RCT
Potential PURL Review Form
PURL Jam Version

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

A. Citiation: Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, Kim H, Obeng Baah J, Marks GB, Long R, Hoeppner V, Elwood K, Al-Jahdali H, Gninafon M, Apriani L, Koesoemadinata RC, Kritski A, Rolla V, Bah B, Camara A, Boakye I, Cook VJ, Goldberg H, Valiquette C, Hornby K, Dion MJ, Li PZ, Hill PC, Schwartzman K, Benedetti A. Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults. N Engl J Med. 2018 Aug 2;379(5):440-453. doi: 10.1056/NEJMoa1714283. PubMed PMID: 30067931.
B. Link to PubMed Abstract: https://www.ncbi.nlm.nih.gov/pubmed/?term=30067931
C. First date published study available to readers: 8/2/2018
D. PubMed ID: 30067931
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L. Assigned Potential PURL Reviewer: Greg Castelli
M. Reviewer Affiliation: UPMC St. Margaret
A. Abstract: BACKGROUND:
A 9-month regimen of isoniazid can prevent active tuberculosis in persons with latent tuberculosis infection. However, the regimen has been associated with poor adherence rates and with toxic effects.

METHODS:
In an open-label trial conducted in nine countries, we randomly assigned adults with latent tuberculosis infection to receive treatment with a 4-month regimen of rifampin or a 9-month regimen of isoniazid for the prevention of confirmed active tuberculosis within 28 months after randomization. Noninferiority and potential superiority were assessed. Secondary outcomes included clinically diagnosed active tuberculosis, adverse events of grades 3 to 5, and completion of the treatment regimen. Outcomes were adjudicated by independent review panels.

RESULTS:
Among the 3443 patients in the rifampin group, confirmed active tuberculosis developed in 4 and clinically diagnosed active tuberculosis developed in 4 during 7732 person-years of follow-up, as compared with 4 and 5 patients, respectively, among 3416 patients in the isoniazid group during 7652 person-years of follow-up. The rate differences (rifampin minus isoniazid) were less than 0.01 cases per 100 person-years (95% confidence interval [CI], -0.14 to 0.16) for confirmed

active tuberculosis and less than 0.01 cases per 100 person-years (95% CI, -0.23 to 0.22) for confirmed or clinically diagnosed tuberculosis. The upper boundaries of the 95% confidence interval for the rate differences of the confirmed cases and for the confirmed or clinically diagnosed cases of tuberculosis were less than the prespecified noninferiority margin of 0.75 percentage points in cumulative incidence; the rifampin regimen was not superior to the isoniazid regimen. The difference in the treatment-completion rates was 15.1 percentage points (95% CI, 12.7 to 17.4). The rate differences for adverse events of grade 3 to 5 occurring within 146 days (120% of the 4-month planned duration of the rifampin regimen) were -1.1 percentage points (95% CI, -1.9 to -0.4) for all events and -1.2 percentage points (95% CI, -1.7 to -0.7) for hepatotoxic events.

CONCLUSIONS:
The 4-month regimen of rifampin was not inferior to the 9-month regimen of isoniazid for the prevention of active tuberculosis and was associated with a higher rate of treatment completion and better safety. (Funded by the Canadian Institutes of Health Research and the Australian National Health and Medical Research Council; ClinicalTrials.gov number, NCT00931736 .).

B. Pending PURL Review Date**:** 3/5/2019

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]

A. Number of patients starting each arm of the study?
2989 in INH group and 3023 in rifampin group.

B. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)

The selected trial sites in Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, and South Korea had extensive experience in previous clinical trials. Trial staff at all the sites received initial training in Good Clinical Practice and trial procedures, and monitoring visits were conducted twice per year (see the Supplementary Appendix, available at NEJM.org).

Adults (18 years of age or older) were enrolled if they had a documented positive tuberculin skin test or interferon-γ–release assay, if they met the criteria for an increased risk of reactivation to active tuberculosis (see the Supplementary Appendix),[6,8] and if their provider recommended treatment with isoniazid. Before randomization, adults underwent medical evaluation, including radiography of the chest, to rule out active tuberculosis. Testing for the human immunodeficiency virus (HIV) was offered to participants who had risk factors for HIV infection. The exclusion criteria were exposure to a patient with active tuberculosis whose isolates were resistant to either trial drug, current or planned pregnancy, the use of medications with potentially serious interactions with either trial drug, history of allergy to either trial drug, or current active tuberculosis. All the eligible patents pro- vided written informed consent.

