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A PARTNERSHIP OF UT HEALTH SCIENCE CENTER AND TCID

this issue…

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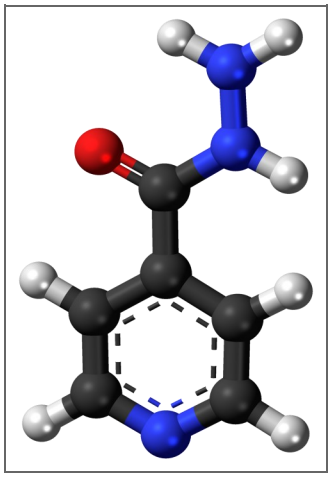
Short-Course (3-Month) Therapy with Weekly Isoniazid-Rifapentine Is NOT RECOMMENDED for HIV-Infected Patients Receiving Antiretroviral Therapy (December 20, 2011)

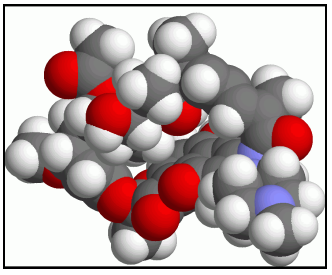
For Specific Article Access:
http://aidsinfo.nih.gov/contentfiles/Short_Course_INH-RPT.pdf



Ball and Stick model of the Isoniazid molecule.

The purpose of this supplemental information is to alert clinicians about the use of short-course therapy with weekly isoniazid plus rifapentine (INH-RPT) for the treatment of latent tuberculosis infection (LTBI) in HIV-infected patients. Pharmacokinetic data are lacking on the interactions between RPT and antiretroviral (ARV) drugs; therefore, until such data are available, the Panel recommends the following:

- **HIV-infected patients receiving antiretroviral therapy (ART) SHOULD NOT receive the 3-month weekly INH-RPT regimen for treatment of LTBI, unless given in the context of a clinical trial (AIII).**
- **Patients receiving ART should receive LTBI treatment according to current recommendations in the guidelines for treatment and prevention of opportunistic infections[1,2](AI).**
- **HIV-infected patients 12 years of age or older who are not receiving ART can be prescribed either a 9-month INH regimen or the 3-month once-weekly INH-RPT regimen by directly observed therapy (DOT), as recommended in the new Centers for Disease Control and Prevention (CDC) guidelines[3]. Clinicians should note that data are limited on efficacy and safety of the 3-month regimen in HIV- infected patients (not on ART).**



Model of the Rifapentine molecule

- **For HIV-infected children 2 to 11 years of age who are not receiving ART, the standard 9-month regimen of daily INH monotherapy is preferable, but the 3-month INH-RPT regimen can be considered on a case-by-case basis. The 3-month INH-RPT regimen is not recommended for children younger than 2 years of age.**

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Background

Treatment of LTBI can prevent progression to active TB. INH given once daily for 9 months is the standard treatment regimen for LTBI. In an open-label, randomized non-inferiority trial, a 3-month combination regimen of INH-RPT, given by DOT once weekly, was compared with the standard 9-month self-administered once daily INH regimen for LTBI treatment[4]. The study results included more than 7,000 enrolled subjects. After 33 months of follow-up, in a modified intention-to-treat analysis, 15 cases of TB were diagnosed in the INH recipients and 7 cases in the INH-RPT recipients (hazard ratio: 0.38 for INH-RPT, confidence interval [CI] 0.15–0.99, $P = 0.05$). The permanent discontinuation rate before treatment completion was higher in the INH alone arm. In this study, only 105 HIV-infected patients who were not receiving ART received the 3-month INH-RPT.

The 3-month regimen of INH-RPT has the advantages of shorter treatment duration, higher completion rate, and efficacy non-inferior to INH alone for 9 months. The results of this study have led to a new CDC recommendation[1] in which 3-month once-weekly INH-RPT given by DOT is considered an equal alternative to the standard 9-month regimen for adults and adolescents (≥12 years old). This regimen, however, is **NOT RECOMMENDED** for HIV-infected patients receiving ART**(AIII)**.

Rationale for NOT Recommending Short Course INH-RPT for Treatment of LTBI in HIV-Infected Patients Receiving ART

RPT is a rifamycin-antibiotic with a long plasma half-life, allowing it to be dosed less frequently than other commonly used rifamycins, such as rifampin and rifabutin. Like other rifamycins, RPT induces the cytochrome P450 enzyme system, which is responsible for the metabolism of many drugs including HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and maraviroc. Rifampin also induces the enzyme UGT-1A1, leading to interaction with raltegravir. No systematic study has been performed to assess the magnitude of the enzyme induction effect of RPT on the metabolism of ARV drugs and other concomitant drugs. Significant enzyme induction can result in reduced ARV drug exposure, which may compromise virologic efficacy. Pharmacokinetic studies and clinical trials to evaluate the impact of RPT on ART are under way or in the planning stages.

References

1. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009; 58 (RR-4): 1-207.

