

HIV and TB: Public Health Pearls

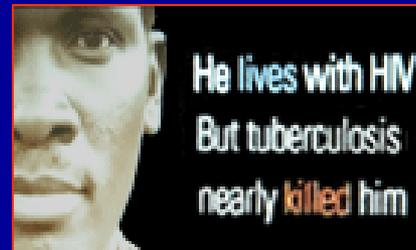


Beth Gadkowski MD

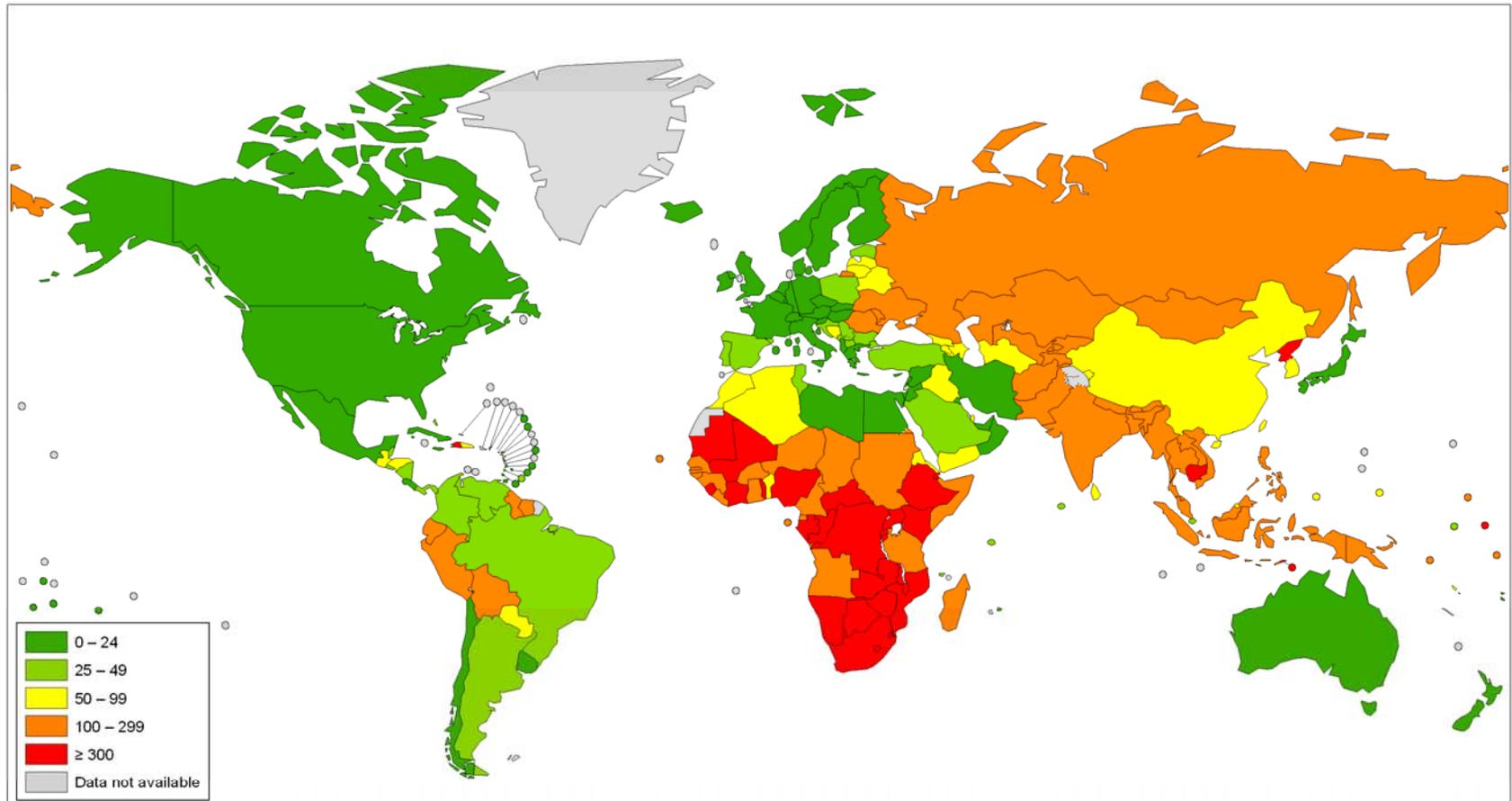
October 27, 2010

HIV and Tuberculosis

- HIV increases the risk of TB reactivation enormously.
- PPD+, HIV- \Rightarrow lifetime risk \sim 10%
- PPD+, HIV+ \Rightarrow YEARLY risk \sim 10%
- A deadly duo



Estimated incidence of tuberculosis (per 100 000 population per year), 2007



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Data Source: World Health Organization
Map Production: Public Health Information
and Geographic Information Systems (GIS)
World Health Organization



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Intensive Tuberculosis Screening for HIV-Infected Patients Starting Antiretroviral Therapy in Durban, South Africa

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S. Africa, country with heaviest HIV burden, to screen all HIV patients for TB within 5 years

By: JENNY GROSS

Associated Press

10/13/10 8:40 AM PDT

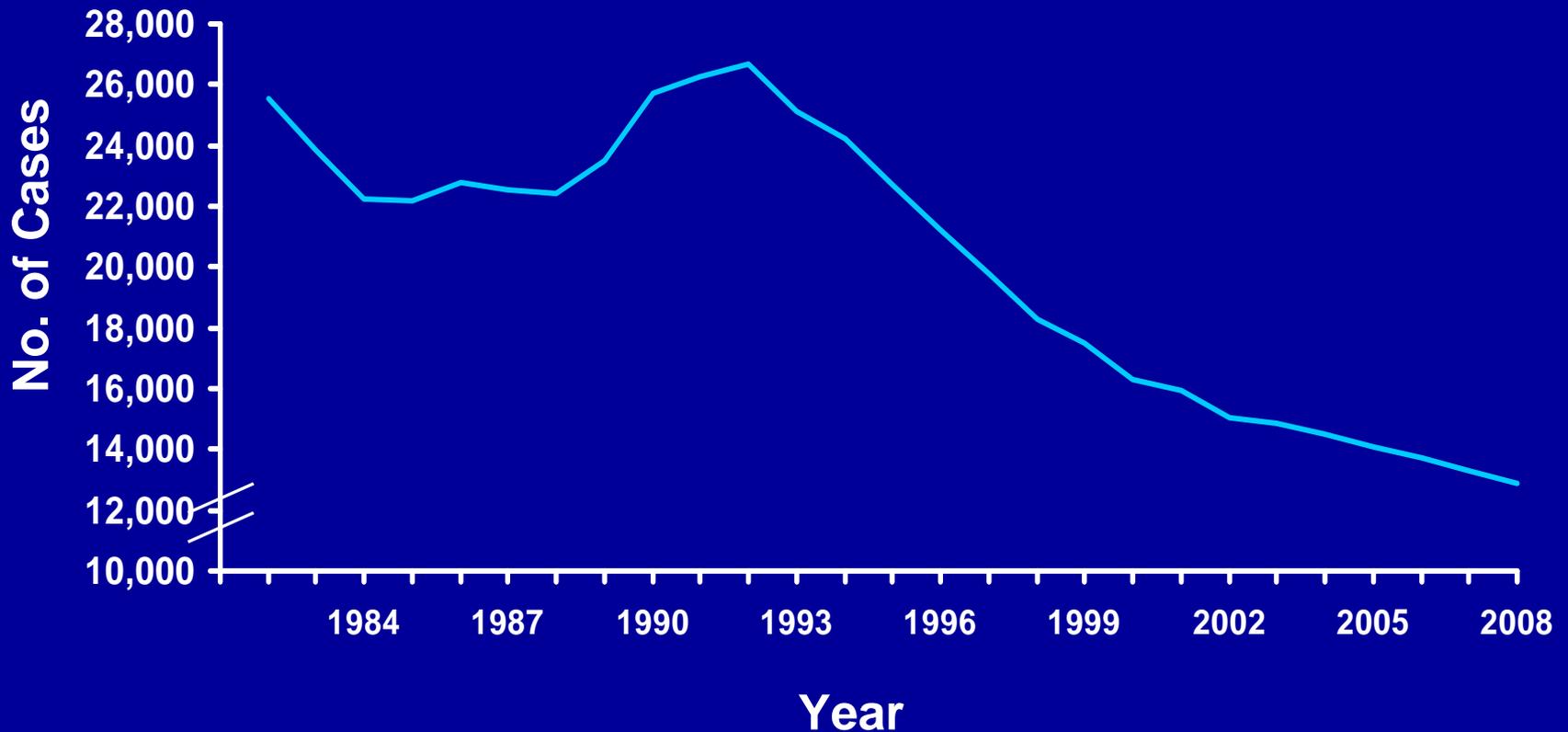
JOHANNESBURG — Health officials in South Africa said Wednesday they recommend screening all HIV patients for tuberculosis and want automatic TB tests for HIV patients to become normal procedure within five years.

