Preventing Tuberculosis through Treatment of Tuberculosis Infection

Connie A. Haley, MD MPH
Faculty, Division of Infectious Diseases and Global Medicine
Consultant, Southeastern National Tuberculosis Center
University of Florida

Learning Objectives

• Recognize the importance of targeted testing and treatment for latent TB infection in the U.S.
• Describe the regimens available for treatment of TB infection including appropriate regimen selection.
• Describe considerations for use of the 3HP regimen.
• Explain 3HP use and outcomes in Virginia.

Global TB Epidemiology*

• In 2012, 8.6 million people fell ill with TB globally
  ▪ 3 million people who developed TB in 2012 were missed by national notification systems
  ▪ Global incidence 122/100,000 population vs. 3.0 U.S.
• About 80% of reported TB cases occurred in 22 countries in 2012
  ▪ Nearly 60% of new TB cases occurred in Asia
  ▪ Sub-Saharan Africa has highest rate of new cases per capita (>1000/100k in some areas)
• 1.3 million deaths, 1.1M with HIV

*World Health Organization (WHO)

Reported TB Cases United States, 1982–2013*

TB Control Priorities in the U.S.

TB control in the United States relies on 3 main strategies:
1. Early diagnosis and treatment of persons with active TB
2. Investigation of contacts of persons with active TB and treatment of those contacts who are found to have active TB or latent TB infection (LTBI)
3. Targeted LTBI testing and treatment of persons at high risk for active TB

Principles for Stopping TB Transmission

Fig. 19 Principles for stopping tuberculosis (TB) transmission. TB control is based on protecting susceptible individuals from becoming infected using vaccination, preventing infected individuals from developing the disease using prophylactic treatment, preventing individuals with TB from having contact with susceptible individuals through early detection and cure, isolation, and infection control measures.

Global Epidemiology of Tuberculosis. Semin Respir Crit Care Med 2013;34:1–18.

- American Indian or Alaska Native
- Asian
- Black or African-American
- Native Hawaiian or Other Pacific Islander
- White
- Hispanic or Latino

*All races are non-Hispanic. **Updated as of June 11, 2014.

Number of TB Cases in U.S.-born vs. Foreign-born Persons, United States, 1993–2013*

- U.S.-born
- Foreign-born

*Updated as of June 11, 2014.

Trends in TB Cases in Foreign-born Persons, United States, 1993 – 2013*

- Number of Cases
- Percentage

*Updated as of June 11, 2014.

TB Case Rates in U.S.-born vs. Foreign-born Persons, United States, 1993 – 2013*

- U.S. Overall
- U.S.-born
- Foreign-born

*Updated as of June 11, 2014.

Reactivation of Latent TB Infection among the Foreign-born in the U.S.

- Studies of TB genotypes in the U.S. suggest that TB among foreign-born individuals is more attributable to reactivation of LTBI likely acquired before arrival to the U.S. instead of recent TB transmission (Geng, NEJM 2002; Jasmer Ann Int Med 1999)
- 4 out of 5 cases among foreign-born persons are due to reactivation (Ricks, PLoS ONE 2011)
- TB case rates declined with increasing time since US entry, but remained higher than among US-born persons—even more than 20 years after arrival. (Cain, JAMA. 2008)
- 50% of foreign-born TB cases occurred among persons who had been in the U.S. for >5 years and, thus, would not qualify as being at high risk for TB according to current guidelines (Cain AJRCCM 2007)

Annual Estimate of Migrants Entering the U.S.*

- Refugees: 70,000-80,000**
- Immigrants: ~1.1 million
- Non-immigrant Visitors: ~36 million
- Border Commuters: 127 million

Total: ~163 million

*Source: U.S. Department of Homeland Security (DHS)
**2011 Refugee Admissions: 56,422
§2011 Non-immigrant Visitors: 36,422
§2011 Border Commuters: 127 million

Total: ~163 million
Percent of Foreign-born with TB by Time of Residence in U.S. Prior to Diagnosis, 2013

### The Scope and Impact of Treatment of LTBI in the United States and Canada.

- **Tuberculosis Epidemiologic Studies Consortium (TBESC)**
  - Task Order 13
  - Conducted a survey of clinics in the U.S. (n=19) and Canada (n=2) that initiated LTBI treatment for ≤10 patients in 2002.
  - Extrapolated study data to the entire U.S. population
    - Used an estimated 20-60% treatment effectiveness and 5% lifetime risk of active TB without treatment,
  - Results: Targeted screening and treatment of LTBI likely prevented between 4,000 and 11,000 active TB cases in the U.S.

