



**USAID**  
FROM THE AMERICAN PEOPLE

# TB/HIV: Global situation and scaling up collaborative activities

Health[e]Foundation Symposium  
Kampala  
October 16, 2010

Yared Kebede Haile, MD, MPH  
TB/HIV coordinator TB CAP



# Presentation outline

- Global TB and HIV epidemiology
  - State of the epidemics
- Collaborative TB/HIV activities
  - Global and regional overview
- Key TB/HIV interventions
  - Evidence & tools
- Challenges, next steps & approaches
- Summary

# Global situation 2008

## TB/HIV

### ■ HIV/AIDS burden

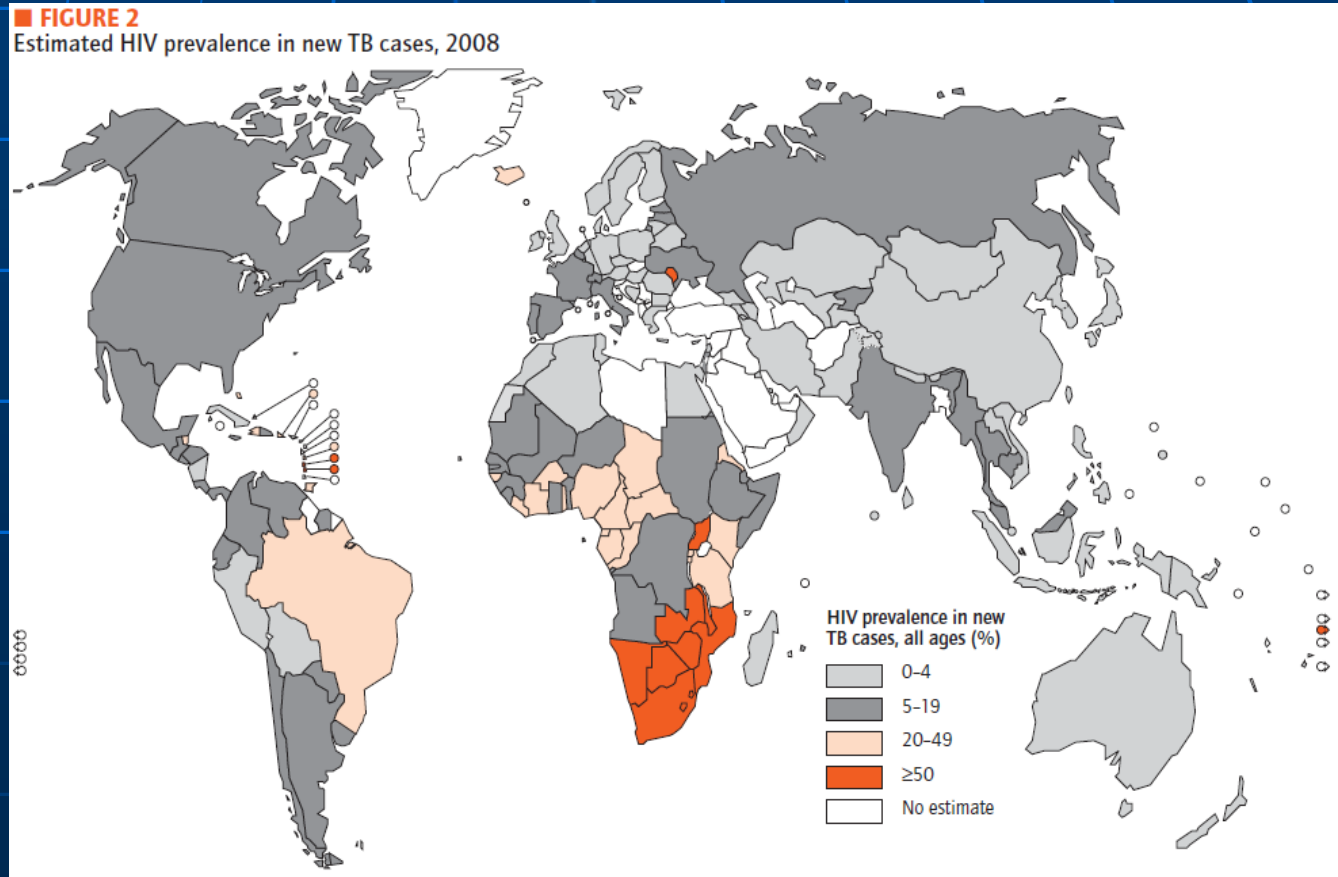
- 33.4 million people living with HIV globally
- 2.7 million newly infected in 2008
- 5.2 million on ART (36%) in 2009
- In high prev. areas, five new HIV infections for every two people newly added on treatment

### ■ TB burden

- 9.4 million (139 per 100,000)
  - Estimated death 1.32 million (20 per 100,000)
- HIV-associated TB 1.4 million (15% of total incid. cases)
  - Estimated death 0.5 million (23% of all HIV deaths)

# HIV Prevalence in New TB Cases WHO 2008

In 8 African countries  
> 60% HIV prevalence  
among TB  
patients.



# TB during the HIV era

- High risk of TB in PLHIV 10%/year
- Increased CFR (HIV co-morbidity)
- Difficult diagnosis (SN & EP)
- Increased adverse drug reactions
- Increased risk of recurrence
- Increased risk of drug res. (MDR/XDR-TB)
- Double stigma
- Management of co-infection - ART
  - Immune Reconstitution (IRIS)
  - Drug-drug interactions (Anti-TB & ARTs)

# Management of TB/HIV co-infection

- High mortality during first 2 months
  - ART - all TB/HIV pts irrespective of CD4 count.
  - Start TB treatment first and ART asap
- Early ART initiation has challenges
  - High pill burden
  - Drug-drug interaction
  - Toxicity
  - IRIS

# IRIS

## ■ Paradoxical TB-IRIS

- Pts on TB treatment and start ART
- 1-4 weeks after ART initiation
- Major risk factors:
  - Low CD4 count, Disseminated TB
  - Short interval between TB treatment and ART

## ■ Unmasking TB-IRIS (ART Associated TB)

- High incidence during first 3 months of ART.
- Severe pulmonary TB, TB abscess, neurological manifestations...
- High mortality (>20%) during first year of ART.

# Management of TB in co-infection (Revised WHO guidelines)

- New TB (PTB and EP) cases: 2HRZE / 4HR
- 2HRZE/6HE regimen should be phased out
- Optimal dosing is daily throughout the course
- In high INH resistance continuation phase: 4HRE
- All previously treated patients: culture and DST
- Failures with DR likelihood: empiric MDR regimen

# Recommended ART for patients with active TB (WHO)

- First-line ART regimen
  - 2 NRTIs plus 1 NNRTI (EFV)
  - Use of triple NRTIs
- Second-line ART: Limited PI options for pts on TB regimen with R.
  - ritonavir boosted PIs (SQV/r or LPV/r)
  - Replacement of rifampicin with **rifabutin**.

