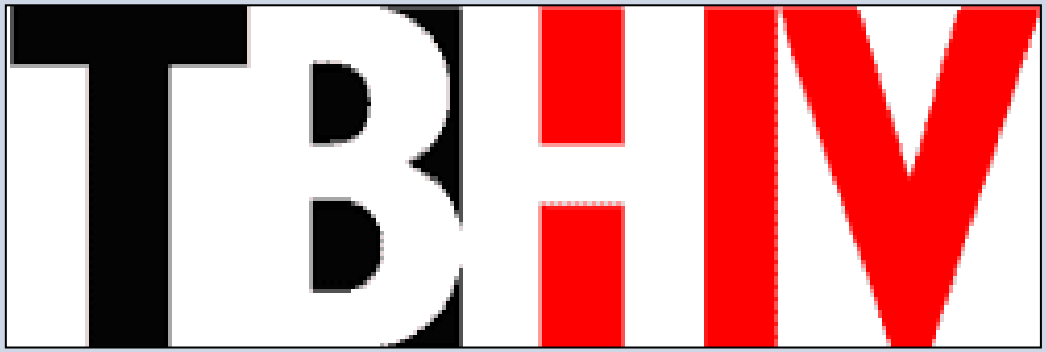
TB and HIV infected persons



L. Masae Kawamura, MD

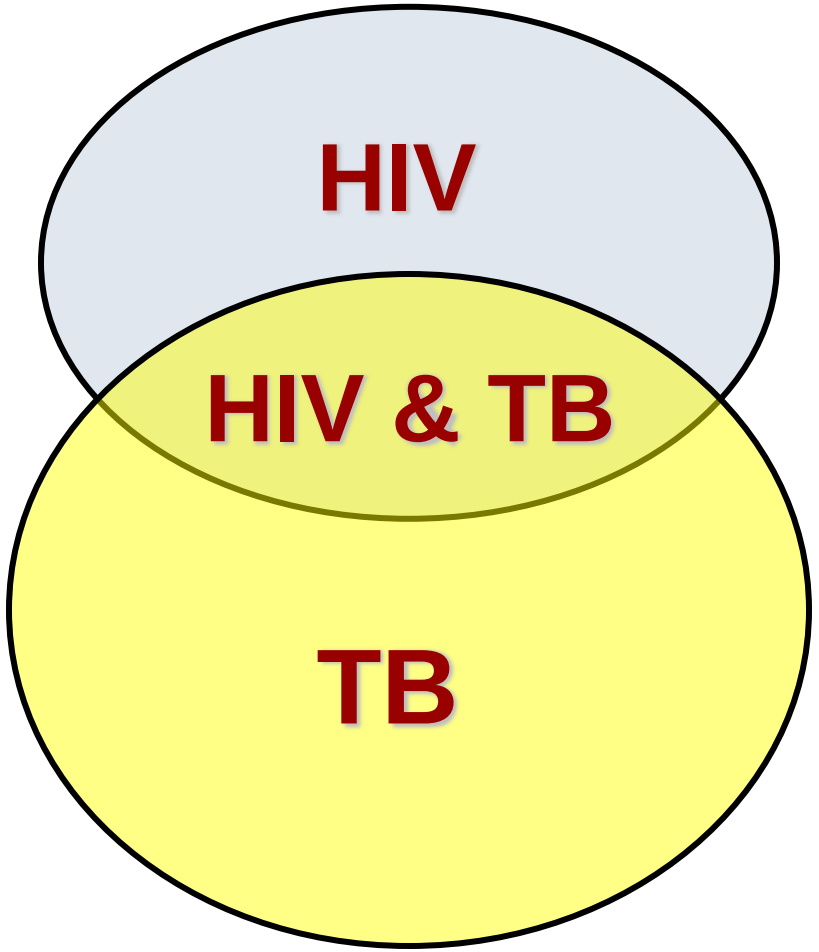
Senior Director, Medical and Scientific Affairs, QIAGEN

