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MAYO CLINIC CENTER FOR TUBERCULOSIS

Tuberculosis in the Setting of HIV Infection

Wisconsin Mycobacteria Laboratory Network (WMLN) Annual Conference
November 17, 2017

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Director, HIV Program

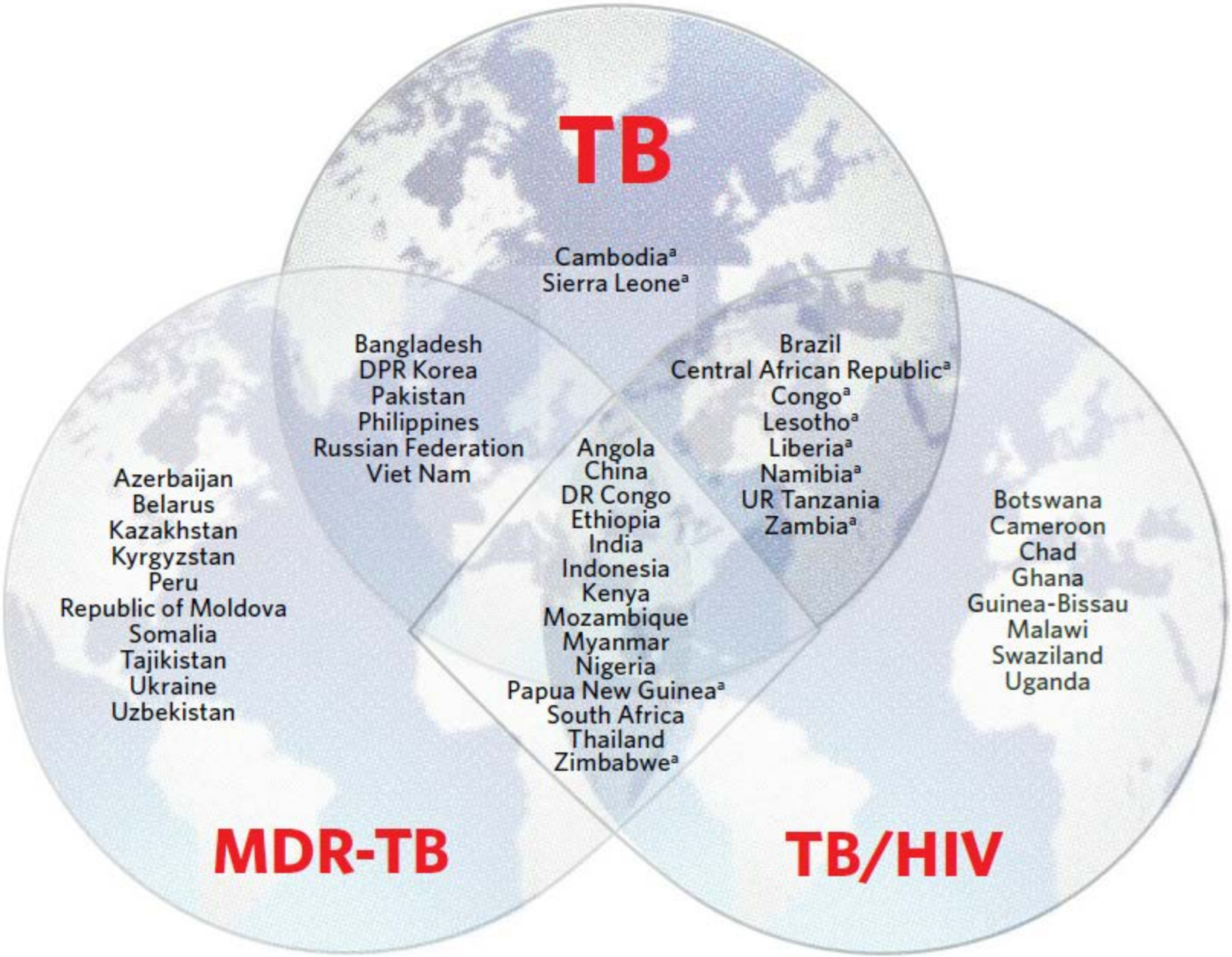
Learning Objectives

At the end of this talk, participants should be able to:

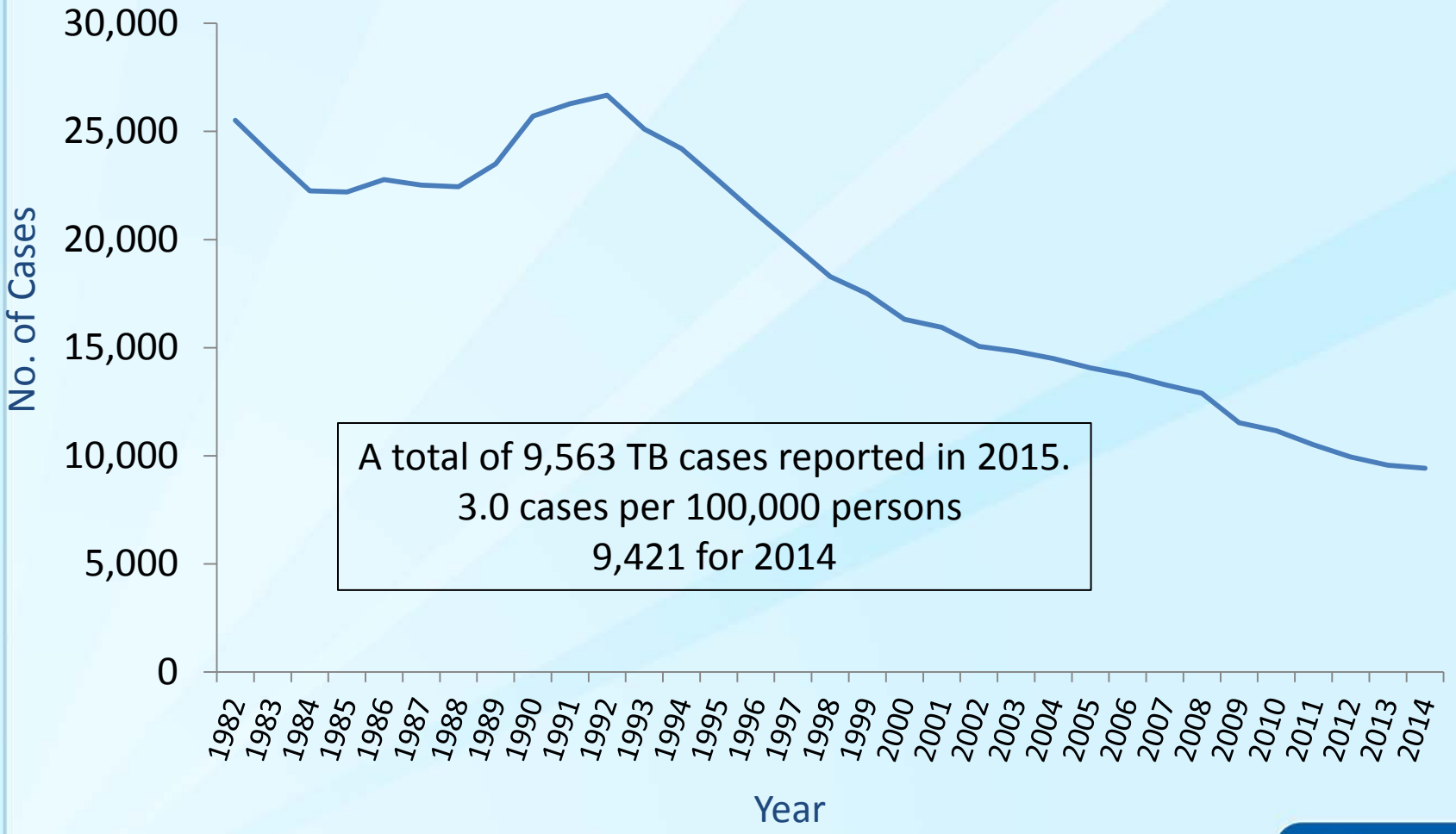
- Describe the overlapping epidemiology of TB and HIV globally and in the United States
- Describe the impact of HIV on the various components of the natural history of TB
- Describe the challenges in the diagnosis and treatment of LTBI in the setting of HIV infection
- Describe the challenges in the diagnosis and treatment of active tuberculosis in the setting of HIV infection

Epidemiology: Tuberculosis

- Tuberculosis (TB) is one of the world's most important infectious diseases.
- In 2015, there were an estimated 10.4 million new (incident) TB cases
  - 5.9 million (56%) among men
  - 3.5 million (34%) among women
  - 1.0 million (10%) among children.
  - People living with HIV accounted for 1.2 million (11%) of all new TB cases.


TB
Cambodia[a]
Sierra Leone[a]
Bangladesh
DPR Korea
Pakistan
Philippines
Russian Federation
Viet Nam
Brazil
Central African Republic[a]
Congo[a]
Lesotho[a]
Liberia[a]
Namibia[a]
UR Tanzania
Zambia[a]
Azerbaijan
Belarus
Kazakhstan
Kyrgyzstan
Peru
Republic of Moldova
Somalia
Tajikistan
Ukraine
Uzbekistan
Angola
China
DR Congo
Ethiopia
India
Indonesia
Kenya
Mozambique
Myanmar
Nigeria
Papua New Guinea[a]
South Africa
Thailand
Zimbabwe[a]
Botswana
Cameroon
Chad
Ghana
Guinea-Bissau
Malawi
Swaziland
Uganda
MDR-TB
TB/HIV

Reported TB Cases
United States, 1982–2014*



*Updated as of June 5, 2015.

