Overview of TB Therapy

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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

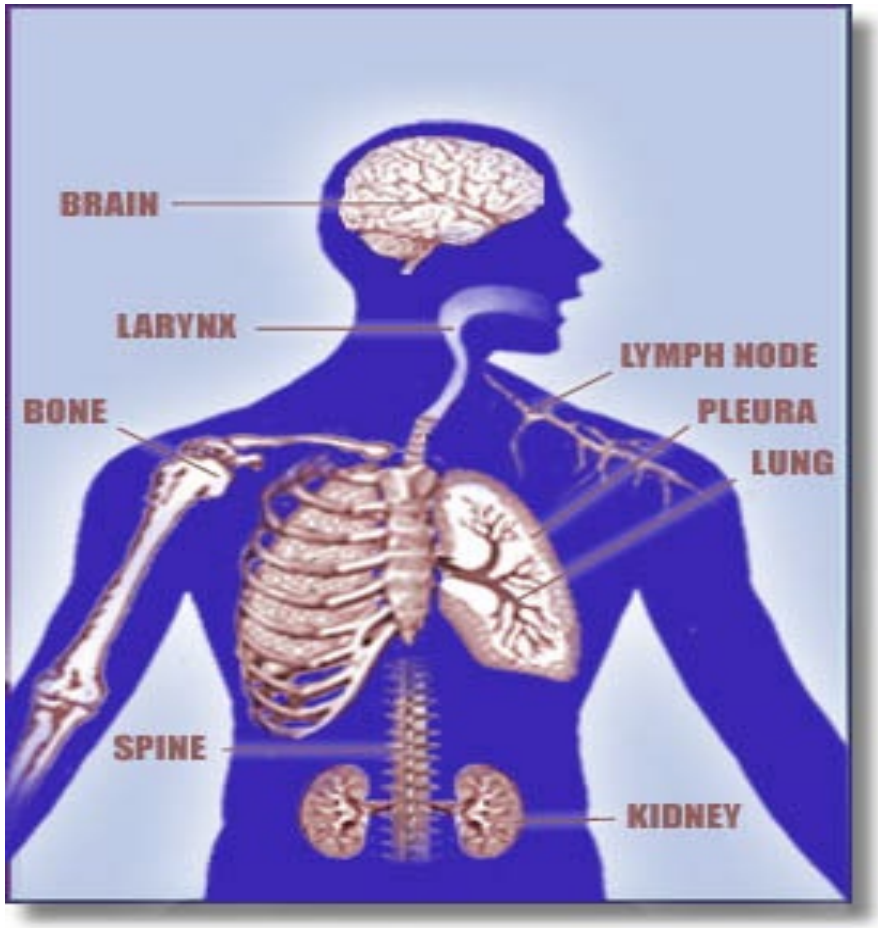
Diagnosing Tuberculosis

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 Disease

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

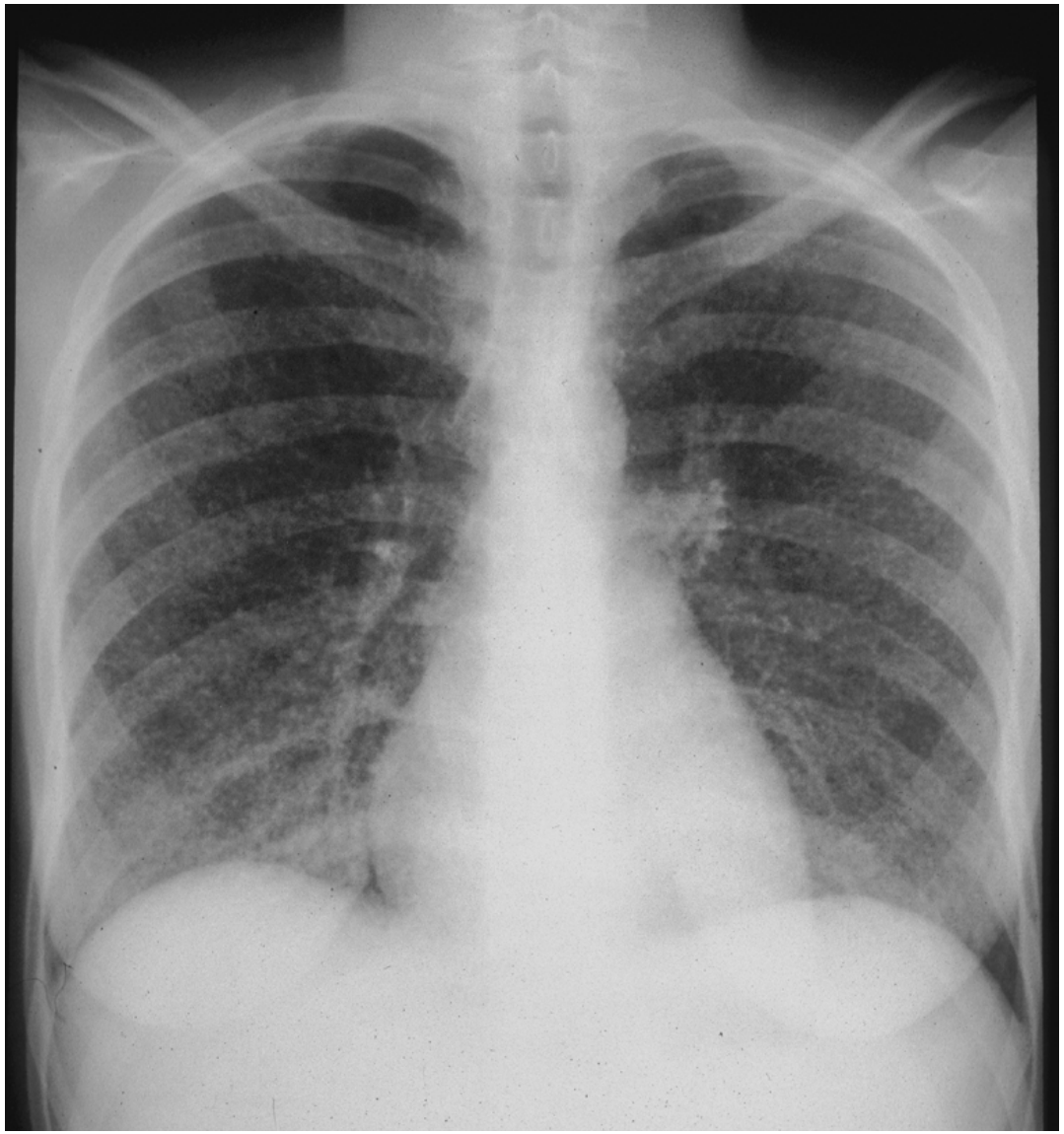
No CXR study shows findings specific for TB

- 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)