Clinician, San Francisco TB Control

TB and HIV: A global problem

~1/3 of the world population has LTBI

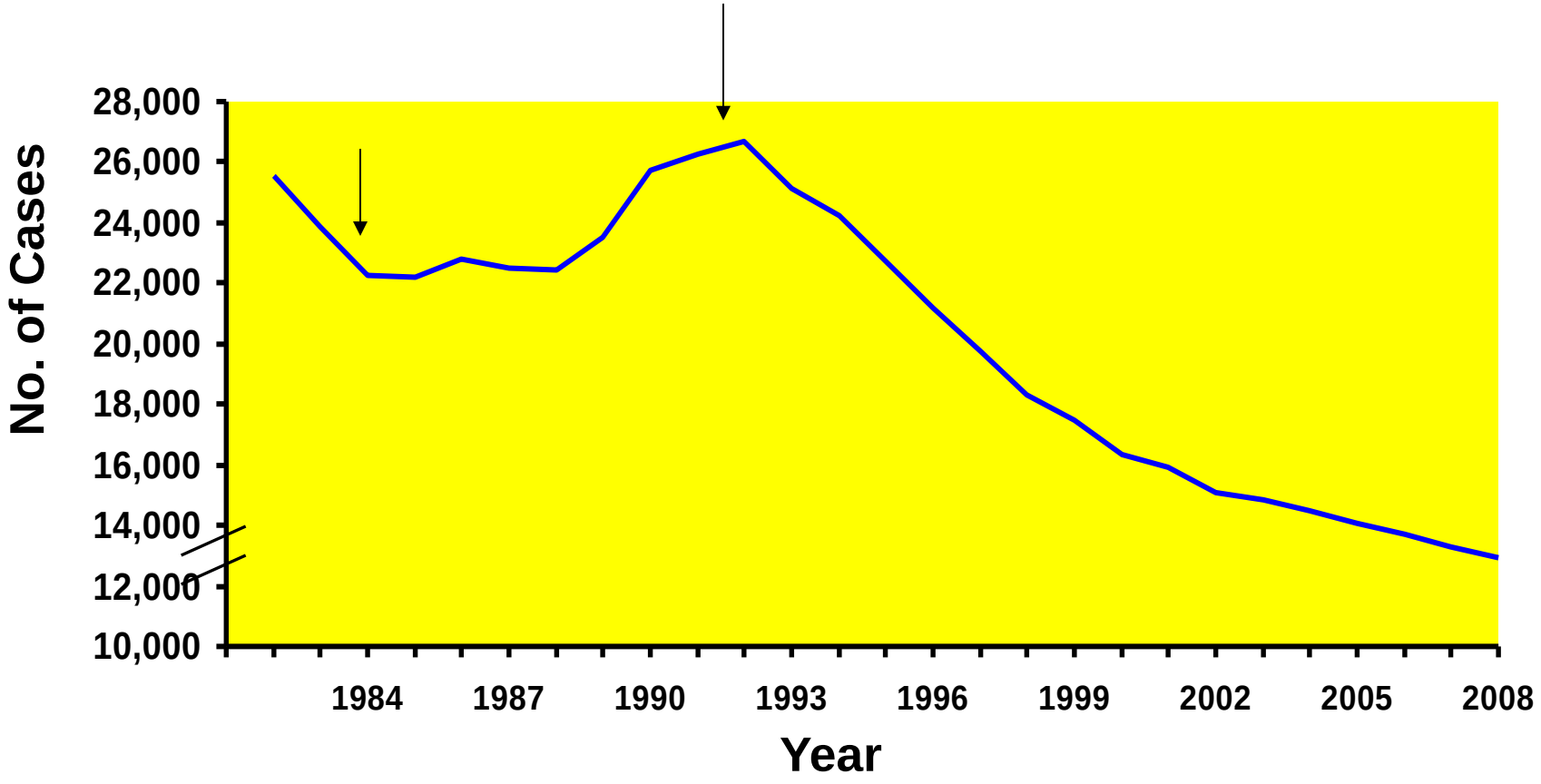
- ~ 1/3 of PLWHA are co-infected with TB
- TB is the leading cause of death in PLWHA, 26% of AIDS related deaths



US example:

HIV changed the epidemiology of TB

Reported TB Cases 1982–2008



Bidirectional Effects: TB on HIV Progression

- TB increases HIV progression
- Dually infected persons often have very high HIV viral loads
- Immuno-suppression progresses more quickly, and survival may be shorter despite successful treatment of TB
- Persons who were co-infected have a shorter survival period than persons with HIV who never had TB disease

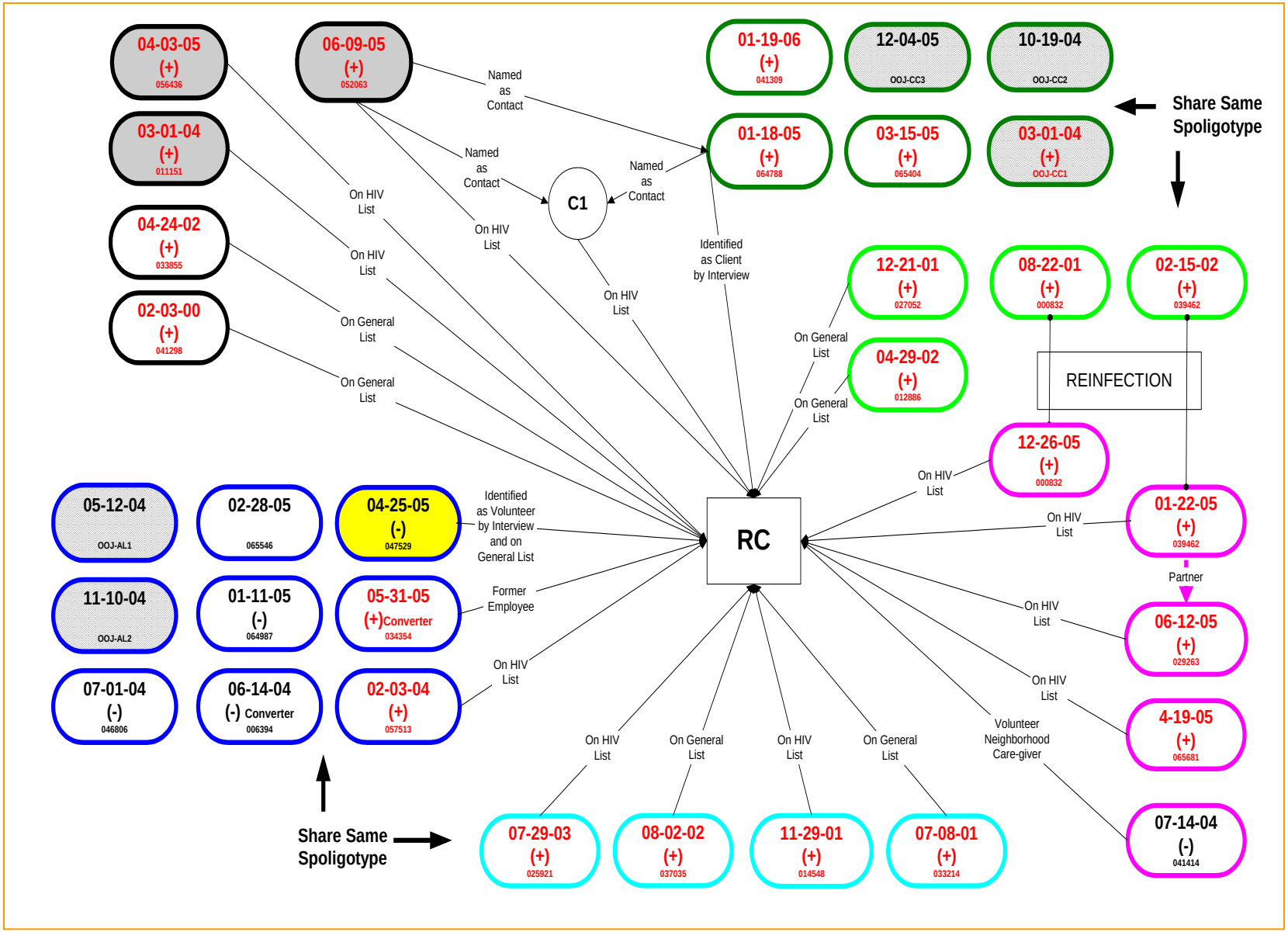
Bidirectional Effects: HIV on TB Progression (2)

