

# **TB associated with HIV infection in the world - WHO strategy for TB / HIV**

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Global Tuberculosis Programme

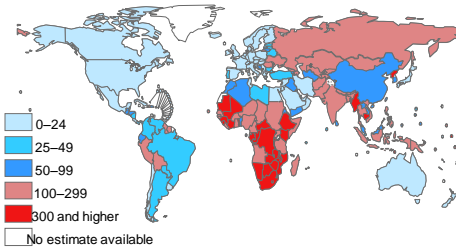
WHO/HQ, Geneva.

# Content

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- Burden and response so far
- Policy to reduce TB/HIV mortality
- Policy to prevent HIV associated TB
- We need to optimize the service delivery model

# The Global Burden of TB, 2012



**Estimated number  
of cases**

**Estimated number  
of deaths**

**HIV-associated TB**

1.1 million (13%)  
(range: 1.0–1.2 million)

320,000  
(range: 400,000–460,000)

**TB is responsible for one in four AIDS deaths**

# Post-2015 Global TB Strategy

## Pillars and Principles

Integrated,  
patient-  
centered  
TB care  
and  
prevention

Bold  
policies and  
supportive  
systems

Intensified  
research  
and  
innovation



Government stewardship and accountability, with monitoring and evaluation

Building a strong coalition with civil society and communities

Protecting and promoting human rights, ethics and equity

Adaptation of the strategy and targets at country level, with global collaboration

# PILLAR I AND COMPONENTS

## Integrated, Patient-centred Care and Prevention

- A. **Early diagnosis** of TB including **universal drug susceptibility testing; systematic screening of contacts and high-risk groups**
- B. Treatment of **all people with TB** including drug-resistant TB, and **patient support**
- C. Collaborative TB/HIV activities; and **management of co-morbidities**
- D. **Preventive treatment** for persons at high-risk and **vaccination for TB**

*New additions to or enhancements of the current strategy are shown in yellow*

# Collaborative TB/HIV activities - 2012



## A. Establish and strengthen the mechanisms for delivering integrated TB and HIV services

A.1. Set up and strengthen a coordinating body for collaborative TB/HIV activities functioning at national level

A.2. Determine HIV prevalence among TB patients and TB prevalence among people living with HIV

A.3. Carry out joint TB/HIV planning to integrate the delivery of TB and HIV services

A.4. Monitor and evaluate collaborative TB/HIV activities

## B. Reduce the burden of TB in people living with HIV and initiate early antiretroviral therapy (the Three I's for HIV/TB)

B.1. Intensify TB case-finding and ensure high quality antituberculosis treatment

B.2. Initiate TB prevention with Isoniazid preventive therapy and early antiretroviral therapy

B.3. Ensure control of TB Infection in health-care facilities and congregate settings

## C. Reduce the burden of HIV in patients with presumptive and diagnosed TB

C.1. Provide HIV testing and counselling to patients with presumptive and diagnosed TB

C.2. Provide HIV prevention interventions for patients with presumptive and diagnosed TB

C.3. Provide co-trimoxazole preventive therapy for TB patients living with HIV

C.4. Ensure HIV prevention interventions, treatment and care for TB patients living with HIV

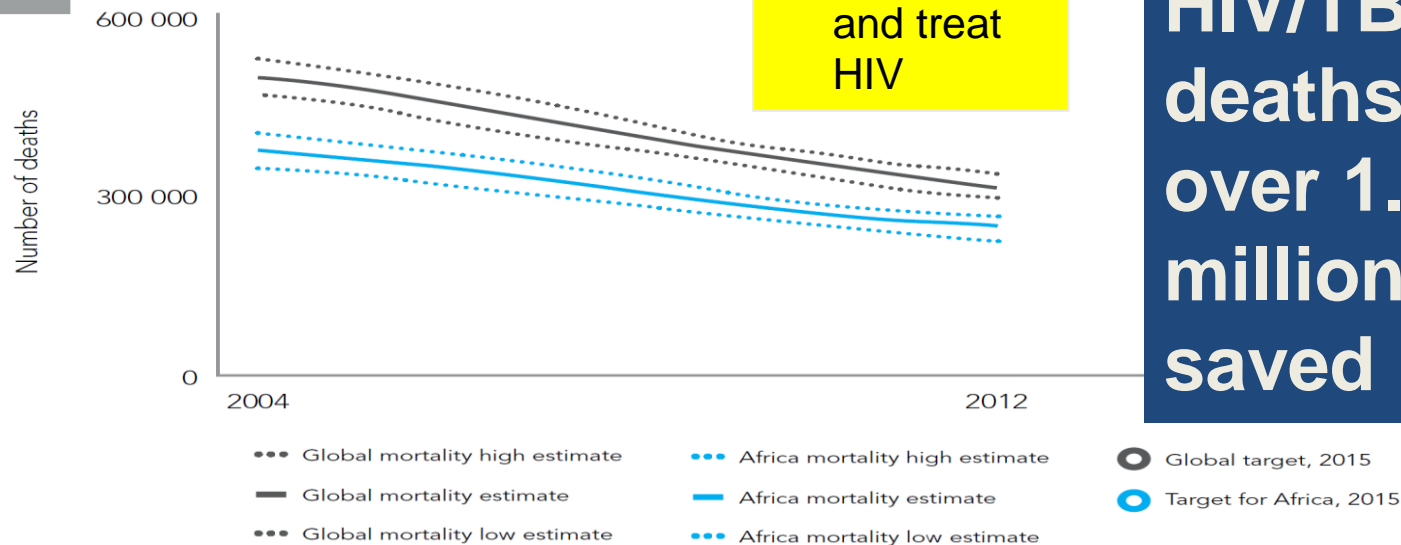
C.5. Provide antiretroviral therapy for TB patients living with HIV

# Policy, advocacy and implementation have produced results



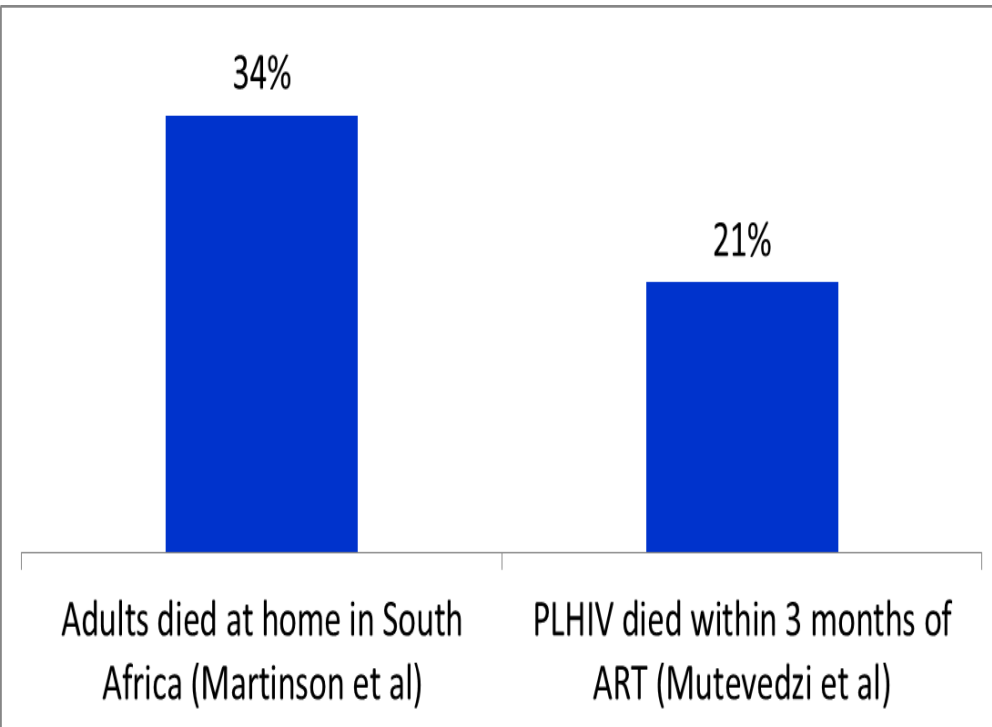
- Diagnose and treat TB
- Diagnose and treat HIV

