

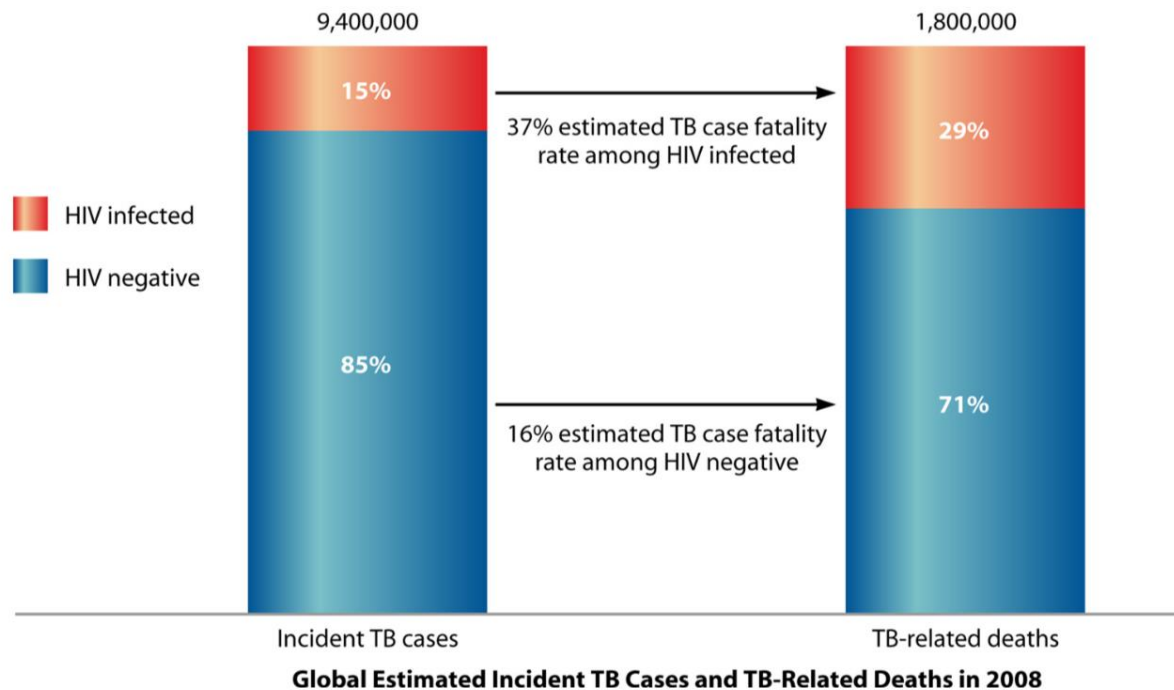
# Modeling the diagnosis of HIV-associated TB: key research questions and data gaps

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# Diagnosis of TB in people living with HIV

- 13% of TB patients with an HIV test result are positive (~500,000 / year)
- Only an estimated 46% of HIV-TB coinfections are notified



WHO Global Tuberculosis Report 2017  
Kwan CK *et al. Clin micro reviews* 2011;**24**:351–76

# Diagnosis of TB in people living with HIV

- Spectrum of immunocompromise
- Risk increases early
- As CD4 counts drop, sensitivity of most diagnostics does too
- Less cavitary disease -> lower sputum bacillary load

**Table 2. Incidence of tuberculosis (TB), by time since HIV seroconversion.**

Category	Pyar	No. of TB cases	Incidence, cases/100 pyar (95% CI)	Rate Ratio (95% CI)			
				Unadjusted		Adjusted <sup>a</sup>	
				Value	<i>P</i> <sub>trend</sub>	Value	<i>P</i> <sub>trend</sub>
HIV-negative miners	36,020	289	0.80 (0.71–0.90)	1		1	
HIV-positive miners, time since HIV seroconversion <sup>b</sup>					.001		.09
<1 year	1849	30	1.62 (1.13–2.32)	2.02 (1.39–2.94)		2.11 (1.45–3.09)	
1–1.9 years	1449	29	2.00 (1.39–2.88)	2.50 (1.70–3.66)		2.25 (1.53–3.31)	
2–2.9 years	1024	37	3.61 (2.62–4.99)	4.50 (3.20–6.34)		3.47 (2.44–4.93)	
3–3.9 years	692	24	3.47 (2.32–5.17)	4.32 (2.85–6.55)		2.94 (1.92–4.51)	
4–7 years	567	18	3.17 (2.00–5.04)	3.96 (2.46–6.37)		2.55 (1.57–4.16)	

**NOTE.** CI, confidence interval; *P*<sub>trend</sub>, *P* for trend of time since HIV seroconversion, calculated within the HIV-positive group; pyar, person-years at risk.

