



## Preventing Tuberculosis through Treatment of Tuberculosis Infection

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### Learning Objectives

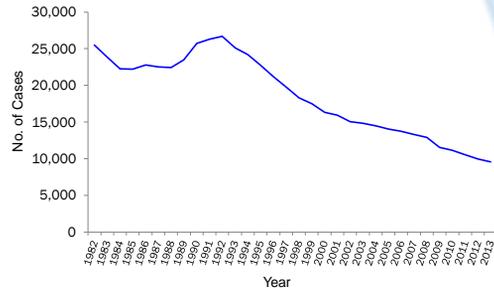
- Recognize the importance of targeted testing and treatment for latent TB infection in the U.S.
- Describe the regimens available for treatment of TB infection including appropriate regimen selection.
- Describe considerations for use of the 3HP regimen.
- Explain 3HP use and outcomes in Virginia.

### 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

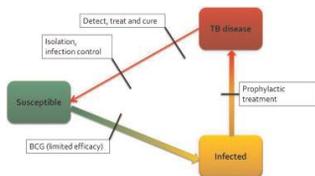
\*World Health Organization (WHO)  
[http://www.who.int/features/factfiles/tb\\_facts/en/index1.html](http://www.who.int/features/factfiles/tb_facts/en/index1.html)

### Reported TB Cases United States, 1982-2013\*



\*Updated as of June 11, 2014.

### Principles for Stopping TB Transmission



**Fig. 10** Principles for stopping tuberculosis (TB) transmission. TB control is based on preventing 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.

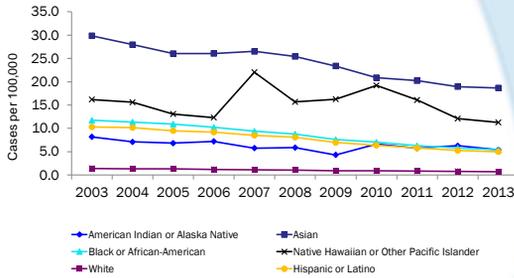
Glaziou et al Global Epidemiology of Tuberculosis. Semin Respir Crit Care Med 2013;34:3-16.

### 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

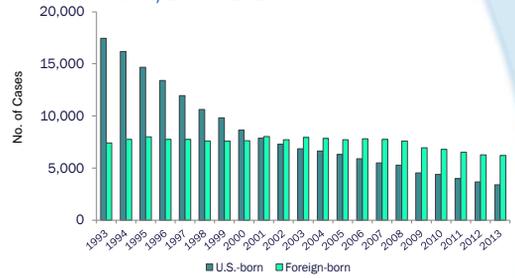
### TB Case Rates by Race/Ethnicity, \* United States, 2003-2013\*\*



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



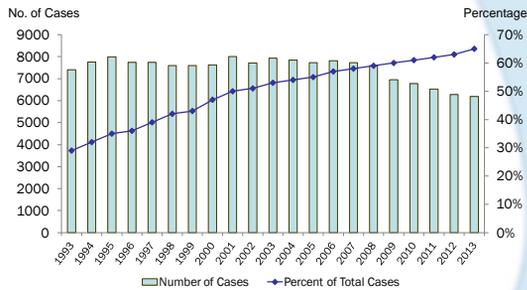
### Number of TB Cases in U.S.-born vs. Foreign-born Persons, United States, 1993-2013\*



\*Updated as of June 11, 2014.



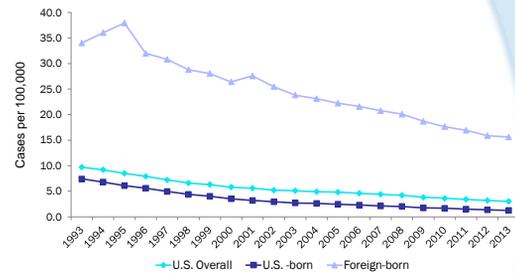
### Trends in TB Cases in Foreign-born Persons, United States, 1993 - 2013\*



\*Updated as of June 11, 2014.



