and rifampin, pyrazinamide, and ethambutol continued for the entire six months of therapy. This regimen may also be prescribed either daily or intermittently.

An alternative regimen for clients with active TB disease resistant to isoniazid alone is the use of rifampin and ethambutol for a minimum of 12 months.

Resistance to Rifampin Alone
Rifampin is a critical component of the standard TB treatment regimen. Regimens that include rifampin are shorter, have faster sputum culture conversion rates, higher cure rates, and lower relapse rates than regimens that do not include rifampin. When laboratory results indicate resistance to rifampin, this resistance should be confirmed with the Bureau of Laboratories (904-791-1571) and another culture be tested to confirm the resistance and expert clinical consultation and assistance should be considered.

For clients with active TB disease resistant to rifampin alone, a drug regimen containing isoniazid, ethambutol, pyrazinamide, and an injectable aminoglycoside should be used for the first six months and should be followed with isoniazid and ethambutol continued for 18 months of total therapy after culture conversion to negative.

A recommended alternative regimen *for HIV negative clients* with resistance to rifampin alone consists of isoniazid, streptomycin, and pyrazinamide for a total of nine months of therapy. This regimen may be prescribed thrice weekly.

Resistance to Isoniazid and Rifampin – MDR-TB
Multidrug-resistant TB (MDR-TB) refers to a strain of *M. tuberculosis* resistant to at least isoniazid and rifampin. All clinicians treating a client with MDR-TB must seek expert

consultation and assistance from the TB Physicians Network at 1-800-4TB-INFO (1-800-482-4636).

The following general principles apply to the treatment of MDR-TB:

- Clients must be treated with a regimen of at least two, and preferably three, anti-TB medications to which the strain is likely to be susceptible.

- A single anti-TB medication should never be added to a regimen that is failing, that is, if the client is not clinically improving or if the cultures remain positive two to four months after the initiation of therapy. At least two, and preferably three, new anti-TB medications to which the strain is likely to be susceptible should be added.

- Treatment for TB strains resistant to at least isoniazid and rifampin should be given for at least 18 months after culture conversion to negative, and for up to 24 months after culture conversion to negative in some HIV positive individuals or those with extensive cavitary disease.

- All clients with MDR-TB should be treated under a program of DOT through the county health department.

Treatment of TB Clients with Chronic Renal Failure

In most clients with chronic renal failure, the regimens for TB treatment must be adjusted. Most clinicians expert in the care of such conditions advise lengthening the interval between conventional doses (intermittent therapy using DOT) as the safest method to accomplish adequate but safe serum drug levels. Because of the potential complications associated with the treatment of TB disease in clients with chronic renal failure, including the possible need to perform periodic serum drug levels, expert clinical consultation and assistance should be considered.

In general, the following anti-TB medications are eliminated by the kidney and may require a regimen adjustment: pyrazinamide, ethambutol, aminoglycosides and capreomycin, para-aminosalicylic acid, cycloserine, and quinolones.

Isoniazid and rifampin can be used in conventional doses in clients with chronic renal failure.

VII. THE USE OF PYRIDOXINE (VITAMIN B_6) IN THE TREATMENT OF TB DISEASE

Pyridoxine (B_6) is often used in conjunction with certain anti-TB medications to prevent side effects in the central and peripheral nervous system. B_6 is safe and well tolerated in clients with normal renal function. Pyridoxine should be considered for clients with the following conditions:

HIV infection
Malnourishment or any wasting disease
Diabetes
Cancer
Chronic Renal Disease (adjust dose)
Pregnancy
Chronic Liver Disease
Alcoholism
Pre-existing Peripheral Neuropathy

Pyridoxine is also indicated for children on a meat-and milk-deficient diet, for breast-feeding infants, and all clients taking cycloserine. The recommended dosages of pyridoxine are 25 mg for 300 mg of isoniazid or 50 mg twice or thrice weekly, if isoniazid is prescribed intermittently.