<sup>a</sup> Adjusted for age and calendar period.

<sup>b</sup> Only the 1962 HIV-positive miners with a seroconversion interval of ≤2 years are included.

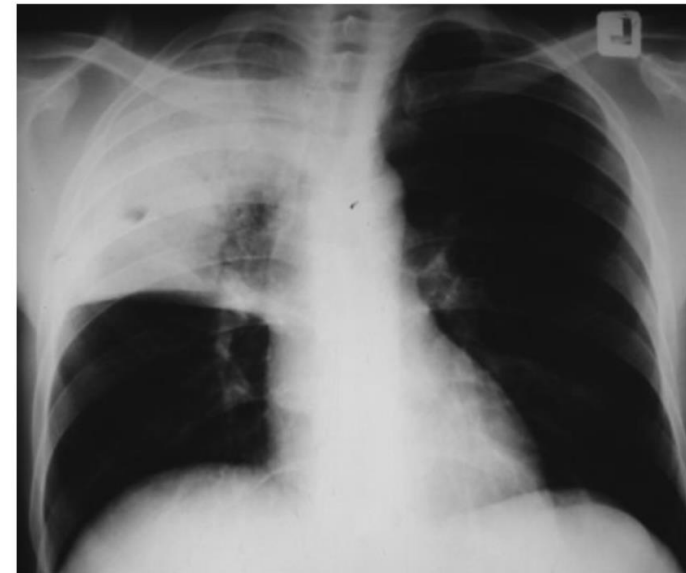
Sonnenberg P et al. J Infect Dis 2005;191:150–8

# CXR Screening

- Study of patients presenting with symptoms of tuberculosis but negative sputum smears
- 54% HIV positive, median CD4 135 cells/ $\mu$ L, not on ART
- CXR read by 2 senior pulmonologists
- Only 14% specificity

**Table 2. Culture Results Versus Chest Radiograph Interpretation**

Radiograph Interpretation	Sputum Culture Positive	Sputum Culture Negative	Total
Radiograph suggestive of tuberculosis	112	205	317
Radiograph not suggestive of tuberculosis	9	34	43
Total	121	239	360



(a)

Cudahy PGT *et al. Open Forum Infect Dis* 2017;**4**  
Kisembo HN *et al. BJR* 2012;**85**:e130–9

# Diagnostic modalities 1 - pulmonary

Diagnostic Tool	Sensitivity	Sensitivity in HIV	Specificity	Specificity in HIV	Comments
Symptom Screening	24%	51-89%	96%	28-70%	
Chest X-ray	87-96%	93-97%	46-89%	14-67%	Low specificity in smear negative disease
Sputum microscopy	65%	20-60%	97%	95%	
Xpert MTB/Rif	89%	79%	99%	98%	
Xpert Ultra	88%	90%	96%	?	63% sensitivity in smear-neg disease
LPA	85%	?	98%	?	

van't Hoog AH et al. WHO 2013  
 Hamada Y et al. Lancet HIV 2018  
 den Boon S et al. IJTLID 2006;**10**:876–82.  
 Cudahy PGT et al. Open Forum Infect Dis 2017;**4**  
 Davis JL et al. Lancet ID 2013;**13**:147–54  
 Kwan CK et al. Clin micro reviews 2011;**24**:351–76

Steingart KR et al. Cochrane Database Syst Rev 2014  
 Dorman SE et al. Lancet ID 2018;**18**:76–84  
 Nathavitharana RR et al. Euro Resp Journal 2017;**49**