Global summary of the AIDS epidemic | 2015

Number of people living with HIV	36.9 million [34.3 million–41.4 million]
People newly infected with HIV in 2014	2 million [1.9 million–2.2 million] New HIV infections have fallen by 35% since 2000.
AIDS deaths in 2014	1.2 million [980 000–1.6 million] AIDS-related deaths have fallen by 42% since the peak in 2004.

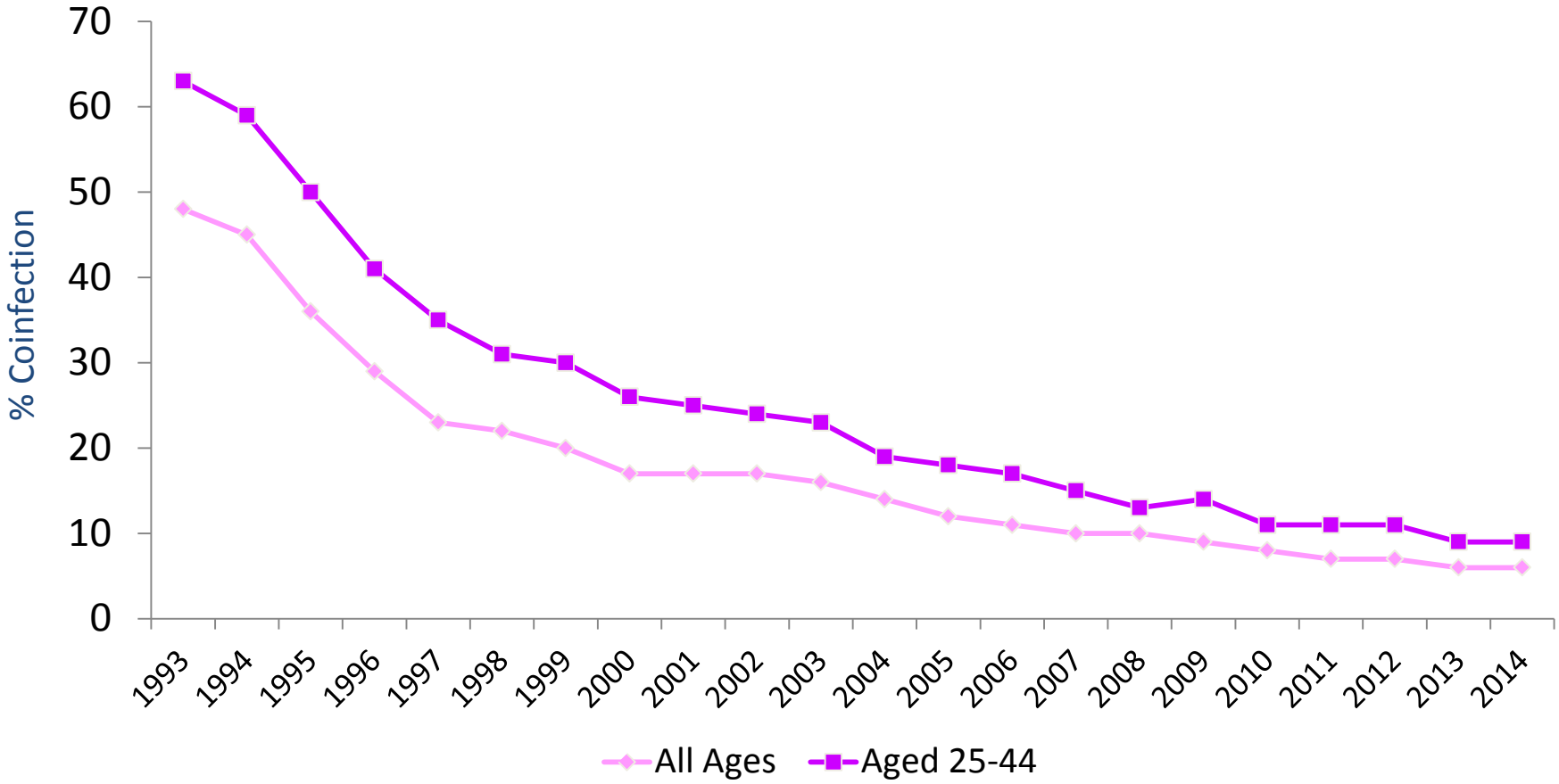
HIV Infection Epidemiology: United States

- About 1.2 million people in the United States are living with HIV
- In 2014, an estimated 44,609 adults and adolescents were diagnosed with HIV infection
  - 81% men
  - 19% women
- During 2013, there were an estimated 16,281 deaths of persons with diagnosed HIV infection.

TB and HIV Co-Infection

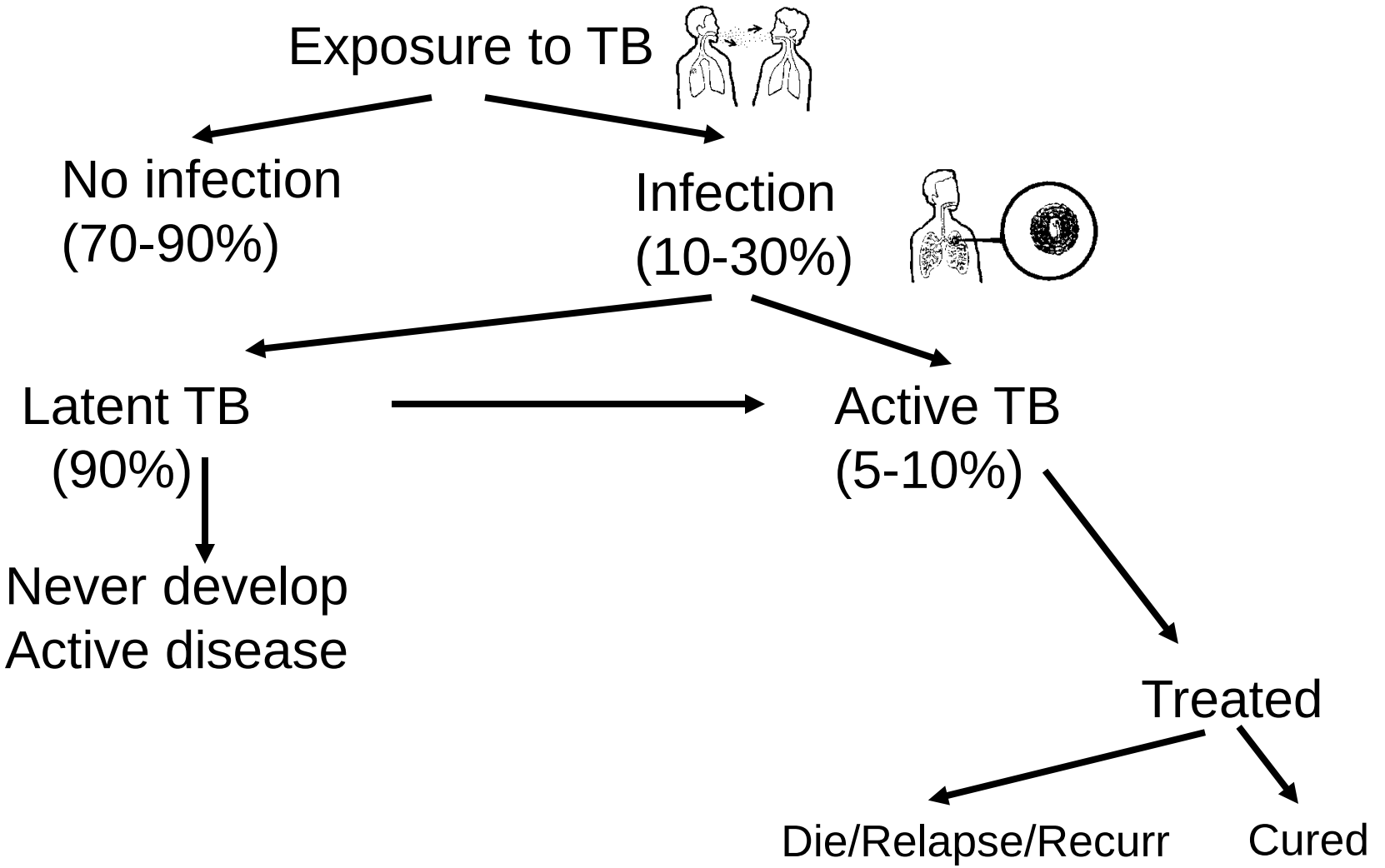
- An estimated 11% of incident TB cases in 2015 were HIV positive.
- > 50% in parts of southern Africa.
- Tuberculosis remains the leading cause of death among people living with HIV
  - 400,000 million deaths from TB among HIV-positive people in 2015.
- The African Region accounts for about four out of every five HIV-positive TB cases and TB deaths.