### LTBI Treatment – Susceptible Disease

#### Recommended regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
<th>Duration</th>
<th>Issues</th>
<th>Abbrev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Daily</td>
<td>9 months (6 months)</td>
<td>Long duration, poor adherence</td>
<td>9H</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Twice weekly</td>
<td>9 months (6 months)</td>
<td>Directly observed, long duration</td>
<td>9H-DOT</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Daily</td>
<td>4 months</td>
<td>Drug interactions</td>
<td>4R</td>
</tr>
<tr>
<td>Isoniazid + rifapentine</td>
<td>Once weekly</td>
<td>3 months</td>
<td></td>
<td>3HP</td>
</tr>
</tbody>
</table>

**Other regimens**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
<th>Duration</th>
<th>Issues</th>
<th>Abbrev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid + rifampin</td>
<td>Daily</td>
<td>3 months</td>
<td>Not in U.S. recommendations</td>
<td>3HR</td>
</tr>
<tr>
<td>Rifampin + pyrazinamide</td>
<td>Daily or 2x/week</td>
<td>2 months</td>
<td>Potentially fatal: NOT RECOMMENDED</td>
<td>2RZ</td>
</tr>
</tbody>
</table>

### LTBI TREATMENT REGIMENS

#### Treatment of LTBI: Isoniazid (INH)

- More than 20 randomized, placebo-controlled trials of LTBI treatment with INH have been conducted involving more than 100,000 subjects.
- The combined average reduction in TB reported in these studies was 60% during the period of observation.
  - These results were based on the total study populations treated, regardless of how regularly medication was taken.
  - Reduction highest during year of treatment
- When analyses were limited to participants who took INH for most of their treatment year, efficacy approximated 90%.
- Protection demonstrable nearly 20 years after treatment.


#### How Much INH is Needed for the Prevention of Tuberculosis? The Bethel Study

- Among those who took 0-9 months, longer duration of therapy corresponded to lower TB rates
- Subgroup analysis, no extra increase in protection among those who took > 9 months

*Therapies were: INH in the Bethel study of 1686 tuberculosis patients according to the number of months of therapy: 9 months = high dose, 0-6 months = low dose. Data from the study by the Getman and the Bethel study authors. Data reported for the first 9 months and the last five observations. See: Getman, S. D. 2002. Your Hand in the Balance: Tuberculosis and Tuberculosis Control. New York: Oxford University Press. Copyright by permission of the World Health Organization World Health Organization World Health Organization.*
INH in Patients with HIV

- Meta-analysis of 7 RCT
  - Mexico, Haiti, the US, Zambia, Uganda and Kenya
  - Conducted between 1985 and 1997
  - INH more effective than placebo in preventing active TB among HIV-infected persons with +TST, reducing the TB incidence by 60-80%
- Some (not all) found association between INH and improved survival
- Preferred regimen for HIV+ persons is 9 months INH
  - If known exposure, treat regardless of TST result

INH: Safety, Tolerability, Completion

- Dose:
  - Daily INH:
    - Adults: 300mg (5mg/kg)
    - Kids: 10-20mg/kg not to exceed 300mg
  - Twice-weekly INH:
    - Adults: 15mg/kg adults
    - Kids: 20-40mg/kg, not to exceed 900mg
    - Must be given by DOPT
  - Adherence for 6-9 months 30-60%
- Adherence for 6-9 months 30-60%
- Monthly clinical assessments (does not mean routine LFT’s)

Shortcomings of LTBI Treatment with INH

- High perceived risk of INH by many providers
- Low perceived benefit for asymptomatic LTBI by patients
- Long duration of treatment (6-9 months)
- Poor adherence by patients
- Need for alternative treatments for patients with drug intolerance
- Need for alternative treatments for patients with drug resistance
- Ideally want shorter, better-tolerated regimens for all patients