References continued from Page 2

2. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR Recomm Rep.* 2009; 58(RR-11): 1-166.
3. Centers for Disease Control and Prevention. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent *Mycobacterim tuberculosis* infection. *MMWR* 2011; 60(48): 1650-3.
4. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *New Engl J Med.* 2011; 365: 2155-66.

Prepared by:

The HHS Panel on Antiretroviral Guidelines for Adults and Adolescents and the HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children, in consultation with:

- The HHS Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents; and
- The HHS Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Children

For more detailed information regarding treatment and care for the HIV-infected patient, consult the AIDS*info* Web site: http://aidsinfo.nih.gov/Guidelines/Default.aspx

INH-RPT Frequently Asked Questions

General Questions

1. Who is this regimen recommended for?

This regimen is recommended for individuals 12 years and older with LTBI who are at high risk for developing tuberculosis (e.g. recent contacts to an infectious case and those with TST or IGRA conversion). Treatment using this regimen is also recommended for patients who have radiographic findings consistent with healed/inactive tuberculosis.

HIV positive patients who are **not** on anti-retroviral therapy (ART) or whose initiation of treatment is **not imminent** may be treated using the 12 week INH-RPT regimen.

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The VISION of Heartland National TB Center is to provide *excellence*, *expertise*, *innovation* in training, medical consultation, and product development to reduce the impact of tuberculosis in our region.

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2. Which patients may be considered for this treatment on a case by case basis?

This treatment regimen may be considered for children ages 2 to 11 years old, IF the completion of the 9 month INH regimen is unlikely AND the likelihood of TB is great. **The preferred regimen for children 2 to 11 years of age is the 9 month INH monotherapy regimen.** The information gathered for children of this age group during this study was insufficient for determining tolerability and efficacy of INH-RPT.

INH-RPT can also be considered on a case by case basis for patients with underlying medical conditions (e.g. diabetes), and for patients who are not likely to complete the 9 month INH monotherapy regimen.

3. Which patients is this regimen not recommended for?

A. This regimen is not recommended for children younger than 2 years of age, due to fact that the safety and pharmacokinetics of Rifapentine have not been established in this age group.
B. Patients who are on ART, or whose initiation of treatment is imminent, should not be treated using the INH-RPT regimen. The drug interactions have not been adequately studied and the efficacy and safety have not been established. The 9 month INH monotherapy regimen is the preferred treatment regimen for patients receiving ART.
C. Pregnant women or women who are expecting to become pregnant should not be placed on an INH-RPT regimen, because the safety of this regimen during pregnancy has not been established. Patients receiving 3 INH-RPT who become pregnant should discontinue this treatment regimen. Completion of LTBI can be with 4 months of rifampin or 9 months of daily INH.
D. This regimen is also not recommended for patients who have LTBI suspected to be INH or Rifampin (rifamycin) resistant.

4. What dosing should be used when administering Isoniazid and Rifapentine?

A. Isoniazid should be administered 15mg per kg rounded **up** to the nearest 50 or 100 mg. 900 mg is the maximum recommended dose.
B. Rifapentine dosing is as follows:
- 300 mg for patients who weigh 10.0- 14.0 kilograms
- 450 mg for patients who weigh 14.1-25.0 kilograms
- 600 mg for patients who weigh 25.1 to 32.0 kilograms
- 750 mg for patients who weigh 32.1 to 49.9 kilograms
- 900 mg for patients who weigh greater than 50 kilograms

5. Are there differences in dosing, based on age?

No. Dosing is the same despite the age.

6. What is the maximum allowed time for receiving the doses?

The CDC recommendations state that treatment will be considered complete if patients receive 11 to 12 doses of INH-RPT in a 16 week period.

7. What is the minimum number of days between doses?

CDC/MMWR recommendations note that doses should be separated by a minimum of 72 hours.

8. Can the regimen be administered in a shorter period of time (e.g. 8 weeks)?

No. The minimum amount of time required for this regimen is 12 weeks.

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9. Which patients should be considered high priority for treatment when there are limited supplies of medication?

Patients who are at high risk for progressing to active tuberculosis due to recent exposure (e.g. recent contacts and TST or IGRA converters) and who are not likely to complete 9 months of INH. Treatment could also be considered high priority for those who are in settings in which INH-RPT offers practical advantages (correctional facilities, refugees, homeless shelters).

****Treatment should not be initiated unless the provider has guaranteed access to sufficient medication to complete the entire treatment course.**

Adverse Effects

10. What adverse effects have been associated with this regimen?

Current known adverse effects associated with this regimen include hepatotoxicity and hypersensitivity. Hepatotoxicity symptoms can be rash, jaundice, and/or tenderness in upper the right quadrant of the abdomen.

11. What precautions should be taken when administering this regimen?

Patients should undergo monthly clinical assessments, including a physical examination, as well as questions regarding signs and symptoms of hepatotoxicity.

