



# **Treatment of Tuberculosis**

Lisa Y. Armitige, MD, PhD

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**Lisa Y. Armitige, MD, PhD** has the following disclosures to make:

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- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity





# Treatment of Tuberculosis

Lisa Y. Armitige, MD, PhD  
Co-Medical Director  
Heartland National TB Center

Professor of Medicine and Pediatrics  
University of Texas HSC at Tyler

*Clinical Infectious Diseases*

**IDSA GUIDELINE**



# Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children

**David M. Lewinsohn,<sup>1,a</sup> Michael K. Leonard,<sup>2,a</sup> Philip A. LoBue,<sup>3,a</sup> David L. Cohn,<sup>4</sup> Charles L. Daley,<sup>5</sup> Ed Desmond,<sup>6</sup> Joseph Keane,<sup>7</sup> Deborah A. Lewinsohn,<sup>1</sup> Ann M. Loeffler,<sup>8</sup> Gerald H. Mazurek,<sup>3</sup> Richard J. O'Brien,<sup>9</sup> Madhukar Pai,<sup>10</sup> Luca Richeldi,<sup>11</sup> Max Salfinger,<sup>12</sup> Thomas M. Shinnick,<sup>3</sup> Timothy R. Sterling,<sup>13</sup> David M. Warshauer,<sup>14</sup> and Gail L. Woods<sup>15</sup>**

<sup>1</sup>Oregon Health & Science University, Portland, Oregon, <sup>2</sup>Emory University School of Medicine and <sup>3</sup>Centers for Disease Control and Prevention, Atlanta, Georgia, <sup>4</sup>Denver Public Health Department, Denver, Colorado, <sup>5</sup>National Jewish Health and the University of Colorado Denver, and <sup>6</sup>California Department of Public Health, Richmond; <sup>7</sup>St James's Hospital, Dublin, Ireland; <sup>8</sup>Francis J. Curry International TB Center, San Francisco, California; <sup>9</sup>Foundation for Innovative New Diagnostics, Geneva, Switzerland; <sup>10</sup>McGill University and McGill International TB Centre, Montreal, Canada;

<sup>11</sup>University of Southampton, United Kingdom; <sup>12</sup>National Jewish Health, Denver, Colorado, <sup>13</sup>Vanderbilt University School of Medicine, Vanderbilt Institute for Global Health, Nashville, Tennessee,

<sup>14</sup>Wisconsin State Laboratory of Hygiene, Madison, and <sup>15</sup>University of Arkansas for Medical Sciences, Little Rock



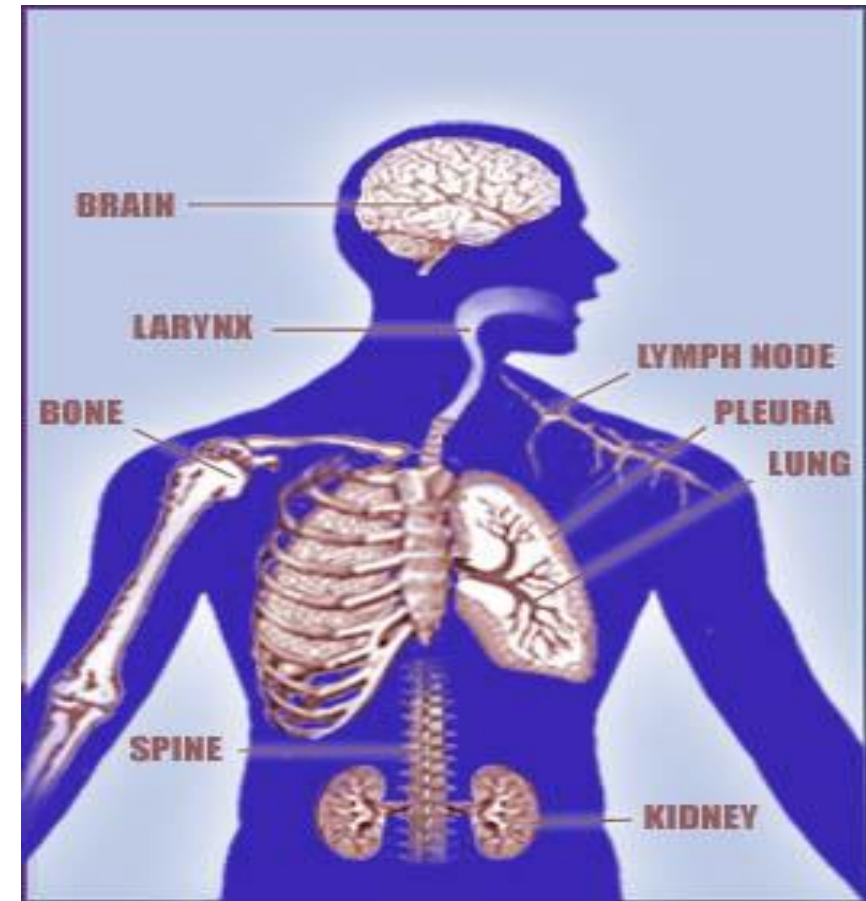
# Diagnosing Tuberculosis

# Sites of TB Disease

- Lungs

## Extrapulmonary:

- Larynx
- Pleural effusion
- Kidneys
- Lymphatics
- Bones & joints
- Miliary (disseminated)



