L'Emilia Romagna dopo ICAR 2014

Tubercolosi e HIV

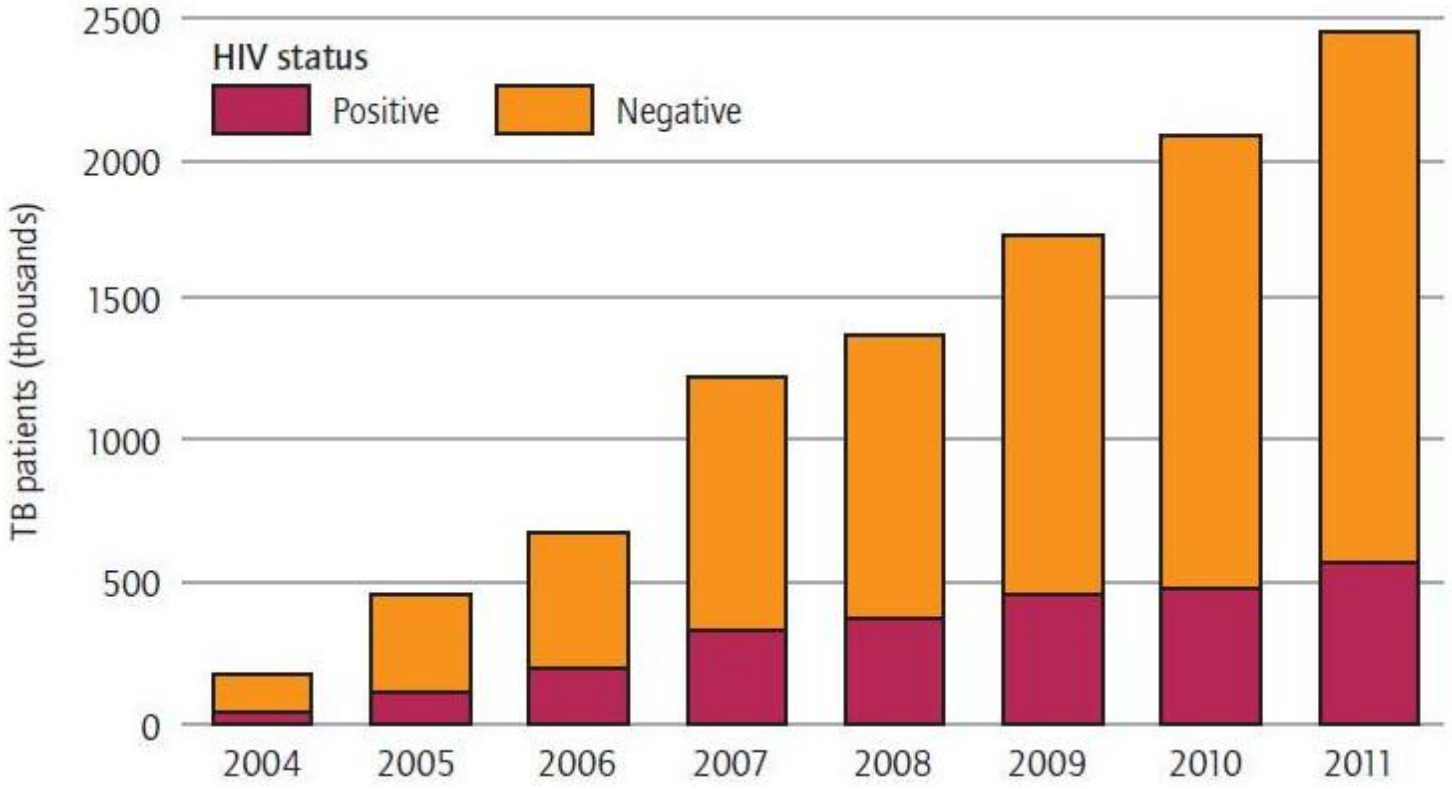
Dr. Pier Francesco Giorgetti

SIMIT
SOCIETA' ITALIANA DI MALATTIE INFETTIVE E TROPICALI

Corso di aggiornamento

18 giugno 2014, Ferrara

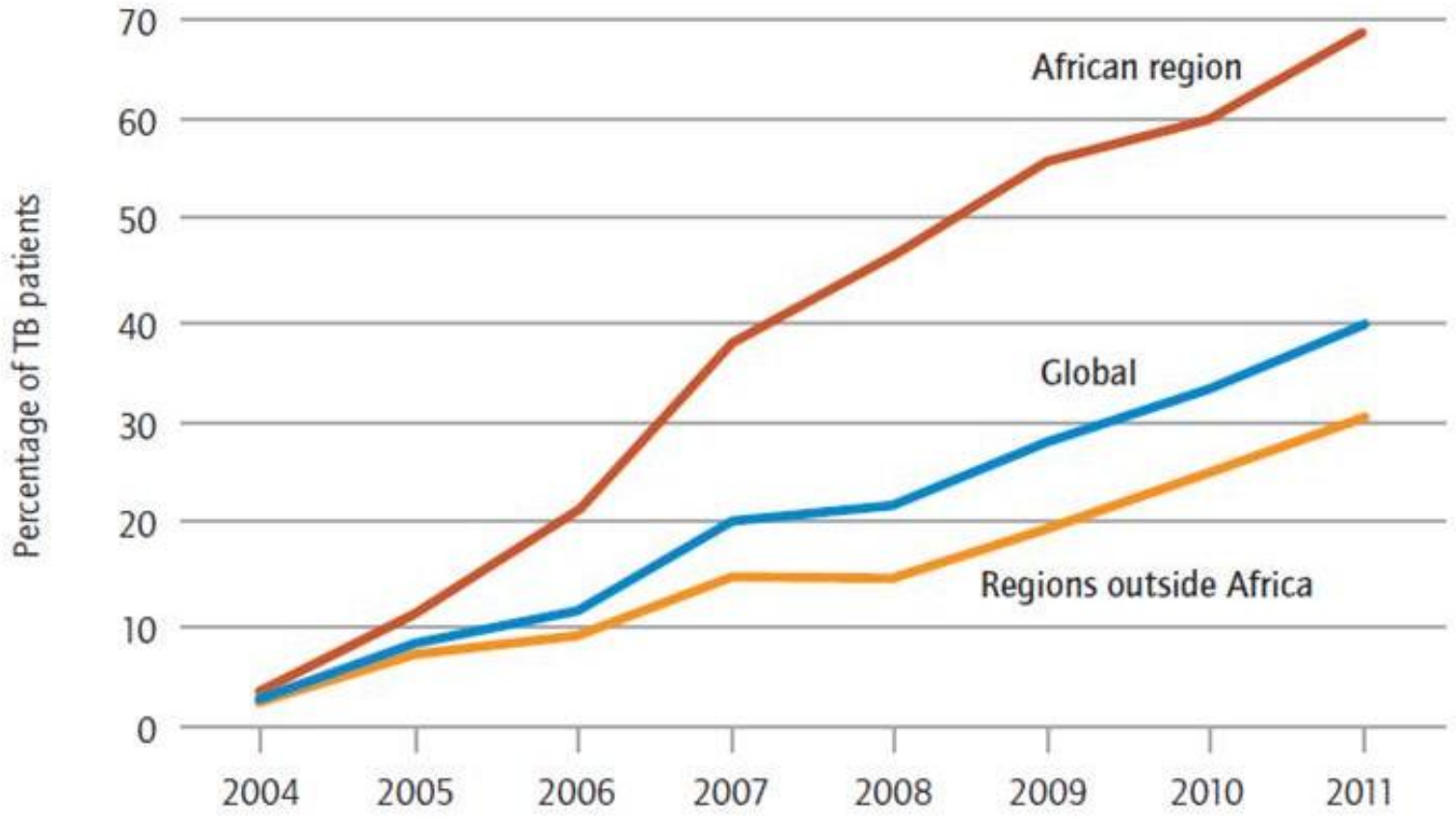
Number of TB patients with known HIV status, 2004-2011



World Health Organization

Collaborative TB/HIV activities, 2011

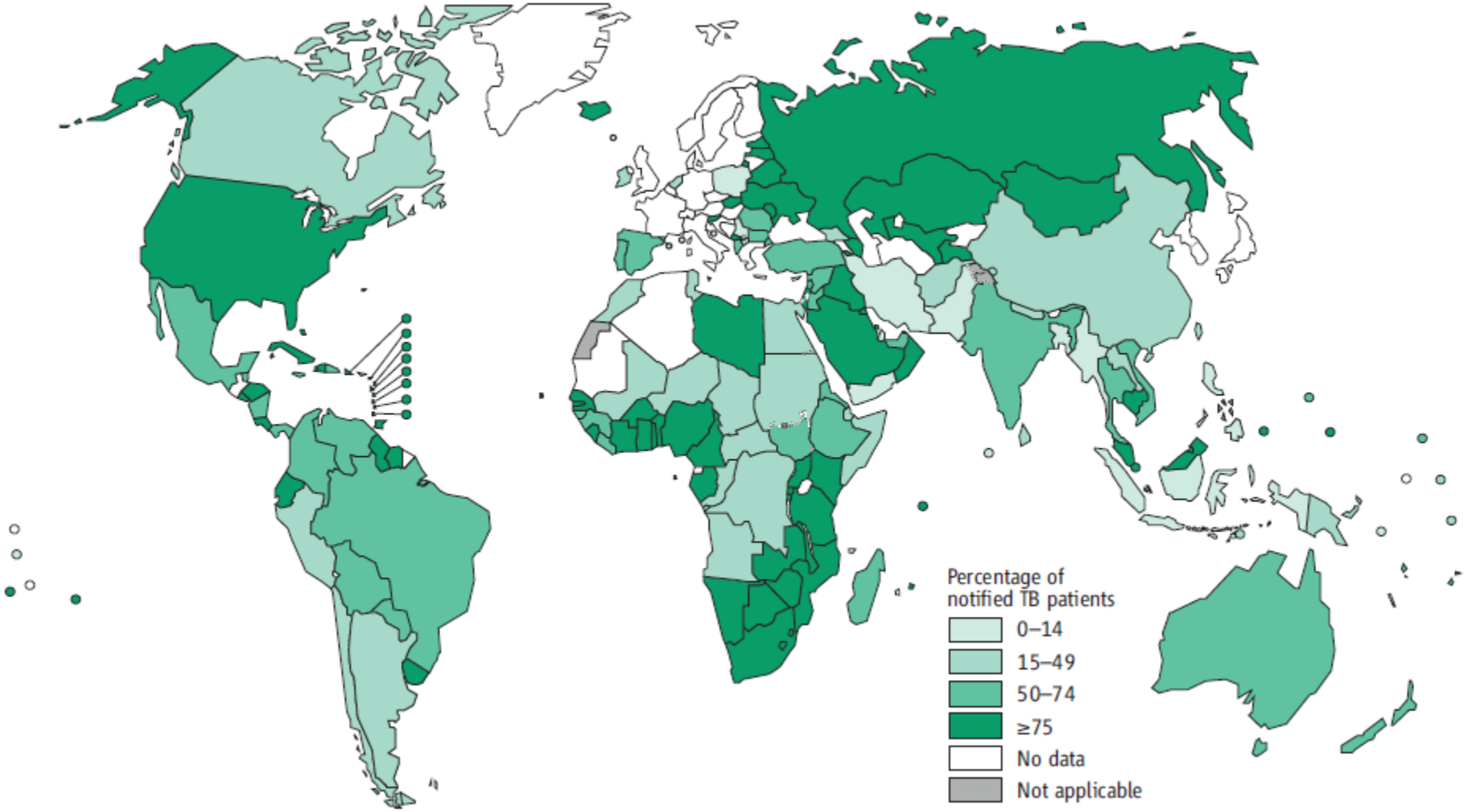
Percentage of TB patients with known HIV status, 2004-2011



World Health Organization

Collaborative TB/HIV activities, 2011

Percentage of TB patients with known HIV status by country, 2011

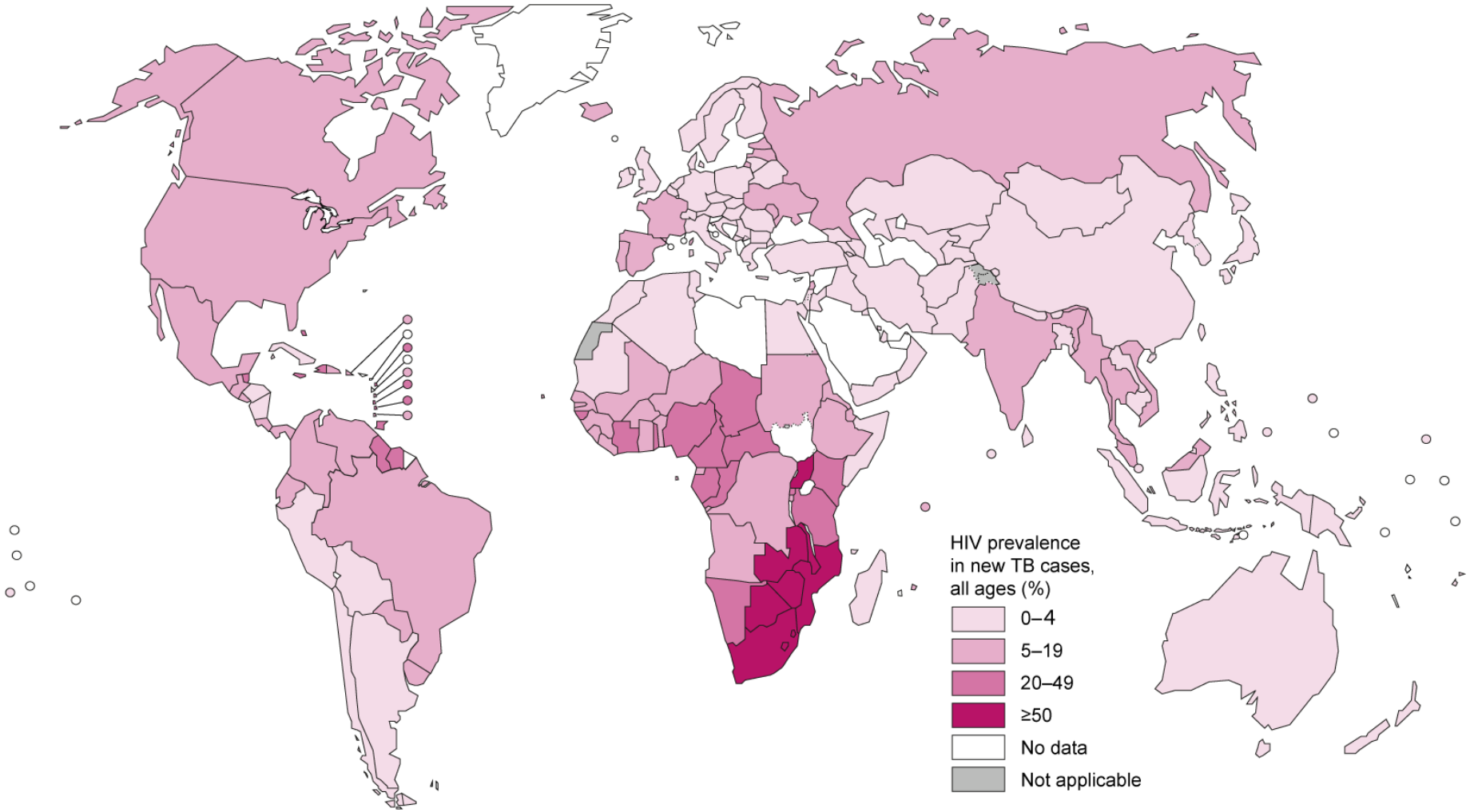


Data for the Russian Federation are for new TB patients only excluding cases in prisons

World Health Organization

Global Tuberculosis Report, 2013

Estimated HIV prevalence in new TB cases, 2012

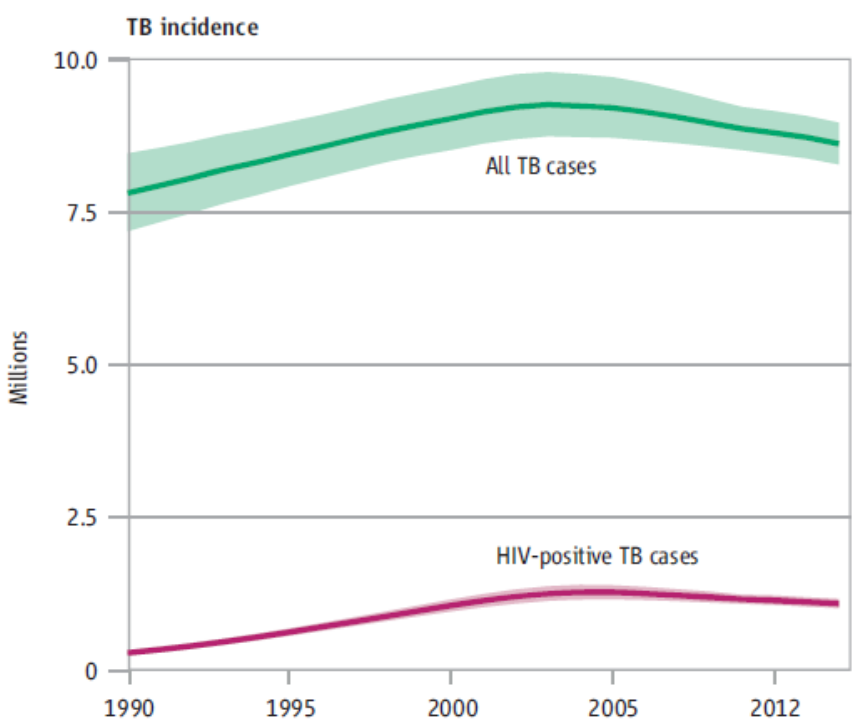


World Health Organization

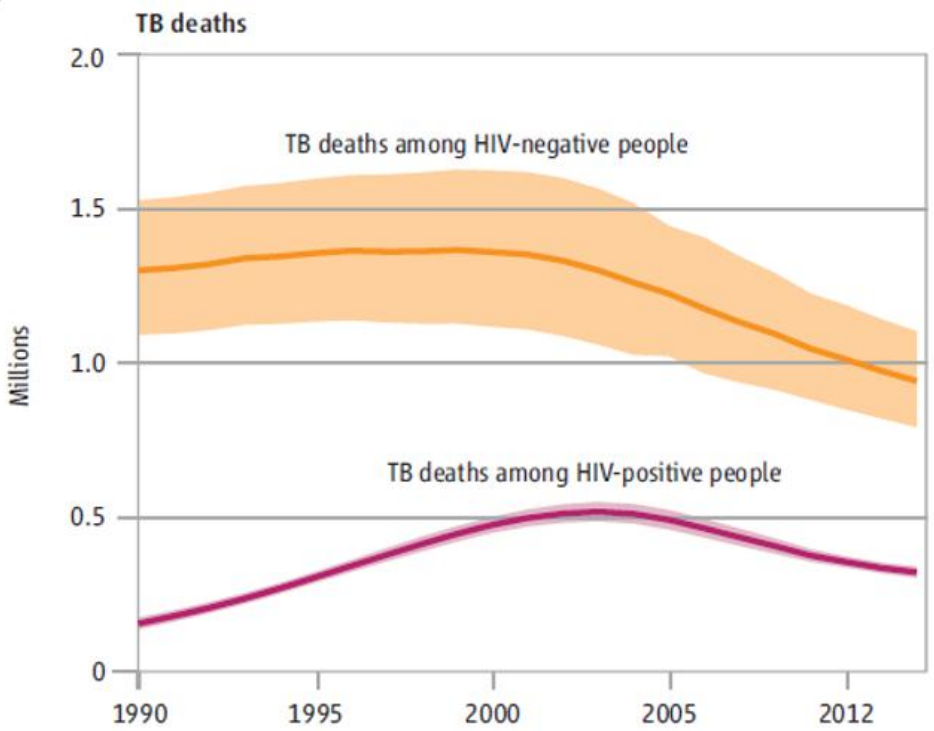
Global Tuberculosis Report, 2013

The burden of TB-HIV confection

Numbers of TB cases, 1990-2012



Numbers of TB deaths, 1990-2012



World Health Organization

Global Tuberculosis Report, 2013

Data of co-epidemics of TB and HIV

	ESTIMATED HIV-POSITIVE INCIDENT TB CASES			NUMBER OF TB PATIENTS WITH KNOWN HIV STATUS	% OF NOTIFIED TB PATIENTS TESTED FOR HIV	% OF TESTED TB PATIENTS HIV-POSITIVE	% OF IDENTIFIED HIV-POSITIVE TB PATIENTS STARTED ON CPT	% OF IDENTIFIED HIV-POSITIVE TB PATIENTS STARTED ON ART	NUMBER OF HIV-POSITIVE PEOPLE SCREENED FOR TB	NUMBER OF HIV-POSITIVE PEOPLE PROVIDED WITH IPT
	BEST	LOW	HIGH							
High TB/HIV burden countries	**1 000**	**960**	**1 100**	**2 454**	**53**	**21**	**80**	**57**	**4 024**	**509**
AFR	830	760	910	1 040	74	43	79	55	2 392	473
AMR	31	28	34	129	56	16	61	76	4.5	19
EMR	11	10	12	58	14	3.5	69	48	15	0.2
EUR	19	17	21	204	60	6.3	67	74	24	18
SEAR	170	160	180	904	39	6.2	89	61	1 352	< 0.01
WPR	24	21	27	451	34	3.1	79	56	308	8.6
Global	**1 100**	**1 000**	**1 200**	**2 787**	**46**	**20**	**80**	**57**	**4 095**	**519**