# Disseminated TB in HIV

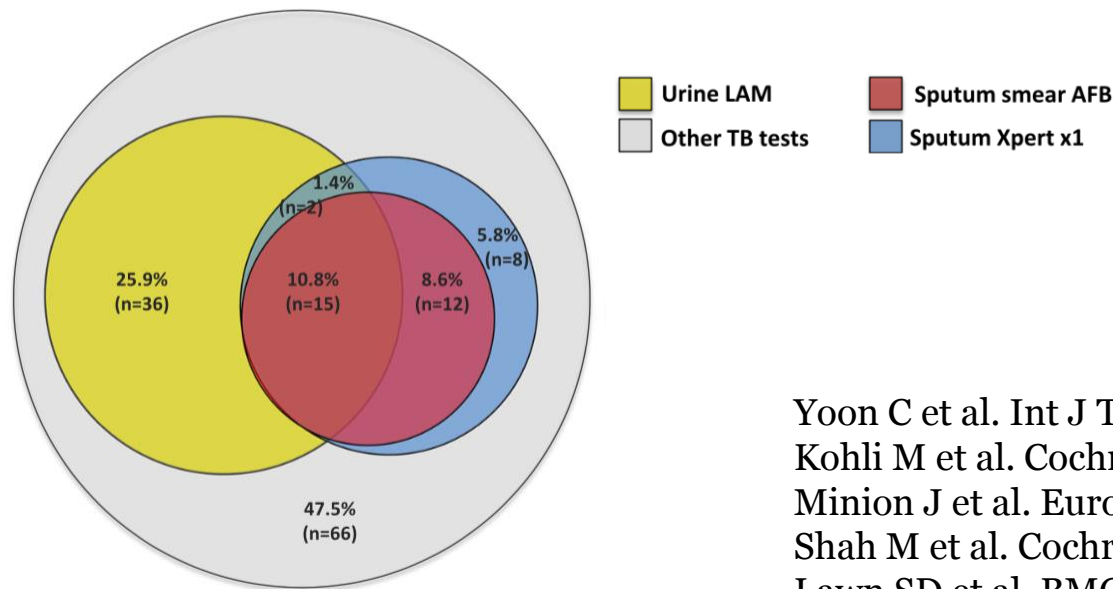
## **Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis**

**Rishi K. Gupta<sup>a</sup>, Sebastian B. Lucas<sup>b</sup>, Katherine L. Fielding<sup>c</sup> and  
Stephen D. Lawn<sup>d,e</sup>**

- Systematic review of >3200 autopsies of people with HIV. TB prevalence was 39.7% in adults
- With increasing immunosuppression, increasing dissemination
- Lungs 85%
- Spleen 83%
- Liver 79%
- Lymph nodes 75%
- CNS 20%

# Diagnostic modalities 2 - disseminated

Diagnostic Tool	Sensitivity	Sensitivity in HIV	Specificity	Specificity in HIV	Comments
Serum CRP	93%	93%	60%	61%	
Urine Xpert	33-100%	?	98%	?	
Urine Ultra	?	?	?	?	
Urine LAM	14%	29-63%	97%	92%	



Yoon C et al. Int J Tuberc Lung Dis 2017;**21**:1013–9  
 Kohli M et al. Cochrane Database Syst Rev 2018  
 Minion J et al. Euro Resp Journal 2011;**38**:1398–405  
 Shah M et al. Cochrane Database Syst Rev 2016  
 Lawn SD et al. BMC Medicine 2017;**15**:67

# Subclinical disease

## **SOA-395-13 Subclinical tuberculosis among HIV positive adults in South Africa: a cohort study**

K Bajema,<sup>1</sup> E Losina<sup>2,3</sup>, S Coleman,<sup>3</sup> J Giddy,<sup>4</sup> D Ross,<sup>5</sup>  
K Freedberg<sup>3,6</sup>, I Bassett,<sup>6</sup> P Drain<sup>1,7,8</sup> <sup>1</sup>University