**Over 40% decline in HIV/TB deaths and over 1.3 million lives saved**



# High burden of HIV/TB deaths

TB not recognized (until autopsy)

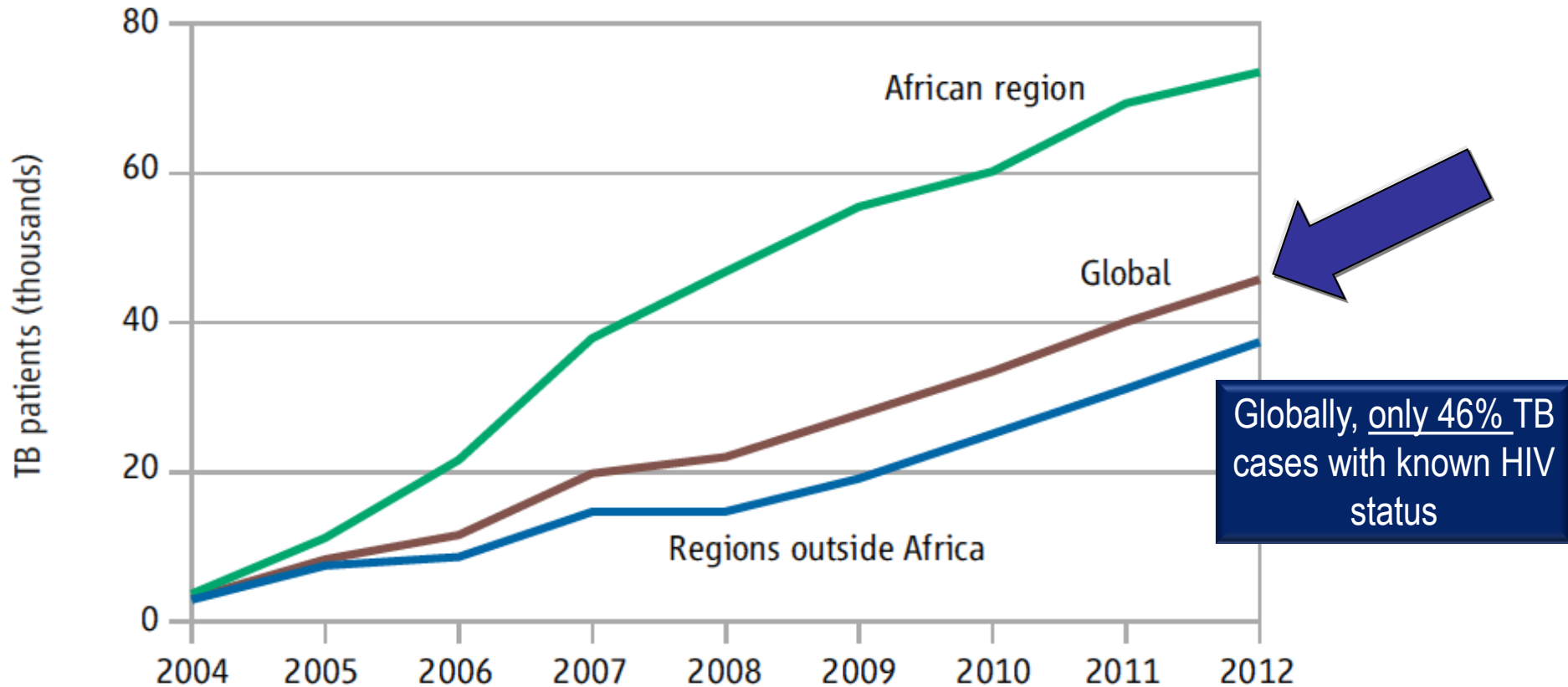


## Some reasons for HIV/TB Deaths

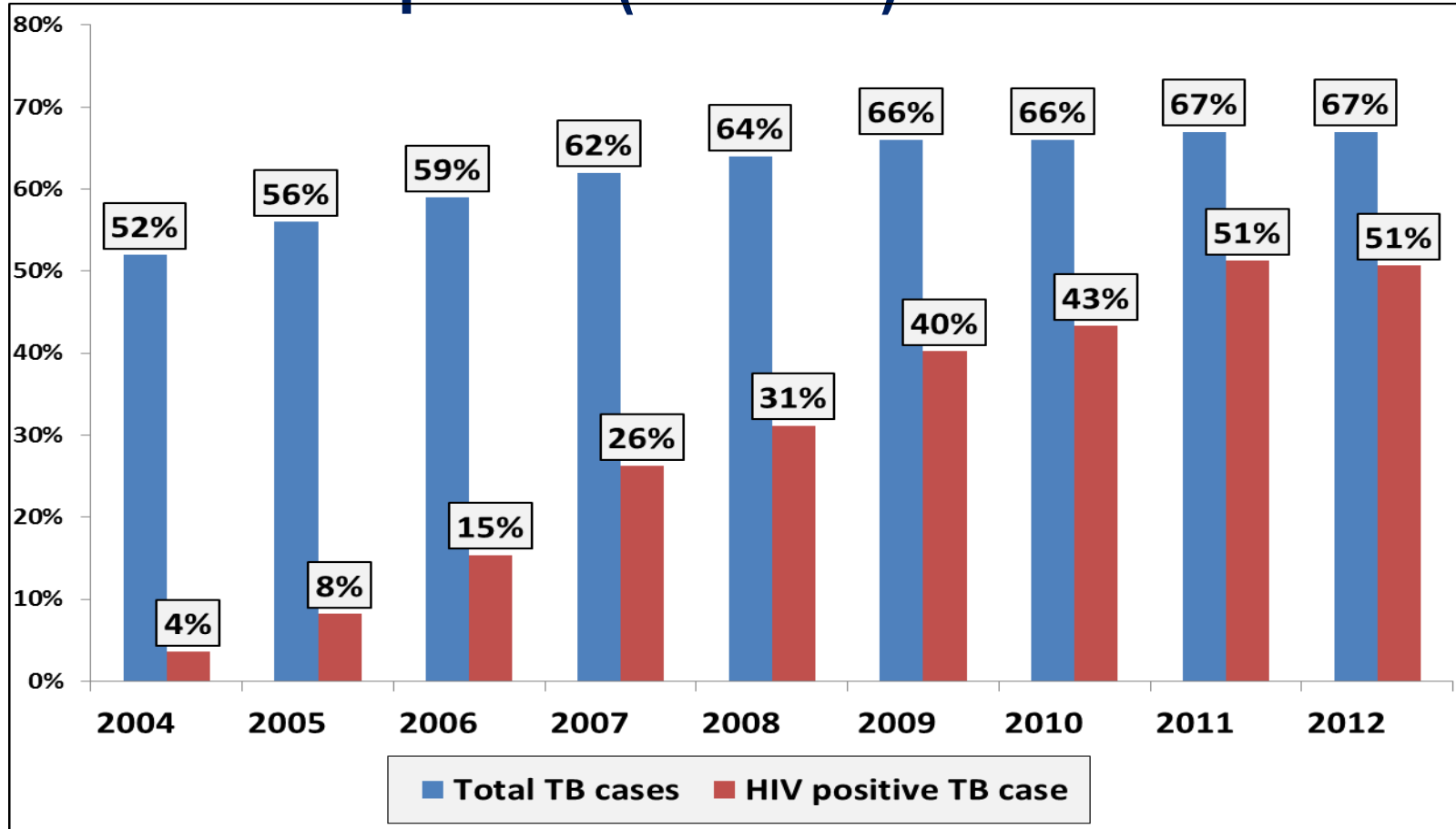
- HIV not diagnosed
- TB not diagnosed
- TB not treated
- HIV not promptly treated
- MDRTB



# HIV is not diagnosed in TB; ART cannot be started

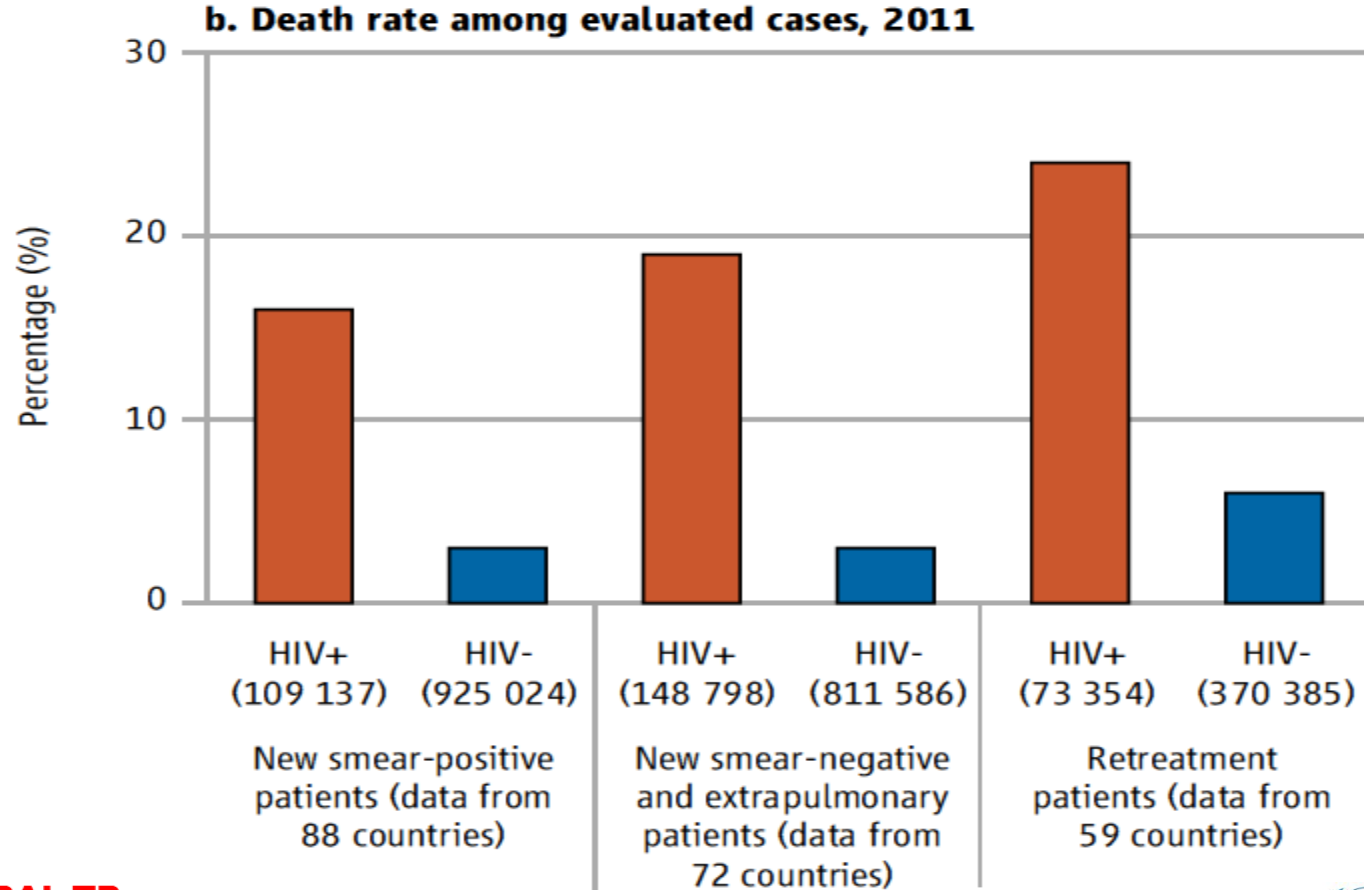


# Only half of PLHIV with TB are reported (reached) in 2012



# Treatment outcomes for HIV-positive and HIV-negative TB patients, 2011.

WHO Global report 2013

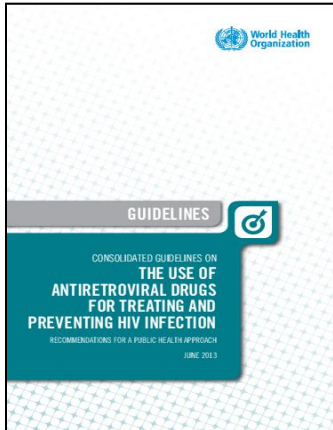


# ART should be given with TB treatment (both first and second line) as soon as possible.

Study	Setting	Arms	Median CD4 (IQR)	Primary endpoint	Findings
CAMELIA	Cambodia	2 vs. 8 weeks	25 (11 - 56)	Death	34% ↓ death (p=0.004)
STRIDE	Multi national	2 vs. 8-12 weeks	77 (36 - 145)	AIDS or death	42% ↓ AIDS/death in <50 CD4 (p=0.02)
SAPIT	South Africa	4 vs. 8-12 weeks	150 (77 - 254)	AIDS or death	68% ↓ AIDS/death in <50 CD4 (p=0.06)

PLHIV with TB should be given ART regardless of CD4 count

# TB and HIV co-treatment in PLHIV



- 6 months rifampicin containing TB treatment regimen throughout the course.
- Daily TB treatment at least during the intensive phase and ideally during the continuation phase
- Start ART irrespective of CD4 count, as soon as possible (within the first 2 weeks) after TB treatment initiation
- Use EFV as the preferred NNRTI

# TB policy 2012 – HIV policy 2013

- Start ART at CD4 <500
- Provide IPT for HIV-positive patients without active TB
- Early diagnosis of TB in people on-ART

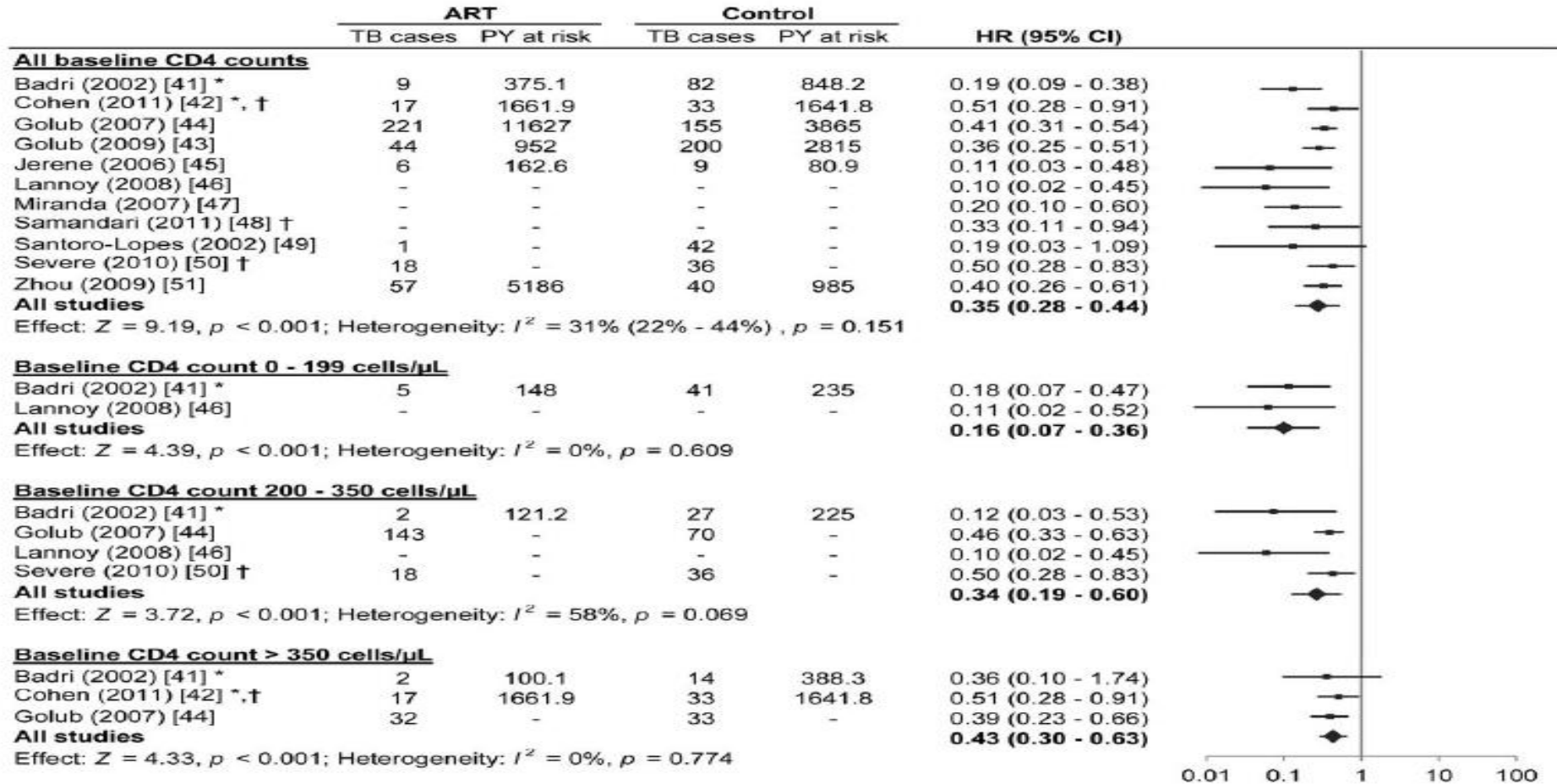
Prevent and Treat HIV and Prevent TB

Reduce HIV/TB deaths  
And HIV morbidity

# 65% reduction in TB incidence during HAART

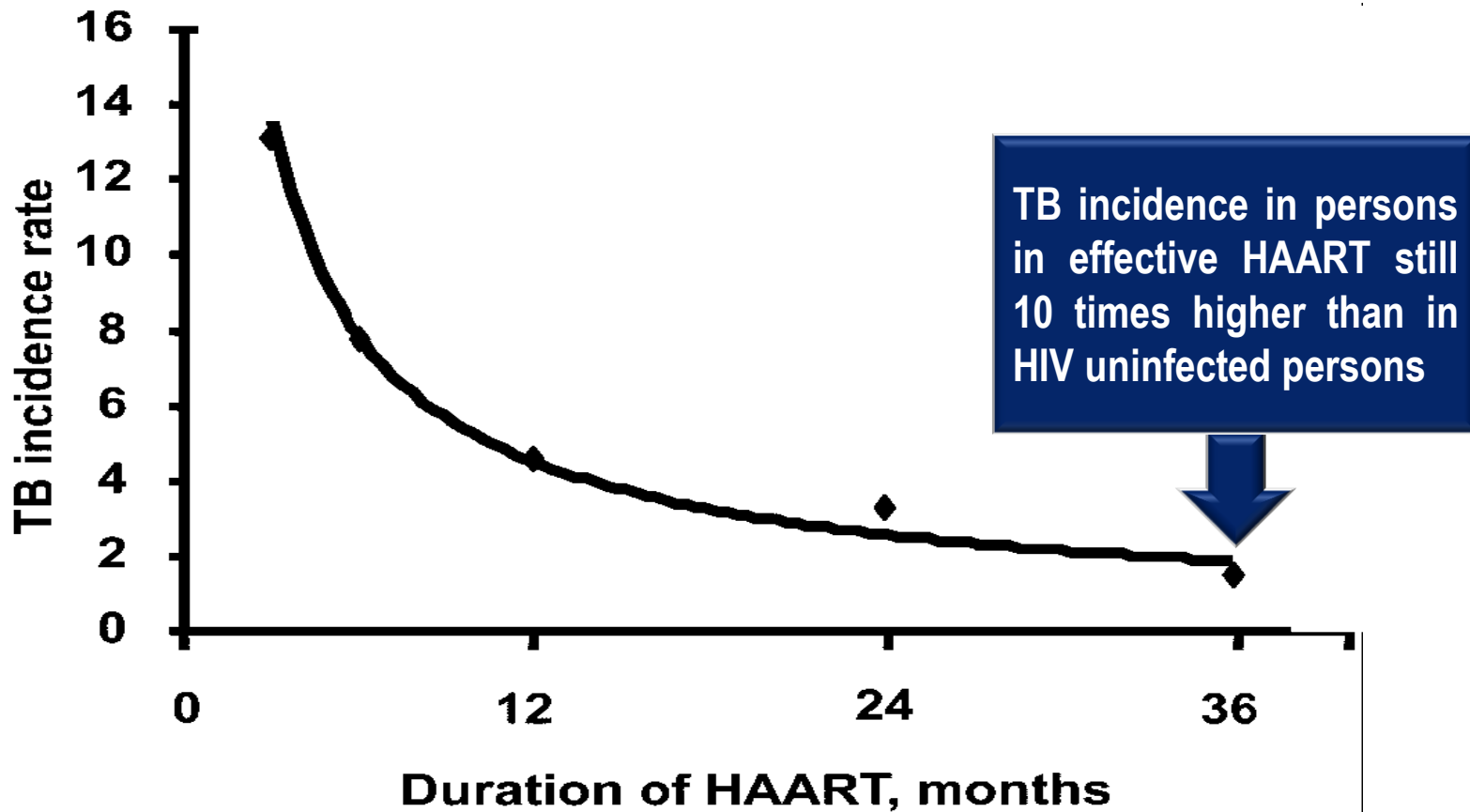
## Antiretroviral Therapy for Prevention of Tuberculosis in Adults with HIV: A Systematic Review and Meta-Analysis

Amitabh B. Suthar<sup>1\*</sup>, Stephen D. Lawn<sup>2,3</sup>, Julia del Amo<sup>4</sup>, Haileyesus Getahun<sup>5</sup>, Christopher Dye<sup>6</sup>, Delphine Sculier<sup>5</sup>, Timothy R. Sterling<sup>7</sup>, Richard E. Chaisson<sup>8</sup>, Brian G. Williams<sup>9</sup>, Anthony D. Harries<sup>10,11</sup>, Reuben M. Granich<sup>1</sup>



