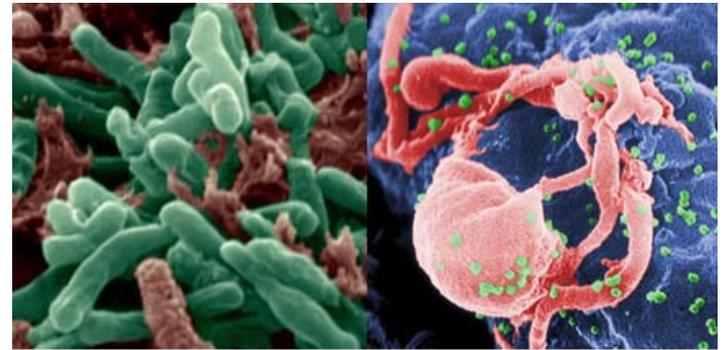


Tuberculosis (TB) and Human Immunodeficiency Virus (HIV)

Melanie Taylor MD, MPH
CDC/NCHHSTP/DSTDP



Tuberculosis (photo: www.tballiance.org/)

HIV (photo: <http://en.wikipedia.org/wiki/Hiv>)

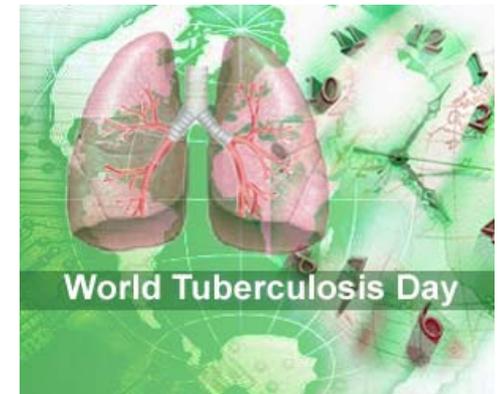
Leadership for a Healthy Arizona



Objectives

- Epidemiology of TB and HIV
- Interaction of TB and HIV
- Treatment issues associated with TB/HIV co-infection

Global TB



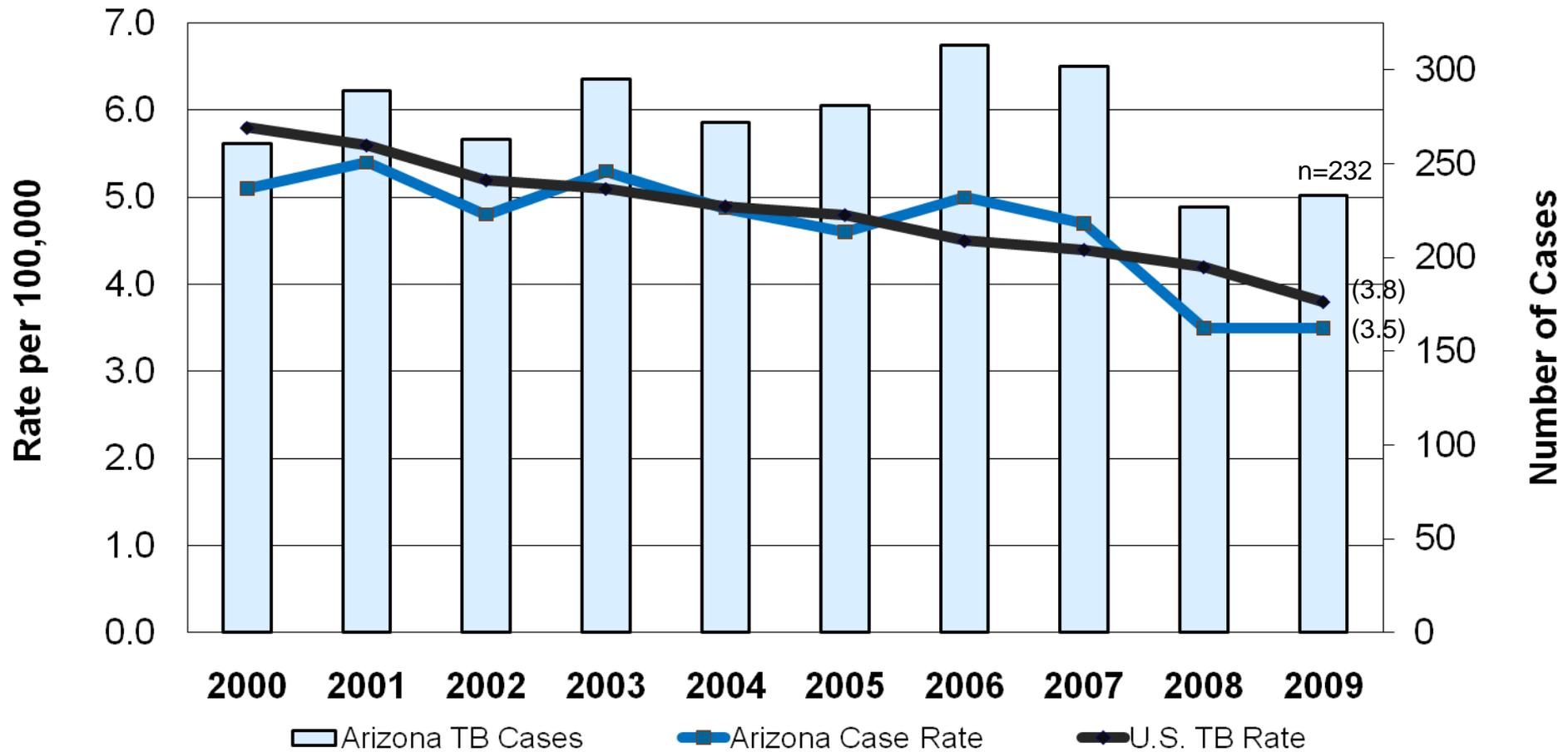
- 2008: 9.4 million incident TB cases
 - 139/100,000 population
 - Between 1.2 & 1.6 million TB cases are HIV+
 - 78% in Africa and Southeast Asia
- TB is the leading cause of death in HIV-infected patients globally
- Case fatality rate is about 40% or higher
- TB kills 2 million people worldwide every year
 - HIV-negative deaths: 1.3 million (28/100,000)
 - >500,000 deaths each year are associated with TB/HIV co-infection, mostly in Africa

Corbett EL et al. Arch Intern Med 2003;163:1009

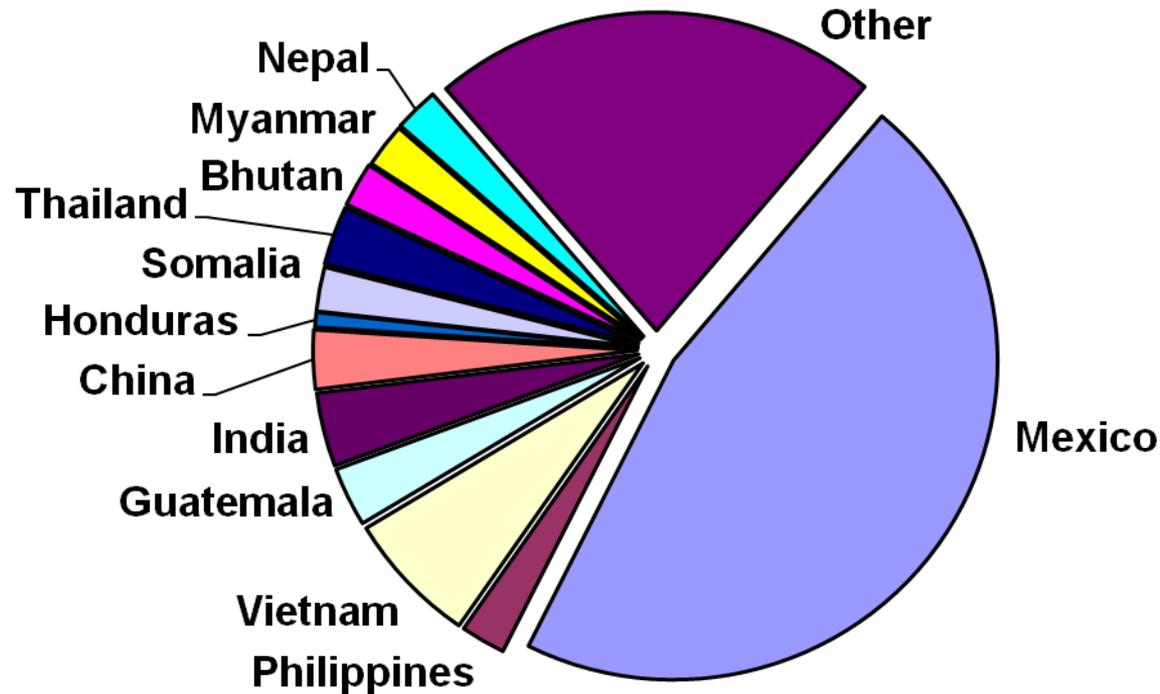
Mukadi YD et al. AIDS 2000;15:143-152

WHO TB report 2009

TB Case Rates per 100,000 population, Arizona & U.S., 2000 - 2009



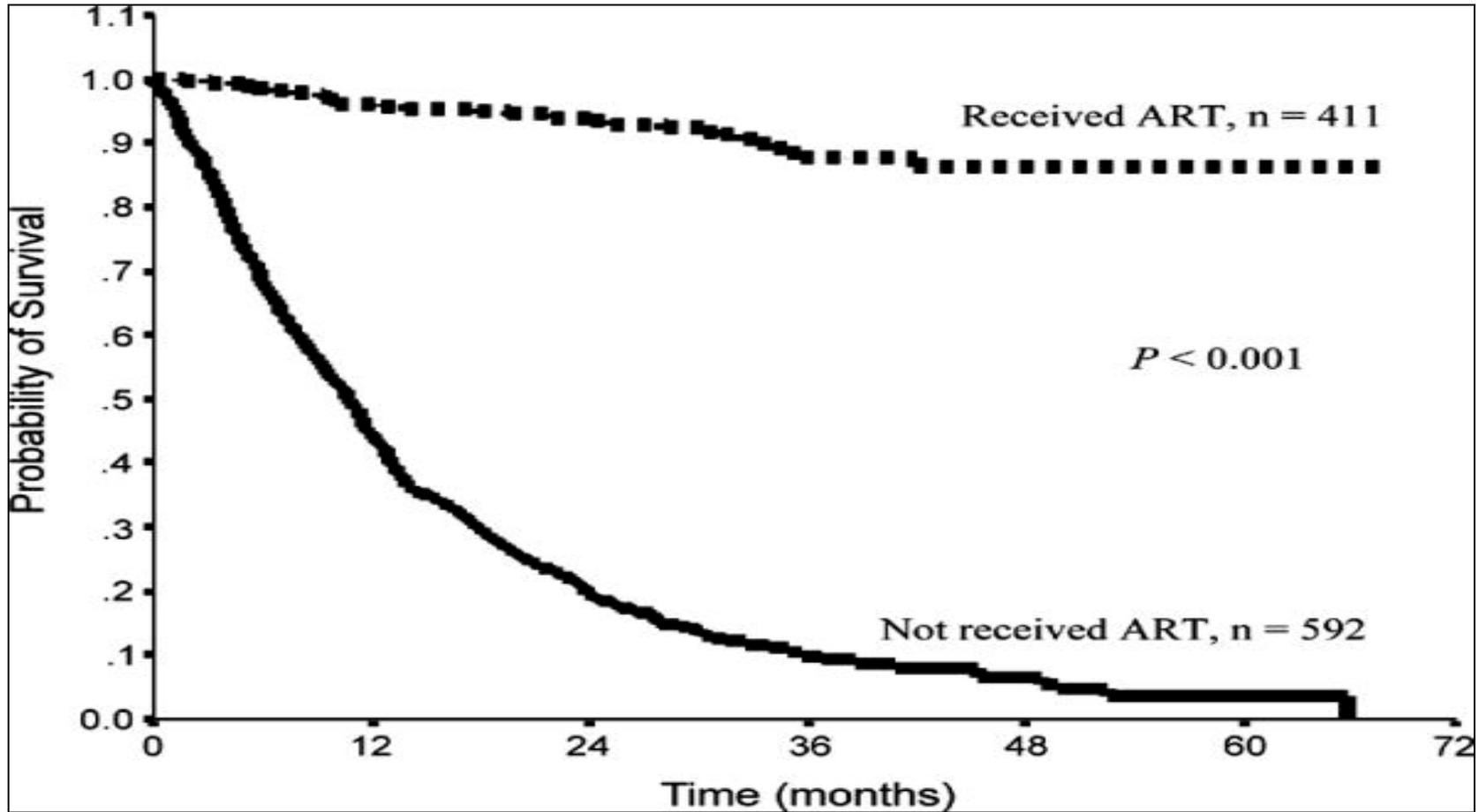
Country of Origin, Foreign-born TB Cases, Arizona, 2009



Risk Factors for TB Cases, Arizona, 2009

Risk Factor	#Cases	%
Correctional Facility Cases	37	17
HIV Positive	16	6.9
Contact of Infectious TB Case, (< 2 years)	10	4.9
Diabetes Mellitus	26	12.6
Excess Alcohol	16	6.9
Non-injecting Drug Use	17	7.3
Injecting Drug Use	3	1.3
Homeless	8	3.4
Long-term Care Facility	2	1.0

Effect of ART on survival



Concomitant HAART markedly improves survival in HIV-infected patients with HIV/TB co-infection. Manosuthi, W et al. JAIDS. 43(1):42-46



Co-pathogenicity of TB and HIV

- Immune activation from TB enhances systemic and local HIV replication
- TB treatment alone results in HIV viral load reduction
- Mortality rate of HIV-infected persons with TB is approx 4 times greater than in those with TB alone

CDC/MMWR 1998;47 (No RR-20).

Mechanisms of Enhanced Viral Replication

- Mycobacterial induction of NF-Kappa-B which binds to the promoter region of HIV
- Macrophages activated by TB release IL-1 and TNF which enhance viral replication in monocyte lines

CDC/MMWR 1998;47 (No RR-20).

Screening for TB in HIV population

- Repeated exposure history
- Screening PPD or IGRAs at presentation and every 12 months depending on exposure risk
- Consider repeat PPD after initiation of anti-retroviral therapy
- CXR

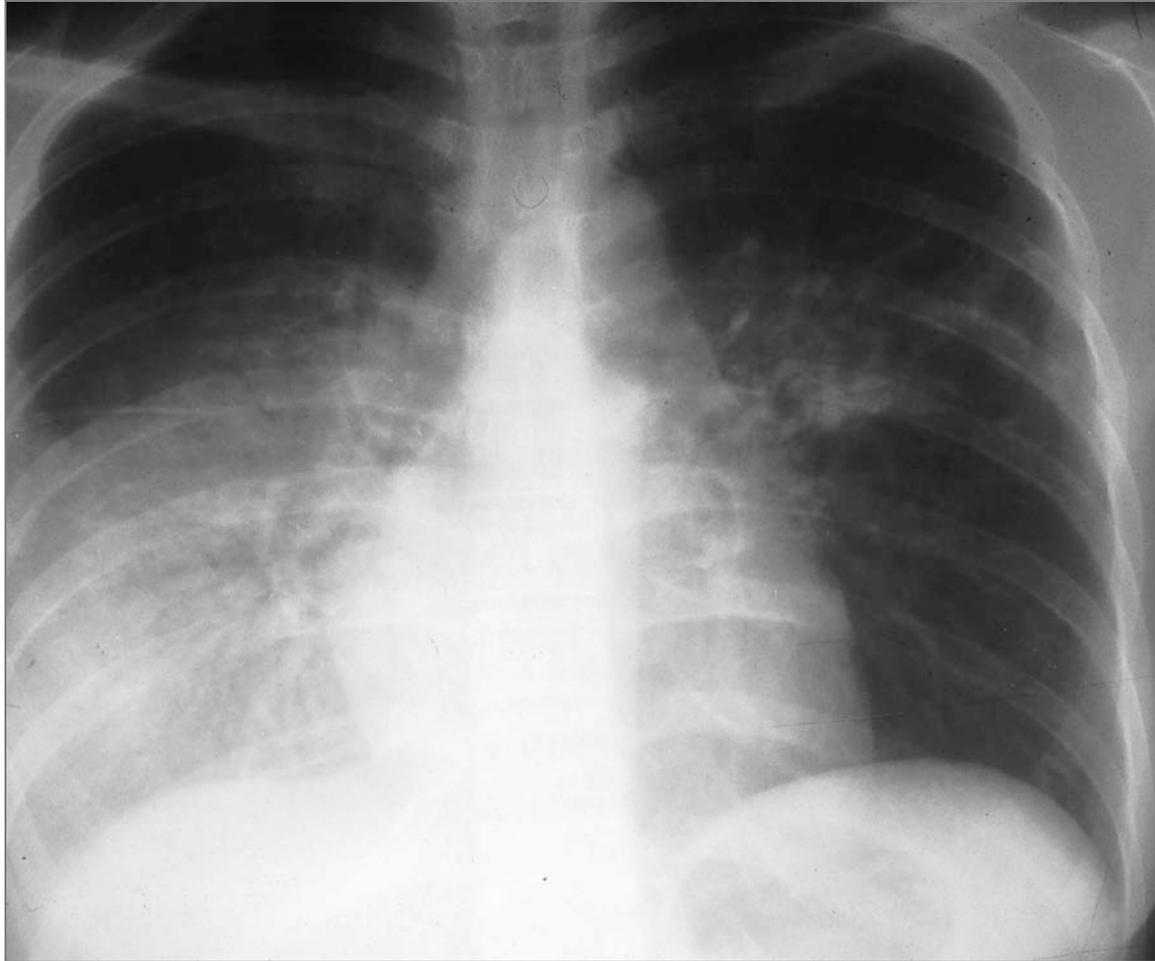
Case 1

- 21 yo F diagnosed with HIV in 2004
- Immigrated from Cameroon, West Africa in 2007
- CD4 count 166
- Had received unknown meds in Cameroon
- At first appointment, she complains of fever, cough, HA

Case 1 (cont)

- Quanteferon TB test positive
- CXR with bilateral lower lobe consolidation c/w bronchial pneumonia
- Admit for rule out meningitis (negative)
- Started on “RIPE” Rifampin, Isoniazid, Pyrazinamide, Ethambutol in March 07’

Primary Pulmonary TB



Case 1 (cont)

- TB Culture positive with pan-sensitive MTB
- HIV therapy deferred
- Completed 4 months of 4 drug therapy and then changed to INH/Rifampin
- TB meds changed to INH/Rifabutin due to interaction with HIV therapy

Case 1 (cont)

- INH/Rifabutin x 2 months
- Rifabutin changed back to Rifampin for final month of therapy
- TB meds stopped after 9 mos of therapy Dec 07'
- HAART attempted in Dec 07 but discontinued due to increasing liver enzymes
- HAART deferred until Feb 08'
- CXR infiltrates resolved

Case 1 Concerns

- IRIS avoidance
- Risk of opportunistic infections (OI) while not on HIV therapy
- Toxicity with HIV medications
- Patient education
- Co-infections
- Communications

The effect of HIV infection on symptoms and signs of TB

Symptom/sign	HIV positive (%)	HIV negative (%)
Dyspnea	97	81
Fever	79	62
Sweats	83	64
Weight loss	89	83
Diarrhea	23	4
Hepatomegaly	41	21
Splenomegaly	40	15
Lymphadenopathy	35	13
No Symptoms		10-20

Chest 1994;106:1471-6



Sites of involvement and HIV status

Site	HIV positive (%)	HIV negative (%)
Pulmonary	40	72
Extrapulmonary	34	16
Both	26	12
Pleural	31	19
Pericardial	15	3
Lymph node	19	3

J Trop Med Hygiene 1993;96:1-11



TB Presentation in HIV Infection

CD4 < 100

- More extrapulmonary
 - 70% patients with CD4 < 100
 - Miliary
 - Meningitis & tuberculomas
 - Peritoneal
- Atypical pulmonary
 - Less cavitory lung disease
 - More lower and middle lobes

TB Presentation in HIV Infection

- CD4 > 350
 - TB presentation more typical
 - Pulmonary disease
 - Apical segments
- TB often precedes other OI by few months to two years

Effect of stage of HIV disease on chest x-ray(CXR) manifestations of TB

Early HIV disease or CD4 > 300

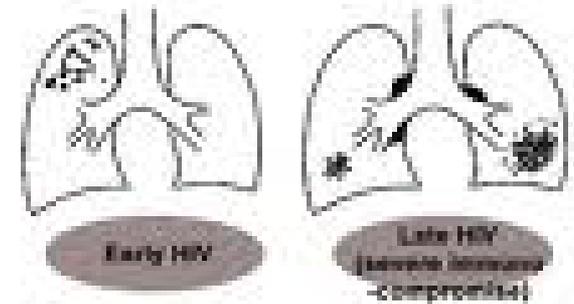
- upper lobe predominance
- cavities
- pleural disease

Advanced HIV disease or CD4 < 200

- lack of cavitation
- intrathoracic adenopathy
- lower and middle lobe infiltrates
- nodular infiltrates
- pleural and pericardial involvement
- MAY BE NORMAL

Patients may present with positive sputum cultures for *M. tuberculosis* even if CXR is negative

X-ray findings in TB patients with HIV infection



Challenges to concurrent HIV and TB therapy

© Cartoon



"I've thrown in some prescription drugs that don't interact well."

- Pill burden
- Overlapping drug toxicities
- Pharmacokinetic drug-drug interactions
- Increased risk of immune restoration inflammatory syndrome

Slide from -Management of HIV in TB Coinfected patients, Awewura Kwara, MD, MPH &TM
Assistant Professor, Alpert Medical School of Brown University Physician, Immunology Center, The Miriam Hospital, Providence, ppt

Treatment of Active TB

- Rifampin is recommended as component of 4-drug regimen:
 - In patients who have not started ARV therapy due to current immune function
 - In patients that for other reasons will not be taking a PI or NNRTI-containing regimen
 - Additional agents should include INH, EMB, PZA

CDC/MMWR 2003;52 (No RR-11)

Co-administering Antiretroviral Drugs with Rifampin

- Dose adjustments of protease inhibitors may still result in liver toxicity
- Non-nucleoside reverse transcriptase inhibitors Nevaripine and Efavirens can be used without dose adjustments
- New CCR5 antagonist
- New integrase inhibitor

<http://www.cdc.gov/nchstp/tb/>

Monitoring Response to Treatment in HIV-Infected Patients with TB

- Monitor patients with mycobacterial cultures monthly until cultures revert to negative
- After 2 months of therapy, if cultures are positive or symptoms do not resolve re-evaluate for:
 - Potential drug resistant disease
 - Non-adherence to drug regimen

CDC/MMWR 1998;47 (No RR-20)

When to start antiretroviral therapy in TB/HIV patients

- No data from randomized trials—yet
- Current thinking:
 - TB clearly needs to be treated; HIV treatment can follow
 - Allow patients to tolerate the 4 TB drugs before starting combination anti-retroviral therapy
 - Risk of paradoxical worsening may be increased during first 2 months of TB therapy

Slide from Management of Challenging TB / HIV Cases by Jennifer Flood M.D., M.P.H., Chief, Surveillance and Epidemiology Section Tuberculosis Control Branch, Division of Communicable Disease Control Center for Infectious Diseases, California Department of Public Health, ppt

Factors to consider when starting antiretroviral therapy(ART) in TB/HIV patients

- High mortality rate in TB/HIV patients
 - TB accelerates HIV disease progression, death
- Beneficial impact of ART on TB/HIV
- ART increases CD4 and could ↓ relapse risk
- Large pill burden for TB and for HIV regimens
- Drug-drug interactions, toxicity
- Paradoxical worsening of TB (IRIS)

Slide from Management of Challenging TB / HIV Cases by Jennifer Flood M.D., M.P.H., Chief, Surveillance and Epidemiology Section Tuberculosis Control Branch, Division of Communicable Disease Control Center for Infectious Diseases, California Department of Public Health, ppt

Immune Reconstitution (Paradoxical reactions)

- Occurs with restoration of immune function after initiation of ARVs
- Can present as worsening of TB disease, fevers, chills, hypotension
- Consider delay of ARVs if situation allows
- May require steroid treatment for inflammatory response

CDC/MMWR 2003;52 (No RR-11)

Types of Immune Reconstitution events among patients with HIV related TB

- Hectic fever
- New or worsening lymphadenitis - peripheral or central nodes
- New or worsening pulmonary infiltrates, including respiratory failure
- New or worsening pleuritis, pericarditis, or ascites
- Intracranial tuberculomas, worsening meningitis
- Disseminated skin lesions
- Epididymitis, hepatosplenomegaly, soft tissue abscesses

Slide from Diagnosis and management of active HIV-related TB by Mailman School of Public Health, Columbia University, ppt



Paradoxical reactions

Management

- Diagnosis of exclusion
 - Treatment failure, drug toxicity, other infection
- Mild-to-moderate reaction
 - Re-assurance
 - NSAIDS
- Severe reactions (hypoxemia, airway obstruction, neurologic impairment, etc.)
 - Corticosteroids

Slide from Management of Challenging TB / HIV Cases
by Jennifer Flood M.D., M.P.H., Chief, Surveillance and
Epidemiology Section Tuberculosis Control Branch
,Division of Communicable Disease Control Center for
Infectious Diseases ,California Department of Public
Health, ppt



Overlapping side effect profiles of first-line antituberculosis drugs and antiretroviral drugs

Side effect	Possible causes	
	Antituberculosis drugs	Antiretroviral drugs
Skin rash	PZA, RIF, INH	NVP, EFV, ABC
Nausea, vomiting	PZA, RIF, INH	ZDV, RIT, AMP, IDV
Hepatitis	PZA, RIF, INH	NVP, PIs, immune reconstitution
Leukopenia, anemia	RIF	ZDV

NVP (nevirapine), EFV (efavirenz), ABC (abacavir), ZDV (zidovudine), RIT (ritonavir), AMP (amprenavir), INH (indinavir), PI (protease inhibitors)

Slide from Diagnosis and management of active HIV-related TB by Mailman School of Public Health, Columbia University, ppt



Case 2

- 23 year old HF diagnosed with HIV in 2005
- PPD + in 2005, 2006, 2007 (5mm) (no treatment for LTBI)
- History of BCG vaccine as a child
- Quantiferon positive January 2008.
- CXR negative
- On HIV therapy, CD4 400, Viral load undetectable

Case 2 Concerns

- Excluding active disease
- Interpretation of PPD in HIV-infected persons
- BCG vaccine
- Initiating treatment for LTBI

Diagnostic Points LTBI & HIV

- False negative PPD
 - Inversely correlated with CD4 counts
 - Up to 65% in AIDS
- AFB positive sputum in AIDS
 - Suspect TB
- Brochoscopy can help when AFB negative
- Miliary disease: Blood cultures + 50%

Treatment of LTBI in HIV-infected patients

- Indications
 - PPD \geq 5 mm
 - High-risk exposure
 - Prior + PPD

Interferon- γ testing for LTBI

- More data is needed on the use of this test for the diagnosis of LTBI in HIV patients
- Quantification of interferon-gamma released from sensitized lymphocytes in whole blood incubated overnight with purified protein derivative from MTB and control antigens
- Does not measure the same components of the immunologic response as the PPD
- Not interchangeable with PPD testing

CDC/MMWR Vol. 51 Dec 18, 2002

Summary: effects of HIV-related immunodeficiency on response to tests for latent TB

- All tests for latent TB rely on an immune response
 - Not surprising that HIV-related immunodeficiency decreases the sensitivity of all of them
 - Negative test does not rule out TB
- Response to Elispot IGRA appears to be better preserved at low CD4 counts

Slide from Diagnosis of latent and active tuberculosis in the setting of HIV disease, William J. Burman, MD, Denver Public Health Tuberculosis Trials Consortium, ppt



Treatment of LTBI Using INH

- PPD of 5mm induration or greater warrants treatment
- Rule out active disease
- 9 months of INH + pyridoxine
- Baseline hepatic studies recommended
- Follow for signs and symptoms of drug toxicity monthly with INH

Adult HIV/AIDS Treatment. 2006. 67

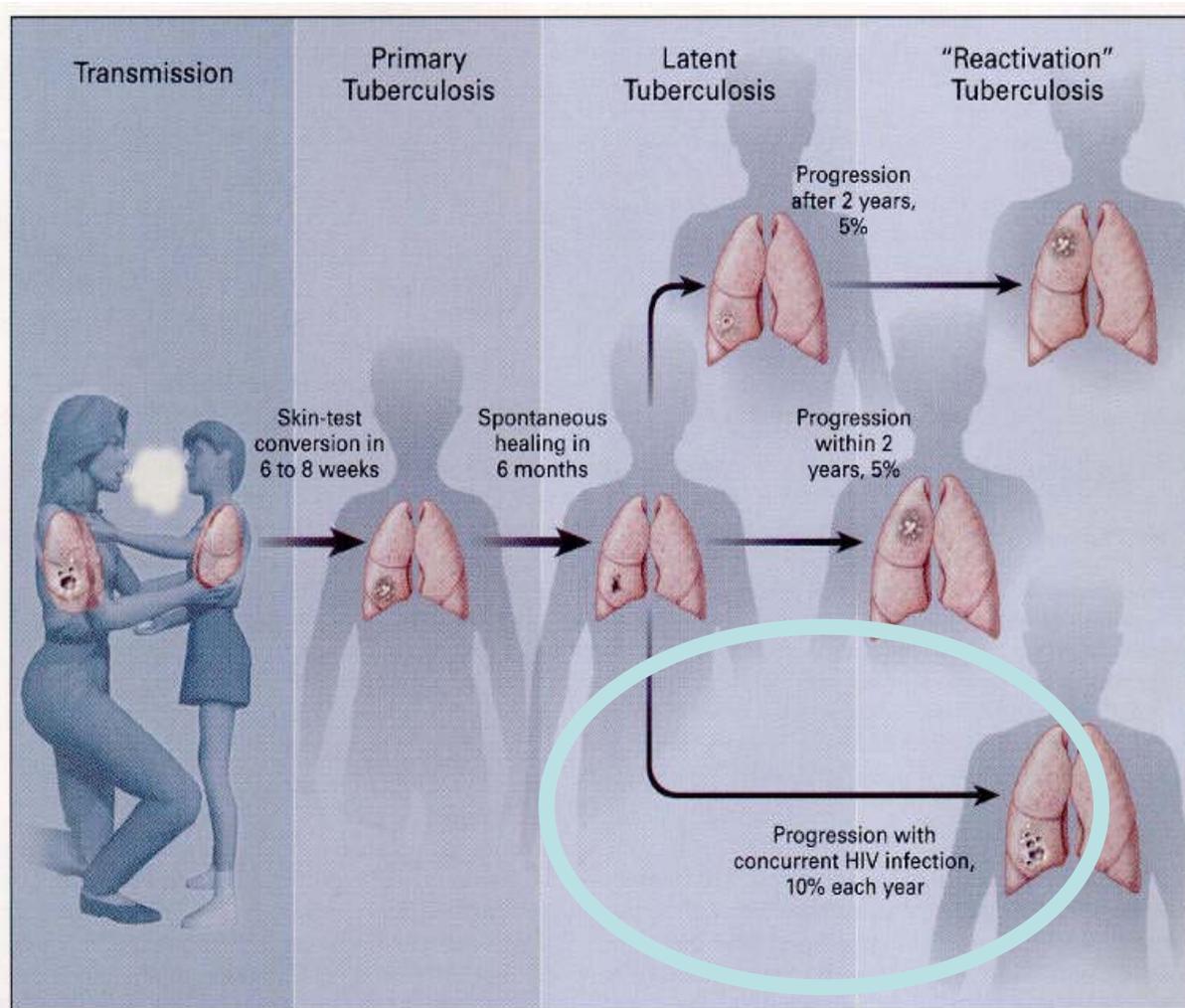
Sputum Testing for TB before LTBI Rx

- Unnecessary if normal chest Xray
- Need sputum if:
 - HIV with symptoms
 - Abnormal chest Xray
 - Parenchymal changes
 - Scarring
 - Upper lobe nodules

When Excluding Active Pulmonary TB with Abnormal Chest x-ray

- Get 3 sputum samples- wait for cultures
- Do not start single drug therapy until active disease is excluded
- Consider 4 drug TB therapy in high risk case
- May need follow up chest X-rays to decide if old scarring or active disease

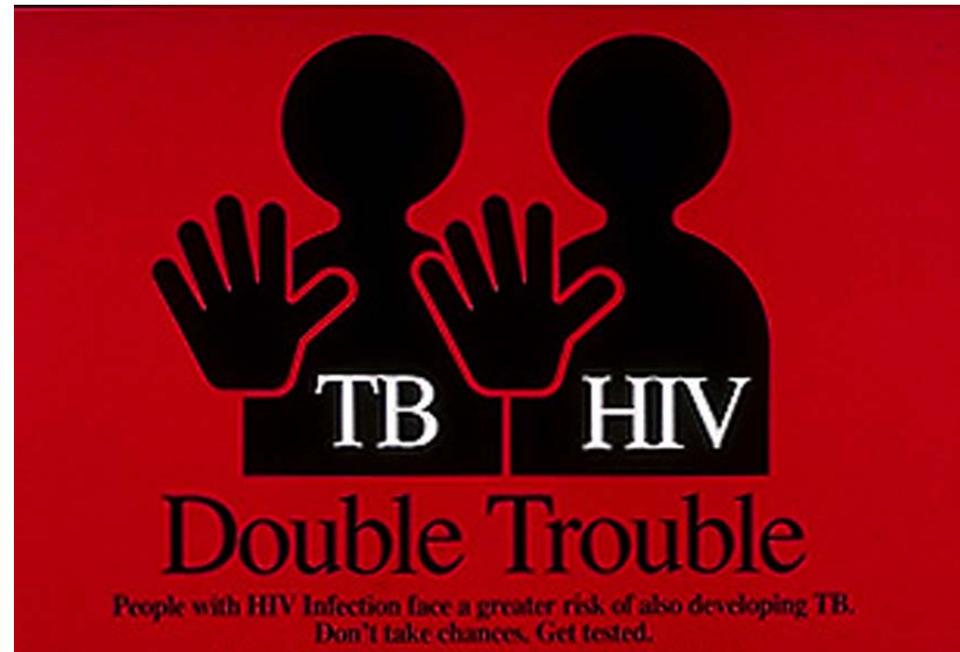
HIV/TB: Profound Effect on Individuals



The annual risk of TB in HIV infected approximates the lifetime risk of HIV uninfected

Small and Fujiwara, N Eng J Med 343:189, 2001

Thank you



Take-Home Points: HIV and TB

- Need to screen all HIV patients for TB
- Need to screen all TB patients for HIV