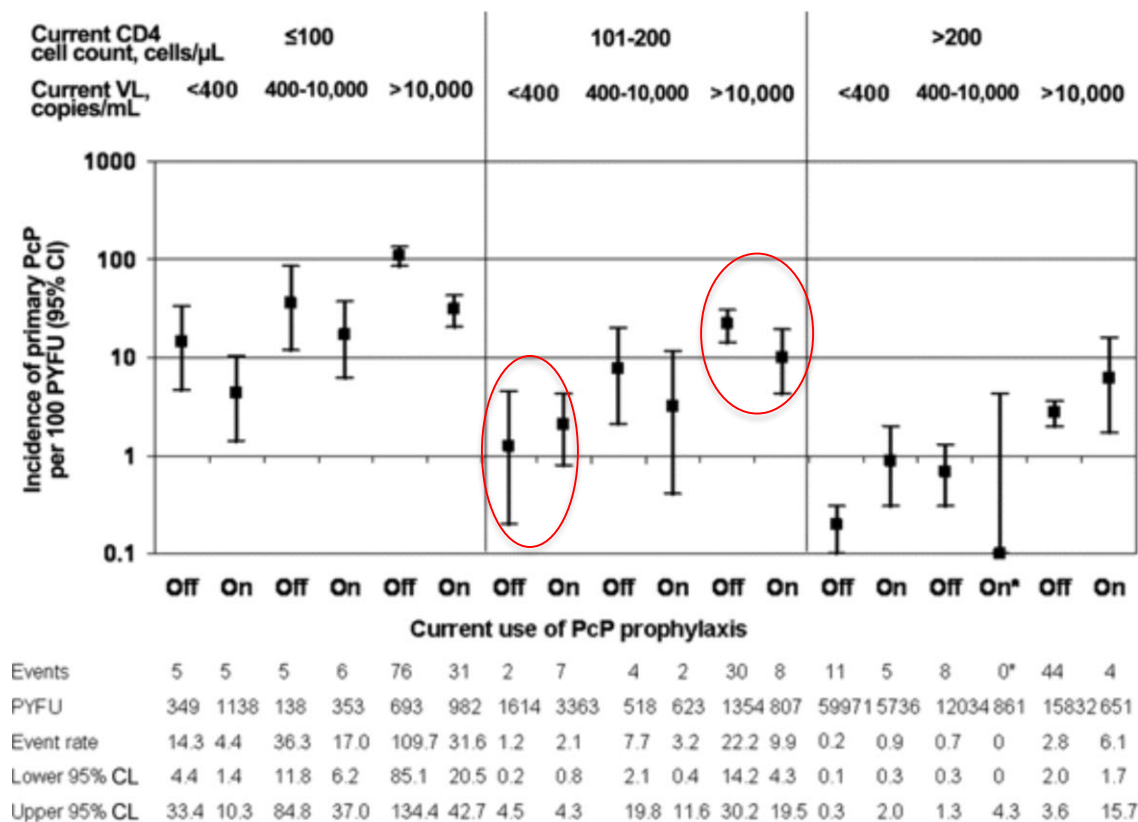
- 670 untreated HIV positive participants screened in Durban
- 16% (n=106) active (symptoms + culture) TB, with 33% urine LAM positive, median CD4 138
- 5% (n=34) subclinical (asymptomatic + culture), with 26% urine LAM positive, median CD4 200
- 41% of subclinical individuals were smear positive vs 22% with active TB,  $P=0.04$
- How does subclinical HIV/TB contribute to transmission?