HIV+ person with LTBI has a 5-10% annual risk of developing active TB (versus 10% lifetime risk among HIV-negative persons)

- greater risk of reactivation of latent TB infection (LTBI)
- more likely to progress to TB disease following infection
- higher risk of TB re-infection, relapse, and death

Source: TB/HIV: A Clinical Manual. Second Edition. WHO, 2004

HIV fuels TB transmission in San Francisco



HIV-TB are sentinels for recent transmission

Karonga District, Malawi: 1995-2003

HIV prevalence in adults: 13%

DNA fingerprinting of 83% culture+ cases

682/948 (72%) *M. tb* strains in clusters

Assuming 1 case per cluster as index:

- 60% of cases due to recent transmission

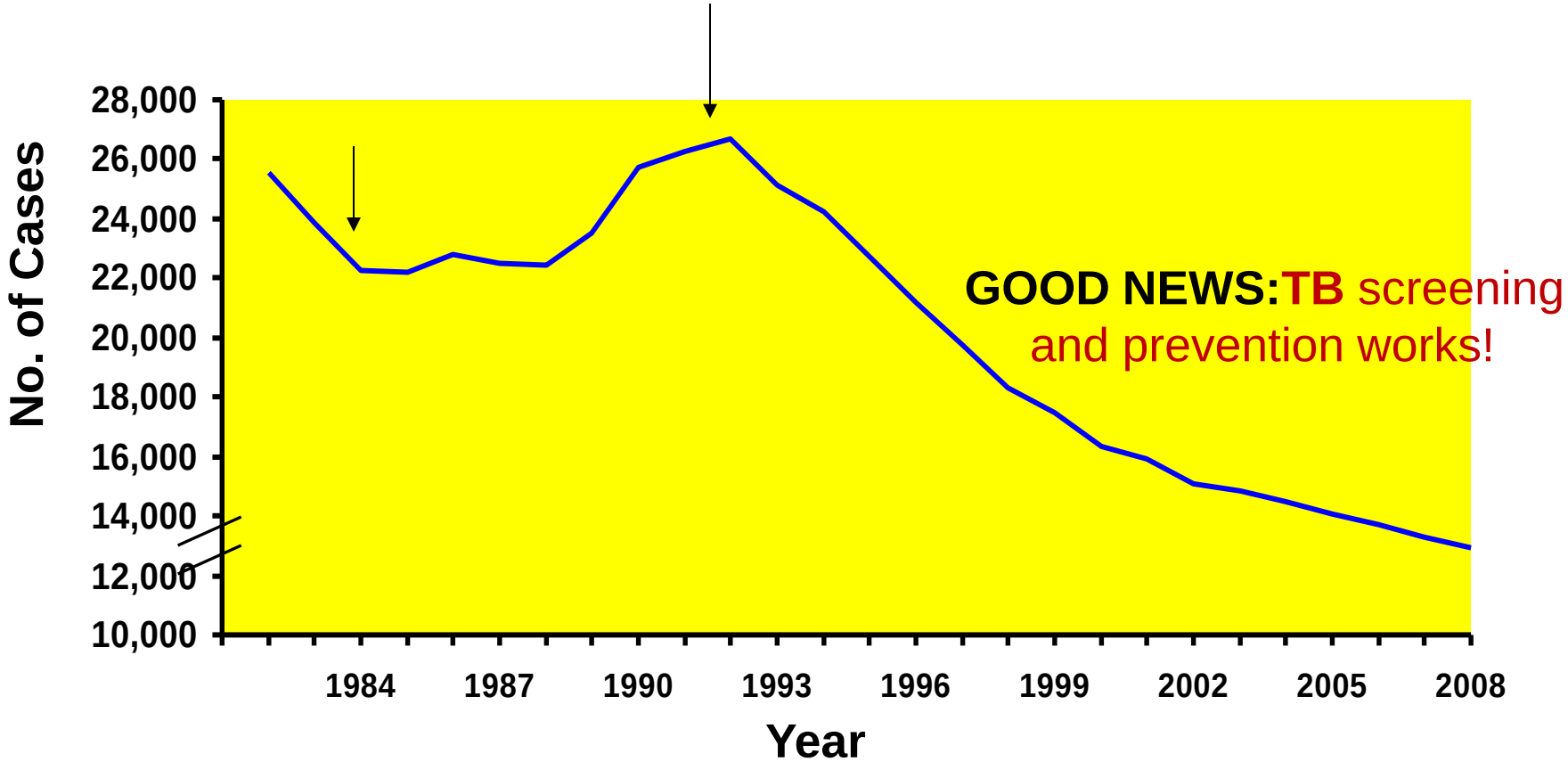
Stresses importance of case finding, treatment

Glynn JR. JID 2005;192:480-7.