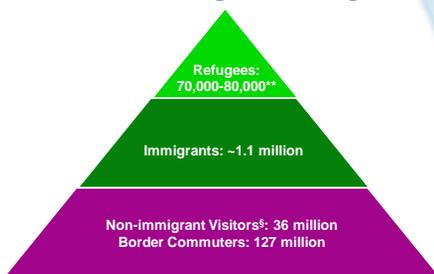
### TB Case Rates in U.S.-born vs. Foreign-born Persons, United States, 1993 - 2013\*



\*Updated as of June 11, 2014.



### Annual Estimate of Migrants Entering the U.S.\*



\*Source: U.S. Department of Homeland Security (DHS)

\*\*2011 Refugee Admissions: 56,422

Note: Immigrants include students, temporary workers and trainees and fiancé(e)s of U.S. citizens.

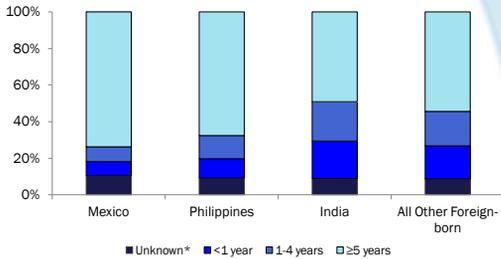


### Reactivation of Latent TB Infection among the Foreign-born in the U.S.

- 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)



### Percent of Foreign-born with TB by Time of Residence in U.S. Prior to Diagnosis, 2013



\*Foreign-born TB patients for whom information on length of residence in the U.S. prior to diagnosis is unknown or missing.



### 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 REGIMENS

### LTBI Treatment – Susceptible Disease

#### Recommended regimens

Drug	Frequency	Duration	Issues	Abbrev
Isoniazid	Daily	9 months (6 months)	Long duration, poor adherence	9H
Isoniazid	Twice weekly	9 months (6 months)	Directly-observed, long duration	9H-DOT
Rifampin	Daily	4 months	Drug interactions	4R
Isoniazid + rifapentine	Once weekly	3 months	DOT	3HP

#### Other regimens

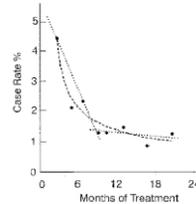
Isoniazid + rifampin	Daily	3 months	Not in U.S. recommendations	3HR
Rifampin + pyrazinamide	Daily or 2x/week	2 months	Potentially fatal: NOT RECOMMENDED	2RZ

Slide adapted from D. Holland



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

Figure 1\*



- 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

\*Tuberculosis case rates (%) in the Bethel Isoniazid Studies population according to the number of months isoniazid was taken in the combined programs. Dots represent observed values; thin line, the calculated curve (y=a-bx); and dotted lines the calculated values based on the first four and the last five observations (y=a-bx). Source: Cornstock, G.W. 1999. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Int. J. Tuberc. Lung Dis. 3:687-850. Reprinted by permission of the International Union Against Tuberculosis and Lung Disease.



### 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.

Ferebee, S. H. 1970. Controlled chemoprophylaxis trials in tuberculosis. A general review. Bibl Tuberc 26:28-106.

International Union Against Tuberculosis Committee on Prophylaxis. 1982. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. Bull World Health Organ 60:555-64.