# Rifabutin

- Added on WHO EML for use in HIV+ TB pts on 2<sup>nd</sup> line ART - ritonavir-boosted PIs
- Equally safe / effective as rifampicin
- Little effect on PI serum concentration
- cost-effective in combination with the standard dose of boosted-PIs.

# Collaborative TB/HIV activities

## A. Establish the mechanism for collaboration

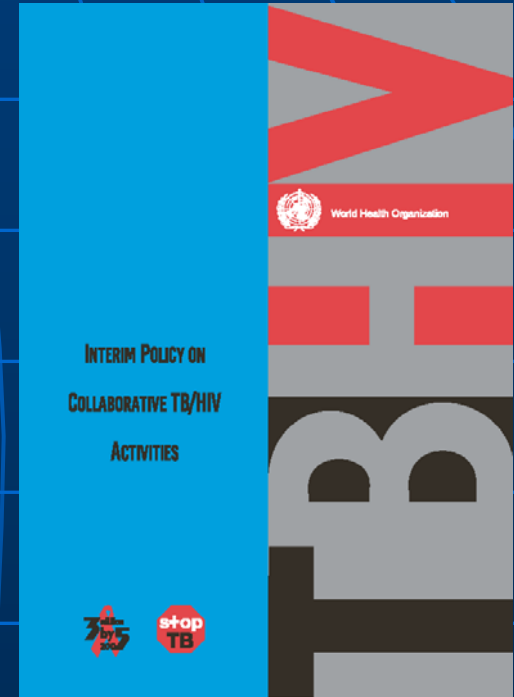
- A.1. TB/HIV coordinating bodies
- A.2. HIV surveillance among TB patient
- A.3. TB/HIV joint planning
- A.4. TB/HIV monitoring and evaluation

## B. To decrease the burden of TB in PLHIV - 3 I's

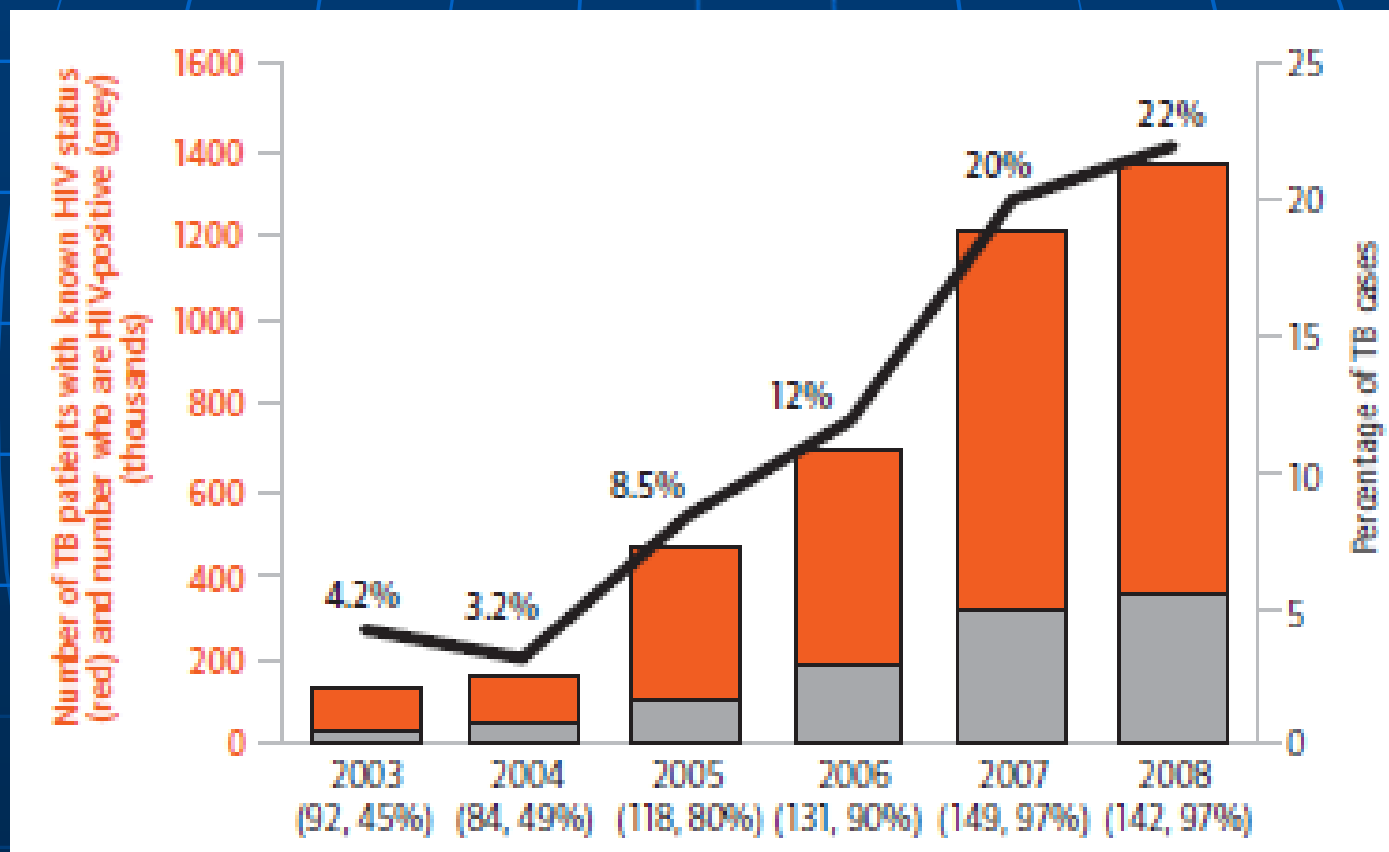
- B.1. Intensified TB case finding (ICF)
- B.2. Isoniazid preventive therapy (IPT)
- B.3. TB infection control in health care and other settings (IC)

## C. To decrease the burden of HIV in TB patients

- C.1. HIV testing and counselling
- C.2. HIV preventive methods
- C.3. Cotrimoxazole preventive therapy
- C.4. HIV/AIDS care and support
- C.5. Antiretroviral therapy to TB patients.

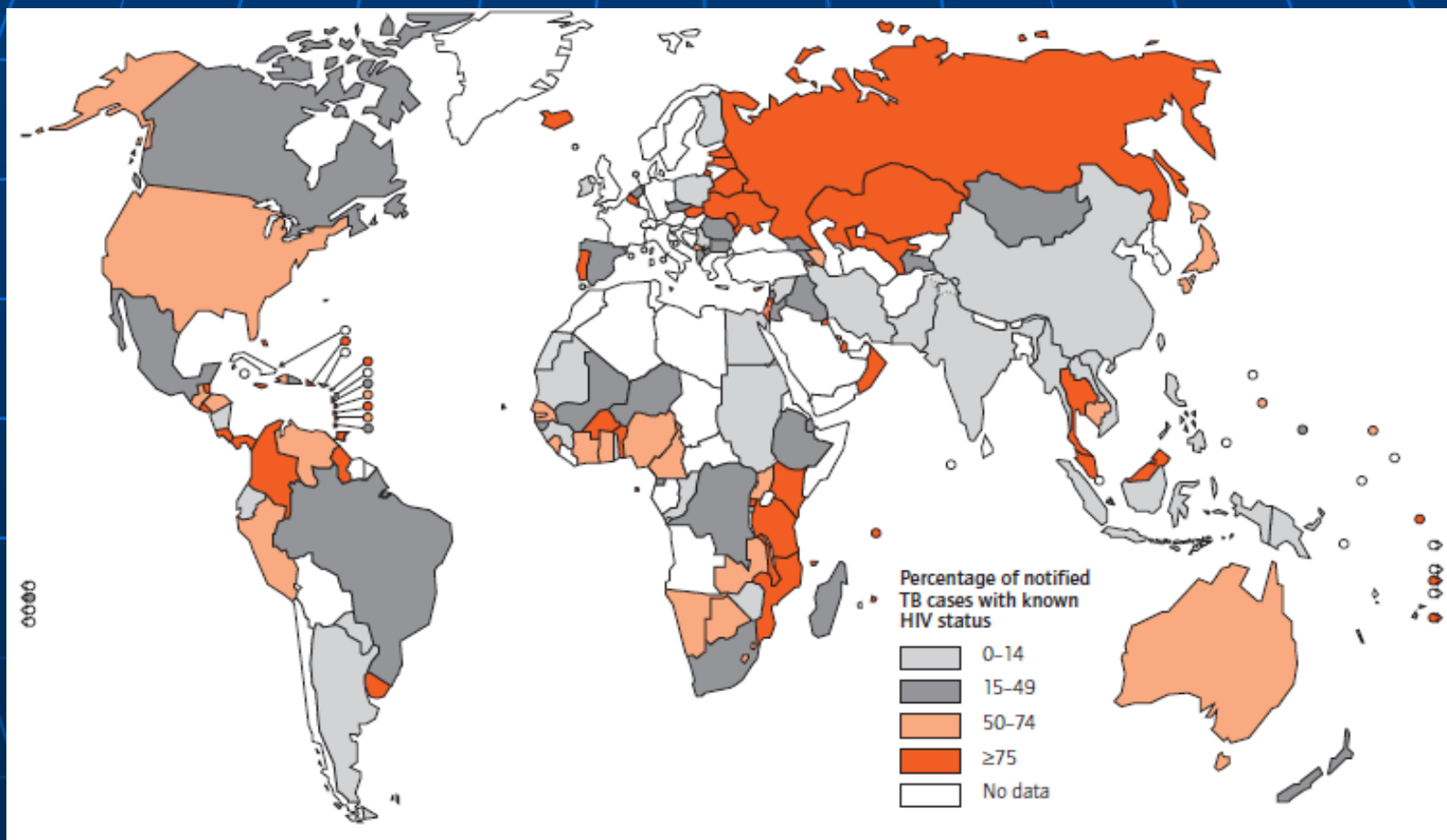


# HIV testing for TB patients 2003–2008 (WHO)



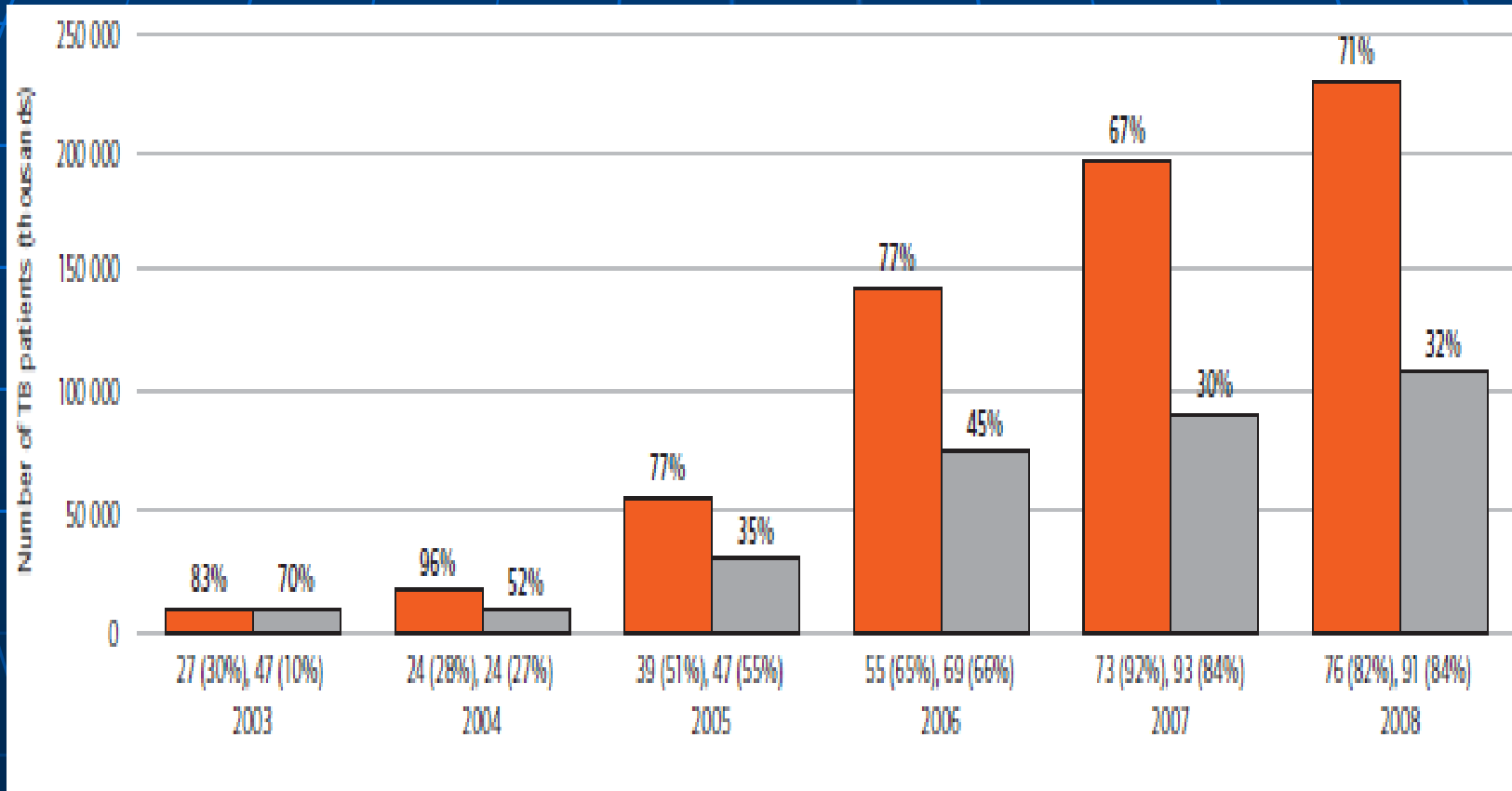
\* Data are only shown for countries for which data were reported on both the number of cases for whom HIV status was known and the number of cases that were HIV-positive.