LTBI Treatment – Susceptible Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
<th>Duration</th>
<th>Issues</th>
<th>Abbrev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Daily</td>
<td>9 months (6 months)</td>
<td>Long duration, poor adherence</td>
<td>9H</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Twice weekly</td>
<td>9 months (6 months)</td>
<td>Directly observed, long duration</td>
<td>9H-DOT</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Daily</td>
<td>4 months</td>
<td>Drug interactions</td>
<td>4R</td>
</tr>
<tr>
<td>Isoniazid + rifapentine</td>
<td>Once weekly</td>
<td>3 months</td>
<td>DOT</td>
<td>3HP</td>
</tr>
</tbody>
</table>

Other regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
<th>Duration</th>
<th>Issues</th>
<th>Abbrev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid + rifampin</td>
<td>Daily</td>
<td>3 months</td>
<td>Not in U.S. recommendations</td>
<td>3HR</td>
</tr>
<tr>
<td>Rifampin + pyrazinamide</td>
<td>Daily or biweekly</td>
<td>2 months</td>
<td>Potentially fatal: NOT RECOMMENDED</td>
<td>2RZ</td>
</tr>
</tbody>
</table>
Rifampin – Efficacy

- One randomized clinical trial
- From 1981 to 1987, a cohort of older Chinese men with silicosis (n=679) randomized to one of three groups:
  - Rifampin for three months (3R)
  - Rifampin plus INH for three months (3HR)
  - Isoniazid for six months (6H)
  - Placebo


So, where do we get “4 months” from?

- 6H < 12H ~ 9H, so 9H is the recommendation
- 3R ~ 6H < 9H, so....
- 4R is the recommendation

*In other words, we have no direct efficacy data for four months of rifampin—yet.

- In situations where RIF cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted (though not studied for LTBI treatment)

Rifamycins

- Inhibit DNA-dependent RNA polymerase
  - Active against dormant and semi-dormant bacteria that characterize LTBI
  - Isoniazid only active against replicating bacteria
- Active against a broad array of bacteria (including M. Tuberculosis)

Examples:
- Rifampin
- Rifabutin
- Rifapentine

Rifampin – Efficacy

Development of active TB:

- The effectiveness of 3 months of RIF vs. placebo was calculated at 50% among persons who completed the 5-year study, and at 46% among all persons who initiated treatment
- (Patients all had silicosis, so TB rates were much higher)

Other Evidence for Rifampin

- 2 small observational studies suggesting efficacy
  - 204 homeless persons in Boston who developed a TST conversion during an epidemic of INH-resistant TB
    - 71 had no therapy–8.6% developed active TB
    - 38 were given INH–7.9% developed INH-resistant TB
    - 49 given RIF only for average of 6 months, none developed TB
  - 157 adolescent contacts to INH-resistant source case who developed TST conversions after M. tuberculosis exposure
    - None developed active TB during 2 years follow up after completion of 6 months of rifampin mono-therapy.

Rifampin – Dose, Adherence and Toxicity

- Dose 600 mg daily x 4 months
  - 6 months in children
- Completion rates much higher, 60-91%
- Well-tolerated
  - Mild skin reactions, GI symptoms, orange body fluids
- Low rates of hepatotoxicity
  - 0.3% versus 1.4% for INH in one study
- Other
  - Hypersensitivity syndrome (“Flu-like” symptoms- fever, malaise, myalgias; Not well-defined
  - Anemia, thrombocytopenia
  - Both more common with intermittent doses
- Carefully rule out TB if HIV (+), avoid with ART

- Dose 600 mg daily x 4 months
  - 6 months in children
- Completion rates much higher, 60-91%
- Well-tolerated
  - Mild skin reactions, GI symptoms, orange body fluids
- Low rates of hepatotoxicity
  - 0.3% versus 1.4% for INH in one study
- Other
  - Hypersensitivity syndrome (“Flu-like” symptoms- fever, malaise, myalgias; Not well-defined
  - Anemia, thrombocytopenia
  - Both more common with intermittent doses
- Carefully rule out TB if HIV (+), avoid with ART
**Rifamycins – Drug Interactions**

- Anticoagulants (oral)
- Chloramphenicol
- Clarithromycin
- Contraceptives (oral)
- Cyclosporine
- Dapsone
- Diazepam
- Disopyramide
- Doxycycline
- Fluconazole
- Haloperidol
- Glucocorticoids
- Itraconazole
- Losartan potassium
- Ketocnazole
- Methadone
- Midazolam or triazolam
- Nifedipine
- Nortriptilene
- Phenyoil
- Quinidine
- Sulfonylureas
- Tacrolimus
- Theophyllyne
- Verapamil

