# Isoniazid-Rifapentine Treatment for Latent TB Infection

## Addendum to "Management of Tuberculosis"

## Federal Bureau of Prisons Clinical Practice Guidelines

## December 2014

## 1. Background

In December 2011, Sterling, et al published results of a large clinical trial that compared the use of 9-month isoniazid (INH) with 3-month isoniazid –rifapentine (INH-RPT) for treatment of latent TB infection (LTBI). INH was given daily for 9 months (self-administered); INH-RPT was administered once weekly for 12 weeks (directly observed). Participants in the study were at high risk for active TB. The authors concluded that 3-month INH-RPT was at least as effective as 9-month INH in preventing active TB which developed in 0.19% (7/3986) of those on INH-RPT and 0.43% (15/3745) among those on INH alone. Completion rates were higher for 3-month INH-RPT versus INH treatment alone (82% vs 69%). Rates of discontinuation were somewhat higher for INH-RPT (4.9% vs 3.7%); however rates of serious hepatotoxicity were lower (0.4% vs. 2.7%)

Centers for Disease Control and Prevention (CDC) has recommended the use of 3-month INH-RPT as an equal alternative to 9-month INH in individuals who are at high risk for developing active TB (i.e., recent exposure, documented tuberculin skin test conversion, chest x-ray findings of healed pulmonary TB, and HIV co-infected persons who are not taking antiretroviral medication). CDC also recommended that 3-month INH-RPT can be considered for treating patients with LTBI in situations where INH-RPT offers significant practical advantages, such as correctional settings. It was emphasized that long term safety monitoring is important.

The BOP has completed a pilot evaluation of 3-month INH-RPT in 7 BOP facilities. Results are available for 243 inmates who started this regimen in 2013. The overall completion rate was 93%. There have been no serious adverse reactions. A total of 10 (4.1%) inmates discontinued medication due to side effects including 2 (0.8%) abdominal pain, 3 (1.2%) elevated LFTs, and 3 (1.2%) nausea/vomiting. INH-RPT appears to be associated with more fatigue, nausea and occasional hypotensive events than INH monotherapy.

Based upon the significant practical advantages of 3-month INH-RPT and the results of the pilot evaluation in the BOP that demonstrated high rates of treatment completion and low rates of adverse reactions, it has been decided that the standard regimen for treatment of LTBI in the BOP will be 3-month INH-RPT. Guidelines for administration of INH-RPT are outlined below. This guidance has been published as an addendum to the BOP Clinical Practice Guideline on Management of Tuberculosis.

## 2. Indications

Inmates who meet the criteria for a positive tuberculin skin test and treatment for latent TB infection in accordance with the BOP Tuberculosis Clinical Practice Guideline should be considered for treatment. In general, INH-RPT is not started on pretrial inmates unless they are at high risk for TB.

## 3. Contraindications

The following are contraindications for 3-month INH-RPT:

**a.** Confirmed or suspected active TB

**b.** HIV co-infected patients on antiretroviral therapy
**c.** Index case is known to have TB organism resistant to rifampin or INH
**d.** Pregnancy
**e.** Warfarin therapy
**f.** Antiepileptic drug therapy – phenytoin, phenobarbital, carbamazepine, clonazepam
**g.** Hypersensitivity to INH or any of the rifamycins (e.g., rifampin, rifabutin)

## 4. Baseline Labs

The following baseline labs should be obtained prior to starting INH-RPT:

**a.** Chest x-ray (negative CXR within previous 3 months for non-HIV co-infected and within one month for HIV co-infected).
**b.** HBsAg, Anti-HCV and HIV (unless previously obtained within the BOP)
**c.** Liver function tests (LFTs) and CBC with platelets

## 5. Clinical Assessment

The recommended clinical assessment prior to starting treatment is outlined below.

