TB and HIV Co-infection – Research Update

Tennessee 2016 Clinical TB Symposium

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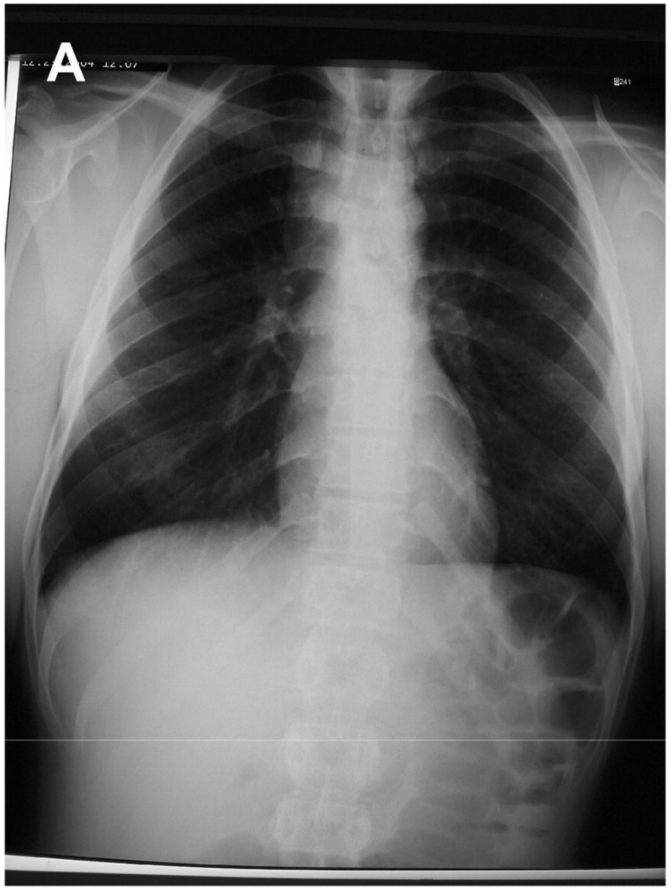
March 30, 2016

Objectives

1. Describe the epidemiology of TB-HIV co-infection nationally, statewide, and locally in order to achieve early diagnosis and timely treatment for this population.
2. Identify risk factors for poor outcomes among TB-HIV co-infected persons to prevent transmission and to improve diagnosis and treatment outcomes.
3. Discuss challenges in the diagnosis and management of TB in persons with HIV co-infection to improve completion of treatment and treatment outcomes.

Case

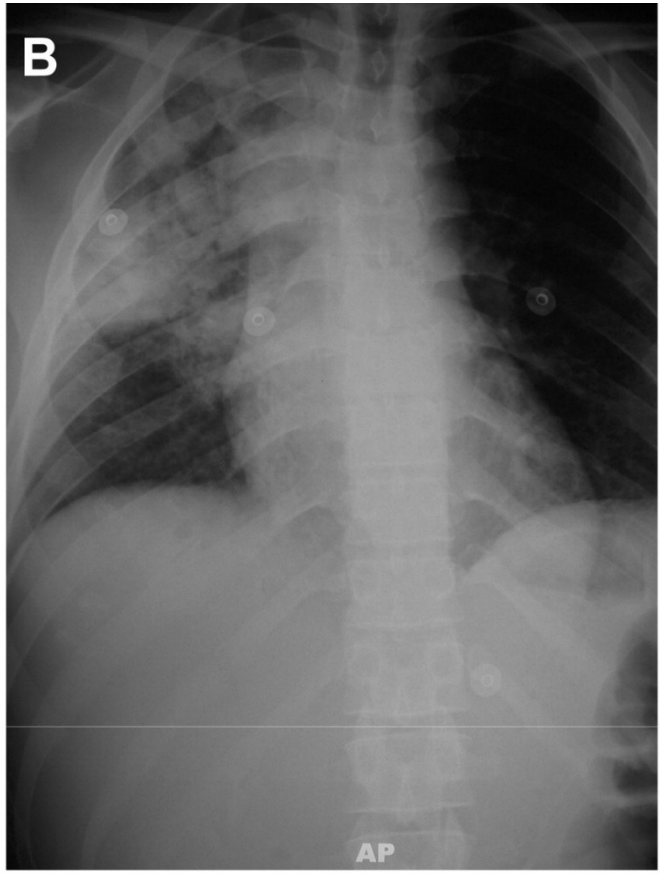
- 25yo African American man with diarrhea, subjective fevers/chills, and 30 pound weight loss—he denies respiratory symptoms.
- PMH: HIV (CD4+ 32, VL 298K)—ART naïve
- PE unremarkable aside from being underweight
- TST no induration
- Patient had no cough and was unable to produce an induced sputum specimen
- ART was initiated



Manabe et. al. JID 2009; 199(3): 437-44.

20 days later….

- Patient presented with fever to 104 and cough
- TST was repeated-24mm induration
- Induced sputum AFB smear negative
- BAL AFB smear negative
- All cultures several weeks later subsequently grew drug-susceptible MTB