*Check everything for potential drug-drug interactions esp. HIV meds*


**Rifapentine**

- Similar to rifampin, but a longer half-life
- Initially approved for once-weekly therapy of active TB in the continuation phase
- Three studies of efficacy for treatment of LTBI (once per week in combination with isoniazid, 3HP)
  1. 399 household contacts in Brazil
     - (Schechter M. Am J Respir Crit Care Med. 2006 Apr 15;173(8):922-6.)
  2. 1,150 HIV+ patients in South Africa
     - (Martinson N et al. 39th IUATLD World Conference on Lung Health, late breaker abstract, Paris, 2008.)
- PREVENT-TB Study (TB Trials Consortium Study 26)

**TB Trials Consortium Study 26 (PREVENT-TB)**

- Multi-center RCT, sites in US, Canada, Brazil, Spain
- 8,053 “high-risk” patients
  - 72% contacts of TB cases, 24% TST converters
  - Very few HIV+ or children 2 years and older
- Randomized to 2 treatment arms and followed for 33 mo.:
  1. Rifapentine/INH weekly for 3 mos by DOT (3HP-DOT)
     - RPT 900 mg (Graduated dosing for persons <50 kg)
     - INH 15-25 mg/kg; 900 mg max.
  2. INH daily for 9 months self-administered (9H-SAT)
     - INH 5-15 mg/kg; 300 mg max.
     - Vitamin B6 (pyridoxine) 50 mg with each INH dose

*Study 26 – results*

- Both arms similar efficacy
  - 15 cases (0.43%) in 9H arm
  - 7 cases (0.19%) in 3HP arm
- Completion much higher with 3HP (80%)
- Toxicity slightly higher with 3HP (5% vs. 3% in 9H)
  - Hepatotoxicity the same
  - “Excess” toxicity was hypersensitivity
  - (There is some evidence that it may have been over-reported.)

**Study 26 – Some caveats**

- DOT was used in the study, so there is no data on completion rates for self-administered therapy
  - Ten pills once per week – adherence could be very different
- Limited data on HIV+ patients
- No data yet on children <2 years

**INH-Rifapentine (3HP) – CDC Recommendations, 2011**

- 3HP: Rifapentine 900 mg plus INH 900 mg once per week for 12 doses
- 3HP is an equal alternative to 9H for the following:
  - Contacts
  - Recent converters
  - Old, healed (Class IV) TB *(rule out active TB)*
- Adults and children ≥12 years
  - Can be used in children 2-11y on “case by case” basis
- HIV+ if healthy and on no ARVs

*MMWR: Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection* [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w)
3HP – CDC Recommendations (2011)

- Choice between INH and INH-RPT depends on:
  - Feasibility of DOT
  - Ability to obtain drugs
  - Ability to monitor side effects
  - Ability to complete treatment
  - Preference of patient and physician

- Practical advantages:
  - Corrections
  - Shelters
  - Clinics for recent immigrants

3HP – CDC Recommendations (2011)

- Precautions:
  - Contacts to INH or Rif
  - HIV patients on ART
  - Recommended in UK and Canada
  - Ability to complete treatment
  - Feasibility of DOT

- Practical advantages:
  - Corrections
  - Shelters
  - Clinics for recent immigrants

3 months INH-Rifampin

- Rifampin 600 mg plus INH 300 mg for 3 months

- Not included in the ATS/CDC guidelines for treatment of LTBI in the United States
  - Recommended in UK and Canada
  - Self-administered, No intermittent option
  - Limited data on efficacy, toxicity/side effects
  - Recent randomized, controlled trial of 3 mos. RH compared to 6 mo. INH in 590 immigrants to Spain:
    - Better adherence in 3 RH vs. 6R (72% vs. 52.4%, P=0.001)
    - Similar effectiveness, liver toxicity, and side effects

LTBI Treatment Regimens for Patients Exposed to Multidrug-Resistant TB

- Contacts of Persons with Multidrug-Resistant TB
  - Consider risk for progressing to MDR disease before recommending LTBI treatment
  - When prescribing treatment for these contacts, consult an MDR TB expert
  - Limited data on most effective treatment regimens
    - Use at least 2 anti-TB drugs, usually a quinolone and PZA or EMB, depending on resistance pattern of source case and patient’s ability to tolerate drugs.
    - Monotherapy with a quinolone also recommended (not cipro)