VIII. ADDRESSING INTERRUPTED OR INCOMPLETE TB TREATMENT

The CDC now defines completion of therapy by number of doses taken within a certain amount of time. See Table 4 - Dosages for Drug Regimens for Drug Susceptible Active TB Disease (TA-TB 6 - p. 16) for details.

When a client has had interrupted or incomplete treatment for TB disease, the clinician must decide the appropriate duration of a new regimen. This decision should be based on an estimate of the load of viable tubercle bacilli remaining in the lungs, or elsewhere, when treatment is restarted, as well as duration of therapy client received prior to interruption of therapy.

In clients with interrupted or incomplete treatment for TB disease and one or more of the following conditions, a full course of therapy should be restarted, that is, the previous doses should be disregarded, if:

a. The client did not receive and/or the client did not adequately respond to the initial phase of therapy, (i.e. client was still culture positive)
b. Treatment that lapsed more than six months ago
c. Extensive disease, especially cavitary
d. Immunosuppression, especially due to HIV infection
e. Prolonged treatment before culture conversion to negative or no culture conversion to negative

Upon retreatment, consideration should be given to adding two medications to which the client had not previously been exposed. The duration of the new regimen should correspond to the length of the original regimen; for example, a new six-month regimen in a client originally prescribed a six-month regimen. In clients with none of the conditions listed above, the regimen should last as long as needed to complete the duration of the regimen originally prescribed.

For clients who originally received two full months of treatment and previously converted their sputum smear and culture to negative, a four-month regimen containing the standard four first line medications may be an option.

When treatment is reinstituted, sputum specimens should be collected for smear and culture. In addition, drug susceptibility testing should be repeated at this time, even if the pretreatment isolates were pansensitive.

DOT must be provided to any client who was previously non-adherent to self-administered therapy. In addition, all clients with suspected or confirmed active TB disease should be educated and counseled about the disease and the importance of anti-TB medications and their potential side effects and adverse reactions. All persons should be educated about the need for client adherence to prescribed anti-TB therapy and medical follow-up. It is highly recommended that all county health departments initiate an Acknowledgement of Tuberculosis Counseling form, DH1179 to every client with suspected or confirmed active TB disease in order to document the provision of such counseling. Clients who demonstrate a pattern of non-

adherence to prescribed therapy or medical follow-up should be evaluated for appropriate legal intervention.

In some cases, either because of drug toxicity or nonadherence to the treatment regimen, the specified number of doses cannot be administered within the targeted period. In such cases the goal is to deliver the specified number of doses within a recommended maximum time. For example, for a 6-month daily regimen the 182 doses should be administered within 9 months.

Usually, it is also recommended that all of the specified number of doses for the initial phase be delivered within 3 months and those for the 4 month continuation phase be delivered within 6 months, so as above the 6 month regimen should be completed within 9 months. Contact the TB Physicians Network at 1-800-4TB-INFO (1-800-482-4636), if the client has not taken TB medications within the specified period of time.

In general, if the client received <80% of the planned total doses and the lapse is 3 months or more in duration, treatment should be restarted from the beginning. If the lapse is less than 3 months in duration, treatment should be continued to complete a full course.

IX. ADDRESSING TB TREATMENT FAILURE OR RELAPSE

Treatment failure should be suspected in clients whose cultures do not convert to negative after two months of therapy and/or who have clinical deterioration due to TB disease or worsening of the chest x-ray due to TB disease.

The most recent positive *M. tuberculosis* culture, if one is available, should be tested for susceptibility to first and second line drugs. It is important to confer with the Department of Health Bureau of Laboratories (904 791-1571) to ensure that proper diagnostic tests are performed.

If sputum smears and/or cultures remain positive after two months of appropriate therapy, three new consecutive daily sputum samples should be sent for smear, culture, and susceptibility testing. For extrapulmonary TB clients, renewed attempts should be made to obtain appropriate specimens for smear, culture, and susceptibility testing.
Clients who are clinically stable may be maintained on the current anti-TB regimen until susceptibility results are available to guide the choice of medications.

Clients who are clinically deteriorating should be given at least two new anti-TB medications, preferably one injectable, to which they had not previously been exposed. When susceptibility results are available, the regimen should be modified accordingly.