Randomization was generated centrally, by computer, in blocks of varying length (2 to 8) and stratified according to center with an assignment ratio of 1:1. All the contacts within the same household were assigned to the same trial group if they were all identified within the same week.

C. Intervention(s) being investigated?

The experimental regimen was oral rifampin at a dose of 10 mg per kilogram (maximum dose, 600 mg) taken daily for 4 months (120 doses).

D. Comparison treatment(s), placebo, or nothing?

The control regimen was oral isoniazid at a dose of 5 mg per kilogram of body weight (maximum dose, 300 mg) taken daily for 9 months (270 doses), with vitamin B_6 (pyridoxine) added for adults who were at risk for neuropathy.[6-8]

E. Length of follow-up? (Note specified end points, e.g., death, cure, etc.)

28 months.

F. What outcome measures are used? List all that assess effectiveness.

The primary objective was to compare the rates of confirmed active tuberculosis in the two groups among all eligible patients during 28 months after randomization. The secondary objectives were to compare the following in the two groups: the rate of confirmed active tuberculosis plus clinically diagnosed active tuberculosis per 100 person-years; the rate of confirmed or clinically diagnosed tuberculosis per 100 person-years among patients who completed the trial therapy per the protocol; the cumulative incidence of adverse events of grades 3 to 5, overall and those considered by the adjudication panel to be drug- related and occurring throughout the course of therapy or within the maximum time allowed for the completion of the rifampin regimen (120% of 4 months, or 146 days); the percentage of patients in each trial group who completed the trial therapy, which was defined as receipt of at least 80% of the doses; and the rate of drug-resistant active tuberculosis per 100 person- years.

G. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CU, p-values, etc.

There were eight cases of confirmed active tuberculosis and nine cases of clinically diagnosed active tuberculosis during active follow-up in the phase 2 and 3 trials combined (Table 3). Seven of the eight patients with confirmed tuberculosis and five of the nine patients with clinically diagnosed tuberculosis had also been reported to the local tuberculosis authorities as having received a diagnosis of active tuberculosis, but no additional cases were detected by passive case- finding procedures.

The differences in rates between the rifampin group and the isoniazid group were as follows: for confirmed tuberculosis in the modified intention-to-treat population, the difference was less than 0.01 cases per 100 person-years (95% CI, −0.14 to 0.16), which is equivalent to a difference in the cumulative incidence over the 28-month period of less than 0.02 (95% CI, −0.33 to 0.37). The difference for confirmed or clinically diagnosed tuberculosis in the modified intention-to-treat population was less than 0.01 cases per 100 person-years (95% CI, −0.23 to 0.22, which is equivalent to −0.54 to 0.51 over the 28-month period); and for confirmed or clinically diagnosed tuberculosis in the per-protocol analysis, the difference was −0.02 cases per 100 person-years (95% CI, −0.30 to 0.26, which is equivalent to −0.70 to 0.61 over the 28-month period). Among the phase 3 trial participants who completed therapy per the proto- col, the rate difference between the rifampin group and the isoniazid group for confirmed plus clinically diagnosed tuberculosis was −0.02 cases per 100 person-years (95% CI, −0.33 to 0.29, which is equivalent to −0.77 to 0.68 over the 28-month period) (Table 4).

In all these analyses, the upper boundary of the 95% confidence interval for the difference in the rates of confirmed active tuberculosis or of confirmed or clinically diagnosed tuberculosis was less than the prespecified margin for non-inferiority. However, the rifampin regimen was not superior to the isoniazid regimen.

H. What are the adverse effects of intervention compared with no intervention?

To account for the potential problem of differen- tial ascertainment, owing to the fact that the duration of the isoniazid

regimen was longer than the duration of the rifampin regimen, we estimated rate differences for adverse events that occurred during the first 146 days after random- ization. The rifampin group had significantly lower rates of adverse events of grades 3 to 5 than the isoniazid group in analyses that included all such adverse events (rate difference, −1.1 per- centage points; 95% CI, −1.9 to −0.4) and in analyses that included only adverse events that were considered by the independent panel to be related to the trial drug (−1.0 percentage point; 95% CI, −1.6 to −0.4) (Table 5).

