



Treatment of Tuberculosis

Lisa Y. Armitige, MD, PhD

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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

- Consultant, SBIR grant for Oak Therapeutics



Diagnosing Tuberculosis Disease

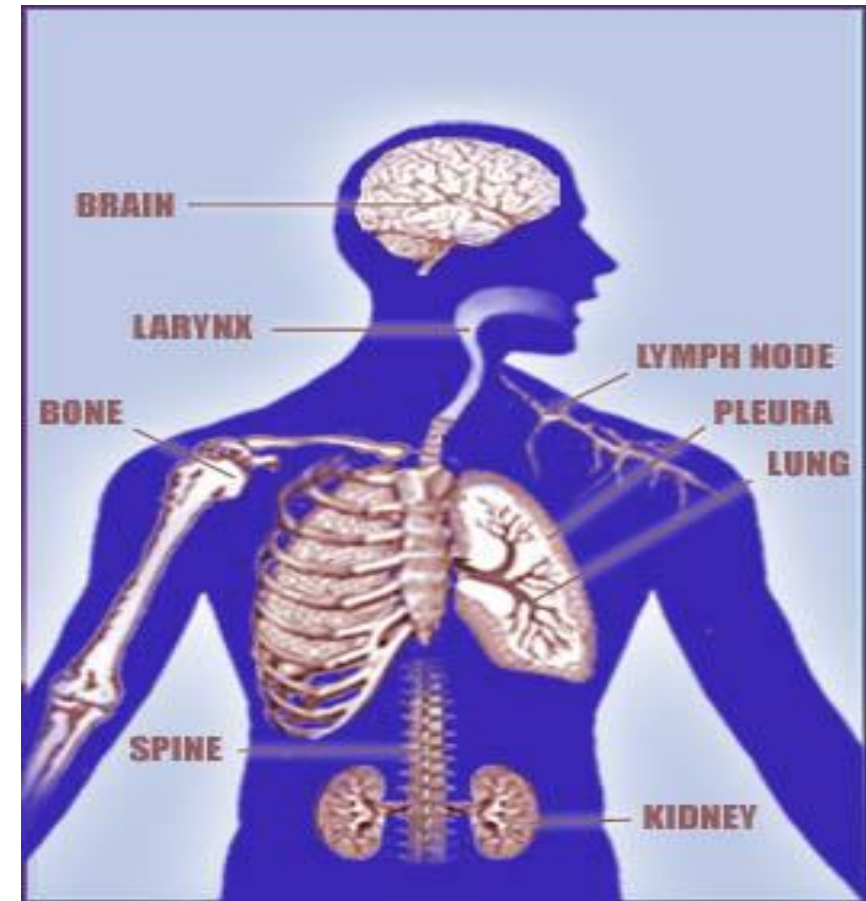


Sites of TB Disease

- 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

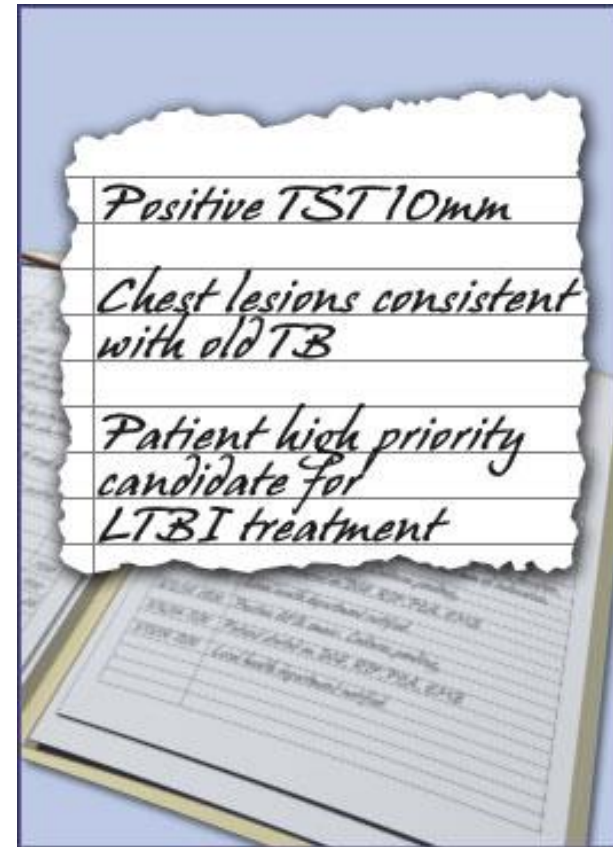
- Medical/social history
- Physical examination
- Testing for TB infection
- Chest radiograph
- Bacteriologic or histologic exam



CXR – old healed TB (TB IV)

- 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)
<i>Very low-dose examinations (<0.1 mGy)</i>	
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
<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
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
- 'Huff cough' or consider gastric aspirates