US example:

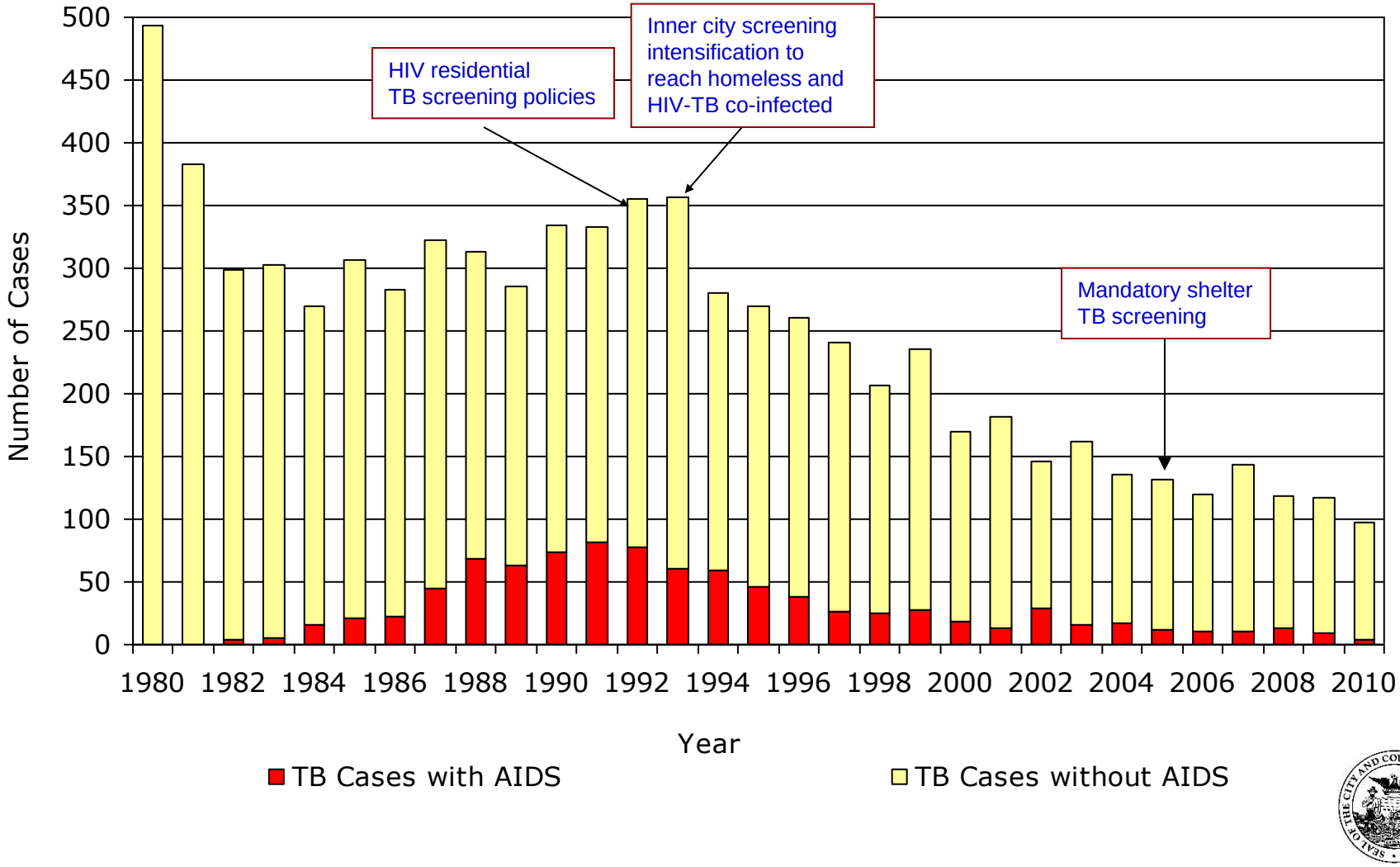
HIV changed the epidemiology of TB

Reported TB Cases 1982–2008



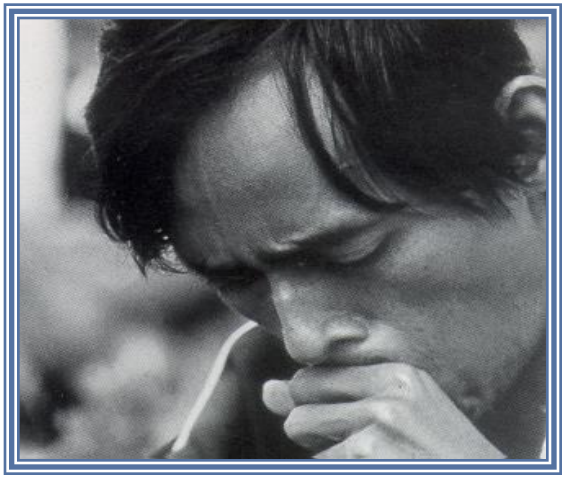
San Francisco TB Case Counts: 1980-2010

Active case finding and prevention works!



Bad News:

No TB or HIV vaccine = No option other than to preventive treatment and early case finding . . . . .



Serial TB screening, ART and LTBI treatment for all HIV-Infected Persons is a national US recommendation

- Preventing TB saves lives
- Prevents amplified transmission in populations that have high rates of HIV
- Is an important matter of public health and maintaining TB control

Rationale for LTBI screening and treatment in HIV infection

- TST+ HIV negative: 5-10% lifetime risk of developing TB (Horsburgh 2004)
- TST+ HIV Infected: 3-10% risk *per year* of developing active TB (Selwyn 1989,1992, Whalen 1997)
- Estimated lifetime risk of active TB in HIV-infected 20% (Horsburgh 2004)

TB Risk in HIV-Infected Persons

HAART Era

TB prevention: A rationale for HAART

TB rate per 100,000 person-years

	No ART	ART	HAART
U.S.	720	470(40% ↓)	190 (80% ↓)
S. Africa	9,700		2,400 (81% ↓)

Jones JL. Int J Tuberc Lung Dis 2000;4:1026—AASD

Badri M. Lancet 2002;359:2059-64.