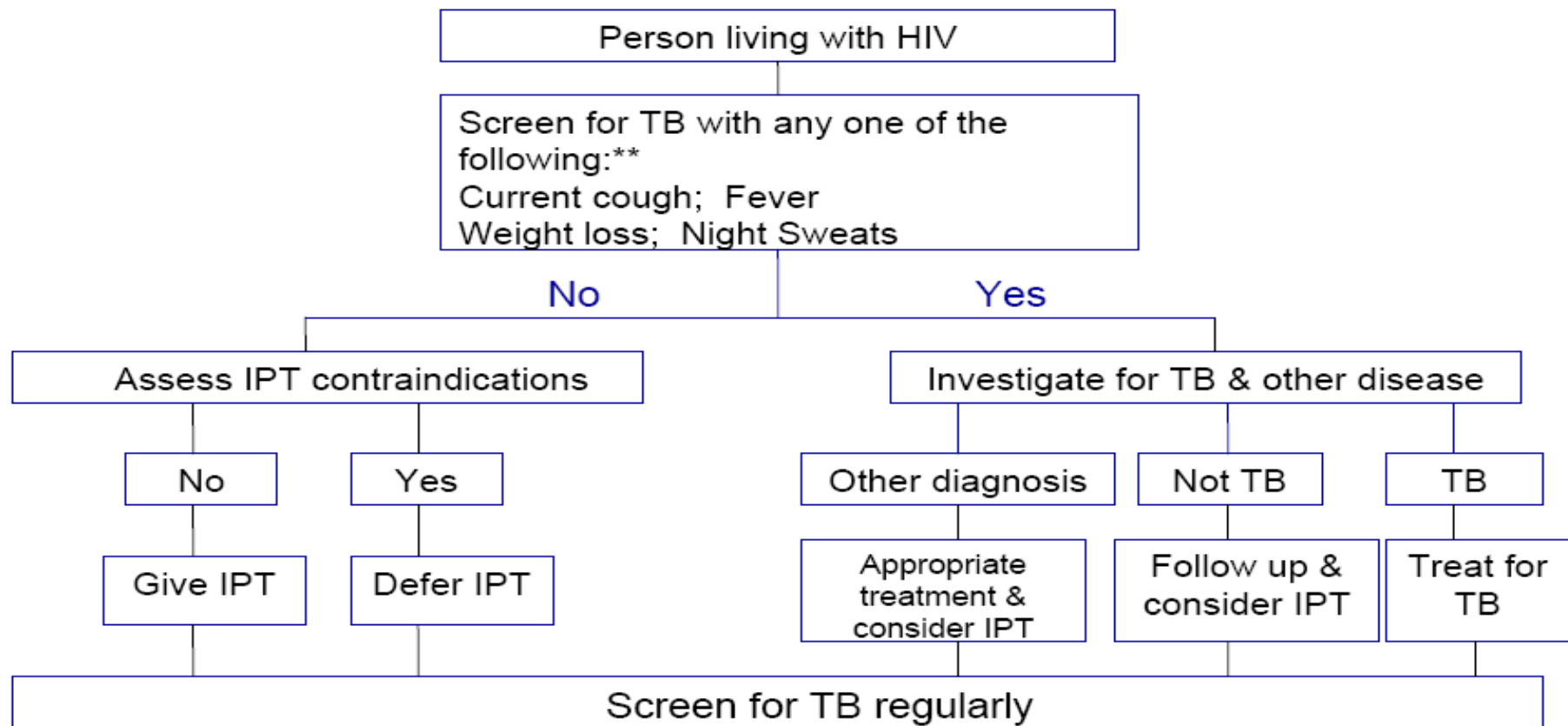
# TB incidence during 3 years of HAART in Europe and North America with regression curve fitted

Number of cases per 1000 person-years of follow-up



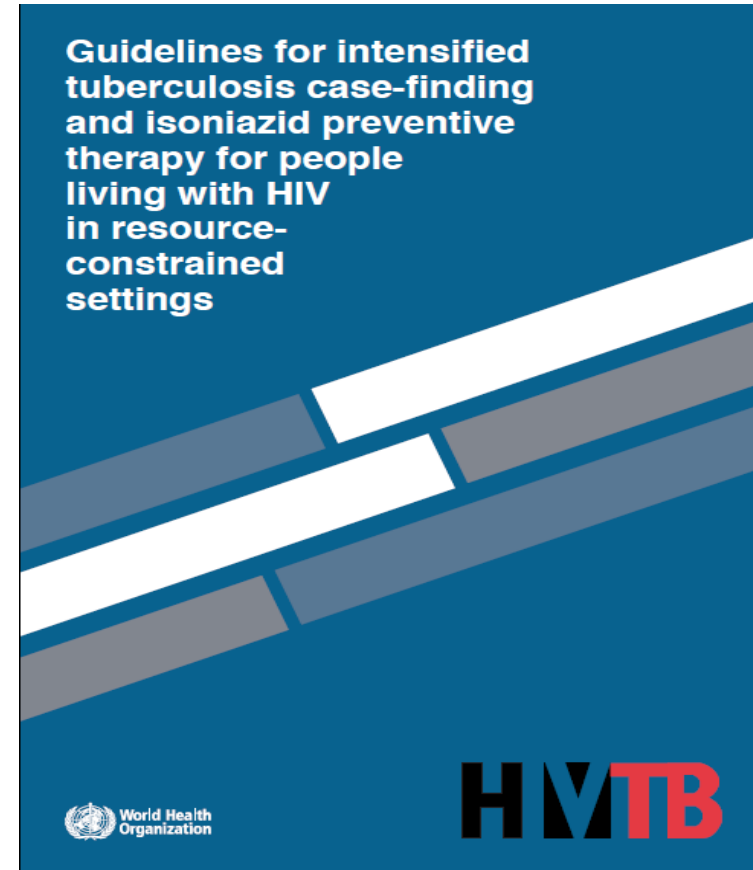


# Algorithm



# Isoniazid preventive therapy in people living with HIV

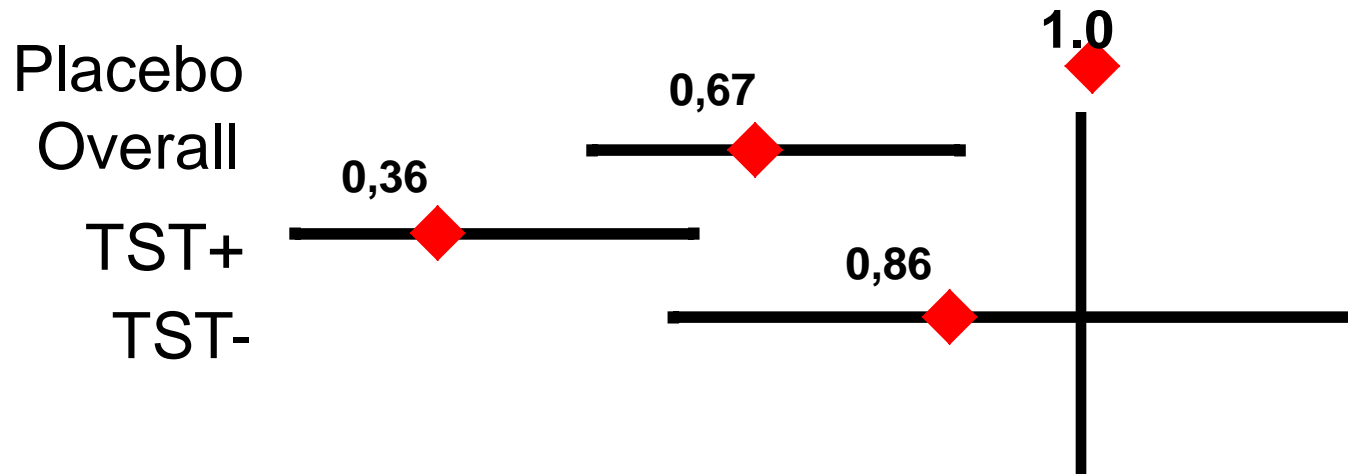
- People living with HIV and:
  - with unknown or positive TST status, and
  - unlikely to have active TBshould receive IPT for **at least 6 months** irrespective of their degree of immunosuppression  
*(strong recommendation)*



# Does IPT work?

Systematic review of clinical trials in PLHIV

## Relative risk, 95% CI



Akolo et al 2010, Cochrane review

# IPT and drug resistant TB

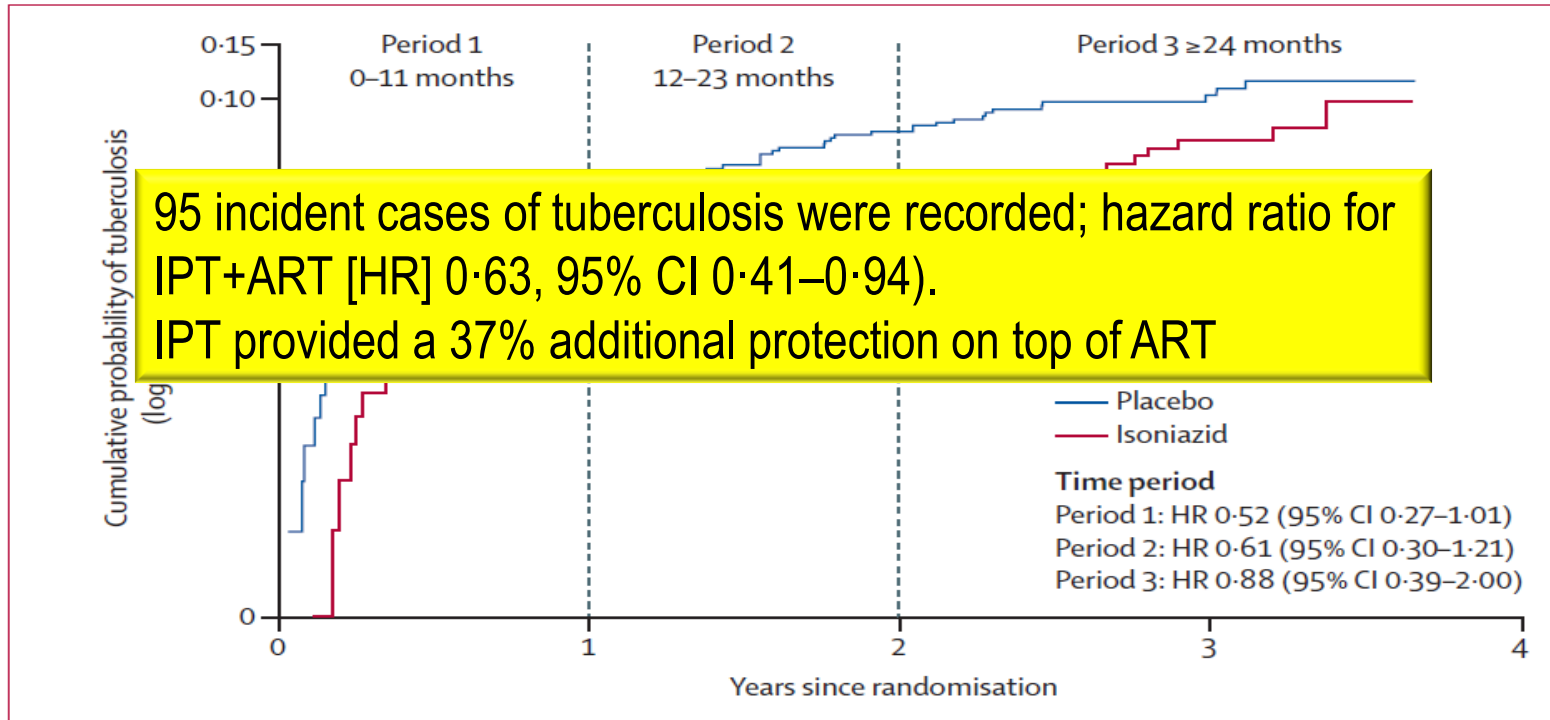
- The use of IPT for PLHIV does not cause drug resistance TB.

*Balcells 2006 meta-analysis*

- Even with 50% baseline INH resistance there will be 50% of the subjects who will benefit from IPT - IPT recommended in Eastern Europe and Central Asia, where INH resistance is the highest

*TB/HIV Working Group of the Partnership  
Focus on European Region, Almaty, May 2010*

# Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial



**Figure 3: Cumulative hazard plot for antiretroviral therapy versus antiretroviral therapy plus isoniazid preventive therapy effect by time since randomisation**

Nelson-Aalen cumulative hazard plot on a logarithmic y-scale to show proportionality of hazards over time periods. HRs shown are unadjusted. Treatment ended 1 year after participants were randomly assigned. Likelihood ratio test for interaction of treatment group with study time  $p=0.61$ , and assuming linear trend for study time  $p=0.34$ . HR=hazard ratio.

# IPT is not toxic to people who use drugs

Outcome	No (%)
Completed treatment correctly	319 (76.9)
Abandoned or changed treatment	71 (17.1)
Elevation in ALT/AST 3-5X normal	34 (8.2)
Hepatotoxicity all	20 (4.8)
Hepatotoxicity clinical	6 (1.4)
Removed for other reasons	5 (1.2)

Source: Fernandez-Villar *et al* *Clinical Infectious Diseases* 2003; 36:293–8

Excessive alcohol consumption (OR 4.2, P=0.002) and underlying liver disease (OR=4.3, P=0.002) are associated with hepatotoxicity

# Xpert MTB/RIF in HIV settings – a vital opportunity



## TUBERCULOSIS DIAGNOSTICS **Xpert MTB/RIF Test**

### ABOUT THE XPERT MTB/RIF TEST

The rapid TB test – known as Xpert MTB/RIF- is a fully-automated diagnostic molecular test. It has the potential to revolutionize and transform TB care and control. The test:

- simultaneously detects TB and rifampicin drug resistance
- provides accurate results in less than two hours so that patients can be offered proper treatment on the same day
- has minimal bio-safety requirements and training needs, and can be housed in non-conventional laboratories.



### UPDATED WHO RECOMMENDATIONS

AS OF OCTOBER 2013

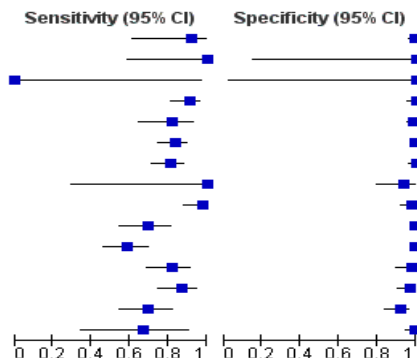
### Strong recommendation:

- Xpert MTB/RIF should be used as the initial diagnostic test in adults and children presumed to have MDR-TB or HIV-associated TB

# Xpert MTB/RIF for the diagnosis of pulmonary TB in PLHIV

## HIV positive

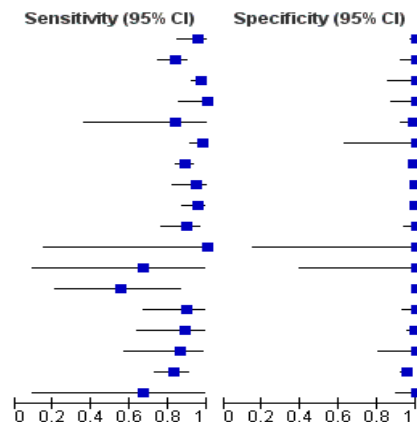
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Balcells 2012	11	1	1	147	0.92 [0.62, 1.00]	0.99 [0.96, 1.00]
Boehme 2010a	7	0	0	2	1.00 [0.59, 1.00]	1.00 [0.16, 1.00]
Boehme 2010b	0	0	1	1	0.00 [0.00, 0.97]	1.00 [0.03, 1.00]
Boehme 2010c	60	0	6	81	0.91 [0.81, 0.97]	1.00 [0.96, 1.00]
Boehme 2010d	27	2	6	141	0.82 [0.65, 0.93]	0.99 [0.95, 1.00]
Boehme 2011c	90	1	18	263	0.83 [0.75, 0.90]	1.00 [0.98, 1.00]
Boehme 2011d	80	0	19	88	0.81 [0.72, 0.88]	1.00 [0.96, 1.00]
Boehme 2011e	3	2	0	31	1.00 [0.29, 1.00]	0.94 [0.80, 0.99]
Carriquiry 2012	44	2	1	84	0.98 [0.88, 1.00]	0.98 [0.92, 1.00]
Hanrahan 2013	36	2	16	325	0.69 [0.55, 0.81]	0.99 [0.98, 1.00]
Lawn 2011	42	2	30	320	0.58 [0.46, 0.70]	0.99 [0.98, 1.00]
Rachow 2011	41	1	9	49	0.82 [0.69, 0.91]	0.98 [0.89, 1.00]
Scott 2011	45	3	7	84	0.87 [0.74, 0.94]	0.97 [0.90, 0.99]
Theron 2011	32	7	14	77	0.70 [0.54, 0.82]	0.92 [0.84, 0.97]
Van Rie 2013	8	1	4	99	0.67 [0.35, 0.90]	0.99 [0.95, 1.00]



**HIV-positive subgroup**  
**Pooled sensitivity = 79% (70,86)**  
**Pooled specificity = 98% (96, 99)**

## HIV negative

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Ateah 2012	42	0	2	127	0.95 [0.85, 0.99]	1.00 [0.97, 1.00]
Boehme 2010a	90	0	18	46	0.83 [0.75, 0.90]	1.00 [0.92, 1.00]
Boehme 2010b	142	0	5	24	0.97 [0.92, 0.99]	1.00 [0.86, 1.00]
Boehme 2010c	23	0	0	26	1.00 [0.85, 1.00]	1.00 [0.87, 1.00]
Boehme 2010d	5	1	1	69	0.83 [0.36, 1.00]	0.99 [0.92, 1.00]
Boehme 2010e	75	0	2	8	0.97 [0.91, 1.00]	1.00 [0.63, 1.00]
Boehme 2011a	161	3	20	252	0.89 [0.83, 0.93]	0.99 [0.97, 1.00]
Boehme 2011b	36	1	2	202	0.95 [0.82, 0.99]	1.00 [0.97, 1.00]
Boehme 2011c	62	1	3	232	0.95 [0.87, 0.99]	1.00 [0.98, 1.00]
Boehme 2011d	41	0	5	56	0.89 [0.76, 0.96]	1.00 [0.94, 1.00]
Boehme 2011e	2	0	0	2	1.00 [0.16, 1.00]	1.00 [0.16, 1.00]
Boehme 2011f	2	0	1	4	0.67 [0.09, 0.99]	1.00 [0.40, 1.00]
Hanrahan 2013	5	0	4	182	0.56 [0.21, 0.86]	1.00 [0.98, 1.00]
Rachow 2011	17	0	2	53	0.89 [0.67, 0.99]	1.00 [0.93, 1.00]
Saffanowska 2012	15	1	2	127	0.88 [0.64, 0.99]	0.99 [0.96, 1.00]
Scott 2011	12	0	2	17	0.86 [0.57, 0.98]	1.00 [0.80, 1.00]
Theron 2011	68	9	14	195	0.83 [0.73, 0.90]	0.96 [0.92, 0.98]
Van Rie 2013	2	0	1	33	0.67 [0.09, 0.99]	1.00 [0.89, 1.00]



*Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults (Review), Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N, The Cochrane Library, 2014, Issue 1*



# Adapting Care: Xpert MTB/Rif for Faster TB detection

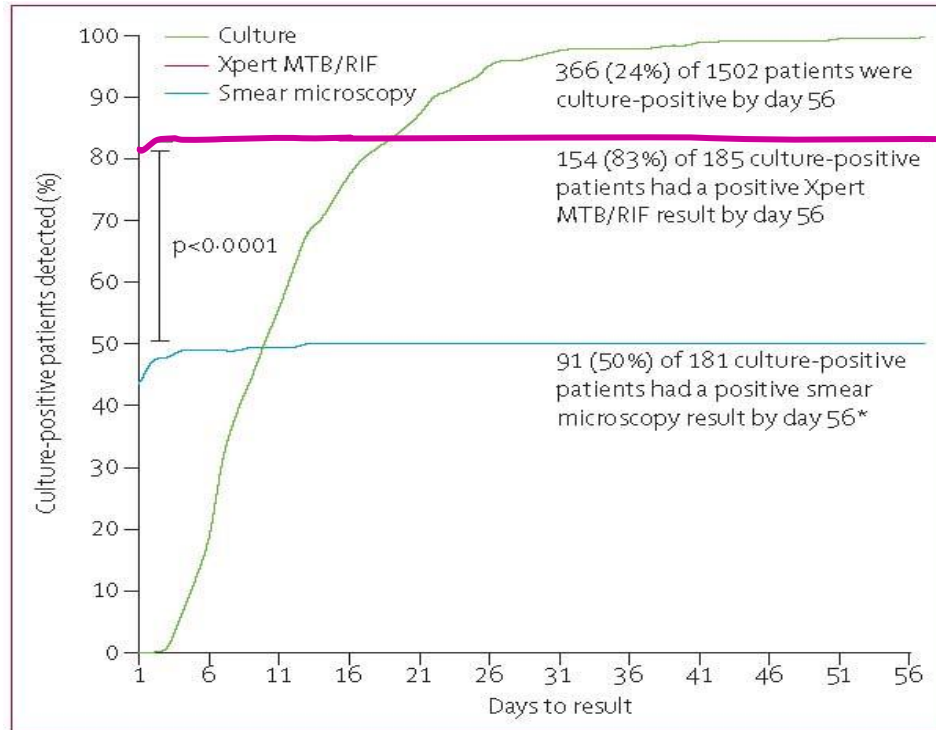
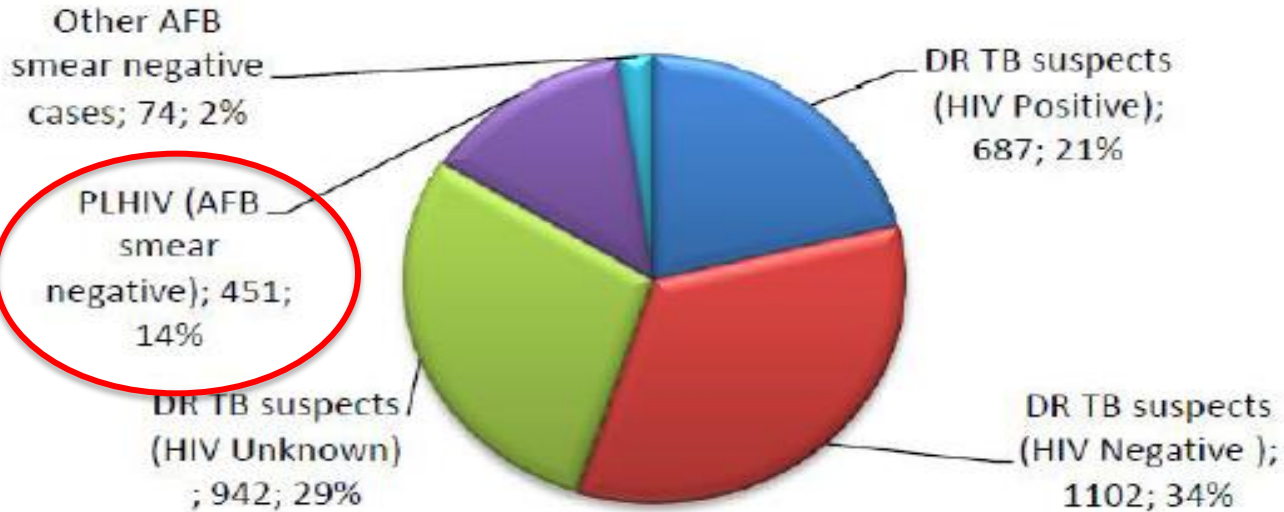


Figure 2: Time to diagnosis by smear microscopy, Xpert MTB/RIF, or liquid culture in culture-positive patients

\*One patient's culture obtained at recruitment was positive after 59 days.

- Nurses coordinated Xpert use
- More TB cases detected from Xpert vs smear
- Time to TB diagnosis less with Xpert and smear vs TB culture
- Time to TB treatment reduced with Xpert

# Initial Testing Algorithms Focused on Presumptive MDR TB Cases



TB CARE I

Xpert MTB/RIF testing at 9 sites in Nigeria (January – December 2012)

# What is the best model for HIV/TB care?

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- The one that is convenient for the patient and delivers quality care
  - Will vary according to HIV and TB prevalence
- Possible HIV/TB clinic models
  - Integrated and co-located models
  - Referral models- 2 separate clinics
- Considerations
  - Integrated models are optimal but require more effort on staff training and considerations such as infection control
  - Co-location not sufficient for optimal delivery of care

*Legidor Quigley, Trop Med Int Health, 2013; Schwartz, IJTLD, 2013; Uyei, Health Policy and Planning, 2014*

# Persons who inject drugs: intersection of HIV/TB/HCV

- One third PWID are HIV-infected; two thirds are HCV infected
- High rates of TB infection
- Human rights violations may drive PWID away from care
- Access and retention in care facilitated by OST programmes

*Getahun, Curr Opin HIV/AIDs, 2012; Grenfell Drug and Alcohol Dependence, 2013; Schluger, Drug and Alcohol Dependence, 2013*

# Incarcerated Populations- Left Behind

- TB spread enhanced in the prison setting
  - 1/11 of TB transmission in prison on high income countries
  - 1/16 of TB transmissions in low and middle income countries
- Crowded conditions
- Limited health access

# Convergence of TB, HIV and injecting drug use in selected high burden countries with high per capita prisoners

Country	Prisoners/ 100,000 <sup>1</sup>	TB incidence/ 100,000 <sup>2</sup>	PWID (n)	Anti-HCV in PWID (%) <sup>3</sup>	Anti-HBV in PWID(%) <sup>3</sup>
Russia	534	106	1825000	73	38
South Africa	318	981	262975	NK	NK
Brazil	261	43	800000	64	56
Thailand	137	137	160528	90	77

*PWID = People who inject drugs; HCV – Hepatitis C virus; HBV – Hepatitis B virus*

References: 1. <http://www.prisonstudies.org/info/worldbrief/> 2. WHO Global TB Control Report 2011

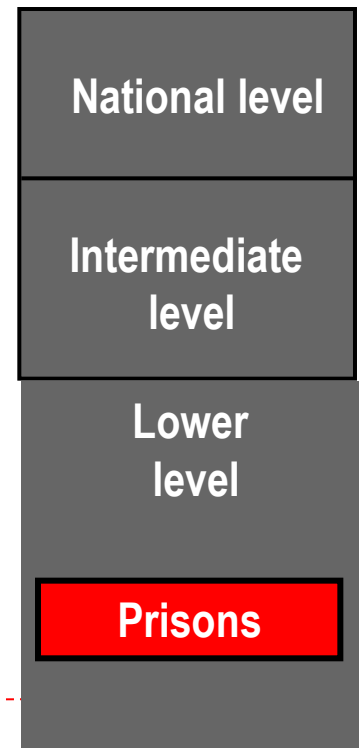
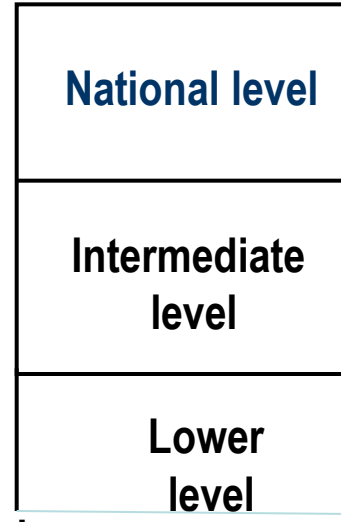
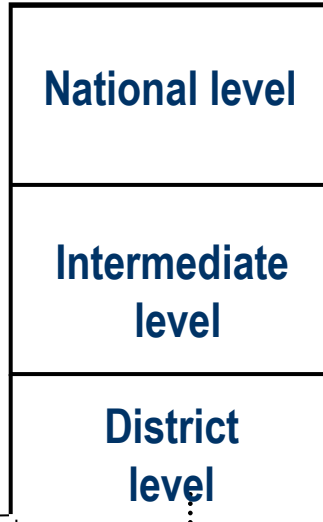
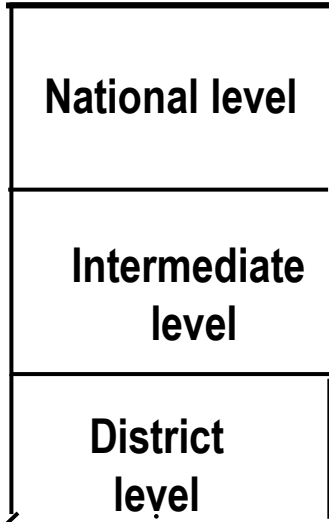
3. Nelson et al *Lancet* 2011, **378**:571-583

# NTP

# NAP

# Narcotic services

# Prison services



TB clinic

ART clinic

ST clinics

Prisons

TB services

HIV services

Primary care services

Community based services

Patient centered – Programme Coordination

# Conclusion

- Reduce mortality due to HIV associated TB (300,000 HIV/TB deaths)
  - PLHIV with TB should get ART within 2 weeks regardless of CD4 count (manage co-morbidities (e.g. hepatitis))
- Prevent TB in PLHIV (>1 million HIV/TB cases)
  - Give earlier ART and provide IPT
  - Ensure TB infection control, especially for PLHIV
  - Screen PLHIV for TB using simple symptom based algorithm.
  - Scale up the use of molecular TB tests (e.g. Xpert MTB/RIF) among PLHIV and in suspected MDR
- Coordinate among TB, HIV, narcotics and prison health programs and deliver integrated services