DOT must be instituted for all clients thought to be failing treatment who are currently on self-administered therapy.

For clients who are thought to be failing treatment, clinical consultation should be sought from the TB Physicians Network by calling 1-800-4TB-INFO (1-800-482-4636) or by contacting local clinicians expert in the care of TB.

X. POTENTIAL ADVERSE DRUG REACTIONS – ANTI-TB MEDICATIONS

Anti-TB medications can cause a variety of adverse reactions, as summarized in Table 2. All clients undergoing treatment for TB disease should be closely assessed, at least monthly, to

identify and address potential adverse reactions. Reactions may range from inconsequential to severe and may be caused by medications other than those prescribed for the treatment of TB disease. The following guidelines pertain to the most common monitoring procedures:

- Baseline measurement of liver enzymes, bilirubin, serum creatinine, complete blood count, and platelet count are suggested for adults. Baseline tests in children are usually not recommended unless special medical conditions exist, such as chronic liver or renal problems or HIV.

- Serum uric acid should be measured, if pyrazinamide is prescribed.

- Clients on aminoglycosides such as streptomycin, kanamycin and amikacin or capreomycin, particularly those with pre-existing renal dysfunction and the elderly, should be closely monitored for renal, vestibular, and auditory toxicity. Serial measurement of BUN, creatinine, and audiograms may be indicated.

- Baseline examination and subsequent monthly evaluation of both visual acuity and red-green color perception for each eye should be performed for all persons when ethambutol is prescribed. If deemed necessary, ethambutol may be used in children if visual testing cannot be performed.

- Routine laboratory monitoring is generally not necessary for clients with normal baseline findings, unless toxicity is suspected.

Expert clinical consultation and assistance in the management of adverse drug reactions caused by anti-TB medications may be obtained from the TB Physicians Network by calling 1-800-4TB-INFO (1-800-482-4636) or by contacting local clinicians expert in the care of TB.

Table 2
Common Adverse Reactions to First-Line Anti-TB Medications

Adverse Reaction	Signs and Symptoms	Usual Causes
Dermatitis	itching, rash, hives, fever, etc.	rifampin, pyrazinamide, isoniazid, rarely ethambutol
Hepatitis	anorexia, nausea, vomiting, jaundice	isoniazid, rifampin, pyrazinamide, rarely ethambutol
Gastritis	anorexia, nausea, vomiting, epigastric pain	rifampin, pyrazinamide
Cholestasis	jaundice, increased SGPT & alkaline phosphatase	rifampin
Peripheral neuropathy	numbness or paresthesias of feet or hands	isoniazid
Joint manifestations	gout-like manifestations, manisfestations like systemic lupus erythematosus	pyrazinamide, isoniazid

Renal manifestations	hematuria, azotemia	rifampin, aminoglycosides, pyrazinamide
Hematologic manifestations	leukopenia, thrombocytopenia	isoniazid, rifampin, pyrazinamide, ethambutol
Visual manifestations	vision loss and color blindness; uveitis	ethambutol, rifabutin
Audiovestibular manifestations	hearing loss, vertigo, new- onset tinnitus	aminoglycosides, capreomycin

XI. POTENTIAL DRUG INTERACTIONS - ANTI-TB MEDICATIONS

Anti-TB medications may interact with prescription and over-the counter medications. Because of this, clinicians should closely monitor persons with TB disease for potential drug interactions. The following guidelines pertain to frequently encountered interactions:

- Isoniazid can increase phenytoin (Dilantin®) serum concentrations. Clinicians should follow phenytoin levels closely and monitor for signs of phenytoin toxicity. Adjust dosages of phenytoin as needed.
- Rifampin interacts significantly with protease inhibitors, a class of potent anti-retroviral agents recommended for combination therapy with reverse transcriptase inhibitors in many HIV infected persons. Rifampin and protease inhibitors should never be used concomitantly. If the use of a rifamycin and protease inhibitors is strongly contemplated, rifabutin should be substituted for rifampin and expert clinical consultation and assistance should be sought.
- Rifampin may accelerate clearance of drugs metabolized by the liver including coumadin, glucocorticoids, estrogen, oral hypoglycemic agents, digitalis, anticonvulsant medications, ketoconazole, fluconazole, and cyclosporin.
- Rifampin may also accelerate the clearance of methadone. Clients on methadone maintenance programs may require increasing the methadone dose up to 50% above its usual dose. In addition, methadone may need to be administered in divided doses.
- Women taking rifampin should be advised to use birth control methods other than oral contraceptives and injectable progesterone-based contraceptives.
- When treatment with rifampin has ended, drug doses of the above drugs must be readjusted to avoid potential overdose/toxicity.
- Ethanol and illicit drugs interfere with the metabolism of rifampin and INH, which may cause a lowering of the therapeutic serum levels of the TB medications, which can lead to treatment failure as well as possible resistance. In addition, the intake of ethanol and illicit drugs can cause adverse effects, which make the administration of the TB medications more difficult. It is for these reasons that clients being prescribed TB medications should be advised to refrain from ethanol or illicit drugs while on TB therapy.

Expert clinical consultation and assistance in the management of potential drug interactions with anti-TB medications may be obtained from the TB Physicians Network by calling 1-800-4TB-INFO (1-800-482-4636) or by contacting local clinicians expert in the care of TB.

Table 3 - Drug Interactions with Anti-Tuberculosis Medications describes, by anti-TB medication, known potential drug interactions. Current literature should be consulted concerning other possible drug interactions.

Table 3

Drug Interactions with Anti-Tuberculosis Medications*

Anti-TB Medication	Drug or Drug Type	Interaction
Isoniazid (INH)	Acetaminophen	Increased toxic metabolites
	Antacids	Decreased isoniazid absorption
	Anticoagulants (oral)	Increased anticoagulant effect
	Benzodiazepines	Increased benzodiazepines toxicity
	Carbamazepines	Increased toxicity of both drugs
	Cycloserine	Increased CNS effect of cycloserine
	Disulfiram	Severe psychotic episodes (avoid concurrent use)
	Enflurane	Increased nephrotoxicity (avoid concurrent use)
	Haloperidol	Increased haloperidol toxicity
	Ketoconazole	Decreased ketoconazole effect
	Phenytoin	Increased phenytoin toxicity
	Theophylline	Increased theophylline toxicity
	Valproate	Increased hepatic and CNS toxicity
Rifampin (RIF) and rifabutin	Aminosalicylic acid	Decreased rifampin absorption
	Anticoagulants (oral)	Decreased anticoagulant effect
	Antidepressants (tricyclic, barbiturates, benzodiazepines)	Decreased antidepressant effect
	Beta-adrenergic blockers (most)	Decreased beta blockade
	Metoprolol	Possible increased beta blockade
	Chloramphenicol	Decreased chloramphenicol effect
	Clofibrate	Decreased clofibrate effect
	Contraceptives (oral)	Decreased contraceptive effect
	Corticosteroids	Marked decreased corticosteroid effect
	Cyclosporine	Decreased cyclosporine effect
	Dapsone	Possible decreased dapsone effect
	DepoProvera	Decreased contraceptive effect
	Digitoxin	Decreased digitoxin effect
Anti-TB Medication	**Drug or Drug Type**	**Interaction**
	Digoxin	Decreased digoxin effect
	Diltiazem	Decreased diltiazem effect
	Disopyramide	Decreased disopyramide effect
	Fluconazole	Decreased fluconazole effect
	Haloperidol	Decreased haloperidol effect
	Itraconazole	Decreased itraconazole effect
	Ketoconazole	Decreased ketoconazole and rifampin effect
	Mephenytoin	Decreased mephenytoin effect
	Mexiletin	Decreased antiarrhythmic effect
	Methadone	Decreased methadone effect
	Nefedipine	Decreased antihypertensive effect
	Nesoldepine	Decreased antihypertensive effect

