TB and HIV Co-infection Update: Global Becomes Local

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TB and HIV Co-infection: Some Resources

- http://www.cdc.gov/tb
- http://www.umdnj.edu/globaltb/home.htm
- AETC Natl Resource Center: http://www.aidsetc.org
- http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf
- http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf
- CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: MMWR 2009; 58 (No. RR-4). http://www.cdc.gov/mmwr/pdf/rr/rr58e324.pdf

Objectives

- Epidemiology of TB and HIV co-infection (Global and Local)
- Impact of HIV Infection on the diagnosis and clinical presentation of TB (and TB on HIV)
- Management issues in TB/HIV co-infection
  - Screening for LTBI and TB disease: TST and IGRA
  - New treatment regimens for LTBI
  - Drug interactions in co-infected patients
  - TB treatment, ART, and IRIS in co-infected patients
- MDR and XDR TB: new diagnostic tools and new drugs

TB: Some Important Terms

- Latent TB Infection (LTBI)
- TB Disease (Tuberculosis, Active Tuberculosis)
- Primary Tuberculosis
- Reactivation Tuberculosis
- Tuberculin skin Test (TST) or PPD
- Interferon Gamma Release Assays (IGRA)
- DOT and DOTS

Clinical Vignette: Patient 1

- A 36 year old woman is referred for management after discharge from the hospital on 4 drug therapy (RIPE) with newly diagnosed smear positive pulmonary tuberculosis
- She was born in South Africa, and has been living in the US for 2 years with her husband and 11 year old child
- She denies any significant past medical history and has no medical records from her arrival in the US
- HIV testing was not performed during her hospital stay

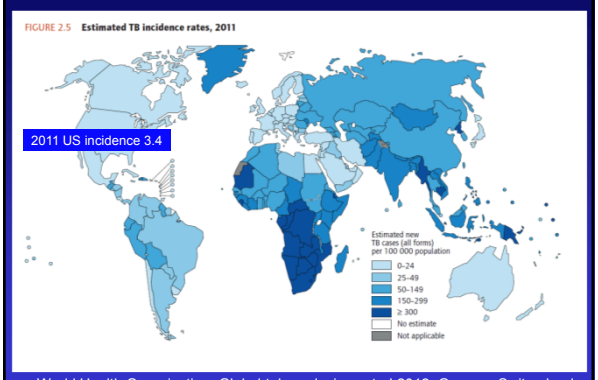
Clinical Vignette: Q1

- Should this woman have HIV testing performed as part of her TB clinical evaluation?
  - A) HIV testing should be offered
  - B) HIV testing should be performed
  - C) No, HIV testing is not necessary or indicated
  - D) Testing is optional as knowledge of HIV status will not affect her TB management

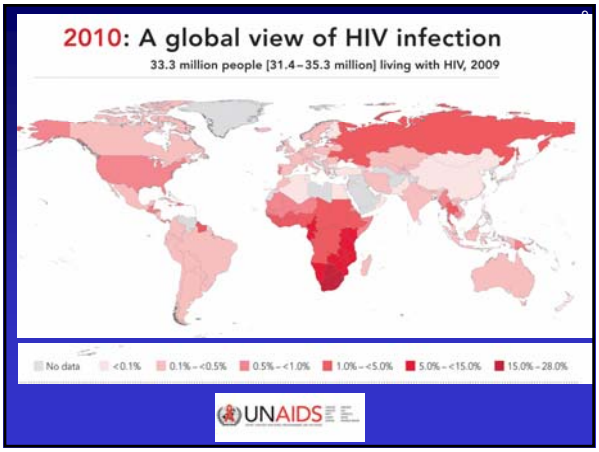
Clinical Vignette: Q2

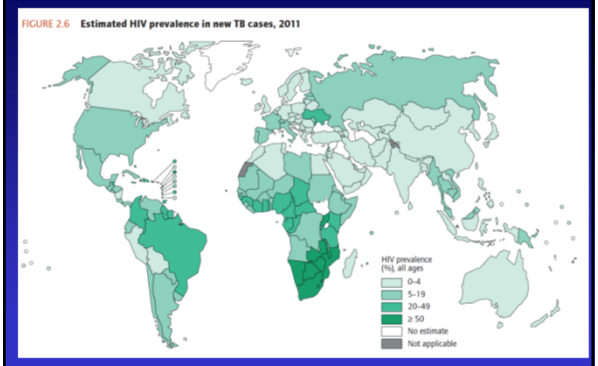
- Based on what you known, what is the likelihood that this woman will have a positive HIV test

A) Less than 5%
B) 5 to 20%
C) 20 to 50%
D) More than 50%



World Health Organization. Global tuberculosis control 2012. Geneva, Switzerland:





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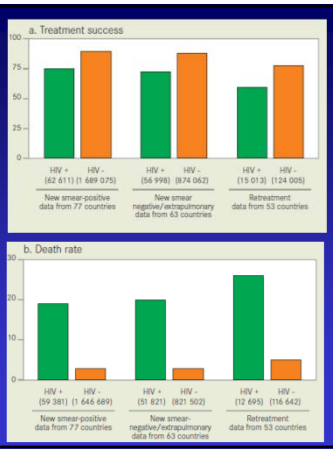
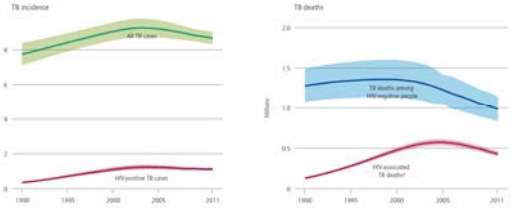


Treatment Outcomes for HIV-positive and HIV-negative TB patients, 2009: Successful treatment outcomes are lower and mortality is > 4x higher in HIV-positive cohort

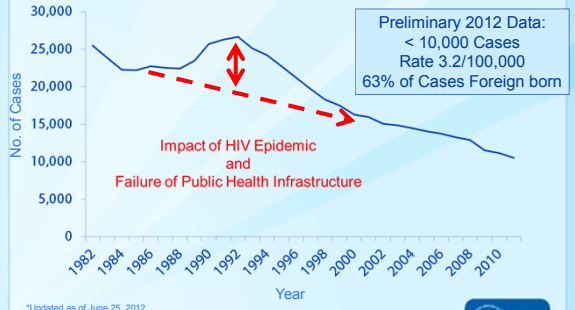
Source: WHO

TB Incidence and TB Deaths: 1990-2011



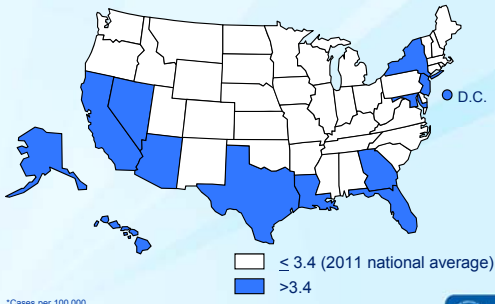
- 1/3 of World's population infected with TB
- 2011: 8.7 million new TB cases, 13% HIV co-infected but more than 80% co-infected in regions of southern Africa
- 1.4 million TB deaths, including 430,000 HIV-positive
- Rates of new TB cases and TB mortality are falling in all regions of the globe, even in Africa and even in HIV +

Reported TB Cases United States, 1982–2011*



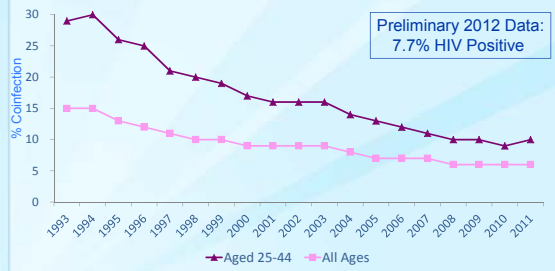
*Updated as of June 25, 2012.

TB Case Rates,* United States, 2011



*Cases per 100,000.

Estimated HIV Coinfection in Persons Reported with TB, United States, 1993 – 2011*



*Updated as of June 25, 2012
Note: Minimum estimates based on reported HIV-positive status among all TB cases in the age group

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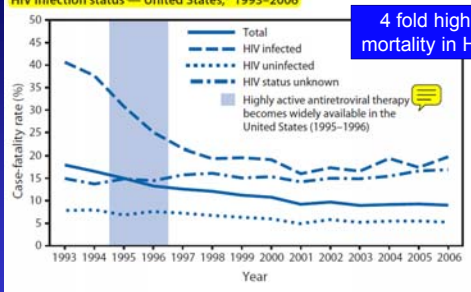
FIGURE 2. Case-fatality rates among culture-confirmed tuberculosis patients who were alive at diagnosis and whose treatment outcomes were known, by HIV infection status — United States,* 1993–2006



4 fold higher mortality in HIV+

* Excludes California data because of lack of HIV data on patients with tuberculosis without AIDS.

CDC. Mortality among patients with tuberculosis and associations with HIV status —United States, 1993–2008. MMWR 2010; 59:1509–13

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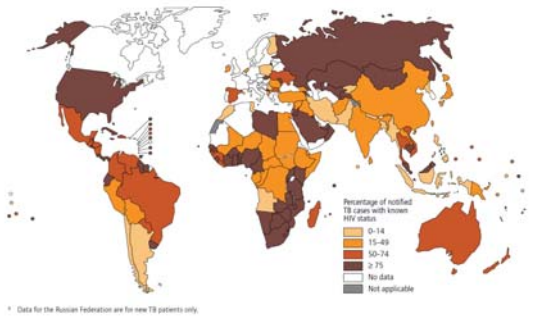
FIGURE 7.3 Percentage of TB patients with known HIV status by country, 2011*



* Data for the Russian Federation are for new TB patients only.

World Health Organization. Global tuberculosis control 2012. Geneva, Switzerland:

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Many Groups are at Higher Risk for Both HIV Infection and TB Infection

- Injection drug users
- Homeless
- Incarcerated/other congregate settings
- Non-injection drug users
- Lower socioeconomic status

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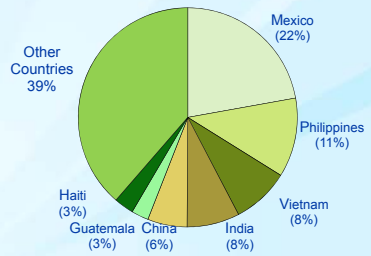
TB, HIV and Immigration

- Rates of TB disease in HIV-infected individuals in developed countries such as the U.S. with low incidence of TB are decreasing
- BUT… immigration of HIV-infected individuals from countries with higher TB prevalence, and spread of HIV infection within poorer immigrant communities will contribute to the persistence of the HIV-TB co-epidemic

Countries of Birth of Foreign-born Persons Reported with TB, United States, 2011



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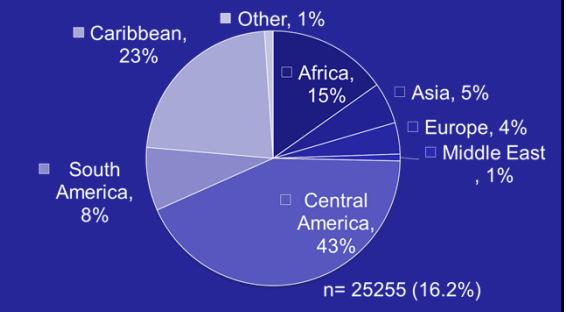
New (US) HIV infections in Patients Born Outside the US: 2007-2010



From: Prosser et al JAMA, 2012

HIV Testing in Patients with Active Tuberculosis (TB Disease) and LTBI

- All patients diagnosed with TB disease should undergo HIV testing at least by the time of initiation of TB therapy (CDC Treatment Guidelines)
  - If HIV +, should also have a CD4 count
- All patients with LTBI should be offered HIV testing
  - Knowledge about HIV infection impacts strongly on management of LTBI

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Direct Impact of HIV and TB Co-infection

- What does HIV infection do to the natural history of TB infection?
  - Risk of progression from LTBI to disease
  - Manifestations of disease
- What does TB infection and TB disease do to the natural history of HIV infection?

Natural History of TB Infection

- Primary TB Infection occurs when tubercle bacilli are inhaled and settle in the lung of immunologically naïve hosts who lack specific anti-TB directed cell mediated immune response
- Organisms replicate in foci in the lung and can disseminate locally or systemically by direct spread and through lymphatic or hematogenous routes
- As specific immune responses evolve, local infection and early disseminated infection is eventually controlled in most individuals
- A **+ TST** or **+ IGRA** test is a (specific) marker of immune response to and thus infection with MTB

Natural History of TB Infection and Risk for TB Disease

- On average, approximately half of the total lifetime risk for developing TB disease (clinical or subclinical) occurs within the 1st few years after exposure (primary disease): 5% risk
  - Genetics, immune status (eg HIV), strain virulence
- Beyond this period, the risk of developing clinical TB disease (reactivation disease) is low but persists throughout life; risk increases in conditions affecting local and systemic immune function
- Re-infection can occur in those with persistent immune deficiencies and ongoing TB exposures

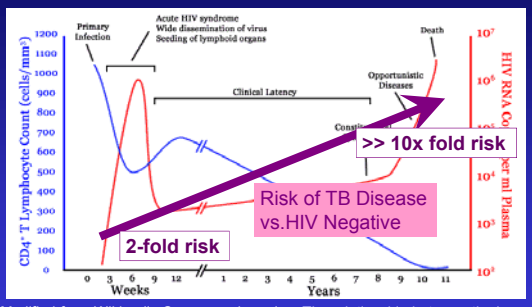
TB and HIV Interactions: Key Points

- During TB infection, T -lymphocytes release IFN-gamma and activated macrophages release other cytokines including TNF and IL-1 that enhance killing of intracellular mycobacteria
- IFN-gamma and TNF accelerate HIV viral replication
- HIV diminishes the host ability to control TB by lowering CD4 T cell counts, decreasing IFN-gamma production and decreasing cell mediated immunity
  - Can't form/maintain granulomas that contain TB
  - Macrophages inefficient in killing mycobacteria

TB as an Opportunistic Infection

- Risk for progression from LTBI to TB disease in HIV infected (7-10% annual risk) is much greater than for HIV-negative patients (lifetime risk 5-10%)
  - Single greatest risk factor for progression from LTBI
- Increased risk for TB at all levels of immune suppression, though relative risk and disease manifestations differ in different CD4 ranges
- Increased risk for TB disease begins early after HIV infection

Risk of TB Disease and Natural History of HIV Infection



Modified from Wikipedia Commons, based on The relationship between the human immunodeficiency virus and the acquired immunodeficiency syndrome, US National Institute of Allergy and Infectious Diseases

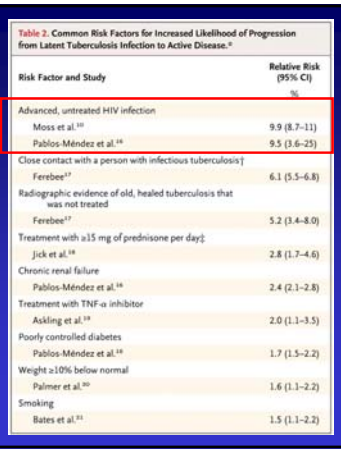


Table 2. Common Risk Factors for Increased Likelihood of Progression from Latent Tuberculosis Infection to Active Disease.*

Risk Factor and Study	Relative Risk (95% CI)
	%
Advanced, untreated HIV infection	
Moss et al.[10]	9.9 (8.7–11)
Pablos-Méndez et al.[16]	9.5 (3.6–25)
Close contact with a person with infectious tuberculosis†	
Ferebee[17]	6.1 (5.5–6.8)
Radiographic evidence of old, healed tuberculosis that was not treated	
Ferebee[17]	5.2 (3.4–8.0)
Treatment with ≥15 mg of prednisone per day‡	
Jick et al.[18]	2.8 (1.7–4.6)
Chronic renal failure	
Pablos-Méndez et al.[16]	2.4 (2.1–2.8)
Treatment with TNF-α inhibitor	
Askling et al.[19]	2.0 (1.1–3.5)
Poorly controlled diabetes	
Pablos-Méndez et al.[16]	1.7 (1.5–2.2)
Weight ≥10% below normal	
Palmer et al.[20]	1.6 (1.1–2.2)
Smoking	
Bates et al.[21]	1.5 (1.1–2.2)

Common Risk Factors for Increased Likelihood of Progression from Latent Tuberculosis Infection to Active Disease.

Horsburgh CR Jr, Rubin EJ. N Engl J Med 2011;364:1441-1448

The NEW ENGLAND JOURNAL of MEDICINE

Impact of Starting Anti-Retroviral Therapy (ART) on Risk of Tuberculosis

- Starting ART decreases rates of tuberculosis in HIV-infected individuals in both developed and resource constrained settings
- Magnitude of effect: 54 to 92% decrease in TB rates, most of this benefit (in high TB prevalence regions) is in the first 2-3 years of ART
- Benefit correlates with increase in CD4 counts
- Despite ART, risk of TB probably never completely falls to that of HIV-negative individuals

TB Disease in HIV

- Increased TB disease occurs from both more progressive primary infections (newly infected) and more reactivation disease (in those with LTBI)
  - High vs Low TB incidence countries
- Re-infection is common, especially in those with more severe immunosuppression in high TB incidence areas
- **But** → with lower CD4 T cell counts, Clinical and X-ray presentation do not always correlate with traditional concepts of primary vs. reactivation disease

Impact of HIV on Presentation of TB

- CD4 counts > 350: Similar to HIV Negative
  - Primarily pulmonary disease with "usual" radiographic appearance (upper lobe fibro-nodular infiltrates with/without cavities)
  - Extra-pulmonary disease does occur more frequently than in HIV-negative
  - Unusual manifestations and disseminated disease uncommon

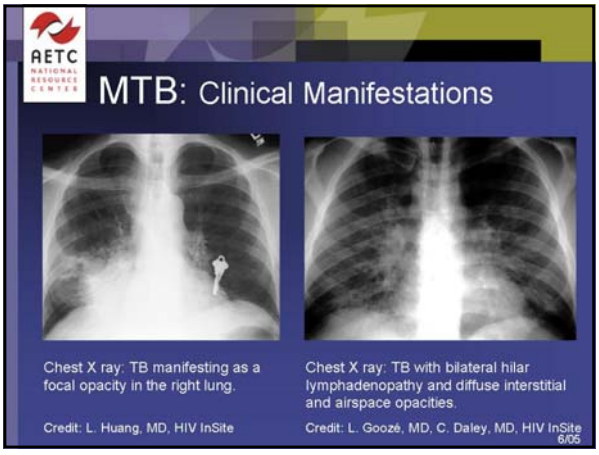
TB Presentations with More Advanced HIV Infection

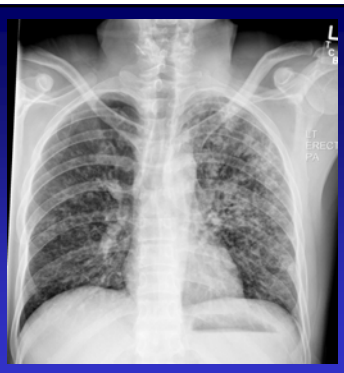
- As CD4 counts fall, extra-pulmonary TB increases
- With severe immunodeficiency (CD4 < 50) extra pulmonary manifestations such as diffuse lymphadenitis, pleuritis, meningitis and pericarditis even more common
- Increase in severe systemic syndromes and sepsis-like presentations that are associated with high mortality
- Organism burdens in these patients high, with high rate of disseminated disease and + mycobacterial blood cultures
- Differences in CXR appearance of pulmonary TB in advanced HIV infection

Pulmonary TB in Advanced HIV Infection

- CXR appearance may be "atypical" i.e., resembling that seen in primary TB infection:
  - Interstitial infiltrates, Lower zone involvement, absence of upper lobe cavitation or fibrosis
  - Can look like bacterial pneumonia or Pneumocystis
  - CXR can be "normal": 20-30% (even if + sputum culture)
  - Sputum smears often negative despite + culture

➢Result: delays in diagnosis, higher mortality





38 year old recent Mexican immigrant with newly diagnosed HIV infection and CD4 count of 258

Clinical Vignette: Patient 2

- A 48 year old homeless man has HIV testing performed by the outreach van in Camden and is found to be positive
- He looks well at this time and denies any symptoms, his CD4 count is 138 cells/mm^3
- He refuses to come to the HIV clinic for evaluation or treatment, but does agree to come to get a "TB test" since he remembers that his mother had TB when he was a child

Clinical Vignette: Q3

- How should this patient be evaluated for possible TB infection or active disease?
  - A) TST using 5 mm as cut off for positive
  - B) An IGRA test
  - C) Either A or B
  - D) Chest X-ray
  - E) Symptom assessment

Testing for LTBI in HIV Infected: TST

- Tuberculin skin test (TST)
- Criteria for a positive TST in HIV infection (at any CD4 count) is 5 mm
- But…likelihood of a positive TST in those with TB infection decreases as CD4 count falls
  - Negative predictive value low for CD4 <200
    - Only 0 to 20% with TB infection will have a positive TST when CD4 < 200

Testing for LTBI in HIV Infected: IGRAs

- Interferon Gamma Release Assays (IGRA's)
  - QuantiFERON® TB-Gold in-Tube
  - T-Spot.*TB*™ Assay
- IGRAs: General considerations
  - Greater specificity for a positive IGRA compared to a positive TST for populations with history of prior BCG
  - Fewer patient visits to complete testing protocol (1 vs 2-4)
  - Less test interpretation bias issues by the test reader (but more logistical problems with processing in the lab)
  - Cost issues

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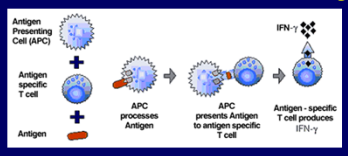
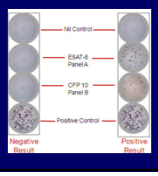
IGRA Assays



Source: Cellestis

Tests	Results Flag	Reference Range	Units
Quantiferon	Detected	(Not Detected)	
Nil	0.07		IU/mL
Mitogen-Nil	>10.00		IU/mL
TB Ag-Nil	>10.00		IU/mL



IGRA vs. TST in HIV Infection

- Incomplete agreement of TST with IGRA, no "gold standard"
- As with TST, rate of positives decreases with more lower CD4, and all tests may be negative or indeterminate in those with active TB disease
- In some studies, IGRA was more "sensitive" than TST in HIV infected, and in other studies T-Spot.*TB*™ performed better at low CD4 counts, but overall superiority of either IGRA (compared to each other or compared to TST) not yet clearly demonstrated
- Do either? Both? CDC/HIVMA/IDSA OI Guidelines and CDC IGRA guidelines recommend either test as appropriate for screening (but not both routinely)

IGRA or TST: What does the CDC tell us?

- IGRA is Preferred for:
  - Groups with low rates of return for TST reading
  - Those with history of BCG vaccination
- TST is preferred for those < 5 years of age
- For most others both tests are interchangeable
- Situations where use of a second test could be appropriate if the first test is negative:
  - In populations where risk of TB infection, risk of progression or risk of poor outcome are higher
    - ➢This would include HIV infected

Practical Issues in Screening

- All newly diagnosed HIV infected patients should be screened for LTBI
  - TST (5 mm cut off) **OR** IGRA **AND** symptom assessment
  - No Sx, TST negative, CD4 > 200→ No Rx
  - No Sx, TST negative, CD4 < 200→ No Rx but …
  - No Sx, TST + (any CD4)→ Evaluate for TB disease and treat for LTBI if active disease excluded
  - If TB Sx regardless of TST result (any CD4)→ Evaluate for TB disease
- HIV+ contacts of infectious cases should be treated regardless of TST or IGRA status, even if prior Rx

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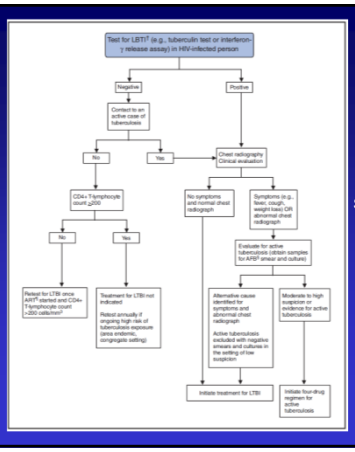

Schema for the diagnosis of LTBI

http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf

Screening for LTBI in HIV

- Negative screening test, no symptoms but CD4 counts < 200 are really "TB status indeterminate"
  - Re-test when CD4 > 200, but ongoing symptom and risk assessment
- How often after baseline testing should repeat TST or IGRA be done in HIV + individuals?
  - Depends on CD4 count, symptoms and risk factors
- Should those with low CD4 and high risk for LTBI (*e.g.,* from TB endemic countries) be treated for LTBI regardless of TST/IGRA results, as WHO recommends for resource-constrained regions?

Clinical Vignette: Patient 3

- 55 year old health care worker with longstanding HIV disease, CD4 count 324 on ART
- She has annual TST at work and has been negative for the past 10 years
- T-Spot.*TB*™ test is done as part of annual assessment in HIV clinic and is positive. She never had an IGRA test performed previously
- No known TB occupational (or other) exposures

Clinical Vignette: Q4

- What Should you do about the positive IGRA test?

A) Nothing – has had a negative TST no further evaluation needed

B) Repeat the TST

C) Repeat the T-Spot.*TB*™ test

D) Perform a Quanti-FERON® TB-Gold in-Tube test

E) Evaluate for active TB disease

Clinical Vignette: Patient 4

- 56 year old MSM with longstanding HIV infection, CD4 800-900 on ART
- Multiple negative TSTs in the past
- QFT-GIT test in 4/2010 (annual screen): Negative
- QFT-GIT test in 7/2011 (annual screen): Positive
- No signs or Sx of active TB
- No known TB exposures

Clinical Vignette: Q5

- What Should you do about the positive IGRA test?

A) Nothing – likely a false positive test

B) Repeat the QFT-GIT

C) Perform a T-Spot.*TB*™ test

D) Perform TST

E) Evaluate for active TB disease

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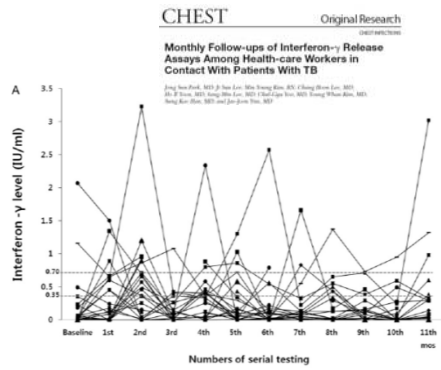
Testing for LTBI in HIV Infection

- There is no "perfect" TB Test
- TB tests (TST or IGRA) need to be interpreted in conjunction with clinical assessment and assessment of risk factors
- All positive tests need further evaluation and in (nearly) all instances should be treated



Results for the 25 (of 48) serially monitored HCW who had inconsistent results on IGRA

Treatment Regimens for LTBI

Table 2. **Latent TB Infection Treatment Regimens**

Drugs	Duration	Interval	Minimum doses
Isoniazid	9 months	Daily	270
		Twice weekly*	76
Isoniazid	6 months	Daily	180
		Twice weekly*	52
Isoniazid & Rifapentine	3 months	Once weekly*	12
Rifampin	4 months	Daily	120

*Use Directly Observed Therapy (DOT).

Four current CDC/USPHS approved options

Estimated Efficacy (prevention of TB Disease) 60-90%, highest rates where adherence is highest

Treatment of LTBI in HIV

- INH: daily for 9 months plus pyridoxine
  - No major interactions with ART though important drug toxicities (Hepatitis and neuropathy)
  - Can use twice weekly (but only if receiving DOT)
  - 6 months of INH est. about 80% as effective as 9 mos
  - ➢ Note: Currently a national INH shortage
- Rifampin: daily for 4 months
  - Used when INH resistance suspected or toxicity concerns (Hepatitis and chronic liver disease common in HIV)
  - Drug interaction issues with ART
  - Rifabutin (dose adjusted) is an alternative if PI are used

Newer LTBI Regimen for HIV

- INH 900 plus Rifapentine 900 weekly by DOT x 12 weeks
  - South African Study: (NEJM, 2011) in HIV+
    - vs INH 900 + Rifampin 600 twice weekly by DOT or INH daily x 6 mos or INH daily for up to 6 years
  - CDC PREVENT TB Study of > 8000 patients
    - vs INH daily x 9 months
    - Included some HIV positive patients
    - Equivalent to 9 mos of INH
- Do Not Use Rifapentine in patients on ART (though some ART regimens being studied in trials)

Clinical Vignette: Patient 2

- Our homeless man has a TST read as 7 mm induration at 48 hours
- On further questioning, now says that he has had a non-productive cough for 2 months and night sweats for a month and has lost 5 pounds over that time
- A CXR is negative

Clinical Vignette: Q6

- What should be done now?

A) Start treatment for LTBI with INH

B) Start treatment for LTBI with Rifampin

C) Start treatment for LTBI with Isoniazid and Rifapentene

D) Collect sputum for Acid Fast Bacilli x 3

E) Initiate 4 drug regimen for active TB

Identifying TB Disease in HIV Infected

- Limitations of "usual" screening tools (CXR and sputum) in HIV+, especially at low CD4
  - Smear negative but culture positive disease
  - CXR negative but culture positive disease

- Symptom assessment
- Pulmonary Symptoms: Prolonged Cough (> 3 weeks), Chest Pain, Hemoptysis
- Systemic Symptoms: Fever, Chills, Night sweats, Appetite loss, Weight loss, Easy fatigability

Treating TB in Co-Infected Patients: Drug Interaction Issues

- Major issue: interactions of Rifamycins with ART
  - PI'S, NNRTI's, integrase inhibitors, CCR5 blockers
- Rifamycins increase metabolism (reduce serum levels) of these classes of ART thru induction of CYP3A or UDG1A1→ increase risk for ART failure
  - Rifampin > rifapentine > rifabutin
  - Effect on PIs (80-90% reduction) greater than NNRTI's (25-40% reduction)
  - PI's increase concentrations of rifabutin thru inhibition of CYP3A

Other Issues with Concurrent Rx for TB and HIV (and other OI's): Overlapping Toxicities

- Hepatotoxicity
  - Many HIV+ also Hepatitis C or B co-infected
- Nausea and vomiting
- Diarrhea
- Peripheral neuropathy
- Rash
- Ocular

Managing Drug Interactions in Treatment of HIV-Related Tuberculosis

Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Last Updated February 13, 2013. at http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf

Note: Current PK data is insufficient for the newest ART agents (rilpivirine, cobicistat/elvitegravir) to recommend use with Rifamycins

Coordination of TB care and HIV is Critical!!

Other Treatment Issues in Management of TB in HIV Infected Individuals

- Treatment principles are the same as those for HIV negative (with some caveats)
- **Early** initiation of Rx when TB is suspected due to higher risk of overwhelming infection/mortality and potential for infectivity without the "usual" clues
- Standard Rx: Initiation of 4 drug regimen: INH + a Rifamycin + Ethambutol + PZA (unless baseline susceptibilities are known or high risk of resistance)
- **DOT** until completion of Rx for HIV co-infection is strongly encouraged, regardless of site of infection

Duration of Treatment in HIV+

- Pulmonary TB: Standard courses (6 mo) for susceptible disease give good cure rates though relapse rates may be higher in HIV infected
- Those who are still sputum culture positive at 2 months even without cavitation should receive longer (9 mo) Rx
- Longer courses for disseminated disease and other complicated extra-pulmonary disease sites
- Slower responses in HIV+ may be due to absorption issues – consider TDM (therapeutic drug monitoring) early if concerns about adequacy of clinical response
- Higher Risk of Rifampin resistance if CD4 <100 using 2x/ week therapy: only use 3x/week or daily therapy

Clinical Vignette: Patient 1

- Our 1st patient, the woman from South Africa, is HIV tested and found to be positive, and her CD4 count is 40 cells/mm^3
- She is improving on treatment for pulmonary TB and is 2 weeks into her course of treatment
- Her isolate is pan-sensitive and she continues on initiation phase treatment with INH 300 mg, RIF 600 mg and PZA 1500 mg daily by DOT
- When should she be started on ART?

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Clinical Vignette Q7

- A) Now
- B) Between 2 and 4 weeks of TB treatment
- C) At completion of her initiation phase of TB treatment (40 doses of INH + RIF + PZA)
- D) At the end of her 6 month course of TB therapy

To Delay or Start ART in Active TB?

Reasons to Delay

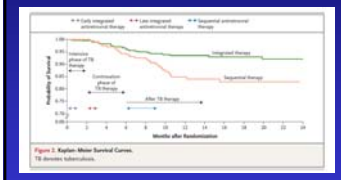
- Multiple drugs, toxicities and interactions
- Potential for decreased adherence
- TB is the priority, HIV is a "chronic" disease and Rx can wait
- ART →IRIS

Reasons to Start

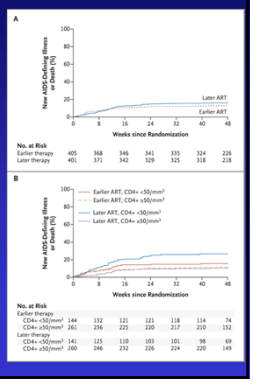
- HIV (esp. advanced HIV) has significant morbidity and mortality
- Earlier ART beneficial for ALL who are HIV+
- Early initiation of ART improves the prognosis of patients with almost all OI's at 6 months

TB and HIV: Timing of Treatment

- TB Rx started in all ASAP
- HIV Rx also started in all, but when?



Karim et al, NEJM 2010 (South Africa),



Havlir DV et al. NEJM 2011 (International ACTG Triall)

Current Recommendations (March 27, 2012 Updated DHHS ART guidelines)

- **All with HIV and TB should be started on ART (AI)**
- **CD4 < 50 → Start ART within 2 weeks (AI)**
- **CD4 ≥ 50→**
  - **With major severity* clinical HIV disease start ART within 2 to 4 weeks (BI:CD4 50-200, BII: CD4 > 200)**
  - **With less severe disease→ can be delayed, but start ART by 8-12 weeks in all (AI:CD4 50-500, BIII: CD4 > 500)**
- **All with MDR or XDR TB → Start ART within 2 to 4 weeks of confirmation of resistance (BIII)**

Clinical Vignette: Patient 1

- Our patient (after a bit of a delay) is started on an ART regimen of Atripla® (Tenofovir 300 mg plus Emtricitabine 200 mg plus Efavirenz 600 mg) daily and she has been on this for 3 weeks and tolerating it well
- She has completed her initiation phase of TB treatment and is now on her continuation phase regimen of INH plus Rifampin by DOT
- She develops new fevers and large, tender cervical lymph nodes

Clinical Vignette: Q8

- What should be done to her TB regimen now?

A) Restart Ethambutol and PZA

B) Add 2 new drugs for possible drug resistant TB

C) Check TB drug levels

D) Obtain lymph node aspirates for AFB culture

E) Stop her ART regimen

TB, HIV and IRIS

Immune Restoration Inflammatory Syndrome

- Enhanced immune mediated inflammatory response to infection already present: "Macrophages gone wild…"
- Multiple infections implicated: TB, MAC, Cryptococcus…many others but globally TB is #1
- Occasionally seen in non-HIV TB patients, especially sicker patients, as they are treated
- Can occur in patients already on TB Rx (paradoxical worsening) **or** as initial manifestation of infection (unmasked infection)
- Does not necessarily indicate treatment failure in patients on appropriate therapy

Manifestations of TB Related IRIS

- New or worsening lymphadenopathy
- High fevers
- New or worsening pulmonary infiltrates
- Pleural effusion, peritonitis, cutaneous lesions, central nervous system lesions (tuberculomas)
- Can be severe and prolonged (months) and even (rarely) fatal; severe cases treated with prednisone

➢ Risks: Lower CD4 (usually < 100) high viral load, more extensive TB, usually in 1st month of ART

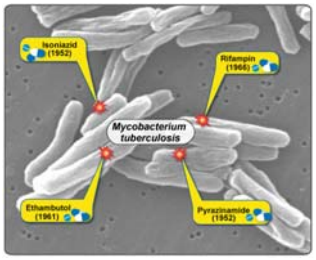
➢ Dx of exclusion: DDx includes treatment failure, adherence, drug toxicity, a new OI

HIV and TB Co-Infection: Key Points

- TB is the most common manifestation of HIV infection in high TB prevalence areas, consider in HIV + immigrants
- HIV infection is the strongest known risk factor for progression from LTBI to TB disease
- Presentation of TB is atypical and disease is more difficult to diagnose and more lethal in advanced HIV infection
- All HIV + should be screened for LTBI but testing is imperfect; LTBI should be treated if diagnosed
- All HIV + with TB should be started on ART,
- Management of TB and HIV is complicated by drug interactions with rifamycins, and by IRIS

Coordination of TB care and HIV care is Critical

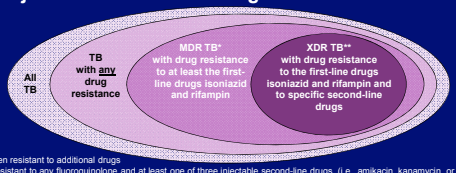
First Line TB Drugs (ATS/IDSA/CDC) Based on Efficacy, Cost, Toxicity



- Isoniazid INH
- Rifampin RIF
- Pyrazinamide PZA
- Ethambutol ETH
- Rifabutin RFB
- Rifapentine RPT

Multidrug-Resistant (MDR) and Extensively Drug-Resistant (XDR) TB

- **MDR TB caused by bacteria resistant to best TB drugs, isoniazid and rifampin**
- **XDR TB caused by organisms resistant to isoniazid and rifampin, plus fluoroquinolones and ≥1 of the 3 injectable second-line drugs**



*Often resistant to additional drugs
**Resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin

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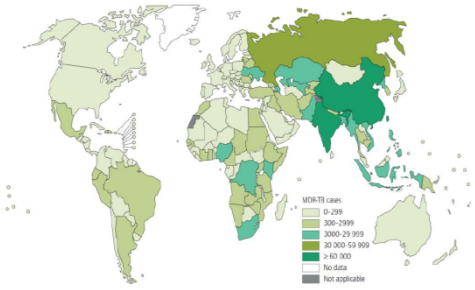
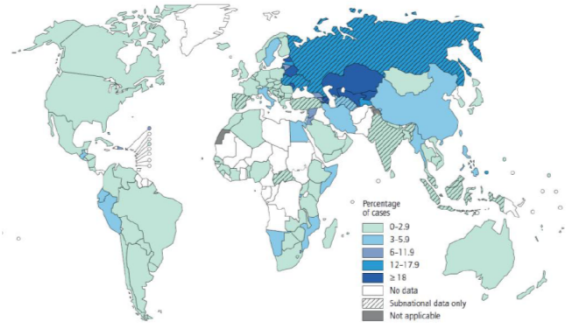
Number of MDR-TB cases estimated to occur among notified pulmonary TB cases, 2011



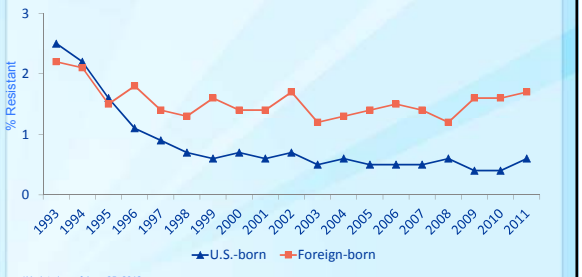
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2012. All rights reserved

Percentage of new TB cases with MDR-TB, latest available data



figures are based on the most recent year for which data have been reported, which varies among countries.

Primary MDR TB in U.S.-born vs. Foreign-born Persons United States, 1993 – 2011*

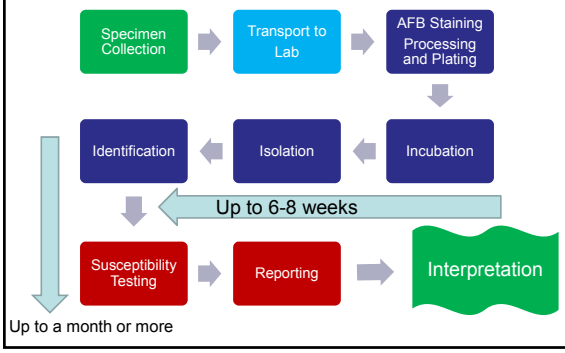


*Updated as of June 25, 2012.
Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.

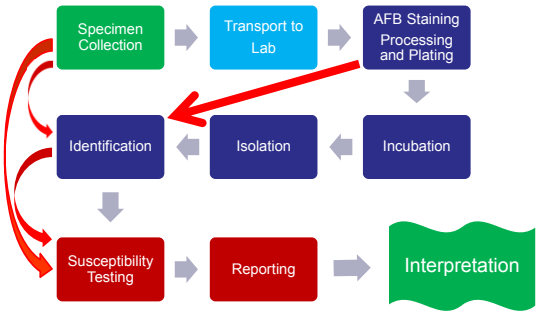
New TB Drugs and New Regimens

- Bedaquiline (TMC207)
  - Diarylquinoline; an oral ATP Synthase inhibitor, first drug specifically developed for MDR TB, 1st new FDA approved TB drug in 4 decades
  - Joint development (Janssen and Global TB Alliance); clinical trials ongoing: rapid sterilization in early trials
  - Toxicity: QT ↑, hepatotoxicity, nausea, arthralgias
- Delamanid (OPC-67683)
  - nitro-dihydro-imidazooxazole, already completed phase 2B in MDR TB (NEJM 2012) and in phase 3 now
- New, shorter course (4 month) TB regimens and 1x weekly DOT regimens for drug susceptible TB

The Clinical Mycobacteriology Process



The Clinical Mycobacteriology Process: Opportunities for Improvement



TB Diagnostic Tests: The Holy Grail

- Rapid
- Simple
- Inexpensive
- Accurate
- Employable on the "Front lines" in resource limited settings
- Detect Drug resistance as well as TB Disease

Original Article

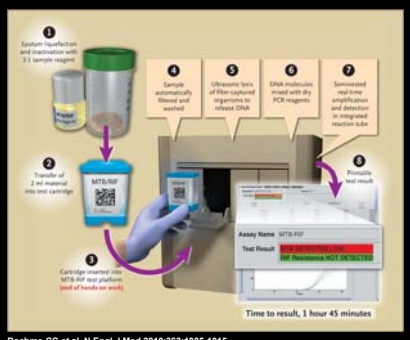
Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillemann, Ph.D., Mark P. Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiorella Krapp, M.D., Jenny Allen, B.Tech., Rasim Tahirli, M.D., Robert Blakemore, B.S., Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.

N Engl J Med
Volume 363(11):1005-1015
September 9, 2010

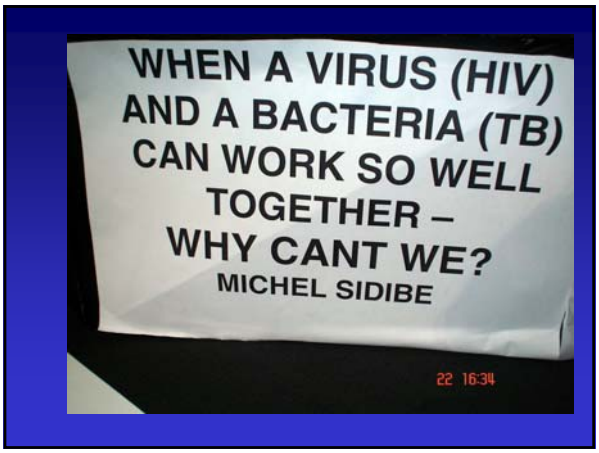
The NEW ENGLAND JOURNAL of MEDICINE

Assay Procedure for the MTB/RIF Test



Boehme CC et al. N Engl J Med 2010;363:1005-1015

The NEW ENGLAND JOURNAL of MEDICINE


WHEN A VIRUS (HIV)
AND A BACTERIA (TB)
CAN WORK SO WELL
TOGETHER –
WHY CANT WE?
MICHEL SIDIBE
22 16:34