Drug-induced hepatitis was the most common adverse event of grade 3 or 4 overall and was significantly less frequent in the rifampin group than in the isoniazid group in analyses that in- cluded all such events, that included only events that were adjudicated as being possibly or prob- ably related to the trial drug, and that included only events occurring in the first 146 days. Table S3 in the Supplementary Appendix shows the results regarding total adverse events in the phase 2 and 3 trials combined, and Table S4 in the Supplementary Appendix shows the results for other types of adverse events.

I. The study addresses an appropriate and clearly focused question.
(select one) Well covered

Comments:

J. Random allocation to comparison groups:
(select one) Adequately addressed

Comments:

K. Concealed allocation to comparison groups:
(select one) Adequately addressed

Comments: open label

L. Subjects and investigators kept “blind” to comparison group allocation:
(select one) Adequately addressed

Comments: This was an open-label trial so researchers and participants were not blind.

M. Comparison groups are similar at the start of the trial:
(select one) Well covered
Comments: yes

N. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential sources of bias. (select one) Well covered
Comments: none

O. Were all relevant outcomes measured in a standardized, valid, and reliable way?
(select one) Well covered
Comments:

P. Are patient oriented outcomes included? If yes, what are they?

Yes. Rates of active TB after treatment.

Q. What percent dropped out, and were lost to follow up? Could this bias the results? How?

95% of patients completed the 28 month follow up. However 64% in the INH group vs 79% in the rifampin group were included in the per protocol analysis.

R. Was there an intention-to-treat analysis? If not, could this bias the results? How?

Yes.

S. If a multi-site study, are results comparable for all sites?

Unknown.

T. Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity?

No. It appears to be funded by grant (MCT-94831) from the Canadian Institutes of Health Research; the Australian National Health and Medical Research Council supported the portion of this trial in Australia.

U. To which patients might the finding apply? Include patients in the study and other patients to whom the findings may be generalized.

Those with active tb infections but not resistant to trial meds.

V. In what care settings might the finding apply, or not apply?

Primary care and infectious disease.

W. To which clinicians or policy makers might the finding be relevant?

Primary care and infectious disease.

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions: For up-to-date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS on editor & current year as publication year.

Example: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert date modified if given.} Accesses February 12, 2009. [whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert date modified if given.} Accessed June 5, 2009. {search date}

A. DynaMed excerpts

Treatment overview:

- presence of active tuberculosis (TB) must be excluded before treatment for LTBI initiated because failure to do so may result in inadequate treatment of disease and development of drug-resistant *M. tuberculosis*
- isoniazid is preferred treatment
  - isoniazid 5 mg/kg/day (maximum 300 mg/day) orally once daily for 9 months is standard regimen (ATS/CDC Grade A, Level II)
  - completion defined as minimum 270 doses within 12 months to allow for minor interruptions in therapy
  - give with vitamin B6 (pyridoxine), especially if patient has condition in which neuropathy is common, is pregnant, breast feeding, or has HIV infection[4]
  - alternative dosing schedules
    - isoniazid 15 mg/kg (maximum 900 mg/dose) orally twice weekly for 9 months with directly observed therapy (DOT) to achieve minimum 76 doses within 12 months (ATS/CDC Grade B, Level II)
    - isoniazid 5 mg/kg/day (maximum 300 mg/day) for 6 months, to achieve minimum 180 doses within 9 months (ATS/CDC Grade B, Level I)
      - can be appropriate for patients with HIV infection (ATS/CDC Grade C, Level I)
      - not recommended for patients with fibrotic lesions
    - isoniazid 15 mg/kg (maximum 900 mg/dose) twice weekly for 6 months with DOT (ATS/CDC Grade B, Level I), including patients with HIV infection (ATS/CDC Grade C, Level I)
- treatments which may be used as alternative to isoniazid
  - rifamycins
    - rifampin 10 mg/kg/day (maximum 600 mg/day) for 4 months in patients intolerant of isoniazid or exposed to isoniazid-resistant *M. tuberculosis*
    - rifabutin 5 mg/kg/day (maximum dose 300 mg) or twice weekly (maximum dose 300 mg) for 4 months if rifampin cannot be used
  - isoniazid plus rifapentine in 12 weekly DOT doses for otherwise healthy patients ≥ 12 years old with LTBI and risk factor for developing active TB
- considerations in patients with HIV infection
  - treat patients with HIV and
    - positive diagnostic test for LTBI and no evidence of active TB disease (CDC/NIH/IDSA Grade A-I)
    - close contact of persons with infectious pulmonary TB (CDC/NIH/IDSA Grade A-II)
  - recommended treatment regimens
    - preferred regimen is isoniazid (INH) and pyridoxine for 9 months given as either
      - INH 300 mg orally once daily plus pyridoxine 25 mg orally once daily (CDC/NIH/IDSA Grade A-II), or
      - INH 900 mg orally twice weekly by DOT plus pyridoxine 25 mg orally once daily (CDC/NIH/IDSA Grade B-II)
    - alternative regimens include
      - rifampin 600 mg/day orally for 4 months (CDC/NIH/IDSA Grade B-III)
      - rifabutin for 4 months, with dose adjusted based on concomitant antiretroviral therapy (ART) (CDC/NIH/IDSA Grade B-III)
  - see Latent tuberculosis infection in patients with HIV for details
- treatment options in patients with known exposure to multidrug-resistant TB (MDR-TB) determined by resistance pattern identified in source case
- consider risk factors for progression to active TB and risk of hepatotoxicity from medication when considering treatment[2]
- completion of therapy based on both total doses administered and duration of therapy[4]

4-month rifampin may be as effective as 9-month isoniazid in adults with LTBI, with higher rates of treatment completion and fewer adverse events (level 2 [mid-level] evidence)

- based on randomized noninferiority trial without blinding
- 6,859 adults with LTBI were randomized to rifampin 10 mg/kg/day (maximum 600 mg/day) orally for 4 months vs. isoniazid 5 mg/kg/day (maximum 300 mg/day) orally for 9 months and followed for 28 months
  - noninferiority of 4-month rifampin defined as cumulative incidence of active TB < 0.75% higher than with 9-month isoniazid at limit of 95% confidence interval for difference
  - comparing 4-month rifampin vs. 9-month isoniazid
    - microbiologically confirmed or clinically diagnosed active TB in 8 patients vs. 9 patients (95% CI for difference in cumulative incidence in 0.54% lower to 0.51% higher, noninferiority met)
    - adverse events within 146 days of randomization in 2.8% vs. 5.8% ($p < 0.001$)
  - in 6,012 adults in phase 3 trial, treatment completed by 78.8% in rifampin group vs. 63.2% in isoniazid group
  - Reference - N Engl J Med 2018 Aug 2;379(5):440 full-text

B. DynaMed citation
Ridzon R. Latent tuberculosis infection: treatment In: DynaMed [database online]. Available at http://www.DynamicMedical.com. Last updated Nov 2018. Accessed March 13, 2019.

C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)
Isoniazid is the preferred treatment.

D. UpToDate excerpts

Selecting a regimen — Thus far, none of the four treatment regimens has been shown to be superior to any of the others. Therefore, the choice of regimen is based largely on the likelihood of adherence, the potential for adverse effects, and preference (of the patient, provider, and/orpublic health program).

Low-incidence settings — For treatment of LTBI in HIV-uninfected adults in low-incidence settings (TB incidence rate <100 per 100,000 population), we favor the following regimens (in order of preference) (table 2):

- Rifampin (RIF) daily for four months (regimen abbreviation: 4R)
- Isoniazid (INH) and RIF daily for three months (regimen abbreviation: 3HR)
- INH and rifapentine (RPT) weekly for three months (regimen abbreviation: 3HP)
- INH daily for nine or six months (regimen abbreviation: 9H or 6H)

We favor 4R because of greater adherence and less hepatotoxicity (relative to 9H) [5,13,14]. In a randomized trial including more than 6800 adults with LTBI treated with 4R or 9H, 4R was not inferior to 9H for prevention of active TB (<0.01 cases per 100 person-years in both groups) and was associated with a higher rate of treatment completion (difference in treatment completion rate 15 percent) and better safety [14]. Issues related to use of rifampin for treatment of LTBI are discussed further below. (See 'Rifampin' below.)

In addition, 4R should be used for patients presumed to have infection with INH-resistant, RIF-sensitive strains of TB [5,15-19]. (See "Epidemiology and molecular mechanisms of drug-resistant tuberculosis" and "Adherence to tuberculosis treatment".)

Alternative choices to 4R include 3HR and 3HP; data on these regimens are limited, and selection between them should be made on an individual basis considering factors such as drug availability, risk for toxicity, adherence, and cost.

- Limited data suggest that 3HR is equally efficacious and not more toxic than 9H [2,5,20-23]. In addition, the treatment completion rate for 3HR is higher than that of 9H [22,24].
- 3HP may be used for otherwise healthy patients age ≥2 years who fall within the four high-risk groups studied. Self-administered therapy (SAT) is acceptable for patients who can reliably take their medications on schedule and inform their providers promptly of side effects (while withholding the next dose pending provider review) [22,24,25]. Otherwise, 3HP should be administered via directly observed therapy (DOT), to facilitate review for side effects and withholding treatment if significant side effects are suspected. (See 'Isoniazid and rifapentine' below.)

Self-administered INH (9H or 6H) is frequently associated with poor adherence. If INH is used, we favor 9H given its established efficacy, and daily treatment achieves greater adherence than intermittent therapy (ie, three times per week or two times per week). 6H provides some

protection; in the setting of difficulty with adherence, providers may prefer to concentrate efforts in ensuring six months of therapy. This approach is favored by the World Health Organization (WHO) [3]. However, regimens shorter than nine months should not be used for patients with fibrotic lesions on chest radiograph. For patients with poor adherence, administration of INH via DOT (implemented daily or twice weekly) may be the optimal approach. (See "Adherence to tuberculosis treatment".)

Pyridoxine supplementation (25 to 50 mg daily) should be administered together with INH for patients with conditions that can predispose to neuropathy (including diabetes, uremia, alcoholism, malnutrition, and HIV infection).

RIF with pyrazinamide (PZA) should NOT be used for treatment of LTBI because of the possibility of severe hepatotoxicity [21,26-28].

High-incidence settings — HIV-uninfected individuals in high-incidence settings (TB incidence rate ≥100 per 100,000 population) who warrant LTBI treatment consist of close contacts of TB cases (table 3). For these individuals, we favor the regimen of RIF daily for four months; the rationale for this approach is discussed above (see 'Low-incidence settings' above). Our approach differs from that of the WHO, which favors the regimen of isoniazid daily for six months [3].

Issues related to treatment of LTBI for HIV-infected individuals are discussed separately. (See "Treatment of latent tuberculosis infection in HIV-infected adults".)

Regimen overview: Administration, toxicity, and efficacy — Regimens for treatment of LTBI include (table 2) [2,3,5,20,25,29]:

- RIF (10 mg/kg [600 mg maximum]) daily for four months (regimen abbreviation: 4R)
- INH (5 mg/kg [300 mg maximum]) and RIF (10 mg/kg [600 mg maximum]) daily for three months (regimen abbreviation: 3HR)
- INH (15 mg/kg [900 mg maximum]) and RPT (dose by weight) weekly for three months (regimen abbreviation: 3HP)
- INH (5 mg/kg [300 mg maximum]) daily for six to nine months (regimen abbreviation: 6H or 9H)

Regimen selection should be made on an individual basis considering factors such as adherence, hepatotoxicity risk, drug-drug interactions, prior treatment for TB (if any), and likelihood of LTBI due to drug-resistant *M. tuberculosis*. (See 'Selecting a regimen' above.)

Previously, RIF with PZA was recommended as a two-month regimen for treatment of LTBI [2], but revised guidelines advise against the use of this combination because of substantial hepatotoxicity [21,26-28].

Rifampin — The efficacy of RIF for reducing the incidence of active TB is estimated to be similar to that of INH [14,30,31]. RIF is well tolerated, with good completion rates and a low rate of hepatotoxicity [14,30,32-34].

In a randomized trial including more than 6800 adults with LTBI treated with 4R or 9H, 4R was not inferior to 9H for prevention of active TB (<0.01 cases per 100 person-years in both groups) and was associated with a higher rate of treatment completion (79 versus 63 percent) and lower rate of adverse events (rate difference -1.1 percentage points for all events; 95% CI -1.9 to -0.4) [14].

These data are preceded by other studies supporting RIF for treatment of LTBI [30,32,35]:

- Findings from a meta-analysis including 53 studies trials evaluating LTBI treatment suggested that regimens containing a rifamycin for at least three months may be more efficacious than INH monotherapy [35]. Compared with placebo, INH for six months, RIF for three to four months, and rifampicin-INH regimens for three to four months were efficacious for treatment of LTBI (odds ratio 0.64, 0.41, and 0.52, respectively).
- In a randomized trial including 679 patients with silicosis, the efficacy of RIF for treatment of LTBI (duration three months) was equivalent to that of INH (administered daily for six months) [30].
- A randomized trial including 847 patients randomized to 4R or 9H noted fewer adverse effects and better adherence among those who received RIF; the study did not evaluate efficacy [32].