	Phenytoin	Decreased phenytoin effect
	Progestine	Decreased progestine effect
	Propaferrone	Decreased propaferrone effect
	Protease inhibitors (saquinavir, ritonavir, indinavir, nelfinavir)	Marked increased serum levels of rifampin and rifabutin. Marked decreased serum levels of protease inhibitor
	Quinidine	Decreased quinidine effect
	Sulfonylurea	Decreased sulfonylurea effect
	Tetracyclines	Decreased tetracycline effect
	Theophyllines	Decreased theophylline effect
	Tocainide	Possible increased tocainide effect
	Trimethoprim- sulfamethoxazole	Possible rifampin toxicity
	Verapamil	Decreased verapamil effect
Aminoglycosides	Amphotericin	Nephrotoxicity (synergism)
	Bumetanide	Increased ototoxicity
	Capreomycin	Increased ototoxicity and nephrotoxicity (additive)
	Cephalosporin	Increased nephrotoxicity
	Cisplatin	Increased nephrotoxicity
	Cyclosporine	Increased nephrotoxicity
	Enflurane	Possible increased nephrotoxicity
	Ethacrynic acid	Increased ototoxicity
	Furosemide	Increased ototoxicity and nephrotoxicity
	Gallium	Increased nephrotoxicity
	Methotrexate kanamycin	Possible increased methotrexate toxicity
	Neuromuscular blocking agents	Increased neuromuscular blockade
	Vancomycin	Increased ototoxicity and nephrotoxicity (additive)
Pyrazinamide	Allopurine	Failure of allopurinol to decrease serum uric acid level
Pyridoxine (B_6)	Barbiturates	Decreased barbiturate effect
	Levodopa	Decreased levodopa effect
	Phenytoin	Decreased phenytoin effect
Anti-TB Medication	**Drug or Drug Type**	**Interaction**
Cycloserine	Alcohol	Increased alcohol effect and seizures
	Isoniazid	Increased CNS effect of cycloserine
Quinolones	Antacid with metal cations (Ca, Mg, Al, Fe)	Reduced absorption of quinolones
	Sucralfate	Reduced absorption of quinolones
	Drugs metabolized by cytochrome P450 (cyclosporine, theophylline, warfarin, phenytoin, sulfonylurea)	Increased action of additional drug
	Non-steroidal anti-inflammatory agents	Increased CNS stimulation and possible convulsions
	Probenecid	Increased serum level of quinolone

Para-aminosalicylic acid (PAS)	Digoxin	Possible decreased digoxin action
Cycloserine	Isoniazid	Increased CNS effect
	Ethionamide	Increased CNS effect of cycloserine
Ethionamide	Cycloserine	Increased CNS effect of cycloserine

There are numerous drug-drug interactions with anti-retroviral medications; consult the updated CDC HIV treatment guidelines at http://aidsinfo.nih.gov/DrugsNew/Default.aspx?MenuItem=Drugs&Search=On. This site is updated regularly as new drugs become available. Also, contact the TB Physicians Network for further information about possible drug-drug interactions between TB and HIV/AIDS medications at 1-800-4TB-INFO (1-800-482-4636).

XII. ADDRESSING POTENTIAL MISDIAGNOSIS OF ACTIVE TB DISEASE

Any person who has a single positive culture (it may rarely be two cultures) but does not have other findings compatible with active TB disease (e.g. asymptomatic, negative CXR, negative PPD, no risk for TB, etc.) should be considered for the possibility of a laboratory cross-contamination or error.

While it is possible to have TB with only one positive culture, whenever the clinical scenario does not match the laboratory results the possibility of laboratory error should be considered. In these cases, consultation with the Bureau of Laboratories (904-791-1571) and the TB Physicians Network at 1-800-4TB-INFO (1-800-482-4636) should be sought.

XIII. SUPPORTIVE DATA:

ATS/CDC/IDSA. *Treatment of TB.* Am J Respir Crit Care Med 2003; 167:603-662.
CDC. *Core Curriculum on Tuberculosis.* U.S. Department of Health and Human Services-Public Health Service, Fourth edition, 2000 (http://www.cdc.gov/nchstp/tb/pubs/corecurr/default.htm).

Garay SM, Rom, WN. *Tuberculosis.* Little, Brown and Company; 2nd edition 2003.

Iseman MD. A Clinicians Guide to Tuberculosis. Lippincott Williams and Wilkins 2000.

Table 4: Dosages for Drug Regimens for Drug Susceptible Active TB Disease

Initial Phase				Continuation Phase		
Regimen	Drugs	Interval and Doses (minimal duration)	§CDC Regimen#	Drugs	Interval and Doses (minimal duration)	Range of Total Doses* (minimal duration)
1	INH RIF PZA EMB	Seven days per week for 56 doses (8 wk)[a] or 5 d/wk for 40 doses (8 wk)[b]	1a 1b 1c	INH/RIF INH/RIF INH/RPT**	Seven days per week for 126 doses (18 wk)[a] or 5d/wk for 90 doses (18 wk)[b] Twice weekly for 36 doses (18 wk)[c] Once weekly for 18 doses (18 wk)[d] **Rifapentine (RPT)	182^{a+a}-130^{b+b} (26 wk) 92^{a+c}-76^{b+c} (26 wk) 74^{a+d}-58^{b+d} (6 wk)
2	INH RIF PZA EMB	Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wks)[e] or 5 d/wk for 10 doses (2 wk), then twice weekly for 12 doses (6 wk)[f]	2a 2b	INH/RIF INH/RPT**	Twice weekly for 36 doses (18 wk)[g] Once weekly for 18 doses (18 wk)[h] **Rifapentine (RPT)	62^{e+g}-58^{f+g} (26 wk) 44^{e+h}-40^{f+h} (26 wk)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)[i]	3a	INH/RIF	Three times weekly for 54 doses (18 wk)i	78^{i+i} (26 wk)

(§ 1a, 1b,1c, 2a, 2b, 3a refer to CDC Regimen #s, see Treatment of Tuberculosis, Am J Respir Crit Care, 2003, Vol 167, p. 605, Table 2)

***Dosages represent variations in the treatment regimen:**

[a+a.] 182 doses = daily treatment for 7 days/wk for 56 doses (8 wks) followed by daily treatment 7 days/wk for 126 doses (26 wks)

[b+b.] 130 doses = treatment for 5 days/wk for 40 doses (8 wks) followed by 5 days/week for 90 doses (26 wks)

[a+c.] 92 doses = daily treatment for 7 days/wk for 56 doses (8 wks) followed by twice weekly for 36 doses (18 wks)

[b+c.] 76 doses = treatment for 5 days/wk for 40 doses (8 wks) followed by twice weekly for 36 doses (18 wks)

[a+d.] 74 doses = daily treatment for 7 days/wk for 14 doses (2 wks) followed by twice weekly for 12 doses (6wks) followed by twice weekly for 36 doses

[b+d.] 58 doses = treatment for 5 days/wk for 40 doses (8 wks) followed by once weekly for 18 doses (18 wks)

[e+g.] 62 doses = daily treatment for 7 days/wk for 14 doses (2 wks) then twice weekly for 12 doses (6 wks) followed by twice weekly for 36 doses (18 wks)

[f+g.] 58 doses = 5 days/wk or 10 doses (2 wks), then twice weekly for 12 doses (6 wks) followed by twice weekly for 36 doses (18 wks)

[e+h.] 44 doses = daily treatment for 7 days/wk for 14 doses (2 wks) then twice weekly for 12 doses (6 wks) followed by once weekly for 18 doses (18 wks)

[f+h.] 40 doses = 5 days/wk or 10 doses (2 wks), then twice weekly for 12 doses (6 wks) followed by once weekly for 18 doses (18 wks)

[i+i.] 78 doses = 3 times weekly for 24 doses (8 wks) followed by 3 times weekly for 54 doses (18) wks

Adapted from Table 2 - MMWR June 20, 2003/Vol. 52/No. RR-11 Treatment of Tuberculosis