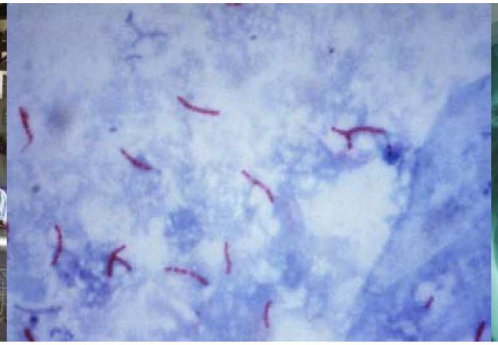
TB and HIV:
Friends with(out) Benefits

Jay K. Varma, MD

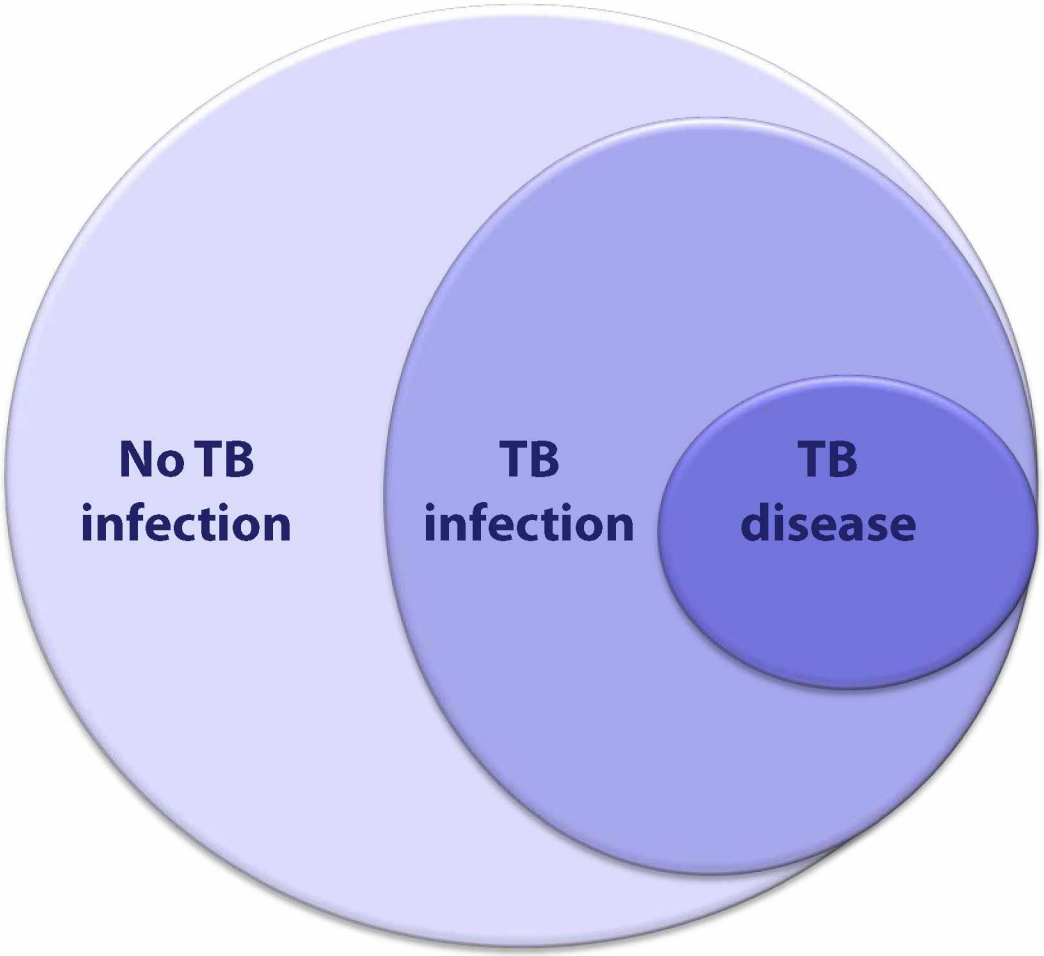
Chief, International Emerging Infections Program—China

Division of Global Disease Detection and Emergency Response

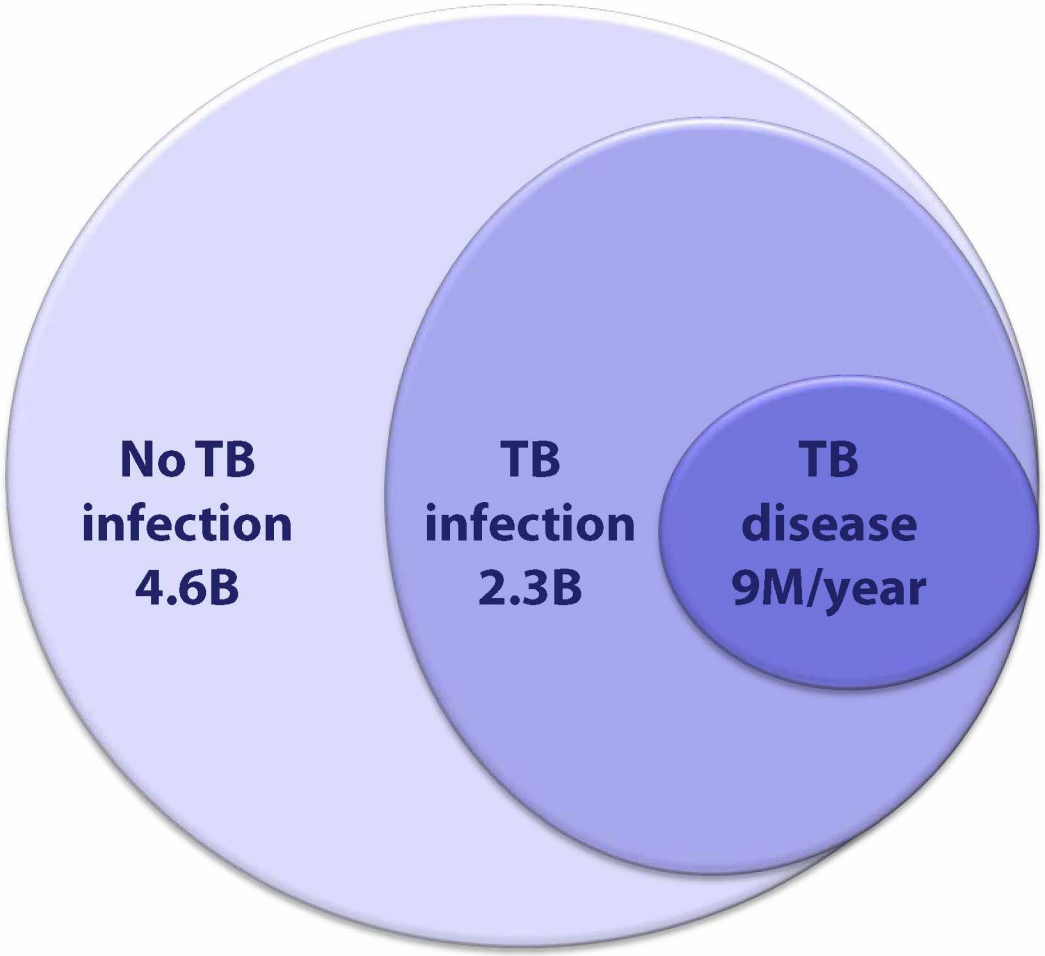
Center for Global Health

Centers for Disease Control and Prevention

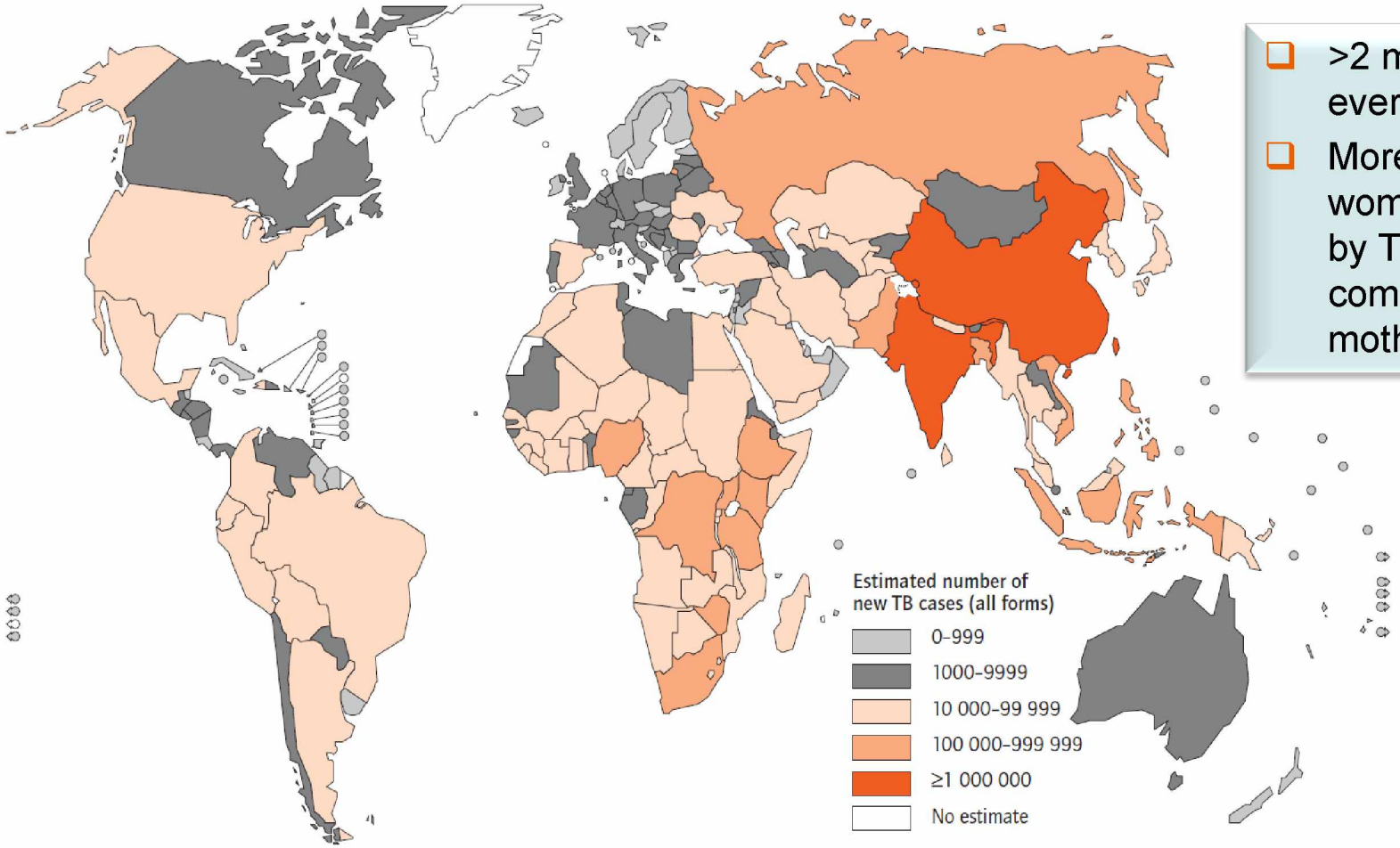
Misconception: TB Is a Single Disease



Misconception: TB Is No Longer a Big Problem



Misconception: TB Is No Longer a Big Problem



- >2 million deaths every year
- More deaths in women caused by TB than complications of motherhood

World Health Organization. Global Tuberculosis Control: WHO report 2010. Geneva, Switzerland
http://www.who.int/tb/publications/global_report/en/

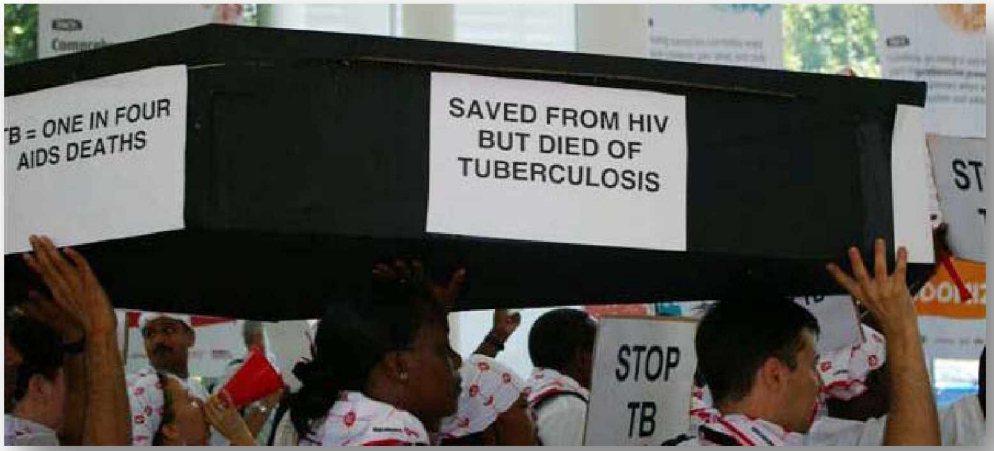
Misconception: TB Is Easy to Diagnose

	Common tests for TB	Challenges
Infection	Tuberculin skin test	Neither sensitive nor specific; difficult to use
Infection	Interferon-γ blood test	Difficult to use; expensive
Disease	Signs and symptoms	Nonspecific
Disease	Antibody blood test	Neither sensitive nor specific
Disease	Chest X-ray	Sensitive for pulmonary TB, but nonspecific
Disease	Sputum acid-fast smear	Only identifies highly infectious TB cases
Disease	Sputum culture	Sensitive, but difficult to use
Disease	Sputum PCR	Sensitive, easy to use, but expensive and only recently validated

PCR, Polymerase chain reaction
γ, gamma

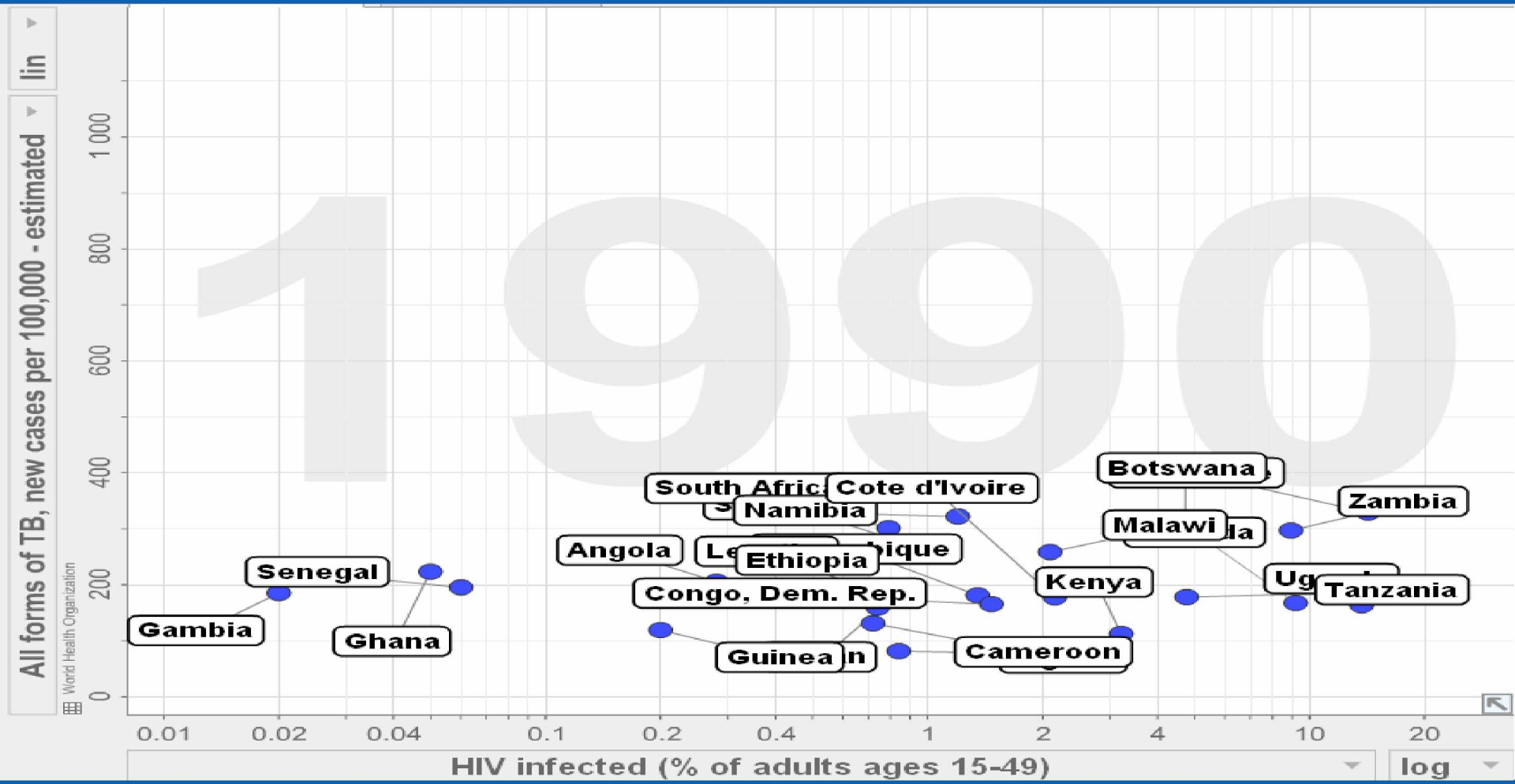
Why HIV and TB Are a Dangerous Duo

- People living with HIV are more likely to develop TB
- In people living with HIV, TB is harder to diagnose and treat
- HIV patients have a high risk of dying during TB treatment



Picture credit: Alex Miranda for WHO

HIV Is the Most Powerful Risk Factor for Progressing from TB Infection to Disease



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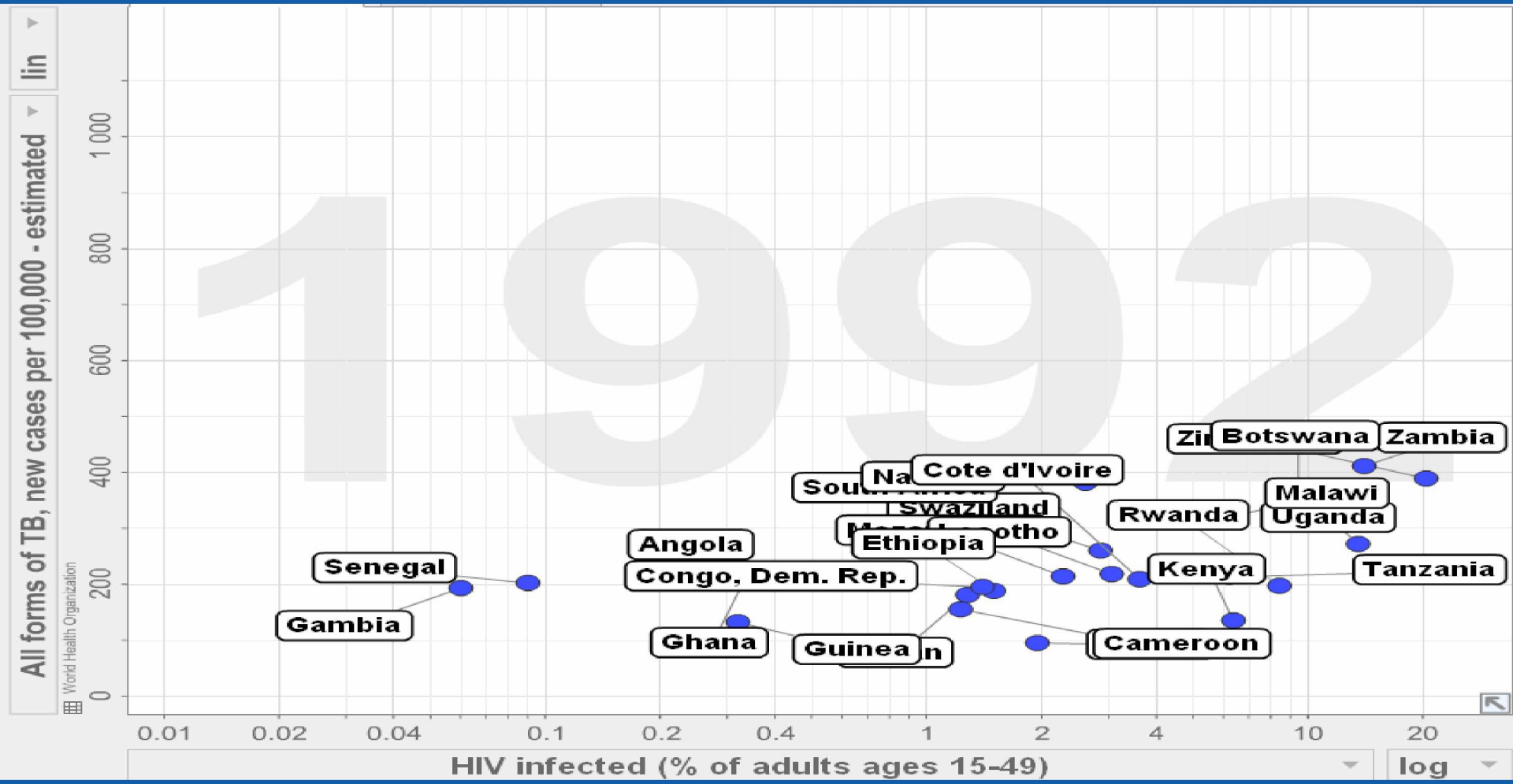

