Tuberculosis, HIV, Diabetes

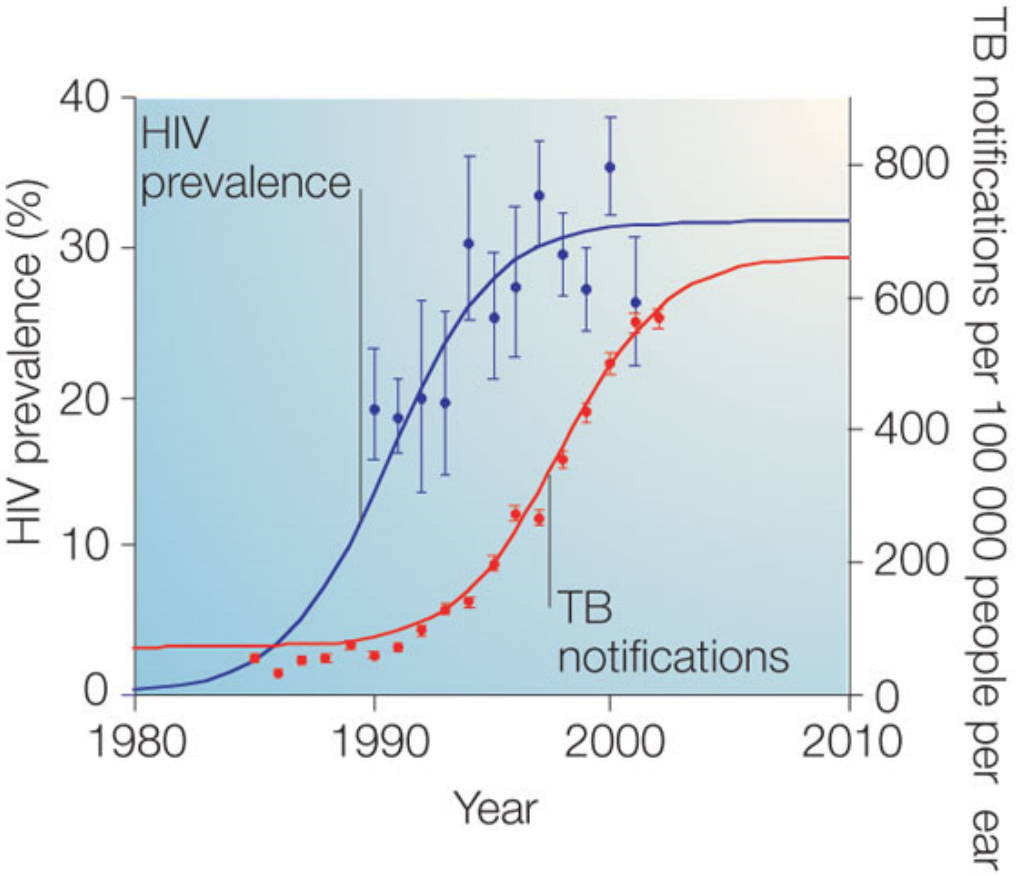
- Overlapping epidemics
- More frequent TB disease
- Atypical clinical aspects
- More severe TB disease
- Interfere with therapy, specially in HIV + patients

TB and HIV Data

- Worldwide, 10.4 million people with TB disease in 2016
- Top five countries (56% of cases): India, Indonesia, China, Philippines, Pakistan
- Around 13% (1.03 million) estimated to be HIV-positive
- 1.3 million TB deaths in 2016; 374 000 in HIV infected individuals . 85% in the WHO Africa and South-East Asia region
- However,
  - the number of people dying from HIV-associated TB peaked at 570 000 in 2004 and had fallen to 374 000 in 2016 (a 34% decrease)
  - Decrease of TB incidence by an average of 1.5% per year since 2000, being now 18% lower than in 2000

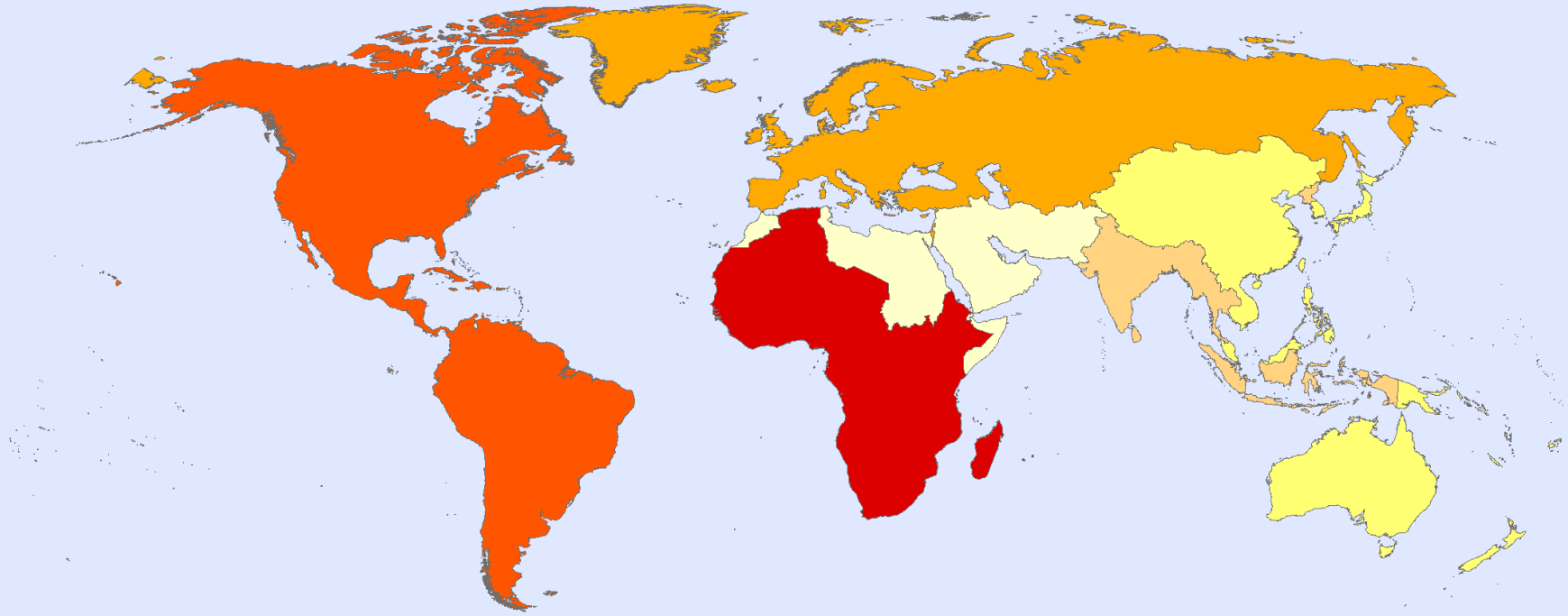
WHO, Global Tuberculosis Report, 2017

HIV Prevalence in Adults and Tuberculosis Notification Rates



Nunn, Nat Rev Immunol, 2005

Prevalence of HIV among adults aged 15 to 49, 2017
By WHO region



Prevalence (%) by WHO region

- Eastern Mediterranean: 0.1 [<0.1−0.1]
- Western Pacific: 0.1 [<0.1−0.2]
- South-East Asia: 0.3 [0.2−0.4]
- Europe: 0.4 [0.4−0.4]
- Americas: 0.5 [0.4−0.6]
- Africa: 4.1 [3.4−4.8]

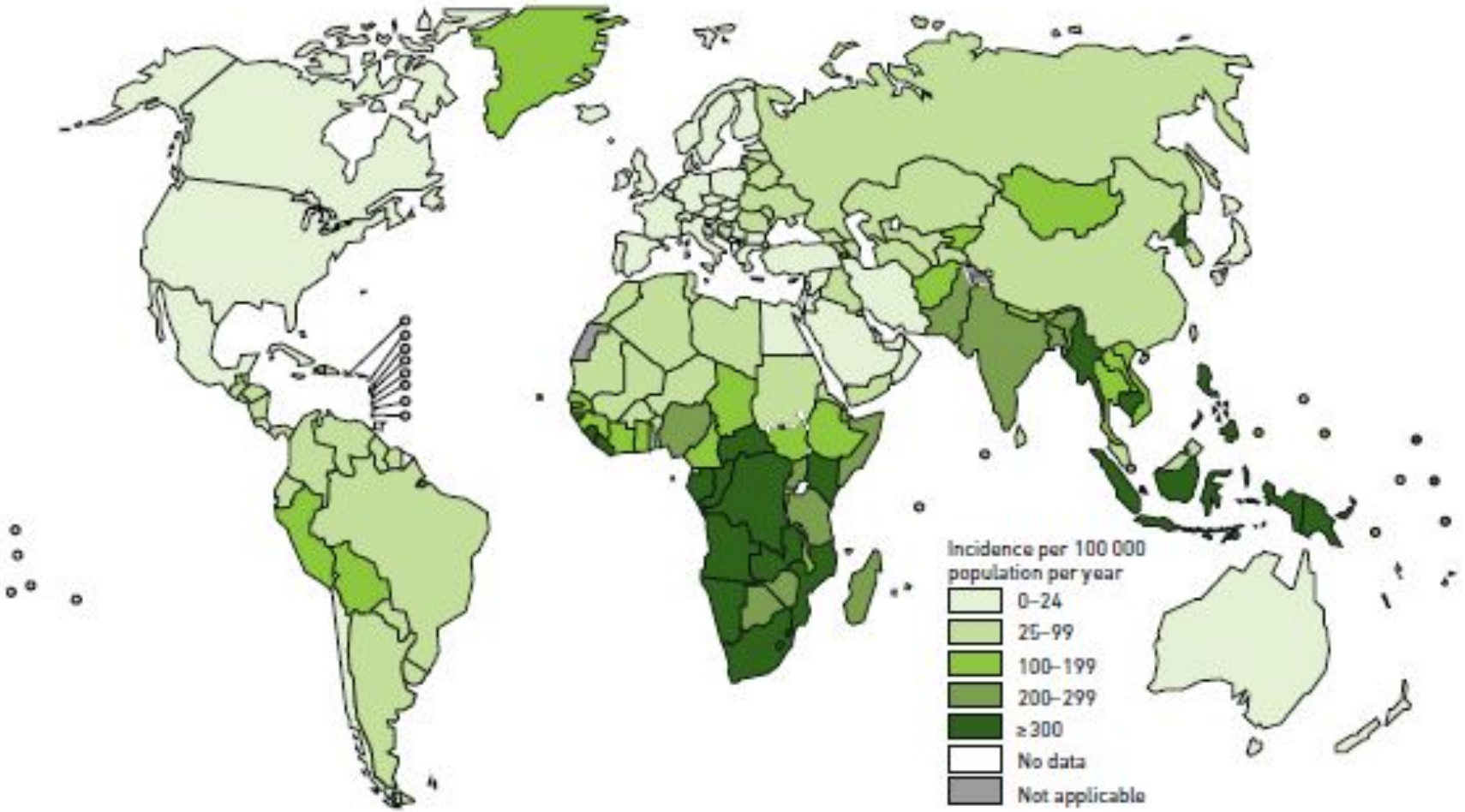
Global prevalence: 0.8% [0.6−0.9]

0 875 1,750 3,500 Kilometers

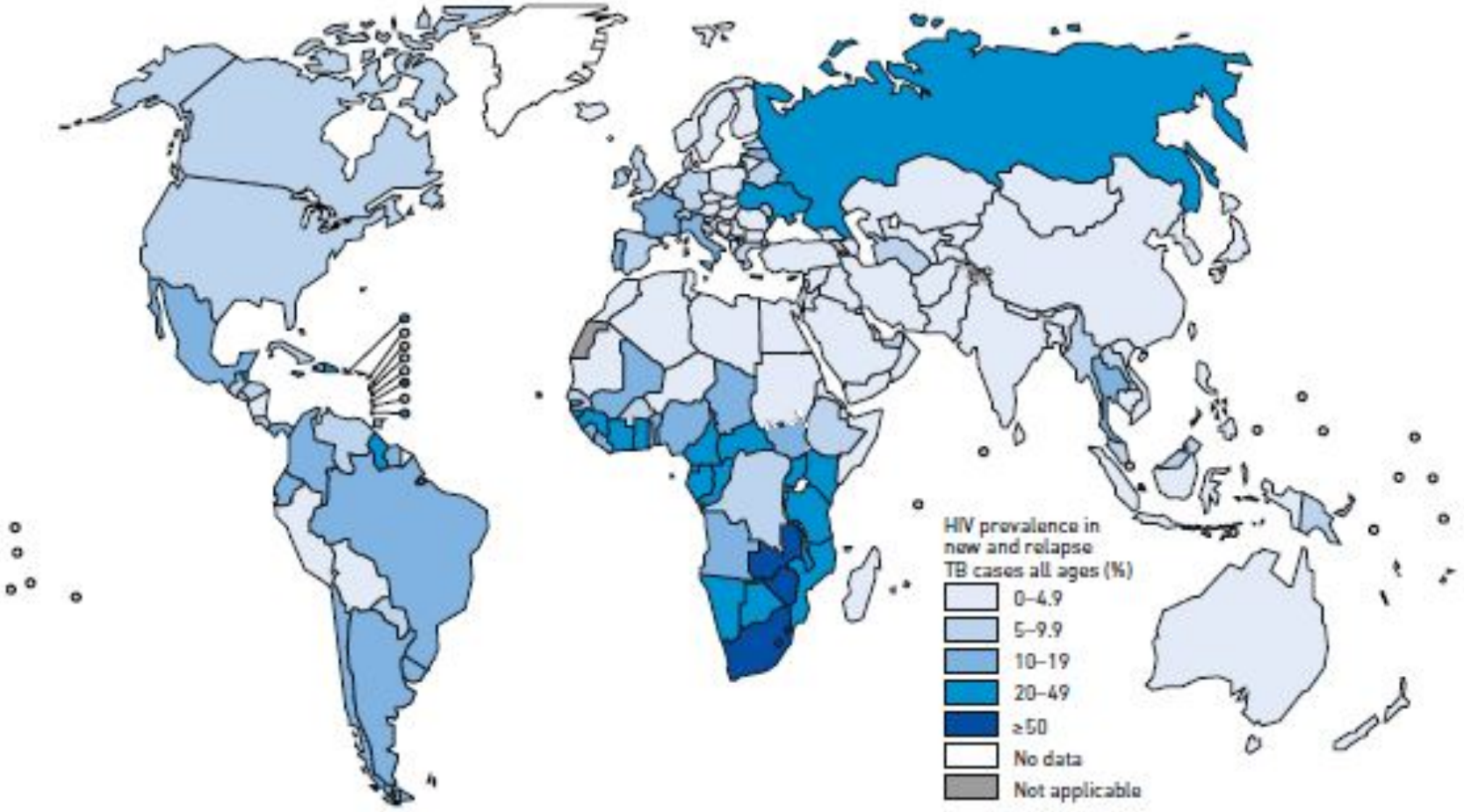
Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization

World Health Organization

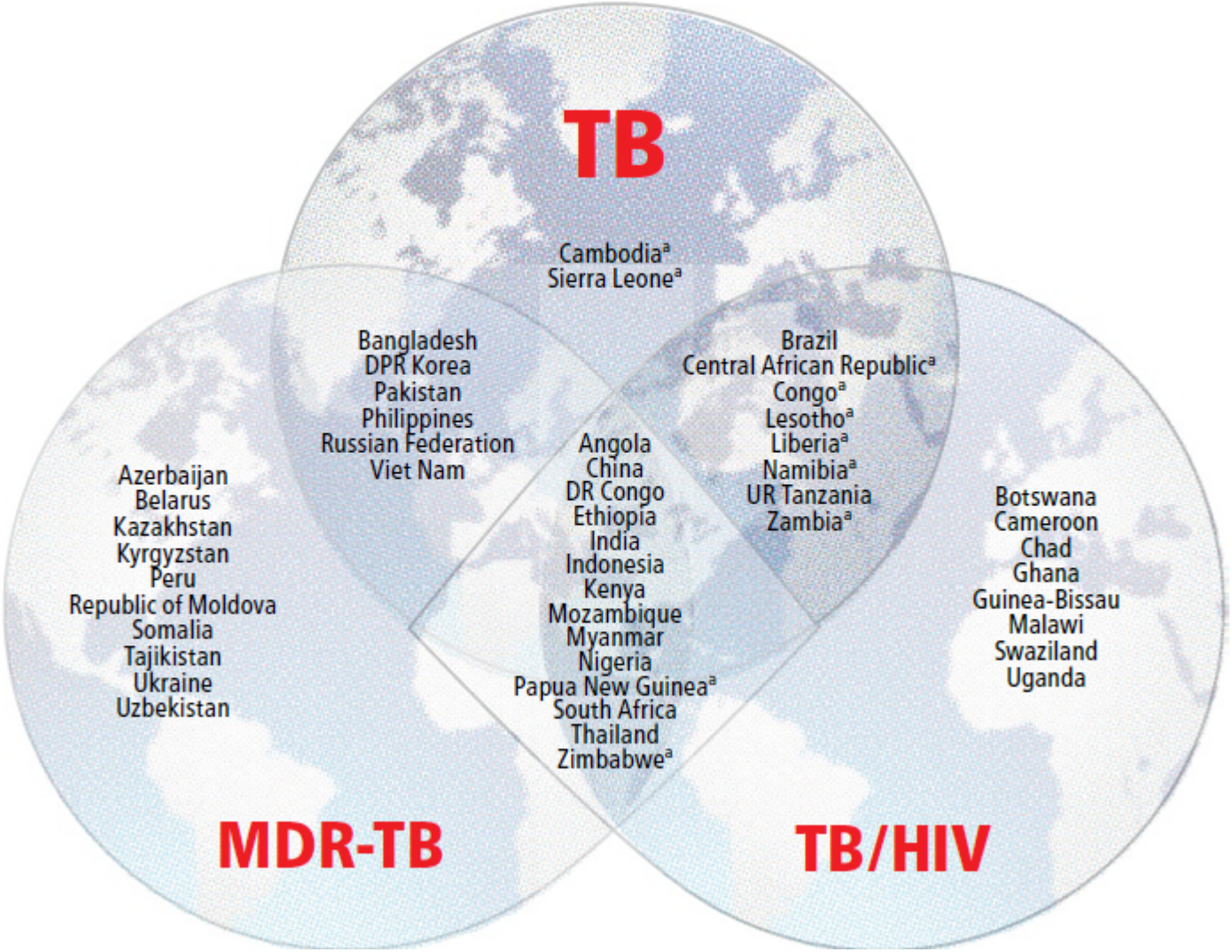
Estimated TB incidence rates, 2017



Estimated HIV prevalence in new and relapse TB cases, 2017

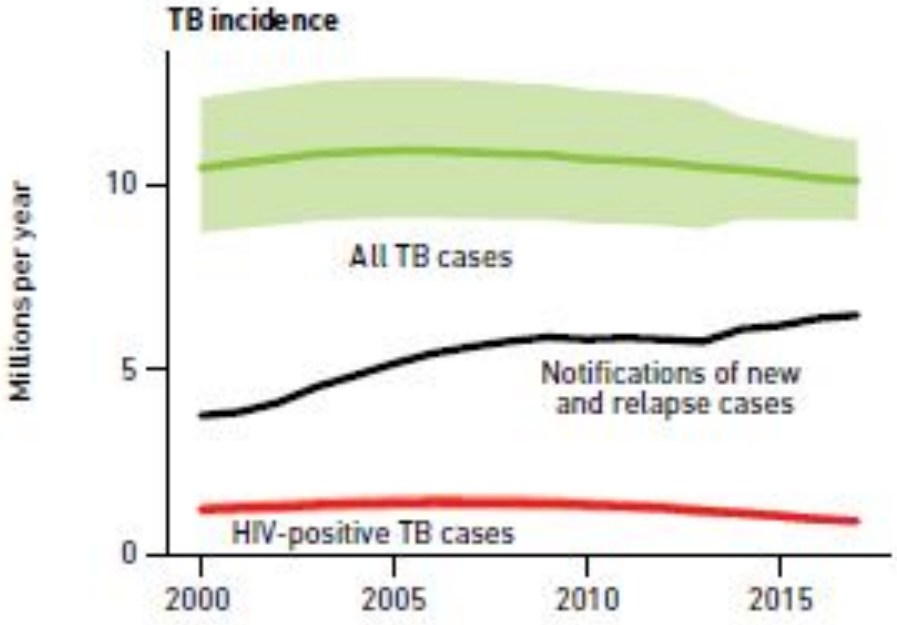


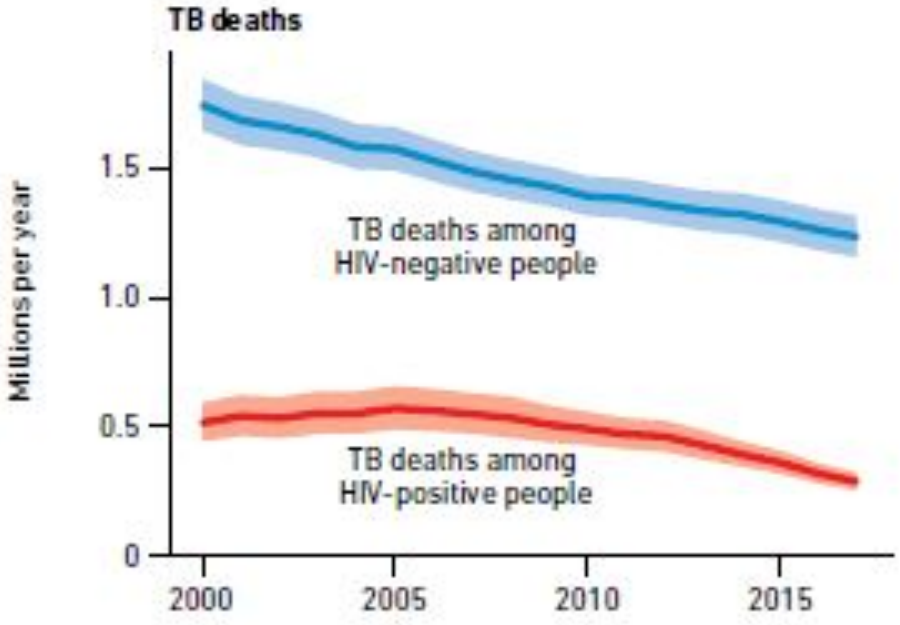
Countries in the 3 high burden country list for TB, TB/HIV and MDR-TB in the period 2016-2020



Evolution of TB deaths

Global trends in the estimated number of incident TB cases and the number of TB deaths (in millions), 2000–2017. Shaded areas represent uncertainty intervals.





