STANDARD
NURSE PROTOCOLS
FOR
TUBERCULOSIS (TB)

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2011-2012 TUBERCULOSIS CLINICAL REVIEW COMMITTEE

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STANDARD NURSE PROTOCOL FOR UNCOMPLICATED PULMONARY TUBERCULOSIS (TB) (AGE 18 AND OVER)

DEFINITION

Tuberculosis (TB) is an infectious disease transmitted through the air in droplet nuclei that are produced when a person with active TB disease of the lung or larynx sneezes, coughs, speaks, or sings. Persons breathing air contaminated with these droplet nuclei may become infected with TB.

Generally, a positive culture or positive Nucleic Acid Amplification (NAA) test for *Mycobacterium tuberculosis* is necessary to confirm the diagnosis of a tuberculosis case. However, suspected cases may be diagnosed on the basis of: a positive sputum smear for acid-fast bacilli (AFB); lung histology showing necrotizing granulomas with or without AFB; or clinical syndrome, even when a culture or pathologic specimen has not been, or cannot be, obtained.

ETIOLOGY

Causative agent of TB is the *Mycobacterium tuberculosis* (*M.tb*) complex (*Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium africanum and Mycobacterium microti)*.

SUBJECTIVE

Individuals with uncomplicated TB:

1. May have history of exposure to a known case.

2. May have one or more of the following:
   a. Productive, prolonged cough (usually more than two or three weeks duration).
   b. Fever.
   c. Chest pain or pleuritic pain.
   d. Chills.
   e. Night sweats.
   f. Easy fatigability.
   g. Loss of appetite.
   h. Weight loss.
   i. Hemoptysis (coughing up blood).

3. If any of these conditions are present, this represents complicated TB and must be treated by a physician:
   a. Currently pregnant or breast-feeding.
   b. Known history of infection or exposure to multiple drug resistant (MDR) *M. tuberculosis*, or drug resistance on susceptibility testing to isoniazid, rifampin, pyrazinamide or ethambutol.

c. Known HIV infection.

d. Other new and/or complicated acute or chronic medical condition.
e. Known allergies to anti-tuberculosis drugs.
f. Treatment with once-weekly isoniazid and rifapentine during the continuation phase.
g. Decision to extend the continuation phase longer than four months.

OBJECTIVE

1. The following criteria are used to diagnose a suspected TB case:
   a. A positive Mantoux tuberculin skin test. (The absence of a reaction to the skin test does not rule out the diagnosis of TB disease or latent TB infection).
   b. Positive staining of acid-fast bacillus (AFB) in sputum(s), bronchial brush, wash or lung tissue biopsy. (However, cases can be smear negative.)
   c. Chest x-ray showing abnormalities compatible with TB.
   d. Response to treatment with anti-tuberculosis drugs.

2. In addition to the above, the following would be necessary to diagnose a case of TB:
   a. Pathology findings compatible with the diagnosis of TB.
   b. Positive culture or positive Nucleic Acid Amplification (NAA**)** test for *Mycobacterium tuberculosis.*

ASSESSMENT

1. Uncomplicated pulmonary tuberculosis.
   OR
2. Uncomplicated suspected case of pulmonary tuberculosis.

PLAN

DIAGNOSTIC STUDIES

1. If documented tuberculin skin test results cannot be verified (including millimeters [mm] of induration), perform a Mantoux tuberculin skin test per programmatic guidelines. **Vaccination with live viruses may interfere with tuberculin skin test reactions. For persons scheduled to receive a tuberculin skin test, testing should be done as follows: Either on the same day as vaccination with live-virus vaccine or 4-6 weeks after the administration of the live-virus vaccine. At least one month after smallpox vaccination.**

2. Collect 3 sputum specimens (on consecutive days) for AFB smear/culture (and sensitivities on first sputum) and send to the State Laboratory in Decatur. The public health nurse (PHN) will obtain the first sputum specimen and provide the client with two

additional containers for collection and mailing of the next two consecutive early morning sputum specimens to the State

Laboratory. Instruction should be given to both client and family on how to properly produce sputum for examination. Seek client confirmation regarding mailing of specimens and check with the laboratory to confirm receipt of specimens. If necessary, the PHN should collect and mail the specimens.

3. Collect blood to obtain baseline measurements for the following lab tests:
   a. Obtain **aspartate aminotransferase** (AST) **[formerly, serum glutamic oxaloacetic transaminase (SGOT)],** alanine aminotransferase (ALT) **[formerly, serum glutamic-pyruvic transaminase (SGPT)],** bilirubin, alkaline phosphatase, CBC with platelet count, serum uric acid, serum creatinine**, and Hepatitis C Ab** for all adults. **If glucose is above normal range, obtain a hemoglobin A1C at next visit. On known diabetics, obtain a hemoglobin A1C with baseline lab tests.** These are not offered by the State Laboratory. (See REFERRAL section on page **6.11-12)**.
   b. **Hepatitis B profile should be obtained for all adults and anyone less than 18 years who is foreign-born.**
   c. All individuals will be tested for HIV using the opt-out approach. Consent is inferred unless client declines testing. If HIV-infected, collaborate with HIV Program to obtain CD4 T-cell count, then refer to consulting physician. (See REFERRAL section on pp. **6**.**11-12)**.

4. Obtain baseline visual acuity testing and red/green color discrimination for clients being placed on ethambutol.

5. Pregnancy test, if indicated.

6. Baseline weight. (Compare client's baseline weight to usual weight for increase or decrease.)

7. **Record height. Calculate current BMI using the tools at the following website:**
   http://www.cdc.gov/healthyweight/assessing/bmi/

THERAPEUTIC

PHARMACOLOGIC

NOTE: Order medications for treatment with directly observed therapy (DOT) from drug stock and send a copy of the drug order(s) to the District Pharmacist or District Drug Coordinator.

