Treatment of Tuberculosis

Lisa Y. Armitige, MD, PhD

June 10, 2025

TB Intensive • June 10 – 12, 2025 • Dallas, Texas

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Has the following disclosures to make:

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

Treatment of Tuberculosis

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Financial Disclosures

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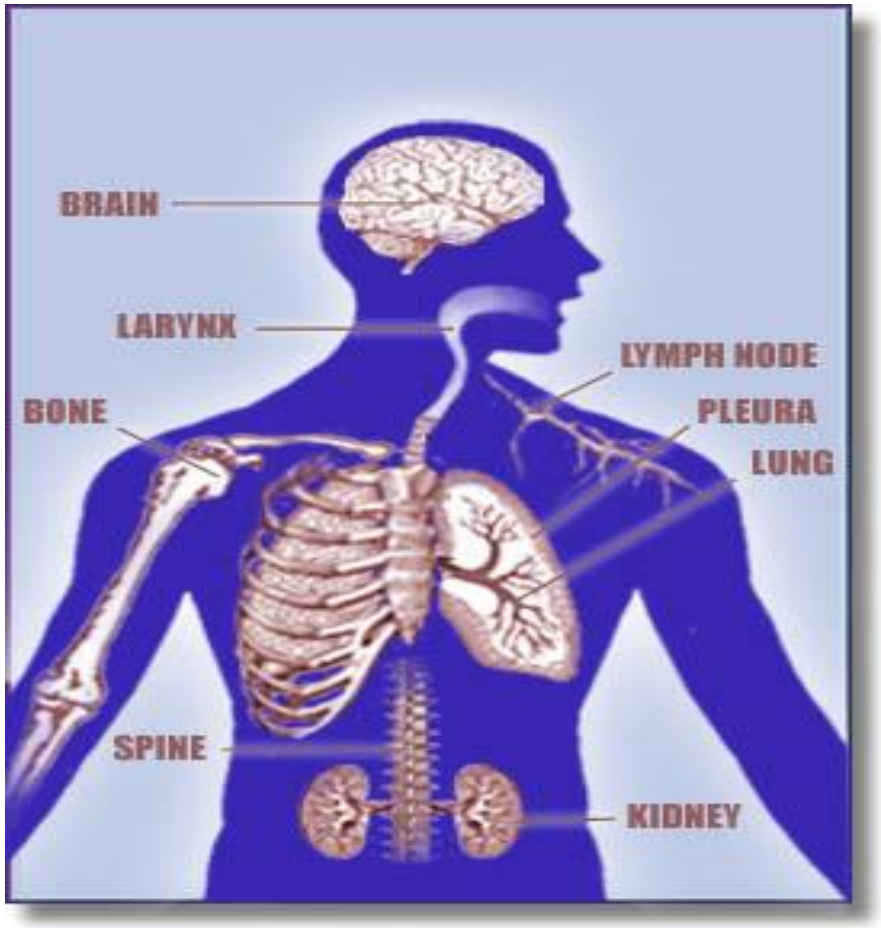
Diagnosing Tuberculosis

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

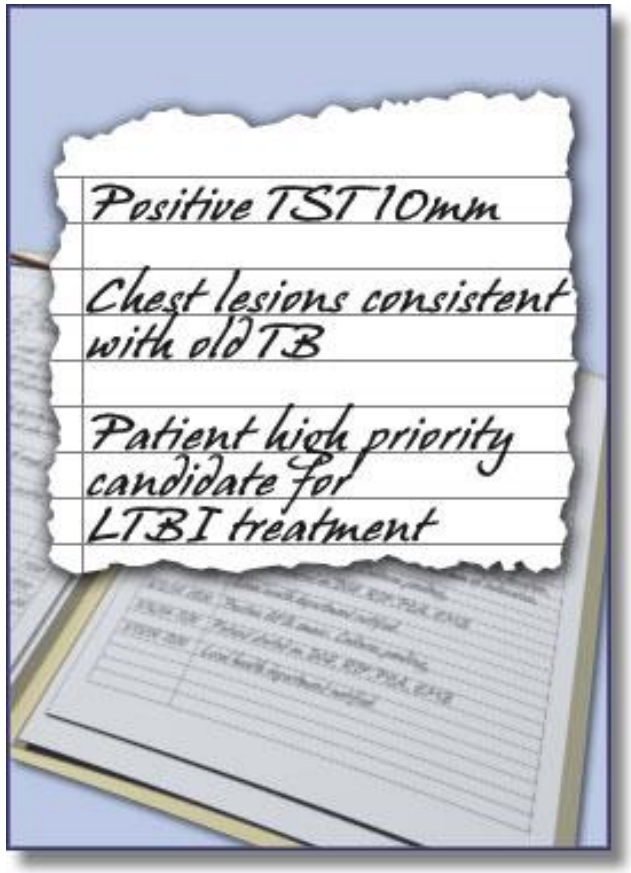
Common mimics of TB =

- 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

This document is endorsed by the American College of Radiology and the American Institute of Ultrasound in Medicine. This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Member contributors included Joshua Copel, MD; Yasser El-Sayed, MD; R. Phillips Heine, MD; and Kurt R. Wharton, MD. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

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

Gestational Period	Effects	Estimated Threshold Dose*
Before implantation (0–2 weeks after fertilization)	Death of embryo or no consequence (all or none)	50–100 mGy
Organogenesis (2–8 weeks after fertilization)	Congenital anomalies (skeleton, eyes, genitals)	200 mGy
	Growth restriction	200–250 mGy
Fetal period	**Effects**	**Estimated Threshold Dose***
8–15 weeks	Severe intellectual disability (high risk)†	60–310 mGy
	Intellectual deficit	25 IQ-point loss per 1,000 mGy
	Microcephaly	200 mGy
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).

†Because this is a period of rapid neuronal development and migration.

Modified from Patel SJ, Reede DL, Katz DS, Subramaniam R, Amorosa JK. Imaging the pregnant patient for nonobstetric conditions: algorithms and radiation dose considerations. Radiographics 2007;27:1705–22.

Table 3. Fetal Radiation Doses Associated With Common Radiologic Examinations ⇦

Type of Examination	Fetal Dose* (mGy)
Very low-dose examinations (<0.1 mGy)	
Cervical spine radiography (anteroposterior and lateral views)	<0.001
Head or neck CT	0.001–0.01
Radiography of any extremity	<0.001
Mammography (two views)	0.001–0.01
Chest radiography (two views)	0.0005–0.01
Low- to moderate-dose examinations (0.1–10 mGy)	
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
Higher-dose examinations (10–50 mGy)	
Abdominal CT	1.3–35
Pelvic CT	10–50
^{18}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