Bajema K. et al., abstr SOA-395-13. 48th Union World Conf Lung Health 2017



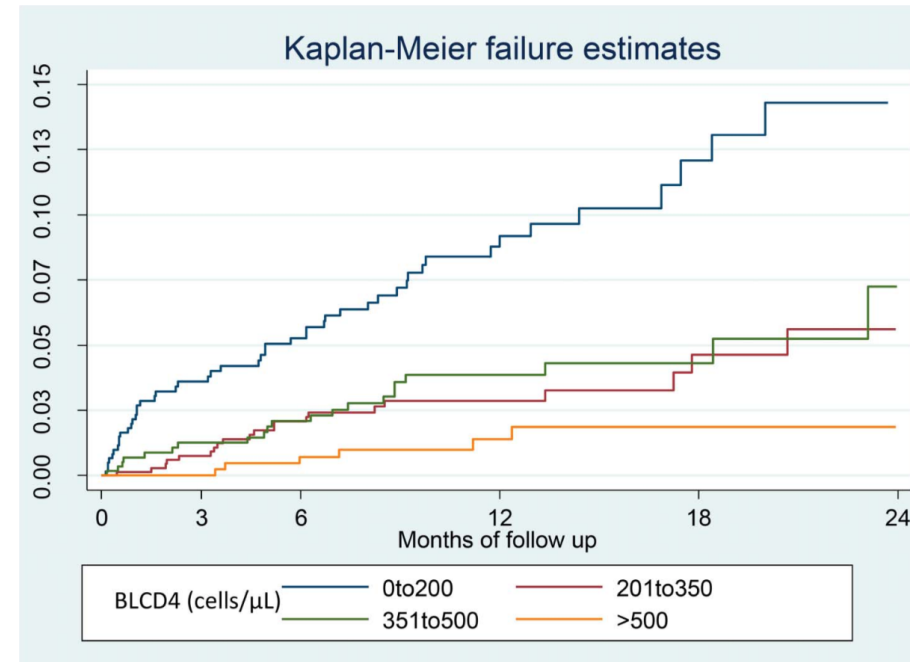
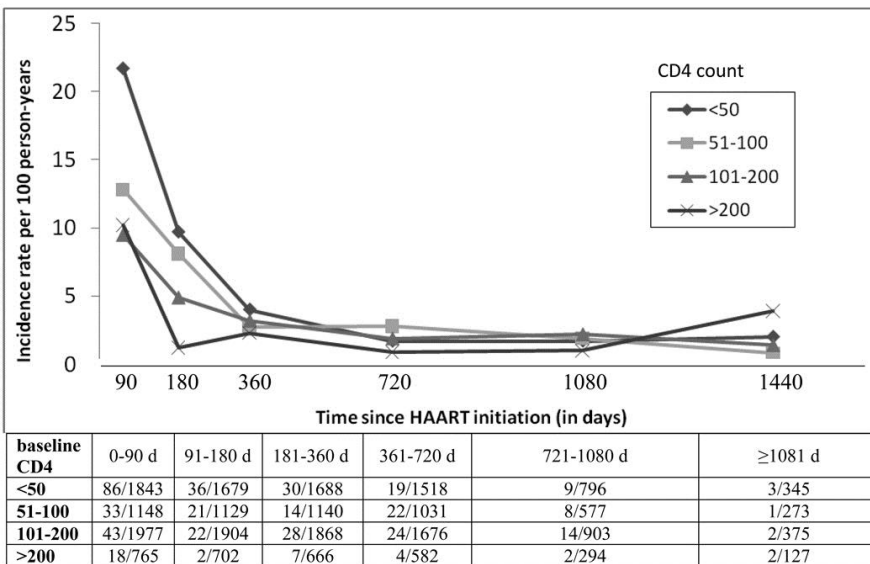
# ART effects?

