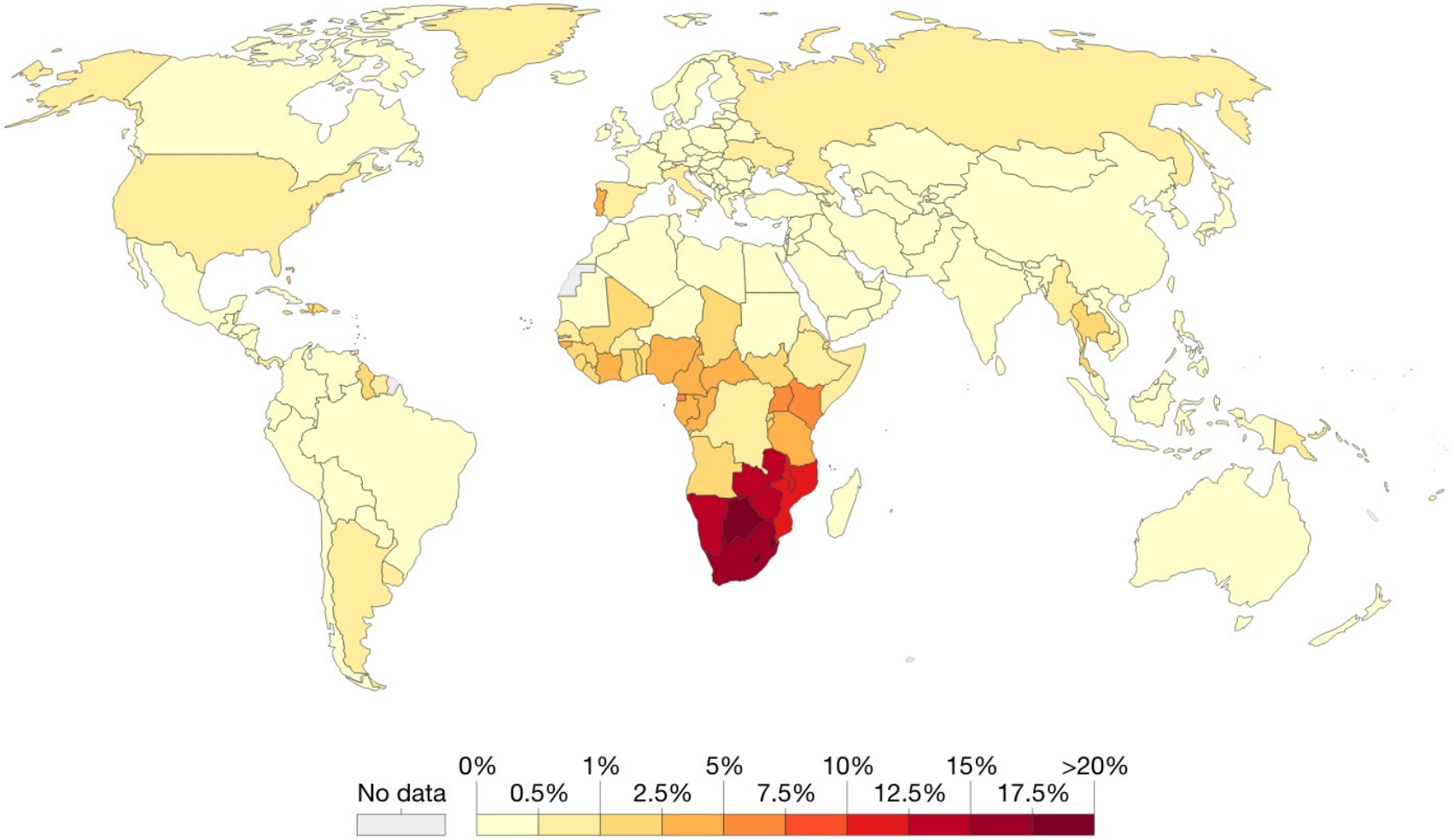
HIV and TB update

HIV/TB BURDEN

Share of the population infected with HIV, 2016

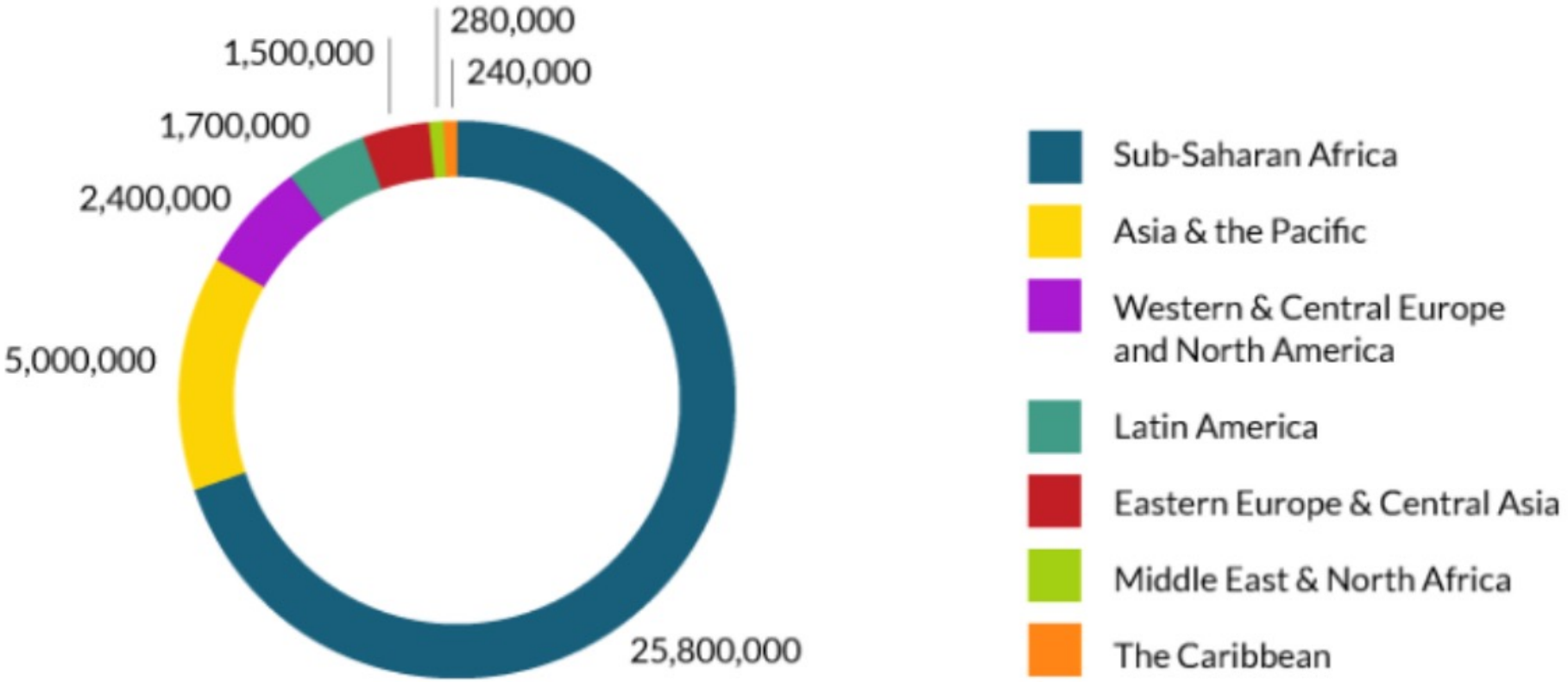
Share of the population aged between 15 and 49 years old infected with HIV/AIDS. This is based on estimates from the IHME, Global Burden of Disease Study.

Our World in Data



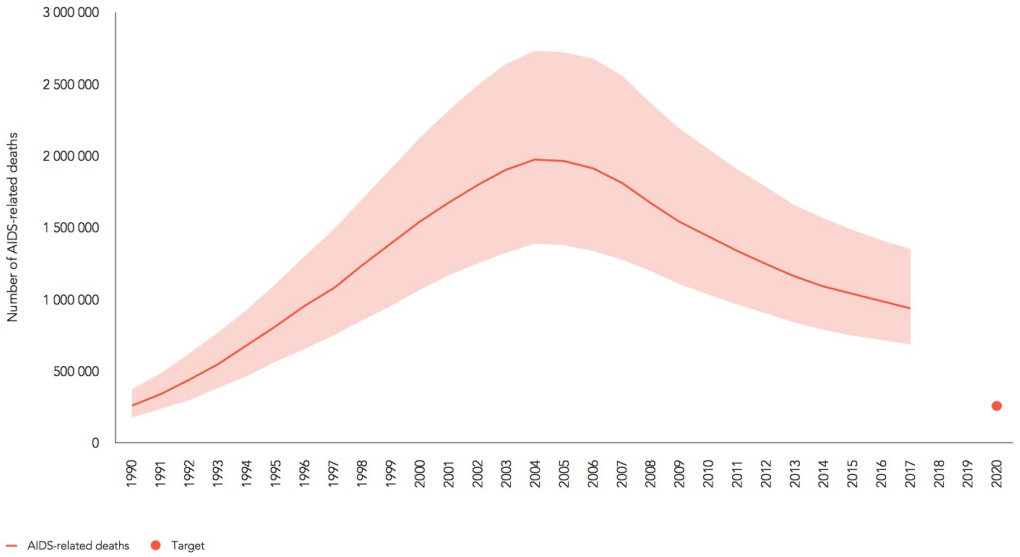
Source: IHME, Global Burden of Disease

HIV Burden by Region



Approaching a 2020 milestone

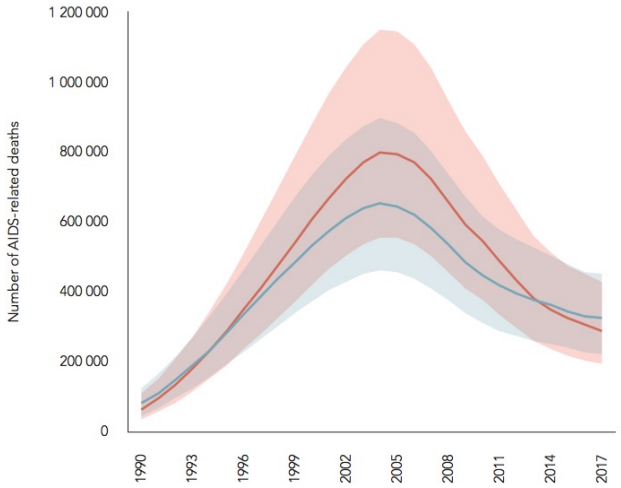
Number of AIDS-related deaths, global, 1990–2017 and 2020 target



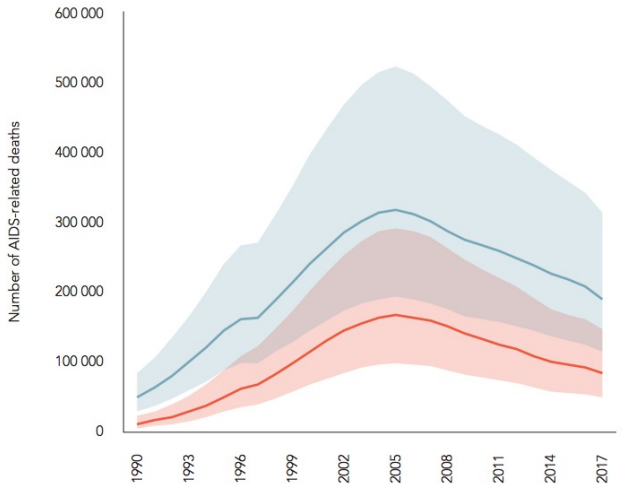
Source: UNAIDS 2018 estimates.

Steep decline in deaths in sub-Saharan Africa

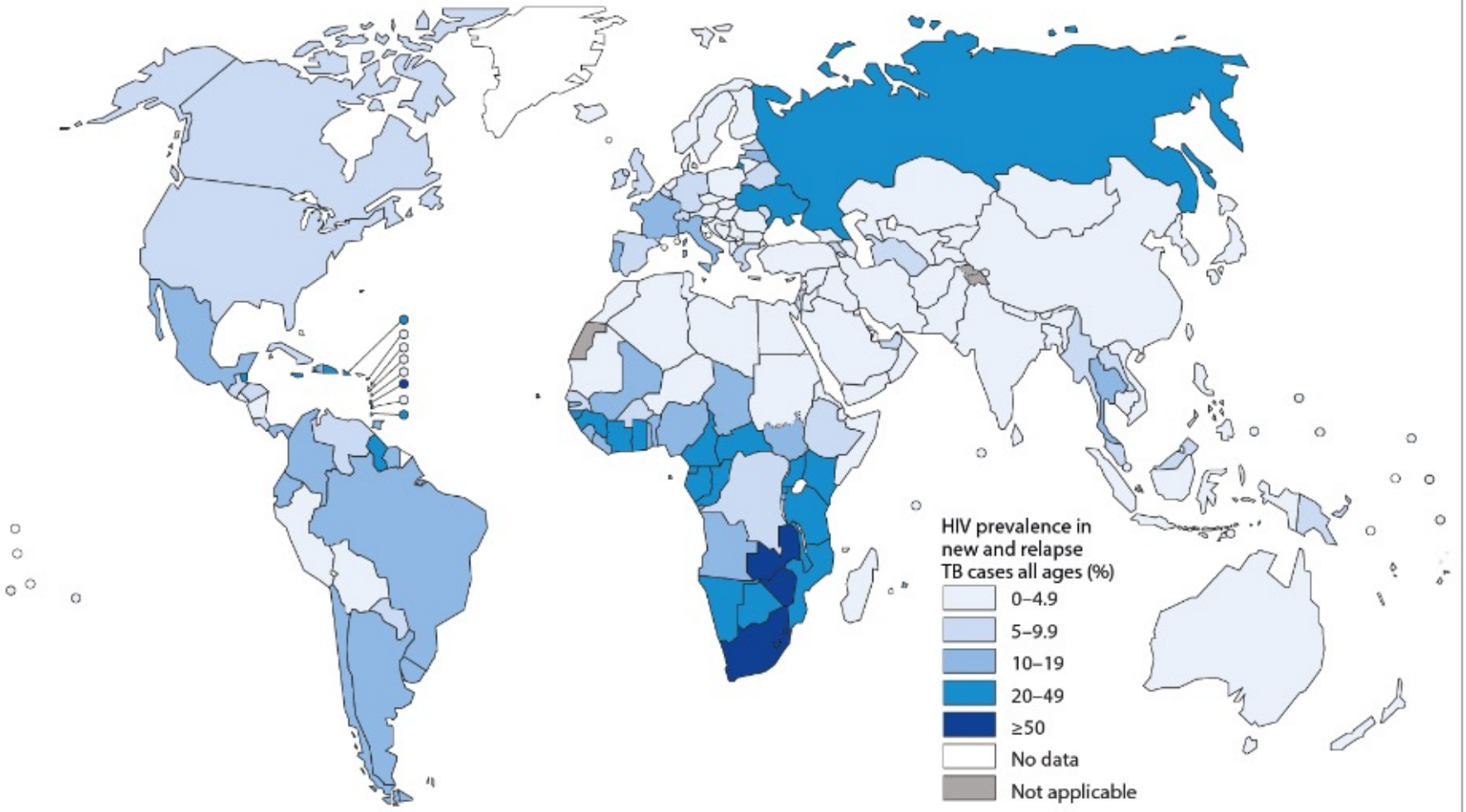
Number of AIDS-related deaths, by sex, sub-Saharan Africa, 1990–2017



Number of AIDS-related deaths, by sex, regions outside sub-Saharan Africa, 1990–2017



Estimated HIV prevalence in new and relapse TB cases, 2017

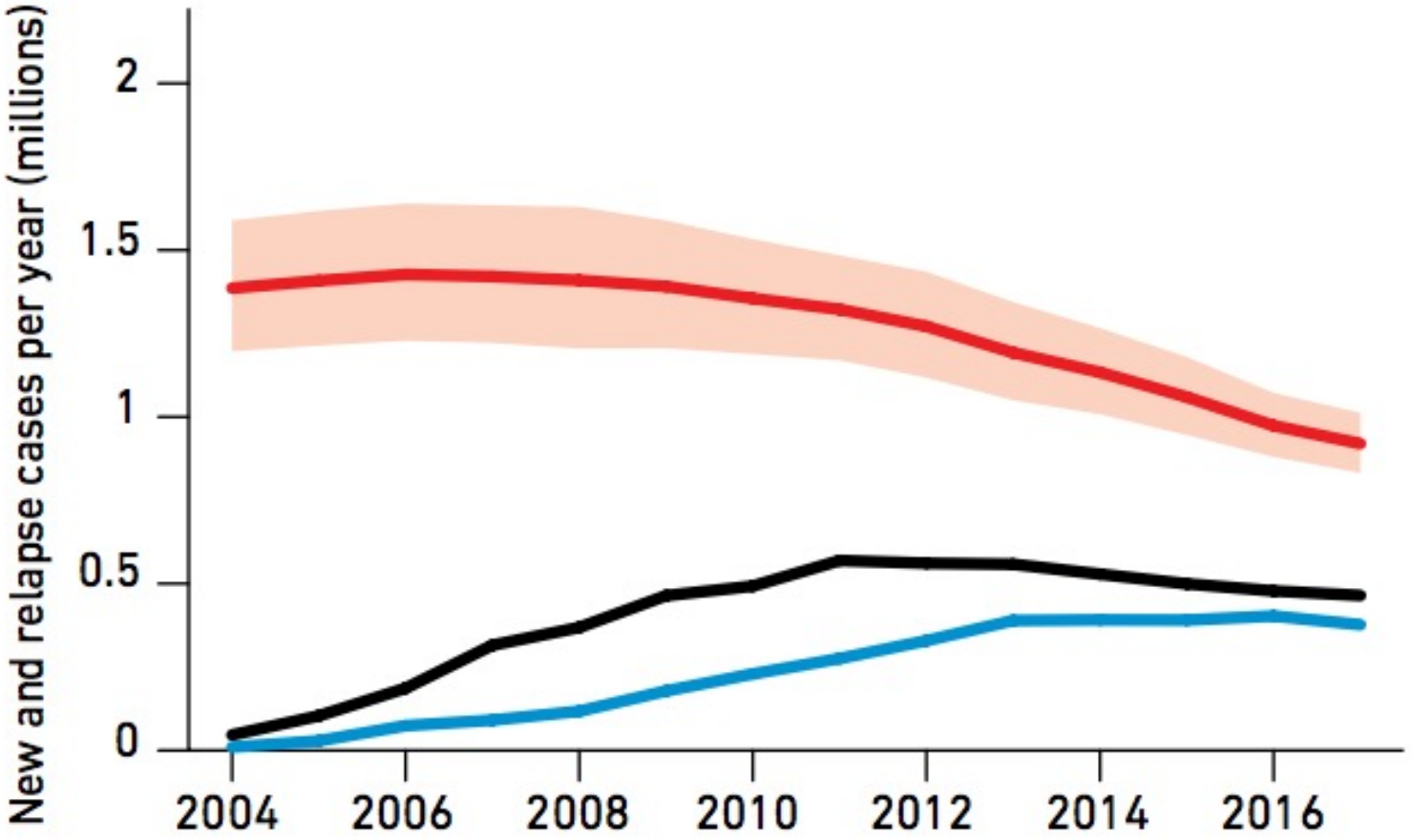


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

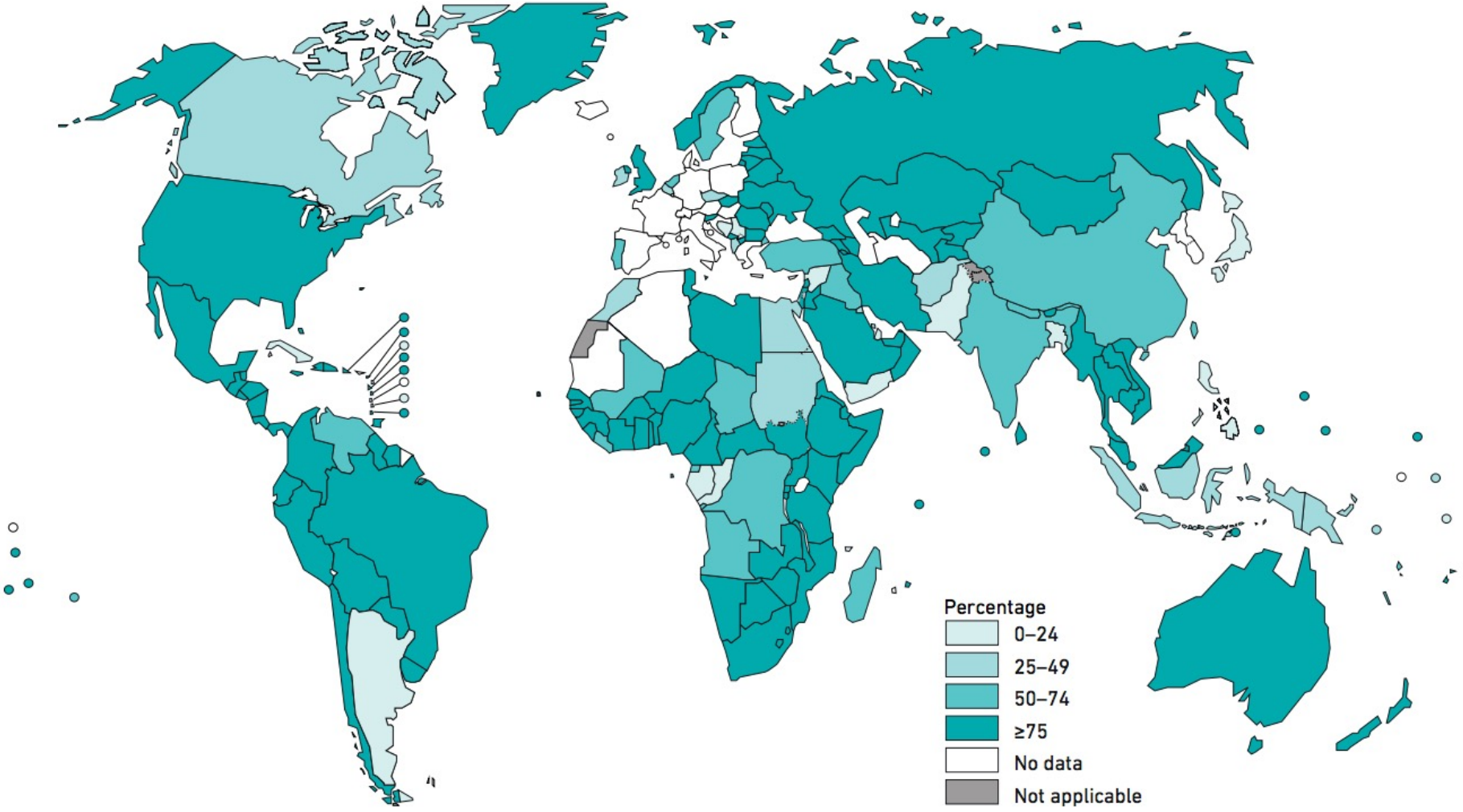
Data Source: *Global Tuberculosis Report 2018*. WHO, 2018.

World Health Organization

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), 2004–2017. Shaded areas represent uncertainty bands.



Percentage of new and relapse TB cases with documented HIV status, 2017[a]

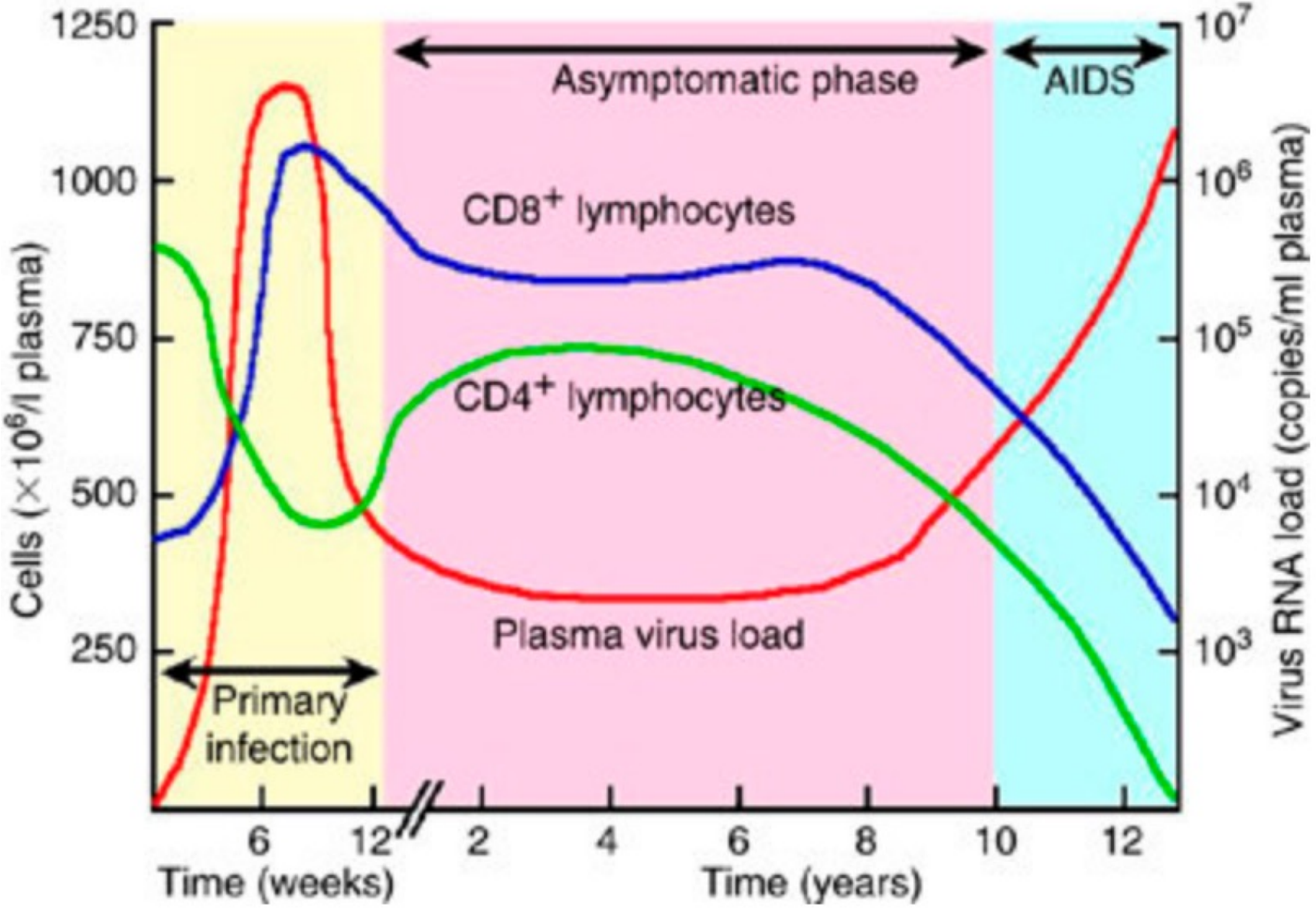


[a] 2016 data were used for 15 countries.

Some TB/HIV Factoids

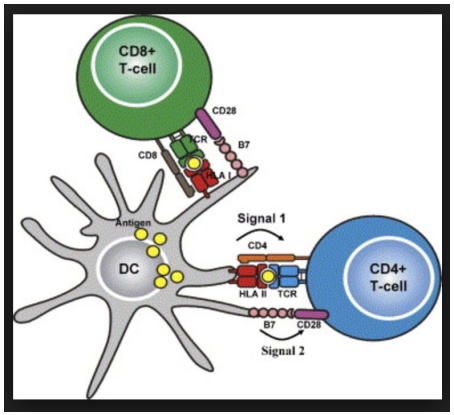
- Top cause of death in PLHIV= TB
- 13-14% TB cases occur in HIV +
- 20X increased risk of TB in HIV
  - Increases risk of reactivation
  - Increases risk of early progression
  - Probably does not alter risk of infection

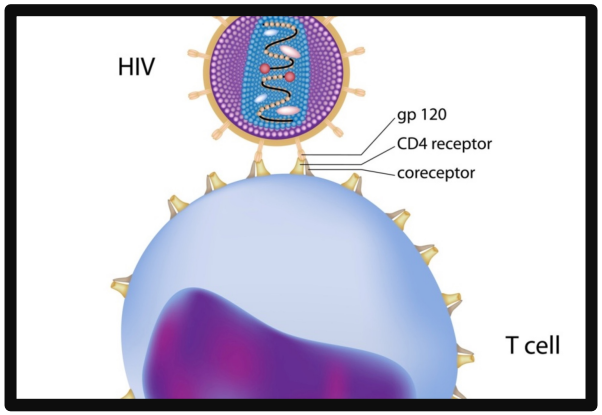
Pathophysiology of Co-infection


1250
1000
750
500
250
Cells (×10⁶/l plasma)
10⁷
10⁶
10⁵
10⁴
10³
Virus RNA load (copies/ml plasma)
Asymptomatic phase
AIDS
CD8⁺ lymphocytes
CD4⁺ lymphocytes
Plasma virus load
Primary infection
6
12
2
4
6
8
10
12
Time (weeks)
Time (years)

What is Cd4

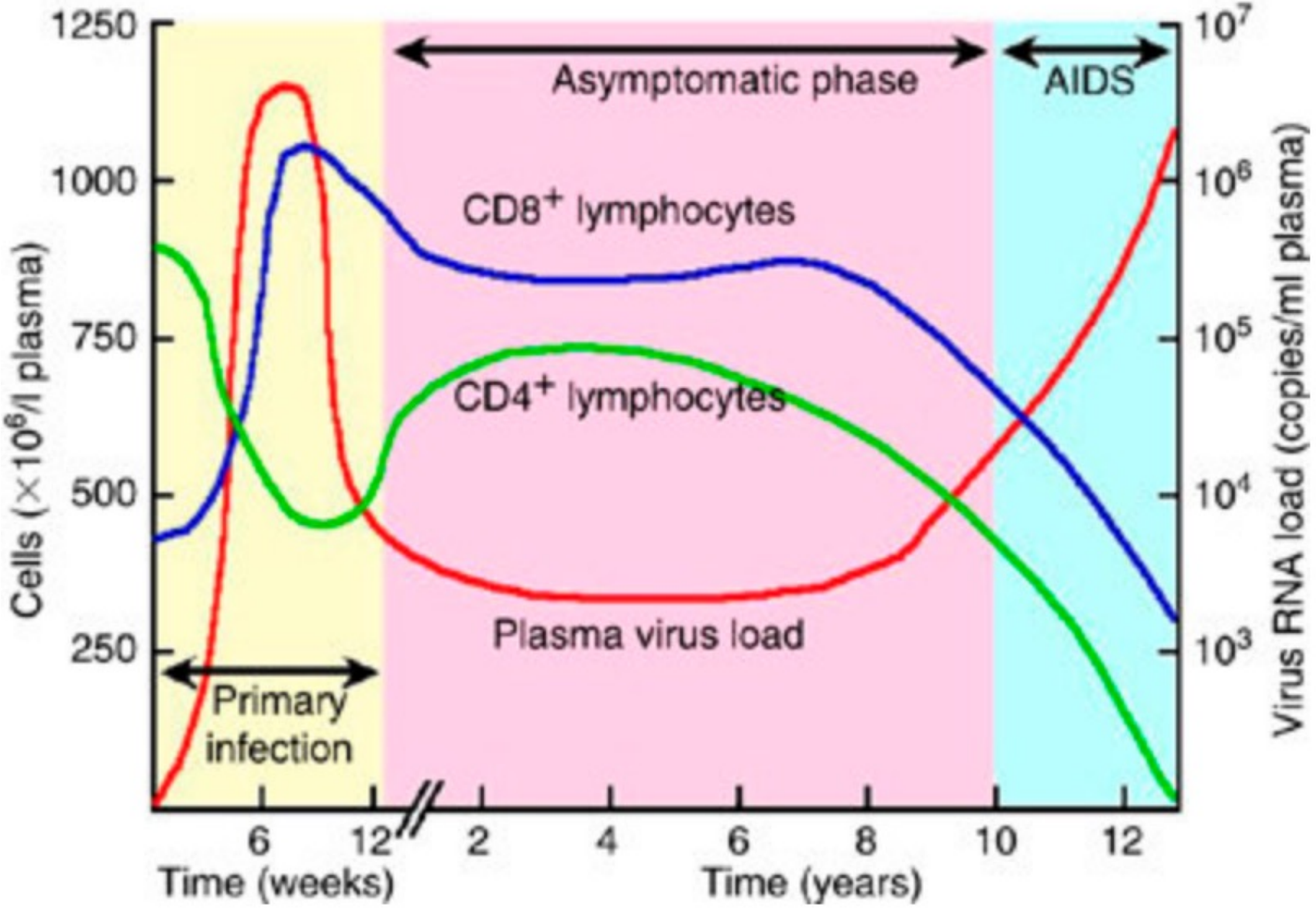
- CD4 (cluster of differentiation) refers to a glycoprotein found in range of immune cells but especially T helper cells.
- T helper cells “help” by producing cytokines that signal other immune cells to kill (Cd8 cells).





Types of T helper cells

- Th1 (anti-bacterial)
- Th2 (anti-helminth)
- Th17 (pro-inflammatory, auto-immune disease)
- Tfh
- T-regs (anti-inflammatory)
- (Th3, Th9)


1250
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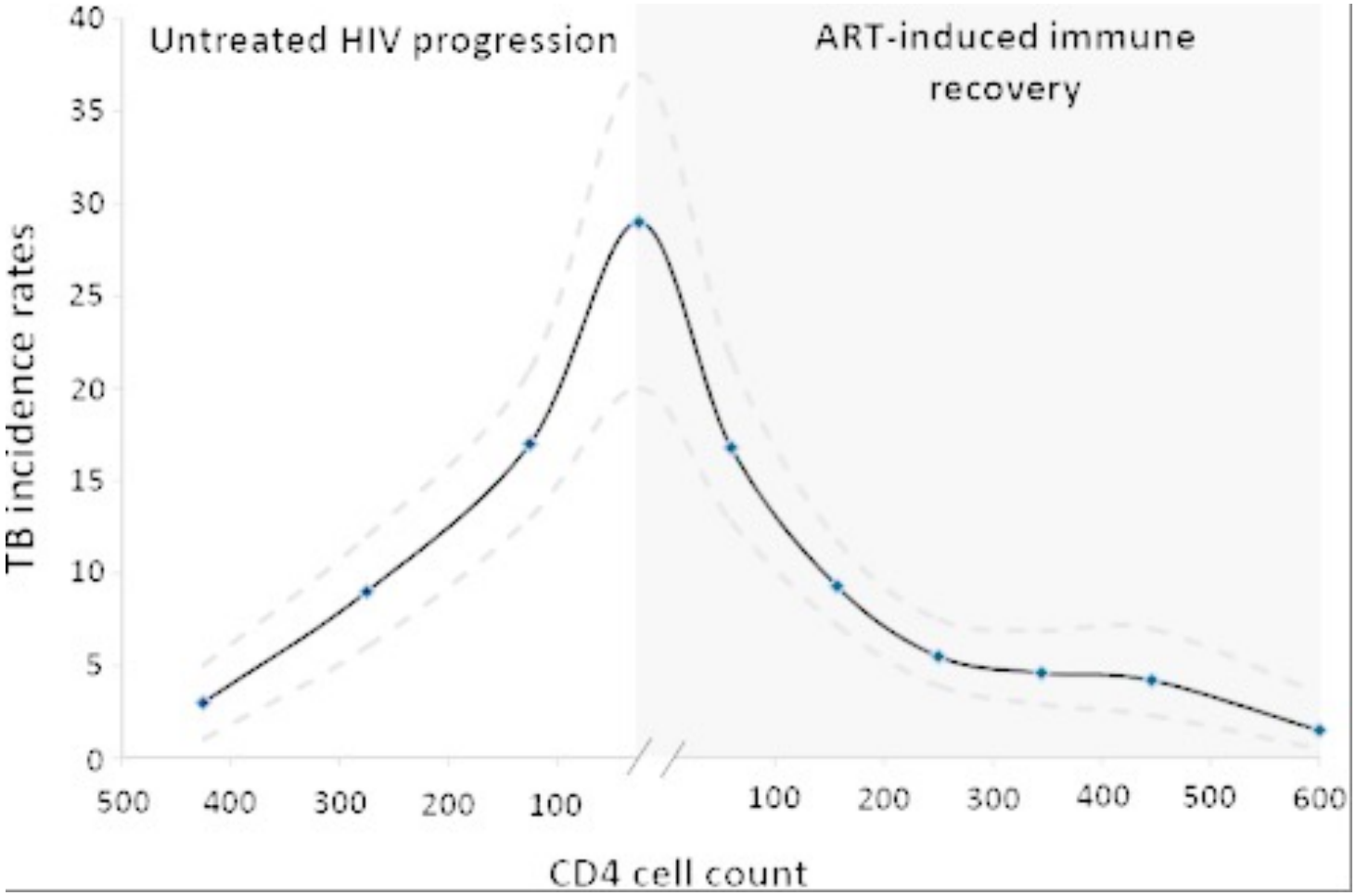
CD4⁺ lymphocytes
Plasma virus load
Primary infection
6
12
2
4
6
8
10
12
Time (weeks)
Time (years)

Risk of TB disease increases as CD4 declines.



BUT

How Soon after Infection with HIV Does the Risk of Tuberculosis Start to Increase? A Retrospective Cohort Study in South African Gold Miners

Pam Sonnenberg,[1] Judith R. Glynn,[1] Katherine Fielding,[1] Jill Murray,[2] Peter Godfrey-Faussett,[1] and Stuart Shearer[3]

Table 2. Incidence of tuberculosis (TB), by time since HIV seroconversion.

Category	Pyar	No. of TB cases	Incidence, cases/100 pyar (95% CI)	Rate Ratio (95% CI)			
				Unadjusted		Adjusted[a]	
				Value	P_{trend}	Value	P_{trend}
HIV-negative miners	36,020	289	0.80 (0.71–0.90)	1		1	
HIV-positive miners, time since HIV seroconversion[b]					.001		.09
<1 year	1849	30	1.62 (1.13 –2.32)	2.02 (1.39–2.94)		2.11 (1.45–3.09)	
1–1.9 years	1449	29	2.00 (1.39–2.88)	2.50 (1.70–3.66)		2.25 (1.53–3.31)	
2–2.9 years	1024	37	3.61 (2.62–4.99)	4.50 (3.20–6.34)		3.47 (2.44–4.93)	
3–3.9 years	692	24	3.47 (2.32–5.17)	4.32 (2.85–6.55)		2.94 (1.92–4.51)	
4–7 years	567	18	3.17 (2.00–5.04)	3.96 (2.46–6.37)		2.55 (1.57–4.16)	

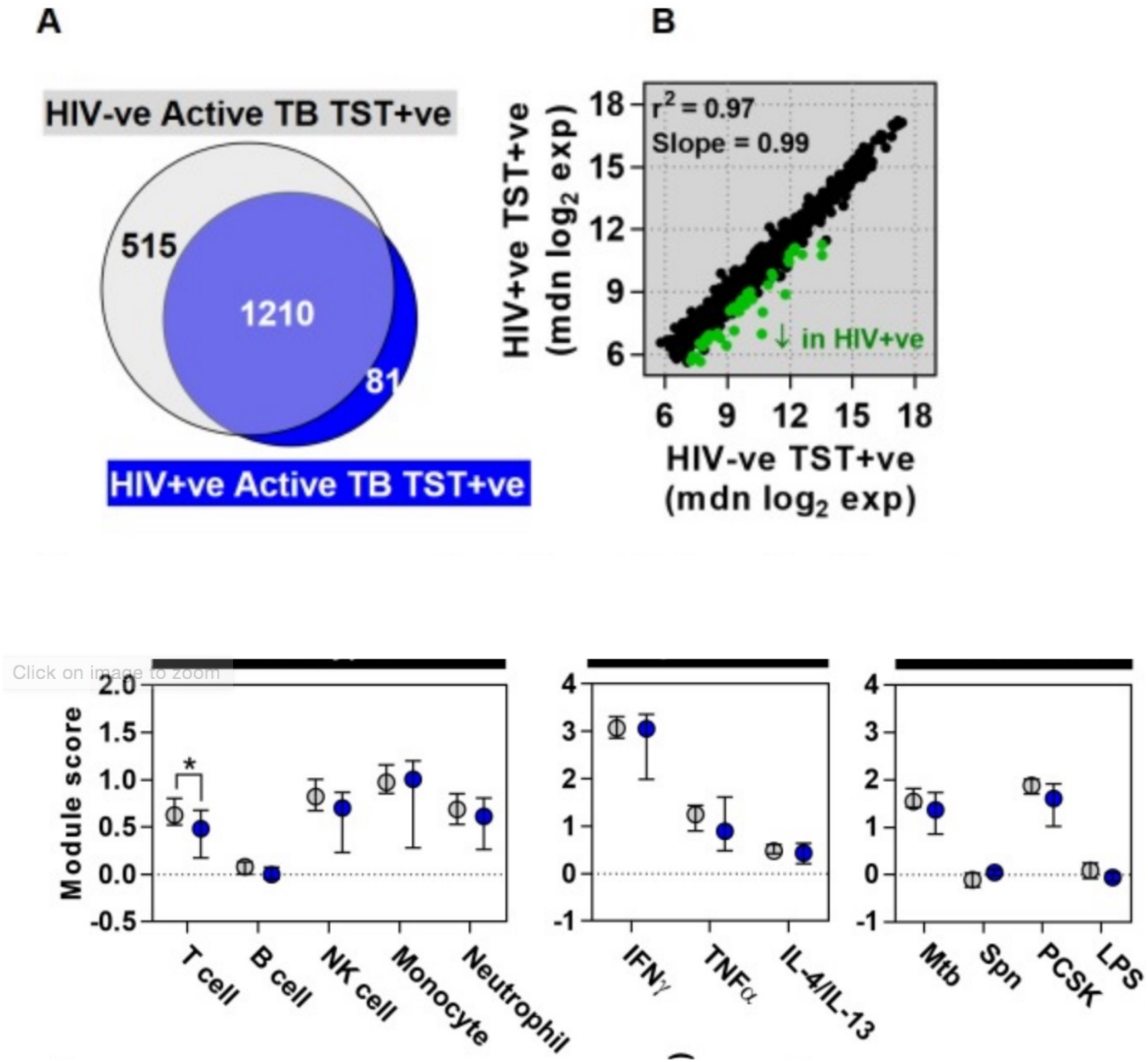
The Journal of Infectious Diseases 2005:191:150–8

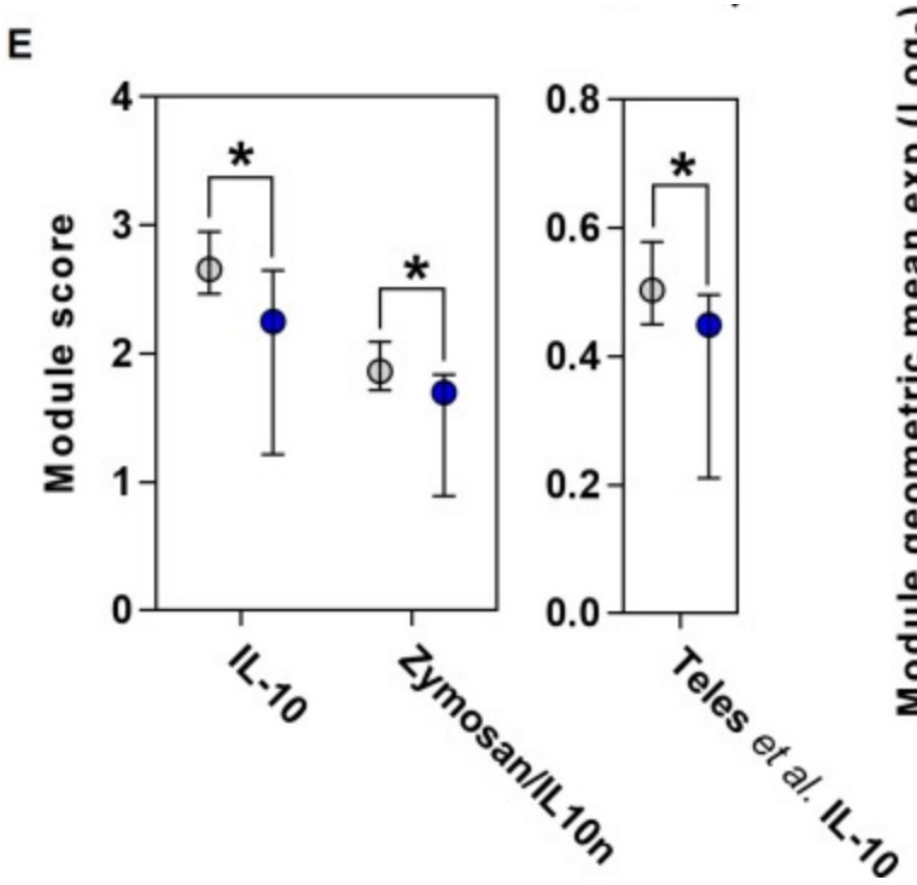
PLoS Pathog. 2016 Mar; 12(3): e1005469.
Published online 2016 Mar 17. doi: 10.1371/journal.ppat.1005469
PMCID: PMC4795555
PMID: 26986567

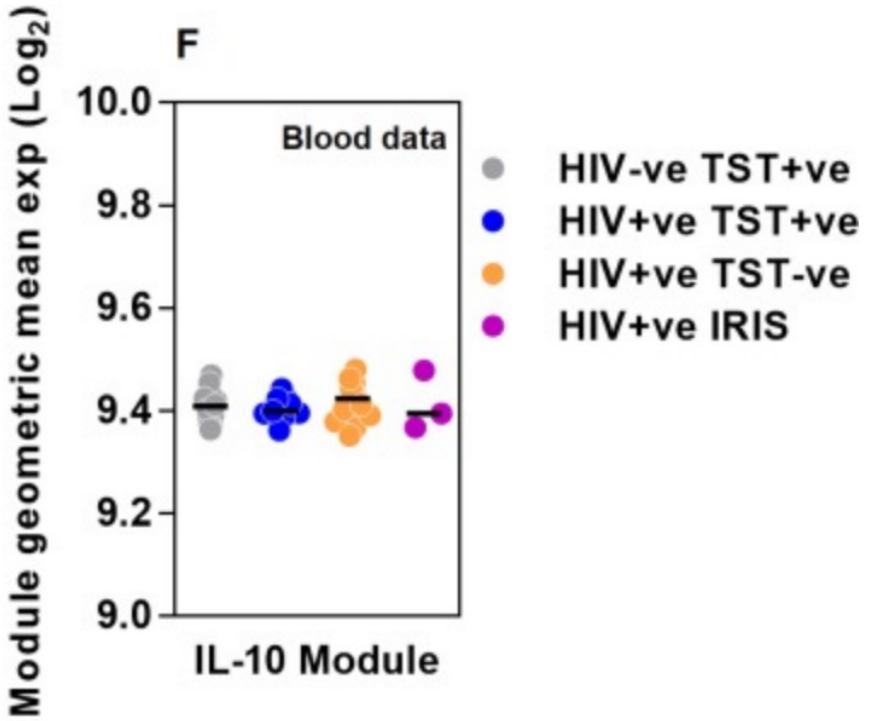
In Vivo Molecular Dissection of the Effects of HIV-1 in Active Tuberculosis

Lucy C. K. Bell, [1] Gabriele Pollara, [1] Mellissa Pascoe, [2] Gillian S. Tomlinson, [1] Rannakoe J. Lehloenya, [2] Jennifer Roe, [1] Richard Meldau, [2] Robert F. Miller, [3] Alan Ramsay, [4] Benjamin M. Chain, [1] Keertan Dheda, [2] and Mahdad Noursadeghi [1,*]

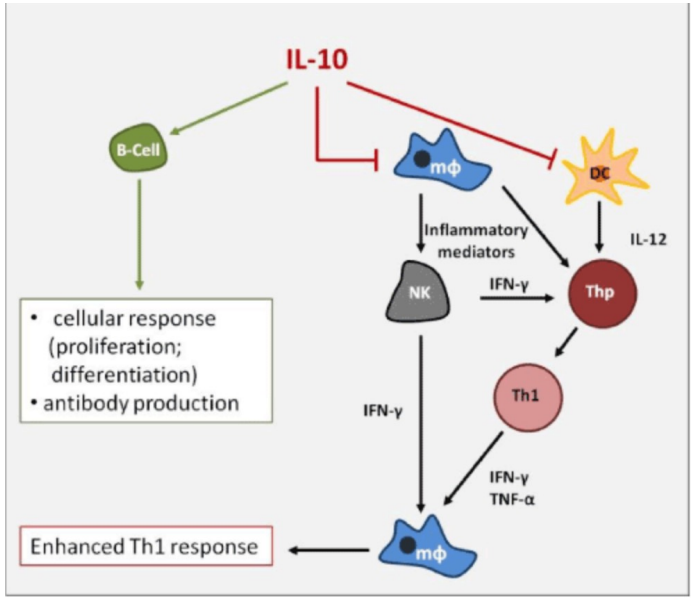
- Used TST as a model for TB disease in HIV + and HIV - TB patients and controls.
- 48 hrs after TST, punch biopsy followed by RNA seq.
- Compared to RNAseq of TB infected lung lesions.


A
HIV-ve Active TB TST+ve
515
1210
81
HIV+ve Active TB TST+ve
B
HIV+ve TST+ve (mdn log2 exp)
r2 = 0.97
Slope = 0.99
↓ in HIV+ve
HIV-ve TST+ve (mdn log2 exp)
Module score
T cell
B cell
NK cell
Monocyte
Neutrophil
IFNγ
TNFα
IL-4/IL-13
Mtb
Spn
PCSK
LPS





Suggests deficient IL-10 immunomodulation with “harmful” inflammatory responses.



CLINICAL IMPLICATIONS

Clinical presentation of culture confirmed pulmonary tuberculosis in HIV positive and negative patients

	HIV-positive		HIV-negative		
Symptoms	*n*	%	*n*	%	*P* value
N	873		1141		
Cough >3 weeks	841	96	1091	96	0.713
Duration of cough, mean, days	99.22		112.81		0.001
Subjective fever	651	75	737	65	<0.001
Sweats	582	67	669	59	<0.001
Weight loss (subjective)	705	81	823	72	<0.001
Malaise	159	18	150	13	0.002
Arthralgias	146	17	133	12	0.001
Hemoptysis	63	7	126	11	0.003
Loss of appetite	574	66	544	48	<0.001
Diarrhea	59	7	29	3	<0.001
Productive sputum	813	93	1072	94	0.068
Signs					
Temperature >37.5°C	321	37	363	32	0.019
Abnormal chest examination	630	72	898	79	<0.001
Abnormal lymph node exam	252	29	142	12	<0.001
Oral thrush	22	3	3	0	0.031
AFB smear-positive	734	84	1075	94	<0.001
Chest X-ray	(*n* = 848)		(*n* = 1085)		
Normal X-ray	71	8	26	2	<0.001
Cavitary disease	338	40	705	65	<0.001
Miliary pattern	35	4	21	2	0.004
Fibrosis	42	5	102	9	<0.001
Adenopathy	62	7	21	2	<0.001
Pleural effusion	73	9	67	6	0.04
Upper lobe disease	622	73	953	88	<0.001
Lower lobe disease	571	67	863	80	<0.001

HIV = human immunodeficiency virus; AFB = acid-fast bacilli.

HIV-infected patients present earlier and are subjectively sicker.

HIV-infected patients have atypical CXR and are less likely to be smear positive.

Lower CD4 counts associated with less clear clinical presentation.