**a. Medical History:**

- Risk factors for TB
- Prior treatment for TB or LTBI
- Signs and symptoms of active TB
- Review of symptoms of hepatitis and liver disease
- Review of preexisting medical conditions that may complicate treatment
- Review of current medications with attention to potential drug interactions with rifapentine (see Table 1)

**Table 1. Examples of Drugs with Interactions with Rifapentine (CYP450 inducer)**

| | |
|---|---|
| • Warfarin (contraindicated)<br>• Antiepileptic drug therapy<br>  ○ Phenytoin<br>  ○ Phenobarbital<br>  ○ Carbamazepine<br>• Calcium channel blockers, including:<br>  ○ Amlodipine<br>  ○ Diltiazem<br>  ○ Felodipine<br>  ○ Isradipine<br>  ○ Nicardipine<br>  ○ Nifedipine<br>  ○ Nisoldipine<br>  ○ Verapamil | • Sulphonylureas, including:<br>  ○ Glipizide<br>  ○ Glyburide<br>  ○ Glimepiride<br>  ○ Chlorpropamide<br>  ○ Tolbutamide<br>• Clarithromycin/Erythromycin<br>• Anti-rejection medications<br>• Azole antifungals<br>• HIV/HCV related therpies should generally not be used concomitantly with rifapentine (seek expert consultation) |

**b. Targeted examination:** should be performed by a clinician for systemic signs of active TB disease (e.g., cough, fever, weight loss, pulmonary findings), as well as signs of hepatitis.

## 6. Patient Education

Review the following key messages.

a. INH-RPT Regimen is provided to prevent the development of active TB.
b. It is a 12-week, once per week regimen.
c. Seek medical attention for adverse effects including: fever, yellow eyes, dizziness, rash, or aches, vomiting, weakness, abdominal pain, tingling of hands or feet, loss of appetite or greater than one day of nausea.
d. RPT will turn urine and eye secretions a reddish color.
e. Medication is administered weekly as determined by the institution. Each institution will have a system in place to ensure doses are not missed and patient is assessed for side effects each week. Do not miss appointments or administered dosing times.
f. CDC Publication Hand-out (CS234967E): What You Need to Know About Your Medicine for Latent Tuberculosis (TB) Infection. Available at: http://www.cdc.gov/tb/publications/PDF/3HP_508.pdf

7. **Medical Hold.** Inmates who are prescribed 3-month INH-RPT shall be placed on Medical Hold (in both BEMR and SENTRY).

**8. Prescribe Medication:** Both INH and RPT are weight based

**Table 2. Dosing Guidelines for INH-RPT Regimen**

| **INH** (15 mg/kg) rounded up to nearest 50 or 100 mg (900 mg maximum) | | |
|---|---|---|
| **Kilograms** | **Pounds** | **INH Dose** |
| ≤ 40 | ≤ 88 | 15mg/kg rounded up to the nearest 50mg (split tablets) |
| 41-46 | 89-101 | 700mg |
| 47-53 | 103-116 | 800mg |
| ≥ 54 | ≥ 117 | 900mg (maximum) |
| INH is formulated as 100 mg and 300 mg tablets | | |
| | | |
| **Rifapentine** | | |
| Kilogram | Pounds | Rifapentine dose |
| 25.1-32 | 55-70 | 600mg |
| 32.1-49.9 | 71-109 | 750 mg |
| ≥ 50 | ≥ 110 | 900 mg (maximum) |
| RPT is formulated as 150 mg tablets (keep sealed until use in blister packs) | | |
| | | |
| **Pyridoxine (Vitamin B-6)** | | |
| Administer 50mg once weekly with each dose of INH-RPT | | |

The treatment regimen consists of 12 once-weekly doses. Pyridoxine 50 mg should be administered with each weekly dose. Directly observe all medication doses. With each dose the inmate should be queried about side effects (see below).

## 9. Side Effect Monitoring

Screening for adverse effects shall be conducted *weekly* and documented using the BOP Electronic Medical Record (BEMR) Latent TB Infection symptom screen adding the following additional symptoms into the comments section (see example in Table 3 below).

a. Diarrhea: Yes or No
b. Dizziness: Yes or No
c. Fever or Chills: Yes or No
d. Rash or Hives: Yes or No
e. Sore Muscles or Joints: Yes or No
f. Other: Yes or No

**Table 3. BEMR Latent TB Infection Screen - Example**

| | | | | | |
|---|---|---|---|---|---|
| Numb Hands/Feet: | ◎ No | Yes | Nausea/Vomiting: | ◎ No | Yes |
| Headache: | ◎ No | Yes | Yellow Skin or Eyes: | ◎ No | Yes |
| Seizure: | ◎ No | Yes | Fatigue: | ◎ No | Yes |
| Vision Decrease: | ◎ No | Yes | Weight Loss: | ◎ No | Yes |
| Memory Loss: | ◎ No | Yes | Abdominal Pain: | ◎ No | Yes |
| Appetite Loss: | ◎ No | Yes | Brown Urine: | ◎ No | Yes |