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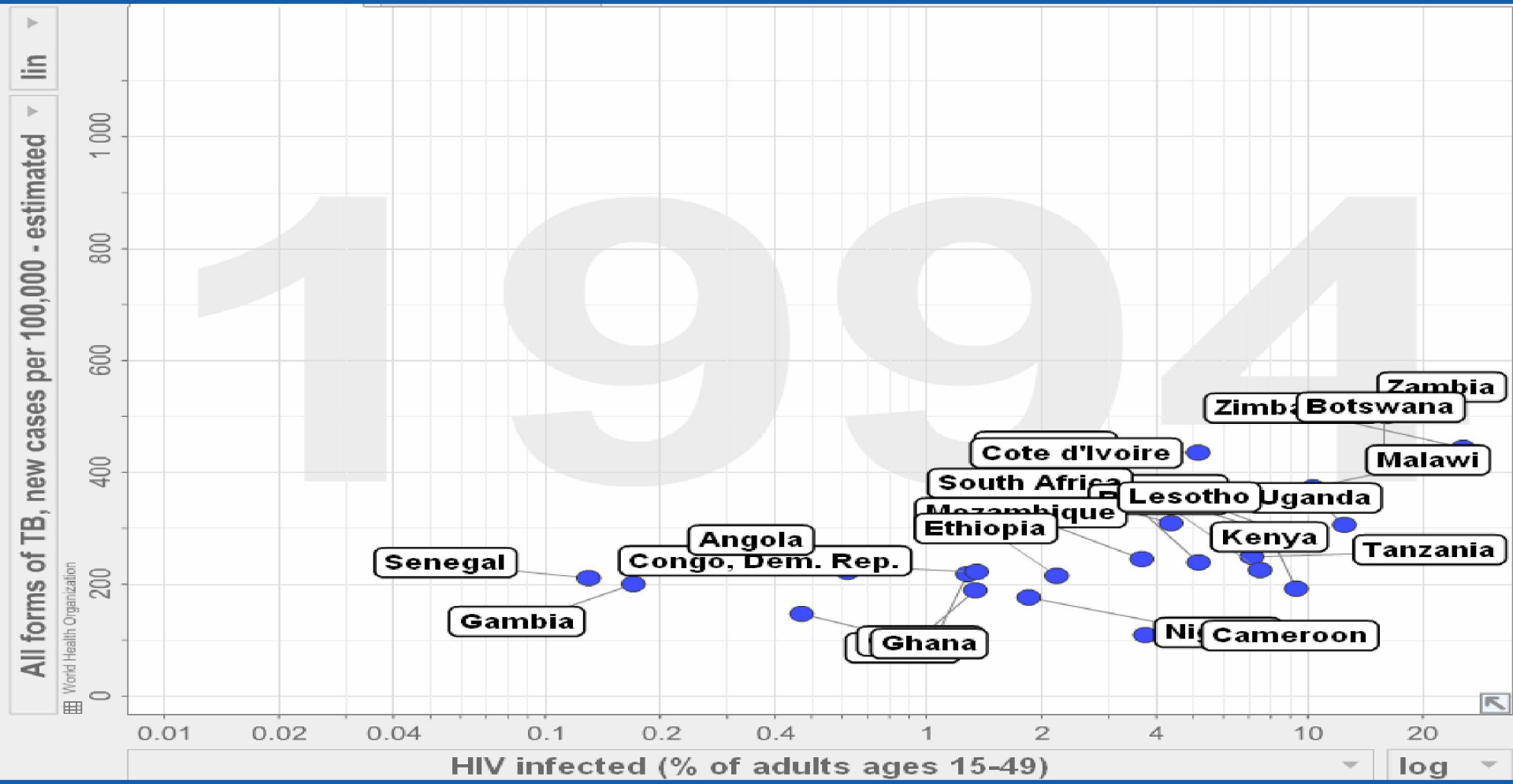

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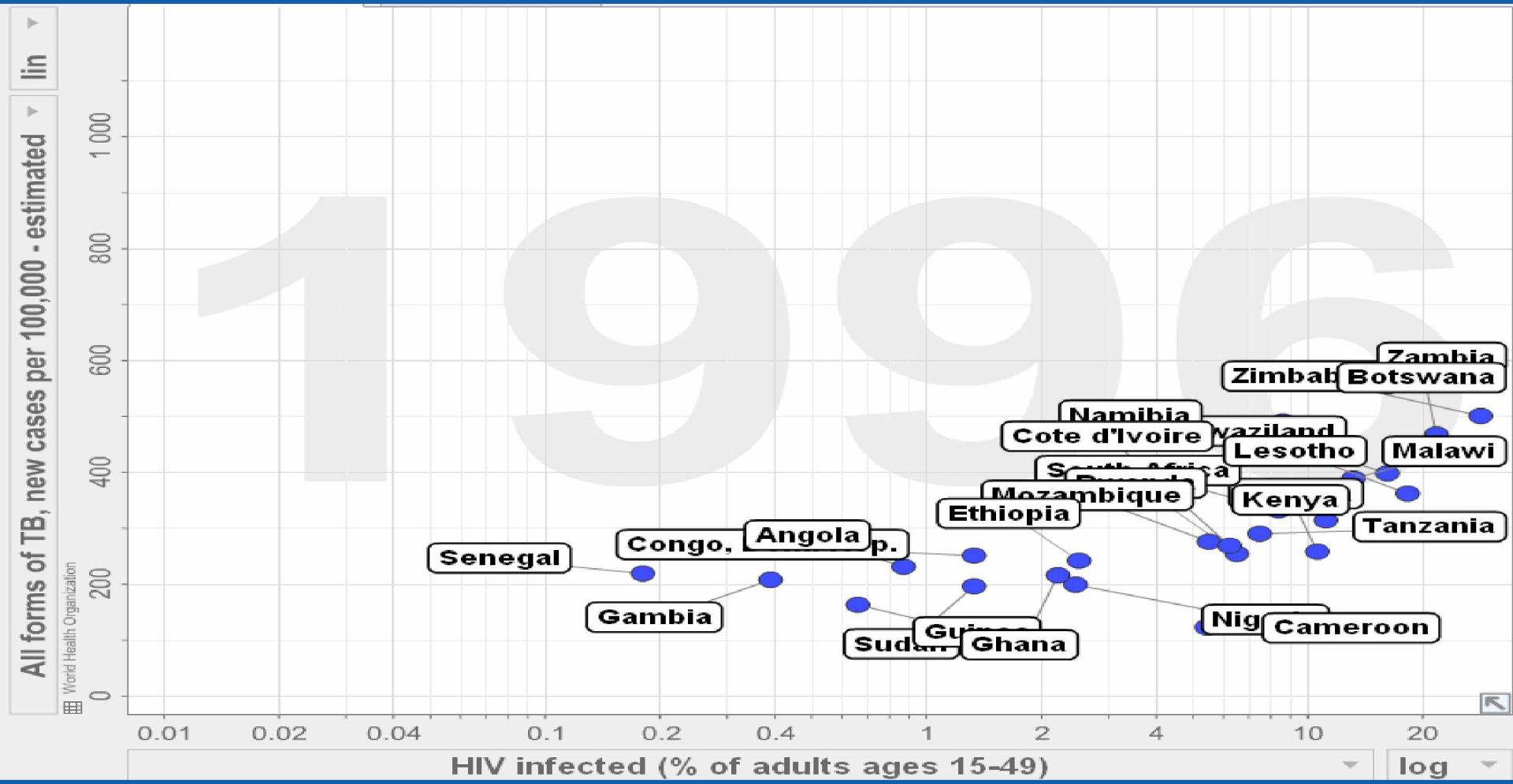

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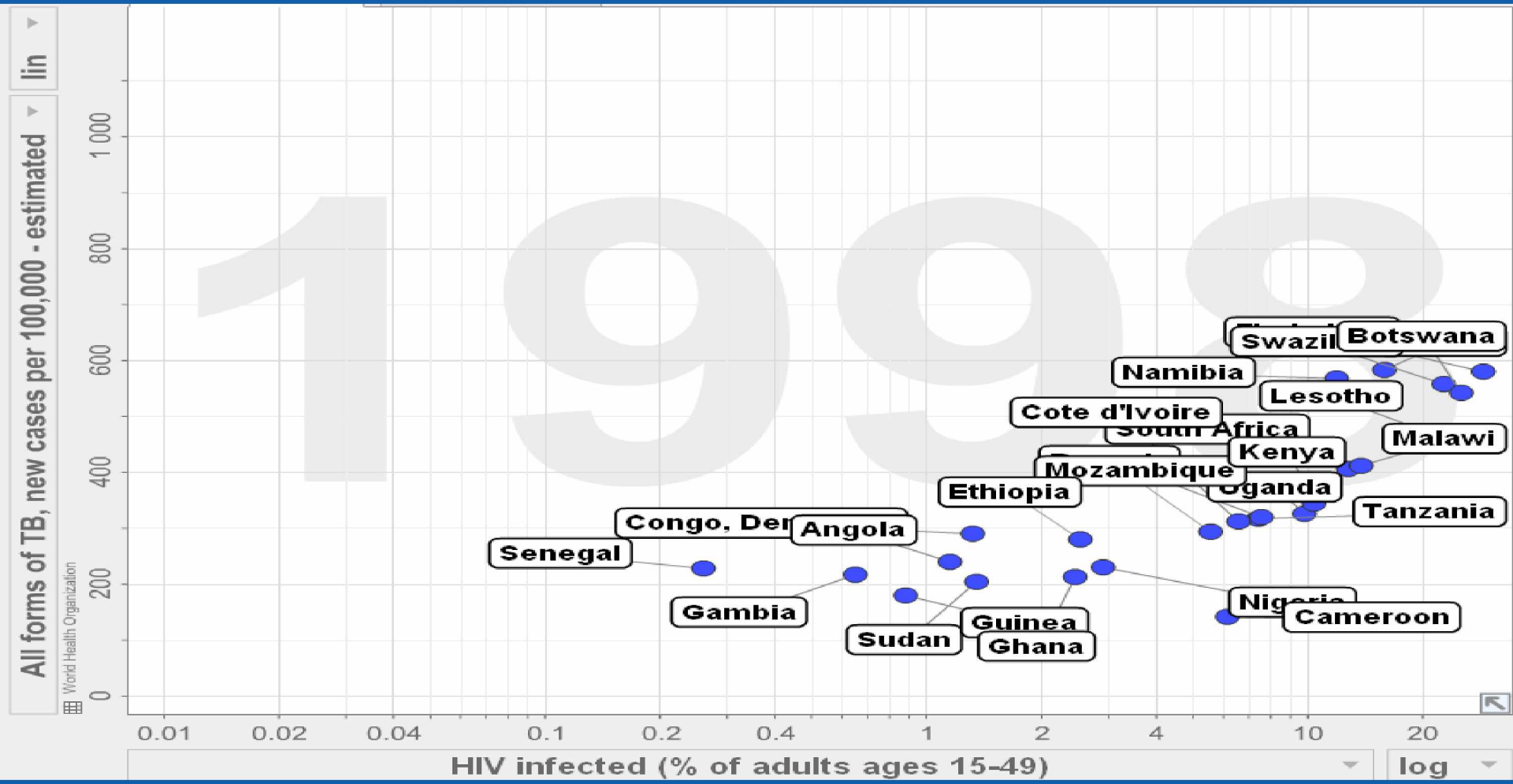

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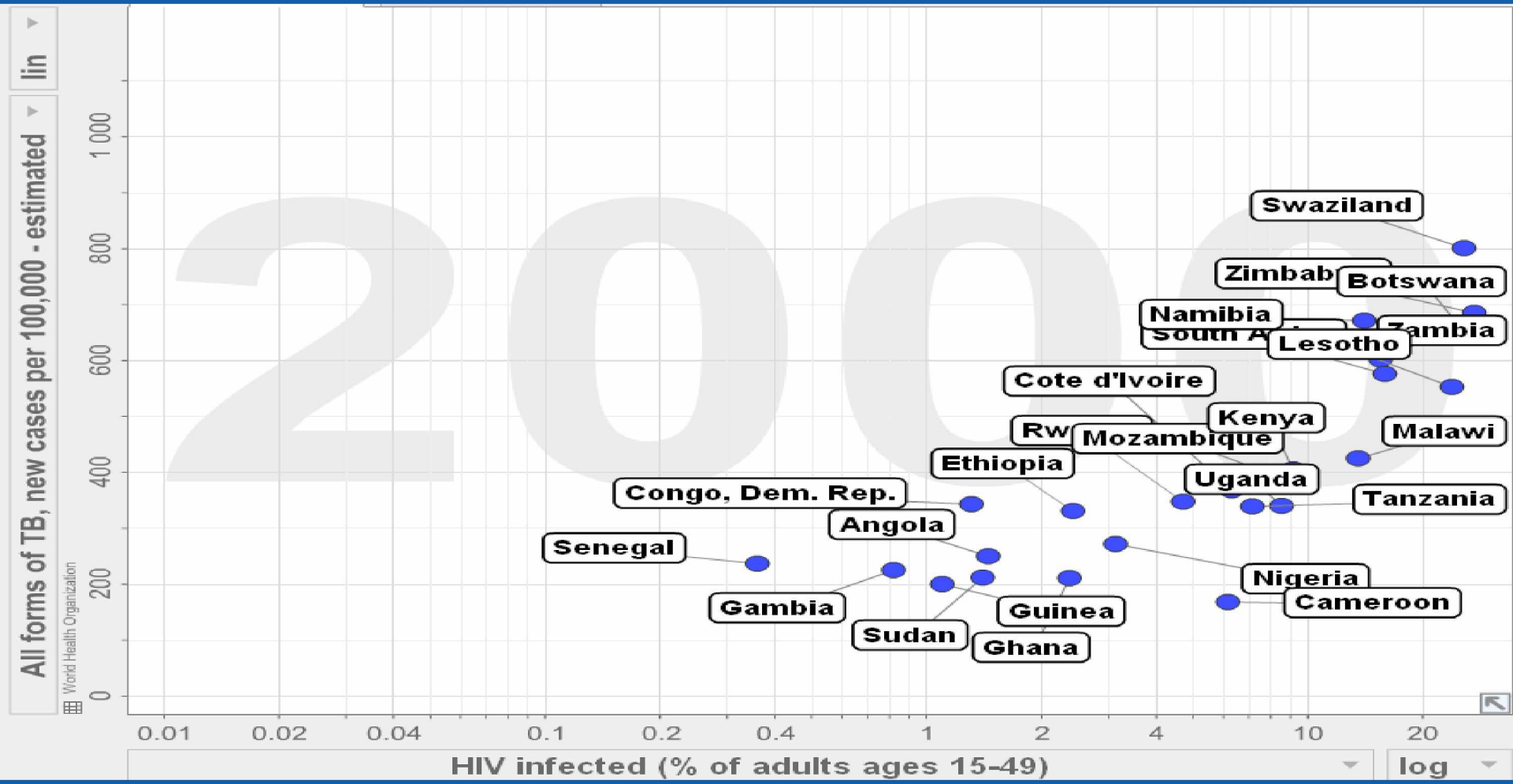

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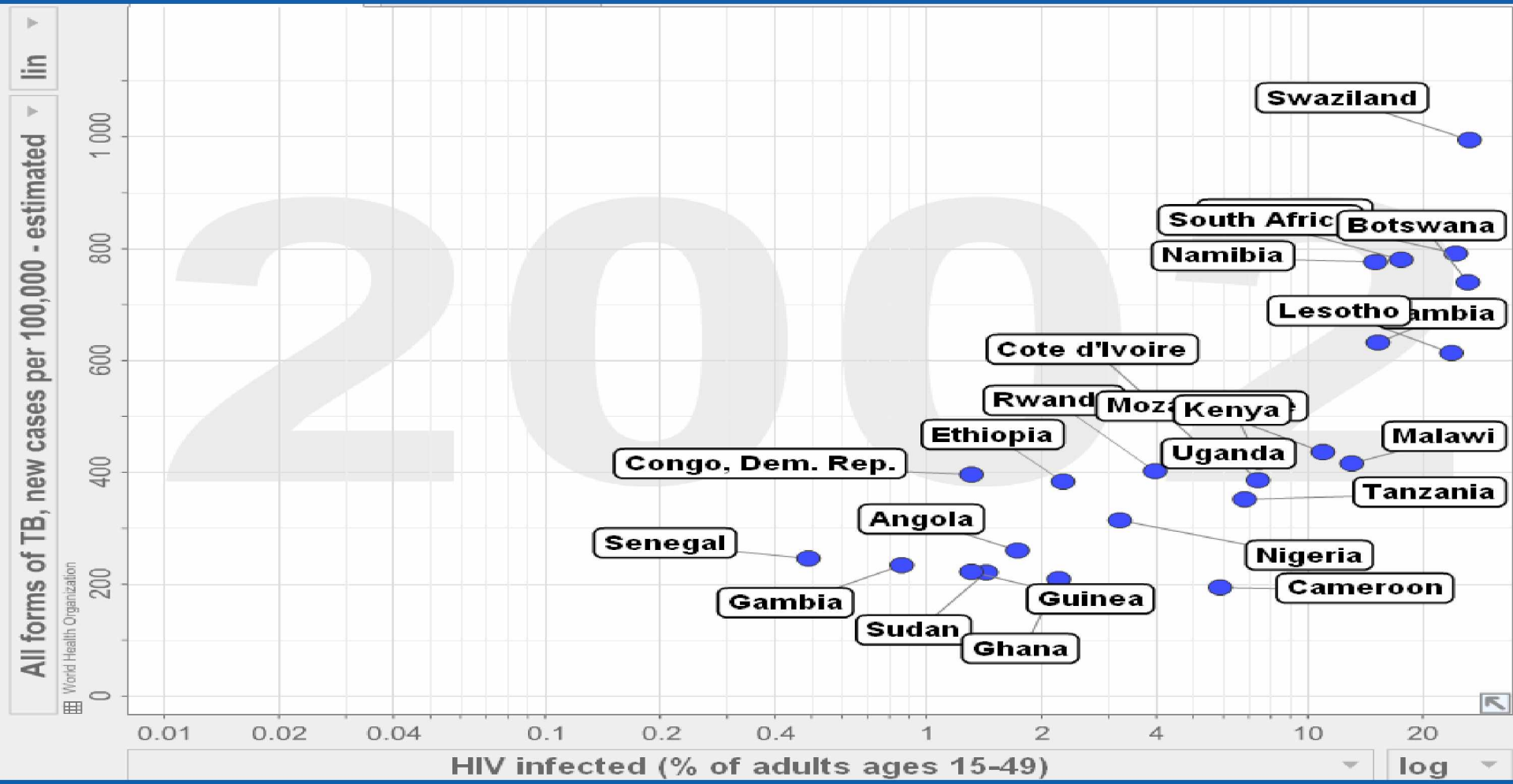