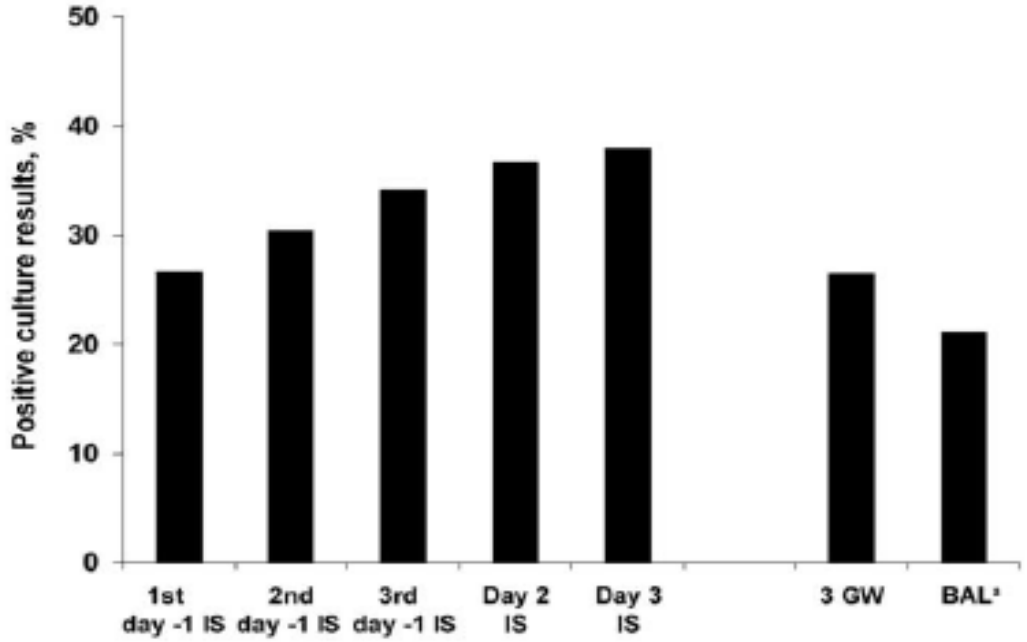


Figure 2. Proportion of subjects with cultures positive for *Mycobacterium tuberculosis*, by diagnostic technique, for 79 subjects with results for all 5 sputum samples obtained by induction with nebulized hypertonic saline (IS) and all 3 gastric washing (GW) specimens. Cumulative proportions are shown 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. [a]Bronchoalveolar lavage (BAL) culture results were available for 19 subjects.

Brown et al Clin Iinfect Dis 2007(44):1415

Bacteriologic and Histologic Examinations

Extrapulmonary Specimens

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

Do NOT collect specimens in Formalin or bacteriostatic saline!

*recovery poor

Laboratory Examination

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

Treatment of Tuberculosis

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

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Lewinsohn et al. CID. 2016

Antituberculosis Drugs
(ATS/CDC/IDSA)

- First-Line drugs (RIPE)
  - Isoniazid
  - Rifampin
  - Rifapentine
  - Rifabutin*
  - Ethambutol
  - Pyrazinamide

  *Not FDA approved for TB

- Second-Line Drugs
  - Cylcoserine
  - Ethionamide
  - Levofloxacin*
  - Moxifloxacin*
  - PAS
  - Streptomycin
  - Amikacin/~~Kanamycin~~
  - ~~Capreomycin~~
  - Bedaquiline
  - Delamanid
  - Pretomanid

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 (replace with a fluoroquinolone)
  - Intermittent regimens (2-3x/wk):
    - GIVEN by DOT ONLY
    - Drug susceptible isolate
    - Regimen contains INH and rifampin

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

	Intensive Phase		Continuation Phase				
Regimen	Drug[a]	Interval and Dose[b] (Minimum Duration)	Drugs	Interval and Dose[b,c] (Minimum Duration)	Range of Total Doses	Comments[c,d]	Regimen Effectiveness
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.	Greater
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[e]	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.	*
							Lesser

Treatment shortening regimen – Drug Sensitive TB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

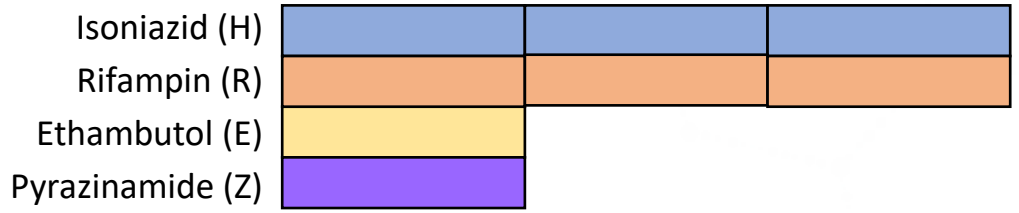
S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, 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

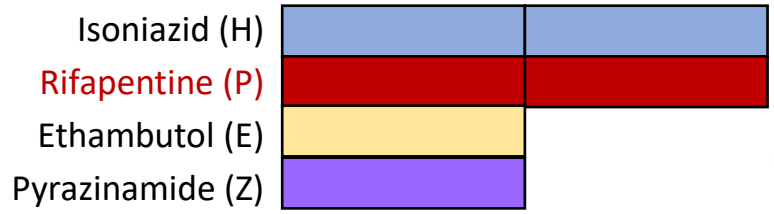
N Engl J Med 2021;384:1705-18.

Study 31/A5349

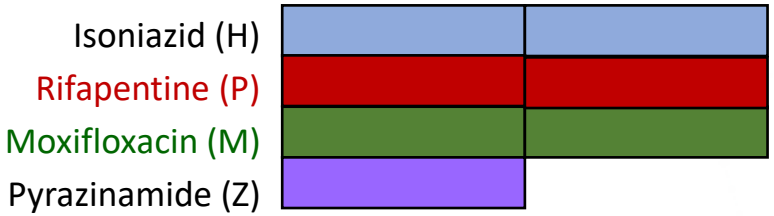
Control
(2HRZE/4HR)



RPT
(2HPZE/2HP)



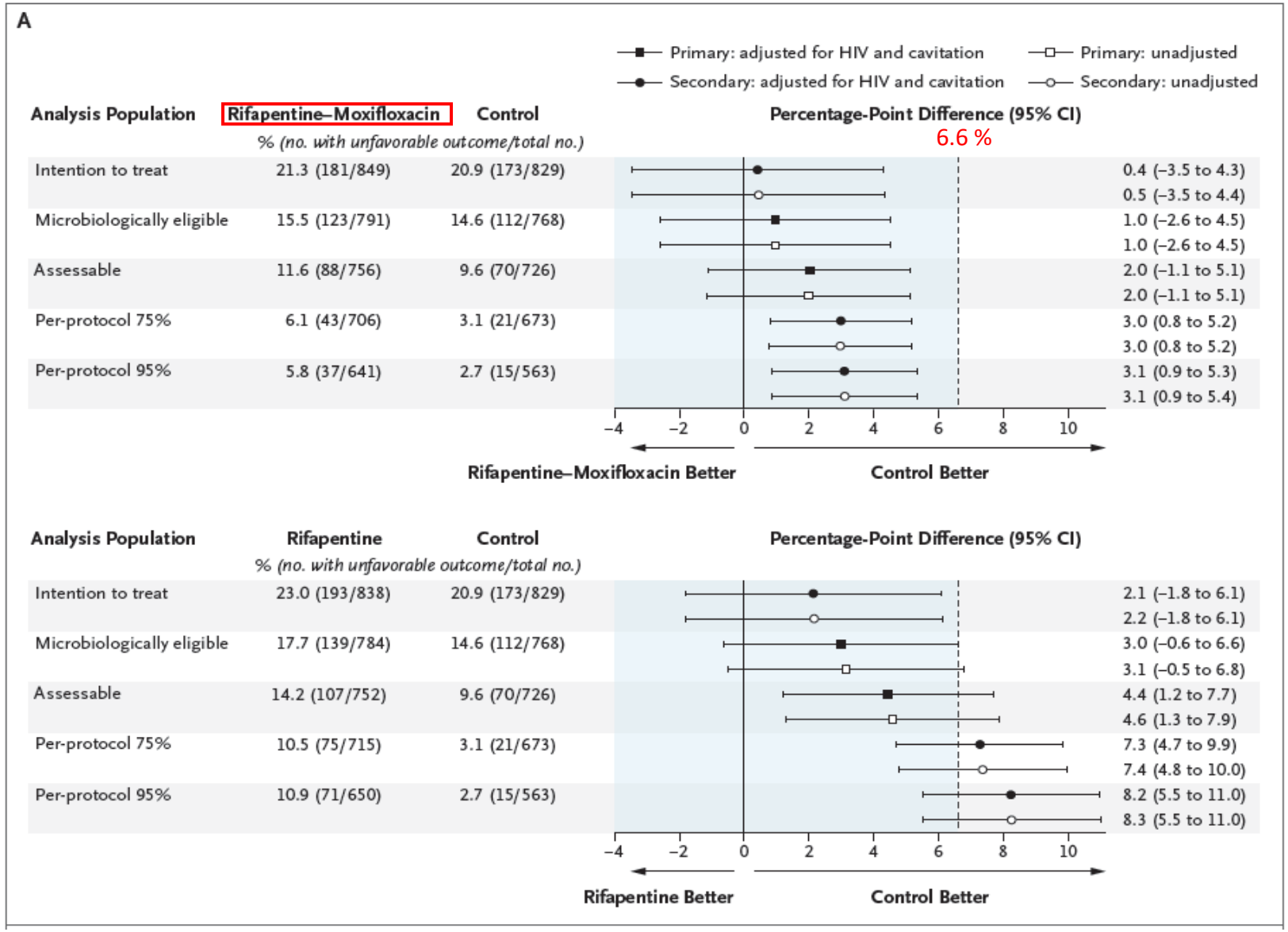
Control
(2HPZM/4HPM)



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



N Engl J Med 2021;384:1705-18.

Groups That May Not Benefit

- Patients< 12 years old and ≥75 years old
- Pregnant women – no studies
- Patients with severe liver disease – Not likely to tolerate INH and PZA
- Patients with severe renal disease – No guidance on renal dosing

Groups That May Not Benefit

- Patients with multiple medication interactions – Rifapentine works like rifampin regarding drug interactions
- The study specifically excluded patients with central nervous system (CNS), bone, miliary, and pericardial TB. Patients with extensive disease, even pulmonary, that would require 9 or more months of standard treatment – Not for bone, CNS, miliary or pericardial disease
- Tiny patients (< 88 lb.) – must weigh at least 40 kg
- Patients with long QTc syndrome – moxifloxacin can prolong QTc

Challenges associated with shorter treatment regimens

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

TB Meningitis – 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 (%)
First-line					
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	-

Expert Review of Clinical Pharmacology, 12:3, 267-288

Drug Penetration of CSF

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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	-

Expert Review of Clinical Pharmacology, 12:3, 267-288

Drug Penetration of CSF

Table 2. (Continued).

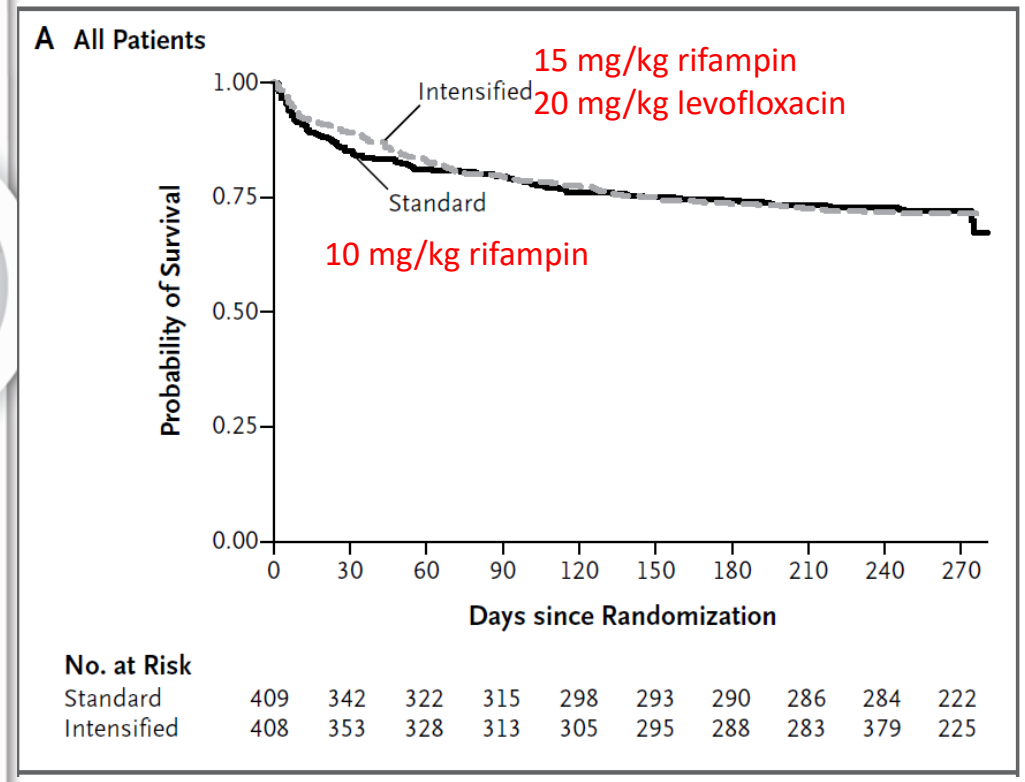
Drug	Forms	Oral bio-availability (%)	Food effect	Plasma protein binding (%)	CNS penetration (%)
Levofloxacin	PO; IV	~100	None	24–38	70–80
Moxifloxacin	PO; IV	90	None	50	70–80
Ethionamide	PO	~100	None	~30	80–90
Cycloserine	PO	65–90	Slight decrease	~0	80–90

Table 2. (Continued).

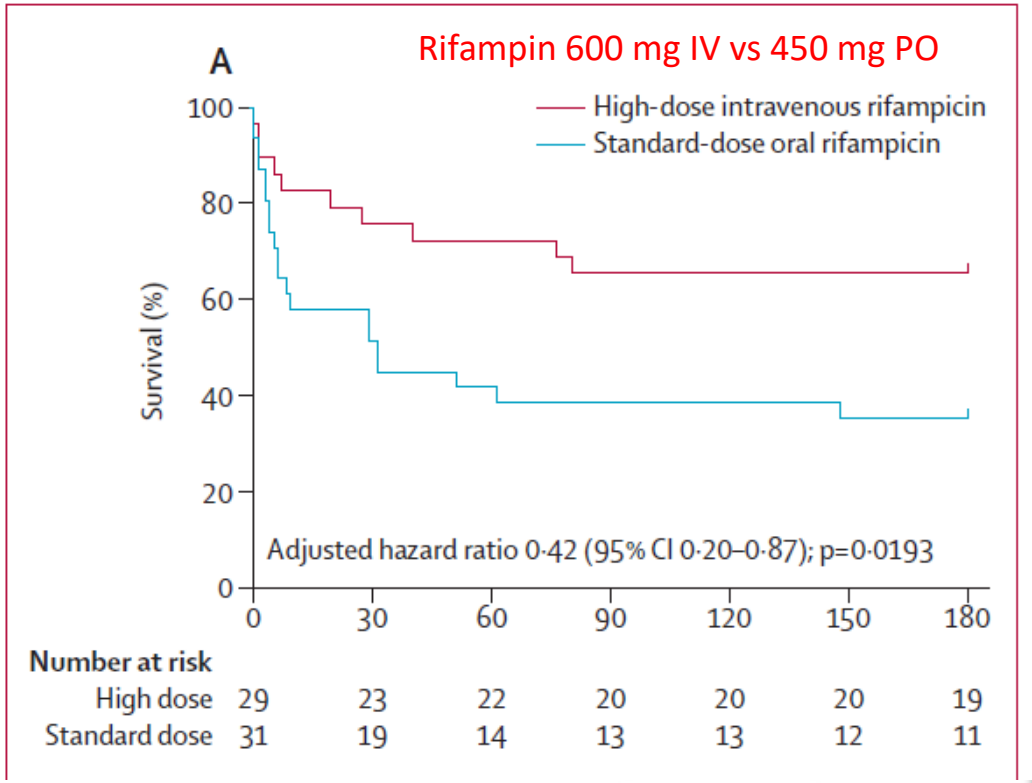
Drug	Forms	Oral bio-availability (%)	Food effect	Plasma protein binding (%)	CNS penetration (%)
Linezolid	PO; IV	~100	–23% with high-fat meals	31	70
Bedaquiline	PO	Unknown	Increase	>99	Likely poor (limited data)
Delamanid	PO	25–47	Increase	>99	No human data
Pretomanid	PO	Unknown	Increase	93	No human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

Expert Review of Clinical Pharmacology, 12:3, 267-288

Intensified Regimen for TBM (Adults)



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



Lancet Infect Dis 2013; 13: 27–35

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults

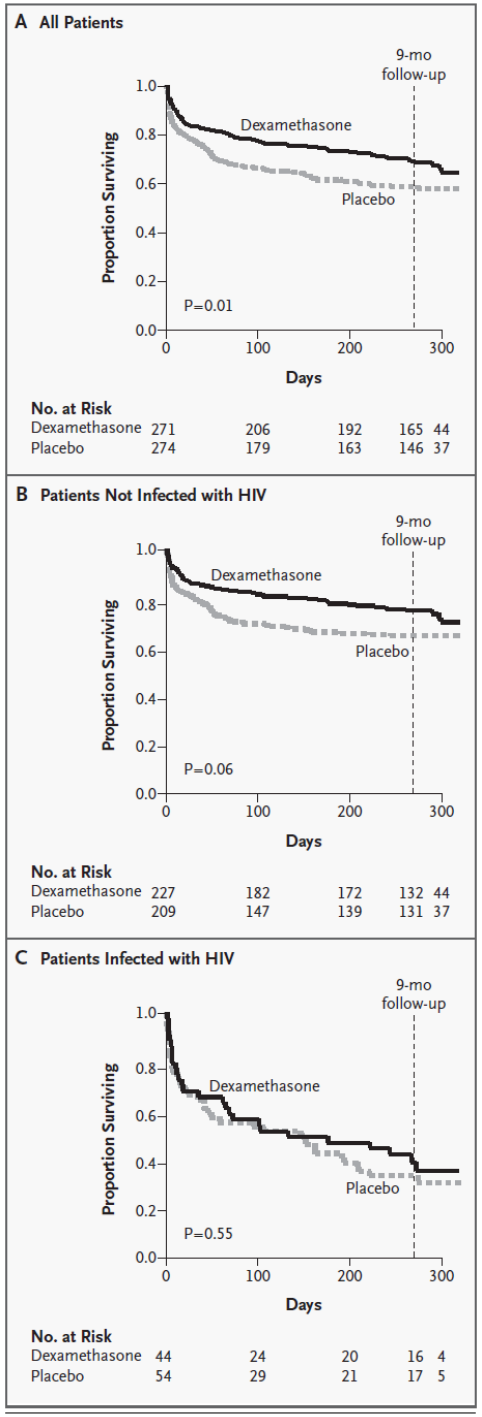
Guy E. Thwaites, M.R.C.P., Nguyen Duc Bang, M.D., Nguyen Huy Dung, M.D., Hoang Thi Quy, M.D., Do Thi Tuong Oanh, M.D., Nguyen Thi Cam Thoa, M.D., Nguyen Quang Hien, M.D., Nguyen Tri Thuc, M.D., Nguyen Ngoc Hai, M.D., Nguyen Thi Ngoc Lan, Ph.D., Nguyen Ngoc Lan, M.D., Nguyen Hong Duc, M.D., Vu Ngoc Tuan, 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
		number (percent)			
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.



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

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"

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.

So, what is ‘liver-friendly/sparing’?

What if they are really, really sick……?

• 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

Sick…..but not dying, liver sparing regimen

• 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
• Pyrazinamide (PZA)		• Kidney (liver metabolites)
• 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, 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 rifampin/INH 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
  - Restart treatment 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

- Cavitary 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

Steroids and TB

Who, What and How

Clinical Infectious Diseases

IDSA GUIDELINE

Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

Payam Nahid,[1] Susan E. Dorman,[2] Narges Alipanah,[1] Pennan M. Barry,[3] Jan L. Brozek,[4] Adithya Cattamanchi,[1] Lelia H. Chaisson,[1] Richard E. Chaisson,[2] Charles L. Daley,[5] Malgosia Grzemska,[6] Julie M. Higashi,[7] Christine S. Ho,[8] Philip C. Hopewell,[1] Salmaan A. Keshavjee,[9] Christian Lienhardt,[6] Richard Menzies,[10] Cynthia Merrifield,[1] Masahiro Narita,[12] Rick O'Brien,[13] Charles A. Peloquin,[14] Ann Raftery,[1] Jussi Saukkonen,[15] H. Simon Schaaf,[16] Giovanni Sotgiu,[17] Jeffrey R. Starke,[18] Giovanni Battista Migliori,[11] and Andrew Vernon[8]

- Severe IRIS
  - 1.25 mg/kg/day (50-80 mg) prednisone
  - 2-4 weeks, then wea over 6-12 weeks or longer

- TB pericarditis
  - Suggested benefit in preventing constrictive pericarditis
  - Consider in patients with large pericardial effusions or at highest risk for inflammatory complications

- TB meningitis
  - Dexamethasone or prednisolone
  - Tapered over 6-8 weeks

Times Steroids Should Absolutely Be Considered

- TB meningitis
- Intrathoracic lymph nodes threatening an airway
- Should consider for:
  - IRIS

Which Steroid is ‘best’?

- Essentially equivalent

- More important to get the equivalence correct if you change from one to another (e.g. from dexamethasone to prednisone)

How should you wean?

- Again, no literature

- Suggestions
  - Wean slowly with large lesions
  - If the patient does not tolerate a drop in steroid dose, go back up on the dose and wean more slowly
  - Look for reasons for worsening disease but don’t be afraid to restart steroids

TB in the Elderly

- Hepatotoxicity as well as other medication toxicities are more common
- Drug-drug interactions are more common
- May want to weigh 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 (*not MDR)*, AND
- Adhering to adequate treatment regimen ≥ 2 weeks (one week if smear negative to start)
  - DOT – YES!
  - Do you know drug susceptibilities?

Questions?

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Or

1-800-TEX-LUNG