HIV&TB: Managing the Minefield of Diagnosis and Treatment

David Ashkin MD FCCP
Medical Director, State Tuberculosis (TB) Program, Florida Department of Health
Co-Principal Investigator, Southeast National TB Center
Adjunct Assistant Professor, University of Florida College of Medicine
Visiting Assistant Professor, Division of Pulmonary and Critical Care Medicine, University of Miami School of Medicine

Objectives

At the completion of this session, the participant will be able to

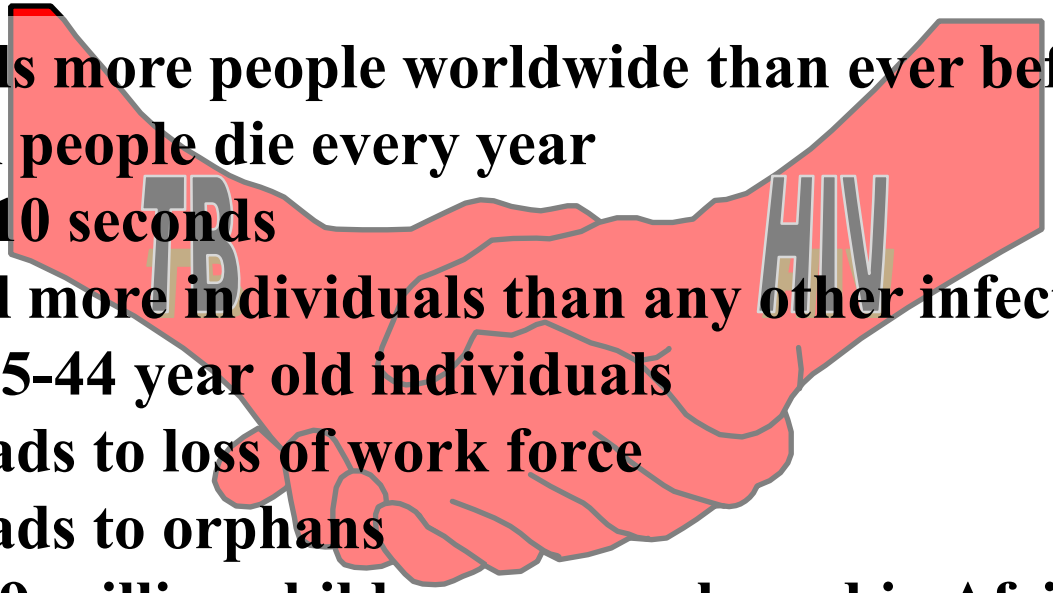
- Describe the increased risk for development of active TB in patients with HIV infection to achieve timely treatment for this population.
- Describe the importance of considering the presence of TB disease in symptomatic HIV infected patients to improve efficacy for diagnosis, treatment and prevent transmission.
- Formulate a plan for treatment of active TB in those with HIV to effectively manage and improve patient outcomes
- Describe Immune Reconstitution Inflammatory Syndrome in patients with HIV and TB, including the diagnosis and management

Copathogenicity of TB and HIV

- (1) T cell depletion caused by HIV causes the immune system not to be able to contain the infection leading to an increased progression to active TB disease as well as disseminated disease
- (2) TB stimulates T cells to replicate enhancing HIV viral replication (-->TB accelerates HIV)
- (3) one-year mortality rate for treated HIV-related TB = 20-35% (!! 4 times higher than HIV(-) !!)

TB and HIV in the 21st Century

The Deadly Partnership



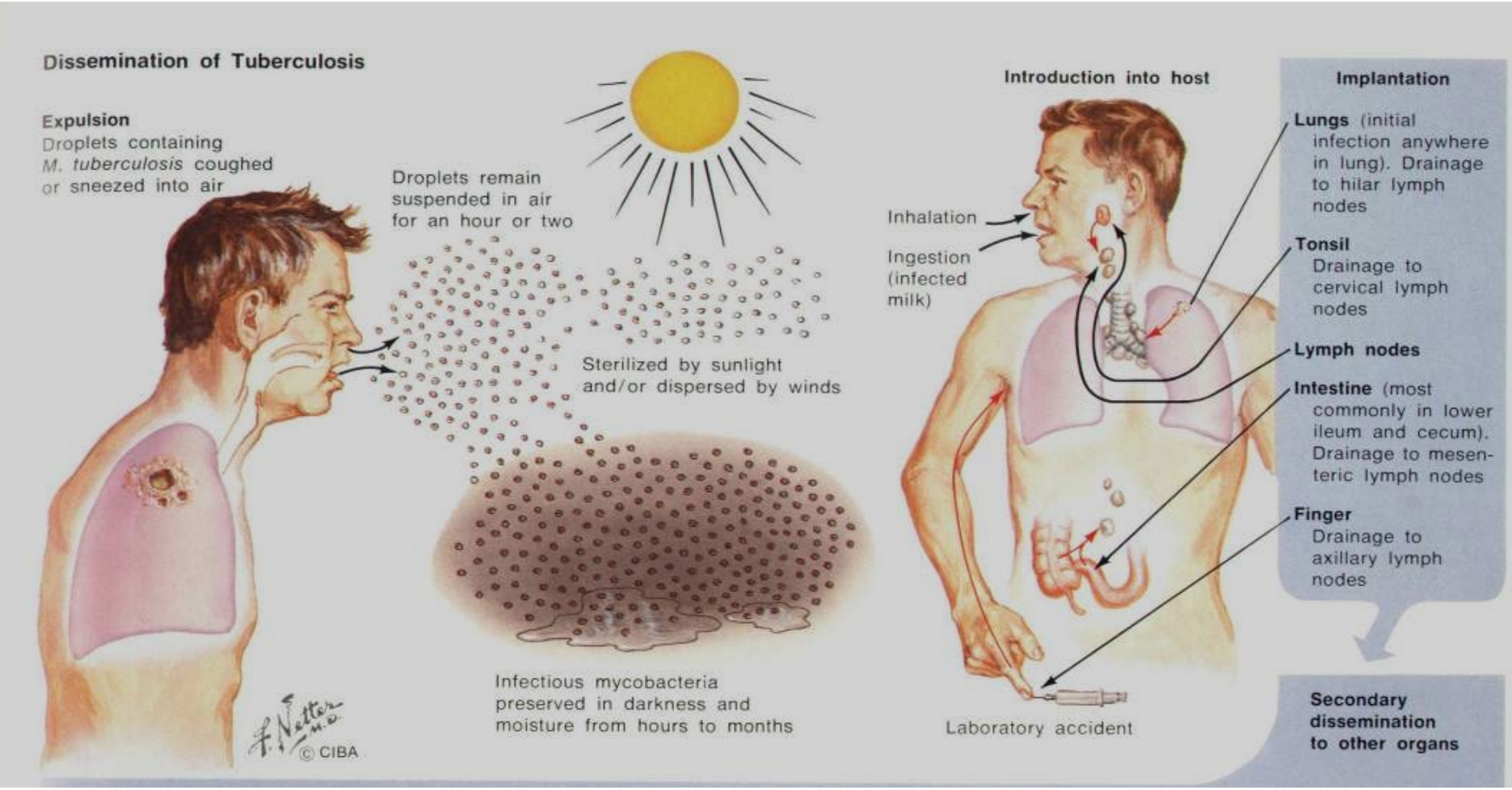
- **TB & HIV kills more people worldwide than ever before**
  - **-2-3 million people die every year**
  - **-one every 10 seconds**
- **TB & HIV kill more individuals than any other infectious diseases**
  - **-Most are 25-44 year old individuals**
    - ***Leads to loss of work force**
    - ***Leads to orphans**
      - **-9 million children are orphaned in Africa**

"Everyone knows the air is terribly infected from the numerous mortals who have died exhaling it"

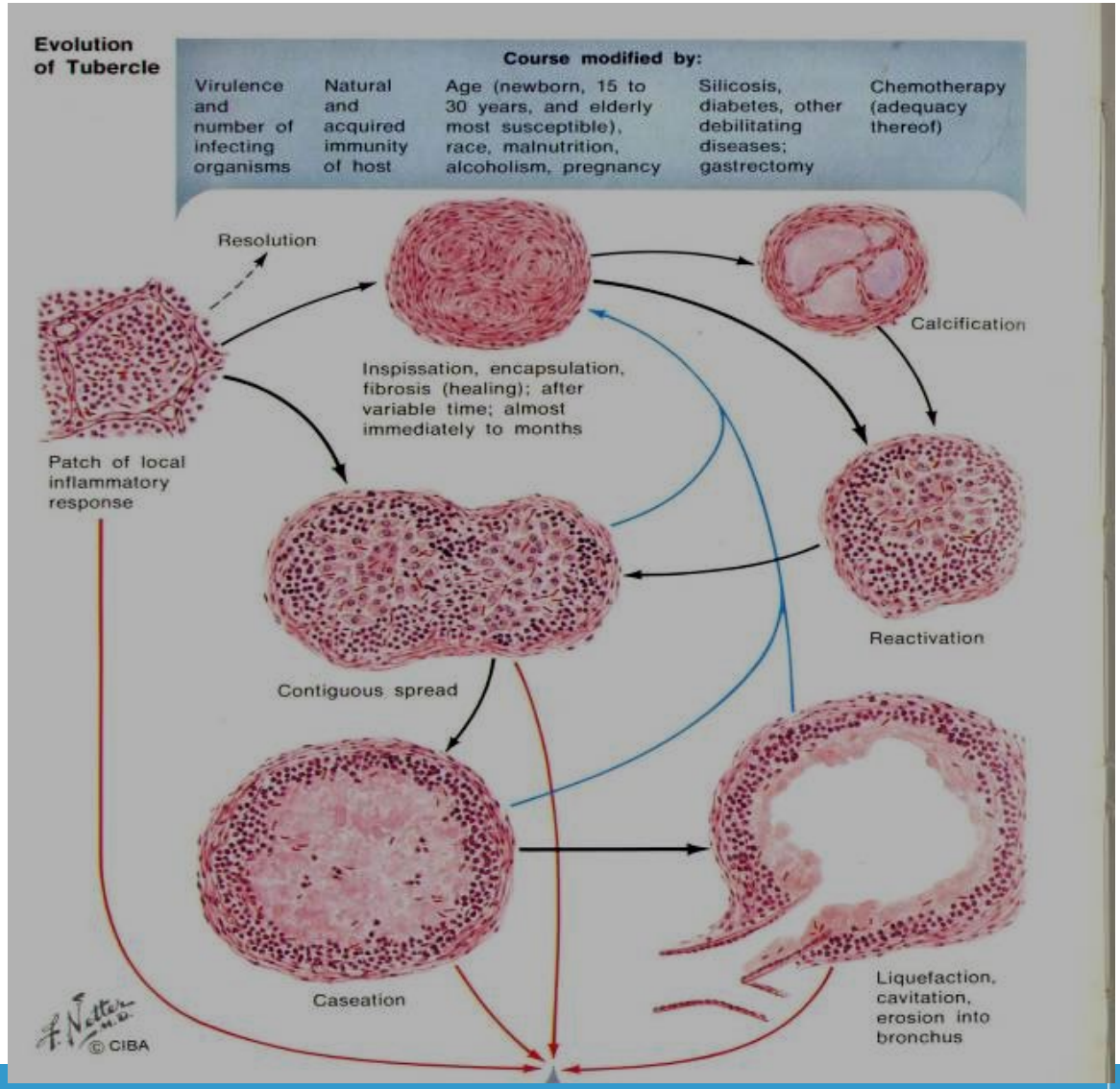
Moby Dick

Herman Melville

Transmission Of Tuberculosis



Pathogenesis of Tuberculosis



Disease Progression

- Progression from infection to disease caused by an inability to contain infection
- 5-10% of all HIV(-) will progress from infection to disease
- Up to 8% per year of PPD(+), HIV(+) pts will progress from infection to disease
- Approximately 25-30% of close contacts become infected on average
- The average patient with active TB infects 30 other individuals

DIAGNOSIS OF TB-THINK TB!!!!
Signs and Symptoms of TB Disease

- **When you have a patient with epidemiologic risk factors (eg hx of being born or lived in area with high rate of TB, congregate living settings, immunosuppression) and have symptoms of:**
- Often of long duration
- General
  - Fatigue, malaise, weight loss, fever, night sweats
- Pulmonary
  - Prolonged cough, coughing up blood
    - Extrapulmonary
  - Depends on site

What to Do When You Suspect A Patient Has Active TB Disease?

- Think TB!!!!
- Isolate!!!!!!!!!!!!!!!!!!!!!!

Nosocomial HIV-Related Multidrug-Resistant Tuberculosis Outbreaks As of August 1992

Facility	Location	Time Period	Total Cases	Resistance Pattern
Hospital A	Miami	1988-91	65	INH, RIF (EMB, ETA)
Hospital B	NYC	1989-91	35	INH, SM (RIF, EMB)
Hospital C	NYC	1989-92	70	INH, RIF, SM (EMB, ETA, KM, RBT)
Hospital D	NYC	1990-91	29	INH, RIF (EMB, ETA)
Hospital E	NYS	1990-91	7	INH, RIF, SM, (EMB, ETA,KM, RBT)
Hospital F	NYC	1990-91	16	INH, RIF, SM (EMB, ETA, KM, RBT)
Hospital I	NJ	1990-92	13	INH, RIF (EMB)
Prison System*	NYS	1990-92	42	INH, RIF (SM, EMB, ETA, KM, RBT)
Total Cases*			277*	

*24 Prison cases are also counted with Hospital C

INH=Isoniazid; RIF=Rifampin; SM=Streptomycin; EMB=Ethambutol; ETA=Ethionamide; KM=Kanamycin; RBT=Rifabutin

CDC
CENTERS FOR DISEASE CONTROL

Florida HEALTH

HIV Prevalence and Mortality of Multidrug-Resistant Tuberculosis Patients As of August 1992

Facility	HIV Infection	Mortality	Median Interval TB Dx to Death
Hospital A	93%	72%	7 weeks
Hospital B	100%	89%	16 weeks
Hospital C	95%	77%	4 weeks
Hospital D	91%	83%	4 weeks
Hospital E	14%	43%	4 weeks
Hospital F	82%	82%	4 weeks
Hospital I	100%	85%	4 weeks
Prison System	98%	79%	4 weeks

CDC
CENTERS FOR DISEASE CONTROL

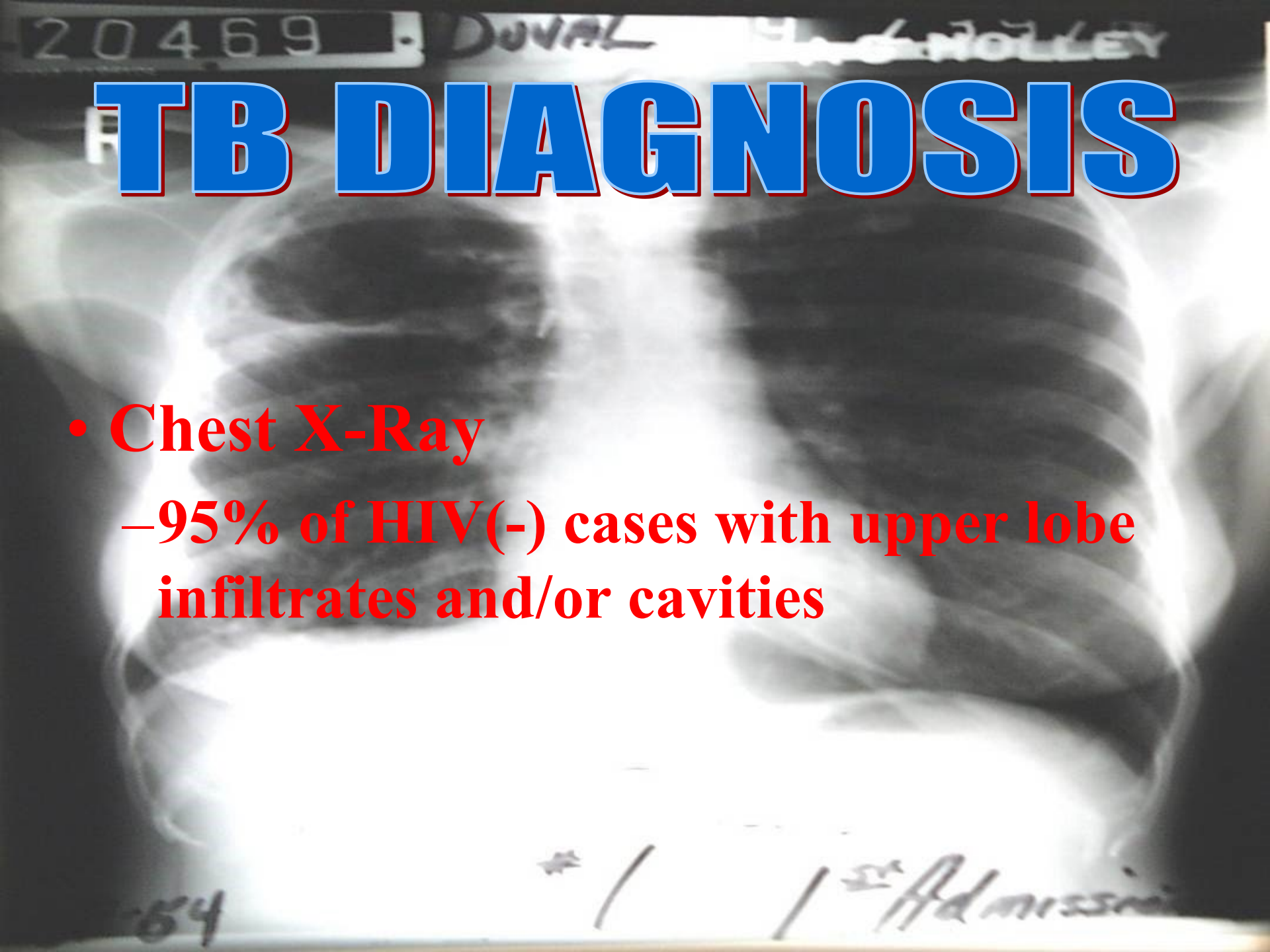
Florida HEALTH

Infection Control

Many Nosocomial outbreaks of TB (including MDR) have occurred

- **THINK TB, ISOLATE & START MEDS**
- **6-8 air exchanges/hr**
- **Negative Pressure**
- **Doors Closed**
- **All entering room wear N95 mask**
- **Keep in isolation until 3 negative smears, on medications and responding clinically**

TB DIAGNOSIS



- **Chest X-Ray**
  - **–95% of HIV(-) cases with upper lobe infiltrates and/or cavities**

TB DIAGNOSIS

- **Up to 30% of HIV (+), active TB cases will have no infiltrates or cavities**

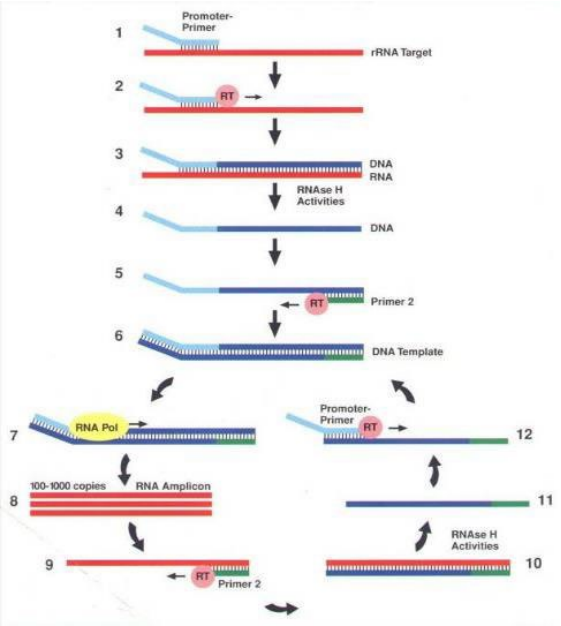
TB Diagnosis

- **Smear-MUST ORDER SEPARATE AFB STUDIES**
  - **Cheap & rapid**
  - **Only 40-60% positive in cases of active TB**

TB Diagnosis

- Culture
  - Positive ~80% of active TB cases
  - Takes 6-8 weeks by conventional
  - Takes 1-3 weeks by liquid media
- Sensitivity
  - Takes 1-2 weeks after positive culture
- Nucleic Acid Amplification
  - Results available in 4-6 hours
  - Specificity ~98% on smear(+) specimens
  - Sensitivity 70-80% on multiple respiratory specimens

TB Diagnosis
Nucleic Acid Amplification



- Results within two hours 99% specificity on smear (+) cases
- Up to 80% sensitivity on three samples
- $30 to $50 per test
- Approved by the FDA for smear-positive and –negative, **untreated cases**
    - May Stay PCR (+) for years-Potential For False Positive Results in Previously Treated Pts
- May have a role in non-pulmonary samples-send to State Lab

GenExpert

HAINS TESTING

FINAL LABORATORY REPORT

Clinical Mycobacteriology Laboratory
Phone: (518) 474-4158 Fax: (518) 408-2264

Testing performed at CLIA# 33D2065937
Specimen Type: Sputum (Isolate)
Specimen Id: IDR1600053390
Submitter's Specimen Id: 200585562

Direct Molecular Detection - Real-time PCR

Mycobacterium tuberculosis complex DNA by real-time PCR*:	DETECTED
Mycobacterium avium complex DNA by real-time PCR*:	Not Detected

Molecular Identification and Drug Susceptibility Prediction: Whole Genome Sequencing

Molecular Identification*:	Mycobacterium tuberculosis

Predicted Resistance Profile*

Rifampin (RIF):	RESISTANT (predicted)	Interpretation
Isoniazid (INH):	RESISTANT (predicted)	
Pyrazinamide (PZA):	RESISTANT (predicted)	
Ethambutol (EMB):	RESISTANT (predicted)	
Streptomycin (SM):	Susceptible (suggested)	
Kanamycin (KAN):	Susceptible (suggested)	
Fluoroquinolones (FLQ):	Susceptible (suggested)	
Ethionamide (ETH):	Susceptible (suggested)	

High-confidence mutations detected*

rpoB (RIF):	Mutation present: Ser531Leu	mutations
katG (INH):	Mutation present: Ser315Thr	
oxyR-ahpC promoter region (INH):	No high-confidence mutation	
mabA-inhA promoter region (INH/ETH):	No high-confidence mutation	
mabA (INH/ETH):	No high-confidence mutation	
pncA (PZA):	Mutation present: Thr47Ile	
pncA promoter region (PZA):	No high-confidence mutation	
embB (EMB):	Mutation present: Gly406Ala	
rpsL (SM):	No high-confidence mutation	
rrs (SM or KAN):	No high-confidence mutation	
eis promoter region (KAN):	No high-confidence mutation	
gyrA (FLQ):	No high-confidence mutation	
gyrB (FLQ):	No high-confidence mutation	

A result of "No high-confidence mutation" does not rule out resistance due to unknown contributory mutations present elsewhere in the genome. CULTURE MUST BE PERFORMED FOR FINAL SUSCEPTIBILITY RESULTS.

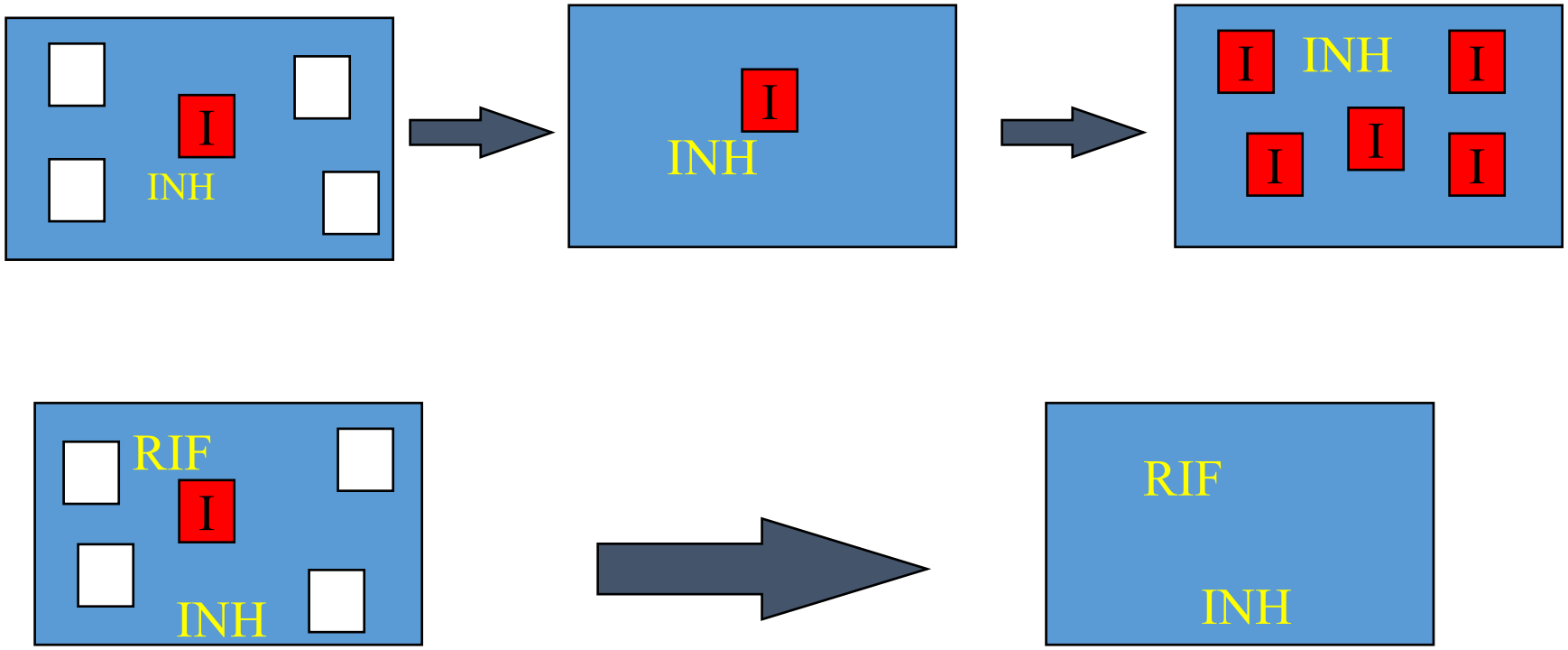
* The performance characteristics of this test were determined by the Wadsworth Center. It has not been cleared or approved by the U.S. Food and Drug Administration.

Gene Sequencing

General Principles of Chemotherapy

- 1) Existence of mutant bacilli with innate resistance to antibiotic action

DEVELOPMENT OF RESISTANCE



General Principles of Chemotherapy

- 1) Existence of mutant bacilli with innate resistance to antibiotic action
- 2)Slow or intermittent growth of mycobacterium which permits the persistence of viable organisms despite prolonged antibiotic treatment, because only actively replicating organisms are killed by antibiotics

TB TREATMENT

- Start with 4 drugs in all patients (in patients from areas where INH resistance exceeds $\geq$ 4%)
  - INH, RIF, PZA and EMB or SM until sensitivities return
  - Once pansensitive, D/C EMB, after 2 months of therapy, D/C PZA
  - Continue INH & RIF for 4 more months for total of 6 months
- Must have culture conversion by 2 months
- 6 month regimen good for HIV(-) and (+)
- Can use TIW regimen
- Monitor adherence and toxicity
- DOT preferred, Combination pills for self administered
- INH and rifampin safe in pregnacy, ?PZA
- Corticosteroids for pericardial constriction, meningitis in children, ? Role in endobronchial disease
- Culture negative (“clinicalTB”)-four months of therapy effective

Causes of Resistance

- Irregular Self Administration with Failure to closely supervise
- Care of patients by non specialists
- Increased immigration

- If pansensitive>95% chance of cure
- If resistant to INH>90% chance of cure
- If resistant to rifampin>70% chance of cure
- If resistant to INH and RIF may be up to a 50% failure rate
- Before chemotherapy~50% chance of cure

"DOT WORKS!!

"DOT THERAPY WORKS!"

- 95% of patients with TB will be cured by DOT
  - Decreases Morbidity & Mortality and cost (~$1500/pt)
  - Decreases Spread of Disease
    - Average patient with TB infects 30 other individuals
  - Decreases resistance
    - MDR costs~$250,000 to cure with only ~80% success
- 5% of patients with Active TB will be unable to complete therapy; requiring legal interventions and facilities to cure them
    - In S.F. one non-compliant patient with MDR-TB was responsible for 40 other cases

CALL YOUR LOCAL HEALTH DEPARTMENT'S TB PROGRAM

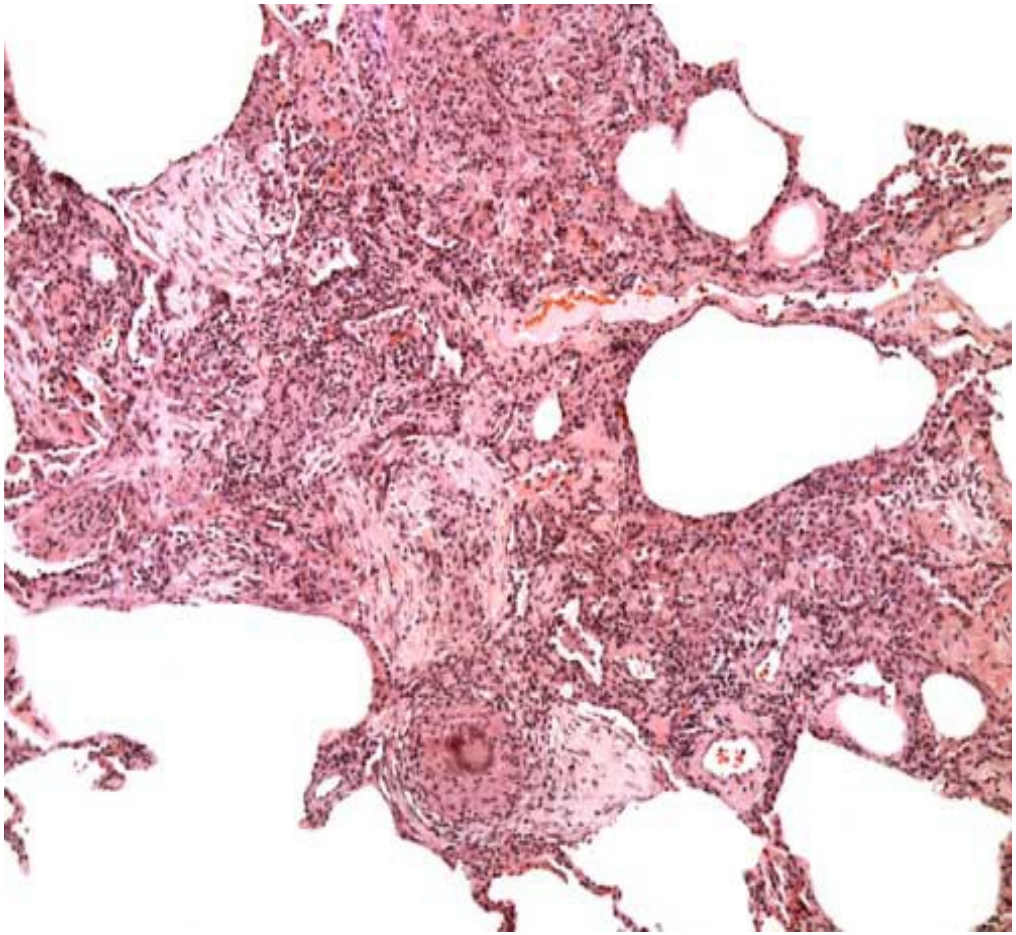
HIV and Tuberculosis:
"The Landmines"

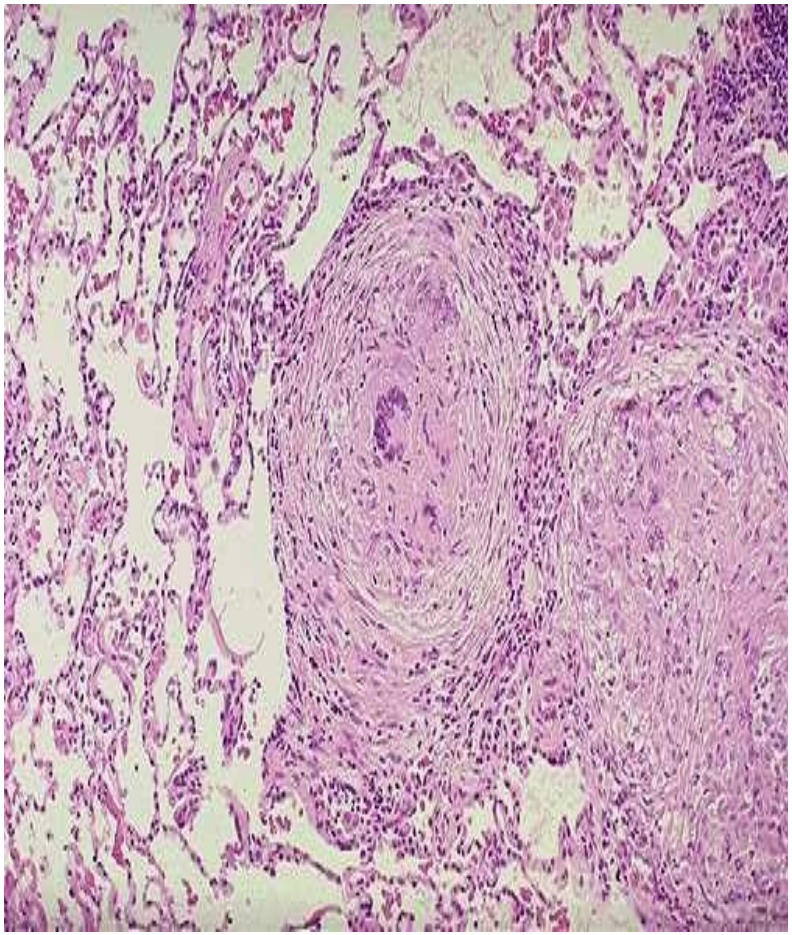
- Increased risk of TB
  - Increased risk with decreased immunity
  - Occurs at any CD4 count
- TB more difficult to diagnose in HIV-infected persons
  - Atypical presentation
- TB + HIV more difficult to manage and treat:
  - Drug-drug interactions
  - Adverse side-effects
  - Possible increased rate of relapse
  - Re-infection after treatment
  - Drug-resistance
- Poorer overall outcomes: ~5-fold increase in mortality

How HIV Changes TB

- HIV mediated immunosuppression impairs granuloma formation; cannot contain the bacilli and cannot form cavities:
  - Extrapulmonary disease
  - Atypical chest radiographs
  - Increased lower lobe involvment
  - Lower concentrations of bacteria in sputum

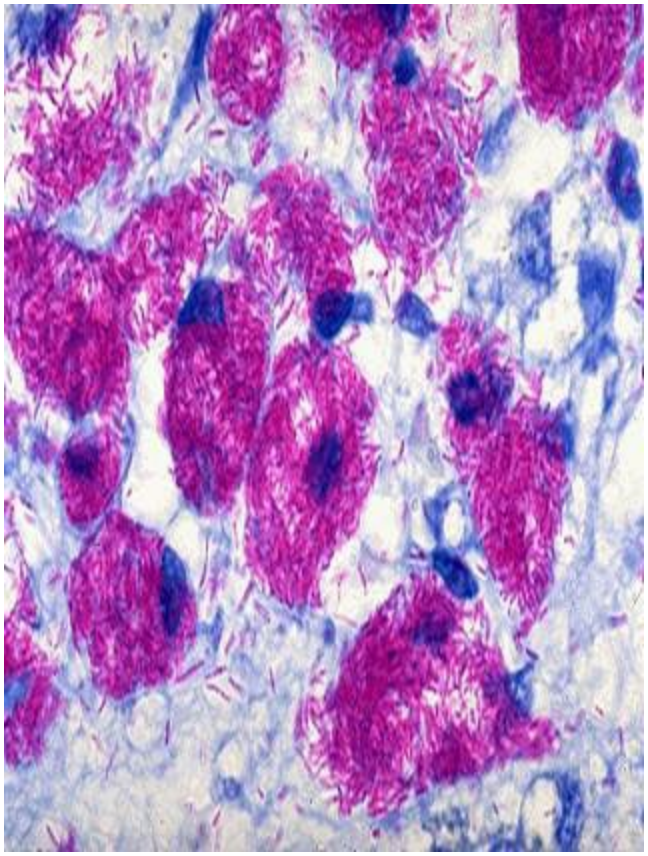
TB in HIV



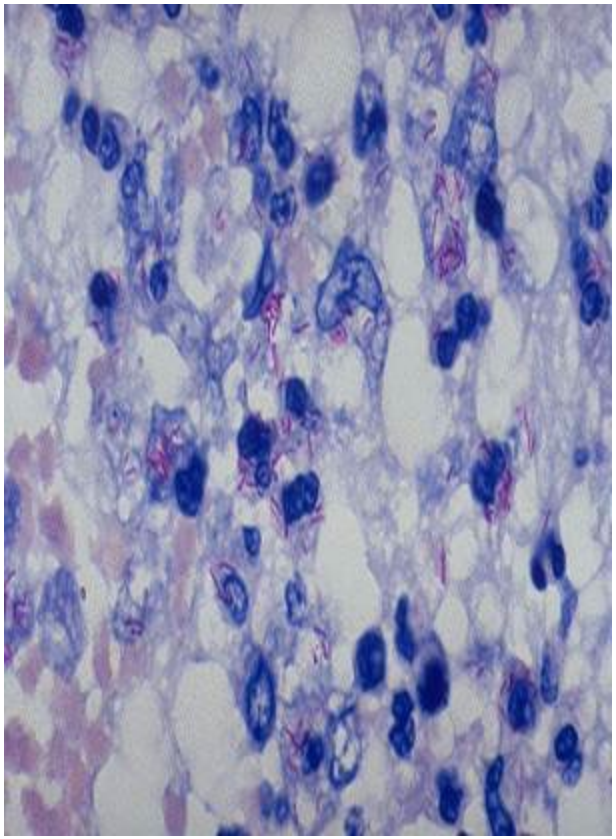


Poorly Formed to No Significant Granuloma Formation in Severely Immunosuppressed HIV (+) Compared to well Formed Granulomas in HIV (-)

Tuberculous Granuloma



Severely Immunosuppressed HIV (+)



HIV (-)

Extra-pulmonary TB

- ~10% in HIV(-)
- HIV(+)
  - 33% with extrapulmonary alone
  - 33% with pulmonary alone
  - 33% both pulmonary and extrapulmonary (many with negative CXRs)
- Any organ has been noted to be involved
  - Pleural dx most common
  - Lymph nodes
  - GU
  - Bone (Need to prolong therapy)
  - Abdominal
  - CNS (Need to prolong therapy)

Impact of Antiretroviral Therapy (ART)

- ART reduces risk of TB
- Rate of TB among patients receiving ART remain persistently higher than among HIV (-) individual

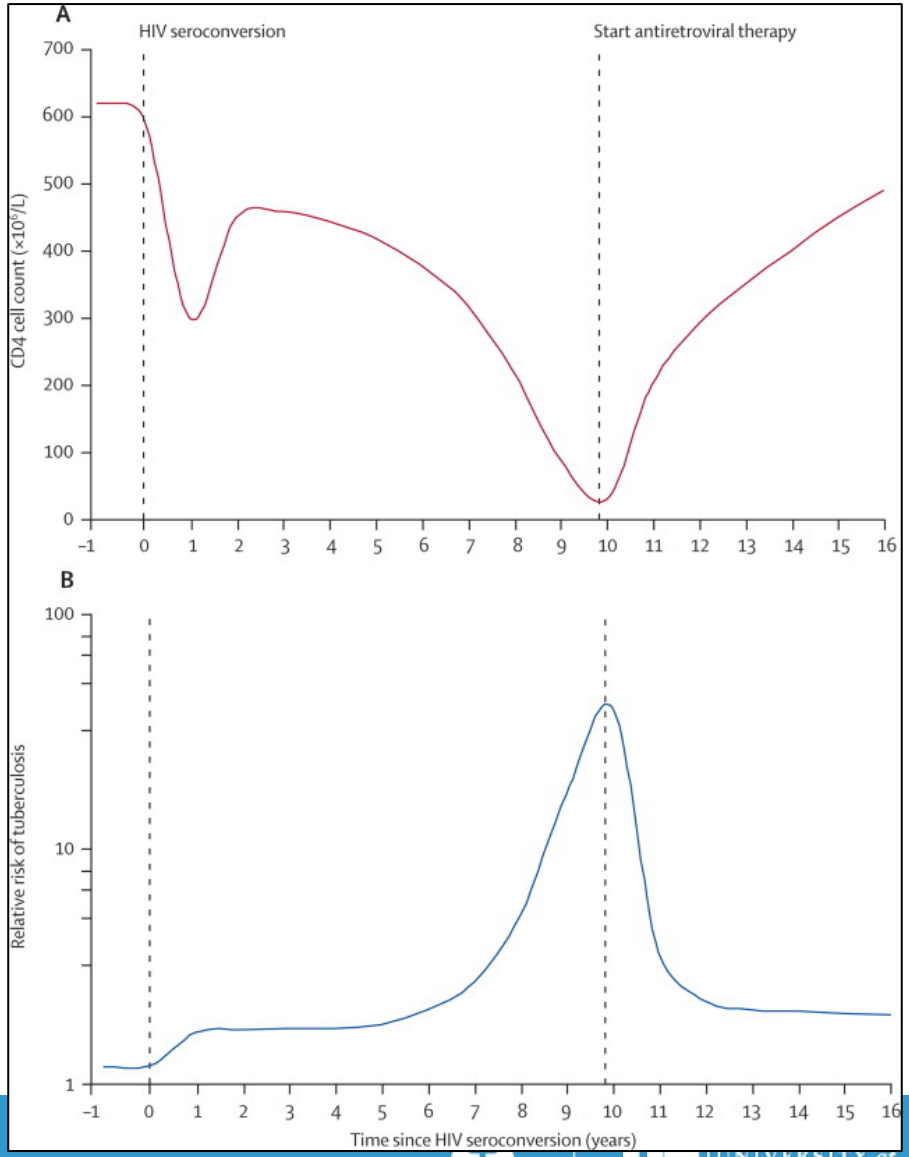


Figure 1. Change in CD4-cell counts (A) and associated risk of TB in an individual from the time of HIV seroconversion (B), during HIV progression, and after initiation of ART

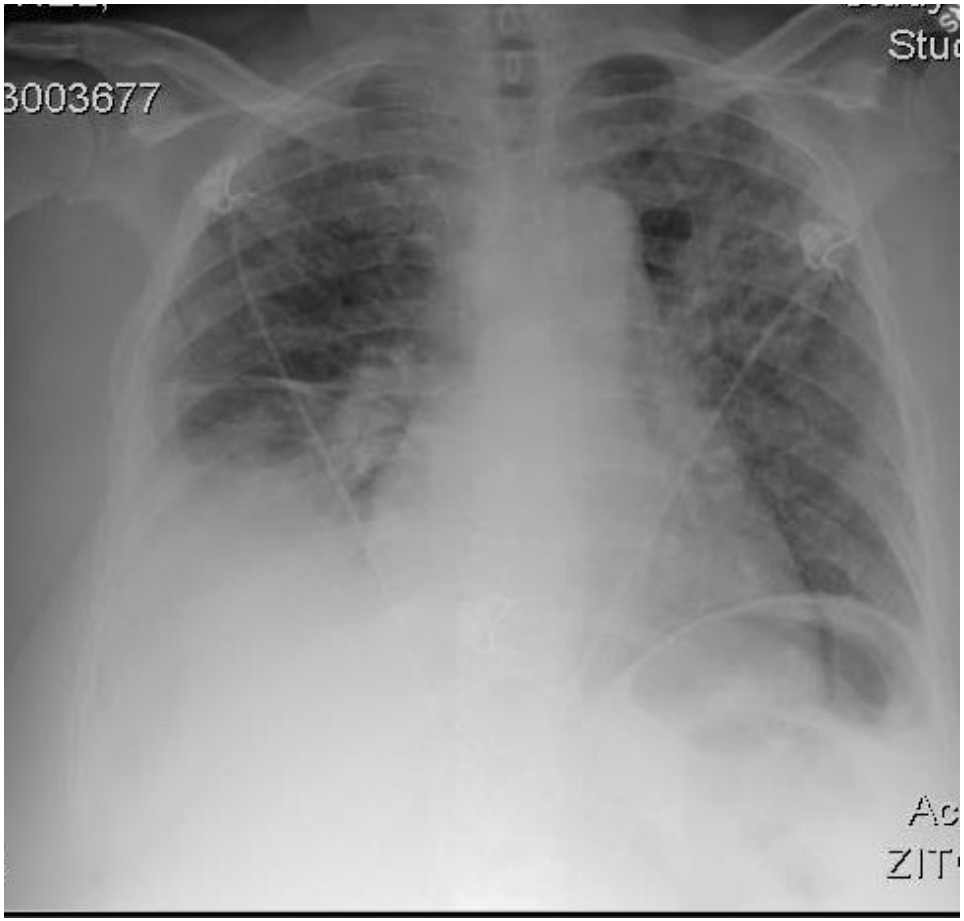
http://dx.doi.org/10.1016/S1473-3099(10)70078-5
SD Lawn et al. Lancet Infect Dis 2010; 10: 489–98

Physician from Zimbabwe

- Dr. K presents to the ER with weakness, fever and productive cough worsening over the past 2 weeks
- Originally from Zimbabwe, she lives in U.S. but travels back and forth to Africa
- Pmhx: Malaria
- Tx for LTBI with INH x 6 months in 1995
- Has cared for many TB patients

Physician from Zimbabwe (con't) Initial Presentation

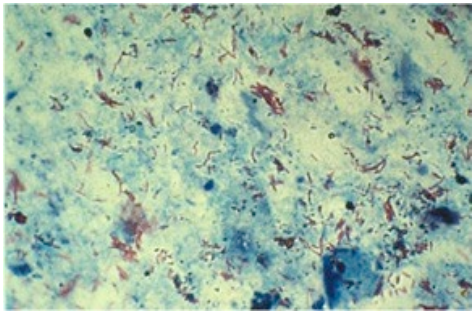
- Temp to 101
- Tachycardic
- ER admits for "Community-acquired pneumonia"



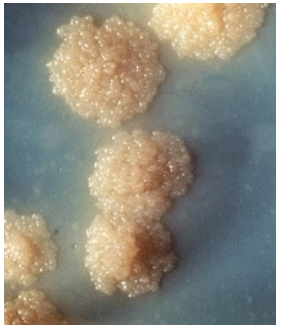
What would you do next?

A. Sputum/blood cultures, start levofloxacin for community acquired pneumonia (CAP)
B. Sputum/blood cultures including AFB, hold treatment until results are known
C. Respiratory isolation, sputum/blood cultures including AFB, TB treatment only if sputum AFB smear is positive
D. Respiratory isolation, sputum/blood cultures including AFB, request geneXPERT, empiric treatment for TB and CAP

Diagnosis of Active TB

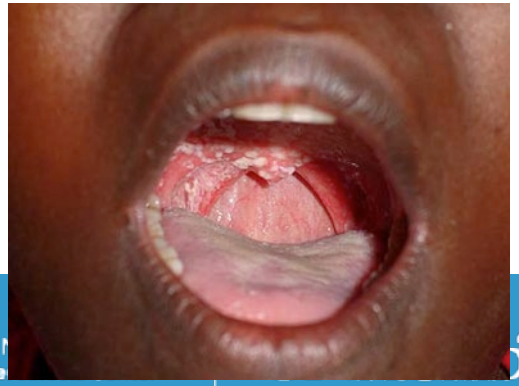


- Same in HIV-infected and HIV (-) Persons
- AFB smear, culture, NAAT at affected site
  - Lungs, lymph nodes, CSF, urine, pleural or pericardial fluid, blood, ascites
- Obtain CXR and sputum even if no pulmonary symptoms
  - Pulmonary involvement common at any CD4 count
  - Sputum C&S can be positive even if normal CXR
  - Obtain NAAT on at least 1 sputum



Physician from Zimbabwe (con't): Hospital Course

- Initiated treatment for pneumonia
- Hospitalist notices "thrush" →HIV test ordered
- Extensive lymphadenopathy on chest CT, abdomen, and pelvis
- Concern for possible lymphoma
- Given history of TB exposure, sputum smears and culture ordered



Physician from Zimbabwe (con't): Hospital Course

- Remains quite ill, no improvement on antibiotics
- Unable to produce sputum
- Bronchoscopy performed; bacterial/fungal/AFB cultures sent
- AFB sputum smear (-), released from respiratory isolation
- Widespread lymphoma felt to be cause of illness → plans for LN biopsy

Physician from Zimbabwe (con't): Hospital Course

- Around this time, CD4 count returns:
  - 178 cells/mm^3
  - Viral Load>2,000,000
  - HIV test results also eventually came back as positive

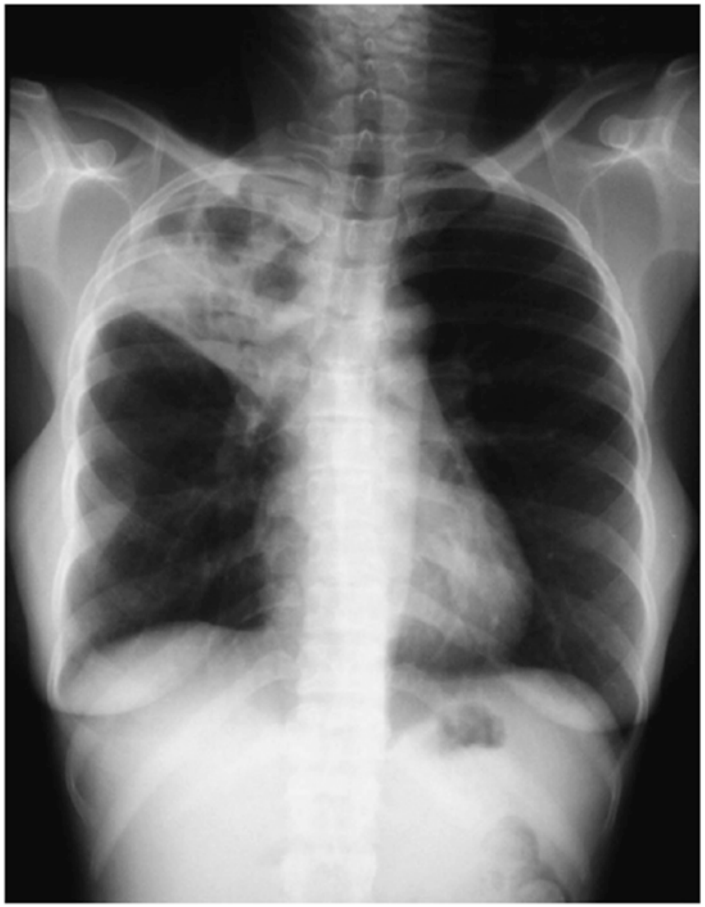
- Axillary lymph node biopsy: "extensive necrotizing granulomas"

Physician from Zimbabwe (con't): Hospital Course

- AFB sputum culture became positive (smear -)
- AFB blood culture also grew *M. tuberculosis* (approximately 4 weeks later)

- Diagnosis: Disseminated TB with pulmonary disease

Clinical Presentation of TB in HIV



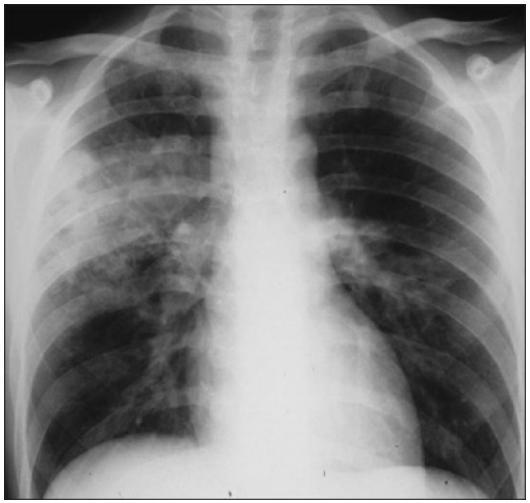
- Presentation of TB influenced by degree of immunodeficiency
- May be typical in early HIV when CD4 > 350
  - Pulmonary disease with cavities on CXR

Rizzi B et al. Clin Radiol 2003 Jun;58(6):469-73

Clinical Presentation of TB in HIV

Advanced HIV

- Extrapulmonary TB more common
  - Pleuritis, lymphadenitis, headache/meningitis, abscesses, pyuria, abdominal pain, disseminated disease
- Sepsis via hematogenous spread
- May have few symptoms
- May have normal or atypical CXR
- Maintain high index of suspicion



Ann Thorac Med [serial online] 2010 [cited 2014 Feb 23];5:201-16. Available from: http://www.thoracicmedicine.org/text.asp?2010/5/4/201/69106

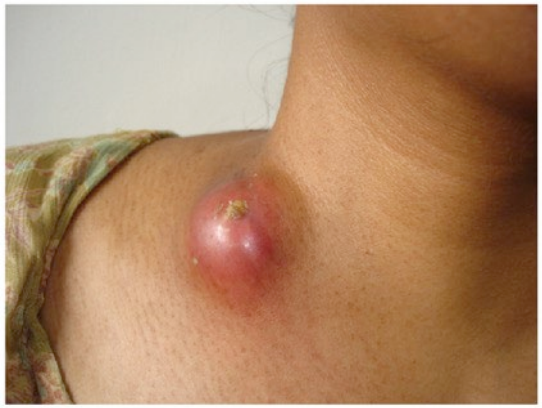


Fig. 1 : Young girl with inflamed, swollen, soft and fluctuant cervical lymph node leading to abscess formation

http://www.japi.org/august_2009/article_06.html. Accessed 2/23/14

Treatment of TB/HIV

Case: Initial Diagnosis with TB and HIV

- 35 yo woman diagnosed with pulmonary TB and AIDS during a single hospitalization
- AFB-smear (+)
- GeneXPERT Mtbc (+), negative for RIF resistance
- No signs or symptoms of extrapulmonary TB
- CD4 count < 20 cells/mm^3
- HIV viral load 1 million copies/mL

How should you proceed with treatment of TB and HIV?

A. Begin HIV treatment, wait for susceptibilities to initiate TB therapy
B. Begin TB therapy, treat HIV after TB treatment completed
C. Begin TB therapy, start HIV therapy in 2 weeks
D. Begin both TB and HIV treatment immediately

Treatment of Active TB in Patients with HIV Infection

- In advanced immunodeficiency, TB can be rapidly progressive and fatal if treatment delayed.

- After collection of specimens for culture and molecular diagnostic tests, start empiric treatment for TB in patients with clinical and radiographic presentation suggestive of HIV-related TB **(AIII)**.

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

Abbreviations: DOT, directly observed therapy; EMB, ethambutol; HIV, human immunodeficiency virus; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.

[a] Other combinations may be appropriate in certain circumstances; additional details are provided in the section "Recommended Treatment Regimens."

[b] When DOT is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses, extensive experience indicates this would be an effective practice. DOT should be used when drugs are administered <7 days per week.

[c] Based on expert opinion, patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week) continuation phase.

[d] Pyridoxine (vitamin B6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (eg, pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.

[e] See [426]. Alternatively, some US tuberculosis control programs have administered intensive-phase regimens 5 days per week for 15 doses (3 weeks), then twice weekly for 12 doses.

Treatment of Drug-Susceptible Tuberculosis Clin Infect Dis. 2016 Oct 1;63(7):853-67

All Patients with HIV/TB Should be Treated with ART

- Reduces mortality rates significantly
- Decreases risk of developing AIDS-related conditions
- ART can be safely given during TB treatment
- Don’t hold ART until TB therapy completed

Official ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis Clin Infect Dis. **2016** Oct 1;63(7):853-67
Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf (Accessed 3/4/2016)

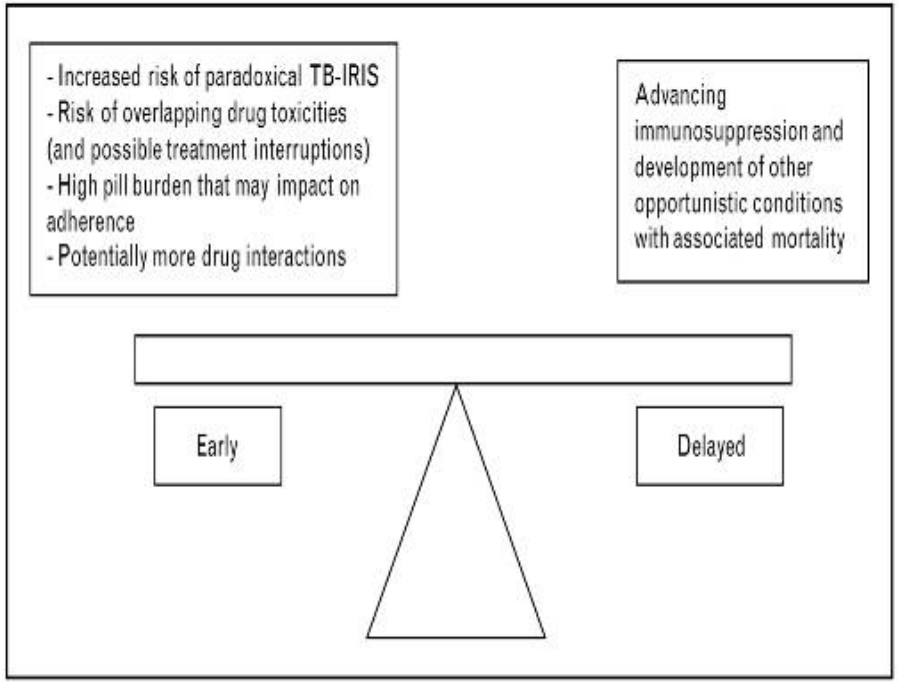
All Patients with HIV/TB Should be Treated with ART

- Important issues to consider:
  - When to start ART;
  - Significant PK drug-drug interactions between anti-TB and ARV agents;
  - The additive toxicities associated with concomitant ARV and anti-TB drug use; and
  - The development of TB-associated immune reconstitution inflammatory syndrome (IRIS) after ART initiation.

Official ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis Clin Infect Dis. **2016** Oct 1;63(7):853-67
Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf (Accessed 3/4/2016)

When to Start ART in HIV/TB

Figure 1 Potential risks associated with early versus delayed antiretroviral therapy in patients with HIV-associated tuberculosis



Cohen et. al. Current Opinion in HIV and AIDS 2010, 5:61–69

When to Start ART in HIV/TB

- If CD4 <50/mm^3: ART within 2 wks of TB treatment
- If CD4 ≥50/mm^3: ART by 8-12 wks of TB treatment

➢ TB meningitis- start ART after 8-10 wks of TB treatment, regardless of CD4 count
  - Higher rate of severe complications and mortality

- Patients already on ART should continue it, with careful monitoring, attention to drug interactions
- DOT and case management for all patients

- Treatment of Drug-Susceptible Tuberculosis Clin Infect Dis. 2016 Oct 1;63(7):853-67
- Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf

Case: Initial Diagnosis with TB and HIV (con't)

- TB treatment started
- Within 2 weeks, sputum smears were AFB (-)
- ART initiated 2 weeks after TB treatment started
- Negative cultures at 2 months of TB therapy, no cavity on initial CXR, on ART
- Completed treatment after 6 months
  - 2 months INH/RIF/PZA/EMB daily therapy
  - 4 months INH/RIF daily therapy (5 days/w)

Choosing ART Regimen During TB Treatment

ART-Naïve Patient

- Use 2 nucleoside reverse transcriptase inhibitors (NRTIs)* in combination with a third drug from one of 3 classes:
  - an integrase strand transfer inhibitor (INSTI),
  - a non-nucleoside reverse transcriptase inhibitor (NNRTI),
  - a protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (booster) (cobicistat or ritonavir).

*NRTI combinations used: ABC/3TC, TDF/FTC , or TAF/FTC

https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

ART-Naïve Patient

- Bictegravir (BIC)/TAF/FTC **(AI)**
- Dolutegravir (DTG)/ABC/3TC **(AI)**
  - if HLA-B*5701 neg
- Dolutegravir + TAF or TDF/FTC **(AI)**
- Raltegravir (RAL) + TAF or TDF/FTC **(BI for TDF, BII for TAF)**

tenofovir alafenamide (TAF); emtricitabine (FTC); abacavir (ABC); lamivudine (3TC); tenofovir disoproxil fumarate (TDF)
https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

TB Treatment in HIV

- **Rifamycins** should be included if possible
  - Rifampin (RIF) or Rifabutin (RFB), *not* Rifapentine (RPT)
  - Refer to tables Tables 19a through 19e for dosing recommendations
- Rifamycins accelerate drug metabolism, significant reduction in ARV exposure

❖Safe to use RIF without dose adjustment:

- NRTIs *except* TAF
- Fusion inhibitor enfuvirtide
- NNRTI Efavirenz (EFV)

https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/283/drugs-not-recommended-with-arv-agents

TB Treatment in HIV (con't)

- Increase ARV doses when **rifampin** used with INSTIs:
  - Dolutegravir (DTG) 50 mg BID dose only in patients without selected INSTI mutations
  - Raltegravir (RAL) increase RAL dose to 800 mg BID
  - CCR5 inhibitor Maraviroc (MVC)

- **Rifampin** not recommended for patients receiving:
  - all PIs (boosted or unboosted)
  - NNRTIs Elvitegravir (EVG), Etravirine (ETR), Rilpivirine (RPV)
  - NRTI TAF

https://aidsinfo.nih.gov/guidelines/html/1/adult-and-ado lescent-arv-guidelines/283/drugs-not-recommended-with-arv-agents

TB Treatment in HIV (con't)

- **Rifabutin (RFB)** weaker inducer of drug metabolism, alternative to RIF with PI- or INSTI-based ARV regimens
  - May be used with MVC;
  - Adjust RFB with NNRTIs or PIs (consider drug monitoring)

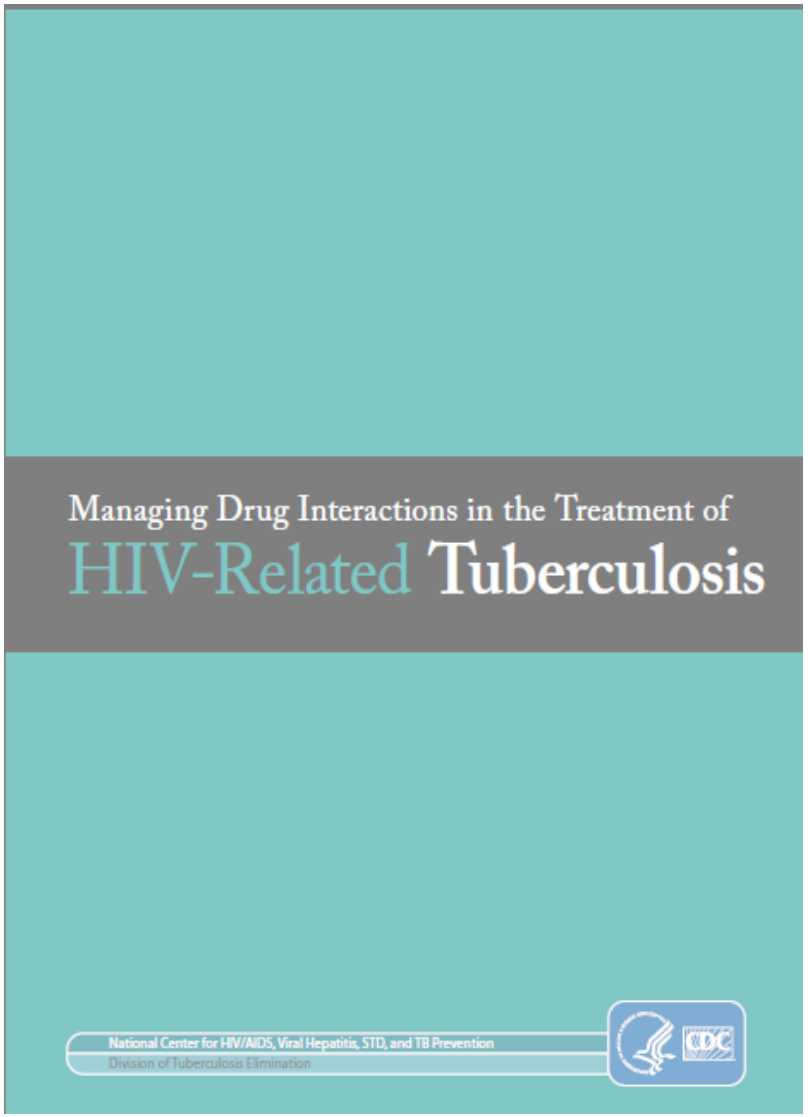
- Expert consultation in TB/HIV recommended for all patients, especially if drug resistance is present
- See Tables 18a through 18e for dosing recommendations

- **RPT not recommended for TB disease**

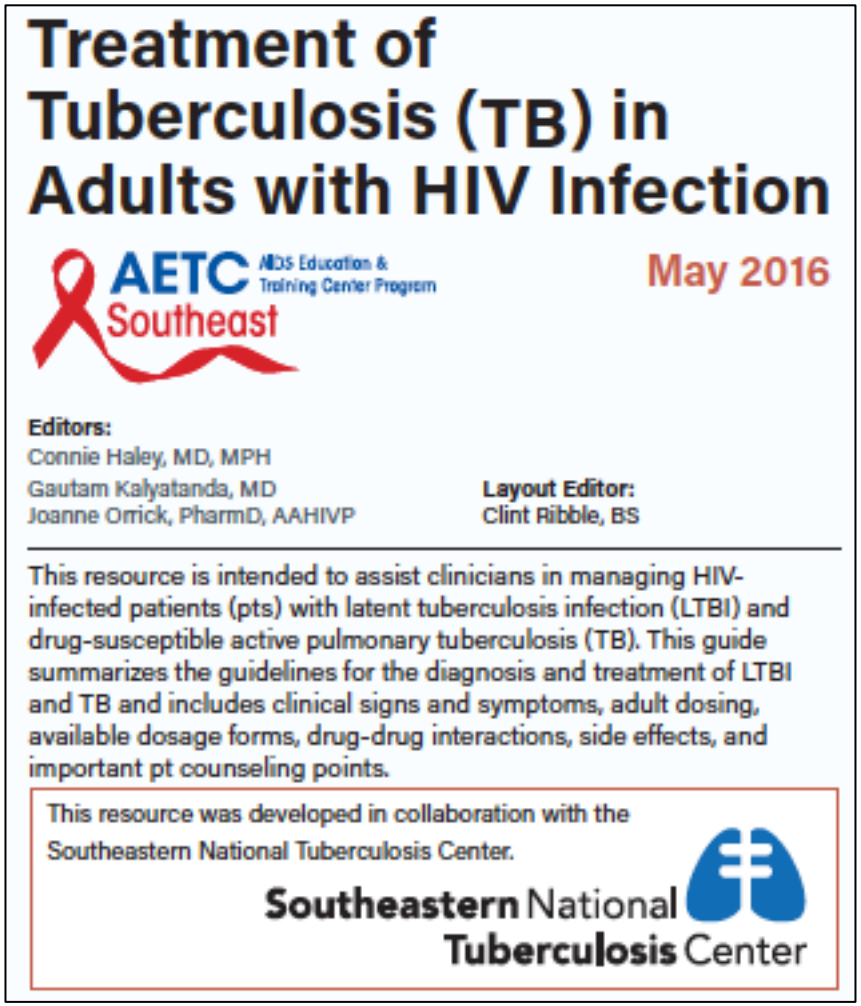
- Treatment of Drug-Susceptible TB Clin Infect Dis. 2016 Oct 1;63(7):853-67
- Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf

Who should have TDM?

- Patients failing treatment
- Resistant patients
- Patients with possible toxic side effects
- Patients with renal or hepatic dysfunction
- Drug interactions
- Compliance checks



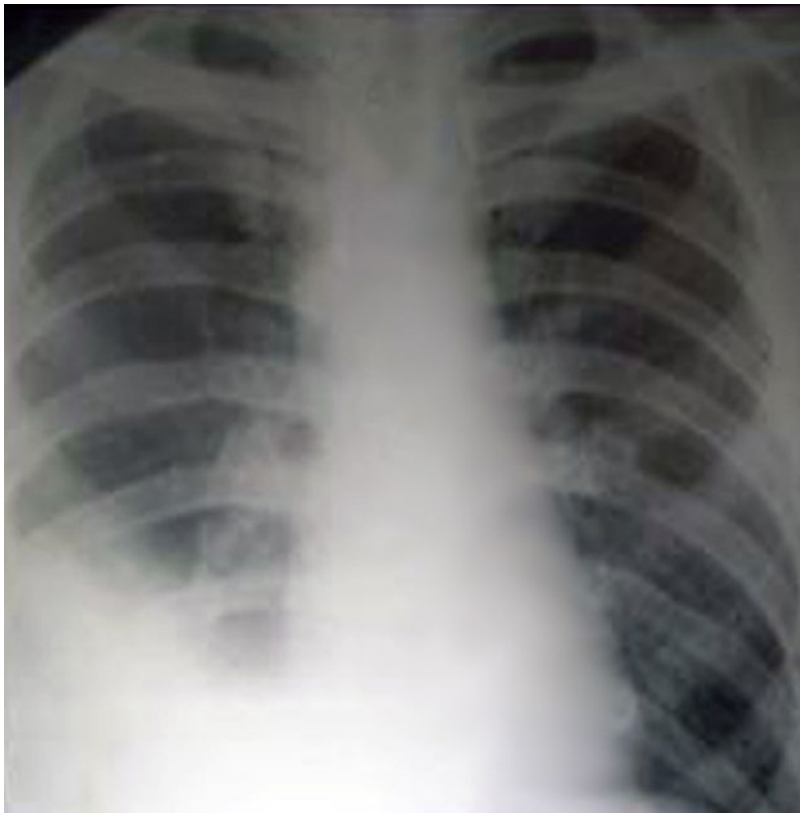
http://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/pdf/tbhiv.pdf



https://sntc.medicine.ufl.edu/Files/Products/TB-HIV%20pocket%20card%205-2016.pdf

Case: 34-year-old HIV-infected man from southern India

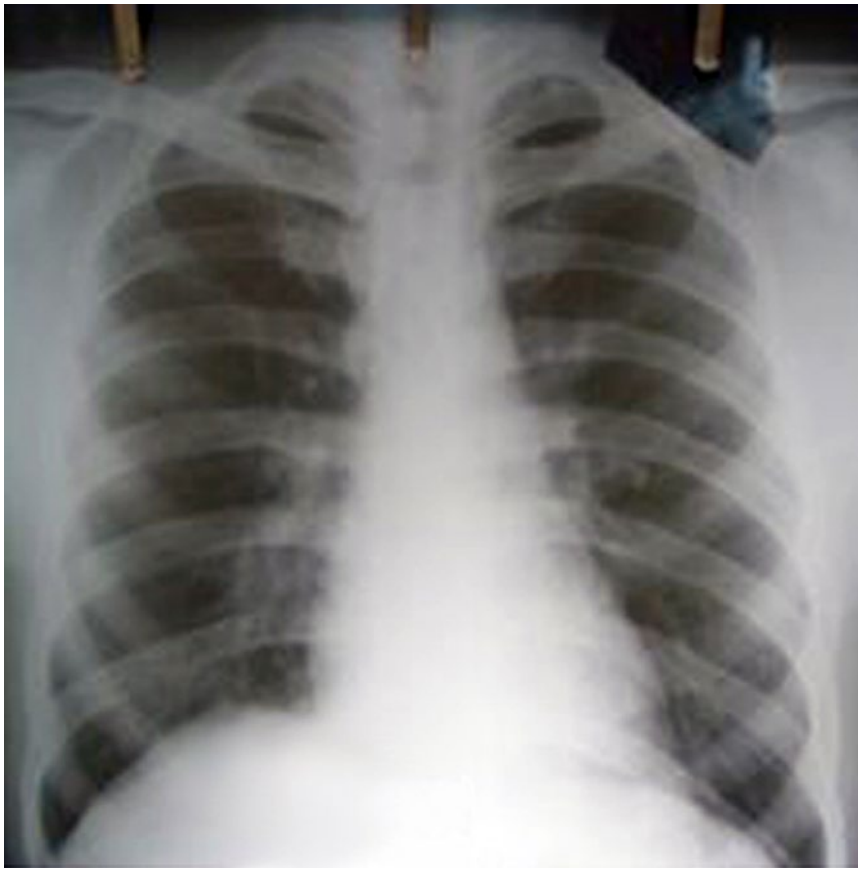
- Hemoptysis and weight loss
- CD4 count 60 cells/mm^3
- Never taken ART
- CXR: R. pleural effusion
- Sputum smear AFB positive
- Baseline labs normal AST, ALT, Bili, Alk Phos, Creat; Total white count low, mildly anemic
- Began INH, RIF, PZA, EMB



http://www.hivwebstudy.org/cases/resource-limited-setting/diagnosis-and-management-tuberculosis-immune-reconstitution

34-year-old HIV-infected man from southern India

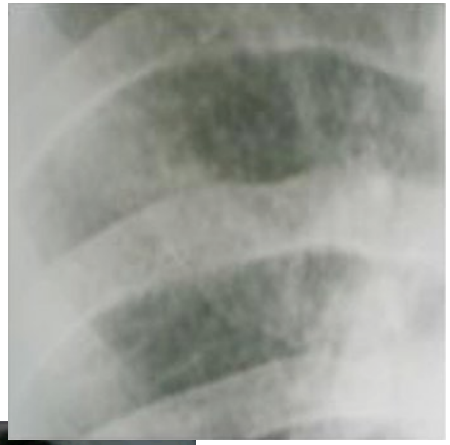
- Two months later, clinically improved, AFB smears are negative
- Repeat CXR: resolution of pleural effusion, no pulmonary infiltrates
- At that time, he begins ART with a regimen of atripla
  - Emtricitabine (FTC)
  - Tenofovir disoproxil fumarate (TDF)
  - Efavirenz (EFV)

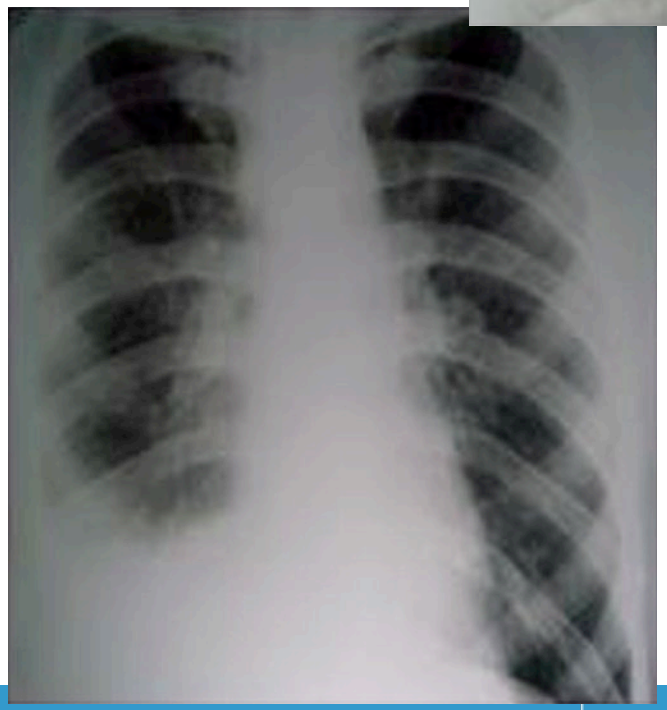


http://www.hivwebstudy.org/cases/resource-limited-setting/diagnosis-and-management-tuberculosis-immune-reconstitution

34-year-old HIV-infected man from southern India

- Returns to clinic 2 months later c/o chest pain, fever
- Vital signs are normal
- CXR: R-sided pleural effusion with R upper lobe infiltrates
- CD4 count now 166 cells/mm3
- Reports taking ART





http://www.hivwebstudy.org/cases/resource-limited-setting/diagnosis-and-management-tuberculosis-immune-reconstitution

What would you recommend regarding the management of this patient?

A. Give steroids, continue TB therapy, and withhold ART until symptoms improve and CXR has cleared.

B. The patient has likely developed MDR-TB; empirically change TB regimen and continue ART.

C. Given CD4 count<200 cells/mm^3, new opportunistic infection best explains worsening clinical course and he should undergo intensive evaluation.

D. Continue ART and TB therapy without change, check drug levels, repeat sputum C&S for drug-resistance, assess DOT, consider steroids if his clinical condition deteriorates further

Tuberculosis immune reconstitution inflammatory syndrome "IRIS"

- ART-induced restoration of pathogen-specific immune response to opportunistic infections such as TB.

- Two Forms:
  - Paradoxical IRIS: deterioration of a treated infection; commonly associated with ART initiation

  - Unmasking IRIS: new presentation of a previously subclinical infection; patients often recognized to have active TB disease within 3 mos of initiating ART therapy

Manabe et al JID 2009:199;437-444
Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf

TB-IRIS (2)

- Rapid recovery of mycobacterial immune responses results in inflammatory reaction to *M. tb* antigen
- Many published cohort studies of TB-IRIS reported incidence 8-43%
- Risk factors include:
  - Low CD4 cell count
  - High HIV viral load
  - Disseminated TB/high burden of TB
  - Short interval between starting TB and ART (though some studies show no difference in starting <2 vs. >2 months)

TB-IRIS (3)
Clinical Presentation

- Most frequently reported features:
  - Fever, enlarging lymph nodes, worsening radiograph, symptoms indicating previously unrecognized extrapulmonary sites
- Usually 2-12 weeks after starting ART, can last 2 months or longer
- Can occur prior to ART, even in HIV (-)
- Study from South Africa reporting high prevalence of rifampin resistant disease associated with IRIS*

*Meintjes et al CID 2009:48:667-678

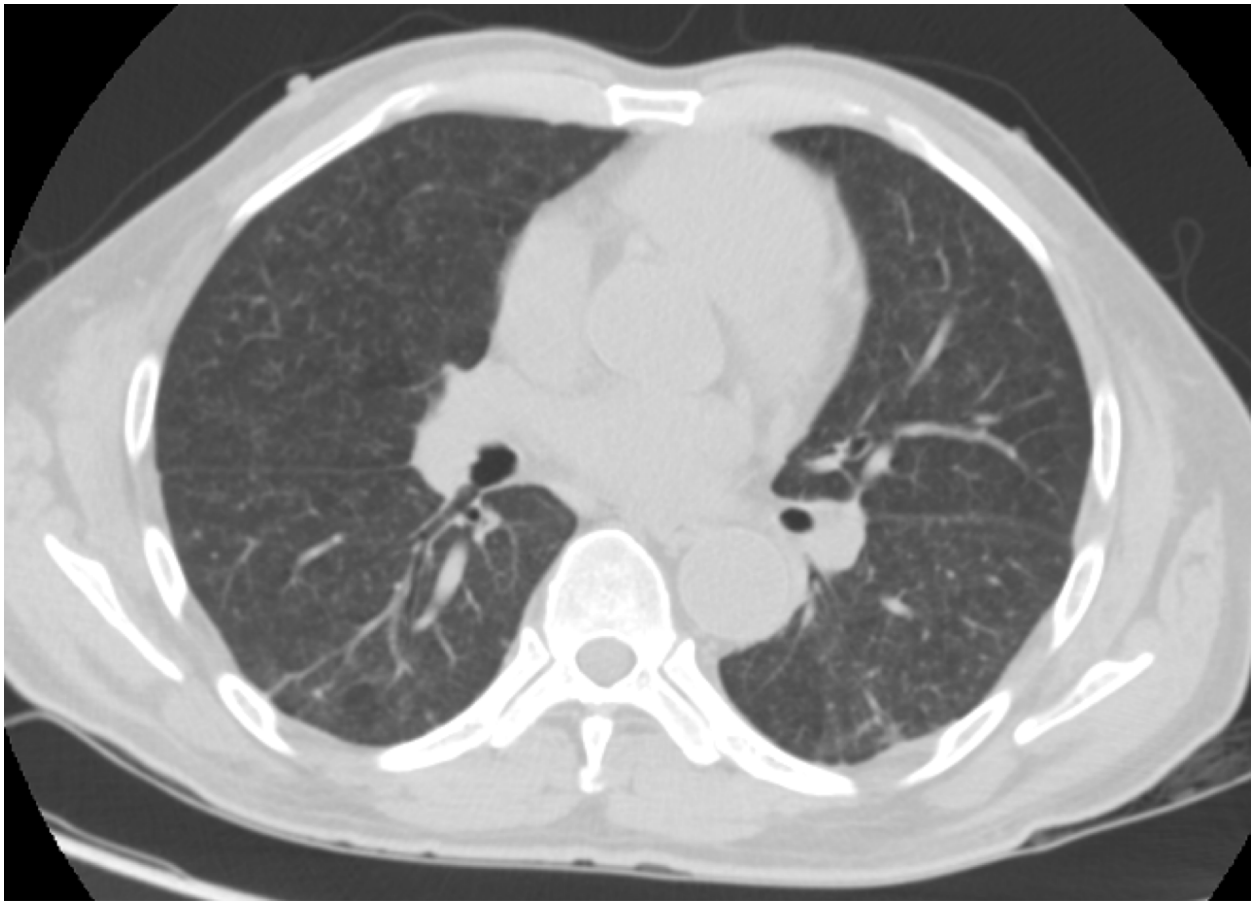
TB-IRIS (4)
Diagnosis

- Diagnosis of exclusion – no specific test available
- Consider other reasons patient may not be improving, or may worsen after initial improvement:
  - Other opportunistic infections
  - Non-adherence
  - Malabsorption of medications
  - Drug Resistant TB
  - Inability of drugs to penetrate affected area

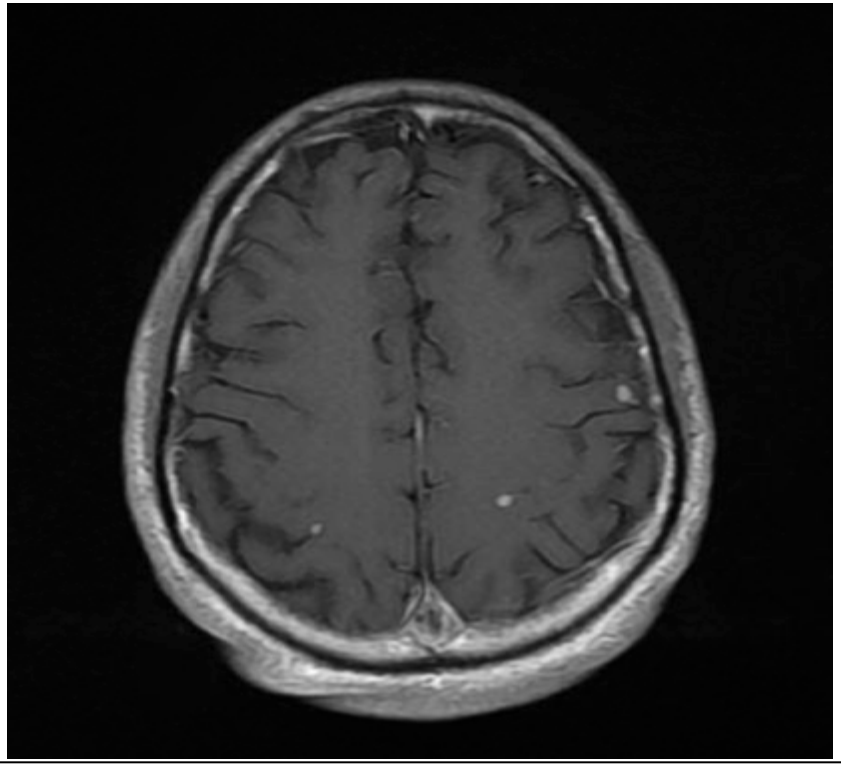
TB-IRIS (5)
Management

- Mortality rare except with CNS involvement
  - Neurologic involvement reported in ~12% of cases
- Most cases treated with supportive care
  - Antipyretics, NSAIDS, IV fluids
- When life threatening, corticosteroids used
  - 1.5 mg/kg/d for 2 wks followed by 0.75mg/kg/d for 2 wks
- Neither TB therapy nor ART should be stopped
  - unless TB-IRIS is severe and slow to respond to steroids or there is concern for drug toxicity

Case: African American with Pneumonia: CT 7/28/2016



Unenhanced chest CT: Diffuse miliary nodular appearance compared to prior studies and therefore primary concern for entities such as miliary TB or other opportunistic infections including fungal.



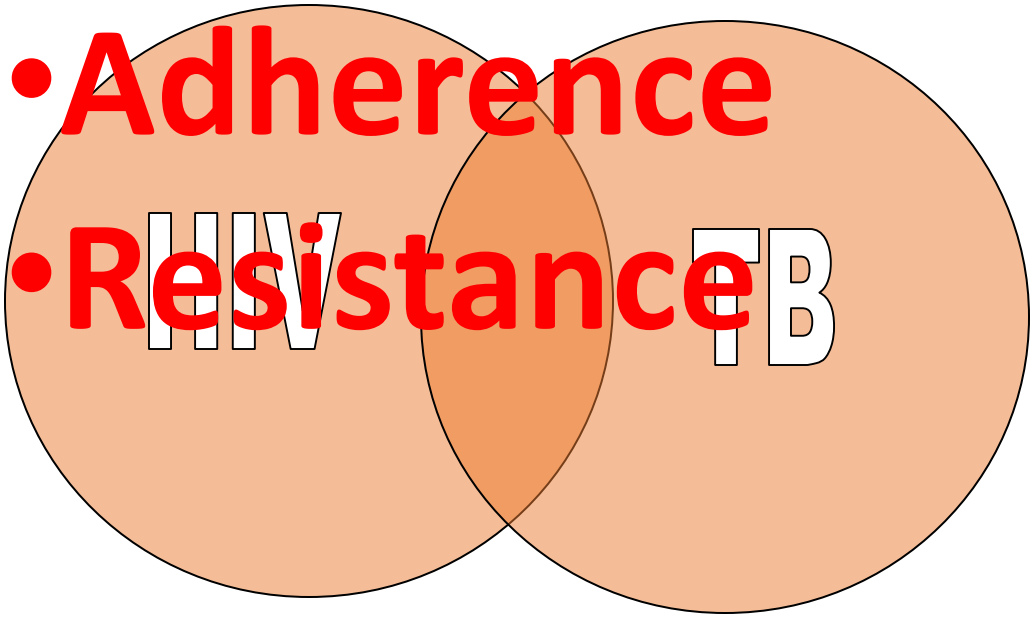
8/1/2016 Brain MRI with contrast:

- Multiple small nodules ranging from 1-6 mm, some larger ones have ring enhancement.
- These findings in this patient with known HIV and a miliary pattern in the lungs raises the possibility of TB.
- Other considerations would include CNS lymphoma and toxoplasmosis along with other bacterial or fungal infections.
- Metastatic disease is considered less likely.

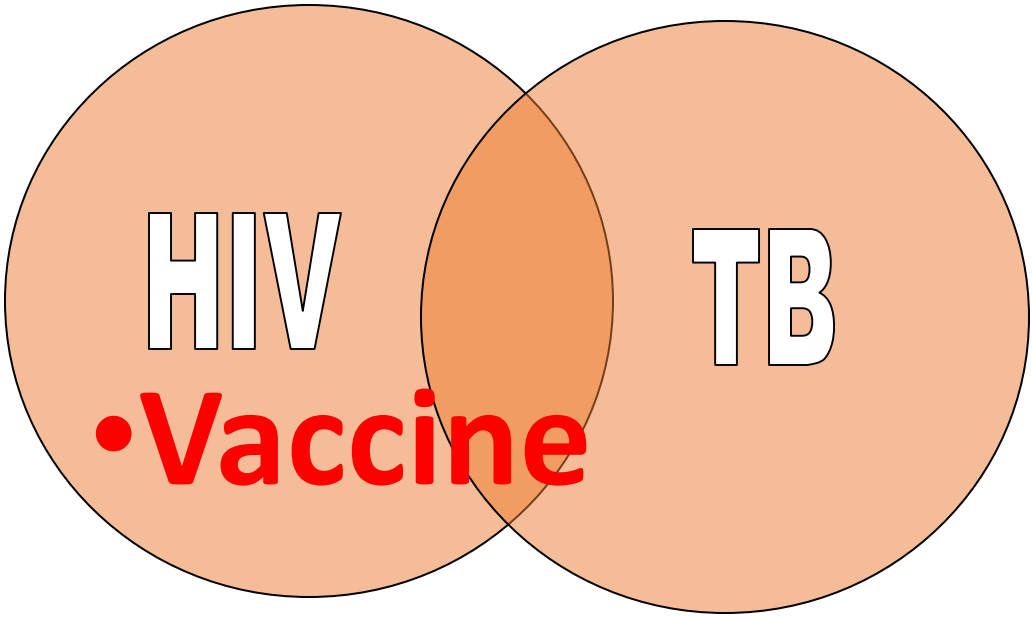
TB/HIV Summary

- HIV markedly increases risk of TB infection and disease
- Diagnosis of TB in HIV (+) patients can be challenging
- TB treatment in HIV (+) similar to HIV (-), more complicated
  - Polypharmacy (pill burden)
  - Tolerability/compliance challenges
  - Drug-drug interactions likely
  - Malabsorption of medications
  - Risk for paradoxical reactions (IRIS)
  - Compliance critical to prevent resistance/treatment failure
- TB treatment usually given with ART; both interventions reduce morbidity and mortality

Common Obstacles



Common Future



TB/HIV Resources

- TB/HIV Pocket card: http://sntc.medicine.ufl.edu/Files/Products/TB-HIV%20pocket%20card%205-2016.pdf
- 2016 Treatment of Drug-Susceptible TB. Clin Infect Dis available at: http://cid.oxfordjournals.org/content/early/2016/07/20/cid.ciw376.full
- Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf
- CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis. 2014. Available from URL: http://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/pdf/tbhiv.pdf
- TB Prevention in the HIV-infected Patient: Screening, Testing, and Treatment of Latent TB Infection (2011), http://www.currytbcenter.ucsf.edu/products/view/tb-prevention-hiv-infected-patientscreening-testing-and-treatment-latent-tb-infection

TB/HIV Resources

- Limiting Liver Toxicity in the HIV-Positive Patient with LTBI http://www.heartlandntbc.org/assets/products/limiting_liver_toxicity_in_the_HIV_positive_patient_with_ltbi.pdf
- Special Considerations for Treatment of TB Disease in Persons Infected with HIV http://www.cdc.gov/tb/publications/factsheets/treatment/treatmenthivpositive.htm
- TB and HIV/AIDS, http://www.cdc.gov/tb/publications/factseries/tbandhiv_eng.htm
- Recommendations for HIV Screening in Tuberculosis (TB) Clinics http://www.cdc.gov/tb/publications/factsheets/testing/hivscreening.htm
- Treatment of Drug-Susceptible TB Disease in HIV-Infected Persons, http://www.cdc.gov/tb/publications/factsheets/treatment/treatmenthivpositive.htm

QUESTIONS???

Image source: https://www.aids.gov/hiv-aids-basics/