UNAIDS official Paul De Lay said that by 2015, all TB patients in South Africa should be automatically screened for HIV. Officials gathered in Johannesburg on Wednesday appealed for international donations to help them develop a new drug regimen to treat TB patients who have developed drug resistance. They said they are also testing four vaccines that they hope to released by 2015.

<http://www.sfoxaminer.com/lifestyle/health/s-africa-country-with-heaviest-hiv-burden-to-screen-all-hiv-patients-for-tb-within-5-years-104856604.html#ixzz136EevUac>

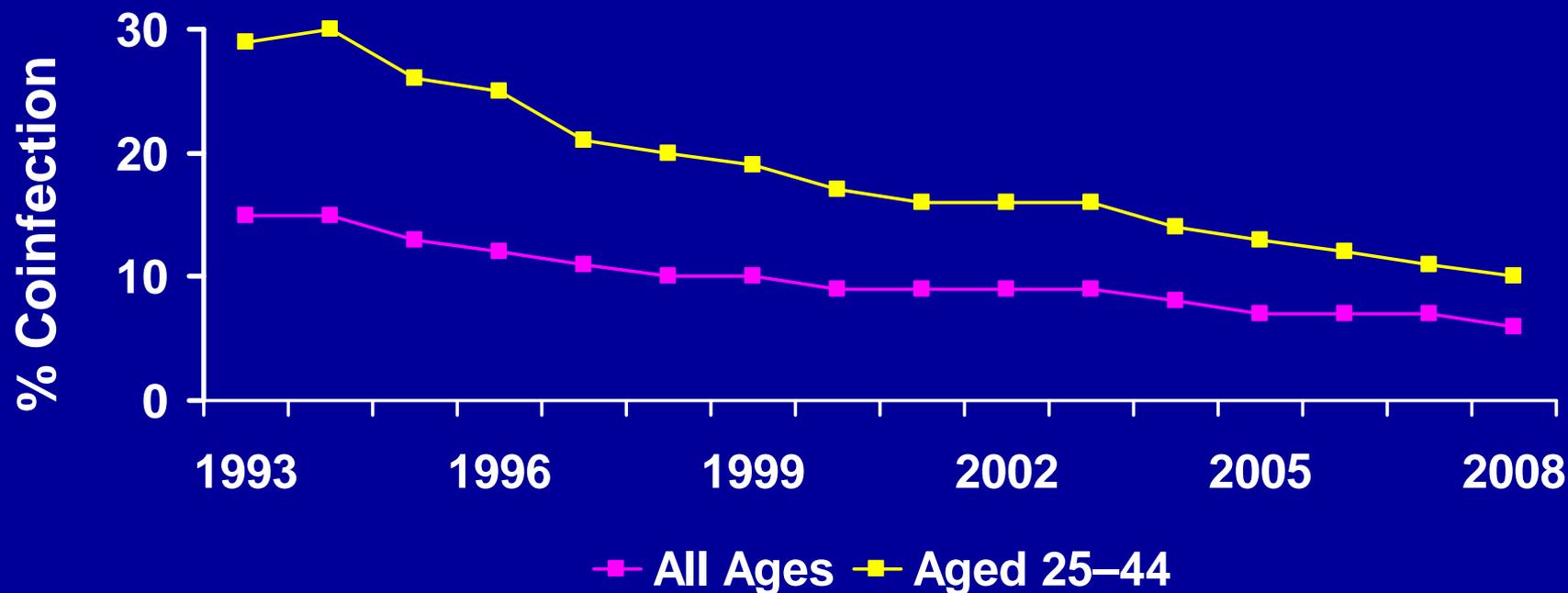
Reported TB Cases*

United States, 1982–2008



*Updated as of May 20, 2009.

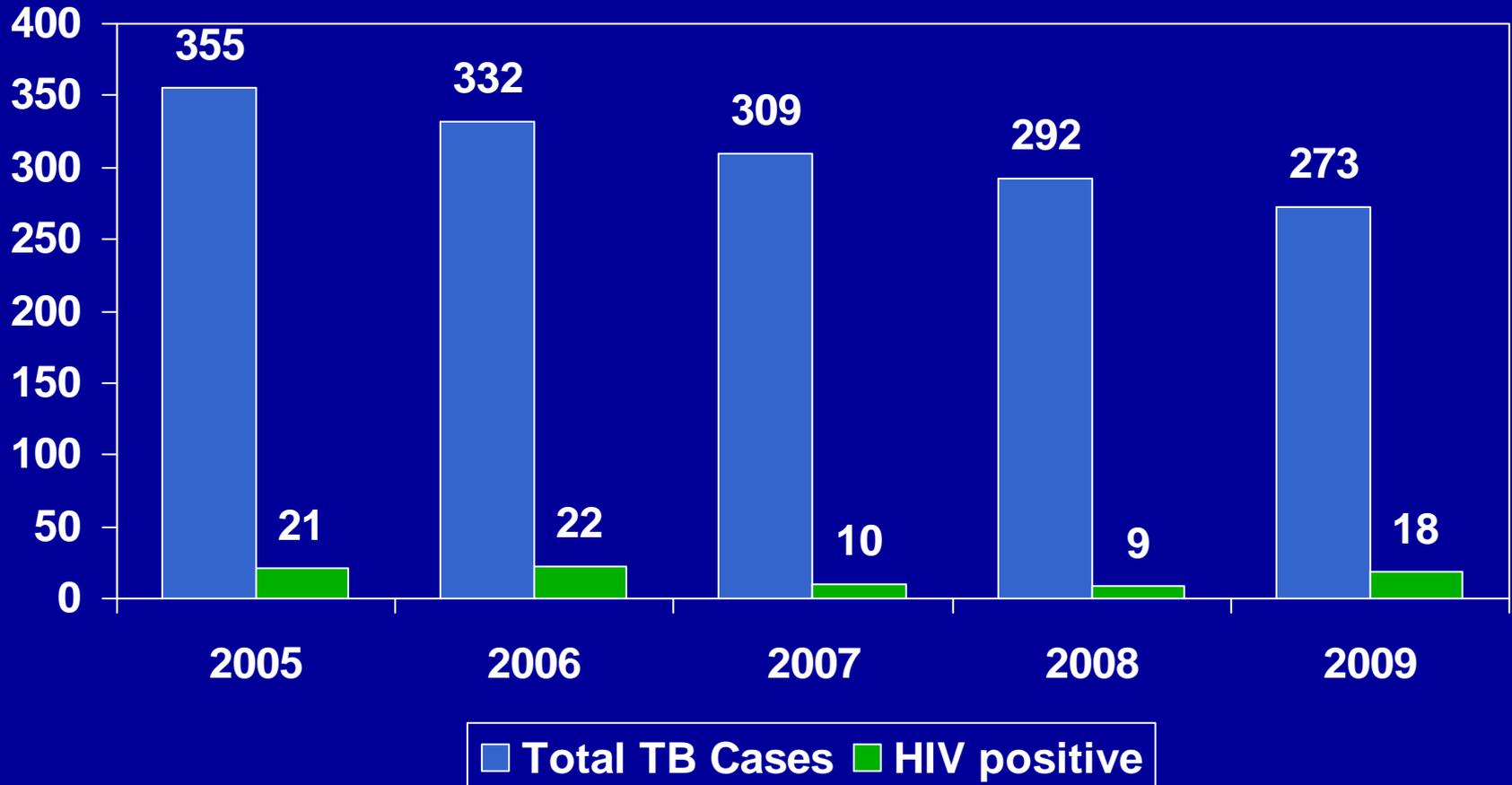
Estimated HIV Coinfection in Persons Reported with TB, United States, 1993–2008*