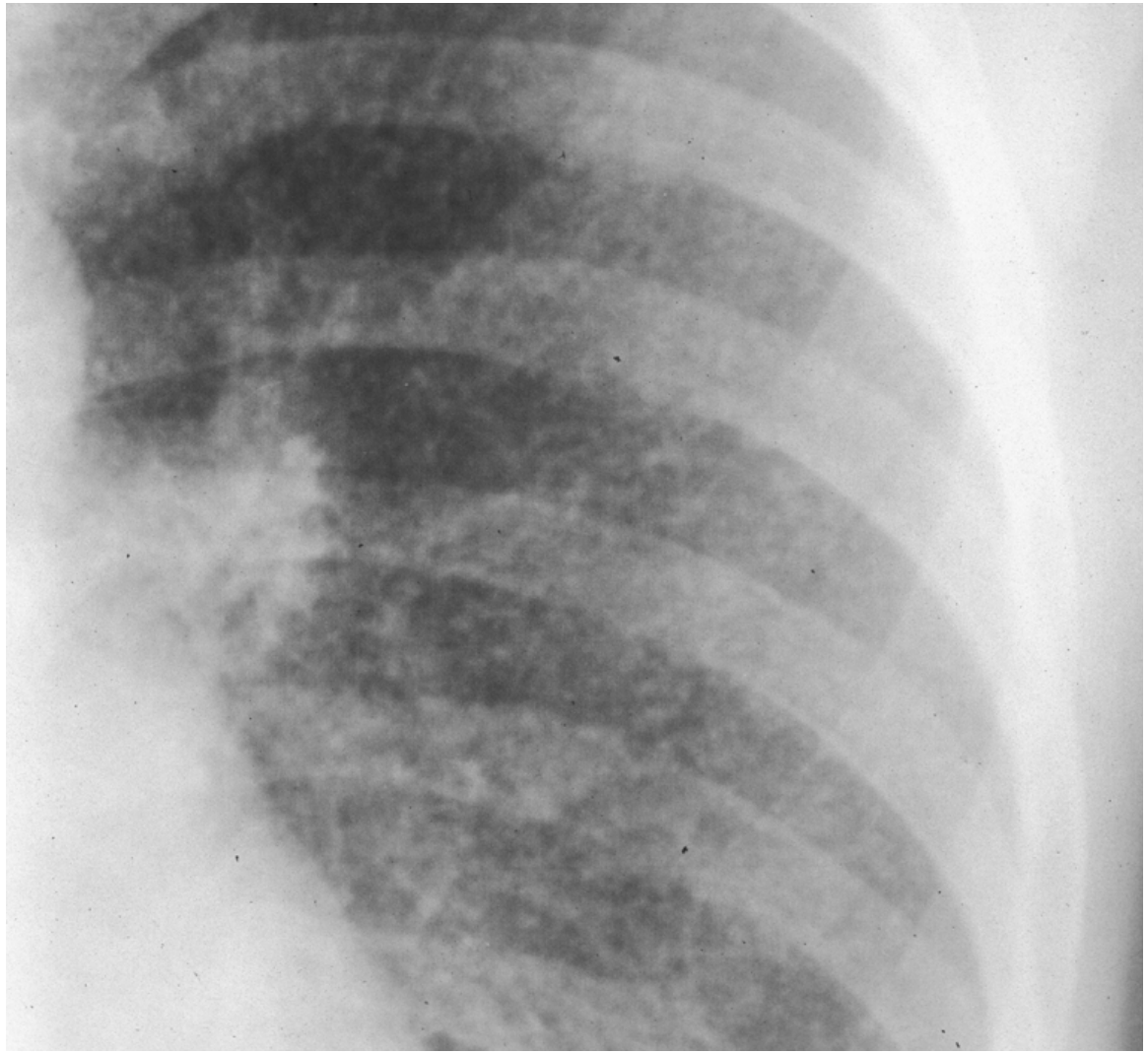
Primary Tuberculosis

- Hilar or paratracheal lymphadenopathy with or without a infiltrates is characteristic.
- Bilateral lymphadenopathy in up to 15%
- Lymphadenopathy may result in lobar atelectasis due to bronchial compression.