- Effect of ART on reversing immunosuppression



COHERE, et al. *Clin Infect Dis* 2010;51:611–9

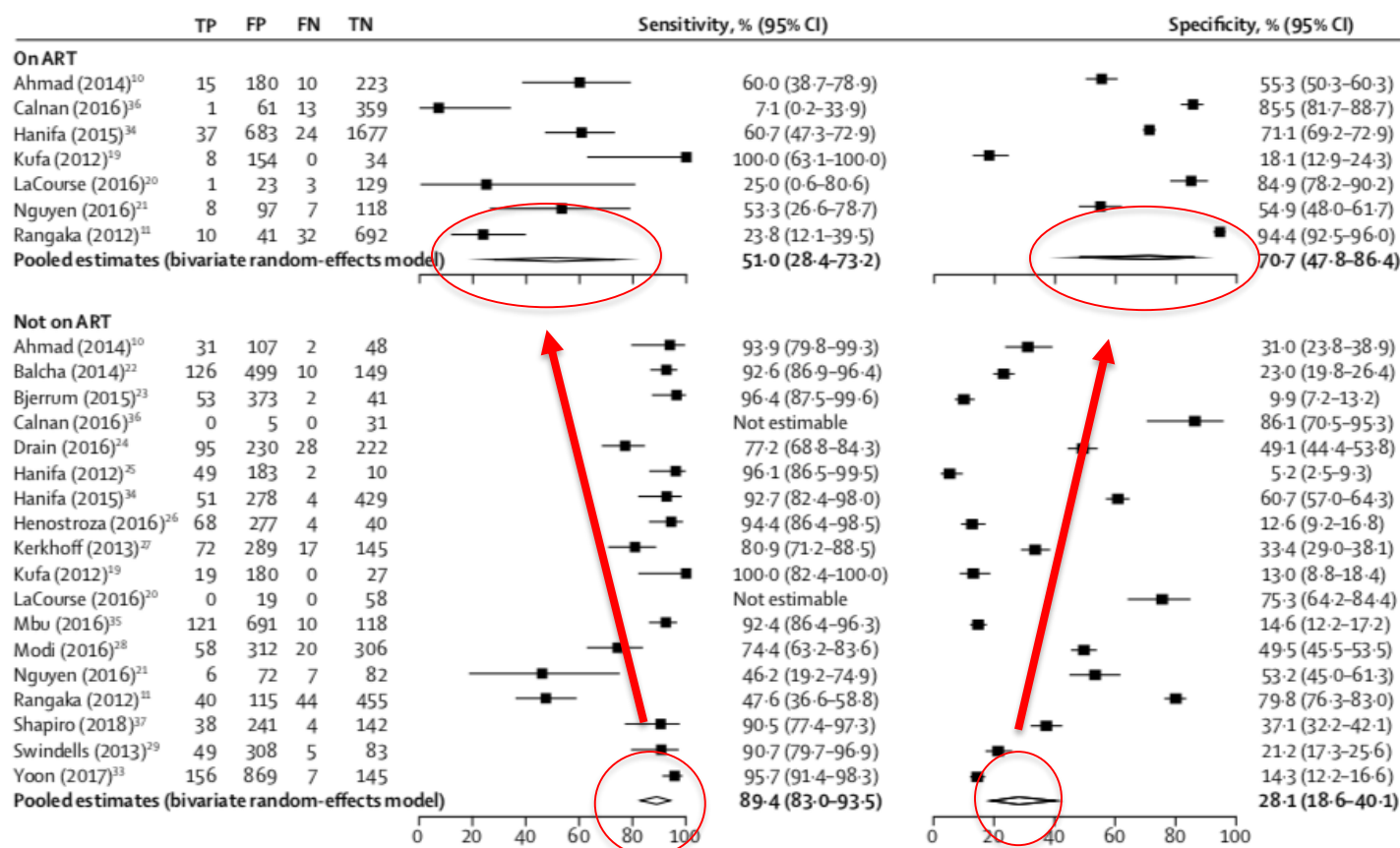
# HIV treatment as TB prevention



Van Rie A et al. J Acquir Immune Defic Syndr 2011;**56**:349–55  
 Bock P et al. J Acquir Immune Defic Syndr 2018;**77**:93–101

# Symptom screening and ART

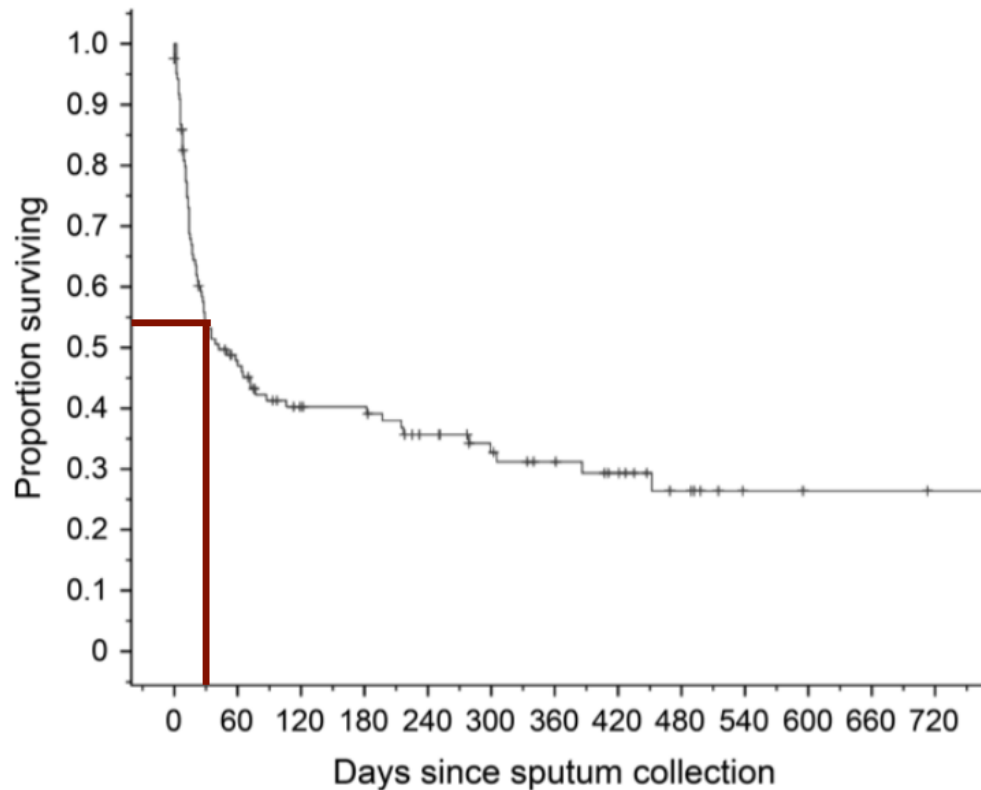
- WHO recommended TB screening in people living with HIV: Cough, weight loss, night sweats or fever



Hamada Y et al. *Lancet HIV* 2018

# The story doesn't end with diagnosis

- Patients with HIV and TB have a high mortality
- Especially bad for HIV and MDR-TB



Gandhi NR *et al. IJTL* 2012;**16**:90–7

# Treatment response monitoring

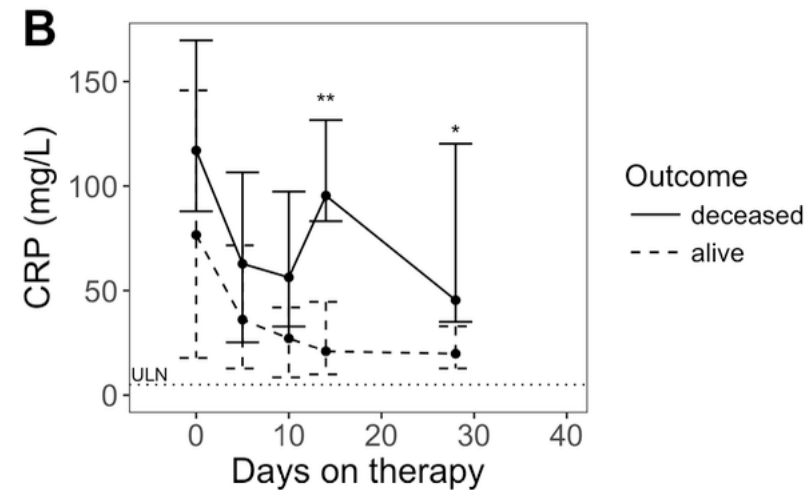
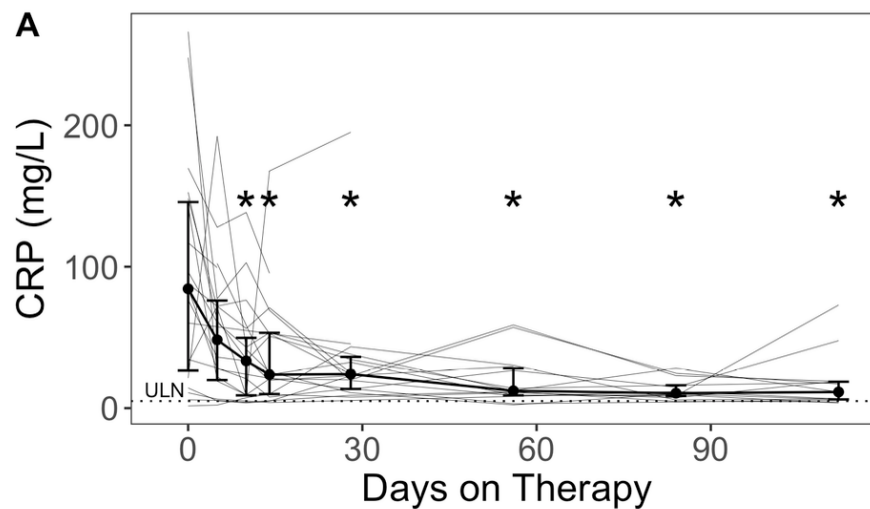
**TABLE 10.1 Activities for monitoring treatment response**