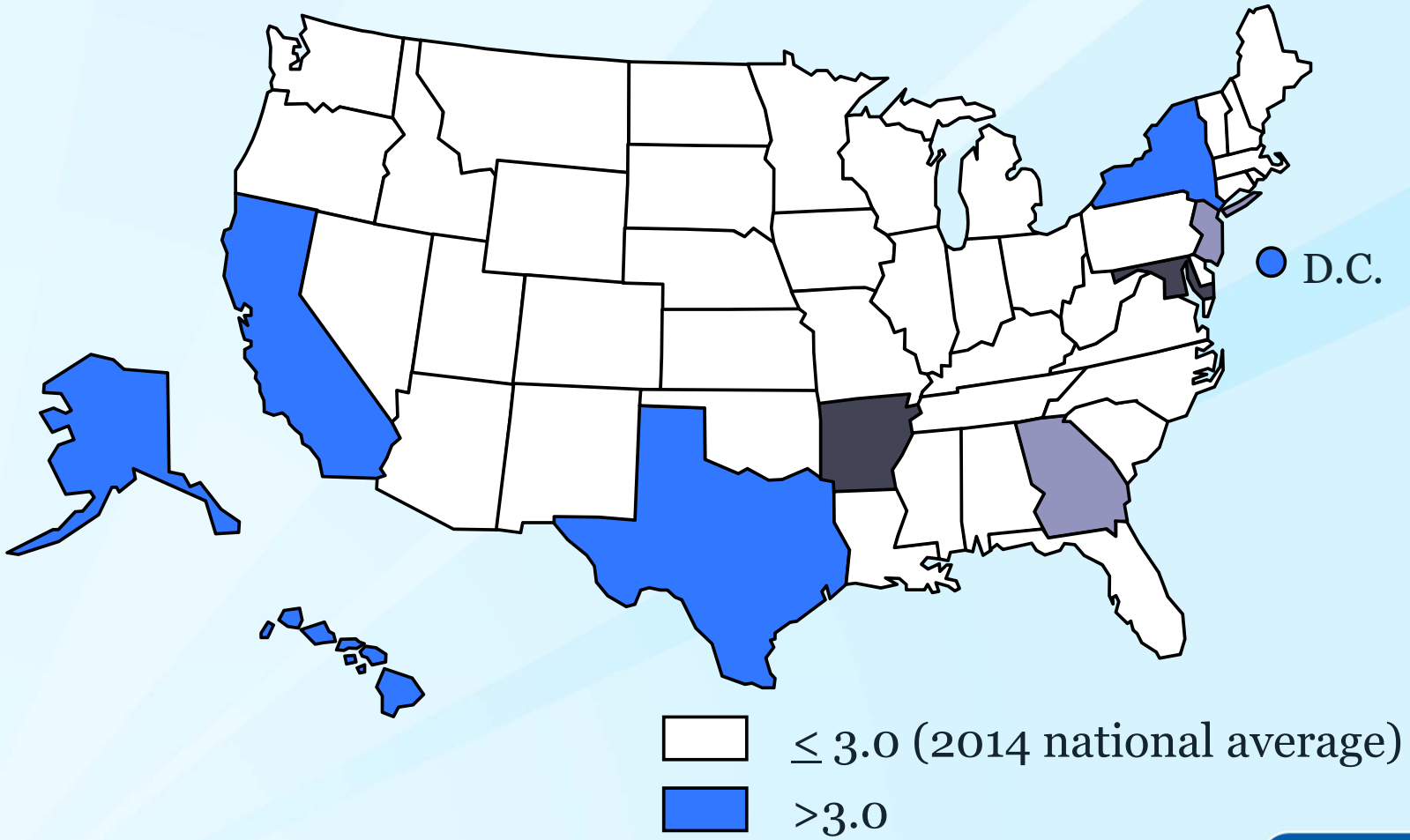


Manabe et. al. JID 2009; 199(3): 437-44.

Outline

- Epidemiology of TB/HIV co-infection
- Risk of TB disease among HIV-infected persons
- Clinical Manifestations
- Diagnosis
- Treatment
- Timing of HAART initiation

TB Case Rates,* United States, 2014



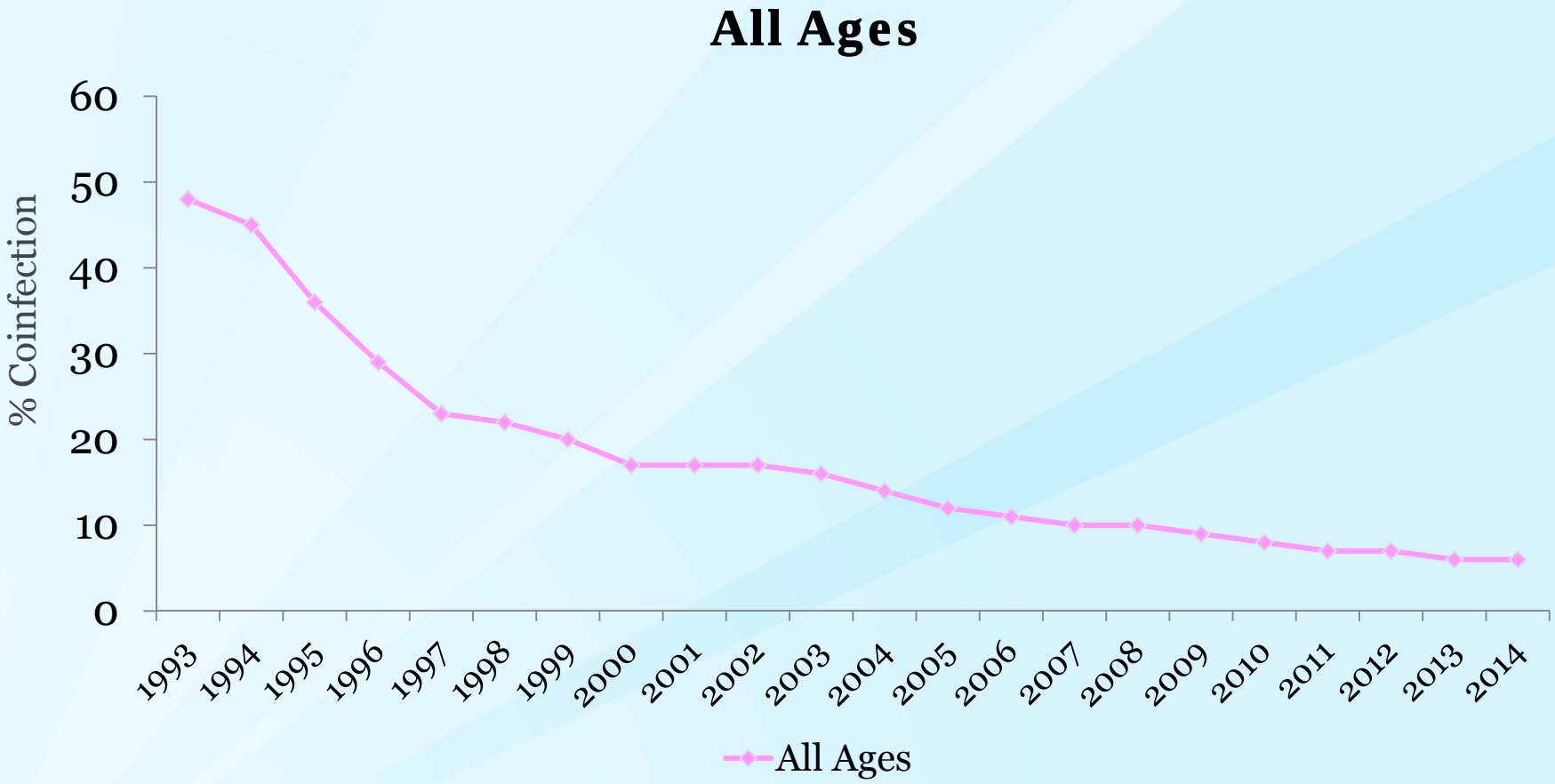
*Cases per 100,000.

Question

What is the estimated proportion of TB cases in the US and Tennessee are co-infected with HIV?

A. 2%
B. 5%
C. 10%
D. 20%

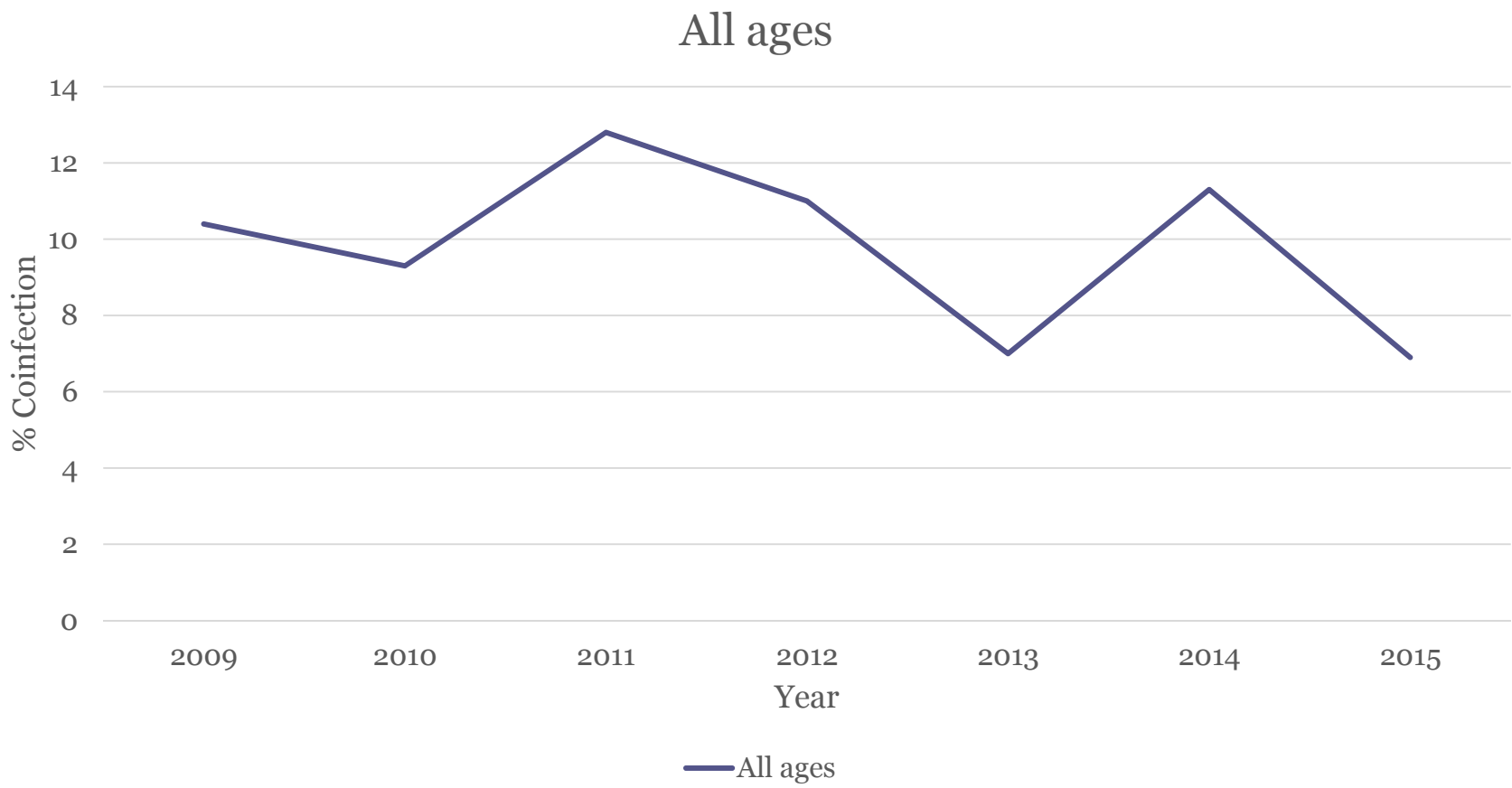
Estimated HIV Coinfection in Persons Reported with TB, United States, 1993 – 2014*



*Updated as of June 5, 2015.