ADHERENCE AND MONITORING DURING LTBI TREATMENT

Completion of LTBI Therapy

- Completion of therapy is based on the total number of doses administered, not on duration alone
- Extend or re-start treatment if interruptions were frequent or prolonged enough to preclude completion
- When treatment has been interrupted for more than 2 months, patient should be examined to rule out TB disease
- Recommend and arrange for DOT as needed

Treatment Completion for LTBI Regimens

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum Doses for completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily</td>
<td>270 within 12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>76 within 12 months</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>Daily</td>
<td>180 within 9 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>52 within 9 months</td>
</tr>
<tr>
<td>Isoniazid &amp; Rifapentine</td>
<td>3 months</td>
<td>Once weekly</td>
<td>12 within 16 weeks</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
<td>120 within 6 months</td>
</tr>
</tbody>
</table>

Identifying Barriers to Initiation and Adherence of LTBI Therapy

- LTBI patient has no symptoms, low perceived risk of TB
- Physician perceptions
- Misinformation about TB or HIV
- Health beliefs and practices
- Cultural and language barriers
- Real or perceived stigma related to LTBI diagnosis or treatment
- Co-existing medical conditions
- Medication side effects (or fear of side effects)
- Limited financial resources
- Appointment hours that conflict with patient’s schedule; inconvenient clinic locations
- Other fears (doctors, government, loss of confidentiality)

Measures to Improve Adherence

- DOT
- Pill boxes, timers, calendars, etc.
- Case management
- Culturally-sensitive education and counseling
- Peer support from community agencies
- Incentives: small rewards that encourage or motivate patients (grocery store vouchers, nutritional supplements, or restaurant coupons)
- Enablers: free van transportation, bus tickets, reminder letters or phone calls, other assistance that makes it easier to keep appointments
- “Cues” as reminders (notes on coffee pot, mirror, etc.

Clinical and Laboratory Evaluation

- Routine baseline laboratory tests (e.g., AST, ALT, and bilirubin) not required, except for:
  - HIV-infected persons
  - Pregnant women or those in early post-partum period
  - Persons with chronic liver disease; use alcohol regularly
  - Liver enlargement or tenderness during examination
- Monthly clinical monitoring for signs or symptoms of possible adverse effects is recommended for all patients
  - Dispensing one month at a time facilitates clinical reassessment
Instruct patient to immediately report signs and symptoms of adverse drug reactions (and stop treatment!!!):
- Fever
- Headache
- Rash
- Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
- Fatigue or weakness
- Dark urine
- Persistent numbness in hands or feet

Monthly visits should include a brief physical exam and a review of:
- Rationale for treatment
- Adherence with therapy
- Symptoms of adverse drug reactions
- Plans to continue treatment

Follow-up lab testing if patient has conditions above, abnormal labs at baseline, or signs or symptoms of adverse drug reaction
- Asymptomatic elevation of hepatic enzymes seen in 10%-20% of people taking INH
  - Levels usually return to normal after completion of therapy
- Discontinue treatment if transaminase level exceeds 3 times the upper limit of normal if patient has symptoms of hepatotoxicity, and 5 times the upper limit of normal if patient is asymptomatic

Consider baseline hepatic chemistry blood test for older patients on individual basis, especially if taking meds for chronic medical conditions.
- Blood tests at subsequent clinical encounters for patients whose baseline testing is abnormal and for others at risk for liver disease.
- Discontinue INH-RPT if serum AST/ALT concentration ≥ 5x ULN even in the absence of symptoms or ≥ 3x ULN in presence of symptoms.
- Be vigilant for drug hypersensitivity reactions, particularly hypotension or thrombocytopenia.
  - Severe condition (e.g., hypotension requiring intravenous fluid support): discontinue INH-RPT; give supportive medical care
  - Mild to moderate condition (e.g., dizziness treated with rest or oral fluids): conservative management of constitutional symptoms, clinical and laboratory monitoring, option for continuing tx under observation

Educate patients to seek medical attention upon the first symptom of a possible adverse event.
- Clinically assess upon first sign/symptom of possible adverse event.
- Monthly interview and brief physical examination for findings of treatment-associated adverse events (e.g., icterus, tenderness of the liver, or rash).
- Baseline hepatic chemistry blood tests (at least aspartate aminotransferase [AST]) for patients with specific conditions:
  - HIV
  - Liver disorders
  - Women in immediate postpartum period (≤3 mo. after delivery)
  - Regular alcohol usage