MONITORING EVALUATION	RECOMMENDED FREQUENCY
<b>Evaluation by clinician</b>	<p><i>During the intensive phase:</i> Every day during the first weeks if hospitalized and at least every week if treated as outpatient, until the treatment is well tolerated.</p> <p>Once stable the patient is seen twice a month or once a month.</p> <p><i>During the continuation phase:</i> Monthly assessments unless there is a medical necessity to see the patient more often. The DOT supporter sees the patient daily between consultations and signals any concerns to the clinician.</p>
<b>Treatment adherence and tolerance</b>	Daily at every DOT encounter by the DOT provider.
<b>Sputum smears and culture</b>	Monitoring smears and culture monthly throughout treatment. (Note: programmes with limited resources may choose to do monthly smears and cultures until conversion and then monthly smears with every other month cultures.)
<b>Weight</b>	At baseline, then every two weeks for first three months and then monthly.
<b>Height</b>	At start of treatment for all (to be able to assess BMI throughout treatment); monthly for children (to assess growth).
<b>Drug susceptibility testing</b>	At baseline for first- and second-line anti-TB drugs. Repeat DST for patients who remain culture-positive or revert after month four (see <a href="#">Chapter 3</a> for more information on DST).
<b>Chest radiograph</b>	At baseline, and then every six months.

Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis 2014

# Outcomes

- Trends in CRP on MDR-TB therapy

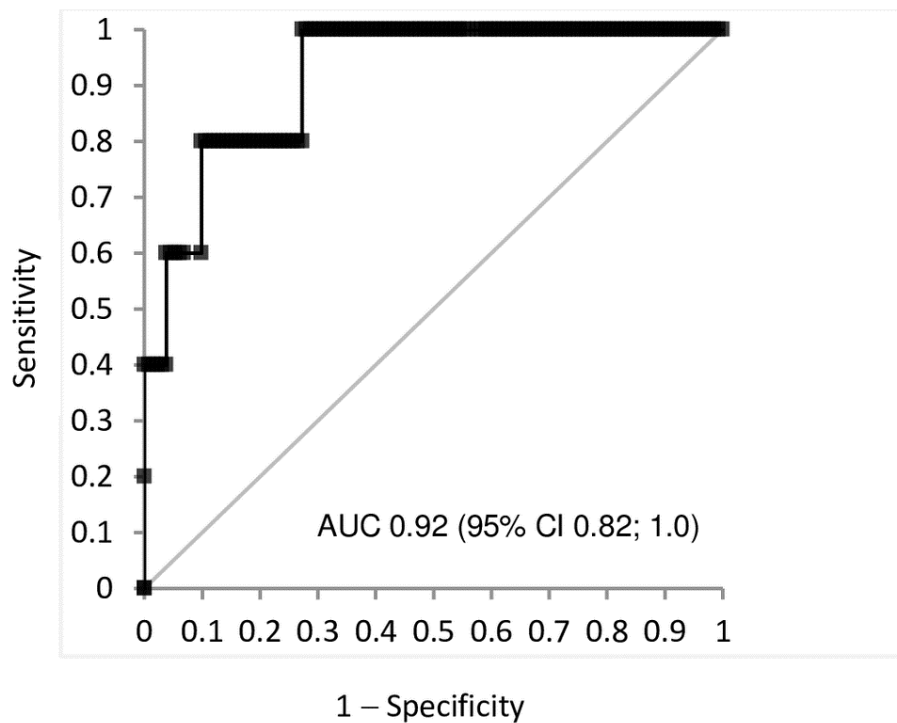


- A) Changes in serum CRP in HIV infected individuals on therapy for MDR-TB. Light grey lines represent individual patient responses.
- B) Changes in serum CRP in HIV infected individuals while on therapy for MDR-TB, stratified by outcome

Cudahy PGT et al. AJTMH 2018 in press

# CRP treatment response performance

- ROC for relative decline in CRP at week 2 to predict hospitalization or death



Wilson D et al. bioRxiv 2018; 400572

# Interventions?

- Rapid drug susceptibility testing
  - Addition of additional antitubercular medications
  - Treatment adherence counseling / monitoring
  - Screen for concurrent illness
- 
- Reduce transmission?
  - Reduce amplification of resistance?



# Questions

- How do we best utilize diagnostics when dealing with a range of immunosuppression, both pre and post ART? Urine vs sputum?
- How can we deploy resources to those at highest risk of treatment failure to improve mortality, TB transmission and amplification of resistance?

# Thanks!

## Yale

- Ted Cohen
- Josh Warren

## South Africa

- Doug Wilson
- Rob Warren (Stellenbosch)

## TGen

- Dave Engelthaler