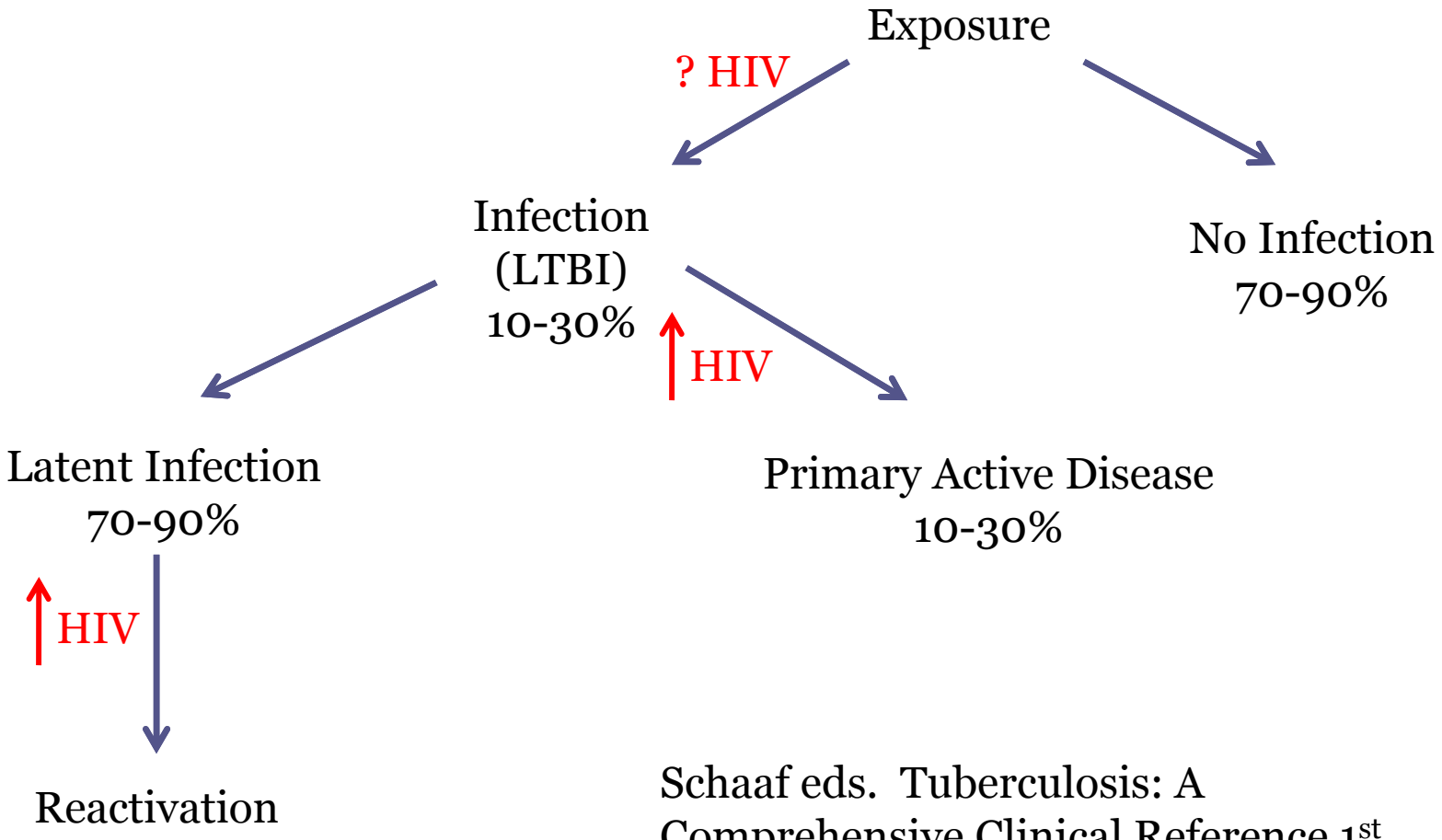
Note: Minimum estimates based on reported HIV-positive status among all TB cases in the age group.

HIV Coinfection in Persons Reported with TB, Tennessee, 2009– 2015



Outline

- Epidemiology of TB/HIV co-infection
- Risk of TB disease among HIV-infected persons
  - CD4, ART, LTBI
- Clinical Manifestations
- Diagnosis
- Treatment
- Timing of HAART initiation



Schaaf eds. Tuberculosis: A Comprehensive Clinical Reference 1st Edition. Elsevier; 2009.

CD4 and TB Risk

- 1130 HIV+ persons not on ART (U.S.: Pulmonary Complications of HIV Study Group)
  - TB risk greater with lower CD4 count
    - CD4 < 200: 1.2 TB cases per 100 p-y
    - CD4 > 200: 0.5 TB cases per 100 p-y
    - RR: 2.4 (95% CI: 1.1, 5.2)

Markowitz et. al. Ann Intern Med 1997;126:123-32.

- 944 HIV+ persons receiving ART (South Africa)
  - TB risk associated only with current CD4 count (within 4 months)
  - 25% decrease in TB risk per 100 cell ↑ in CD4 count

Lawn et. al. AIDS 2006;20:1605-12.