# HIV testing for TB patients, 2008

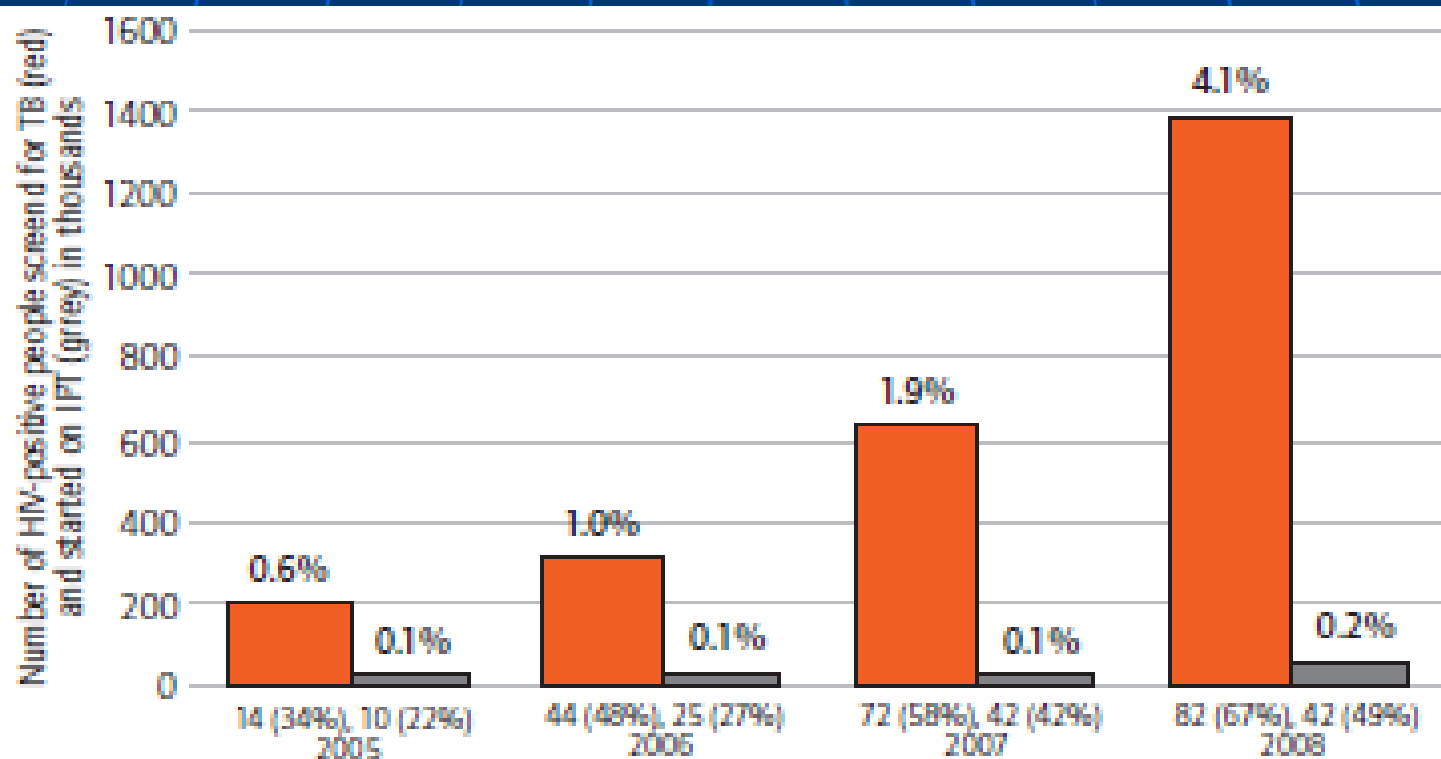


In 50 countries at least 75% of TB patients knew their HIV status, including 11 African countries

# Co-trimoxazole preventive therapy and antiretroviral therapy for HIV-positive TB patients, 2003–2008.



# Intensified TB case-finding and IPT provision among HIV positive people.



<sup>a</sup> Percentages for IPT figures are calculated using the estimated number of HIV-positive people without active TB.

# Global summary (by WHO regions – 2008)

Region	% of notified TB patients tested for HIV	% of tested TB patients HIV positive	% of identified HIV+ TB patients started on CPT	% of identified HIV+ TB patients started on ART	Number of HIV+ people screened for TB (thousands)	Number of HIV+ people provided IPT (thousands)
AFR	45	46	73	30	729	26
AMR	49	15	36	67	48	12
EMR	5.4	4.1	39	55	12	0.7
EUR	79	3.3	61	29	205	9.2
SEA	4.1	18	54	35	300	0.2
WPR	11	7.0	55	28	90	0.7
Global	22	26	71	32	1384	48

# TB care for PLHIV (Key interventions)

- **HCT** - 22%
- **ICF** - 4% screened ~1.4m
- **IPT** - 0.2% ~50,000
- **ART** - 32%
- **TB-IC** at early stage - Good indicators needed

**Scaling-up urgent!!**  
**Tools and evidence?**

# Intensified Case Finding (ICF) (the gateway)

- High CFR for HIV-infected TB pts
  - 25-50% during TB treatment
  - >50% deaths occur within 2 months
- Early diagnosis and treatment
  - Reduces transmission and case-fatality
  - Improve safety of ART initiation
  - Improve uptake of IPT
- Challenges:
  - Diagnostic difficulty (AFB, X-ray, clinical)
  - Evidence-based TB screening

# IPT and ART

## ■ IPT

- Effective in reducing TB incidence in PLHIV and safe
- Overall 36% reduction in TB incidence
- Upto 62% reduction in TST positives
- Does not contribute to increased INH resistance

## ■ ART

- Reduces TB incidence in PLHIV
- Reduces mortality in TB patients co-infected with HIV.