In 2012, **1.1 million (13%) of 8.6 million people who developed TB worldwide were HIV-positive**. The African Region accounted for 75% of the estimated number of HIV-positive incident TB cases

The number of people dying from HIV-associated TB has benn falling since 2003. However, there were stil **320000 deaths from HIV-associated TB in 2012**

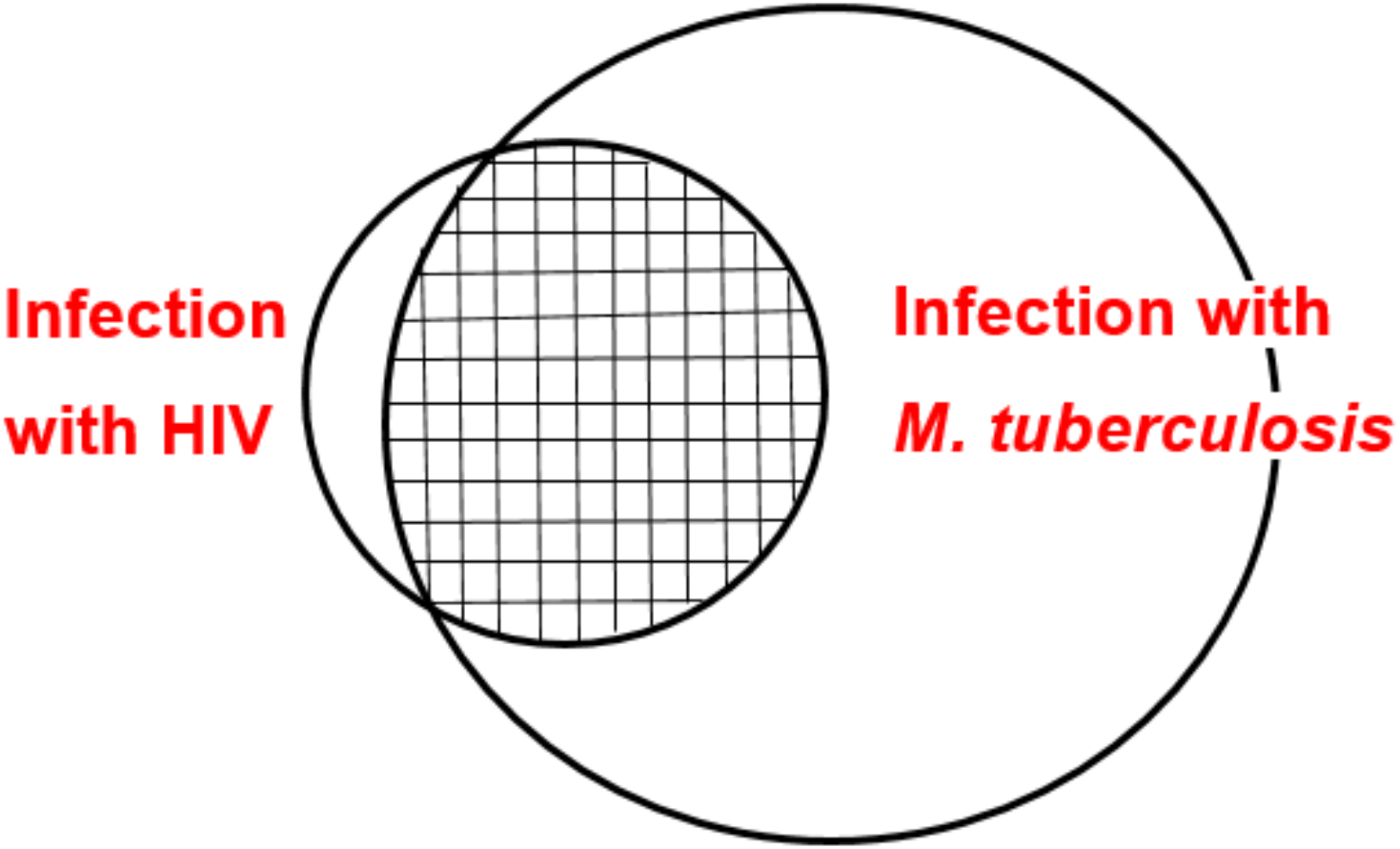
The prevalence of HIV co-infection among TB patients is highest in the **African Region**. Of TB patients with an HIV test result, **43% tested positive in 2012**, ranging from 9.6% in Angola and Ethiopia to 77% in Swaziland

World Health Organization

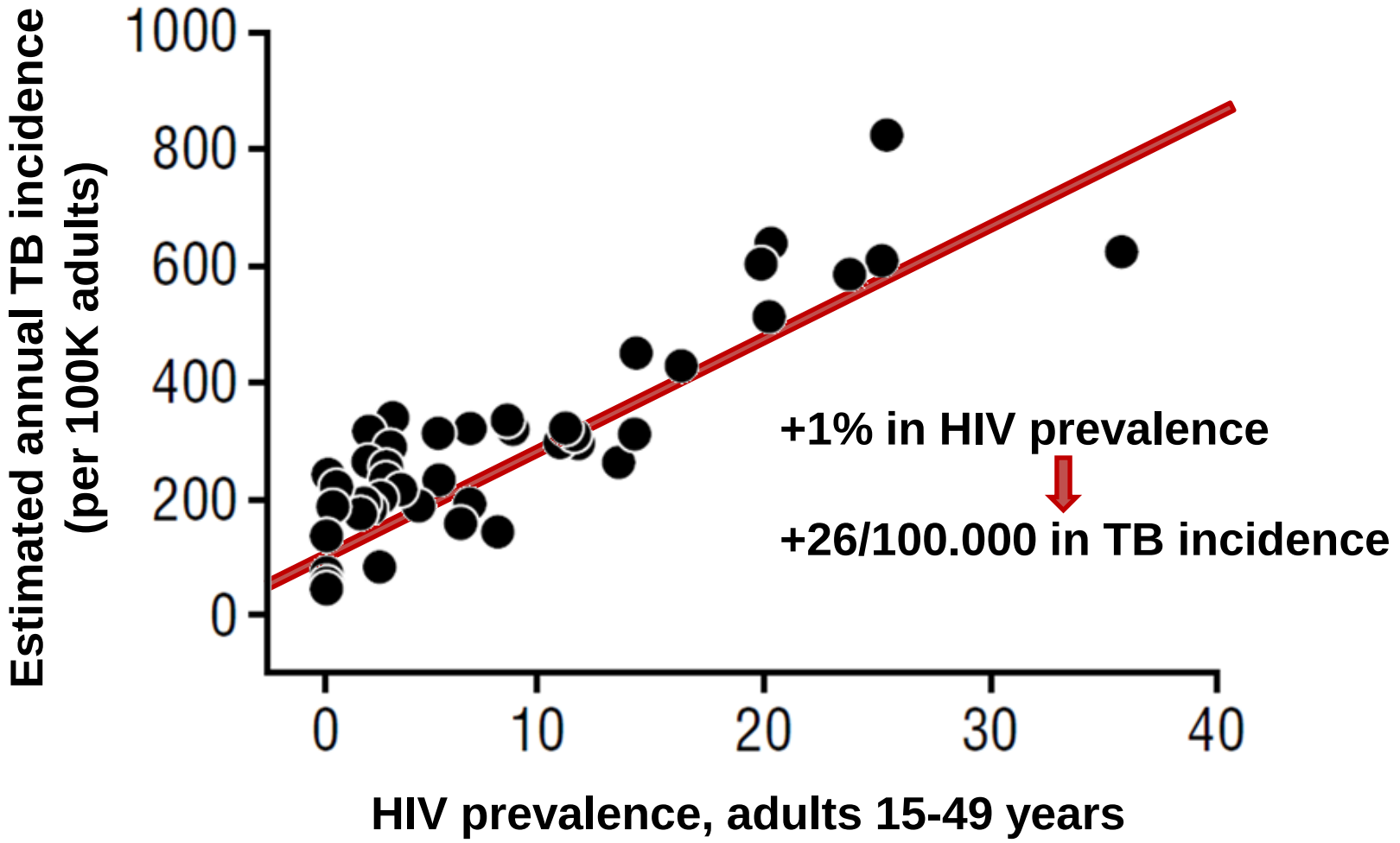
Global Tuberculosis Report, 2013

TB-HIV coinfection

Sub-Saharan Africa

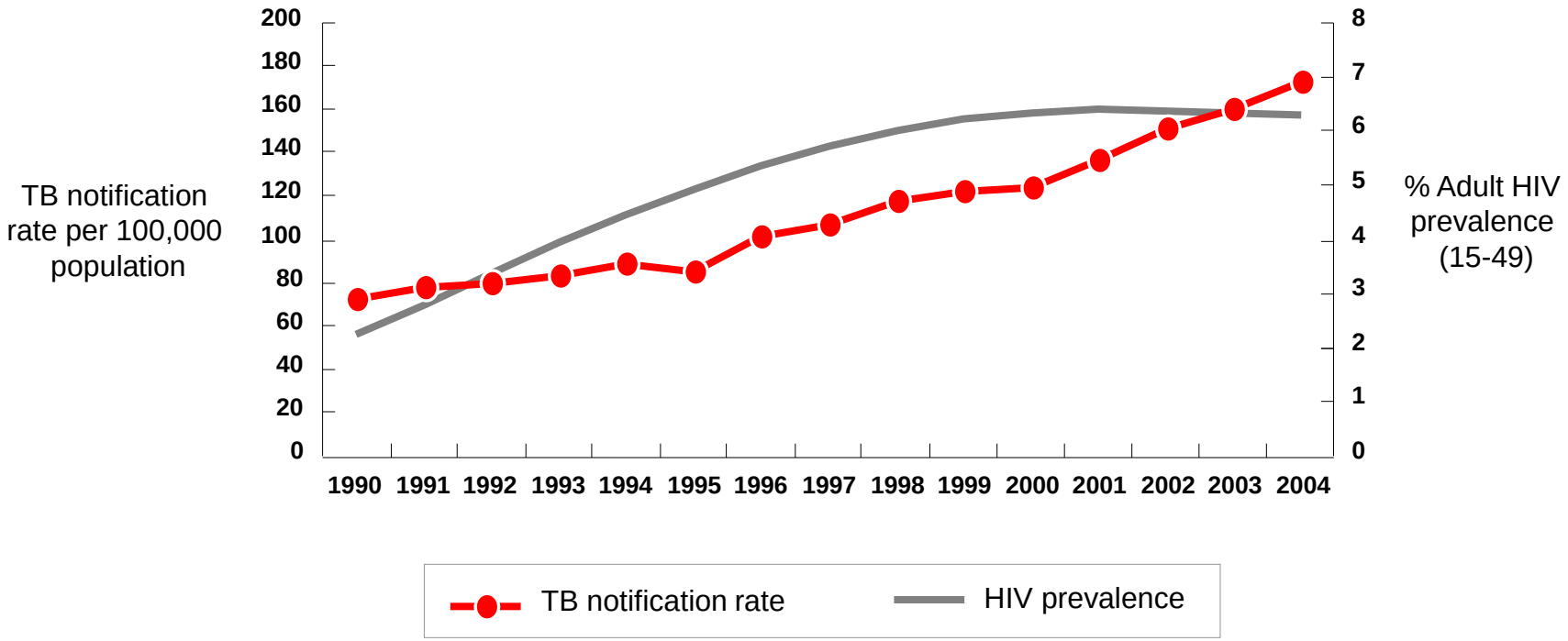


Estimated TB incidence vs. HIV prevalence in high burden countries



Corbett EL, Arch Intern Med. 2003;163:1009-1021

TB notification rate in 20 African countries* versus HIV prevalence in sub-Saharan Africa, 1990–2004

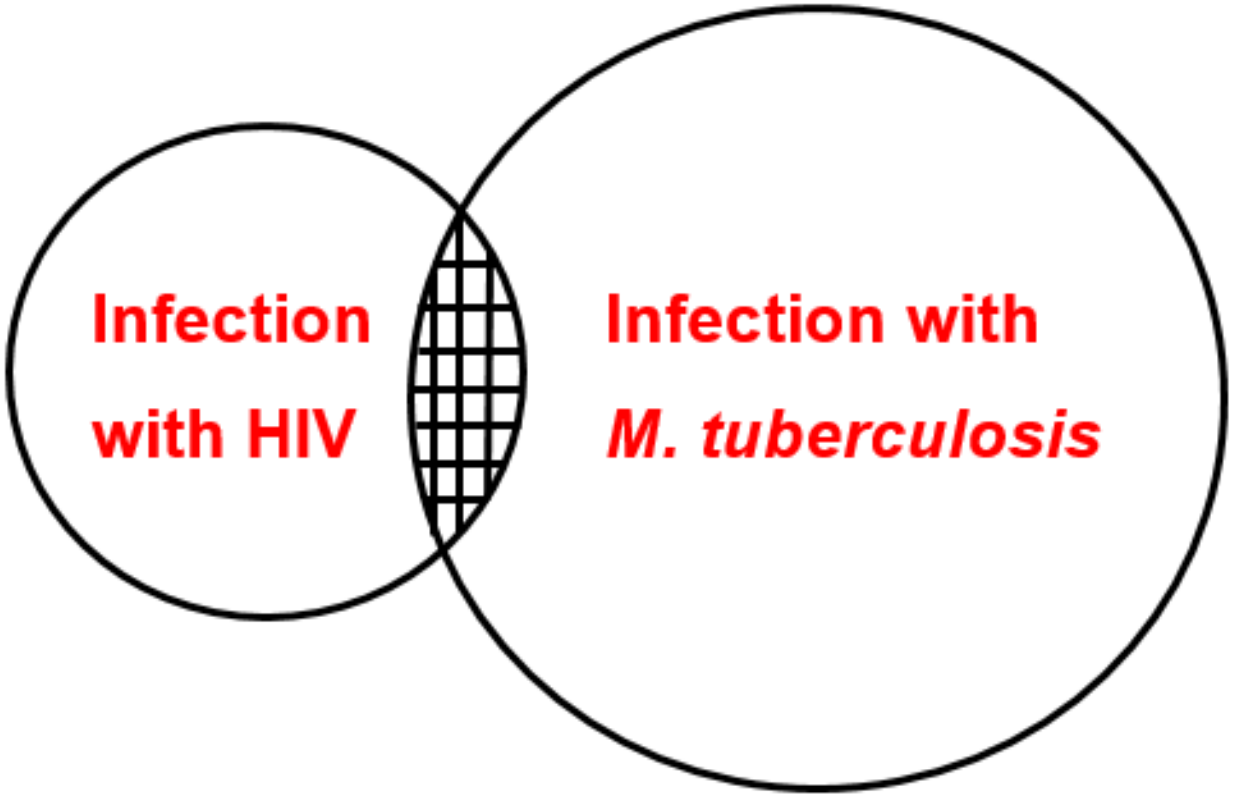


- ***Consistently reporting each year*: Algeria, Angola, Botswana, Cameroon, Comoros, Congo, Côte d'Ivoire, Democratic Republic of Congo, Ghana, Guinea, Kenya, Malawi, Mauritius, Mozambique, Nigeria, Senegal, South Africa, Uganda, United Republic of Tanzania, Zimbabwe**

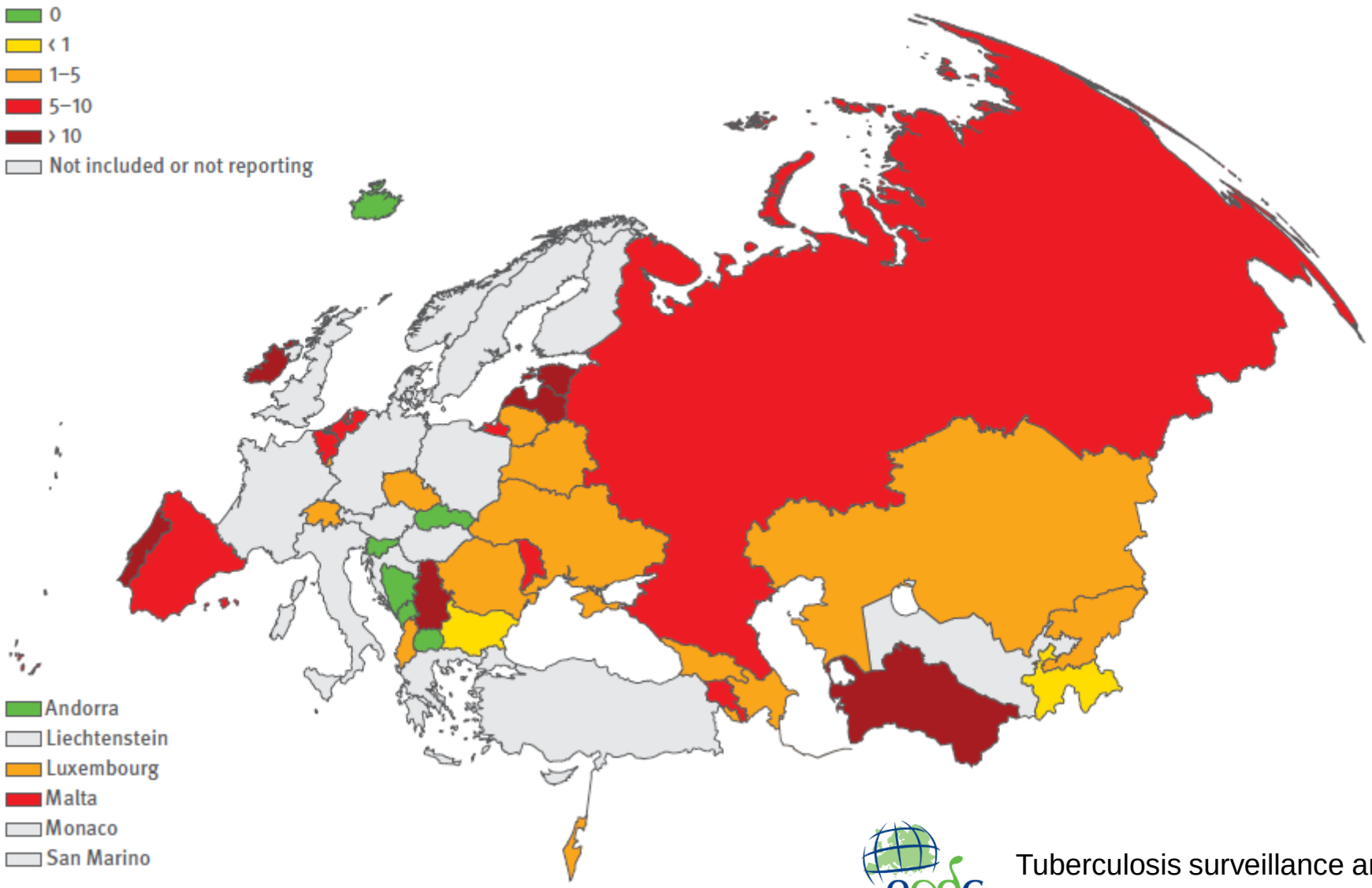
Sources: World Health Organization (2006), Global TB database; UNAIDS (2006)