# Signs & Symptoms Pulmonary TB

## Pulmonary Symptoms:

- Productive prolonged cough of over 3 weeks duration
- Chest pain
- Hemoptysis

## Systemic Symptoms:

- Fever
- Chills
- Night sweats
- Appetite loss
- Weight loss
- Easy fatigability



# Evaluation for TB

- Medical history
- Physical examination
- Testing for TB infection
- Chest radiograph
- Bacteriologic or histologic exam





# No CXR study shows findings specific for TB

Cavitary process are more likely to be TB

Common mimics of TB =

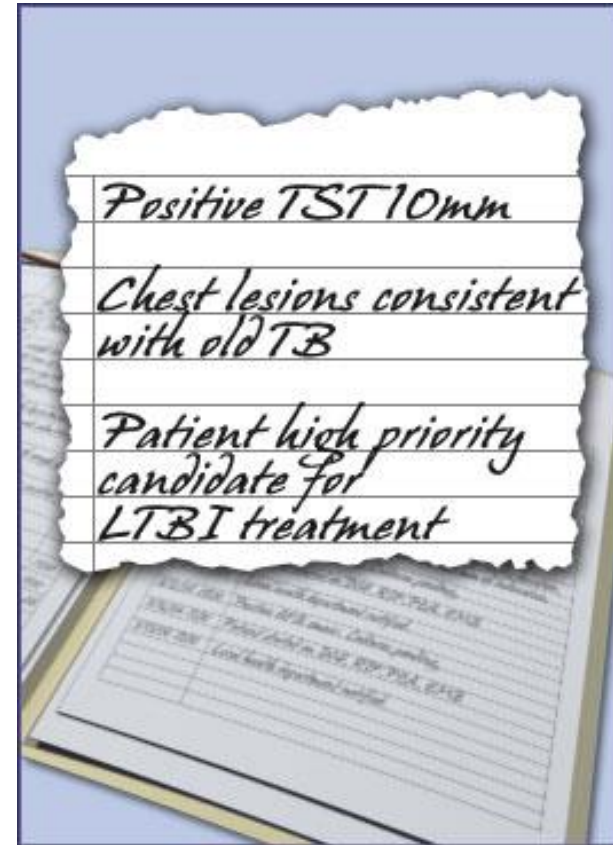
- Non-tuberculous mycobacteria (NTM)
- fungal infection
- bacterial abscesses
- necrotic neoplasm (especially lung neoplasm)



# CXR – old healed TB

- Nodules & fibrotic lesions may contain slowly multiplying bacilli = potential for progression
- CXR consistent with old TB and + TST/IGRA = high priority for LTBI treatment

*Calcified nodular lesions (calcified granuloma) pose a very low risk for future progression*



# CXR - special situations

- Pregnant persons who are highly suspected of having TB and are being evaluated for active disease should undergo a CXR without delay, even during the first trimester
- Patients suspected of extrapulmonary TB should have a CXR to R/O pulmonary TB



# Yes! You can X-ray a pregnant patient!



The American College of  
Obstetricians and Gynecologists  
WOMEN'S HEALTH CARE PHYSICIANS

## ACOG COMMITTEE OPINION

Number 723 • October 2017

(Replaces Committee Opinion Number 656, February 2016)

### Committee on Obstetric Practice

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**Table 2.** Effects of Gestational Age and Radiation Dose on Radiation-Induced Teratogenesis ↵

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16–25 weeks	Severe intellectual disability (low risk)	250–280 mGy*

\*Data based on results of animal studies, epidemiologic studies of survivors of the atomic bombings in Japan, and studies of groups exposed to radiation for medical reasons (eg, radiation therapy for carcinoma of the uterus).