## ■ ART + IPT

- synergistic in reducing risk of TB in PLHIV

# Evidence and tools

1. THIBELA TB IPT study: Outcome of massive "IPT" scale-up among miners in South Africa" – IAS 2009, Capetown
2. Botswana IPT trial - Cancun UNION 2009 and CROI2010
3. TB incidence in HIV infected patients in Rio – impact of ART and IPT- Golub J et al, AIDS 2007, 21:1441–1448
4. IPT, HAART and TB risk in HIV infected adults in SA – prospective study - Golub J et al AIDS 2009, 23:631–636
5. *Widespread ART is associated with decline in TB prevalence.* Middelkoop K et al. 5th IAS Conference, Cape Town, abstract WeLBB105, 2009
6. CAMELIA: Survival With Early vs Late Therapy in TB-Coinfected Patients - Blanc FX, et al. AIDS 2010. Abstract THLBB206.
7. WHO ICF and IPT draft guidelines – AIDS 2010 Vienna.
8. WHO policy on TB Infection Control 2009

# 1. THIBELA TB IPT study (CREATE)

- Two arms
  - Standard TB control
  - Standard TB control *plus* Community wide IPT
- Large scale: >27,000 consented
  - 88% eligible, 98% started

# THIBELA TB IPT study (findings)

- Safe: 126 AEs, 4 SAEs, 33 deaths all causes
- TB screening effective
  - High prevalence (1.2%) – contributed to TB case finding
  - 26 cases missed among 8116 screened [0.3%]
- Community mobilisation essential
- No evidence of increased INH resistance

# TB drug susceptibility after IPT

## IAS 2009 - Thibela TB\*

	First episode			Re-treatment episode	
	TB after IPT group	Control cluster	Laboratory sub-study	TB after IPT group	Control cluster
Any INH resistance	7/58 (12.1%)	12/182 (6.6%)	32/270 (11.8%)	1/13 (7.7%)	12/67 (17.9%)
MDR-TB	1.58 (1.7%)	6/182 (3.3%)	21/269 (7.8%)	1/13 (7.7%)	8/67 (11.9%)

- TB episode with drug resistance in TB after IPT group not significantly different from those in comparison group

- Most TB episodes after IPT have good treatment outcome.

- Data don't support concerns about drug resistance following IPT

van Halsema et al; Tuberculosis outcomes and drug susceptibility in individuals exposed to isoniazid preventive therapy in a high HIV prevalence setting, AIDS2010)

Poster + oral presentation IAS 2009

## 2. Botswana IPT trial

Cancun UNION 2009 and CROI2010

- Randomized double-blind placebo-controlled trial
- 6 months (989) vs 36 months (1,006)
  - 23% TST positive in 6H
  - 26% TST positive in 36H
- By 6 months 45% had initiated ART
- 11 LFU, 176 with drawals, 36 deaths
- Adherence at 36m: 78% attended >80% of their visits.

# Botswana IPT trial (findings)

- The benefit of 6 months of IPT was lost in less than 6 months after treatment completion.
- Overall 36 months IPT reduced TB by 56%.
- Continuous IPT prevented TB in TST+ with 92% efficiency.
- In TST negatives, 36m IPT did not prevent TB any better than placebo.
- SAE not more common in 36H than 6H
- Provision of IPT did not result in increased INH-R

# Botswana IPT trial

INH RESISTANCE BY TREATMENT ARM  
(from enrolment and after 36 months)

Botswana  
Background  
9% INH resistance  
in new TB patients

18% INH R  
expected in trial if  
no additional  
contribution by IPT

	6H (989)	36H (1009)
DST test available	24	14
INH mono R	3	1
MDR -TB	1	1
Any INH R # (%)	4 (17%)	2 (14%)

### 3. TB incidence in HIV infected patients in Rio – impact of ART and IPT

Incidence rate of tuberculosis for primary exposure categories.

Exposure category	IR (per 100 PY)	Incidence rate ratio
Naive	4.01 (3.40–4.69)	1.0 (REF)
ART only	1.90 (1.66–2.17)	0.48 (0.39–0.59)
IPT only	1.27 (0.41–2.95)	0.32 (0.10–0.76)
<b>Both</b>	<b>0.80 (0.38–1.47)</b>	<b>0.20 (0.09–0.91)</b>
Total	2.28 (2.06–2.52)	

Golub J etal, AIDS 2007, 21:1441–1448

## 4. IPT, HAART and TB risk in HIV infected adults in SA – prospective study

Incidence rate of tuberculosis for primary exposure categories.

IPT & HAART history	IR (per 100 PY)	Incidence rate ratio
Naive	7.1 (6.2–8.2)	REF
HAART only	4.6 (3.4–6.2)	0.65 (0.46–0.91)
IPT only	5.2 (3.4–7.8)	0.73 (0.44–1.13)
<b>IPT and HAART</b>	<b>1.1 (0.2–7.6)</b>	<b>0.15 (0.004–0.85)</b>

Golub J etal AIDS 2009, 23:631–636

## 5. Widespread ART is associated with decline in TB prevalence

	HIV Negative			HIV Positive		
	2005n=584	2008n=899	p-value	2005 n=174	2008n=306	p-value
<b>Current Notified TB</b>	<b>0.7%</b>	<b>0.7%</b>	<b>0.97</b>	<b>4.0%</b>	<b>2.3%</b>	<b>0.24</b>
<b>Previously Undiagnosed TB</b>	<b>0.5%</b>	<b>0.4%</b>	<b>0.84</b>	<b>5.2%</b>	<b>1.3%</b>	<b>0.01</b>
<b>TOTAL</b>	<b>1.2%</b>	<b>1.1%</b>	<b>0.98</b>	<b>9.2%</b>	<b>3.6%</b>	<b>0.02</b>

Middelkoop K et al. *Widespread ART is associated with decline in TB prevalence.* 5th IAS Conference on HIV Treatment, Pathogenesis and Prevention, Cape Town, abstract WeLBB105, 2009.