TB-HIV coinfection

Europe

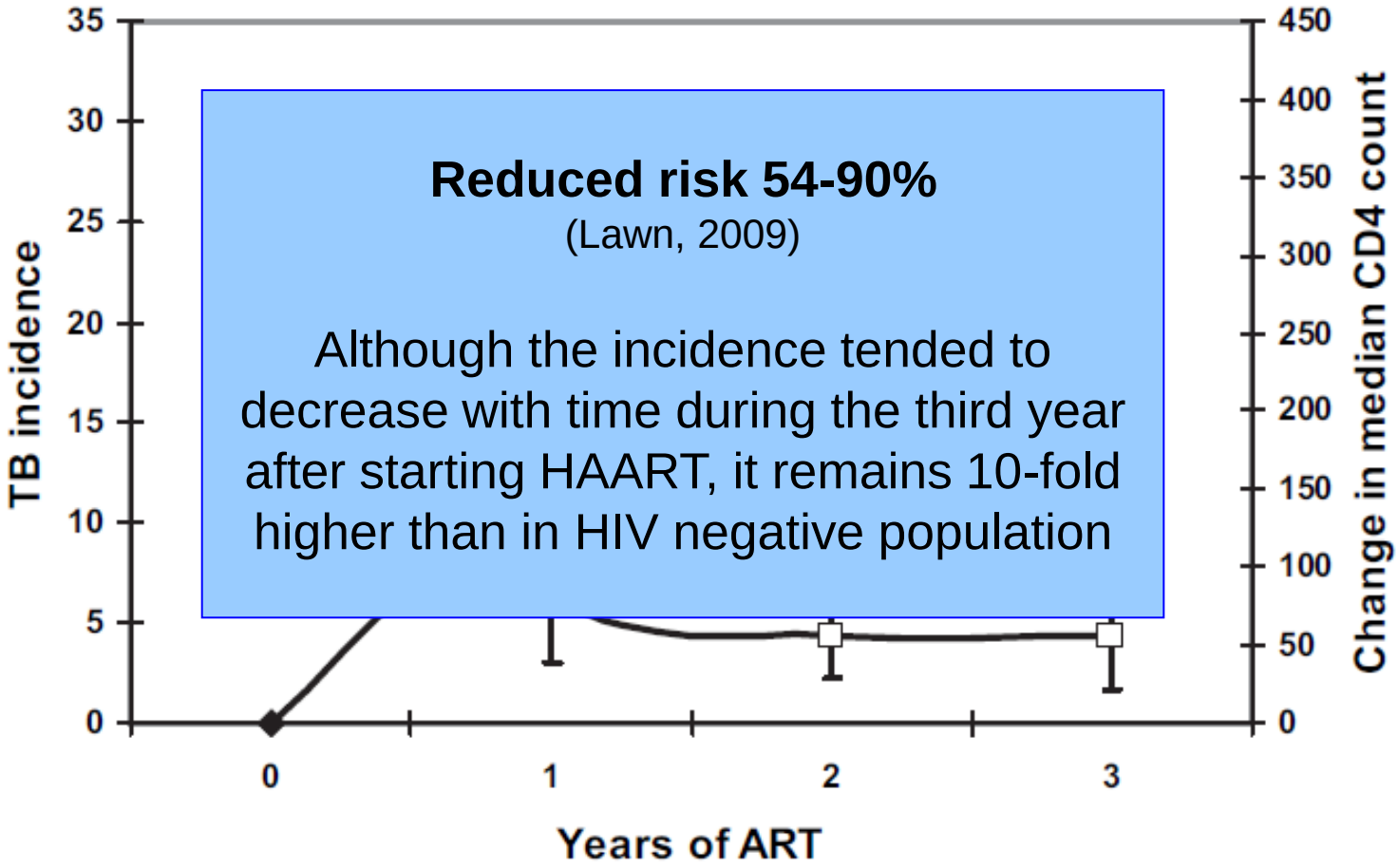


Percentage of HIV-positive TB cases among all TB cases with known HIV status, European Region, 2012



Tuberculosis surveillance and monitoring in Europe, 2014

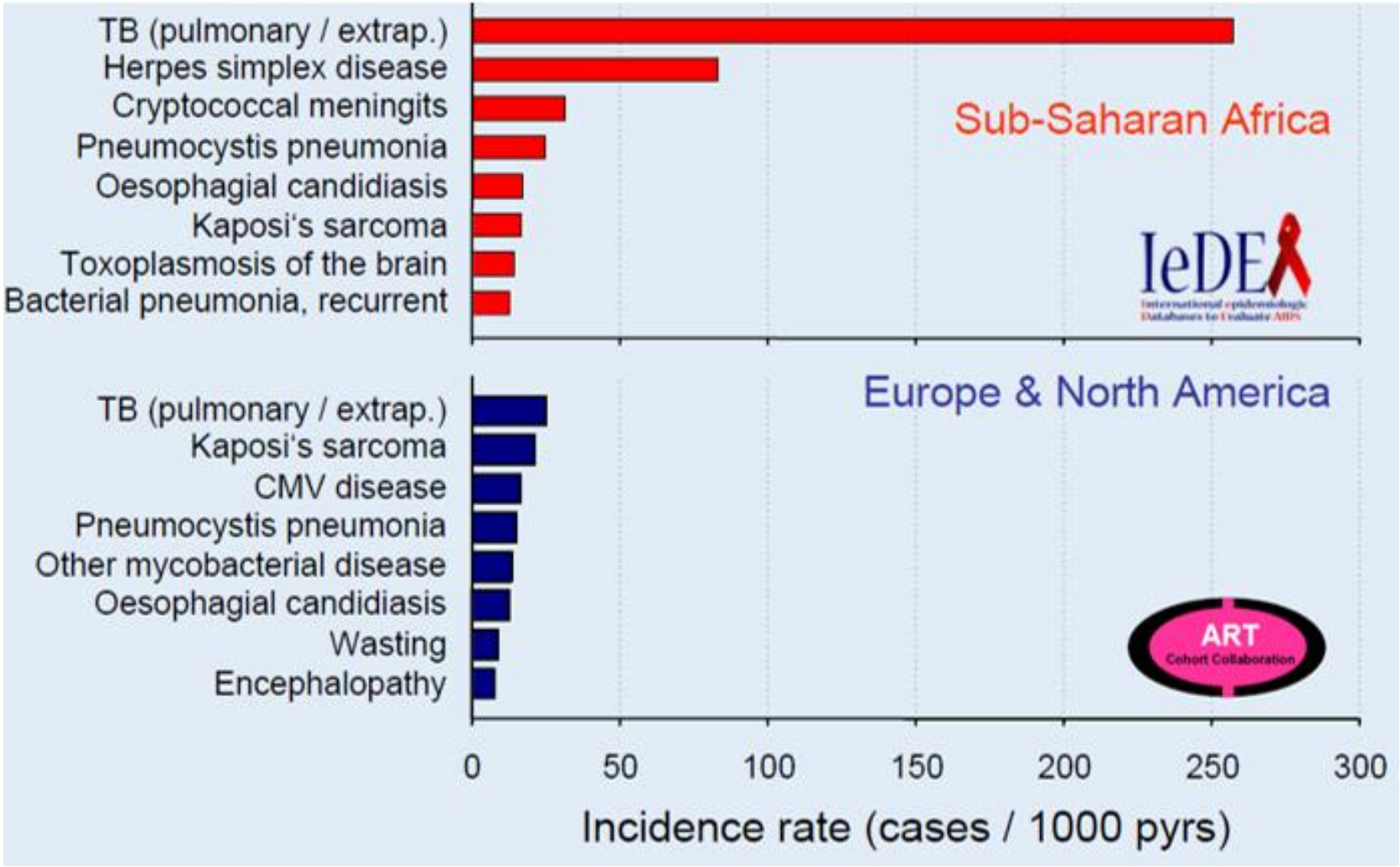
Riduzione del rischio di TB in corso di ART



Decreasing TB incidence rates (cases/100 person-years) and rising median CD4 cell counts (cells/mL). Data from a cohort in Cape Town, South Africa

Lawn SD, Clin Chest Med. 2009; 30: 685-699

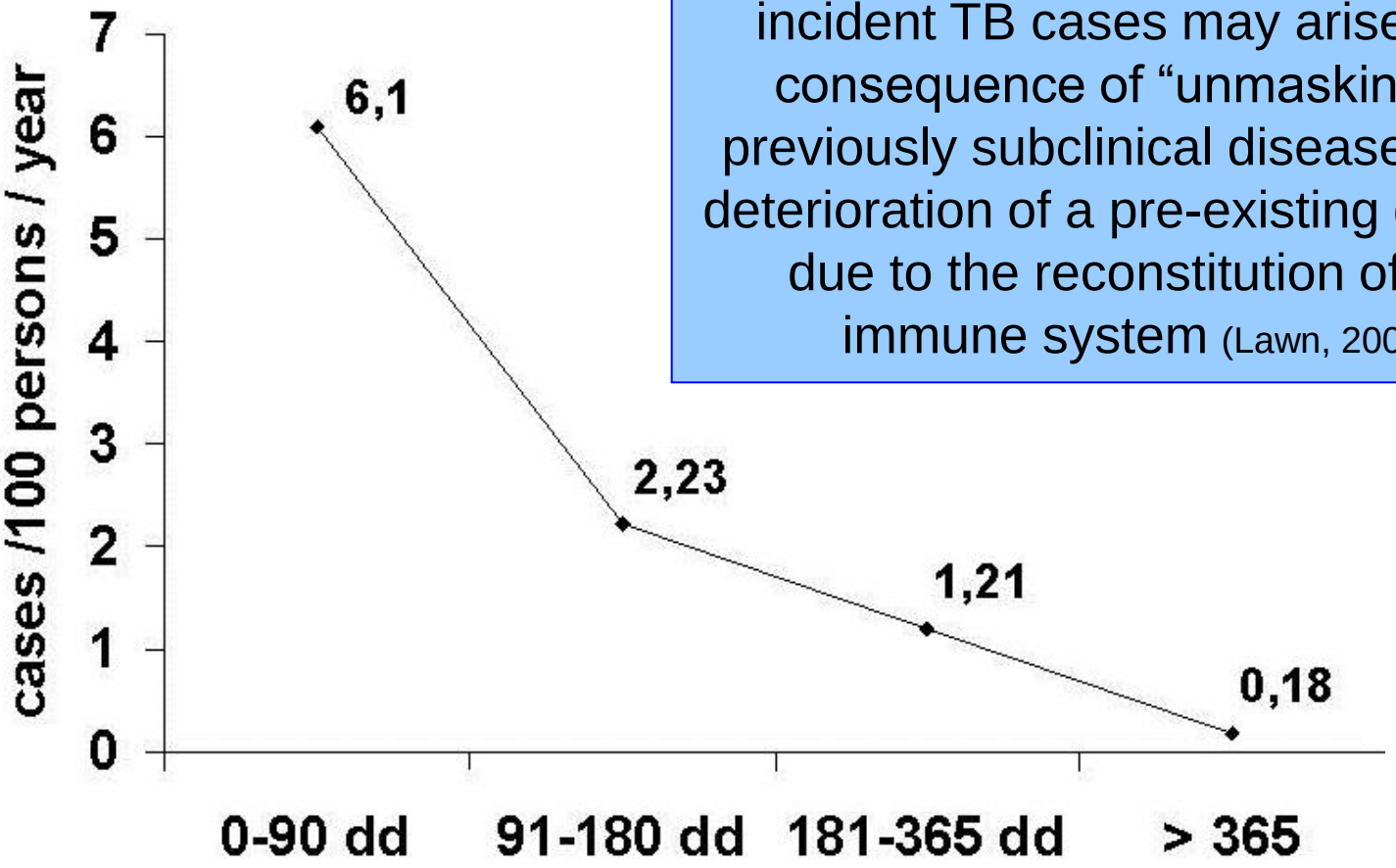
Commonest illness among PLHIV on ART



ART Cohort Collaboration
ArchIntern Med. 2005;165:416-423

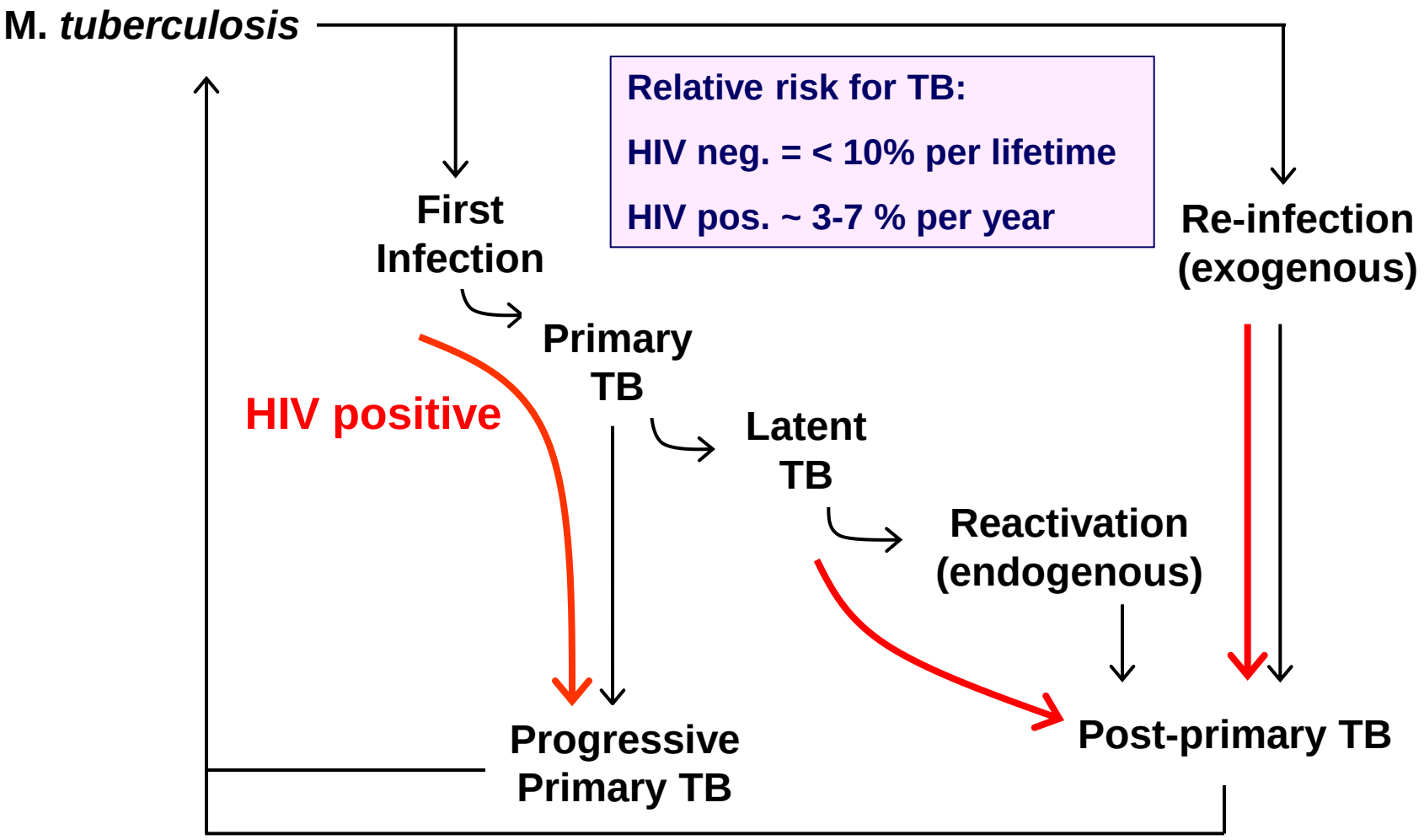
Incidence of tuberculosis among HIV seropositive patients by timing after initiation of HAART

During the initial months of HAART incident TB cases may arise as a consequence of “unmasking” of previously subclinical disease or the deterioration of a pre-existing disease due to the reconstitution of the immune system (Lawn, 2005)