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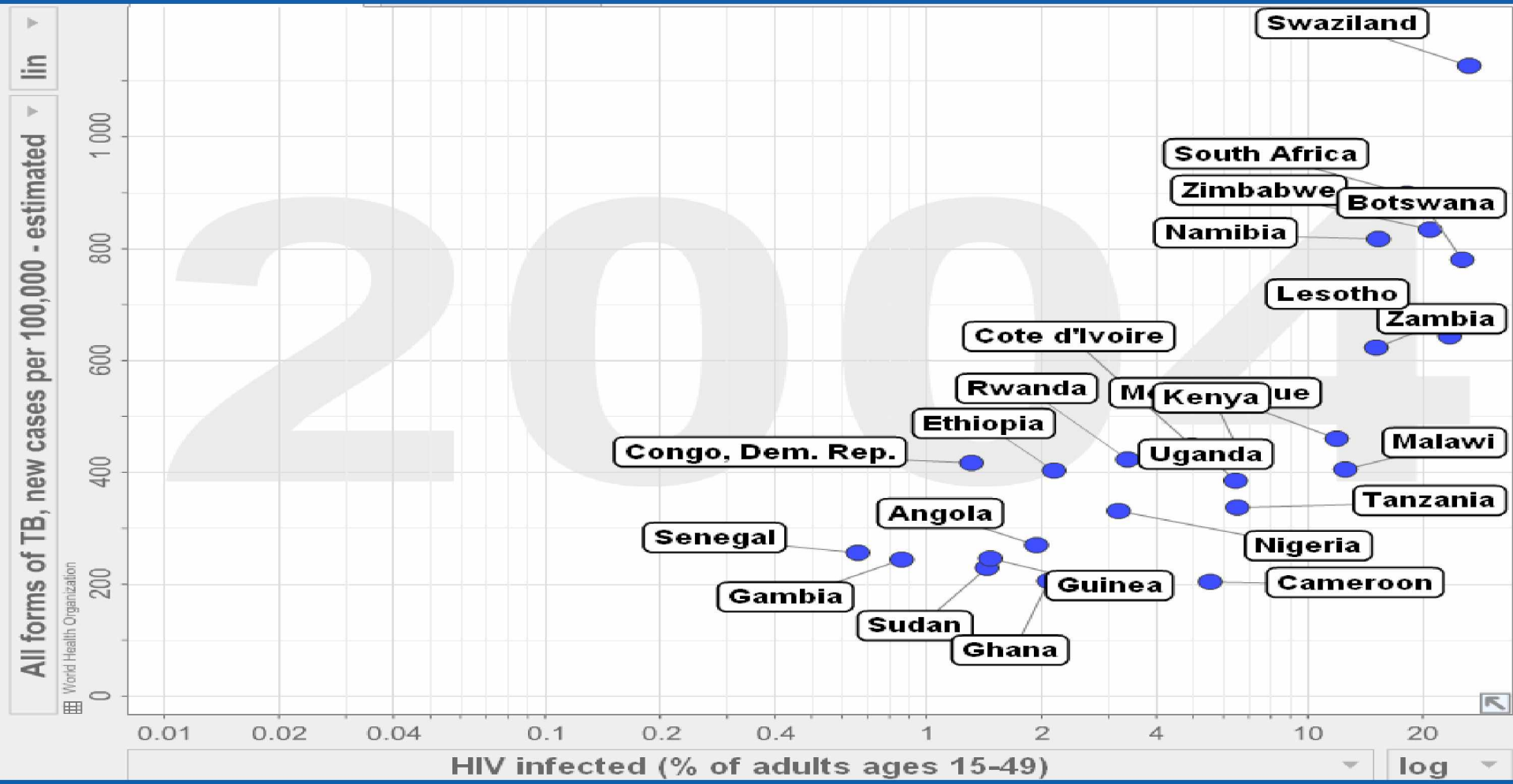
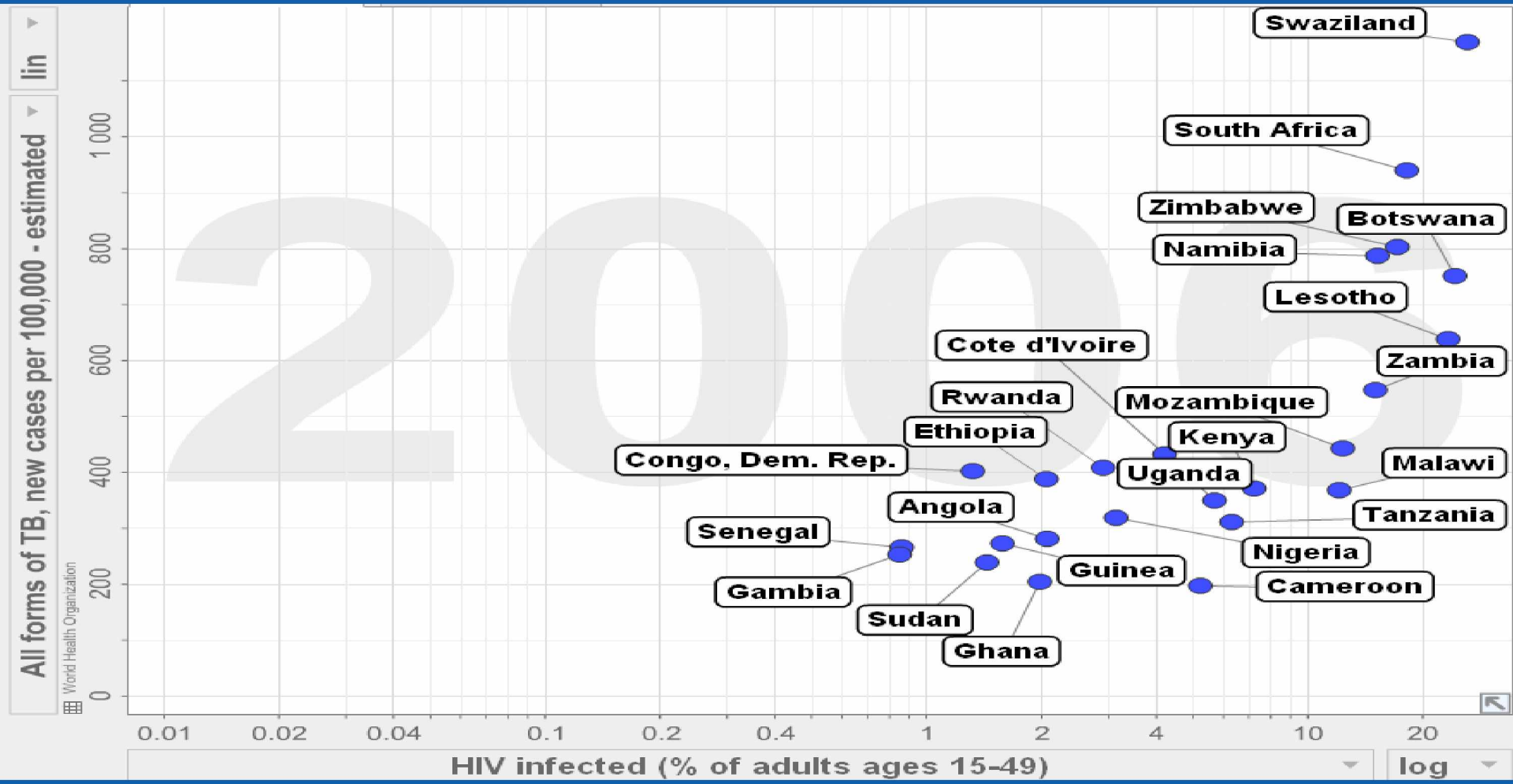


HIV Is the Most Powerful Risk Factor for Progressing from TB Infection to Disease



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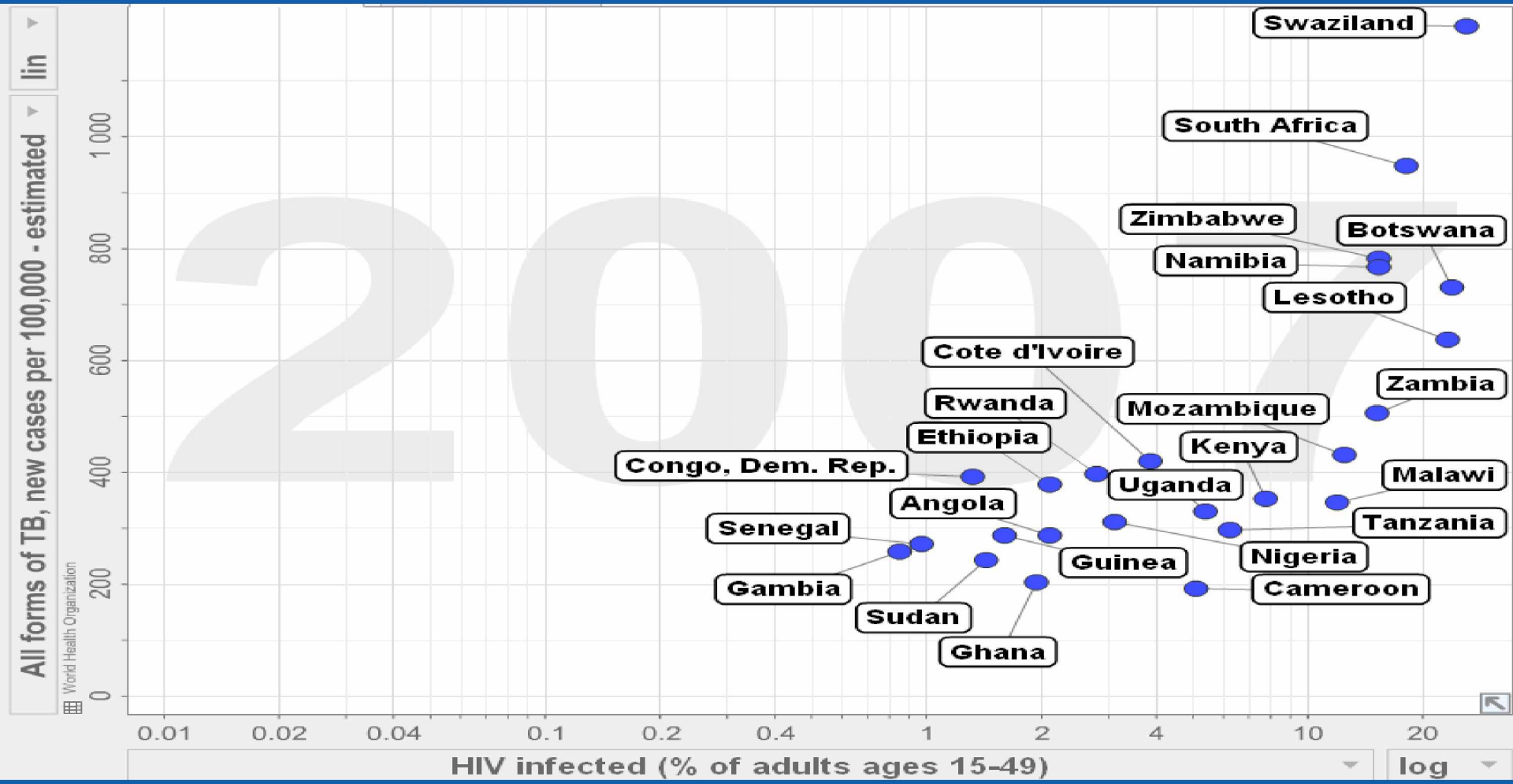


In People Living with HIV, TB is Harder to Diagnose Many Are Ill, but Don't Know They Have TB

- Pulmonary TB: Frequently smear and chest X-ray negative
- Extra-pulmonary TB can occur in any anatomic site

Setting	No. of studies	Median prevalence of TB disease in HIV patients	No. needed to screen to find a TB case
HIV diagnosis clinics	10	8%	12
HIV treatment clinics	24	8%	12
Maternal health clinics for HIV-infected persons	3	2%	44

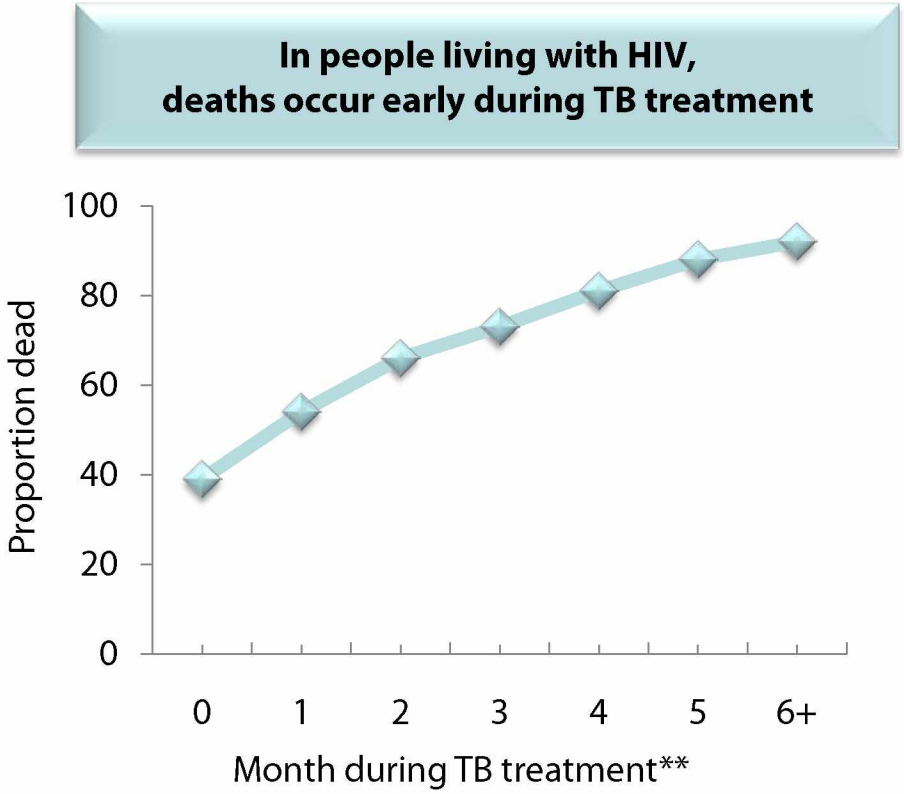
Kranzer K, et al. Lancet ID 2010;10;93-102

In People Living with HIV, TB Is Harder to Treat

- Many pills to take several times every day
- Drugs interact with each other
- Drugs have overlapping toxicity

People Living with HIV Have High Risk of Dying during TB Treatment

Location	Case fatality rate
Sub-Saharan Africa	6–39%
Thailand*	43–50%
Cambodia	27%
Vietnam	26–30%



Month of death for 334 HIV-infected TB patients that died during TB treatment
*Multiple provinces,Thailand, 2004–2005
**Six references are available at http://www.cdc.gov/about/grand-rounds/index.htm

TB Can Be Prevented in People Living with HIV

- **Find and treat people with TB disease**
- **Give isoniazid for at least 6 months to people who do not have TB disease**
  - Isoniazid preventive therapy (IPT)
  - In 2009, only 0.3% of people with HIV received IPT
    - Finding TB disease is difficult with limited lab resources
    - IPT is not always durable; some develop TB again

IPT, Isoniazid preventive therapy

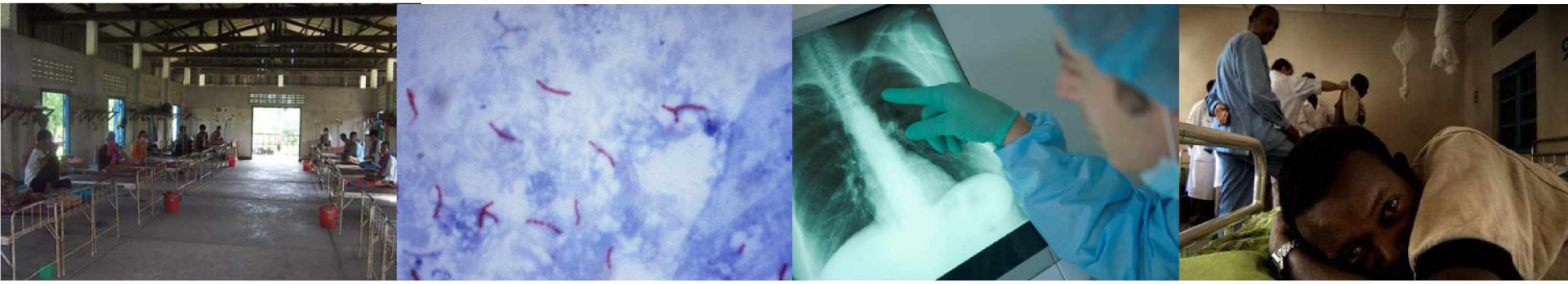
Improving TB Prevention among PLHIV in Resource-limited Settings

Questions to Answer

- **Persons not yet diagnosed with TB**
  - Is there a simple clinical algorithm that frontline health care workers can use to identify patients who do not have TB disease?
- **Persons screened and found not to have TB disease**
  - Can treatment of TB infection for periods longer than 6 months prevent reinfection with TB?

PLHIV, People living with HIV

Ruling out TB: The First Step for TB Diagnosis and Prevention



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Centers for Disease Control and Prevention

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

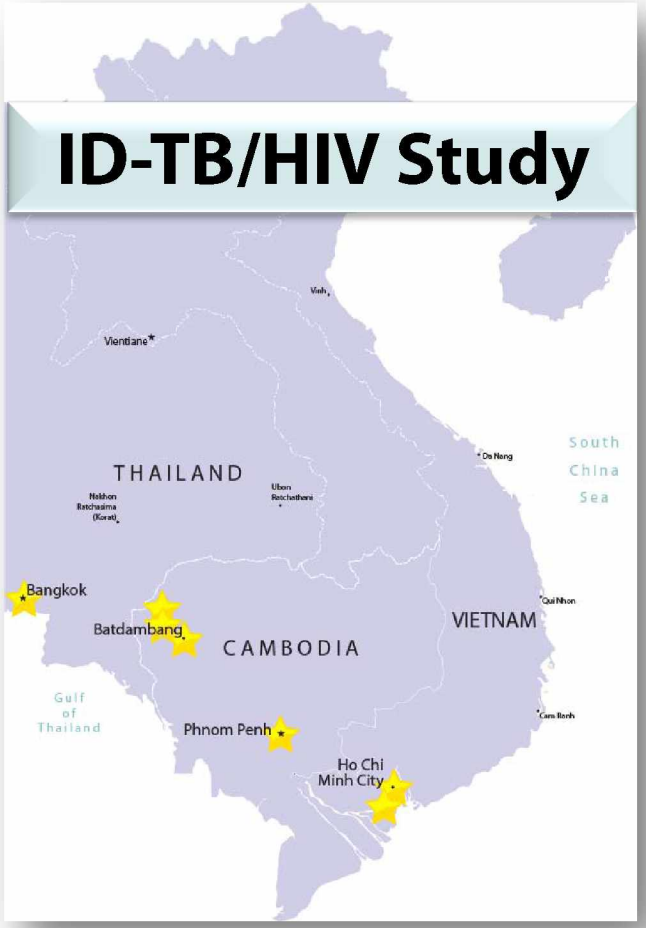
Diagnosing TB
2007 WHO Guidelines

- **All people with HIV should be screened for TB**
  - Screening based on presence of chronic cough
  - Diagnosis based on smear microscopy of sputum and chest X-ray
  - Based on expert opinion from pre-HIV era and not validated in PLHIV
- **Problems**
  - In PLHIV: Small studies suggest low sensitivity of chronic cough, smear microscopy, and chest X-ray
  - <5% of PLHIV screened for TB, and <1% started on TB prevention
  - In PLHIV with TB: High case-fatality rate

PLHIV, People living with HIV

WHO. World Health Organization. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents, 2007. http://whqlibdoc.who.int/hq/2007/WHO_HTM_TB_2007.379_eng.pdf

Improving Diagnosis of TB in People Living with HIV Study (ID-TB/HIV)



- 6 sites in Cambodia, Vietnam, and Thailand
- Initiated in 2006
- Funded by USAID
- Conducted at sites supported by PEPFAR
- Goal: Develop simple, sensitive rule for TB screening in PLHIV

PEPFAR, President's Emergency Plan for AIDS Relief
USAID, US Agency for International Development
PLHIV, People living with HIV

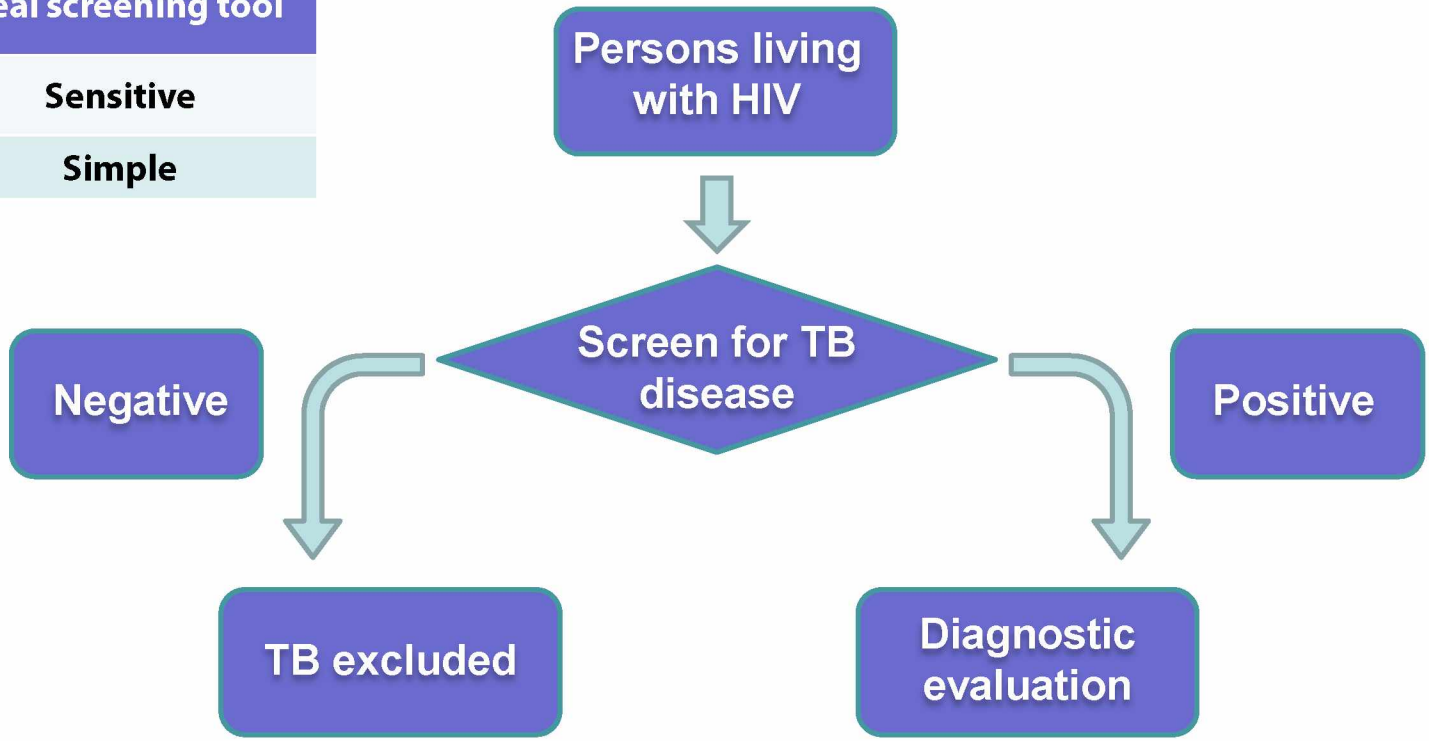
ID-TB/HIV Study
Standardization of Methods across all Sites