Tuberculosis in Patients Dying in Zambia

125 autopsies on patients who died in University Hospital in Lusaka, Zambia, 2012-13

	Overall (n=125)	HIV + (n=101)	HIV – (n=24)	P value
TB (all forms)	78 (62%)	66 (66%)	12 (50%)	0.16
Extrapulmonary*	35 (28%)	33 (33%)	2 (8%)	0.017
Pulmonary only	43 (34%)	33 (33%)	10 (42%)	0.40

* All also had pulmonary tuberculosis

26% of tuberculosis were not diagnosed ante-mortem

Bates, Lancet ID, 2015

Many Groups are at Higher Risk for HIV Infection and TB Infection

- Foreign born
- Prisoners
- Homeless/marginally housed
- Drug Users
- Racial/ethnic minorities
- Recent contact to TB
- Lower socio-economic status

Tuberculosis and Diabetes

- **Pathophysiology –** diabetes, especially when poorly-controlled, causes relative immunocompromise and increases likelihood of reactivation of TB
- **Epidemiology** – dramatic increase of diabetes
- **Demographics** – diabetes disproportionately affects lower socioeconomic groups and ethnic minorities that also have higher prevalence of TB
- **Hidden epidemic** – estimated that ¼ of people with diabetes don't know they have it

TB and DM burdens

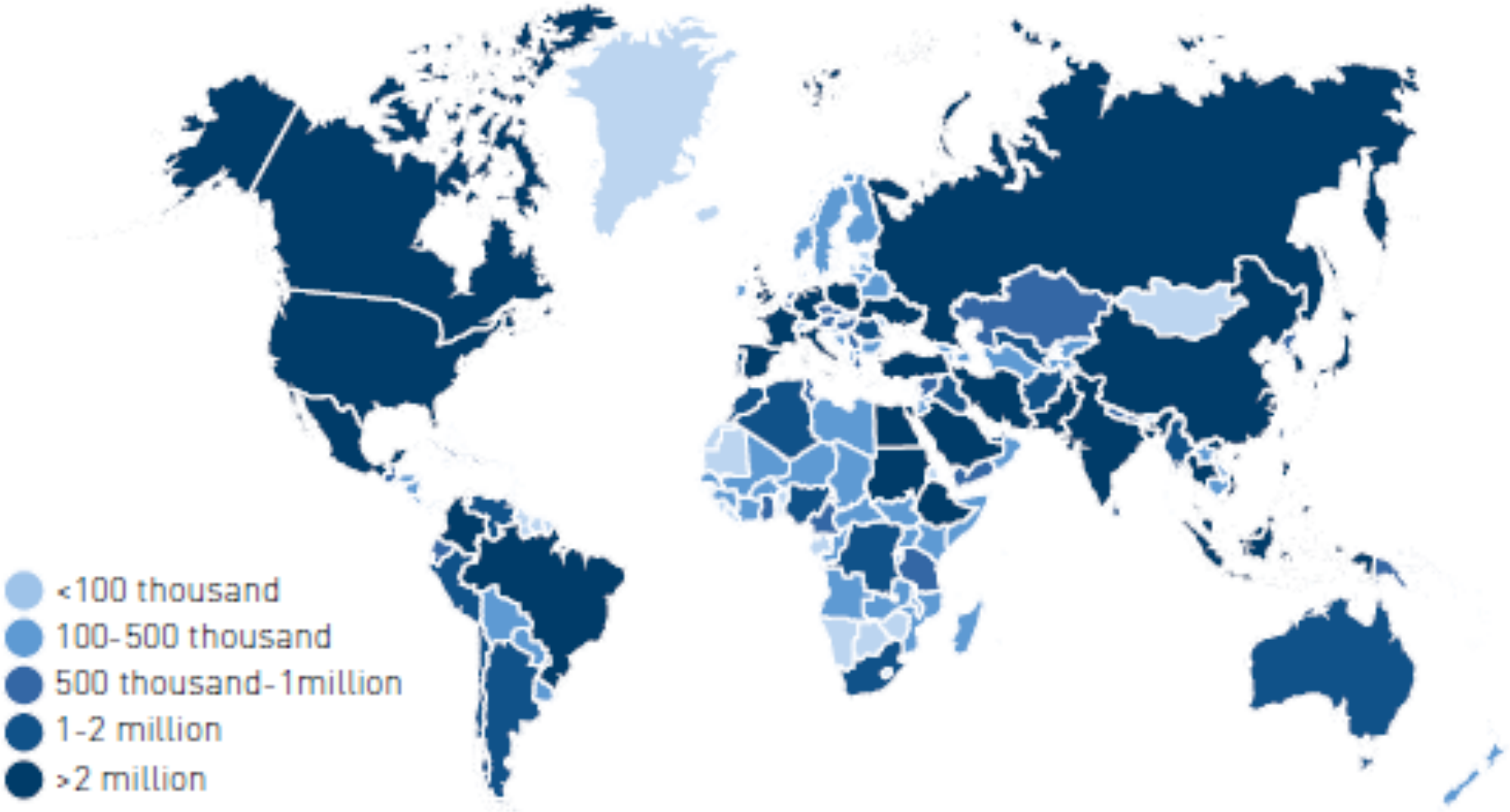
DM Burden

- 422 million people living with DM in 2015
- 3.7 million people died of DM in 2012
- Prevalence increased from 4.7% in 1980 to 8.5% in 2014

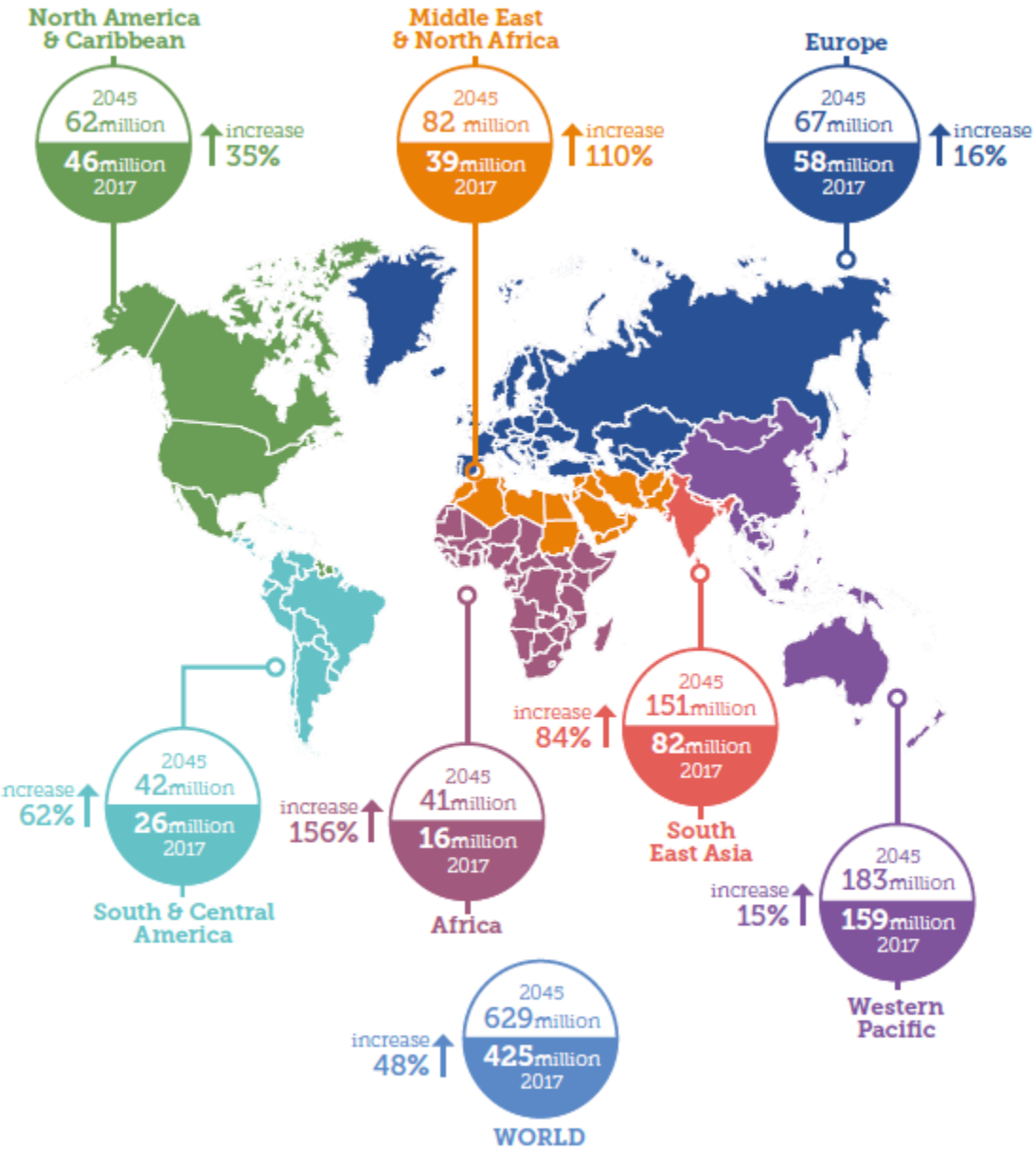
TB Burden

- 10.4 new tuberculosis cases worldwide in 2016
- 1.3 million people died of TB in 2016

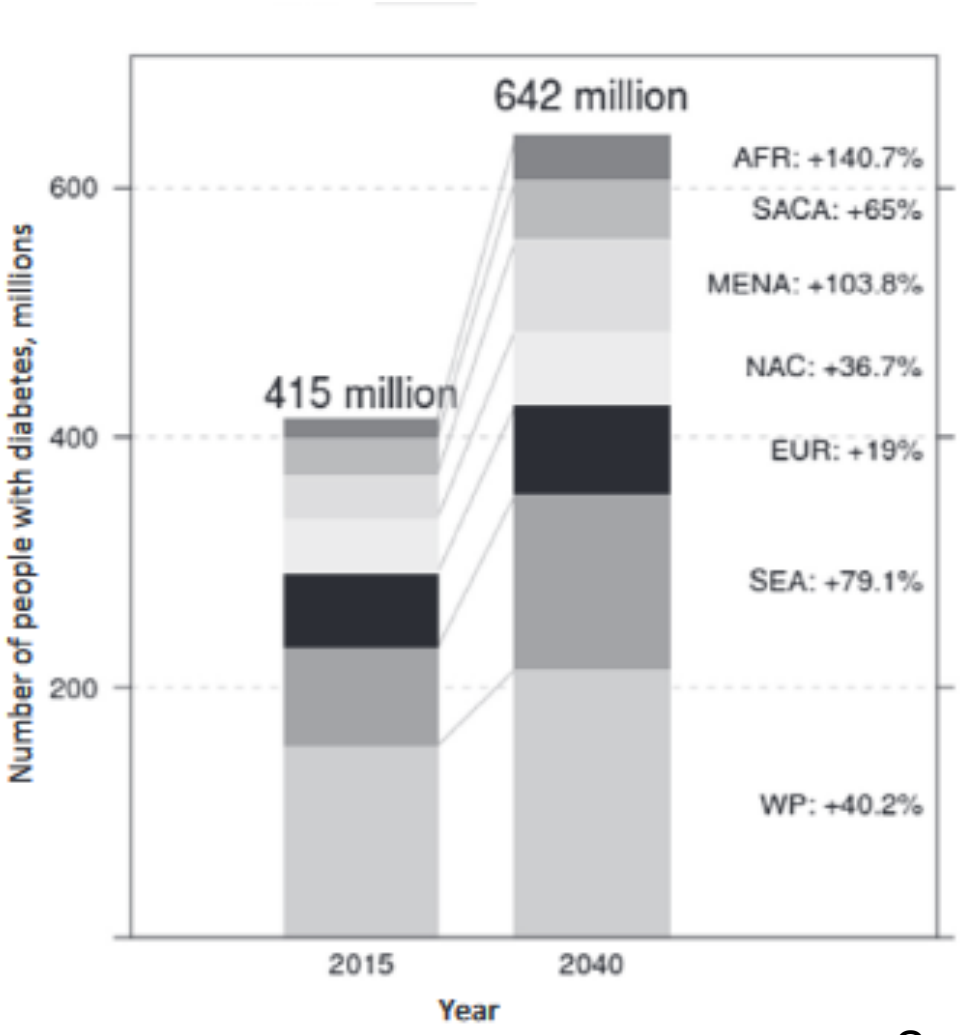
Map 3.2 Estimated total number of adults (20-79 years) living with diabetes, 2017



Number of people with diabetes worldwide and per region in 2017 and 2045 (20-79 years)

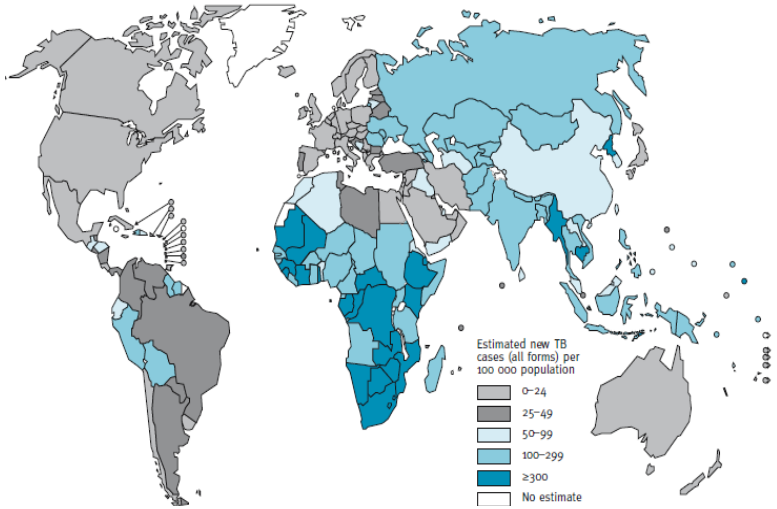


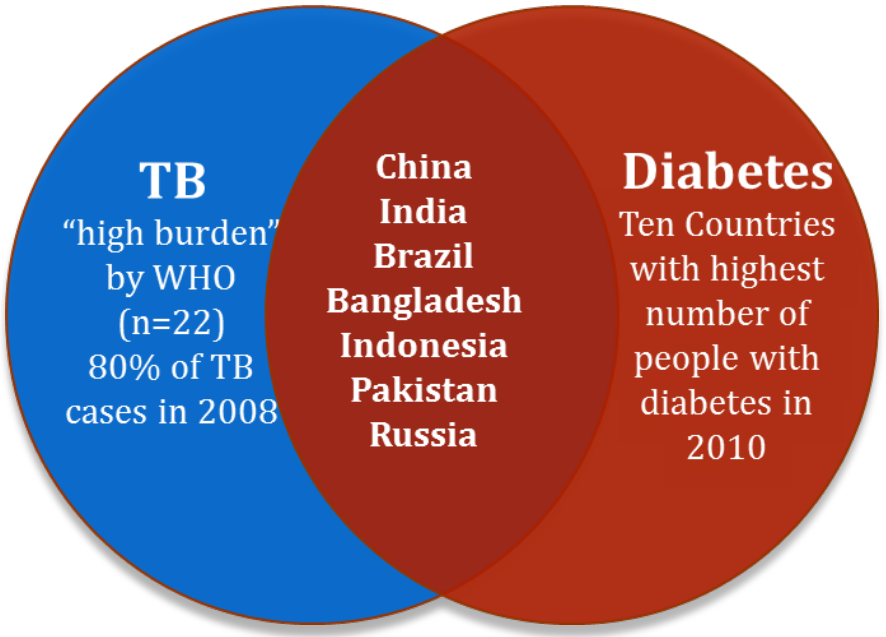
Total Number of Adults with Diabetes by Region

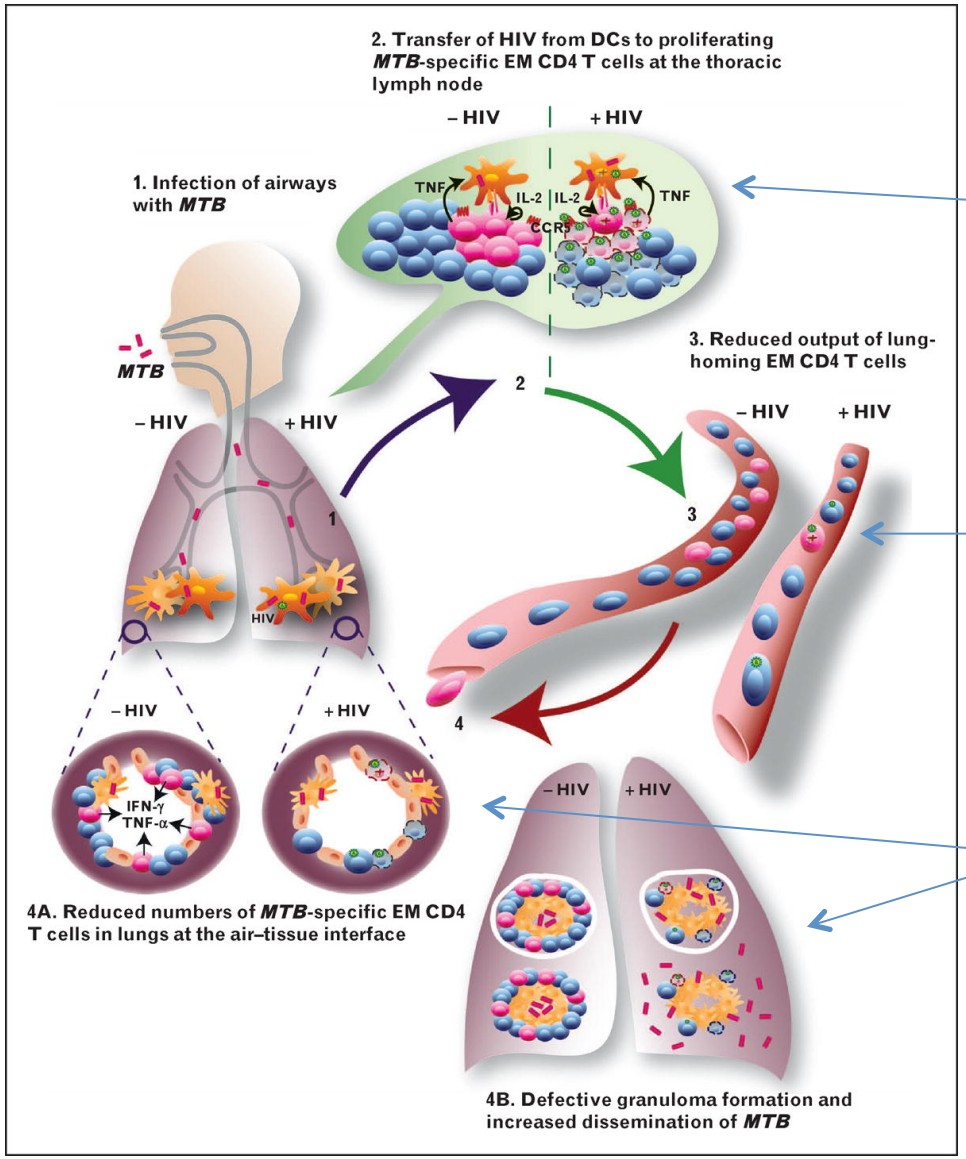


Ogurtsova, Diabetes Res Clin Prac, 2017

Diabetes and Tuberculosis - the converging pandemics







HIV kills TB-specific CD4 cells and impairs macrophages activation

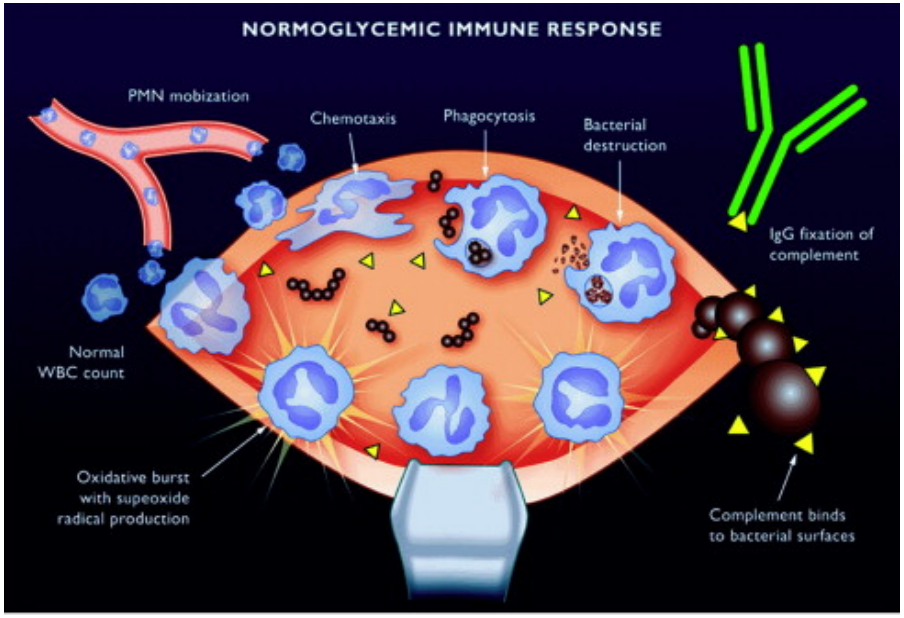
Reduced numbers of lung-homing CD4 cells

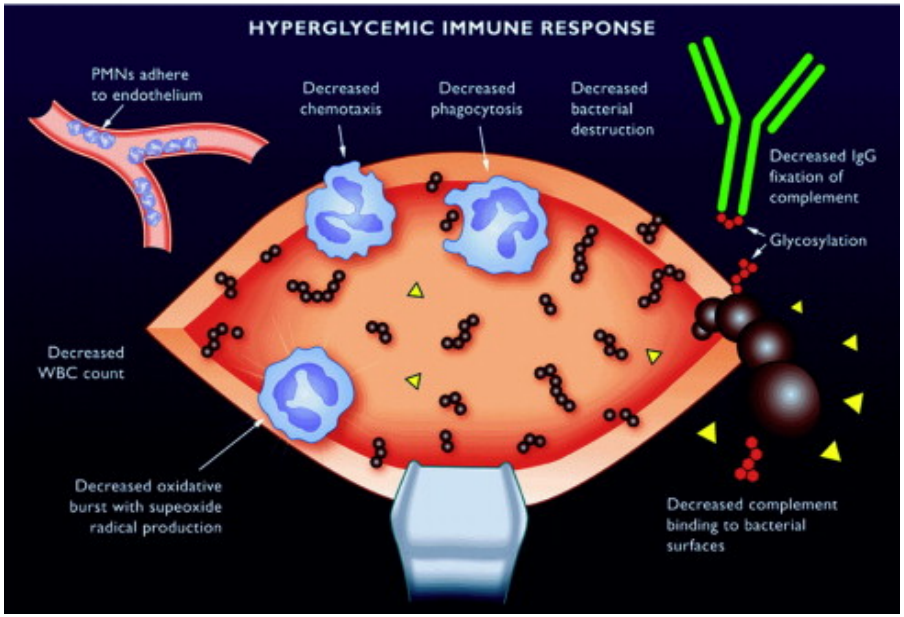
Defective granuloma formation

Loss of control of infection

Geldmacher, Curr Opin HIV AIDS 2012

Normoglycemic vs. Hyperglycemic





Adapted from Shilling AM, Raphael J. Diabetes, hyperglycemia, and infections. Best Practice & Research Clinical Anaesthesiology. 2008;22(3):519-535. http://ars.sciencedirect.com/content/image/1-s2.0-S1521689608000566-gr3.jpg

Natural history of tuberculosis

- Primary TB infection occurs when tubercle bacilli are inhaled and settle in the lung of immunologically naive hosts
- Local and disseminated disease is controlled in most individuals
- In average, 10% of subjects will develop the disease:
  - 5% in the first years, 5% throughout whole life
  - Risk is increased in case of altered immune fonctions
- Reinfection can occur, specially with immune deficiency

Risk Factors for Progression from LTBI to Active Disease.