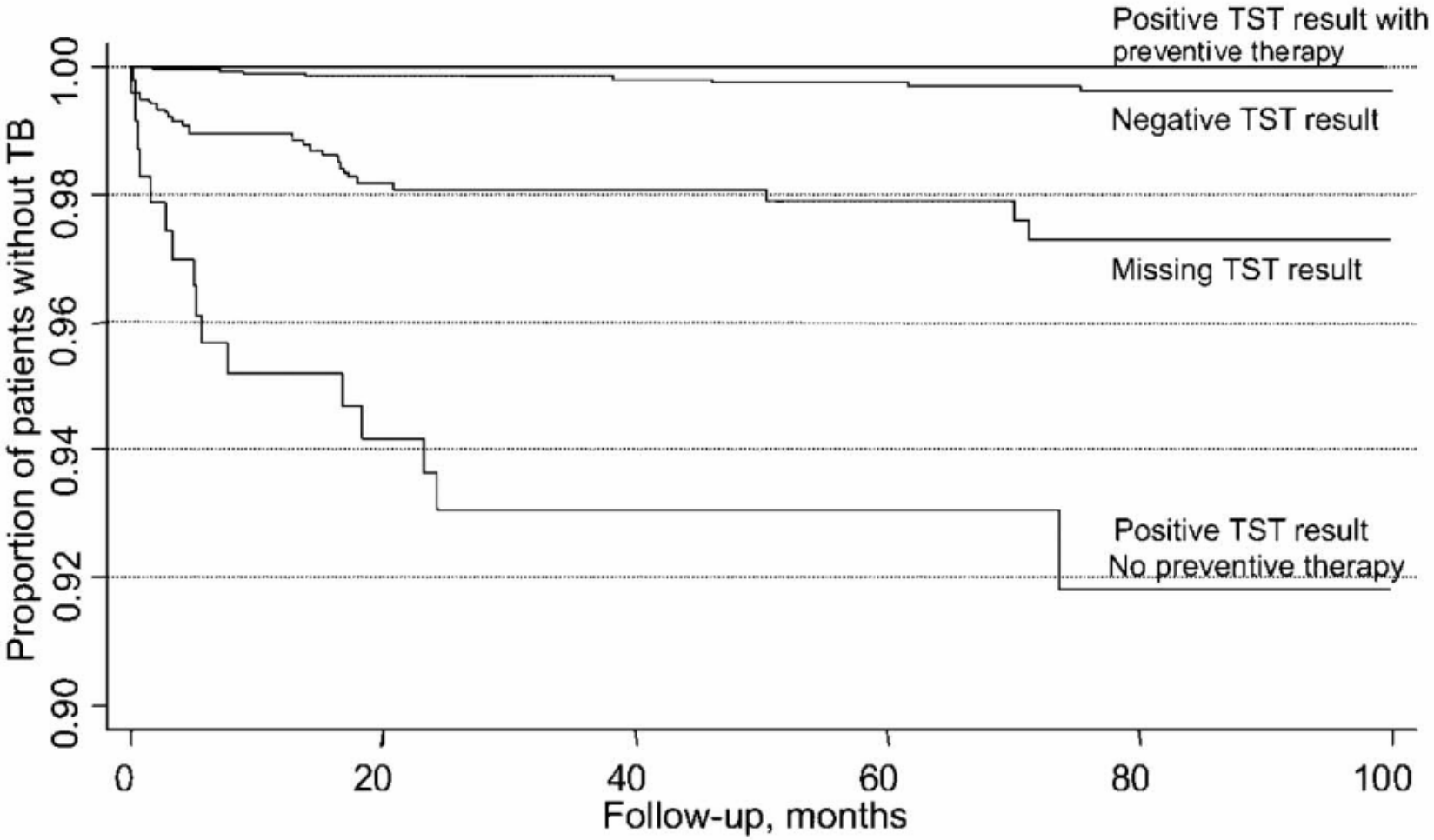


Dembele M, Int J Tub Lung Dis 2010, 14: 318

How HIV influences the TB natural history



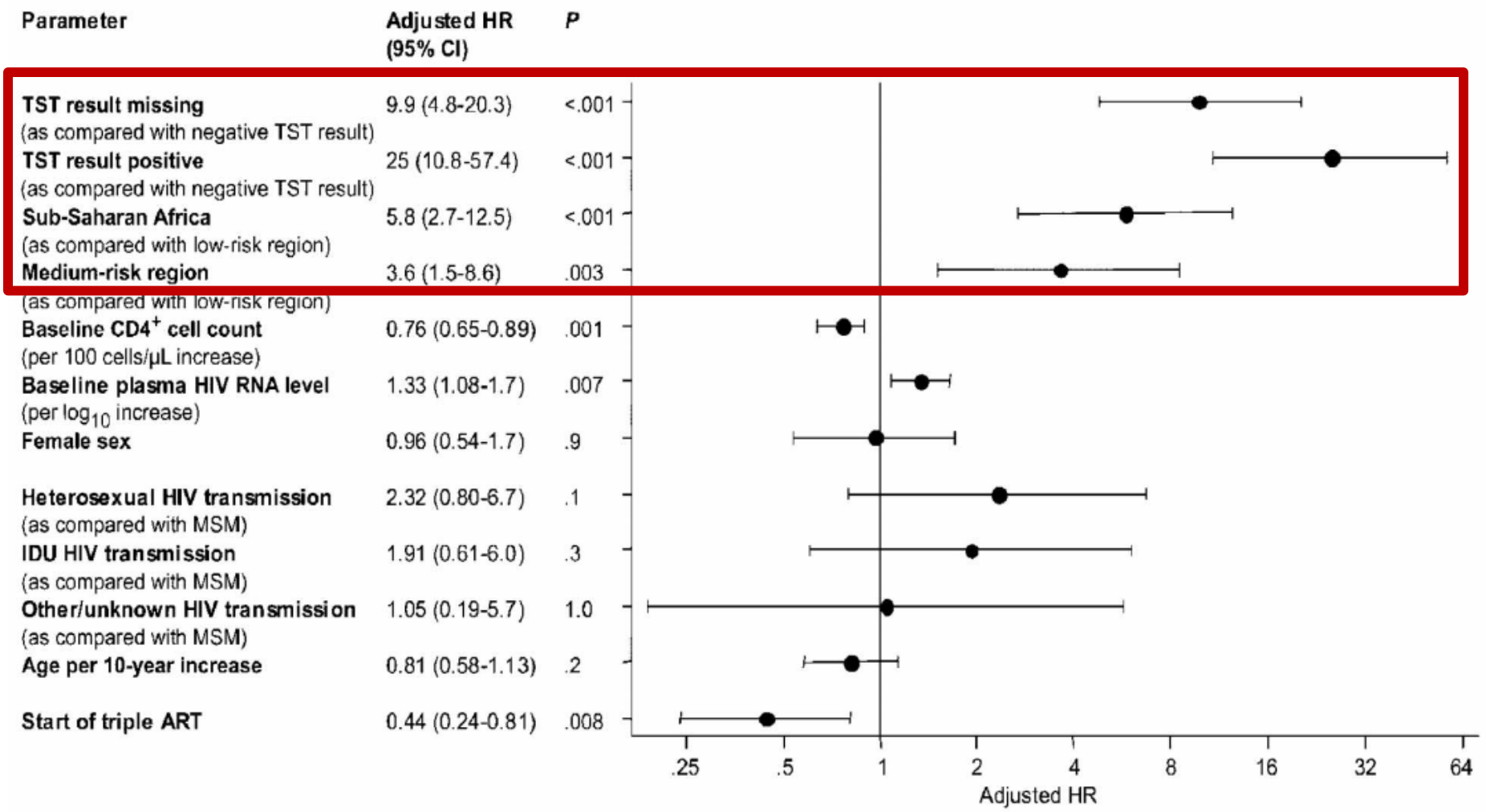
Risk of TB according to TST result



Swiss HIV Cohort Study

Elzi L, CID, 2007

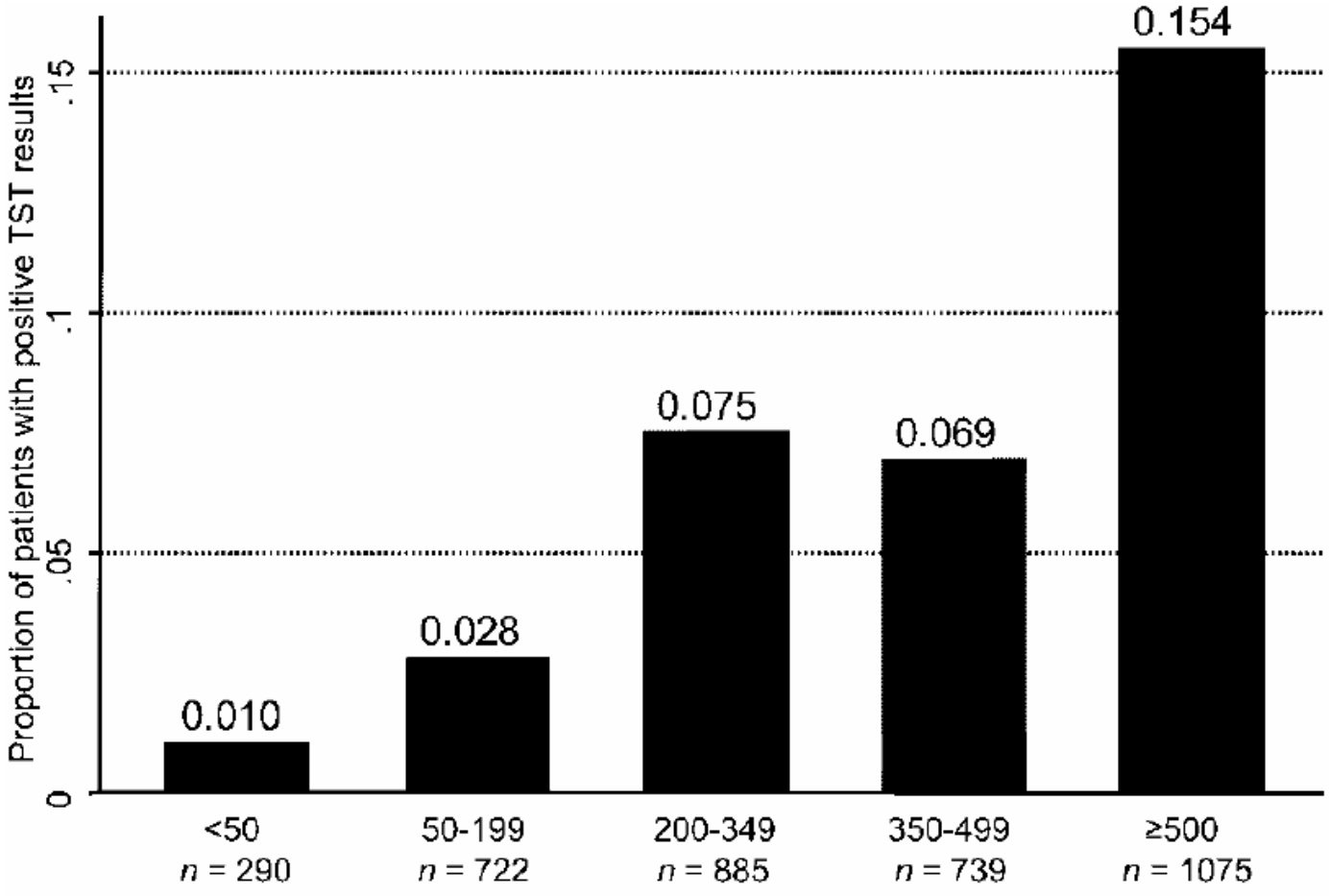
Risk of TB according to TST result



Swiss HIV Cohort Study

Elzi L, CID, 2007

The probability of a positive TST test is associated to the level of immune suppression



Swiss HIV Cohort Study

Elzi L, CID, 2007

Do IGRAs help for screening of LTBI in HIV+ subjects ?

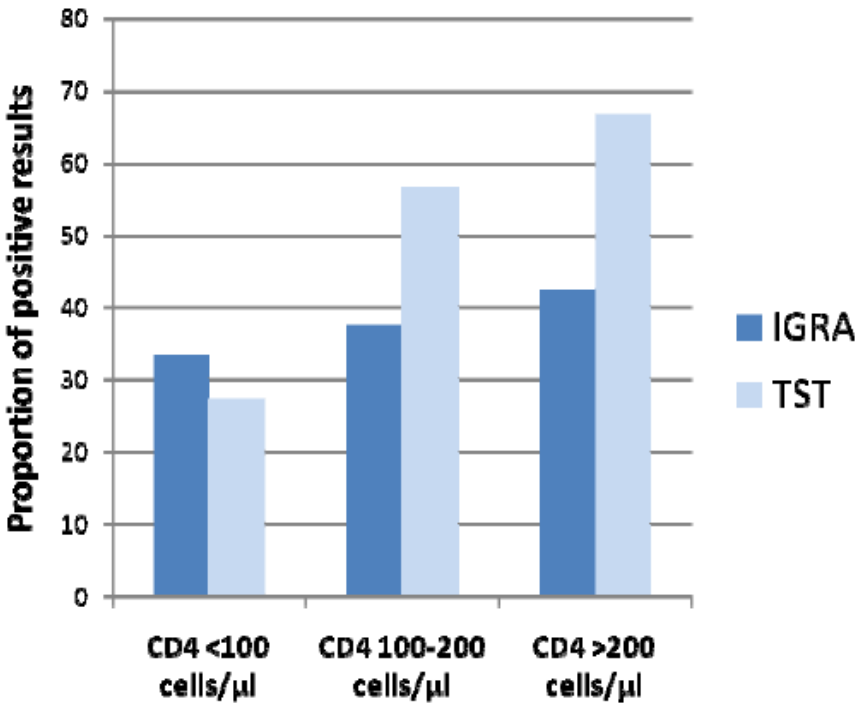
Characteristics of 64 HIV-infected individuals	
Median age (IQR)	35 (31-42)
Males	64%
Non-white ethnicity	54%
Prior AIDS-defining condition	18%
Median CD4 cell count (IQR)	223 (103-339)

IGRA (T Spot-TB®)

- Positive: 39%
- Indeterminate: 33%

Sensitivity of T Spot-TB®: 58%* (43-74)
Sensitivity of TST: 50% (35-65)

**if indeterminate results excluded*



Swiss HIV Cohort Study

Elzi L, CID, 2007

Do IGRAs help for screening of LTBI in HIV+ subjects ?

ELISA (Quantiferon TB-Gold in-tube test)

and

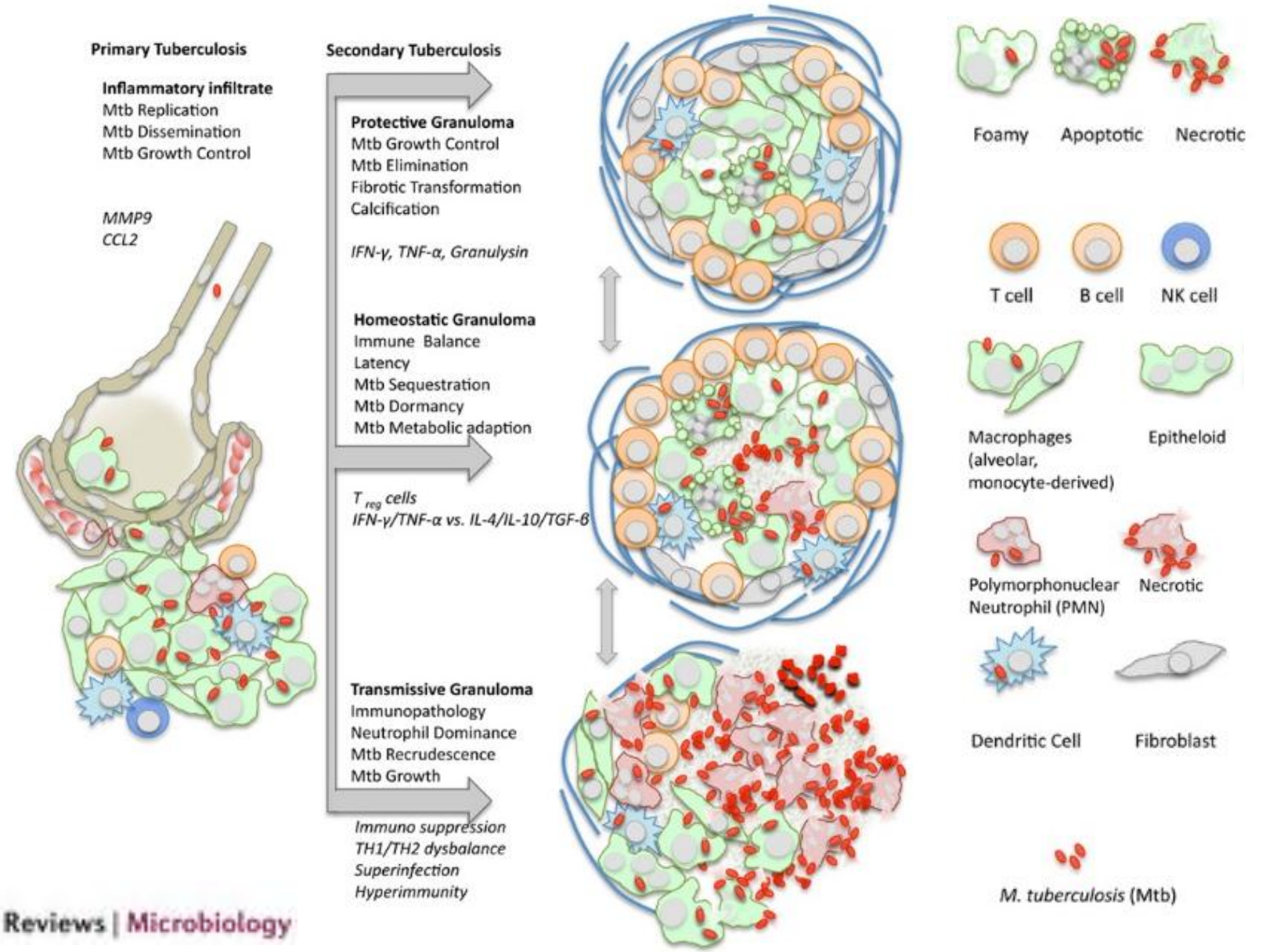
ELISPOT (T-SPOT.TB Test)

We have to consider:

- **better sensitivity for the ELISPOT** assay in HIV infection (Lawn 2007, Mandalakas 2008)
- **ELISPOT test result is much less dependent on the level of CD4 T cells** (Rangaka 2007a, Hammond 2008, Stephan 2008, Kim 2009), while the IFN-gamma response in the ELISA strongly correlates to the CD4 T cell count (Leidl 2009)

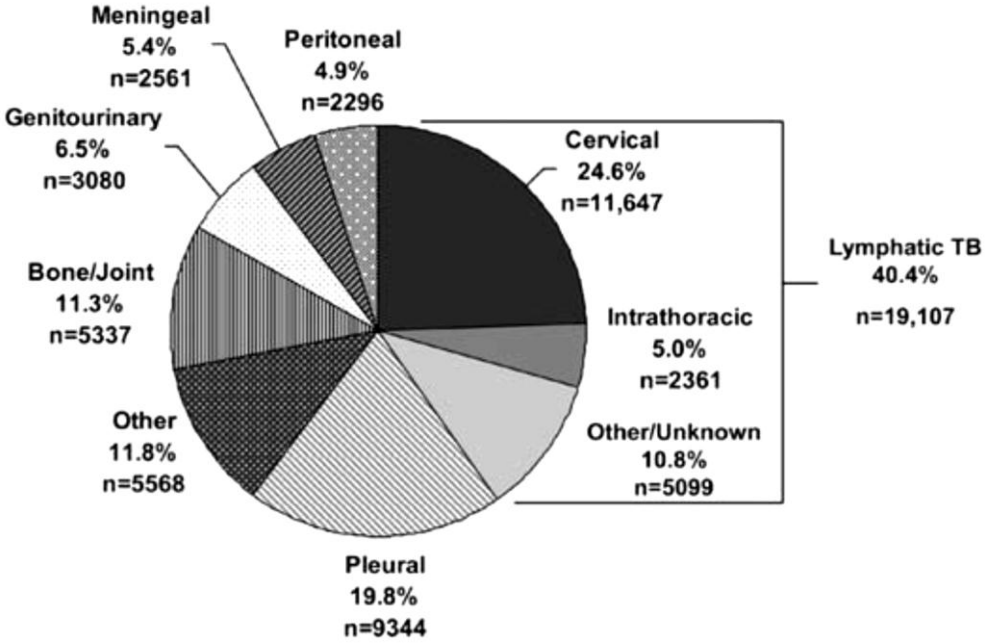
Cattamanchi A. JAIDS 2011; 56:230-8

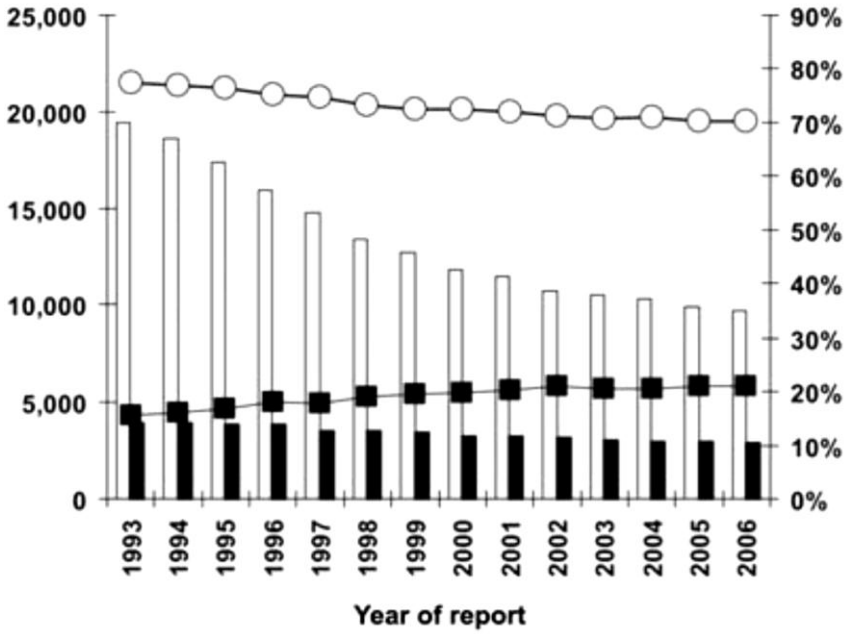
Evolution of tubercular granuloma



Nature Reviews | Microbiology

Extrapulmonary tuberculosis (EPTB)



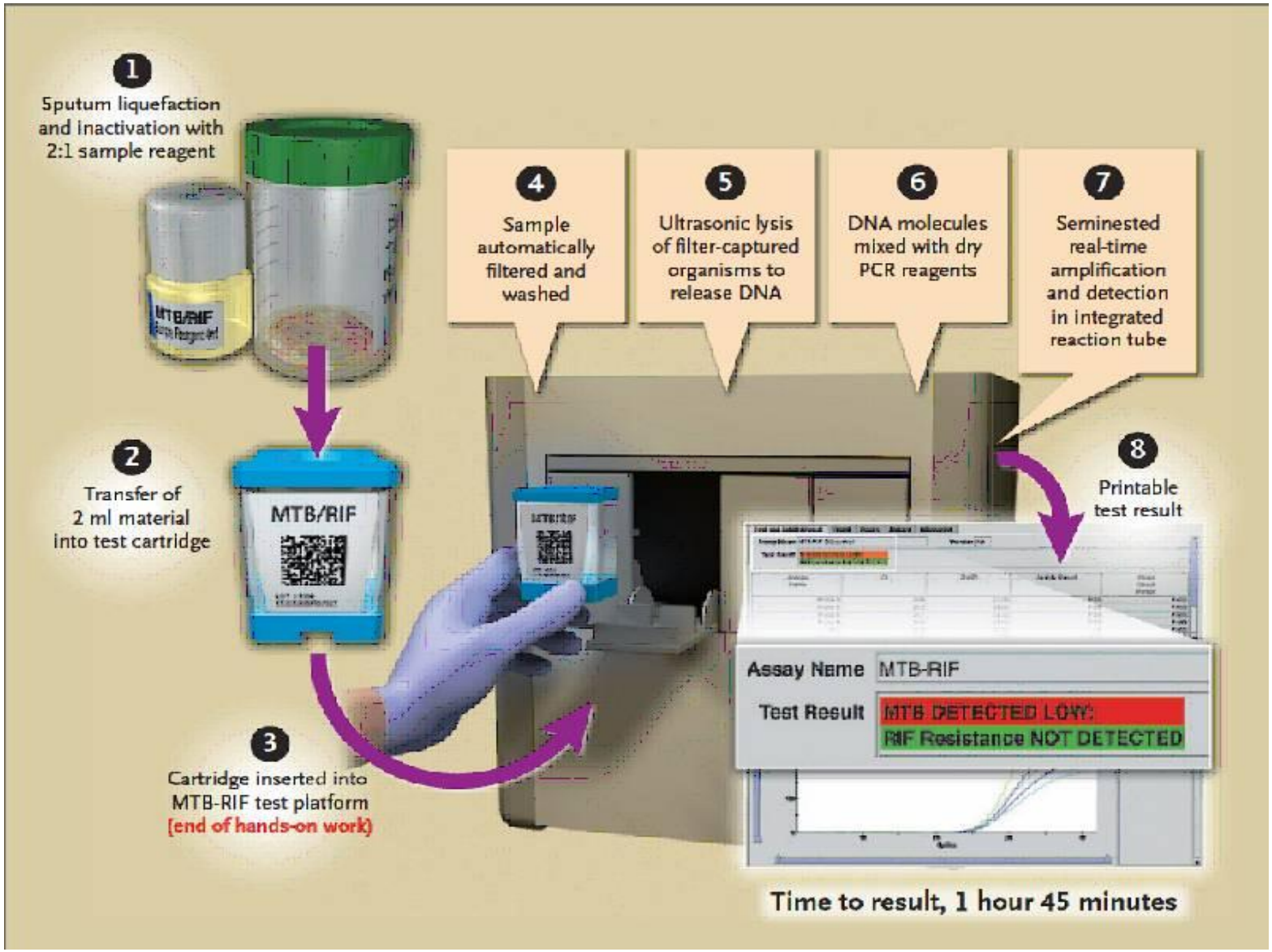


Among 253.299 cases, 73,6% were PTB and **18,7% were EPTB** (N = 47.293)