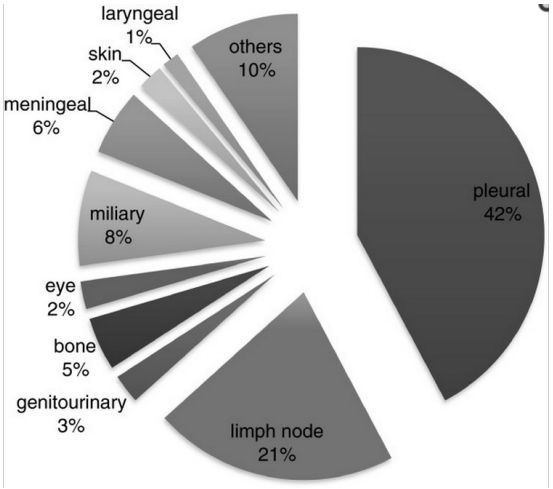
Table 3 Predictors of a normal CXR at initial presentation among patients with pulmonary tuberculosis

Characteristic	Normal CXR *n/N*	%	Crude OR	Adjusted OR	95%CI	*P* value
Immune status						
CD4 ≤ 150	52/323	16	7.82	5.32	3.07–9.23	<0.001
CD4 > 150	19/525	4	1.53	1.05	0.54–2.04	0.897
HIV-negative	26/1085	2	Reference	Reference		
AFB smear-negative						
Yes	53/202	26	12.96	10.36	6.41–16.74	<0.001
No	47/1760	3	Reference	Reference		
History of tobacco use						
Yes	15/490	3	0.50	0.36	0.18–0.74	0.005
No	84/1412	6	Reference	Reference		
Sex						
Male	52/1126	5	0.74	1.02	0.61–1.70	0.934
Female	48/780	6	Reference	Reference		
Age (for every 10-year increase)	NA		NA	1.2	0.91–1.56	0.194
Cough duration (for every 30-day increase)	NA		NA	0.98	0.92–1.05	0.613

Significant variation in presentation of pulmonary tuberculosis across a high resolution of CD4 strata

G. Chamie,* A. Luetkemeyer,* M. Walusimbi-Nanteza,† A. Okwera,‡ C. C. Whalen,§ R. D. Mugerwa,† D. V. Havlir,* E. D. Charlebois¶

HIV associated with extra-pulmonary TB



Clinical sites of extra-pulmonary TB among 57,217 ETB cases in Brazil: 2007-2011

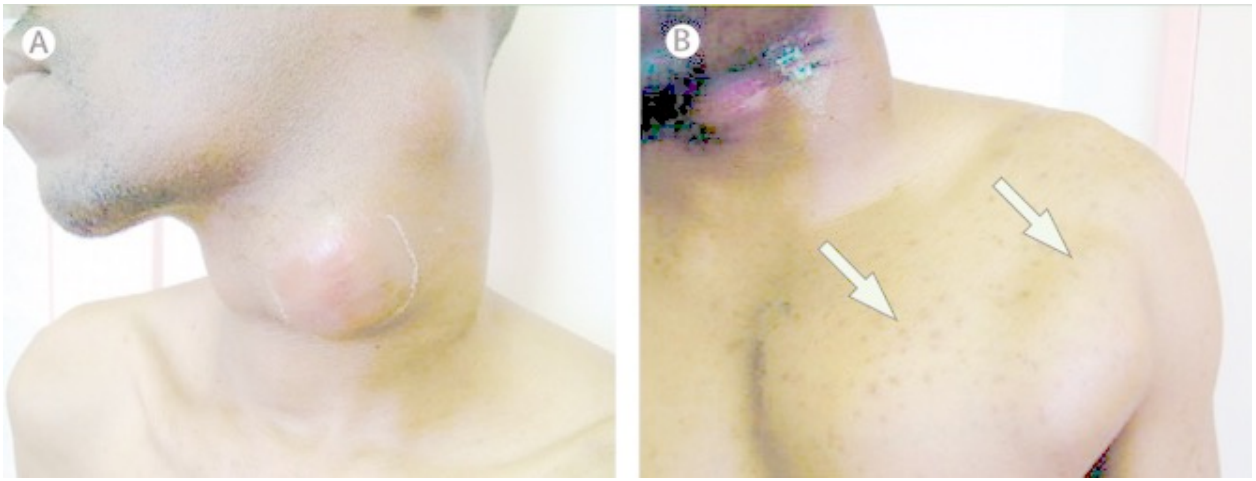
Research article

Highly accessed Open Access

Epidemiology of extrapulmonary tuberculosis in Brazil: a hierarchical model

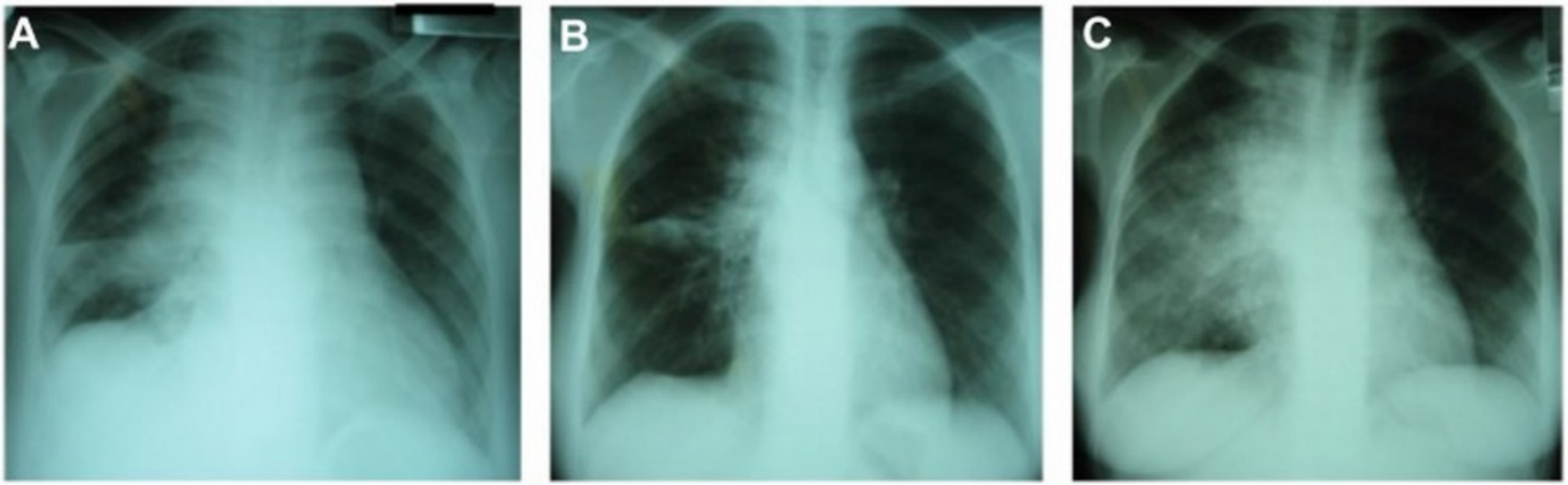
Teresa Gomes[1], Bárbara Reis-Santos[1], Adelmo Bertolde[2], John L Johnson[3], Lee W Riley[4] and Ethel Leonor Maciel[1]*

Risk factors	OR	95% CI
Female sex	1.3	
HIV	2.15	2.09-2.21
Age <15	2.52	2.39-2.65
Alcohol	.45	.43-.46
DM	.54	.51-.57



BMC Infectious Diseases

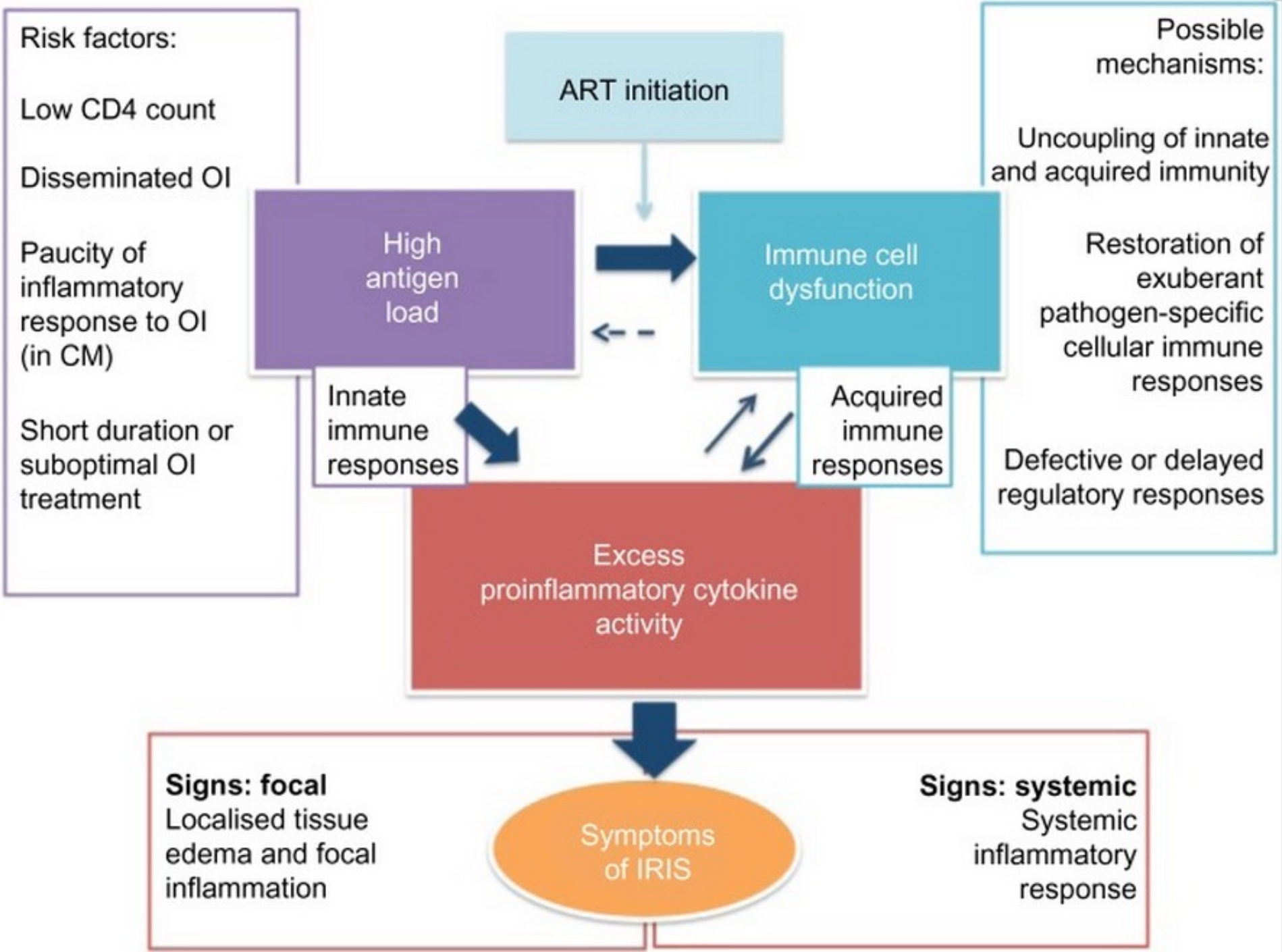
Immune reconstitution inflammatory syndrome



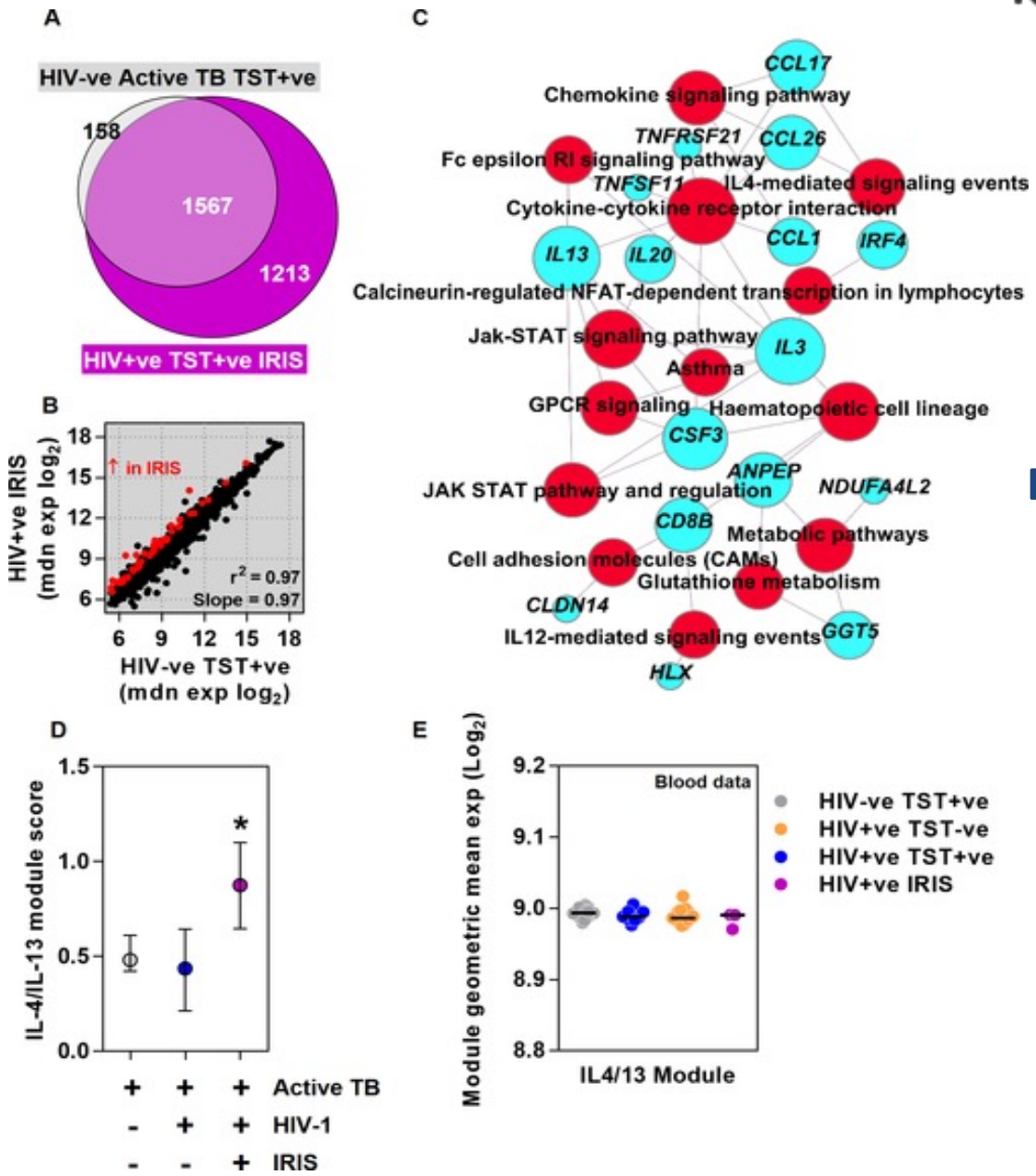
Patient presents with cough, weight loss, fever; right middle and upper lobe infiltrates. Culture positive for DS TB.

10 weeks later: Improved symptoms and reduced infiltrate. Starts ART.

9 days later: Recurrence of cough, fatigue, weight loss with worsening infiltrate.


Risk factors:
Low CD4 count
Disseminated OI
Paucity of inflammatory response to OI (in CM)
Short duration or suboptimal OI treatment
ART initiation
High antigen load
Immune cell dysfunction
Innate immune responses
Acquired immune responses
Excess proinflammatory cytokine activity
Possible mechanisms:
Uncoupling of innate and acquired immunity
Restoration of exuberant pathogen-specific cellular immune responses
Defective or delayed regulatory responses
Signs: focal
Localised tissue edema and focal inflammation
Symptoms of IRIS
Signs: systemic
Systemic inflammatory response

PLOS | PATHOGENS



Exaggerated Th2 responses in HIV-1 infected patients with unmasking TB-IRIS.

DIAGNOSTICS

Diagnosing latent TB infection in HIV +

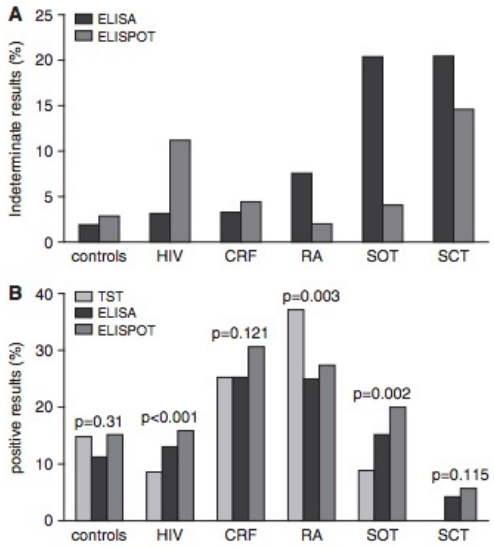
- Tuberculin skin testing
- Interferon gamma release assay (IGRA)

Predictors of indeterminate versus determinate IGRA results

Patient factor	Indeterminate vs determinate IFN-γ response		
	Odds ratio	95% CI	*P* value
HIV infected	2.36	1.10–5.08	0.028
Presence of a BCG scar	2.48	1.23–5.01	0.011
Lived in Khayelitsha for >1 year	0.30	0.11–0.80	0.016

Oni T, et al. . Risk factors associated with indeterminate gamma interferon responses in the assessment of latent tuberculosis Infection in a high-incidence environment. Clin Vaccine Immunol. 2012 ;19(8):1243-7..

Diagnosis of latent TB



HIV reduces concordance of three tests for latent TB.

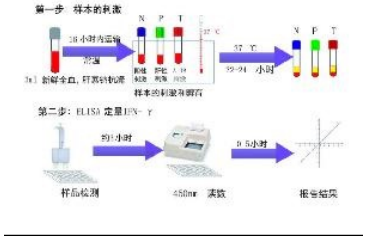


Table E6: Follow-up active tuberculosis in HIV-infected patients 1, 2 and 5 years after testing for latent infection with *M. tuberculosis*.

			1 year			2 years			5 years		
	test-result[§]	n	PY at risk	TB cases	Incidence*	PY at risk	TB cases	Incidence*	PY at risk	TB cases	Incidence*
TST	positive	59	55.3	3	5.42 (1.75-16.8)	92.2	3	3.26 (1.0-10.1)	124.5	4	3.21 (1.21-8.56)
	negative	642	622.9	2	0.32 (0.08-1.28)	1094.4	3	0.27 (0.09-0.85)	1763.4	6	0.34 (0.15-0.76)
ELISA	positive	88	85.1	2	2.35 (0.59-9.39)	145.8	2	1.37 (0.34-5.48)	236.0	3	1.27 (0.41-3.94)
	negative	599	587.4	2	0.35 (0.09-1.38)	1019.0	2	0.20 (0.05-0.78)	1627.5	5	0.31 (0.13-0.74)
ELISPOT	positive	95	92.2	3	3.25 (1.05-10.09)	166.6	3	1.80 (0.58-5.58)	275.2	4	1.45 (0.55-3.87)
	negative	515	497.0	2	0.40 (0.10-1.61)	873.6	3	0.34 (0.11-1.06)	1407.5	5	0.36 (0.15-0.85)

*Incidence is given per 100 person-years (PY); the rates refer to the cumulative rates after 1, 2, and 5 years after testing for latent infection with *M. tuberculosis*; [§]This analysis includes all patients with valid test results (positive or negative), while indeterminate test results were not considered in this analysis.

But TST predicts future disease more reliably than ELISA or ELISPOT.

Sester M, et al; TBNET. Risk assessment of tuberculosis in immunocompromised patients. A TBNET study. Am J Respir Crit Care Med. 2014 Nov 15;190(10):1168-76.

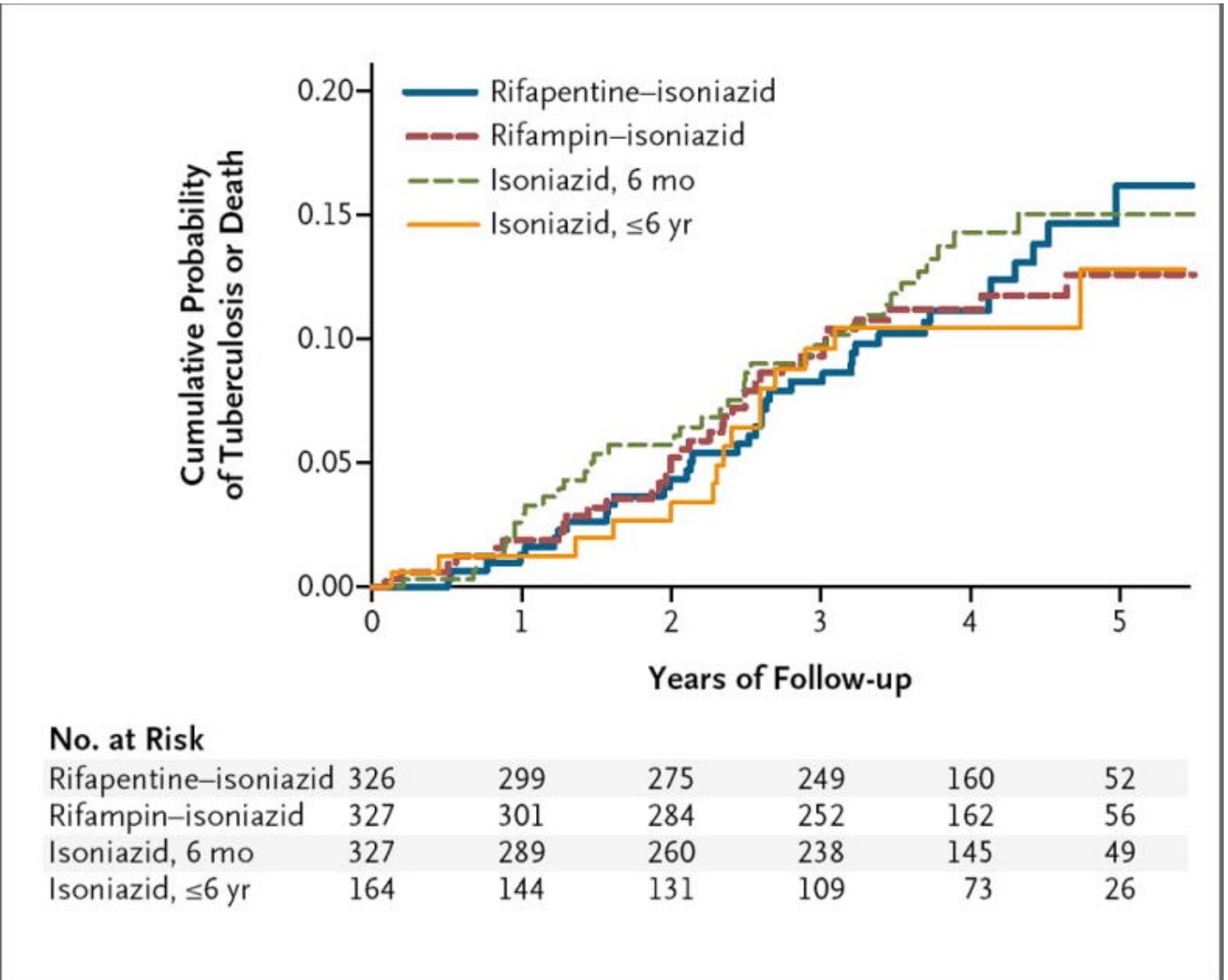
PREVENTIVE THERAPY

Treatment of latent TB infection

- Cochrane review 2010
  - Summarized 12 trials, 8578 patients
  - RR of TB .38 among treated PPD+ PLHIV
  - RR of TB .89 among treated PPD- PLHIV
  - No difference among different regimens used for different durations (INH, Rif and PZA, others).
  - No impact on all cause mortality.

Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD000171.

Continuous PT



No. at Risk

Rifapentine–isoniazid	326	299	275	249	160	52
Rifampin–isoniazid	327	301	284	252	162	56
Isoniazid, 6 mo	327	289	260	238	145	49
Isoniazid, ≤6 yr	164	144	131	109	73	26

Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med. 2011;365(1):11–20.

Mass IPT for TB control (in high HIV burden setting)

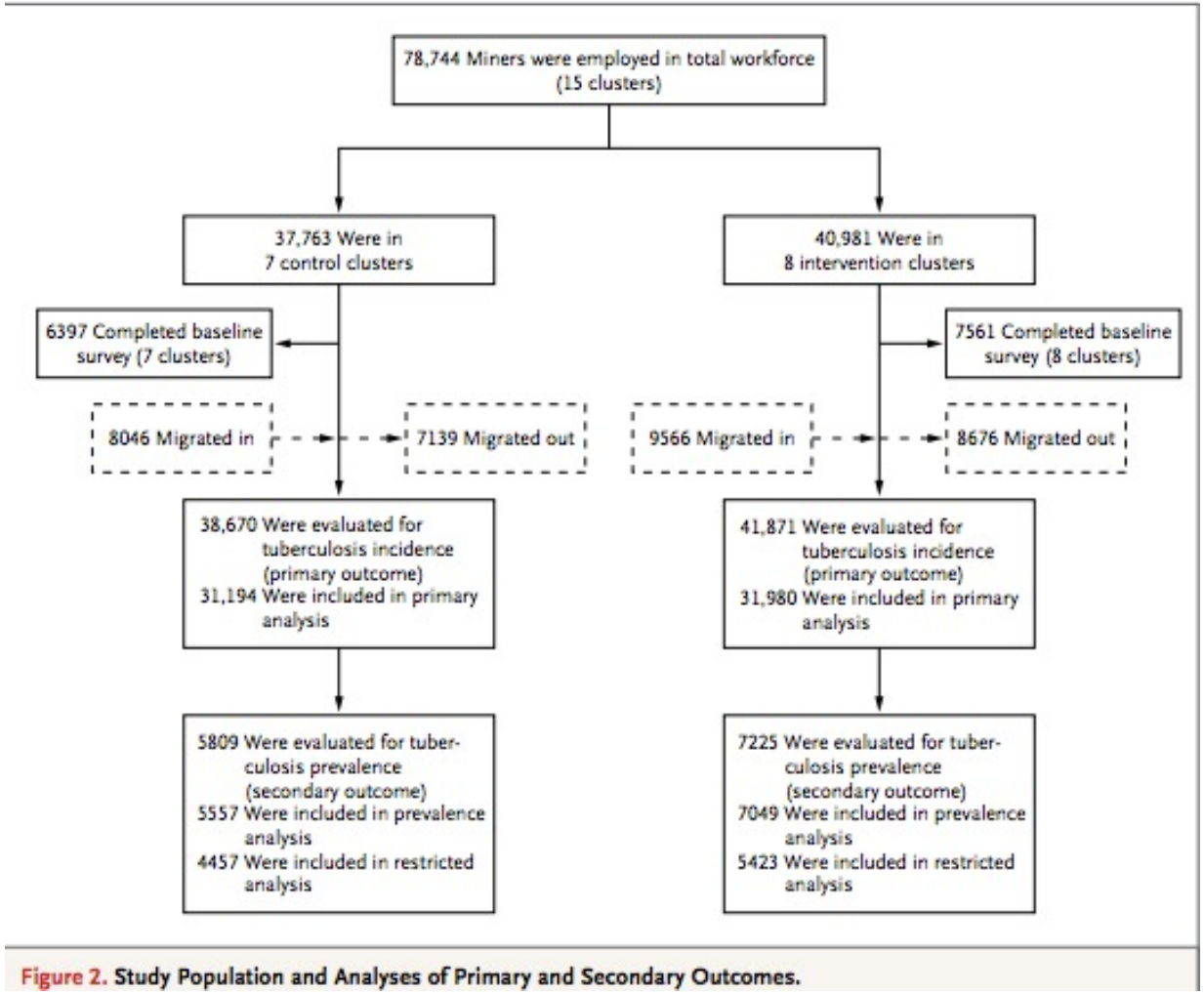


Figure 2. Study Population and Analyses of Primary and Secondary Outcomes.

Impact in communities randomized to PT intervention

Table 2. Overall Effect of Community-wide Isoniazid Preventive Therapy: Tuberculosis Incidence and Prevalence.

Outcome	Control Clusters		Intervention Clusters		Rate Ratio (95% CI)*			
	Cases	Rate	Cases	Rate	Unadjusted	P Value	Adjusted†	P Value
	no./no. of person-yr	*per 100 person-yr‡*	*no./no. of person-yr*	*per 100 person-yr‡*				
Primary outcome: tuberculosis incidence§								
Any	856/29,014	2.95	887/29,352	3.02	1.00 (0.75–1.34)	0.98	0.96 (0.76–1.21)	0.71
Definite or probable	656/29,014	2.26	703/29,352	2.40	1.07 (0.70–1.64)	0.72	1.04 (0.73–1.48)	0.80
					Prevalence Ratio (95% CI)*			
	no. of cases/ total no.	*%‡*	*no. of cases/ total no.*	*%‡*				
Secondary outcome: tuberculosis prevalence¶								
All employees	119/5557	2.14	166/7049	2.35	1.05 (0.60–1.82)	0.86	0.98 (0.65–1.48)	0.90
Employees in work-force at the time of cluster enrollment	97/4457	2.18	128/5423	2.36	1.05 (0.62–1.78)	0.85	1.01 (0.66–1.55)	0.94

Churchyard GJ, Fielding KL, Lewis JJ, Coetzee L, Corbett EL, Godfrey-Faussett P, Hayes RJ, Chaisson RE, Grant AD; Thibela TB Study Team. A trial of mass isoniazid preventive therapy for tuberculosis control. N Engl J Med. 2014 Jan 23;370(4):301-10.

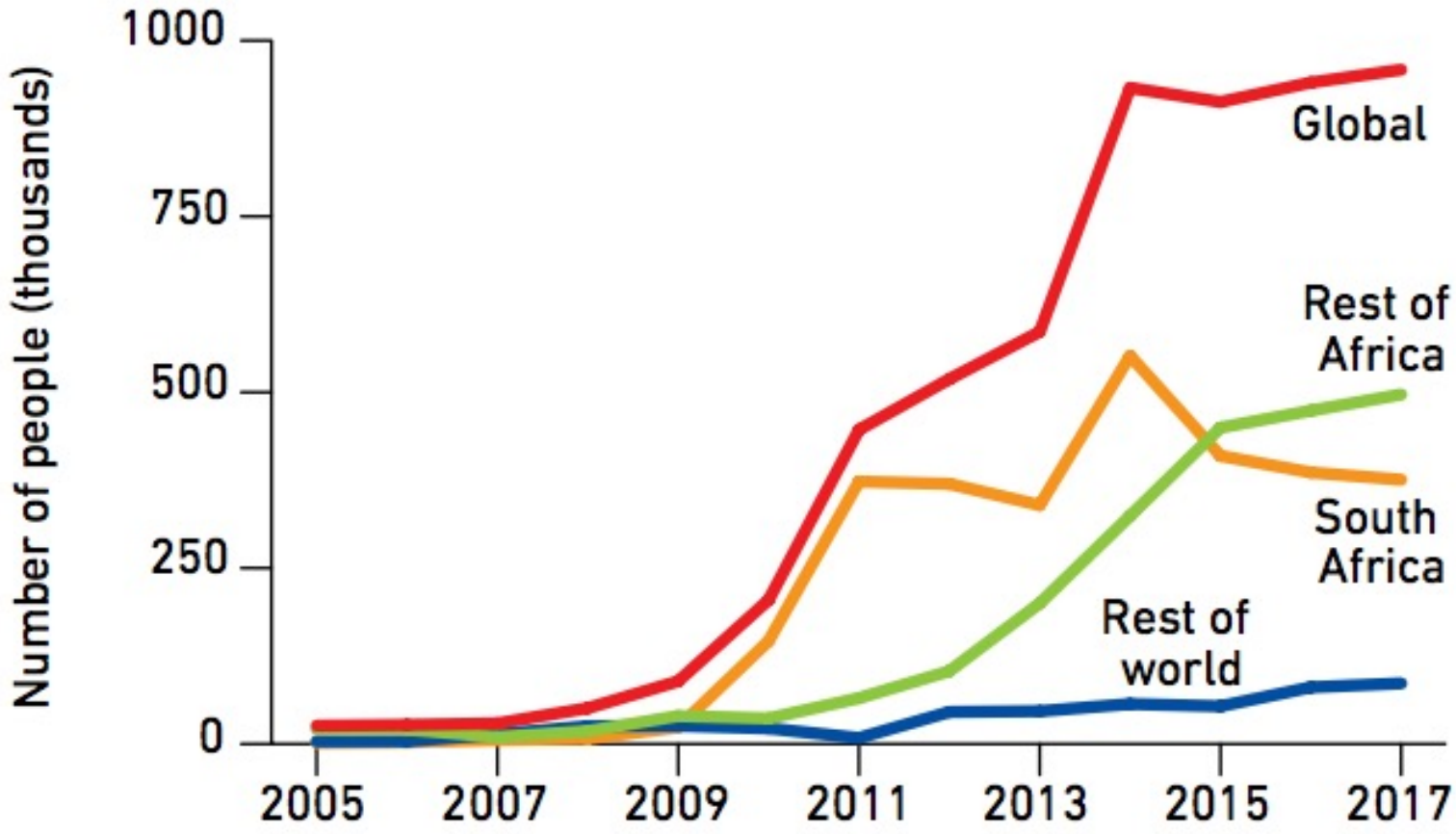
Impact among people getting IPT

Table 3. Direct Effect of Isoniazid Preventive Therapy as Shown by Tuberculosis Incidence, According to the Time Interval after Enrollment.*

Time Interval	Control Cohort (N = 6263)		Isoniazid Cohort (N = 4646)		Rate Ratio (95% CI)			
	Cases	Rate†	Cases	Rate†	Unadjusted	P Value	Adjusted‡	P Value§
	no./no. of person-yr	*per 100 person-yr*	*no./no. of person-yr*	*per 100 person-yr*				
Overall	382/13,776	2.77	175/9163	1.91	0.77 (0.52–1.15)	0.18	0.82 (0.58–1.15)	0.23
0–9 mo¶	133/4,564	2.91	37/3358	1.10	0.38 (0.19–0.75)	0.01	0.42 (0.20–0.88)	0.03
>9–18 mo	115/4,243	2.71	74/3156	2.34	0.97 (0.57–1.65)	0.89	0.93 (0.53–1.61)	0.93
>18 mo	134/4,970	2.70	64/2649	2.42	0.83 (0.54–1.27)	0.35	0.95 (0.62–1.46)	0.95

FIG. 5.1

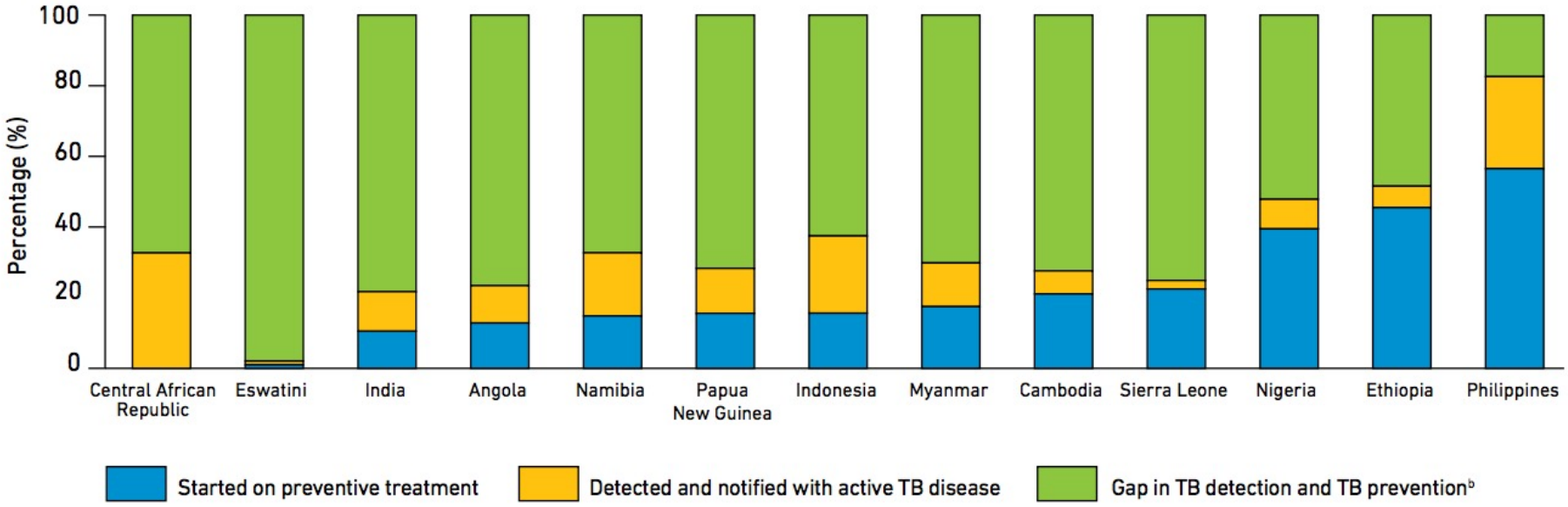
Provision of TB preventive treatment to people newly enrolled in HIV care,[a] 2005–2017



[a] For seven countries, data are for people currently enrolled in HIV care: Congo, Ecuador, Grenada, Kenya, Mozambique, Nepal and Ukraine.

FIG. 5.2

Gaps in TB prevention and TB detection for people who were newly enrolled in HIV care in 2017, selected countries[a]



Screening for active TB

Screening for active TB in HIV positive patient

- All HIV patients should be screened for symptoms of active TB and if positive, receive diagnostic test: “intensified case finding.”

- Symptoms screening algorithms
  - Cough, fever, night sweats or weight loss

- Patients who test negative started on ART if indicated and IPT.
- Patients who test positive go on to diagnostic testing.

But clinical screening can miss a significant proportion of cases……

N	Positive screen, *N* (%)	PTB, *N* (%)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	PTB cases missed, *N* (%
All participants							
705	540 (76.6)	62 (8.8)	85.5 (74.2–93.1)	24.3 (21.0–27.8)	9.8 (7.4–12.6)	94.6 (89.9–97.5)	9 (14.5)
ART							
505	368 (72.9)	30 (5.9)	76.7 (57.7–90.1)	27.4 (23.4–31.6)	6.3 (4.0–9.2)	94.9 (89.8–97.9)	7 (23.3)
No ART							
200	172 (86.0)	32 (16.0)	93.8 (79.2–99.2)	15.5 (10.4–21.9)	17.4 (12.1–24.0)	92.9 (76.5–99.1)	2 (6.3)

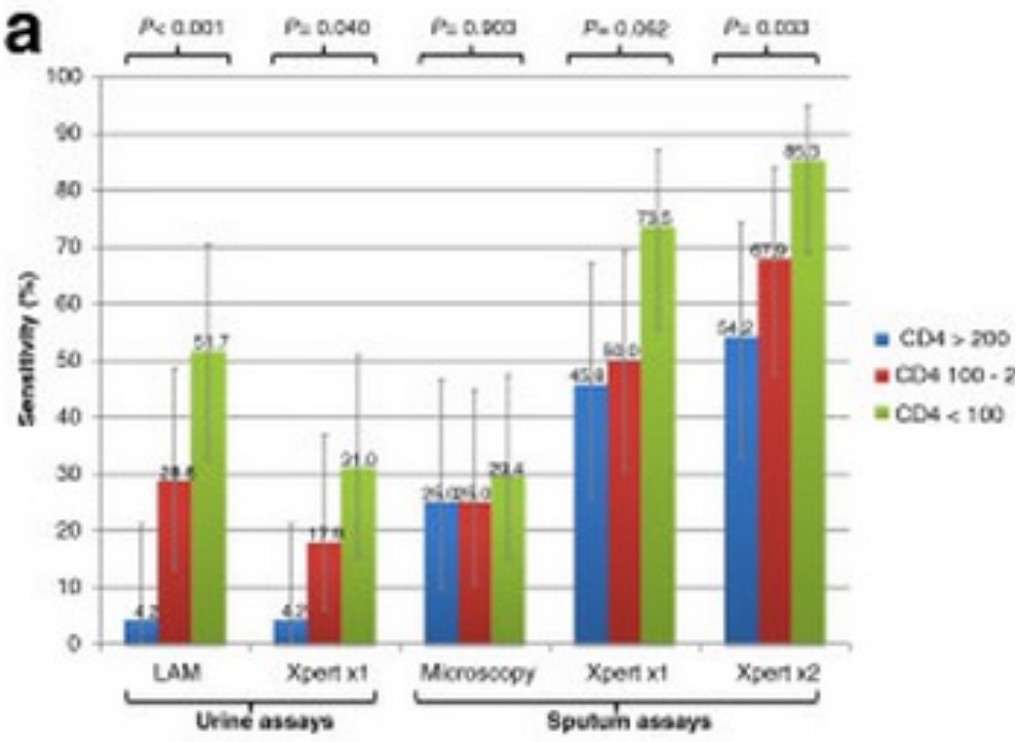
Performance of symptom-based tuberculosis screening among people living with HIV: not as great as hoped. Ahmad Khan, Faiz; Verkuijl, Sabine; Parrish, Andrew; Chikwava, Fadzai; Ntumy, Raphael; El-Sadr, Wafaa; Howard, Andrea

AIDS. 28(10):1463-1472, June 19, 2014.