Primary Tuberculosis



Primary Tuberculosis

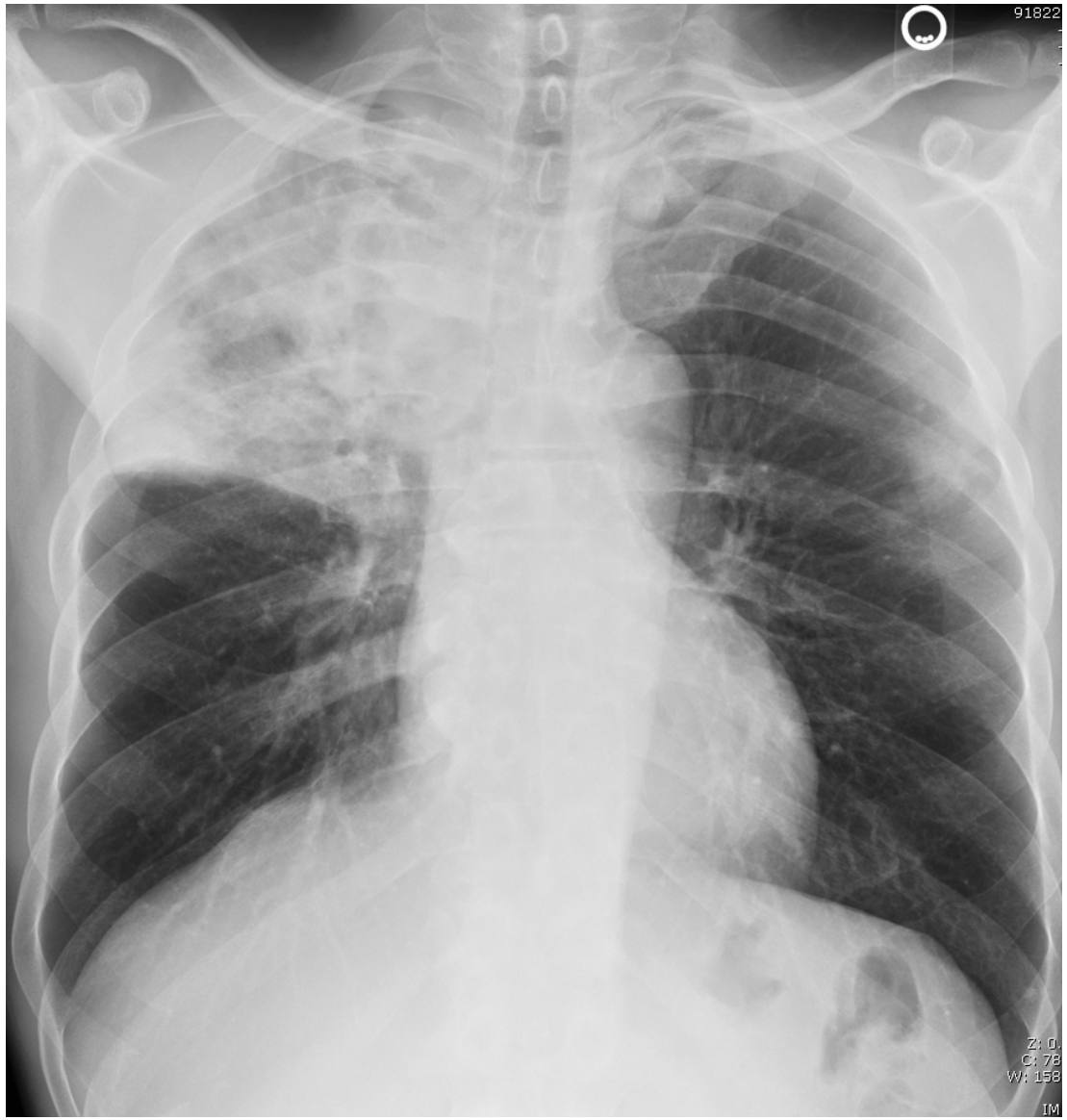


Primary Tuberculosis

Post primary or reactivation tuberculosis

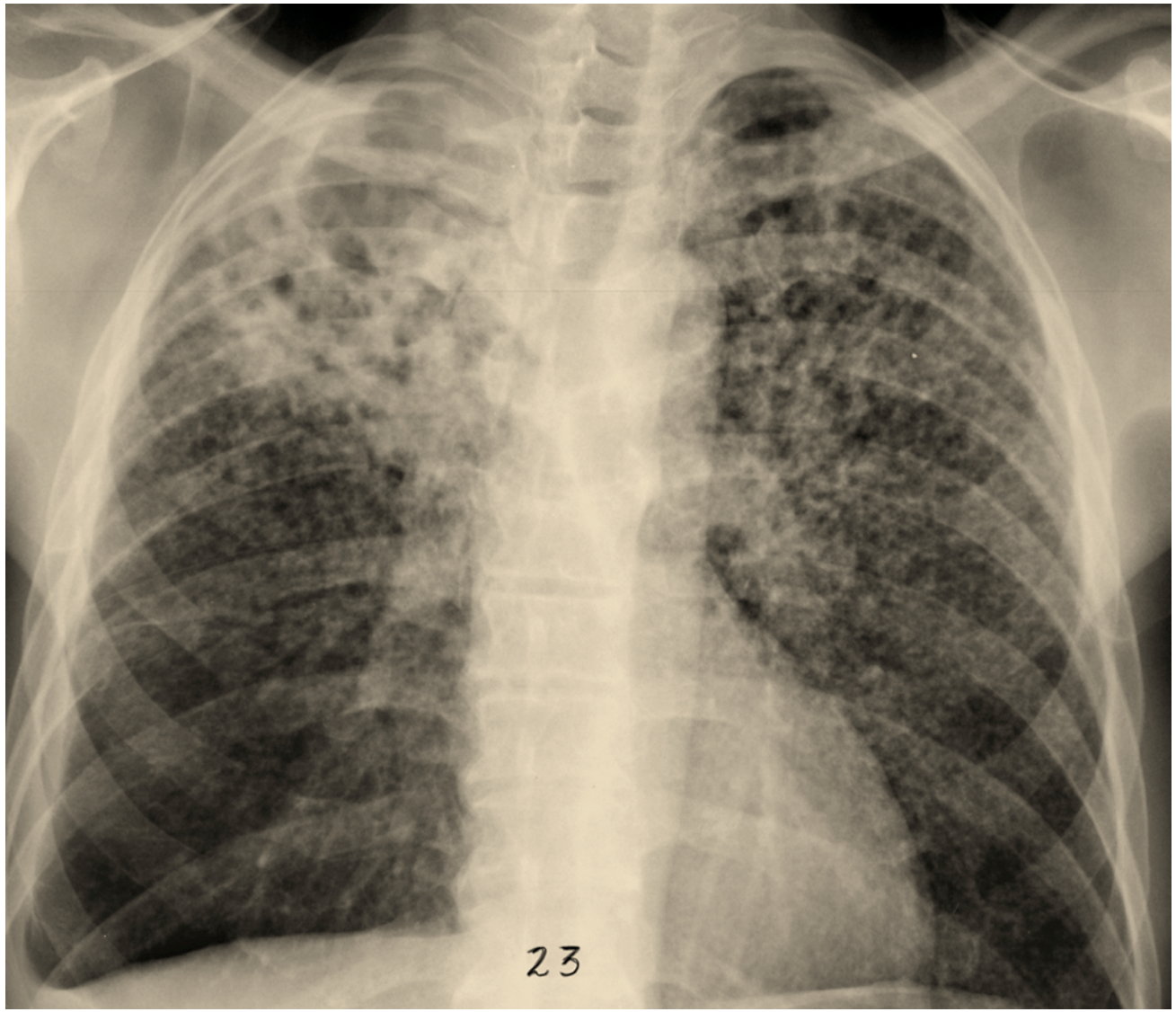
- Cavitation is the hallmark, hematogenous dissemination (miliary), and bronchogenic spread (tree-in-bud)
- Fibrosis and calcification are seen after healing
- Characterized by upper lobes predilection, cavitation and absence of lymphadenopathy
- Manifestations are: parenchymal disease, airway involvement, and pleural extension

Post primary or reactivation tuberculosis



Post primary or reactivation tuberculosis

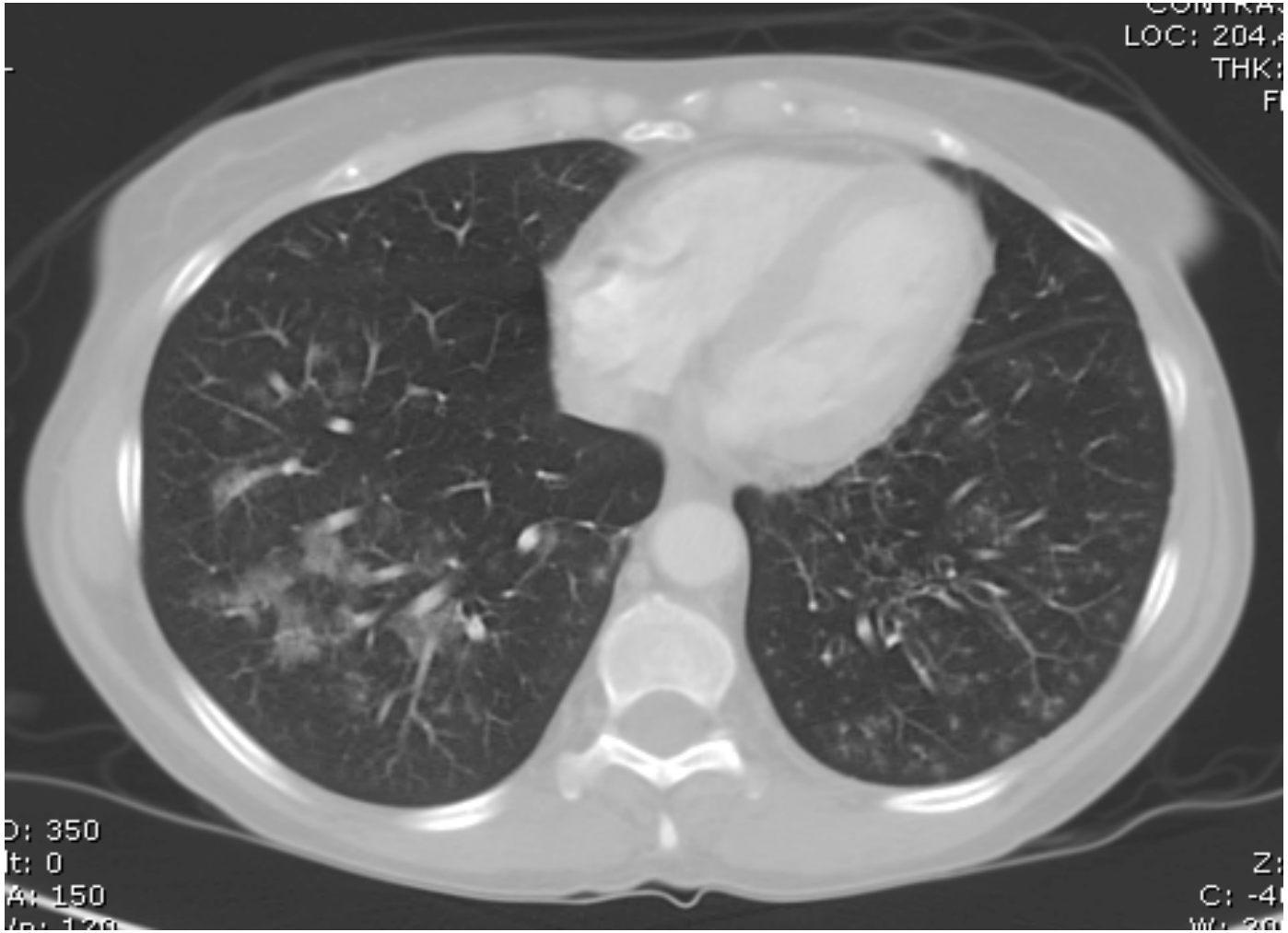
Post primary or reactivation tuberculosis



Tree in Bud……

http://www.jellosalad.com/pic/favorites/index.html

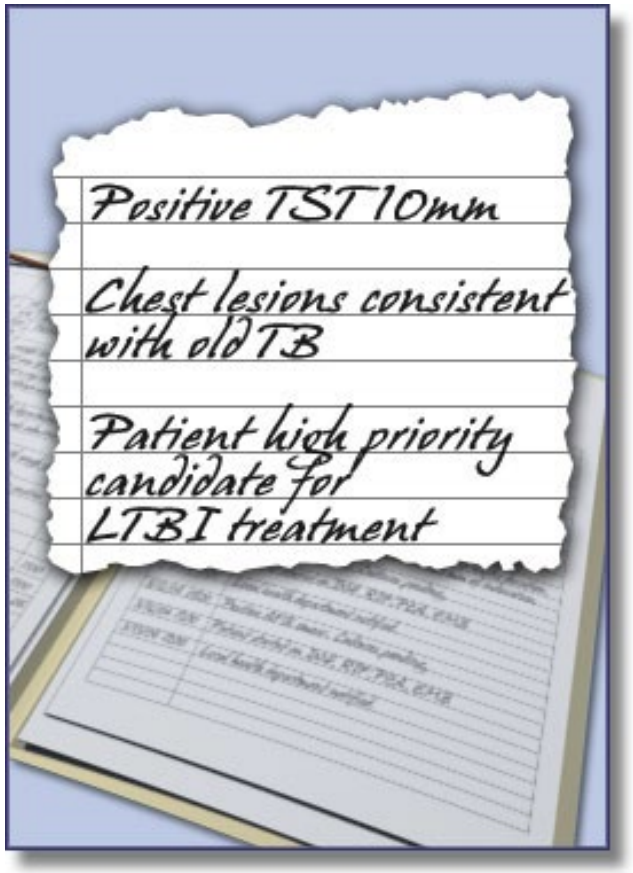
Post primary or reactivation tuberculosis



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 women 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 one observed specimen

Culture Yield

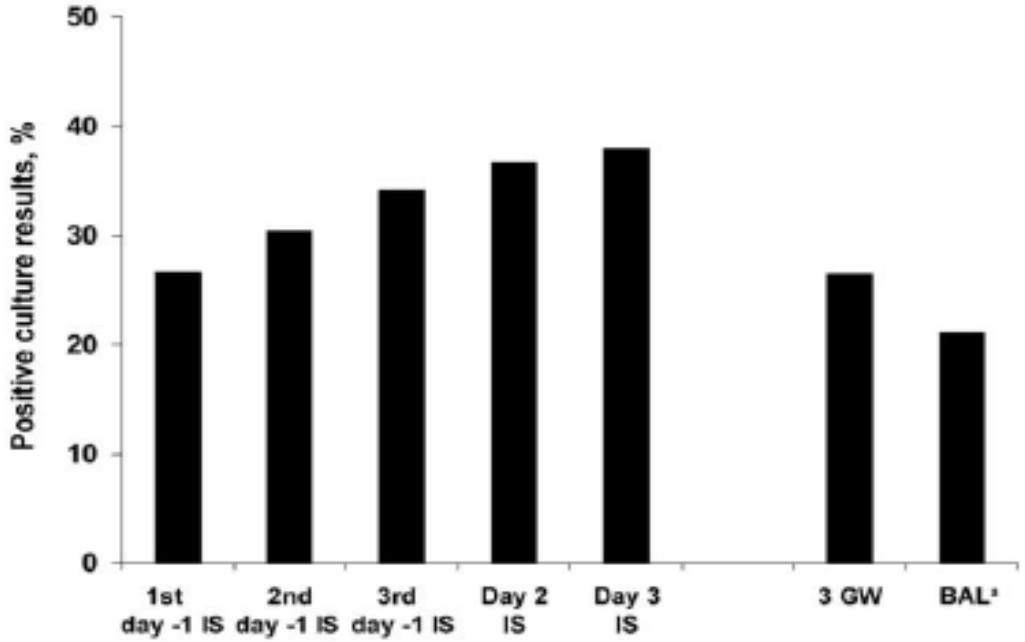


Figure 2. Proportion of subjects with cultures positive for *Mycobacterium tuberculosis*, by diagnostic technique, for 79 subjects with results for all 5 sputum samples obtained by induction with nebulized hypertonic saline (IS) and all 3 gastric washing (GW) specimens. Cumulative proportions are shown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

TB Infection Treatment Options

- CDC Recommended Treatment regimens:
  - INH/Rifapentine x 3 months (3HP)
    - Once weekly DOT x 12 weeks
    - Average of 10 pills at once
  - Rifampin x 4 months
    - Daily (10 mg/kg: 600 mg max)
  - INH +rifampin x 3 months
    - INH daily (5 mg/kg: 300 mg max) + rifampin daily (10 mg/kg: 600 mg max)
  - INH x 6-9 months
    - Daily (5 mg/kg: 300 mg max) or BIW (15 mg/kg: 900 mg max)

ATS/IDSA/NTCA. November 2018.

Treatment of Culture-Positive Drug Susceptible Pulmonary TB

- General conclusions from the literature for HRZE regimen
  - 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
    - Treat with rifampin/PZA/ethambutol + a fluoroquinolone
  - 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
  - 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:
  - Without PZA - minimum duration is 9 months
  - Without rifampin – 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

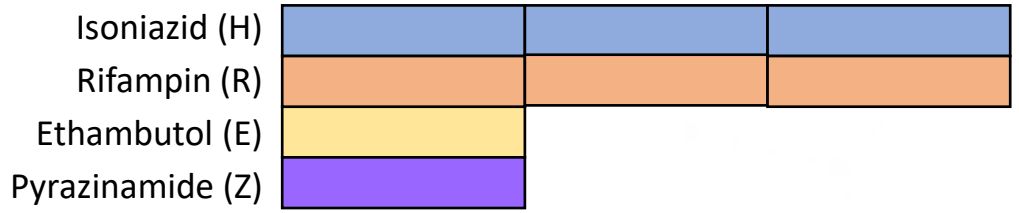
S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott,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

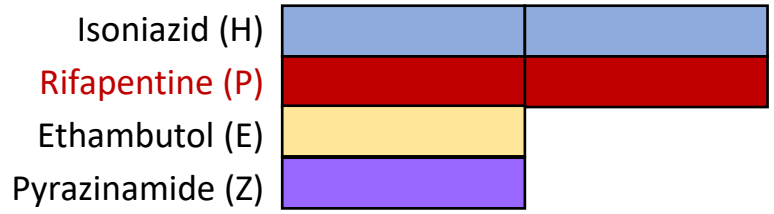
N Engl J Med 2021;384:1705-18.

Study 31/A5349

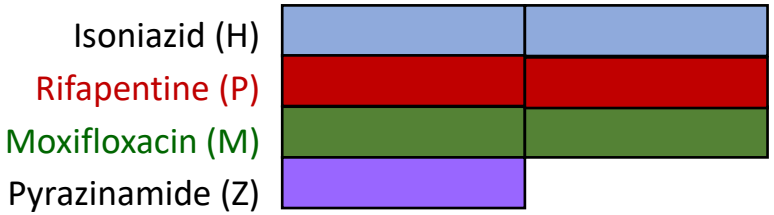
Control
(2HRZE/4HR)



RPT
(2HPZE/2HP)