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Radiography of any extremity	<0.001
Mammography (two views)	0.001–0.01
Chest radiography (two views)	0.0005–0.01
<i>Low- to moderate-dose examinations (0.1–10 mGy)</i>	
Radiography	
Abdominal radiography	0.1–3.0
Lumbar spine radiography	1.0–10
Intravenous pyelography	5–10
Double-contrast barium enema	1.0–20
CT	
Chest CT or CT pulmonary angiography	0.01–0.66
Limited CT pelvimetry (single axial section through the femoral heads)	<1
Nuclear medicine	
Low-dose perfusion scintigraphy	0.1–0.5
Technetium-99m bone scintigraphy	4–5
Pulmonary digital subtraction angiography	0.5
<i>Higher-dose examinations (10–50 mGy)</i>	
Abdominal CT	1.3–35
Pelvic CT	10–50
<sup>18</sup> F PET/CT whole-body scintigraphy	10–50

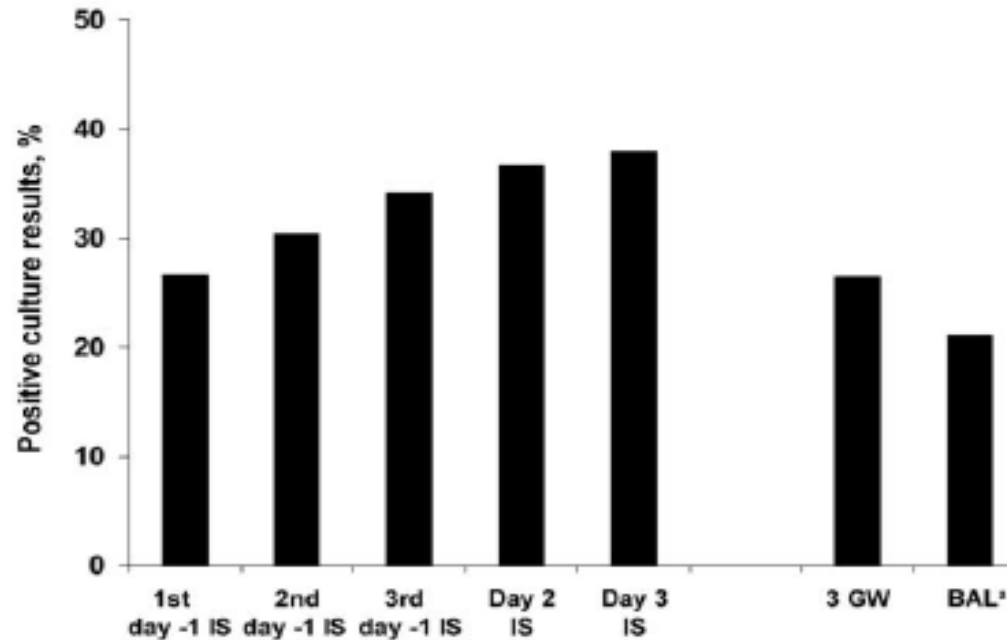
# Bacteriologic and Histologic Examinations

When lung or larynx is site of disease:

- 3 sputum specimens for AFB smear and culture
- Collected 8-24 hours apart with at least 1 early morning specimen



# Culture Yield



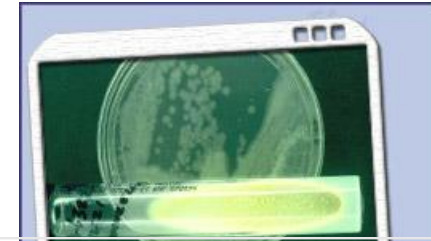
**Figure 2.** Proportion of subjects with cultures positive for *Mycobacterium tuberculosis*, by diagnostic technique, for 79 subjects with results for all 5 sputum samples obtained by induction with nebulized hypertonic saline (IS) and all 3 gastric washing (GW) specimens. Cumulative proportions are shown for the 5 IS samples.  $P = .25$ , by paired binomial probability test comparing diagnostic yield of all 5 IS samples versus 3 day 1 IS samples. \*Bronchoalveolar lavage (BAL) culture results were available for 19 subjects.

# Bacteriologic and Histologic Examinations

## Extrapulmonary Specimens

- Urine
- Cerebrospinal fluid \*
- Pleural fluid \*
- Pus
- Biopsy specimens

\*recovery poor



**Do NOT collect  
specimens in Formalin  
or bacteriostatic saline!**



# Laboratory Examination

- AFB smear
- AFB culture
- Nucleic acid amplification test (NAAT)
  - GeneXpert
  - Molecular Detection of Drug Resistance (MDDR)





# Treatment of Tuberculosis



# Treatment of Culture-Positive Drug Susceptible Pulmonary TB

- General conclusions from the literature

- 6 mo (26 wk) is the **MINIMUM** duration of Rx
- 6 mo regimens require rifampin throughout and PZA for the first 2 months
- 6 mo regimens are effective without INH
- Intermittent regimens (2-3x/wk):
  - **GIVEN by DOT ONLY**
  - Drug susceptible isolate
  - Regimen contains INH and rifampin



# Antituberculosis Drugs

(ATS/CDC/IDSA)

- First-Line drugs (RIPE)