- **Standardized laboratory diagnosis: Mycobacterial culture and smear of 6–7 specimens**
  - 3 sputum specimens
  - 1 each of urine, stool, blood, and lymph node aspirate (if enlarged)
- **Case definition: Positive culture for TB from any site**
- **Standardized data collection**
  - Clinical signs and symptoms
  - Chest X-ray, CD4 count, complete blood count
- **Calculated performance as individual predictors and >80 million combinations**
- **Calculated yield of different diagnostic tests**

PLHIV, People living with HIV

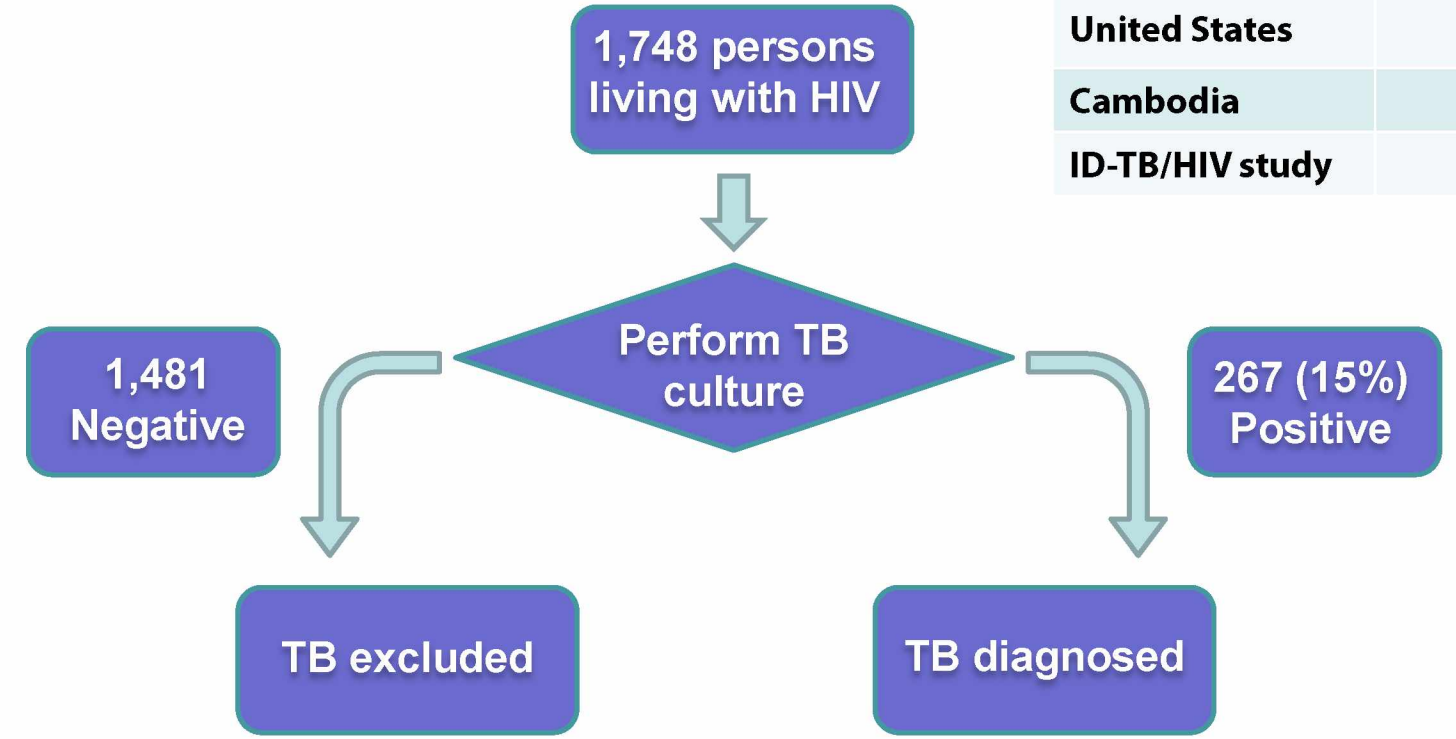
Screening for TB Disease

Ideal screening tool
Sensitive
Simple



Screening for TB Disease

Population	TB prevalence per 100,000
United States	5
Cambodia	700
ID-TB/HIV study	15,000



High prevalence of TB disease in PLHIV

PLHIV, People living with HIV

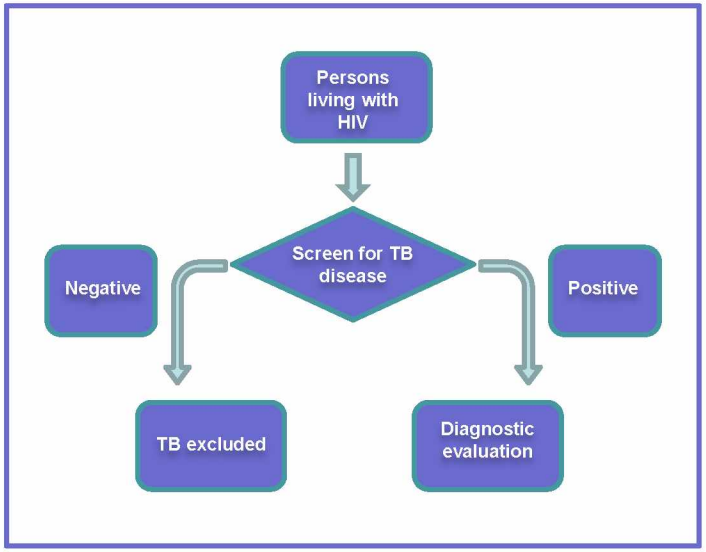
Sensitivity and Specificity of Predictors

Predictor	Sens (%)	Spec (%)
Cough ≥2 weeks	33	82
2 sputum smears for AFB	38	99
Abnormal chest radiograph	65	85
Cough	71	53
Weight loss	73	54
Fever	74	55
At least 1 of: Cough or fever of any duration or night sweats ≥3 weeks	93	36

67% of patients
with TB
will NOT be detected using chronic cough as a screening approach and will have undiagnosed TB

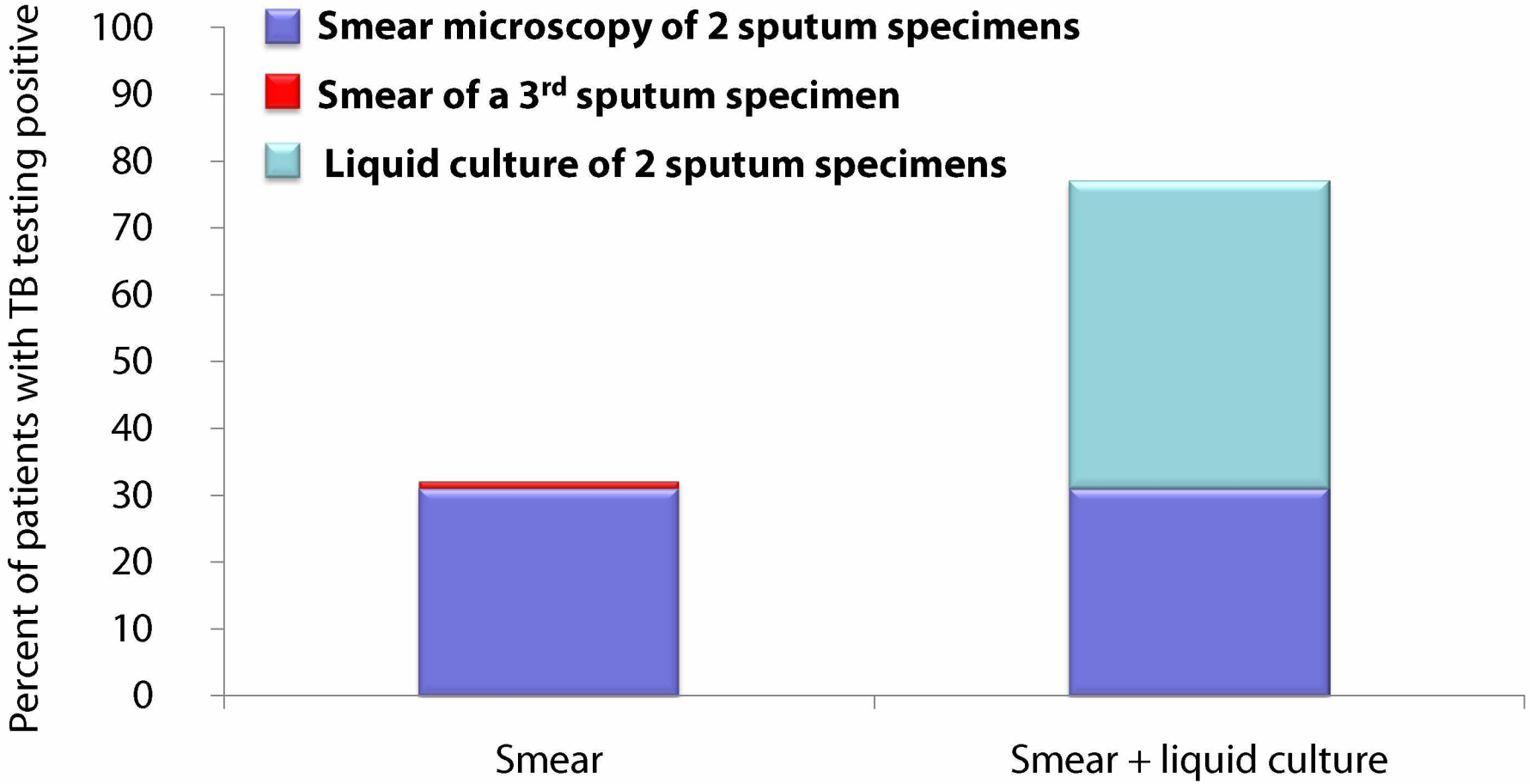
AFB, Acid fast bacilli

Screening for TB Disease



Predictor	Misclassified as not having TB	
	%	No. of patients
Cough ≥ 2 weeks	67	179 (of 267)
Cough, fever, or night sweats ≥ 3 weeks	7	18 (of 267)

Sputum Smears Alone Miss Many TB Cases in PLHIV that Can Be Detected by Culture



This analysis is limited to patients enrolled in Vietnam and Thailand
PLHIV, People living with HIV

Potential Applications Based on ID-TB/HIV Study

- **15% of people with HIV had TB disease**
- **Ruling out TB disease**
  - 3-symptom combination (or similar) should be used
  - Chronic cough should not be used for TB screening
  - Patients with none of the 3 symptoms have TB excluded
- **Ruling in TB disease: Patients with ≥1 symptoms should have ≥2 sputum specimens collected for both smear and culture**

Cain KP, et al. N Engl J Med 2010;362(8):707-16
Monkongdee P, et al . J Respir Crit Care Med 2009;180(9):903-8

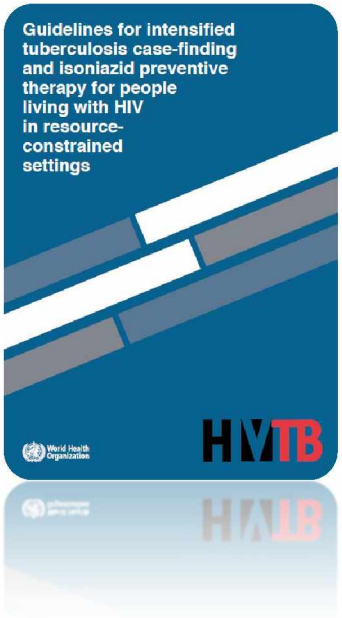
TB Diagnosis: Challenges and Opportunities

- **Challenges**
  - Liquid culture rarely available, difficult to implement
  - Massive scale-up of laboratory services needed
- **An exciting new opportunity: Xpert™ MTB/Rif assay**
  - Endorsed by WHO as the initial diagnostic test of choice for PLHIV
  - Results in >2 hours for both presence of TB and drug resistance
  - Sensitivity approaches that of TB culture
  - Need to demonstrate ability to scale-up

Boehme, et.al. N Engl J Med 2010 Sep 9;363(11):1005-15

Can Data from the ID–TB/HIV Study Be Extrapolated Globally

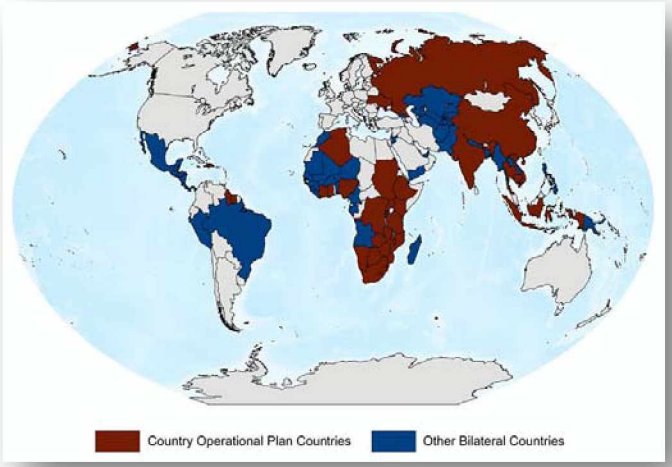
- **Based on the data from the ID-TB/HIV study, WHO determined that policy change was needed**
- **WHO and CDC collaborated on a meta-analysis**
  - Individual patient-data meta-analysis
  - 12 studies: 9 from Africa, 3 from Asia
- **Best combination: At least 1 of**
  - Current cough
  - Fever
  - Weight loss (subjective)
  - Night sweats (any duration)
- **Sensitivity is 90% in clinical settings**



Getahun H, et al. PLoS Med;8(1):e1000391

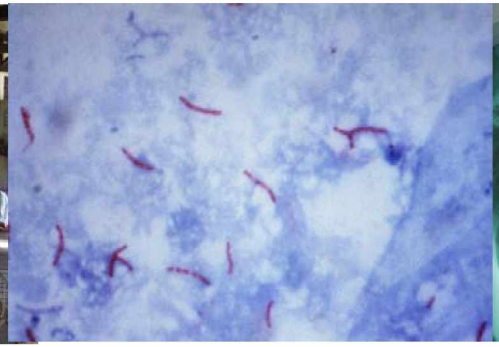
From Guidance to Practice

- **WHO 2011 guidelines are being implemented globally**
  - Nearly $150 M in PEPFAR TB/HIV funding allocated in FY2011
  - CDC implements TB/HIV activities with PEPFAR funding in 26 countries and 1 regional office



- **Collaborations are essential to address research questions successfully and to translate research to policy and practice**

If Finding TB is So Difficult, Why Not Just Prevent It?

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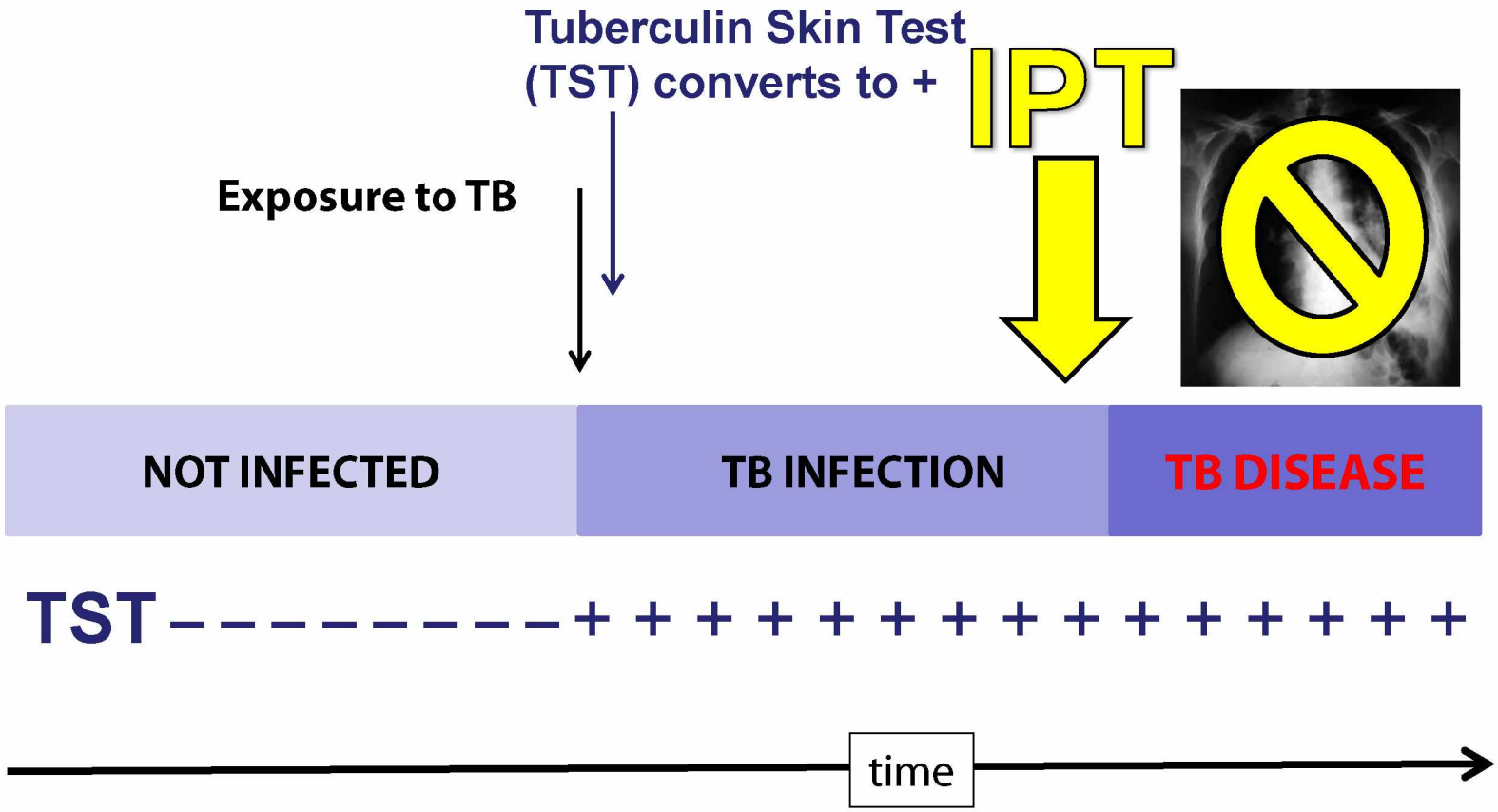
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

" An Ounce of Prevention Is Worth a Pound of Cure"
– Benjamin Franklin

"I'll have an ounce of prevention."

TB Infection, TB Disease, and the Tuberculin Skin Test (TST)



IPT, Isoniazid preventive therapy
TST, Tuberculin skin test

Anti-retroviral Therapy (ART) for TB Prevention in TB-endemic Settings

- **ART reduces the risk of TB in PLHIV by 50–80%**
- **Increasing use of ART increases CD4 lymphocyte count and thereby reduces the risk of TB**
- **Rate of TB among PLHIV receiving ART remains unacceptably high in TB-endemic settings**
  - 2-7 TB cases per 100 person-years

8 references are available at http://www.cdc.gov/about/grand-rounds/index.htm
PLHIV, People living with HIV
ART, Anti-retroviral therapy

Isoniazid Preventive Therapy (IPT) for PLHIV

Study or subgroup	Treatment (INH) n/N	Control n/N	Risk ratio M-H, Fixed, 95% CI	Weight	Risk ratio M-H, Fixed, 95% CI
TST +					
Hawken 1997	5/67	8/69		6.3%	0.64 [0.22, 1.87]
Mwinga 1998	4/52	11/60		8.2%	0.42 [0.14, 1.24]
Pape 1993	2/38	6/25		5.8%	0.22 [0.05, 1.00]
Whalen 1997	7/536	21/464		18.0%	0.29 [0.12, 0.67]
Subtotal (95% CI)	**693**	**618**		**38.3%**	**0.36 [0.22, 0.61]**

6-month IPT reduces the risk of TB by 64% in TST-positive PLHIV

TST –					
Subtotal (95% CI)	**1,297**	**1,193**		**43,9%**	**0.86 [0.59, 1.26]**

6-month IPT does NOT significantly reduce the risk of TB in TST-negative PLHIV

Akolo C, et al. Cochrane Database Syst Rev 2010;1:CD000171
INH, Isoniazid
PLHIV, People living with HIV
TST, Tuberculin skin test

Isoniazid Preventive Therapy (IPT) for PLHIV

Study or subgroup	Treatment (INH) n/N	Control n/N	Risk ratio M-H, Fixed, 95% CI	Weight	Risk ratio M-H, Fixed, 95% CI
Total (95% CI)	2,152	1,984		100.0%	0.67 [0.51, 0.87]

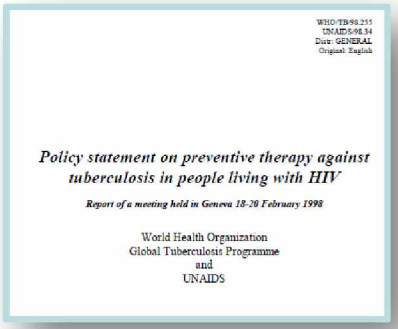
Overall IPT reduces the risk of TB by 33% in PLHIV (TST-positive, TST-negative, TST-unknown)

Akolo C, et al. Cochrane Database Syst Rev 2010;1:CD000171
INH, Isoniazid
PLHIV, People living with HIV
TST, Tuberculin skin test

WHO 1998 Isoniazid Preventive Treatment (IPT) Recommendation

- **Provide 6 months daily IPT to HIV-infected adults**
- **If not feasible and >30% of the population was infected with TB, do not perform tuberculin skin test (TST)**

http://whqlibdoc.who.int/hq/1998/WHO_TB_98.255.pdf


WHO/TB/98.255
UNAIDS/98.34
Distr: GENERAL
Original: English

Policy statement on preventive therapy against tuberculosis in people living with HIV

Report of a meeting held in Geneva 18-20 February 1998

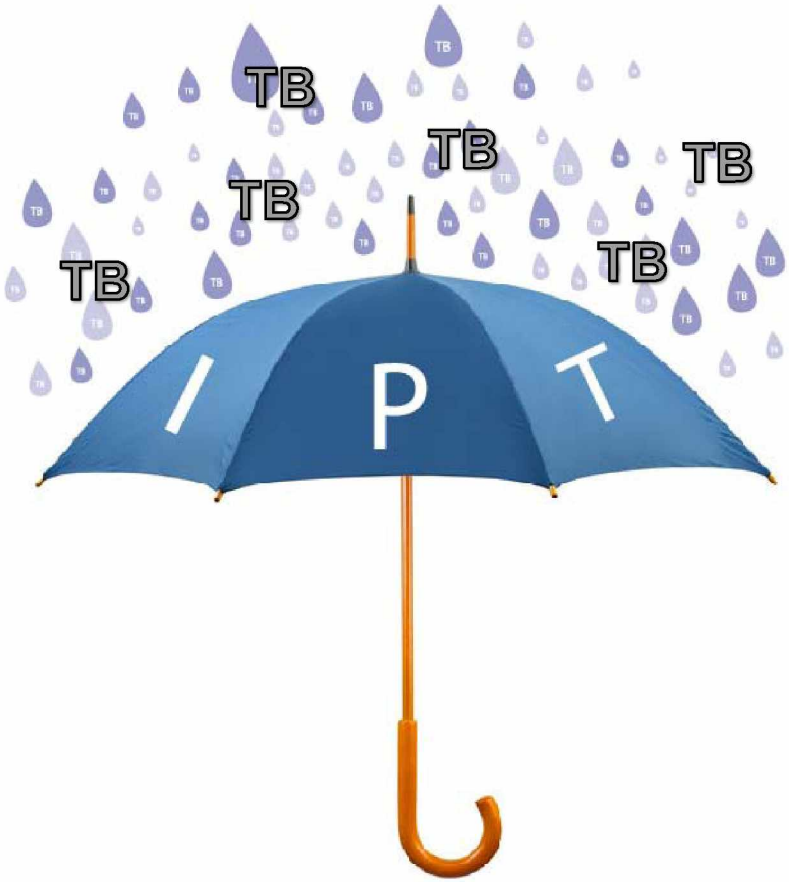
World Health Organization
Global Tuberculosis Programme
and
UNAIDS

- **IPT benefit lost in 6-18 months**
  - Failure of eradication vs. reinfection
- **Later, molecular epidemiology in TB-endemic countries showed infection with new strains of TB is very common (42–88%)**

IPT, Isoniazid preventive therapy
TST, Tuberculin skin test

Quigley M,, et al. AIDS 2001;15:215
Johnson J, et al. *AIDS* 2001;15:2137
9 additional references are available at http://www.cdc.gov/about/grand-rounds/index.htm

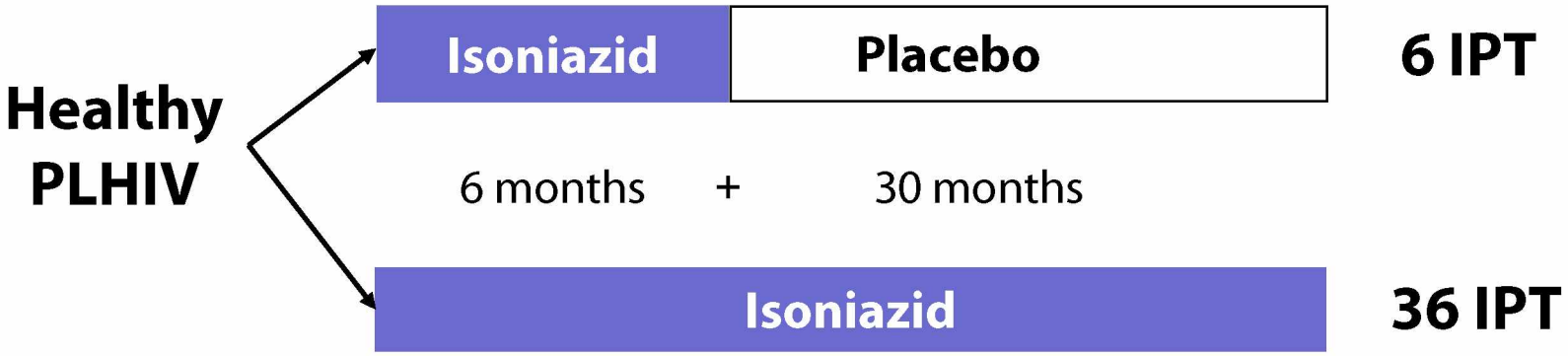
"So Long as It's Raining, You Need an Umbrella"



TB, Tuberculosis
IPT, Isoniazid preventive therapy

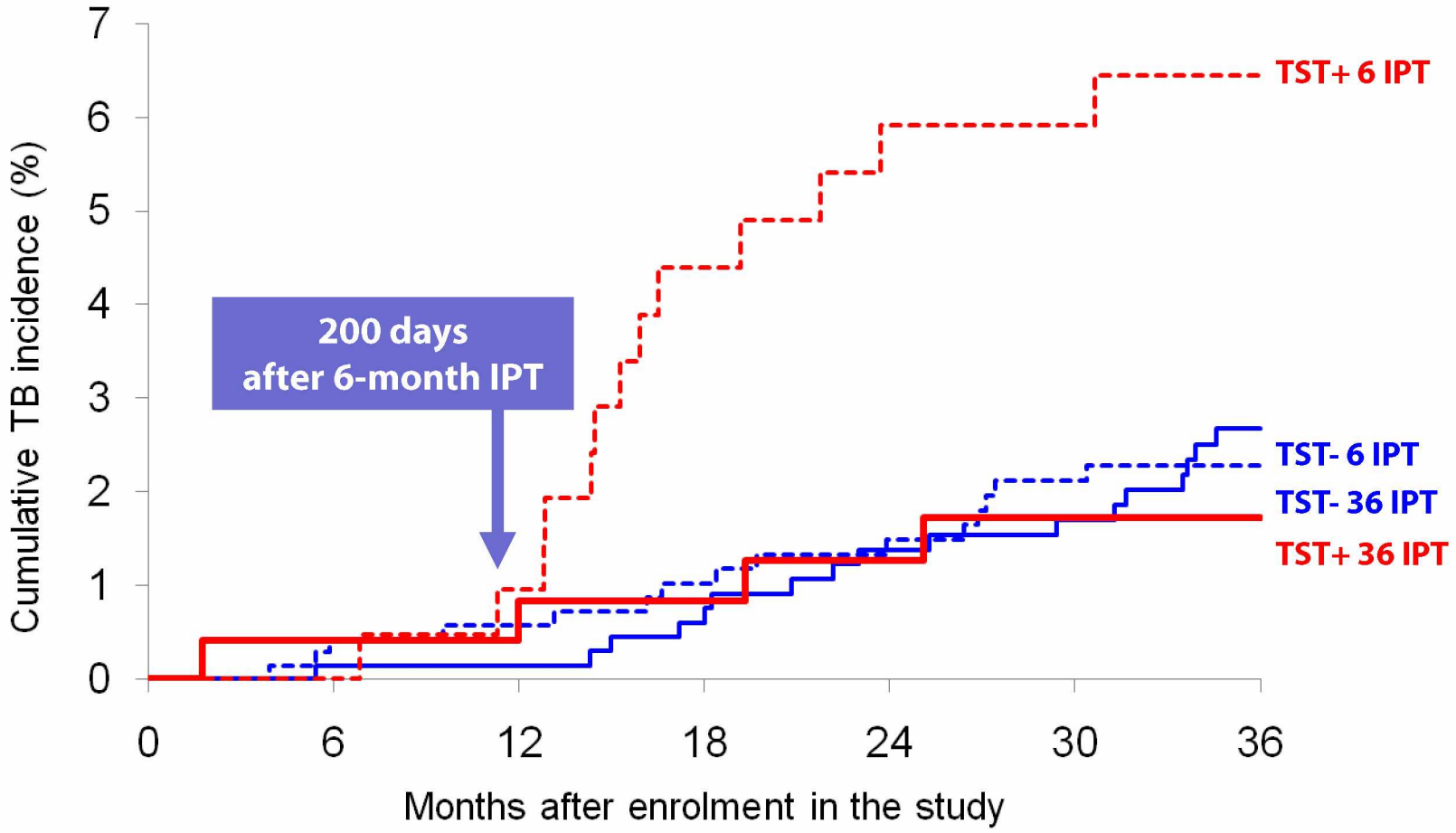
Botswana IPT Trial 2004–2009

- **Randomized, double-blind, placebo-controlled trial**
- **ART provided as needed through national program**
  - When CD4 <200 cells/µL



PLHIV, People living with HIV
IPT, Isoniazid preventive therapy
ART, Anti-retroviral therapy

Continuous IPT for 36 Months Prevents TB Better than IPT for 6 Months in TST-positive PLHIV



Samandari T, et all. *Lancet* 2011 *in press*
IPT, Isoniazid preventive therapy
PLHIV, People living with HIV
TST, Tuberculin skin test

Efficacy of 36 Months IPT vs 6 Months IPT

ART Provided if CD4<200/µL in TST+ PLHIV

	Arm	No. of pts	TB cases	TB rate 100 /year	Hazard ratio	Efficacy
All enrolled	6 IPT	989	34	1.26	ref	
	36 IPT	1006	20	0.72	0.57*	43%
All TST+ enrolled	6 IPT	216	13	2.22	ref	
	36 IPT	252	4	0.57	0.26*	74%

* $P<0.05$

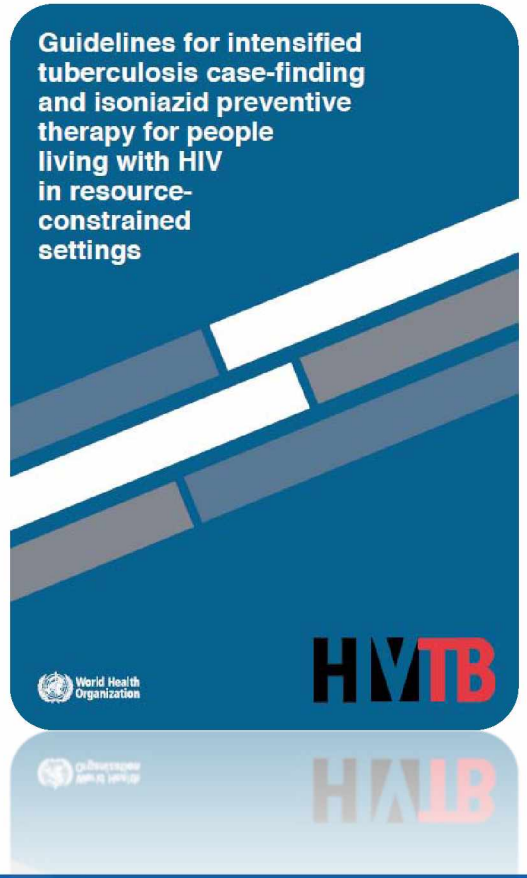
**ART reduced the risk of TB additively by 50%
in both arms and was independent of IPT's protective effect**

Samandari T, et al. *Lancet* 2011, *in press*
PLHIV, People living with HIV
IPT, Isoniazid preventive therapy
TST, Tuberculin skin test
ART, Anti-retroviral treatment

From Evidence to Guidance

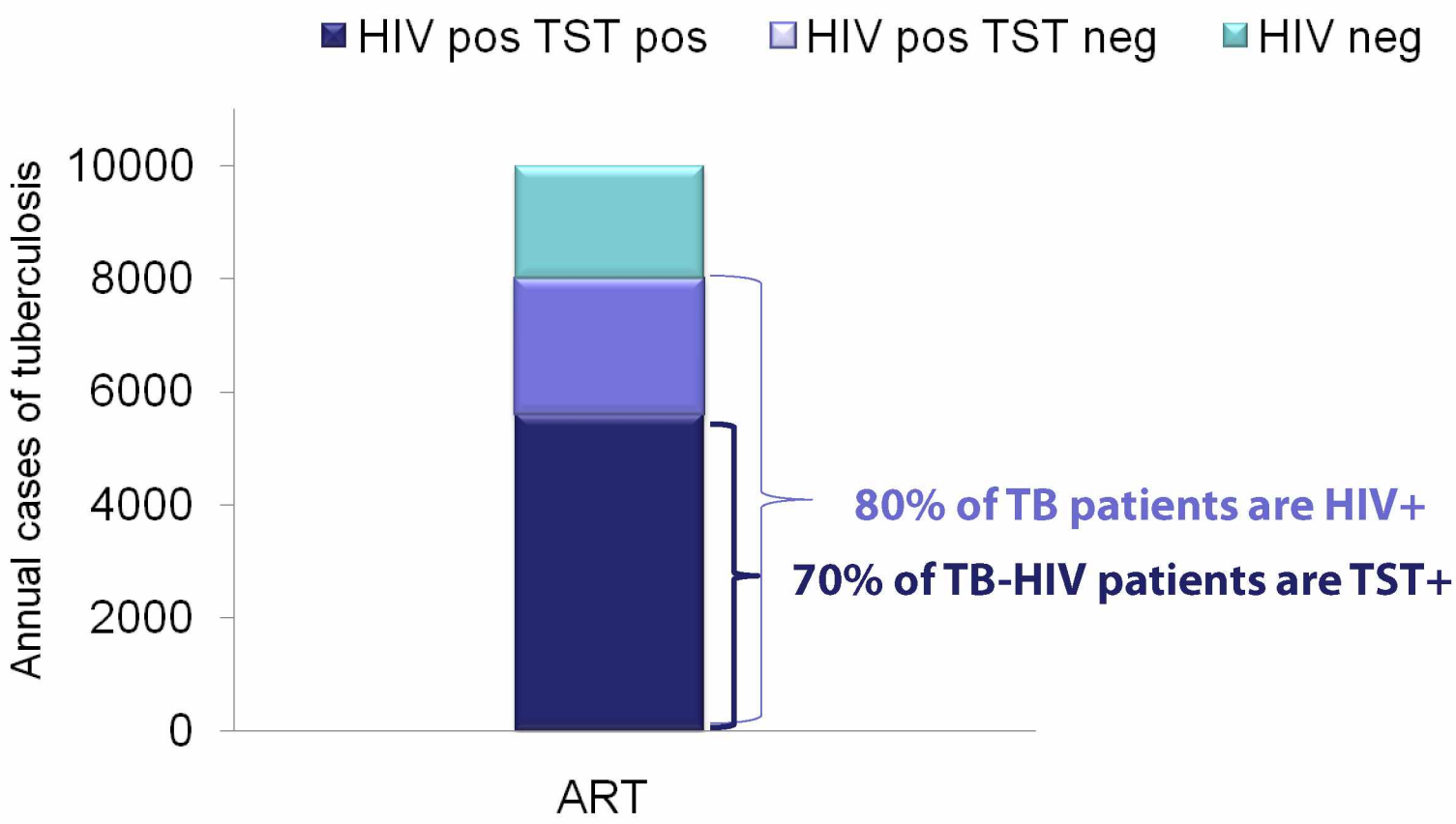
- **WHO 2011 guidelines for TB screening and prevention in PLHIV**

  "IPT for a duration of 36 months is conditionally recommended in settings with a high transmission of TB … tuberculin skin testing is not a requirement for initiating IPT … in some settings where it is feasible, [TST] can help to identify those who would benefit most from IPT"



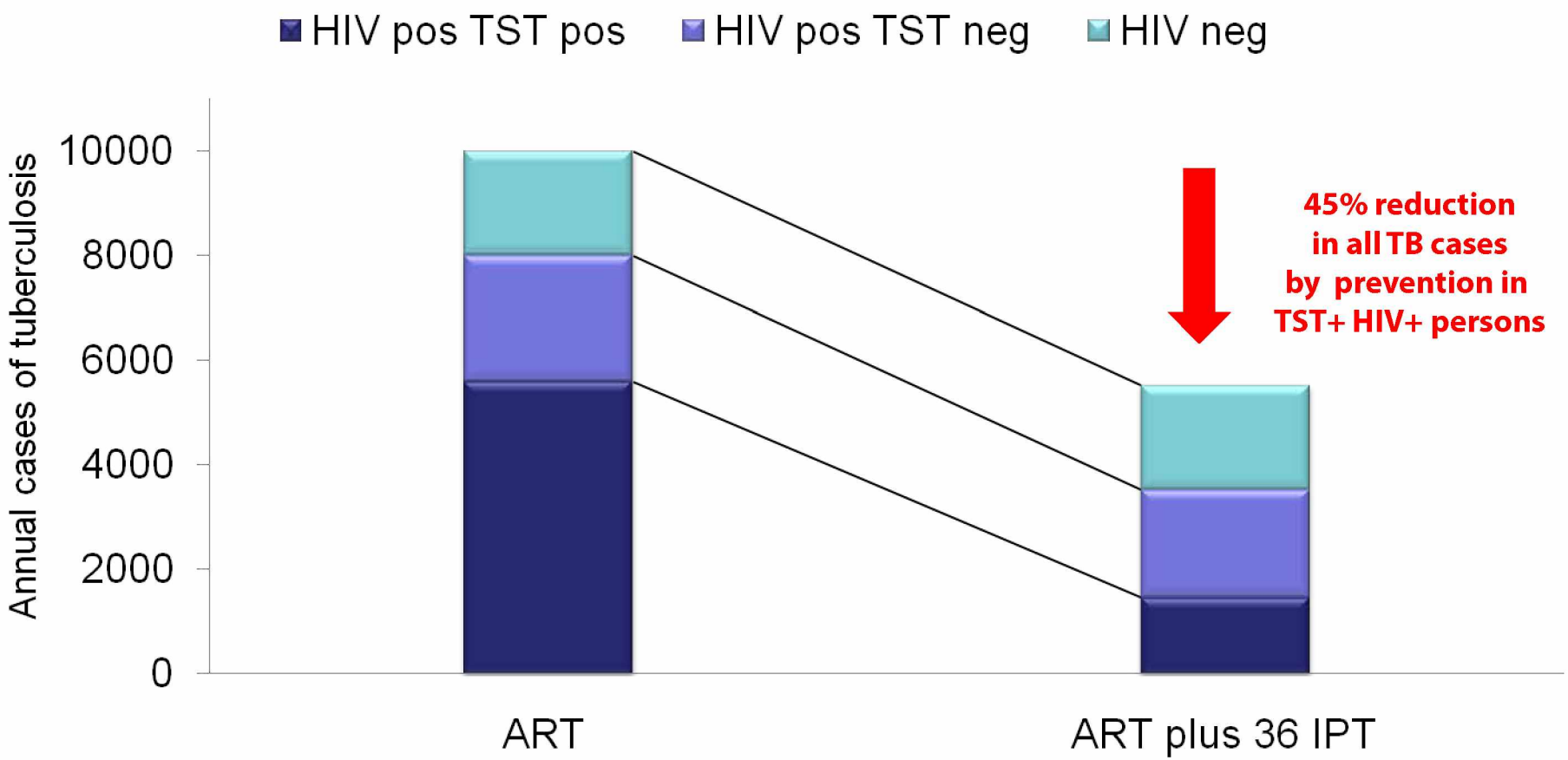
http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf
PLHIV, People living with HIV
IPT, Isoniazid preventive therapy

Potential Public Health Impact of Continuous IPT on Annual TB Cases in Botswana



Antiretroviral therapy provided to all HIV-infected persons if CD4<250 per μL^{-1}
IPT, Isoniazid preventive therapy
PLHIV, People living with HIV
TST, Tuberculin skin test

Potential Public Health Impact of Continuous IPT on Annual TB Cases in Botswana



Antiretroviral therapy provided to all HIV-infected persons if CD4<250 /μL^{-1}
IPT, Isoniazid preventive therapy
ART, Anti-retroviral treatment
PLHIV, People living with HIV

Cost Effectiveness Analysis for TB Prevention 36 Months IPT, TST, and ART

- **Initiation of ART at higher CD4 thresholds further reduces tuberculosis disease**
  - Is it necessary to include IPT?
  - Is it cost effective to use the TST when implementing IPT?
- **Botswana cost analysis for 10,000 PLHIV over 3 years**
  - 36 months IPT + ART at CD4<250
    - Equivalent or superior prevention vs. ART initiation at higher CD4 thresholds (350 or 500)
    - Saves $2–4 million
  - Addition of TST to target 36 months IPT for TST-positive PLHIV
    - Reduces TB by 30%
    - At a cost of $80,000

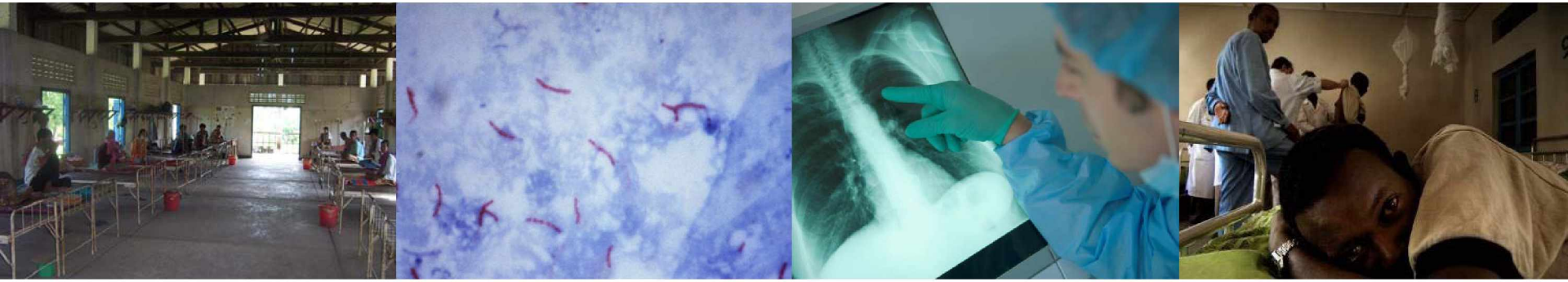
IPT, Isoniazid preventive therapy
ART, Anti-retroviral therapy
TST, Tuberculin skin testing
PLHIV, People living with HIV

Some Additional Research Needs for TB Prevention in PLHIV

- Operationalize TST in resource-limited settings
- Improve control of TB transmission in the communities with high TB endemicity
- Identify better anti-TB drugs and new vaccines to prevent TB
- Determine whether intermittent short courses (6–12 months) of IPT are as efficacious as continuous IPT for TST- positive PLHIV
- Reduce causes of early mortality (such as from TB) in PLHIV initiating ART

TST, Tuberculin skin testing
PLHIV, People living with HIV
ART, Anti-retroviral treatment

From Science to Policy to Impact



Mario C. Raviglione, MD
Director, Stop TB Department
World Health Organization (WHO)
Geneva, Switzerland

WHO THE STOP TB DEPARTMENT

With appreciation for support and engagement to Haileyesus Getahun Stop TB, WHO

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Overview

- **TB science and policy, hand-in-hand**
  - WHOs perspectives on the science of TB/HIV
  - Policies to control TB
  - Potential impact of TB/HIV interventions
- **Challenges and opportunities to eliminate TB**

Process for Developing WHO Guidelines

- **Compose the external guidelines panel; declare COI**
- **Formulate questions and relevant outcomes**
- **Assess available evidence**
  - Retrieval, evaluation (using GRADE) and synthesis
  - Benefit, equity, and cost
- **Develop recommendations (strong, conditional)**
- **Evaluate impact of recommendations**
- **Identify areas of further research**
- **Establish peer review process**
- **Finalize and define expiration date**

COI, Conflict of interest
GRADE, WHO handbook for guideline development 2010 http://www.bmj.com/content/328/7454/1490.full

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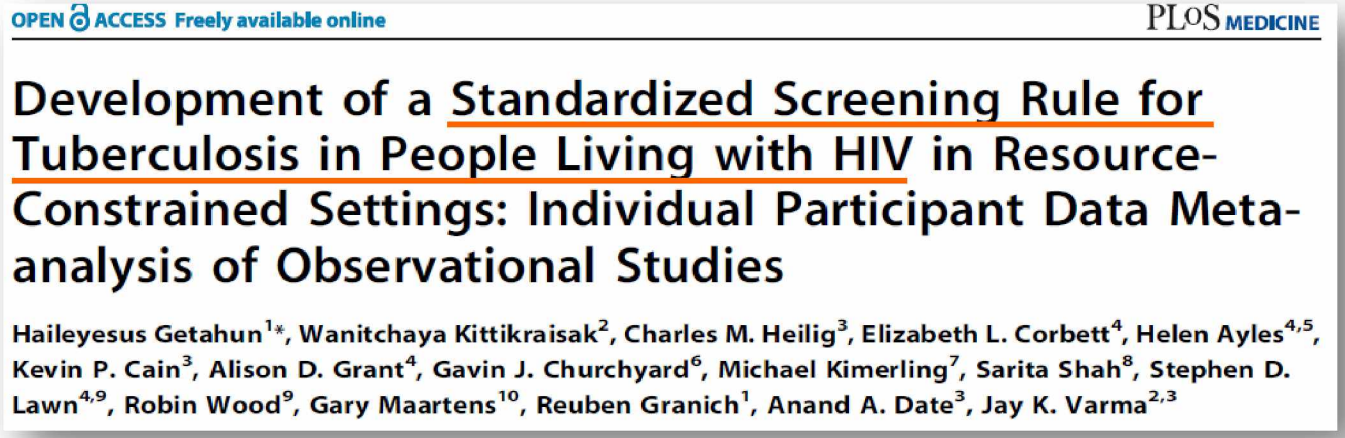
WHO–CDC Collaboration in the Area of TB/HIV



OPEN ACCESS Freely available online PLoS MEDICINE

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

Haileyesus 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[4,9], Robin Wood[9], Gary Maartens[10], Reuben Granich[1], Anand A. Date[3], Jay K. Varma[2,3]

Inclusion criteria for studies

- Collected sputum specimens from PLHIV regardless of signs or symptoms
- Used mycobacterial culture of at least 1 specimen to diagnose TB
- Collected data about signs and symptoms

PLHIV, People living with HIV

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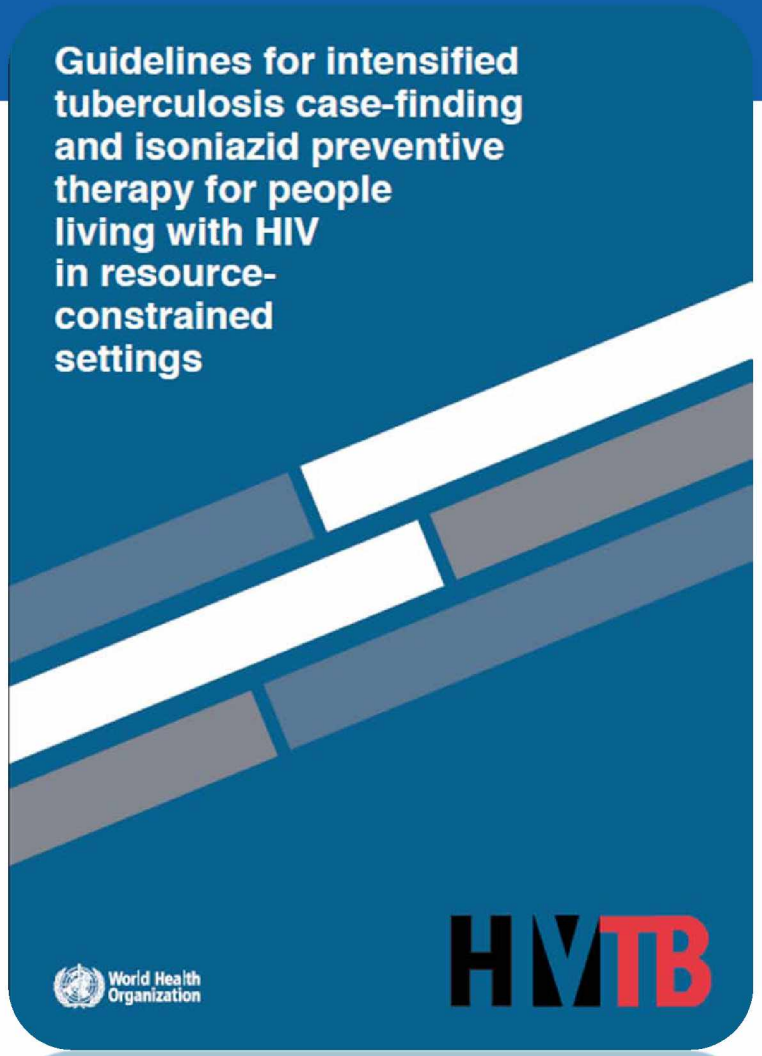

http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf

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Recommendation 1
Isoniazid Preventive Therapy (IPT)

Adults and adolescents living with HIV should be screened with a clinical algorithm and those *who do not report* any one of

- Current cough
- Fever
- Weight loss
- Night sweats

are *unlikely to have active TB* and should be offered IPT

Strong recommendation, moderate quality evidence

IPT, Isoniazid preventive therapy

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Recommendation 2
TB Screening

Adults and adolescents living with HIV should be screened with a clinical algorithm and those *who reported* any one of

- Current cough
- Fever
- Weight loss
- Night sweats

may have active TB **and should be evaluated for TB and other diseases**

Strong recommendation, moderate quality evidence

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Recommendation 3
Duration of Isoniazid Preventive Therapy

Adults and adolescents who are living with HIV and

- Have tuberculin skin test-positive or unknown status and
- Are unlikely to have active TB

should receive IPT for *at least 6* months

Strong recommendation, high quality evidence

IPT, Isoniazid preventive therapy

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Recommendation 4
Duration of Isoniazid Preventive Therapy

Adults and adolescents who are living with HIV

in settings with higher TB transmission **and**

- Have tuberculin skin test-positive or unknown status and
- Are unlikely to have active TB

should receive IPT for *at least 36* months

Conditional recommendation, moderate quality evidence

Need To Simplify

... Simplicity, simplicity, simplicity! I say, let your affairs be as two or three, and not a hundred or a thousand; instead of a million count half a dozen, and keep your accounts on your thumbnail... Simplify, simplify....

—Henry D. Thoreau, Walden, 1854

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Summary
What's New in these Policy Recommendations?

- Screening for TB using only symptom-based algorithm is sufficient to start IPT for PLHIV
- No mandatory chest X-ray and tuberculin skin test requirement for IPT
- Regular screening of those on IPT at every visit
- Pregnant women, children, those on ART, and those who completed TB treatment should receive IPT
- Conditional recommendation of 36 months IPT for settings with high TB transmission among PLHIV

Simplification

PLHIV, People living with HIV
IPT, Isoniazid preventive therapy
ART, Antiretroviral treatment

WHO THE STOP TB DEPARTMENT

Can IPT Impact Epidemiology of TB/HIV?

- IPT is highly effective in clinical trials among TB-infected PLHIV (64% reduction in incidence)
- Feasibility of IPT in field conditions is still questioned, although individual benefits are obvious
- New modelling of impact of large-scale IPT is ongoing, whereas previous model showed little impact

Currie CS, et al. BMC Public Health 2005: 5:130
Akolo et al Cochrane Database Syst Rev. 2010;Jan 20
Charalambous S, et al AIDS. 2010;24 (sup 5) s5-s13

PLHIV, People living with HIV
IPT, Isoniazid preventive therapy

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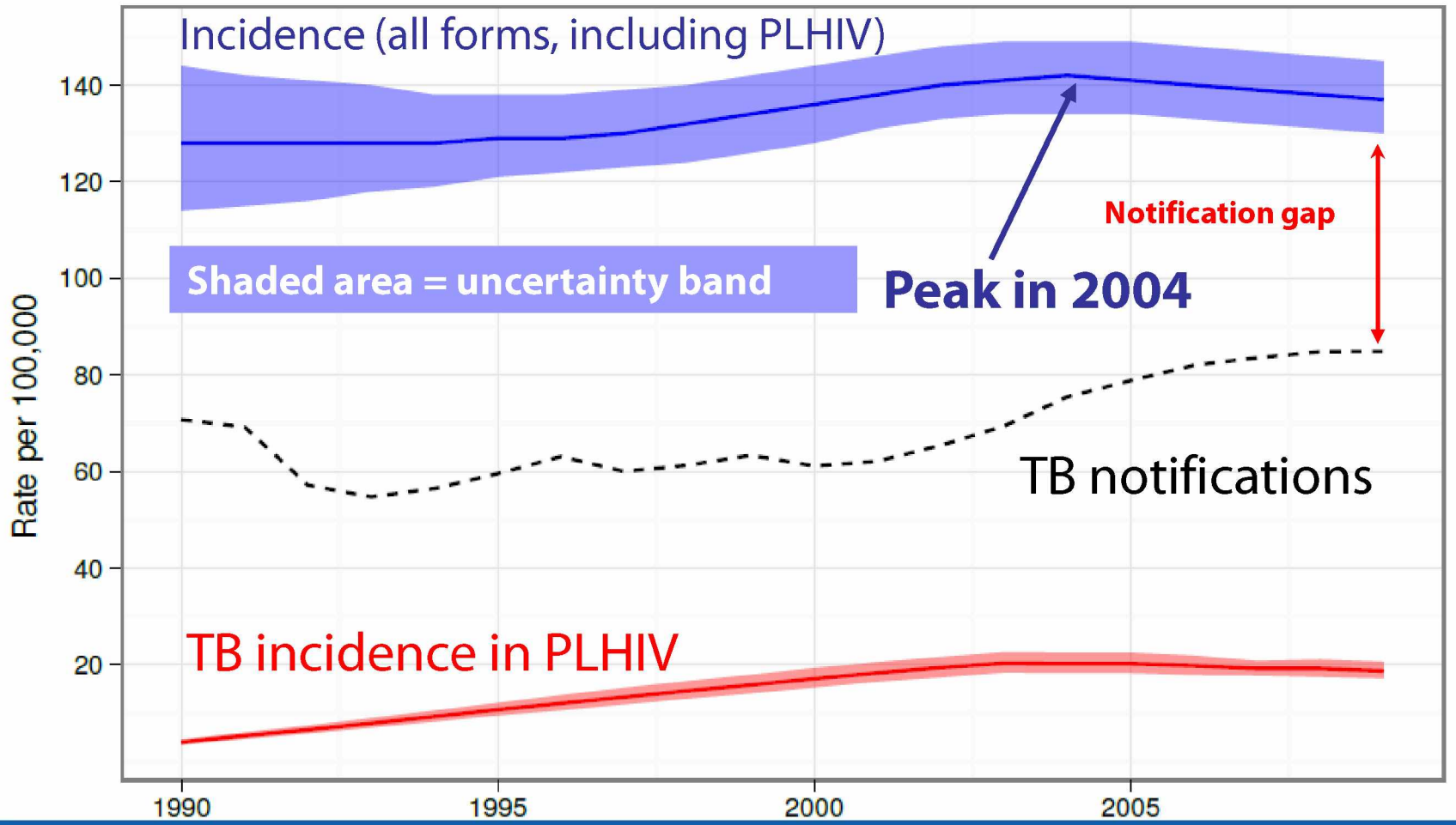
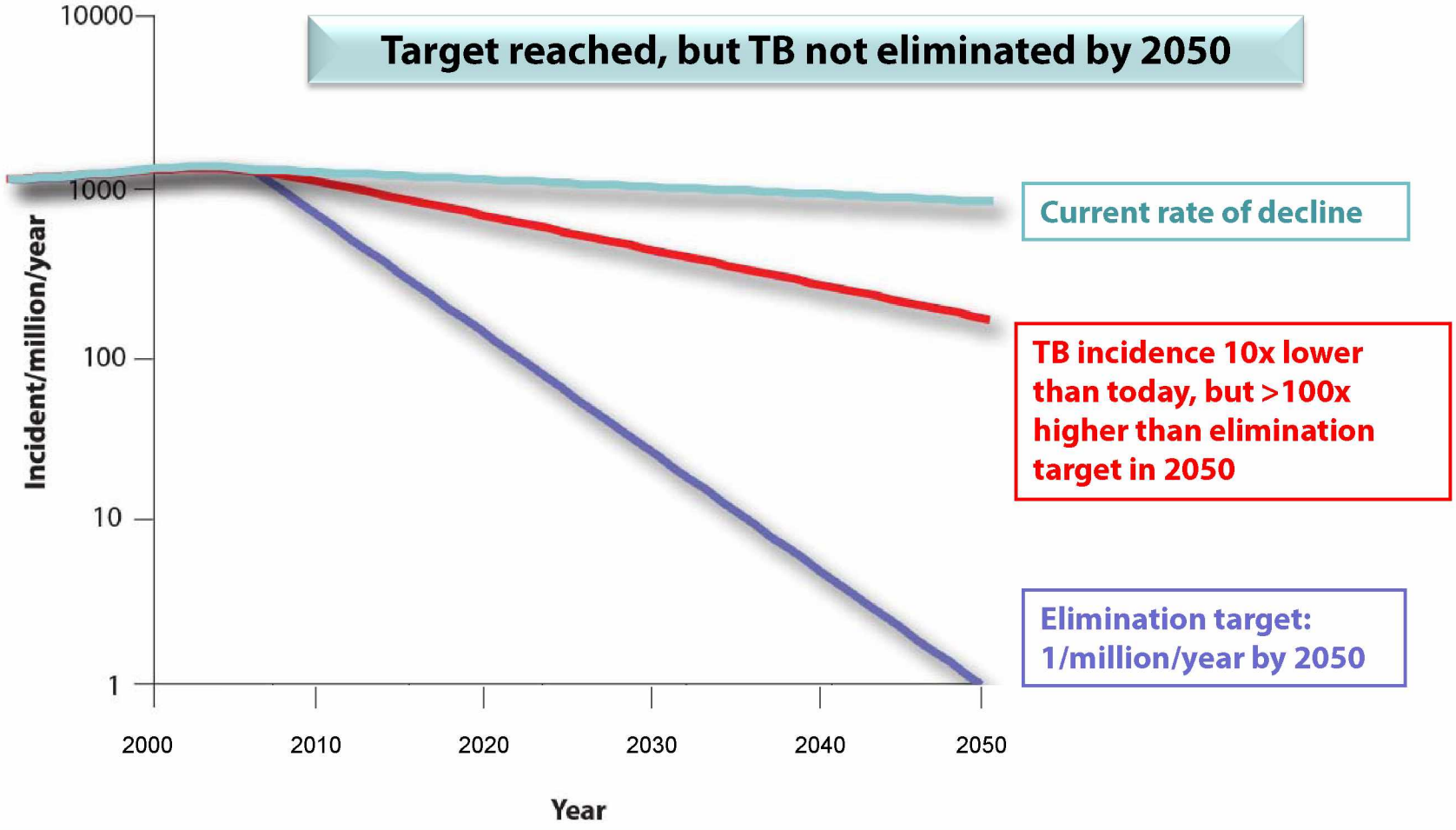
TB Incidence Rates Falling Globally after Peak in 2004, but Only at <1%/year



PLHIV, People living with HIV

Full Implementation of the Global Plan to Stop TB
2015 Millenium Development Goal