1. Order DOT for all doses until completion of treatment (see Tables 1 and 2 on pages **6.5** and **6.6** for options and dosages).

2. Pyridoxine (Vitamin B_6) 25 - 50 mg PO daily, to prevent the development of isoniazid-induced peripheral neuropathy.

Table 1: Regimen Options - Treatment of Clients with Drug-Susceptible TB

Option	Total Duration (Months)	Initial Phase		Continuation Phase		Comments
		Drugs*	Interval, Duration & # of Doses	Drugs	Interval, Duration & # of Doses	
1	6	Isoniazid Rifampin Pyrazinamide Ethambutol	Daily DOT for 40 doses	Isoniazid Rifampin	Daily DOT for 90 doses OR Twice-Weekly DOT for 36 doses **OR** Thrice-Weekly DOT for 54 doses	Regimen must be directly observed Continue ethambutol until susceptibility to isoniazid and rifampin is demonstrated.
2	6	Isoniazid Rifampin Pyrazinamide Ethambutol	Daily DOT for 10 doses, then twice-weekly DOT for 12 doses	Isoniazid Rifampin	Twice-Weekly DOT for 36 doses	Regimen must be directly observed. Include ethambutol in initial phase. After the initial phase, continue ethambutol until susceptibility to isoniazid and rifampin is demonstrated.

NOTE: DOT 5 days/week = Monday through Friday. Weekend doses will not be counted toward the total doses.

* Pyridoxine (Vitamin B_6) 25- 50 mg/daily should be added to all regimens to prevent development of isoniazid-induced peripheral neuropathy.

NOTE: Split dosing should be avoided.

NOTE: Rifamate, a fixed combination of Rifampin 300 mg, and Isoniazid 150 mg, may be used to minimize the number of pills. Intermittent dosing is not recommended with fixed combination medications.

NOTE: Refer to current drug reference or drug package insert for a complete list of adverse drug reactions and drug interaction

Table 2: First-Line TB Drugs

Drugs	Adult Dose in mg per kg* (Maximum Dose)			Adverse Reactions
	Daily	Twice-Weekly	Thrice-Weekly	
Isoniazid	5 **mg/kg** (Maximum Dose 300 mg)	15 **mg/kg** (Maximum Dose 900 mg)	15 **mg/kg** (Maximum Dose 900 mg)	Hepatic enzyme elevation, Hepatitis, Peripheral neuropathy, Mild effects on central nervous system, Drug interactions, Gastrointestinal (GI) upset.
Rifampin**	10 **mg/kg** (Maximum Dose 600 mg)	10 **mg/kg** (Maximum Dose 600 mg)	10 **mg/kg** (Maximum Dose 600 mg)	GI upset, Drug interactions, Hepatitis, Bleeding problems, Influenza-like symptoms, Rash, Orange discoloration of body fluids and secretions.
Pyrazinamide	15-30 **mg/kg** (Maximum Dose 2 gm)	50-70 **mg/kg** (Maximum Dose 4 gm)	50-70 **mg/kg** (Maximum Dose 3 gm)	Hepatitis, Rash, GI upset, Joint aches, Hyperuricemia Gout (rare).
Ethambutol***	15-25 **mg/kg** (Maximum Dose 1.6 gm)	50 **mg/kg** (Maximum Dose 4 gm)	25-30 **mg/kg** (Maximum Dose 2.4 gm)	Optic neuritis.

*Formula used to convert pounds to kilograms: Divide pounds by 2.2 to get kilograms.
Example: Client weighs 154 pounds ÷ 2.2 = 70 kilograms.

**Adults should receive 600 mg of Rifampin. If their weight is 44 kg or less, use 10 mg per kg.

NOTE: Ethambutol is generally not recommended for children whose visual acuity cannot be monitored (less than six years of age).

*** Calculate Ethambutol dosage based on total body weight (TBW). **NOTE:** Round up fractions of a dose to the nearest whole number. Massively obese clients are considered complicated cases. (See *Referral Section*, item # 2).

Directly Observed Therapy (DOT) is mandatory.

NOTE: Refer to current drug reference or drug package insert for a complete list of adverse drug reactions and drug interactions.

Note: EMB, PZA dosage adjustment may be needed if there is renal impairment (See reference #17: Lexicomp).

CLIENT EDUCATION/COUNSELING

Education/communication should use methods adapted to client's cultural and linguistic background. Provide education to the client and his/her family, when family is available**,** regarding the following:

1. TB transmission.

2. TB isolation measures.

3. A client is considered infectious until he/she has met all of the following requirements:
   a. Is on adequate therapy (minimum of 2 weeks),
   b. Has had a significant clinical response to therapy, AND
   c. Has had three consecutive negative AFB sputum smear results from sputum collected on different days.

4. Confinement of the client to a room in an institution or at home, with as few visitors as possible. Anyone entering the room/home should wear respiratory protection (N95 particulate respirator).

5. The use of the surgical mask by the client, especially when going to a doctor's office, during the period when he/she is still considered to be infectious.

6. The use of tissues to cover the nose/mouth when coughing/sneezing and proper tissue disposal.

7. The rationale for continuous uninterrupted chemotherapy.

8. The importance of regularly scheduled visits for medical supervision.

9. Signs and symptoms of possible side effects of the anti-tuberculosis medications and what the client should do if symptoms should occur. Instruct client to report immediately any symptoms suggesting hepatitis or adverse reactions: loss of appetite, nausea, vomiting, persistently dark urine, jaundice (yellowish skin/sclera), malaise, unexplained fever for three or more days, abdominal tenderness**,** flu-like symptoms, peripheral neuropathy and joint pain/swelling.