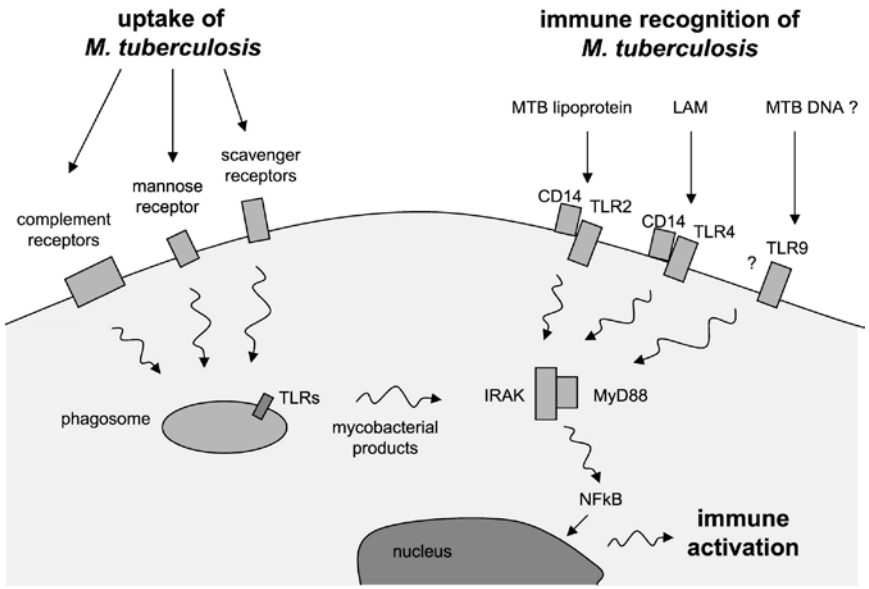
Estimated HIV Coinfection in Persons Reported with TB, United States, 1993 – 2014*

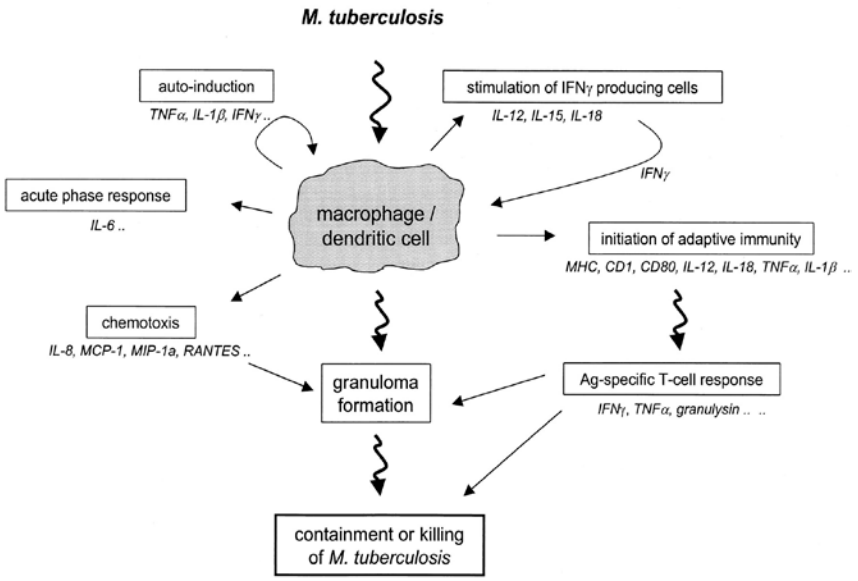


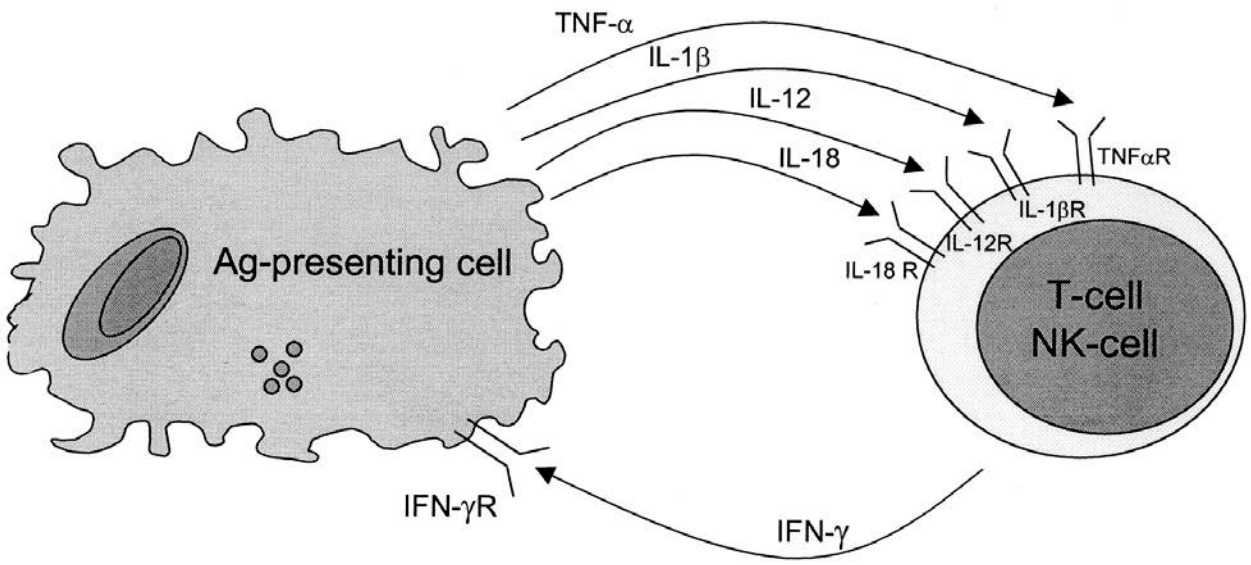
Natural History

Natural History of TB Infection in Patients Without HIV









van Crevel R et al. Clin. Microbiol. Rev. 2002;15:294-309

HIV Immune Deficiency

- Diminished T cell repertoire
- Reduced lymphocyte function - decreased
- Delayed hypersensitivity response to recall antigens
- Phagocytosis
- Chemotaxis
- Intracellular killing
- Natural killer cell-mediated killing
- Loss of specific antibody responses
- Increased immune activation
- disruption of immunoregulatory cytokine expression and production
- Decreased IL-2, γ interferon, and IL-12
- Increased IL-1, IL-6, TNFα

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An Outbreak of Tuberculosis with Accelerated Progression among Persons Infected with the Human Immunodeficiency Virus — An Analysis Using Restriction-Fragment—Length Polymorphisms

Charles L. Daley, M.D., Peter M. Small, M.D., Gisela F. Schecter, M.D., M.P.H., Gary K. Schoolnik, M.D., Ruth A. McAdam, D.Phil., William R. Jacobs, Jr., Ph.D., and Philip C. Hopewell, M.D.

N Engl J Med 1992; 326:231-235 | January 23, 1992 | DOI: 10.1056/NEJM199201233260404

Tuberculous infection progressed to active disease within 106 days of acquiring the infection in 37 percent (11 of 30) of HIV-infected patients.

Tuberculosis did not develop in any of 28 staff members with exposures, although there were 6 with documented tuberculin conversions and 8 others had positive tuberculin reactions of unknown duration.

THE LANCET

Volume 334, Issues 8678–8679, 30 December 1989, Pages 1502–1504

Hospital Infection

NOSOCOMIAL EPIDEMIC OF ACTIVE TUBERCULOSIS AMONG HIV-INFECTED PATIENTS

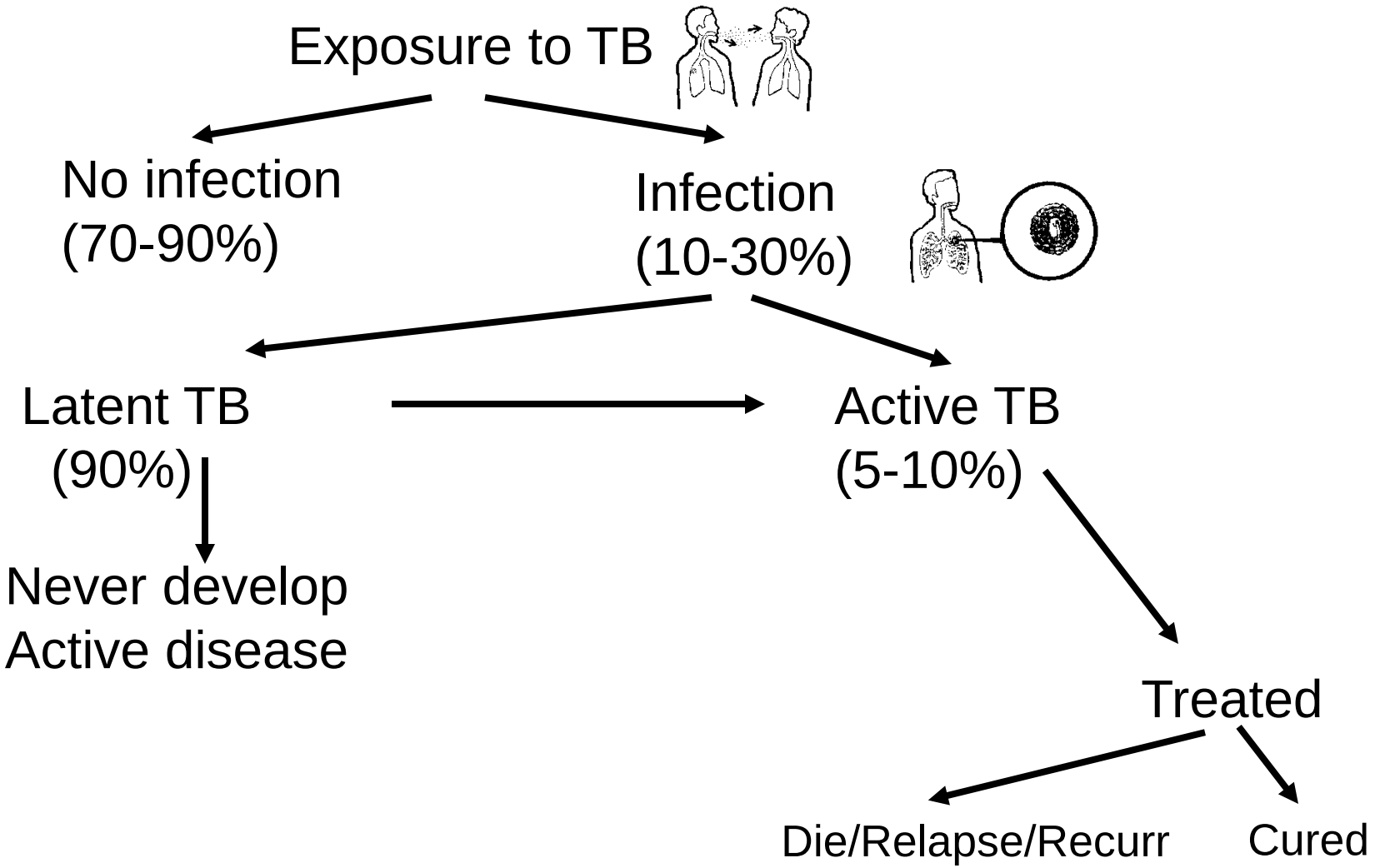
DiPerri Giovanni[a], Maria Chiara Danzi[a], Giovanna De Checchi[a], Sergio Pizzighella[b], Maurizio Solbiati[a], Mario Cruciani[a], Roberto Luzzati[a], Marina Malena[a], Romualdo Mazzi[a], Ercole Concia[a], Dante Bassetti[a]