INH works to prevent TB in HIV

Exposure category	Person-Years	TB cases	IR (per 100 PYs)	IRR
Naïve	3,865	155	4.01 (3.40-4.69)	1.0
ART only	11,627	221	1.90 (1.66-2.17)	0.48 (0.39-0.59)
IPT only	395	5	1.27 (0.41-2.95)	0.32 (0.10-0.76)
Both	1,253	10	0.80 (0.38-1.47)	0.20 (0.09-0.91)
TOTAL	17,142	391	2.28 (2.06-2.52)	

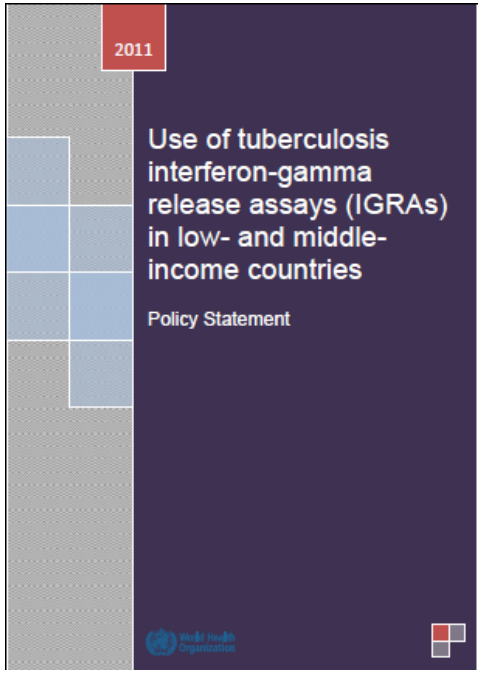
ART prevents TB as well

(CIPRA HT001)

Golub, AIDS, 2007

WHO LTBI guidelines for low and middle income countries

- Advises preventive treatment without testing:
  - Asymptomatic HIV infected
  - Household contacts under age 5

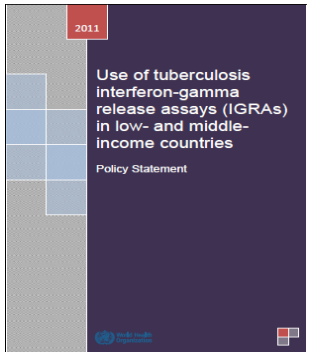


2011 WHO IGRA Policy statement still stands for low and middle income countries public health programs

→ IGRAs NO!

WHO_IGRA_factsheet_oct2011

2011 WHO IGRA recommendations for low and middle-income countries

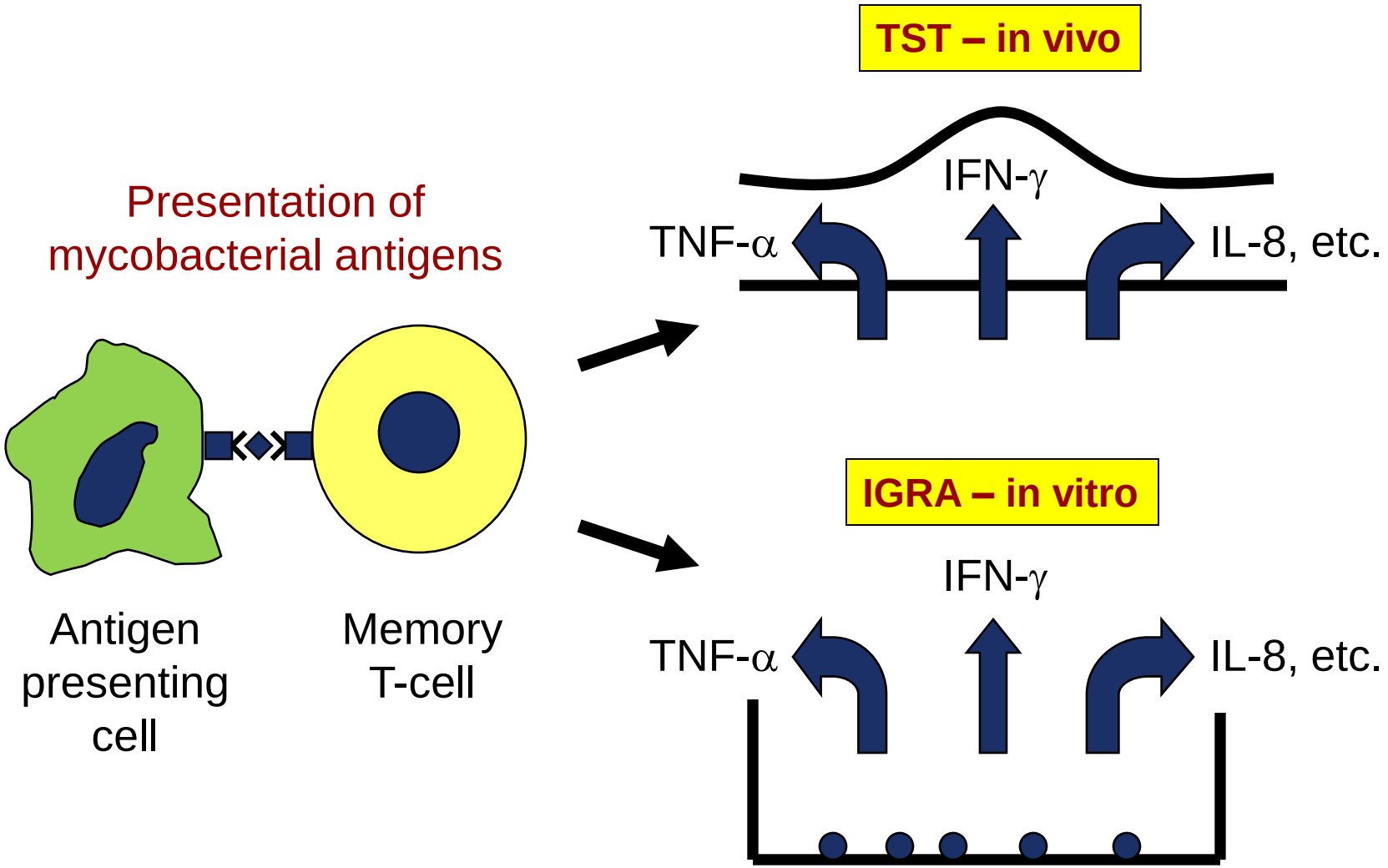


Overall conclusions

- **Insufficient data and low quality evidence** on IGRA performance, particularly in high burden setting
- IGRAs and the TST **cannot accurately predict the risk** of infected individuals developing active TB disease
- IGRAs are **more costly and technically complex** to do than the TST.
- Given comparable performance but increased cost, replacing the TST by IGRAs as a public health intervention in resource-constrained settings is not recommended.

