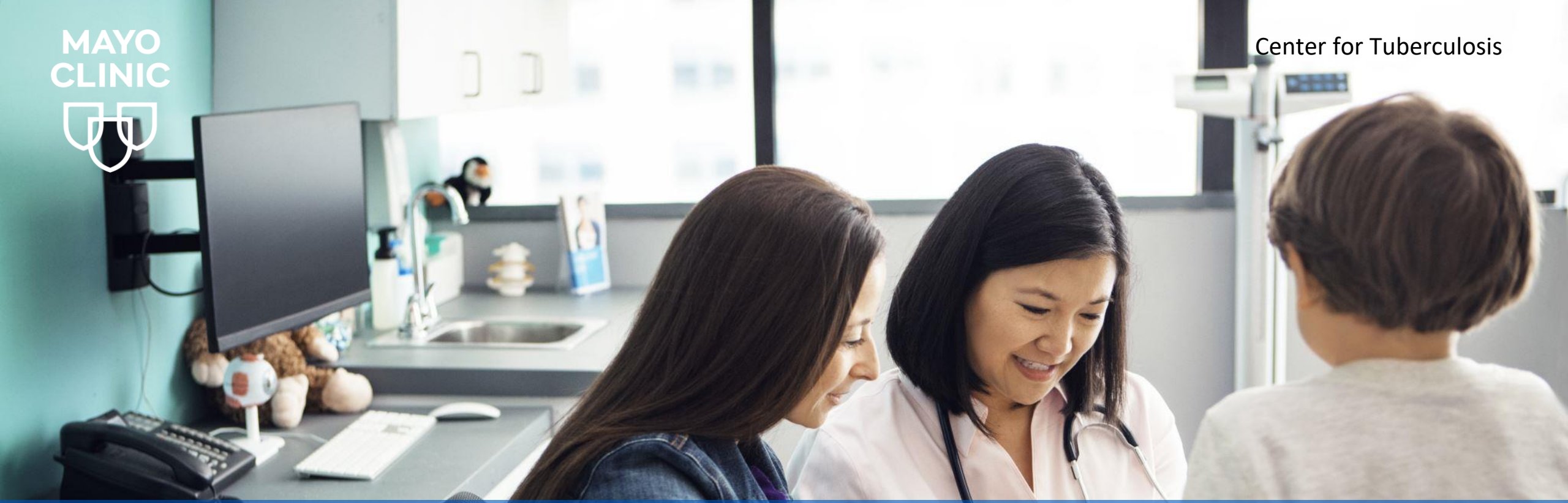


MAYO CLINIC

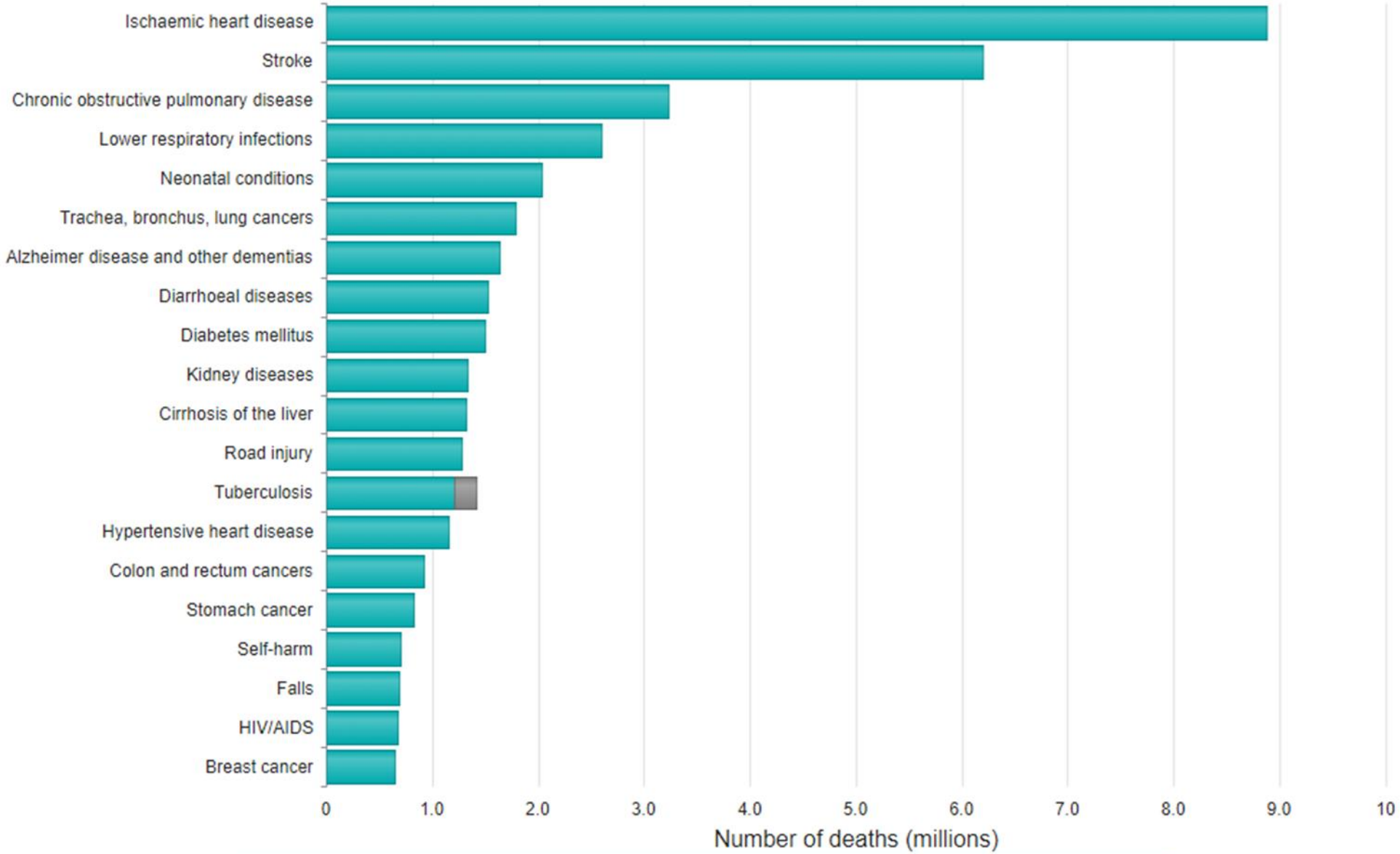
Center for Tuberculosis

Tuberculosis in the Setting of HIV Infection

Zelalem Temesgen, MD FIDSA
Professor of Medicine
Principal Investigator, Mayo Clinic Center for Tuberculosis
Editor-in-Chief, Journal of Clinical Tuberculosis and Other Mycobacterial Diseases
Editor-in-Chief, IDCases

Learning Objectives

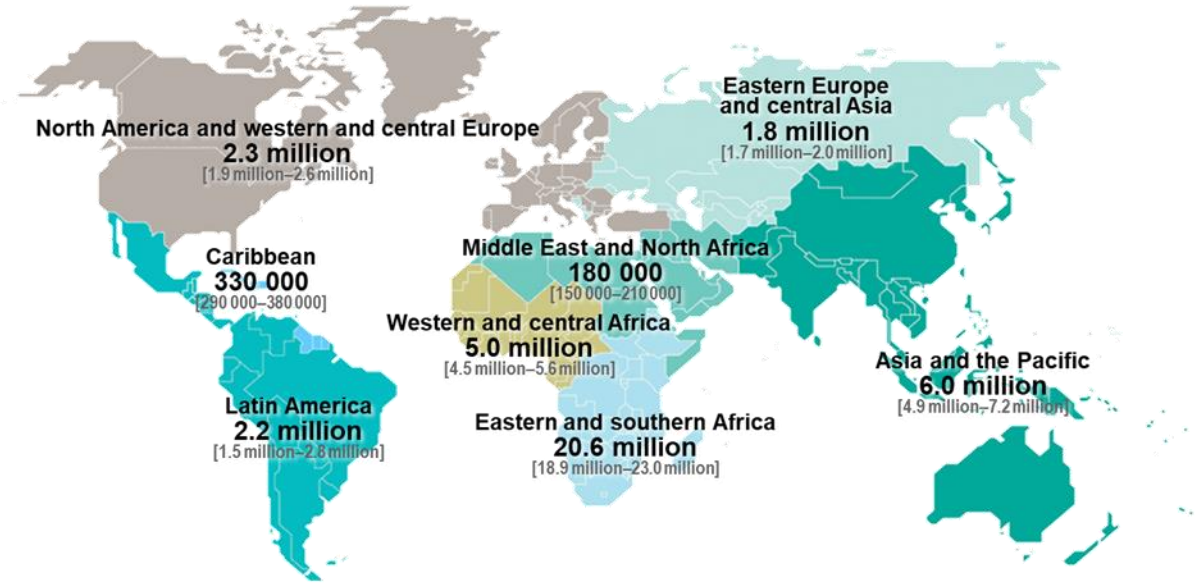
Describe	how HIV impacts TB natural history
Describe	how HIV impacts TB diagnosis
Describe	how HIV impacts TB treatment