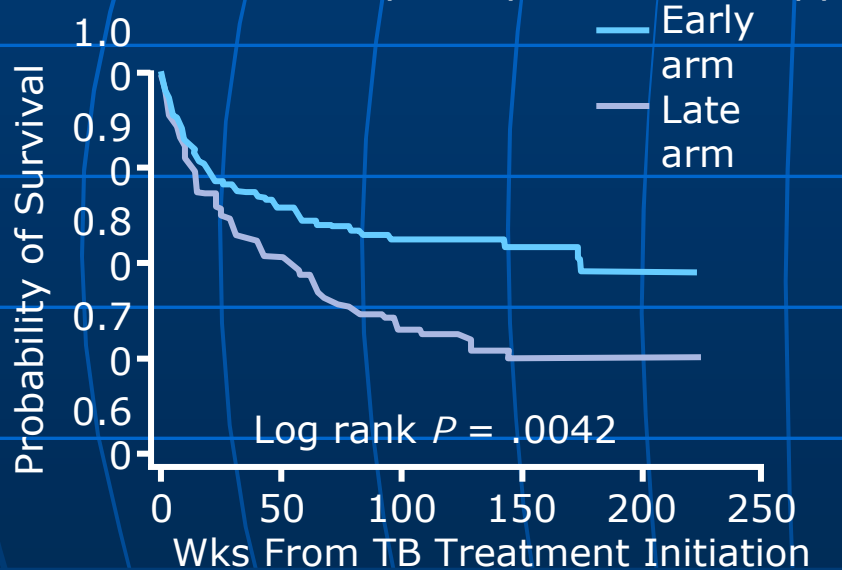
# 6. CAMELIA: ART Initiation at Wk 2 vs Wk 8 of TB Therapy in HIV-Coinfected Patients

- WHO 2010 guidelines recommend to
  - Initiate HAART in all HIV-infected patients with TB, regardless of CD4+ cell count
  - Initiate TB therapy before HAART, with HAART added as soon as possible
- CAMELIA: randomized, open-label trial of HIV-infected patients with newly-diagnosed AFB+TB and CD4 cell count  $\leq 200$  cells/mm<sup>3</sup> [2]
  - Compared HAART initiation (d4T + 3TC + EFV) at
    - Wk 2 (n = 332) vs
    - Wk 8 (n = 329) of TB therapy
  - All patients received standard TB therapy for 6 mos

Blanc FX, et al. AIDS 2010. Abstract THLBB106.

# CAMELIA: Survival With Early vs Late Therapy in TB-Coinfected Patients

Survival Probability, Early vs Late Therapy



Wk	Survival Probability, % (95% CI)		P
	Early Arm	Late Arm	
50	86.1 (81.8-89.4)	80.7 (76.0-84.6)	.07
100	82.6 (78.0-86.4)	73.0 (67.7-77.6)	.006
150	82.0 (77.2-85.9)	70.2 (64.5-75.2)	.002

- Significantly higher incidence of IRIS with early vs late HAART
  - 4.03 vs 1.44 per 100 person-mos, respectively ( $P < .0001$ )

Blanc FX, et al. AIDS 2010. Abstract THLB206. Graphic used with permission..

# 7. ICF and IPT WHO draft guidelines 2010

WHO-CDC meta-analysis - TB screening

## Objective

Sensitive clinical algorithm to develop simple, standardized TB screening tool and develop standardized evidence-based guidelines for TB screening and IPT for PLHIV.

## Results

- 12 studies and >9000 cases included in study (retrospective)
- Top performing rules outlined
  - C24,F, NS, WL - Sensitivity (79%), Sp (56%), NPV (98%)
- Draft guidelines and algorithms developed

# Recommendation 1 : TB screening

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 or
- night sweats

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

- Irrespective of immunosuppression
- Including those on ART
- Previously treated for TB
- Pregnant women

# Recommendation 2 : TB screening

Adults and adolescents living with HIV screened with a clinical algorithm and reported one of the following;

- current cough,
- fever,
- weight loss or
- night sweats

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

# Recommendation 3

Adults and adolescents who are living  
With HIV and:

- have unknown or positive TST status and;
  - unlikely to have active TB
- should receive IPT for at least 6 months

# Recommendation 4

Adults and adolescents who are living With HIV in settings with higher TB transmission

and:

- have unknown or positive TST status and;
- unlikely to have active TB

**Conditionally** receive IPT for at least 36 Months

- Settings for 36 months should be determined by national guidelines
- Local context (feasibility, resources, safety and relevance)
- Higher TB prevalence and transmission

# Recommendation 5

- **Tuberculin Skin Test (TST)**
  - Not a requirement for initiating IPT
  - TST can be used if feasible
  - TST positives benefit more from IPT

# Recommendation 6

- **Chest radiography**
  - Could be used to augment screening but less feasible due to workload, cost, availability and qualified staff.
  - Implement symptom based rule regardless of radiography.

# Recommendation 7

## IPT and drug resistance

- IPT does not increase INH resistance
- Concerns of INH resistance should not be barriers to providing IPT.