Table 2. Common Risk Factors for Increased Likelihood of Progression from Latent Tuberculosis Infection to Active Disease.*

Risk Factor and Study	Relative Risk (95% CI) %
Advanced, untreated HIV infection	
Moss et al.[10]	9.9 (8.7–11)
Pablos-Méndez et al.[16]	9.5 (3.6–25)
Close contact with a person with infectious tuberculosis†	
Ferebee[17]	6.1 (5.5–6.8)
Radiographic evidence of old, healed tuberculosis that was not treated	
Ferebee[17]	5.2 (3.4–8.0)
Treatment with ≥15 mg of prednisone per day‡	
Jick et al.[18]	2.8 (1.7–4.6)
Chronic renal failure	
Pablos-Méndez et al.[16]	2.4 (2.1–2.8)
Treatment with TNF-α inhibitor	
Askling et al.[19]	2.0 (1.1–3.5)
Poorly controlled diabetes	
Pablos-Méndez et al.[16]	1.7 (1.5–2.2)
Weight ≥10% below normal	
Palmer et al.[20]	1.6 (1.1–2.2)
Smoking	
Bates et al.[21]	1.5 (1.1–2.2)

* Relative risk was calculated as described in Horsburgh.[5] CI denotes confidence interval, HIV human immunodeficiency virus, and TNF tumor necrosis factor.
† Relative risk was calculated for the first 3 years after exposure.
‡ The drug was taken for 2 weeks or more.

Horsburgh CR Jr, Rubin EJ. N Engl J Med 2011

Risk factors for tuberculosis

- Exposure
  - Household contacts
  - Foreign-born from TB endemic regions, ethnic minorities
  - Congregate settings- shelters, prisons, hospitals
  - Poverty, homeless, IV drug users
- Impaired immunity (host factors)
  - Substance abuse: IVDA, Smoking,Heavy ETOH
  - Nutritional status: underweight, Vit D
  - Systemic disease: silicosis, HIV, DM, renal dz; gastric bypass, celiac sprue
  - Immune compromise: HIV, steroids, TNF inhibitors, transplant
  - Age

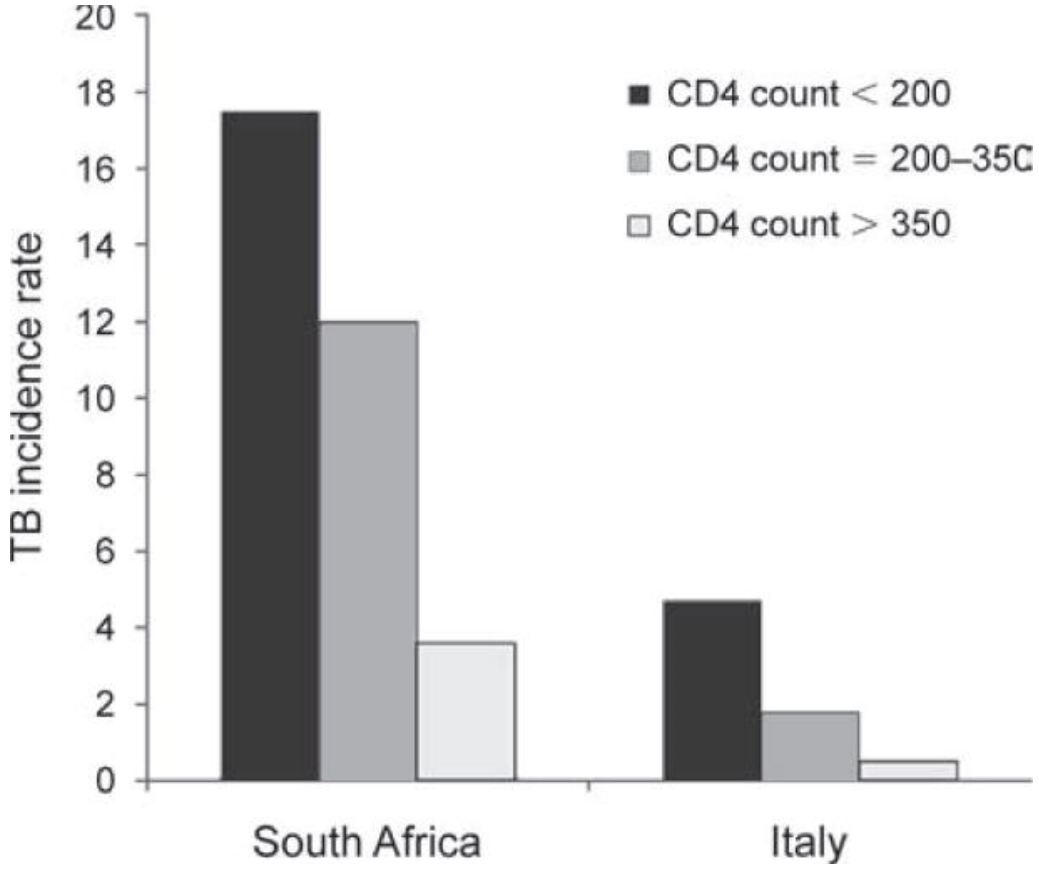
TB as an Opportunistic Infection

- Risk progression from LTBI to TB disease in HIV infected (7-10% annual risk) is much greater than for HIV-negative patients (5%-10% lifetime)
- Increased risk for TB at all levels of immuno-suppression, although relative risk and disease differ in different CD4 ranges
- Increased risk for TB disease begins early after HIV infection

Treatment for LTBI

- Treating LTBI reduces the risk that *M. tuberculosis* infection will develop into TB disease
- Certain groups have higher risk for developing TB disease after infection; should be treated
- Before beginning treatment for LTBI
  - Exclude diagnosis of TB
  - Ensure patient has no history of adverse reactions resulting from prior LTBI treatment

Pathogenesis and Natural History



Wood, Int J Tuberc Lung Dis, 2010

TEMPRANO: Immediate or Deferred ART Initiation ± IPT for African Pts

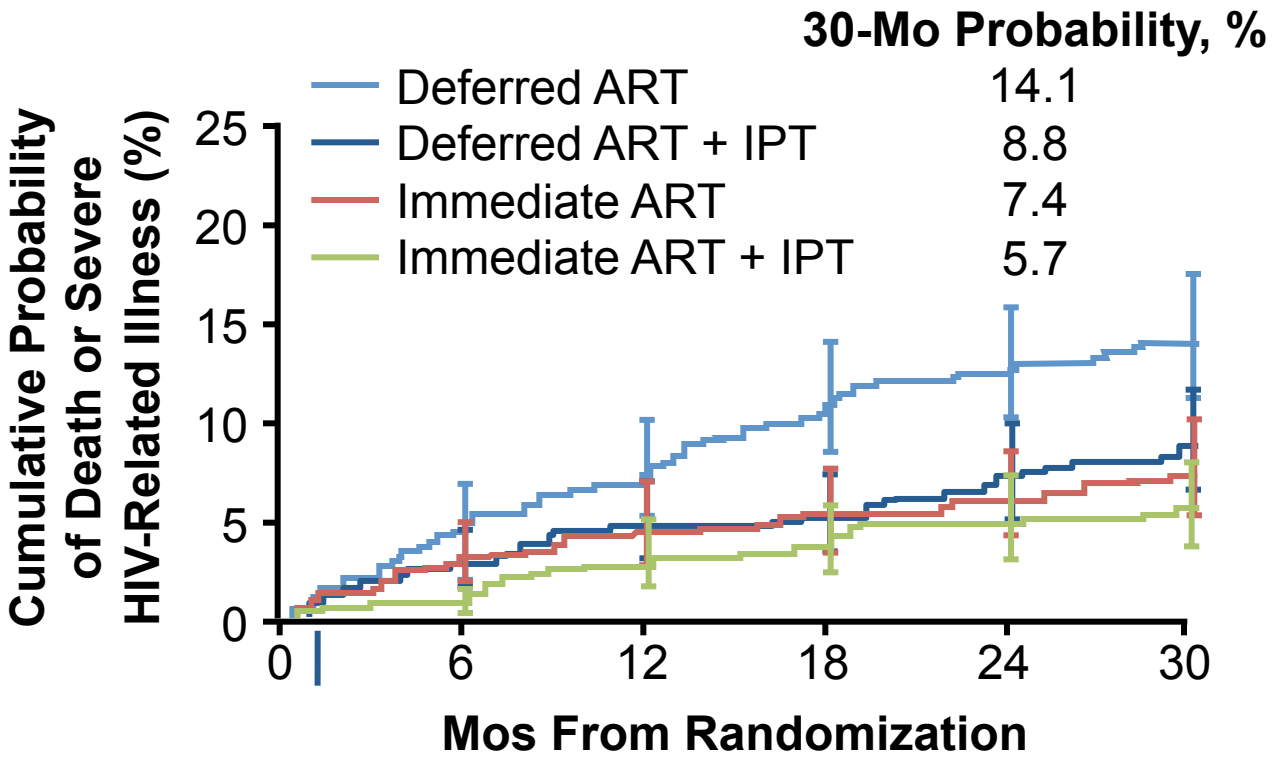
- Randomized, controlled, unblinded, multicenter (Ivory Coast), 2 x 2 factorial

*WHO criteria evolved during the study (updates 2006, 2010, 2013). †ART initiated immediately following randomization. ‡IPT = 300 mg daily isoniazid initiated 1 mo after enrollment and terminated 7 mos after enrollment. §Deferred until meeting WHO criteria for initiating ART.

- Pts in the treatment arms well matched at baseline
  - First-line ART primarily EFV + TDF/FTC (68% to 71%) or LPV/RTV + TDF/FTC (22% to 24%)
- Median duration of follow-up: 29.9 mos

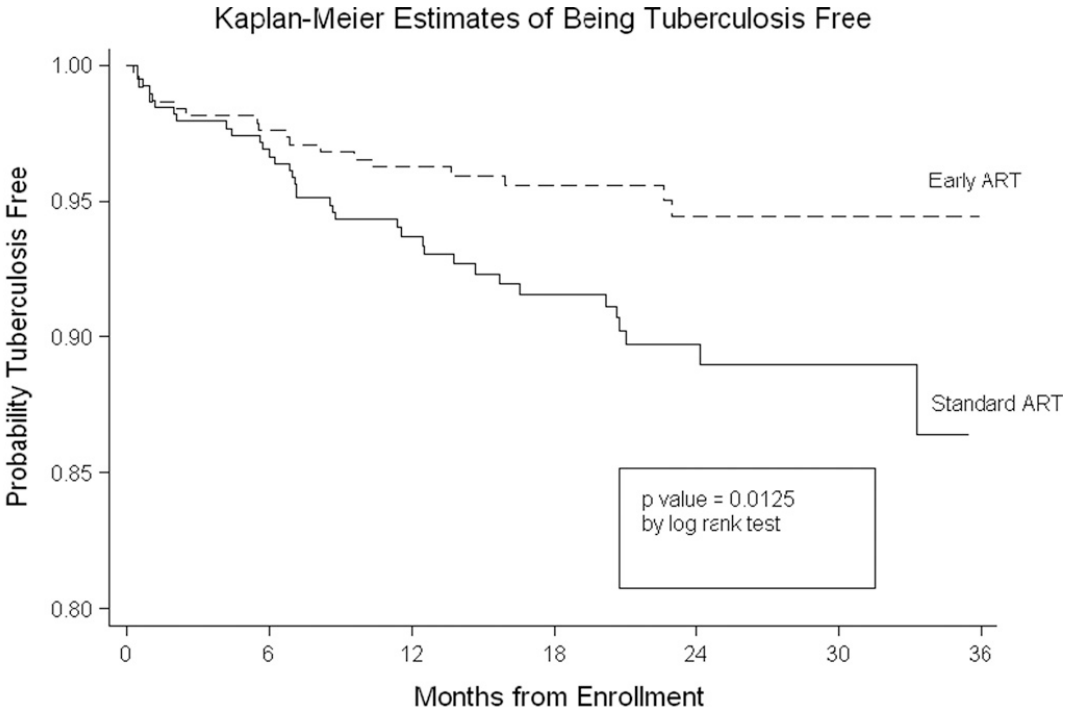
TEMPRANO ANRS 12136 Study Group. N Engl J Med. 2015;[Epub ahead of print].

TEMPRANO: Immediate vs Deferred ART Initiation and IPT Delivery for African Pts



TEMPRANO ANRS 12136 Study Group. N Engl J Med. 2015;[Epub ahead of print].

Effect of ART on Tuberculosis: Haiti



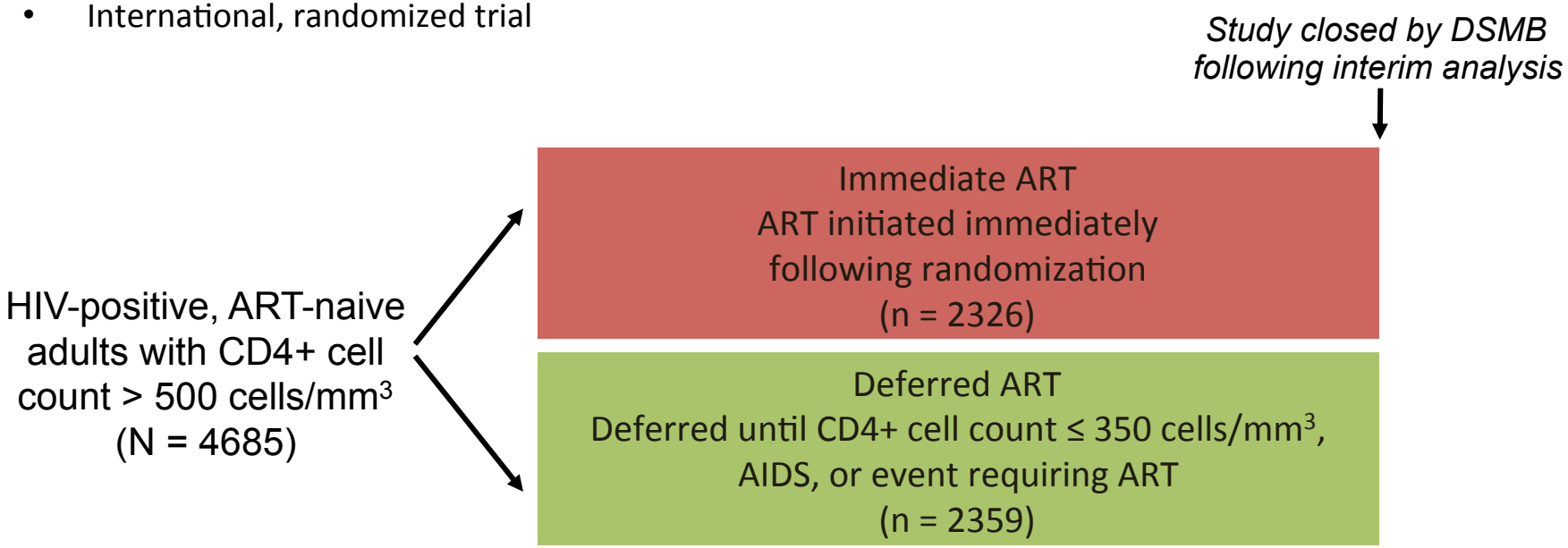
No at risk:

Early	380	302	140	20
Standard	393	288	122	16

Severe, NEJM, 2010

START: Immediate vs Deferred Therapy for Asymptomatic, ART-Naive Pts

- International, randomized trial



- Composite primary endpoint: any serious AIDS-related (AIDS-related death or AIDS-defining event) or non-AIDS–related event (non-AIDS–related death, CVD, end-stage renal disease, decompensated liver disease, non-AIDS–defining cancer)
- Mean follow-up: 3 yrs; median baseline CD4+ cell count: 651 cells/mm^3; median baseline HIV-1 RNA: 12,759 copies/mL
- Median CD4+ cell count at initiation of ART for deferred group: 408 cells/mm^3

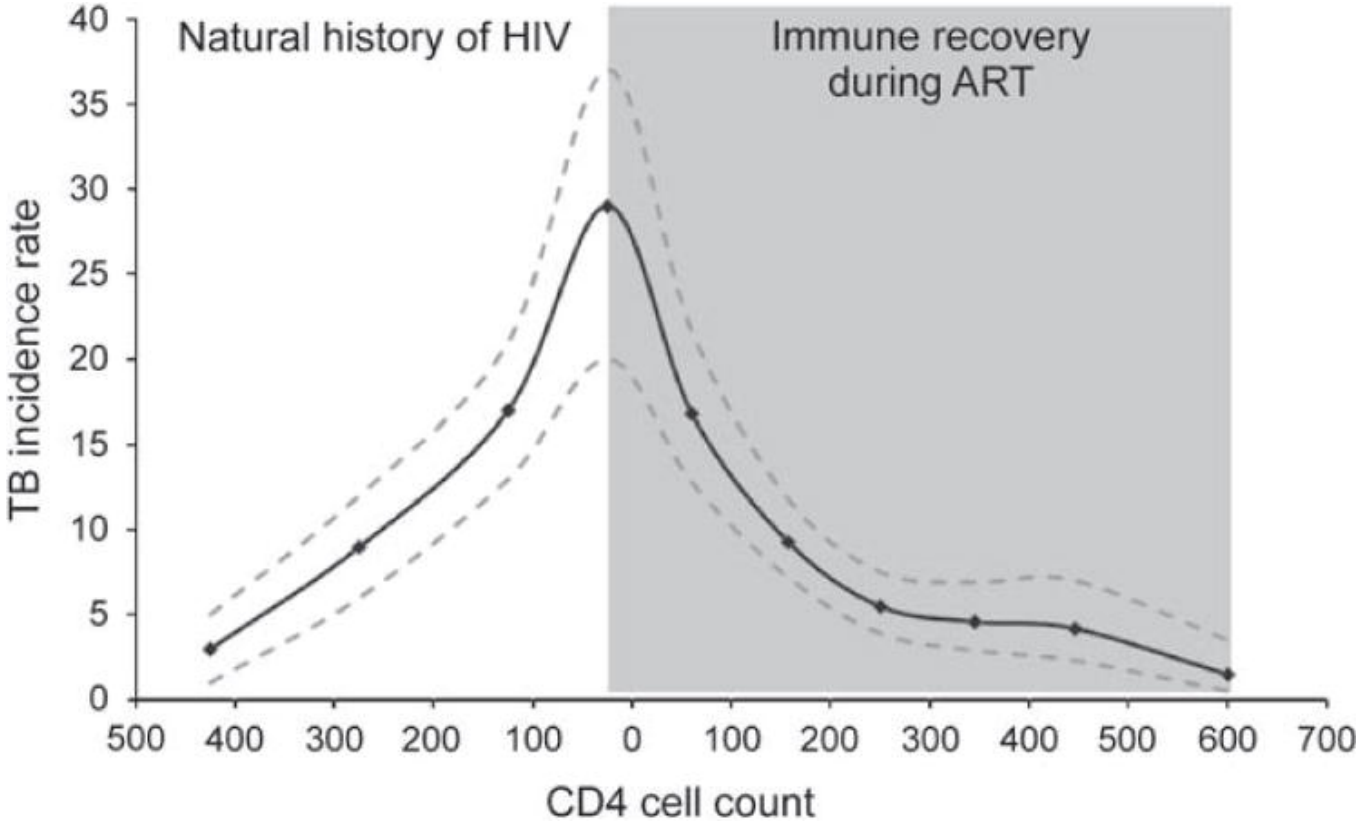
INSIGHT START Study Group. N Engl J Med. 2015;[Epub ahead of print]. Lundgren J, et al. IAS 2015. Abstract MOSY0302.

START: Primary Endpoint Components With Immediate vs Deferred ART

Endpoint	Immediate ART (n = 2326)		Deferred ART (n = 2359)		HR (95% CI)	*P* Value
	N	Rate/100 PY	N	Rate/100 PY		
Serious AIDS-related event	14	0.20	50	0.72	0.28 (0.15-0.50)	< .001
Serious non-AIDS–related event	29	0.42	47	0.67	0.61 (0.38-0.97)	.04
All-cause death	12	0.17	21	0.30	0.58 (0.28-1.17)	.13
Tuberculosis	6	0.09	20	0.28	0.29 (0.12-0.73)	.008
Kaposi's sarcoma	1	0.01	11	0.16	0.09 (0.01-0.71)	.02
Malignant lymphoma	3	0.04	10	0.14	0.30 (0.08-1.10)	.07
Non-AIDS–defining cancer	9	0.13	18	0.26	0.50 (0.22-1.11)	.09
CVD	12	0.17	14	0.20	0.84 (0.39-1.81)	.65

INSIGHT START Group. N Engl J Med. 2015;[Epub ahead of print]. Lundgren J, et al. IAS 2015. Abstract MOSY0302.

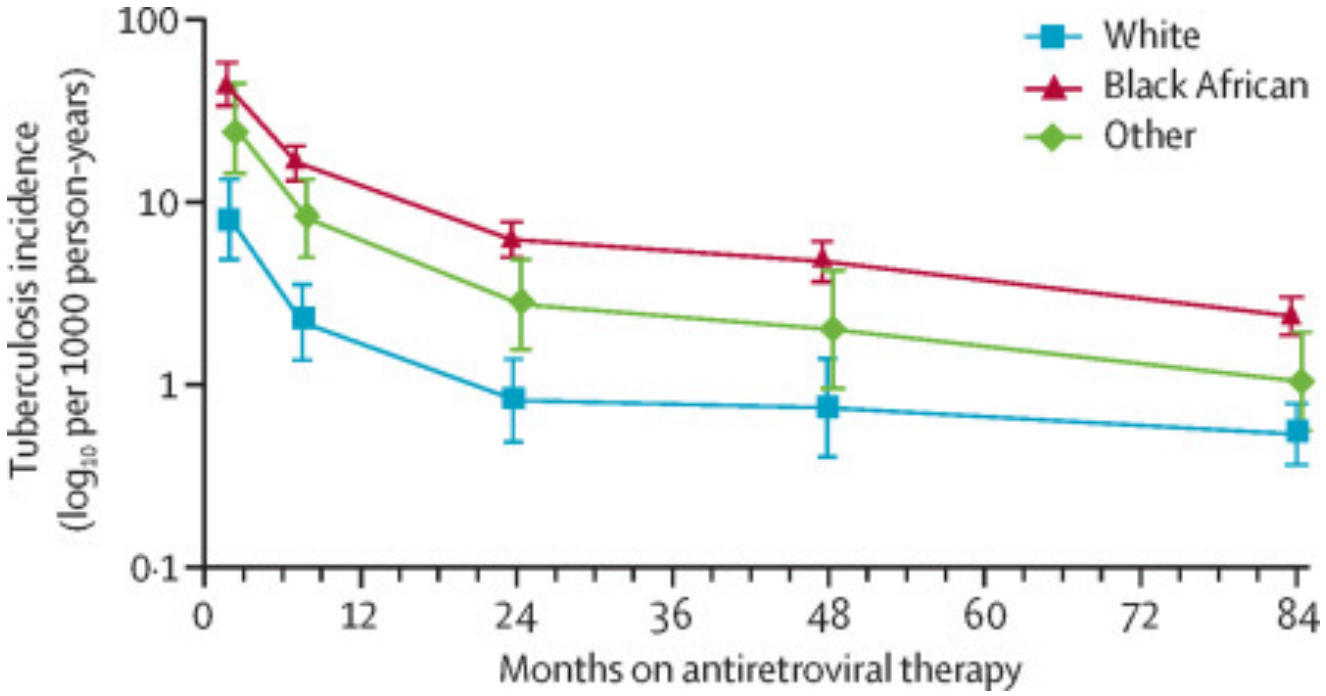
HIV, TB and ART



Lawn, J Infect Dis, 2011

Does ARV reduce Tuberculosis incidence to background rate in HIV + Patients ?

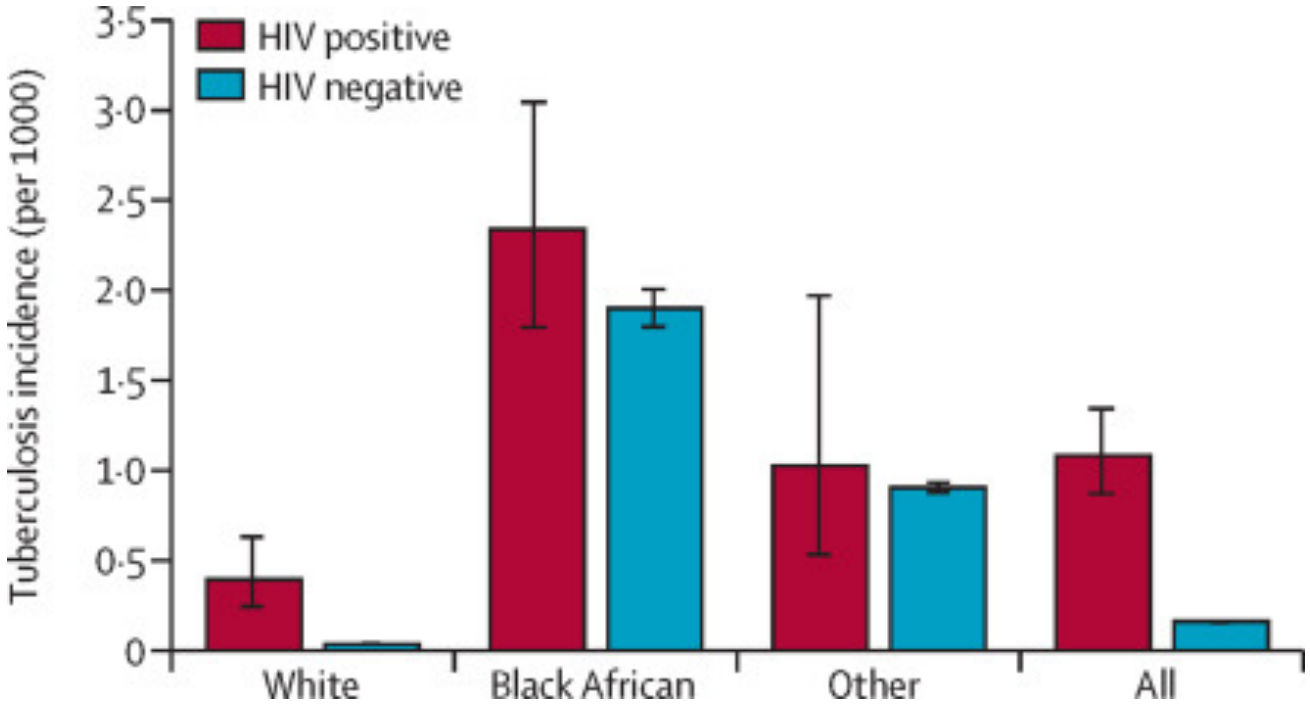
A national observational cohort study from England, Wales, and Northern Ireland



Tuberculosis incidence by months on antiretroviral therapy in the national HIV cohort in England, Wales, and Northern Ireland

Gupta, Lancet HIV, 2015

Does ARV reduce Tuberculosis incidence to background rate in HIV + Patients ?



Tuberculosis incidence in national HIV cohort compared with that in background HIV-negative population in 2009

Data shown for patients with HIV receiving antiretroviral therapy and with most recent CD4 count of at least 500 cells per µl

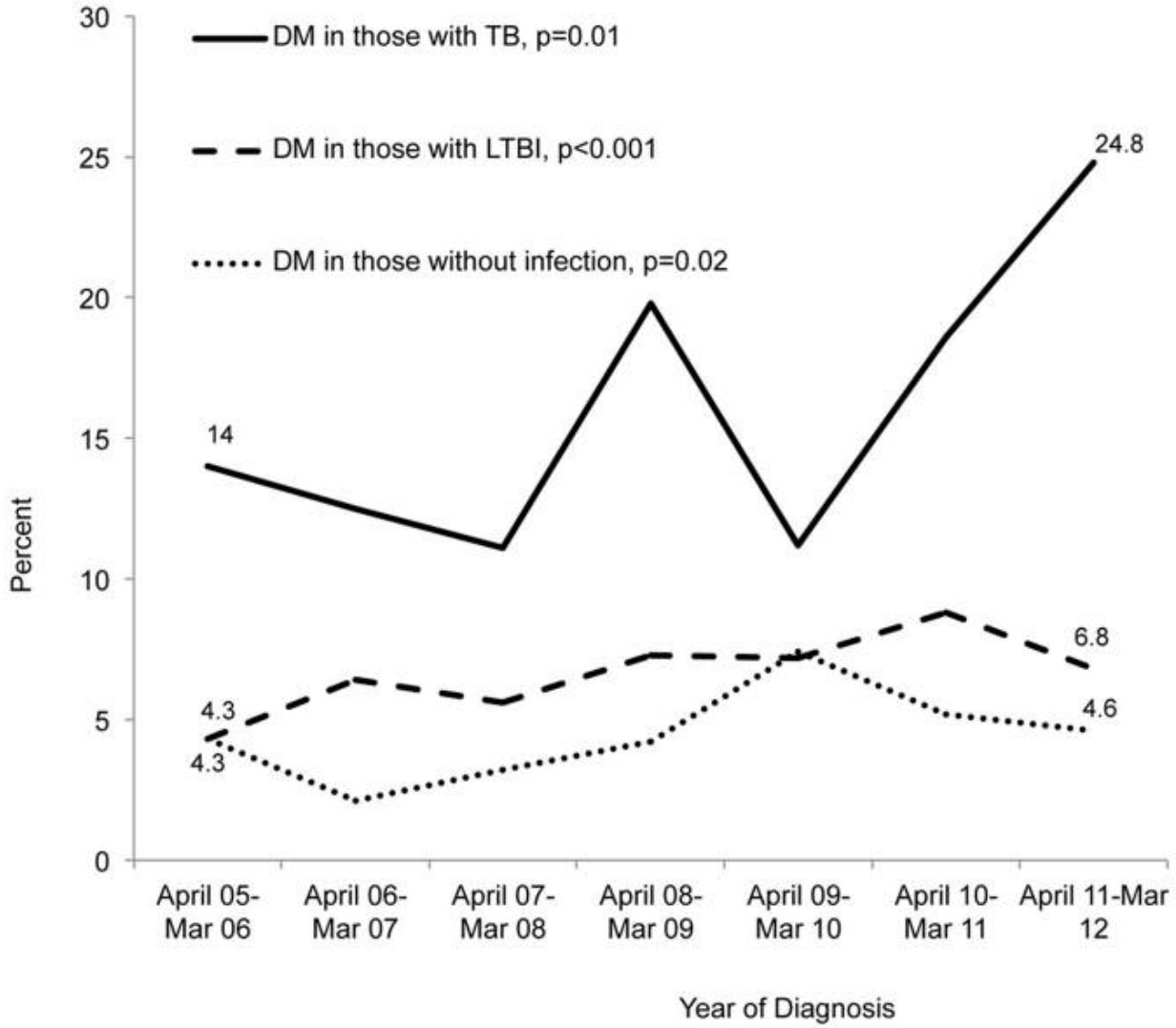
Gupta, Lancet HIV, 2015

Association between DM and TB

- Study in US and foreign-born persons attending the San Francisco Tuberculosis Clinic.
- Between 2005 and 2012:
  - 4371 (19.0%) individuals without evidence of TB infection,
  - 17,856 (77.6%) with latent tuberculosis
  - 791 (3.4%) with tuberculosis.
- The prevalence of diabetes was the highest among individuals with tuberculosis and increased during the study period.
- There was a disproportionate association of TB and DM relative to LTBI and DM among Filipinos in individuals older than 45 years old.

Suwanpimolkul, PLoS ONE 2014

Association between DM and TB



Suwanpimolkul, PLoS ONE 2014

DM is associated with Tuberculosis in Indonesia

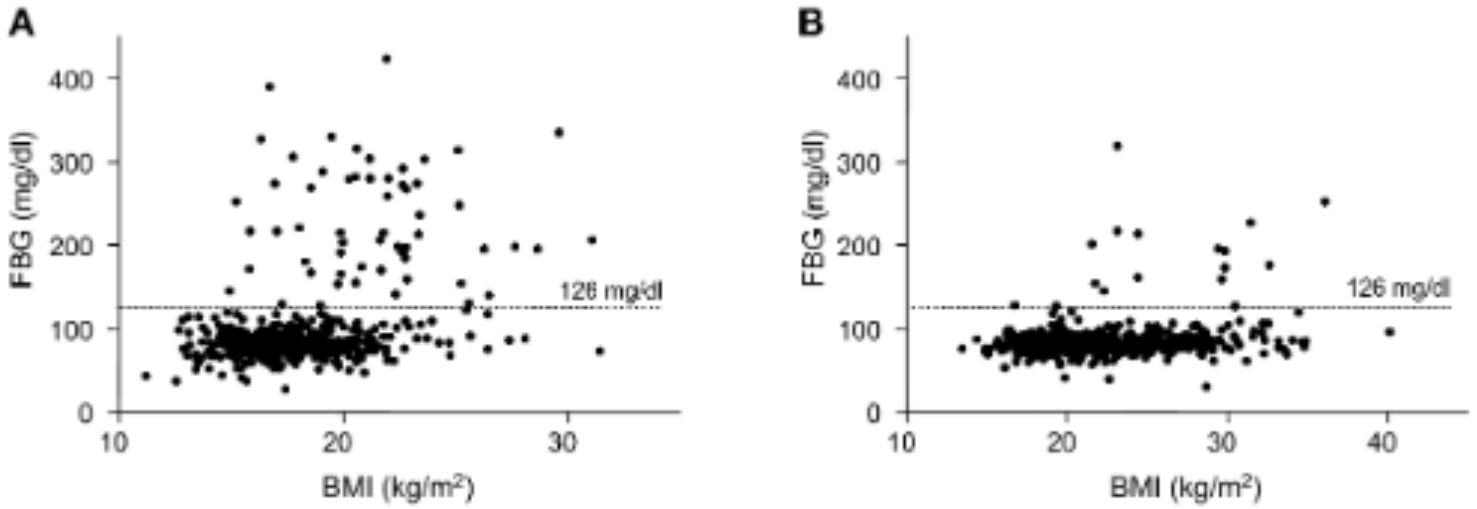
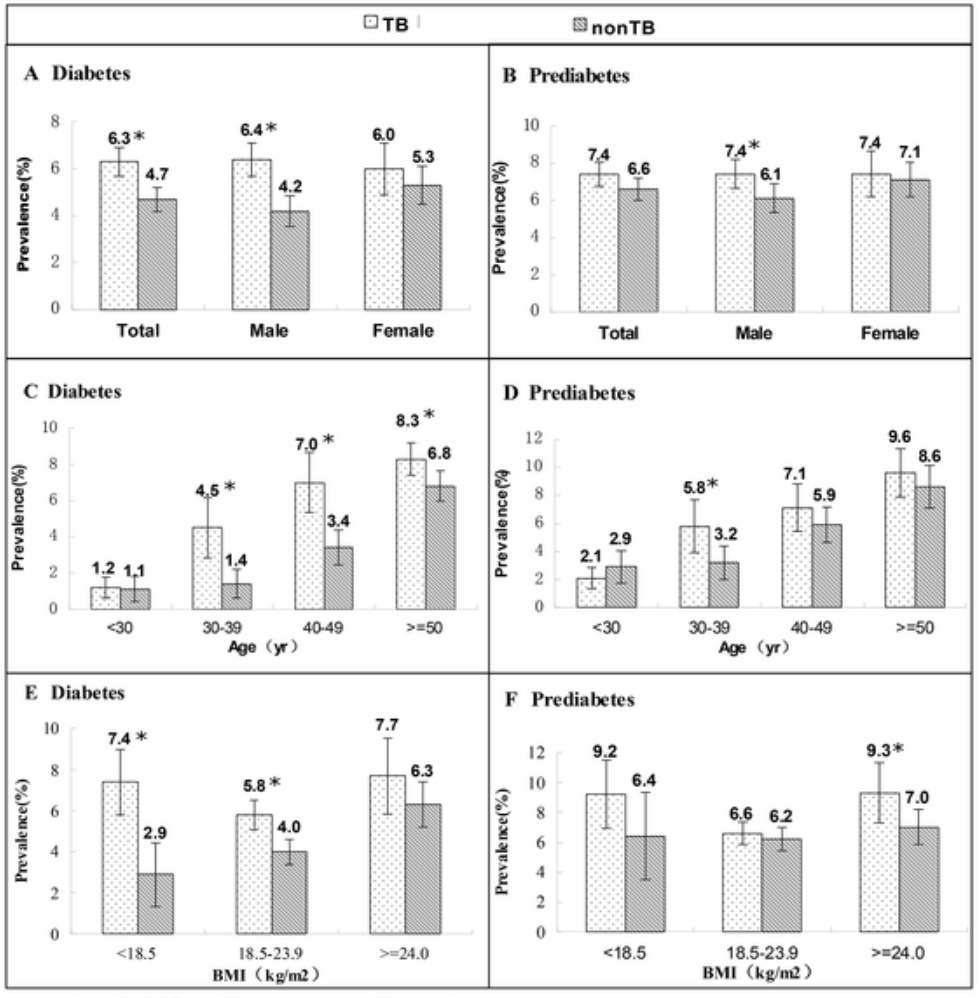


Figure Fasting blood glucose concentrations according to body mass index among TB patients (**A**) and control subjects (**B**).

Alisjabanah B, Int J Tuberc Lung Dis, 2006

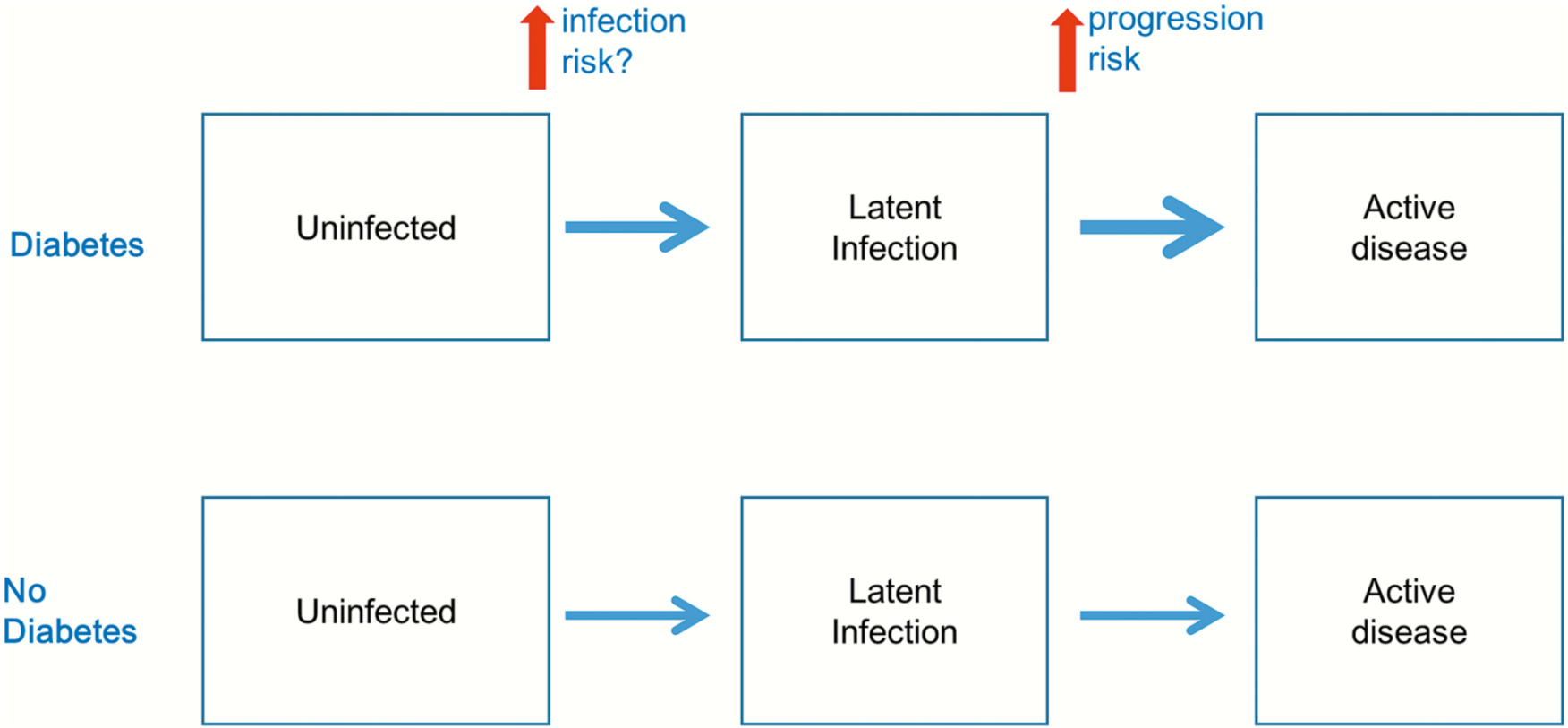
The prevalence of diabetes and prediabetes in TB and non-TB.



Note: *P<0.05 for difference with non-TB controls

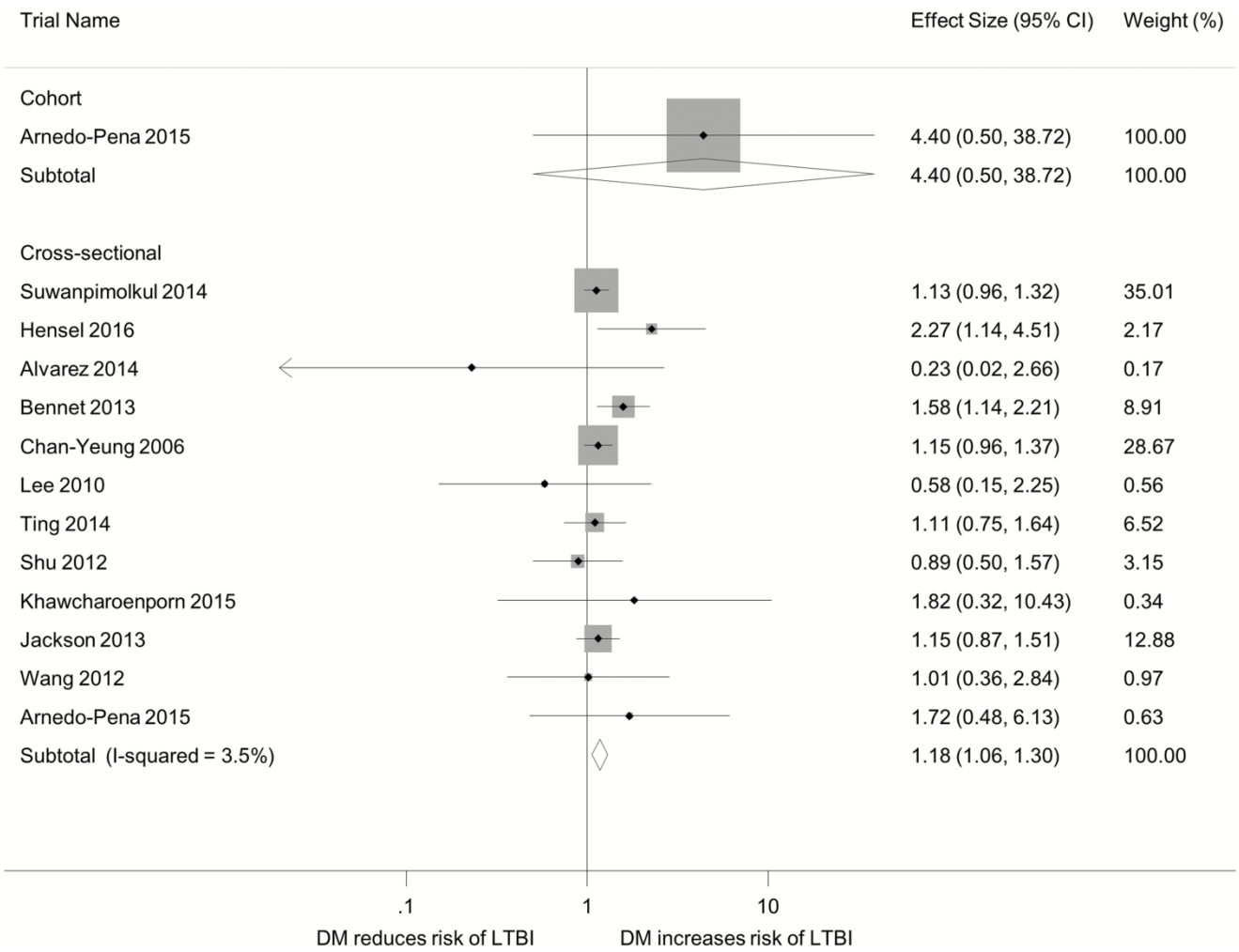
Wang Q, Ma A, Han X, Zhao S, Cai J, et al. (2013) Prevalence of Type 2 Diabetes among Newly Detected Pulmonary Tuberculosis Patients in China: A Community Based Cohort Study. PLOS ONE 8(12): e82660. https://doi.org/10.1371/journal.pone.0082660
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0082660

DM and Tuberculosis



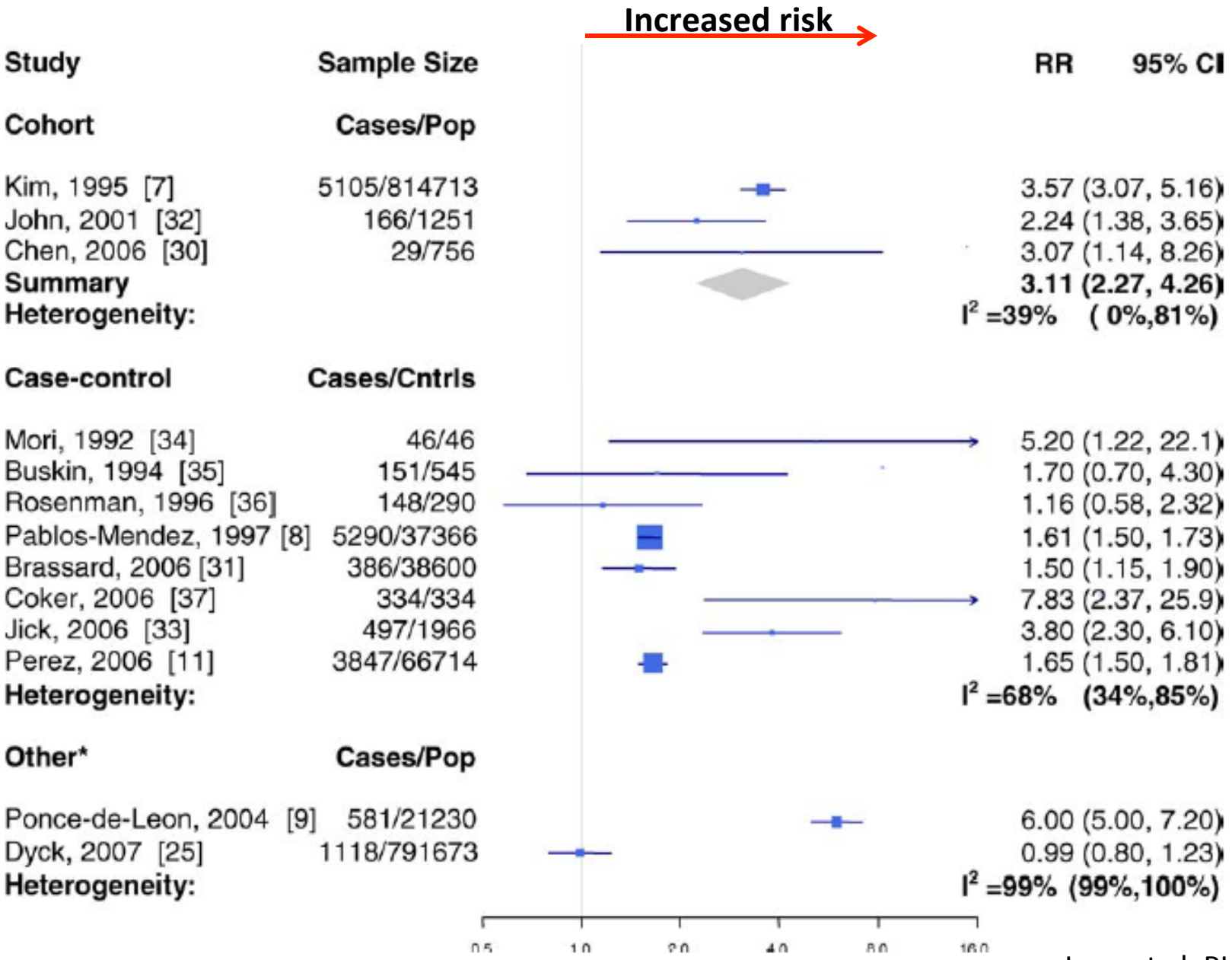
From: Diabetes Mellitus and Latent Tuberculosis Infection: A Systemic Review and Metaanalysis
Clin Infect Dis. 2016;64(6):719-727. doi:10.1093/cid/ciw836

Is Diabetes a Risk Factor for LTBI ?