*Updated as of May 20, 2009.

Note: Minimum estimates based on reported HIV-positive status among all TB cases in the age group.

TB/HIV in Virginia



Tuberculosis



The Connection between TB and HIV (the AIDS virus)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control
and Prevention



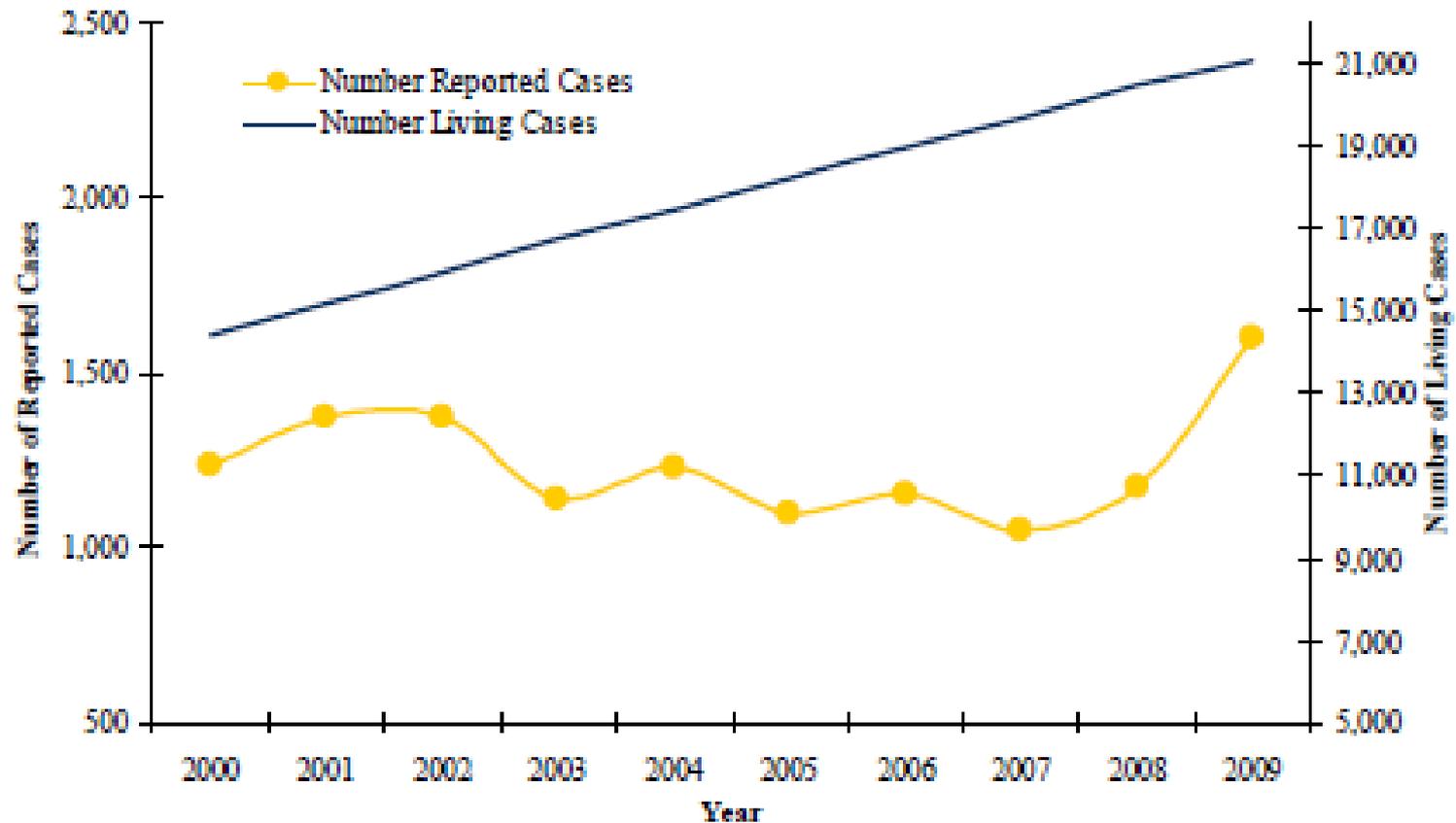
Take steps to control TB.

“I got a skin test for TB at the clinic. My TB skin test was positive. Other tests showed that I had TB disease. I started on the TB pills as the doctor suggested. Because I have HIV, I was pretty upset when I found out I had TB too. I just didn’t want to take any more pills. But—I also wanted to be healthy, so I took the pills. It was not easy, but I managed to get through. After months of treatment, the TB germs were gone.”



“When you have HIV infection your system is weak, so, you catch things pretty easily. It is hard enough dealing with HIV. When the doctor at the clinic told me I had TB disease I said, just tell me what I need to do and I’ll do it.”

2000-2009: Reported and Living HIV Cases, Virginia



Who should be tested for HIV in the TB clinic?

- A. 68 yo lady whose husband was just diagnosed with pulmonary TB
- B. 22 yo lady from the Philippines who is a currently a TB suspect
- C. 52 yo gentleman just discharged from hospital with diagnosis of clinical TB (not culture proven)
- D. 18 yo college student who is the room mate of an active pulmonary case
- E. All of the above

Recommendations for Human Immunodeficiency Virus (HIV) Screening in Tuberculosis (TB) Clinics

What are the recommendations for human immunodeficiency virus (HIV) screening in tuberculosis (TB) clinics?

In revised recommendations from 2006, CDC recommends HIV screening for all TB patients after the patient is notified that testing will be performed, unless the patient declines (i.e., opt-out screening). Routine HIV testing is also recommended for persons suspected of having TB disease and contacts to TB patients. Persons at high risk for HIV infection should be screened for HIV at least annually. Prevention counseling and separate written consent for HIV testing should no longer be required.

How do the new 2006 recommendations for HIV screening differ from previous ones?