Comments: Diarrhea NO
RASH OR HIVES NO
FEVER OR CHILLS NO
SOREMUSCLES OR JOINTS NO
OTHER

## 10. Laboratory Monitoring

Recommended laboratory monitoring is summarized in Table 4 (below). Routinely obtain LFTs at dose number 4. Inmates with risk factors for hepatotoxicy shall also have LFTs periodically throughout treatment. Risk factors for hepatotoxicity include:

a. Abnormal baseline liver transaminases
b. HIV
c. Chronic liver disease from alcohol, viral hepatitis or other etiologies
d. Other potentially hepatotoxic drugs concurrently prescribed
e. History of previous adverse reactions to the medications used in treating LTBI

| **Table 4. Summary of Laboratory Monitoring** | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Dose** | **Baseline** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
| HIV | X* | | | | | | | | | | | | |
| HBsAg | X* | | | | | | | | | | | | |
| Anti-HCV | X* | | | | | | | | | | | | |
| CBC | X | | | | | | | | | | | | |
| LFTs | X | | | | X | periodically if hepatic risk factors | | | | | | | |
| * Only obtain if not previously documented in the BOP and continuously incarcerated since that test. | | | | | | | | | | | | | |

INH-RPT should ordinarily be discontinued if:

- Liver transaminases exceed 3 times the upper limit of normal (if associated with symptoms of hepatitis) and 5 times the upper limit of normal ( if the inmate is asymptomatic).
- Severe drug hypersensitivity reactions, e.g., hypotension.

If treatment is stopped because of elevated LFTs or other adverse effects, consideration should be given to rechallenging the inmate with the same regimen or with rifampin (4-month daily) or INH (9 months twice weekly) in accordance with the BOP Clinical Practice Guideline on Management of Tuberculosis.

**11. Interruptions/Continuation of Therapy**

a. **Managing interruptions in therapy.** The following practical decision rule should be applied when reinstituting therapy for inmates who have stopped taking their medications for LTBI or who have had therapy interrupted for medical reasons:
   - If 50% or fewer of doses have been missed within the intended treatment period, then add doses onto the end of treatment.
   - If greater than 50% of doses have been missed within the intended treatment period, then restart therapy.

   In either situation, when therapy is reinstituted after an interruption of more than 2 months, a medical examination to rule out active TB is indicated.

b. **INH-RPT for inmates who arrive while on treatment with INH.** If an inmate arrives on INH-RPT treatment then it should be continued. INH-RPT can be considered for continuation of treatment of LTBI for inmates who arrive on INH in the following circumstance. If an inmate has documentation of less than 6 months of treatment on INH, then the inmate can be "restarted" on INH-RPT and finish the treatment in 3 months. If the inmate has documentation of 6 months or more INH treatment, then continue INH.

## 12. Documentation of treatment regimen

Treatment of LTBI should be documented by the responsible physician and other health care staff as follows:

- At the baseline evaluation and initiation of treatment.
- Whenever treatment is interrupted or discontinued.
- At the completion of treatment.

Inmates who refuse treatment for LTBI should sign a refusal form, to be filed in BEMR, documenting their declination of treatment.

## 13. Strategies for Success

Clinicians involved in the BOP 3-month INH-RPT pilot evaluation report that the high rate of completion (93%) may have been achieved for more reasons than the simple fact that the regimen was simpler and shorter.

- **One health care professional was dedicated to oversee the program** who conducted the weekly symptom reviews and administered medication. This health care worker was selected on the basis of available staff resources at the institution (e.g., nurse, infection control staff, pharmacist, mid-level practitioner). Thus inmates received ongoing individual support from one health professional for promoting compliance and completing the regimen.

- **Weekly call-outs were used to structure the INH-RPT clinics** rather than lengthy pill-lines. The weekly call-out system resulted in groups of inmates waiting together to be seen resulting in the formation of informal support groups for completing the regimen.

- **Pilot sites frequently started the inmates on INH-RPT in cohorts** to facilitate tracking of the baseline evaluations and lab monitoring which was found to be an efficient approach. Education can then be provided to groups of inmates who are all starting the regimen at the same time.

## 14. References

Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med* 2011; 365:2155-2166 . Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa1104875#t=articleTop

Centers for Disease Control and Prevention.. Recommendations for use of an isoniazid-rifapentine regimen for direct observation to treat latent *Mycobacterium tuberculosis* infection. *MMWR* 2011;60: 1650-1653. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm