MAYO CLINIC

Center for Tuberculosis

Tuberculosis (TB) Treatment Principles

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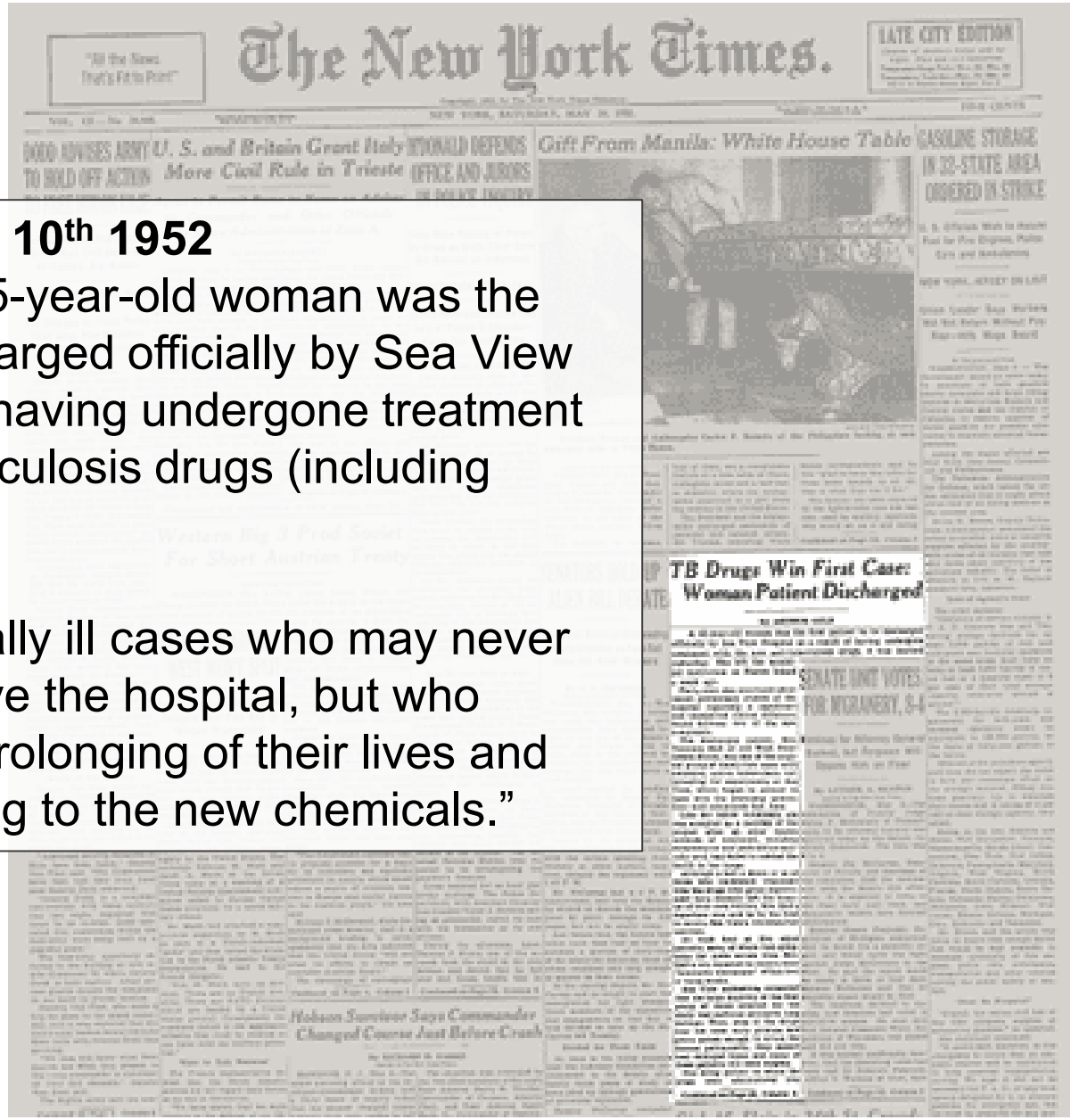
Learning Objectives

- Review current treatment protocols for managing drug-susceptible TB
- Identify clinical assessments to treat TB effectively
- Identify clinical monitoring strategies to treat TB effectively

New York Times, May 10th 1952

Mrs. Veronica Hall a 45-year-old woman was the first patient to be discharged officially by Sea View Hospital as a result of having undergone treatment with the new anti-tuberculosis drugs (including isoniazid)

“There are some critically ill cases who may never get well enough to leave the hospital, but who nonetheless owe the prolonging of their lives and their sense of well being to the new chemicals.”


The New York Times.

LATE CITY EDITION

Gift From Manila: White House Table

TB Drugs Win First Case: Woman Patient Discharged

https://www.nytimes.com/1952/05/10/archives/tb-drugs-win-first-case-woman-patient-discharged-new-tb-drugs-win.html

SIX-MONTH HRZE REGIMEN

SIX-MONTH HRZE REGIMEN

Intensive phase
2 months of INH, RIF, PZA, EMB

EMB can be discontinued once drug susceptibility results confirm susceptibility to INH and RIF

Continuation phase
4 months of INH and RIF

Extend continuation phase for an additional 3 months if cavitary disease and culture positive at end of intensive phase

- Once daily administration preferred throughout treatment
- Alternative intermittent 2-3 times per week dosing is not preferred (if done should be DOT only, confirmed drug susceptible TB, using both INH + RIF)

Saukkonen JJ et al. Am J Respir Crit Care Med 2025 Jan 1;211(1):15–33

DURATION OF TREATMENT

- Duration of the continuation phase depends on the microbiological status at the end of the intensive phase of treatment
- Risk factors for relapse
  - Positive sputum culture at completion of the intensive phase of treatment (2 months)
  - Cavitation on initial chest radiograph
- Cavitation + positive culture at 2 months → 20% relapse rate
- No cavitation + negative culture at 2 months → 2% relapse rate

Jo KW et al. Respir Med 2014; 108:654–9
Chang KC et al. Am J Respir Crit Care Med 2004; 170:1124–30

EXTENSION OF TREATMENT

- Extend continuation phase for an additional 3 months
  - Cavitation + positive culture at 2 months
  - PZA not used in regimen
- Consider extending continuation phase, if either cavitation *or* positive culture at 2 months and at least one of the following:
  - Greater than 10% below ideal body weight
  - Active smoker
  - Diabetes
  - HIV
  - Immunosuppression
  - Extensive pulmonary disease

Saukkonen JJ et al. Am J Respir Crit Care Med 2025 Jan 1;211(1):15–33

TREATMENT COMPLETION

- Intensive phase
  - 56 doses over minimum 8 weeks
  - Maximum 12 weeks
  - Restart treatment if more than 2 weeks missed

- Continuation phase
  - 126 doses over 18 weeks
  - Maximum 24 weeks (36 weeks if 7 month continuation phase)

Saukkonen JJ et al. Am J Respir Crit Care Med 2025 Jan 1;211(1):15–33

FOUR-MONTH RIFAPENTINE-MOXIFLOXACIN REGIMEN

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

PARTICIPANTS

Inclusion Criteria

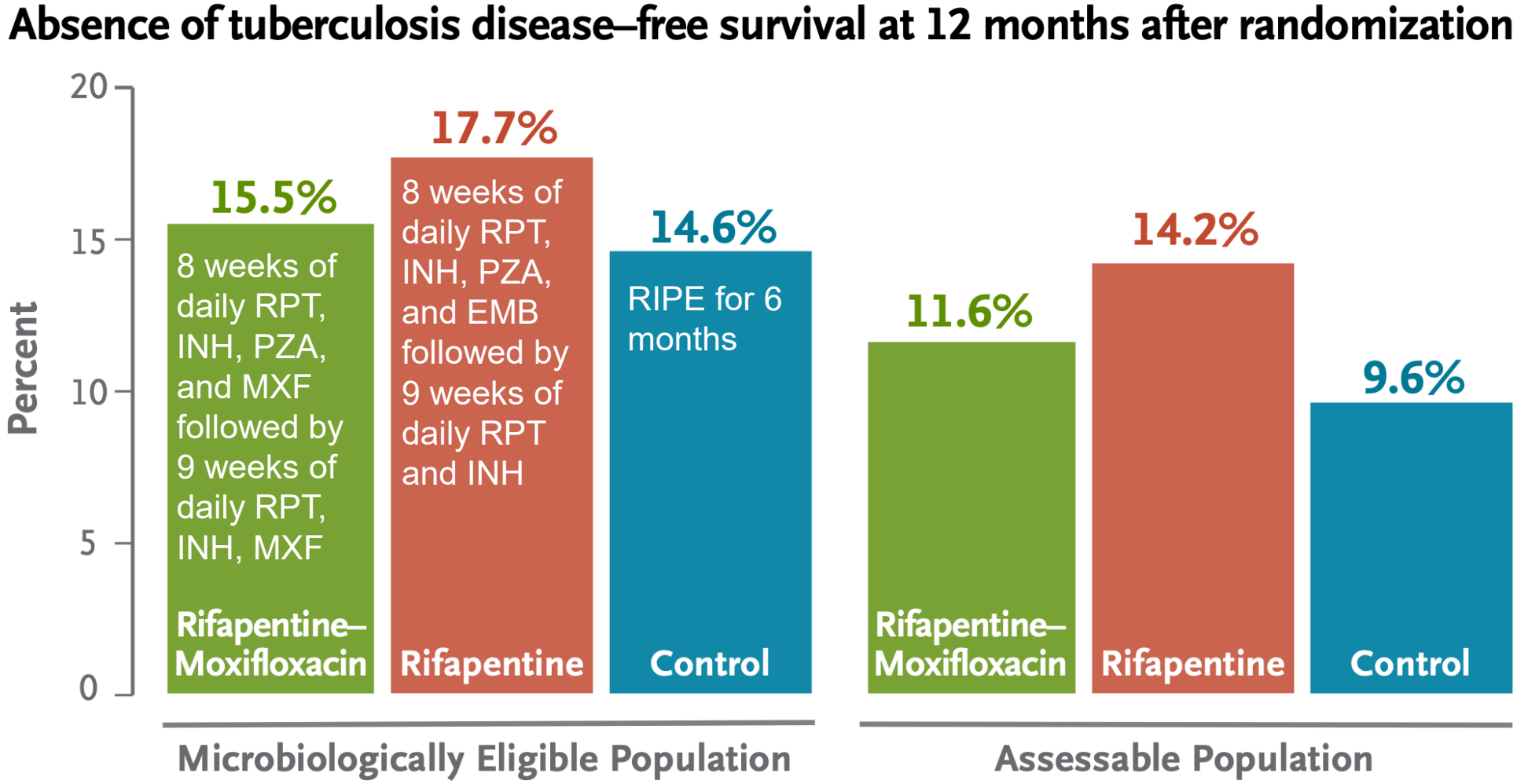
- Drug susceptible pulmonary tuberculosis
- Age 12 years or older
- Weight > 40 kg
- Positive acid-fast smear or NAAT
- HIV with CD4 ≥ 100, on or starting ART without clinically significant drug-drug interactions with HPMZ

Exclusion Criteria

- Pregnant or breastfeeding
- More than 5 days of TB or LTBI treatment within prior 6 months
- Prolonged QT syndrome
- Extrapulmonary TB
- Known drug resistance

Dorman SE et al. N Engl J Med 2021;384:1705–18

Open-label RCT of 2343 people with pulmonary drug susceptible TB, found no difference in outcomes between 4 months of of RPT-MXF therapy and 6 months of typical therapy



Dorman SE et al. N Engl J Med 2021;384:1705–18

ADVERSE EVENTS

- No difference in adverse events across treatment groups
  - Control group 19.3%
  - Rifapentine–moxifloxacin group18.8%
  - Rifapentine group 14.3%
- Similar transaminitis and DILI events across treatment groups
- Significant cardiac events in 3 participants in RPT-MXF group
  - 2 deemed to be unlikely to be related to drug
  - 1 with palpitations, borderline prolonged QT interval

Dorman SE et al. N Engl J Med 2021;384:1705–18

FOUR-MONTH RIFAPENTINE-MOXIFLOXACIN REGIMEN (2HPZM/2HPM)

Isoniazid	300 mg daily for 17 weeks
Rifapentine	1200 mg daily for 17 weeks
Pyrazinamide	Weight-based (actual BW) dosing daily for 8 weeks 40 - 55 kg: 1000 mg 55 - 75 kg: 1500 mg > 75 kg: 2000 mg
Moxifloxacin	400 mg daily for 17 weeks

DOT 5 of 7 days per week
Administer with food; avoid milk, antacids and other cations
Pyridoxine 25-50 mg daily with isoniazid

Saukkonen JJ et al. Am J Respir Crit Care Med 2025 Jan 1;211(1):15–33

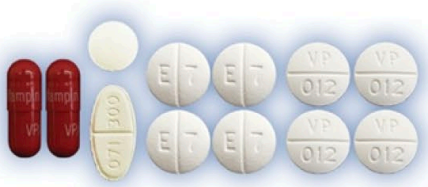
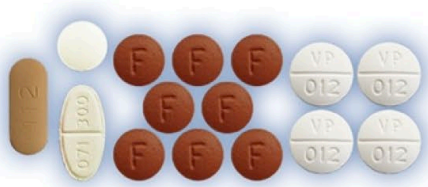
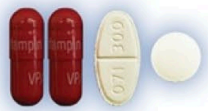
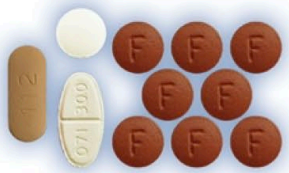
POTENTIAL BENEFITS

- Shorter duration may benefit patients and healthcare systems
- Smear conversion at 8 weeks
  - Standard 63%
  - RPT/MXF 78%
- Different drug-drug interactions

Saukkonen JJ et al. Am J Respir Crit Care Med 2025 Jan 1;211(1):15–33

POTENTIAL DRAWBACKS

- Higher daily pill burden: 1 INH, 8 RPT, 1 MXF, 1 pyridoxine + weight based PZA

	Standard Regimen (HRZE) >75Kg	Short course regimen (HPMZ) >75Kg
Intensive Phase	8 weeks  Isoniazid Rifampin Pyrazinamide Ethambutol Vitamin B6	8 weeks  Isoniazid Rifapentine Moxifloxacin Pyrazinamide Vitamin B6
Continuation Phase	16-28 weeks  Isoniazid Rifampin Vitamin B6 Photos courtesy of George Lee, RN	9 weeks  Isoniazid Rifapentine Moxifloxacin Vitamin B6

https://www.tbcontrollers.org/docs/resources/4-Month-HPMZ-TB-Regimen_NTCA-FAQ.pdf

POTENTIAL DRAWBACKS

- Higher daily pill burden
- Requires food for optimal absorption
- Different drug-drug interactions
- Programmatic cost
- Potential fluoroquinolone side effects may be more common in low incidence settings (older, comorbidities, other QTC prolonging medications)
- No data on drug substitutions
- No data on extension of therapy
- Cannot swap from RIPE or give credit for doses from another regimen

Saukkonen JJ et al. Am J Respir Crit Care Med 2025 Jan 1;211(1):15–33

TREATMENT COMPLETION

- Intensive phase: 56 doses
  - 8 weeks
  - Must be completed within 70 days
- Continuation phase: 63 doses
  - 9 weeks
  - Must be completed within 84 days
- Total: 119 doses
  - 17 weeks
  - Must be completed within 22 weeks
- No data on treatment extension, drug or regimen changes

Preferred treatment if:

- Age ≥ 12 years
- Body weight ≥ 40 kg (88 lb)
- Pulmonary tuberculosis
- Drug susceptible tuberculosis
- No other contraindications or medication interactions

Consider alternative if:

- Age <12 years and ≥ 75 years
- Prolonged QTc, long QT syndrome
- Weight < 40 kg (88 lb)
- Pregnancy, breastfeeding (limited data)
- Advanced liver disease (INH + PZA)
- Advanced kidney disease (limited data)
- Drug interactions
- Extensive pulmonary TB disease
- Extrapulmonary TB disease

TB DRUGS

ISONIAZID

- Dose: 300 mg daily
- Adverse effects
  - Peripheral neuropathy
  - Hepatotoxicity
  - Less common
    - GI (nausea, abdominal pain)
    - CNS (seizures, dysphoria, irritability)
    - Drug induced lupus (Positive ANA 20%, clinical lupus <1%)
    - Optic neuritis
    - Hypersensitivity Reactions: fever, rash
- Potential drug interactions: Carbamazepine, phenytoin, valproate, warfarin

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RIFAMPIN

- Dose: 10 mg/kg/d (usually 600 mg daily)
- Orange discoloration of body fluids
- Adverse effects
  - GI (anorexia, nausea, abdominal pain)
  - Less common
    - Rash
    - Hepatotoxicity (cholestatic)
    - Leukopenia, thrombocytopenia, hemolytic anemia
- Potential drug interactions
  - Strong inducer of P-gp, cytochrome P450
  - Interactions with HIV antiretrovirals, hormonal contraceptives, warfarin, DOACs, levothyroxine, many other medications…

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RIFAPENTINE

- Dose: 1200 mg daily
- Generally well tolerated
- Similar adverse effects to rifampin
- Potential drug interactions – inducer cytochrome P450

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RIFABUTIN

- Similar adverse effects to rifampin
- Uveitis – rare, dose related
- Generally weaker enzyme induction and drug interactions

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PYRAZINAMIDE

- Dose
  - 40-55 kg 1000 mg daily
  - 56-75 kg 1500 mg daily
  - 76-90 kg 2000 mg daily
- Adverse effects
  - GI (nausea, vomiting)
  - Hepatoxicity
  - Asymptomatic hyperuricemia (inhibits uric acid excretion at renal tubules)
  - Polyarthralgia (up to 40%, can continue drug)
  - Acute gout flares – with pre-existing gout

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ETHAMBUTOL

- Dose
  - 40-55 kg 800 mg daily
  - 56-75 kg 1200 mg daily
  - 76-90 kg 1600 mg daily

- Optic neuropathy
  - Change in visual acuity, red-green color blindness
  - Typically after 3-5 months of therapy
  - Reversible in most

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MOXIFLOXACIN

- Dose: 400 mg daily
- Adverse effects
  - GI (nausea, discomfort, bloating)
  - QTc prolongation
  - Tendinopathy, rupture (MFX > LFX)
  - CNS – anxiety, confusion, insomnia, irritability
  - Lower seizure threshold

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MONITORING ON TREATMENT

BASELINE EVALUATION

Clinical Assessment

- Symptom review
- Weight, nutritional status
- On EMB: Baseline visual acuity and color discrimination

Labs

- AST, ALT, ALP, bilirubin, creatinine, platelets
- HIV screen
- If at risk: hepatitis B (IVDU; born in Asia, Africa etc) and hepatitis C screen (IVDU, high risk sex behavior)
- Diabetes screen if at risk (age >45, BMI >25, first degree relative, ethnicity)

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BASELINE EVALUATION

Microbiology

- Sputum smear, culture
- Phenotypic drug susceptibility for first line TB drugs
- Rapid molecular drug resistance test (GeneXpert)

Imaging: Chest radiograph or other imaging

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MONITORING ON TREATMENT

Monthly Clinical Assessment

- Symptom review
  - Improvement in TB symptoms (cough, fever, fatigue, night sweats)
  - Symptoms concerning for drug adverse effects (jaundice, nausea, vomiting, abdominal pain, dark urine, rash, fever, neuropathy)
- Weight – adjust drug doses if needed
- On EMB: Monthly color discrimination, inquiry about visual disturbance

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MONITORING ON TREATMENT

Microbiology

- Monthly sputum smear and culture until 2 consecutive negative specimens
- Consider more frequent sputum testing (every 2 weeks) to assess early response to treatment
  - Smear positive at diagnosis
  - High risk of transmission
- Sputum smear and culture at completion of month 2 of therapy
- Obtain phenotypic and molecular drug susceptibility testing if culture positive after 3 months of appropriate TB therapy
- Positive smear + negative culture may reflect non-viable bacilli…not treatment failure…

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MONITORING ON TREATMENT

Labs

- Consider monthly AST, ALT, ALP, bilirubin, creatinine, platelets
  - Abnormal at baseline
  - Risk of liver disease (alcohol, HBV, HCV, HIV, liver disease, prior DILI)

Imaging

- Negative culture at diagnosis - repeat chest radiograph at 2 months and completion of therapy to assess for improvement
- Positive culture at diagnosis – consider repeat chest radiograph at 2-3 months and completion of therapy
- Consider EPTB imaging at end of treatment

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Baseline and Follow-up Evaluations on TB Treatment

Activity	Baseline	Month of Treatment Completed 1	2	3	4	5	6	7	8	End of Treatment Visit
MICROBIOLOGY										
Sputum smears and culture[1]	☐	☐	☐	☐	☐					☐
Drug susceptibility testing[2]	☐			☐						
IMAGING										
Chest radiograph or other imaging[3]	☐		☐							☐
CLINICAL ASSESSMENT										
Weight[4]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Symptom and adherence review[5]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Vision assessment[6]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
LABORATORY TESTING										
AST, ALT, bilirubin, alkaline phosphate[7]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Platelet count[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Creatinine[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
HIV[9]	☐									
Hepatitis B and C screen[10]	☐									
Diabetes Screen[11]	☐									

Shaded boxes are optional or contingent on other information

ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Inf Dis 2016;63(7):e147–95

DRUG ADVERSE EFFECTS

GI ADVERSE EFFECTS

- Common, especially early in treatment
- Nausea, vomiting, abdominal pain ⇢ physical examination, LFTs
- Evaluate for potential serious adverse effects (hepatotoxicity)
- Strategies: Bedtime administration, antacids
- Consider PPi, light low-fat snack

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HEPATOTOXICITY

- Most frequent serious drug adverse effect
- Evaluate for biliary disease, alcohol, pre-existing liver disease, other hepatotoxic drugs and supplements, viral hepatitis (A, B, C)
- PZA, INH, RIF
- Approach depends on:
  - Severity of TB disease - disseminated or CNS disease?
  - Immune compromised host?
  - Critically ill?

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HEPATOTOXICITY

- If not stable for drug holiday, consider liver sparing regimen (EMB, MXF, RIF, LFX, amikacin, linezolid…)

- If stable enough for drug holiday:
  - Hold all TB drugs if drug induced liver injury
    - ALT ≥3 x upper limit of normal with hepatitis symptoms
    - ALT ≥5 x upper limit of normal without hepatitis symptoms
  - Restart TB drugs sequentially once ALT < 2 x upper limit of normal
    - One week apart with ALT monitoring
    - RIF → INH → if tolerated, presume PZA related
    - If PZA not resumed, consider extending treatment to 9 months

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RASH

- Uncomplicated pruritic rash without systemic symptoms
  - Symptomatic management with antihistamines
  - Continue TB drugs
- Petechial rash
  - Consider rifamycin related thrombocytopenia
- Generalized erythematous rash, fever, mucus membrane involvement
  - Consider more severe systemic reaction (SJS, TENS, hypersensitivity syndrome, DRESS etc)
  - May require systemic corticosteroid treatment
  - Consider inpatient monitoring with stepwise drug rechallenge every 2-3 days after improvement in rash (RIF > INH > EMB > PZA)

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TREATMENT INTERRUPTIONS & FAILURE

TREATMENT INTERRUPTIONS

- Interruptions are common
- Greater impact of interruption
  - Earlier in treatment
    - Highest bacillary load and chance of developing drug resistance
  - Longer duration of interruption
  - Bacteriologic status

Interruption in intensive phase	< 14 days	Complete planned total number of doses (as long as all doses completed within 3 months)
	≥ 14 days	Restart treatment from beginning
Interruption in continuation phase	≥80% of doses received and negative initial sputum smear	Further treatment may not be needed
	≥80% of doses received and positive initial sputum smear	Continue treatment until all doses completed
	<80% of doses received and cumulative lapse < 3 months	Continue treatment until all doses completed. If cannot be completed within recommended time frame, restart from intensive phase.
	<80% of doses received and cumulative lapse ≥ 3 months	Restart treatment from intensive phase onwards

ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Inf Dis 2016;63(7):e147–95

TREATMENT FAILURE

- Positive cultures after 4 months of treatment

⚐ Delayed culture conversion (> 2 months), worsening symptoms or imaging at 2 months

- Higher risk: Cavitary, extensive, diabetic
- Repeat drug susceptibility testing (molecular and culture based)
- Don’t add a single new drug to a failing regimen

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TREATMENT RELAPSE

- Cultures convert and remain negative on treatment, then develop positive cultures or clinical/radiologic disease consistent with active TB disease after completion of treatment
- Most occurs within 6-12 months of completing treatment
- Increased risk of acquired drug resistance

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APPROACH TO POSSIBLE TREATMENT FAILURE

- Assess adherence
- Assess for development of drug resistance
  - Repeat molecular and culture-based drug susceptibility testing
- Assess for malabsorption
- Assess for drug-drug interactions affecting exposure
- Therapeutic drug monitoring
  - Severe GI issues (gastroparesis, short bowel, chronic diarrhea with malabsorption)
  - Drug-drug interactions may be affecting drug exposure
  - Impaired renal clearance

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EXTRAPULMONARY TUBERCULOSIS

EXTRAPULMONARY DRUG SUSCEPTIBLE TB

- Total treatment duration of 6-9 months is adequate for most drug susceptible extrapulmonary tuberculosis
- Once daily (rather than intermittent) dosing is recommended
- Sputum specimens should be obtained if pulmonary involvement
- Treatment response typically based on clinical and imaging findings

EPTB site	Duration	
Pleural	6 months	No role for routine corticosteroids
Lymph node	6 months	
Pericardial	6 months	Consider adjunctive corticosteroids if early signs of constriction, large pericardial effusion, high inflammatory cells in pericardial fluid
Bone, joint, spine	6-9 months	Consider extending total treatment duration to 12 months if extensive hardware present No additional benefit to debridement for uncomplicated spinal TB
GI TB	6 months	
GU TB	6 months	
Disseminated	6 months	
TB meningitis	12 months	Adjunctive corticosteroids tapered over 6-8 weeks High morbidity & mortality

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TUBERCULOSIS SURVIVORS & ADVOCATES

https://www.weareetb.com

Summary

- Recommended treatment for drug susceptible TB
  - 4-month HPMZ for select cases
  - 6-month HRZE
    - Extend continuation phase for an additional 3 months if cavitary disease and culture positive at end of intensive phase
- Daily oral therapy is preferred to intermittent 1-3 times weekly therapy

RESOURCES

ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

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NTCA Guidance on HPMZ 4-month regimen

https://www.tbcontrollers.org/resources/hpmz-4-month-regimen/