Culture Yield

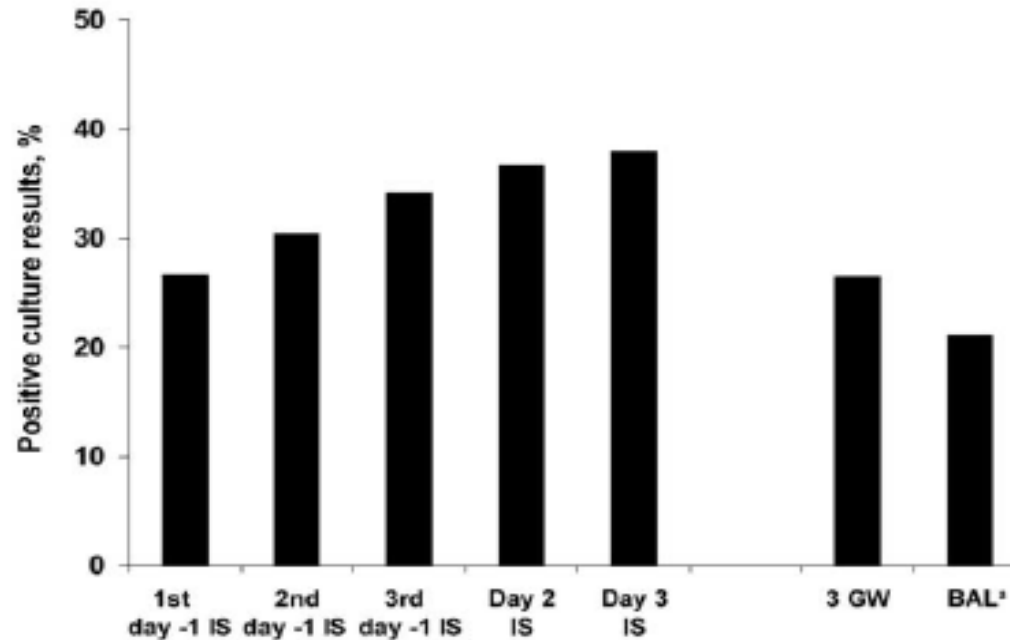


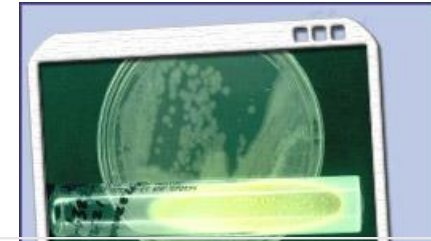
Figure 2. Proportion of subjects with cultures positive for *Mycobacterium tuberculosis*, by diagnostic technique, for 79 subjects with results for all 5 sputum samples obtained by induction with nebulized hypertonic saline (IS) and all 3 gastric washing (GW) specimens. Cumulative proportions are shown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



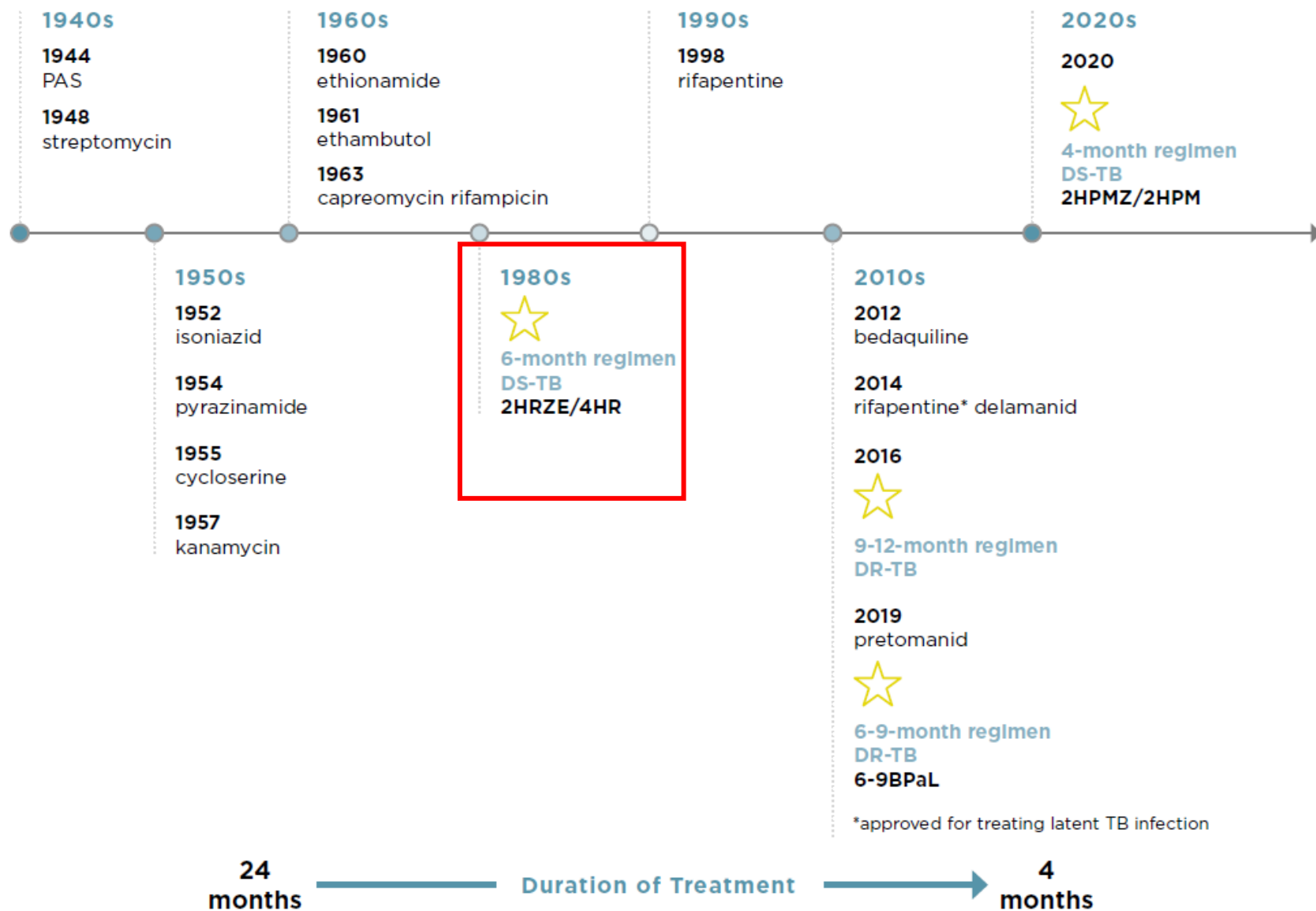
**Do NOT collect
specimens in Formalin
or bacteriostatic saline!**