- Isoniazid
- Rifampin
- Rifapentine
- Rifabutin\*
- Ethambutol
- Pyrazinamide

\*Not FDA approved for TB

- Second-Line Drugs

- Cycloserine
- Ethionamide
- Levofloxacin\*
- Moxifloxacin\*
- PAS
- Streptomycin
- Amikacin/Kanamycin
- ~~Capreomycin~~
- Bedaquiline
- Delamanid
- Pretomanid



# Treatment of Culture-Positive Drug Susceptible Pulmonary TB


- General conclusions from the literature:

- Without PZA - minimum duration is 9 months
- Without rifampin – see Dr. Seaworth's talk but, basically, treat like MDR
- Streptomycin and ethambutol (EMB) are approximately equivalent in effect (BUT concern about increasing Streptomycin resistance among foreign born leads to preference of EMB for initial therapy)



# ATS recommendations for treatment of tuberculosis

**Table 2. Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms**

Regimen	Intensive Phase		Continuation Phase		Range of Total Doses	Comments <sup>c,d</sup>	Regimen Effectiveness
	Drug <sup>a</sup>	Interval and Dose <sup>b</sup> (Minimum Duration)	Drugs	Interval and Dose <sup>b,c</sup> (Minimum Duration)			
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)	182–130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	 <p>Greater</p> <p>Lesser</p>
2	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110–94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	
4	INH RIF PZA EMB	7 d/wk for 14 doses then twice weekly for 12 doses <sup>e</sup>	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.	

# Treatment for TB disease in Pregnancy

- A person diagnosed with or strongly suspected of having TB disease should be started on treatment without delay
- All first line drugs are generally considered safe in pregnancy
- Treatment regimen
  - PZA or no PZA?
  - Rifampin, INH, EMB for 9 months if PZA is excluded



# Yes! You can X-ray a pregnant patient!



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Abdominal CT	1.3–35
Pelvic CT	10–50
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# PZA in Pregnancy

- The WHO and IUATLD endorse use of PZA in the treatment of TB in pregnancy
- The CDC 2003 treatment guidelines did not endorse use of PZA in pregnancy due to lack of studies to show safety
- Current (2016) CDC/IDSA/ATS treatment guidelines state
  - Clinicians should evaluate risk/benefit of prescribing PZA, discuss with patient, informing patient that benefits may outweigh risk
  - Patients with HIV, extrapulmonary or severe disease should receive PZA in their treatment regimen





# Suspected Active TB at Delivery

- Protect the delivery team
- Try to find a negative pressure room for delivery or perhaps a room further away from the general floor, like a surgical suite
- Delivery team should wear N95 masks
- Make arrangements to send placenta for pathologic evaluation and AFB culture



# After-Delivery Concerns

- Should you separate the patient from their infant?
  - Only if the patient is suspected of having MDR TB
  - If patient is infectious, put the baby on INH or rifampin and have the patient wear a surgical mask while holding the baby until they are no longer infectious
- Can the patient breastfeed?
  - Yes
  - First line TB drugs all into the breastmilk in low but safe levels



# Drug Penetration of CSF

Table 2. Anti-tuberculosis drugs used in TBM treatment [31–34,164].

Drug	Forms	Oral bio-availability (%)	Food effect	Plasma protein binding (%)	CNS penetration (%)
<b>First-line</b>					
Rifampicin	PO; IV	70	–30%	89	10–20
Isoniazid	PO; IV; IM	~100	–50% $C_{max}$	0–10	80–90
Pyrazinamide	PO	>90	None	~10	90–100
Ethambutol	PO	75–80	None	20–30	20–30
Rifabutin	PO	50	Decreased rate of absorption	85	50
Rifapentine	PO	70	None	98	-

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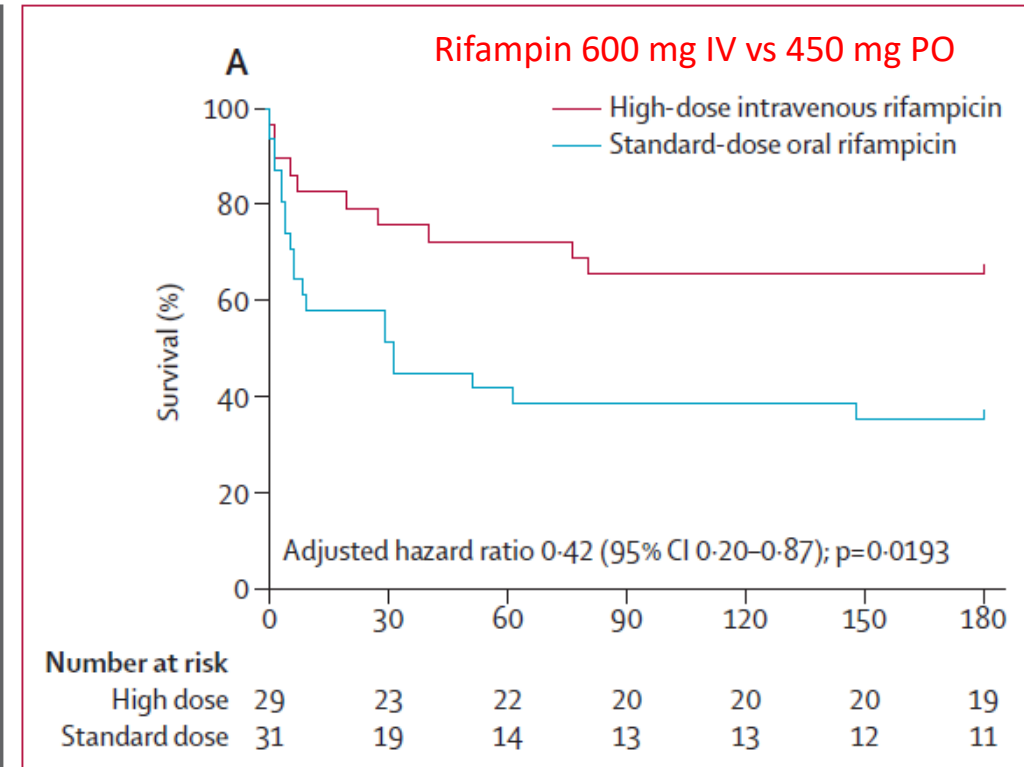
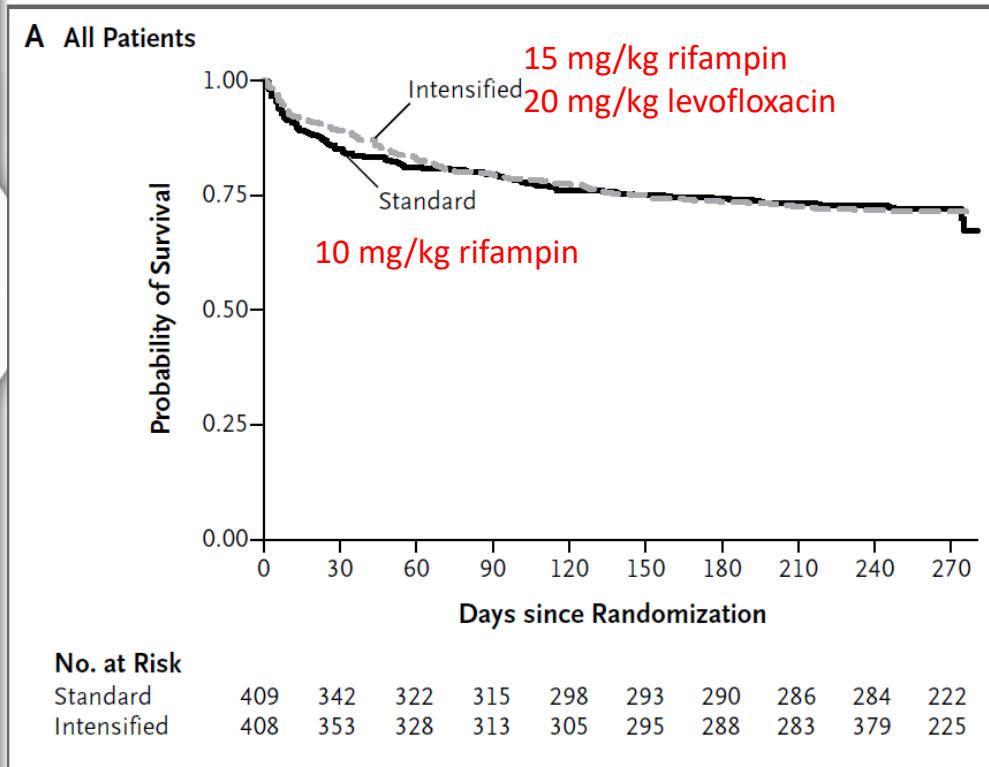
Table 2. (Continued).

Drug	Forms	Oral bio-availability (%)	Food effect	Plasma protein binding (%)	CNS penetrator (%)
Levofloxacin	PO; IV	~100	None	24–38	70–80
Moxifloxacin	PO; IV	90	None	50	70–80
Ethionamide	PO	~100	None	~30	80–90
Cycloserine	PO	65–90	Slight decrease	~0	80–90

Table 2. (Continued).

Drug	Forms	Oral bio-availability (%)	Food effect	Plasma protein binding (%)	CNS penetration (%)
Linezolid	PO; IV	~100	–23% with high-fat meals	31	70
Bedaquiline	PO	Unknown	Increase	>99	Likely poor (limited data)
Delamanid	PO	25–47	Increase	>99	No human data
Pretomanid	PO	Unknown	Increase	93	No human data

# Intensified Regimen for TBM (Adults)



N Engl J Med 2016;374:124-34.

Lancet Infect Dis 2013; 13: 27-35

## ORIGINAL ARTICLE

# Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults

Guy E. Thwaites, M.R.C.P., Nguyen Duc Bang, M.D., Nguyen Huy Dung, M.D., Hoang Thi Quy, M.D., Do Thi Tuong Oanh, M.D., Nguyen Thi Cam Thoa, M.D., Nguyen Quang Hien, M.D., Nguyen Tri Thuc, M.D., Nguyen Ngoc Hai, M.D., Nguyen Thi Ngoc Lan, Ph.D., Nguyen Ngoc Lan, M.D., Nguyen Hong Duc, M.D., Vu Ngoc Tuan, M.D., Cao Huu Hiep, M.D., Tran Thi Hong Chau, M.D., Pham Phuong Mai, M.D., Nguyen Thi Dung, M.D., Kasia Stepniewska, Ph.D., Nicholas J. White, F.R.C.P., Tran Tinh Hien, M.D., and Jeremy J. Farrar, F.R.C.P.

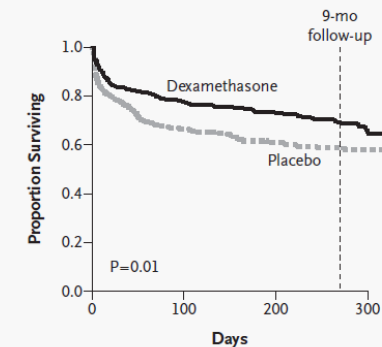
N ENGL J MED 351;17 WWW.NEJM.ORG OCTOBER 21, 2004

**Table 3. Outcomes of 545 Patients Nine Months after Randomization.**

Group	No. of Patients	Outcome			
		Good	Inter- mediate	Severe Disability	Death
		<i>number (percent)</i>			
Dexamethasone*	274	104 (38.0)	49 (17.9)	34 (12.4)	87 (31.8)
Placebo	271	95 (35.1)	42 (15.5)	22 (8.1)	112 (41.3)

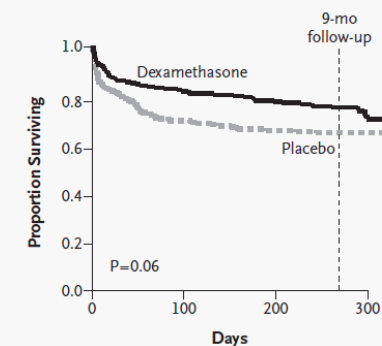
\* Because of rounding, the percentages for the dexamethasone group do not total 100.

## A All Patients



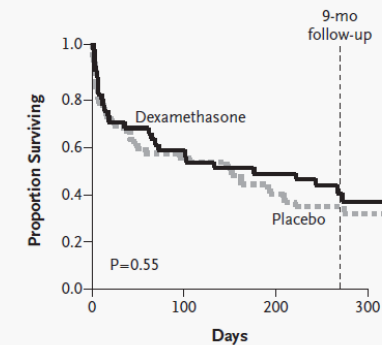
No. at Risk					
Dexamethasone	271	206	192	165	44
Placebo	274	179	163	146	37

## B Patients Not Infected with HIV



No. at Risk					
Dexamethasone	227	182	172	132	44
Placebo	209	147	139	131	37

## C Patients Infected with HIV



No. at Risk					
Dexamethasone	44	24	20	16	4
Placebo	54	29	21	17	5

# TB Drugs Cleared by the Kidneys

- Ethambutol (EMB)
- Pyrazinamide (PZA)
- Levofloxacin
- Cycloserine
- Anything that is injected
  - Streptomycin
  - Amikacin
  - Capreomycin
  - Kanamycin





# Treatment Regimen: Active TB with renal insufficiency

- Renal insufficiency counted at CrCl <30
- Initial Phase (first two months):
  - INH 300mg po daily
  - Rifampin 600mg po daily
  - Ethambutol 15-25mg/kg po *thrice weekly*
  - PZA 25-35mg/kg po *thrice weekly*
  - Vitamin B6 50mg daily
- Continuation
  - INH and Rifampin x 4 – 7 months




# Hepatotoxicity – What to do about it

- First, can you stop medications safely?
  - Is the patient really sick (ICU, septic sick)?
  - Does he have a form of TB you really don't want going untreated (disseminated disease, meningitis, associated with HIV or poorly controlled diabetes)?
- If the patient is ill, pick something liver-sparing and continue treatment.
- If the patient is stable, stop the medications until the liver cools off and do a drug challenge.



# Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active TB

(Yee, AJRCCM 2003; 167: 1472)

- 
- PZA: 1.48/100 person months of exposure
  - INH: 0.49/100 person months
  - Rif : 0.43/100 person months
  - EMB: 0.07/100 person months

*“The drug most likely responsible for the occurrence of hepatitis or rash during therapy for active TB is PZA”*

So, what is  
'liver-friendly/sparing'?




# What if they are really, really sick.....?

- INH
- Rifampin
- Rifabutin
- Ethambutol (EMB)
- Pyrazinamide (PZA)
- Moxifloxacin ←
- Levofloxacin
- Amikacin ←
- Linezolid ←


- Liver
- Liver
- Liver/kidney
- Kidney
- Kidney (liver metabolites)
- Liver, but.....
- Kidney
- Kidney
- Neither liver or kidney



# Liver sparing but not dying

- 
- |                      |   |                              |
|----------------------|---|------------------------------|
| • INH                |   | • Liver                      |
| • Rifampin           |   | • Liver                      |
| • Rifabutin          |   | • Liver/kidney               |
| • Ethambutol (EMB)   | ← | • Kidney                     |
| • Pyrazinamide (PZA) |   | • Kidney (liver metabolites) |
| • Moxifloxacin       | ← | • Liver, but.....            |
| • Levofloxacin       |   | • Kidney                     |
| • Amikacin           |   | • Kidney                     |
| • Linezolid          | ← | • Neither liver or kidney    |

# Liver-friendly

- 
- |                      |   |                              |
|----------------------|---|------------------------------|
| • INH                |   | • Liver                      |
| • Rifampin           | ← | • Liver                      |
| • Rifabutin          |   | • Liver/kidney               |
| • Ethambutol (EMB)   | ← | • Kidney                     |
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| • Moxifloxacin       | ← | • Liver, but.....            |
| • Levofloxacin       |   | • Kidney                     |
| • Amikacin           |   | • Kidney                     |
| • Linezolid          |   | • Neither liver or kidney    |

# What is a proper 'drug challenge'?

- Stop the medications. Cool the patient off.
- When LFTs have returned to  $< 2$  times the ULN, you are ready to challenge
- Start with rifampin and ethambutol, then INH (or moxifloxacin if there is a shortage....), then strongly consider whether you need PZA
  - Wait 3-7 days between additions
  - Check LFTs before starting the next drug (and wait for the results, please)
  - If LFTs rise stop the last drug added and go to the next





# Smear Negative Pulmonary TB

- Sputum has been collected and has resulted smear and culture negative
- Treatment recommendations are for RIPE x 2 months, then RI for 2 more months
- Consider leaving all 4 drugs or at least INH/rifampin/EMB



# *M. bovis*

- Unpasteurized milk products
  - Travel, gifts from foreign places
- Bladder instillation with BCG
  - Fever, **sterile pyuria**!
- **Resistant to PZA**, susceptible to INH, rifampin and EMB
  - Note: PZA monoresistance likely *M. bovis* or *M. kansasii*



# Management of Treatment Interruptions

- Initial phase of therapy
  - <14 days –complete standard # of doses
  - >14 days – restart from the beginning
- Continuation phase
  - >80% doses by DOT – if initial smear negative, may stop
  - Repeat culture
    - >3 month interruption restart from beginning
    - <3 month interruption, culture positive, restart
    - <3 month interruption, culture negative, give an additional 4 months



# Relapsed Tuberculosis

- Most relapses occur within the first 6 – 12 months after stopping therapy but some occur 5 or more years later
- Nearly all drug susceptible patients who were treated with a rifamycin and received DOT will relapse with drug susceptible organisms
  - Treat with standard RIPE regimen
- Patients with a history of poor adherence, self administration or self administration should have additional sputum collected and careful selection of a treatment regimen



# Medical Factors Associated With Relapse of Tuberculosis

- Cavitory TB
- Extensive disease on CXR; bilateral infiltrates
- Positive 2 month culture
- Associated medical conditions
  - Diabetes
  - HIV
  - Malabsorption of TB drugs
- Tuberculous lymphadenitis
- Underweight at diagnosis and failure to gain
- Drug resistant disease
- Prior treatment for tuberculosis



# TB Elderly

- Hepatotoxicity and as well as other medication toxicities are more common
- May want to weight the risk/benefit of using PZA



# Criteria to Be Considered Noninfectious

Patients no longer considered infectious if:

- 3 consecutive negative sputum smears
  - collected at least 8 hours apart
  - one early morning specimen
- Their symptoms have improved, AND
- Adhering to **adequate** treatment regimen  $\geq 2$  weeks (one week if smear negative to start)
  - DOT – YES!
  - Do you know drug susceptibilities?