[a] Istituto di Malattie Infettive, University of Verona, United Kingdom

[b] Microbiology Laboratory, Ospedale Borgo Trento , Verona, Italy

7 of 18 (39%) HIV-infected inpatients developed active tuberculosis within 60 days of diagnosis of the index case

Natural History of TB Infection in Patients Without HIV



ORIGINAL ARTICLE ARCHIVE

A Prospective Study of the Risk of Tuberculosis among Intravenous Drug Users with Human Immunodeficiency Virus Infection

Peter A. Selwyn, M.D., M.P.H., Diana Hartel, M.P.H., Victor A. Lewis, M.D., Ellie E. Schoenbaum, M.D., Sten H. Vermund, M.D., Robert S. Klein, M.D., Angela T. Walker, M.D., and Gerald H. Friedland, M.D.

N Engl J Med 1989; 320:545-550 | March 2, 1989 | DOI: 10.1056/NEJM198903023200901

- Forty-nine HIV-seropositive subjects and 62 HIV-seronegative subjects had a positive TST response.
- 7/8 cases of TB occurred in HIV-seropositive subjects with a prior positive PPD test (7.9 cases per 100 person-years, vs. 0.3 case per 100 person-years in those without a prior positive PPD test; rate ratio, 24.0; P<0.0001).

Relative Risk of Reactivation Tuberculosis among Persons with Medical Conditions That Impair Immune Control of *M. tuberculosis*.

Table 3. Relative Risk of Reactivation Tuberculosis among Persons with Medical Conditions That Impair Immune Control of *M. tuberculosis*.*

Condition	Study	Relative Risk (95% CI)
Advanced HIV infection	Pablos-Mendez et al.[27] Moss et al.[26]	9.9 (8.7–11.3)† 9.4 (3.5–25.1)
Old, healed tuberculosis	Ferebee,[13] Ferebee et al.[20]	5.2 (3.4–8.0)
Chronic renal failure	Pablos-Mendez et al.[27]	2.4 (2.1–2.8)†
Infliximab therapy	Keane et al.[28]	2.0 (0.7–5.5)†
Poorly controlled diabetes	Pablos-Mendez et al.[27]	1.7 (1.5–2.2)†
Silicosis	Cowie[29] Corbett et al.[30] Kleinschmidt and Churchyard[31]	1.7 (1.3–2.1)† 1.3 (1.1–1.7)† 1.2 (1.0–1.5)†
Underweight (≤10 percent below normal)	Palmer et al.,[22] Edwards et al.[23]	1.6 (1.1–2.2)
Gastrectomy	Thorn et al.[32] Steiger et al.[33]	1.4 (1.1–1.9)† 1.3 (1.2–1.4)†

* CI denotes confidence interval, and HIV human immunodeficiency virus.
† The relative risk is estimated, as described in the Methods section.

Horsburgh CR Jr. N Engl J Med 2004;350:2060-2067.

OPEN ACCESS Freely available online

PLOS | ONE

Incidence of HIV-Associated Tuberculosis among Individuals Taking Combination Antiretroviral Therapy: A Systematic Review and Meta-Analysis

Tendesayi Kufa[1,2]*, Tonderai Mabuto[1]*, Evans Muchiri[1], Salome Charalambous[1,2], Dominique Rosillon[3], Gavin Churchyard[1,2], Rebecca C. Harris[4]

PLoS One. 2014; 9(11): e111209

- 42 studies describing 43 cohorts
  - 32 (74%) from high/intermediate burden
  - 11 (26%) from low burden

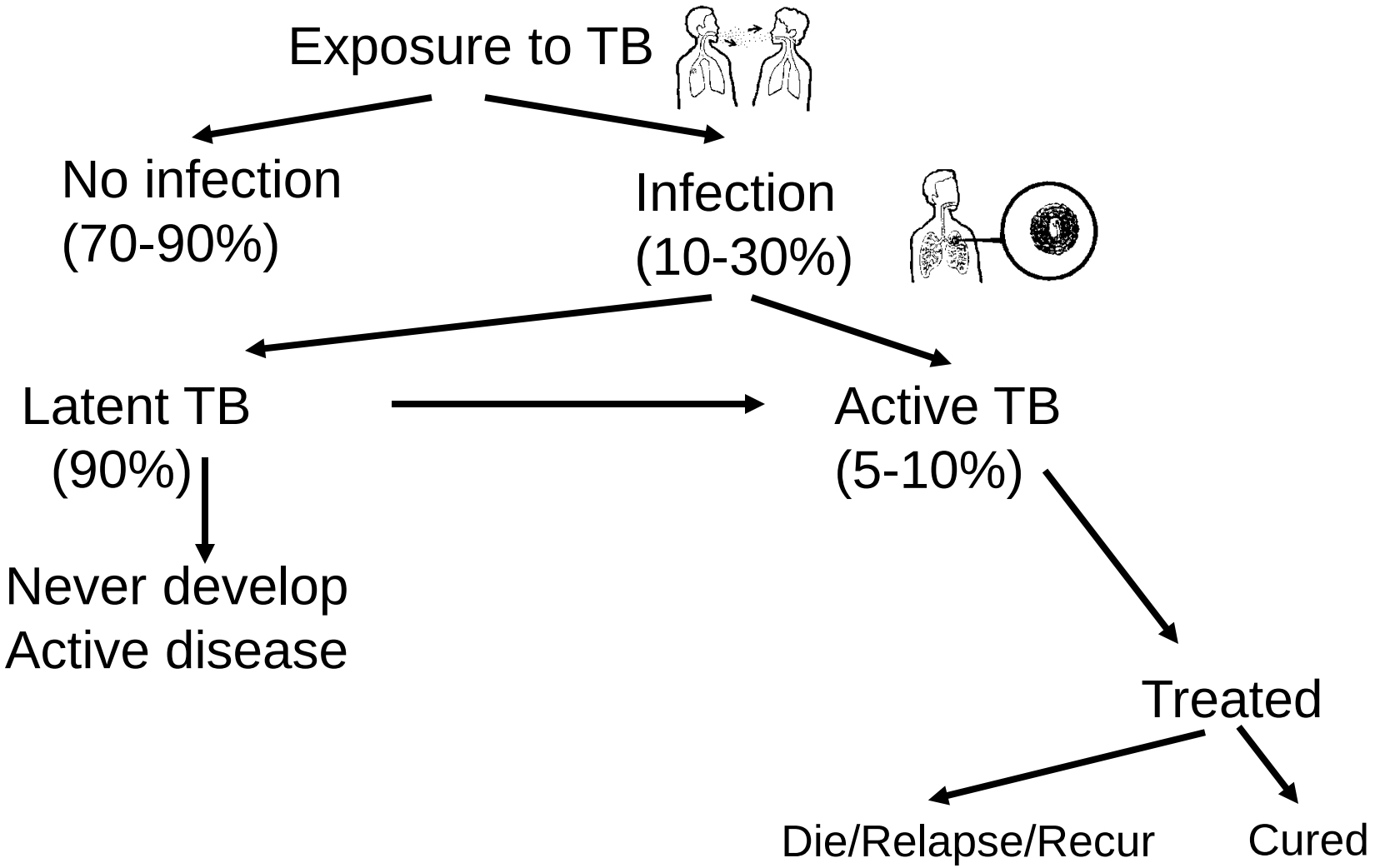
- Incidence rates in cohorts from high/intermediate burden settings are higher than rates in cohorts those from low burden settings
- HIV disease stage impacts TB incidence
- ART and duration of ART impacts TB incidence

HIV and Risk of Reactivation of TB

- Advanced HIV infection vs non HIV - Increased
- Untreated HIV infection that is less advanced vs. advanced - decreased risk of TB
- HIV infection on effective ART vs. untreated - decreased risk of TB
- HIV infection on effective ART vs. non HIV – increased risk
- ART failure - reversion to the higher level of risk.

Horsburgh CR Jr. N Engl J Med 2004;350:2060-2067; Girardi et al. AIDS 2000, 14:1985±1991
Jones, et al. The International Journal of Tuberculosis and Lung Disease, 2000 4(11):1026-1031; Kufa et al. PLoS One. 2014; 9(11): e111209

Natural History of TB Infection in Patients Without HIV



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PLoS one

When Tuberculosis Comes Back: Who Develops Recurrent Tuberculosis in California?