From: Diabetes Mellitus and Latent Tuberculosis Infection: A Systemic Review and Metaanalysis
Clin Infect Dis. 2016;64(6):719-727. doi:10.1093/cid/ciw836

Diabetes is consistently a risk factor for developing active TB



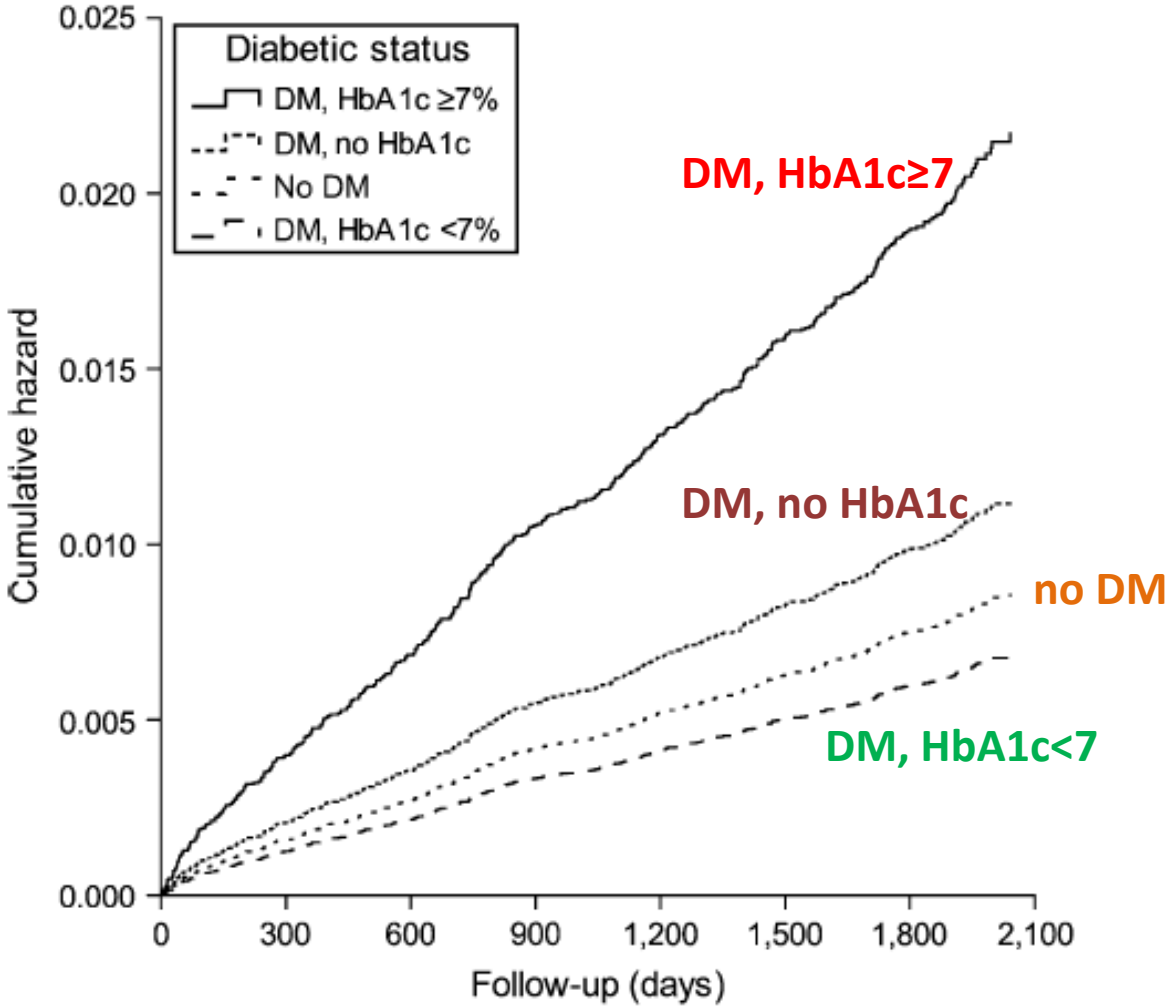
Jeon et al. PLoS Med 2008

Effect of DM on the Risk of developing TB

- Prospective cohort study: 17 715 Taiwanese persons
- DM significantly associated with TB
- Risk of TB increased as the number of complications of DM increased (P = .0016), with >3-fold risk if ≥2 DM-related complications (OR 3.45; 95% CI, 1.59–7.50).
- Similarly, the risk increased among those with higher Diabetes Complications Severity Index scores (P = .0002).

Baker, CID, 2012

Severity of diabetes increases the risk for TB



42,000 adults >65 years old from Hong Kong*

Diabetes with HbA1C≥7 compared to <7; odds for developing active PTB were **3.63 (1.79-7.33)***

1. Pablos-Mendez et al. *Am J Pub Health* 1997

*2. Leung et al. *Am J Epi* 2008

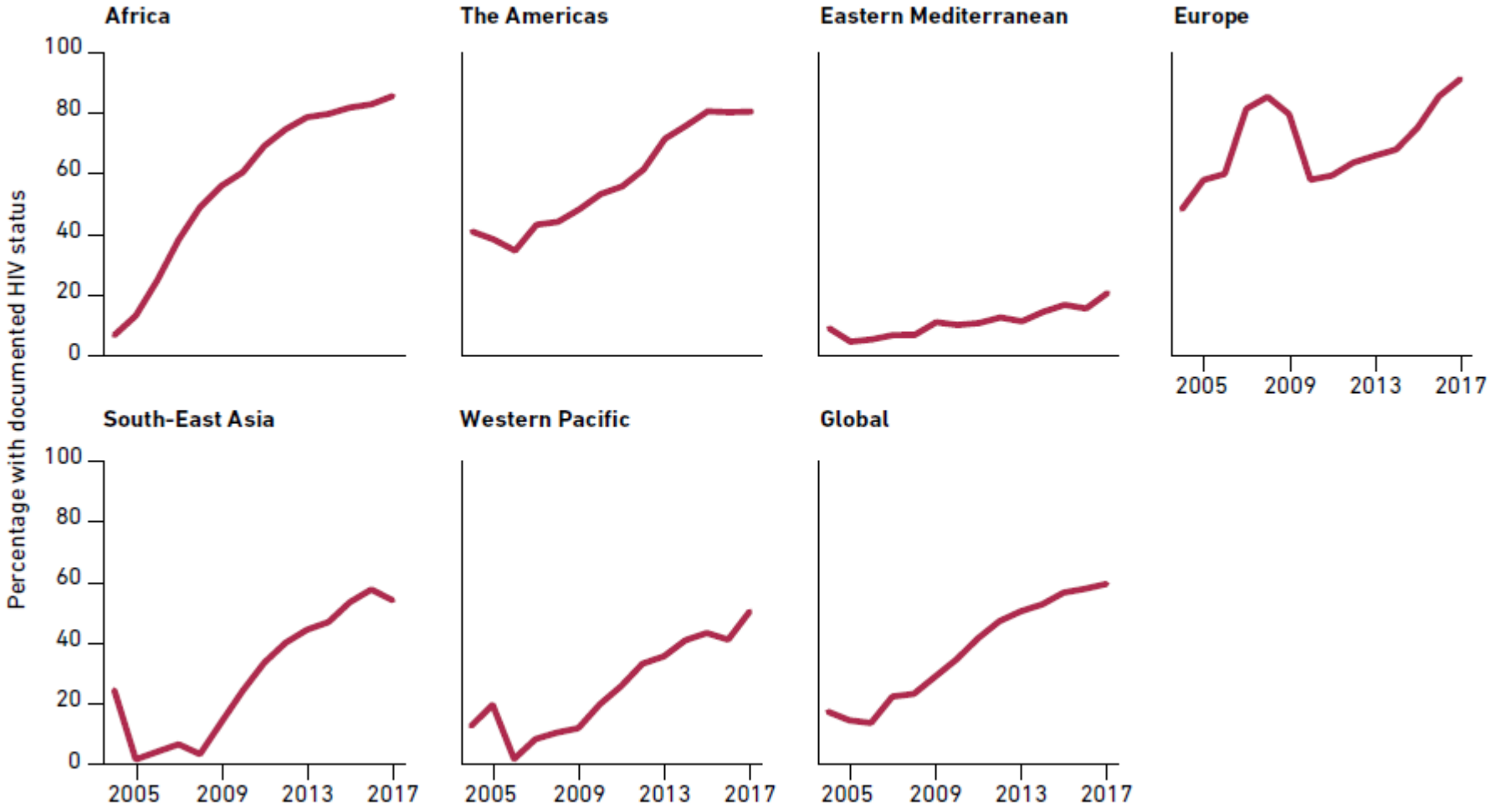
Improve Screening !

TB and HIV Screening

Globally in 2016, 57% of notified TB patients had a documented HIV test result, up from 55% in 2015 and a 19-fold increase since 2004.
In the WHO African Region, where the burden of HIV-associated TB is highest, 82% of TB patients had a documented HIV test result.
A total of 476 774 TB cases among HIV-positive people were reported and of these, 85% were on antiretroviral therapy (ART).

The highest proportion of HIV-positive cases among those tested for HIV was the WHO African Region (34%).
Overall, the percentage of TB patients testing HIV-positive has been falling globally since 2008.
This decline is evident in all WHO regions with the exception of the WHO European Region, where the proportion of TB patients testing HIV-positive has increased from 3% in 2008 to 15% in 2016.

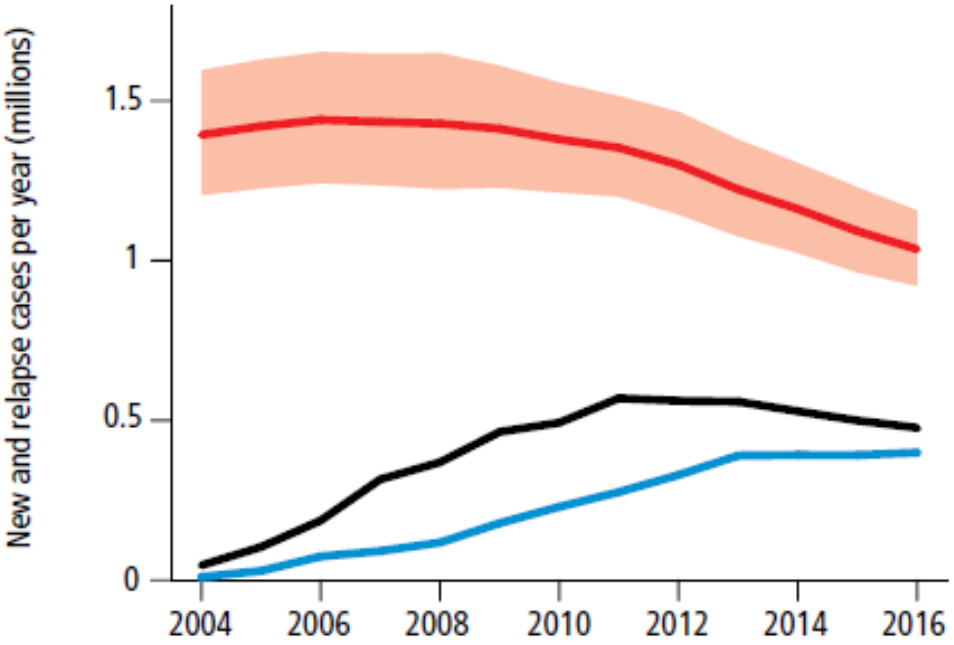
Percentage of new and relapse[a] TB cases with documented HIV status, 2004–2017, globally and for WHO regions[b]



[a] The calculation is for all cases in years prior to 2015.
[b] Countries were excluded if the number with documented HIV status was not reported to WHO.

HIV, TB and ART

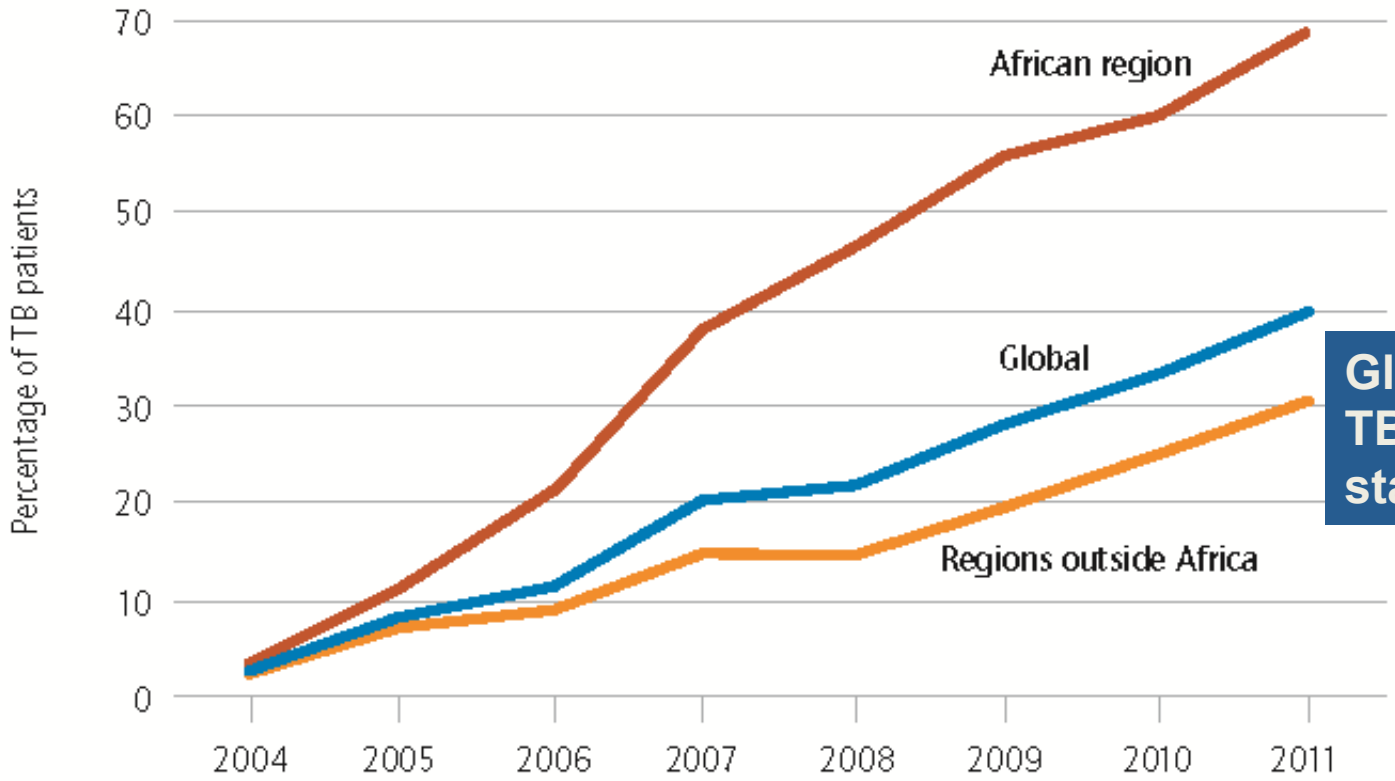
Global numbers of notified new and relapse cases[a] known to be HIV-positive (black), number started on antiretroviral therapy (blue) and estimated number of incident HIV-positive TB cases (red), 2004–2016. Shaded areas represent uncertainty bands.



WHO, 2017 report

HIV is not diagnosed in TB; ART cannot be started

FIGURE 7.2 **Percentage of TB patients with known HIV status, 2004–2011**



Globally, Only 40% TB cases HIV status known

Global TB report, 2012

Screening for diabetes in new TB patients can be highly effective (India)

	Number of TB patients whose DM status was ascertained [a]	Number with previously known DM [b]	Number of DM newly diagnosed [c]	Additional Yield [c/(b+c)*100]	Number needed to screen (NNS) [(a−b)/c]
Type of TB					
New Smear Positive Pulmonary TB	307	87	70	45%	3.1
New Smear Negative Pulmonary TB	37	4	7	64%	4.7
New Extra-pulmonary TB	128	15	21	58%	5.3
Relapse	35	12	8	40%	3.3
Treatment after Failure	19	7	2	22%	6.0
Treatment after Default	26	3	7	70%	3.3

Overall, number of **TB patients needed to screen** (with HbA1c) in order **to detect one new case of diabetes was just 4.**

Balakrishnan, Plos One 2012

Screening for DM in persons with TB

- Every patient with TB over the age of 18 should be screened for DM
  - A fasting plasma glucose > 125 mg/dl = DM
  - A random plasma glucose > 200 mg/dl = DM
  - A Hemoglobin A1c > 6.5% = DM

- Abnormal glucose values should be repeated in patients who have no symptoms of DM

Clinical Presentation in HIV Patients

- Presentation depends on immune state
- Extra-pulmonary disease occurs in 40 to 80%
- CNS TB develops in 5 to 10% of HIV + patients (< 2% of HIV – patients)
- Bacteremia more frequent

Clinical presentation

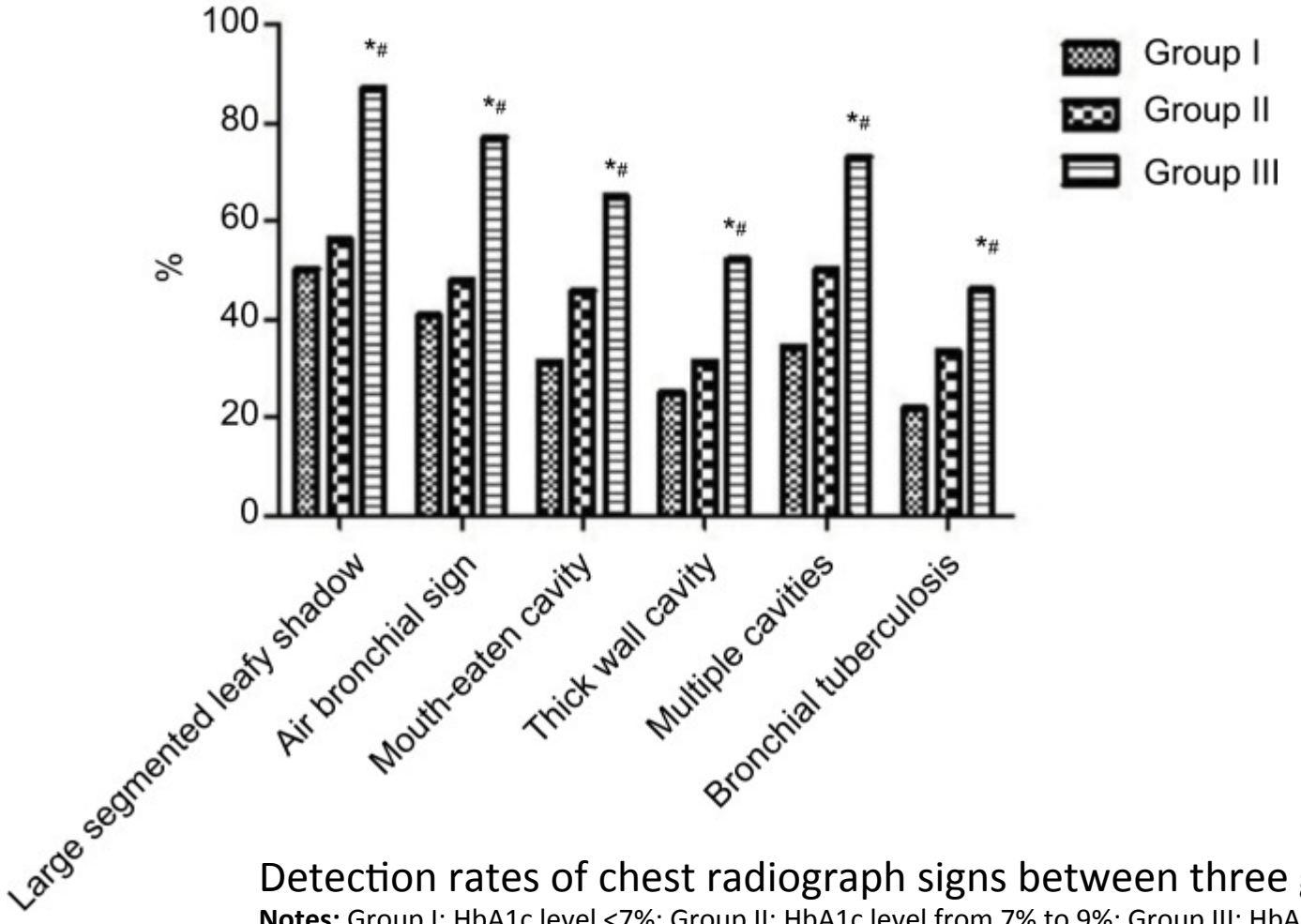
	Late HIV (CD4 < 200)	Early HIV
Pulm / Extra pulm	50/50	80/20
Chest X ray - Lymph node - Lower lobes - cavitation	 Common Common Rare	 Rare Rare Common
Anergy	Common	Rare
Smear +	Less common	Common
Adverse drug reaction	Common	Rare

Clinical Characteristics of TB Associated with DM

- A population-based study in adults diagnosed with TB between 2000 and 2013 in Barcelona.
- Of 5849 TB patients, 349 (5.9%) had DM.
- Factors associated with DM were:
  - being Spanish-born (OR 1.46, 95%CI 1.11-1.96),
  - age ≥40 years (OR 6.08, 95%CI 4.36-8.66),
  - cavitary patterns on chest X-ray (OR 1.42, 95%CI 1.08-1.86),
  - experiencing more side effects due to anti-tuberculosis treatment (OR 1.86, 95%CI 1.28-2.64)
  - hospitalization at the time of diagnosis (OR 1.8, 95%CI 1.40-2.31).