ART and TB Risk

TB rate per 100,000 person-years:

	No ART	ART	HAART
U.S.	720	470(40%↓)	190 (80%↓)
S. Africa	9700		2400 (81%↓)

Jones et. al. Int J Tuberc Lung Dis 2000;4:1026-31

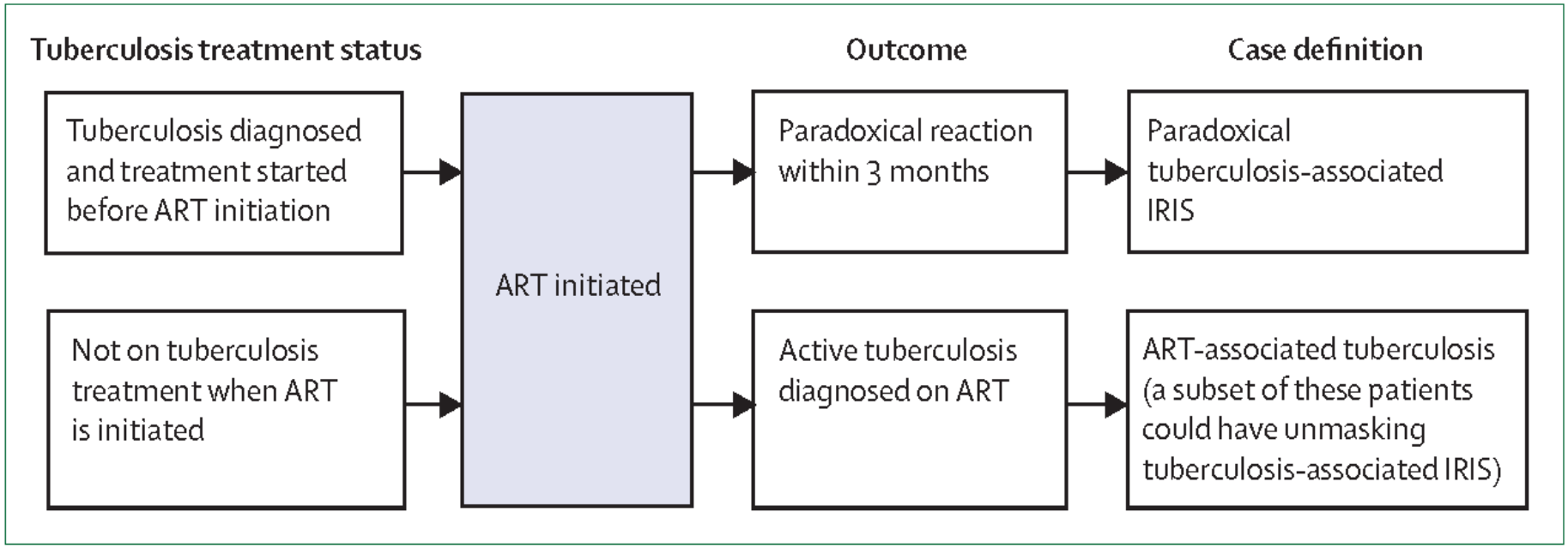
Badri et. al. Lancet 2002;359:2059-64

ART and TB risk

	Intention to Treat (ITT)		
Time Interval	TB cases	Follow-up (p-y)	TB incidence (per 100K p-y)
Off HAART	31	33,371	93 63, 132
HAART initiation-≤3 months	8	5,217	153 66, 302
>3 months -≤6 months	13	5,112	254 135, 434
>6 months	42	103,857	40 29, 55
Overall	94	147,557	64 51, 78

Pettit et. al. JAIDS (in press).

Hypothesis 1: Immune Reconstitution Inflammatory Syndrome (IRIS)



Meintjes et. al. Lancet Infect Dis. 2008 August ; 8(8): 516–523.

Hypothesis 2: ART Started at low CD4

Marginal Structural Model

Adjusting for time-updated CD4 and ART exposure

Characteristic	ITT Analysis aOR* (95% CI)
HAART status	
Not on HAART	Reference
≤6 months of HAART	0.65 (0.28, 1.51)
>6 months of HAART	**0.29 (0.16, 0.53)**

Pettit et. al. JAIDS (in press).

LTBI Prevalence

Characteristic	Est popln N x (1,000)	TST		QFT-GIT	
		LTBI Prev (95% CI)	Est. popln w/ LTBI x (1,000)	LTBI Prev (95% CI)	Est. popln w/ LTBI x (1,000)
All participants	282,460	4.4 (3.1-6.1)	12,398 (8,869-17,230)	4.8 (4.0-5.8)	13,628 (11,411-16,241)

Characteristic	# of NHANES subjects	TST		QFT-GIT	
		LTBI Prev (95% CI)	Est. popln w/ LTBI x (1,000)	LTBI Prev (95% CI)	Est. popln w/ LTBI x (1,000)
All participants	16	0	0	7.7 (2.0-25.4)	49 (13-164)

Mancuso et. al. AJRCCM 2016 [Epub ahead of print].

HIV and LTBI reactivation risk

	Est # Cases	Est % of US Popln w/ LTBI	Est US popln	Est p-y at risk for TB	Est Rate TB per 100 p-y
HIV+	2,198	4.2	961,000	121,100	1.82 (1.74-1.89)
HIV-	16,568	4.2	182,243,000	22,850,000	0.073 (0.070-0.075)

>20x

Shea et. al. AJE 2014; 179(2): 216-25.

Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Recommendations from the Centers for Disease Control, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

Mycobacterium tuberculosis Infection and Disease (Last updated May 7, 2013; last reviewed May 7, 2013)

Question

CDC Guidelines for the prevention of TB disease state that testing for latent TB infection should occur for ALL HIV-infected persons:

A. At the time of HIV diagnosis AND yearly after the first test regardless of risk
B. At the time of HIV diagnosis regardless of risk AND yearly after the first test only if other risk factors are identified
C. At the time of HIV diagnosis only if other risk factors are identified AND subsequent testing is not indicated

LTBI Testing Guidelines

- All persons should be tested for LTBI at the time of HIV diagnosis regardless of risk
- Persons with negative diagnostic tests for LTBI and CD4+ <200 should be retested once they start ART and CD4+>200
- Annual testing with high risk persons: incarceration, congregate settings, active drug users, etc

Outline

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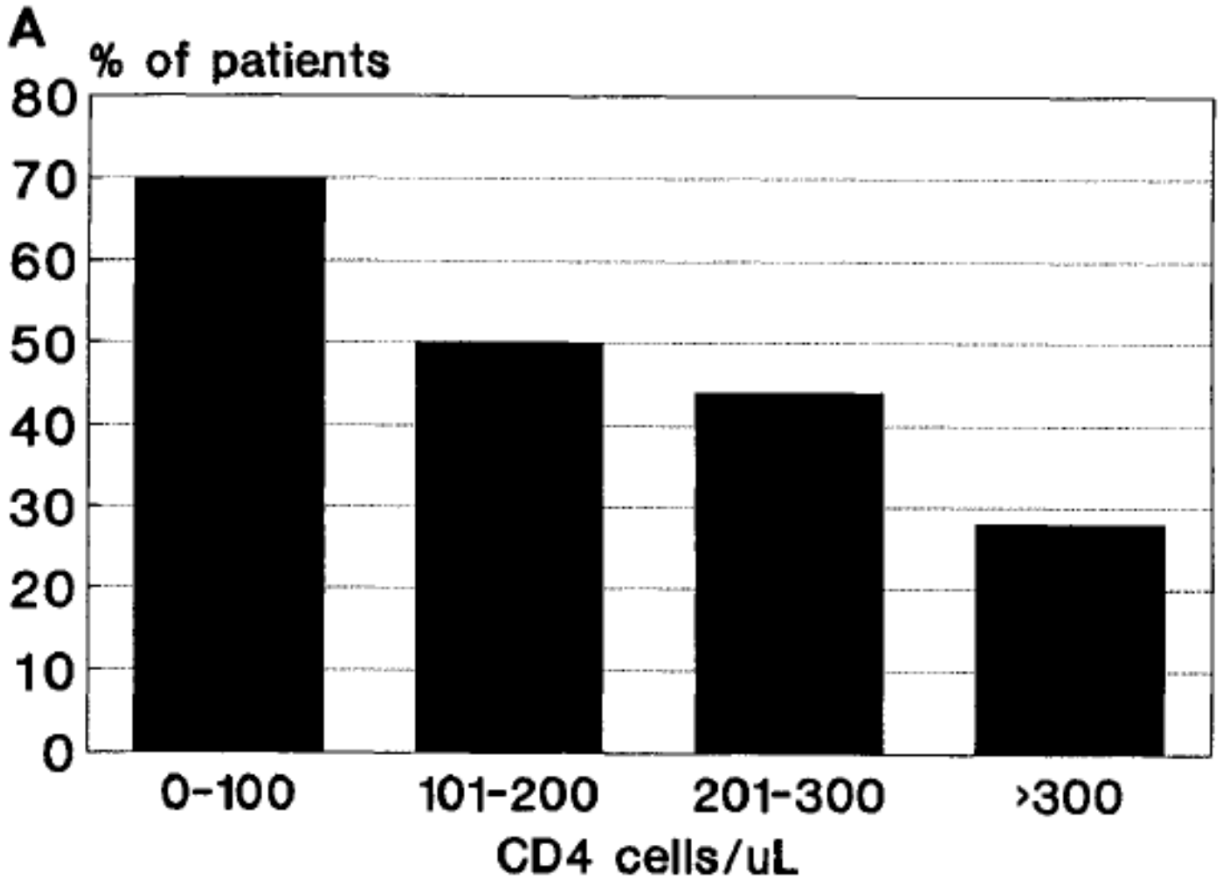
Clinical Manifestations

Symptom	Sensitivity 95% CI	Specificity 95% CI	Likelihood Ratio Negative
Cough	38.5 (19.2–62.2)	81.8 (65.3–91.5)	0.753 (0.724–0.783)
Fever	42.8 (22.2–66.3)	79.8 (62.4–90.4)	0.716 (0.695–0.738)
Night sweats	31.4 (14.8–54.6)	82.2 (65.9–91.7)	0.835 (0.780–0.893)
Weight loss	49.3 (27.0–71.9)	71.1 (50.8–85.5)	0.712 (0.693–0.733)
Any	78.9 (58.3–90.9)	49.6 (29.2–70.1)	0.426 (0.349–0.520)

Getahun et. al. PLoS Medicine 2011; 8 (1): e10000391.

Extrapulmonary TB



Jones et. al. AJRCCM 1993; 148: 1292-7.

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Diagnosis-Chest Radiography

CXR N=124	HIV+ N=72	HIV- N=52	P-value
Focal infiltrate	38 (53%)	46 (89%)	<0.01
Upper lobe infiltrate	19 (26%)	32 (62%)	<0.01
Cavitary Disease	5 (7%)	23 (44%)	<0.01
LAD	28 (39%)	6 (12%)	<0.01
Normal	8 (11%)	3 (6%)	NS

Alpert et. al. CID 1997; 24: 661-8.

Diagnosis-Sputum Smear

Smear status N=107	HIV+ N=64	HIV- N=43
AFB+, Number (%)	35 54.3%	32 74.5%
AFB-, Number (%)	29 45.7%	11 25.5%

Alpert et. al. CID 1997; 24: 661-8.

Diagnosis-Sputum Culture

Culture status N=189	HIV+ N=165	HIV- N=124
Culture+, Number (%)	109 66.1%	110 88.7%
Culture-, Number (%)	56 33.9%	14 11.3%

Crampin et. al. IJTLD 2001; 5(11): 994-9.

Diagnosis-Xpert MTB/RIF

HIV Status	Overall Sensitivity	Smear Negative Sensitivity	Smear Positive Sensitivity
All	86 (76, 92)	67 (60-74)	98 (97-99)
Positive	79 (70, 86)	61 (40-81)	97 (90-99)

Steingart et. al. Cochrane Review 2014.

