Protocol for Isoniazid-Rifapentine ("3HP") Regimen for Treatment of TB Infection

Treatment for Mycobacterium tuberculosis infection (TBI) is essential to controlling and eliminating TB disease in the United States. The Centers for Disease Control and Prevention (CDC) has published recommendations for the treatment of TBI using a regimen of isoniazid (INH) and rifapentine (RPT) given once-weekly for 12 weeks and administered by Directly Observed Therapy (DOT). This regimen, also commonly known as the "3HP regimen," is recommended by CDC as an equal alternative to the 9-month daily self-administered INH regimen for treatment of TB infection, and is both safe and effective in children as young as two (2) years old. The 3HP regimen offers the practical advantages of once-weekly administration of 12 doses, and higher rates of TBI treatment completion to prevent TB disease.

**Purpose:** To provide a safe, short and effective regimen for treatment of TBI.

**Indication:** Treatment of TBI as an alternative to 9 months of daily self-administered INH.

**Programmatic priorities for treatment of TBI with the “3HP” regimen:**

1. Recent contacts of persons with infectious TB disease
2. Recent arrivals to the U.S. (< 5 years) from high-prevalence countries
3. Other persons at high risk for progression to TB disease for whom shorter therapy by DOT is advantageous (see TB Manual, Module III, Table III-2)
4. The 12-dose 3HP regimen by DOT for treatment of TBI is preferred over a 9-month regimen of daily self-administered INH in patients who have underlying liver disease or risk for hepatotoxicity

I. ELIGIBILITY

A. **Inclusion Criteria (must meet BOTH criteria):**

1. Otherwise healthy patient age ≥ 2 years; **AND**
2. Positive indirect test for TB infection: either an interferon-gamma release assay (IGRA) or tuberculin skin test (TST)

B. **Exclusion Criteria (must NOT meet any criteria below):**

1. Previously completed an adequate treatment course for TB disease or TB infection

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1 Centers for Disease Control and Prevention. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. MMWR 2011;60:1650-1653.


3 Bliven-Sizemore EE, Sterling TR, et al, for the TB Trials Consortium. Three months of weekly rifapentine plus isoniazid is less hepatotoxic than nine months of daily isoniazid for treatment of LTBI. Int J Tuberc Lung Dis 19(9); 1 September 2015:1039-1044. Published online 10 August 2015. doi: http://dx.doi.org/10.5588/ijtld.14.0829.
2. Has a combination of symptoms and/or signs suggestive of active TB disease (pulmonary or extra-pulmonary), regardless of chest X-ray result
3. HIV-positive and taking antiretroviral medications (HIV expert consultation is required)
4. Has TBI that is known or presumed to be resistant to INH and/or rifampin (RIF)
5. Pregnancy, or patient expects to become pregnant during treatment for TBI, or currently in immediate post-partum period (≤ 3 months since delivery)
6. Allergy to rifamycins or isoniazid
7. Underlying liver disease with elevated baseline transaminases (ALT or AST) ≥ 3X the upper limit of normal (ULN) with or without symptoms, or low platelet count (< 140k/ul)
8. Unable or unlikely to adhere to a once-weekly plan for DOT for 12 weeks

II. BASELINE SCREENING AND EVALUATION
A. Complete TB Risk Assessment Tool (RAT) – if “high risk,” continue below
B. Test for TB infection (TBI) – IGRA or TST (see TB Program Manual, Module 2)
C. Chest X-ray (CXR) – if provider or radiologist’s review suggests active TB disease, immediately refer to TB physician for full evaluation; if no evidence of active TB disease, continue below
D. Clinical evaluation (by TB physician or nurse practitioner)
   1. Baseline vital signs, including weight
   2. Review medical history – note history of liver disease, seizure disorder, symptoms consistent with TB disease, substance abuse (e.g., alcohol, injecting drug, non-injecting drug, etc.), all current medications
   3. Examination including head, neck, lymph nodes, chest, heart, abdomen
   4. If abnormal, evaluate for active TB disease including extra-pulmonary TB or other process; if unremarkable, continue below
E. Diagnosis of TB infection (TBI) – based on clinical and radiographic evaluation
F. Selection of TBI treatment regimen
   1. Clinician to discuss with patient (parent or guardian, if a minor) what the diagnosis of TBI means (especially, as distinguished from active TB disease), and the risks/benefits of treatment for TBI
   2. Discuss regimen options for TBI treatment (see TB Manual, Module 3)
   3. Review inclusion and exclusion criteria for use of 3HP regimen, and patient’s eligibility
   4. Determine and document patient’s interest, preference, and willingness to complete TBI treatment with 3HP regimen by DOT in the health department setting:
      • Take up to 10 tablets at each DOT visit
      • Commit to 12 weeks of treatment
• Availability for DOT as scheduled in the local health department clinic (unless specifically approved by the TB clinician for DOT in another setting)

• Awareness of RPT causing orange body fluids (saliva, sweat, tears, urine, stool, etc.), possible permanent staining of contact lenses and clothing

• Women of child-bearing age need barrier method (e.g., condom, diaphragm, etc.), even if using a hormonal family planning (FP) method

G. Clinician’s orders:

1. Baseline lab tests:
   • Children (age 2 to 17 years) – no laboratory testing generally is necessary; however, consider a urine pregnancy test for adolescent women of childbearing age, if applicable
   • Adults (≥18 years old) – obtain baseline CMP, CBC with platelets, HIV screen (if status unknown); urine pregnancy test for women of childbearing age, if applicable

2. Medication orders:
   • Include all medications (INH, RPT; add pyridoxine for adults age ≥ 18 years old), total mg/dose, dosing frequency (once weekly), and total number of weekly doses (12)
   • Specifically document that the initial dose must be administered in the health department clinic, and subsequent doses may be administered in another setting; ALL doses of 3HP must be administered by DOT.
   • Dosages (see Table 1 below)

<table>
<thead>
<tr>
<th>Patient Weight</th>
<th>Medications &amp; Recommended Dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kilograms</td>
<td>Isoniazid (INH)</td>
</tr>
<tr>
<td>10.0 – 14.0 kg</td>
<td>200 mg/dose</td>
</tr>
<tr>
<td>14.1 – 25.0 kg</td>
<td>300 mg/dose</td>
</tr>
<tr>
<td>25.1 – 32.0 kg</td>
<td>450 mg/dose</td>
</tr>
<tr>
<td>32.1 – 49.9 kg</td>
<td>500 - 800 mg/dose</td>
</tr>
<tr>
<td>50.0 – 59.9 kg</td>
<td>800 – 900 mg/dose</td>
</tr>
<tr>
<td>≥ 60.0 kg</td>
<td>900 mg/dose (max.)</td>
</tr>
</tbody>
</table>

- INH dosage: 15 mg/kg, rounded up to the nearest 50 or 100 mg, 900mg maximum dosage; formulated as 100 mg and 300 mg tablets.

- RPT dosage: per table, 900 mg maximum dosage; formulated as 150 mg tablets packed in blister packs that should be kept sealed until usage.
3. **Monitoring orders:**
   - Monthly LFTS and/or CBC with platelets are generally not necessary for children or adults
   - Consider monthly LFTs and/or CBC with platelets if baseline results are abnormal or older patient on hepatically metabolized medications or with interactions with INH and/or rifamycins
   - Additional timely lab tests as indicated if symptoms suggest intolerance/toxicity, possible pregnancy, and other tests, as indicated

### III. NURSING

A. **Confirm clinician’s orders**

B. **Obtain lab tests as ordered**

C. **Provide patient education**
   1. “What You Need to Know About Your Medicine for Tuberculosis Infection (TBI)” (handout)
   2. Provide copy of patient education sheet with TB clinic contact information (included)
   3. Document education provided in patient record

D. **Administration of medications and documentation** (see TTBEP “DOT Medication Record – ‘3HP Regimen’”)
   1. Confirm patient identity
   2. Complete “TB Infection Treatment Plan” section on TTBEP “DOT Medication Record – ‘3HP Regimen’”
   3. Ensure patient is well-hydrated prior to administering medication
   4. Before administering each dose of medications, ask the patient about adverse effects. Document findings on the TTBEP “DOT Medication Record- 3HP Regimen.” (See instructions for how to complete the TTBEP “DOT Medication Record – ‘3HP Regimen’”)
      - If patient develops GI upset after ingesting medication, consult with TB clinician for consideration of adding an antiemetic prior to each dose of medication
   5. Administer all required medications and confirm that patient has swallowed each tablet
   6. Review patient education as needed
   7. Confirm next appointment for DOT
   8. Schedule the patient in TB clinic for a clinical reassessment, as indicated or ordered by the TB clinician.
   9. Document administration of medications on TTBEP “DOT Medication Record – ‘3HP Regimen’”
   10. Document all reports of symptoms or signs of possible adverse effects or toxicity in progress notes
IV. TREATMENT MONITORING

A. Educate patients to seek medical attention upon the first symptom of a possible adverse event.

B. Clinically assess upon the first sign or symptom of a possible adverse event.

C. Periodic laboratory tests as ordered by TB clinician:
   - Monthly LFTs in all patients with elevated baseline liver function tests
   - Monthly LFTs and CBC/platelets in patients with a history of liver disease, HIV infection, or of regular alcohol use
   - Other tests as indicated for patients taking medications for other chronic conditions
   - Urine pregnancy test upon suspicion of possible pregnancy, and hold DOT if positive

D. Discontinuation of INH-RPT – If a serum aminotransferase concentrations (ALT or AST) are ≥ 3 times the upper limit of normal in the presence of symptoms, or ≥ 5 times the upper limit of normal even in the absence of symptoms.

E. Vigilance for drug hypersensitivity reactions – particularly hypotension or thrombocytopenia
   - Severe condition (e.g., hypotension requiring intravenous fluid support): discontinuance of INH-RPT; supportive medical care
   - Mild to moderate condition (e.g., dizziness treated with rest or oral fluids): conservative management of constitutional symptoms, clinical and laboratory monitoring, the option for continuing treatment under observation

F. Report all adverse events promptly to TTBEP Central Office (C.O.)

G. Adverse event resulting in hospitalization or death – should be reported on the Food and Drug Administration (FDA) MedWatch Form 3500. This form should be sent to TTBEP Central Office for reporting.
   - The MedWatch Form 3500 and instructions can be found at: [http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf](http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf)
   - Instructions for completing the form can be found at: [http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm149236.htm](http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm149236.htm)

V. DOCUMENTATION

A. Baseline screening and evaluation - Clinician
   1. Clinician’s progress notes – including pertinent history and current medications, physical examination (include patient’s weight), diagnosis of TBI, laboratory results (if available), patient’s eligibility status for 3HP regimen; record per routine in patient record
   2. Chest X-ray report – hard copy in patient record
   3. Clinician’s orders – record per routine in patient record
B. Nursing
   1. Risk Assessment Tool (RAT)—enter per routine in PTBMIS
   2. TB test (TST or IGRA)—enter per routine in PTBMIS (if test is performed by an outside provider, enter the result on the RAT in PTBMIS)
   3. Routine documentation in progress notes of patient assessment and education
   4. Record administration of each medication dose on TTBEP “DOT Medication Record – ‘3HP Regimen’ ”
   5. Document all reported or witnessed adverse events in patient record
   6. Completion of therapy for TBI
      • Patients are given 12 once-weekly DOT doses within a 16-week period to be considered complete. To ensure patient is on track with the regimen, no less than three (3) doses or more than five (5) doses should be given in any 28 day period. If the patient misses three (3) doses within any 28 day period, the regimen should be discontinued and not restarted
      • Discuss with patient and check calendar (consider holidays) to determine the best day for DOT
      • Doses should ideally be spaced seven (7) days apart, with a minimum of 5 days between doses
      • Doses are not considered missed if given within 48 hours of the scheduled dose; missed doses or altered dosing intervals could jeopardize efficacy or safety of this regimen.
      • NOTE: near the end of the treatment period, the TB clinician may consider completion of therapy for TBI with only 11 once-weekly DOT doses within a 16-week period under rare and insurmountable circumstances in which the patient cannot take an additional (12th) dose by DOT.

C. Documentation to TTBEP C.O.
   1. DOT Medication Record – “3HP Regimen” – upon initiation of 3HP regimen (PTBMIS label and TB infection treatment plan included on form)
   2. DOT Medication Record—“3HP Regimen” – upon discontinuation of 3HP regimen

VI. RESOURCES
   B. MMWR reference - Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection. MMWR 2011;60:1650–1653
   C. TTBEP patient education sheet adapted from CDC – “What You Need to Know About Your Medicine for Tuberculosis Infection” (English and Spanish versions)
   D. TTBEP “DOT Medication Record – ‘3HP Regimen’ ”
E. FDA MedWatch 3500 Form and Instructions