# Treatment shortening regimen – Drug Sensitive TB

*The NEW ENGLAND JOURNAL of MEDICINE*

ORIGINAL ARTICLE

## Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley,  
M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens,  
N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham,  
S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje,  
E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson,  
for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

2234 participants (194 PLHIV, 1703 with cavity on CXR)

Randomized 1:1:1 to 3 arms

Noninferiority study





# Study 31/A5349

Control  
(2HRZE/4HR)

Isoniazid (H)			
Rifampin (R)			
Ethambutol (E)			
Pyrazinamide (Z)			

RPT  
(2H<sup>P</sup>ZE/2H<sup>P</sup>)

Isoniazid (H)		
Rifapentine (P)		
Ethambutol (E)		
Pyrazinamide (Z)		

Control  
(2H<sup>P</sup>Z<sup>M</sup>/4H<sup>P</sup><sup>M</sup>)

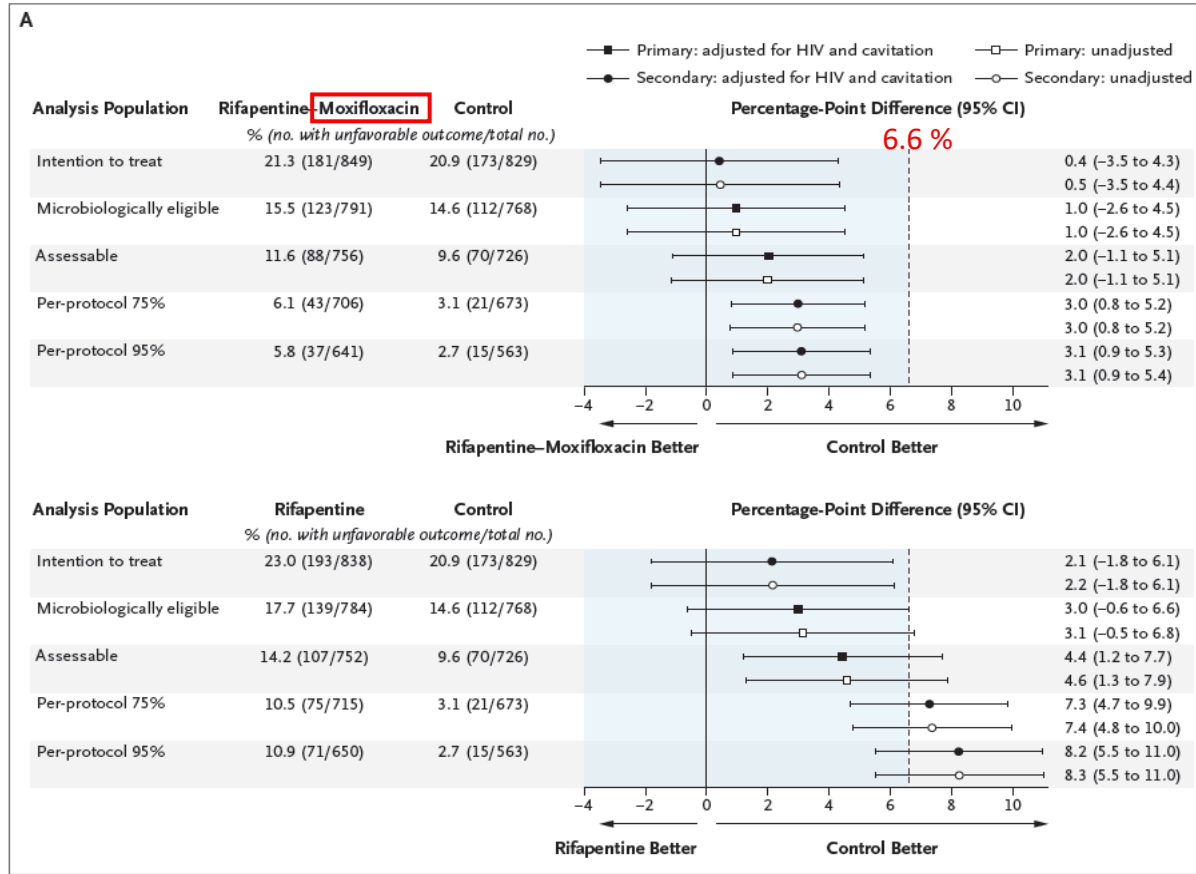
Isoniazid (H)		
Rifapentine (P)		
Moxifloxacin (M)		
Pyrazinamide (Z)		

## Notes:

- HRZE dosed at standard doses
- Dosed daily, 7 days/week, observed 5 days/week
- Rifapentine 1200 mg (8 tablets)
- Moxifloxacin 400 mg



# Study 31 - Results



# Challenges associated with shorter treatment regimens

- Pill burden
- Tolerability (versus safety, efficacy)
- Familiarity with the regimen
- Drug shortages (first rifapentine, now INH)



# Questions?

[Lisa.Armitige@dshs.texas.gov](mailto:Lisa.Armitige@dshs.texas.gov)

Or

**1-800-TEX-LUNG**