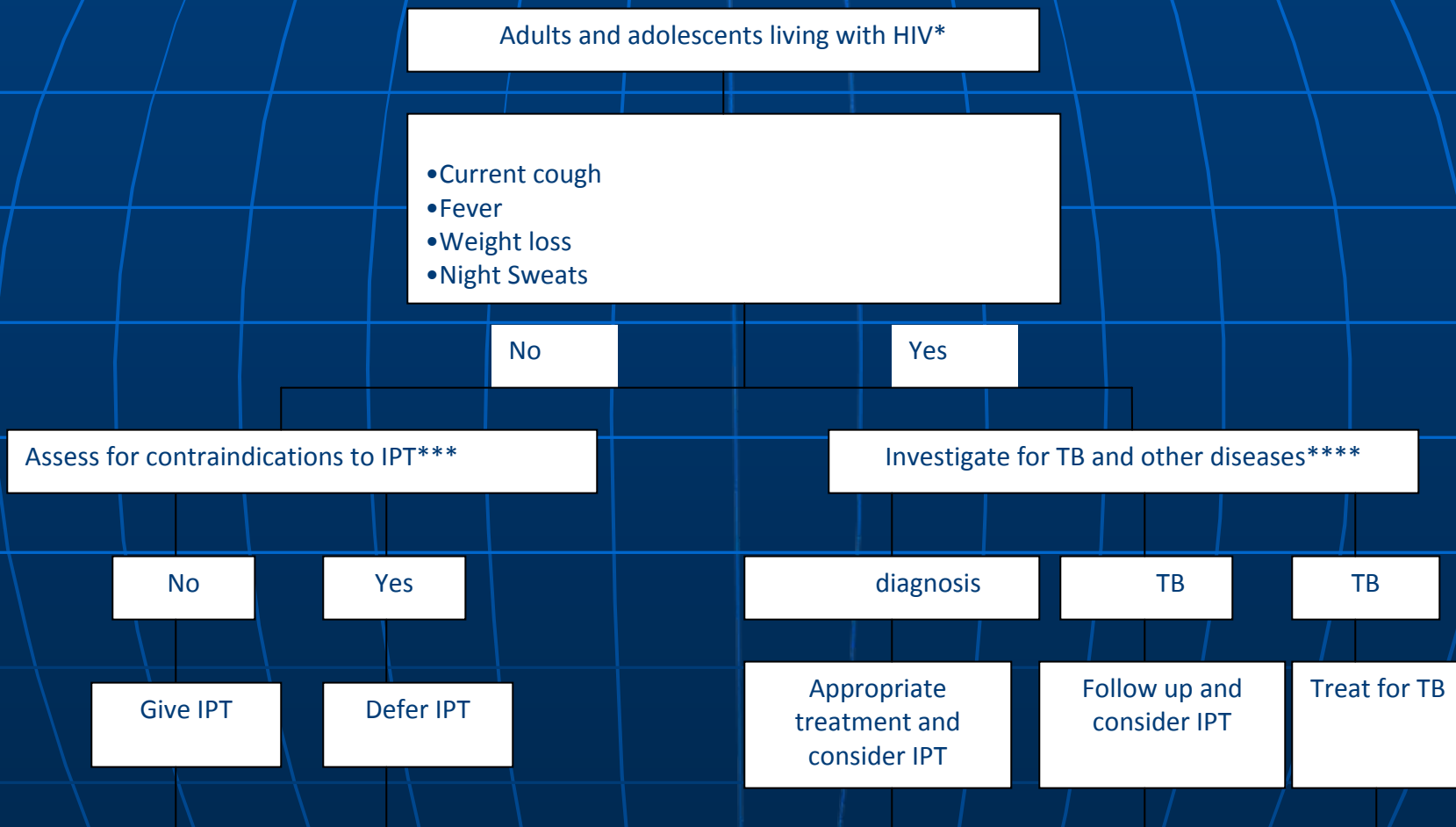
# Recommendation 8

## Children living with HIV and IPT (1)

- IPT should be offered to children without poor weight gain, fever or concurrent cough.
- Children (with HIV) after TB treatment should receive additional 6 months of IPT

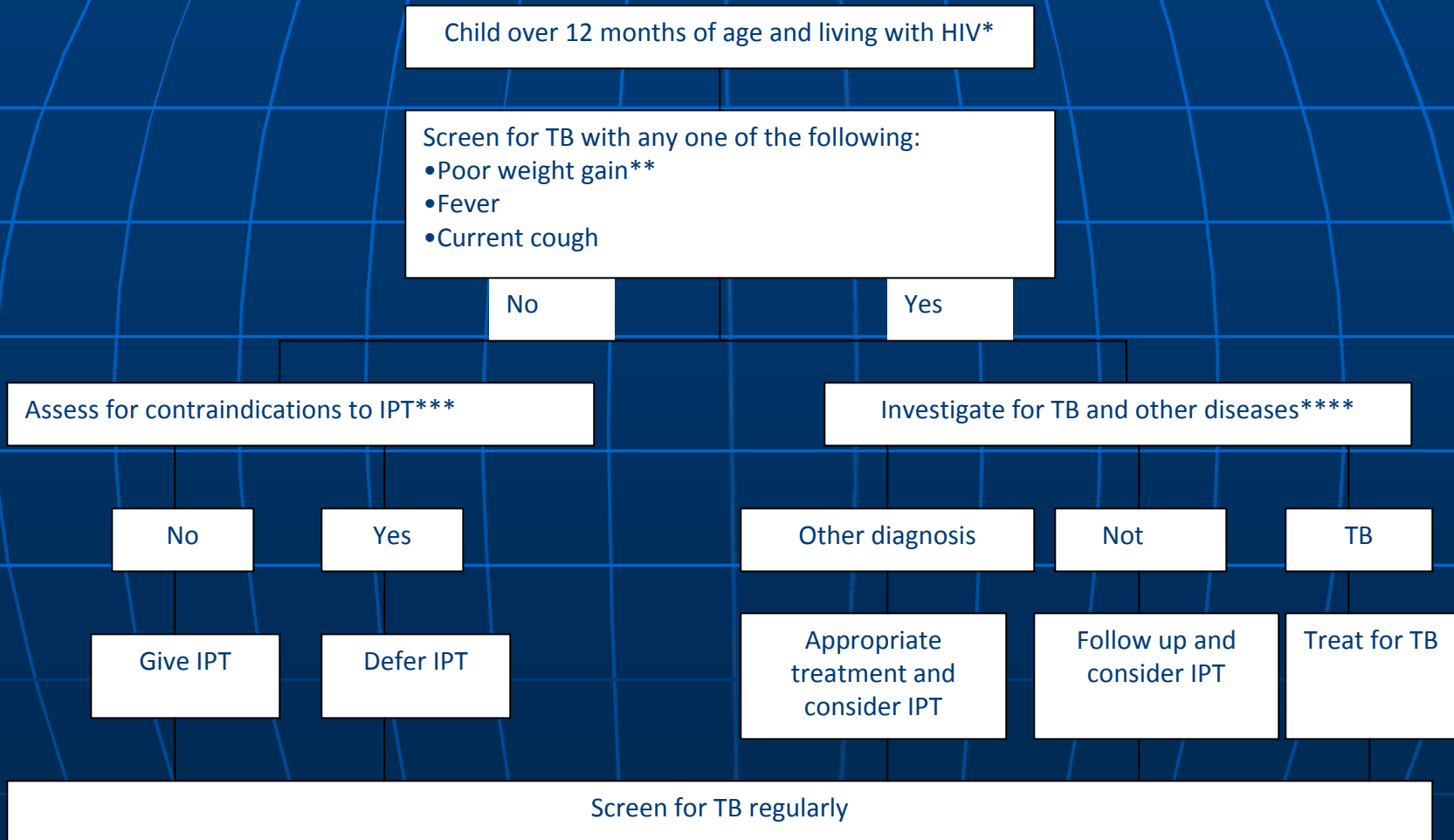
All children with TB contact history should receive 6 months of IPT.