Diagnosis-Xpert

Sample	Pooled Sensitivity Estimate
CSF	Cannot Calculate
Pleural Fluid	34 (24-44%)
Non-pleural serous Fluid	Cannot Calculate
All tissue	88 (77-95%)
Lymph node	96 (72-99%)
Gastric Aspirate	78 (69-86%)
Smear positive	95 (91-100%)
Smear negative	69 (60-80%)

Maynard-Smith et. al. BMD Infec Dis 2014; (14): 709.

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Initiation Phase=2 months HRZE

- Interval
  - Daily throughout (5-7 days per week) as DOT
  - Intermittent therapy associated with treatment failure or relapse with acquired rifamycin resistance

CDC. MMWR 2003. Vol 52. No-RR11.

Initiation Phase=2 months HRZE

- Regimen
  - INH 300mg daily
    - No ART interactions
  - PZA dosed by weight
    - No ART interactions
  - EMB dosed by weight and discontinued when susceptibilities known (unless PZA not used)
    - No ART interactions

CDC. MMWR 2003. Vol 52. No-RR11.

Initiation Phase=2 months HRZE

- Rifampin 600mg daily
  - If patient is on NNRTI (usually Nevirapine or Efavirenz) based regimen
  - Weight-based dosing of Efavirnez is not required
- Rifabutin 300mg daily
  - If patient is on PI-based regimen, decrease Rifabutin dose to 150mg daily
  - If patient is on Integrase Inhibitor based therapy (Raltegravir), no dosing changes are needed

CDC. MMWR 2003. Vol 52. No-RR11.

Question

The dosing interval in the continuation phase for HIV-infected persons can be:

A. Daily
B. Once-weekly
C. Twice-weekly
D. Three times weekly
E. A or D

Continuation Phase

- Interval
  - Daily throughout (5-7 days per week) as DOT
  - Once or twice weekly intermittent therapy associated with treatment failure or relapse with acquired rifamycin resistance
  - Thrice weekly intermittent therapy
    - Not studied adequately in clinical trials
    - No increased risk of adverse outcomes in observational studies and meta-analyses

CDC. MMWR 2003. Vol 52. No-RR11.

Continuation Phase

- Regimen
  - INH 300mg daily or 900mg tiw
  - RIF 600mg daily /tiw OR RBT 300mg daily /tiw
- Duration-optimum unknown
  - 4 months is recommended
  - 4-7 months for bone/joint
  - 7 months
    - +ve cultures after intensive phase
  - 7-10 months for CNS disease

CDC. MMWR 2003. Vol 52. No-RR11.

HIV and Relapse

Adjusted Odds of Relapse Stratified by Use of ART

	Relapse, aOR (95% CI)[a]	
	ART	
Covariate	None/NR[b]	All/Some[c]
Duration of rifamycin		
2 months	**6.7 (2.4, 18.5)**	$\sim 1 \times 10^{-5}$ [d] (~0, ~∞)
6 months	**3.1 (1.4, 6.7)**	0.2 (.01, 2.2)
≥8 months (reference)	1.0	1.0
Overall significance of factor, *P* value[e]	**0.001**	0.40

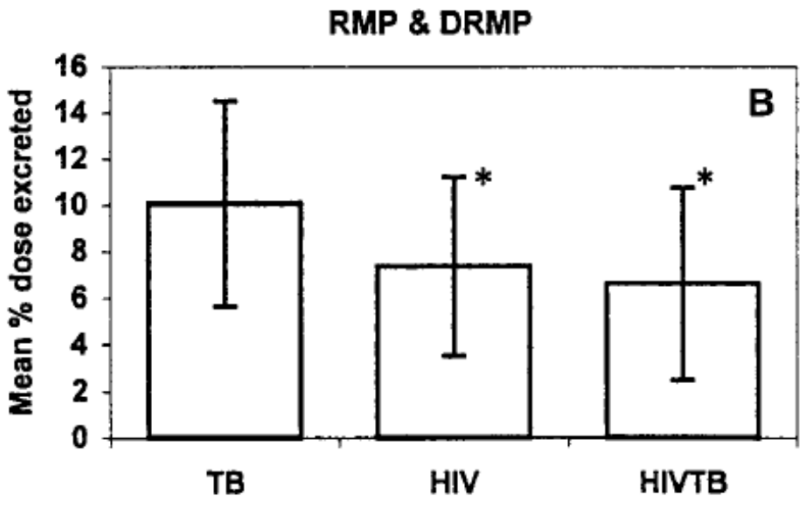
Khan et. al. CID 2012; 55: 1154-1163.

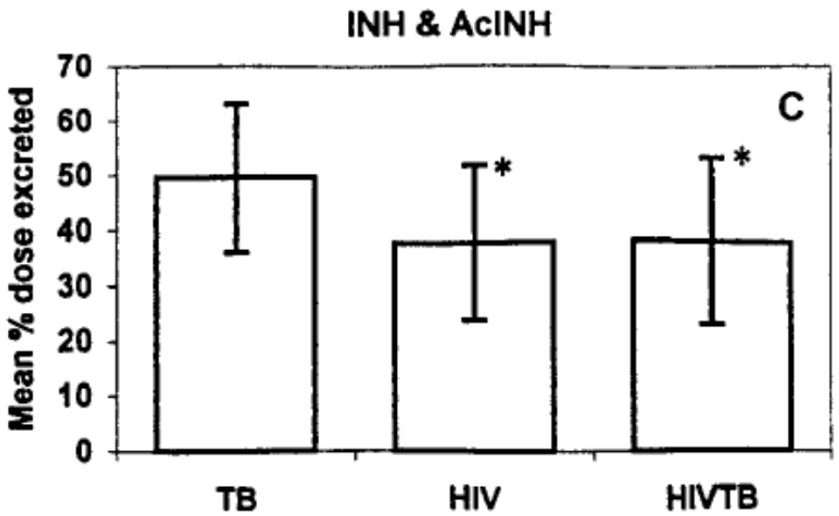
Therapeutic Drug Monitoring

- HIV-infected persons have MANY reasons for low anti-TB drug levels
  - Drug-drug interactions due to
    - Antiretroviral medications
    - Treatment for other opportunistic infections
    - Multi-way interactions between treatment for both of the above
  - Malabsorption in the setting of malnutrition or diarrhea

Alsultan& Peloquin. Drugs 2014; 74: 839-854.

Therapeutic Drug Monitoring





*Significant correlation between CD4 and urinary RMP.

Gurumurthy et. Al. CID 2004; 38: 280-3.

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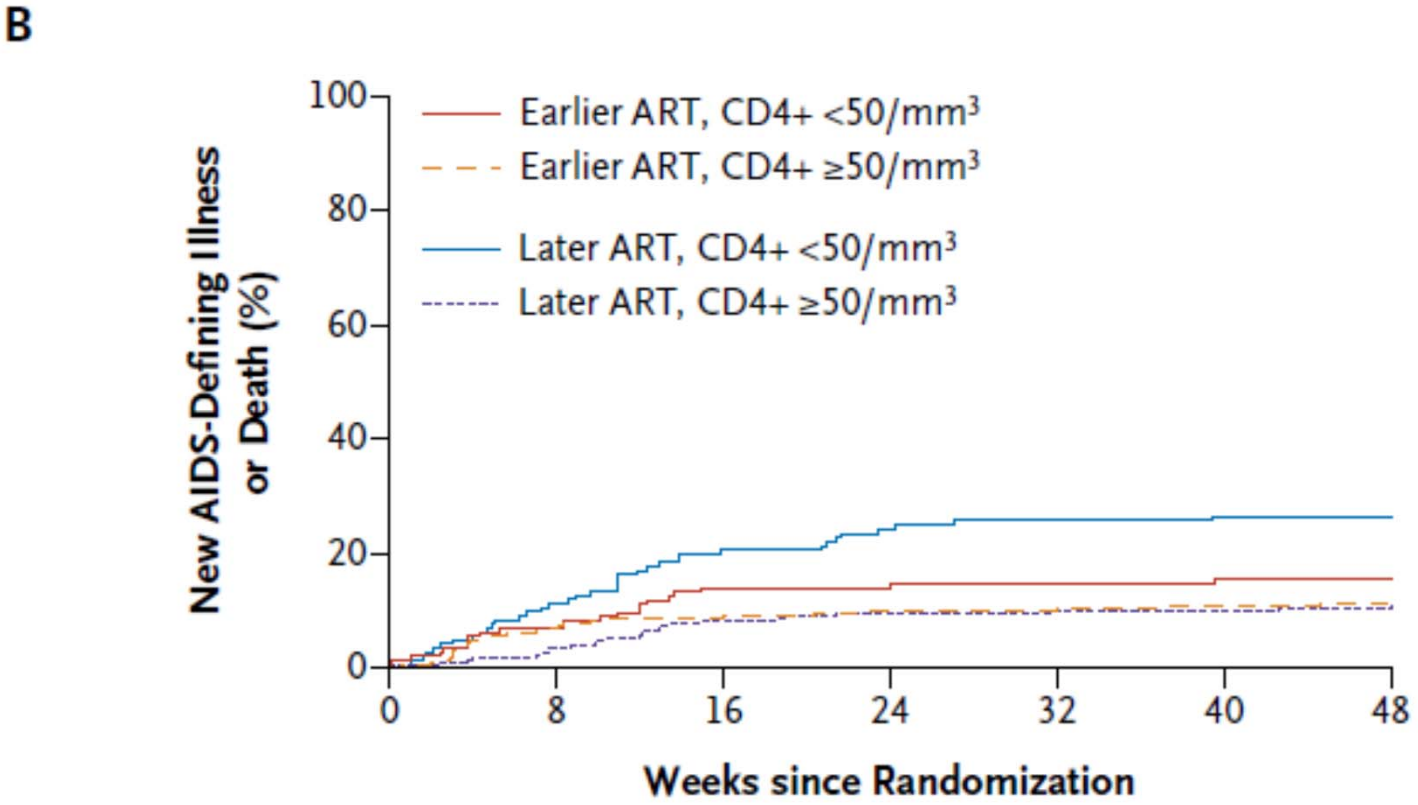
When to Start ART

- Favors early start:
  - Improved survival
  - Decreased risk of additional opportunistic infections
  - May improve TB outcomes
- Favors delayed start:
  - Large pill burden leads to decreased adherence
  - Drug-drug interactions
  - Overlapping side effects
  - Immune reconstitution inflammatory syndrome (IRIS)

ACTG 5221 STRIDE Study

- Immediate (within 2 weeks of TB tx) to early ART (within 8-12 weeks of TB tx)



Havlir et. al. NEJM 2011; 365 (16):1482-91

Guidelines-When to Start ART

- ART is recommended in all HIV-infected persons with TB (AI)
- Sequential treatment NOT recommended
  - Within 2 weeks if CD4<50 (AI)
  - Within 8-12 weeks if CD4>50 (AI)

Conclusions

- TB/HIV coinfection remains an important public health problem in the US.
- CD4, antiretroviral therapy, and latent TB infection are all important risk factors for TB disease in HIV-infected person.
- TB disease can be difficult to diagnose in HIV-infected persons.
- If clinical improvement is slower than expected, consideration should be given to longer continuation phase duration and/or therapeutic drug monitoring.

Questions?