

HIV Module: HIV and Tuberculosis

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Objectives:

1. Describe the epidemiology of Tuberculosis (TB) including transmission
2. Describe the clinical manifestations of TB and clinical course
3. Define latent TB infection and current guidelines for secondary prophylaxis
4. Describe strategies for diagnosis and management of active TB infection
5. Explain the classifications of drug resistant TB and its epidemiology
6. Describe unique challenges in TB-HIV co-infection pertaining to the above topics

Case 1. Mr. Pott is a 47 year old man with HIV/AIDS, hypertension, chronic tobacco use and active alcohol use disorder. His HIV is well-controlled on combination antiretroviral therapy (cART) and recent CD4 count was 500 cells/mm³ with undetectable viral load. He is currently homeless and has a history of incarceration. He presents to clinic because he has been accepted to an inpatient rehabilitation facility and needs a PPD. He wants to know if he is at risk for TB.

1. Describe the epidemiology of TB and HIV. How is TB transmitted? Does the risk of active TB differ in patients with and without HIV? What are other risk factors?

TB is the leading cause of death among people with HIV worldwide. In the US, TB burden has been decreasing; of the 9,412 TB cases reported in 2014, 506 were HIV/TB co-infections.

Mycobacterium tuberculosis bacilli are transmitted when a patient with active pulmonary TB coughs, sneezes or speaks, releasing airborne droplet nuclei which are inhaled by a new host. Given their small size (5-10 microns in size), the droplets are able to enter the alveoli, where they are ingested by alveolar macrophages. Cytokines, neutrophils and monocytes are activated and form a granulomatous collection called a tubercle to contain the bacilli. However if bacterial replication continues unabated, the bacilli can escape through lymphatics to the hilar lymph nodes (called a "Ghon complex"), and from there can travel further to establish itself in virtually any organ, most commonly the lungs (with preference for the upper lobes where oxygen content is high and lymphatic flow is poor, hindering clearance), as well as lymphatics, abdomen, genitourinary system, skeletal system, and central nervous system. The bacilli can also enter the blood stream and cause disseminated disease, known as "miliary" TB due to appearance similar to millet seeds spread throughout organs.

In the weeks following primary infection, a cellular immune response is mounted that in the majority of cases contains the infection locally and controls bacterial replication, resulting in latent

infection. Without intervention, 5-10% of patients with latent infection will eventually develop reactivation TB disease, in which the bacteria begin replicating again where seeding had previously occurred during primary infection. If cellular immunity is intact, infectious foci will be walled off forming abscesses or, in the lung tissue, cavities (areas of tissue necrosis surrounded by thick wall of inflammatory material). If the cellular immune response is poor (such as in advanced HIV/AIDS, use of corticosteroids or TNF-alpha inhibitors, lymphoma, diabetes), risk of reactivation is increased – for example, for a person with HIV/AIDS, reactivation risk is approximately 10% per year.

Other populations especially at risk include the current/formerly incarcerated, residents of homeless shelters, smokers, travelers/immigrants/refugees from high burden settings, close contacts of active pulmonary TB cases, health care workers, and employees/residents of congregate settings including homeless shelters.

Case 1 continued: You conduct a thorough ROS and Mr. Pott denies experiencing recent cough, hemoptysis, fever, night sweats, weight loss, lymphadenopathy, fatigue, or malaise. You place a PPD (TST) for Mr. Pott. When he returns 72 hours later, there is an area of induration 7 mm in diameter.

2. Define latent TB infection (LTBI). What are the current guidelines for screening of LTBI in HIV+ patients? How would you interpret Mr. Pott's PPD?

LTBI occurs when a person becomes infected with *M. tuberculosis*, but the immune system is able to control the infection and they remain asymptomatic despite harboring live bacteria. A person with LTBI will be completely asymptomatic, without positive sputum studies or imaging findings.

All patients with HIV should be tested for LTBI with Interferon-Gamma Release Assays (IGRA) – such as Quantiferon-TB Gold or T-SPOT – or tuberculin skin test (TST) with purified protein derivative (PPD) at the time of HIV diagnosis, even in the absence of obvious exposure to TB, and then yearly if ongoing risk of exposure is present. Given that both IGRA and TST are less sensitive in patients with advanced HIV disease, patients with negative initial testing and CD4 <200 should be re-tested after starting ART and CD4 rises above 200 cells/mm³.

Though TST is generally less expensive, disadvantages include inconvenience of returning for read within 48-72 hours and higher rate of false positives in patients who received BCG vaccination. IGRAs have higher specificity (approx. 95%) and less cross-reactivity with BCG vaccination. However, as HIV disease advances both TST and IGRAs lose sensitivity, and agreement between IGRA and TST is poor (57% in one studyii).