WHO_IGRA_factsheet_oct2011

Can HIV cause test problems? Yes, TST and IGRAs rely on immunocompetence



Andersen P, et al. Lancet 2000;356:1099

2017: Where are we today on IGRA evidence and experience

- Sufficient and high quality evidence on IGRA performance in high burden settings- HIV and children
- Prediction of disease: QFT superior to TST with new evidence in S. African infants
- IGRA blood testing more patient centered than TST, less subjective and programmatically efficient
- COST: savings on false positive CXR, medical evaluation and treatment, and side effects from false-positive TST
- Given the better performance of IGRAs, it can replace the TST, and is preferred for BCG-vaccinated adults and children >5 yrs old (US, Canada, Western Europe, Australia, Japan, Taiwan, Singapore, Korea, etc. (list is growing)

New ATS-CDC-IDSA guidelines: December 2016

Guidelines define what TST and IGRA results mean in the context of risk and have recommendations on retesting

- **Low to intermediate risk of progression (IGRA testing preferred)**
  - No recommendation for repeat testing
  - Consider INFECTED if single test is positive
- **Unlikely to be infected (IGRA testing preferred)**
  - Consider repeat or dual testing to maximize SPECITFICITY]
  - A negative results from either test would be considered NEGATIVE
  - Considered infected only if BOTH tests are positive
- **High risk of progression (IGRA or TST without preference)**
  - Consider dual testing to maximize SENSITIVITY
  - A positive results from either test would be considered POSITIVE

Optimizing the detection of recent TB infection in children in a high-burden HIV-TB setting

Mandalakas A et al, AJRCCM, Vol 191: 7 2015

- Prospective S. African community-based study 3-way head to head assay comparison using robust contact scoring system
- Total cohort size: 1343 (age 6 mo - <15 years)
  - 836 contacts
  - 507 no exposure
  - 299 (22%) HIV positive (18% with TB exposure)

KEY FINDING: 8% of contacts developed active TB within 3 months

	TST	QFT	T-Spot	TST and Tspot	TST and QFT	QFT and Tspot
Initial positive (ALL)	39.9% 529/1325	41.2% 520/1261	30.5% 302/991			
Test Conversion	11%	9.1%	10.6%			
Test reversion	14.8%	8.3%	10.6%			
Sensitivity: TB cases developing within 3 mos	75%	79%	71%	83%	84%	88%

Optimizing the detection of recent infection in childern in a high-burden HIV-TB setting

Mandalakas A et al, AJRCCM , Vol 191: 7 2015

KEY FINDINGS continued:

- All assay results correlated to contact score, however IGRAs correlated better than TST (p=0.0011)
- NOT perfect: All tests negatively impacted by HIV infection and chronic malnutrition
- 8% contacts had discordant IGRA+/TST- results (magnitude of results argues against false positive results)
  - Discordant pattern more common with QFT, more TB exposure and HIV- status
  - Suggests that IGRAs to confirm TST may under detect LTBI
- IGRAs more strongly associated with contact score in younger children (age<2 yrs) than TST
- No difference between IGRA performance (*Elispot performed with blood <8hrs old)
- Children younger than age 5 have sufficient immunologic capacity

Pregnancy Differentially Impacts Performance of Latent Tuberculosis Diagnostics in a High-Burden Setting

Mathad J et al, PLOS, March 2014 | Volume 9 | Issue 3

Design: Cross-sectional study of 401HIV-negative pregnant women tested with TST and QFT-GIT antepartum (154), delivery (148) and postpartum (99). 60 followed longitudinally

RESULTS:

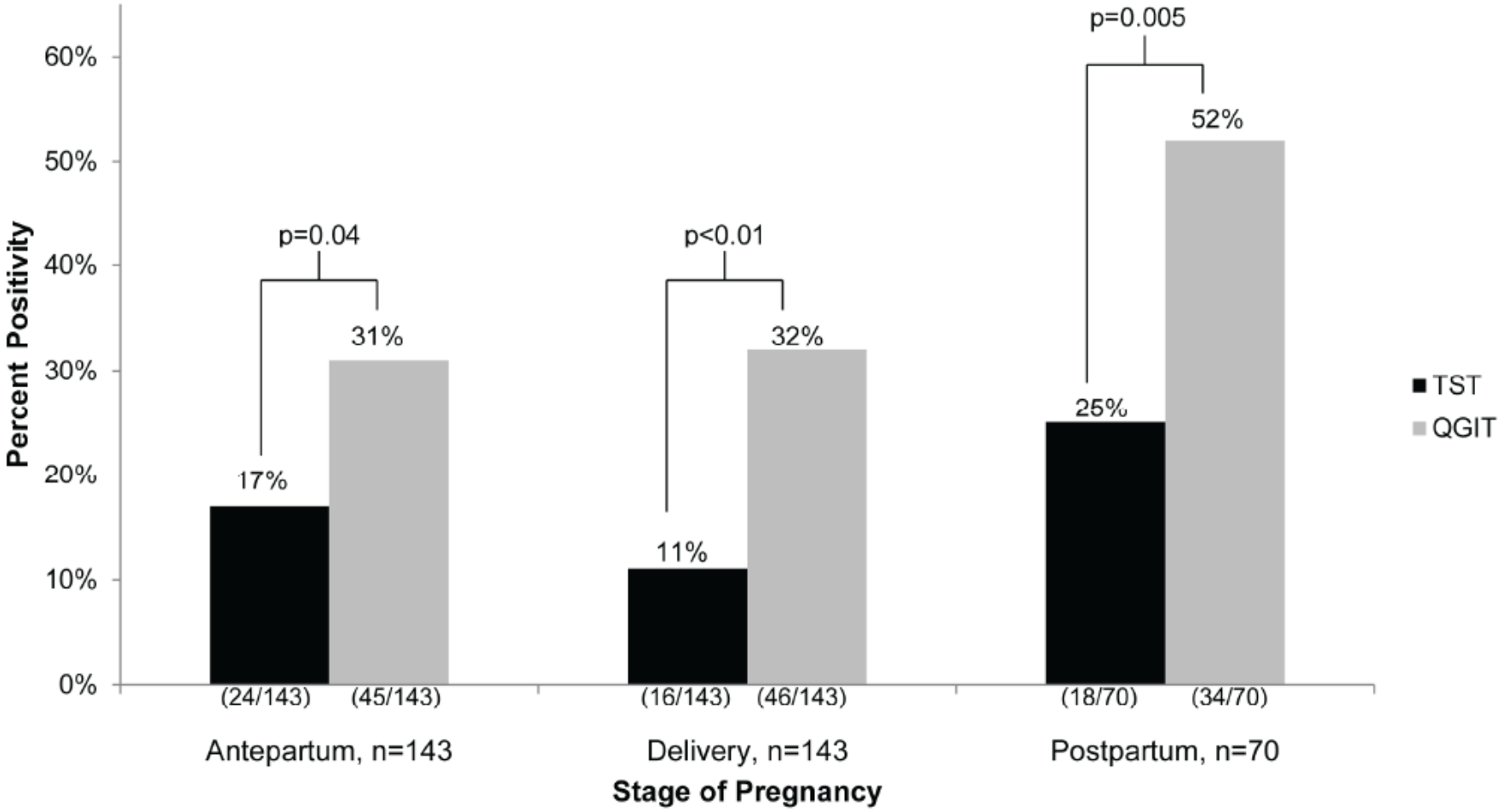
- More positive by QFT: 150 (37%) QFT+ vs. 259 (14%) TST+ (p=0.005)
- Agreement (n=356):
  - Positives: 46 (13%) were concordant positive
  - 91 (25%) were discordant, 79 (22% IGRA+/TST-)
- Unlike TST, QFT percent positivity remained stable between antepartum QFT quantitative values lower at delivery
- Postpartum, both QFT and TST had significantly increased positives (QGIT 31% vs 32% vs 52%, p = 0.01; TST 17% vs 11% vs 25%, P=0.005)

CONCLUSIONS :

- Timing and choice of LTBI test during pregnancy impact results
- QGIT was more stable and more closely approximated the LTBI prevalence in India.
- Pregnancy stage clearly affects both tests

Pregnancy Differentially Impacts Performance of Latent Tuberculosis Diagnostics in a High-Burden Setting

Mathad J et al, PLOS, March 2014 | Volume 9 | Issue 3



Quantitative IFN-γ,IL-2 response and latent tuberculosis test discordance in HIV-infected pregnant women

Mathad J et al, AJRCCM online.Published on 14-January-2016, 10.1164/rccm.201508-1595OC

Design: Cross-sectional study of 252 HIV-infected pregnant women tested with TST and QFT-GIT during their 2nd/3rd trimester and at delivery. 50 studied longitudinally

RESULTS:

- More positive by QFT: 71 (28%) QFT+ vs. 27 (10%) TST+ ($p<0.005$)
- Agreement: 75% (kappa = 0.25 fair)
  - 20% had IGRA+/TST- discordance during pregnancy and delivery
- Association with known TB contact: QFT > TST (OR 3.6, CI 1.2-11.1, p=0.02)

Substudy: IGRA+/TST- women produced significantly less IFN-γ and IL-2 than IGRA+/TST+

- IFN-γ (1.85 vs 3.48 IU/mL, p=0.02)
- IL-2 (46.17 vs 84.03 pg/mL, p=0.01)

TB cases: 5/252 (2%) developed TB postpartum within one year

- All positive by QFT 100% sensitivity, PPV 7%
- 3 had IGRA+/TST- results during pregnancy

CONCLUSIONS: Choice of assay affects results and IGRA+/TST- discordance may represent higher risk group for active TB postpartum

What we know…IGRAs in HIV (preferred by US and European HIV Clinics)

- **NOT PERFECT**: QFT-GIT and TSpot are less sensitive in HIV-infected patients vs HIV-uninfected (1, 2, 3) – false negatives will occur
- **IGRAs cannot rule out active TB**

- **BUT….**
  - IGRAs are **more sensitive than the TST** in HIV-infected patients (1, 2)
  - IGRAs contain **internal positive controls** which assist discrimination between true and false negative TB results (1)
  - IGRAs are **not affected by BCG** vaccination (4)
  - **Single visit** of IGRAs overcomes the TST issue of poor return rates (1, 5) –PATIENT CENTERED (can be done with routine VL testing)

1. Hoffmann et al (2010) *European Infectious Disease* 56(3):230-238
2. Ramos et al (2012) *BMC Infectious Diseases* 12:169
3. Aabye et al (2009) *PlOs One* 4(1) e4220
4. Wolf et al (2013) J *Infect* 66(4):376-80
5. Cheallaigh et al (2013) *PlOs One* 8(1) e53330

Performance of QFT vs. TST vs. TSpot in HIV-infected patients

Cheallaigh CN et al., 2013

- Comparison of IGRAs and TST in low TB burden setting
- 256 HIV+ adults enrolled – 67% low burden (Dublin, Ireland)
  - CD4+ T-cell counts and HIV viral loads recorded

Test Method	N	Positive	Negative	Indeterminate/ Invalid/ Unavailable
TST	93	9 (9.7%)	84 (90.3%	43% did not return
QFT	256	46 (18.0%)	204 (79.7%)	6 (2.3%)
T-SPOT.TB	256	28 (10.9%)	201 (78.5%)	27 (10.5%)

Low TST return rates are common among HIV patients

Cheallaigh CN et al. IGRA for the diagnosis of LTBI in HIV-infected individuals in low TB burden country. PLoS One. 2013;8(1):e53330.