Moreno Martinez, Int J Tuberc Lung Dis 2015

Clinical Characteristics of TB Associated with DM

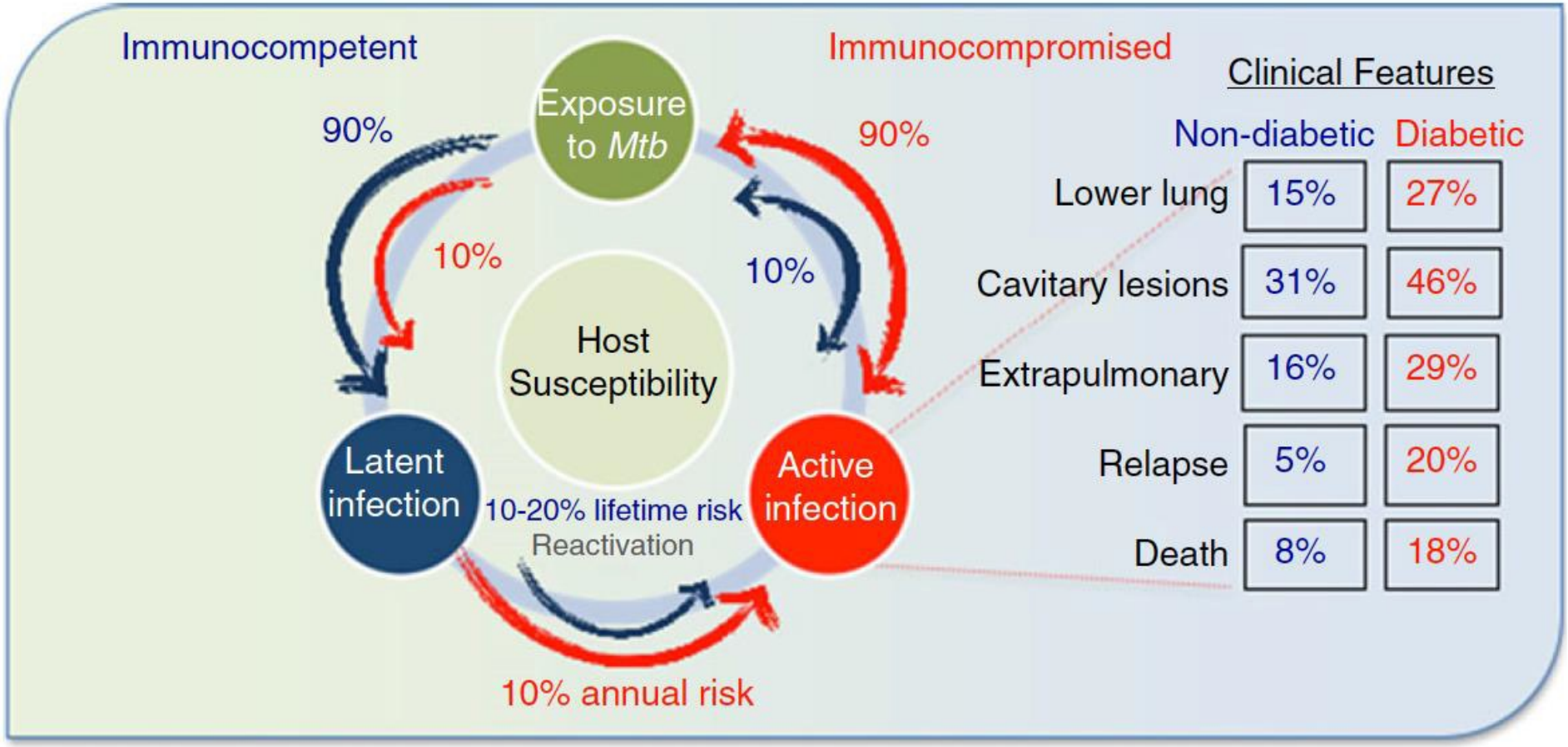


Detection rates of chest radiograph signs between three groups.

Notes: Group I: HbA1c level <7%; Group II: HbA1c level from 7% to 9%; Group III: HbA1c level >9%. **p*<0.05 compared with Group I, #*p*<0.05 compared with Group II.

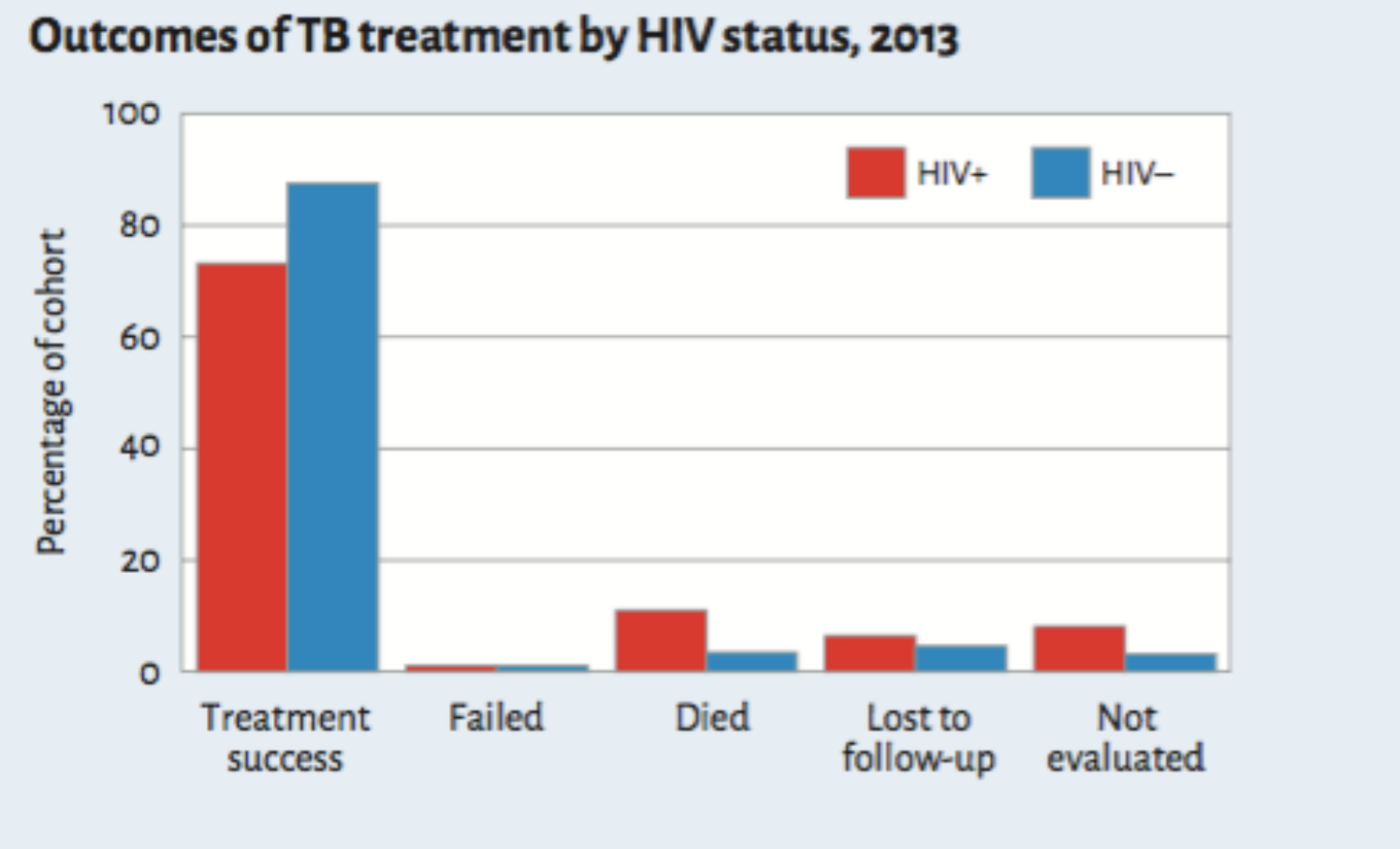
Xia LL, Infection and Drug Resistance, 2018

The impact of diabetes on tuberculosis infection



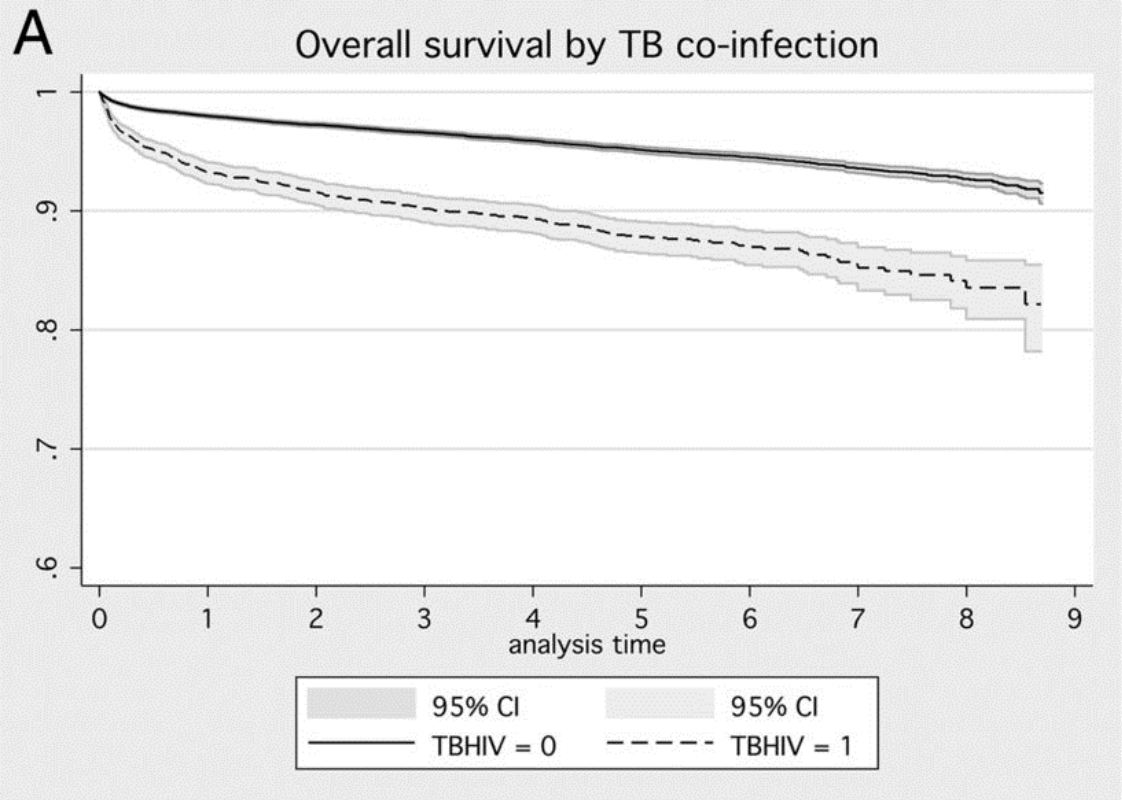
Hodgson et al, Immunology 2015, 144:171

Influence of HIV on TB Evolution



WHO, 2015 report

Tuberculosis and Death in UK in HIV + Patients



HR for death for TB/HIV co-infected persons: 4.77

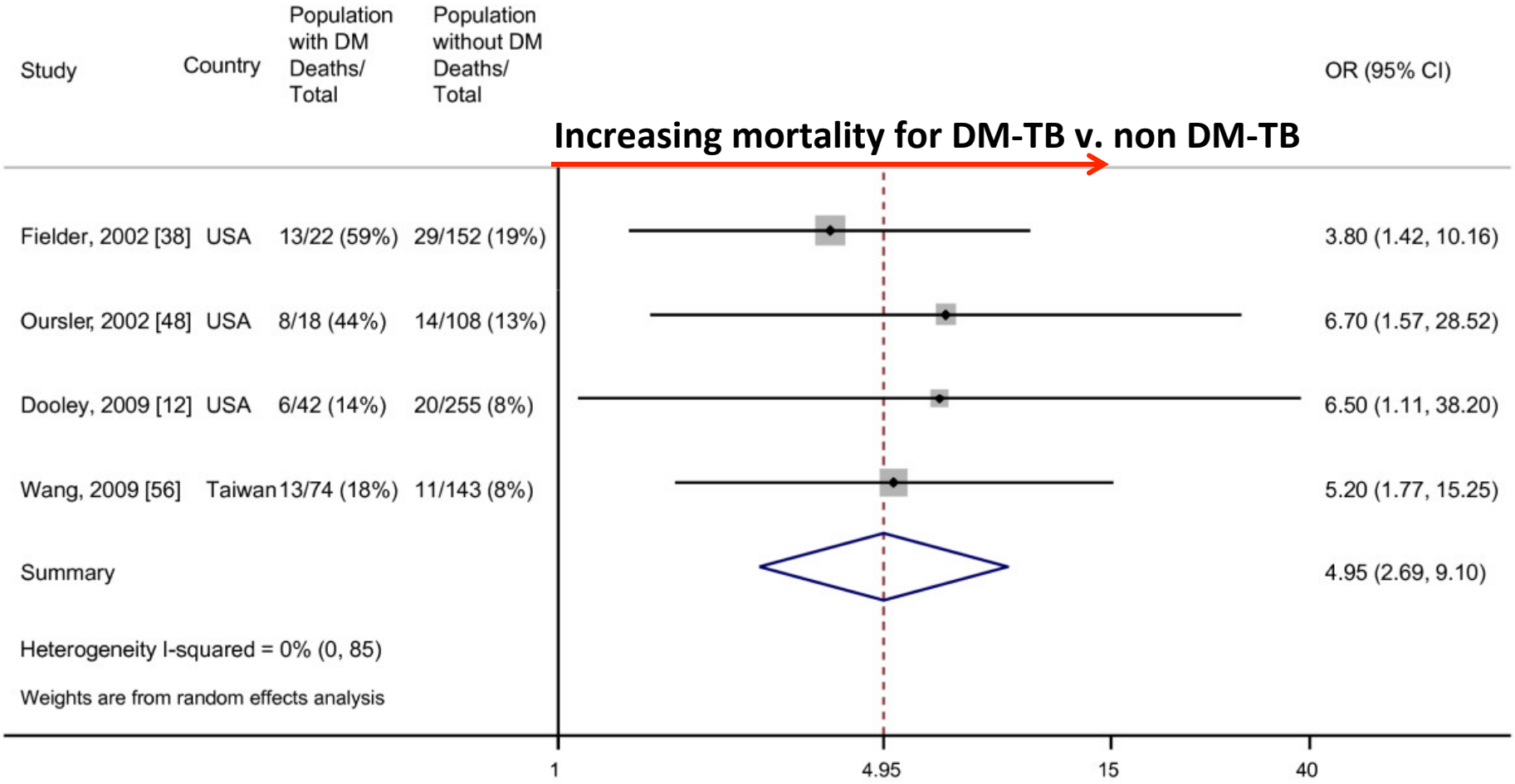
Zenner, Thorax, 2015

Outcome in TB associated with DM

- Prospective study in Southern Mexico
- The prevalence of DM among 1262 Pts with pulmonary TB was 29.63% (n=374)
- Pts with DM and pulmonary TB had:
  - More frequent cavities of any size(aOR 1.80)
  - Delayed sputum conversion (aOR 1.51)
  - Higher probability of treatment failure (aOR 2.93), recurrence (aHR=1.76) and relapse (aHR=1.83)
- Most of second episodes among Pts with DM were due to bacteria with the same genotype but in 5/26 (19%), reinfection with a different strain occurred

Jimenez-Corona, Thorax, 2013

All cause mortality increased in diabetics during TB treatment (compared to non-diabetics)



Baker et al. *BMC Med* 2011

TB/HIV Co-infection: Principles of Treatment

- Standard course in susceptible disease (4 drugs for 2 months and 2 drugs for 4 months)
- Increase to 9 months if suboptimal response (culture + after 2 months)
- Longer courses (9 to 12 months) in disseminated disease and some extra-pulmonary sites (skeletal TB, CNS TB)
- If using regimens without INH or a rifamycin, duration should be 12 to 15 months

Interactions of Rifamycins with ART: The P450 system

- Isoform CYP 3A is induced by NNRTIs
- Isoform CYP 3A is inhibited by protease inhibitors
- Rifamycins induce CYP 3A
  - Rifampin > rifapentine > rifabutin
  - Rifampin is not metabolized by CYP 3A: level not affected by other drugs the influence CYP 3A
  - Rifabutin is metabolized by CYP 3A: level is affected by other drugs that affect CYP 3A

Protease Inhibitors and Rifampin

- Rifampin will reduce the level of Pis by 75-90%
  - Super-boost or double dose of LPV/r may be used but can induce hepatotoxicity
- Rifabutin may be substituted for rifampin but:
  - Need to reduce the dose to avoid rifabutin toxicity (uveitis, cytopenia)
  - If patient interrupts ARV treatment, the dosage of rifabutin will not be sufficient

Interactions between ARV and Rifamycins: Dose Adjustments

Antiretroviral	Rifampin	Rifabutin
NNRTI		
Efavirenz	EFV 600mg, increase to 800mg if > 60 kg	Increase rifabutin to 450 – 600 mg daily
Nevirapine	Risky	No dose adjustment (300mg daily)
Etravirine	Not recommended	No dose adjustment
Rilpivirine	Do not co-administer	Increase rilpivirine ?
PI/r	Do not co-administer	Decrease rifabutin to 150 mg OD or every other day
Integrase Inhibitors		
Raltegravir	Consider to increase to raltegravir to 800mg bid	No dose adjustment
Dolutegravir	Increase dolu to 50mg bid	No dose adjustment
Nucleosides	No dose adjustment	No dose adjustment
Enfuvirtide	No dose adjustment	No dose adjustment

Tuberculosis and HAART

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 20, 2011 VOL. 365 NO. 16

Earlier versus Later Start of Antiretroviral Therapy in HIV-Infected Adults with Tuberculosis

François-Xavier Blanc, M.D., Ph.D., Thim Sok, M.D., Didier Laureillard, M.D., Laurence Borand, Pharm.D., Claire Rekacewicz, M.D., Eric Nerrienet, Ph.D., Yoann Madec, Ph.D., Olivier Marcy, M.D., Sarin Chan, M.D., Narom Prak, M.D., Chindamony Kim, M.D., Khemarin Kim Lak, M.D., Chanroeurn Hak, M.D., Bunnet Dim, M.D., Chhun Im Sin, M.D., Sath Sun, M.D., Bertrand Guillard, M.D., Borann Sar, M.D., Ph.D., Sirenda Vong, M.D., Marcelo Fernandez, M.D., Lawrence Fox, M.D., Ph.D., Jean-François Delfraissy, M.D., Ph.D., and Anne E. Goldfeld, M.D., for the CAMELIA (ANRS 1295–CIPRA KH001) Study Team*

CAMELIA (Cambodia)

Integration of Antiretroviral Therapy with Tuberculosis Treatment

Salim S. Abdool Karim, M.B., Ch.B., Ph.D., Kogieleum Naidoo, M.B., Ch.B., Anneke Grobler, M.Sc., Nesri Padayatchi, M.B., Ch.B., Cheryl Baxter, M.Sc., Andrew L. Gray, M.Sc.(Pharm.), Tanuja Gengiah, M.Clin.Pharm., M.S.(Epi.), Santhanalakshmi Gengiah, M.A.(Res.Psych.), Anushka Naidoo, M.Med.Sci.(Pharm.), Niraksha Jithoo, M.B., Ch.B., Gonasagrie Nair, M.B., Ch.B., M.P.H., Wafaa M. El-Sadr, M.D., M.P.H., Gerald Friedland, M.D., and Quarraisha Abdool Karim, Ph.D.

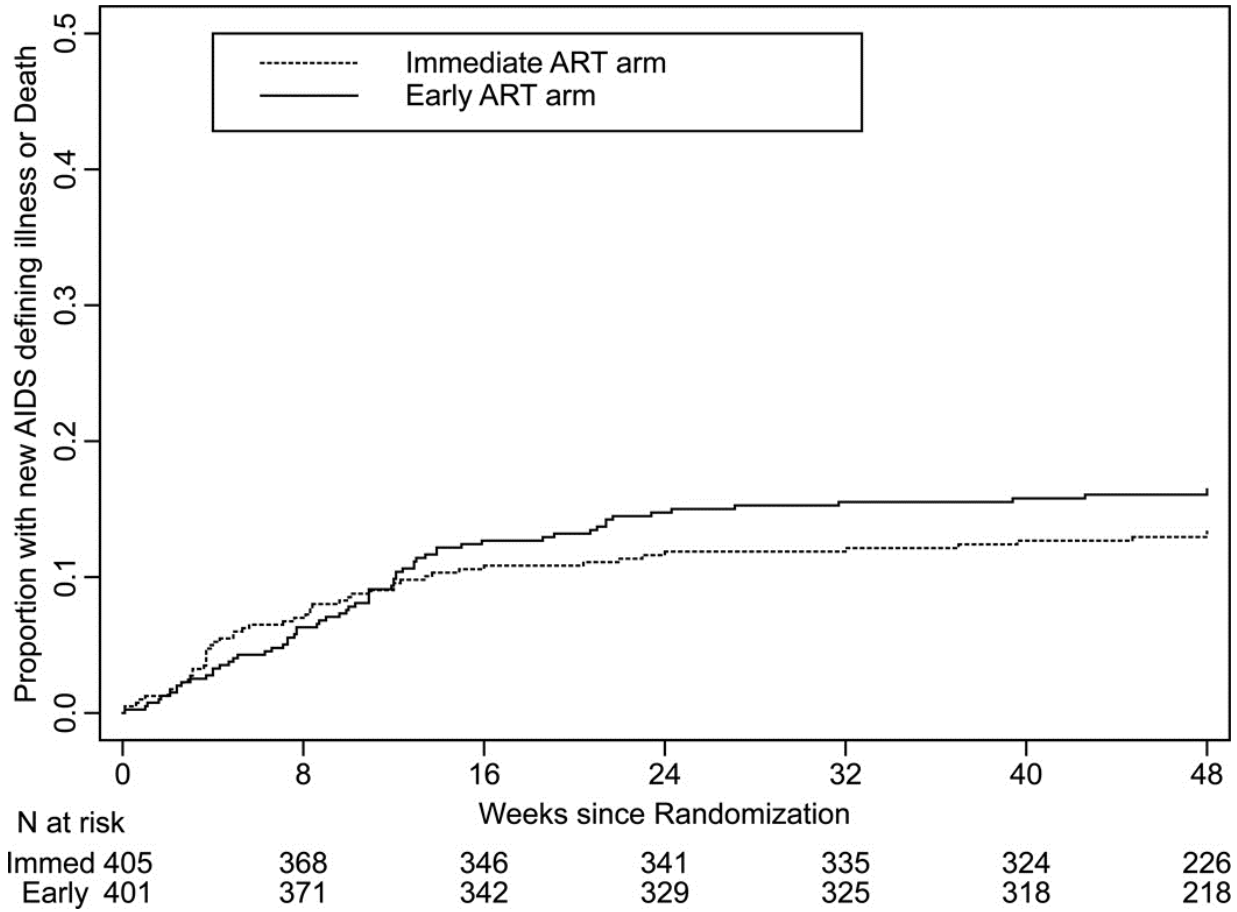
SAPIT (South Africa)

Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis

Diane V. Havlir, M.D., Michelle A. Kendall, M.S., Prudence Ive, M.D., Johnstone Kumwenda, M.B., B.S., Susan Swindells, M.B., B.S., Sarojini S. Qasba, M.D., Anne F. Luetkemeyer, M.D., Evelyn Hogg, B.A., James F. Rooney, M.D., Xingye Wu, M.S., Mina C. Hosseinipour, M.D., Umesh Lalloo, M.B., Ch.B., Valdilea G. Veloso, M.D., Fatuma F. Some, M.B., Ch.B., N. Kumarasamy, M.D., Nesri Padayatchi, M.D., Breno R. Santos, M.D., Stewart Reid, M.D., James Hakim, M.B., Ch.B., Lerato Mohapi, M.D., Peter Mugyenyi, M.D., Jorge Sanchez, M.D., Javier R. Lama, M.D., Jean W. Pape, M.D., Alejandro Sanchez, M.D., Aida Asmelash, M.D., Evans Moko, M.B., Ch.B., Fred Sawe, M.B., Ch.B., Janet Andersen, Sc.D., and Ian Sanne, M.D., for the AIDS Clinical Trials Group Study A5221*

STRIDE (multicontinent)

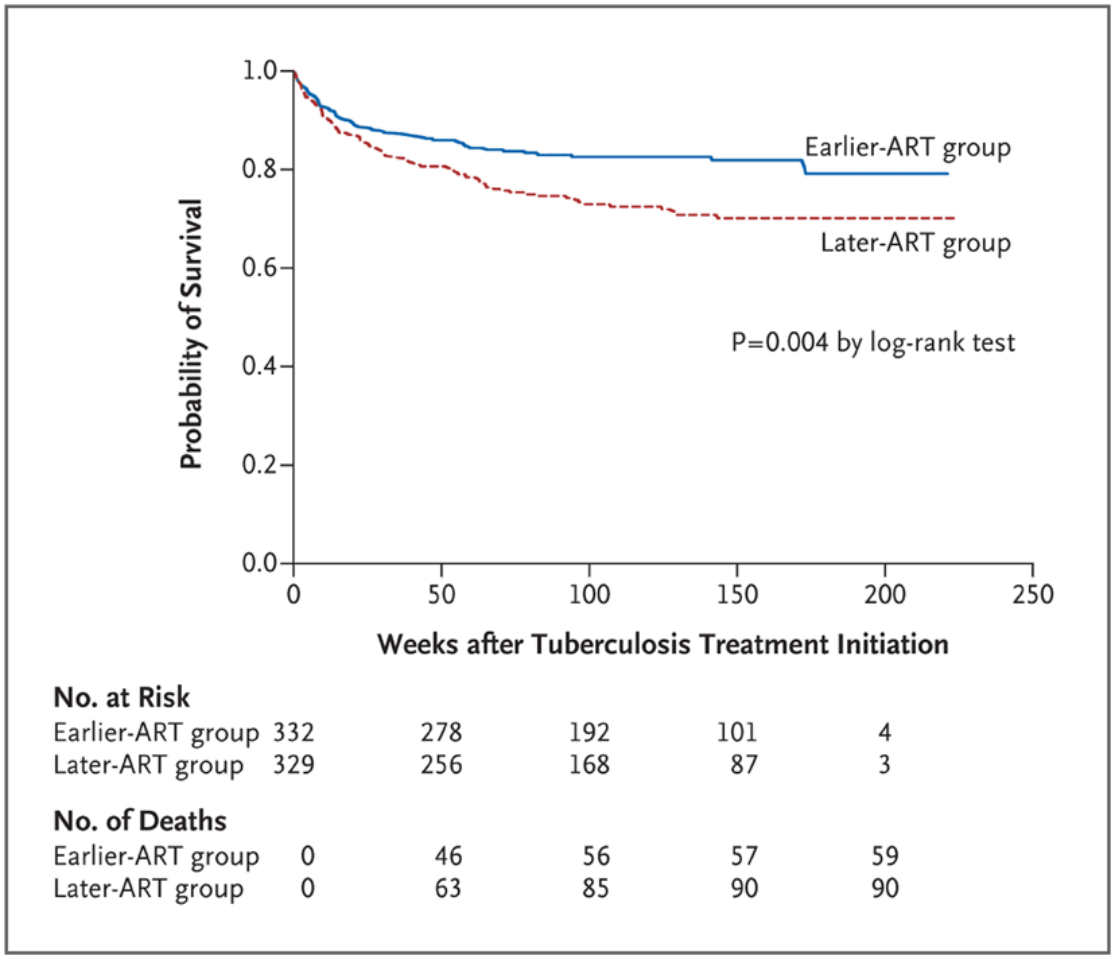
Tuberculosis and HAART



Havlir, NEJM, 2011

Tuberculosis and HAART: Camelia

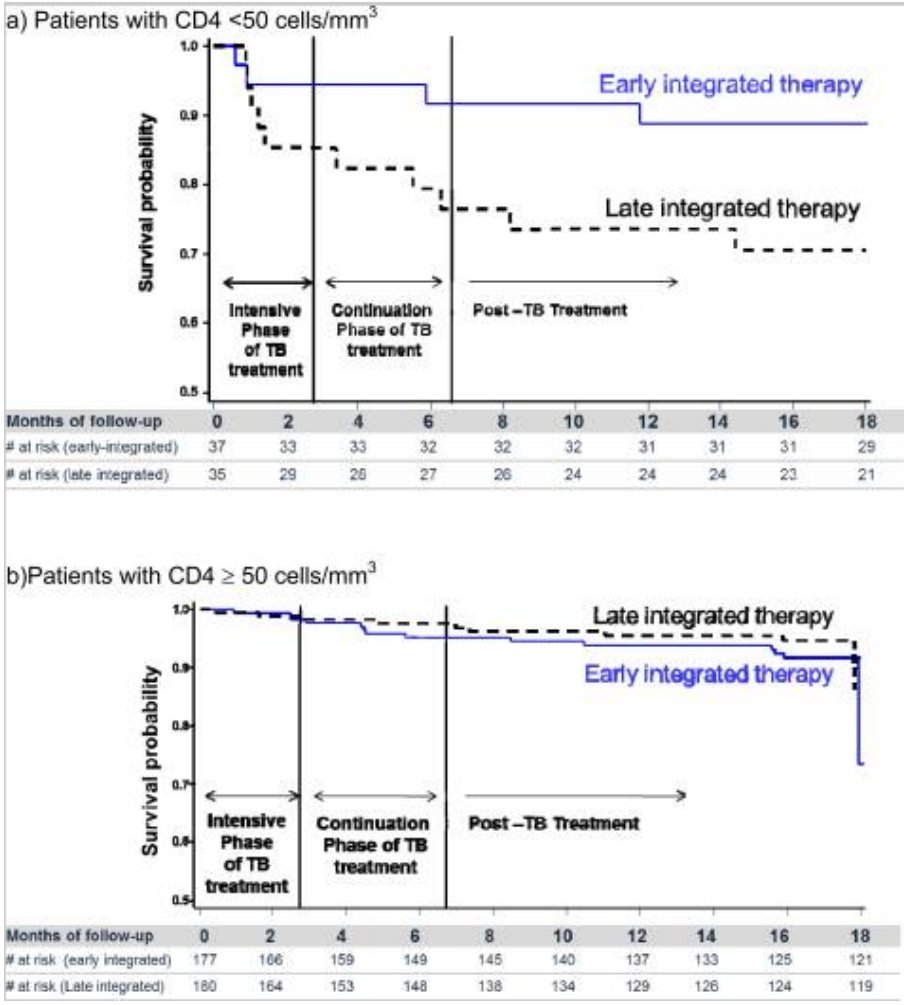
Kaplan–Meier Survival Estimates According to Study Group.



No. at Risk					
Earlier-ART group	332	278	192	101	4
Later-ART group	329	256	168	87	3
No. of Deaths					
Earlier-ART group	0	46	56	57	59
Later-ART group	0	63	85	90	90

Blanc, NEJM, 2011

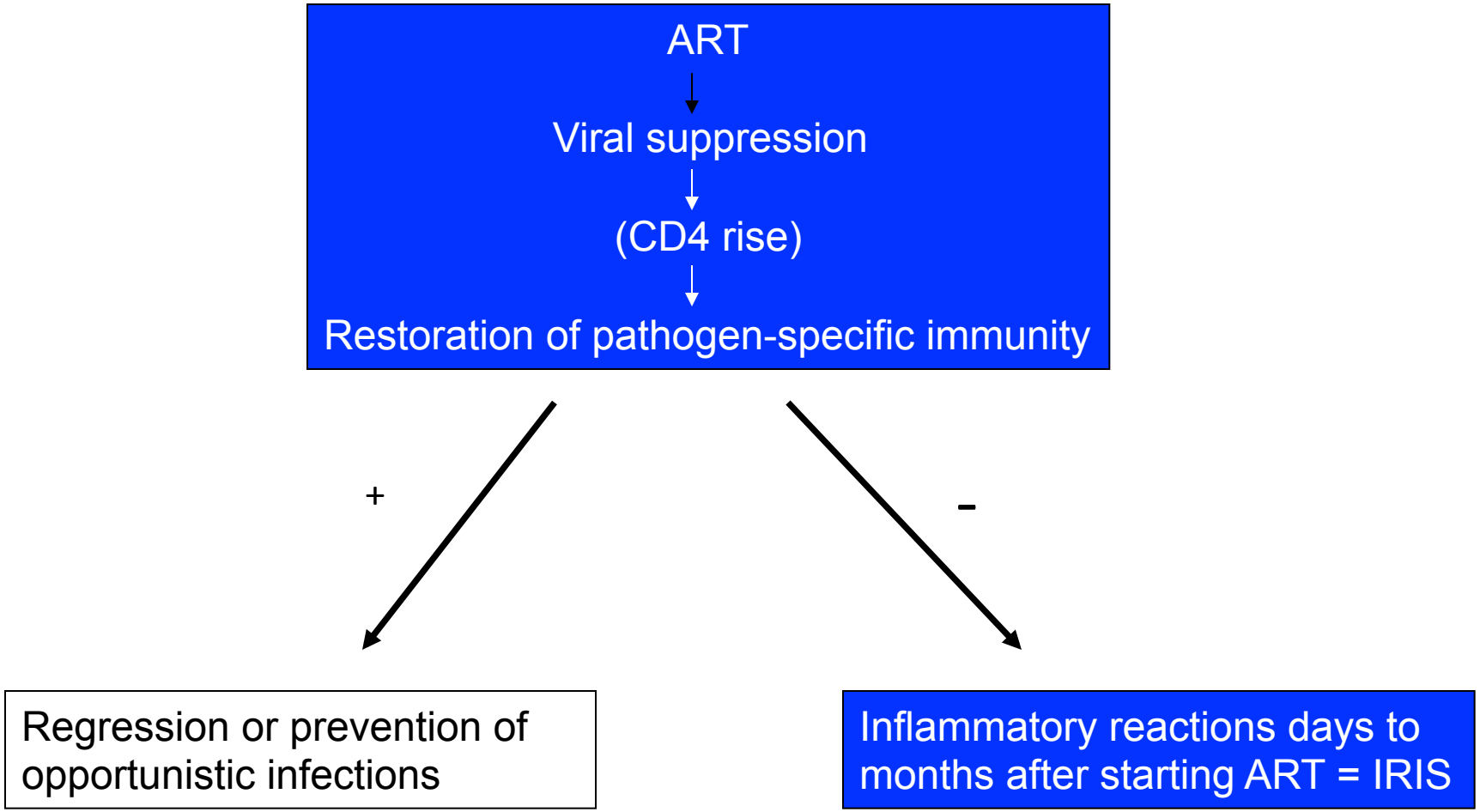
Tuberculosis and HAART



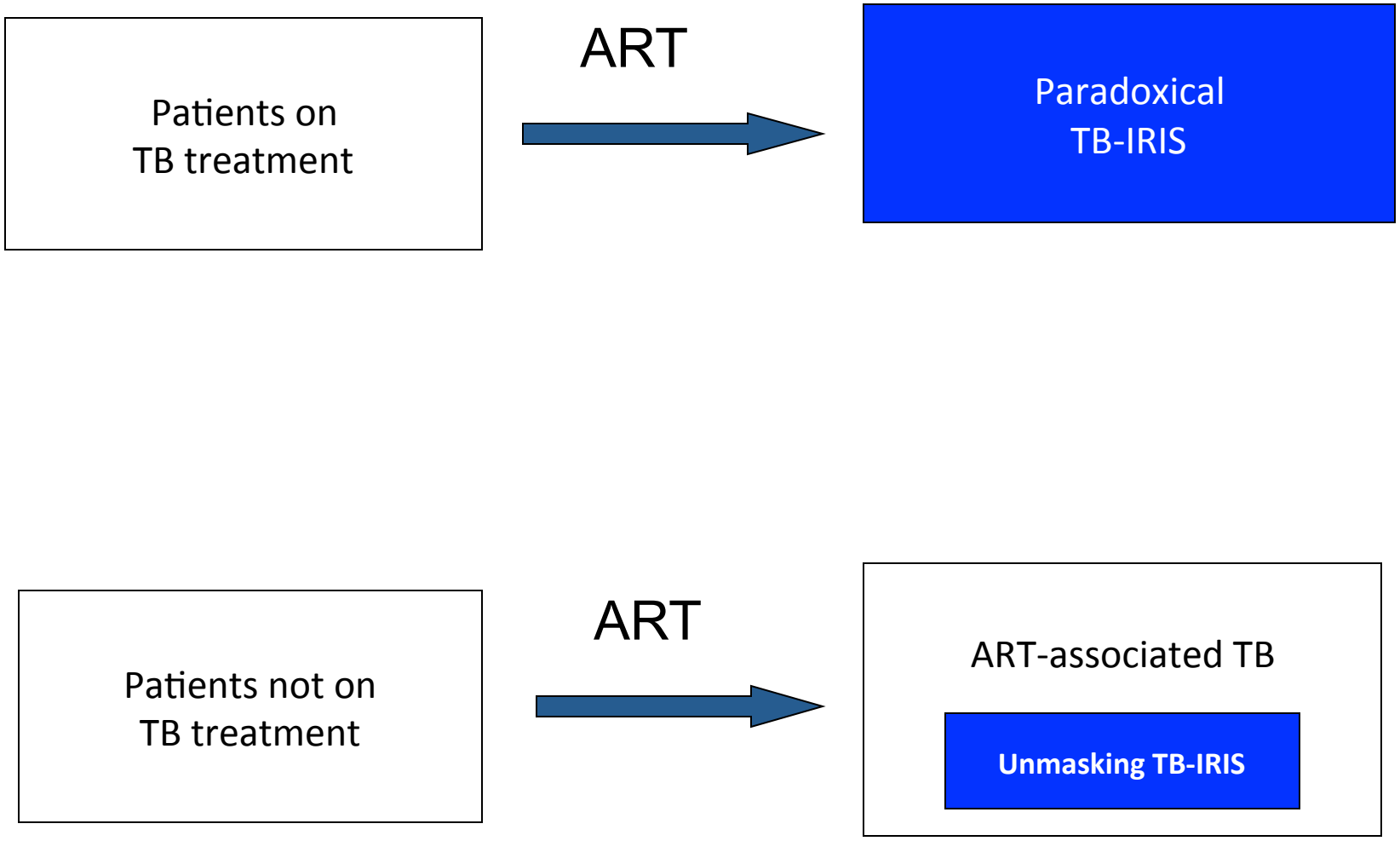
Abdoul Karim, NEJM, 2011

Tuberculosis and HAART

Study	Patients	ARV timing	IRIS	Outcome
Blanc	N = 661 Median CD4 = 25	2 vs 8 wks	HR 2.51 for early ARV	HR for death 0.62 (for early ARV)
Havlir	N = 809 Median CD4 = 77	Median of 10 vs 70 days	Early 11% Late 5%	Death rate: overall 12.9% vs 16.1% (NS) CD4<50: 15.5% vs 26.6% (p=0.02)
Abdool Karim	N = 642 Median CD4 = 150	Median of 21 vs 97 days	HR of 2.62 for early ARV	AIDS or death: no difference overall CD4<50: 8.5 vs 26.3 per 100 py (p=0.06)



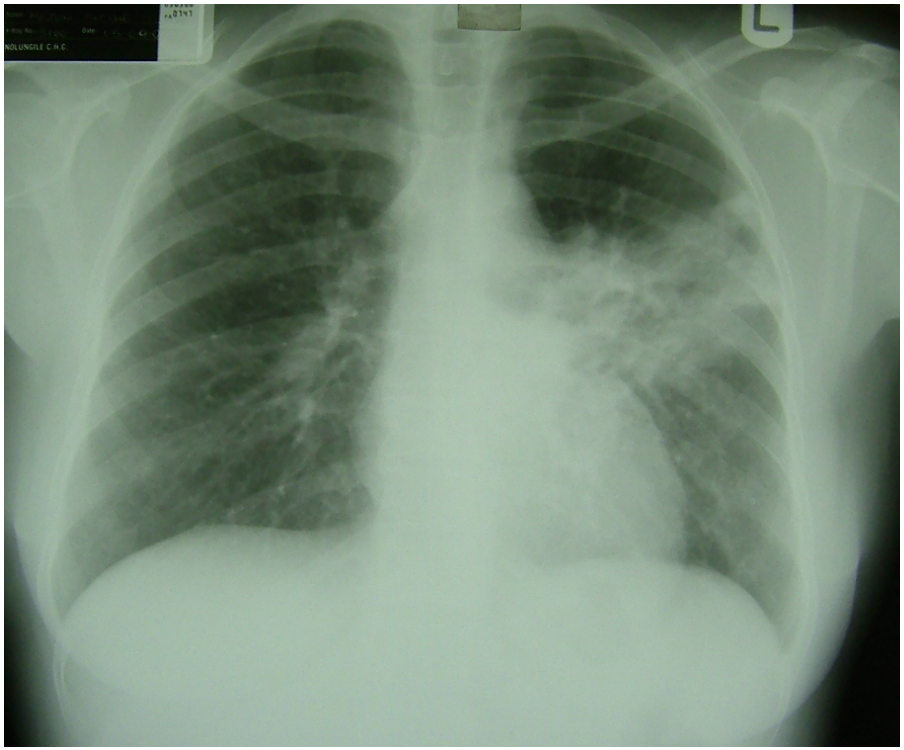
IRIS = Immune Reconstitution Inflammatory Syndrome
IRD = Immune Restoration Disease

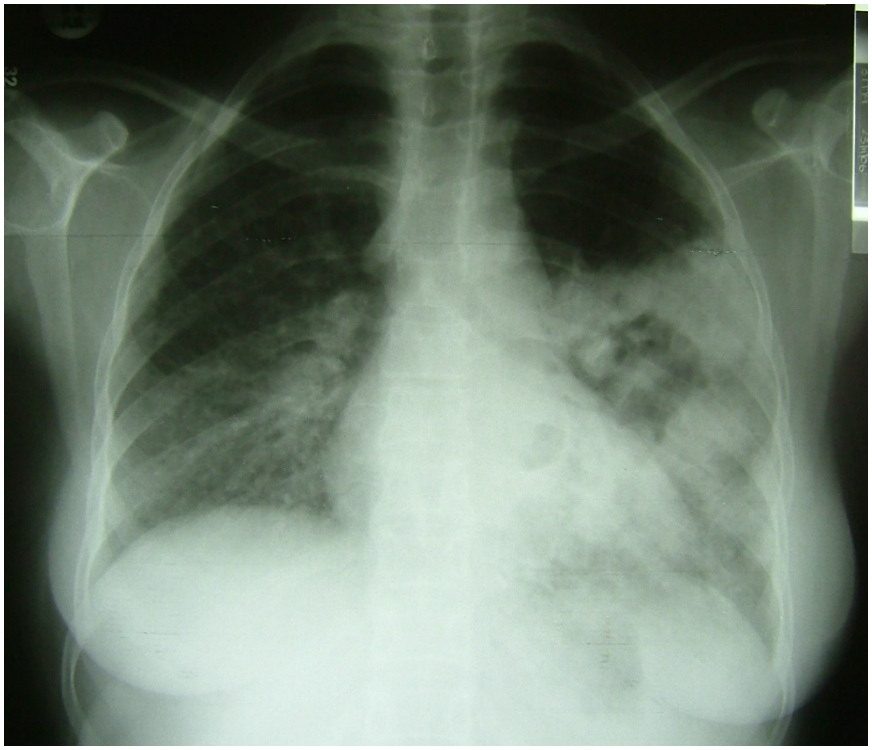

Patients on
TB treatment
ART
Paradoxical
TB-IRIS
Patients not on
TB treatment
ART
ART-associated TB
Unmasking TB-IRIS

Paradoxical TB-IRIS characteristics

- Incidence 8 – 54% (15.7% in meta-analysis)
- Onset of symptoms: Median 14 days from ART start
- Focal and systemic inflammatory features
  - Fever, tachycardia, weight loss
- Hospitalisation in up to 48%
- Median duration 2-3 months
- Mortality infrequent
  - Meta-analysis 3.2% (substantially higher if CNS IRIS)

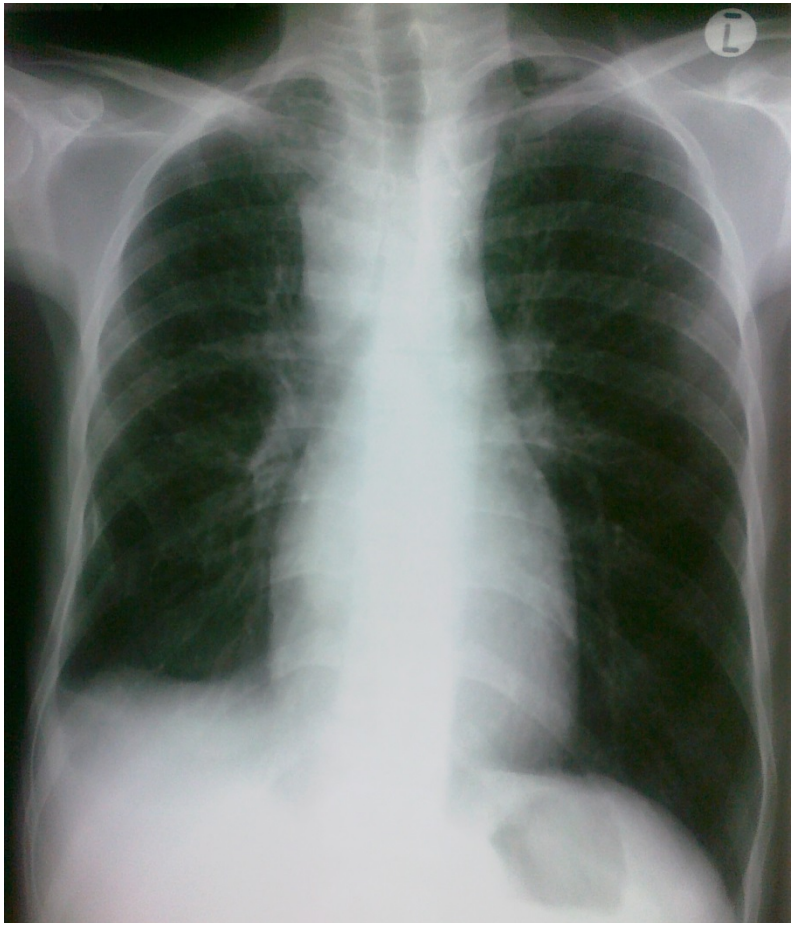
Meintjes Lancet Infect Dis 2008;8:516, Muller Lancet Infect Dis 2010;10:251, Agarwal AIDS Res Ther 2012;9:17, Meintjes Clin Infect Dis 2009;48:667, Burman IJTLD 2007;11:1282