	>=5 mm		>=10 mm		>=15 mm
1.	HIV infection	5.	Recent immigrant	10.	All others

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|----|-------------------|----|---|
| 2. | Immunosuppressed | 6. | IVDU |
| 3. | Active TB contact | 7. | Resident/employee of high risk setting* |
| 4. | CXR changes | 8. | Other clinical risk factor |
| | | 9. | Children <5 years |

* health care workers, group homes, lab workers, incarceration, homelessness, shelters

Mr. Pott's TST would be considered positive given that it was >5 mm with HIV infection.

11. Given his positive TST, how can Mr. Pott's risk of developing active TB be reduced?

Given that he is asymptomatic, he likely has LTBI. Absence of cough, fever, night sweats, weight loss, and LAD has >90% negative predictive value for culture+ TB. Ordering a chest X-ray increases sensitivity but decreases specificity. Symptom screening + CXR should be performed on HIV+ patients testing positive on IGRA or TST to exclude active TB. Sputum culture is not cost-effective or indicated for screening asymptomatic patients.

Mr. Pott should be started on cART as soon as is feasible, given reduction in overall mortality as demonstrated in the START study. Furthermore, cART has been shown to reduce progression of LTBI to active TB disease by 56%.ⁱⁱⁱ

Isoniazid (INH) prophylaxis can also decrease Mr. Pott's risk of progressing to active TB. A Cochrane review found that TB prophylaxis reduced active TB incidence in HIV+ patients with positive TST by 62%; benefit was less clear for patients with negative TST. In low TB-burden settings like the US, INH prophylaxis is indicated for HIV+ patients with a positive LTBI test OR history of close contact with TB and negative LTBI test. The preferred regimen is INH 300 mg PO daily for 9 months, together with pyridoxine (vitamin B6) 25-50 mg PO daily to prevent peripheral neuropathy. Alternative regimens may also be effective.^v

HIV+ patients on INH prophylaxis should be evaluated monthly to assess for adherence and adverse events, particularly drug-induced liver injury (DILI). They should be educated to watch and immediately report symptoms indicating drug toxicity (RUQ pain, nausea, vomiting, jaundice, icterus, rash, bilirubinuria, numbness and tingling of extremities). At baseline they should be screened for factors that increase the risk of DILI including heavy alcohol use, viral hepatitis, underlying liver disease, pregnancy and concomitant hepatotoxic drugs. Liver function tests including AST, ALT and total bilirubin should be tested at baseline, and again if the patient has other underlying risk factors, if baseline transaminases were elevated, or if the patient becomes symptomatic. In 10-20% of patients, transaminases will increase within the first 3 months of INH therapy then normalize in the absence of intervention; clinically overt hepatitis occurs in <1% of patients. Patients who develop asymptomatic transaminitis > 5 times the upper limit of normal (ULN) or symptomatic hepatitis with transaminitis >3 times ULN should

stop chemoprophylaxis, and risks and benefits of hepatotoxicity vs activation of TB disease should be carefully weighed with specialist input.

Case 2: Ms. Calmette is a 26-year-old woman with newly diagnosed HIV who presents with cough x 4 weeks. The cough has worsened gradually over the past month and she now has hemoptysis. It is associated with fever, weight loss, night sweats. She does not have any additional known medical problems and does not take any medications. She denies alcohol or other substance use and current sexual activity. ROS is notable for headaches and white patches on tongue.

1. Ms. C. has the classic symptoms of pulmonary TB (hemoptysis, fever, weight loss, night sweats). What other clinical signs/symptoms may be seen in pulmonary TB? Extrapulmonary TB? What else is on the differential?

The cardinal symptoms of active pulmonary TB are fever, cough, weight loss, and night sweats. Fever is present in 30-70% of cases, and usually begins as low grade temperature that worsens over days to weeks, classically peaking in the afternoon and at night. Cough is noted in one third to one half of cases, also progressing subacutely from nonproductive morning cough to productive of yellow sputum with or without blood streaks, later occurring throughout the day and throughout the night in advanced, cavitated disease. Weight loss and fatigue occur in over half of cases, and dyspnea in one third. Chest pain is present in one third of cases and can indicate presence of effusion or empyema when pleuritic, or bronchial lymphadenopathy when retrosternal. Hemoptysis, present in a quarter of cases, manifests late in disease course with erosion of the endobronchus due to caseous sloughing; massive blood loss is rare. More rarely, continuous swallowing of infectious sputum after coughing can lead to development of oropharyngeal or gastrointestinal ulcers. Spread to endobronchial tissue can present with wheezing, bronchorrhea, or barking cough. Voice changes may signal laryngeal TB.

Physical exam findings in pulmonary TB are nonspecific and more easily appreciated in advanced disease. Dullness and decreased tactile fremitus can be observed when effusion is present. Crackles can denote an infiltrate. "Amphoric" breath sounds, similar to that produced blowing across a jar (amphora), can be auscultated over large cavities in advanced disease. Clubbing of fingers can be seen in advanced fibrotic disease.

The differential for pulmonary TB includes other infectious pneumonia (including bacterial and fungal pathogens such as PJP, histoplasmosis, blastomycosis, atypical mycobacteria, tularemia), PE, malignancy, autoimmune disorders (eg Sarcoidosis).

2. In the clinic with Ms. C, what are your next steps? How would you go about working up her symptoms?

The first step in Ms. C's management would be to place her in airborne isolation in a negative pressure room. Anyone entering the room should wear a properly fitted N-95 respirator. In the event that she needs to leave the room for imaging or other reason, the patient should wear a respirator.

The following sputum studies should be performed:

1. Acid fast bacteria (AFB) smear microscopy – 3 specimens, collected 8 hours apart
2. Mycobacterial culture with drug sensitivity testing
3. Nucleic acid amplification testing (Cepheid Xpert MTB/Rif test or other NAAT/PCR depending on lab availability)

If a patient is not able to expectorate sputum, sputum induction should be performed in order to increase sensitivity of sputum testing. If sputum induction fails, or if AFB microscopy is repeatedly negative and there is strong clinical suspicion for military TB, bronchoscopy can be performed to collect sample.

Imaging should also be performed depending on suspected site of clinical involvement. In active pulmonary TB, the vast majority of CXR abnormalities are seen in the upper lobes. Infiltrates are present in 70-87% and cavities in 19-40%; cavities may show air fluid levels. Right middle lobe collapse can be seen due to hilar adenopathy. A uniform reticulonodular infiltrate may be seen in pulmonary miliary TB disease. Fibrocalcific changes can be seen in healed pulmonary TB. Plain X-ray films can be useful diagnostic tools in extrapulmonary TB as well. In spinal TB, anterior vertebral body osteolysis may be seen, and other musculoskeletal sites may show soft tissue swelling or calcifications, osteopenia and bone destruction.

CT is more sensitive than CXR for pulmonary TB findings and in addition to cavities, infiltrates, and effusions, can help identify fibrotic lesions, adhesions, and bronchiectasis. CT may also reveal miliary lung involvement with scattered 2-4 mm nodules and diffuse ground glass opacities. CT and ultrasound are useful in evaluating abdominal and genitourinary TB. For CNS TB, MRI is more sensitive than CT and may show abnormal meningeal enhancement in basal cisterns, hydrocephalus, or tuberculomas.

If there is clinical or radiographic evidence of extrapulmonary TB involvement, fluid or tissue specimens from suspected sites (pleural, pericardial, ascitic, synovial, CSF, urine) should be evaluated with cell count, gram stain, AFB microscopy, AFB culture, cell count, and NAAT testing (if available – currently off-label) performed. Adenosine deaminase (ADA) levels are highly sensitive and specific for TB in ascites (LR 26.8 for ADA >39 IU/L)iv, pleural and synovial fluid, and may also be useful in CSF. Sterile pyuria is suggestive of genitourinary TB.

Other systemic laboratory findings, while not specific for TB, can help make the diagnosis. C-reactive protein is elevated in up to 85% of patients. Hematologic manifestations include normocytic anemia, leukocytosis, monocytosis, or pancytopenia in the setting of miliary TB bone involvement. Hyponatremia may occur due to SIADH or adrenal insufficiency.

TST and IGRA are not clinically useful when diagnosing active TB, since positive test does not distinguish between active and latent disease, and false negative test can occur due to anergy in up to

one-third of patients with active TB.v In one meta-analysis of studies mostly conducted in African populations, the sensitivity of IGRAs for active TB was around 65%.¹

Case 2 continued: Ms. Smith has a positive AFB sputum smear microscopy, and NAAT test is positive for MTB. Sputum mycobacterial culture results are pending. CXR shows a cavitory lesion in the right upper lobe. HIV test is positive; CD4 is 250 cells/mm³ with VL 43,000 copies/mm³.

4. Describe the management of active pulmonary and extrapulmonary TB.

In addition to airborne isolation and notifying the DOH of this new TB case you have diagnosed, Ms. Smith should start “RIPE” treatment : Rifampin (RIF), Isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB).

Table 2. Recommendations for Treating Mycobacterium Tuberculosis Infection and Diseasevi

¹ Metcalfe et al. Interferon-gamma Release Assay for Active Pulmonary Tuberculosis Diagnosis in Adults in Low- and Middle-Income Countries: Systematic Review and Meta-Analysis. The Journal of Infectious Diseases 2011;204:S1120-29.

Intensive Phase (2 Months)

- INH + (RIF or RFB) + PZA + EMB (AI); if drug susceptibility report shows sensitivity to INH & RIF then EMB may be discontinued

(Table reproduced from: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf)

Drug susceptibility testing (DST) for first-line drugs (RIPE) should be performed on all isolates at baseline. Repeat AFB smear and culture should be performed monthly to document conversion to negative (defined as at least 2 negative samples in consecutive months). If after 4 months cultures are still positive, or if tests become positive after previously converting to negative, DST should be performed for second line drugs including fluoroquinolones.

The optimal duration of therapy for extrapulmonary TB is not known, and guidelines are based on expert recommendation (see above). Corticosteroids are indicated in certain circumstances, with increased overall survival in CNS TB, and potentially reducing the impact of constrictive pericarditis in pericardial TB disease.

5. Ms. C wants to know when she should start antiretroviral medication for her HIV. What do you tell her? What specific considerations would you take into account regarding concurrent TB treatment and antiretroviral medications?

Treatment of TB disease in the setting of HIV is complicated due to drug-drug interactions, immunosuppression and disease severity, and immune reconstitution inflammatory syndrome (IRIS). Patients with HIV/AIDS and drug-susceptible TB should be given the standard 6-month daily RIPE regimen, and should receive combination antiretroviral therapy (cART) concurrently to TB treatment. Patients already taking cART should continue it. If not yet started on cART, patients with CD4 <50 should start within 2 weeks. Due to higher risk of IRIS with earlier cART initiation, patients with CD4 >50 should start cART 8-12 weeks after starting TB treatment. In the case of TB meningitis, cART should not be started until after 2 months of appropriate treatment. Antiretroviral classes that interact significantly with anti-TB drugs include protease inhibitors, non-nucleoside reverse transcriptase inhibitors and

integrase strand inhibitors; these interactions can usually be managed with dose adjustments (see table below reproduced from CDC).

Table 3. Recommended Doses of First-Line Drugs for Treatment of Tuberculosis in Adults and Adolescents^{vii}

Drug	Daily Dose
Isoniazid	5 mg/kg (usual dose 300 mg)
Rifampin ^a Note: Rifampin is not recommended in patients receiving HIV PIs, ETR, RPV, EVG/COBI or TAF	10 mg/kg (usual dose 600 mg)
Rifabutin ^a without HIV PIs, EFV, RPV	5 mg/kg (usual dose 300 mg)
with HIV PIs	150 mg ^b
with EFV	450–600 mg
with TAF or EVG/COBI containing regimens	not recommended
Pyrazinamide (weight-based dosing)	
40–55 kg	1000 mg (18.2–25.0 mg/kg)
56–75 kg	1500 mg (20.0–26.8 mg/kg)
76–90 kg	2000 mg (22.2–26.3 mg/kg)
>90 kg	2000 mg ^c
Ethambutol	
40–55 kg	800 mg (14.5–20.0 mg/kg)
56–75 kg	1200 mg (16.0–21.4 mg/kg)
76–90 kg	1600 mg (17.8–21.1 mg/kg)
>90 kg	1600 mg ^c

^a For more detailed guidelines on use of different antiretroviral drugs with rifamycin, clinicians should refer to the [Drug Interactions section of the Adult and Adolescent ARV Guidelines](#)

^b Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150 mg twice weekly dosing together with ritonavir-boosted PIs. May consider therapeutic drug monitoring when rifabutin is used with a ritonavir-boosted PI and adjust dose accordingly.

^c Monitor for therapeutic response and consider therapeutic drug monitoring to assure dosage adequacy in patients who weigh >90 kg.

Key to Acronyms: COBI = cobicistat; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide

Immune reconstitution can cause paradoxical worsening of TB disease after cART initiation despite appropriate treatment, or unmasking of unknown TB disease after cART initiation. It can be managed symptomatically with anti-inflammatory agents such as ibuprofen in most cases. Corticosteroids are used in moderate and severe cases of IRIS.

Case 2 Continued: Ms. Calmette is started on RIPE while in the hospital. HLA B5701 is negative and you plan to start her on Triumeq 8 weeks after RIPE initiation.

6. What other adverse effects are you concerned about?

As with INH prophylaxis, drug induced liver injury (DILI) is a big concern in patients on TB treatment, and can also be caused by rifamycins and pyrazinamide in addition to INH. If criteria for DILI are fulfilled (see LTBI treatment section above), all drugs that are potentially contributing to hepatotoxicity should be stopped. The patient should be evaluated for concomitant risk factors (alcohol use, gallbladder disease, viral hepatitis, hepatotoxic medications). Depending on clinical status, a “bridging regimen” can be started with second line drugs while the cause of hepatotoxicity is elucidated. When transaminitis and symptoms resolve (decrease in ALT to <2.5 ULN or to baseline levels if abnormal at baseline), the patient can be re-challenged with the potentially hepatotoxic medications, added back one at a time every 7 days, starting with the rifamycin, then INH, then anti-HIV medications if appropriate.

Rash can occur, especially with RIF and INH. If minor and limited in area, the patient can be monitored and pruritis can be treated with antihistamines. If the patient develops diffuse rash, fever, desquamation or mucous membrane involvement, all suspected medications should be stopped immediately. Re-challenge should be pursued similar to DILI protocol detailed above.


Self-limited GI upset can occur with INH, PZA and RIF and can be mitigated by taking with food and pre-medicating with anti-emetic. Peripheral neuropathy associated with INH occurs in 2% of patients, and can be prevented with pyridoxine (vitamin B6). Pyrazinamide can cause elevated uric acid and precipitate gout or nephrolithiasis. Ethambutol can cause optic neuritis with blurry vision and red/green color blindness, which is usually reversible if ethambutol is immediately stopped. Thrombocytopenia can occur with rifampin.

Bonus Case:

Mr. Sofuba is a 42 year old man with longstanding well-controlled HIV disease. He returned from a stint as a Peace Corps volunteer in Kazakhstan 1 year ago at which time he had a positive IGRA and completed 9 months of INH prophylaxis. However, for the past 3 months he has had progressive cough that has become blood-streaked, fevers, night sweats, and a 20-pound weight loss. A sputum sample is positive for AFB on microscopy and *Mtb* on NAAT. PCR testing also reveals mutations associated with resistance to both RIF and INH. He is started on second line regimen. Eight weeks later, cultures with second-line drug sensitivity testing result with *Mtb* that is sensitive to moxifloxacin and capreomycin.

1. How would you classify Mr. S's TB disease? How should he be managed?

Mr. S has evidence of TB that is resistant to both Isoniazid and Rifampin, which is classified as Multiple Drug Resistant (MDR) TB. Extensively Drug Resistant (XDR) TB is resistant to INH, RIF, any fluoroquinolone, and a second line injectable (amikacin, kanamycin, capreomycin). Thus, Mr. S's TB would be classified as MDR-TB, which he likely contracted in his time in Kazakhstan, one of the countries with high MDR-TB burden.^{viii} In the US, the treatment regimen for a patient with MDR- or XDR-TB should be designed with expert consultation according to drug sensitivity profile, but will include a combination of medications from the classes listed in the figure reproduced below.^{ix}

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(Accessed at: http://www.currytbcenter.ucsf.edu/sites/default/files/tb_sg3_book.pdf)

Resources:

ATS/CDC/IDSA Clinical Practice Guidelines for Drug-Susceptible TB

Available at: https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf

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. Available at:

<https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciw778>

USDHHS Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents, Section on Mycobacterium tuberculosis Infection and Disease, updated September 2017.

Available at https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf

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ii Elzi et al. Improved sensitivity of an interferon-gamma release assay (T-SPOT.TB™) in combination with tuberculin skin test for the diagnosis of latent tuberculosis in the presence of HIV co-infection. *BMC Infect Dis*. 2011 Nov 15;11:319. doi: 10.1186/1471-2334-11-319.

iii Elz et al <https://academic.oup.com/cid/article/44/1/94/434184?searchresult=1>

iv <https://www.ncbi.nlm.nih.gov/pubmed/16940883>

v <https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/325/tb>

vi USDHHS Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents, Section on Mycobacterium tuberculosis Infection and Disease, updated September 2017. Accessed at https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf

vii <https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/356/tb-drug-dosing>

viii <http://www.stoptb.org/countries/tbdata.asp>

ix http://www.currytbcenter.ucsf.edu/sites/default/files/tb_sg3_book.pdf