Treatment of Tuberculosis



FIGURE 1: TUBERCULOSIS TREATMENT SHORTENING MILESTONES



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,^{1,a} Michael K. Leonard,^{2,a} Philip A. LoBue,^{3,a} David L. Cohn,⁴ Charles L. Daley,⁵ Ed Desmond,⁶ Joseph Keane,⁷ Deborah A. Lewinsohn,¹ Ann M. Loeffler,⁸ Gerald H. Mazurek,³ Richard J. O'Brien,⁹ Madhukar Pai,¹⁰ Luca Richeldi,¹¹ Max Salfinger,¹² Thomas M. Shinnick,³ Timothy R. Sterling,¹³ David M. Warshauer,¹⁴ and Gail L. Woods¹⁵

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

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

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

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
- Linezolid



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)



Regimen	Intensive Phase		Continuation Phase		Range of Total Doses	Comments ^{c,d}	Regimen Effectiveness	
	Drug ^a	Interval and Dose ^b (Minimum Duration)	Drugs	Interval and Dose ^{b,c} (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.		
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.		*



FIGURE 1: TUBERCULOSIS TREATMENT SHORTENING MILESTONES

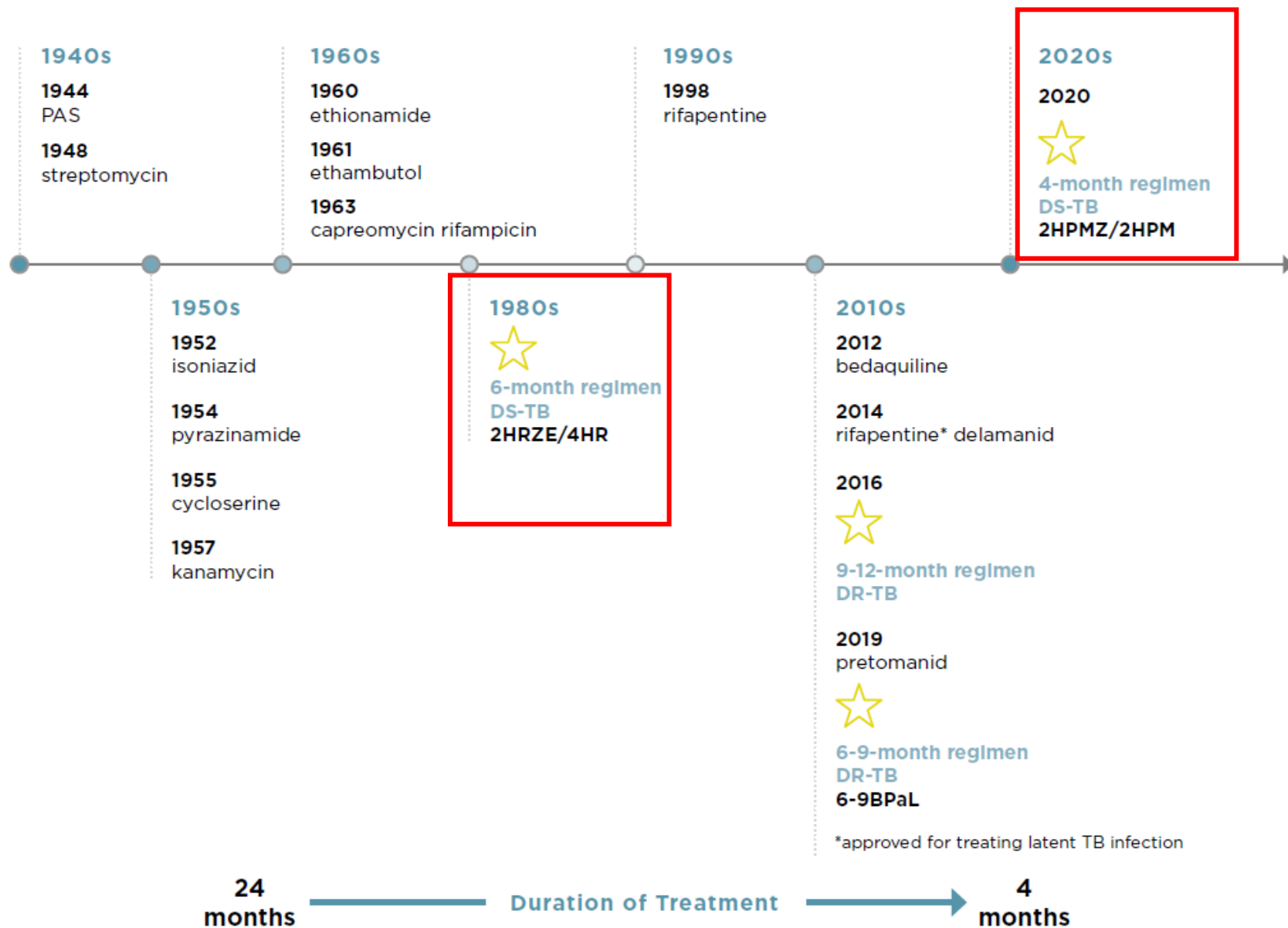
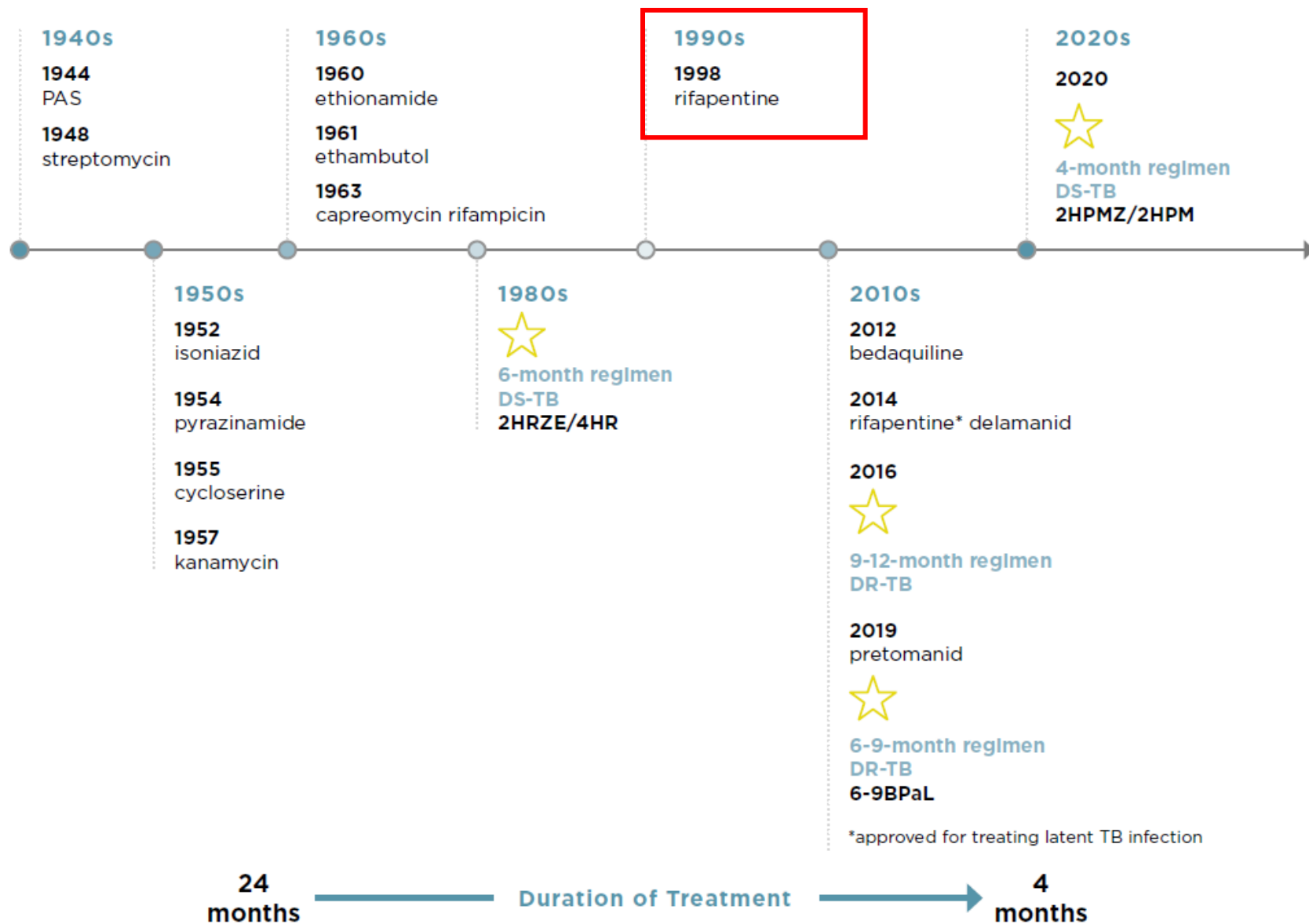


FIGURE 1: TUBERCULOSIS TREATMENT SHORTENING MILESTONES



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^PZE/2H^P)

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

Control
(2H^PZ^M/4H^P^M)