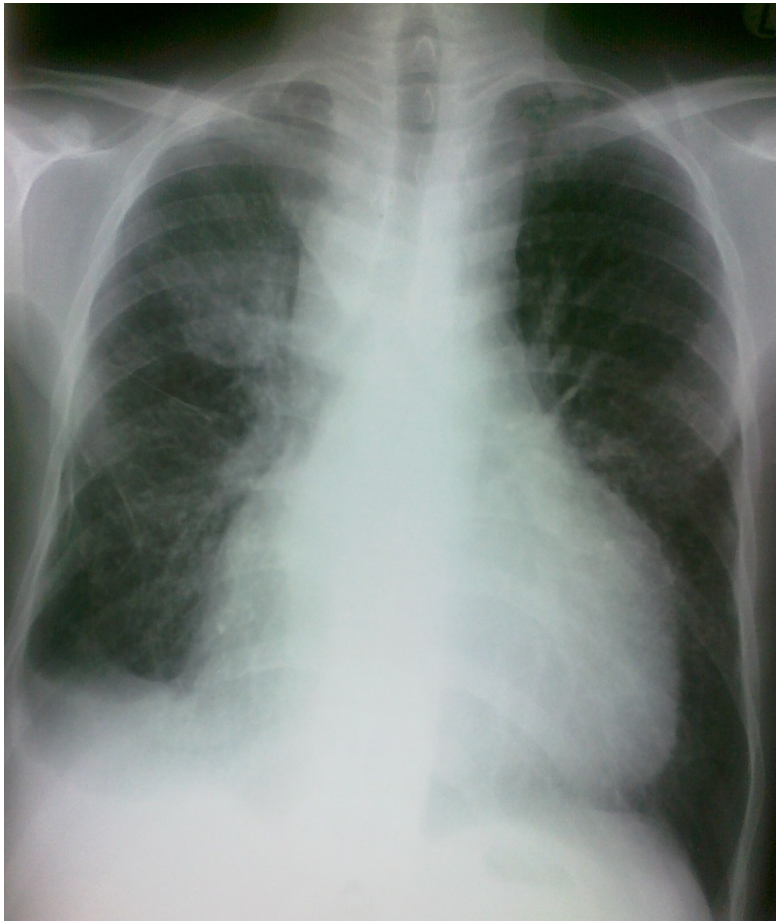


Worsening pulmonary infiltrate and cavitation due to TB-IRIS

Pericardial tamponade due to paradoxical TB-IRIS



On TB treatment prior to ART



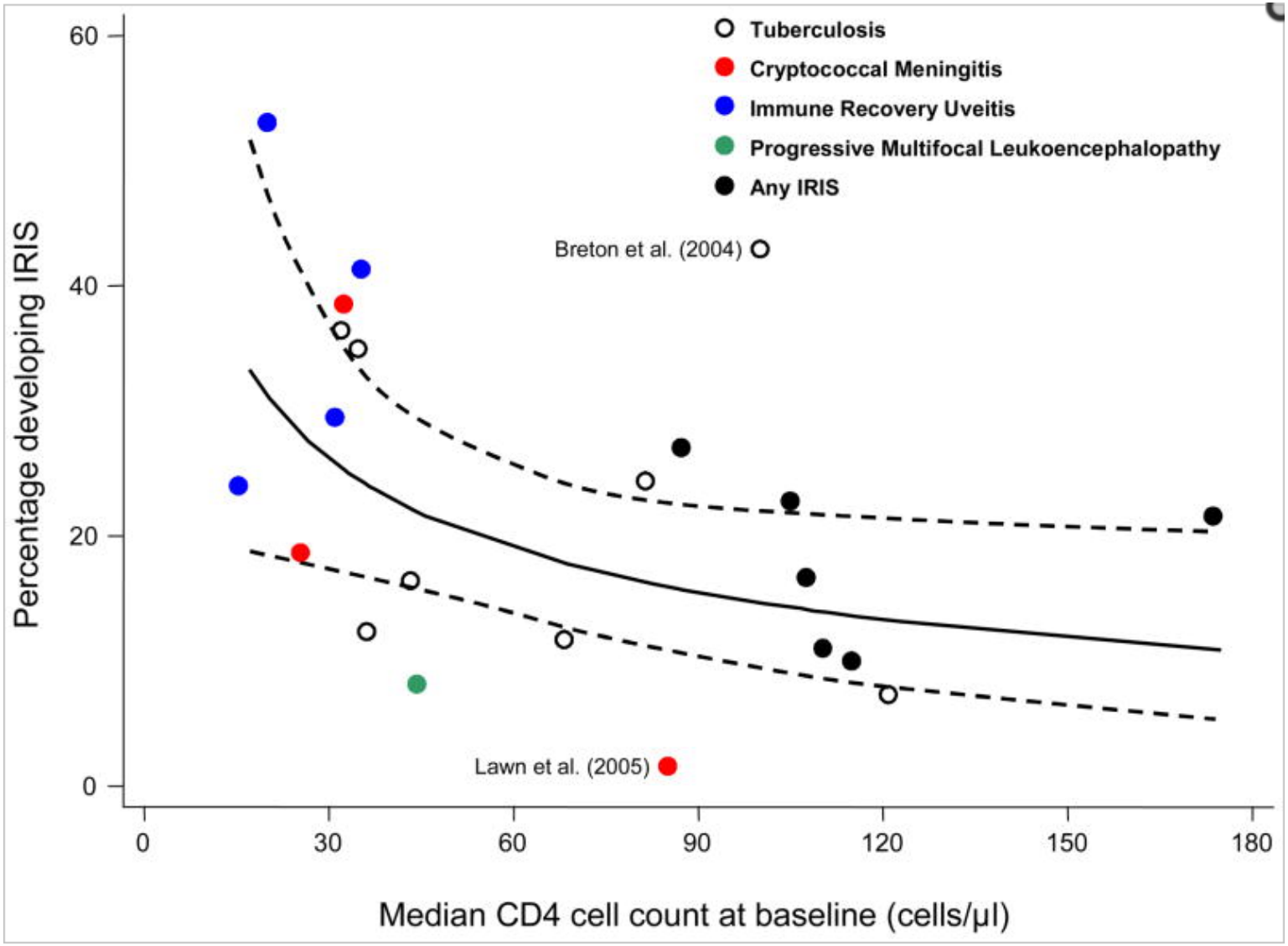
3 weeks on ART
(1 litre drained at pericardiocentesis)

Major TB-IRIS risk factors

- Low CD4 count
- Short interval between TB treatment and ART
- Disseminated TB

Lawn AIDS 2007;21:335
Meintjes Lancet Infect Dis 2008;8:516
Burman IJTLD 2007;11:1282

Immune Reconstitution Inflammatory Syndrome



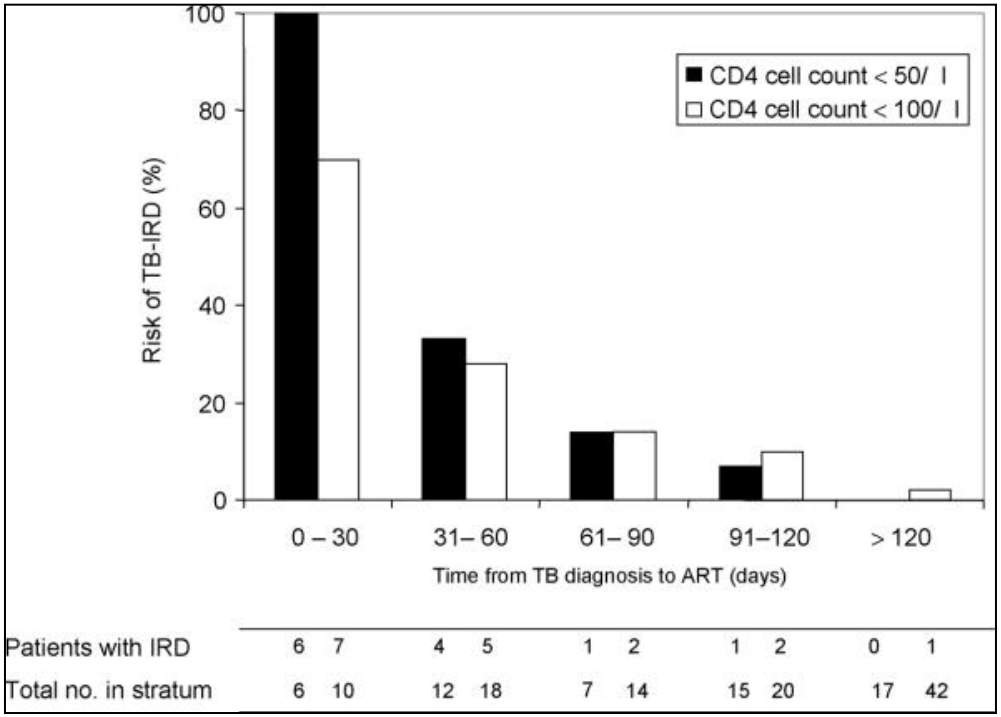
Müller, Lancet ID, 2010

IRIS: Timing

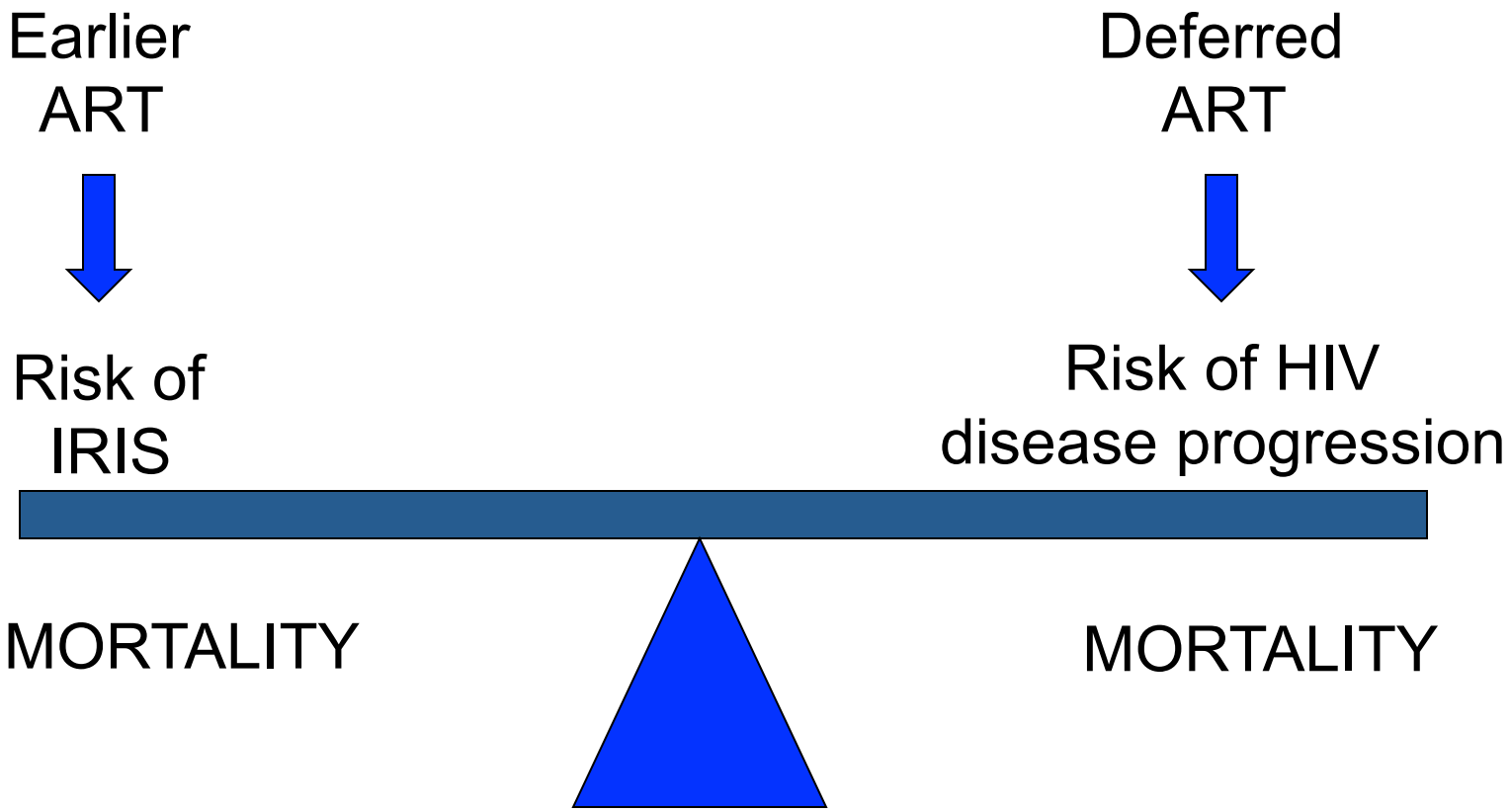
TB-associated IRIS in South Africa

- 160 patients receiving treatment for TB at the time HAART was initiated
- Median CD4 68
- IRIS in 12% overall, 32% in those who started HAART wihtin 2 months of TB treatment

Graph showing the risk of TB-IRD among patients stratified by baseline CD4 cell count and by the interval between TB diagnosis and initiation of ART (days)



Lawn, AIDS, 2007

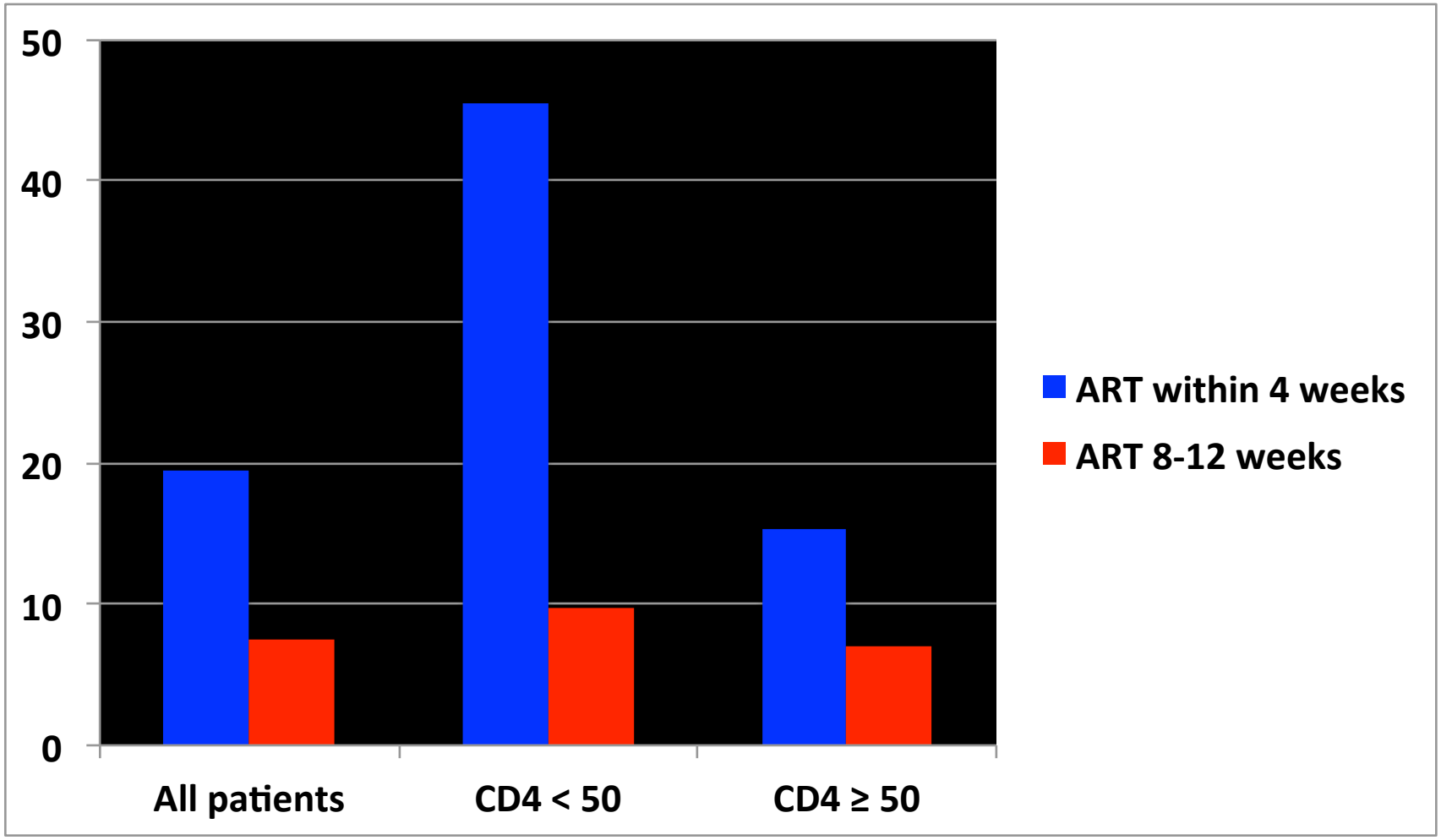


When to start ART after recent diagnosis of TB?

3 recent large RCTs (SAPIT, STRIDE, CAMELIA)

SAPiT IRIS incidence

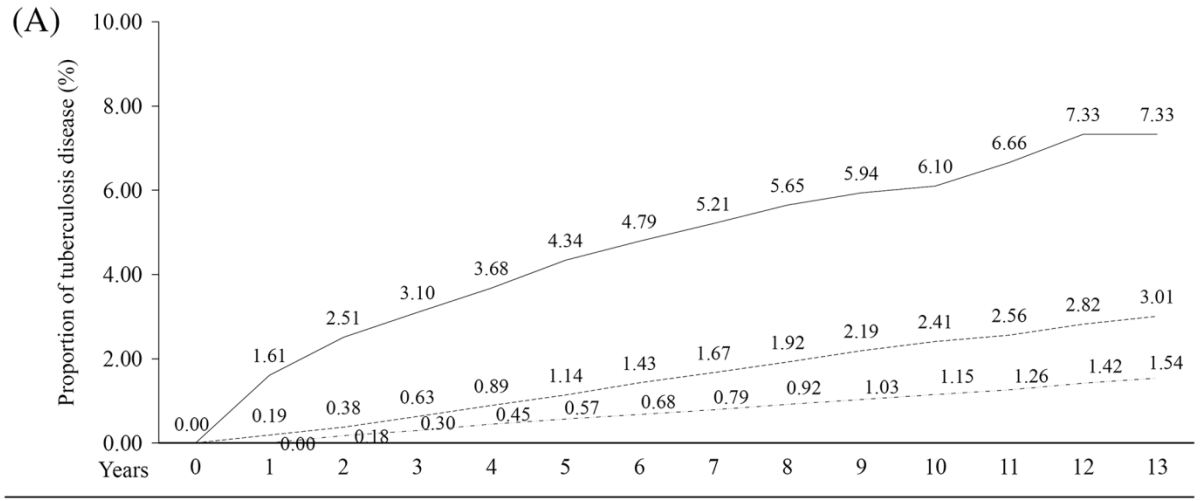
(IRIS cases/100 person years)



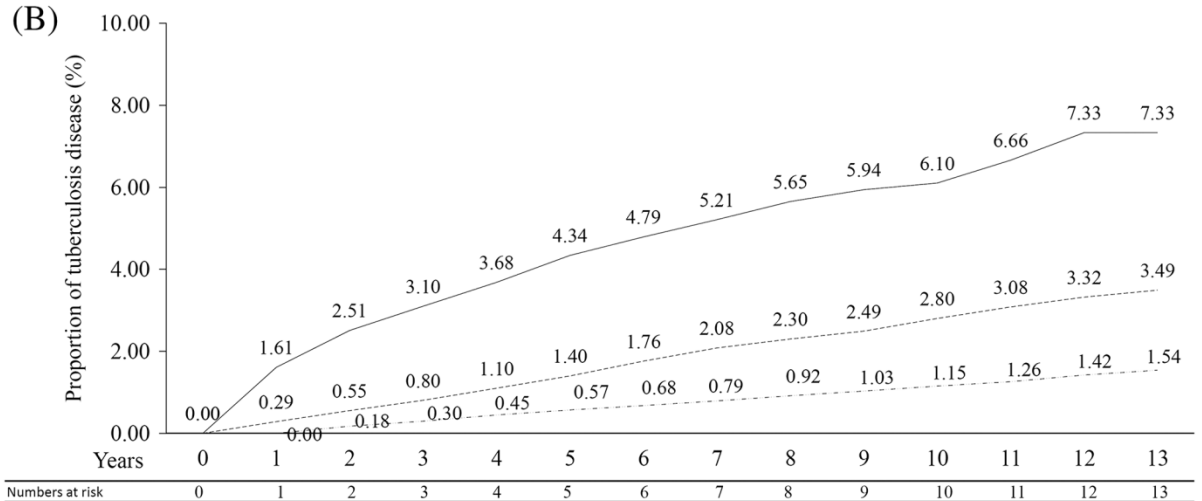
Treatment of TB in persons with DM

- Ensure that TB treatment is appropriately adjusted in persons with DM
  - Check creatinine for diabetic nephropathy
  - May need to adjust frequency of PZA and EMB administration
  - Give B6 to prevent INH induced peripheral neuropathy

Metformin and Risk of Active Tuberculosis in Pts with T2DM



Numbers at risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Compared group	49028	49028	48942	48883	48810	48749	48697	48641	48579	48523	48464	48410	48334	48271
Without metformin use	5026	4945	4414	3892	3409	2968	2516	2096	1769	1407	1041	624	205	0
With metformin use	44002	42034	37589	33218	29124	25441	22066	18704	15878	13167	10699	8590	6467	4371



Numbers at risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Compared group	49028	49028	48942	48883	48810	48749	48697	48641	48579	48523	48464	48410	48334	48271
Without metformin use	5026	4945	4414	3892	3409	2968	2516	2096	1769	1407	1041	624	205	0
With metformin use	5026	4761	4227	3654	3118	2681	2293	1943	1657	1403	1147	923	673	478

(– – –) Compared group,
(—) without metformin use,
(– – –) with metformin use.

Lin SH, Respirology, 2018

HIV and TB: Key Points

- TB is the most common manifestation of HIV infection in high TB prevalence areas, consider in HIV positive immigrants
- HIV is the strongest known risk factor for progression from LTBI to TB disease
- Presentation of TB is atypical and TB is more severe in advanced HIV infection
- All HIV+ should be screened for LTBI
- All HIV+ with TB should be started on ART; management is complicated by drug interactions and by IRIS

Tuberculosis and Diabetes: Key Points

- People with diabetes have a 2-3 times higher risk of developing TB disease compared to people without diabetes.
- Diabetes must be screened in every subject with TB
- People with TB and coexisting diabetes have 4 times higher risk of death during TB treatment and higher risk of TB relapse after treatment.
- People with TB and coexisting diabetes are more likely to be sputum positive, to have lung cavitations and take longer to become sputum negative.
- Diabetes may adversely affect TB treatment outcomes by delaying the response time to treatment.
- Diabetes may interfere with the activity of TB medications
- Toxicity of TB medications should be carefully monitored