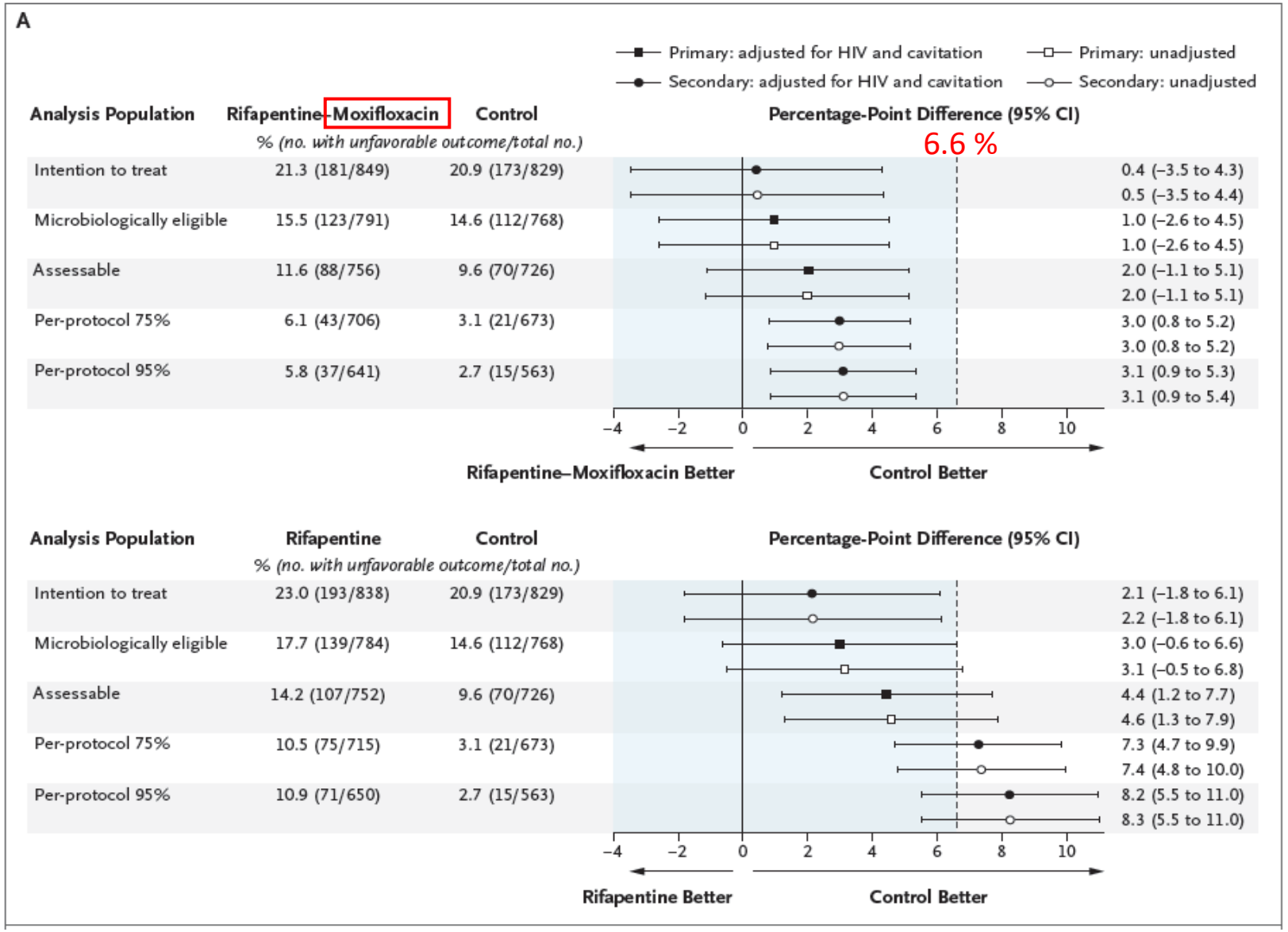
RPT/Moxi
(2HPZM/4HPM)



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.

Safety and Efficacy Study 31/A5349

TABLE 1. EFFICACY AND SAFETY OUTCOMES IN S31/A5349

	EFFICACY		SAFETY	
Regimen	**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

	EFFICACY				SAFETY			
Regimen	**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)

https://www.treatmentactiongroup.org/publication/an-activists-guide-to-shorter-treatment-for-drug-sensitive-tuberculosis/

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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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

Table 2. (Continued).

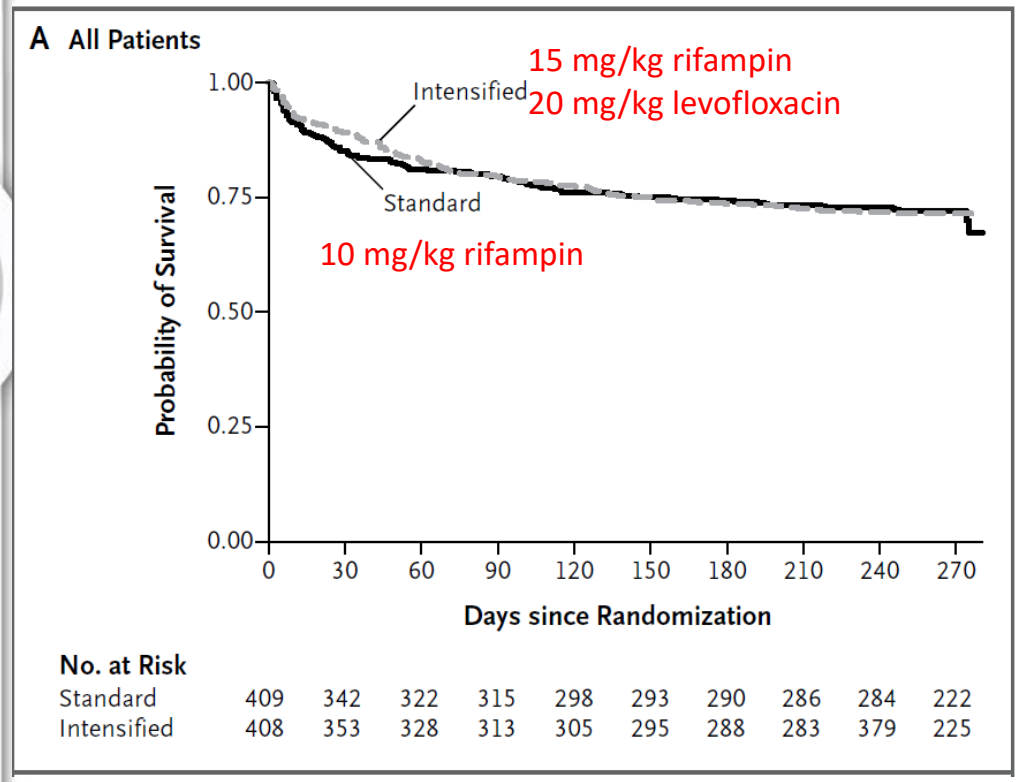
Drug	Forms	Oral bio-availability (%)	Food effect	Plasma protein binding (%)	CNS penetratior (%)
Levofloxacin	PO; IV	~100	None	24–38	70–80
Moxifloxacin	PO; IV	90	None	50	70–80
Ethionamide	PO	~100	None	~30	80–90
Cycloserine	PO	65–90	Slight decrease	~0	80–90

Table 2. (Continued).

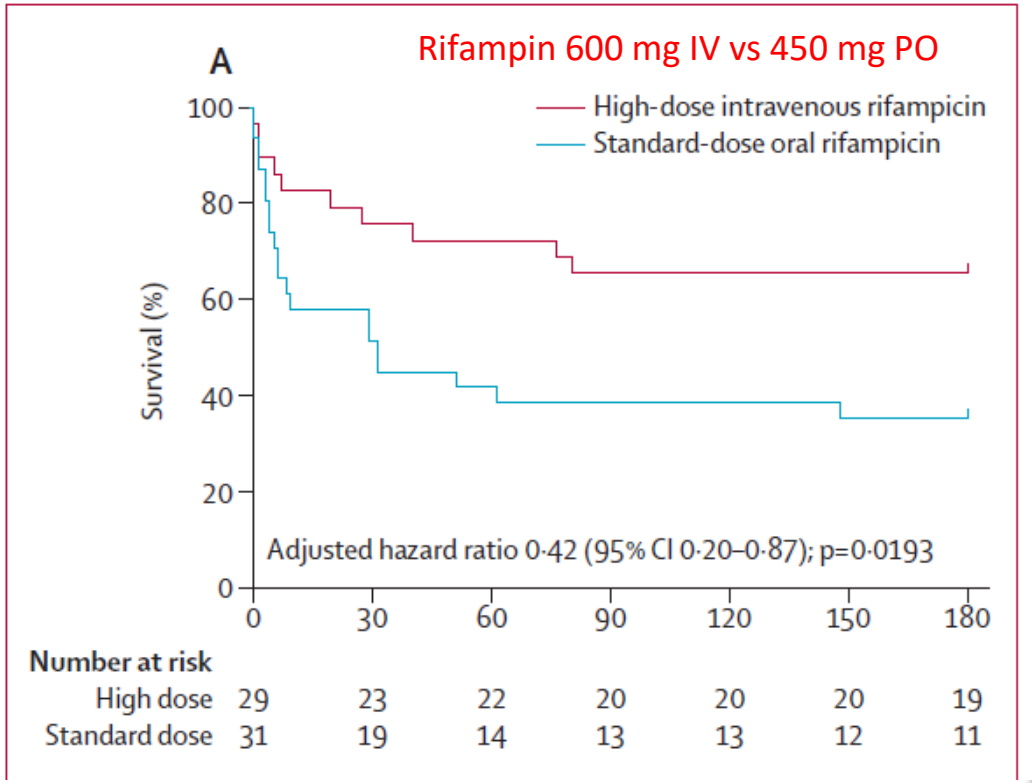
Drug	Forms	Oral bio-availability (%)	Food effect	Plasma protein binding (%)	CNS penetration (%)
Linezolid	PO; IV	~100	–23% with high-fat meals	31	70
Bedaquiline	PO	Unknown	Increase	>99	Likely poor (limited data)
Delamanid	PO	25–47	Increase	>99	No human data
Pretomanid	PO	Unknown	Increase	93	No human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

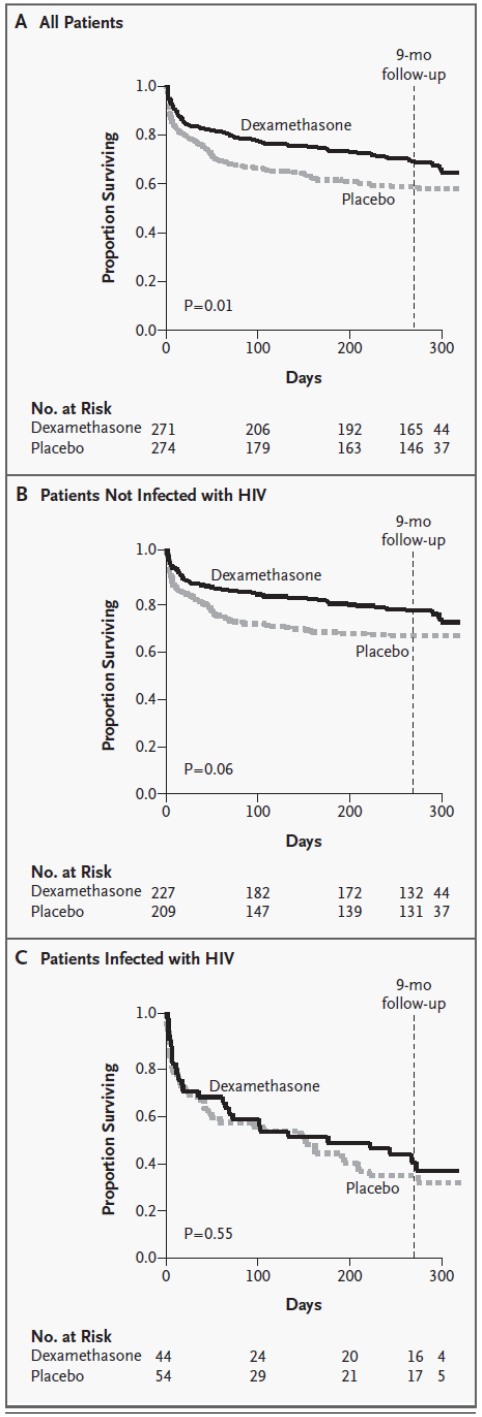
Guy E. Thwaites, M.R.C.P., Nguyen Duc Bang, M.D., Nguyen Huy Dung, M.D., Hoang Thi Quy, M.D., Do Thi Tuong Oanh, M.D., Nguyen Thi Cam Thoa, M.D., Nguyen Quang Hien, M.D., Nguyen Tri Thuc, M.D., Nguyen Ngoc Hai, M.D., Nguyen Thi Ngoc Lan, Ph.D., Nguyen Ngoc Lan, M.D., Nguyen Hong Duc, M.D., Vu Ngoc Tuan,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



Treatment of Drug Resistant TB

Standard of Care for Treatment of MDR TB pre-2019

- 20-24 months of treatment
- 6-8 months of an injectable
- 4-6 less effective second line drugs
- 50% cure, 10% mortality

BPaL Regimen (Nix Trial)

Bedaquiline-Pretomanid-Linezolid

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 5, 2020 VOL. 382 NO. 10

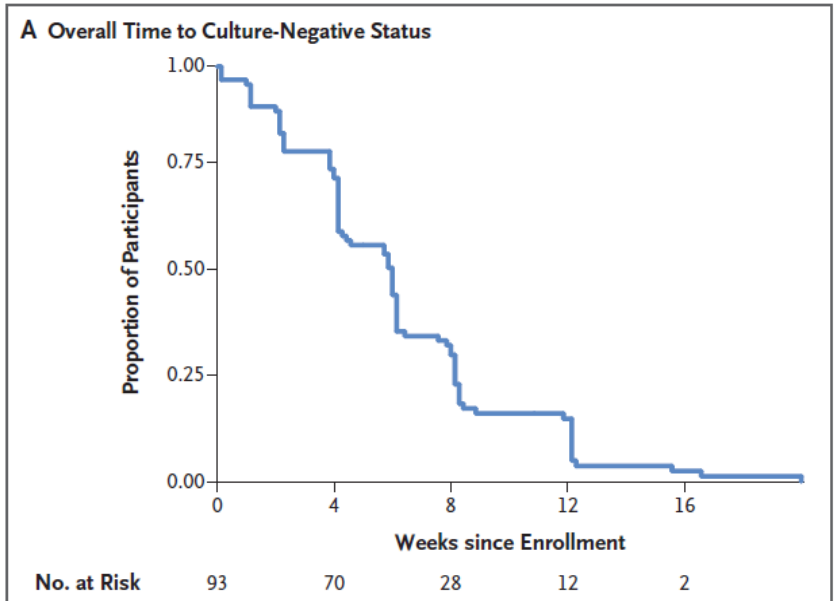
Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D., Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

- Open label, single group study
- All oral regimen
- 109 patients with MDR or XDR TB unresponsive to treatment or intolerant of other second line treatment
- Primary end point: unfavorable outcome

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Value (N=109)
Median age (range) — yr	35 (17–60)
Male sex — no. (%)	57 (52)
Race — no. (%)†	
Black	83 (76)
Mixed race	25 (23)
White	1 (1)
Median BMI (range)‡	19.7 (12.4–41.1)
HIV-positive — no. (%)	56 (51)
Median time since HIV diagnosis (range) — yr	4.0 (0.2–14.3)
Median CD4 cell count (range) — cells/mm^3§	343 (55–1023)
Cavities present on chest radiograph — no. (%)	
No	17 (16)
Unilateral	51 (47)
Bilateral	41 (38)
Karnofsky score — no. (%)¶	
100	9 (8)
90	50 (46)
80	29 (27)
70	19 (17)
60	2 (2)
<60	0
Median no. of tuberculosis drugs taken in month before enrollment (range)	7 (3–13)
Median time since original tuberculosis diagnosis (range) — mo	12 (<1–141)



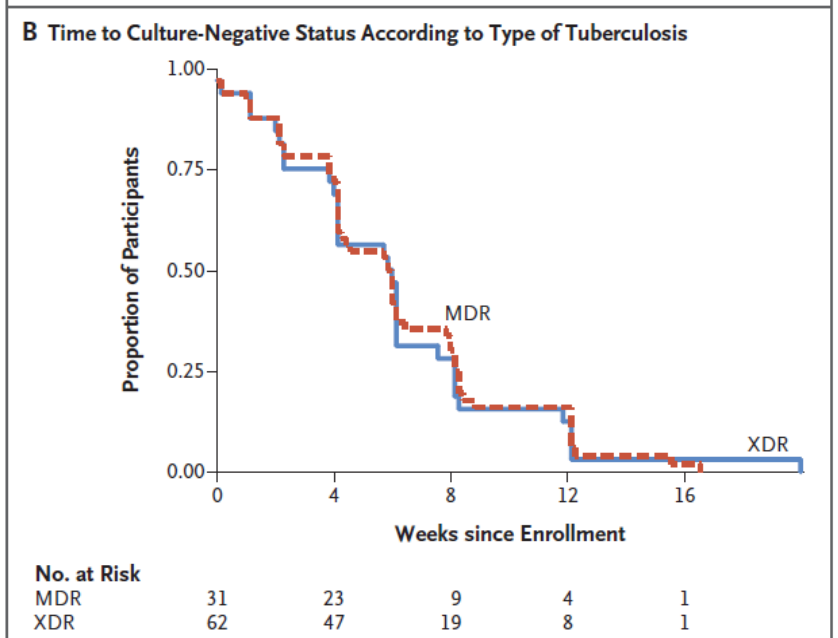


Figure 2. Time to Culture-Negative Status among Patients Who Were Positive at Baseline (Intention-to-Treat Population).

Table 2. Primary Efficacy Analysis.*

Outcome	XDR	MDR	Overall
Intention-to-treat population†			
No. of patients	71	38	109
Favorable outcome			
No. of patients	63	35	98
Percent of patients (95% CI)	89 (79–95)	92 (79–98)	90 (83–95)
Unfavorable outcome — no. (%)	8 (11)	3 (8)	11 (10)
Deaths — no.	6	1	7
Withdrawal during treatment — no.	1	0	1
Lost to follow-up after end of treatment — no.	0	1	1
Relapse — no.	1	1	2‡
Modified intention-to-treat population†			
No. of patients	70	37	107
Favorable outcome			
No. of patients	63	35	98
Percent of patients (95% CI)	90 (80–96)	95 (82–99)	92 (85–96)
Unfavorable outcome — no. (%)	7 (10)	2 (5)	9 (8)
Deaths — no.	5	1	6
Withdrawal during treatment — no.	1	0	1
Relapse — no.	1	1	2‡
Per-protocol population			
No. of patients	68	37	105
Favorable outcome			
No. of patients	62	35	97
Percent of patients (95% CI)	91 (82–97)	95 (82–99)	92 (86–97)
Unfavorable outcome — no. (%)	6 (9)	2 (5)	8 (8)
Deaths — no.	5	1	6
Relapse — no.	1	1	2‡

N Engl J Med 2020;382:893-902.

BPaL Adverse Events

Table 3. Adverse Events That Occurred or Worsened during Treatment.

Event*	HIV Status		Linezolid Regimen		Overall (N=109)
	Negative (N=53)	Positive (N=56)	600 mg Twice Daily (N=44)	1200 mg Daily (N=65)	
	number (percent)				
Adverse event	53 (100)	56 (100)	44 (100)	65 (100)	109 (100)
Adverse event leading to death	3 (6)	3 (5)	4 (9)	2 (3)	6 (6)
Serious adverse event	10 (19)	9 (16)	13 (30)	6 (9)	19 (17)
Grade 3 or 4 adverse event	27 (51)	35 (62)	27 (61)	35 (54)	62 (57)

* A patient could have had more than one type of event.

BPaL Adverse Events

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ZeNix Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

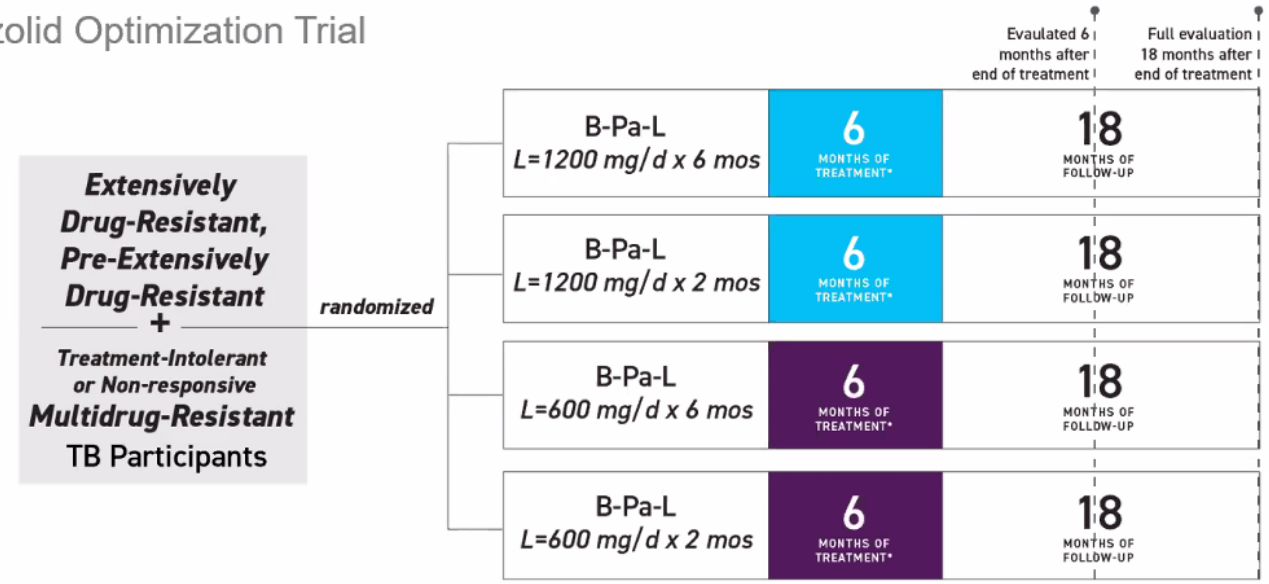
F. Conradie, T.R. Bagdasaryan, S. Borisov, P. Howell, L. Mikiashvili, N. Ngubane, A. Samoilova, S. Skornykova, E. Tudor, E. Variava, P. Yablonskiy, D. Everitt, G.H. Wills, E. Sun, M. Olugbosi, E. Egizi, M. Li, A. Holsta, J. Timm, A. Bateson, A.M. Crook, S.M. Fabiane, R. Hunt, T.D. McHugh, C.D. Tweed, S. Foraida, C.M. Mendel, and M. Spigelman, for the ZeNix Trial Team*

Study Design

IAS 2021 18–21 July

ZeNix

Linezolid Optimization Trial



*Additional 3 months if sputum culture positive between week 16 and week 26 treatment visits

Pa pretomanid dose = 200 mg daily
B bedaquiline dose = 200 mg x 8 weeks, then 100 mg x 18 weeks

Pre-2021 WHO Definitions of XDR-TB and Pre-XDR-TB

N Engl J Med 2022;387:810-23

ZeNix - Efficacy

Table 2. Primary End-Point Efficacy Analysis.*

Population and Outcome	Bedaquiline–Pretomanid–Linezolid Regimen				Total (N=181)
	Linezolid, 1200 mg, 26 wk (N=45)	Linezolid, 1200 mg, 9 wk (N=46)	Linezolid, 600 mg, 26 wk (N=45)	Linezolid, 600 mg, 9 wk (N=45)	
Modified intention-to-treat population					
Not assessable					
Violent or accidental death during treatment period — no.	0	1	0	0	1
Lost to follow-up during follow-up period — no.	1	0	0	0	1
Withdrawn for other reason during follow-up period — no.	0	0	0	1	1
All participants — no. (%)	1 (2)	1 (2)	0	1 (2)	3 (2)
Assessable — no. (%)	44 (98)	45 (98)	45 (100)	44 (98)	178 (98)
Favorable outcome — no./total no. (%)	41/44 (93)	40/45 (89)	41/45 (91)	37/44 (84)	159/178 (89)
95% CI for favorable outcome — %	81–99	76–96	79–98	70–93	84–93
97.5% CI for favorable outcome — %	—	74–97	77–98	—	—
Unfavorable outcome — no./total no. (%)	3/44 (7)	5/45 (11)	4/45 (9)	7/44 (16)	19/178 (11)
Confirmed relapse during follow-up period — no.†	0	2	1	1	4
Lost to follow-up during treatment period — no.	0	0	0	1	1
Retreatment during follow-up period — no.‡	2	0	1	1	4
Withdrawn during treatment period — no.					
Because of adverse event	1	1	0	2	4
Because of investigator or sponsor decision	0	0	1	0	1
Because of participant decision	0	2	1	1	4
Treatment failure during treatment period†	0	0	0	1	1
Intention-to-treat population					
Not assessable — no. (%)	0	0	0	0	0
Assessable — no. (%)	45 (100)	46 (100)	45 (100)	45 (100)	181 (100)
Favorable outcome — no./total no. (%)	41/45 (91)	40/46 (87)	41/45 (91)	37/45 (82)	159/181 (88)
95% CI for favorable outcome — %	79–98	74–95	79–98	68–92	82–92

ZeNix – Safety Analysis

Table 3. Safety Analysis.*

Variable	Bedaquiline–Pretomanid–Linezolid Regimen				Total (N = 181)
	Linezolid, 1200 mg, 26 wk (N = 45)	Linezolid, 1200 mg, 9 wk (N = 46)	Linezolid, 600 mg, 26 wk (N = 45)	Linezolid, 600 mg, 9 wk (N = 45)	
	number of participants (percent)				
≥1 Grade 3 or higher adverse event	14 (31)	11 (24)	9 (20)	11 (24)	45 (25)
≥1 Serious adverse event	3 (7)	4 (9)	1 (2)	3 (7)	11 (6)
Death from any cause	0	1 (2)	0	0	1 (1)
Tuberculosis-related death	0	0	0	0	0

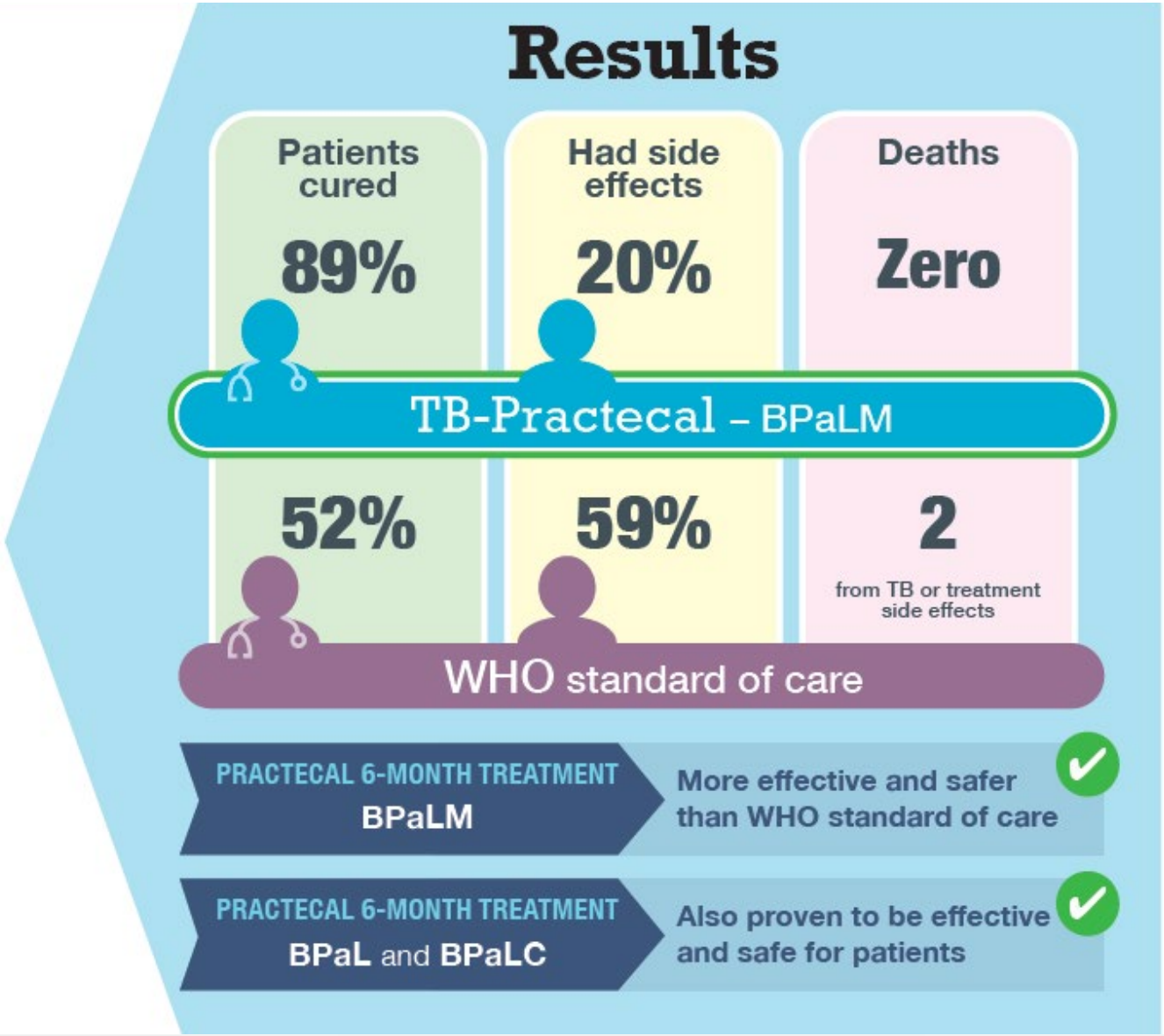
TB PRACTECAL

- Regimen 1:
- bedaquiline + pretomanid + linezolid + moxifloxacin for 24 weeks

- Regimen 2:
- bedaquiline + pretomanid + linezolid + clofazimine for 24 weeks

- Regimen 3:
- bedaquiline + pretomanid + linezolid for 24 weeks

TB PRACTECAL



Assessment of epidemiological and genetic characteristics and clinical outcomes of resistance to bedaquiline in patients treated for rifampicin-resistant tuberculosis: a cross-sectional and longitudinal study

Lancet Infect Dis 2022; 22: 496–506

Nazir Ahmed Ismail, Shaheed Vally Omar*, Harry Moultrie*, Zaheda Bhyat, Francesca Conradie, M Enwerem, Hannetjie Ferreira, Jennifer Hughes, Lavania Joseph, Yulene Kock, Vancy Letsaolo, Gary Maartens, Graeme Meintjes, Dumisani Ngcamu, Nana Okozi, Xavier Padanilam, Anja Reuter, Rodolf Romero, Simon Schaaf, Julian te Riele, Ebrahim Variava, Minty van der Meulen, Farzana Ismail†, Norbert Ndjeka†*

- 8041 patients starting bedaquiline-based treatment had samples collected at baseline, month 2, month 6
- Baseline BDQ resistance was 3.8%
  - BDQ naïve 72/2023, 3.6%
  - Prior BDQ or clofazimine, 4/19, 21.1%
- BDQ resistance was associated with previous exposure to bedaquiline or clofazimine (OR 7.1)
- Rv0678 mutations were associated with resistance
- Resistance emerged in 12/695 (2.3%) of patients on treatment with median time to emergence of 90 days (range 21-654 days)
- Successful treatment outcomes were lower in patients with bedaquiline resistance

TB Treatment Regimens

- TB Infection (LTBI)
  - 3HP, 4R, 3HR, 6H/9H
  - 1HP, 1.5P
- Drug susceptible TB
  - RIPE, HPMZ
- Drug resistant TB
  - Bedaquline, linezolid, FQ, pretomanid regimens

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

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/isoniazid for 2 more months
- Consider leaving all 4 drugs or at least INH/rifampin/EMB

M. bovis

- Unpasteurized milk products
  - Travel, food gifts from places where *M. bovis* rates are high
- 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*
- Treatment requires at least 9 months of therapy without PZA

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 HRZE 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

Criteria to Be Considered Noninfectious….. For now

Patients no longer considered infectious if:

- 3 consecutive negative sputum smears
  - collected at least 8 hours apart
  - one early morning specimen

- TB symptoms have improved, AND
- Adhering to adequate treatment regimen ≥ 2 weeks (one week if smear negative to start)
  - DOT – YES!
  - Do you know drug susceptibilities?

Questions?