10. Directly observed therapy (DOT) and how the client and the health care worker will be working together to make DOT successful.

11. The signs and symptoms of disease, with instructions to report to the health department or their physician if this should occur.

12. The relationship between HIV infection and TB.

13. The importance of HIV testing for all clients with suspected or active tuberculosis.

14. The rationale and importance of a contact investigation.
15. The rationale for using an alternative or back-up method of birth control (e.g., copper-bearing IUD such as ParaGard, condoms, diaphragm) is that when rifampin is prescribed, it reduces effectiveness (degree depending on method) of combined oral contraceptives, progestin-only oral contraceptives, levonorgestrel implants, Depo-Provera, patch and ring. Advise condom back- up. (Table **4** on page **6**.**14** – Drug Interactions - Rifampin).

16. The client's immunization status. Assess and administer vaccines indicated according to the current Advisory Committee on Immunization Practices (ACIP) childhood or adult immunization schedule. **Although no data exist regarding whether measles, varicella or live varicellla vaccine exacerbates TB, vaccination is not recommended for persons who have untreated active TB.** See the Georgia Immunization Program Manual, Recommended Schedule and Guidelines, for current ACIP schedules and administration guidelines for each vaccine. The Georgia Immunization Manual may be accessed on line at **http://www.health.state.ga.us/programs/immunization/publications.asp**

17. If smoker or tobacco user, refer to a local cessation program and/or the Georgia Tobacco Quit Line, 1-877-270-STOP (7867).

18. If substance abuse known or suspected, refer for appropriate counseling.

FOLLOW-UP

1. Continued client management/follow-up by a case management team comprised of the client, nurse, physician and others determined by an individual needs assessment.

2. After the nursing assessment, the Public Health Nurse (PHN) will forward the following clinical data to be reviewed by the district TB coordinator, the district's contract physician and the state office:

a. Complete health history and pertinent physical findings.
b. Hospital discharge summaries (if available).
c. Treatment assessment and plan for DOT.
d. All other pertinent clinical data (e.g., prior chest x-rays, if available, and lab work).

3. Monitor client(s) monthly for adverse drug reactions, drug-drug interactions, drug-food interactions, drug-lab interactions, infectious status, and clinical and bacteriologic response to therapy (see Tables **3, 4 and 5** on pages **6.**1**3 – 6**.1**6** for drug interactions).

4. Provide HIV test results with post-test counseling to client and, if positive, appropriate referral to HIV care. Seek confirmation that client kept referral appointment for HIV care.

5. Conduct a contact investigation following the *Georgia TB Program Policy and Procedure Manual* (current edition) and the *CDC Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis* (current edition) to include:
   a. The initial interview of the index **client** should be done by the PHN or designee (e.g., Communicable Disease Specialist) for all cases and suspects in the hospital (preferred) or within one to three working days of health department notification. The follow-up interview should occur 1-2 weeks later, preferably in the **client's** home.
   b. Start screening with high priority contacts in home, work, school and social environments. High priority contacts would be those persons with the greatest intensity, frequency and duration of exposure with the person who has infectious TB. Take into consideration risk factors (see item c) as well as exposure in determining high priority contacts. **NOTE:** High-priority contacts should be examined within seven working days. Medium priority contacts should be examined within fourteen calendar days. Low priority contacts should be examined within thirty calendar days.
   c. High priority contacts who are considered a medical risk should be examined immediately regardless of initial TST results. Those persons are at particularly high risk of developing TB disease once infected with *M. tuberculosis* and would include children less than 5 years of age and persons with immune systems compromised by HIV infection, immunosuppressive medications (prednisone, cancer chemotherapy, anti-rejection drugs for cancer therapy, tumor necrosis factor alpha agents antagonists) and certain medical conditions (diabetes mellitus, silicosis,

end stage renal disease, cancer of the head and neck, reticuloendothial diseases [e.g., lymphoma, leukemia], gastric or jejunoileal bypass surgery). Those contacts should have a chest x-ray and be placed on isoniazid if the chest x-ray is negative for active TB disease for either window period treatment or a full course of treatment (see current edition of *Georgia TB Program Policy and Procedure Manual* on Contact Investigation).

d. Expand the contact investigation if there is evidence of recent transmission such as a higher than expected infection rate in high priority contacts, a secondary case of TB disease, infection in a child less than five years, or a converter.

e. Contact information should be entered on the *TB Contact Investigation Report Form* (Form #3126) and promptly entered into SENDSS.

6. Obtain a sputum specimen for AFB smear/culture upon completion of the initial phase of treatment (a minimum of 22 doses) to identify clients at increased risk for relapse. Obtain a monthly sputum specimen for AFB culture after client is culture negative.

7. Perform the following blood chemistry tests monthly to monitor reactions to TB drugs: AST (SGOT), ALT (SGPT), bilirubin, alkaline phosphatase and CBC with platelets. Perform serum uric acid and serum creatinine monthly if there are abnormalities at baseline or there are clinical reasons to obtain the measurements (e.g., hepatitis B or C virus infection, alcohol abuse, abnormal kidney function).

8. Discontinue the isoniazid or rifampin and report immediately to the consulting physician if any of the following occur:
   a. AST/ALT levels equal to or greater than 3 times the upper limit of normal in the presence of symptoms of adverse events.
   b. AST/ALT levels equal to or greater than 5 times the upper limit of normal in an asymptomatic client.
   c. Client reporting symptoms of adverse reactions.

9. Monitor the vision of clients taking ethambutol by providing vision checks monthly, including visual acuity and red/green color discrimination.

10. Use incentives and enablers to enhance adherence to therapy. These may be as simple as offering a cup of coffee and talking

with a client who is waiting in the clinic, or as complex as providing food and housing for a homeless client.

11. Observe the client for isoniazid-induced peripheral neuropathy during the course of therapy and report to the delegating physician. (Consulting physician may recommend pyridoxine to correct these complaints, if not already on pyridoxine, or increasing the pyridoxine dosage).

12. Treatment completion is defined by the number of doses taken as well as the duration of treatment. The number of doses required is listed in Table 1, page **6**.5.

CONSULTATION

Consult with the consulting physician:

1. Before changing to the continuation phase of Regimen Options (1) or (2) (see Table 1, page **6.5**), and regarding complications that would require reevaluation of the client and possible new treatment recommendations.

2. If susceptibility results show resistance to any of the first-line drugs.

3. If the client remains symptomatic or smear or culture positive after two months.

4. If the client's HIV test result is positive.

5. If the client refuses HIV testing.

6. To discuss abnormal laboratory test results.

7. If the client is not compliant with DOT.

REFERRAL

1. Refer clients for other medical and social services as needed, particularly alcohol or drug abuse treatment, **diabetes care (if hemoglobin A1C is 6.5% or higher)** and HIV care.

2. Refer all of the following categories of complicated suspects/cases to the consulting physician: drug-resistant, multidrug-resistant, extrapulmonary, children, HIV-infected clients, pregnant women, breast-feeding women, clients with acute or

chronic medical conditions (e.g., diabetes, cancer, renal disease), relapse cases and morbidly obese clients **(BMI over 30).**

3. Refer client to a licensed dietitian (LD), if indicated. This will be especially important if the client has a history of drug or alcohol abuse, is breast-feeding, is HIV-infected, has GI side effects from TB drugs or if desirable weight is not maintained.

4. Refer client to other resources for laboratory tests such as AST (**formerly SGOT**), ALT (**formerly SGPT**), bilirubin, alkaline phosphatase, CBC with platelet count, serum uric acid, serum creatinine, **hemoglobin A1C and Hepatitis C Ab.**

5. Refer to the Georgia TB Reference Guide (current edition) for treatment timelines.

Table 3: TREATMENT OF TB - DRUG INTERACTIONS (Format 1)

DRUG INTERACTIONS - RIFAMPIN

Drug	Effects on Drug
Anticoagulants (warfarin, coumadin)	↓ serum concentration
Cardiac glycosides (digoxin)	↓ serum concentration
Oral hypoglycemics	↓ serum concentration
Oral contraceptives, contraceptive implants, patch, ring, Depo-Provera	↓ efficacy
Corticosteroids	↓ serum concentration
Narcotics/analgesics (methadone)	↓ serum concentration
Dapsone	↑ clearance
Cyclosporin	↓ serum concentration
Quinidine	↓ peak serum concentration
Protease inhibitors	↓ serum concentration

DRUG INTERACTIONS – ISONIAZID

Drug	Effects on Drug
Diazepam (valium)	↓ clearance ↑ half life (time to xcreted)
Phenytoin (dilantin)	↑ plasma concentration ↑ toxicity

NOTE: Refer to current drug reference or drug package insert for a complete list of adverse drug reactions and drug interactions.

Table 4: TREATMENT OF TB - DRUG INTERACTIONS (Format 2)

DRUG INTERACTIONS - RIFAMPIN

Rifampin (Rifadin) plus...	
Adefovir	Increases risk of side effects.
Amprenavir	Should not be used together.* Significantly decreases amprenavir levels in blood.
Anticoagulants	May decrease effectiveness of anticoagulants.
Atovaquone	Decreases atovaquone levels by 50% in blood.
AZT	May decrease AZT levels in blood.
Barbiturates	May decrease effectiveness of barbiturates.
Clarithromycin	Decreases clarithromycin levels by 120% in blood.
Corticosteroids	May decrease corticosteroid levels in blood.
Cyclosporine	May decrease cyclosporine levels in blood.
Dapsone	Decreases dapsone levels by 7- to 10-fold in blood.
Delavirdine	Should be taken together otherwise delavirdine levels in blood significantly decreased.
Diazepam	May decrease effectiveness of diazepam.
Digitalis	May decrease effectiveness of digitalis.
Disopyramide	May decrease effectiveness of disopyramide.
Efavirenz	Decreases efavirenz levels by 26% in blood.
Estrogen	May decrease effectiveness of estrogen.
Ethinyl Estradiol (birth control pills)	May decrease ethinyl estradiol levels in blood.
Fluconazole	Decreases fluconazole levels by 23% in blood.
Halothane	May increase risk of liver toxicity.
Indinavir	May increase rifampin levels in blood. Should not be used together.*
Isoniazid	May increase risk of liver toxicity.
Itraconazole	May decrease itraconazole levels in blood.
Ketoconazole	Significantly decreases ketoconazole levels in blood. Should not be used together.*
Lopinavir/ritonavir	Decreases lopinavir levels by 75% in blood. Should not be used together.
Methadone	May decrease effectiveness of methadone.
Mexilitine	May decrease effectiveness of mexilitine.
Nelfinavir	Decreases nelfinavir levels by 82% in blood. Should not be used together.*
Nevirapine	May affect rifampin and/or nevirapine levels in blood.
Probenecid	Increases rifampin levels in blood.
Progesterone	May decrease effectiveness of progesterone.
Quinidine	May decrease quinidine levels in blood.
Ritonavir	Decreases ritonavir levels by 35% in blood.
Saquinavir (hard gel)	Decreases saquinavir levels by 80% in blood. Should not be used together.*
Saquinavir (soft gel)	Decreases saquinavir levels by 84% in blood.

Rifampin (Rifadin) plus...	
Sulfonylureas (oral hypoglycemic drugs)	May decrease sulfonylurea levels in blood.
Theophylline	May decrease theophylline levels in blood.
Verapamil	May decrease effectiveness of verapamil.