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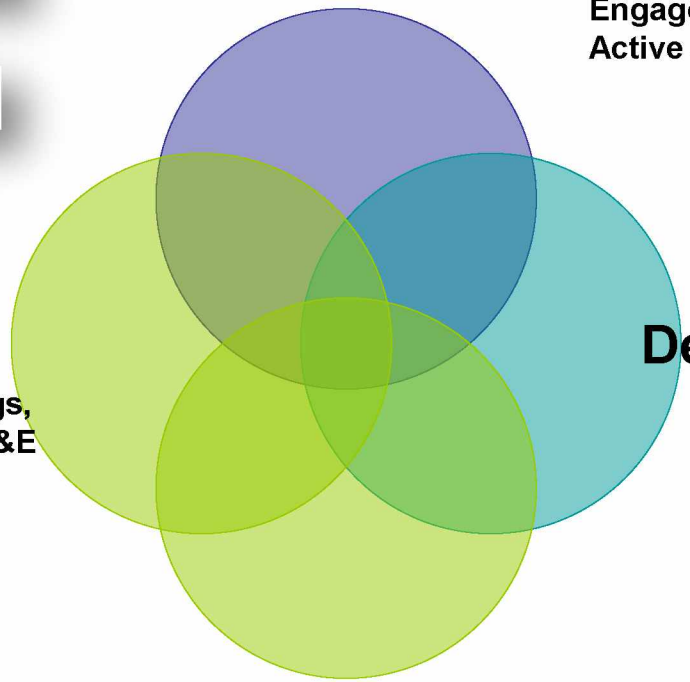
Innovative Actions Needed in 4 Areas

TB care and control

Early & increased case detection: new tools
Scale-up TB/HIV and MDR-TB interventions
M&E and impact measurement
Engage all care providers
Active screening among at-risk populations



Health systems and policies

Free services, labs, quality drugs, regulated private care, better M&E

Development agenda

Socio-economic factors: living conditions, food insecurity, awareness, risk behaviour, access to care

Research *sensu lato*

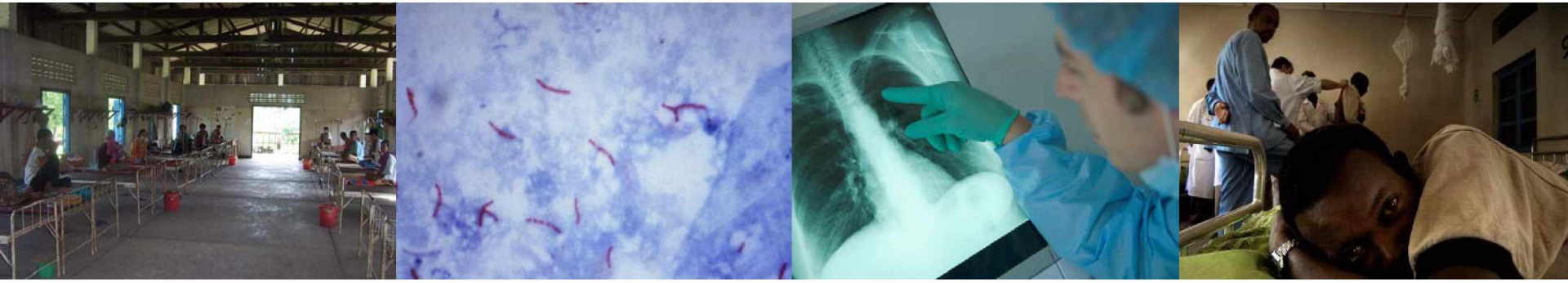
New tools
Operational research
Transfer of technology

MDR-TB, Multi drug resistant TB
M&E, Monitoring and evaluation

Conclusions

- **New WHO Guidelines**
  - Incorporate outcomes of latest research and simplify interventions: "Simplicity, simplicity, simplicity"
  - Potential impact of TB/HIV interventions on TB incidence and mortality could be important
  - Need for operational research and field assessment beyond mathematical modelling
- **Fast decline of TB incidence globally will depend on**
  - Quality of core TB control efforts, including rapid detection
  - Bold health system policies
  - Socioeconomic development
  - Availability of new tools

Fundamentals Are Fundamental



Thomas R. Frieden, MD, MPH
Director, Centers for Disease Control and Prevention
Administrator, Agency for Toxic Substances and Disease Registry

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

What Is the A
What Is the Q

- Save lives?
- Prevent MDR-TB?
- Reduce incidence?

MDR-TB, Multidrug resistant TB

Answer?
Question?

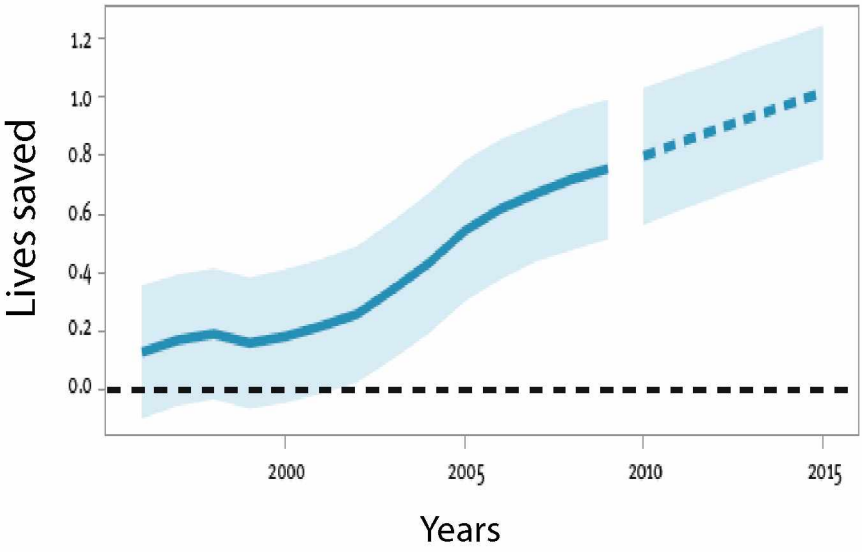
What Is the
What Is the

- **Save lives?**
- **Prevent MDR-TB?**
- **Reduce incidence?**

WHO. Global Tuberculosis Control: WHO Report 2010.
http://www.who.int/tb/publications/global_report/2010/en/index.html

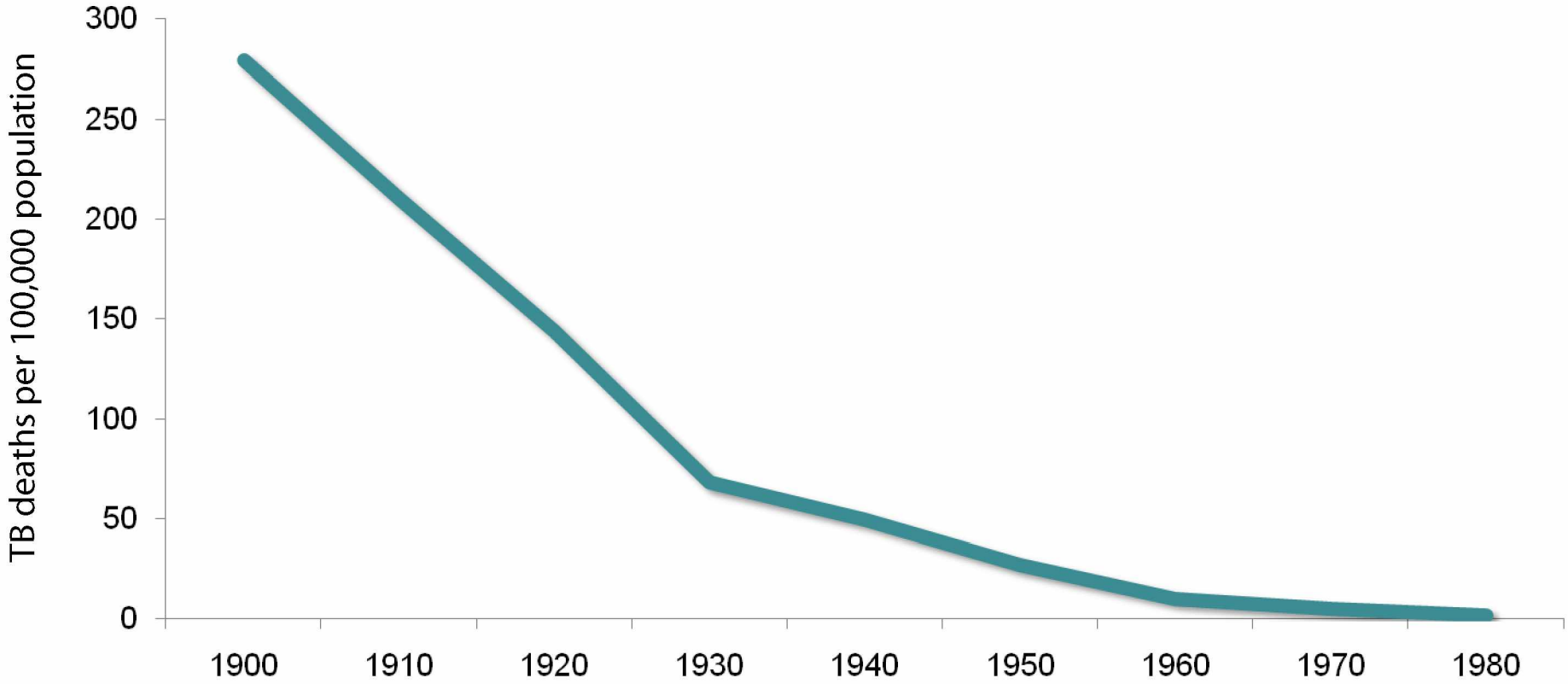
e Answer?
Question?

Estimated number of lives saved annually (in millions), 1996–2009, and projections for 2010–2015



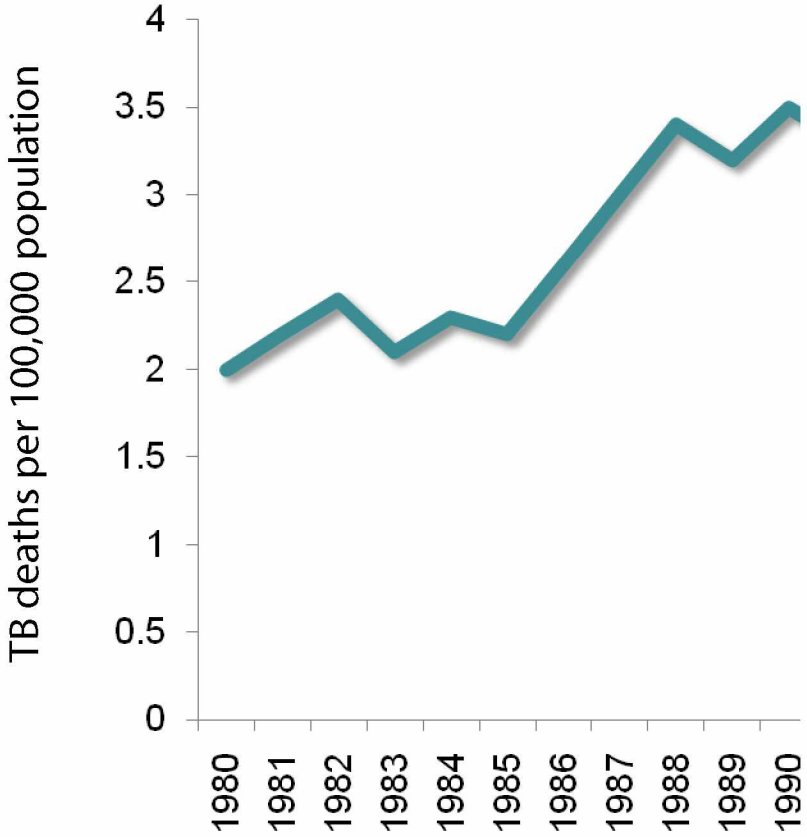
New York City Example

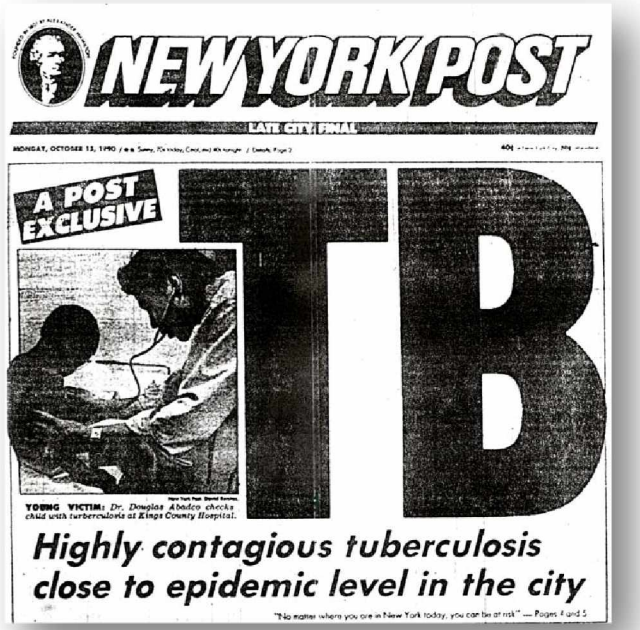
TB Death Rate Declined Dramatically During Most of the 20th Century …



NYC DOHMH. New York Is Stopping TB. Bureau of Tuberculosis Control Annual Summary 2008. http://nyc.gov/html/doh/downloads/pdf/tb/tb_annualsummary08.pdf

… But Increased Sharply with the HIV Epidemic and Low Rates of TB Diagnosis and Cure




NEW YORK POST

LATE CITY FINAL

A POST EXCLUSIVE

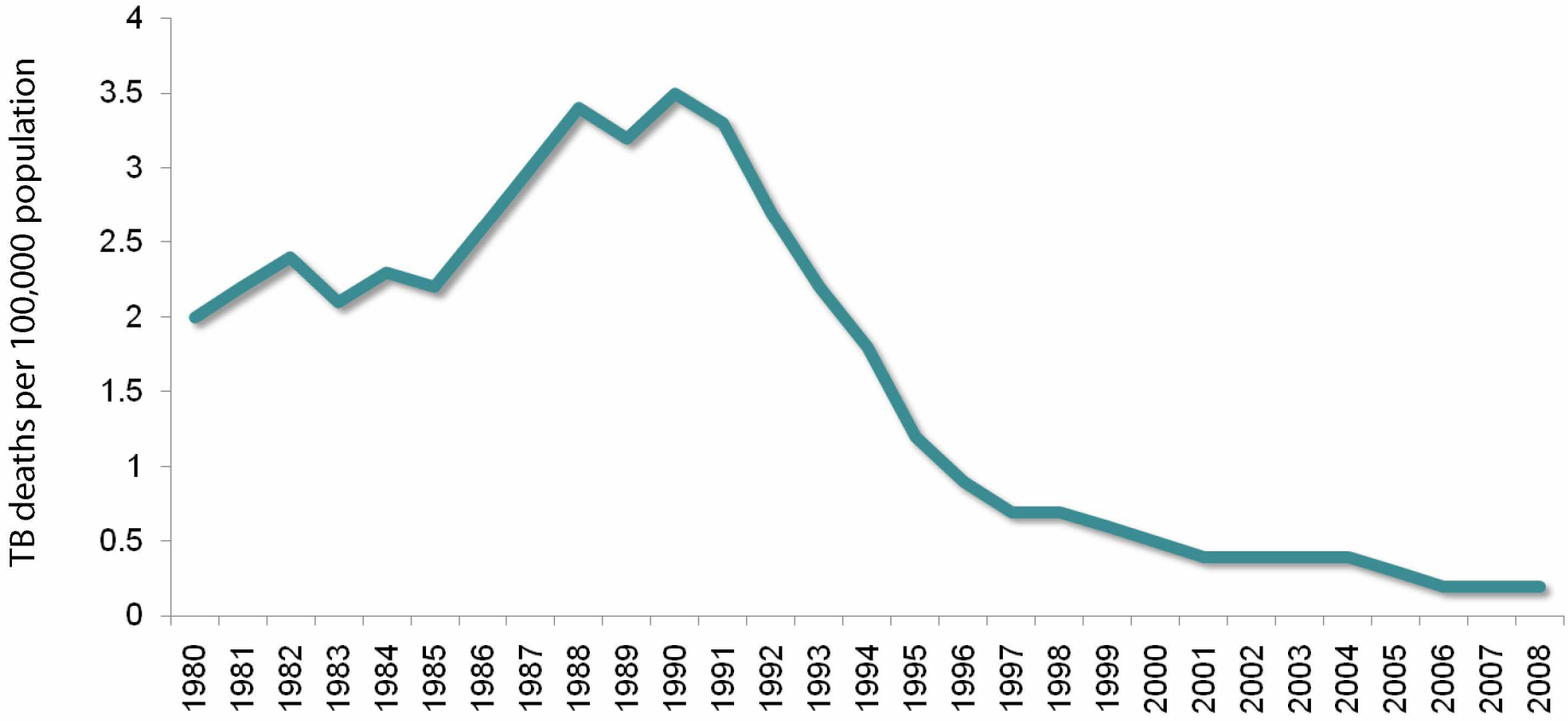
TB

YOUNG VICTIM: Dr. Douglas Abadco checks child with tuberculosis at Kings County Hospital.

Highly contagious tuberculosis close to epidemic level in the city

NYC DOHMH. New York Is Stopping TB. Bureau of Tuberculosis Control Annual Summary 2008. http://nyc.gov/html/doh/downloads/pdf/tb/tb_annualsummary08.pdf

… Until Effective Diagnosis, Treatment, Treatment Observation, and Infection Control Led to a Rapid Decline



NYC DOHMH. New York Is Stopping TB. Bureau of Tuberculosis Control Annual Summary 2008. http://nyc.gov/html/doh/downloads/pdf/tb/tb_annualsummary08.pdf

TB Control Efforts Are Saving Lives – But We Can Save More Lives

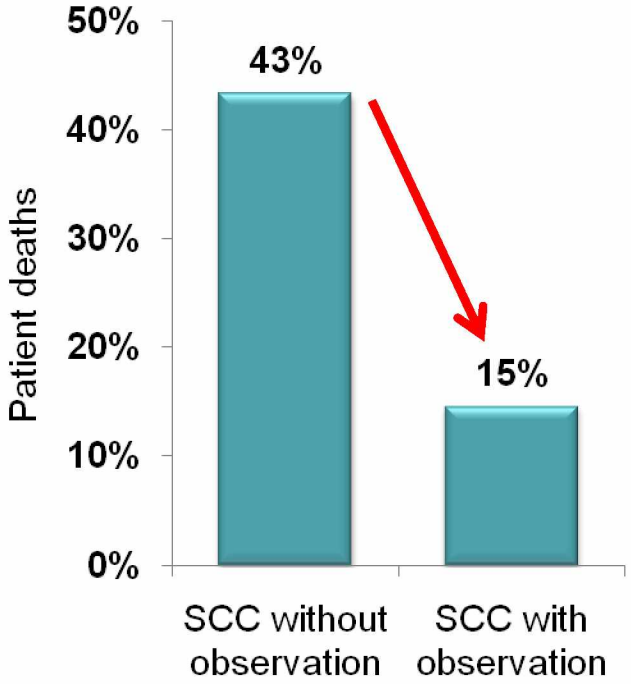
- **Prompt diagnosis of TB and HIV**
  - More rapid and accurate TB diagnosis
    - Many patients who are not diagnosed die of TB
    - TB diagnosis can → HIV testing → ARV Rx
- **Expanded prevention**
  - Reducing TB spread, especially in health care facilities
  - Isoniazid preventive treatment (cf. cotrimoxazole?)
  - Preventing TB and HIV, including testing and early ART (especially if started with CD4>350)

ART, Anti-retroviral treatment

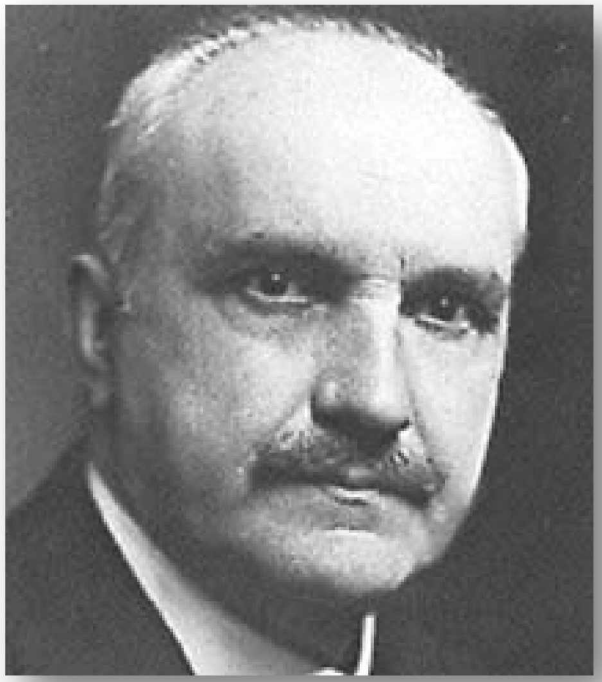
TB Control Efforts Are Saving Lives – But We Can Save More Lives

- **More prompt and more effective treatment**
  - ART treatment for HIV+ people with TB disease
  - Adjunctive treatments (e.g., steroids for TB meningitis, pericardial effusions)
  - Improved case management of all patients (including direct observation)

Treatment observation prolongs survival of HIV+ people with TB disease



Alwood K, et al. AIDS 1994;8:1103-1108
ART, Anti-retroviral treatment
PLHIV, People living with HIV
SCC, Short-course chemotherapy



"Those who cannot remember the past are condemned to repeat it."