Top causes of death worldwide in 2019

Estimated TB incidence rates, 2021

Adults and children estimated to be living with HIV | 2021

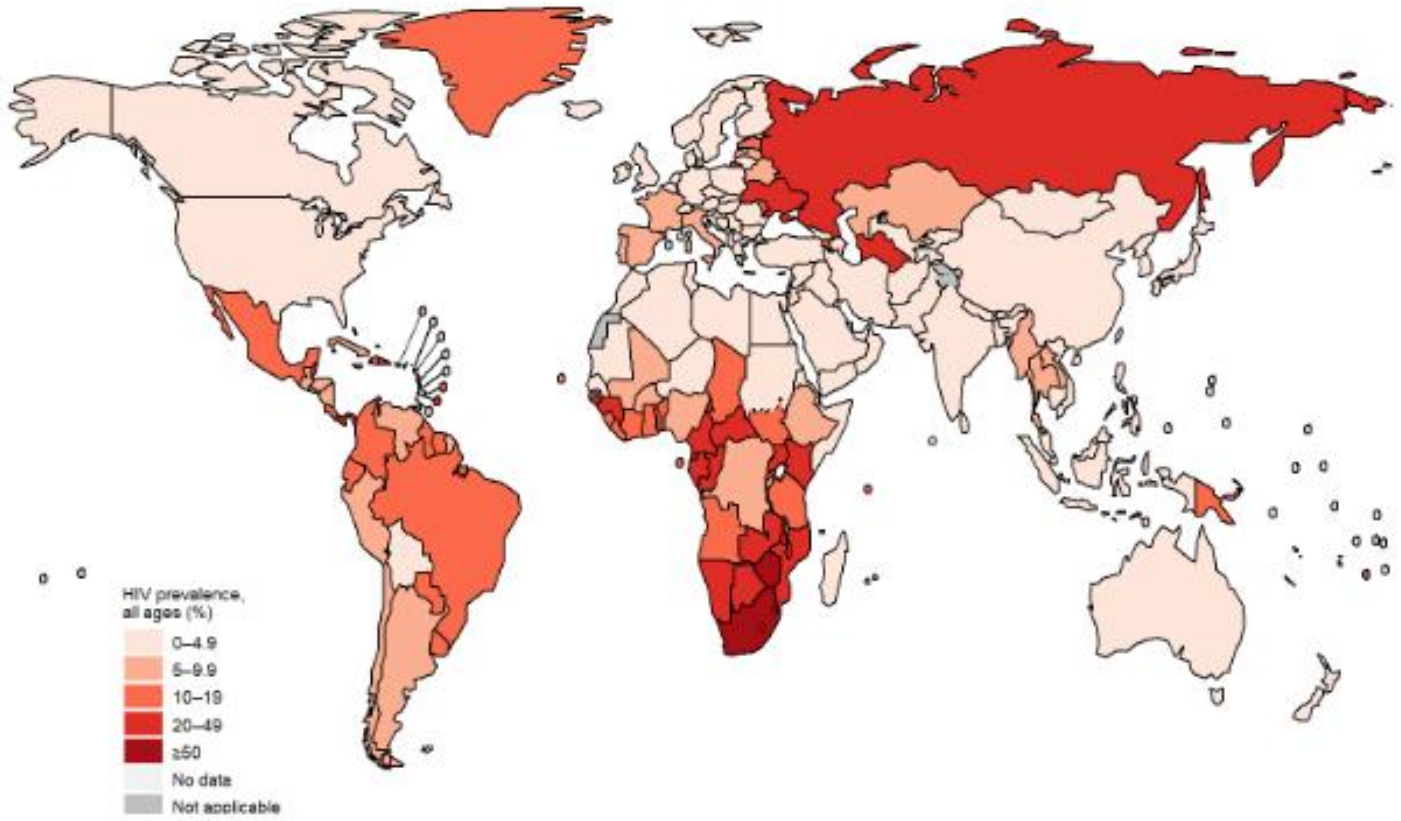


Total: 38.4 million [33.9 million–43.8 million]

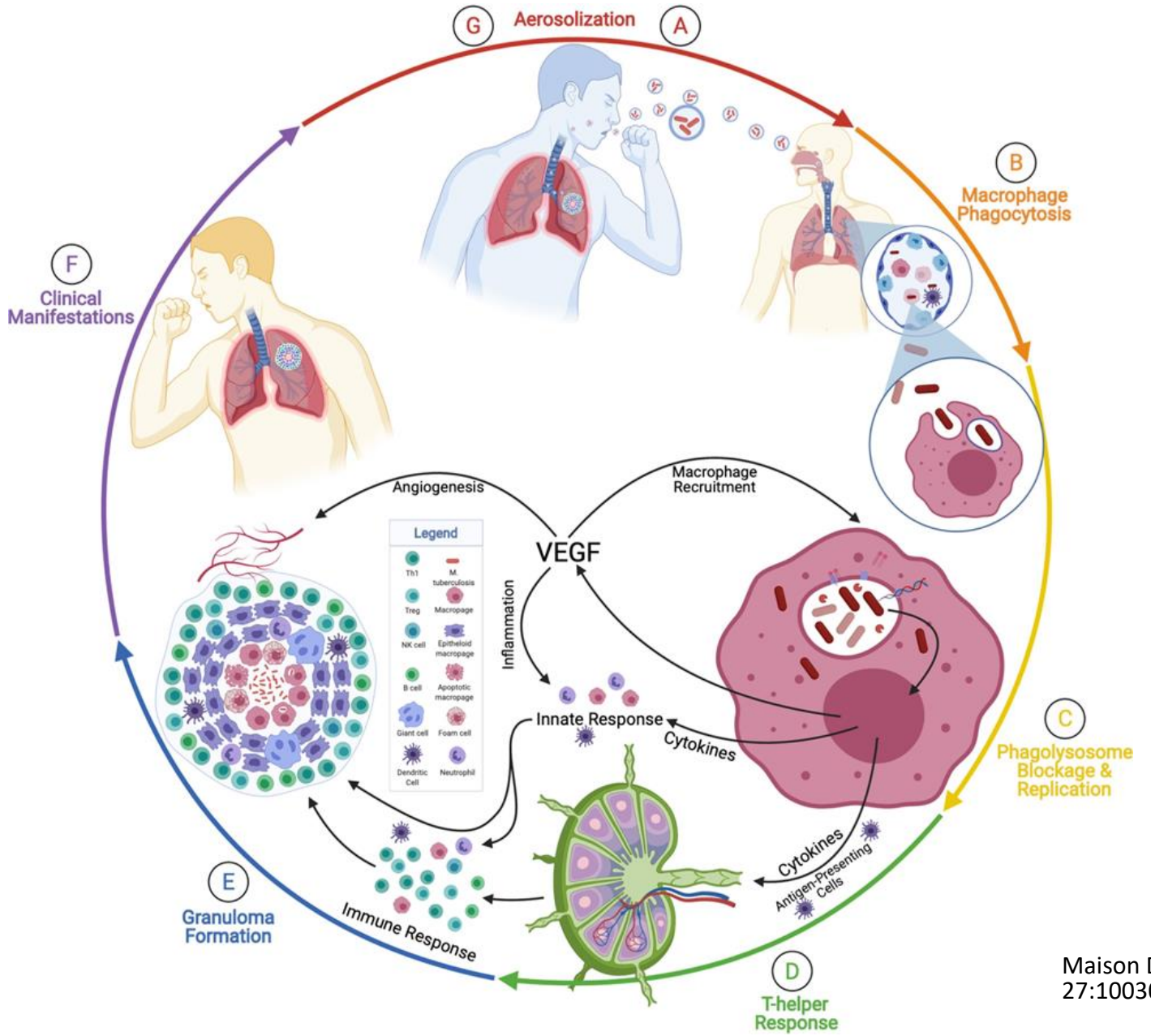
WHO Global Tuberculosis Report 2022

UNAIDS Global AIDS Update 2022

Estimated HIV prevalence in people with new or relapse TB, 2021



It is not just a geographic overlap of 2 epidemics

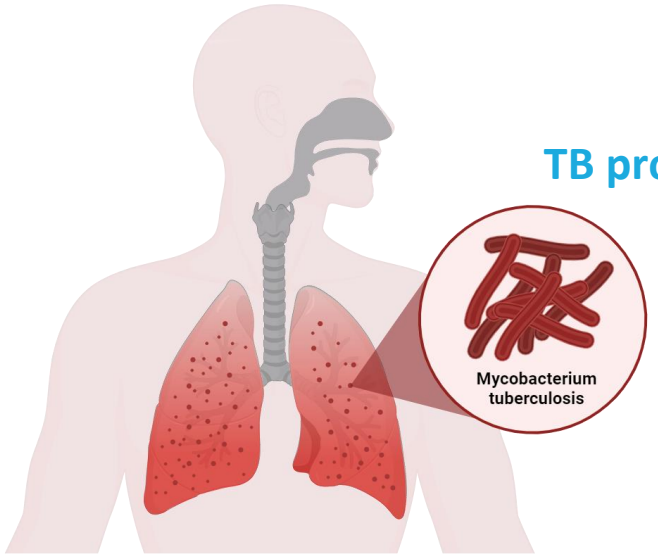


Maison DP. J Clin Tuberculosis Other Mycobact Dis (2022) 27:100300. doi: 10.1016/j.jctube.2022.100300

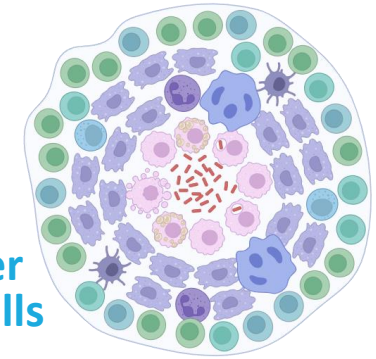
HIV Immune Deficiency

- Diminished T cell repertoire
- Reduced lymphocyte function
- Delayed hypersensitivity response
- 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, IL-12
- Increased IL-1, IL-6, TNFα

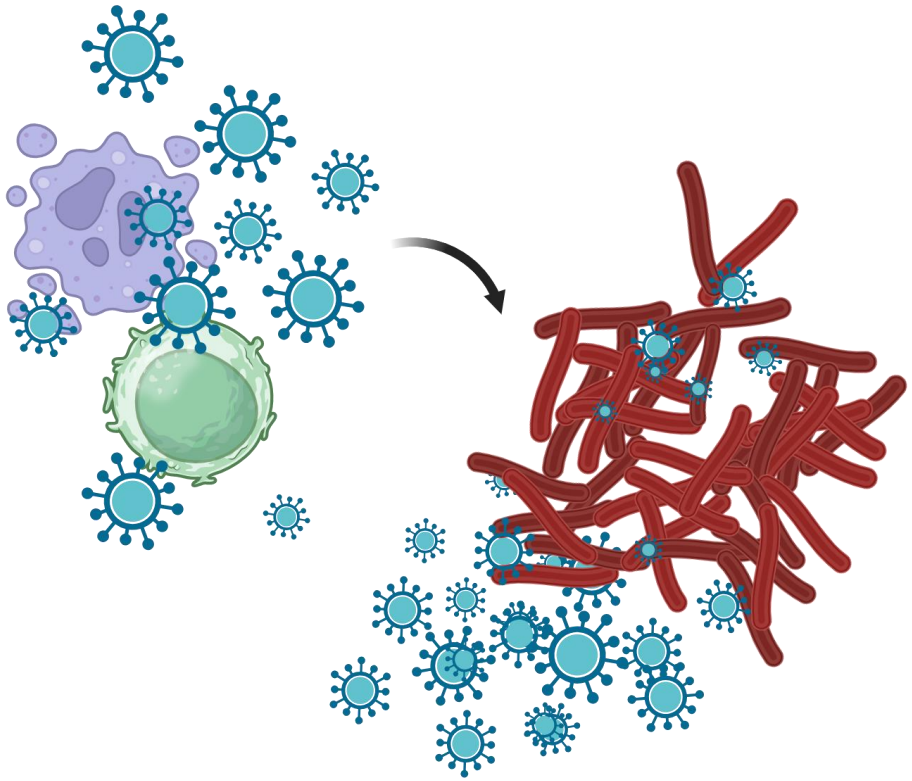


TB proliferates inside alveolar macrophages

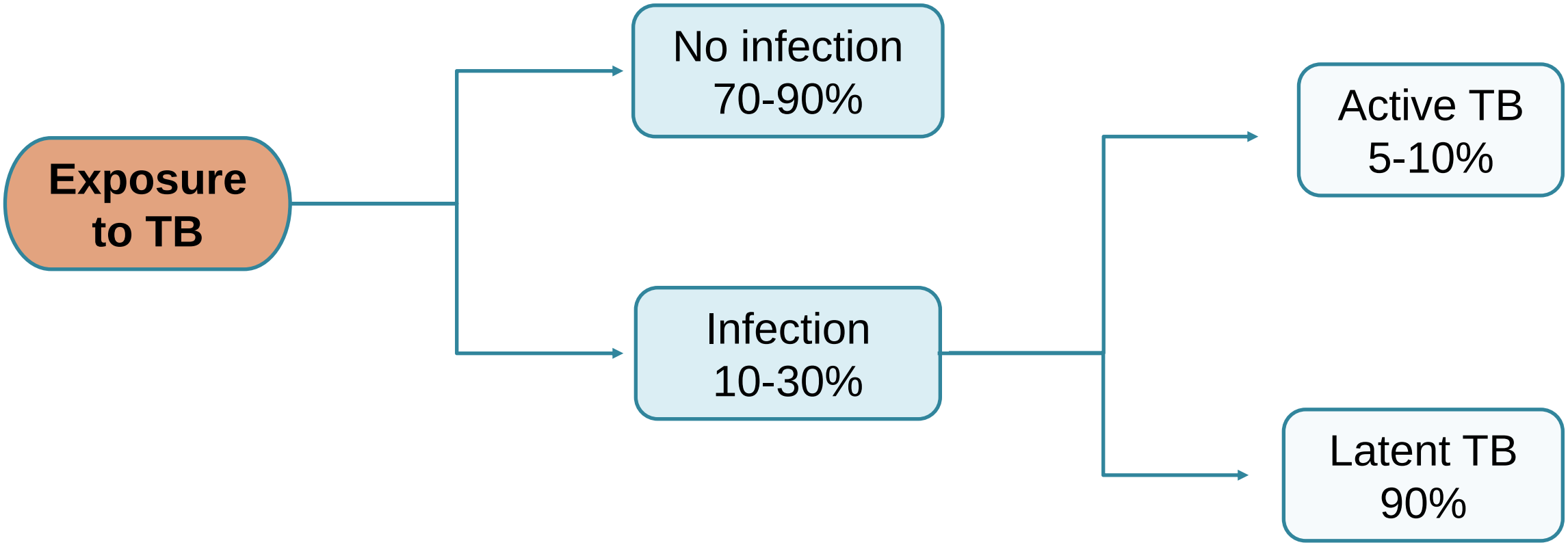


Macrophages recruit other phagocytic and immune cells to form a granuloma

HIV infection dysregulates TB immune response



Natural History of Tuberculosis



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 was diagnosed in 11/30 (37 percent) residents of a housing facility for PLWH**
- **In the preceding six months, two patients being treated for tuberculosis had been admitted to the facility.**
- **Organisms isolated from all 11 had similar RFLP patterns to the previous 2 patients.**
- **Tuberculous infection progressed to active disease within 106 days of acquiring the infection.**

Tuberculosis did not develop in any of 28 staff members with exposures.

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

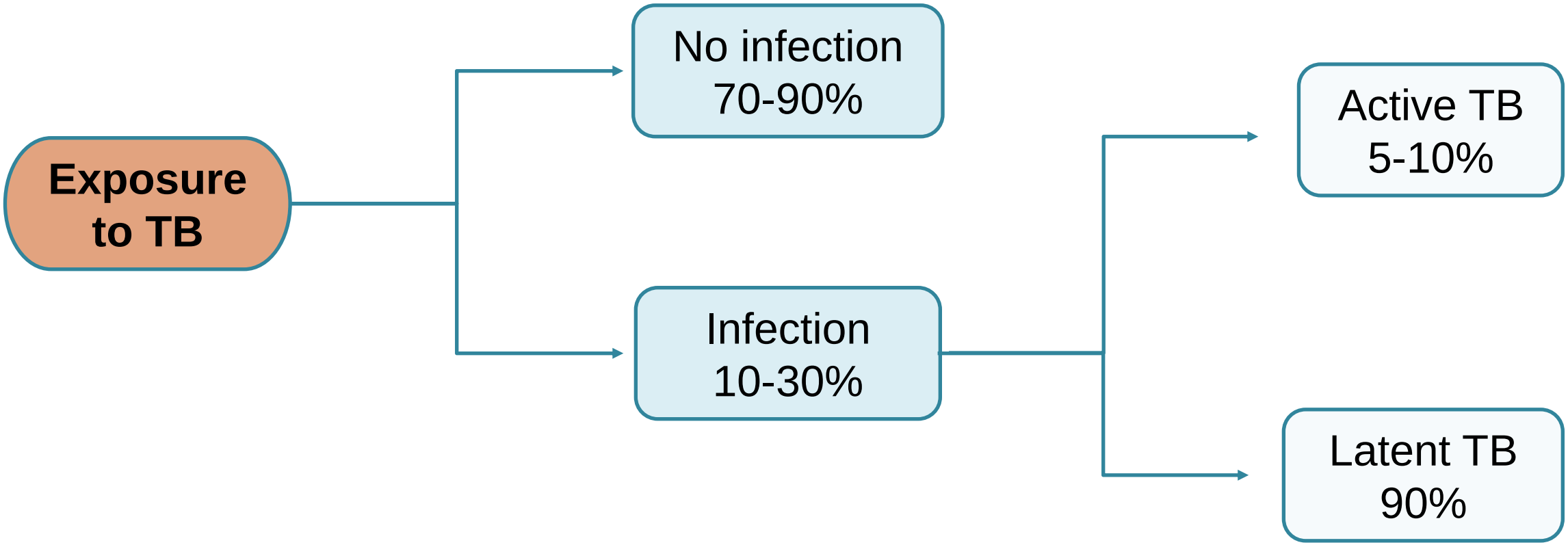
[b] Microbiology Laboratory, Ospedale Borgo Trento , Verona, Italy

18 HIV-infected inpatients were exposed to TB.

8 (44%) developed active TB.

7/8 developed active tuberculosis within 60 days of diagnosis of the index case

Natural History of Tuberculosis



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

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

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.

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)¥.