# Algorithm for TB screening in adults and adolescents living with HIV in HIV prevalent and resource constrained settings (WHO)



Screen for TB regularly at each encounter with a health worker or visit to health facility

# Algorithm for TB screening in children more than one year old and living with HIV (WHO)

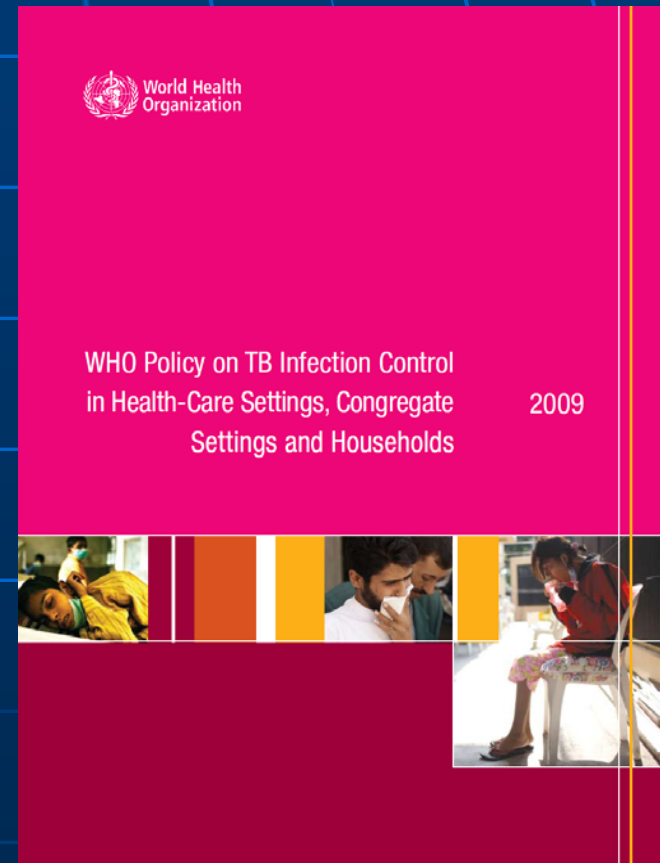


# Summary WHO guidelines

- Symptom based screening for TB
- Algorithm is sufficient to start IPT for PLHIV
- No mandatory CXR and TST 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

# TB Infection Control (TB-IC)

- Facility level measures
- Administrative measures
- Environmental measures
- Personal protection



# Key challenges

## Coordination and collaboration

- Health System structure and capacity
- Centralized HIV vs Decentralized TB (models)
- Weak referral systems, M&E systems
- Strategies for vulnerable populations

## HIV care for TB patients

- Low ART coverage
- High mortality (quality of care)

## TB care for PLHIV

- Policy support and implementation of IPT
- Implementation of WHO ICF/IPT guidelines
- MDR-TB/HIV co-infection
- High mortality (quality of care)

# NEXT STEPS

## OBJECTIVE

Reduced mortality (<10%)  
among new  
HIV co-infected TB patients

## PRIORITY ACTIVITY

Scale up TB screening, prevention,  
diagnosis and treatment in PLHIV  
Scale up early ART for TB patients  
co-infected wth HIV

# Key approach



## Monitoring and Evaluation

- Collect and analyze stratified data
- Use harmonized TB/HIV indicators

## Service integration and scale up



- Engage and coordinate with all care providers
- HIV implementers ownership of 3I's
- Enhance community strategy
- 3 tier strategy (global, national and facility level)

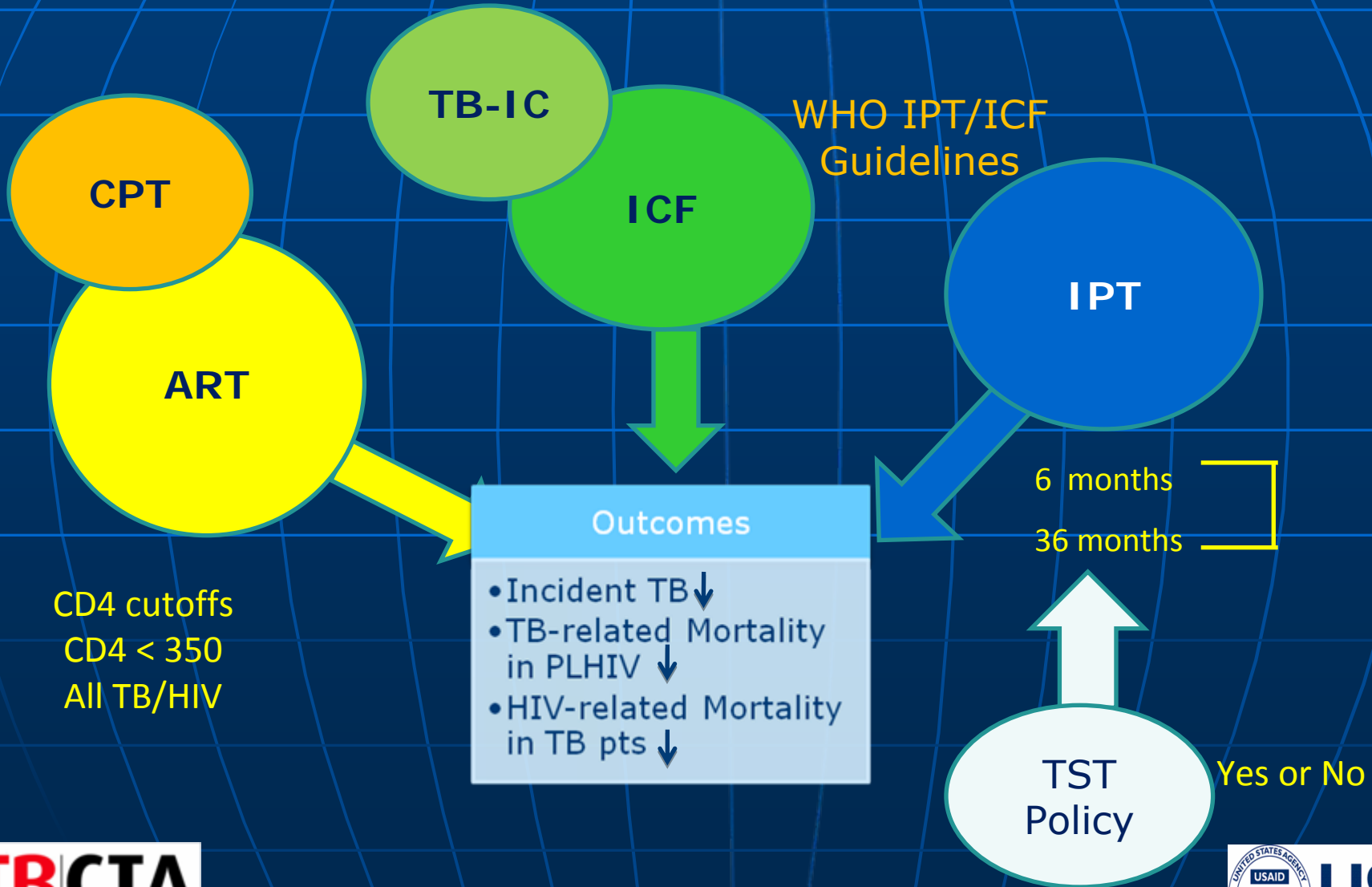


## Enhance diagnostic capacity

- X-ray for case finding in children and smear -ve
- Improved smear microscopy (LED, FM)
- Culture and DST (LPA, XpertTB...)

# Summary

## Key interventions and outcomes



**Thanks you**

[WWW.tbcta.org](http://WWW.tbcta.org)