Treatment of TB Disease

Treatment of Tuberculosis

- Responsibility for the successful treatment is assigned to the health care provider, **not** to the patient
- Focus on individual case management with directly observed therapy (DOT)
  - Case management is a patient-centered strategy
  - Case managers are responsible for ensuring that patients are educated about TB and treatment, ensuring that therapy is continuous and complete, and confirming that all contacts are evaluated
  - DOT is a component of case management that helps ensure patients adhere to therapy
- Tailoring treatment regimens to individual patient circumstances

Treatment of TB: Objectives

- The treatment of TB is centered on curing the individual patient and decreasing the transmission of TB bacteria to other people
- The objectives of TB therapy are:
  - Cure the individual patient and minimize risk of death and disability
  - Reduce transmission of *M. tuberculosis* to other persons
  - Prevent the development of drug resistance during therapy

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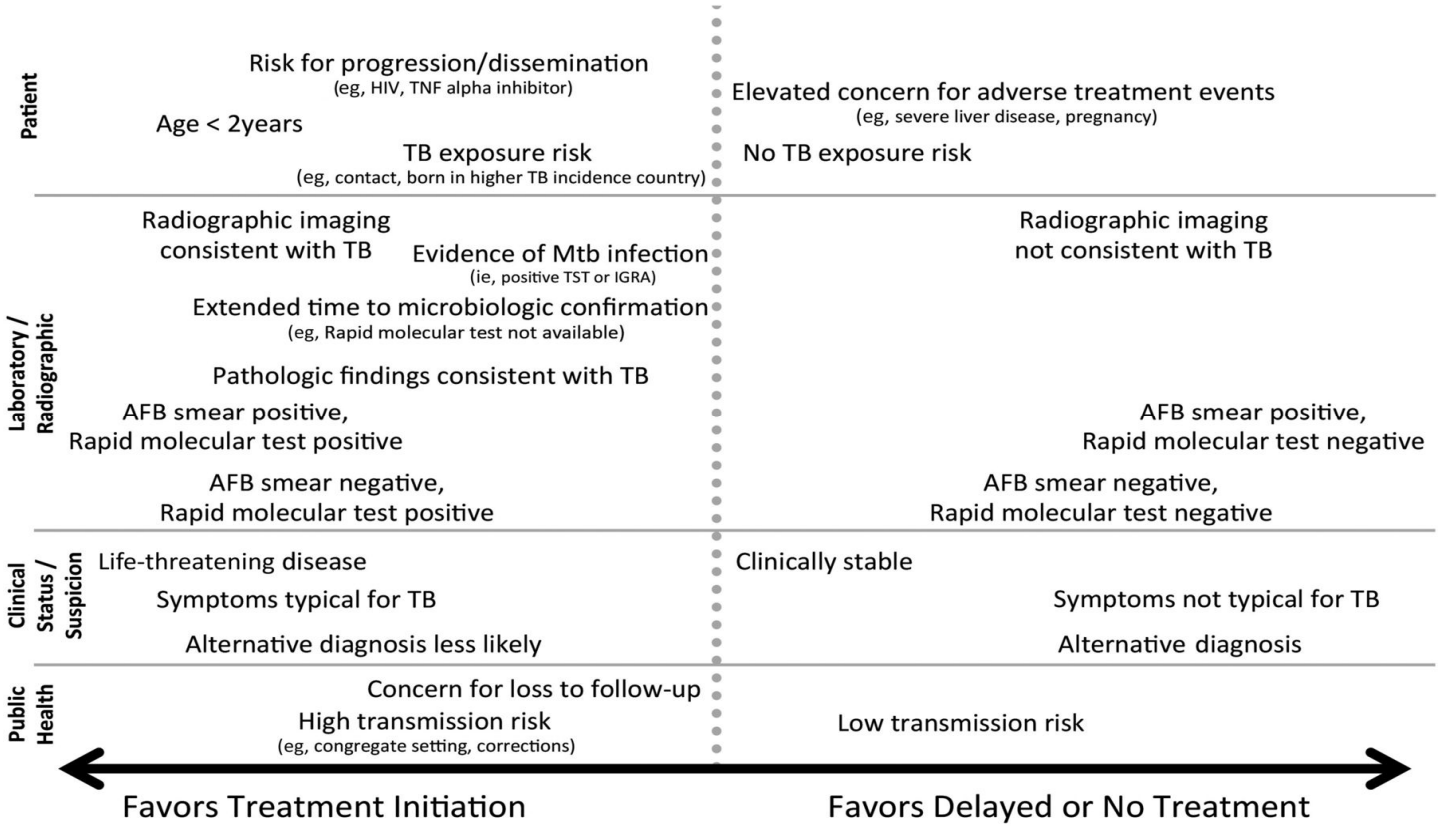
Goals of Anti-TB Therapy

- Rapid killing of tubercle bacilli
- Minimize potential for organisms to develop drug resistance: Combination chemotherapy
- Sterilize host tissues: Sufficient length of treatment
- Result: Patient is cured with very small likelihood of relapse

Initiation of Therapy

- Often is based on high index of suspicion
  - Do not delay treatment waiting for smear and culture results, especially in ill and vulnerable patients
  - Absence of AFB on smear or granulomas on biopsy does not rule out tuberculosis, nor does negative TB culture
  - A positive TST or IGRA is only supportive, may be negative in 15-25% of cases

Figure 1. Factors to be considered in deciding to initiate treatment empirically for active tuberculosis



Clin Infect Dis, Volume 63, Issue 7, 1 October 2016, Pages e147–e195, https://doi.org/10.1093/cid/ciw376

Drugs in Current Use

First-line	**Second-line**	**xxx-line**
Isoniazid (INH)	Cycloserine	Linezolid*
Ethambutol (EMB)	Levofloxacin*	Bedaquiline
Rifampin (RIF)	Ethionamide	Pretomanid
Rifabutin* (RBT)	Moxifloxacin*	
Rifapentine (RPT)	*p*-Aminosalicylic acid (PAS)	
Pyrazinamide (PZA)	Capreomycin	
Streptomycin (SM)	Gatifloxacin*	
	Amikacin/Kanamycin*	

** Not approved by FDA for use in tuberculosis*

2017

Role of Multi-Drug Therapy

- Drugs differ in their activity against TB
- Standard of care is weight based four-drug therapy (Rifampin, Isoniazid, Pyrazinamide, Ethambutol – RIPE)
- Kill actively multiplying bacteria (initial phase)
  - Most bacteria are killed during the first 8 weeks of treatment
  - Improve symptoms & prevent death
  - Prevent transmission to others
  - Prevent emergence of resistance
- Sterilize disease sites (continuation phase)
  - Persistent organisms targeted
  - Cure the disease

Why Do We Use These Drugs?

- Each drug has a special role in TB therapy
  - Isoniazid (H, INH): Early bactericidal activity (kill the dividing bacteria)
  - Rifampin (R, Rif): Sterilizing activity (prevents relapse)
  - Pyrazaminide (Z, PZA): Special “shortening” activity
  - Ethambutol (E, EMB): Fortify the regimen to prevent drug resistance

TB Treatment Phases

Phase	Purpose	Treatment
Initial phase	• Kills most of the tubercle bacilli during the first 8 weeks of treatment, but some bacilli can survive longer • Prevents the emergence of drug resistance • Determines the ultimate outcome of the regimen	Initial 2-month treatment regimen • Includes four drugs in the treatment (usually INH, RIF, PZA, and EMB) • Each of the drugs plays an important role for short-course regimens with high cure rates • Multiple drugs are needed to prevent the development of drug-resistant TB disease
Continuation phase	• Kills remaining tubercle bacilli (after initial phase) • If treatment is **not** continued long enough, the surviving bacilli may cause TB disease in the patient at a later time	An addition of either 4 or 7 months of treatment • 4 months is used for majority of patients • 7 months is recommended only for persons » Who have drug-susceptible cavitary or extensive pulmonary TB disease and whose sputum culture obtained at the time of completion of 2 months of treatment is positive » Whose initial phase of treatment did **not** include PZA
Treatment completion	Defines the number of doses ingested within a specified time frame Duration depends on • Drugs used • Drug susceptibility test results of the isolate • Patient's response to therapy	Most patients with previously untreated pulmonary TB disease can be treated with • 6-month regimen (preferred) containing INH, RIF, and initially PZA • 4 month RPT/Moxi containing regimen – in certain pt populations

Treatment & Monitoring Plan

- Treatment and monitoring plan should be developed for the individual patient and include:
  - Description of the TB treatment regimen
  - Methods of assessing and ensuring adherence to the TB treatment regimen
  - Methods to monitor for adverse reactions
  - Methods for evaluating treatment response

Baseline Monitoring

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]	☐									

- Before starting treatment, adult patients should have certain baseline blood and vision tests to help detect any underlying problems that may complicate treatment
- For children, only vision tests are necessary unless there are other medical conditions that may complicate treatment

ATS/IDSA/CDC 2016 Treatment Guidelines

Monitoring During Treatment

Patient	Recommended Test
All patients	Repeat at least monthly clinical evaluations to • Identify possible adverse reactions to medications • Assess adherence
Patients who are taking EMB	• Question monthly regarding visual disturbances • . JIOCGT >JGJM?IN>MH DI<OJI O@NON
Patients who have extrapulmonary TB disease	Evaluation depends on • Sites involved • Ease with which specimens can be obtained

Evaluating Response to Treatment

- Important to evaluate the patient's response to treatment
- Patients should have monthly clinical evaluations to:
  - Identify possible adverse drug reactions
  - Assess adherence
  - Determine treatment efficacy

Response to Treatment

- May be rapid (days)
  - Signs/symptoms
- Expect > 90% sputum culture conversion by 3 months
- ~70% by 2 months
  - If slow conversion – evaluate and consider longer treatment
- Allow return to home/work environment based on individual considerations
  - Infectiousness of case (look for clinical response, declining organisms on smear)
  - Risk of others becoming infected (contacts)

Response to Treatment for Pulmonary TB Disease

Bacteriologic Status	Recommendations for Response to Treatment
Positive sputum cultures prior to treatment	• Obtain specimens for culture at least monthly until two consecutive specimens are negative on culture • Perform monthly sputum AFB smears and cultures on MDR TB patients for entire course of treatment • A repeat chest radiograph after 2 months of treatment may be useful but is **not** essential
Negative sputum cultures prior to treatment	• Repeat chest radiograph at intervals based on clinical circumstances and differential diagnosis • If radiograph does not improve after patient has received 2 months of treatment, abnormality may be due to » Previous (not current) TB disease » Another reason
Cultures have **not** become negative after 3 months of therapy	Reevaluate for • Potential drug-resistant disease • Potential failure to adhere
Cultures are still positive after 4 months of treatment	Consider as having failed treatment and manage accordingly

Follow-up Evaluations

- For pulmonary TB
  - Sputum smear/culture monthly until 2 consecutive samples are culture negative
    - Repeat drug susceptibility testing, other investigations, if culture-positive still at 3 months
  - If initial culture positive - consider repeat CXR at 2 mos, and consider CXR at completion of therapy
  - If initial culture negative – perform 2 mos CXR to assess response; consider CXR at completion of therapy
- For extra-pulmonary TB
  - Frequency and types of evaluations depend on site

Hospital Discharge Planning

- Start when TB diagnosed or suspected:
  - Clinical/laboratory evidence or patient on TB drugs
- Pre-discharge conference:
  - Include nurse case manager, providers, discharge planners
- Home assessment by nurse case manager necessary to:
  - Prevent putting potentially vulnerable household members at-risk - especially children
  - Coordinate community follow-up for continuation and completion of therapy

Case management / Monitoring

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										
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https://academic.oup.com/cid/article/63/7/e147/2196792?login=true

TB Treatment Guidelines, CID, 2016

Factors that Lead to Drug Resistance

- Birth/ residence in country with high incidence of drug resistant TB
- U.S. residents who travel to high-risk areas
- Exposure to patient with relapse or failure
- Previous episode of TB treatment

- Inadequate treatment regimen for TB
- Relapse/Failure in a patient not on DOT
- Poor adherence
- Malabsorption

Completion of Therapy

- Completion of treatment primarily defined by number of ingested doses within specified time frame (not solely on duration of therapy)
- For example:
    1. 6-month daily regimen (7 days/wk) = at least 182 doses of INH and RIF, and 56 doses of PZA
    2. 6-month daily regimen (5 days/wk) = at least 130 doses

Completion of Therapy

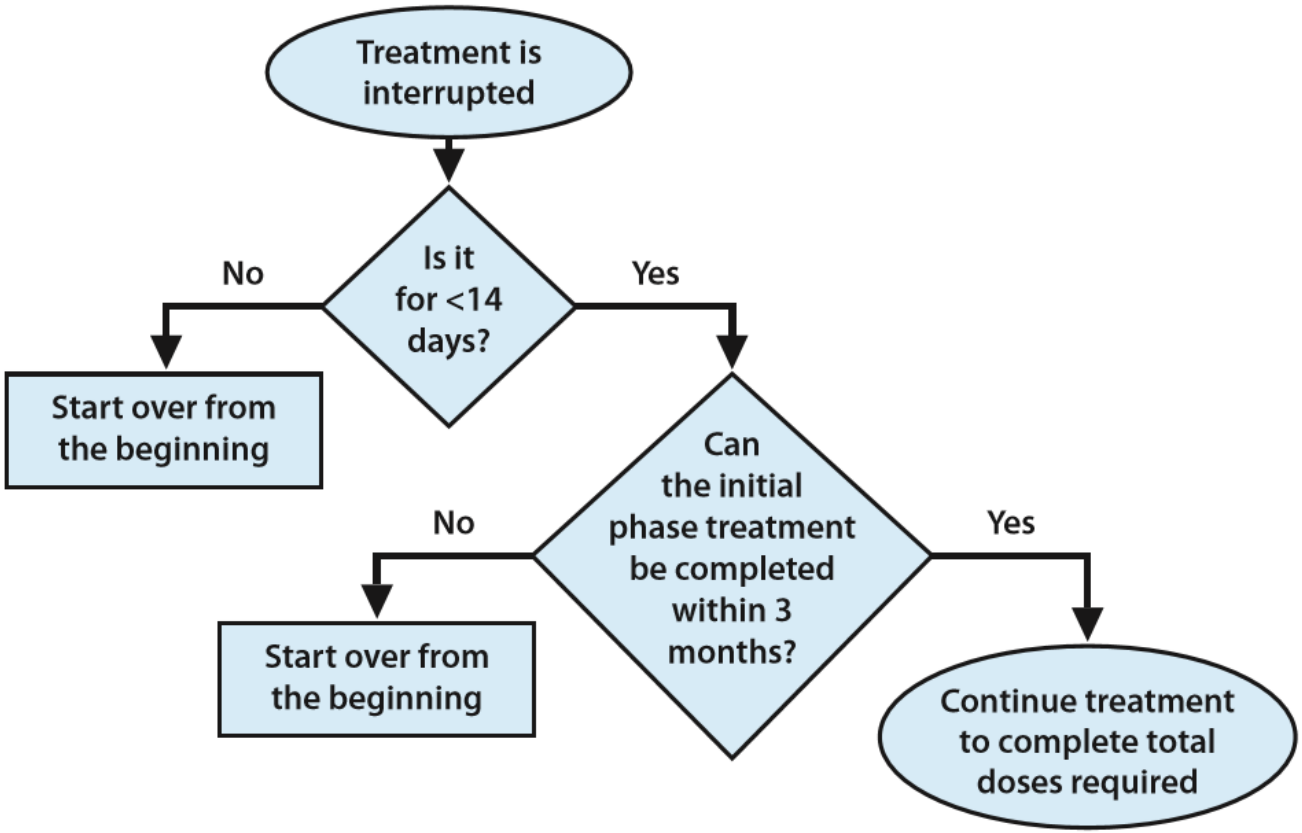
- In cases of drug toxicity or non-adherence to regimen or other interruptions, all specified number of doses must be administered within:
  - 3 months for initial phase
  - 6 months for 4-month continuation phase

- If the specified number of doses is not administered within the targeted time period, patient is considered to have interrupted therapy

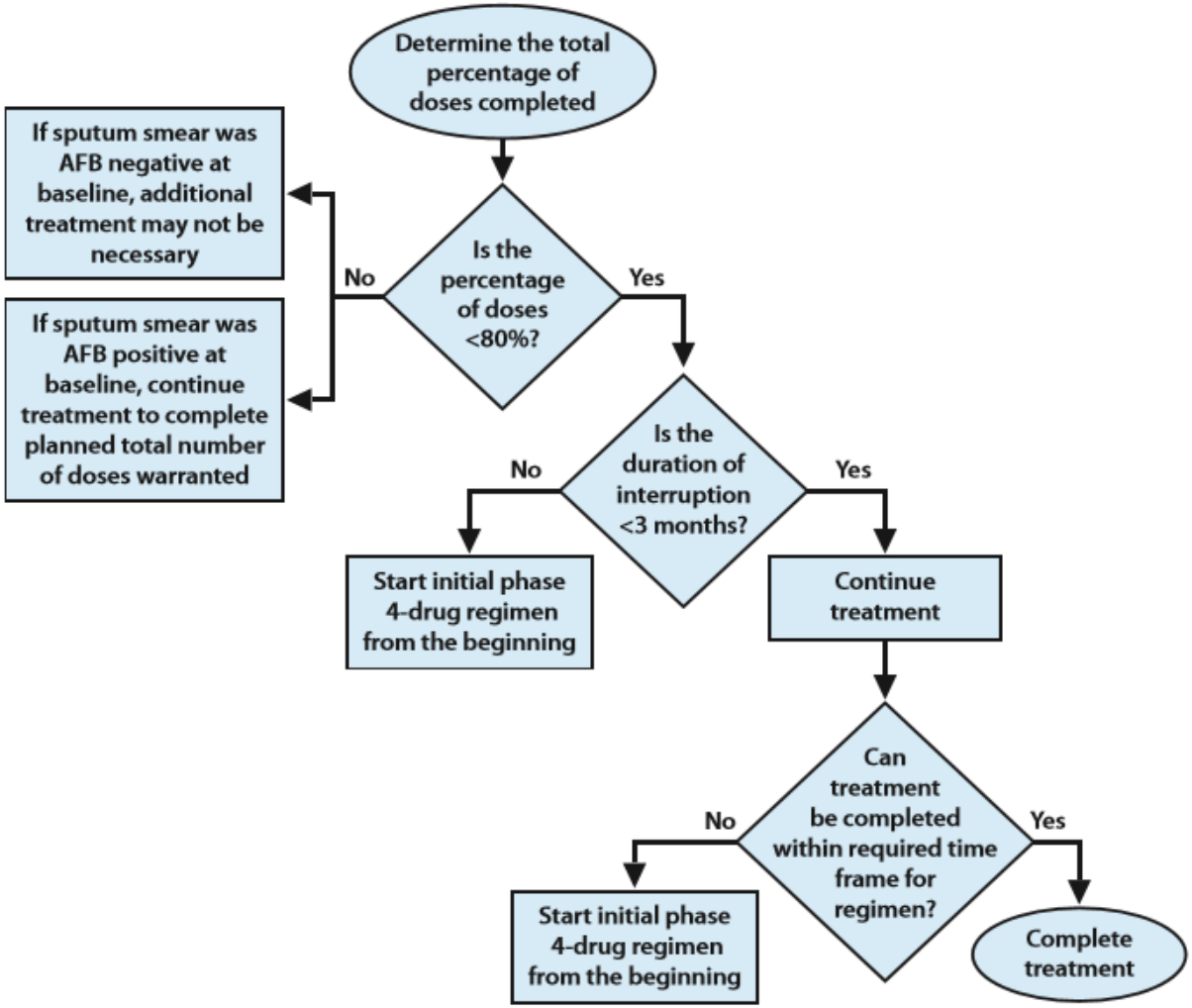
Interruptions in Therapy

- Interruptions in the treatment of TB disease are common
- Decisions about restarting or continuing treatment should be based on when the interruption occurred (intensive v continuation phase) and the duration of the interruption
- Different guidance applies depending on whether interruption occurred during the initial phase or continuation phase

Algorithm for Management of Initial Phase Treatment Interruptions



Algorithm for Management of Continuation Phase Treatment Interruptions



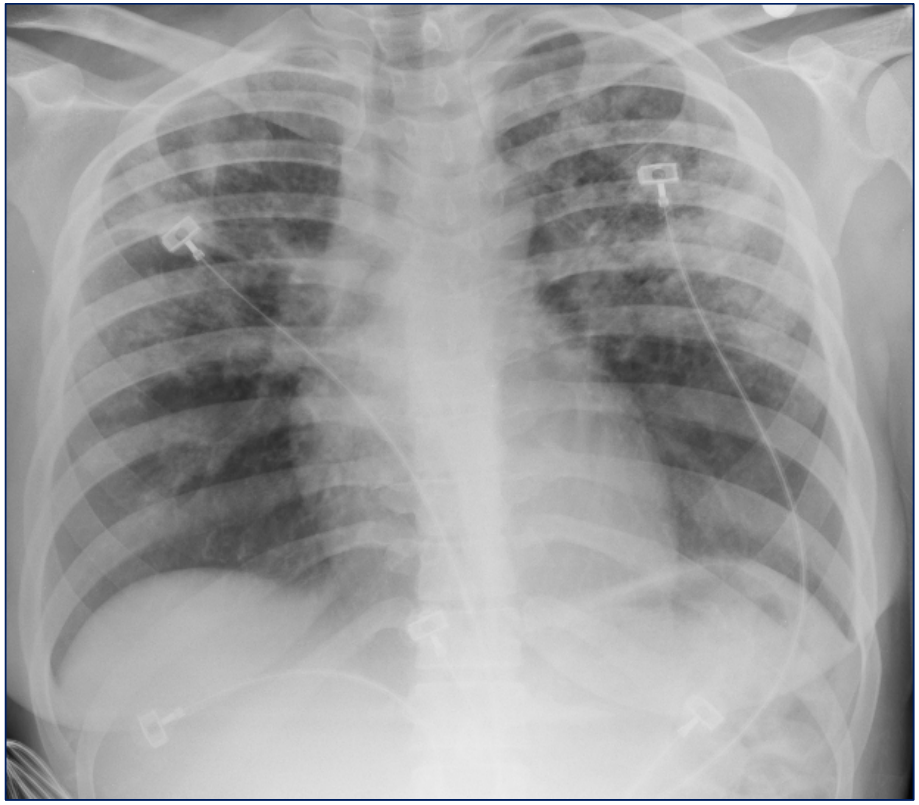
Drug Susceptible TB Treatment - Summary

- Person-centered case management is standard of care
- When prescribing treatment
  - Use preferred regimens
  - Extend treatment for cavitation and/or + sputum cultures at 2 months
  - Calculate # doses within prescribed time frame
  - Use DOT as a tool to ensure treatment adherence
- Special situations
  - Be mindful of additional guidelines for pregnant or breastfeeding women, HIV (+) persons, patients with renal or liver disease

Case 1

29 year old physician from India presents with dry cough for several weeks. No weight loss, night sweats or fevers.

Pre-employment IGRA positive 12 months ago. LTBI treatment declined. CXR normal at that time



Case 1 Questions (use chat)

- What do you see on CXR?
- What studies/tests would you order next?
- Should the physician continue working?
- Would you consider any empiric treatment while awaiting sputum results?

Case 2

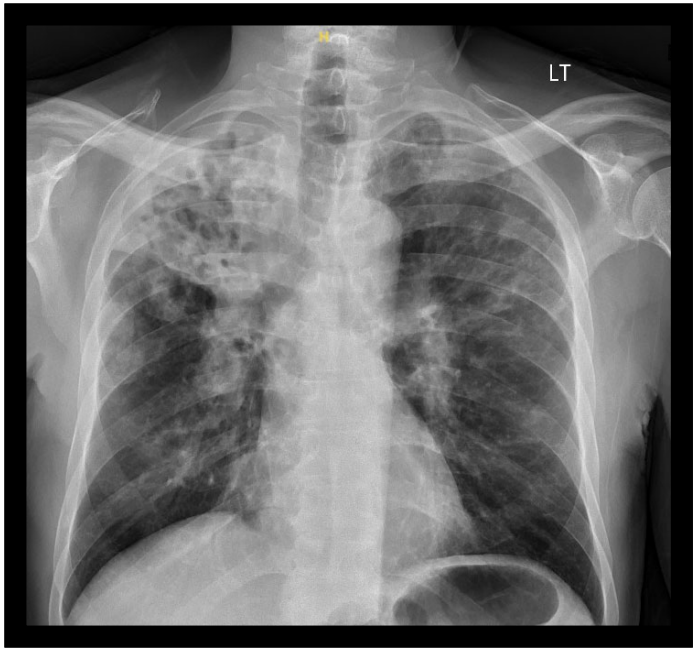
60 yo man with chronic kidney disease HTN, DM presenting with cough, weight loss and fevers for 3 months.

Sputum AFB – smear positive, culture positive for MTB, pansusceptible

Started on 4 drug standard treatment via video DOT. Tolerating treatment well. Cough improving, weight unchanged. Completed intensive phase, now in continuation phase on INH and Rifampin.

Unable to produce sputum at month 2.

Month 3 sputum returned smear 1+; culture MTB positive



Case 2 Questions

- Is this treatment failure?
- What are some factors that might lead to delayed response in this pt?
- What questions do you have for the treatment and case management team?
- Would you order any additional testing at this time?