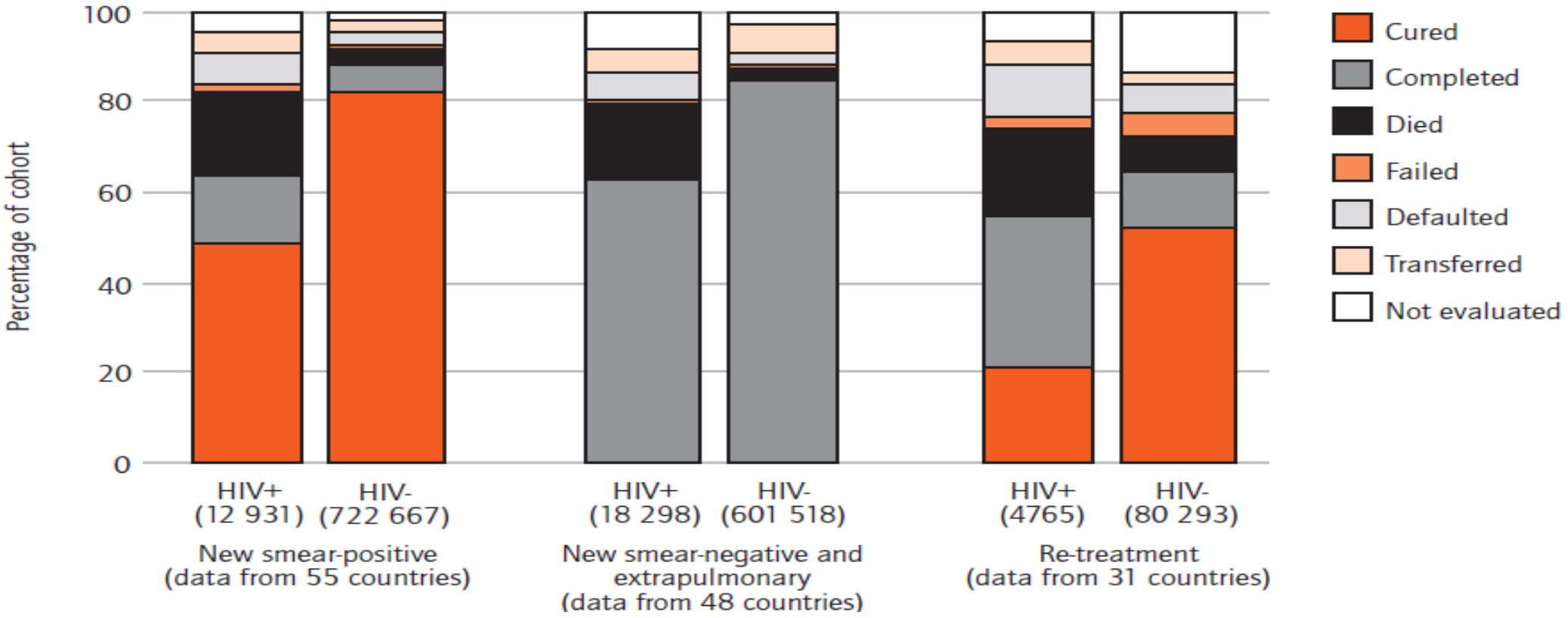
Characteristics	Total		Unadjusted Odds Ratio (95% CI)	*P-value**	Adjusted Odds Ratio (95% CI)[F]	*P-value**
	N	%				
HIV Status				*0.019*		*0.003*
HIV positive	1,275	56%	1.00		1.00	
HIV negative	989	44%	1.34 (1.05–1.72)		1.49 (1.14–1.94)	
Gender				*0.005*		*0.002*
Male	1,400	62%	1.00		1.00	
Female	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			

*P-value for likelihood ratio test,
[F]Adjusted for sex, age, HIV status and TB registration year,
¥Treatment success = cured/completed treatment.
doi:10.1371/journal.pone.0056248.t003

Tweya H, Feldacker C, Phiri S, Ben-Smith A, Fenner L, 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. https://doi.org/10.1371/journal.pone.0056248
https://journals.plos.org/plosone/article?id=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

OPEN ACCESS Freely available online

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 had 1 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)**

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

Differential diagnosis is broader

- HIV itself
- Other opportunistic infections

Extrapulmonary

- 35-80% vs. 15-50%

Laboratory and Radiographic 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 Active Tuberculosis in the Setting of HIV

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

Treatment of Active Tuberculosis in the Setting of HIV

Drug interactions

Sequencing of TB and HIV treatment

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

When to start ART following initiation of treatment for TB?