EPTB was almost equally associated with HIV status (OR, 1.1; CI, 1.1–1.1)

Peto HM. CID. 2009; 49:1350-7

Xpert MTB/RIF



Boehme et al. N Engl J Med 2010; 363: 1005

The NEW ENGLAND JOURNAL of MEDICINE

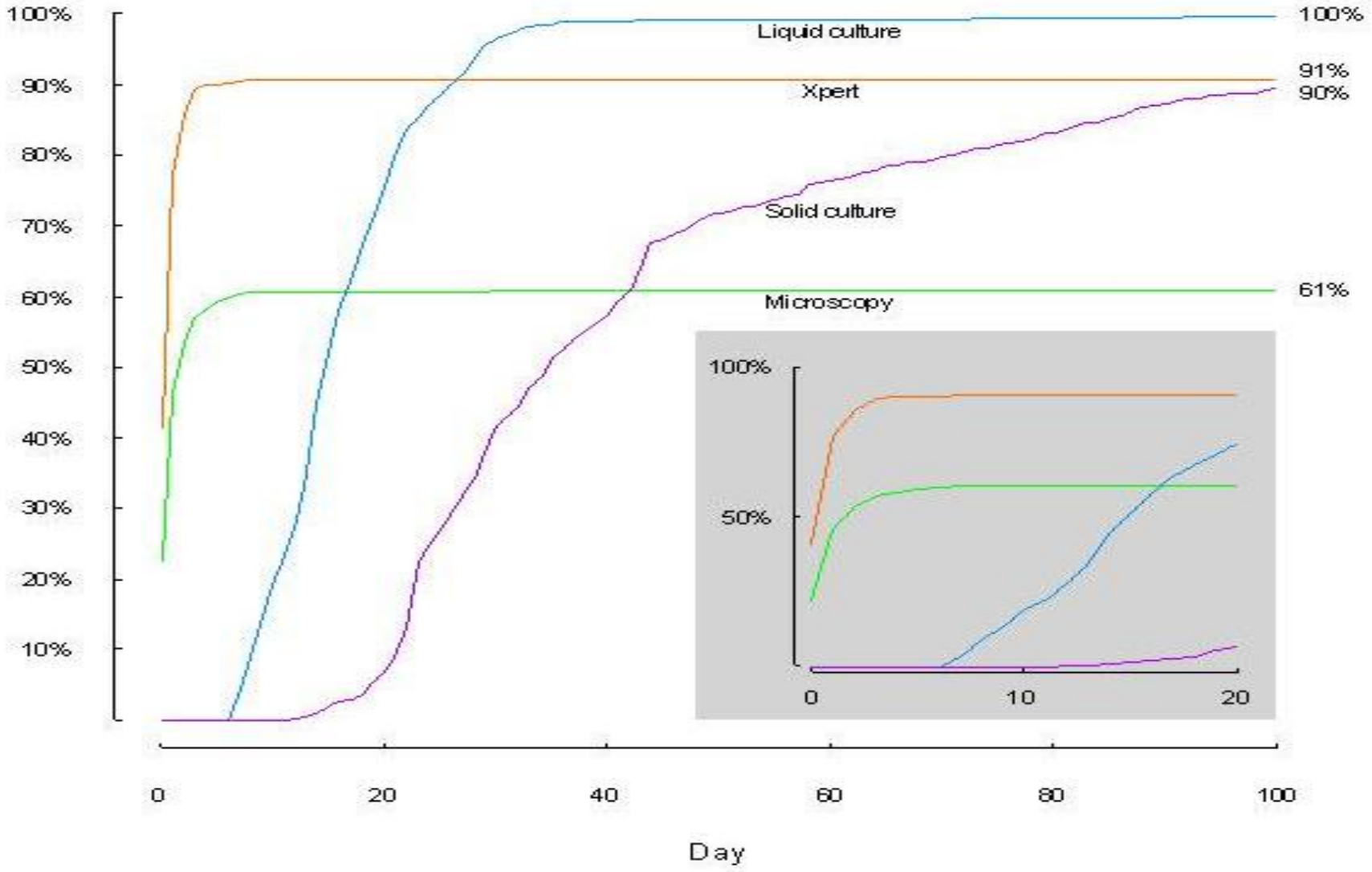
Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillemann, Ph.D., Mark P. Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiorella Krapp, M.D., Jenny Allen, B.Tech., Rasim Tahirli, M.D., Robert Blakemore, B.S., Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.

Among culture-positive patients, a single, direct MTB/RIF test identified 551 of 561 patients with smear-positive TB (98.2%) and 124 of 171 with smear-negative TB (72.5%). The test was specific in 604 of 609 patients without tuberculosis (99.2%).

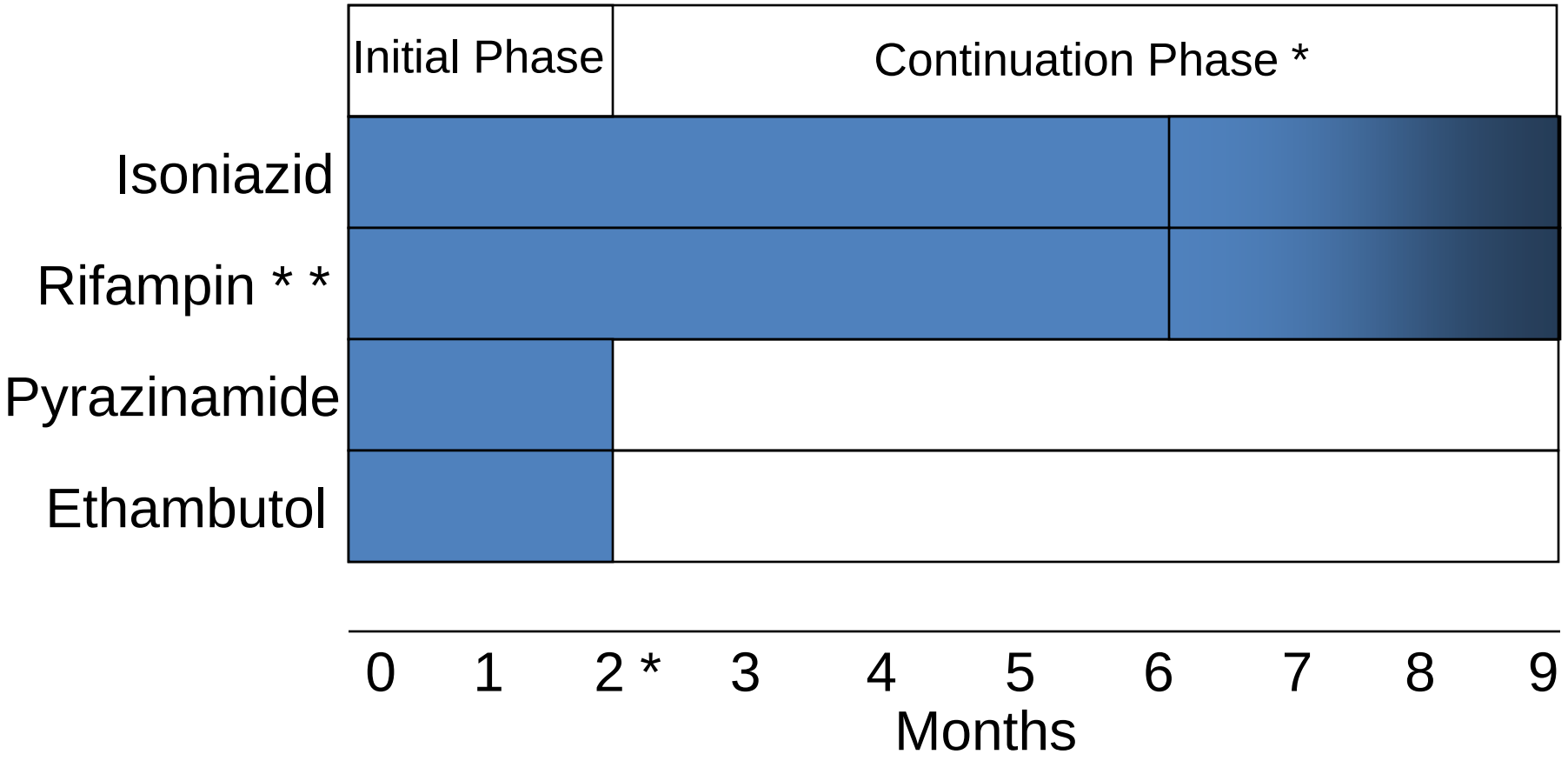
MTB/RIF testing correctly identified 200 of 205 patients (97.6%) with rifampin-resistant bacteria and 504 of 514 (98.1%) with rifampin-sensitive bacteria.

Proportion of TB cases detected and time to detection



Treatment of tuberculosis in HIV

Daily or 3 times weekly therapy only

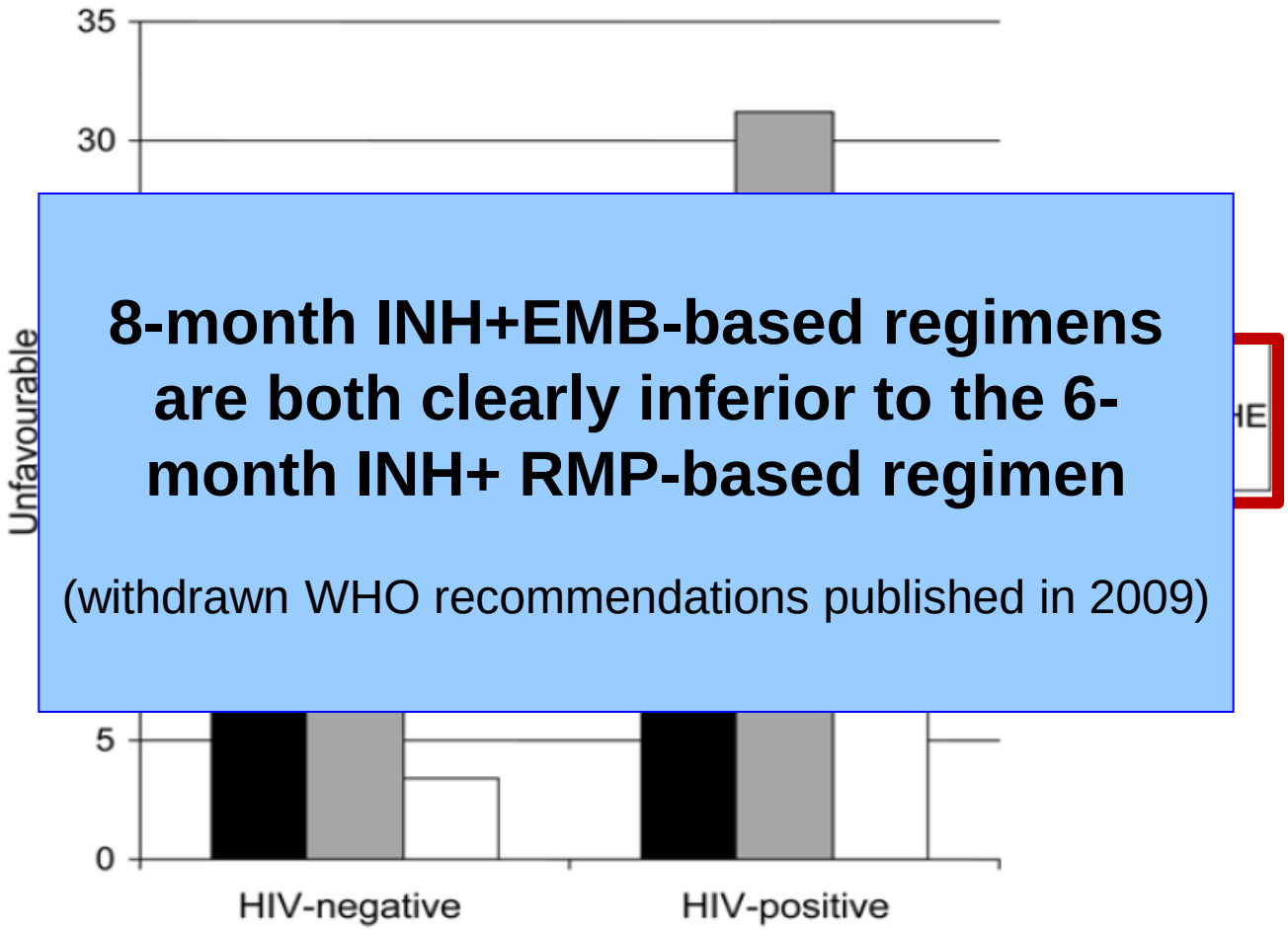


* If culture positive at 2 months and cavitation, extend therapy to 9 months

* * Substitute rifabutin if using protease inhibitors

CDC , ATS and Infectious Diseases Society of America Guidelines

Duration of treatment



8-month INH+EMB-based regimens are both clearly inferior to the 6-month INH+ RMP-based regimen

(withdrawn WHO recommendations published in 2009)

Nunn AJ. Int J Tuberc Lung Dis, 2011 15(6):741–745

Is a 6-month therapy duration the best one?

Pooled Estimates of Major Outcomes Stratified by Duration of Rifampin

Outcome, d	No. of		Pooled event rate	(95% CI)
Failure				
2 Months				(0–0.71)
6 Months				(0–0.54)
≥8 Mont				(0–0.62)
Relapse				
2 Months				(0.61–0.87)
6 Months				(0.89–0.94)
≥8 Mont				(0–0.64)
Death during treatment				
2 Months	12	205/1077	16.6 (10.2–22.9)	0.94 (0.91–0.96)
6 Months	19	196/1573	10.5 (6.8–14.3)	0.76 (0.63–0.84)
≥8 Months	9	60/501	11.7 (5.9–18.4)	0.41 (0–0.73)

Maybe not!

"… rates of treatment failure and relapse were lower with longer duration of rifamycin, whereas mortality was higher in groups treated with 2-month rifamycin regimens, although **none of these differences were statistically significant**."

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

Factors influencing treatment success

Adjusted risk ratios (aRRs) of treatment failure, relapse, and death in patients coinfected with HIV

Variable	reat- CI)	P^b
Duration of		
2 Months		.03
6 Months		
⩾8 Month		
Intermittent		
Initial phas		.42
Initial phas		
Receipt of A		
Some or a		.39
None or n		
Dispersion p	31)	

Our data suggest that:

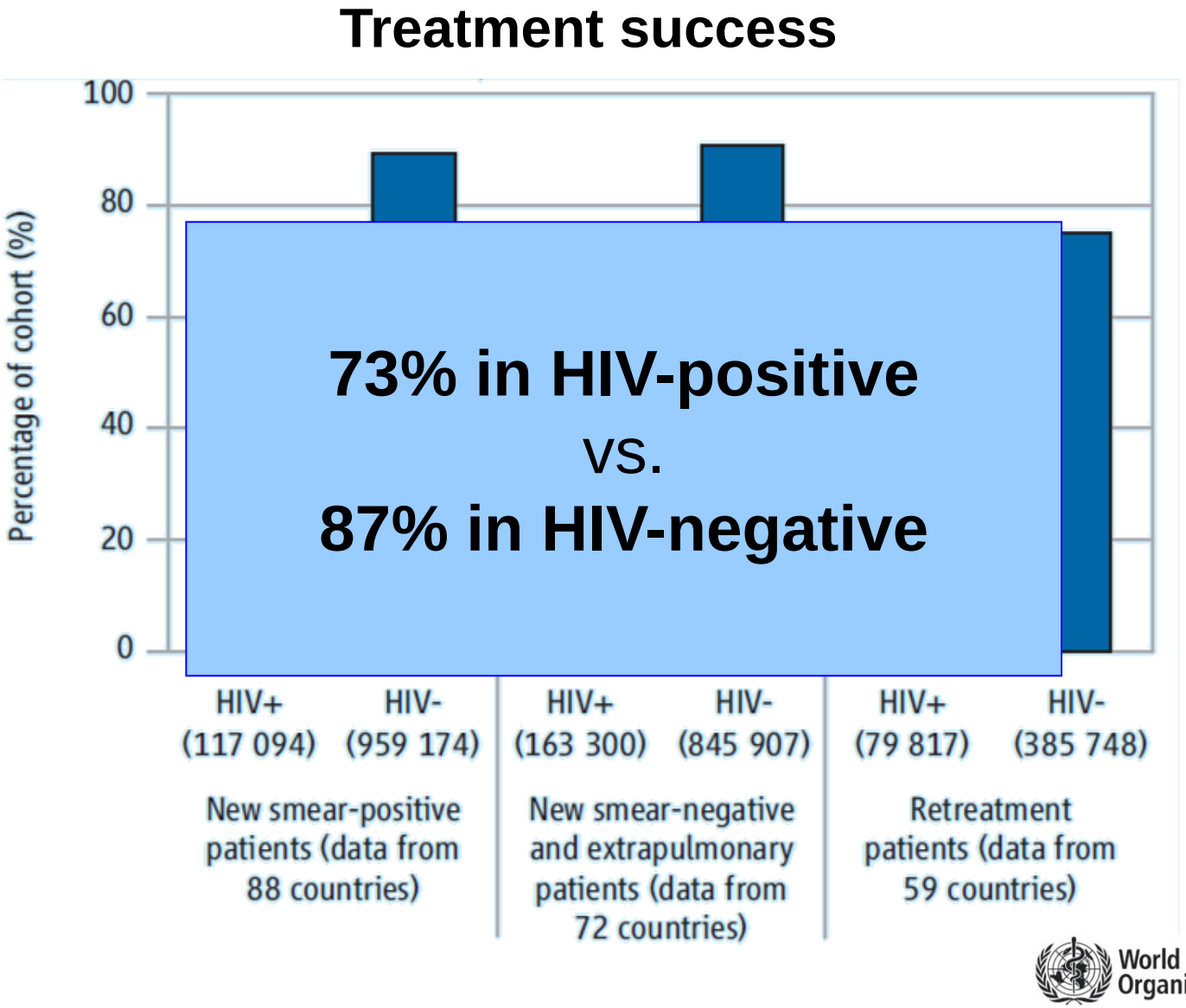
- **longer duration of rifamycin therapy** (at least 8 months)
- **daily dosing in the initial phase**
- **concurrent ART**

… might be associated with better outcomes.

[d] Nonoverlapping 95% CIs, which indicate a statistically significant difference between substrata

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

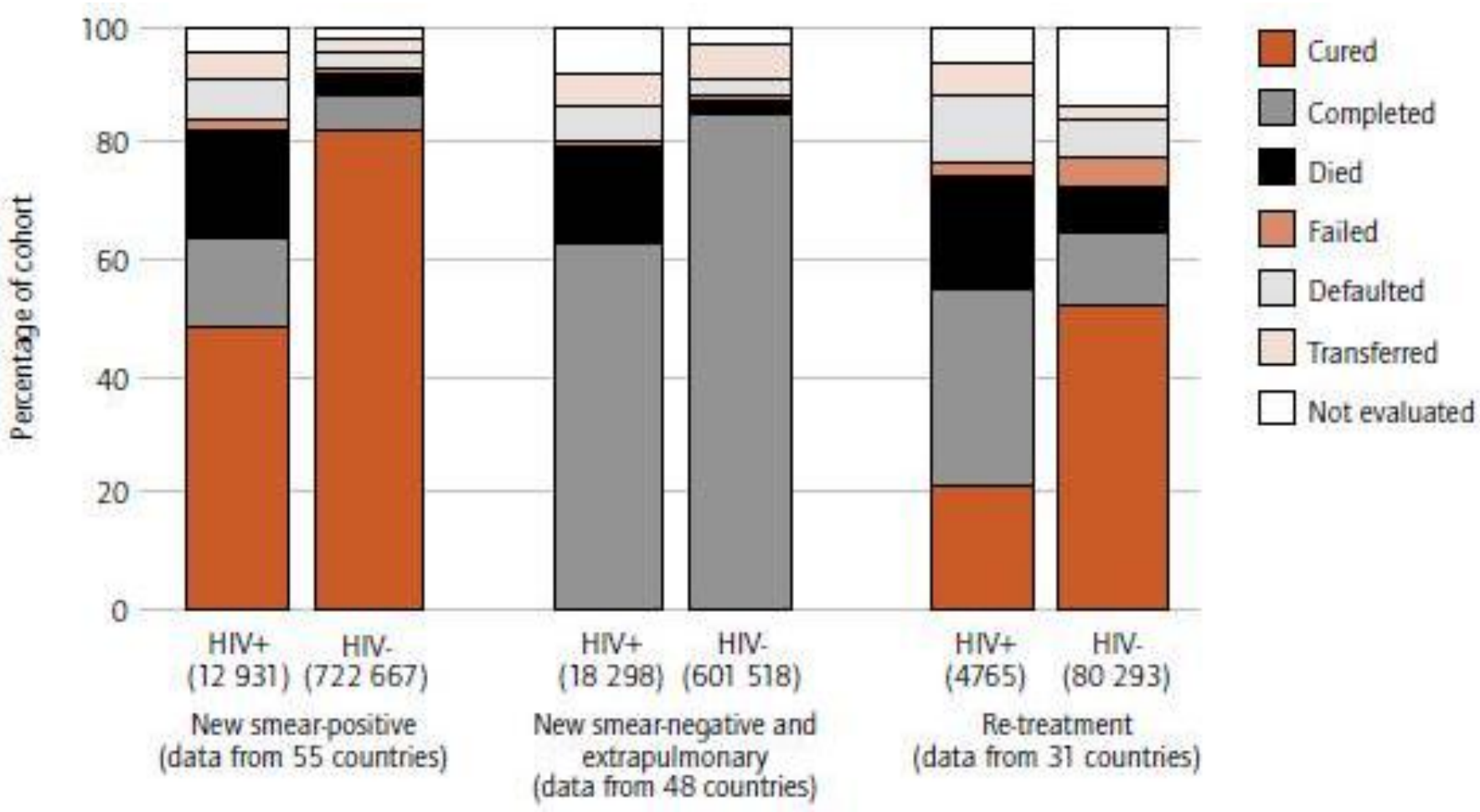
Treatment outcomes in HIV-positive patients, 2011



World Health Organization

Global Tuberculosis Report, 2013

Programmatic outcomes for TB/HIV patients are poor



Treatment outcomes, 2006 cohort

ART for HIV/tuberculosis co-infection

WHO recommendation

- Use **efavirenz** as the preferred non nucleoside reverse transcriptase inhibitor in patients starting ART while on treatment

(strong recommendation – High quality of evidence)

WHO, 2010: Rapid Advice on ART

Efavirenz, no doubts

Advantages

- Is a first line option for HIV treatment
- In the most widely used first line drug in resource limited settings
- Allows for standard TB therapy
- Allows for once a day therapy with minimal pill burden (Atripla)
- Clinical trials available from South Africa and Thailand

EFV dose in TB/HIV co-infection treated with RMP (600 versus 800 mg)

- **Reduction in EFV levels: 20-25%**
- Clearance of EFV lower in in Afro-Americans and Hispanics than Caucasians (impact on safety profile); **body weight also important** (60 kg threshold)
- In Caucasian > 60 Kg EFV 800 mg + RIF give AUC similar to EFV 600 mg
- In Thailand and South Africa studies show effective, pharmacological, clinical, immunological and virologic response with conventional 600 mg EFV dose

Efavirenz vs Nevirapine

Rifampicin is a **potent inducer of CYP3A4** (55-fold) and it **increases the expression of CYP2B6** (9-fold)

nevirapine is metabolized by both isoenzymes 3A4 and 2B6, whereas efavirenz is mainly metabolized by cytochrome P450 isoenzyme 2B6 only

Efavirenz may be the better NNRTI for concomitant treatment of HIV-1 infected patients with TB who are also receiving rifampicin

Efavirenz Nevirapine

One-fifth of patients in the **nevirapine group** having l**ow C_{12} drug levels** at both time points

Manosuthi W. CID. 2009; 48:1752–9

Linee Guida Italiane SIMIT (novembre 2013)

NRTI

○ Un **regime cART di scelta** da associare ad una terapia antitubercolare che includa rifampicina è rappresentato da un **backbone nucleosidico più efavirenz** (EFV) (*)	[AI]
○ L'uso di **nevirapina** (#) in associazione a rifampicina può essere considerato nei **pazienti che non tollerano EFV**	[CII]
○ L'uso di **rilpivirina in associazione con rifampicina o rifabutina è sconsigliato** per la riduzione dei livelli plasmatici di rilpivirina	[CII]

* = Limitazione rappresentata dall'uso in gravidanza. La posologia raccomandata di EFV è di 600 mg al dì salvo nei soggetti di peso > 60 Kg dove è 800 mg.

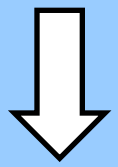
= L'impiego di nevirapina in associazione a rifabutina è possibile, ma questa combinazione non presenta vantaggi e può anzi presentare svantaggi in termini di tossicità epatica rispetto ad altre opzioni terapeutiche

What if efavirenz cannot be used ?

Effect of **RFM** on serum concentrations of **PIs and NNRTI**

PI		NNRTI	
Saquinavir	↓ 80%	Nevirapine	↓ 37-58%
Ritonavir	↓ 35%	Efavirenz	↓ 13-26%
Indinavir	↓ 90%		
Nelfinavir	↓ 82%		
Amprenavir	↓ 81%		
Lopinavir/ritonavir	↓ 75%		
Atazanavir	↓ 60%		

Significantly ↓ PI exposure (>75%) despite ritonavir boosting



Co-administration should be avoided

Clin Infect Dis 1999; 28: 419-30

DHHS, 2013

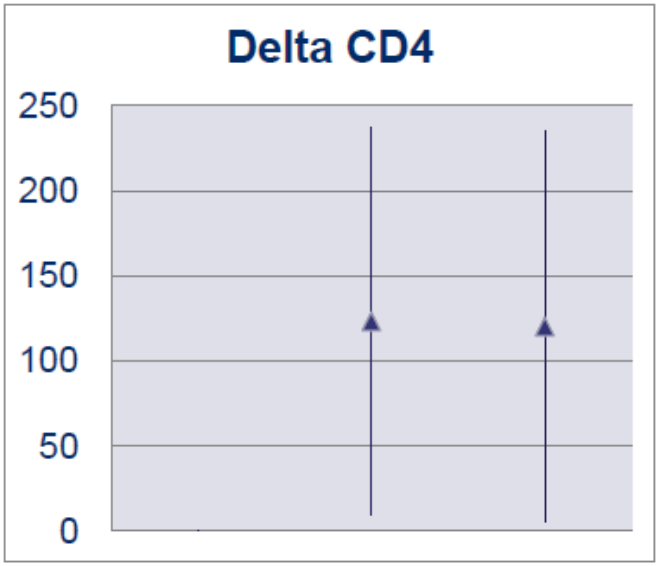
CYP-P450 mediated metabolism of PI, NNRTIs and Maraviroc

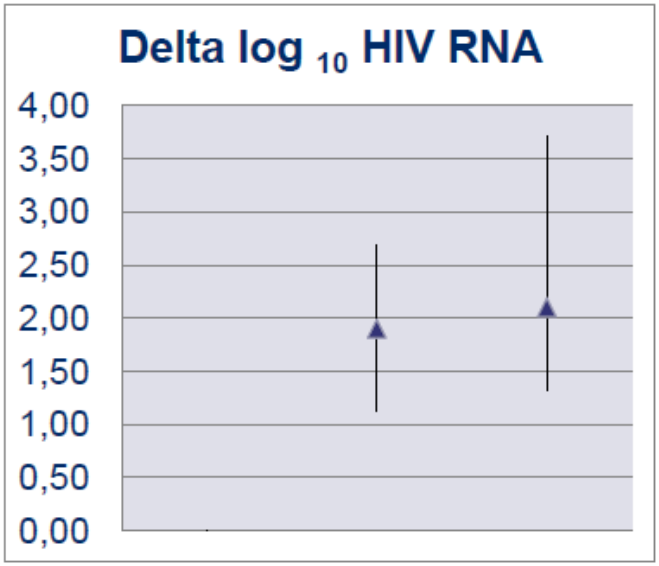
- **PIs**
  - **All PIs** are metabolized via CYP 450 (primarily via 3A4 isoenzyme)
  - **Ritonavir** and **most PIs** - 3A4 substrate and inhibitor
- **NNRTIs**
  - ***Delavirdine*** - 3A4 Inhibitor
  - ***Efavirenz*** - mixed inducer and inhbitor
  - ***Etravirine*** - 3A4 substrate and inhibitor, 2C9 and 2C19 substrate and inhibitor
  - ***Nevirapine*** - 3A4 inducer
- **CCR5 Antagonist**
  - ***Maraviroc*** - 3A4 substrate

Efavirenz vs PIs

RHZE + FTC/TDF/EFV vs RbHZE + TC/TDF/LPV-r

	EFV + RFP (49 pz)	PI + RBT (47 pz)	p
Completamento terapia	28 (57%)	22 (47%)	0.41
Effetti collaterali gravi	5 (10%)	8 (17%)	0.38
Persi al follow-up	9 (18%)	12 (25%)	0.55
Decessi	2 (4%)	2 (4%)	1.0





Matteelli A, CROI 2013

Rifabutin and PIs

Available data allows for the use of **Lopinavir, Atazanavir, Fosamprenavir, Darunavir, Tipranavir** always with **Ritonavir** boosting

- 9/10 patients with low C_{max} values (<30mg/ml)

  (Boulanger C, CID 2009)

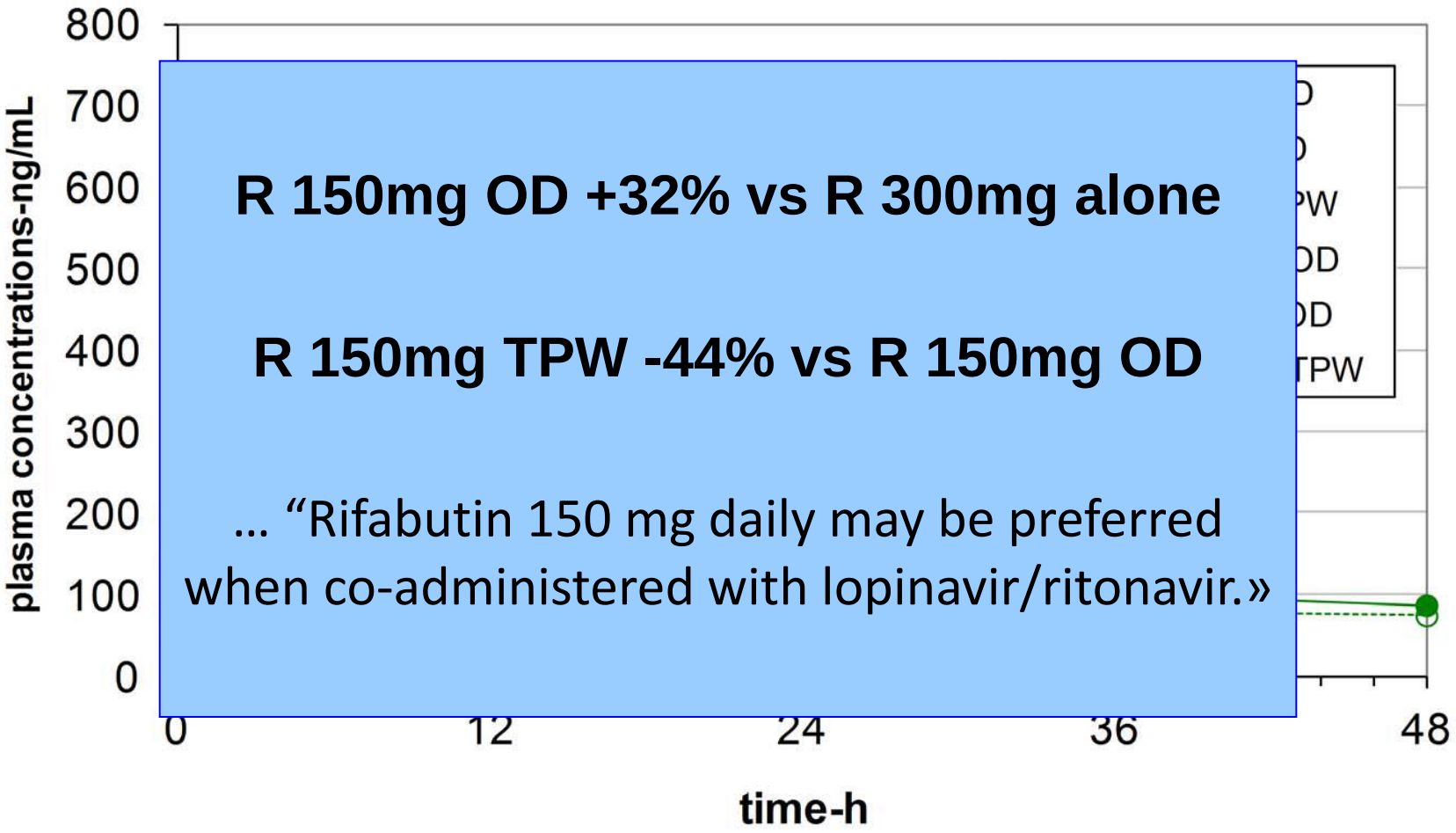
- 5/5 patients with low C_{max} values (<45mg/ml)

  (Khaci H, JAC 2009)

- AUC significantly reduced compared to the standard in 16 TB/HIV patients in South Africa. AUC reverted by 150 mg daily during LPV/r treatment

  (Naiker S, 18° ICAAR, 2011)

Rifabutin TPW vs OD



R 150mg OD +32% vs R 300mg alone

R 150mg TPW -44% vs R 150mg OD

… “Rifabutin 150 mg daily may be preferred when co-administered with lopinavir/ritonavir.»

Lan NTN. PLoS ONE 9(1): e84866. doi:10.1371

Linee Guida Italiane SIMIT (novembre 2013)

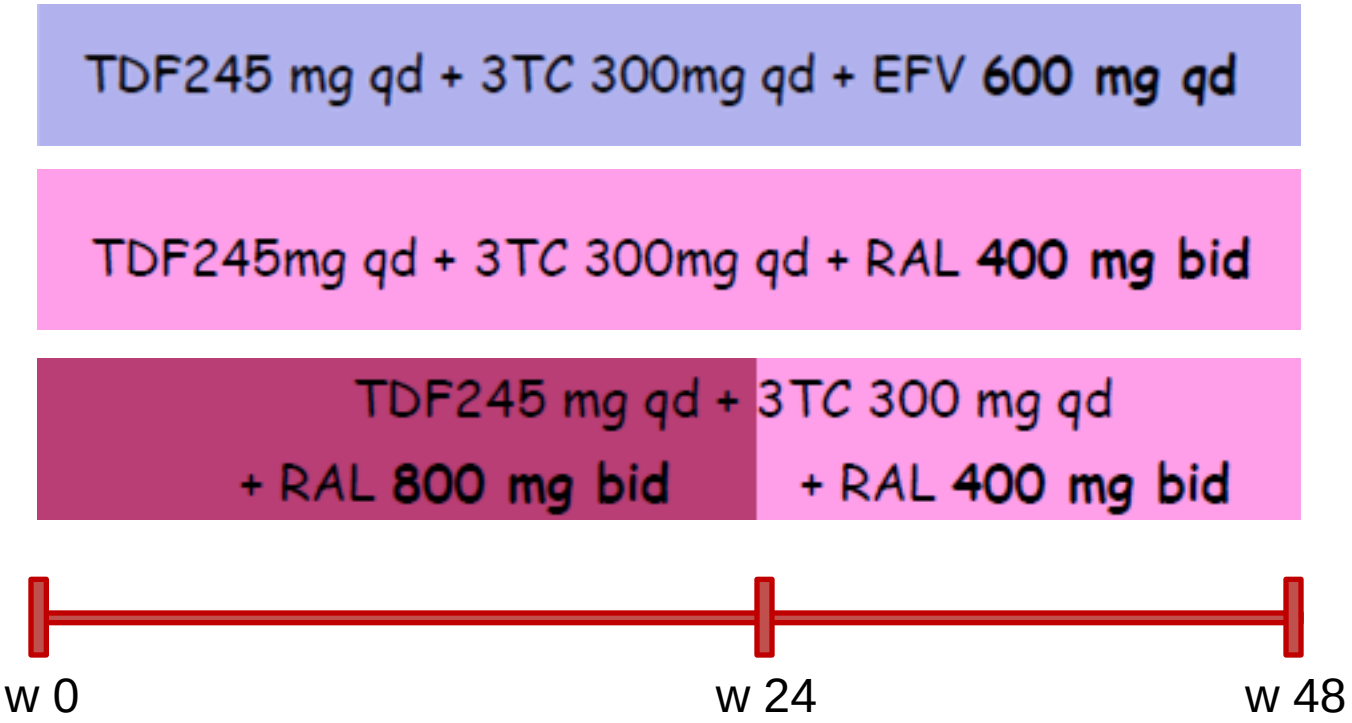
PIs

○ L'utilizzo di **IP/r è possibile se associato a rifabutina**	[BI]
○ La **dose di rifabutina** deve essere ridotta a **150 mg una volta al giorno** se in associazione a un inibitore delle proteasi	[AII]
○ Si raccomanda l'**esecuzione della TDM di rifabutina** nei pazienti in terapia con tutti gli IP	[BI]
○ Regimi cART più complessi (es. associazioni di due IP più ritonavir ovvero di IP e NNRTI) è da riservare a casi in cui l'impiego sia strettamente indispensabile e sotto attento monitoraggio clinico e di TDM	[CI]

L'associazione di IP e rifabutina trova indicazione elettiva in pazienti con resistenza o intolleranza agli NNRTI

Use of Raltegravir in TB-HIV coinfection

ANRS 12 180 Reflate TB Study



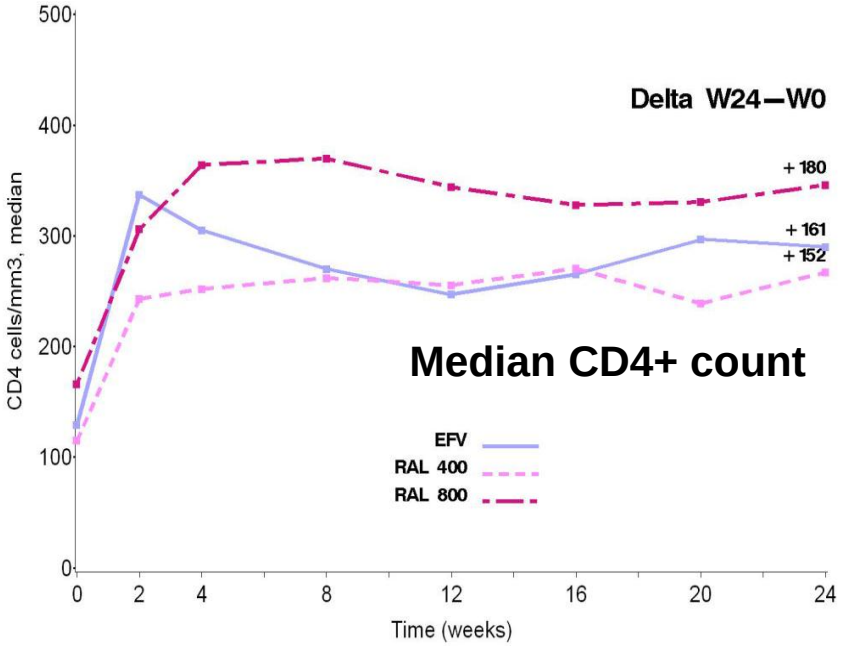
Anti-TB regimen: HRZE for 2 months + HR for 4 months

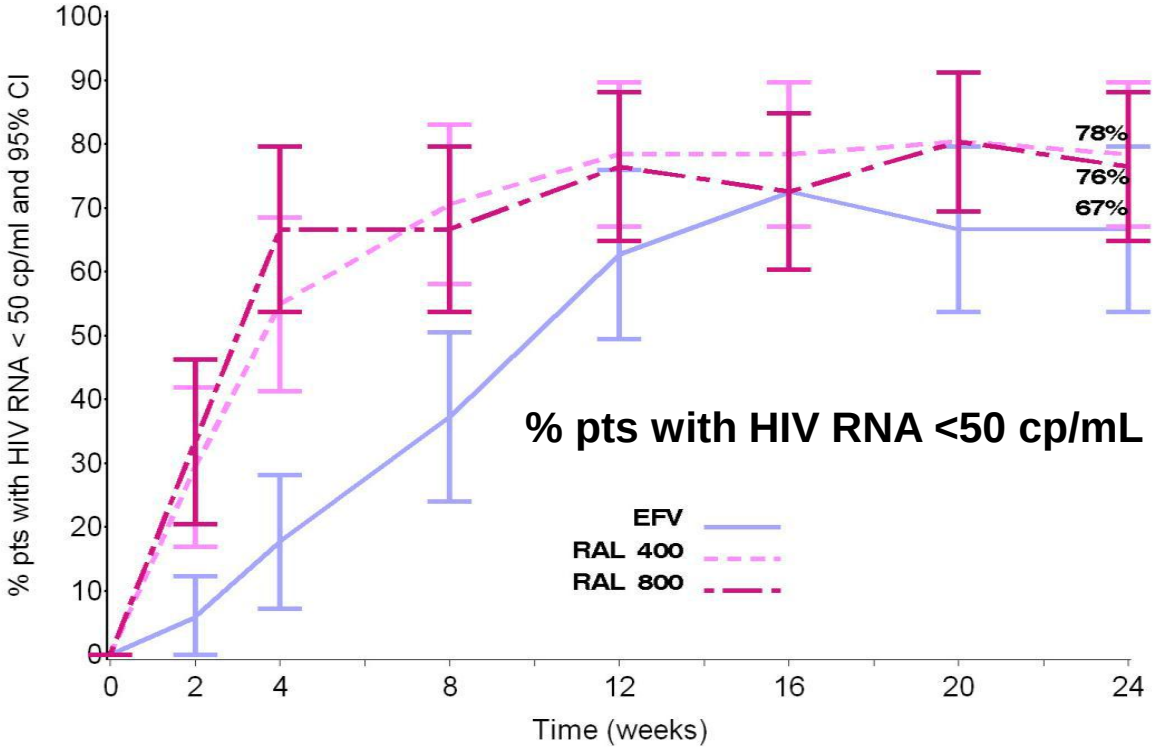
Criteria:

- **HIV-RNA > 1000 cp/ml**
- **ART naive**

Grinsztejn B. Lancet Infect Dis 2014; 14: 459–67

Raltegravir in TB-HIV coinfection





… "Raltegravir 400 mg twice daily might be an alternative to efavirenz for the treatment of patients co-infected with HIV and tuberculosis"

Linee Guida Italiane SIMIT (novembre 2013)

INI

○ L'utilizzo di **raltegravir**, alla dose di 800 mg BID, in associazione a **rifampicina** dovrebbe essere **considerato con cautela in assenza di TDM di raltegravir e solo in assenza di alternative valide**	[CII]
○ L'utilizzo di raltegravir può essere **considerato in associazione a rifabutina senza modifiche di dosaggio**	[BII]

Rifampicina induce l'enzima UGT1A1 portando all'aumento della glucoronidazione e alla conseguente **riduzione dei livelli plasmatici di raltegravir**. Tuttavia, iniziali esperienze "real life" hanno riportato risultati incoraggianti in termini di tollerabilità, sicurezza e efficacia di regimi contenenti raltegravir (800 mg BID) in associazione a rifampicina

Non sono state segnalate significative interazioni farmacologiche nell'utilizzo concomitante di raltegravir e rifabutina, cosi come di dolutegravir e rifabutina

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Anti-CCR5

○ **L'associazione di rifampicina e maraviroc è controindicata**	[BII]
○ **Rifabutina può essere utilizzata in pazienti che assumono Maraviroc**, e la dose di Maraviroc (150 mg BID o 300 mg BID) è definita sulla base della cosomministrazione di altri farmaci che non inducano, o inducano, rispettivamente, il sistema CYP3A	[BIII]

Rifampicina diminuisce di oltre l'80% i livelli plasmatici di maraviroc. Nonostante il dosaggio di maraviroc possa essere aumentato a 600 mg BID, non ci sono però evidenze cliniche che supportino in maniera controllata l'efficacia farmacocinetica di questa combinazione

Al momento **non ci sono invece dati in letteratura riguardo l'utilizzo combinato e l'interazione farmacologica tra maraviroc e rifabutina**

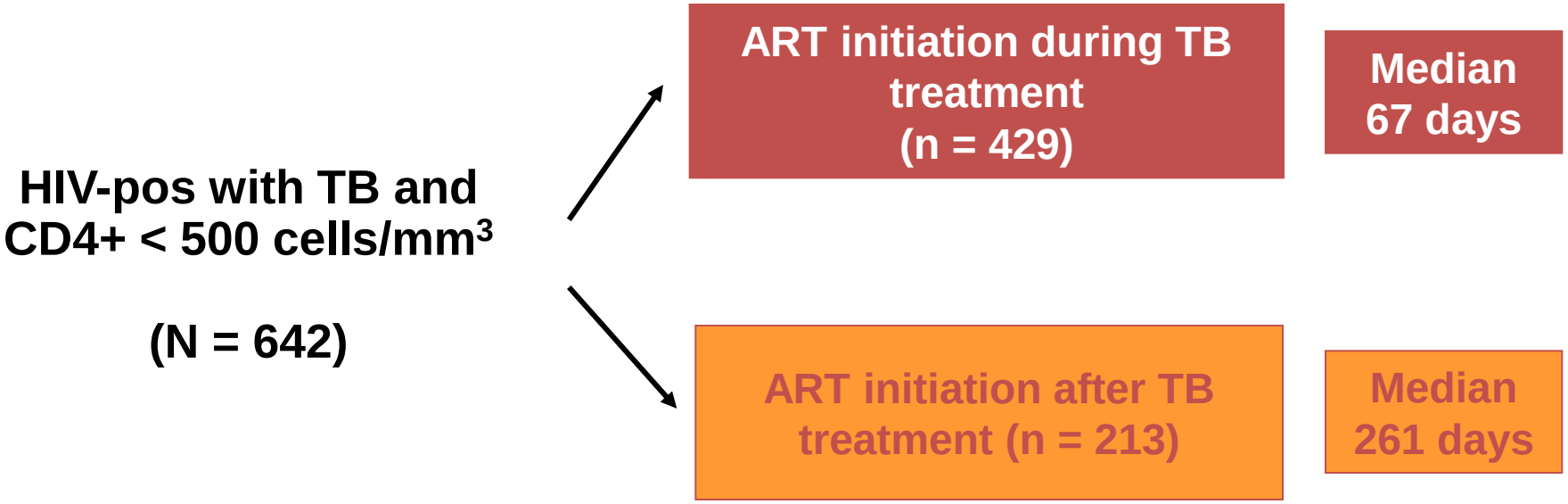
Drug Interactions: Rifampicin and other HIV drugs

- **NNRTIs**
  - Rifampicin decreases **Etravirin** exposure “significantly”. Combination not recommended
- **Integrase inhibitors**
  - Rifampicin reduces **raltegravir** exposure by 40-60%. Raltegravir 800 mg BID suggested, but optimal concentration range of this drug is unknown
  - Rifampicin decreases **Elvitegravir** (and **Cobicistat**) exposure “significantly”. Combination not recommended
- **CCR5 Inhibitors**
  - Rifampicin reduces **maraviroc** exposure by 63%. Maraviroc doses could theoretically be doubled (600mg BID) but no clinical experience

Drug Interactions: Rifabutin and other HIV drugs

- **NNRTIs**
  - No significant interactions with efavirenz and nevirapin (but no advantage over rifampicin). With **efavirenz** rifabutin dose need to be increased to 450 mg daily
- **Integrase inhibitors**
  - Rifabutin does not alter **raltegravir** exposure to a clinically meaningful degree (Brainard DM et al. J Clin Pharmacol 2010)
  - Rifabutin decreases **elvitegravir** by 67% and elvitegravir increases rifabutin metabolite exposure by 625%
- **CCR5 Inhibitors**
  - No clinical data

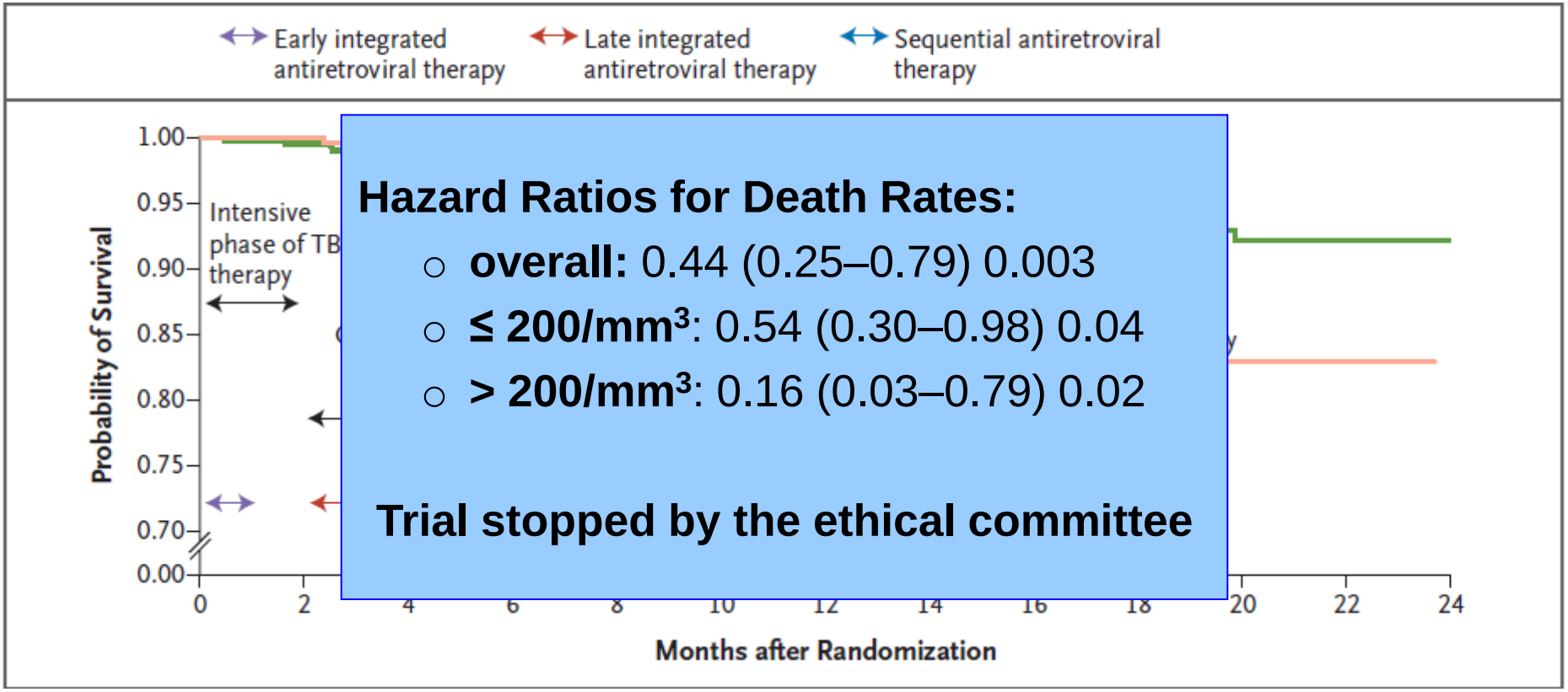
SAPiT Trial: Initiating ART during TB treatment significantly increases survival



Primary Endpoint: mortality rate (any cause)

Abdool Karim SS, N Engl J Med 2010; 362:697-706

SAPiT Trial: Initiating ART during TB treatment significantly increases survival



Hazard Ratios for Death Rates:

- **overall:** 0.44 (0.25–0.79) 0.003
- **≤ 200/mm³**: 0.54 (0.30–0.98) 0.04
- **> 200/mm³**: 0.16 (0.03–0.79) 0.02

Trial stopped by the ethical committee

Abdool Karim SS, N Engl J Med 2010; 362:697-706

Timing of ART in HIV/tuberculosis patients

WHO recommendation

- Start **ART in all HIV infected individuals with active tuberculosis** irrespective of CD4 cell count

(strong recommendation – Low quality of evidence)

WHO, 2010: Rapid Advice on ART

Early (2 weeks) vs. late (8 weeks) after initiation of HAART

CAMELIA study

1.0

Mortality was reduced by 34% when HAART was initiated 2 weeks vs 8 weeks after onset of TB treatment

Consider:

- **median CD4+ T-cell count** = 25
- **patients with ≤ 50/mm³** = 71.4% in earlier-ART and 72.3% in later-ART

Weeks after Tuberculosis Treatment Initiation

Survival probability (95% CI)	Early arm	Late arm	Log-rank *p*-value
Week 50	86.1 (81.8 – 89.4)	80.7 (76.0 – 84.6)	0.07
Week 100	82.6 (78.0 – 86.4)	73.0 (67.7 – 77.6)	0.006
Week150	82.0 (77.2 – 85.9)	70.2 (64.5 – 75.2)	0.002

Blanc FX, N Engl J Med 2011;365:1471-81

Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis

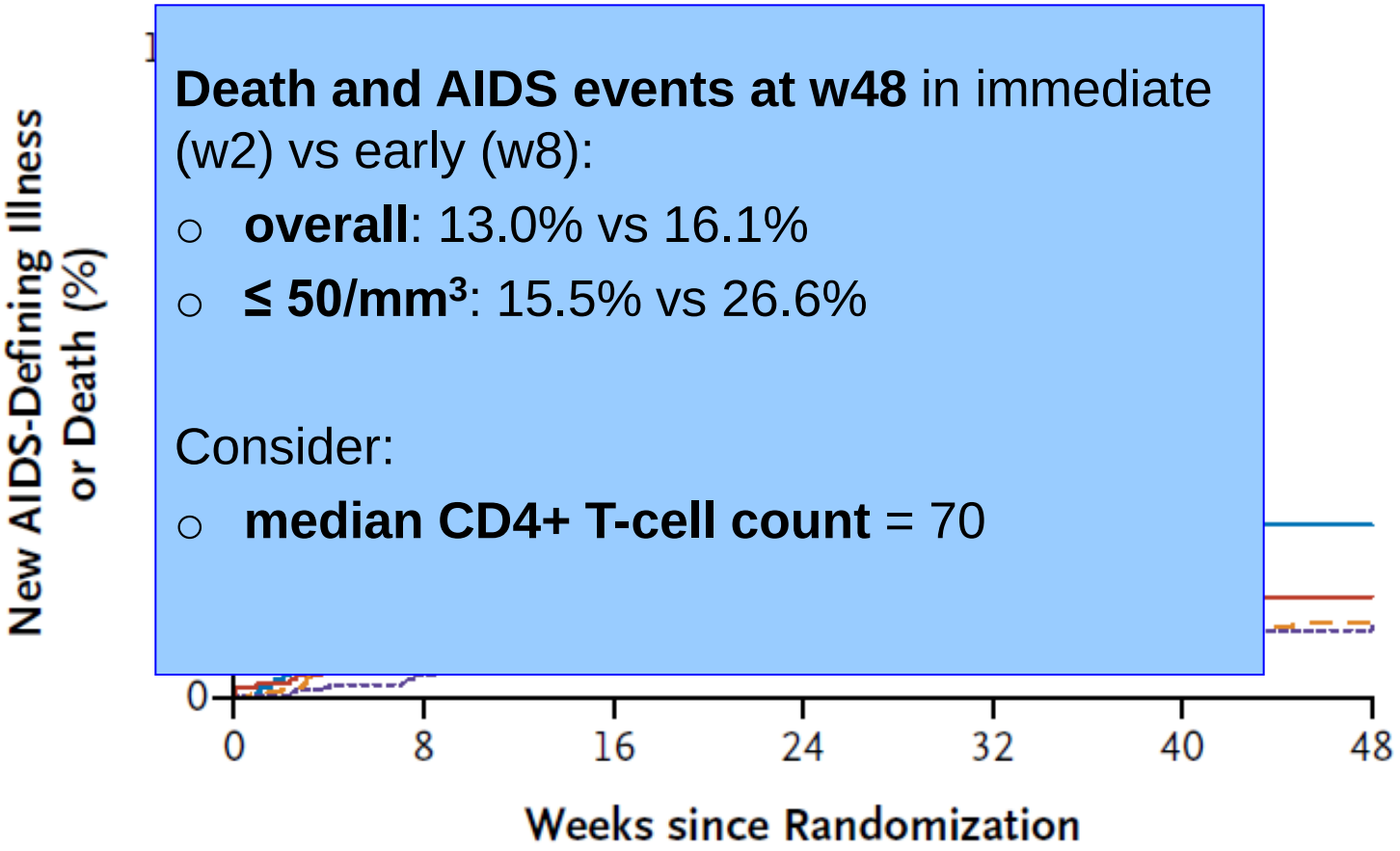
STRIDE study

Death and AIDS events at w48 in immediate (w2) vs early (w8):

- **overall**: 13.0% vs 16.1%
- **≤ 50/mm³**: 15.5% vs 26.6%

Consider:

- **median CD4+ T-cell count** = 70



Havlir DV, N Engl J Med 2011;365:1482-91

ART Initiation in TB Meningitis – A Randomized Trial in Vietnam

- **Immediate** – ART within 7 days after TB
- **Deferred** – ART initiated 2 months after TB

	Immediate	Deferred
Number	127	126
Died	76	70
Survival	40%	45%
		p=0.52

Torok et al. ICAAC 2009, Abstract H-1224

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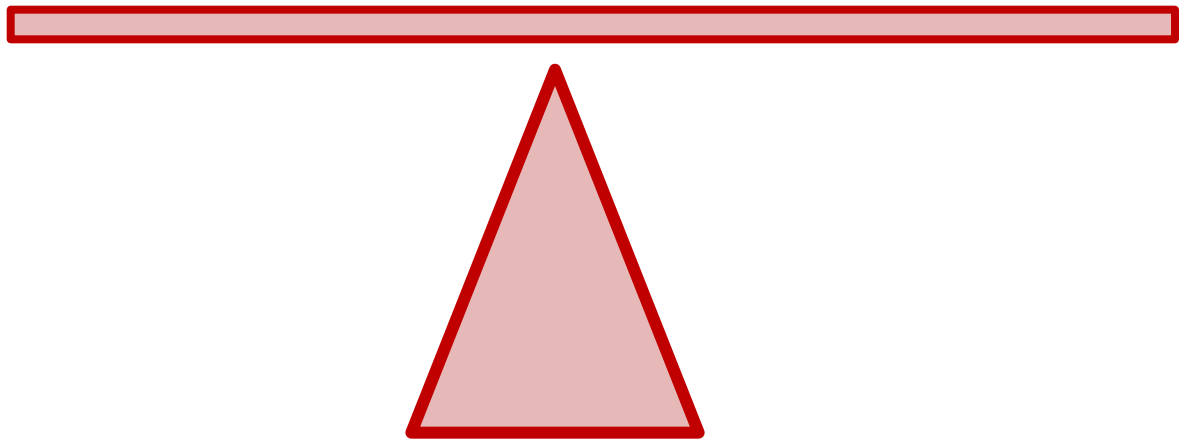
Quando iniziare?