Diagnostic testing for TB in HIV infected patients

- Sputum smear microscopy
- Liquid or solid culture
- Molecular diagnostic tests
  - Cepheid GeneXpert
- Urine LAM (lipoarabinomannan)

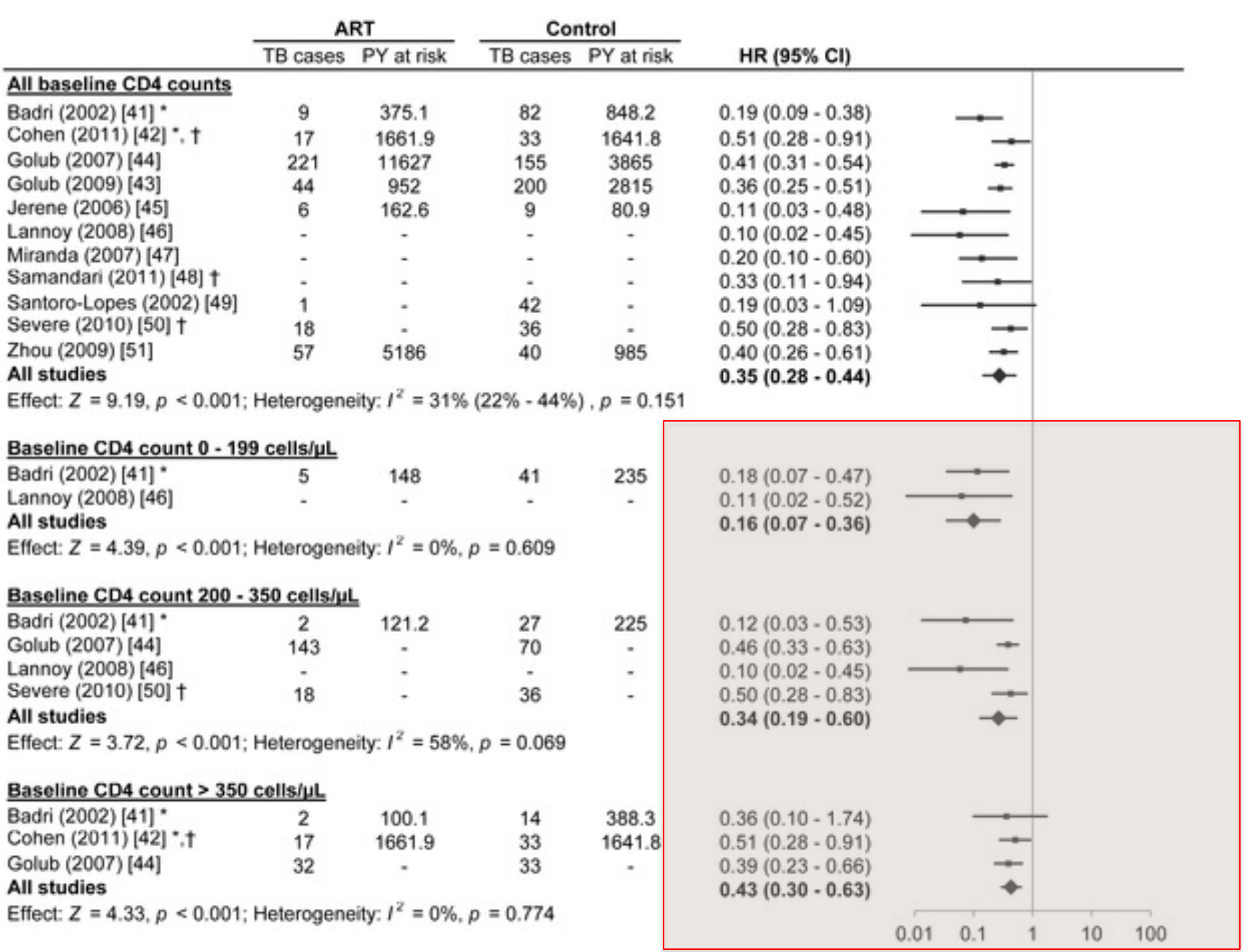
Diagnosis of active TB



Low sensitivity of smear microscopy in HIV-infected patients does not vary by CD4 while urine LAM and GeneXpert have higher sensitivity with lower CD4.

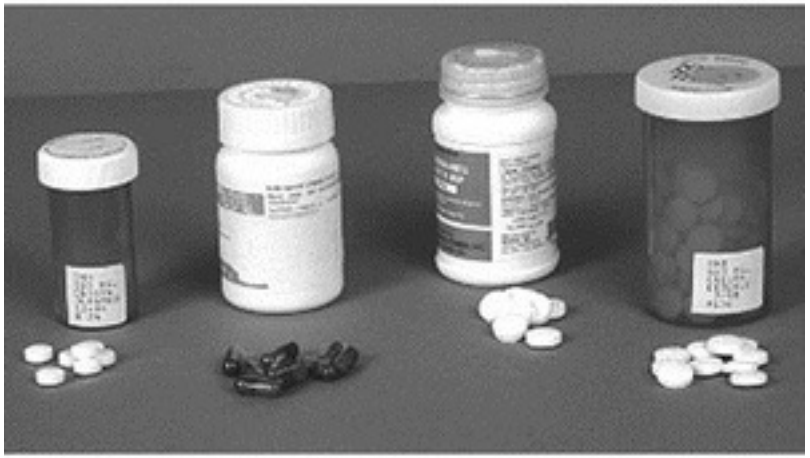
Lawn SD, Kerkhoff AD, Vogt M, Wood R. HIV-associated tuberculosis: relationship between disease severity and the sensitivity of new sputum-based and urine-based diagnostic assays. BMC Med. 2013 Oct 29;11:231

Treatment



Suthar AB, Lawn SD, del Amo J, Getahun H, Dye C, et al. (2012) Antiretroviral Therapy for Prevention of Tuberculosis in Adults with HIV: A Systematic Review and Meta-Analysis. PLoS Med 9(7): e1001270.

Treatment of active TB: treatment duration, intermittent therapy and ART



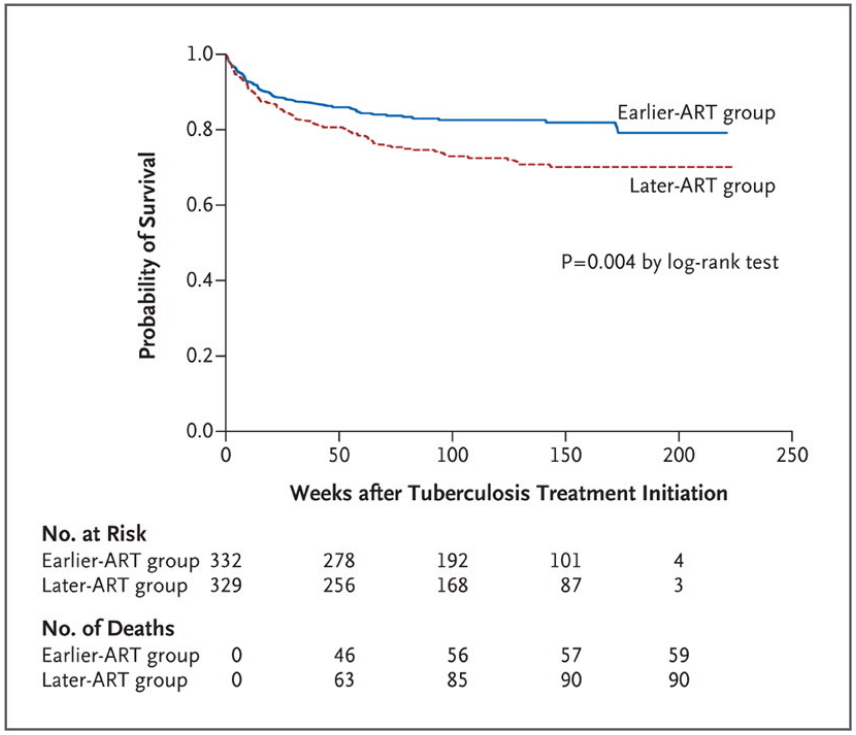
Standard four drug therapy

- 2 months of INH, Rifampicin, Ethambutol and Pyrazinamide
- 4 months of INH and Rifampicin

Table 6. Adjusted Risk Ratios (aRRs) of Treatment Failure, Relapse, and Death in Patients Coinfected with Human Immunodeficiency Virus and Tuberculosis (TB), from Negative Binomial Regression

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)	

Camelia Study

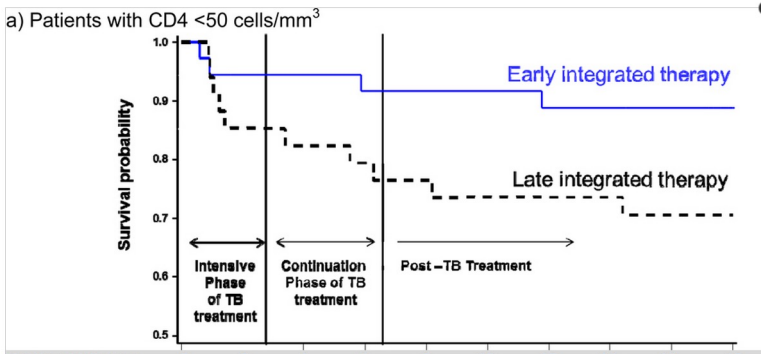


No. at Risk					
Earlier-ART group	332	278	192	101	4
Later-ART group	329	256	168	87	3

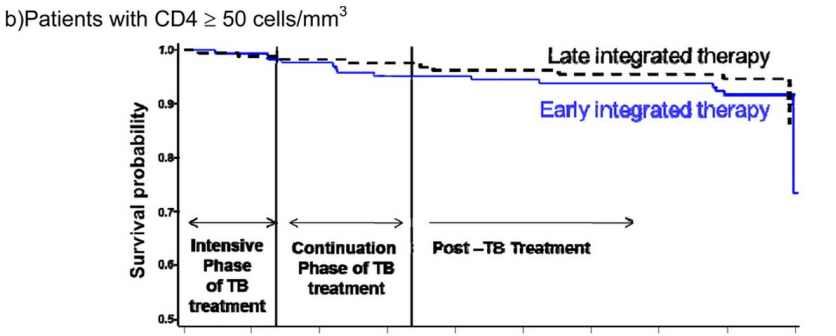
No. of Deaths					
Earlier-ART group	0	46	56	57	59
Later-ART group	0	63	85	90	90

Blanc F et al. N Engl J Med 2011;365:1471-1481.

Sapit trial



Months of follow-up	0	2	4	6	8	10	12	14	16	18
# at risk (early-integrated)	37	33	33	32	32	32	31	31	31	29
# at risk (late integrated)	35	29	28	27	26	24	24	24	23	21



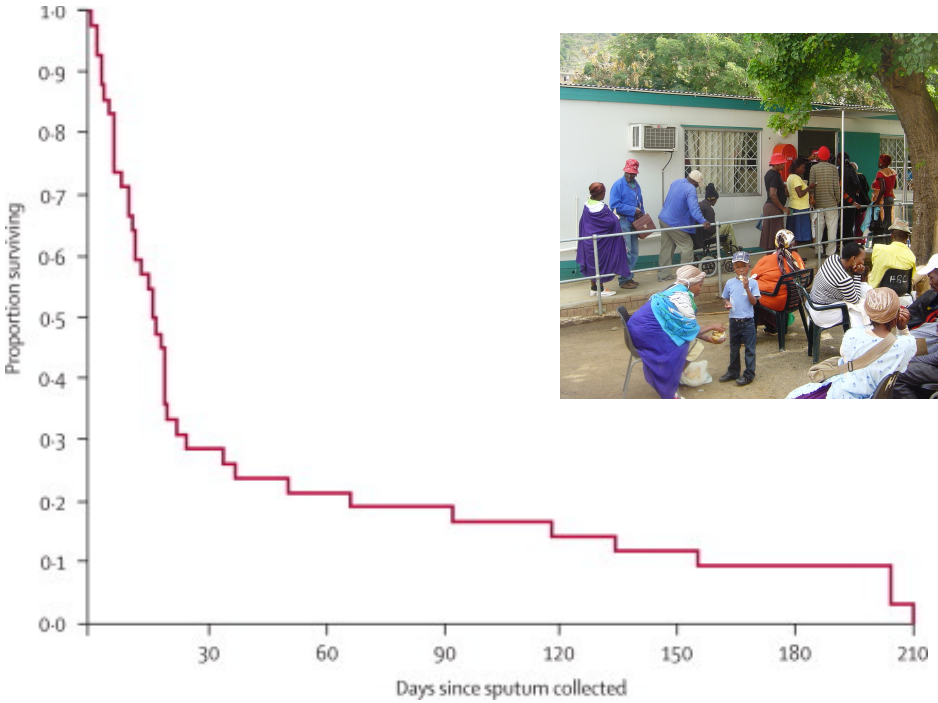
Months of follow-up	0	2	4	6	8	10	12	14	16	18
# at risk (early integrated)	177	166	159	149	145	140	137	133	125	121
# at risk (Late integrated)	180	164	153	148	138	134	129	126	124	119

EARLY is GOOD

Abdool Karim Sset al. N Engl J Med. 2010 Feb 25;362(8):697-706

Emergence of XDR TB

Tugela Ferry



Survival after sputum collection in patients with XDR tuberculosis with confirmed dates of death (n=42)

Characteristics of patients with XDR tuberculosis

	Number (%)
Tuberculosis characteristics (n=53)	
Pulmonary tuberculosis alone	40 (75%)
Pulmonary and extrapulmonary tuberculosis	13 (25%)
Sputum-smear positive	42 (79%)
Sputum-smear negative	11 (21%)
Previous tuberculosis treatment (n=47)	
No previous treatment	26 (55%)
Previous treatment: cure or completed treatment	14 (30%)
Treatment default or failure	7 (15%)
Previous admission in past 2 years (n=42)	
Admitted for any cause	28 (67%)
No previous admission	14 (33%)
HIV characteristics (n=44)	
HIV-infected	44 (100%)
On antiretroviral therapy	15 (34%)

Neel R Gandhi , et al. **Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa,** The Lancet, Volume 368, Issue 9547, 2006, 1575 - 1580

Impact of HIV on TB pathogenesis transitions

1. Infection leading to latent TB
2. Progression on to primary disease
3. Re-activation of latent TB
4. Re-infection leading to disease
5. Cure
6. Death
7. Relapse