HIV: European 6-yr follow-up study

ERJ Express. Letter Published on May 2, 2014

Christian Soborg, Morten Ruhwald, Peter H. Andersen and Pernille Ravn

6-year follow-up of 522 HIV-positive individuals screened for Mycobacterium tuberculosis infection in Denmark

- CD4 >200 cells/uL = 90%
- On ARV = 80%

PPV of 7% (two out of 28) and a NPV of 100% (478 out of 478) for developing active TB using the QFT-IT

Number needed to treat with INH to avoid one TB case =14

Number needed to test to identify one QFT-IT-positive individual =18.6

QFT-IT: safe test for ruling out risk of TB among immunocompetent HIV-positive

	QFT N=522
Positive (overall)	5% (28)
Negative (overall)	91% (478)
Indeterminate (overall)	4% (16)
Non-Caucasians positive rate	13.3% (14/105)
Caucasians positive rate	3.5% (14/401)

Cost effectiveness of IGRAs

IGRA was cost effective compared to TST

*Linas B, et al. Am J Respir Crit Care Med 2011; 184(**5**):590-601*

Evaluated CDC-defined risk-groups referenced in current U.S. LTBI screening guidelines

- Contacts
- HIV
- Immigrants – regardless of time living in the US
- Base case cost used: IGRA - $52 and TST- $22

QFT-Plus

- QFT-Plus developed to improve sensitivity without loss of specificity
- Novel CD8 antigens
  - showing excellent performance in registration studies and early independent studies.
  - early promise as indicators of intracellular bacillary load in active TB and response to treatment
- Ongoing independent studies involving over 20,000 patients in all regions of the world (HIV, contacts, disease progression, pregnant women, HCWs, pediatrics)….STAY TUNED!

QuantiFERON®-TB Gold Plus

The latest evolution of QFT – will replace QFT

1st generation QuantiFERON®-TB	2nd generation QuantiFERON®-TB Gold (liquid antigen)	3rd generation QuantiFERON®-TB Gold (QFT® in tube)	4th generation **QuantiFERON®-TB Gold Plus** (QFT®-Plus)
2001 – FDA-approved	**2004 – FDA-approved**	**2007 – FDA-approved**	**Q4 2014 CE-IVD / 2016 FDA submission**
Measured the cell-mediated immune response to the same tuberculin purified protein derivative (PPD) used for the TST (*M. avium*)	Used antigens specific for *M. tuberculosis* complex organisms	Blood collection tubes as incubation vessels	Increased sensitivity, improved performance in immune-compromised patients Improved handling and performance, extended patent protection.
	 	 	

New peptide antigens

	QuantiFERON Gold In tube	QFT-Plus
Peptide length	ESAT-6, CFP-10 and TB7.7 polypeptides • MHC-class II peptides (CD4)	ESAT-6 and CFP-10 polypeptides • MHC-class II peptides (CD4) • **MHC class I peptides (CD8)**
Stimulated cell population	Primarily $CD4^+$ T helper lymphocytes	CD4+ T helper lymphocytes **CD8+ cytotoxic T lymphocytes**
Targeted product performance improvement		**Potential Increased sensitivity** **Application in CD4-low populations** • HIV+ subjects **Additional clinical information** • Research tool

First Independent Evaluation QFT-PLUS

EUROPEAN RESPIRATORY *journal*
OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

First independent evaluation of QuantiFERON-TB Plus performance

L. Barcellini [1], E. Borroni[1], J. Brown[2], E. Brunetti[3], L. Codecasa[4], F. Cugnata[5], P. Dal Monte[6], C. Di Serio[5], D. Goletti[7], G. Lombardi[6], M. Lipman[2], P.M.V. Rancoita[5], M. Tadolini[8] and D.M. Cirillo[1]

Study design: Prospective multi-center study, 6 sites Italy and UK (Nov 2014 to Sept 2015)

RESULTS

Sensitivity: 88% (102/116), 100% in subjects co-infected with HIV/TB (n=4)

Specificity: 97% (103/106)

Indeterminate: 1.3% (3/225) overall

- All three indeterminate were from active TB cohort (2.5% (3/119)

Correlation with QFT (in a sub-cohort of 73 where QFT results were available): 94%

Barcellini et al., 2016 ERJ: Author's conclusions

SENSITIVITY ADVANTAGE

- Sensitivity (88%) higher than culture-confirmed active TB patients in the most recent meta-analysis for QFT, *"suggesting that the QFT-Plus does indeed offer improved sensitivity."*

CD8 POTENTIAL

- Difference between TB2 and TB1 was higher in smear-positive compared to smear-negative patients (significant difference). *"Considering the difference between the two antigen tubes as surrogate marker of the magnitude of CD8+ T-cell responses, the last finding is in agreement with what observed in flow-cytometry studies."*

ADVANTAGE IN IMMUNOSUPPRESSION

- "*The increased IFN-γ release by combined stimulation of CD4+ and CD8+ T-cells observed in the newly added antigen tube (TB2) might be advantageous for improving the assay's accuracy in patients with low CD4+ T-cell counts."*

Serial TB screening, ART and LTBI treatment for all HIV-Infected Persons is key in controlling TB

- Saves lives
- Prevents amplified transmission in populations that have high rates of HIV
- TB-HIV prevention is a matter of public health and maintaining TB control