Lisa Pascopella[1]*, Kathryn DeRiemer[2], James P. Watt[3], Jennifer M. Flood[1]

1 Tuberculosis Control Branch, Division of Communicable Disease Control, Center for Infectious Diseases, California Department of Public Health, Richmond, California, United States of America, **2** School of Medicine, University of California Davis, Davis, California, United States of America, **3** Division of Communicable Disease Control, Center for Infectious Diseases, California Department of Public Health, Richmond, California, United States of America

- 23,517 culture-positive, pulmonary tuberculosis patients from the California tuberculosis case registry from 1993 to 2007 who completed anti-tuberculosis therapy.
- 148 (0.63%) had a late recurrence.
- Human immunodeficiency virus infection (adjusted hazard ratio, 1.81; p = 0.0149

The Journal of Infectious Diseases

The Journal of Infectious Diseases 2010; 201:704–711

High Rates of Recurrence in HIV-Infected and HIV-Uninfected Patients with Tuberculosis

Judith R. Glynn,[1] Jill Murray,[3,4] Andre Bester,[5] Gill Nelson,[3,4] Stuart Shearer,[5] and Pam Sonnenberg[2]

[1]Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, and [2]Research Department of Infection and Population Health, University College London, London, United Kingdom; [3]National Institute for Occupational Health, National Health Laboratory Service, [4]School of Public Health, University of the Witwatersrand, and [5]Gold Fields Limited, Johannesberg, South Africa

- Retrospective cohort study of South African gold miners, men with known dates of seroconversion to HIV (from 1991 to 1997) and HIV-negative men were followed up to 2004.
- 342 HIV-positive and 321 HIV-negative men who had had1 previous episode of tuberculosis,
- Rates of tuberculosis recurrence:
  - HIV-positive 19.7 cases per 100 person-years at risk (95% confidence interval [CI], 16.4–23.7)
  - HIV-negative 7.7 cases per 100 PYAR (95% CI, 6.1–9.8)

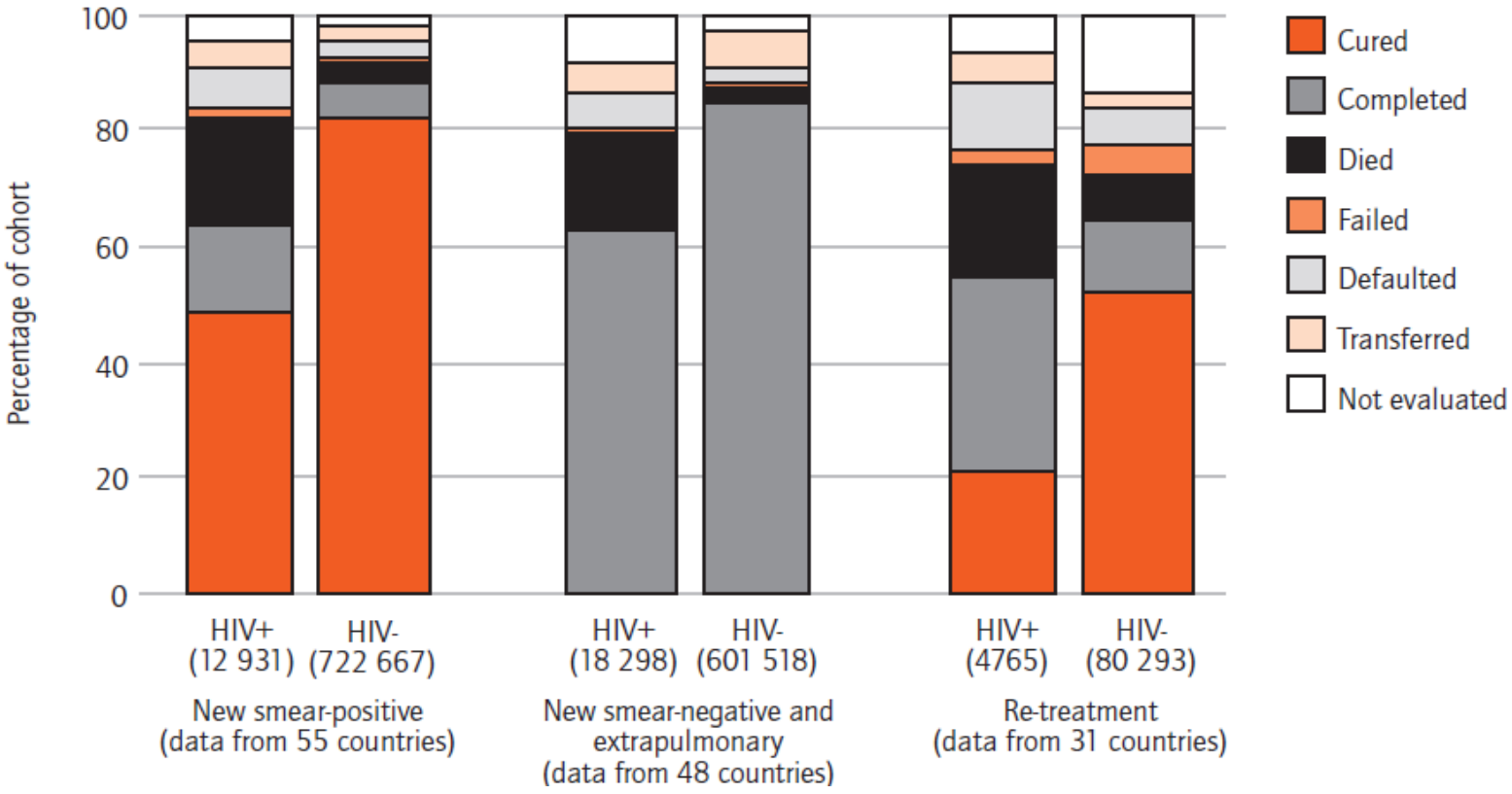
Factors associated with TB treatment success among new smear-positive TB patients at Martin Preuss Centre between January 2008 and December 2010 (N = 2,264)¥.

Characteristics	Total		Unadjusted Odds Ratio (95% CI)	*P-value**	Adjusted Odds Ratio (95% CI)[¥]	*P-value**
	N	%				
HIV Status				*0.019*		*0.003*
HIV positive	1,275	*56%*	1.00		1.00	
HIV negative	989	*44%*	1.34 (1.05–1.72)		1.49 (1.14–1.94)	
Gender				*0.005*		*0.002*
Male	1,400	*62%*	1.00		1.00	
Female	864	*38%*	1.45 (1.12–1.87)		1.52 (1.17–1.99)	
Age category				*0.323*		*0.065*
15–24	460	*20%*	0.90 (0.65–1.25)		0.76 (0.54–1.06)	
25–34	985	*44%*	1.00		1.00	
35–44	505	*22%*	0.98 (0.71–1.36)		1.07 (0.77–1.48)	
45–54	173	*8%*	0.71 (0.46–1.10)		0.70 (0.45–1.10)	
≥55	141	*6%*	0.66(0.41–1.06)		0.57 (0.35–0.93)	
TB Registration year				*<0.001*		*<0.001*
2008	791	*35%*	1.80 (1.34–2.43)		1.79 (1.33–2.41)	
2009	843	*37%*	1.00		1.00	
2010	630	*28%*	1.23 (0.92–1.65)		1.22 (0.91–1.63)	
TB Treatment site				*0.147*		
MPC	912	*40%*	1.20 (0.94–1.53)		-	
Other	1,352	*60%*	1.00			

Tweya H, Feldacker C, Phiri S, Ben-Smith A, et al. (2013) Comparison of Treatment Outcomes of New Smear-Positive Pulmonary Tuberculosis Patients by HIV and Antiretroviral Status in a TB/HIV Clinic, Malawi. PLoS ONE 8(2): e56248. doi:10.1371/journal.pone.0056248 http://www.plosone.org/article/info:doi/10.1371/journal.pone.0056248

FIGURE 1.26

Treatment outcomes for HIV-positive and HIV-negative TB patients, 2006 cohort. The numbers under the bars are the numbers of patients included in the cohort.



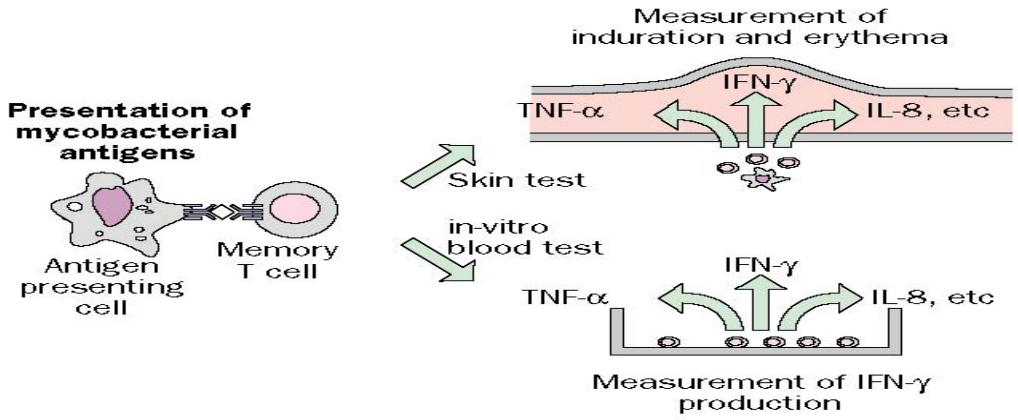
Global Tuberculosis Control: Epidemiology, Strategy, Financing : WHO Report 2009

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

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

- Testing for LTBI at the time of HIV diagnosis should be routine regardless of epidemiologic risk factors
- All patients with tuberculosis should be tested for HIV
- Annual testing for LTBI only in those with ongoing exposure
- If negative screen for LTBI while CD4 count is low, repeat testing post cART once CD4 is above 200.

Diagnosis of LTBI in HIV-Infected Individuals: Which Test?



