Shorter Course Regimens for Treatment of LTBI

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Objectives

- Describe short course LTBI treatment regimens
- Pros and cons: 4mos Rifampin *vs* 3HP
- Strategies for implementation in primary care
- 3HP by DOT *vs* Self Administration

- Conflicts: None to declare

TABLE 3. Recommendations for regimens to treat latent tuberculosis infection

Priority rank*	Regimen	Recommendation (strong or conditional)	Evidence (high, moderate, low, or very low)
Preferred	3 mos isoniazid plus rifapentine given once weekly (**3HP**)	Strong	Moderate
Preferred	4 mos rifampin given daily (**4R**)	Strong	Moderate (HIV Negative)[†]
Preferred	3 mos isoniazid plus rifampin given daily (**3HR**)	Conditional Conditional	Very low (HIV negative) Low (HIV positive)
Alternative	6 mos isoniazid given daily (**6H**)	Strong[§] Conditional	Moderate (HIV negative) Moderate (HIV positive)
Alternative	9 mos isoniazid given daily (**9H**)	Conditional	Moderate

MMWR Recomm Rep 2020;69 (No. RR-1):1–11

Isoniazid

- Cheap
- Effective
- Historical standard of care

Risk reduction from various durations of INH in patients with LTBI*

Group	3 months	6 months	12 months
Overall	21%	65%	75%
Completers	31%	69%	93%

* n 27,830; Fibrotic CXR, 7 countries.
INH or placebo; 5yr active follow-up

Bull. WHO. 1982, 60(4): 555

INH: Major Issues

- Length of treatment
  - Poor adherence; <50% in some programs
- Toxicity
  - Requires at least monthly monitoring visits
- INH resistance
  - More than 9% of U.S. cases are INH resistant (2019)

Rifamycins

- Rifampin, Rifabutin, Rifapentine
- Inhibit DNA-dependent RNA polymerase
  - Active against non-replicating bacteria
  - Active against a broad array of bacteria
- Much less hepatotoxicity than INH
- However:
  - Multiple drug interactions
  - Other toxicities:
    - “Hypersensitivity” syndrome
    - Thrombocytopenia, anemia

Rifamycins
Some Drug Interactions

Oral anticoagulants
Cyclosporine
Itraconazole
Methadone
Phenytoin
Theophylline
β-Adrenergic blocking agents
Clarithromycin
Diazepam
Diltiazem
Doxycycline
Haloperidol
Nifedipine
Sulfonylureas
Tocainide

Oral contraceptives
Glucocorticoids
Ketoconazole
Midazolam or triazolam
Quinidine
Verapamil
Chloramphenicol
Dapsone
Digoxin (oral)
Disopyramide
Fluconazole
Losartan potassium
Nortriptyline
Tacrolimus

Rifamycin Hypersensitivity?

- Refers to a variety of syndromes
  - "Flu-like" symptoms (fever, malaise, myalgias)
  - GI upset (nausea)
  - Dizziness, syncope
  - Can be minor to severe
- Most commonly seen with intermittent regimens
- Mechanism(s) not understood
  - May not be same for each drug or side effect
    - Anti-rifampin antibodies found in patients with Rif-induced hemolytic anemia
    - NO antibody found in CDC substudy of 3HP-induced syncope

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults

D. Menzies, M. Adjobimey, R. Ruslami, A. Trajman, O. Sow, H. Kim, J. Obeng Baah, G.B. Marks, R. Long, V. Hoeppner, K. Elwood, H. Al-Jahdali, M. Gninafon, L. Apriani, R.C. Koesoemadinata, A. Kritski, V. Rolla, B. Bah, A. Camara, I. Boakye, V.J. Cook, H. Goldberg, C. Valiquette, K. Hornby, M.-J. Dion, P.-Z. Li, P.C. Hill, K. Schwartzman, and A. Benedetti

N Engl J Med 2018;379:440-53.

Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults

- Open label, randomized trial
  - 6,859 patients, 9 countries
- 4 months Rifampin *vs* 9 months INH
- 28 month follow-up
- Efficacy and safety
- Principal findings:
  - 4 mos Rif was noninferior to 9 mos INH (8 *vs* 9 TB cases)
  - Rate of completion better in Rif group (79 *vs* 62%)
  - Toxicity (grade 3-5, esp hepatotoxicity) was lower in Rif group

Menzies, *et al*. NEJM 379:440, 2018.

Rifapentine

- Similar to rifampin; longer half-life
  - Similar drug interaction profile
- Initially approved for once-weekly therapy in the continuation phase of active TB
- Few studies of *efficacy for treatment of LTBI*, once weekly in combination with INH
  - 1 study in children >2 y/o

3HP Evidence

- Sterling, *et al*: **TBTC Study 26** (NEJM 12/8/11)
  - 3HP (DOT) *vs* 9H (SAT)
  - 7,731 adults (>12y/o) with increased RISK:
    - 5,466 close contacts,
    - 1,925 TST converters,
    - 161 HIV-infected,
    - 179 with CXR changes c/w healed pulmonary TB

    96%
  - Non-inferiority data analysis
    - Low event rate; loss to follow-up
  - 3HP
    - As effective as 9H (rate of TB appr. 50% that of 9H)
    - Higher completion (82 *vs* 69%*)
    - Higher permanent discontinuation for AE (4.9 *vs* 3.7%*)
    - Higher incidence of "Hypersensitivity" (2.9 *vs* 0.4%*)
    - Less hepatotoxicity (0.3 *vs* 2.0%*)

* $p < 0.01$

3HP - Risks

- Drug interactions
  - Rifamycins interact with multiple drugs
    - Articulated in Guidelines and Fact Sheet, with reference to major drugs (oral contraceptives, warfarin, sulfonureas, and methadone)
- Adverse events
  - Hepatotoxicity
    - Less than 9H
  - Pregnancy
  - "Hypersensitivity"
    - Includes "Flu-like syndrome", nausea, light-headedness, syncope – usually following a 2nd or 3^{d} dose with prodrome following previous dose
- Requires DOT: adherence AND safety
  - HCW reviews symptoms following prior dose before next dose administration; if significant reaction is reported, dose is not given

3HP Safety Studies

- 7552 TBTC Study 26 subjects who received ≥1 dose of study drug*; 153 had SAE:
  - 138/3893 (3.5%) with 3HP *vs* 15/3659 (0.4%) with 9H ($p < 0.001$)
  - 3HP arm:
    - 87 (63%) had flu-like syndrome and 23 (17%) had cutaneous reactions
    - 13/3893 (0.3%) had severe reactions: 6 were hypotensive and 6 (0.15%) reported syncope
      - Study did not account for held doses if subject reported symptoms following previous dose; likely underestimates significance of problem
- Post marketing surveillance (CDC)
  - Programs voluntary reporting SAE
  - No denominator data
  - No communication with FDA *Medwatch* Program

* Sterling, et al. *Clin Infect Diseases* 61:527, 2015

3HP: DOT?

- **TBTC Study 33:** *An evaluation of **adherence** to LTBI treatment with 12 doses of once weekly rifapentine and isoniazid given as self-administered versus directly-observed therapy: iAdhere**
  - Compared SAT with DOT and "reminder" SAT; 4 countries
    - SAT *non-inferior* to DOT for completion *in US cohort only*
    - *NOT* powered for safety analysis, but says "*similarly safe*"
- For now, safety concerns may preclude SAT for 3HP
  - Especially pre-syncope/syncope
  - Guidance statement from CDC is suggests SAT is acceptable (most patients)

*Belknap, R., *et al*. Annals Int Med. 2017*, in press*.

So …

Shorter course regimens for treating LTBI?

Basically, 3 options are available:

Regimen 1: 4 months Daily Rif (4R)

- Strengths
  - Most experience
  - Better completion rates versus 9H
  - Less toxic than 9H
  - Can be used in children
  - Can be self-administered
- Issues
  - Multiple drug interactions may need to be accommodated
  - No intermittent option

Regimen 2: 3 months Weekly INH + Rifapentine (3HP)

- Strengths
  - Efficacy has been shown best in contacts and TST/IGRA converters: non-inferior to 9H
    - Limited data on non-recently infected persons
  - Enhanced completion rates *versus* 9H
- Issues
  - Limited data on HIV+ and others not recently infected
  - Number of tablets per dose (±10 tablets/week)
  - DOT (?)
    - Safety and efficacy
  - Toxicity – especially hypersensitivity (syncope)

Regimen 3: 3 months Daily INH + Rif (3HR)

- Strengths
  - Commonly used in Europe; not used in U.S.
  - Can be self-administered
- Issues
  - Limited data on efficacy
  - Toxicity (with INH)
  - No intermittent option

But …

Not So Fast …

- FDA recently notified providers about discovery of excess **nitrosamine impurities** in Rifampin and Rifapentine
  - These are common compounds, found in many foods and beverages – but have carcinogenic potential
  - Risk is believed to be extremely low, requiring long term exposure
- In order to maintain the supply of these drugs for treatment of TB disease, FDA raised the maximum acceptable limits for these contaminants in these drugs
  - By 31x for Rifampin, 200x for Rifapentine*
- National TB Controllers Association (NTCA) and CDC are in dialog with FDA and manufacturers

* 10/2020

Nitrosamines and Rifamycins. Recommendations, MDPH*

- **Treatment of TB disease:**
  - Continue use of rifampin *if acceptable to the patient*, as the risk of not taking rifampin likely outweighs any potential risk from nitrosamine impurities.
- **Treatment of latent TB infection:**
  - **Currently receiving rifampin or rifapentine:** continue this treatment, although a change to isoniazid (INH) is acceptable *if preferred by the patient*.
  - **Newly diagnosed LTBI**: Until more information becomes available, consider alternative treatment strategies *in discussion with the patient*.

* 12/2020

Monitoring

- All patients on LTBI treatment with any regimen must be clinically monitored at least monthly
  - Rifampin only: Consider base and monthly liver enzymes and CBC/platelets for anyone with:
    - HIV+
    - Regular alcohol use
    - Underlying liver disease
  - Rifamycin with INH: also follow standard INH monitoring procedures
- **Check for possible drug interactions**
- For HIV+ on antiretrovirals, seek expert TB medical consultation and communicate with the patient's HIV physician before starting rifampin or rifapentine

Summary

- Rifamycins allow for shorter treatment of LTBI with better completion rates
  - Rifampin (4 months) is well-tolerated, effective, and safe
  - Rifapentine with INH for 3 months has good data on efficacy in limited, high risk groups but should be given by DOT for safety
  - Shorter course regimens using rifamycins are less toxic and less expensive than isoniazid monotherapy with higher completion rates
    - … but for Nitrosamines contamination