These recommendations only address health care settings and do not replace previous recommendations for HIV testing in non-clinical, outreach, or field settings. The recommendations are aimed to eliminate missed opportunities for HIV screening and reduce significant barriers to HIV testing in health care settings by

- Using opt-out HIV screening;
- Annually screening persons at high risk for HIV;
- Eliminating the need for separate written consent for HIV testing; and
- Eliminating the need for prevention counseling as part of routine HIV screening.

What is opt-out screening?

Opt-out screening is defined as performing HIV testing after notifying the patient that the test will be performed, and although the patient may decline or defer testing, it is strongly recommended. Assent is inferred unless the patient declines testing.

Why does CDC recommend that TB clinics screen their patients for HIV infection?

HIV infection is the most important known risk factor for progression from latent TB infection to TB disease. Progression to TB disease is often rapid among HIV-infected persons and can be deadly. In addition, TB outbreaks can rapidly expand in HIV-infected patient groups.

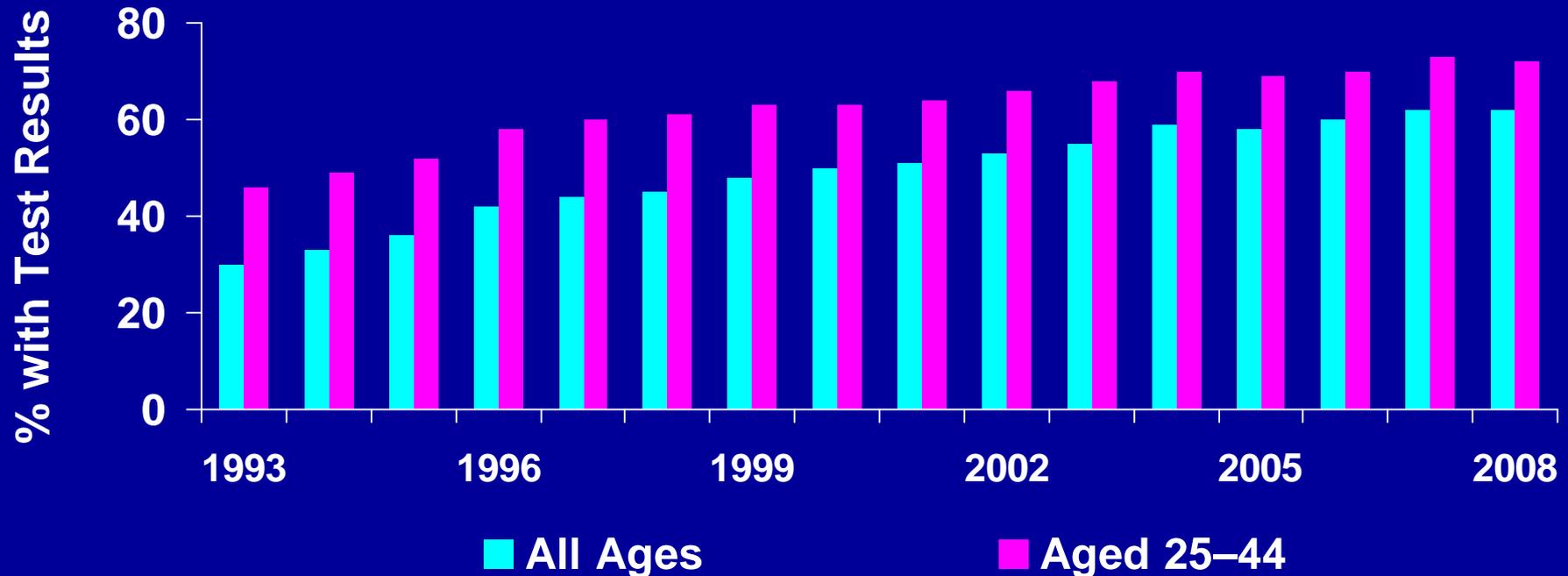
Targeted HIV testing based on provider assessment of patient risk behaviors fails to identify a substantial number of persons who are HIV infected. This is because many individuals may not perceive themselves to be at risk for HIV or do not disclose their risks. Routine HIV testing also reduces the stigma associated with testing.

When HIV is diagnosed early, appropriately timed interventions can lead to improved health outcomes, including slower progression and reduced mortality. Identifying TB patients, suspects, and contacts who are HIV infected allows for optimal TB testing of these groups and provides opportunities to prevent TB in those without disease.

Who should be tested for HIV in TB clinics?

All patients in TB clinics should be tested for HIV. This includes TB suspects, patients, and contacts.

Reporting of HIV Test Results in Persons with TB by Age Group United States, 1993–2008*

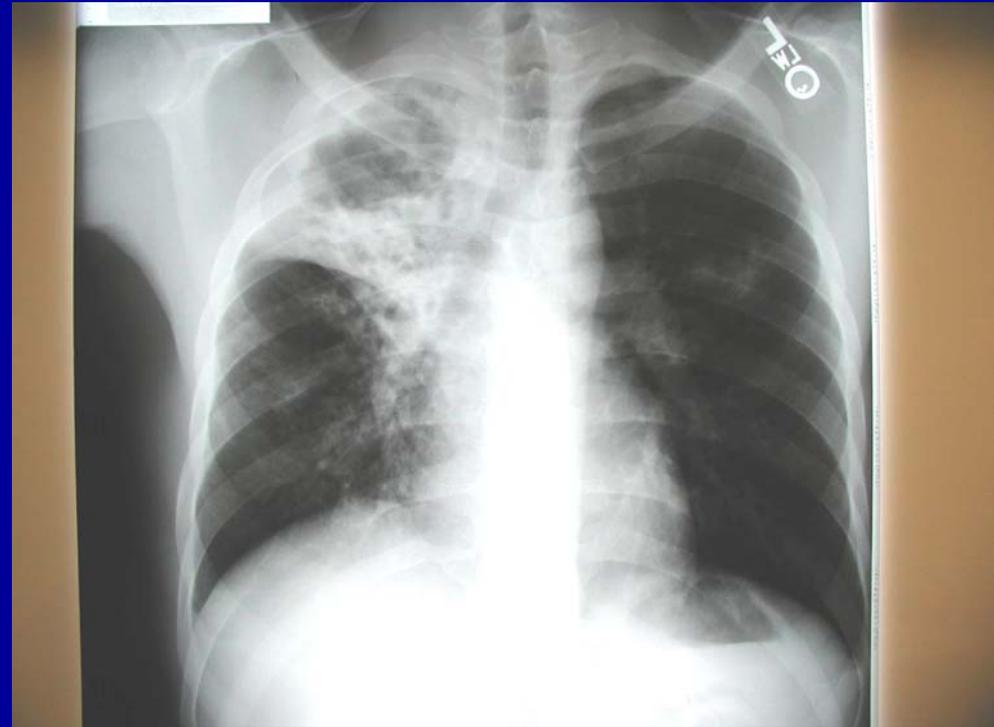


*Updated as of May 20, 2009.