Comparison of sensitivity of IGRAs between HIV-infected and HIV-uninfected patients with culture-confirmed tuberculosis

Reference	Country	Sensitivity in HIV-pos	Sensitivity in HIV-neg
		n/N (%)	n/N (%)
QFT-GIT			
Tsiouris et al. [19]	South Africa	17/26 (65)	11/15 (73)
Chee et al. [20]	Singapore	4/7 (57)	220/273 (81)
Garcia-Gasalla et al. [25]	Spain	12/13 (92)	85/105 (81)
Legesse et al. [29]	Ethiopia	13/19 (68)	20/31 (65)
Ling et al. [31]	South Africa	29/43 (67)	67/82 (82)
Dheda et al. [33]	South Africa	1/5 (20)	11/15 (73)
T-SPOT.TB			
Chee et al. [20]	Singapore	7/7 (100)	247/267 (93)
Ling et al. [31]	South Africa	35/43 (81)	70/82 (85)
Dheda et al. [33]	South Africa	5/5 (100)	14/15 (93)

Head-to-Head Comparison of Sensitivity Between IGRAs and TST in HIV-infected Patients with Culture-Confirmed Tuberculosis

Reference	Country	IGRA	Sensitivity IGRA	Sensitivity TST
			n/N (%)	n/N (%)
Tsiouris et al. [19]	South Africa	QFT-GIT	17/26 (65)	22 (85)
Aichelburg et al. [22]	Austria	QFT-GIT	10/11 (91)	8 (80)*
Kabeer et al. [23]	India	QFT-GIT	29/44 (66)	11 (25)
Garcia-Gasalla et al. [25]	Spain	QFT-GIT	9/13 (69)	5 (42)**
Rangaka et al. [32]	South Africa	QFT-GIT	32/50 (64)	34 (68)
Vincenti et al. [38]	Italy	T-SPOT.TB	11/13 (85)	6 (46)†

Head-to-Head Comparison of Sensitivity Between QFT-GIT and T-SPOT.TB in HIV-Infected Patients with Culture-Confirmed Tuberculosis

Reference	Country	Sensitivity QFT-GIT	Sensitivity T-SPOT.TB
		n/N (%)	n/N (%)
Chee et al. [20]	Singapore	4/7 (57)	7/7 (100)
Markova et al. [21]	Bulgaria	12/13 (92)	8/13 (62)
Leidl et al. [24]	Uganda	13/19 (68)	17/19 (89)
Ling et al. [31]	South Africa	29/43 (67)	35/43 (81)
Dheda et al. [33]	South Africa	1/5 (20)	5/5 (100)

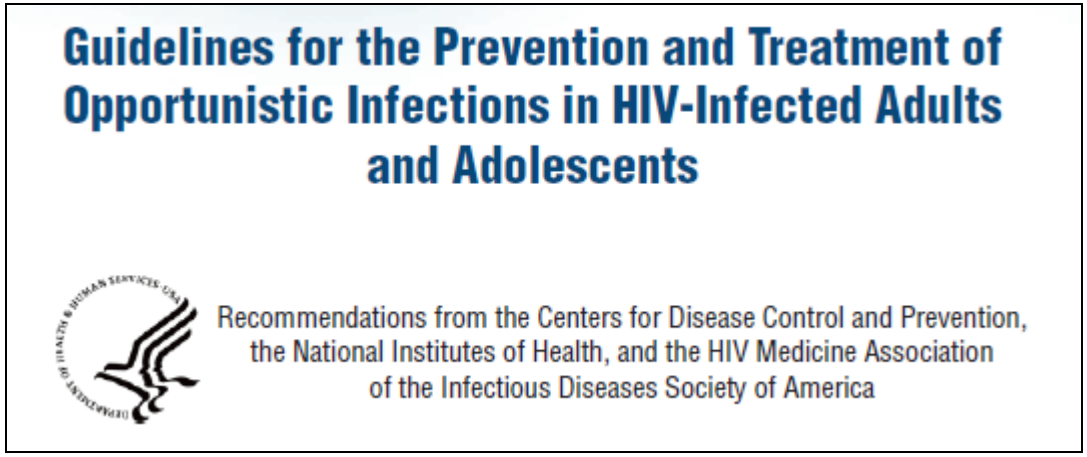
infected

Patients in Four Systematic

	Cattamanchi (Ref. [10])	Metcalfe (Ref. [11])	Chen (Ref. [12])	Santin Current SR
Sensitivity*				
High-burden TB settings				
-QFT-GIT	61% (47–75)	65% (52–77)	N.D.	61% (53–69)
-T-SPOT.TB	72% (62–81)	68% (56–80)	N.D.	65% (54–74)
Low-burden TB settings				
-QFT-GIT	67% (47–83)†	N.D.	N.D.	59% (46–71)
-T-SPOT.TB	94% (73–100)†	N.D.	N.D.	69% (47–99)†
Overall				
-QFT-GIT	N.D.	N.D.	69% (62–71)	61% (54–67)
-T-SPOT	N.D.	N.D.	66% (60–71)	65% (56–74)

Which IGRA is better for CD4 < 200

- Three studies evaluated the effect of CD4 + cell counts on sensitivity of QFT-GIT
  - One study reported a decrease in its sensitivity with fewer than 200 circulating CD4 +T-cell counts
  - Another found no differences in CD4 + T-cell counts between patients with positive and negative QFT-GIT results
  - Another study found higher sensitivity in patients with <200 CD4 + cells than in those with > 200 CD4 + cells
- None of the three studies assessing TSPOT. TB reported a relationship between lower sensitivity and lower CD4 + T-cell counts
  - The sensitivity of T-SPOT.TB in one study was higher in patients with CD4 + cells < 200 than in those with CD4+ cells > 200 cells



- Progressive immunodeficiency is associated with decreased sensitivity of IGRAs
  - It may have less impact on the sensitivity of IGRAs than on the sensitivity of TST
- Both TST and FDA-approved IGRAs are appropriate for TB screening in HIV-infected individuals
- No definitive comparison favoring one over the other
- Routine use of both TST and IGRAs to screen for LTBI is not recommended

Diagnosis of Active Tuberculosis in the Setting of HIV

TB in the Setting of HIV: Clinical Presentation

- In general, similar to that seen in HIV-uninfected patients
- However, differential diagnosis broader
  - HIV itself
  - Other opportunistic infections
- Extrapulmonary
  - HIV main risk factor
  - 35-80% vs. 15-50%
  - Bones and joints, lymph nodes, the pleura, peritoneum, CNS

Laboratory Diagnosis of Active TB

- Sputum smear
  - HIV-infected patients are more likely to have smear-negative pulmonary TB
  - Range 31 – 81%
- CXR
  - Individuals with advanced HIV are likely to have atypical presentations
    - Lower lobe locations
    - Less cavities
    - Consolidation
    - Intrathoracic LAD
    - May appear normal

Treatment of Tuberculosis

Treatment of LTBI

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

Factors associated with TB treatment success among new smear-positive TB/HIV co-infected patients at Martin Preuss Centre between January 2008 and December 2010 ¥ (N = 1,275).

Characteristics	Total		Unadjusted Odds Ratio (95% CI)	P-value*	Adjusted Odds Ratio (95% CI)‡	P-value*
	N	%				
ART Status				0.005		0.001
On ART	492	39%	1.61 (1.15–2.25)		1.83 (1.29–2.60)	
Not on ART	783	61%	1.00		1.00	
Gender				0.031		0.032
Female	520	41%	1.43 (1.03–1.97)		1.44 (1.03–2.01)	
Male	755	59%	1.00		1.00	
Age at TB registration				0.515		0.373
15–24	169	13%	0.76 (0.48–1.19)		0.70 (0.44–1.12)	
25–34	619	49%	1.00		1.00	
35–44	350	27%	0.98 (0.67–1.43)		1.06 (0.72–1.55)	
45–54	200	8%	0.70 (0.40–1.21)		0.73 (0.42–1.28)	
≥55	37	3%	1.35 (0.47–3.90)		1.43 (0.49–4.17)	
TB Registration year				0.004		<0.001
2008	421	33%	1.90 (1.30–2.79)		2.17 (1.46–3.22)	
2009	496	39%	1.00		1.00	
2010	358	28%	1.31 (0.91–1.90)		1.22 (0.84–1.78)	

Tweya H, Feldacker C, Phiri S, Ben-Smith A, et al. (2013) Comparison of Treatment Outcomes of New Smear-Positive Pulmonary Tuberculosis Patients by HIV and Antiretroviral Status in a TB/HIV Clinic, Malawi. PLoS ONE 8(2): e56248. doi:10.1371/journal.pone.0056248
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0056248

A comparison of TB treatment outcomes in HIV-TB co-infected patients diagnosed with TB taking and not taking ART

Treatment outcome	*Not on ART (n = 1024) N (%)*	*On ART (n = 4016) N (%)*	*OR (95% CI)*
Treatment success	552 (54)	3191 (79.5)	1.47 (1.39-1.56)
Death	256 (25)	541 (13.5)	0.53 (0.47-0.61)
Default	105 (10.3)	118 (3)	0.28 (0.22-0.36)
Failure	10 (1)	13 (0.3)	0.33 (0.14-0.75)

Shastri et al. BMC Public Health 2013 13:838 doi:10.1186/1471-2458-13-838

TB and HIV coinfection: Treatment Issues

- Drug-drug interactions
- Overlapping drug toxicities
- Pill Burden
- Immune-reconstitution inflammatory syndrome (IRIS)
- Sequencing with antiretroviral therapy
- Highly intermittent Dosing
- TB treatment outcome in HIV
- ART treatment effect on TB incidence

Treatment of Active Tuberculosis in HIV-Coinfected Patients: A Systematic Review and Meta-Analysis

Faiz A. Khan,[1] Jessica Minion,[1] Madhukar Pai,[1,2] Sarah Royce,[3] William Burman,[4] Anthony D. Harries,[5] and Dick Menzies[1]

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Clinical Infectious Diseases 2010; 50(9):1288–1299

Meta-analysis of 27 studies

Duration of rifamycin therapy of ⩾6 months and daily therapy in the initial intensive phase were associated with lower risk of failure and/or relapse in HIV-positive patients with active TB.

Variable	Treatment failure, aRR[a] (95% CI)	P^b	Relapse, aRR[a] (95% CI)	P^b	Death during TB treatment, aRR[a] (95% CI)	P^b
Duration of rifampin therapy[c]						
2 Months	1.3 (0.4–4.1)	.67	3.6 (1.1–11.7)[d]	.14	1.8 (1.0–3.1)[d]	.03
6 Months	1.0 (0.4–2.8)		2.4 (0.8–7.4)		1.0 (0.6–1.6)	
⩾8 Months	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Intermittent therapy[c]						
Initial phase daily	1.0 (reference)	.02	1.0 (reference)	.002	1.0 (reference)	.42
Initial phase thrice weekly	4.0 (1.5–10.4)[d]		4.8 (1.8–12.8)[d]		1.3 (0.7–2.3)	
Receipt of ART[c]						
Some or all patients	1.0 (reference)	.10	1.0 (reference)	.21	1.0 (reference)	.39
None or not stated	3.8 (0.9–16.4)		3.5 (0.5–26)		0.8 (0.5–1.5)	
Dispersion parameter for model	0.3 (−0.1 to 0.7)		0.22 (−0.04 to 0.53)		0.13 (−0.02 to 0.31)	

Acquired Rifamycin Resistance with Twice-Weekly Treatment of HIV-related Tuberculosis

William Burman, Debra Benator, Andrew Vernon, Awal Khan, Brenda Jones, Claudia Silva, Chris Lahart, Stephen Weis, Barbara King, Bonita Mangura, Marc Weiner, Wafaa El-Sadr, and the Tuberculosis Trials Consortium

Denver Public Health; University of Colorado Health Sciences Center, Denver, Colorado; Veterans Affairs Medical Center of Washington, DC; George Washington University Medical Center, Washington, DC; Centers for Disease Control and Prevention, Atlanta, Georgia; Los Angeles County–University of Southern California Medical Center, Los Angeles, California; Baylor College of Medicine, Houston; Tarrant County Public Health Department; University of North Texas Health Sciences Center, Fort Worth; University of Texas Health Science Center; South Texas Veterans Health Care System, San Antonio, Texas; University of Medicine and Dentistry of New Jersey–New Jersey Medical School National Tuberculosis Center, Newark, New Jersey; Harlem Hospital Center; and Columbia University College of Physicians and Surgeons, New York, New York

Am J Respir Crit Care. 2006;173:350–356

- 169 HIV-infected patients with culture-confirmed TB
- Median CD4 cell count 90 cells/mm3
- Median HIVRNA 5.3 log10 copies/ml

- DOT rifabutin, isoniazid, pyrazinamide, and ethambutol for 2 months (given daily, thrice-weekly, or twice-weekly per the local tuberculosis control program)
- Followed by rifabutin plus isoniazid for 4 months twice weekly.

Nine (5.3%) patients had culture-positive treatment failure (n=3) or relapse (n=6).
Eight of these nine (89%) cases had isolates with acquired rifamycin resistance.

Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid

*Lancet.*1999;353(9167):1843-1847

Andrew Vernon, William Burman, Debra Benator, Awal Khan, Lorna Bozeman, for the Tuberculosis Trials Consortium

- 61 adults with culture-positive, drug-susceptible pulmonary tuberculosis
- Completed 2 months of isoniazid, rifampin, pyrazinamide, ethambutol
- Median CD4 cell count 118 cells/mm^3 for the once weekly arm and 137 cells/mm^3 for the twice weekly arm

- Randomly assigned to (for an additional 16 weeks, DOT)
  - 9 0 0 mg isoniazid and 600 mg rifapentine once weekly or
  - 900 mg isoniazid and 600 mg rifampin twice weekly.

- Five of 30 patients in the once-weekly isoniazid/rifapentine group relapsed, compared with three of 31 patients in the twice weekly isoniazid/rifampin group (p=0·41).

- Four of five relapses in the once-weekly isoniazid/rifapentine group had monoresistance to rifamycin, compared with none of three in the rifampin group (p=0·05).

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

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

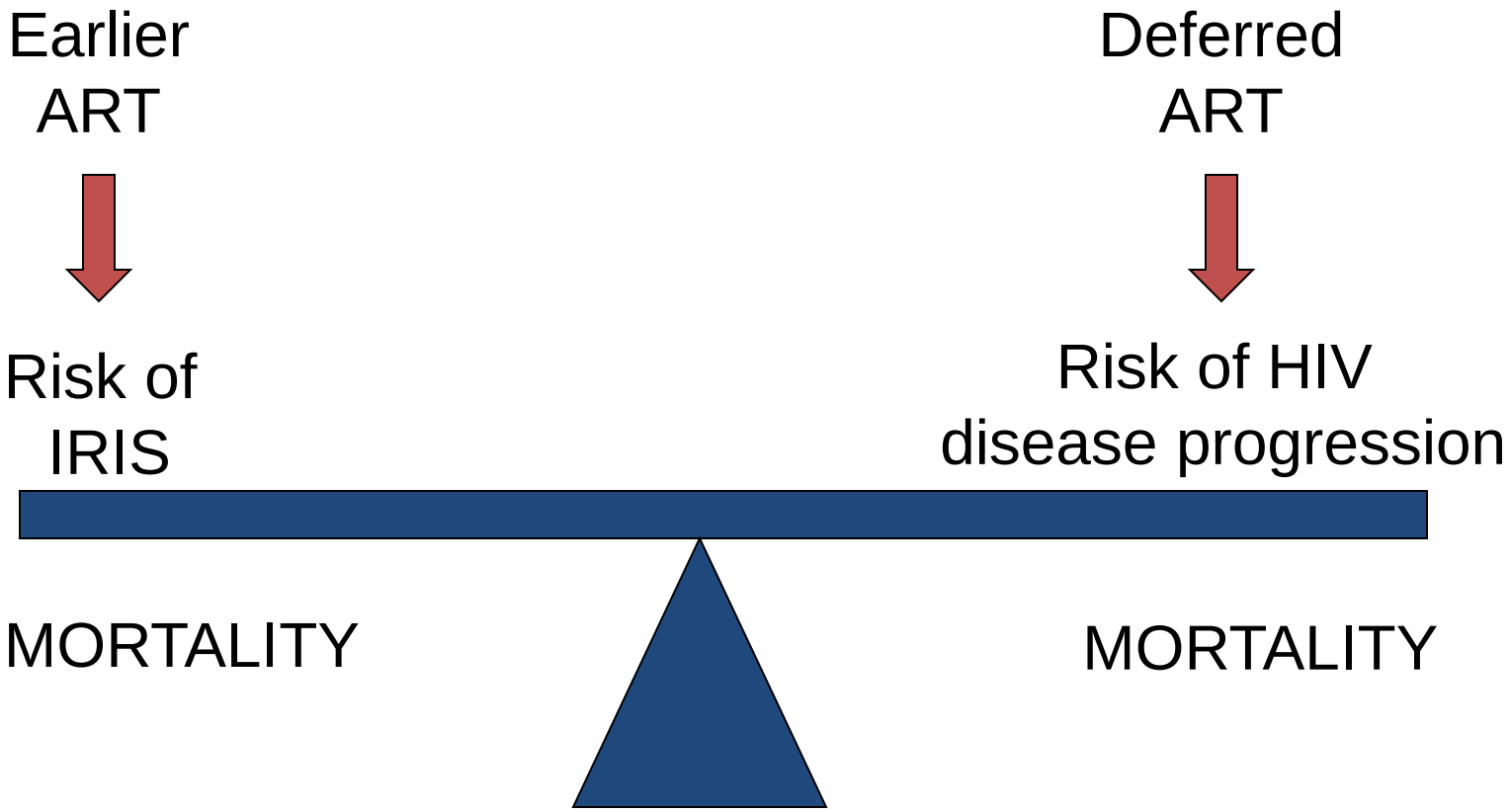
- Treatment of TB in HIV-infected individuals is the same as for those who are HIV uninfected
- Treatment of TB in HIV-infected individuals should include an initial 4-drug combination of isoniazid, rifampin, pyrazinamide, and ethambutol
- DOT is recommended for all patients with suspected HIV-related TB
- Daily therapy (5–7 days per week) given as DOT is recommended during the intensive phase
- Daily (5–7 days per week) or thrice-weekly dosing is recommended during the continuation phase
- Once- or twice-weekly dosing during the continuation phase assoc. with treatment failure/relapse with acquired rifamycin resistance

TB/HIV Treatment Issues: Drug Interactions

- Rifamycins induce hepatic cytochrome P450 (CYP3A4) enzymes, accelerating metabolism of:
  - Protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), etc.
  - Rifampicin >> Rifabutin
- For patients receiving PIs or NNRTIs, substitute rifabutin for rifampin, if available
- Alternative non-rifamycin regimens less optimal, longer duration of therapy

Co-treatment of OI and ART

Potential challenges	Potential benefits
IRIS Co-toxicities Drug-drug interactions Absorption Pill burden Adherence counseling	Reduced HIV progression Reduced mortality Clearance of OI Prevent OI recurrence



When to start ART after recent diagnosis of OI?

IRIS

Immune Reconstitution Inflammatory Syndrome (IRIS)

- Clinical worsening in the setting of an adequate response to ART
  - "Paradoxical" worsening of previously known treated (completed or ongoing) opportunistic pathogen
  - "Unmasking" of subclinical opportunistic pathogen

Incidence of Tuberculosis Immune Reconstitution Inflammatory Syndrome (IRIS) in Human Immunodeficiency Virus (HIV)–Tuberculosis Coinfection.