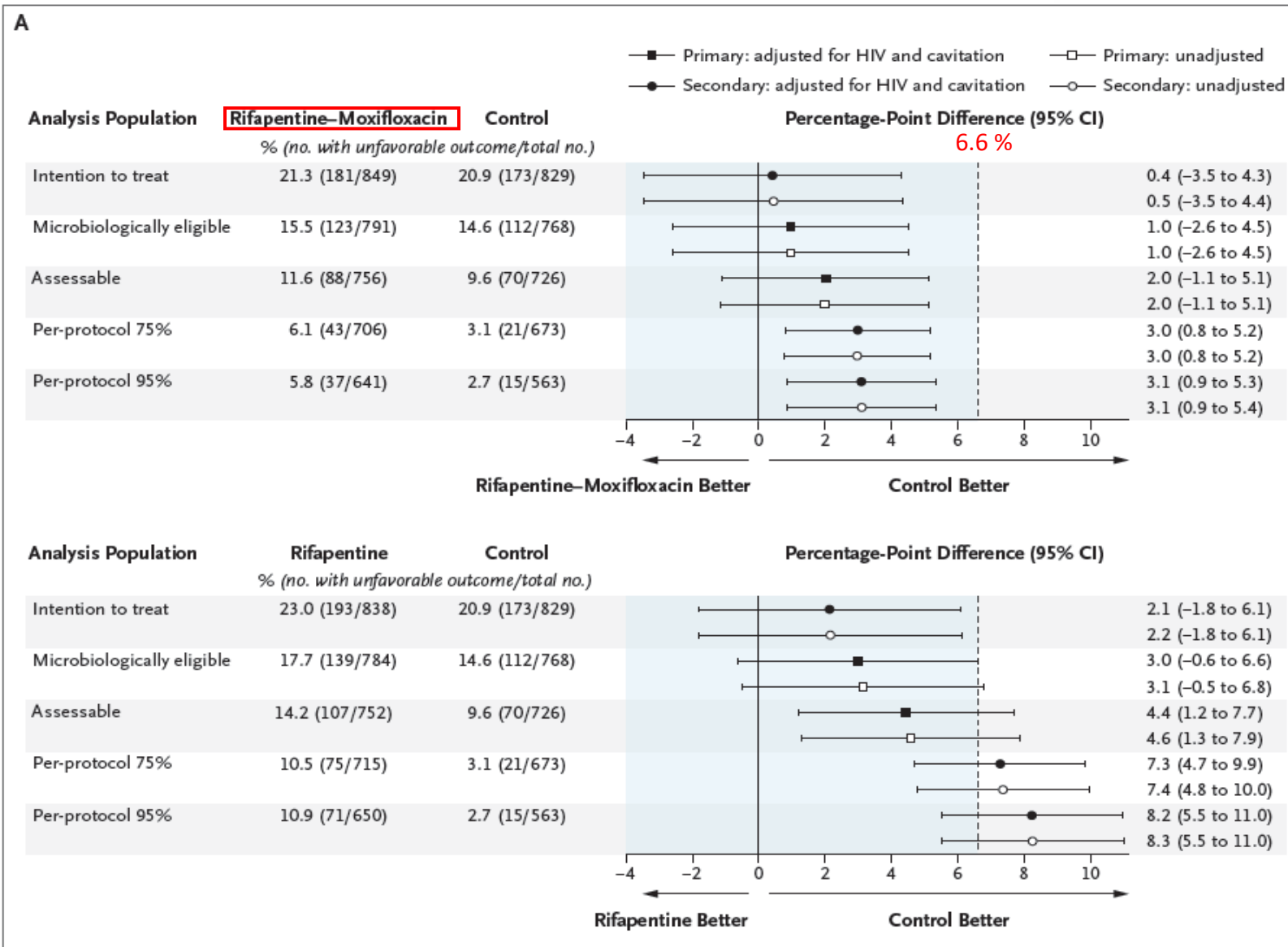
Isoniazid (H)		
Rifapentine (P)		
Moxifloxacin (M)		
Pyrazinamide (Z)		

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



Groups Not Included

- Patients < 12 years old and ≥75 years old – not studied
- Pregnant women – not studied
- 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



Safety and Efficacy Study 31/A5349

TABLE 1. EFFICACY AND SAFETY OUTCOMES IN S31/A5349

Regimen	EFFICACY		SAFETY	
	Favorable outcomes	Unfavorable outcomes	Grade 3 or higher AEs	All-cause mortality
Control (2HRZE/4HR)	90.4% (656/726)	9.6% (70/726)	19.3% (159/825)	0.8% (7/825)
RPT-MOX (2HPZM/2HPM)	88.4% (668/756)	11.6% (88/756)	18.8% (159/846)	0.4% (3/846)

TABLE 2. EFFICACY AND SAFETY OUTCOMES IN S31/A5349 AMONG PLHIV

Regimen	EFFICACY				SAFETY			
	Favorable outcomes		Unfavorable outcomes		Grade 3 or higher AEs		All-cause mortality	
	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Control (2HRZE/4HR)	84.7% (50/59)	90.8% (605/666)	15.3% (9/59)	9.2% (61/666)	21.4% (15/70)	19.1% (144/755)	2.9% (2/70)	0.7% (5/755)
RPT-MOX (2HPZM/2HPM)	91.4% (53/58)	88.1% (615/698)	8.6% (5/58)	11.9% (83/698)	13.9% (10/72)	19.3% (149/774)	0% (0/72)	0.4% (3/774)

CTCAE SEVERITY GRADING – QUICK REFERENCE

Based on Common Terminology Criteria for Adverse Events (CTCAE) v5.0

i Grade refers to the severity of the adverse event (AE) and guides clinical decision-making, documentation, and reporting.

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
 DESCRIPTION	 MILD Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	 MODERATE Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.	 SEVERE Severely or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.	 LIFE-THREATENING Life-threatening consequences; urgent intervention indicated.	 DEATH Death related to the adverse event.
 EXAMPLES (not all inclusive)	• Mild nausea • Rash <10% BSA • Lab abnormality (e.g., mild ↑ AST/ALT) • Fatigue relieved by rest	• Moderate pain • Nausea interfering with eating • Oral medications indicated • Rash 10–30% BSA	• Severe pain • Dehydration requiring IV fluids • Neutropenic fever • Transfusion indicated • Depressive symptoms interfering with self care	• Respiratory distress • Hemodynamic instability • Life-threatening arrhythmia • Severe bleeding • Anaphylaxis	• Death due to an adverse event
 IMPACT ON ADL:	 No limitation in daily activities.	 Limits instrumental ADL (e.g., shopping, handling finances, using phone).	 Limits self-care ADL (e.g., bathing, dressing, using toilet, taking medications).	 Unable to perform self-care ADL; urgent care required.	N/A



ADL = Activities of Daily Living

Instrumental ADL: preparing meals, shopping,

Self-care ADL: bathing, dressing, feeding self,

managing money, using telephone, etc.

using toilet, taking medications.



REMEMBER

Clinical judgment is essential. CTCAE provides standardized language to improve communication and patient safety.

Potential Challenges

- Pill burden
 - 1 INH, 8 rifapentine, 1 moxifloxacin, 1 pyridoxine (everybody gets these) + PZA for weight (up to 15 pills total)
 - Continuation phase is 11 pills vs 4 pills
- Access to VDOT or other mode of 7 day/week dosing
- Tolerability (versus safety, efficacy)
- Familiarity with the regimen
 - Substitutions?
 - There is no guidance on substituting any of the drugs
 - EOT and they need more treatment?
 - There is no real guidance on how long to extend treatment
- Drug shortages!



4 Month Rifapentine Regimen in Actuality

- NY experience - 36 patients enrolled
 - 46% of patients with TB were eligible
 - 36% completed the regimen
 - 42% discontinued due to adverse events
- SF experience - 22 patients enrolled
 - 18.8% of patients with TB were eligible
 - 41% completed treatment
 - 81% had adverse events
- Texas experience - 26 patients enrolled
 - 69% completed treatment



‘What If My Patient Has....’



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	–

Drug Penetration of CSF

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

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Drug Penetration of CSF

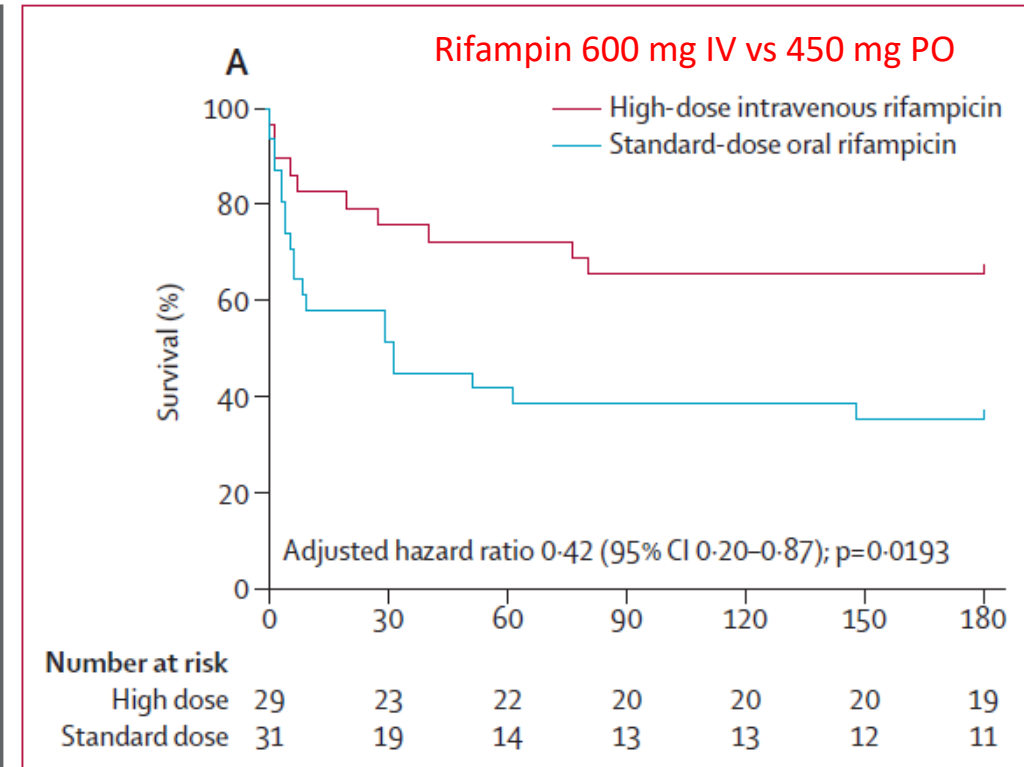
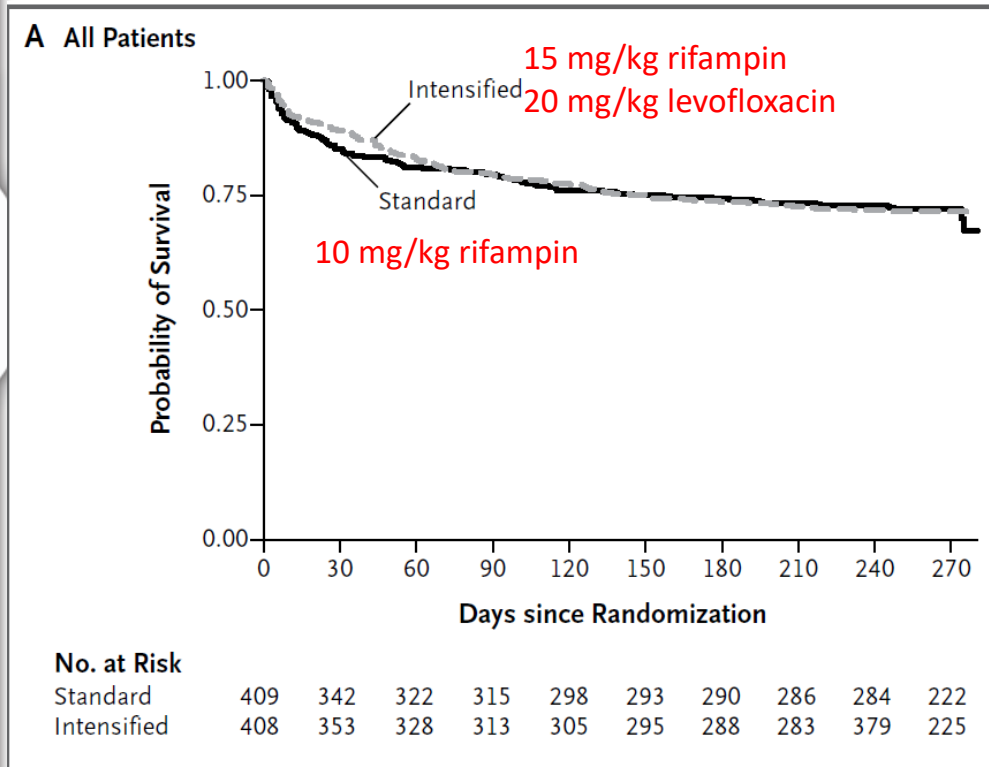
Table 2. (Continued).

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

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.

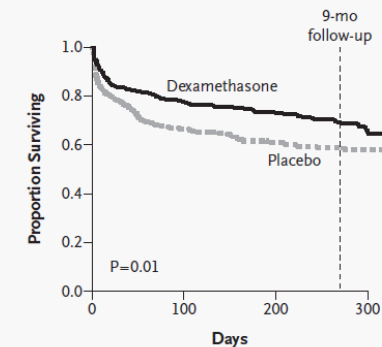
N ENGL J MED 351;17 WWW.NEJM.ORG OCTOBER 21, 2004

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)

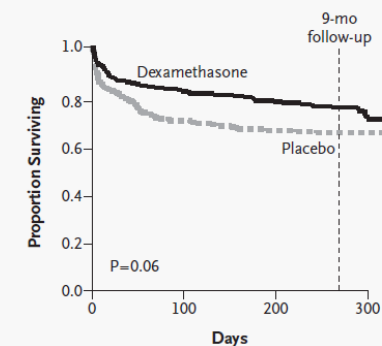
* Because of rounding, the percentages for the dexamethasone group do not total 100.

A All Patients



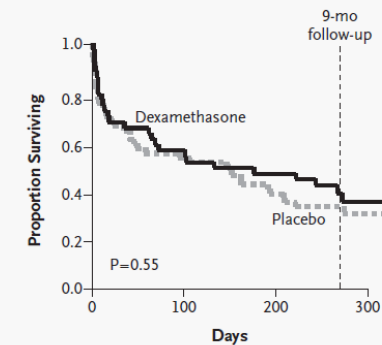
No. at Risk					
Dexamethasone	271	206	192	165	44
Placebo	274	179	163	146	37

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

Steroids and TB

Who, What and How



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 Vernon⁸

- 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 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.....?

What are my IV options?

- 
- 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

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 options

- 
- | | | |
|----------------------|---|------------------------------|
| • 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
- Assess any barriers to cure. In order for the patient to cure, the drugs have to get to the bug and kill it
- 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

- 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



Steroids and TB

Who, What and How



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 Vernon⁸

- 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 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



PZA

- 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

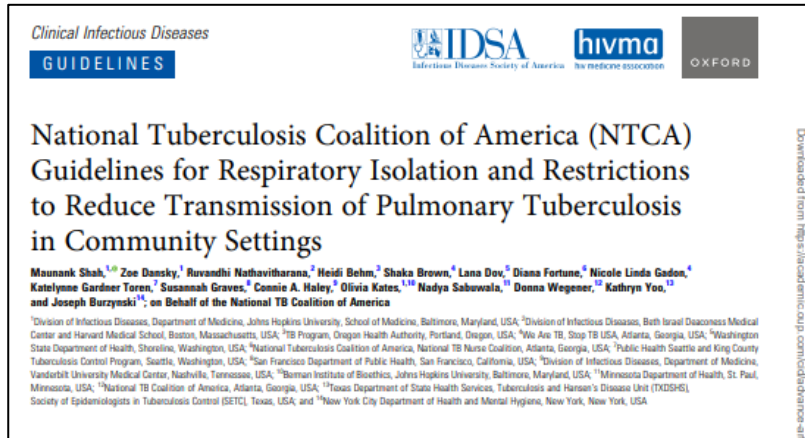


TB in the Elderly

- 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

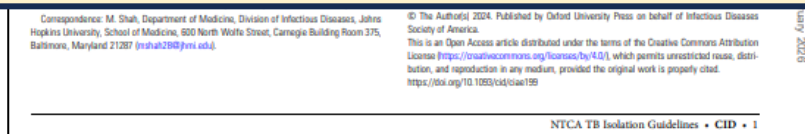


TB Isolation References

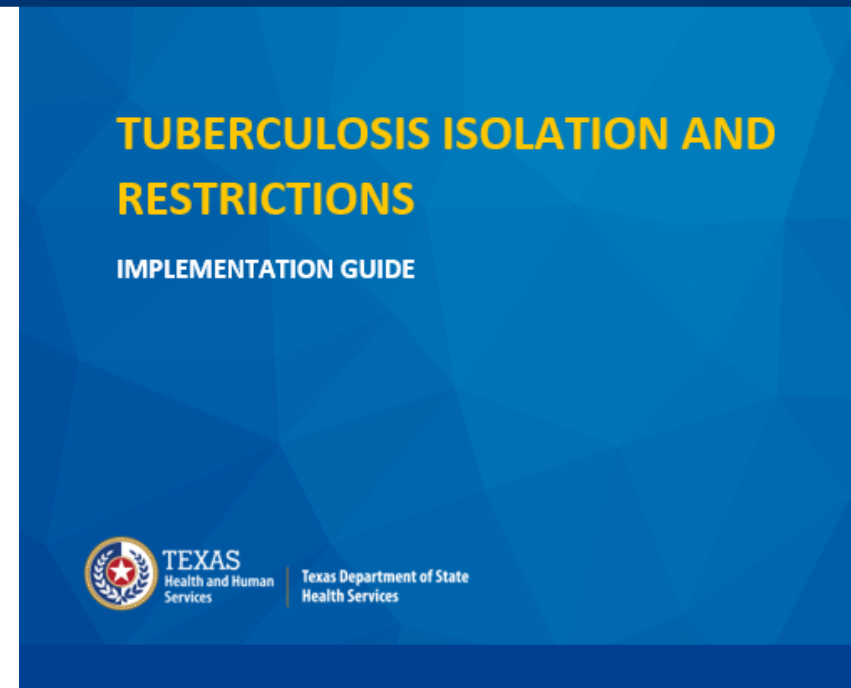


National Tuberculosis Coalition of America (NTCA) Guidelines for Respiratory Isolation and Restrictions to Reduce Transmission of Pulmonary Tuberculosis in Community Settings, 2024.

<https://doi.org/10.1093/cid/ciae199>



*Texas Department of State Health Services
Tuberculosis Isolation and Restrictions
Implementation Guide (Implementation
Guide), 2026.*



Take Home from New Approach to Release from Isolation

- Isolation can be psychologically damaging
- Smear positivity is not necessarily the best indicator of infectiousness once the patient is on adequate therapy
- After 5 days, if the patient is adherent to treatment, has low likelihood of drug resistant disease and are improving clinically, they can be released from isolation in most instances
- High risk environments and high risk contacts need to be carefully considered



Table 5. Criteria to Release Patients from TB Isolation and Restrictions.

When to Release	A: Release Based on Bacteriology	B: Release After 5 ATT Doses	C: Release After 10-14 ATT Doses	D: Release After Consultation
Criteria to Release	1. Patients who live, work, or visit High-Risk Transmission Settings (Table 3). 2. Patients who are non-adherent to the treatment plan or are not tolerating ATT. The above patients may be released after having: • Three negative AFB sputum smears 8-24 hours apart; • 10-14 DOT doses[‡]; • symptom improvement; and • adherence to and tolerance of ATT. [‡]If patient never had a positive sputum smear, release from TB isolation and restrictions after 5 ATT doses- see column B #1.	1. Patients on ATT who never had a positive AFB sputum smear*, are adherent with and tolerating ATT (<i>regardless of setting</i>). 2. Patients on ATT who were initially sputum smear positive and who <u>do not</u> live, work, or visit High-Risk Transmission Settings (Table 3) AND who: a) May** live, work, or visit Other Congregate Settings (Table 4); and/or b) baseline TB symptoms are not worsening (Appendix 3); and c) are not likely† to expose previously unexposed, vulnerable contacts.	1. Patients on ATT and who <u>do not</u> live, work, or visit High-Risk Transmission Settings (Table 3) who were initially sputum smear positive AND who: a) May** live, work, or visit Other Congregate Settings (Table 4) and the PHR or LHD decides longer than 5 ATT doses is necessary before release. b) Have delayed but subsequent improvement of baseline TB symptoms (Appendix 3).	1. Patients on ATT who <u>do not</u> live, work, or visit High-Risk Transmission Settings (Table 3), who remain AFB sputum smear positive, and who remain in TB isolation and restrictions after 10-14 ATT doses. Medical consultation is strongly recommended to determine when patients should be released from TB isolation and restrictions.

*Obtain three initial sputum specimen collected consecutively, 8-24 hours apart, ideally the first specimen observed. Refer to DSHS TB Section's SDOs.

**PHRs and LHDs may consider releasing certain patients who live, work or frequent settings listed in [Table 4](#) on a case-by-case basis. Consider baseline bacteriology results, patient symptoms, setting, and likelihood of exposing previously unexposed vulnerable contacts when making that decision.

†Consider known exposures to new vulnerable contacts (children under age 5 and immunocompromised individuals) such as household contacts or planned time around such individuals where masking would still be required (and at minimum, low level restrictions would be needed).

Questions?

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