Consider baseline hepatic chemistry blood test for older patients on individual basis, especially if taking meds for chronic medical conditions.
- Blood tests at subsequent clinical encounters for patients whose baseline testing is abnormal and for others at risk for liver disease.
- Discontinue INH-RPT if serum AST/ALT concentration ≥ 5x ULN even in the absence of symptoms or ≥ 3x ULN in presence of symptoms.
- Be vigilant for drug hypersensitivity reactions, particularly hypotension or thrombocytopenia.
  - Severe condition (e.g., hypotension requiring intravenous fluid support): discontinue INH-RPT; give supportive medical care
  - Mild to moderate condition (e.g., dizziness treated with rest or oral fluids): conservative management of constitutional symptoms, clinical and laboratory monitoring, option for continuing tx under observation


LTBI Pretreatment Clinical Evaluation and Counseling
Monitoring for Hepatotoxicity During LTBI Treatment

INH for 9 mo. preferred for children <12y, HIV patients on ART, and pregnant women or those wanting to become pregnant

Rifamycins allow for shorter treatment of LTBI with better completion rates
- Rifampin for 4 months well-tolerated; limited efficacy data
- INH-Rifapentine for 12 weeks has good efficacy data; DOT
- Shorter rifampin-based LTBI regimens are more effective and less expensive than INH monotherapy
- DOT may be justified for high-risk patients.

LTBI treatment is cost-effective (prevention saves $$)

Virginia's Experience with INH + Rifapentine therapy for TB Infection

- 19 of 35 health districts in Virginia have used the 12 week INH/Rifapentine (3HP) regimen through 10/31/14.
- Data is only received at central office after completion or if discontinued for a serious side effect.
- 255 know to have started treatment with 3HP
  - 222 (87%) completed therapy
  - 2 still on treatment
  - 28 (10%) stopped treatment
    - 17 (7%) stopped due to side effects
    - 0 stopped due to death
    - 6 (2%) stopped lost to follow-up

Virginia's Experience with INH + Rifapentine therapy for TB Infection

- 10 districts had 1 or more clients with an adverse event form filed.
- Outcomes from adverse event forms
  - Continued 3HP – 6
  - Switched to INH for 9 months – 5
  - Switched to rifampin for 4 months – 0
  - Stopped any LTBI treatment – 14
  - Unknown – 1

Mississippi 3HP Experience (SETBC 10/20/2014)

- Since deployment in 2011, 1,478 patients have started 3HP
- 1,345 patients have realized completion or have stopped receiving treatment
  - 1,095 patients (81.3%) have successfully completed 3HP
  - 72 (5.3%) starting 3HP completed alternate regimen
- Overall completion rate for persons starting 3HP and completing any regimen – 86.6%
  - 156 (11.6%) stopped therapy due to adverse reaction
  - 72 (5.3%) stopped by choice or other reason
  - 27 (2%) lost to follow-up

Most frequently reported symptoms associated with treatment being stopped or held
- Rash/hives – 6
- Nausea or vomiting – 5
- Fatigue – 2
- Appetite loss – 2
- Sore muscles – 2
- Diarrhea – 1
- Numbness – 1
- Dizzy/faint -1
- Abdominal pain – 1
- Other – 6
Duval County, FL 3HP Experience (1)  
(SETBC 10/20/2014)

- Duval Co. jail screens approximately 45,000 inmates annually
  - House 2500 at any given time
  - Average length of stay is 42 days
- TB therapy provided
  - 3HP DOT Qw x12weeks
  - 9INH SA x 9 months or 4R SA x4 mo.
- Contact Investigation in Jail, 40 inmates identified, 35 offered treatment
  - 29 have completed treatment
  - 2 are still currently being treated
  - 2 have been transferred to state facilities
  - 2 have been ‘lost’ once released from jail

Questions?

Duval Co., FL 3HP Experience (2)  
(SETBC 10/20/2014)

- Lessons learned:
  - DOT helps to build rapport
  - Continuity/adherence improved by DIS worker that DOT’s while incarcerated continues DOT once inmate is released
  - Appeal of once weekly dosing vs. daily
  - Inmate is vested in treatment and wants to complete treatment
  - Inmate is more willing to provide contact information once released.