Study no.	Study, year	Years studied	Incidence of tuberculosis IRIS among HIV-positive patients with tuberculosis, proportion (%)	Median baseline parameters			Median time, days	
				Age of patients, years	CD4 cell count, cells/μL	Viral load, $\log_{10}$ copies/mL	From tuberculosis diagnosis and treatment to IRIS	From start of ART to IRIS
1	Narita et al [82], 1998	1996–1997	12/33 (36)	40[a]	51[a]	5.8	109[a]	15[a]
2	Breton et al [83], 2004	1996–2001	16/37 (43)	35	100	5.36	48	12
3	Breen et al [84], 2004	1997–2002	14/50 (28)	36	NA	NA	33	11
4	Kumarasamy et al [85], 2004	2000–2003	11/144 (8)	29	123	NA	42	22
5	Lawn et al [80], 2007	2002–2005	19/160 (12)	35	68	4.84	105	14

NOTE. ART, antiretroviral therapy; NA, not available.

[a] Mean.

Swaminathan S et al. Clin Infect Dis. 2010;50:1377-1386

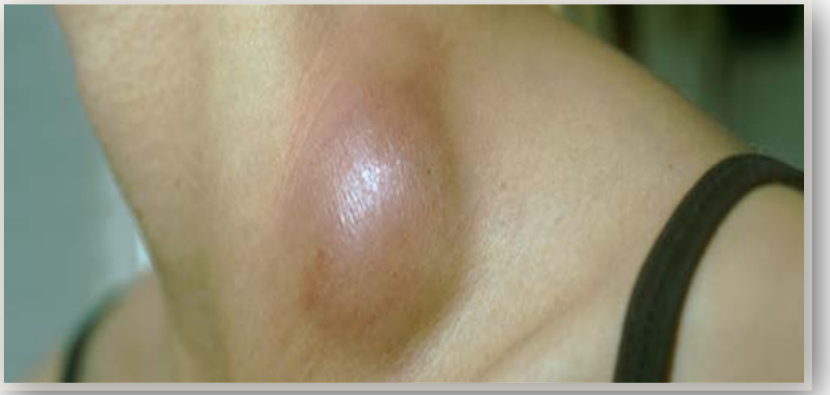
IRIS

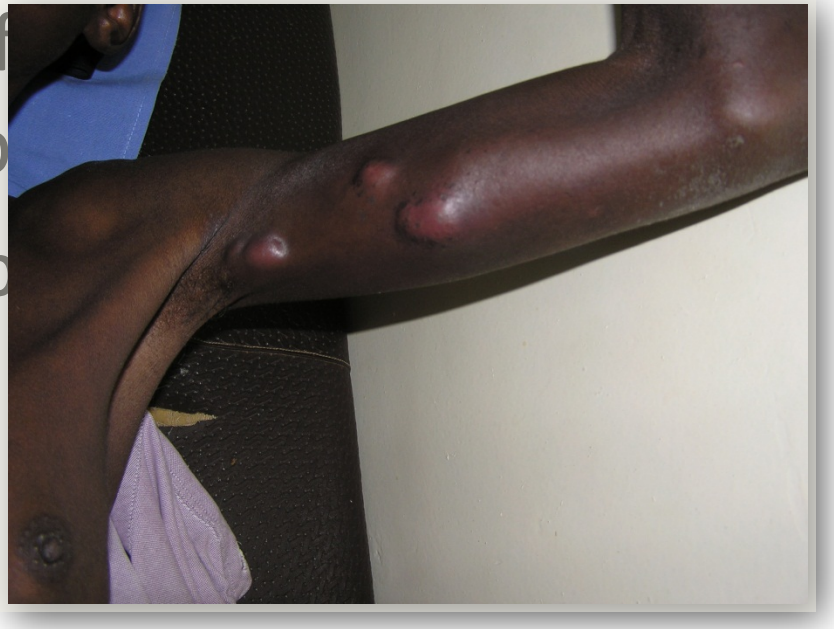
- **Risk factors**
  - Disseminated TB
  - Shorter delay between onset of TB and ART drugs
  - Low baseline CD4, higher baseline viral load
  - Greater CD4 or viral load response to ART
- **Timing of onset**
  - Usually within first 6 weeks of ART (often 2–3 weeks, but can be months after ART started)

IRIS

Clinical presentation:

- Fever
- Nodal enlargement
- Worsening pulmonary inf
  without respiratory symp
- Local worsening in extrap





IRIS Differential Diagnosis

- TB treatment failure
- Drug-resistant TB
- ART failure
- Other opportunistic (or non-opportunistic) infections
- Lymphoma, Kaposi's sarcoma
- Hypersensitivity drug reactions

IRIS Management

- Continue TB treatment
- Continue ART
- Exclude TB treatment failure
  - Adherence
  - Drug resistance
- Exclude additional/new diagnosis
- Consider NSAIDS, steroids
- Drainage of lesions

Randomized Trials of Early Versus Late ART in Patients co-infected with HIV and Tuberculosis

Study	SAPIT	SAPIT	CAMELIA	STRIDE	TIME	TB-HAART
Number of patients	642 (429 vs 213)	429 (214 vs 215)	661 (332 vs 329)	806 (405 vs 401)	156 (79 vs 77)	1538 (767 vs 771)
Trial design	Open label	Open label,	Open label,	Open label,	Open label,	DB, PC
Baseline CD4 (median; cells per µL)	<500 (150)	<500 (150)	≤200 (25)	<250 (77)	<350 (43)	>220 (367)
Early ART group	≤4 weeks	≤4 weeks	≤2 weeks	≤2 weeks	≤4 weeks	≤2 weeks
Late ART group	At 6 months	≤8 weeks	≤8 weeks	8-12 weeks	≤12 weeks	At 6 months
Median follow-up (months)	12.1	17.7	25	25	12	24
IRR (95% CI; p value), early vs late ART Deaths or AIDS (per 100 person years)	0·44 (0·25 to 0·79; p=0·003)	0·96 (0·44 to 2·10; p=0·91) IRR 0·32, 95% CI 0·07–1·13; p=0·06 for CD4 ≤ 50	0·62 (0·44 to 0·86; p=0·006)	0·32 (–1·8 to 8·1; p=0·45) Fewer new AIDS and death For CD4 ≤ 50	0·84 (0·25 to 2·90; p=0·99)	0·91 (0·64 to 1·30; p=0·9)

Timing of Initiation of Antiretroviral Therapy in Human Immunodeficiency Virus (HIV)–Associated Tuberculous Meningitis

M. Estee Török,[1,2] Nguyen Thi Bich Yen,[3] Tran Thi Hong Chau,[4] Nguyen Thi Hoang Mai,[4] Nguyen Hoan Phu,[4] Pham Phuong Mai,[4] Nguyen Thi Dung,[4] Nguyen Van Vinh Chau,[4] Nguyen Duc Bang,[3] Nguyen Anh Tien,[3] N. H. Minh,[3] Nguyen Quang Hien,[3] Phan Vuong Khac Thai,[3] Doan The Dong,[3] Do Thi Tuong Anh,[3] Nguyen Thi Cam Thoa,[3] Nguyen Ngoc Hai,[3] Nguyen Ngoc Lan,[3] Nguyen Thi Ngoc Lan,[3] Hoang Thi Quy,[3] Nguyen Huy Dung,[3] Tran Tinh Hien,[4] Nguyen Tran Chinh,[4] Cameron Paul Simmons,[2,5] Menno de Jong,[2,6] Marcel Wolbers,[2,5] and Jeremy James Farrar[2,5]

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Clinical Infectious Diseases 2011;52(11):1374–1383

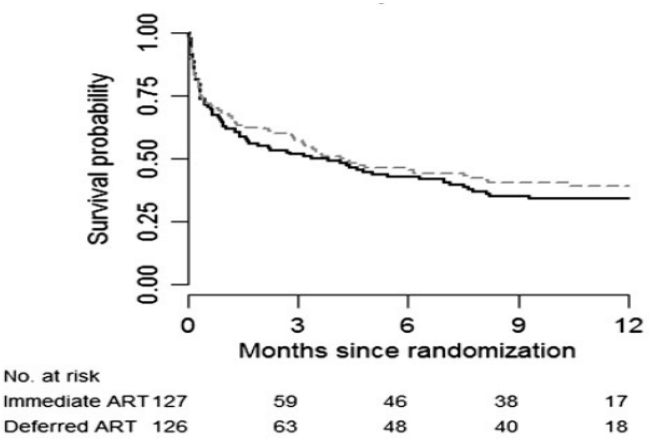
ART-naïve, TBM suspects (N = 253)

Immediate ART within 1 wk post TB Rx (n = 127)

EFV+ZDV+3TC

Deferred ART 2 months post TB Rx (n = 126)

Median CD4+ 40
Median viral load
5.4 log10 copies



High mortality in both groups at 9 months but no significant difference:
76 in the immediate ART vs. 70 in the deferred ART (HR 12; 95% confidence interval, .81–1.55; P 5 .50).

Immediate ART associated with more grade 4 adverse events

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

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

CD4	Start ART
≤50 cells/µL	Within 2 weeks of TB Rx
≥50 cells/µL	Can defer ART beyond 2 weeks but should start within 8 weeks

In patients with TB meningitis and low CD4 cell counts, early ART may pose a risk that calls for careful monitoring and consultation with experts.

Tuberculosis in the Setting of HIV Summary

- Substantial global disease burden, individually and as coinfection
- HIV adversely affects the entire spectrum of the natural history of tuberculosis
- Difficulties in diagnosis and treatment
- Simultaneous ART and TB treatment is challenging, but manageable
- ART is critical for a positive outcome of tuberculosis and HIV

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