* The information on interactions with rifampin and **HIV antiretroviral therapy (ART)** is constantly changing. Consult with the consulting physician/contract physician. In general, only certain **HIV medications** can be used and rifampin may be replaced by rifabutin. Rifabutin is in the formulary at the state pharmacy.

NOTE: Refer to current drug reference or drug package insert for a complete list of adverse drug reactions and drug interactions.

Table 5: DRUG INTERACTIONS – ISONIAZID

Isoniazid plus...	
Alcohol	May increase risk of isoniazid associated hepatitis.
Antacids	Should be taken two hours apart otherwise isoniazid will have no effect.
Carbamazepine	Decreases carbamazepine metabolism.
Cycloserine	May increase risk of central nervous system toxicity.
Ethionamide	May increase risk of encephalopathy (dysfunction of the brain) and may increase isoniazid levels in blood.
Phenytoin	Decreases phenytoin metabolism.

NOTE: Refer to current drug reference or drug package insert for a complete list of adverse drug reactions and drug interactions.

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STANDARD NURSE PROTOCOL FOR LATENT TUBERCULOSIS INFECTION (LTBI)

DEFINITION

Latent tuberculosis infection (LTBI) means that a person has been infected with *Mycobacterium tuberculosis* but has no clinical or radiographic evidence of TB. Individuals who are infected but do not have active disease are not infectious but, if not adequately treated, are at risk for developing disease and becoming infectious in the future.

Candidates for treatment of LTBI include:

1. Persons in the following high-risk groups should be given treatment for LTBI if they have positive skin test results of equal to or greater than 5 mm:
   a. HIV-positive persons.
   b. Recent contacts to a TB case.
   c. Persons with fibrotic changes on chest radiograph consistent with old TB.
   d. Persons with organ transplants and other immuno-suppressed persons (those receiving the equivalent of equal to or greater than15 mg daily of prednisone for 1 month or longer).

2. Persons in the following high-risk groups should be considered for treatment of LTBI if their reaction to the tuberculin skin test is equal to or greater than10 mm:
   a. Recent arrivals (less than 5 years) from high prevalence countries.
   b. Injection drug users.
   c. Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes and other long-term facilities for the elderly, homeless shelters, residential facilities for AIDS clients, hospitals and other health care facilities).
   d. Mycobacteriology laboratory personnel.
   e. Persons with clinical conditions that place them at high risk of progression to TB disease (e.g., substance abuse, infection with *M. tuberculosis* within the past two years, diabetes, hematologic or reticuloendothelial malignancies, chronic renal failure, post-gastrectomy, silicosis, immunosuppressive therapy, chronic malabsorption syndromes or candidates being considered for treatment with tumor necrosis factor (TNF) antagonists such as injectable Remicade [Infliximab] for rheumatologic conditions or ulcerative colitis prior to initiation of therapy).
   f. Children less than 5 years of age, or children and adolescents exposed to adults in high-risk groups.

3. Persons with no risk factors for TB should be considered for treatment of LTBI if their reaction to the tuberculin skin test is greater than or equal to 15 mm.

Treatment of LTBI might NOT be indicated for:

1. Persons at increased risk for adverse reactions to isoniazid and persons for whom isoniazid is contraindicated.

2. Persons who cannot tolerate isoniazid or rifampin.

3. Persons likely to be infected with drug-resistant *M. tuberculosis*. **NOTE:** They should be referred to the consulting physician.

4. Persons who are not likely to complete a course of treatment for LTBI (e.g., some homeless persons or migrant farm workers).

Treatment of LTBI might NOT be completed on:

1. Persons who are a contact to a TB suspect later found not to have TB. NOTE: They should be referred to the consulting physician.

ETIOLOGY The agent is the *Mycobacterium tuberculosis* complex.

SUBJECTIVE

1. May have a history of known exposure to TB.

2. Negative history of risk factors indicating special precautions needed for persons receiving isoniazid therapy:
   a. Concurrent use of any other medications on a long-term basis, or medications that may cause interactions.
   b. Alcohol abuse.
   c. Previous discontinuation of isoniazid because of side effects.
   d. Chronic liver disease.
   e. Peripheral neuropathy.
   f. Pregnancy.
   g. Injection drug abuse.

3. No known allergies to anti-tuberculosis drugs.

4. Absence of symptoms of TB.

OBJECTIVE

1. A positive Mantoux tuberculin skin test per current

programmatic guidelines and no clinical symptoms of active disease,

AND

2. Chest x-ray negative for evidence of tuberculosis disease,

AND

3. Absence of clinical signs of TB**,** both pulmonary and extra-pulmonary.

4. Negative sputum smears (3 consecutive) and culture with evaluation by clinician if signs and symptoms of TB disease are evident.

ASSESSMENT

1. Latent tuberculosis infection (LTBI) (without signs/symptoms of tuberculosis disease).

2. No contraindications to isoniazid or rifampin.

3. No history of documented infection from or exposure to drug-resistant *M. tuberculosis* source case.

PLAN **DIAGNOSTIC STUDIES**

1. If documented tuberculin skin test results cannot be verified (including millimeters [mm] of induration), perform a Mantoux tuberculin skin test per programmatic guidelines. **Vaccination with live viruses may interfere with tuberculin skin test reactions. For persons scheduled to receive a tuberculin skin test, testing should be done as follows: Either on the same day as vaccination with live-virus vaccine or 4-6 weeks after the administration of the live-virus vaccine. At least one month after smallpox vaccination.**

2. Baseline weight. (Compare client's baseline weight to usual weight for increase or decrease).

3. Collect blood to obtain baseline measurements for the following lab tests:

   a. AST (SGOT), ALT (SGPT), alkaline phosphatase and bilirubin.
   b. All individuals will be tested for HIV using the opt-out approach. Consent is inferred unless client declines testing.
   c. Hepatitis B and C profile, if indicated (e.g., history of injection drug use, foreign birth in Asia or Africa, HIV infection).