Note: Includes TB patients with positive, negative, or indeterminate HIV test results. Persons from California reported with AIDS only through 2004. (HIV test results are not reported from California)

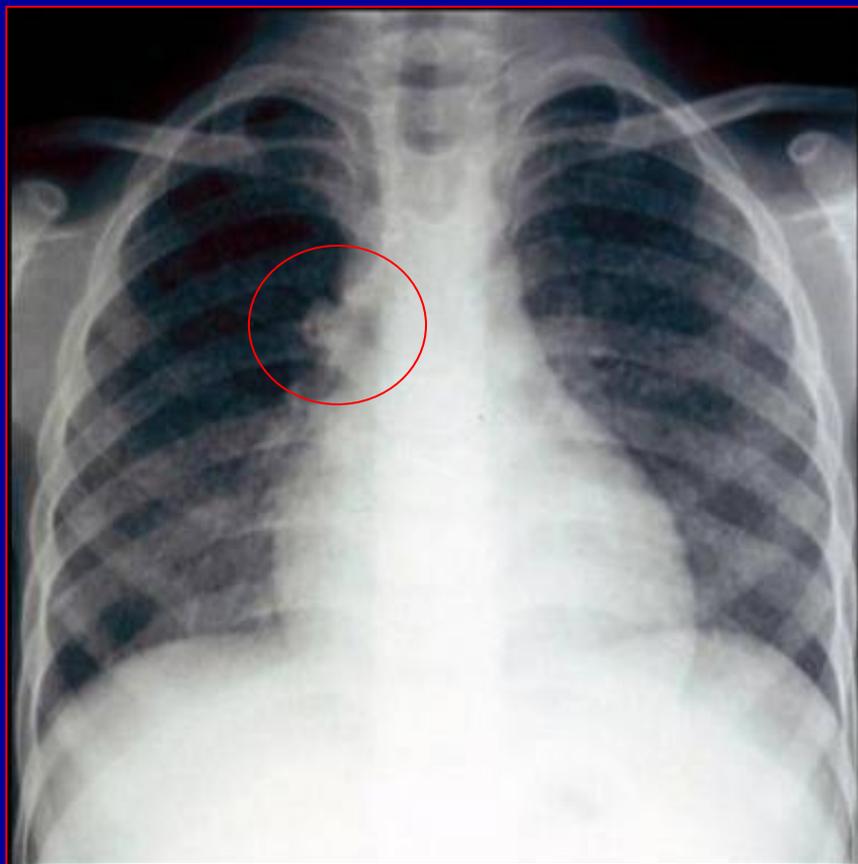
TB and HIV coinfection (1)

- Active TB can occur in an HIV-positive individual at any level of immunodeficiency:
 - it is very important to know CD4 count
- In 2000, TB was the second most common opportunistic infection reported in new AIDS cases in New York City
- TB may also:
 - increase the risk for developing other opportunistic infections in HIV-positive patients
 - may accelerate the course of HIV disease

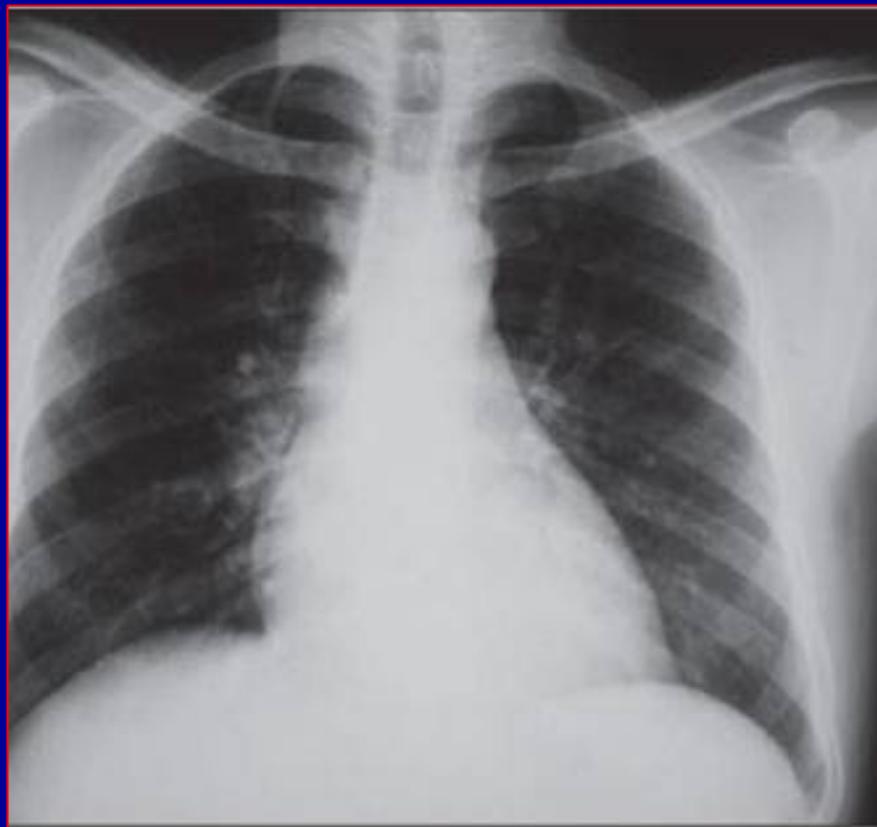


Which HIV-positive patient has TB?

A.

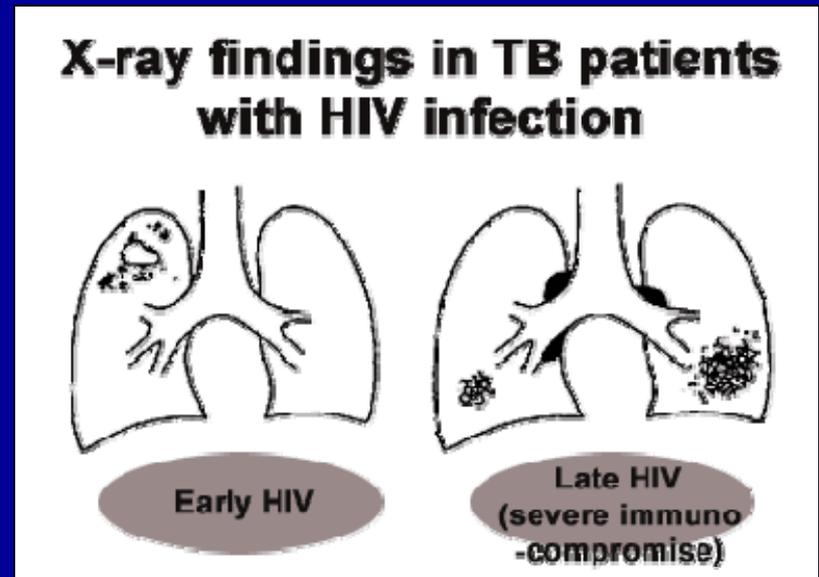


B.



TB and HIV coinfection (2)

- More likely to have smear negative pulmonary disease than HIV-negative counterparts
- May result in increased lag time between presentation for care and institution of TB therapy
- Leads to increased morbidity and mortality



http://www.searo.who.int/EN/Section10/Section18/Section356/Section421_1626.htm

TB and HIV coinfection (3)

- Extrapulmonary TB more common in HIV-positive patients
- Most common manifestations:
 - Lymphadenitis
 - Blood
 - Pleural
- Often disseminated
- Difficult to diagnose which can lead to delayed institution of proper therapy