Additional Resources

- Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection  
  MMWR 2000; 49 (No. RR-6)  
  http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm
- Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection  
  http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w
- Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection — United States, 2010  
  http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5908a3.htm?s_cid=mm5908a3_e
- Latent Tuberculosis Infection: A Guide for Primary Health Care Providers  

Additional Resources

  http://ajrccm.atsjournals.org/content/174/8/935.full.pdf+h
  http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5908a3_e
- Latent Tuberculosis Infection: A Guide for Primary Health Care Providers  

Additional Resources

- Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis  
- CDC TB Website  
  http://www.cdc.gov/tb
- Southeastern National TB Center  
  http://sntc.medicine.ufl.edu
- National TB Controllers Association  
  www.ntca-tb.org/
- CDC’s Morbidity and Mortality Weekly Report  
  http://www.cdc.gov/tb/publications/reportsarticles/mmwr/default.htm
- American Thoracic Society  
  http://www.thoracic.org/statements/
Thank You!

1-800-4TB-INFO

Animal Studies and INH Dosing

- Before clinical trials in humans, the effective dose of isoniazid was established in guinea pigs
- Varying doses of INH was given to guinea pigs after challenge with virulent TB bacilli
- Those challenged with at least 5mg/kg were protected
- This formed the basis of using 5mg/kg for humans

Outbreak of Severe Hepatitis, Capitol Hill 1971

- A highly infectious case of TB was identified on Capitol Hill resulting in a large contact investigation.
- Congressional staffers, politicians, and journalists were involved.
- Over 1000 started on INH
- Within months there were several cases of severe hepatitis including two deaths...both were journalists.

 ADDITIONAL EVIDENCE FOR TREATMENT OF LTBI

---

**Table 4. Efficacy of various durations of isoniazid preventive therapy for persons with fibrotic lesions, by length of treatment**—International Union Against Tuberculosis (IUAT) Trial, 1980–1987

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>12 wk</th>
<th>26 wk</th>
<th>52 wk</th>
<th>104 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>14.3</td>
<td>11.2</td>
<td>5.0</td>
<td>3.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Adverse participants*</td>
<td>7.1</td>
<td>4.1</td>
<td>4.0</td>
<td>4.0</td>
<td>3.3</td>
</tr>
<tr>
<td>Continuous exposure</td>
<td>5.7</td>
<td>2.9</td>
<td>2.9</td>
<td>3.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Pulmonary lesions</td>
<td>1.6</td>
<td>1.2</td>
<td>1.2</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Alveolar lesions</td>
<td>3.3</td>
<td>2.9</td>
<td>2.9</td>
<td>3.2</td>
<td>3.0</td>
</tr>
</tbody>
</table>

* For INH per person-year.

---

**Mortality from INH hepatitis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>Age</th>
<th>Mortality (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPHS surveillance</td>
<td>1971-72</td>
<td>&lt; 35</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 35</td>
<td>45</td>
</tr>
<tr>
<td>IUAT trial</td>
<td>1969-72</td>
<td>35-65</td>
<td>14</td>
</tr>
<tr>
<td>CDC surveillance</td>
<td>1972-73</td>
<td>All</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>1974-83</td>
<td>All</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>1984-88</td>
<td>All</td>
<td>6</td>
</tr>
<tr>
<td>Solpeter survey</td>
<td>1983-92</td>
<td>&lt; 35</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 35</td>
<td>2.4</td>
</tr>
</tbody>
</table>
Early Studies with Rifapentine as part of LTBI Therapy

- Study from 2006 in Brazil with 399 household contacts
- Compared RZ daily with RPN/INH once weekly
- Greater toxicity from RZ than RPN/INH perhaps better efficacy with RZ

### Table 1: Adverse Events during Follow-up

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>INH1</th>
<th>RZ1</th>
<th>INH2</th>
<th>RZ2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Grade ≥ 3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other grade ≥ 2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>任何 grade ≥ 1</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Definition of abbreviations: INH = isoniazid; RIF = rifampicin; RZ = rifazid.

### Schecter, AJRCCM 2006

Adherence to LTBI Therapy

- Percent LTBI treatment completion by duration of treatment.

Failure to complete LTBI treatment, by month in which last dose was taken, as a percent of all persons taking treatment at the beginning of that month (among those taking the 9-month INH regimen, the 6-month isoniazid regimen, or the 4-month rifampin regimen...