Mycobacterial Infections in HIV-positive Patients in Low-income Countries (LICs)

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Bellvitge University Hospital-IDIBELL
University of Barcelona

Tuberculosis and other mycobacterial infections in low-income countries

24th ECCMID 2014, Barcelona

Disclaimer

I have no conflicts of interest

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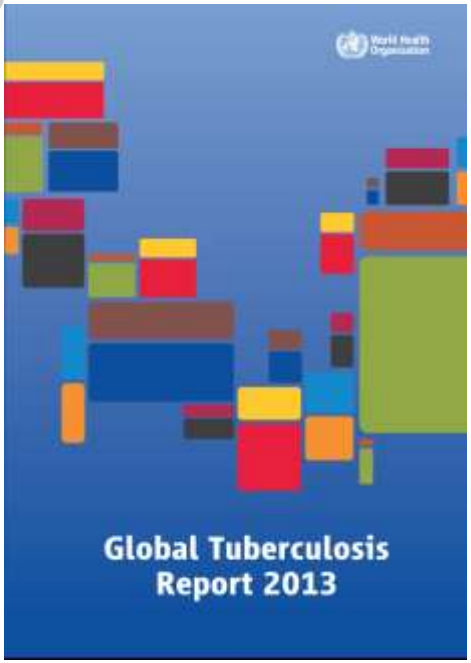
TB and HIV Co-infection.

A deadly synergy

In 2012

- 8.6 million TB cases
- 1.1 (13%) million of TB/HIV
- 320,000 died from HIV-associated TB



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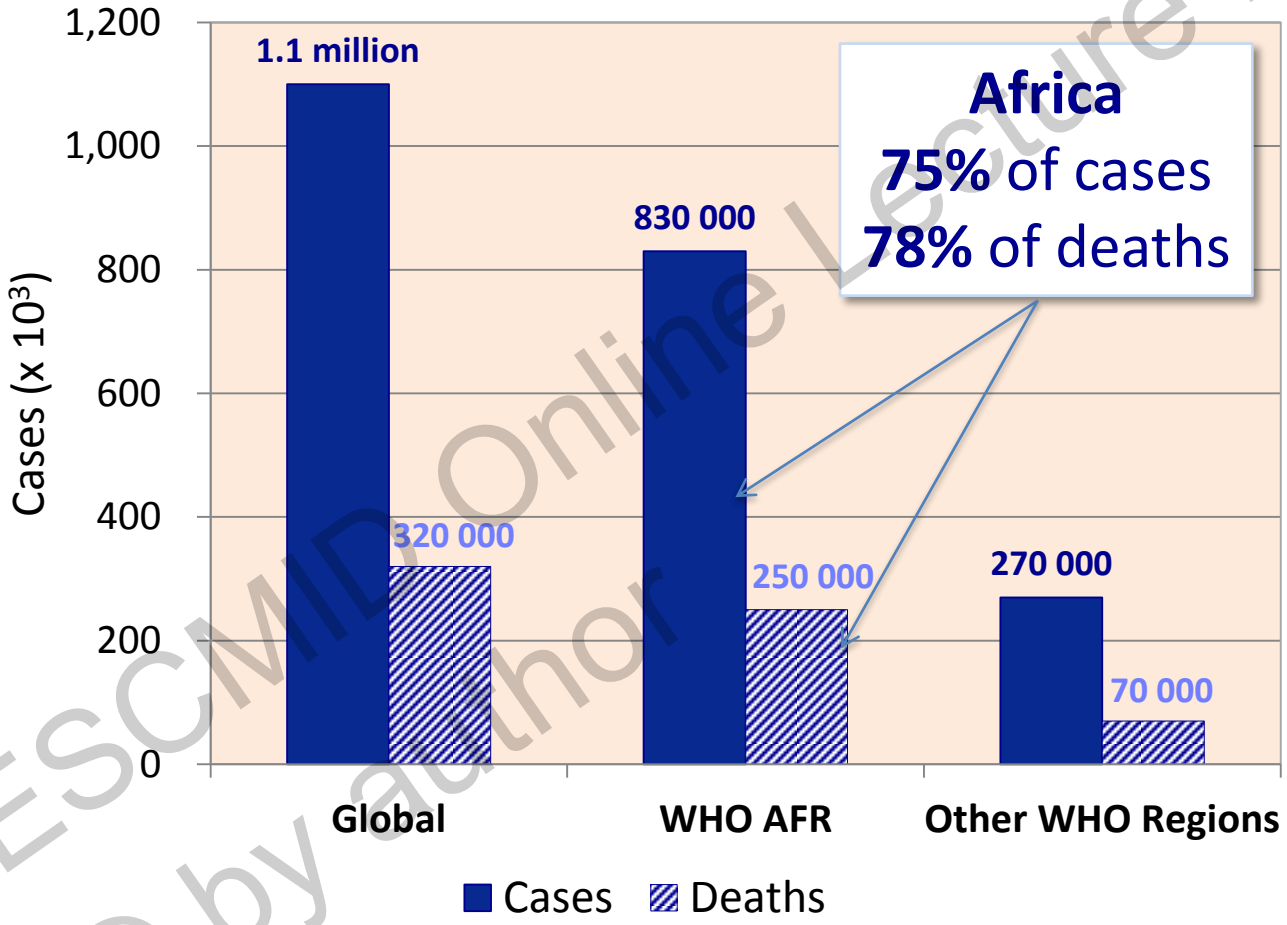
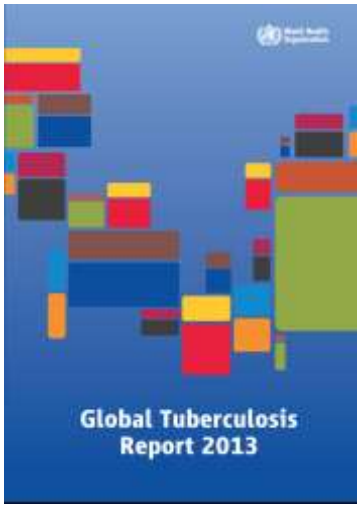
TB/HIV Incident Cases and Deaths

(WHO 2012)





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HIV and TB epidemics

HIV shaped TB

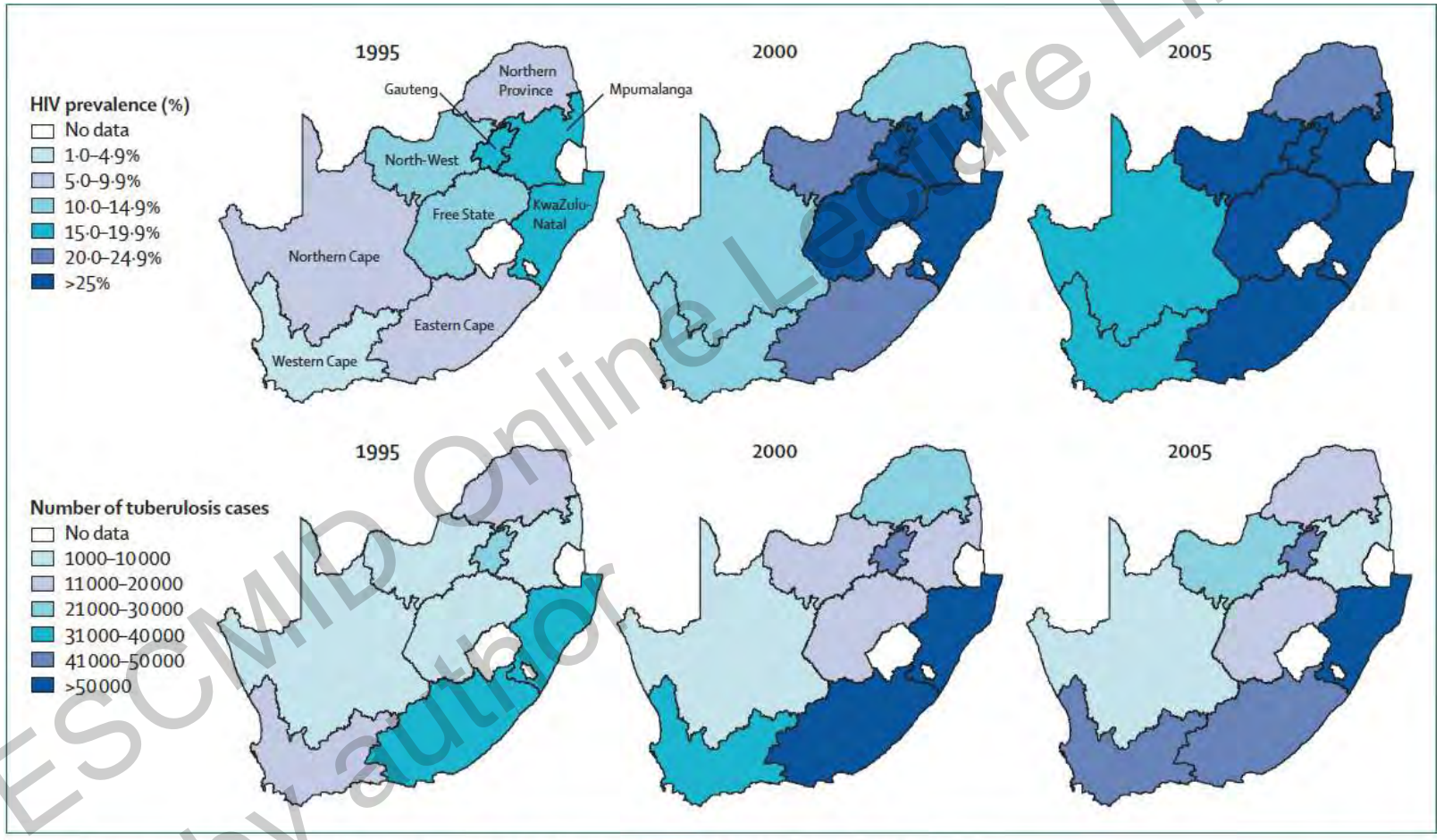

Figure 3: Geographical distribution of HIV and tuberculosis infections in South Africa in 1995, 2000, and 2005

Karim SSA. Lancet 2009

The HIV-associated tuberculosis epidemic—when will we act?

Anthony D Harries, Rony Zachariah, Elizabeth L Corbett, Stephen D Lawn, Ezio T Santos-Filho, Rhehab Chimzizi, Mark Harrington, Dermot Maher, Brian G Williams, Kevin M De Cock

Lancet 2010; 375: 1906–19

The 2012 WHO Policy on Collaborative TB/HIV Activities

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 functional at all levels
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

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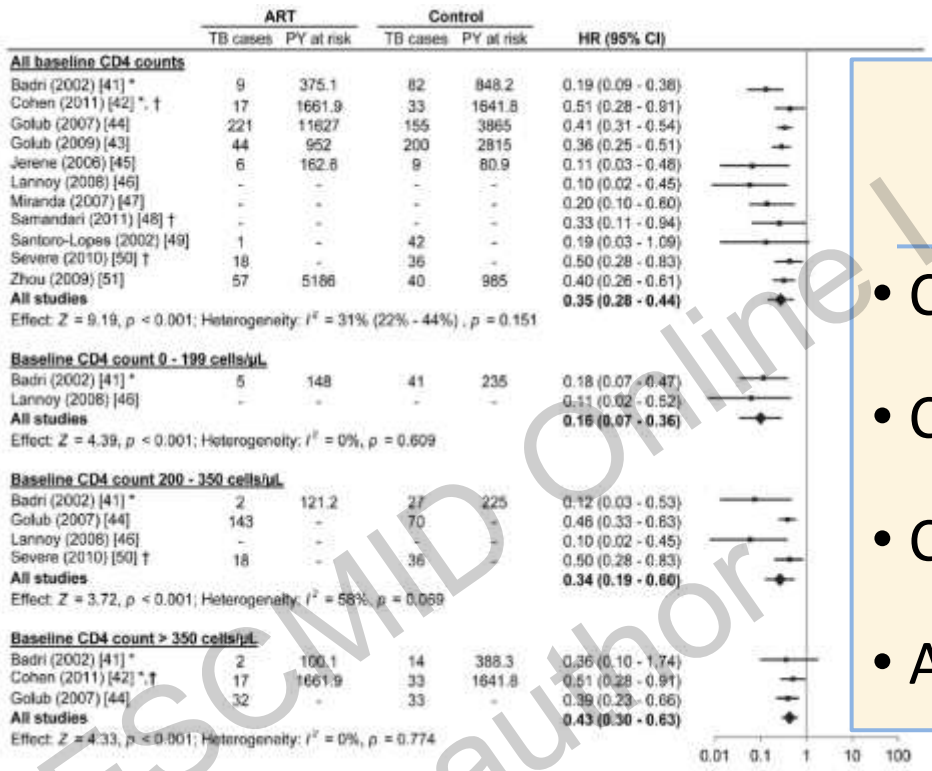
The 2012 WHO Policy on Collaborative TB/HIV Activities

- Role of Antiretroviral Therapy (ART) in preventing TB in HIV-infected people.

ART Prevents HIV-associated TB



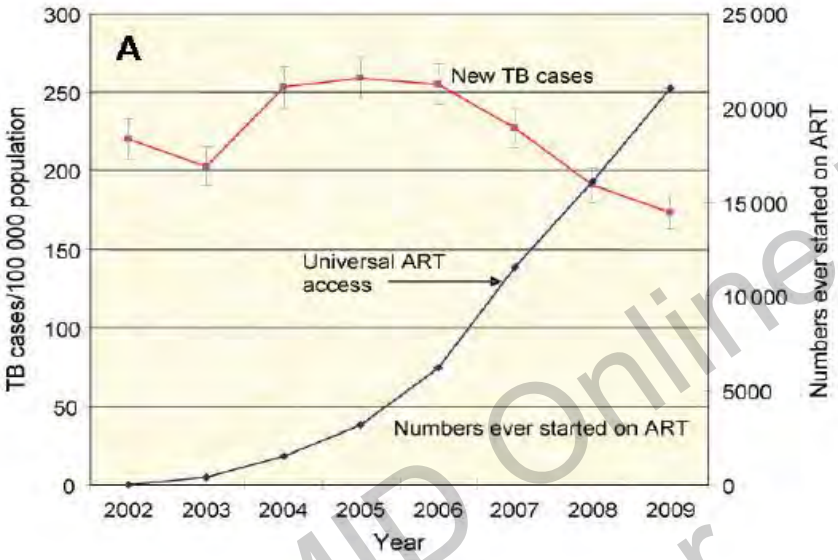
Hazard of TB by Baseline CD4 count

- CD4 0-199 0.16 (0.1-0.4)
- CD4 200-350 0.34 (0.2-0.6)
- CD4 >350 0.43 (0.3-0.6)
- All CD4 counts 0.35 (0.3-0.4)

Adapted from: Suthar AB. PLoS ONE 2012

ART Prevents HIV-associated TB

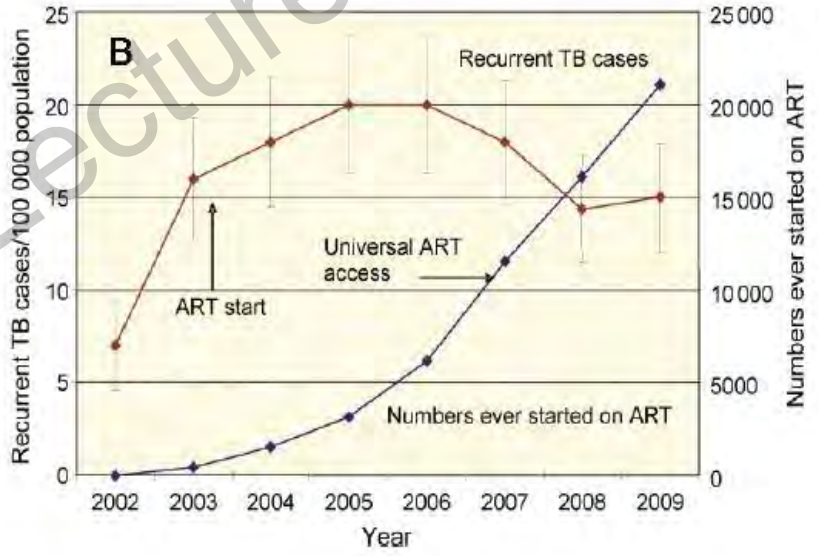
New TB cases



Cumulative reduction (2005-09)

33%

Recurrent TB cases



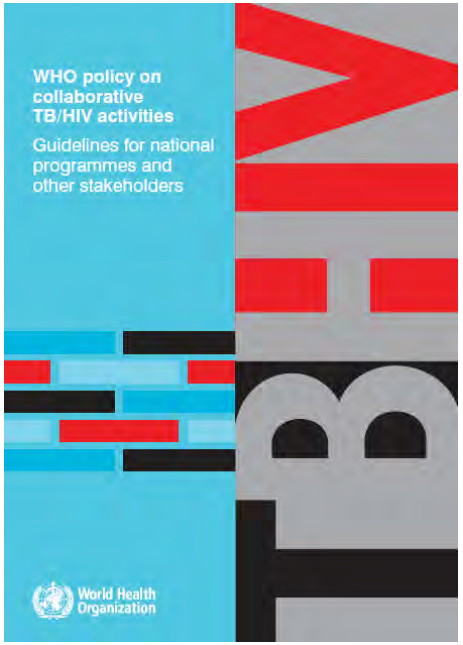
Cumulative reduction (2006-09)

25%

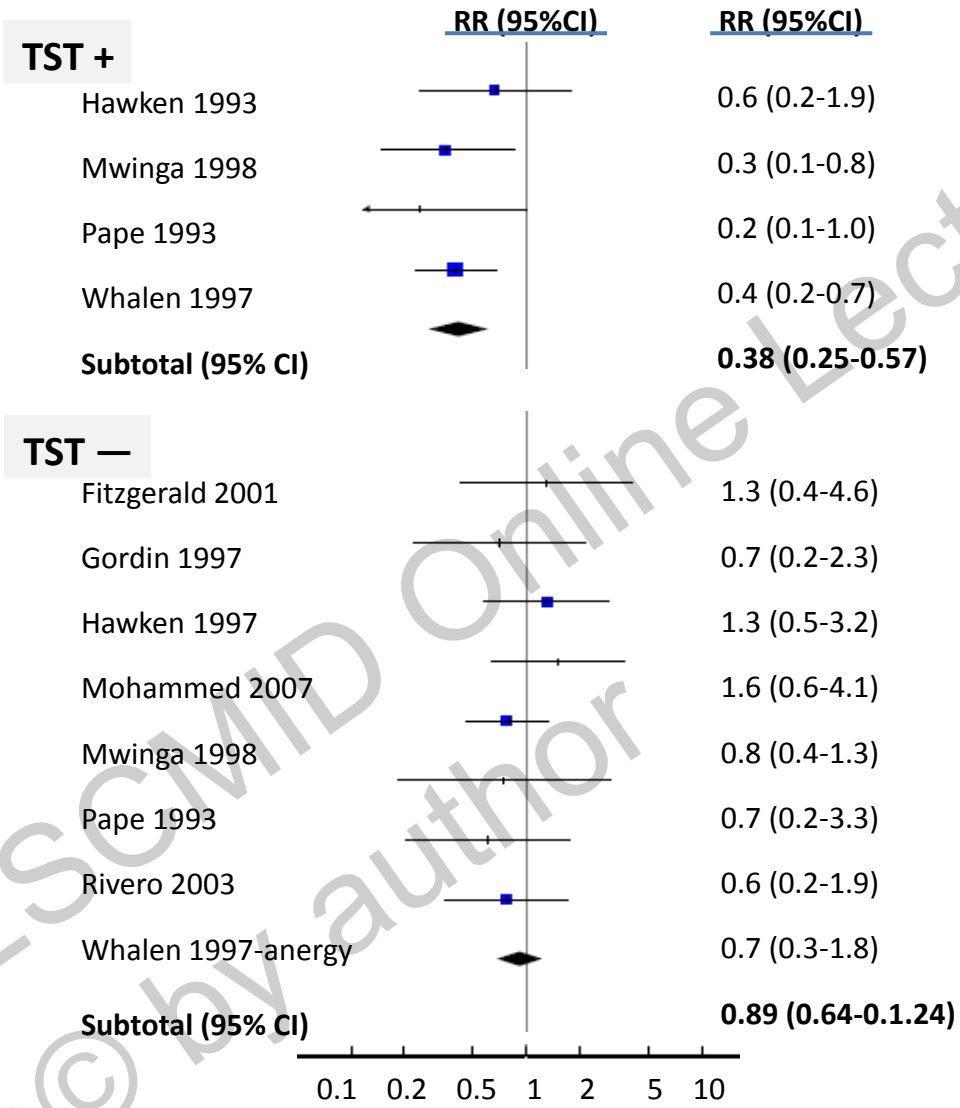
Zachariah R. Reduced TB notifications with ART in rural Malawi. IJTLD 2011.

The 2012 WHO Policy on Collaborative TB/HIV Activities

- Isoniazid Preventive Therapy (IPT)



TB Preventive Therapy in PLHIV



Adapted from:
Akolo C. Cochrane Database of Syst. Reviews 2010.

← **No benefit**

Difficulties for IPT Rollout in PLHIV in LICs

- **TST assessment.**
- **Concerns regarding how to exclude active TB.**
- Low acceptance and completion rates.
- Incomplete protection (6 months) for those TST (+).
- Need for clinical monitoring for toxicity.
- Adherence.
- Cost of DOT (if instituted).

TST not needed for initiating IPT in PLHIV in LICs

4. Tuberculin skin test (TST) is not a requirement for initiating IPT in people living with HIV *(strong recommendation, moderate quality of evidence)*. People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals *(strong recommendation, high quality of evidence)*.

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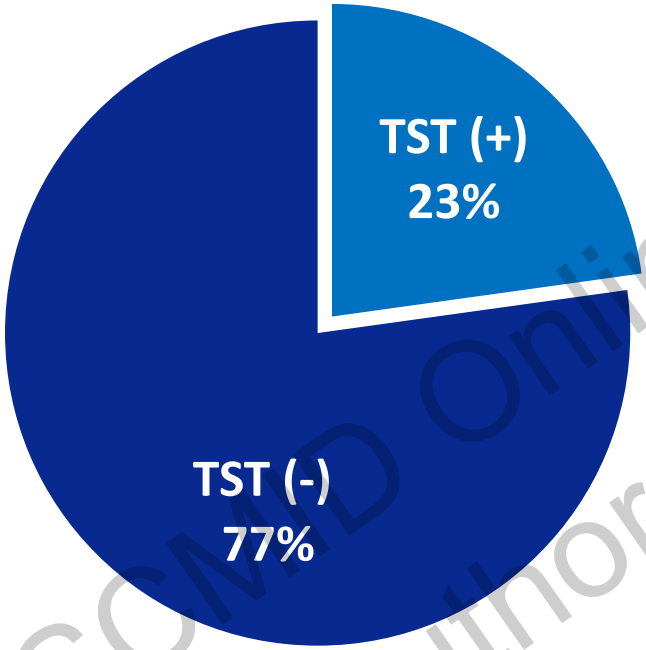
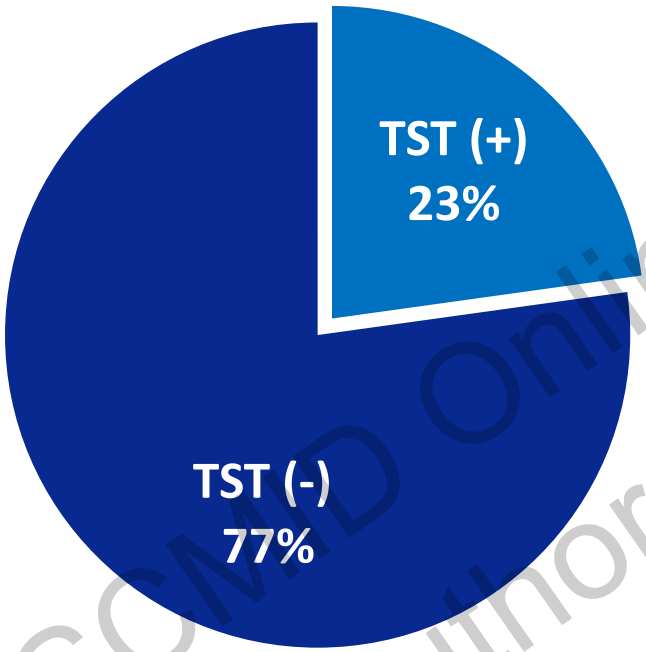
PLHIV Testing TST (+) in LICs



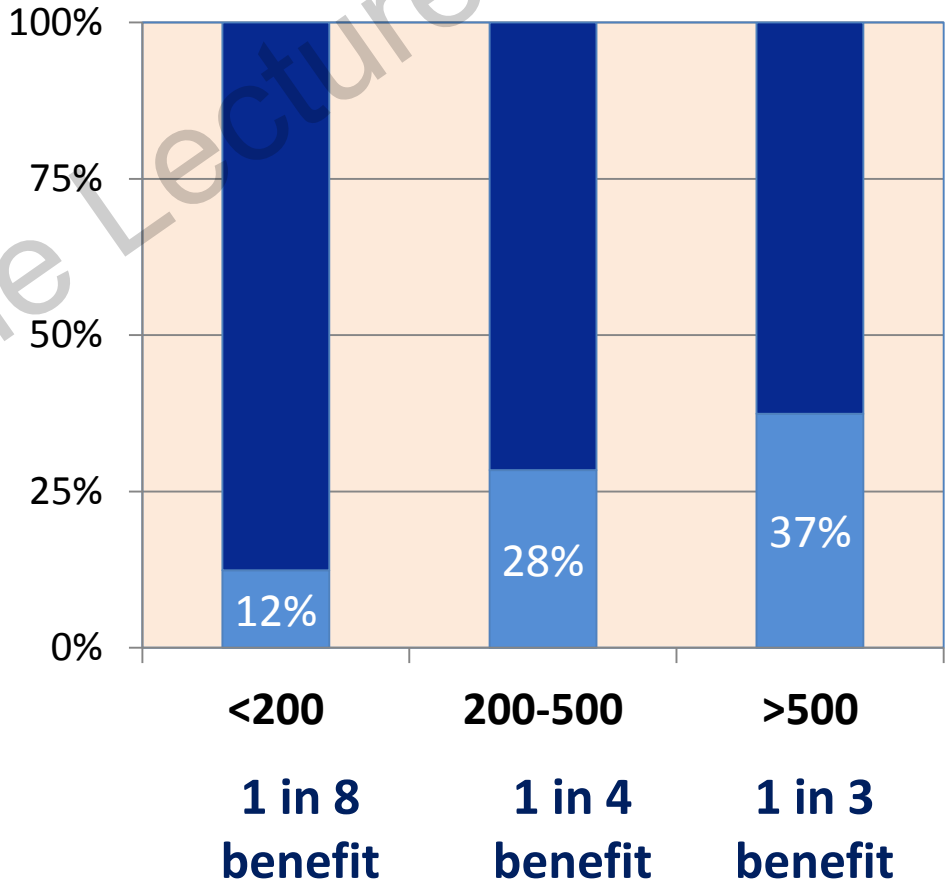
1 in 4
benefit

Kerkhoff AD. PLoS ONE 2012

PLHIV Testing TST (+) in LICs



1 in 4
benefit



Kerkhoff AD. PLoS ONE 2012

Screening for TB in PLHIV in LICs

- **Cough, Fever, Night sweats or Weight loss (CFSW)**
  - *Sensitivity: 79%*
  - *Specificity: 47%*
  - *NPV for TB:*
    - *97.7% (prevalence TB in HIV of 5%)*
    - *90% (prevalence TB in HIV of 20%)*
- **Chest X-ray** increases sensitivity to 91%

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Development of a Standardized Screening Rule for Tuberculosis in People Living with HIV in Resource-Constrained Settings: Individual Participant Data Meta-analysis of Observational Studies

Halleyesus Getahun[1*], Wanitchaya Kittikraisak[2], Charles M. Heilig[3], Elizabeth L. Corbett[4], Helen Ayles[4,5], Kevin P. Cain[3], Alison D. Grant[4], Gavin J. Churchyard[6], Michael Kimerling[7], Sarita Shah[8], Stephen D. Lawn[1,9], Robin Wood[9], Gary Maartens[10], Reuben Granich[1], Anand A. Date[3], Jay K. Varma[2,3]

Abstract

Background: The World Health Organization recommends the screening of all people living with HIV for tuberculosis (TB) disease, followed by TB treatment, or isoniazid preventive therapy (IPT) when TB is excluded. However, the difficulty of reliably excluding TB disease has severely limited TB screening and IPT uptake in resource-limited settings. We conducted an individual participant data meta-analysis of primary studies, aiming to identify a sensitive TB screening rule.

Methods and Findings: We identified 12 studies that had systematically collected sputum specimens regardless of signs or symptoms, at least one mycobacterial culture, clinical symptoms, and HIV and TB disease status. Bivariate random-effects meta-analysis and the hierarchical summary relative operating characteristic curves were used to evaluate the screening performance of all combinations of variables of interest. TB disease was diagnosed in 557 (5.8%) of 9,626 people living with HIV. The primary analysis included 8,148 people living with HIV who could be evaluated on five symptoms from nine of the 12 studies. The median age was 34 years. The best performing rule was the presence of any one of current cough (any duration), fever, night sweats, or weight loss. The overall sensitivity of this rule was 78.9% (95% confidence interval [CI] 58.9%–90.9%) and specificity was 49.6% (95% CI 29.2%–70.1%). Its sensitivity increased to 90.1% (95% CI 76.3%–96.2%) among participants selected from clinical settings and to 88.0% (95% CI 76.5%–94.4%) among those who were not previously screened for TB. Negative predictive value was 97.7% (95% CI 97.4%–98.0%) and 90.0% (95% CI 88.6%–91.3%) at 5% and 20% prevalence of TB among people living with HIV, respectively. Abnormal chest radiographic findings increased the sensitivity of the rule by 11.7% (90.6% versus 78.9%) with a reduction of specificity by 10.7% (43.9% versus 54.9%).

Conclusions: Absence of all of current cough, fever, night sweats, and weight loss can identify a subset of people living with HIV who have a very low probability of having TB disease. A simplified screening rule using any one of these symptoms can be used in resource-constrained settings to identify people living with HIV in need of further diagnostic assessment for TB. Use of this algorithm should result in earlier TB diagnosis and treatment, and should allow for substantial scale-up of IPT.

Please see later in the article for the Editors' Summary.

Citation: Getahun H, Kittikraisak W, Heilig CM, Corbett EL, Ayles H, et al. (2011) Development of a Standardized Screening Rule for Tuberculosis in People Living with HIV in Resource-Constrained Settings: Individual Participant Data Meta-analysis of Observational Studies. PLoS Med 8(1): e1000391. doi:10.1371/journal.pmed.1000391

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Competing Interests: HG and RG are staff members of the World Health Organization. The author alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the World Health Organization.

Abbreviations: ART, antiretroviral treatment; CDR, CD4 T-lymphocyte cell count; CI, confidence interval; IQR, interquartile range; IPT, isoniazid preventive therapy; TB, tuberculosis

*E-mail: getahuch@who.int

Getahun H. PLoS Med 2011

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Duration of IPT in PLHIV in LICs

3. Adults and adolescents living with HIV who have an unknown or positive TST status and who are unlikely to have active TB should receive at least **36 months** of IPT. IPT should be given to such individuals irrespective of the degree of immunosuppression… *(conditional recommendation, moderate quality of evidence)*.

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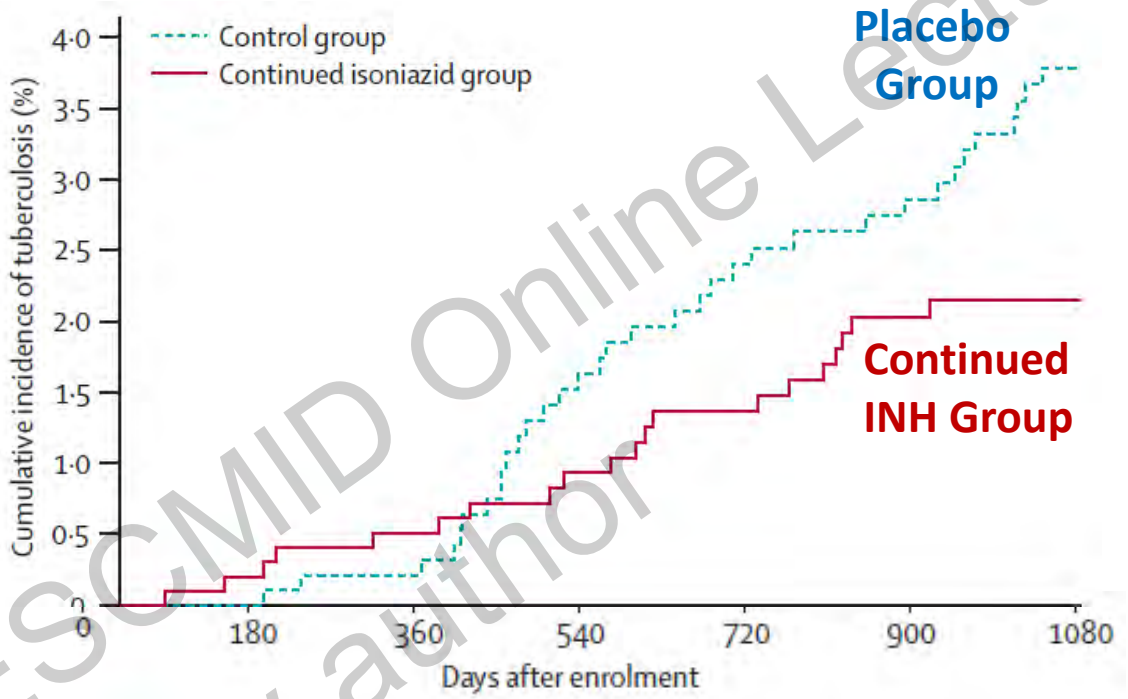
IPT Therapy in PLHIV in LICs

Shorter or longer?



6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial

Samandari T. Lancet 2011

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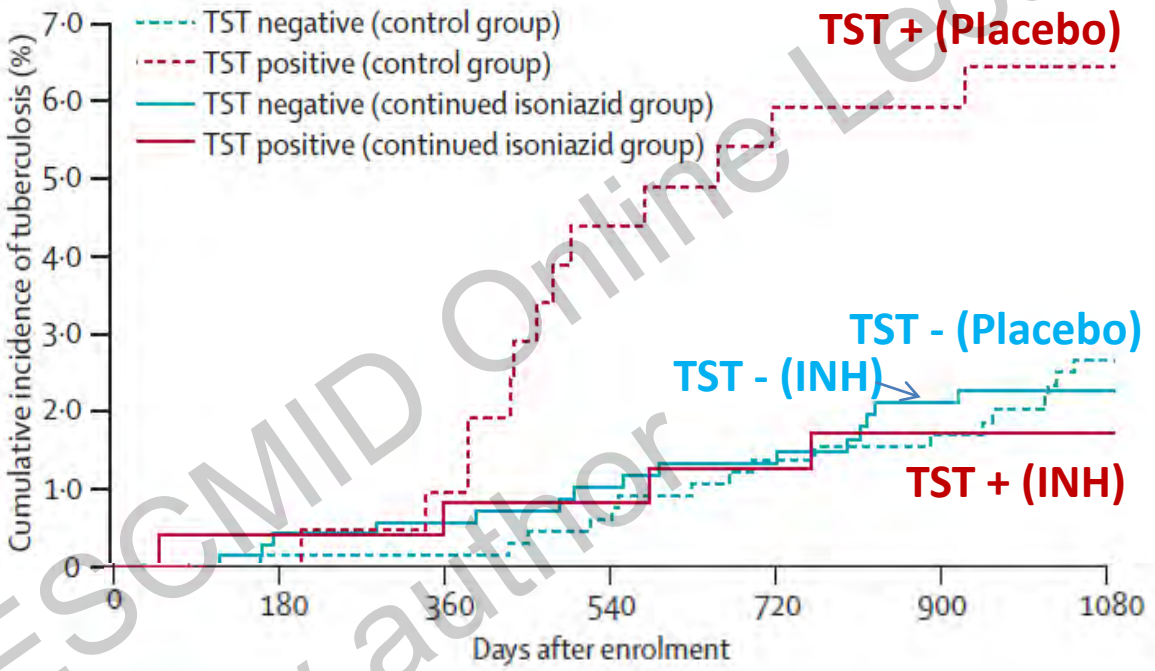
IPT Therapy in PLHIV in LICs

Shorter or longer?



6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial

Samandari T. Lancet 2011

The 2012 WHO Policy on Collaborative TB/HIV Activities

- ART for all TB patients living with HIV.

Timing of ART in TB Patients with HIV

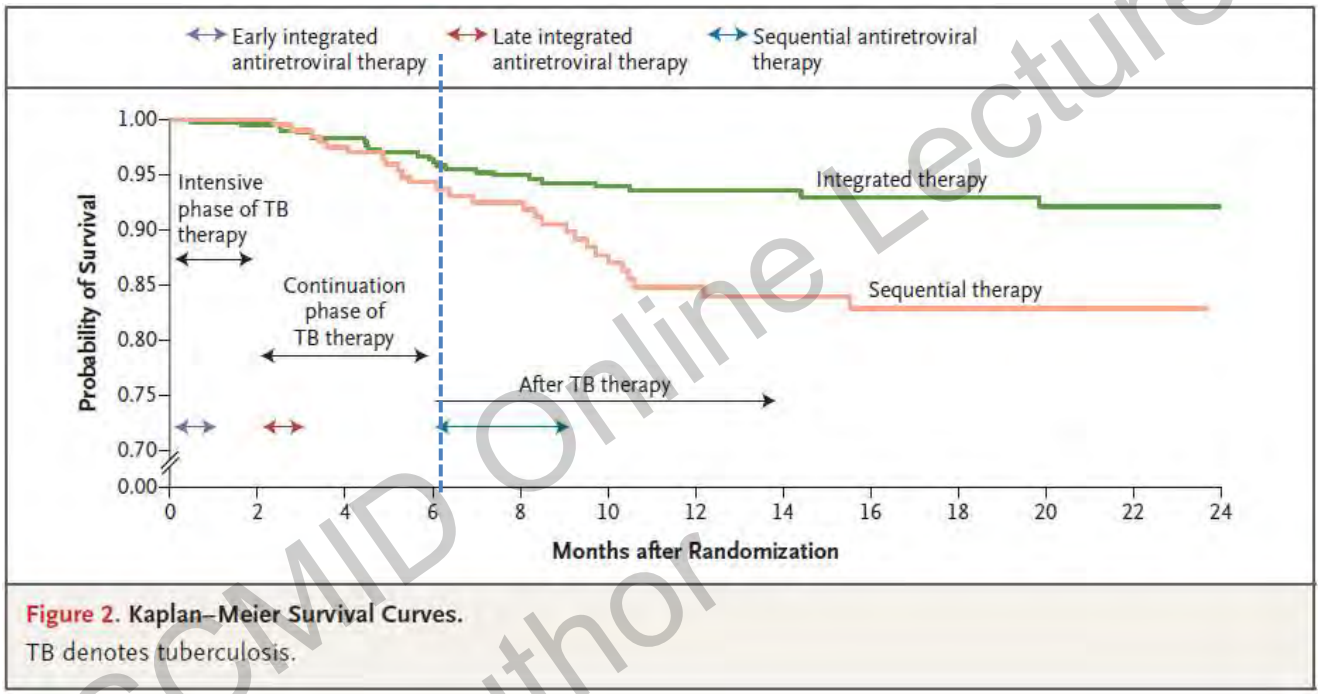


Figure 2. Kaplan–Meier Survival Curves.
TB denotes tuberculosis.

Timing of Initiation of Antiretroviral Drugs during Tuberculosis Therapy

56% reduction in mortality in the integrated ART

Karim SSA. NEJM 2010

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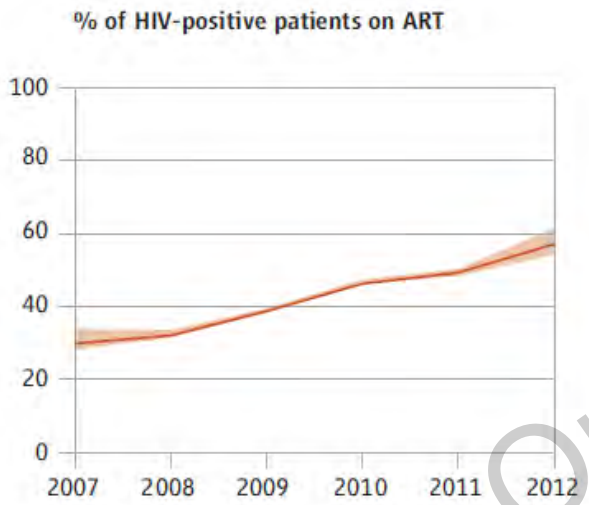
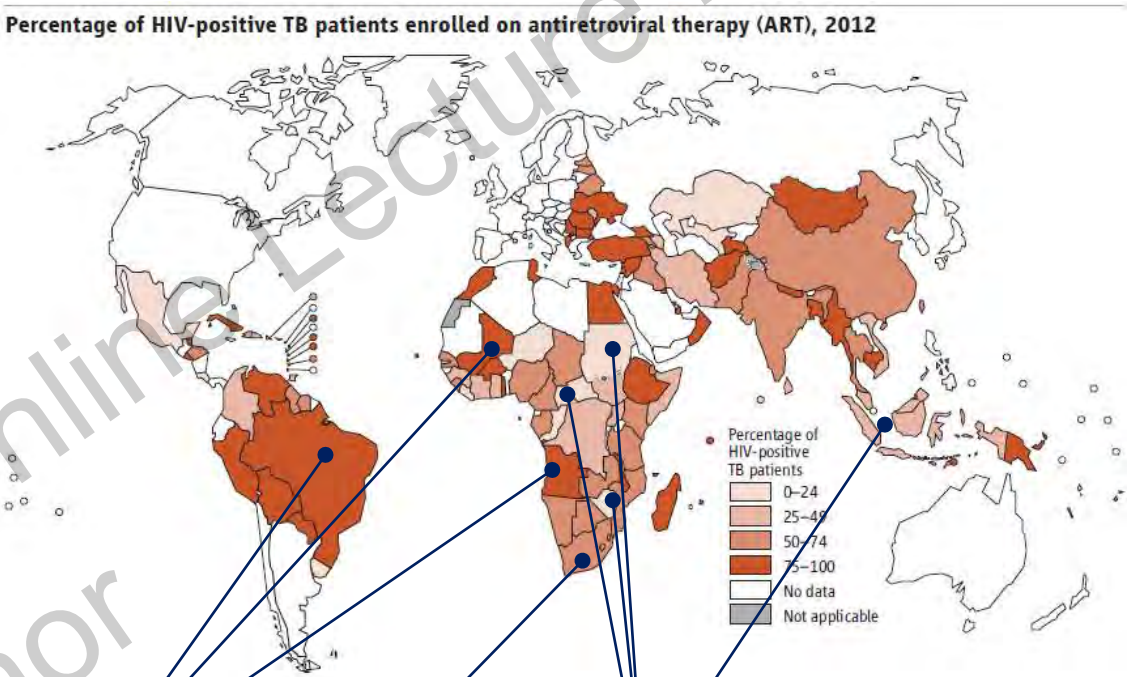
Timing of ART in TB Patients with HIV

	SAPIT n= 429 (S. Africa)	CAMELIA n= 661 (Cambodia)	STRIDE n= 809 (Multin.)
Type study	RCT	RCT	RCT
Pts. included	<500 CD4	≤200 CD4	<200 CD4
Intervention			
-Early-ART	Within 4 wks after the start of TB Rx	2 wks after the start of TB Rx	Within 2 wks after the start of TB Rx
-Late-ART	Within 4 wks of the continuation phase of TB Rx	8 wks after initiation TB Rx	Within 4 wks of the continuation phase of TB Rx
Early vs late ART	Early ART improved AIDS-free survival in pts. with <50 CD4	Early ART improved survival (No diffs. between < and > 50 CD4)	Early ART improved survival and prevent AIDS events in pts. with <50 CD4

Karim SSA. NEJM 2011; Blanc F. NEJM 2011; Havlir DV. NEJM 2011

ART Coverage for TB/HIV-positive Patients





ART coverage (2012)
High TB/HIV Countries
57%

Brasil
Mali **100%**
Angola

S. Africa
54%

Sudan
Congo
CA Republica **<25%**
Zimbawe
Indonesia

Global TB Report 2013
World Health Organization

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PLoS NEGLECTED TROPICAL DISEASES

Viewpoints

Non-Tuberculous Mycobacteria in TB-Endemic Countries: Are We Neglecting the Danger?

Krishnamoorthy Gopinath, Sarman Singh*

Division of Clinical Microbiology, Department of Laboratory Medicine, All India Institute of Medical Sciences, New Delhi, India

NTMs in HIV Patients in LICs

- **Longitudinal study** (Cotrame ANRS 1203 Cohort. Côte d'Ivore)
- **Period:** 1996-2004
- **Patients:** 718 HIV-positive adults
- **CD4** cell count (median): 297 cells/mm3
- **Follow-up** (median): 28 months

	N	Time at risk (person-years)	Cases NTMs	Incidence (cases/ 100 p-y)
Overall	718	1841	34*	1.9
Baseline CD4				
< 100	109	99	12	**12.2**
≥ 100	609	1742	22	**1.3**

*All isolates were *M. avium* or *M. intracelullare*

Bonard D. AIDS 2004

Prevalence of NTMs in HIV Patients in LICs

Country (Study period)	Patients	N	Prevalence
• **South Africa** (1998)	Hospitalized black men with advanced HIV infection (<100 CD4)	100	HIV (+): 10% *(16% of Mycobacterial infections in HIV pts.)*
• **Zambia** (2001-03)	Pts suspected of having Pulmonary TB	173 126 HIV (+)	Overall: 31% HIV (+): 36% *(53% of Mycobacterial infections in HIV pts.)*
• **Kenya** (2007-09)	Pts suspected of having Pulmonary TB	872 272 HIV (+)	Overall: 1.7% HIV (+): 2.6% *(6% of Mycobacterial infections in HIV pts.)*
• **Nigeria** (2010-11)	Pts suspected of having Pulmonary TB	1369	Overall: 5% *(15.5% of Mycobacterial infections)*

Pettipher CA, CID 2001; Buitjels PC, Asian Pacific J Trop Med 2010; Nyamogoba H, Afr Health Sciences 2012; Aliyu G, PONE 2013

Document heading

Misdiagnosis of tuberculosis and the clinical relevance of non-tuberculous mycobacteria in Zambia

Patricia CAM Buijtels[1*], Michael D Iseman[2], Shelagh Parkinson[3], Cas S de Graaff[4], Henri A Verbrugh[5], Pieter LC Petit[6], Dick van Soolingen[7,8]

Asian Pacific Journal of Tropical Medicine (2010)386-391

Concluding remarks

- HIV co-infection threatens TB control programmes in high-endemic HIV/TB countries.
- Currently, early ART is the mainstay for preventing HIV-associated TB.
- IPT complements ART, but longer courses of treatment may be needed in high-endemic TB settings.
- Although all HIV TB patients are eligible for ARV, in LICs <60% are put on treatment.
- Incidence of NTMs in HIV patients in LICs is comparable to developed countries and has implications on diagnosis and empirical treatment of TB.

Thank You!