### 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*

UF UNIVERSITY OF FLORIDA Bucher et al. 1999. Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized controlled trials. AIDS 13:501-7. Southeastern National Tuberculosis Center

### 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%
- Monthly *clinical* assessments (does not mean routine LFT's)

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### INH: Safety, Tolerability, Completion

- Adverse events:
  - 10-20% will develop liver enzyme abnormalities (most are transient and not clinically significant)
  - Hepatotoxicity ~0.1%-0.5%
    - Increased risk with age, liver disease, HCV, alcohol use, prior INH hepatotoxicity, other hepatotoxic medications
  - Peripheral neuropathy uncommon at doses of 5 mg/kg.
    - Persons with risk factors for neuropathy (e.g., diabetes, uremia, alcoholism, malnutrition, HIV infection), pregnant women, and persons with seizure disorder may be given pyridoxine (vit B<sup>6</sup>) 10-50 mg/day with INH
    - Patients who develop signs and symptoms of peripheral neuropathy may also be started on vitamin B<sup>6</sup>.
  - Mortality rate 0.3/1000 (increases w/ age, alcohol use)

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### 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

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## Rifampin Based Regimens

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### LTBI Treatment – Susceptible Disease

#### Recommended regimens

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Isoniazid	Daily	9 months (6 months)	Long duration, poor adherence	9H
Isoniazid	Twice weekly	9 months (6 months)	Directly-observed, long duration	9H-DOT
Rifampin	Daily	4 months	Drug interactions	4R
Isoniazid + rifapentine	Once weekly	3 months	DOT	3HP

#### Other regimens

Isoniazid + rifampin	Daily	3 months	Not in U.S. recommendations	3HR
Rifampin + pyrazinamide	Daily or 2x/week	2 months	Potentially fatal: NOT RECOMMENDED	2RZ

UF UNIVERSITY OF FLORIDA Slide adapted from D. Holland Southeastern National Tuberculosis Center

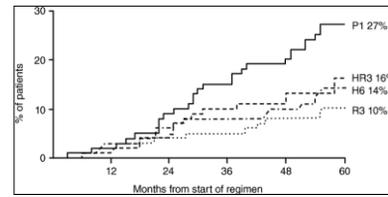
## Rifampin – Efficacy

- 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

Hong Kong Chest Service. Am Rev Respir Dis. 1992 Jan;145(1):36-41.

## 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)

## 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)

## 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
    - Polesky, et al. 1996. Am J Respir Crit Care Med 154:1473-7.
  - 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.
    - Villarino et al. 1997. Am J Respir Crit Care Med 155:1735-8.

## 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 – 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

## Rifamycins – Drug Interactions

- Anticoagulants (oral)
- Chloramphenicol
- Clarithromycin
- Contraceptives (oral)
- Cyclosporine
- Dapsone
- Diazepam
- Digoxin (oral)
- Diltiazem
- Disopyramide
- Doxycycline
- Fluconazole
- Haloperidol
- Glucocorticoids
- Itraconazole
- Losartan potassium
- Ketoconazole
- Methadone
- Midazolam or triazolam
- Nifedipine
- Nortriptyline
- Phenytoin
- Quinidine
- Sulfonyleureas
- Tacrolimus
- Tocainide
- Theophylline
- Verapamil

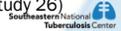
Check everything for potential drug-drug interactions-esp. HIV meds

[http://www.cdc.gov/tb/publications/guidelines/TB\\_HIV\\_Drugs/default.htm](http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm)



## 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.)



## 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  $\leq$ 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



N Engl J Med, Volume 365(23):2155-2166



## 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.)



N Engl J Med, Volume 365(23):2155-2166



## 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



N Engl J Med, Volume 365(23):2155-2166



## 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  $\geq$ 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

UNIVERSITY OF FLORIDA Southeastern National Tuberculosis Center  
 \*MMWR. Recommendations for Use of an Isoniazid–Rifampentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection.  
[http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?\\_cid=mm6048a3\\_w](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?_cid=mm6048a3_w)

### 3HP – CDC Recommendations (2011)

- INH-RPT NOT recommended for:
  - Children under 2y
  - HIV patients on ART
  - Pregnant women or women wanting to become pregnant
  - Contacts to INH or Rif-resistant TB

\*MMWR. Recommendations for Use of an Isoniazid–Rifampentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection.  
[http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?\\_cid=mm6048a3\\_w](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?_cid=mm6048a3_w)

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### 3HP – CDC Recommendations (2011)

- Precautions:
  - RPT rarely can cause neutropenia, increased liver enzymes, hypersensitivity reactions (fever, dizziness, musculoskeletal pain, rash, pruritus)
  - RPT induces increased metabolism of many medications, particularly those metabolized by cytochrome P450 enzymes – avoid with methadone, coumadin and hormonal birth control
  - Women who use any form of hormonal birth control should be advised to add, or switch to a barrier method

\*MMWR. Recommendations for Use of an Isoniazid–Rifampentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection.  
[http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?\\_cid=mm6048a3\\_w](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?_cid=mm6048a3_w)

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### 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

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### 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*)

UNIVERSITY OF FLORIDA Francis J. Curry National Tuberculosis Center, and California Department of Public Health. 2008. Drug-resistant tuberculosis: a survival guide for clinicians. Southeastern National Tuberculosis Center

### LTBI Treatment Regimens for Patients Exposed to MDR-TB

Drug resistance pattern of source case isolate	Recommended regimen†
INH, RIF	FQN monotherapy or PZA and EMB or FQN and PZA or FQN and EMB
INH, RIF, EMB	FQN monotherapy or FQN and PZA
INH, RIF, PZA	FQN monotherapy or FQN and EMB
INH, RIF, EMB, PZA	FQN monotherapy or FQN and ethionamide
INH, RIF, EMB, PZA, ethionamide	FQN monotherapy or FQN and cycloserine
INH, RIF, PZA, EMB, and FQN	Cycloserine and PAS or PAS and ethionamide or ethionamide and cycloserine

† Recommendations are not evidence-based; there have been no clinical trials for the use of these regimens in contacts of patients with MDR TB. Recommendations are based on expert opinion. FQN in vitro activity against M. Tuberculosis strains: Moxifloxacin = Gatifloxacin > Levofloxacin >> Ofloxacin > Ciprofloxacin. Selection of FQN should take this activity into consideration (More active preferred).

UNIVERSITY OF FLORIDA Southeastern National Tuberculosis Center  
 Lobue, P, and D. Menzies. 2010. Treatment of latent tuberculosis infection: An update. Respirology. 15(4):603

## 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

Drug(s)	Duration	Interval	Minimum Doses for completion
Isoniazid	9 months	Daily	270 within 12 months
		Twice weekly	76 within 12 months
	6 months	Daily	180 within 9 months
		Twice weekly	52 within 9 months
Isoniazid & Rifapentine	3 months	Once weekly	12 within 16 weeks
Rifampin	4 months	Daily	120 within 6 months

## 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*

### Clinical Monitoring - 1

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



### Clinical Monitoring - 2

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



### Laboratory Monitoring

- 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



### 3HP – CDC Recommendations, 2011

Early detection and management of adverse effects during treatment of LTBI with INH and RPT (12 Qw doses by DOT)

- 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



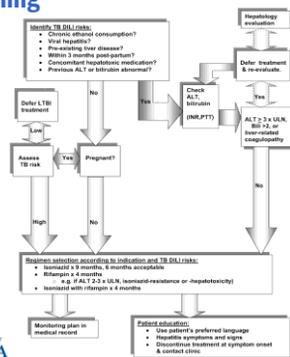
### 3HP – CDC Recommendations, 2011

Early detection and management of adverse effects during treatment of LTBI with INH and RPT (12 Qw doses by DOT)

- 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



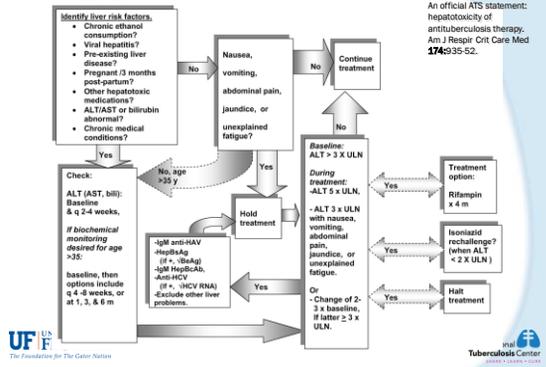
### LTBI Pretreatment Clinical Evaluation and Counseling



Saukkonen et al. 2006. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 174:995-52.



### Monitoring for Hepatotoxicity During LTBI Treatment



### LTBI Treatment Summary

- 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
    - 5 (2%) stopped other

### 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

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

- 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

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

- Since deployment in 2011, 1478 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

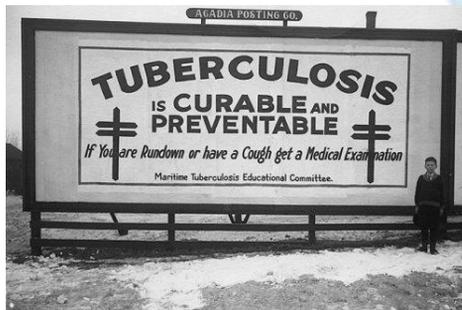
## Duval County, FL 3HP Experience (1) (SETBC 10/20/2014)

- 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

## 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.

## Questions?



## 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-Rifampentine 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)
- Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection --- United States, 2010  
[http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1\\_e](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1_e)

## Additional Resources

- Saukkonen, et al. 2006. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 174:935-52.  
<http://ajrcm.atsjournals.org/content/174/8/935.full.pdf+html>
- Severe Isoniazid-Associated Liver Injuries Among Persons Being Treated for Latent Tuberculosis Infection --- United States, 2004–2008.  
[http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5908a3.htm?s\\_cid=mm5908a3\\_e](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5908a3.htm?s_cid=mm5908a3_e)
- Latent Tuberculosis Infection: A Guide for Primary Health Care Providers  
<http://www.cdc.gov/tb/publications/LTBI/default.htm>

## Additional Resources

- Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis  
[http://www.cdc.gov/tb/publications/guidelines/TB\\_HIV\\_Drugs/default.htm](http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm)
- 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/](http://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**



**ADDITIONAL EVIDENCE FOR TREATMENT OF LTBI**



**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



**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, 1969–1977**

Group	5-yr Tuberculosis incidence* (% reduction)			
	Placebo	12 wk	24 wk	52 wk
All participants (n = 27,830) <sup>†</sup>	14.3	11.3 (21)	5.0 (65)	3.6 (75)
Adherent participants <sup>‡</sup> (n = 21,635) <sup>‡</sup>	15	9.4 (31)	4.7 (69)	1.1 (93)
Fibrotic lesions <2 cm <sup>2</sup> (n = 16,663) <sup>‡</sup>	11.6	9.2 (20)	4.0 (66)	4.2 (64) <sup>††</sup>
Fibrotic lesions >2 cm <sup>2</sup> (n = 8,426) <sup>‡</sup>	21.3	16.2 (24)	7.0 (67)	2.4 (89)

\* Per 1000 person-years.  
<sup>†</sup> Comparing placebo to 24 and 52 wk, p < 0.05; differences between placebo and 12 wk and between 24 and 52 wk not significant.  
<sup>‡</sup> Collected pill calendars for "almost all" of the months assigned for their regimen and had taken at least 80% of the pills from the calendar by the time of the next monthly visit.  
<sup>††</sup> For all isoniazid regimens comparisons (p < 0.05).  
<sup>‡‡</sup> Persons who developed tuberculosis on 52-wk regimens and had small fibrotic lesions were less likely to have collected pill calendars (47%) than all other groups (≥80%) (p < 0.001).  
 Source: International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid therapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull. WHO* 1982;60:555-64.



**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.

Mortality from INH hepatitis				
Study	Years	Age	Mortality (per 100,000)	
USPHS surveillance	1971-72	< 35	0	
		> 35	98	
IUAT trial	1969-72	35-65	14	
CDC surveillance	1972-3	All	54	
		1974-83	All	14
		1984-8	All	6
Salpeter survey	1983-92	< 35	0.6	
		> 35	2.4	



### 4 months Rifampin vs 9 months INH A retrospective review (non-randomized) Patient characteristics *(Page et al, Archives Int Med, 2006; 166: 1863-1870)*

	9 INH	4 RIF	(Pvalue)
Patients starting therapy	770	1379	
Age	30.1	34.2	(.001)
Sex (% females)	59%	54%	(.03)
HIV positive	1.8%	0.7%	(.01)
Abnormal baseline LFT's	5.7%	4.3%	(NS)
<b>Percent completing</b>	<b>53%</b>	<b>72%</b>	<b>(.001)</b>



## Early Studies with Rifapentine as part of LTBI Therapy

TABLE 3. ADVERSE EVENTS DURING FOLLOW-UP

Variable	RPT/INH	RZ	All
Death	1	3	4
Grade 3 hepatotoxicity*	2	14	16
Grade 4 hepatotoxicity†	0	11	11
Labor grade 3 or 4 toxicity*	2	20	22
Pregnancy	1	4	5

Definition of abbreviations: INH = isoniazid; RPT = rifapentine; RZ = rifampin and pyrazinamide.  
\* Grade 3 hepatotoxicity defined as aspartate aminotransferase or alanine aminotransferase 5 to 10 times upper limit of normal; grade 4 hepatotoxicity defined as aspartate aminotransferase or alanine aminotransferase > 10 times upper limit of normal. If initial abnormality was grade 3 but subsequent testing revealed grade 4, patients were counted in both categories.

- 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

Schecter, AJRCCM 2006



Table 2. Number of Subjects with Tuberculosis and Event Rates.\*

Population and Study Group	No. of Subjects	Subjects with Tuberculosis		Difference in Cumulative Rate†	Upper Limit of 95% CI for Difference in Cumulative Rate	
		no.	per patient-yr			
<b>Modified intention-to-treat analysis</b>						
Isoniazid only	3745	15	0.16	0.43	-0.24	0.01
Combination therapy	3986	7	0.07	0.19		
<b>Per-protocol analysis</b>						
Isoniazid only	2585	8	0.11	0.32	-0.19	0.06
Combination therapy	3273	4	0.05	0.13		

\* Combination therapy consisted of 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg). Isoniazid-only therapy consisted of 9 months of self-administered daily isoniazid (300 mg). Data are shown for a period up to 33 months after study enrollment.  
† The difference is the rate in the combination-therapy group minus the rate in the isoniazid-only group.

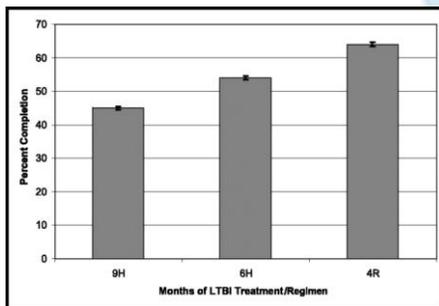
Sterling TR et al. N Engl J Med 2011;365:2155-2166



## Adherence to LTBI Therapy



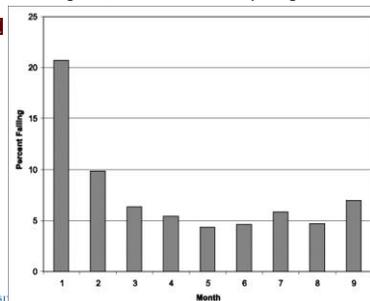
Percent LTBI treatment completion by duration of treatment.



Horsburgh CR et al. Chest 2010;137:401-409



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 regime...)



Horsburgh CR et al. Chest 2010;137:401-409