—Jorge Agustín Nicolás Ruiz de Santayana

What Is the A
What Is the Q

- Save lives?
- **Prevent MDR-TB?**
- Reduce incidence?

Answer?
Question?

A Single Patient Can Infect Many Others

- **Clustering of TB cases indicates likelihood that groups of patients are acquiring infection from the same source**
- **In New York City in a one-month study in 1991, molecular epidemiology showed**
  - About 30% of all TB cases *and more than half of MDR-TB cases* were clustered
  - 41% of HIV-infected patients with TB were in a cluster
  - A third of patients in clusters of 4 or more cases had evidence of nosocomial TB acquisition

Frieden TR, et al. Tuberc Lung Dis 1996;77:407-413
MDR-TB, Multidrug resistant TB

Preventing MDR-TB

- **Treating patients for ethical and public health reasons**
  - Ethical: Everywhere, but harm can outweigh the benefits if treatment is not followed through to cure or detracts from treatment of the larger number of patients with drug-susceptible TB
  - Public health, e.g., high HIV prevalence, crowded living conditions
- **Testing for drug resistance**
  - Can reduce treatment costs and improve outcomes
- **Stopping spread in congregate facilities**
  - Hospitals, homeless shelters, mines, etc.

No TB control program can treat MDR-TB as fast as a bad program can create it

MDR-TB, Multi drug resistant TB

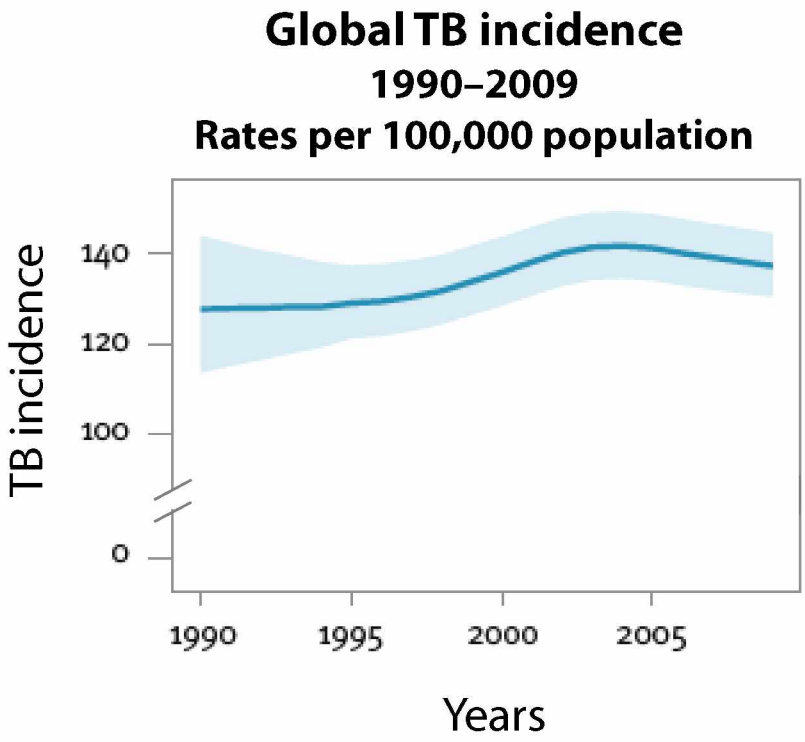
Suarez P, et al. Lancet 2002;359:1980-1989
Resch S, et al. PLoS Medicine 2006;3:e241

What Is the
What Is the

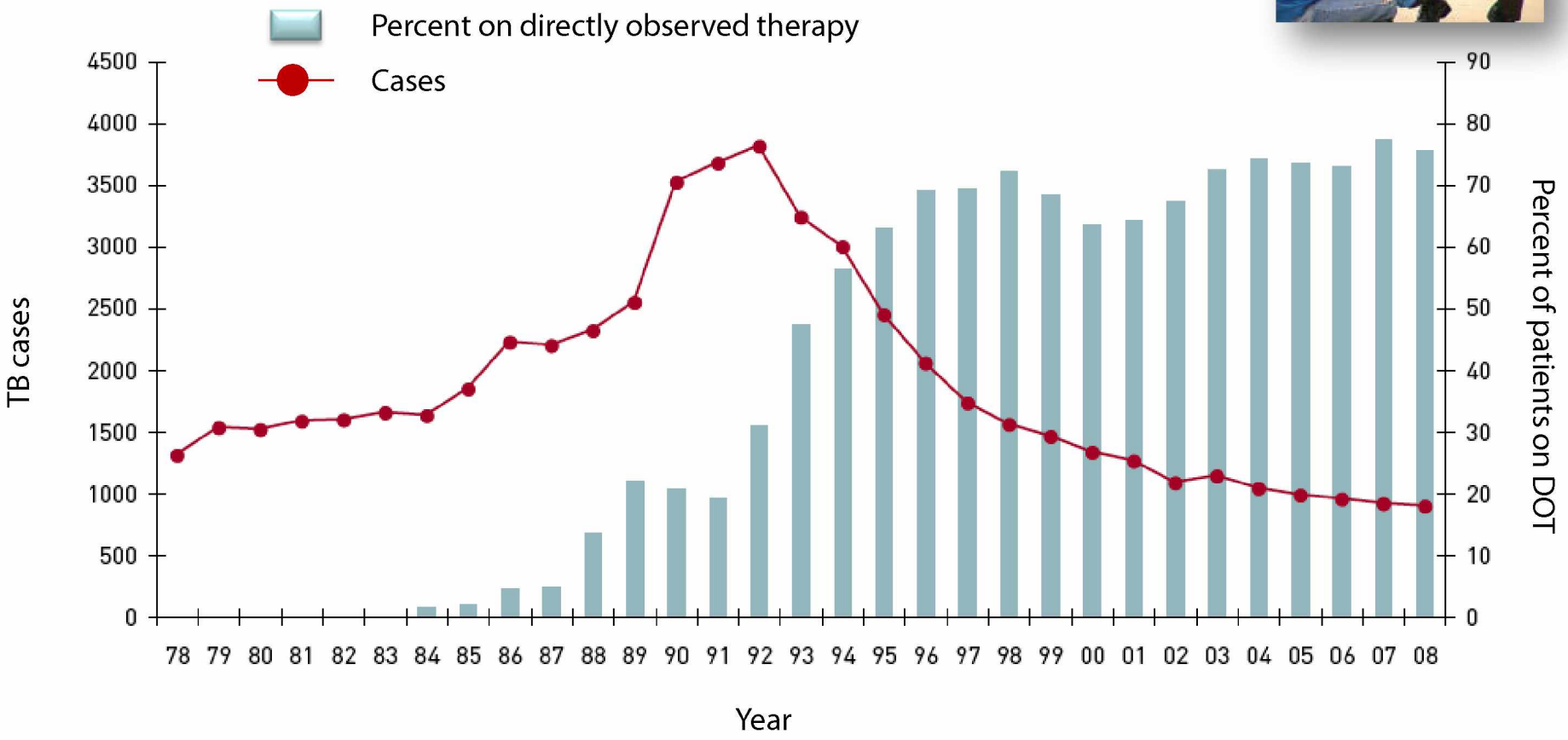
- Save lives?
- Prevent MDR-TB?
- **Reduce incidence?**

WHO. Global Tuberculosis Control: WHO Report 2010.
http://www.who.int/tb/publications/global_report/2010/en/index.htm

e Answer?
Question?

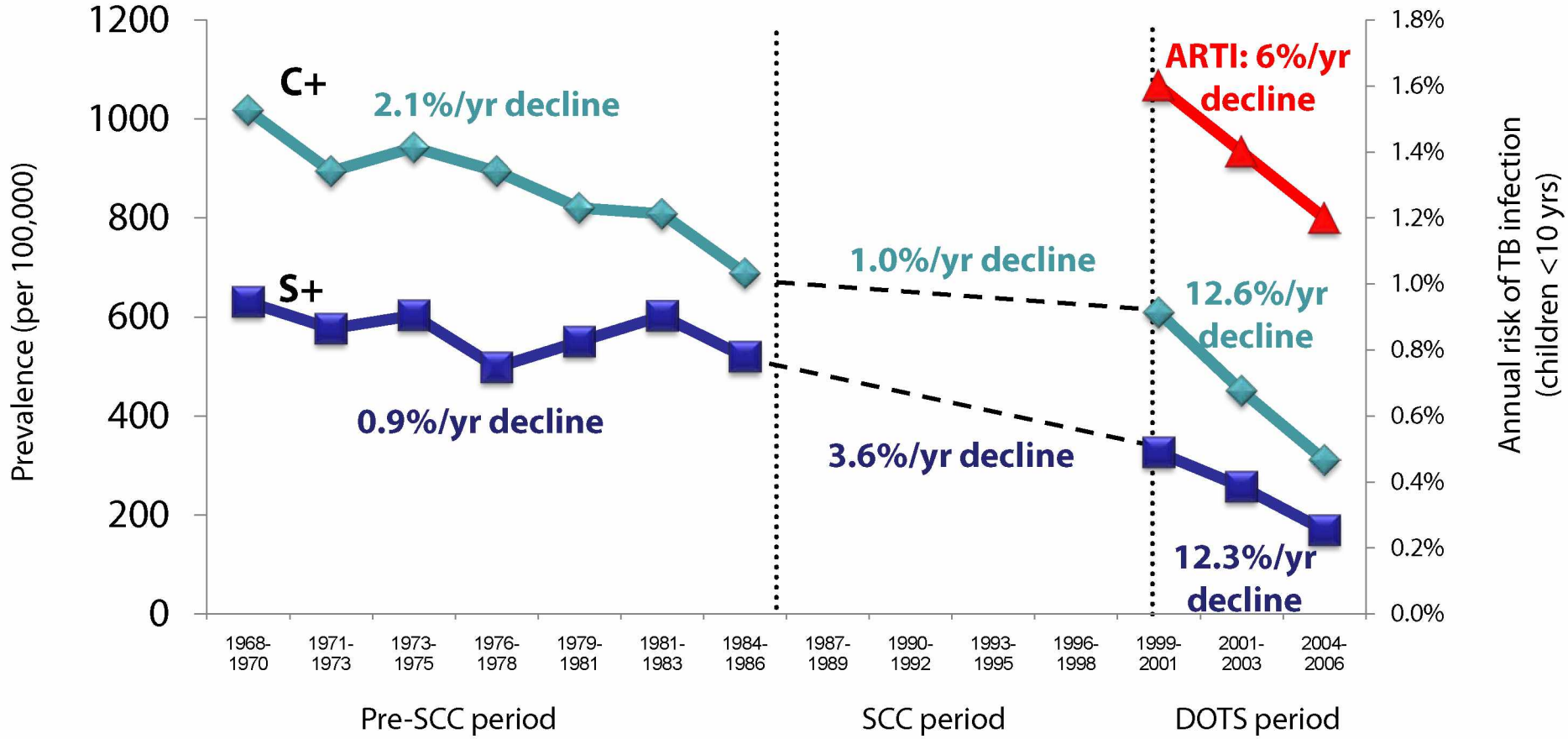


Substantial Decrease in TB as More Patients Were Given DOT New York City, 1978–2008



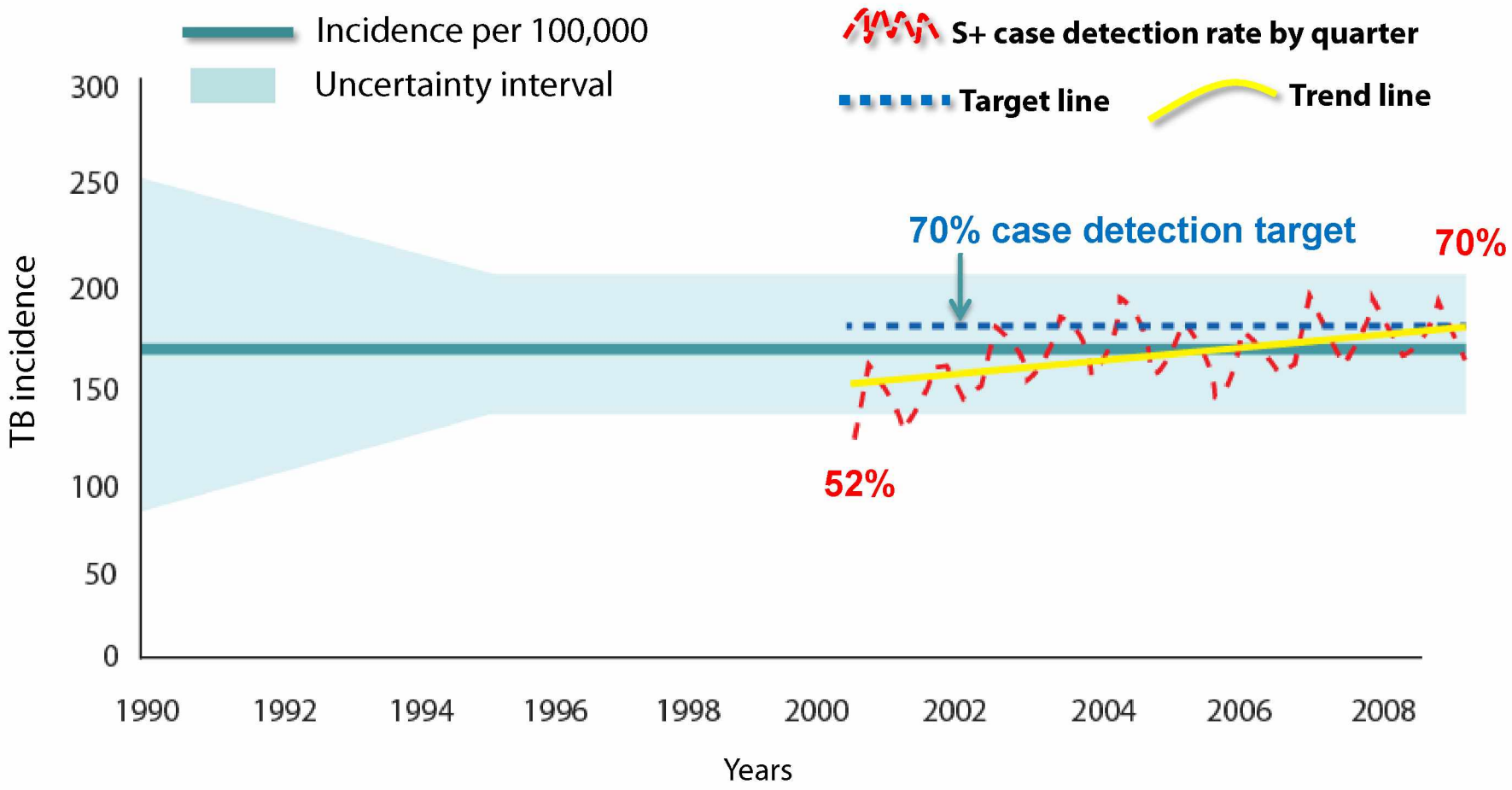
NYC DOHMH. New York Is Stopping TB. Bureau of Tuberculosis Control Annual Summary 2008. http://nyc.gov/html/doh/downloads/pdf/tb/tb_annualsummary08.pdf
DOT, Directly observed therapy

DOTS Implementation in India Significantly Accelerated Reduction of TB Prevalence and Risk of Infection Tiruvallur, India, 1968–2006



Subramani R, et al. IJE 2007;36:387-393; Subramani R et al. IJTLD 2008;12:916-920.
Gopi PG, et al. IJTLD 2006;10:346-348
ARTI, Annual risk of TB infection
SCC, Short-course chemotherapy

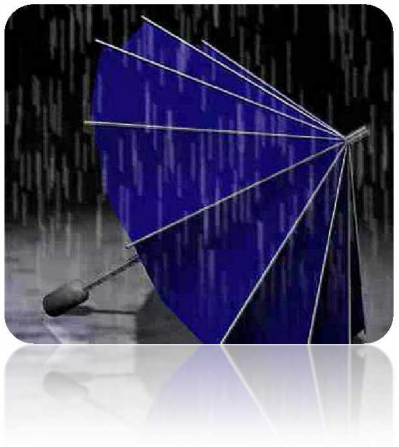
But … in India, Estimated TB Incidence Has Remained Unchanged Despite Increasing Case Detection and Cure 1990–2008



WHO. Global Tuberculosis Control: WHO Report 2010.
http://www.who.int/tb/publications/global_report/2010/en/index.html
India Revised National Tuberculosis Control Programme. TB India 2010: RNTCP Status Report.
http://www.tbcindia.org/pdfs/TB%20India%202010.pdf

Why is TB Incidence Falling only Gradually
Bad DOTS vs. Reactivation vs. Need for Social Change

- **Bad DOTS? Continued spread (rain)**
  - Insufficient case finding – diagnosing too little, too late
  - Not registering all diagnosed patients
  - Not ensuring treatment continuation/completion
  - Not stopping spread of infection
    - In the community
    - In health care facilities, where many TB infections occur but can be prevented



Implication

- **Improve diagnosis, treatment, and infection control**

DOTS, formerly Directly Observed Treatment Short-course

Why is TB Incidence Falling only Gradually
Bad DOTS vs. Reactivation vs. Need for Social Change

- **Reactivation: Waves crashing on beach**
  - Preventing reactivation of latent TB disease (or disease previously considered cured)
  - Example: In Hong Kong, risk of developing TB from reactivation of previously cured infection is much higher than developing TB from primary infection

Implication

- **Preventive treatment if indicated**
- **Research into new ways to identify and treat those most likely to have reactivation of past infection**
- **Persistence – and recognition that results may not be immediate**

DOTS, formerly Directly Observed Treatment Short-course

Why is TB Incidence Falling only Gradually
Bad DOTS vs. Reactivation vs. Need for Social Change

- **Need for social change**
  - Changes in social determinants
    - Poverty
    - Housing
    - Education
  - Better control of modifiable risk factors

TB attributable to selected risk factors in 22 high-burden countries*

Risk Factor	Proportion of TB attributable to risk
Undernutrition	27%
Indoor air pollution	22%
Smoking	16%
HIV	11%
Alcohol misuse	10%
Diabetes	8%

Implication

- **Achieve sustainable long-term change**

Lönnroth,K, et al. Lancet 2010;375:1814-1829

*Multiple risk factors may be present

DOTS, formerly Directly Observed Treatment Short-course

DOTS Is the Foundation of Effective TB Treatment

DOTS has been effective

- Good quality diagnosis, good-quality treatment, and adherence to treatment through completion
- Powerful information systems and commitment to observational research
- Great model for other public health programs

Further strengthening and enhancement of DOTS

- Optimize TB diagnosis with new tools (e.g., fluorescent LED microscopy)
- Implement rapid tests for active TB and drug resistance (e.g., GeneXpert)
- Improve case management (including patient-centered treatment observation)
- Ensure supplies of high-quality drugs
- Reinforce program monitoring and supervision

DOTS, formerly Directly Observed Treatment Short-course
LED, Llight-emitting diode

Early Diagnosis and Drug Treatment to Interrupt TB Transmission Remain the Top Priorities

"[TB] control programs have been less effective than expected in cutting transmission mainly because patients are not diagnosed and cured quickly enough. The priority now is not to abandon the basic principles of chemotherapy, but rather to implement them with greater vigor."

Dye C and Williams BG. Science 2010;328:856-861

Challenges for TB-HIV Control

- **HIV continues to drive the TB epidemic in Africa**
  - Expansion of HIV prevention and treatment is critical
  - Isoniazid preventive treatment of people who have both HIV and TB infections could reduce TB
- **Strengthening diagnosis and treatment for TB and HIV**
  - Effective screening and prompt, accurate diagnosis to facilitate early treatment initiation for both TB and HIV
  - Screening of TB patients for HIV
  - Providing ART to all people who have HIV and TB disease
- **Effective case management for both TB patients and people living with HIV**
- **Infection control**

ART, Anti-retroviral treatment
PLHIV, People living with HIV
IPT, Isoniazid preventive therapy

Focus on Basics + New Strategies and Tools = Success in TB Control

- **Tremendous progress over the past several decades using current tools and strategies**
  - DOTS has saved 6 million lives in the past 15 years – and nearly a million this year alone
- **Better application of existing tools can further decrease deaths and, to some extent, incidence**
- **Persistence, patient-centeredness, and zealous adherence to technical rigor and program excellence are essential**
- **Current tools and strategies will not eliminate TB**
- **New approaches will be required to control TB in Africa and, globally, to reduce TB incidence drastically**

DOTS, formerly Directly Observed Treatment Short-course

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

PUBLIC HEALTH GRAND ROUNDS

Office of the Director

March 24, 2011

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention