Updated Recommendations for use of Once-weekly INH and Rifapentine (3HP)
Bob Belknap, MD
November 22, 2019

Medical Consultant Meeting
November 22, 2019
San Antonio, Texas

Friday, November 22, 2019

Medical Consultant Meeting

Speakers:
Barbara J. Seaworth, MD; Heartland National TB Center
Dick Brostrom, MD; Centers for Disease Control and Prevention
Manasa Velagapudi, MBBS; Creighton University Medical Center
Lisa Y. Armitige, MD, PhD; Heartland National TB Center
Bob Belknap, MD; Denver Health and Hospitals Metro TB Program
Jim McAuley, MD; Whiteriver Indian Health Services
Janice Louie, MD; San Francisco Department of Public Health

Today’s presenters, CME Committee, staff and planning committee have indicated they have no commercial affiliations to disclose.
Updated Recommendations for use of Once-weekly INH and Rifapentine (3HP)

Bob Belknap MD
Director, Denver Metro TB Program
November 22, 2019

Disclosure

• None

“I’ll have an ounce of prevention.”
Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Phase 3 Clinical Trial
9 months of daily, self-administered INH vs 3 months of INH/Rifapentine once weekly by directly observed therapy (DOT)
- > 8,000 patients
- Proved both safe and effective

PREVENT TB Trial
Once-weekly INH and Rifapentine for 3 months by Directly Observed Therapy (DOT)

Sterling NEJM 2011 365; 23
• Original guidance in 2011 recommending use of 3HP in HIV-negative persons ≥ 12 years old
• Update focused on newer data
  – Systematic literature review
    • Used the Guide to Community Preventive Services (a method for conducting reviews that is different than GRADE)
  – Expert Consultation

MMWR June 29, 2018 / Vol 67 / No 25

Updated Recommendations

1. Expanded recommendation to use in children aged 2-17 years

2. Use of 3HP recommended in persons living with HIV and taking medications with acceptable drug-drug interactions

3. Use of 3HP by directly observed therapy (DOT) or self-administered therapy (SAT)
3HP in younger children

**Water dispersible rifapentine**
- Mango flavored
- Coming soon (hopefully)

3HP in HIV-positive

- Rifapentine and rifampin can be safely given with efavirenz
  - But efavirenz isn’t first-line for HIV anymore

- DOLPHIN Study (Dooley et al CROI 2019)
  - Co-administered once daily dolutegravir with 3HP
  - Decrease in DTG levels by 29% but viral loads remained undetectable and no increased AEs
Why do another LTBI study using 💝 once-weekly INH and rifapentine?

• Directly observed therapy is good

• Intermittent therapy for treating TB evolved as a way to make DOT easier

• The cost of DOT is the limiting factor when considering broad use of the once weekly, 12 dose regimen
2011 - how will 3HP be used?

1. Reserved for specific subsets of LTBI patients
   or
2. Given as self-administered therapy where the adherence is unknown

Cost and Inconvenience are Barriers

Figure 1  Cost of a complete course of treatment for latent tuberculous infection with either 9H or 3HP administered by DOT

Shepardson IJTLD Dec 2013, update 2014
Would Text Reminders Help?

http://www.patient-reminders.com

iAdhere: Protocol Summary

Primary Objective:
Evaluate treatment completion by DOT vs self-administered with or without text reminders

• Phase 4 (drugs are approved for latent TB)
• Open label (everyone knows what drugs they are getting)
• Randomized to one of the 3 arms
• Target Population: Adults with latent tuberculosis
iAdhere: Study Design

- Enrolled adults only (> 18)
  - measuring individual and not parental adherence
  - INH by DOT was used as the standard
- Study Sites: U.S., Spain, South Africa and Hong Kong
- Ensured ≥ 75% from U.S. sites for a pre-planned sub-analysis
- Sample size to detect a difference of 15% or greater between DOT and SAT arms

Measuring Adherence to SAT - Direct

Urine  Blood
Consultation with Adherence Experts

• Pill counts and self-report (indirect measures)
  – Both tend to overestimate true adherence

• Medication Event Monitoring System (MEMS)
  – Gold Standard in adherence literature

Enrollment

• Enrollment: September 2012 - April 2014
• 1002 patients
Treatment Completion

<table>
<thead>
<tr>
<th></th>
<th>DOT</th>
<th>SAT</th>
<th>SAT w/ texts</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Participants</td>
<td>87%</td>
<td>74%</td>
<td>76%</td>
</tr>
<tr>
<td>U.S. Only</td>
<td>85%</td>
<td>78%</td>
<td>77%</td>
</tr>
</tbody>
</table>

- DOT completion was higher than in Study 26
- SAT completion varied by country of enrollment

iAdhere: Results

Differences in Completion Rates: DOT minus SAT and DOT minus eSAT: Total and U.S. only

21

22
iAdhere: Summary

- Population enrolled was broadly representative of adult patients with LTBI (generalizable)

- Treatment completion by SAT was
  - comparable to DOT in the USA
  - was better than 9 months of INH in Study 26 and historical experience
  - Similar to 4 months of rifampin

3HP SAT in Denver

Aiona et al., NTCA 2018
Patient Choice

1. **Once-weekly INH and Rifapentine**
   Pros: 3 months, shortest current regimen
   Cons: ~ 10 pills / dose (120 pills total); flu-like illness in some

2. **Daily Rifampin**
   Pros: 4 months (short), only 2 pills / dose
   Cons: 240 pills

3. **Daily INH**
   Pros: far fewer drug-drug interaction
   Cons: 6-9 months and it’s INH (fatigue, headaches, GI)
Questions?

"The last thing he said was 'I'm going to go and look up the word 'dictionary' in the dictionary, and then the universe kind of collapsed around him.'"