Barriers to adoption of routine use of RIF for treatment of LTBI include the possibility of inadvertent treatment of active TB resulting in RIF-resistant disease, interactions between RIF and many other drugs, concerns about efficacy, and cost [36,37].

RIF has important interactions with the following drugs: warfarin, oral contraceptives, some antihypertensives, some antiarrhythmics, some antidepressants, some anticonvulsants, methadone, and the protease inhibitor class of antiretroviral drugs. Specific interactions can be determined by use of the Lexicomp drug interactions tool included within UpToDate. (See "Rifamycins (rifampin, rifabutin, rifapentine)".)

Isoniazid and rifampin — Data on use of INH and RIF in HIV-uninfected patients are limited [20,30]. In a prospective randomized trial among HIV-infected individuals, a three-month regimen of daily INH and RIF provided 60 percent protection [38]. Although this regimen has not been studied in a large trial among HIV-uninfected persons, a meta-analysis of small studies in this population suggests that it is equally efficacious and not more toxic than isoniazid for nine months [20].

We favor pyridoxine coadministration (25 to 50 mg daily) for individuals on an LTBI regimen containing INH; this is particularly important for those with risk factors for INH neurotoxicity (diabetes, uremia, alcoholism, malnutrition, HIV infection, pregnancy, seizure disorder).

Isoniazid and rifapentine — RPT is a rifamycin derivative with a long half-life and greater potency against *M. tuberculosis* than RIF. A three-month regimen of weekly INH and RPT given as DOT (table 2) was shown to be noninferior to a nine-month self-administered regimen of daily INH in a randomized trial including 7731 predominantly HIV-uninfected individuals at high risk for progression from latent to active TB infection in four low-incidence countries (Brazil, Canada, Spain, and the United States) for up to 33 months of follow-up [22]. Patients were ≥12 years of age and belonged to one of the following four high-risk categories:

- Close contact of patient with culture-confirmed contagious TB and positive tuberculin skin test (TST)
- Conversion from negative to positive TST result
- HIV-infected patients not on antiretroviral medications with positive TST or who have had close contact with known TB case (regardless of TST status)
- Positive TST with fibrotic changes on chest radiograph consistent with previously untreated TB

Most participants in the trial were presumed to be recently infected; infected contacts of infectious cases and recent TST converters made up approximately 96 percent of patients. TB developed in 7 of 3986 patients in the combination therapy group (cumulative rate 0.19 percent) and 15 of 3745 patients in the INH-only group (cumulative rate 0.43 percent). Hepatotoxicity was observed more frequently in the INH group than the combination therapy group (2.7 versus 0.4 percent), while "hypersensitivity" was observed more frequently in the combination therapy group than the INH group (3.8 versus 0.5 percent).

The completion rate was 82 percent for the combination therapy group and 69 percent for INH. At least some of the higher completion rate for combination therapy (and thus some of the efficacy) can be attributed to administration of combination therapy via DOT, while INH was administered without DOT.

The trial also observed an association between weekly INH plus RPT and flu-like syndrome or other systemic drug reaction [39]. These reactions occurred in 3.5 percent of 3893 mostly HIV-uninfected patients; risk factors included white ethnicity, older age, and lower body mass index. The reactions were serious (hypotension or syncope) in 0.3 percent of cases; none was associated with serious sequelae or death. This phenomenon remains poorly understood and difficult to predict; therefore, careful monitoring of patients on this regimen is important.

Implementation of a three-month regimen of weekly INH and RPT with DOT in 16 health care settings throughout the United States was associated with a treatment completion rate of 87 percent [40]. Such implementation in New York City Health Department clinics (302 patients) was also associated with a significant increase in treatment completion (65 versus 34 percent) [41].

Administration of weekly INH and RPT via DOT facilitates review for side effects and withholding treatment if significant side effects are suspected. SAT is acceptable for patients who can reliably take their medications on schedule and inform their providers promptly of side effects (while withholding the next dose pending provider review) [25]. Important side effects include symptoms of "hypersensitivity" (eg, light headedness, dizziness, headache, nausea or vomiting, syncope, rash, or angioedema) experienced following ingestion of the previous dose.

This approach is based on a randomized trial that included a subgroup of 774 patients with LTBI in the United States treated with INH and RPT given once weekly for 12 weeks via DOT, self-administration, or self-administration with reminders; completion rates were 85, 78, and 77 percent, respectively [24]. However, the study was not powered for safety analysis and patients on this regimen still require monthly provider visits to review for signs or symptoms of hepatic or hematologic toxicity.

Use of INH-RPT for treatment of LTBI should not be used for patients in the following categories: children <2 years of age, individuals with presumed infection with INH- or RIF-resistant TB, and pregnant women [22,23].

RPT has important and potentially prolonged drug interactions with the following: warfarin; oral contraceptives; some antihypertensives, antiarrhythmics, antidepressants, and anticonvulsants; methadone; and the protease inhibitor class of antiretroviral drugs. (See "Rifamycins (rifampin, rifabutin, rifapentine)".)

We favor pyridoxine coadministration (25 to 50 mg daily) for individuals on an LTBI regimen containing INH; this is particularly important for those with risk factors for INH neurotoxicity (diabetes, uremia, alcoholism, malnutrition, HIV infection, pregnancy, seizure disorder).

Isoniazid — The effectiveness of INH for reducing the incidence of active TB (compared with placebo) in clinical trials is 60 to 90 percent. However, the efficacy in practice is lower (25 to 92 percent), because of adherence issues [42,43].

In the only study comparing the efficacy of different durations of INH therapy, six months of treatment was 65 percent effective and 12 months of treatment was 75 percent effective (but not statistically different from six months) in preventing TB among patients with radiographic abnormalities suggestive of inactive infection [44]. By extrapolation of data from randomized trials, the optimal duration of INH treatment for LTBI has been determined to be nine months [2,44,45].

The most important side effect of INH is hepatitis; the incidence is about 1 per 1000 persons, although asymptomatic mild liver enzyme abnormalities are relatively common [46-48]. The most important risk factor for the development of INH-induced hepatitis is alcohol consumption; patients should be advised to abstain from alcohol while taking INH. In addition, all individuals on INH should be educated about the symptoms of hepatitis and instructed to seek prompt evaluation of symptoms to reduce risk for progression to severe disease. (See 'Monitoring and adherence' below.)

INH interference with metabolism of pyridoxine leads to peripheral neuropathy in up to 2 percent of patients [12]. In the setting of conditions that can predispose to neuropathy (including diabetes, uremia, alcoholism, malnutrition, and HIV infection) as well as in the setting of pregnancy and seizure disorders, patients on INH should receive pyridoxine supplementation (25 to 50 mg daily). Pyridoxine should also be administered to infants of breastfeeding mothers receiving INH.

E. UpToDate citation
Horsburgh CR. Treatment of latent tuberculosis infection in HIV-uninfected nonpregnant adults. In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. Jan 4, 2019. Access March 13, 2019.

F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)
Not any of the regimens appears to be more effective than another.

G. Other excerpts (USPSTF; other guidelines; etc.)

H. Citations for other excerpts

I. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]

[to be revised by the Pending PURL Reviewer as needed]

A. **Validity**: Are the findings scientifically valid? Yes

B. If **A** was coded "Other, explain or No", please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

C. **Relevance**: Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in the US such that results can be generalized?
Yes

D. If **C** was coded "Other, explain or No", please provide an explanation.

E. **Practice changing potential**: If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation?
Yes

F. If **E** was coded as "Yes", please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

Patients with latent TBI can be prescribed rifampin for 4 months due to a a shorter treatment course and potentially less side effects.

G. **Applicability to a Family Medical Care Setting**:
Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? Yes

H. Please explain your answer to **G**.
Latent TBI is common in family medicine practices both inpatient and outpatient.

I. **Immediacy of Implementation**:
Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market? Yes

J. If **I** was coded "Other, explain or No", please explain why.

K. **Clinically meaningful outcomes or patient oriented outcomes**:
Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective?
Yes

L. If **K** was coded “Other, explain or No”, please explain why.

M. In your opinion, is this a pending PURL? Yes

1. Valid: Strong internal scientific validity; the findings appear to be true.

2. Relevant: Relevant to the practice of family medicine.

3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.

4. Applicability in medical setting.

5. Immediacy of implementation

N. Comments on your response for question M.
My group felt that this was a PURL. I have some reservations about the study. It was open label. This was likely done to look at adherence rates and not overburden patients with multiple doses. However, this is definitely a source of bias.