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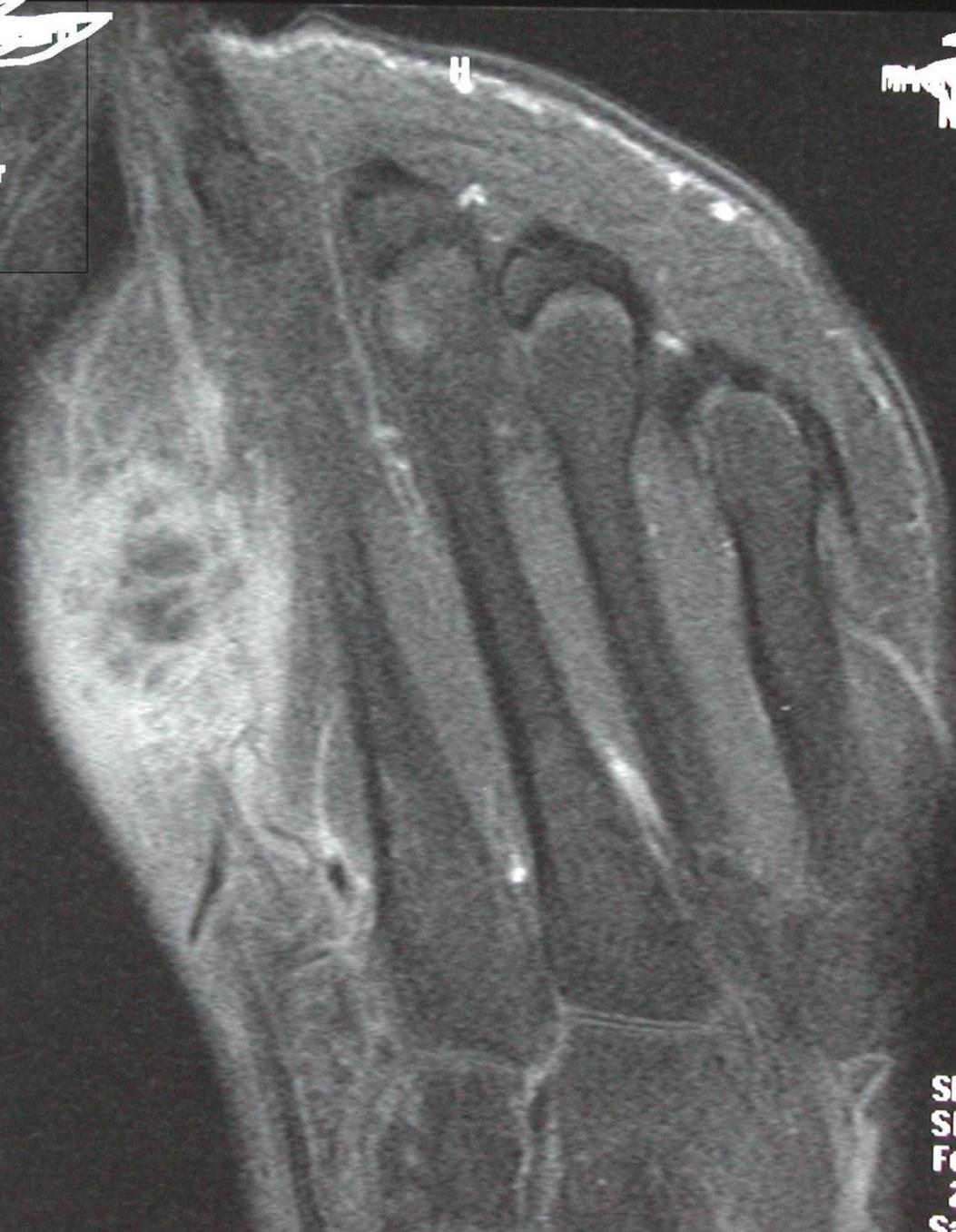
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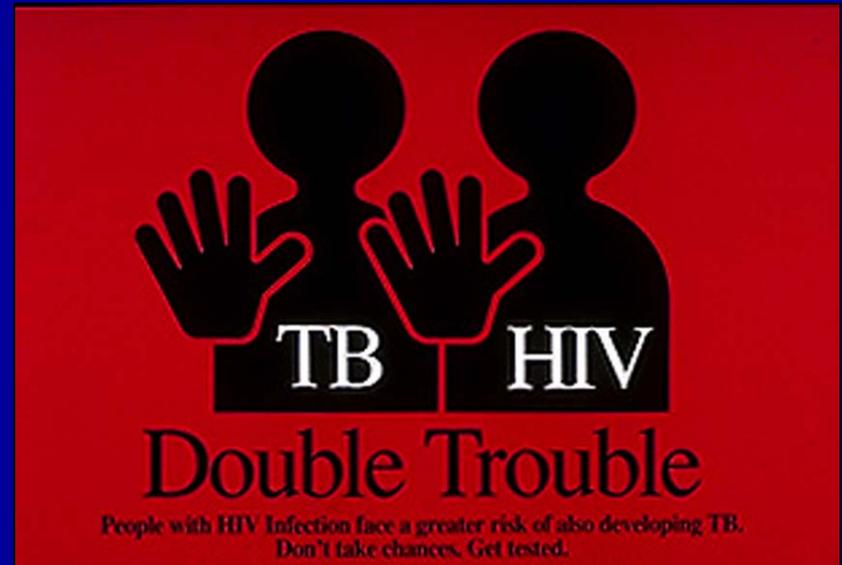
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Starting TB Treatment in HIV/TB coinfected patients

- Necessary to know CD4 count
- Patients with late-stage HIV (CD4<100)
 - Relapse with rifampin-resistant disease
 - CDC recommends daily therapy for a full 6 months
 - Consider drug-levels to ensure absorption
- What other medications are they on?

TB and HIV Coinfection (4)

- Many coinfecting patients are unaware of their HIV-positive status at the time of TB diagnosis
- Those who know HIV-positive status are often not receiving HIV care
- Care and further treatment complicated by homelessness, illicit drug use, unemployment and incarceration



Which of the following are the most important to consider when starting HIV therapy in an HIV/TB coinfecting patient?

- A. Timing of HAART in relation to when TB therapy was started
- B. Concern for drug interactions
- C. Immune reconstitution inflammatory syndrome (IRIS)/paradoxical reaction
- D. Concern for an increase in adverse events
- E. All of the above

Timing of Highly Active Antiretroviral Therapy (HAART) (1)

- A decision analysis to assess timing of HAART during TB treatment in patients with CD4 count < 200 found:
 - Greatest mortality benefit occurred when HAART started within first two months of TB therapy
 - When severe IRIS, drug toxicity, AIDS-defining illness and mortality were considered together, greatest overall benefit was seen when HAART started early
 - deferred HAART preferred when IRIS-related mortality rates are high, such as in meningitis or pericarditis

Timing of Highly Active Antiretroviral Therapy (HAART) (2)

- CD4 count < 100: start within 2 weeks of initiation of TB therapy
- CD4 count > 100: start after initial phase of TB therapy has been completed (8 weeks)

Starting HAART: Highly Active Antiretroviral Therapy

- DHHS Guidelines 2009 suggest starting either:

-2 NRTIs

or

- 2 NRTIs

-1 NNRTI

-1 Boosted PI



Concerns and considerations for concurrent TB/HIV therapy

- High pill burden
- Increase in adverse events:
 - Sustiva (one of three drugs in Atripla, generic name: efavirenz) can cause neurological side effects, bizarre dreams, worsen mental health issues in patients with mental health diagnosis such as bipolar or schizophrenia
- Overlapping drug toxicities:
 - Reyataz (atazanavir) causes an asymptomatic increase in bilirubin that could be mistaken for hepatotoxicity
 - Norvir (ritonavir) can cause nausea/diarrhea that might be confused with GI upset secondary to hepatotoxicity

Drug interactions between TB medications and HAART

Managing Drug Interactions in the Treatment of **HIV-Related Tuberculosis**



Department of Health and Human Services
Centers for Disease Control and Prevention

HAART regimens in TB

- Necessary to include a rifamycin in TB treatment
- TB treatment regimens in which rifampin is not included, or are only included in the first two-months are associated with increased relapse and failure
- Rifamycins are inducers of cytochrome P450
- Rifampin is one of the most potent inducers of cytochrome P450

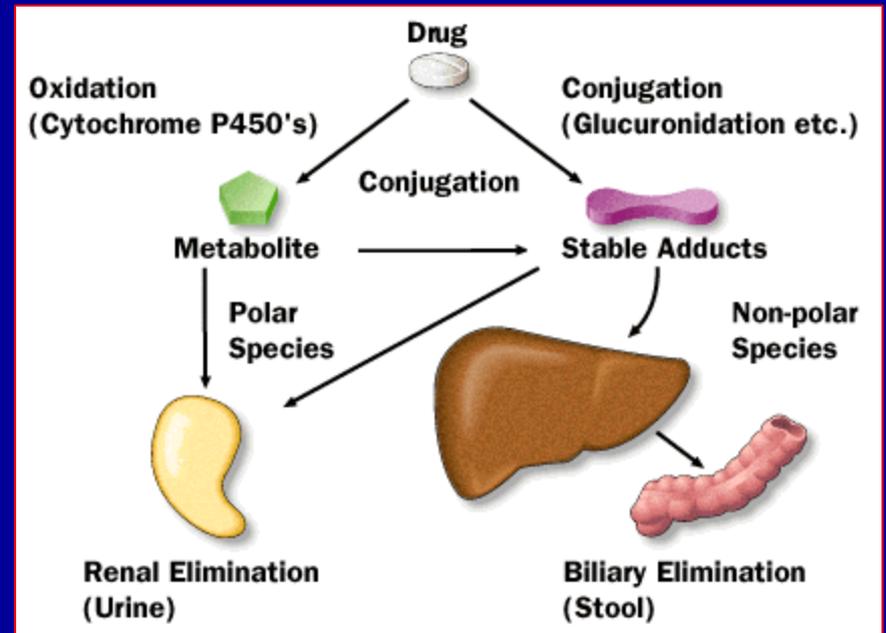


Table 1. Recommendations for regimens for the concomitant treatment of tuberculosis and HIV infection

Combined regimen for treatment of HIV and tuberculosis	PK effect of the rifamycin	Tolerability / toxicity	Antiviral activity when used with rifampin	Recommendation (comments)
Efavirenz-based ART* with rifampin-based TB treatment	Well-characterized, modest effect	Low rates of discontinuation	Excellent	Preferred (efavirenz should not be used during the first trimester of pregnancy)
PI-based ART* with rifabutin-based TB treatment	Little effect of rifabutin on PI concentrations, but marked increases in rifabutin concentrations	Low rates of discontinuation (if rifabutin is appropriately dose-reduced)	Favorable, though published clinical experience is not extensive	Preferred for patients unable to take efavirenz †
Nevirapine-based ART with rifampin-based TB treatment	Moderate effect	Concern about hepatotoxicity when used with isoniazid, rifampin and pyrazinamide	Favorable	Alternative for patients who cannot take efavirenz and if rifabutin not available
Zidovudine / lamivudine / abacavir / tenofovir with rifampin-based TB treatment ¹⁰	50% decrease in zidovudine, possible effect on abacavir not evaluated	Anemia	No published clinical experience	Alternative for patients who cannot take efavirenz and if rifabutin not available
Zidovudine / lamivudine / tenofovir with rifampin-based TB treatment	50% decrease in zidovudine, no other effects predicted	Anemia	Favorable, but not evaluated in a randomized trial	Alternative for patients who cannot take efavirenz and if rifabutin not available
Zidovudine / lamivudine / abacavir with rifampin-based TB treatment	50% decrease in zidovudine, possible effect on abacavir not evaluated	Anemia	Early favorable experience, but this combination is less effective than efavirenz-based regimens in persons not taking rifampin	Alternative for patients who cannot take efavirenz and if rifabutin not available
Super-boosted lopinavir-based ART with rifampin-based TB treatment	Little effect	Hepatitis among healthy adults, but favorable experience, among young children (< 3 years)	Good, among young children (< 3 years)	Alternative if rifabutin not available; preferred for young children when rifabutin not available

ART: antiretroviral therapy

*with 2 nucleoside analogues

† includes patients with NNRTI-resistant HIV, those unable to tolerate efavirenz, women during the first 1-2 trimesters of pregnancy

Rifabutin

- Less potent inducer of cytochrome p450
- Little effect on protease inhibitors
- Not available in developing countries
- Very expensive:
 - 150 mg \$8.83 per pill
 - vs. 300 mg \$1.99 for rifampin

Table 2. Recommendations for coadministering antiretroviral drugs with RIFAMPIN – 2007

Non-nucleoside reverse transcriptase inhibitors			
	Recommended change in dose of antiretroviral drug	Recommended change in dose of rifampin	Comments
Efavirenz	None (some experts recommend 800 mg for patients > 60 kg)	No change (600 mg/day)	Efavirenz AUC ↓ by 22%; no change in rifampin concentration. Efavirenz should not be used during the 1 st trimester of pregnancy.
Nevirapine	No change	No change (600 mg/day)	Nevirapine AUC ↓ 37-58% and C _{min} ↓ 68% with 200 mg 2x/day dose.
Delavirdine	Rifampin and delavirdine should not be used together		Delavirdine AUC ↓ by 95%
Etravirine	Etravirine and rifampin should not be used together		Marked decrease in etravirine predicted, based on data on the interaction with rifabutin
Single protease inhibitors			
	Recommended change in dose of antiretroviral drug	Recommended change in dose of rifampin	Comments
Ritonavir	No change	No change (600 mg/day)	Use with caution. Ritonavir AUC ↓ by 35%; no change in rifampin concentration. Monitor for antiretroviral activity of ritonavir.
fos-Amprenavir	Rifampin and fos-amprenavir should not be used together		
Atazanavir	Rifampin and atazanavir should not be used together		Atazanavir AUC ↓ by >95%
Indinavir	Rifampin and indinavir should not be used together		Indinavir AUC ↓ by 89%.
Nelfinavir	Rifampin and nelfinavir should not be used together		Nelfinavir AUC ↓ 82%
Saquinavir	Rifampin and saquinavir should not be used together		Saquinavir AUC ↓ by 84%

Table 3. Recommendations for coadministering antiretroviral drugs with RIFABUTIN – 2007

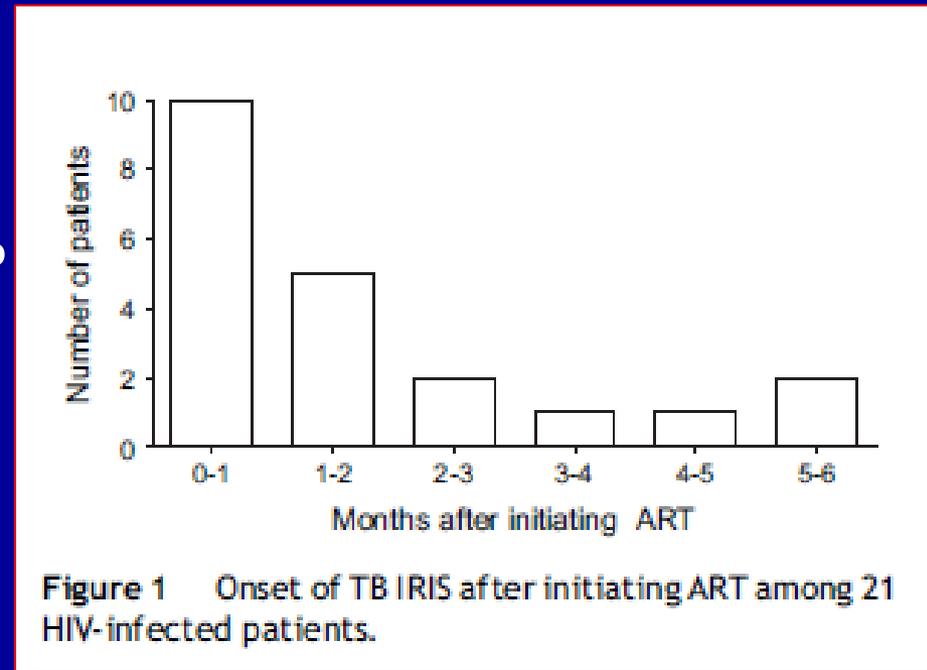
Non-nucleoside reverse-transcriptase inhibitors			
	Antiretroviral dose change	Rifabutin dose change	Comments
Efavirenz	No change	↑ to 450-600 mg (daily or intermittent)	Rifabutin AUC ↓ by 38%. Effect of efavirenz + protease inhibitor(s) on rifabutin concentration has not been studied. Efavirenz should not be used during the 1 st trimester of pregnancy.
Nevirapine	No change	No change (300 mg daily or thrice-weekly)	Rifabutin and nevirapine AUC not significantly changed.
Delavirdine	Rifabutin and delavirdine should not be used together		Delavirdine AUC ↓ by 80%; rifabutin AUC ↑ by 100%.
Etravirine	No change	No change (300 mg daily or thrice-weekly)	No clinical experience; etravirine C _{min} ↓ by 45%, but this was not thought to warrant a change in dose
Single protease inhibitors			
	Antiretroviral dose change	Rifabutin dose change	Comments
fos-Amprenavir	No change	↓to 150 mg/day or 300 mg 3x/week	No published clinical experience
Atazanavir	No change	↓to 150 mg every other day or 3x/week	No published clinical experience. Rifabutin AUC ↑ by 250%
Indinavir	1000 mg every 8 hours	↓ to 150 mg/day or 300 mg 3x/week	Rifabutin AUC ↑ by 170%; indinavir concentrations ↓ by 34%
Nelfinavir	No change	↓ to 150 mg/day or 300 mg 3x/week	Rifabutin AUC ↑ by 207%; insignificant change in nelfinavir concentration

Paradoxical Reaction/Immune Reconstitution Inflammatory Response (IRIS)

- Well-described in HIV-negative TB patients, especially those with lymphadenitis
- Temporary exacerbation of symptoms:
 - High fever
 - Enlarging, draining lymph nodes
 - Worsening of pulmonary infiltrates or pleural effusions
- Needs to be distinguished from treatment failure

Paradoxical Reaction/IRIS (2)

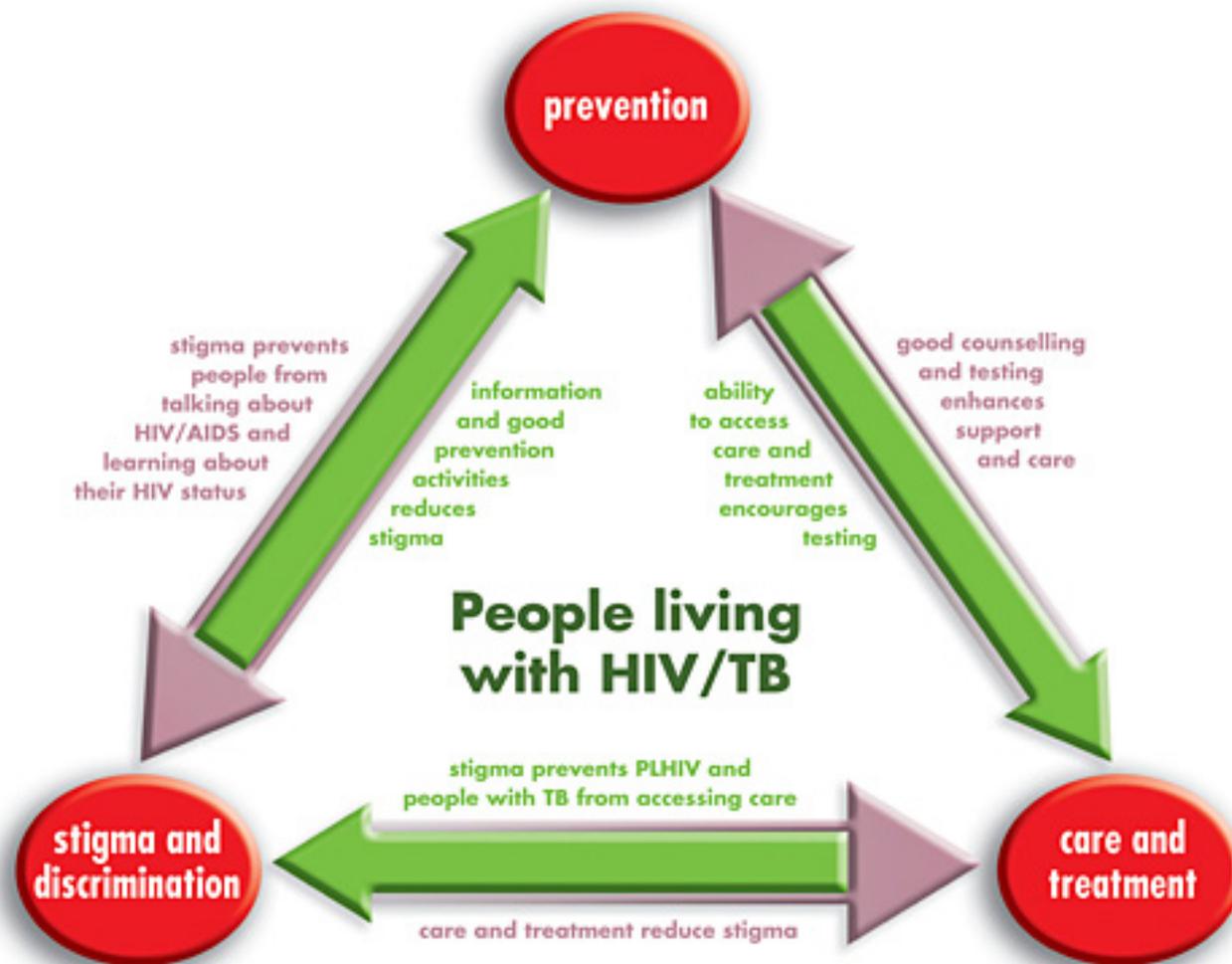
- More commonly seen in HIV-positive patients who have initiated TB and HAART therapy
- Has been described in 10-36% of patients
- Risk increased in CD4 count <100 and if HAART started within two months of TB therapy
- Median time for occurrence: 15 days after starting antiretrovirals



Manosuthi et al. Journal of Infection (2006) 53, 357-363.

Diagnosing and Managing IRIS

- Make sure patient is NOT failing TB therapy:
 - check sputum smear/culture, make sure they are compliant with therapy, consider drug levels
- Consider timing of worsening of symptoms in relation to starting of HAART
- Check CD4 count and viral load
- Rule out other opportunistic infections
- Symptoms often resolve without any specific
- Continue TB medications
- Continue HIV medications



Resources

- <http://www.cdc.gov/tb/topic/TBHIVcoinfection/default.htm>
- http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/PDF/tbhiv.pdf
- http://www.vdh.state.va.us/epidemiology/DiseasePrevention/Programs/Tuberculosis/documents/TBAnnualReport_2009.pdf