12. Should baseline hepatic chemistry tests be performed prior to starting treatment?

For otherwise healthy individuals baseline hepatic chemistry tests are not required. Establishing baseline hepatic chemistry is recommended for patients who are HIV infected, have a history of liver disease, those in the immediate postpartum period and those who regularly use alcohol. Patients older than 50 should be considered for baseline hepatic chemistry tests on a case by case basis.

****If baseline testing is abnormal (performed prior to starting treatment), hepatic chemistry testing should be conducted at every clinical assessment or more often if symptoms of hepatotoxicity develop.**

13. When should treatment be discontinued?

- If the patient is asymptomatic, and has an AST or ALT concentration ≥ 5 times the upper limit of normal, treatment should be discontinued pending further evaluation.
- If the patient has symptoms, treatment should be discontinued if the AST or ALT is ≥ 3 times the upper limit of normal.
- If the patient experiences severe hypersensitivity reactions, such as hypotension requiring intravenous fluid support or thrombocytopenia, treatment should be discontinued and further evaluation completed. Treatment may be continued under strict clinical and laboratory monitoring in the case of mild to moderate hypersensitivity reactions (e.g. dizziness treated with rest or oral fluids).

14. Is there are a high risk for drug-drug interactions with this regimen?

Yes. Rifapentine (like rifampin) is a potent inducer of the cytochrome p450 enzyme system and has the potential for a variety of interactions. As a result of this interaction, the concentration of many medications can be reduced to sub-therapeutic/effective levels (e.g. hormonal contraceptives, warfarin, methadone, etc.) It is important to be aware of all the medications that the patient is receiving and be aware of any potential interactions.

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Pediatrics

15. Can children younger than 12 years old be considered for this regimen?

This treatment regimen may be considered for children ages 2 to 11 years old, IF both 1) the completion of the 9 month INH regimen is unlikely **AND** 2) the likelihood of TB is great. **The preferred regimen for children 2 to 11 years of age is the 9 month INH monotherapy regimen.** The number of children of this age group during who participated in this study was insufficient for determining tolerability and efficacy of INH-RPT. Children in this age group receiving the 12 dose INH-RPT should be have careful clinical monitoring.

This regimen is not recommended for children younger than 2 years of age. The safety and pharmacokinetics of Rifapentine has not been established in this age group.

16. Are there any special considerations/ precautions that need to be taken for children 12 to 17?

No. The safety, tolerability and efficacy of this regimen were established by the study.

17. Are there any pediatric dosing recommendations?

No, the dosing recommendations provided in the CDC recommendations apply to all age groups.

Pregnancy

18. Is this regimen recommended for pregnant patients? **No, Refer to Question 3C.**

HIV

Is this regimen recommended for HIV positive/infected patients?

HIV positive patients who are **not** on Anti-retroviral therapy (ART) or whose initiation of treatment is not imminent may be treated using the 12 week INH-RPT regimen. Patients receiving anti-retroviral therapy or who are starting ART treatment should receive the daily 9 month INH regimen.

Resources

TB LINKS

TB Education and Training Network
http://www.cdc.gov/tb/education/Tbetn/default.htm

Find TB Resources
www.findtbresources.org

Tuberculosis Epidemiologic Studies Consortium (TBESC)
http://www.cdc.gov/tb/topic/research/TBESC/default.htm

Regional Training and Medical Consultation Centers' TB Training and Education Products – (Joint RTMCC Products Page)
https://sntc.medicine.ufl.edu/rtmccproducts.aspx

Program Collaboration and Service Integration (PCSI)
http://www.cdc.gov/nchhstp/programintegration/Default.htm

****If your organization has any additional links for TB resources you would like published, please send them to Alysia.gibbons@uthct.edu****

UPCOMING TRAININGS

2012 HNTC Training Calendar

Date	Course	Location
April 3 – 6	TB Intensive	San Antonio, Texas
May 31, June 7, 21	Introduction to TB Nurse Case Management	ONLINE COURSE
June 5 – 6	Contact Investigation and Handling Outbreaks	Lisle, Illinois
July 18 – 20	TB Nurse Case Management	San Antonio, Texas
July 20	TST Practicum	San Antonio, Texas
August 7 – 10	TB Intensive	San Antonio, Texas

The calendar will be updated in every newsletter as well as on the website to show trainings that have been confirmed

Please visit our website: **http://www.heartlandntbc.org/training.asp** to find detailed information concerning registration and participation.
Proposed topics are subject to change; check website for the latest updates.

Products from the Heartland National TB Center are available for download at **http://www.heartlandntbc.org/products.asp**

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New TB Patient Fact Sheet from the Minnesota Department of Health

The MDH TB Program is pleased to announce a new patient fact sheet titled "Tuberculosis (TB) Blood Test (IGRA)." This one-page fact sheet is available in English and 12 other languages. MDH has other TB patient fact sheets in the following 15 languages: Amharic, Arabic, Bosnian/Serbian/Croatian, French, Hmong, Karen, Khmer, Lao, Nepali, Oromo, Russian, Somali, Spanish, Tibetan, and Vietnamese. To view and download, go to www.health.state.mn.us/divs/idepc/diseases/tb/education.html#patients.

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