NOTE: The baseline lab measurements are not mandatory for children less than 16 years of age, unless a complicating medical condition (e.g., HIV, liver disease, renal disease, cardiac disease) or lifestyle is known or suspected.

4. Pregnancy test, if indicated.

THERAPEUTIC

PHARMACOLOGIC

Refer to options, dosages and interactions of isoniazid and rifampin in Tables A – **G** on pages **6.26 - 6.33**.

1. Order medication for treatment in children and adults from drug stock and send copies of the drug orders to the District Pharmacist/Drug Coordinator.

2. Add pyridoxine (Vitamin B_6) 25-50 mg PO daily for adults on isoniazid, to prevent the development of isoniazid - induced peripheral neuropathy (see FOLLOW-UP on page **6**.2**3**).

   NOTE: Directly Observed Preventive Therapy (DOPT) is recommended for all children up to the age of 15 years. DOPT should also be considered for clients who are at high risk for TB and whose adherence to LTBI therapy is questionable.

CLIENT EDUCATION/COUNSELING

Education/communication should use methods adapted to client's cultural and linguistic background. Provide education to the client and his/her family regarding the following:

1. The rationale for treatment of LTBI and the importance of attending regularly scheduled clinic appointments.

2. The difference between "latent TB infection" (LTBI) and "TB disease" and what a "positive skin test" means.

3. The signs and symptoms of TB disease and the need to report immediately if anyone has these symptoms.

4. The symptoms of adverse reactions to isoniazid/rifampin, including: GI disturbances (anorexia, heartburn, nausea, vomiting, gas, cramps, diarrhea), hepatitis (loss of appetite, persistently dark urine, yellowish skin/sclera, malaise, unexplained fever for three or more days, abdominal tenderness) and peripheral neuropathy (see Table C on page **6**.**28**). Advise the client to report immediately to the Public Health Nurse or clinician if any such symptoms occur during treatment.

5. The relationship between HIV infection and TB infection and the importance of HIV testing for all TB-infected individuals.

6. The rationale for using an alternative or back-up method of birth control (e.g., copper-bearing IUD such as ParaGard, condoms, diaphragm) is that when rifampin is prescribed, it reduces effectiveness (degree depending on method) with combined oral contraceptives, progestin-only oral contraceptives, levonorgestrel implants, Depo-Provera, patch and ring. Advise condom back-up (see Tables D and E on pages **6**.**29** – **6.30**).

7. The client's immunization status. Assess and administer vaccines indicated according to the current Advisory Committee on Immunization Practices (ACIP) childhood or adult immunization schedule. **Although no data exist regarding whether measles, varicella or live varicellla vaccine exacerbates TB, vaccination is not recommended for persons who have untreated active TB.** See the Georgia Immunization Program Manual, Recommended Schedule and Guidelines, for current ACIP schedules and administration guidelines for each vaccine. The Georgia Immunization Manual may be accessed on line at **http://www.health.state.ga.us/programs/immunization/publications.asp**

8. If smoker or tobacco user, refer to a local cessation program and/or the Georgia Tobacco Quit Line, 1-877-270-STOP (7867).

9. If substance abuse known or suspected, refer for appropriate counseling.

FOLLOW-UP

1. At least once a month, evaluate for:

   a. Adherence to the prescribed regimen.
   b. Symptoms of hepatitis (nausea, loss of appetite, vomiting, persistently dark urine, yellowish skin, malaise,

unexplained elevated temperature for more than three days, abdominal tenderness and/or right upper quadrant tenderness).

c. Symptoms of neurotoxicity such as paresthesia of hands or feet.
d. Maintenance of desirable weight.
e. Adverse effects of prescribed regimen.

2. At follow-up visits, ask clients about adherence to therapy.

3. Provide the HIV test result with post-test counseling and, if the test is positive, appropriately refer for HIV care. Seek confirmation that client kept referral appointment for HIV care.

4. **All clients on isoniazid or rifampin should be assessed for presence of symptoms of hepato-toxicity at every encounter.**

   Clients considered at risk of hepato-toxicity (i.e., those with any admission of alcohol use, HIV, Hepatitis B, Hepatitis C, IV drug use, chronic liver disease, pregnancy/post-partum state) need to have aspartate aminotransferase (AST) [formerly, serum glutamic oxaloacetic transaminase (SGOT)], alanine aminotransferase (ALT) [formerly, serum glutamic-pyruvic transaminase (SGPT)], done monthly.

5. Observe for isoniazid-induced peripheral neuropathy during the course of isoniazid therapy. When peripheral neuropathy is present and/or persists, report to the consulting physician.

6. **Pregnant** women, particularly African-American and Hispanic women, may be at increased risk for fatal hepatitis associated with isoniazid, according to some reports. This risk may be increased during the postpartum period. These clients should be closely monitored for adverse reactions throughout the course of treatment. **The risk of hepatitis from INH in pregnant/post-partum women does NOT preclude treatment of LTBI in such a woman who is extremely high risk for developing active TB (e.g., close contact, HIV-infected, or with documented recent infection or conversion.**

7. Discontinue the isoniazid or rifampin and report immediately to the consulting physician if any of the following occur:
   a. AST/ALT levels equal to or greater than 3 times the upper limit of normal in the presence of symptoms of adverse events.

b. AST/ALT levels equal to or greater than 5 times the upper limit of normal in an asymptomatic client.

c. **If the client reports any symptoms of adverse reactions obtain AST/ALT immediately and notify consulting physician.**

d. **Any hospital admissions or deaths due to adverse reactions are to be reported immediately to the State TB Program.**

8. A clinical symptom screen is required for all clients who have a lapse in treatment. A repeat chest x-ray/evaluation is required for clients who are symptomatic or who have had a lapse in therapy for LTBI for two month or more.

9. **Treatment completion is defined by the number of doses taken as well as the duration of treatment. The number of doses required is listed in Tables A and B, pp. 6.26 – 6.27.**

CONSULTATION

Consult with the TB Program medical consultant or consulting physician:

1. Regarding any complications of treatment for LTBI with clients placed on isoniazid or rifampin (see Table A on page **6.26** and Tables C, D, E and F on pages **6**.2**8** – **6**.3**0** for drug interactions, drug adverse reactions and drug monitoring).

2. If a client's HIV test result is positive, or if a client at risk refuses HIV testing.

3. About any abnormal lab test results.

REFERRAL

1. Refer clients for other medical and social services as needed, particularly alcohol or drug abuse treatment and HIV care.

2. Refer all clients with complications (pregnant women **with active TB disease**, breast-feeding women, clients with acute or chronic conditions, clients infected with drug-resistant TB, HIV-infected clients taking protease inhibitors) to the consulting physician.

Table A: TREATMENT OF LATENT TUBERCULOSIS INFECTION (LTBI) - FIRST- LINE DRUG AND REGIMEN OPTIONS

Drug	Dose in mg/kg* (Maximum Dose)					Adverse Reactions	Monitoring	Comments
	Option One Daily		Option Two Twice-Weekly*		Option Three Thrice-Weekly*			
	Children***	Adults	Children	Adults	Adults			
Isoniazid**	10-20 mg/kg (Maximum Dose 300 mg) PO•	5 mg/kg (Maximum Dose 300 mg) PO•	20-40 mg/kg (Maximum Dose 900 mg) PO•	15 mg/kg (Maximum Dose 900 mg) PO•	15 mg/kg (Maximum Dose 900 mg) PO•	Hepatic enzyme elevations, Hepatitis, Peripheral neuropathy, Mild effects on central nervous system, Drug interactions, GI upset	Baseline measurements of hepatic enzymes for adults Repeat measurements: – if baseline results are abnormal – if client is at high-risk for adverse reactions – if client has symptoms of adverse reactions	Hepatitis risk increases with age and alcohol consumption Pyridoxine can prevent isoniazid-induced peripheral neuropathy

Isoniazid

*Formula used to convert pounds to kilograms: Divide pounds by 2.2 to get kilograms. *Example: Client weighs 154 pounds ÷ 2.2 = 70 kilograms*.

Should consider adding pyridoxine 25 - 50 mg **daily (Vitamin B_6) as part of routine preventive treatment of isoniazid-induced peripheral neuropathy for adults.

***Refer to **Table G on page 8.31** for daily pediatric dosages of isoniazid.

• Medication may be given by mouth or compounded for rectal or oral administration.

NOTE: Regarding treatment of LTBI with isoniazid in children: The number of treatments and time duration for treatment is the same for children and adults. The mg/kg dose is different for children (see Table B: **Treatment of LTBI**).

Table B: TREATMENT OF LTBI - RECOMMENDED DRUG REGIMENS FOR ADULTS

Drug	Interval and Duration	Adult Dosage mg/kg * (maximum)	Criteria for Completion	Comments
Isoniazid	Daily self-adm for 9 mo Daily DOT for 9 mo ♦ Twice-Weekly DOT for 9 mo**	5 **mg/kg** (**Maximum dose** 300 mg) PO 5 **mg/kg** (**Maximum dose** 300 mg) PO 15 **mg/kg** (**Maximum dose** 900 mg) PO	270 doses within 12 mo **190** doses within 12 mo 76 doses within 12 mo	*Preferred regimen for all persons.* In HIV-infected clients, isoniazid may be administered concurrently with NRTIs, protease inhibitors, or NNRTIs. *DOT must be used with twice-weekly dosing.* **NOTE:** Not recommended for HIV-infected clients.
Isoniazid	Daily self-adm for 6 mo Daily DOT for 6 mo ♦ Twice-Weekly DOT for 6 mo	5 **mg/kg** (**Maximum dose** 300 mg) PO 5 **mg/kg** (**Maximum dose** 300 mg) PO 15 **mg/kg** (**Maximum dose** 900 mg) PO	**180** doses within 9 mo 130 doses within 9 mo 52 doses within 9 mo	Offer if preferred or alternative regimens not feasible. Not indicated for persons with HIV infection or fibrotic lesions. Not indicated for children. *DOT must be used with twice-weekly dosing.*
Rifampin	Daily self-adm for 4 mo (18 weeks) Daily DOT for 4 mo (18 weeks) ♦	10 **mg/kg** (**Maximum dose** 600 mg) PO	120 doses within 6 mo **90** doses within 6 mo	For persons who are contacts of clients with isoniazid-resistant, rifampin susceptible TB.

♦ DOT 5 days a week = Monday - Friday.

*Formula used to convert pounds to kilograms: Divide pounds by 2.2 to get kilograms. *Example: Client weighs 154 pounds ÷ 2.2 = 70 kilograms.*

NOTE: One month is 4.3 weeks.

Table C: TREATMENT OF LTBI - DRUG ADVERSE REACTIONS AND MONITORING

Drug	Adverse Reactions	Monitoring	Comments
Isoniazid	Hepatic enzyme elevations, hepatitis, peripheral neuropathy, mild effects on central nervous system, drug interactions, gastrointestinal (GI) upset.	Baseline measurements of AST for adults. Repeat measurements: – if baseline results are abnormal – if client is at high-risk for adverse reactions – if client has symptoms of adverse reactions	Hepatitis risk increases with age and alcohol consumption. Pyridoxine can prevent isoniazid-induced peripheral neuropathy.
Rifampin	GI upset, drug interactions, hepatitis, thrombocytopenia, rash, fever, Influenza-like symptoms, orange discoloration of body fluids (secretions, tears, urine).	Complete blood count, platelets and liver function tests. Repeat measurements if: – baseline results are abnormal – client has symptoms of adverse reactions	Hepatitis risk increases with age and alcohol consumption.

Table D: TREATMENT OF LTBI - DRUG INTERACTIONS (Format 1)

DRUG INTERACTIONS - RIFAMPIN

Drug	Effects on Drug
Anticoagulants (warfarin, coumadin)	↓ serum concentration
Cardiac glycosides (digoxin)	↓ serum concentration
Oral hypoglycemics	↓ serum concentration
Oral contraceptives, contraceptive implants, patch, ring, Depo-Provera	↓ efficacy
Corticosteroids	↓ serum concentration
Narcotics/analgesics (methadone)	↓ serum concentration
Dapsone	↑ clearance
Cyclosporin	↓ serum concentration
Quinidine	↓ peak serum concentration
Protease inhibitors	↓ serum concentration

DRUG INTERACTIONS – ISONIAZID

Drug	Effects on Drug
Diazepam (valium)	↓ clearance ↑ half life (time to excreted)
Phenytoin (dilantin)	↑ plasma concentration ↑ toxicity

NOTE: Refer to current drug reference or drug package insert for a complete list of adverse drug reactions and drug interactions.

Table E: TREATMENT OF LTBI - DRUG INTERACTIONS (Format 2)

DRUG INTERACTIONS - RIFAMPIN

Rifampin (Rifadin) plus...	
Adefovir	Increases risk of side effects.
Amprenavir	Should not be used together.* Significantly decreases amprenavir levels in blood.
Anticoagulants	May decrease effectiveness of anticoagulants.
Atovaquone	Decreases atovaquone levels by 50% in blood.
AZT	May decrease AZT levels in blood.
Barbiturates	May decrease effectiveness of barbiturates.
Clarithromycin	Decreases clarithromycin levels by 120% in blood.
Corticosteroids	May decrease corticosteroid levels in blood.
Cyclosporine	May decrease cyclosporine levels in blood.
Dapsone	Decreases dapsone levels by 7- to 10-fold in blood.
Delavirdine	Should be taken together otherwise delavirdine levels in blood significantly decreased.
Diazepam	May decrease effectiveness of diazepam.
Digitalis	May decrease effectiveness of digitalis.
Disopyramide	May decrease effectiveness of disopyramide.
Efavirenz	Decreases efavirenz levels by 26% in blood.
Estrogen	May decrease effectiveness of estrogen.
Ethinyl Estradiol (birth control pills)	May decrease ethinyl estradiol levels in blood.
Fluconazole	Decreases fluconazole levels by 23% in blood.
Halothane	May increase risk of liver toxicity.
Indinavir	May increase rifampin levels in blood. Should not be used together.*
Isoniazid	May increase risk of liver toxicity.
Itraconazole	May decrease itraconazole levels in blood.
Ketoconazole	Significantly decreases ketoconazole levels in blood. Should not be used together.*
Lopinavir/ritonavir	Decreases lopinavir levels by 75% in blood. Should not be used together.
Methadone	May decrease effectiveness of methadone.
Mexilitine	May decrease effectiveness of mexilitine.
Nelfinavir	Decreases nelfinavir levels by 82% in blood. Should not be used together.*
Nevirapine	May affect rifampin and/or nevirapine levels in blood.
Probenecid	Increases rifampin levels in blood.
Progesterone	May decrease effectiveness of progesterone.
Quinidine	May decrease quinidine levels in blood.
Ritonavir	Decreases ritonavir levels by 35% in blood.
Saquinavir (hard gel)	Decreases saquinavir levels by 80% in blood. Should not be used together.*
Saquinavir (soft gel)	Decreases saquinavir levels by 84% in blood.

Rifampin (Rifadin) plus...	
Sulfonylureas (oral hypoglycemic drugs)	May decrease sulfonylurea levels in blood.
Theophylline	May decrease theophylline levels in blood.
Verapamil	May decrease effectiveness of verapamil.

* The information on interactions with Rifampin and **HIV antiretroviral therapy (ART)** is constantly changing. Consult with the consulting physician/contract physician. In general, only certain **HIV medications** can be used and Rifampin may be replaced by rifabutin. Rifabutin is in the formulary at the state pharmacy.

NOTE: Refer to current drug reference or drug package insert for a complete list of adverse drug reactions and drug interactions.

Table F: DRUG INTERACTIONS – ISONIAZID

Isoniazid plus...	
Alcohol	May increase risk of isoniazid associated hepatitis.
Antacids	Should be taken two hours apart otherwise isoniazid will have no effect.
Carbamazepine	Decreases carbamazepine metabolism.
Cycloserine	May increase risk of central nervous system toxicity.
Ethionamide	May increase risk of encephalopathy (dysfunction of the brain) and may increase isoniazid levels in blood.
Phenytoin	Decreases phenytoin metabolism.

NOTE: Refer to current drug reference or drug package insert for a complete list of adverse drug reactions and drug interactions.

Table G: PEDIATRIC DOSAGE

DAILY DOSAGE OF ISONIAZID IN CHILDREN AND ADOLESCENTS

Child's Weight (lbs.)	kg	Daily Dose (mg)
15-21	7-9.5	100
22-29	10-13	150
30-40	14-18	200
41-51	19-23	250
52+	23.5+	300

NOTE: Isoniazid Syrup should not be refrigerated (keep at room temperature). Isoniazid tablets can be crushed for oral administration. Isoniazid tablets are also scored.

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