Immune Reconstitution Inflammatory Syndrome

Paradoxical

Unmasking

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

Immune Reconstitution Inflammatory Syndrome

Risk factors

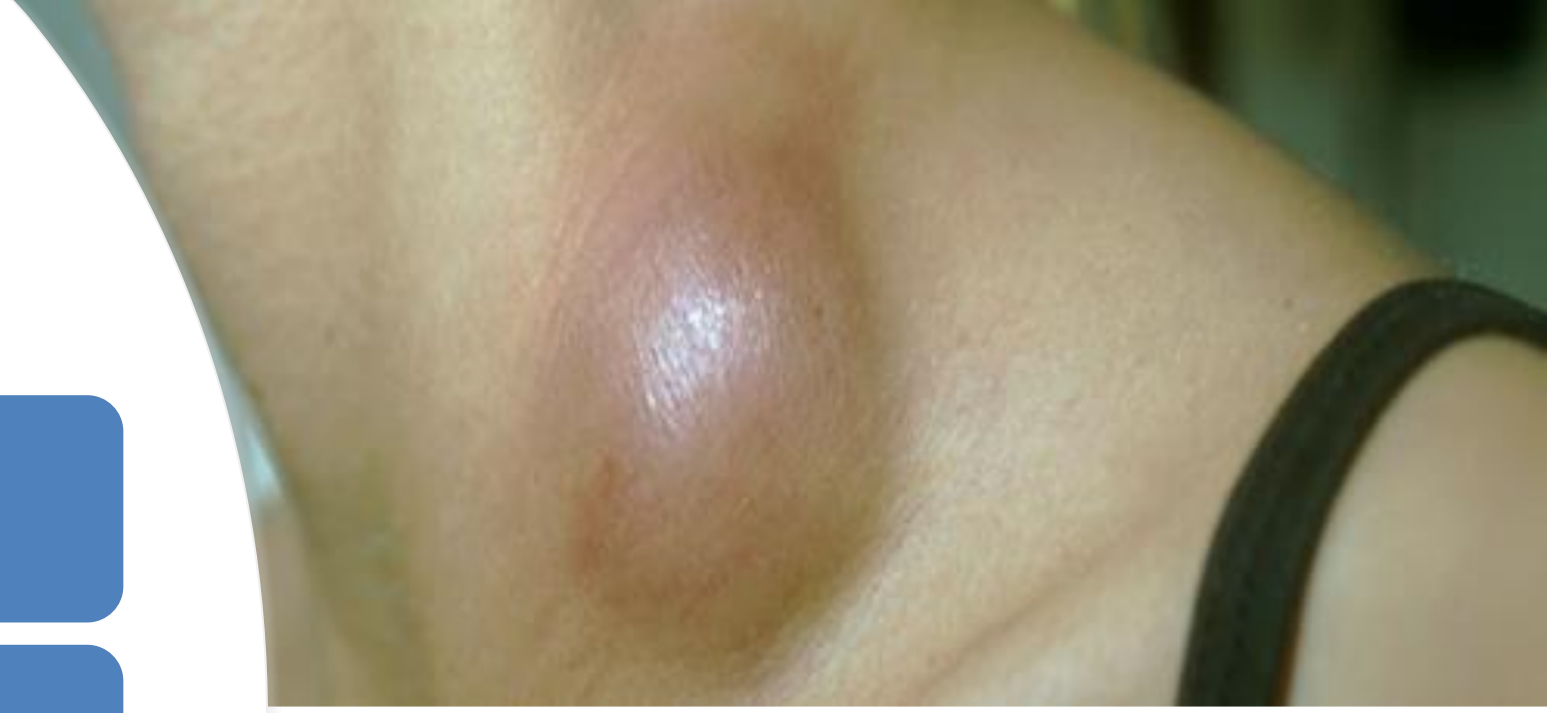
- Disseminated TB
- Shorter delay between onset of TB and ART drugs
- Low baseline CD4, higher baseline viral load
- Greater CD4 Response to ART
- Greater viral load response to ART

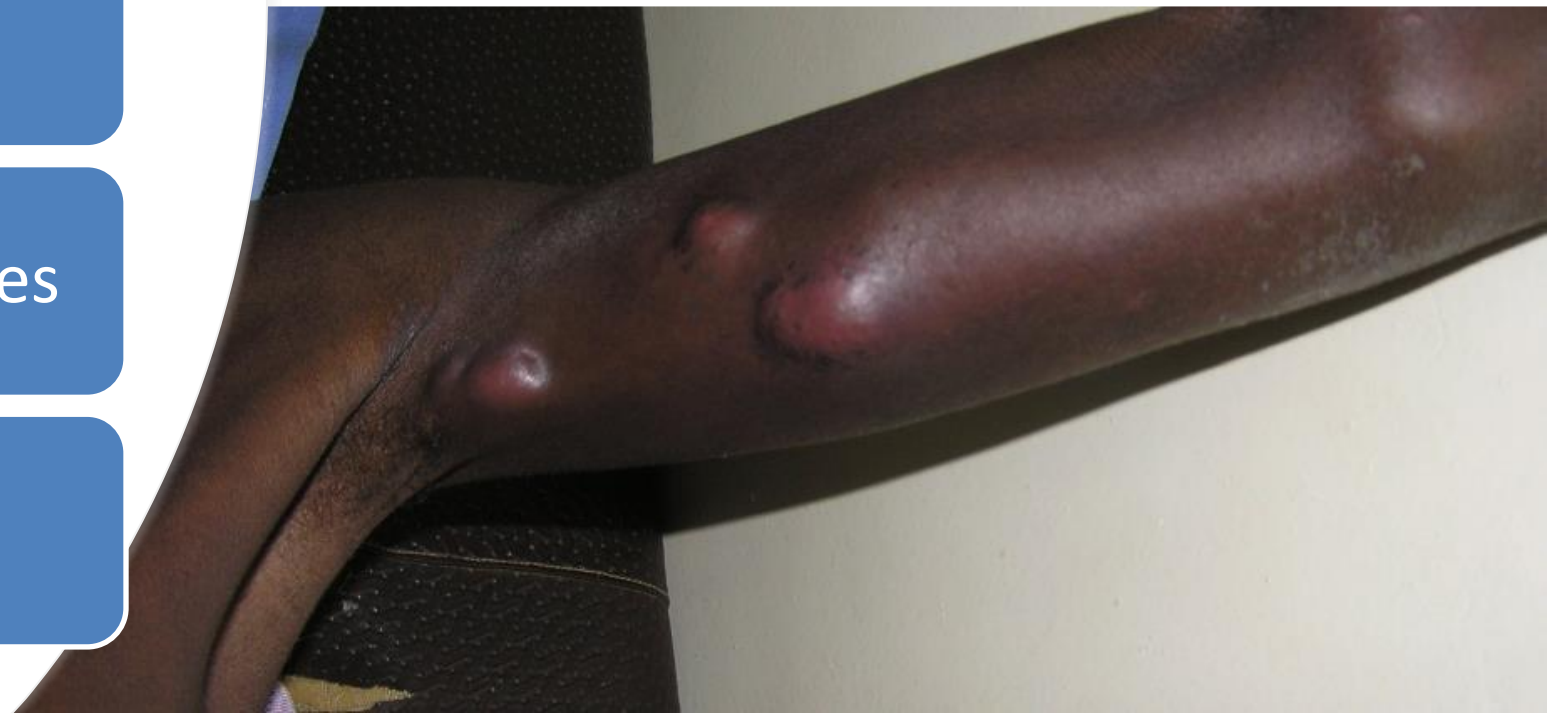
Onset

- Usually within first 6 weeks of ART
- Can be months after ART started

IRIS

- Fever
- Nodal enlargement
- Worsening pulmonary infiltrates
- Local worsening in extrapulmonary sites





IRIS Differential Diagnosis

- TB treatment failure
- ART failure
- Other opportunistic (or non-opportunistic) infections
- Adverse drug reactions

IRIS Management

Continue TB treatment

Continue ART

Exclude TB treatment failure

- Adherence
- Drug resistance
- Absorption

Exclude additional/new diagnosis

Consider NSAIDS, steroids

Drainage of lesions

WHO Systematic Review

- Incidence of IRIS is increased with immediate ART
- Incidence of AIDS-defining evens similar with immediate vs. deferred ART
- Mortality related to IRIS was uncommon.
- Mortality is similar with immediate vs. deferred ART

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]

[1]Department of Infectious Diseases, Cambridge University Hospitals National Health Service Foundation Trust, Cambridge, United Kingdom; [2]Wellcome Trust Major Overseas Programme and Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam; [3]Pham Ngoc Thach Hospital, Ho Chi Minh City, Vietnam; [4]Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam; [5]Centre for Tropical Medicine, University of Oxford, Oxford, United Kingdom; [6]Department of Medical Microbiology, Amsterdam Medical Centre, University of Amsterdam, Amsterdam, Netherlands

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

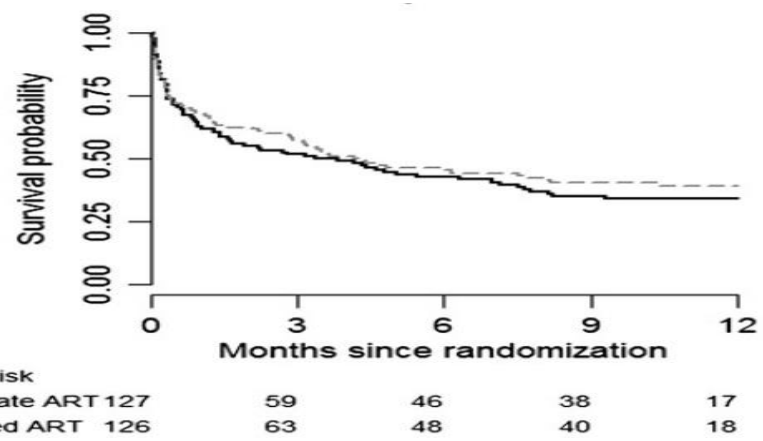
ART-naïve, TBM suspects (N = 253)

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

EFV+ZDV+3TC

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

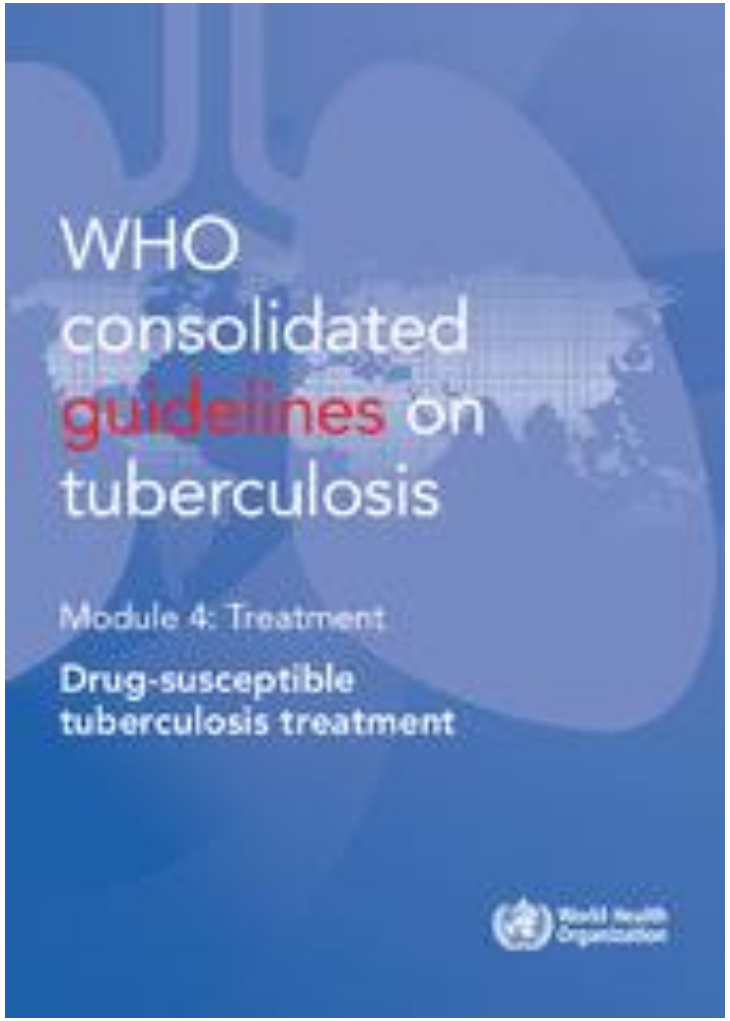
Median CD4+ 40
Median viral load
5.4 log10 copies



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



ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count

For TB meningitis: Do not start ART before 8 weeks of TB treatment is completed, regardless of CD4 count. CDC/ATS/IDSA

For TB meningitis, use adjuvant corticosteroid therapy over 6–8 weeks

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

Thank you