○ In **pazienti con T CD4+ < 50 cellule/mL** è fortemente raccomandato l'inizio della cART **a due settimane dall'inizio della TAT**	[AI]
○ In pazienti con **linfociti T CD4+ compresi tra 50 e 500 cellule/mL** è fortemente raccomandabile l'inizio della terapia antiretrovirale **tra 2 settimane e due mesi dall'inizio della TAT**	[AI]
○ In pazienti con **linfociti T CD4+ > 500 cellule/mL**, dato l'aumentato rischio di progressione dell'infezione da HIV in presenza di una tubercolosi attiva anche ad elevati livelli di linfociti T CD4+, il **timing della cART andrà stabilito nei singoli casi sulla base di valutazioni costo-beneficio**	[BII]
○ In **pazienti con tubercolosi del SNC** la cART dovrebbe essere iniziata **a 2 mesi dall'inizio della terapia antitubercolare** indipendentemente dalla conta dei T CD4+ iniziale	[BII]

Expected mortality should steer decision on optimal timing of combined TB and HIV therapy

Risk of death while awaiting HAART

Risk of death as a consequence of HAART (IRIS)



Definition of IRIS

(A) Antecedent requirements

- Diagnosis of tuberculosis before starting ART
- Initial response (stabilised or improved) to tuberculosis treatment

(B) Clinical criteria

- Onset of manifestations within 3 months of ART
- *Plus at least one major or two minor criteria*
  - ***Major criteria***

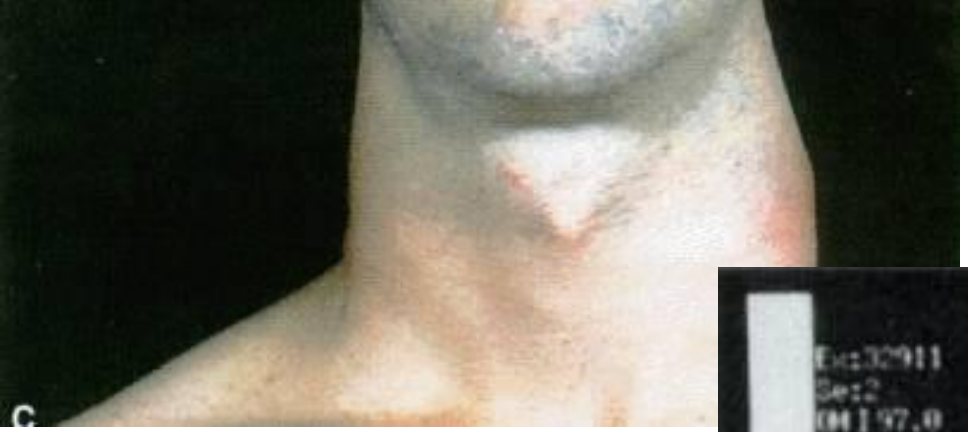
    1) New or enlarging lymph nodes, or similar cold abscesses, 2) New or worsening radiological features of TB; 3) New or worsening CNS TB; 4) New or worsening serositis
  - ***Minor criteria***

    1) New or worsening constitutional symptoms; 2) New or worsening respiratory symptoms; 3) New or worsening abdominal pain

(C) Alternative explanations for clinical deterioration must be excluded if possible

- Failure of tuberculosis treatment because of tuberculosis drug resistance
- Poor adherence to tuberculosis treatment
- Another opportunistic infection or neoplasm
- Drug toxicity or reaction

Meintjes G. Lancet ID 2008; 8-516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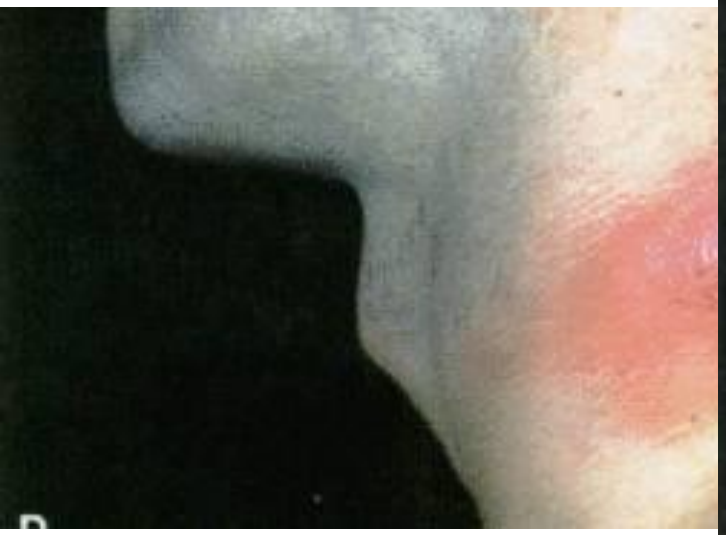
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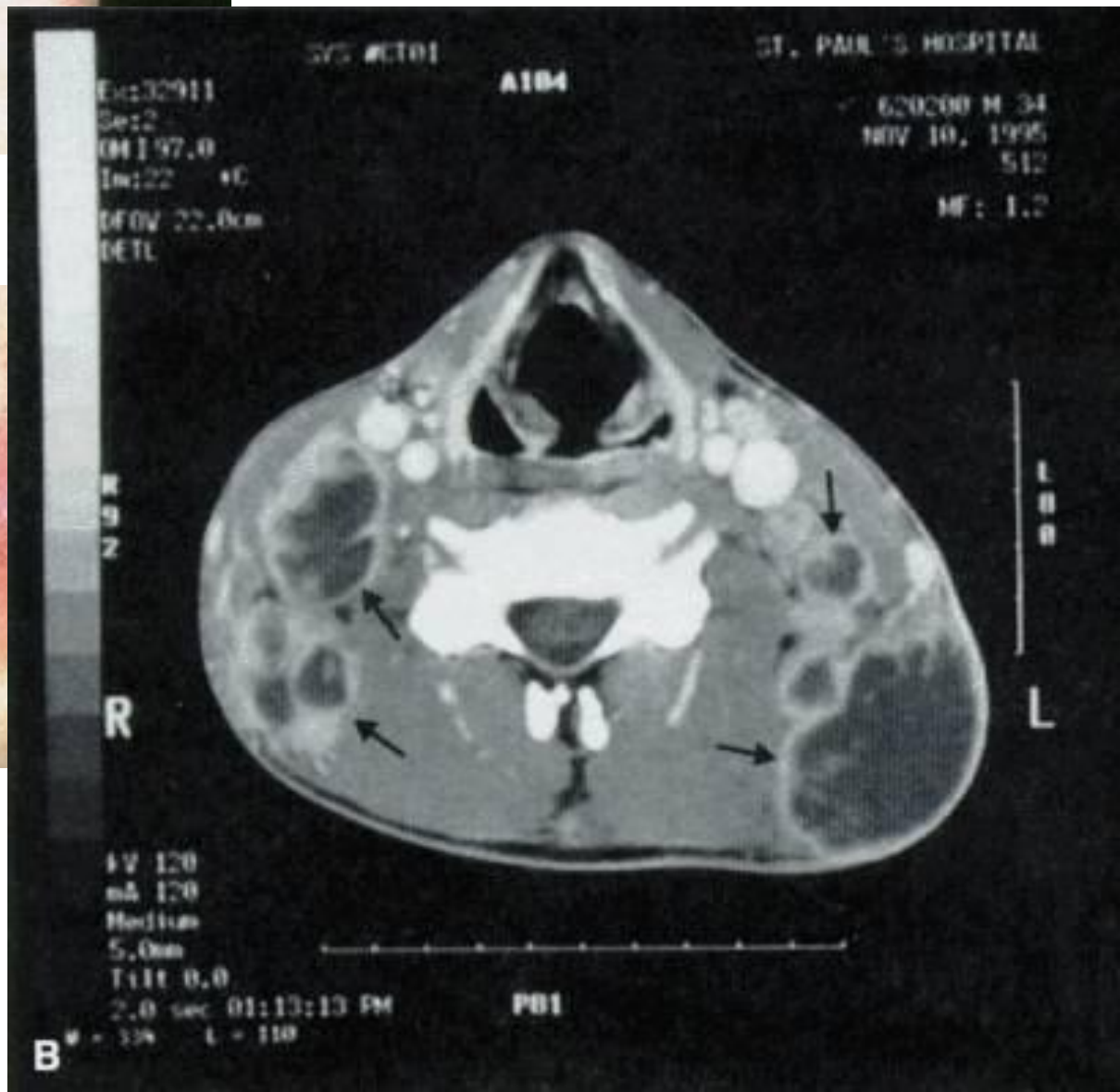
A184
ST. PAUL'S HOSPITAL
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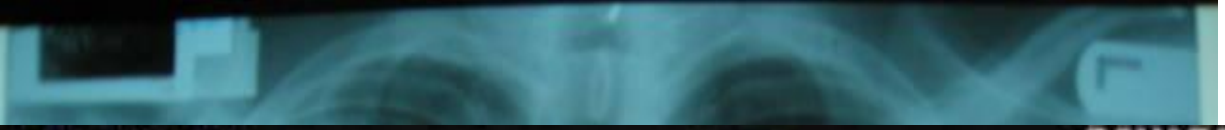
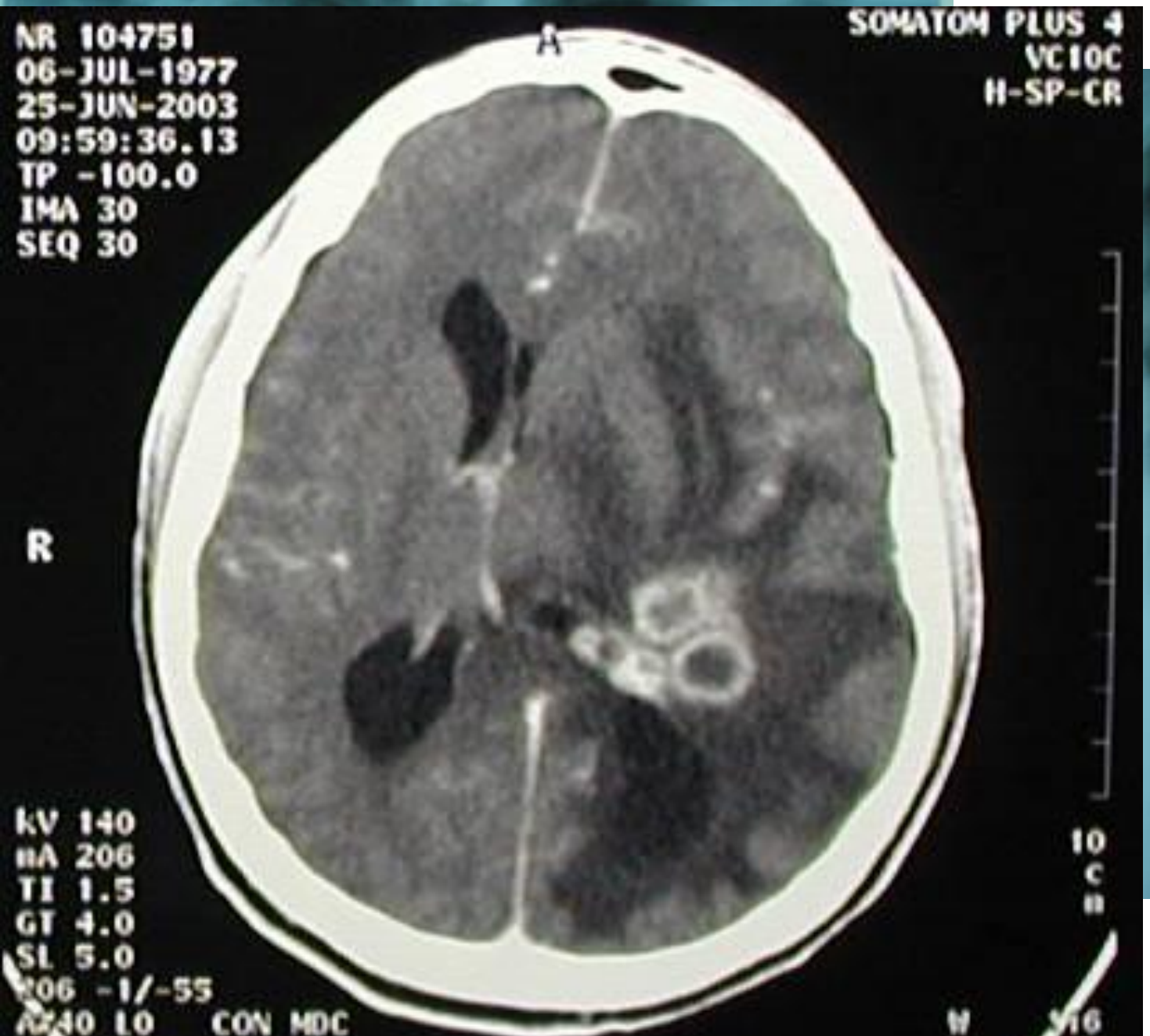
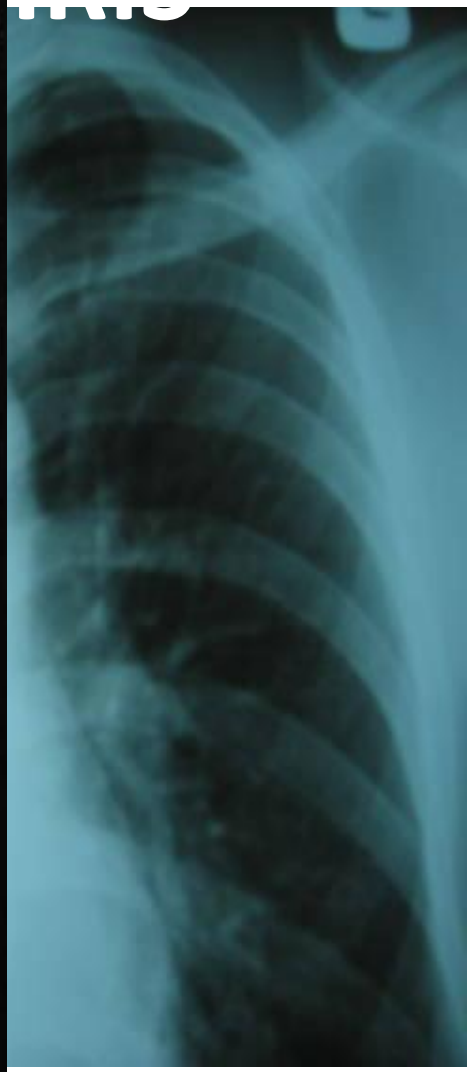
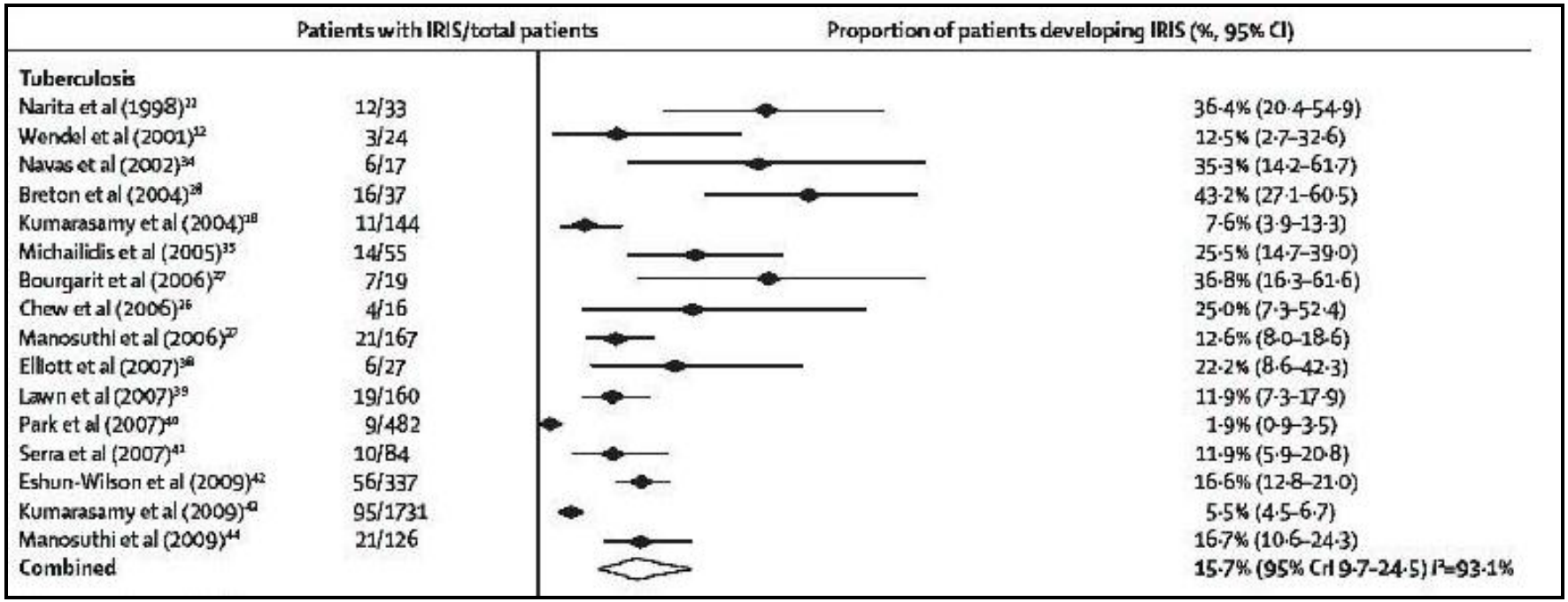



NR 104751
06-JUL-1977
25-JUN-2003
09:59:36.13
TP -100.0
IMA 30
SEQ 30
SOMATOM PLUS 4
VC10C
H-SP-CR
A
R
kV 140
mA 206
TI 1.5
GT 4.0
SL 5.0
CON MDC
10 cm



Do patients die because of IRIS ?



	Patients with IRIS/total patients	Proportion of patients developing IRIS (%, 95% CI)
Tuberculosis		
Narita et al (1998)[21]	12/33	36·4% (20·4–54·9)
Wendel et al (2001)[32]	3/24	12·5% (2·7–32·6)
Navas et al (2002)[34]	6/17	35·3% (14·2–61·7)
Breton et al (2004)[28]	16/37	43·2% (27·1–60·5)
Kumarasamy et al (2004)[18]	11/144	7·6% (3·9–13·3)
Michailidis et al (2005)[35]	14/55	25·5% (14·7–39·0)
Bourgarit et al (2006)[27]	7/19	36·8% (16·3–61·6)
Chew et al (2006)[26]	4/16	25·0% (7·3–52·4)
Manosuthi et al (2006)[37]	21/167	12·6% (8·0–18·6)
Elliott et al (2007)[38]	6/27	22·2% (8·6–42·3)
Lawn et al (2007)[39]	19/160	11·9% (7·3–17·9)
Park et al (2007)[40]	9/482	1·9% (0·9–3·5)
Serra et al (2007)[41]	10/84	11·9% (5·9–20·8)
Eshun-Wilson et al (2009)[42]	56/337	16·6% (12·8–21·0)
Kumarasamy et al (2009)[43]	95/1731	5·5% (4·5–6·7)
Manosuthi et al (2009)[44]	21/126	16·7% (10·6–24·3)
Combined		**15·7% (95% CrI 9·7–24·5) I^2=93·1%**

3.2% (0.7–9.2) of patients with tuberculosis-associated IRIS died

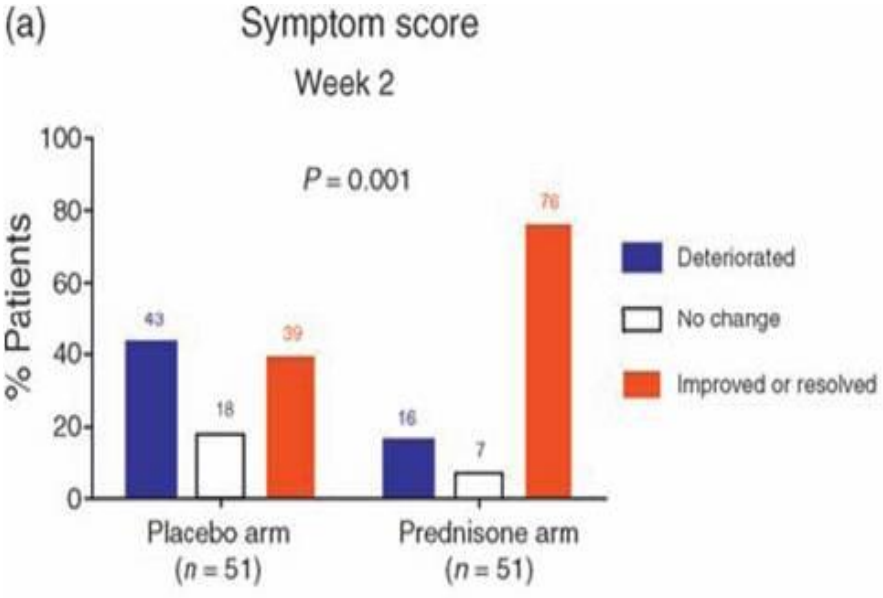
Muller M. Lancet Infect Dis, 2010 10: 251 (metanalysis)

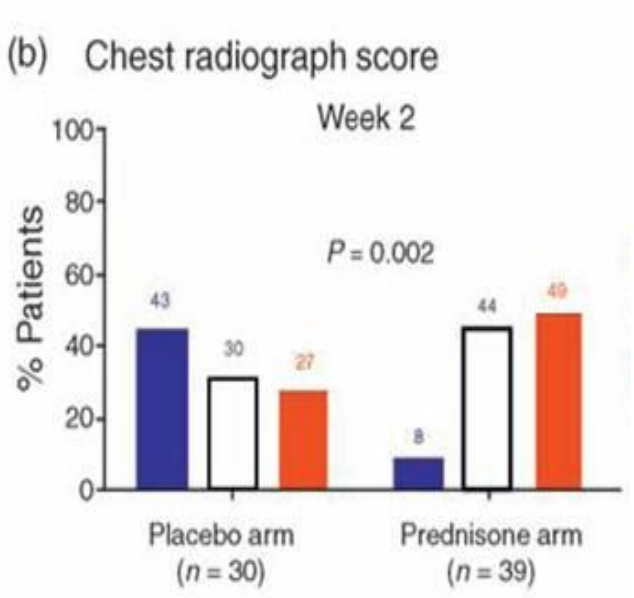
Management of IRIS

- Make certain of diagnosis
  - rule out MDR TB or new opportunistic infection
- **TB treatment should be continued**
- **ARV treatment should be continued**
- Surgical drainage
- **Non-steroidal anti-inflammatory drugs**
- **Steroids (1.5 mg/kg prednisone)**

Corticosteroids and IRIS outcome

- 109 TB/HIV patients with clinical definition of IRIS in South Africa
- **Randomised, placebo controlled trial of 1.5 mg/kg/day (2 weeks) + 0.75 mg/kg/day (2 weeks)**
- Cumulative hospital days: 282 vs 463
- Median hospital stay: 1 vs 3 (p=0.05)





Meintjes G. AIDS, 2010

Grazie per l'attenzione