NATIONAL HEALTH LABORATORY SERVICE

Screening for active TB: who, when and how?

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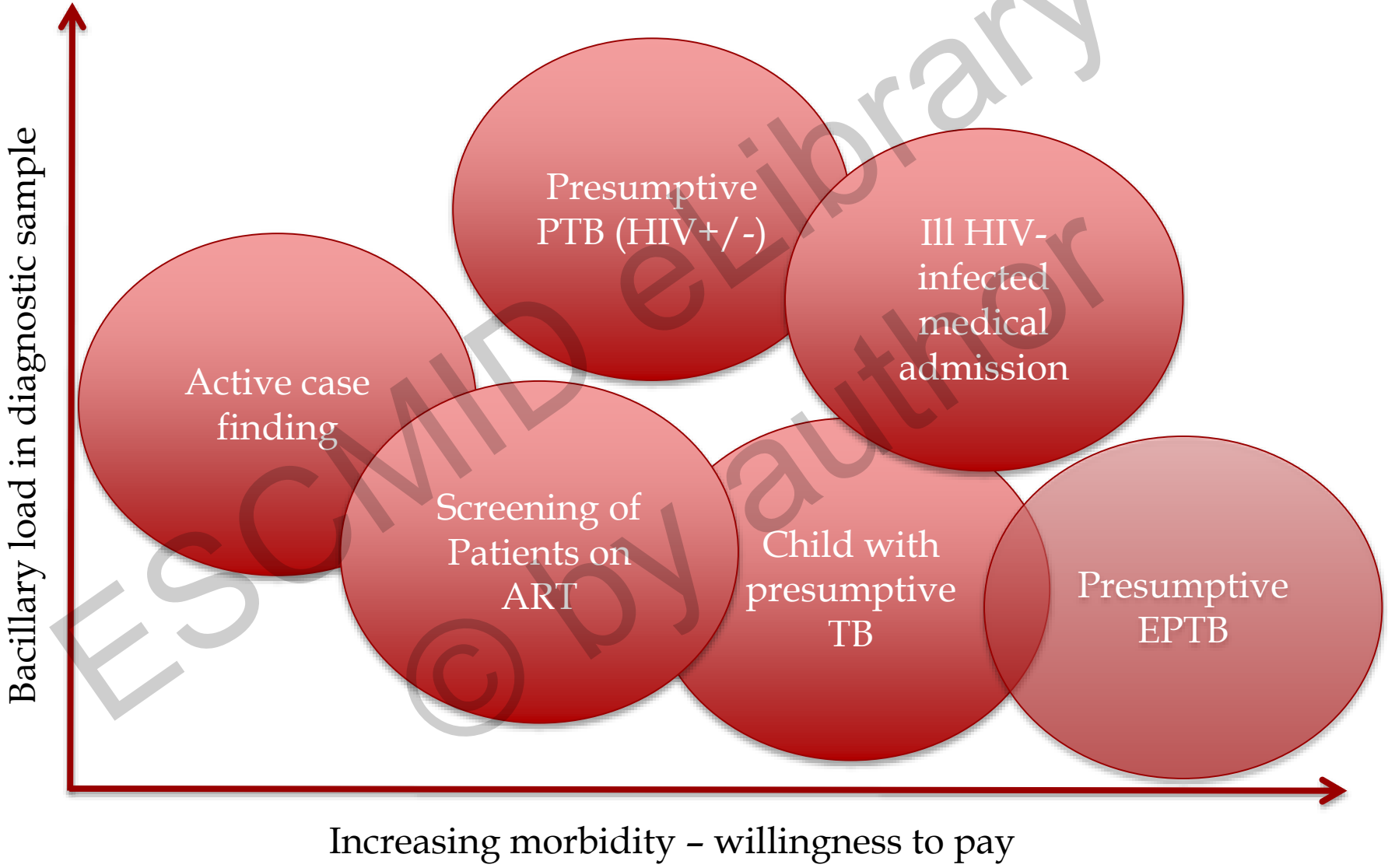
Disclosures

Mark Nicol has received research grants awarded to his institution from the Foundation for Innovative New Diagnostics, NIH, SA MRC and Bill and Melinda Gates Foundation, to conduct studies evaluating Xpert MTB/RIF, Xpert MTB/RIF Ultra, LAM and other diagnostics.

Complex mix of patients requiring testing



Test requirements:

Accurate
Low-cost
Point of care
Drug-resistance screen

Sensitivity of Xpert MTB/RIF

- Adults: case detection (vs. culture)
  - Sensitivity 88% (83-92)
  - Smear-negative 68%
  - PLHIV 80% (Steingart KL Cochrane Review 2013)

- Children: case detection
  - Sensitivity lower than for adult TB
    Substantial incremental benefit for 2 tests
    - 1 x Xpert 46-69%; 2 Xpert 61-76%

The impact gap

- ✓ Reduced time to treatment
- ✓ Increased bacteriological confirmation
- ✗ Little increase in number of patients on treatment
- ✗ No impact on mortality (outpatient largely)

Lack of apparent impact driven largely by empiric TB treatment

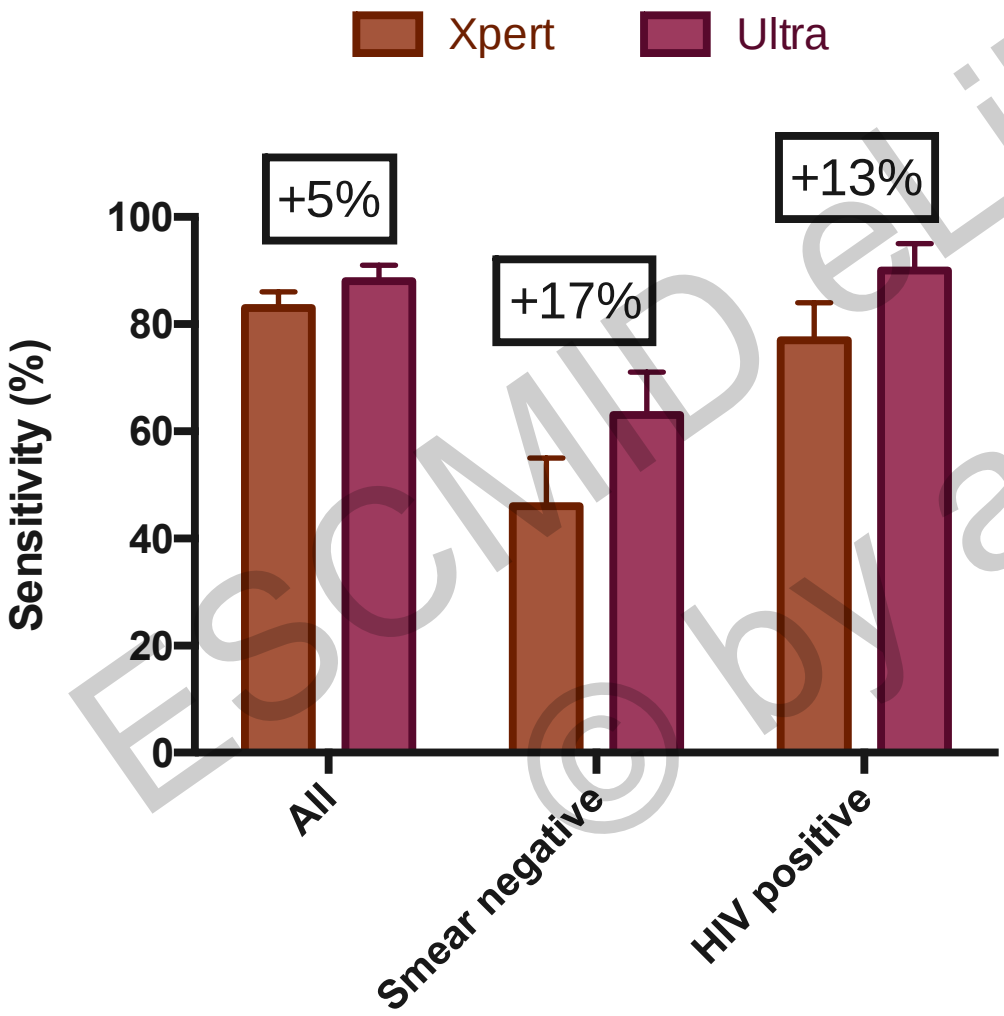
Theron et al. Lancet 2014, Cox et al. PLoS Med 2014, Durovni B et al PLoS Med 2014, Churchyard, Lancet Global Health 2015

Xpert Ultra

- Increased sensitivity
  - Fully nested (vs. semi-nested) PCR
  - Additional multi-copy targets (*IS*6110, *IS*1081)
    - Trace calls (no RIF result)
  - Increased volume in reaction chamber
  - Analytical LOD 16 CFU/ml sputum (vs. 131)
- Melt curve analysis for RIF resistance detection
  - Improved specificity, better for mixed infection?
- Quicker (75 minutes)

Information courtesy of Cepheid and David Alland

Accuracy of Ultra for case detection:
multi-centre diagnostic accuracy study



Improved sensitivity, but reduced specificity:
- Xpert 98%
- Ultra 96% (Δ-2.7%)

If trace calls regarded as negative, specificity = 98%

Accuracy for RIF resistance similar to Xpert

Dorman Lancet ID 2018

Implications of reduced specificity of Ultra on test choice and interpretation

Scenario 1

- Active case-finding campaign in a high-burden urban community in India.
  - Symptom screen (cough >2 weeks) followed by Ultra test for all individuals with a positive screen.
  - Expected prevalence of TB is 5% in individuals being tested with Ultra.

How would you manage a relatively well individual with a positive Ultra test (RIF S) in this campaign?

1. Start first line TB treatment

2. Confirm the Ultra result with TB culture before making a treatment decision.

3. Only treat if Ultra result is 'fully' positive (not trace).

4. Repeat trace-positive Ultra test before making a treatment decision.

5. Regard trace-positive results as negative in individuals previously treated for TB.

Specificity: implications for PPV

(the proportion of individuals with a positive test who actually have TB)

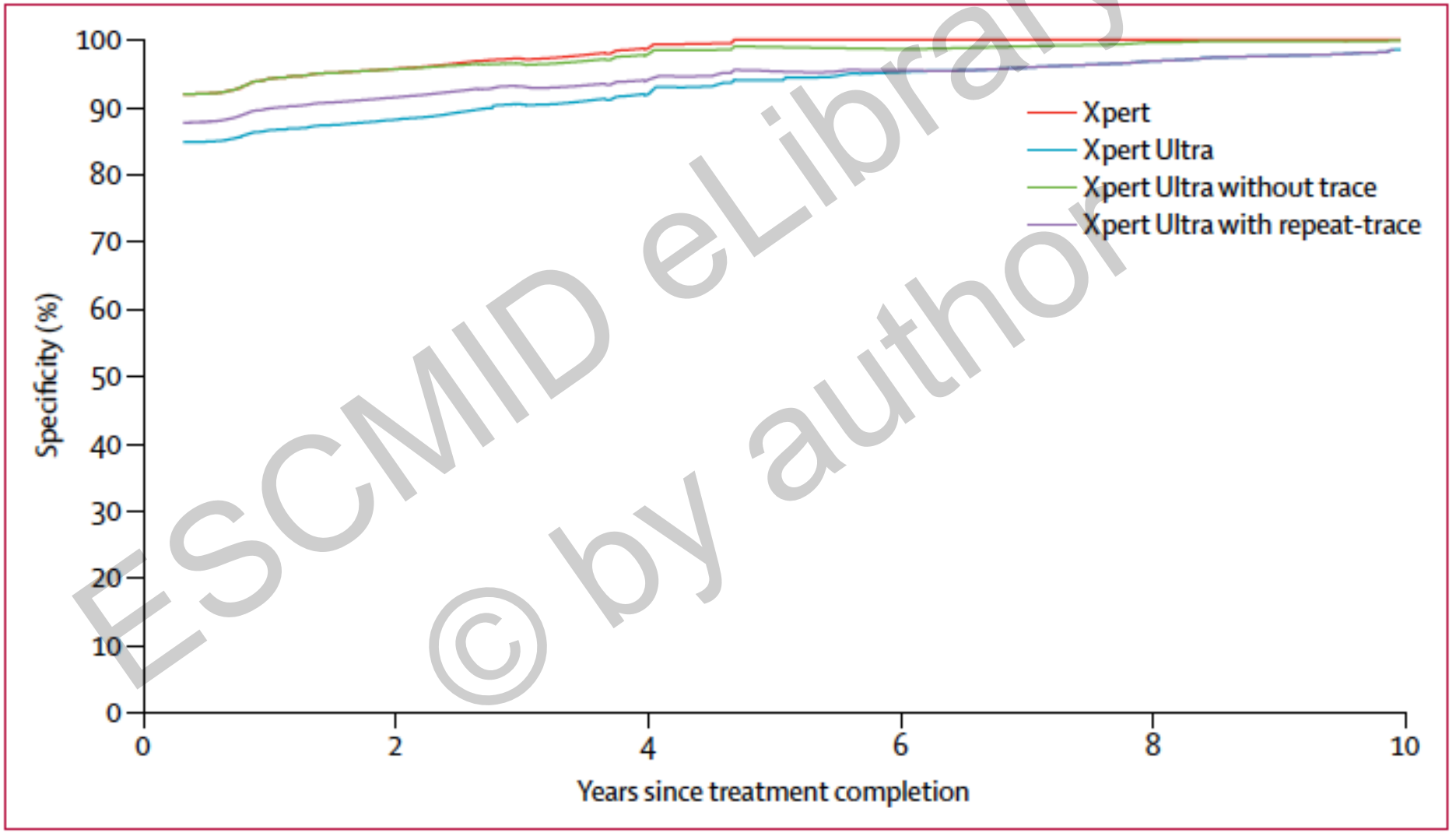
	Have TB	Don't have TB		
Ultra +	132	34	166	PPV=132/166 (80%)
Ultra -	18	816	834	NPV=816/834 (98%)
	150	850	1000	

Prevalence 15%, sens 88%, spec 96%

	Have TB	Don't have TB		
Ultra +	44	38	82	PPV=44/82 (54%)
Ultra -	6	912	918	NPV=912/918 (99%)
	50	950	1000	

Prevalence 5%, sens 88%, spec 96%

Impact of previous TB treatment on specificity of Ultra



Dorman Lancet ID 2018

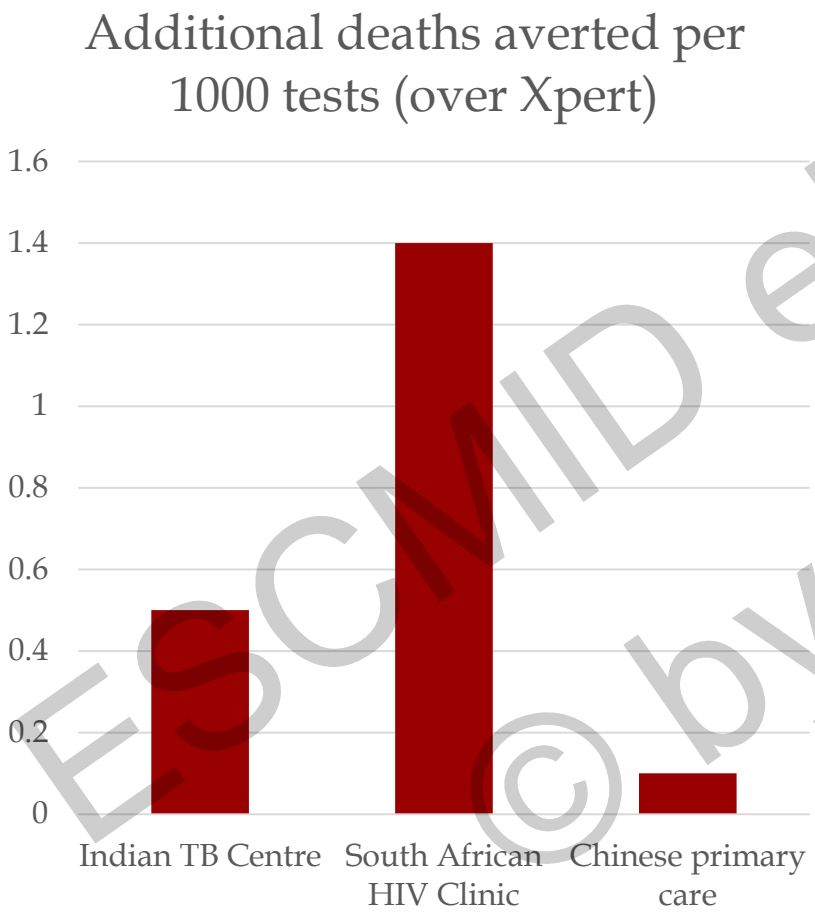
Options for improving PPV of Ultra

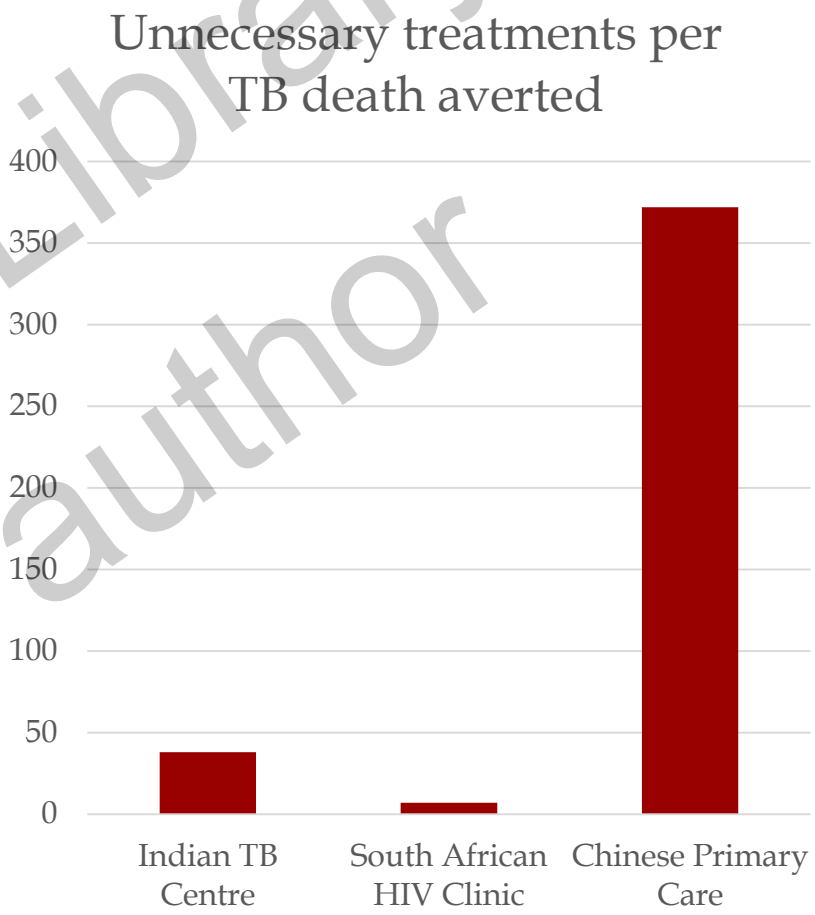
- Manage trace calls differently

	Sens. smear neg %	Specificity %
Trace reported positive	63	96
Report trace calls as negative	54	98
Repeat Ultra for trace calls	61	97
Report trace calls as negative in patients previously treated for TB	61	97

- Confirm trace calls using culture

Trade off:
Deaths averted vs. unnecessary treatment



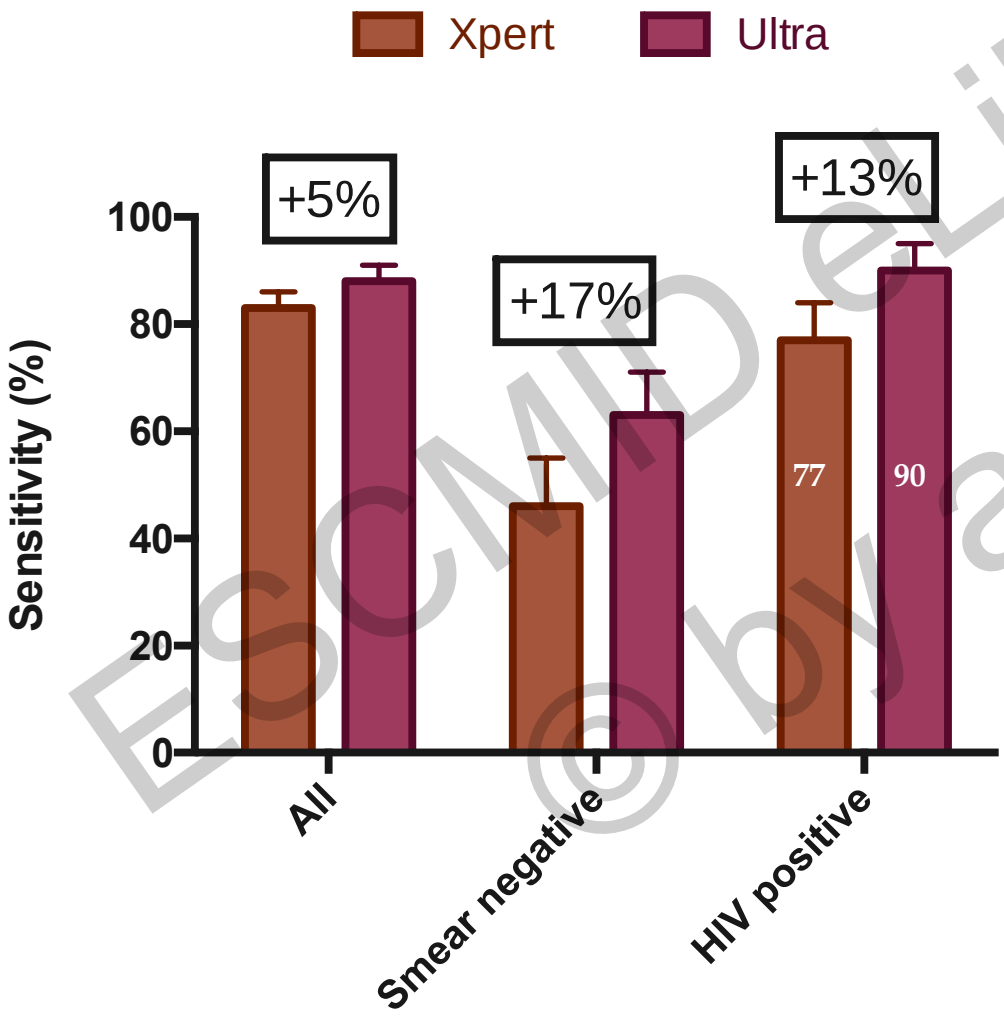


Kendall EA. PLoS Med 2017

How would you manage a relatively well individual with a positive Ultra test (RIF S) in this campaign?

1. Start first line TB treatment
   - But PPV only 54%
2. Confirm the Ultra result with TB culture before making a treatment decision.
   - Delay, LTFU
3. Only treat if Ultra result is 'fully' positive (not trace).
   - Trace called negative: PPV 70%, but reduced sensitivity
4. Repeat trace-positive Ultra test before making a treatment decision.
   - Trace repeat: PPV 61%
5. Regard trace-positive results as negative in individuals previously treated for TB.
   - Conditional trace: PPV 61%

Implications of improved sensitivity of Ultra for diagnostic algorithms



Improved sensitivity, but reduced specificity:

- Xpert 98%
- Ultra 96% (Δ-2.7%)
- Reporting trace calls as negative increases specificity to 98%

Accuracy for RIF resistance similar to Xpert

Dorman Lancet ID 2018

Scenario 2

- South African HIV-infected man, stable on ART, presenting to out-patient clinic with history of coughing for 2 weeks.
  - Good sputum sample is obtained and Ultra test is negative.
  - Prevalence of TB in this patient population is 15%

How would you manage this patient further?

1. Collect a further sputum sample for TB smear and culture.

2. Collect a further sputum sample for repeat Ultra.

3. If not acutely ill, consider antibiotic therapy and review after a week.

4. 1 and 3, above

5. 1, 2 and 3, above

Negative predictive value of Ultra

In multi-centre evaluation, sensitivity of Ultra (vs. culture) was 90% in HIV-infected patients

	Have TB	Don't have TB		
Ultra +	135	34	169	PPV=135/169 (80%)
Ultra -	15	816	831	NPV=816/831 (98%)
	150	850	1000	

Prevalence 15%, sens 90%, spec 96% (Trace pos)

- Amongst patients with a negative Ultra test, 2% will have a positive culture for TB.
- Incremental benefit of repeat Ultra will be even lower.

How would you manage this patient further?

1. Collect a further sputum sample for TB smear and culture.
   - Relatively low incremental yield; cost effective?

2. Collect a further sputum sample for repeat Ultra.
   - Likely very low incremental yield (no data)

3. If not acutely ill consider antibiotic therapy and review after a week.
   - Most cost-effective?

4. 1 and 3, above
   - Probably best practice but costly

5. 1, 2 and 3, above
   - Even more costly…

Scenario 3

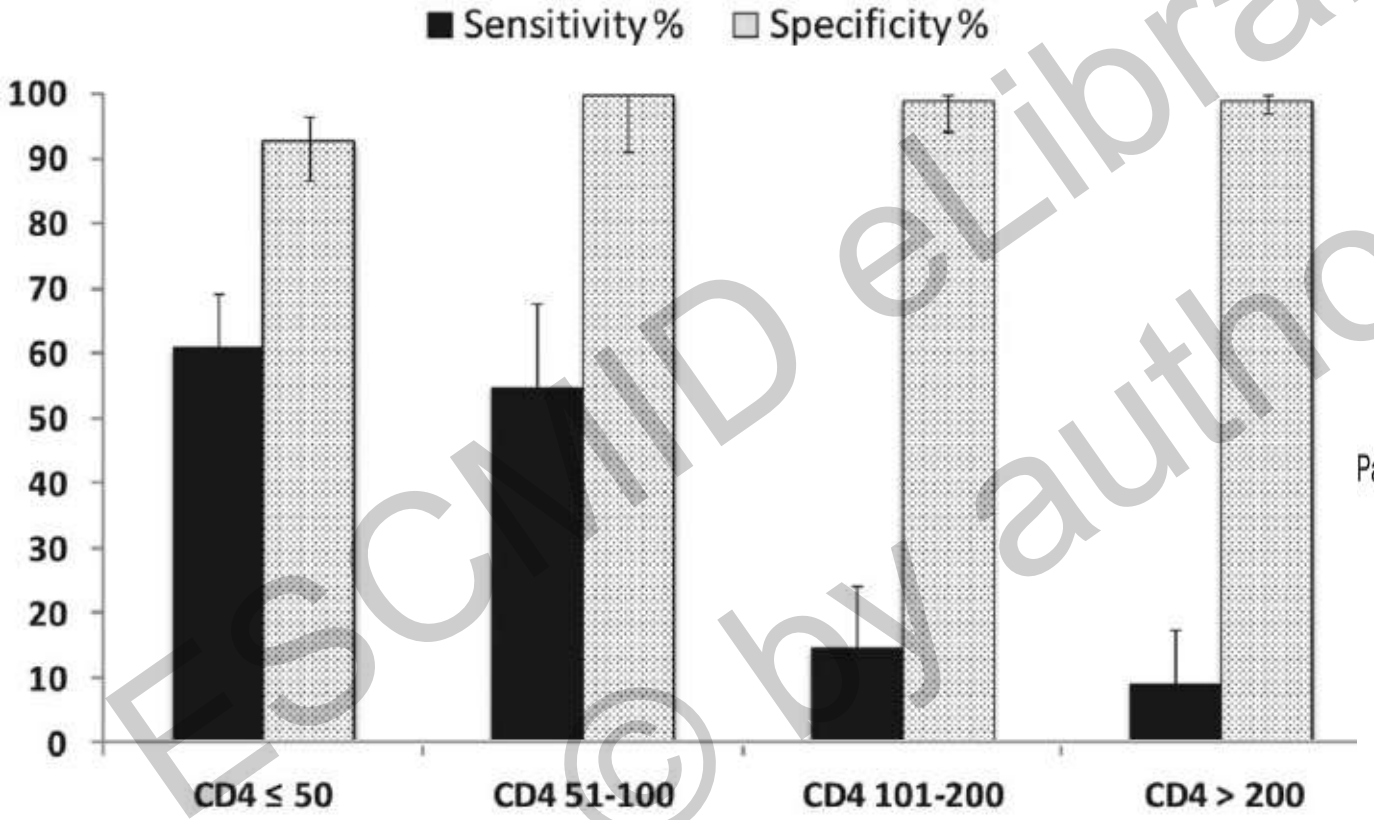
- Ill Malawian woman with advanced HIV-infection, admitted to general medical ward with fever and weight loss. Unable to produce a sputum sample on admission.

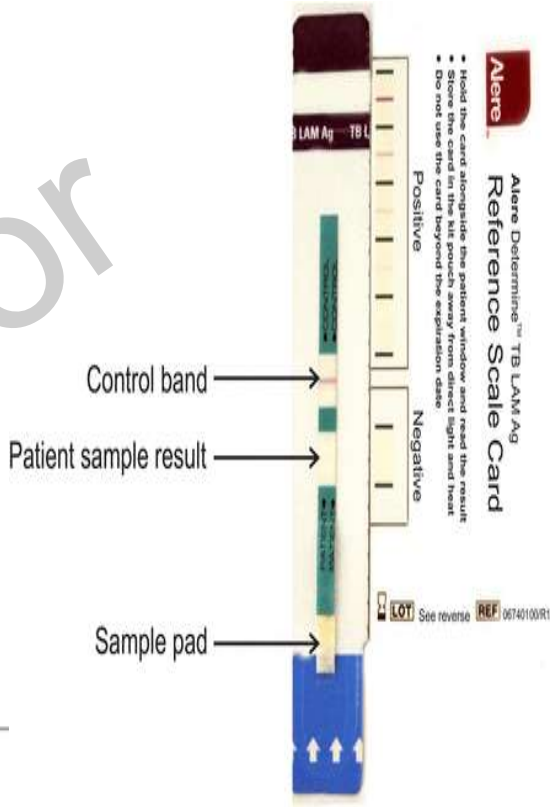
If you could choose one TB diagnostic test which would it be?

1. Induced sputum for Ultra
2. Induced sputum for TB culture
3. Urinary LAM test
4. Xpert (or Ultra) test on a concentrated urine sample
5. Mycobacterial blood culture

Urinary LAM lateral flow assay accuracy

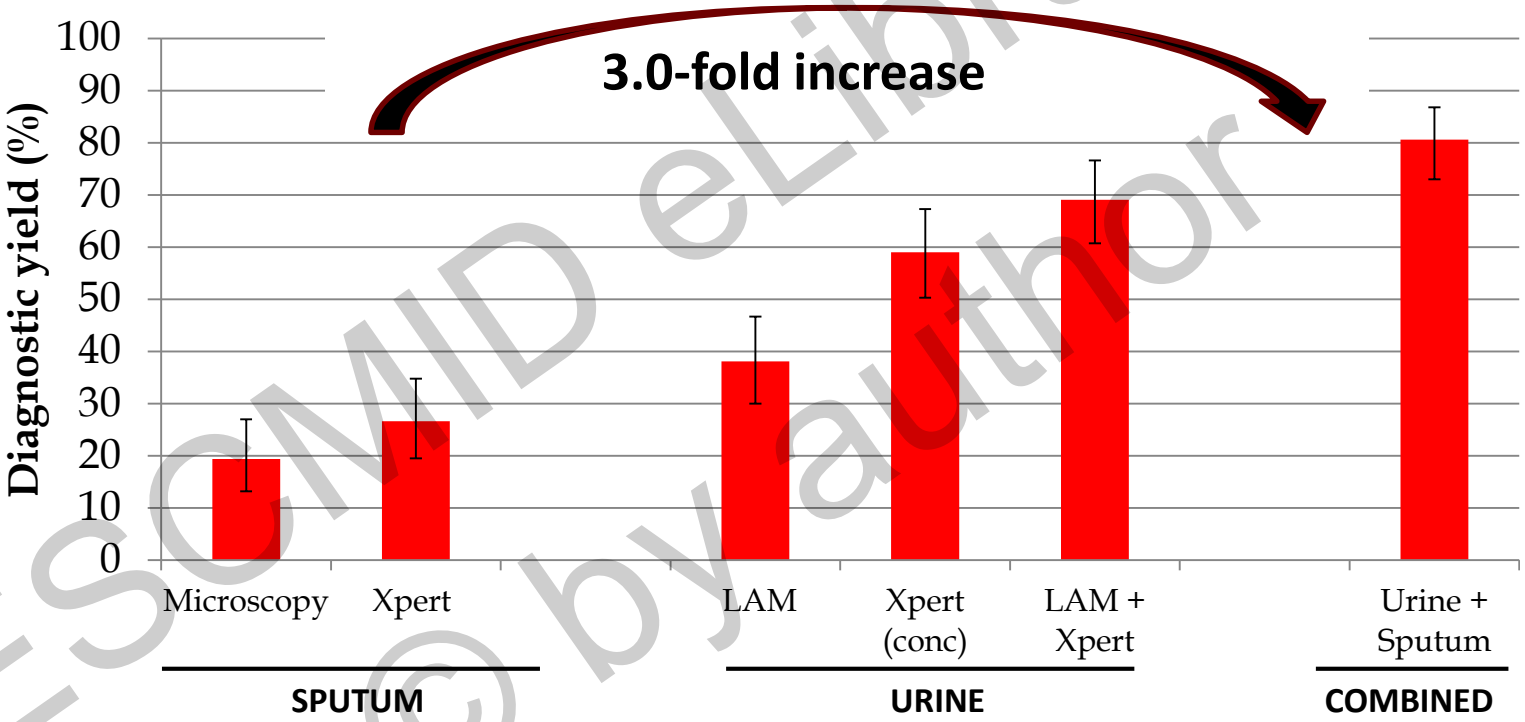
TB CDRC study: Uganda and South Africa





Nakiyingi et al. JAIDS 2014

Incremental yield from rapid urine testing of samples obtained within 24 hours of admission



Slide courtesy of Liz Corbett

Lawn BMC Med 2016

STAMP trial: a pragmatic, multi-country randomized controlled trial

2600 UNSELECTED adult HIV+ admissions
Irrespective of TB symptoms

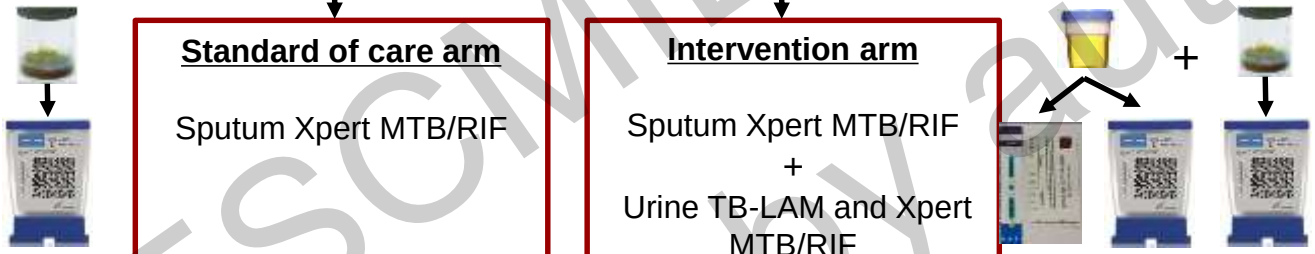
Exclude:
- <18 years old
- TB treatment in last 12 months
- IPT in last 6 months
- Outside follow-up area
- Admitted >48 hours
- Unable to provide consent

Standard of care arm

Sputum Xpert MTB/RIF

Intervention arm

Sputum Xpert MTB/RIF
+
Urine TB-LAM and Xpert MTB/RIF



Edendale, KZN, South Africa

Zomba, Malawi

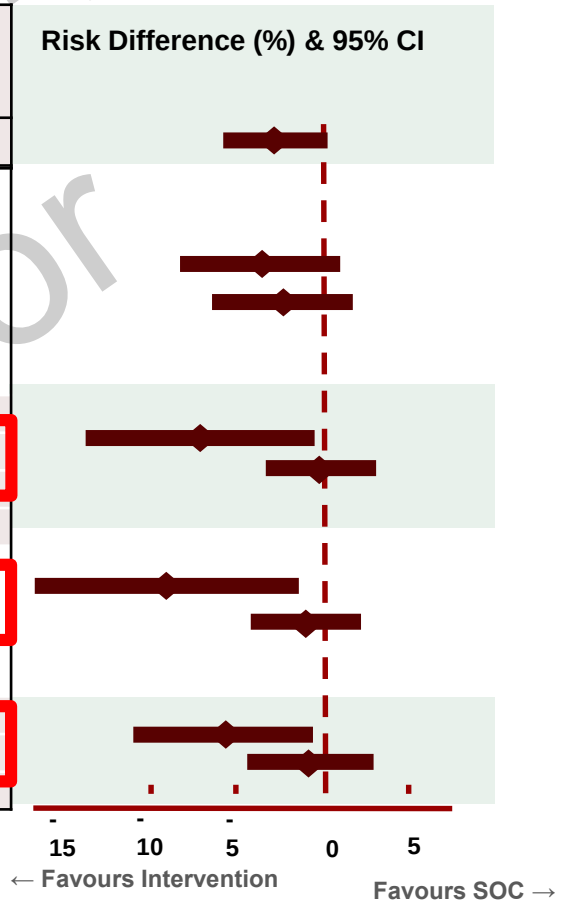
Primary outcome: mortality risk at 56-days

Ankur Gupta-Wright, Elizabeth L Corbett, Joep J van Oosterhout, Doug Wilson, Daniel Grint, Melanie Alufandika, Jurgens A Peters, Lingstone Chiume, Stephen D Lawn & Katherine Fielding

STAMP primary outcome: mortality at 56-days

	Standard of Care [SOC] n (%)	Intervention n (%)	Risk Difference* % (95% CI)	p-value	Interaction p-value
Intervention - SOC	272 (21.1)	235 (18.3)	-2.8 (-5.8, 0.3)	0.074	
Subgroup analyses:					
Site					0.668
Zomba, Malawi	161 (24.4)	137 (20.9)	-3.5 (-8.0, 1.0)	0.128	
Edendale, South Africa	111 (17.7)	98 (15.5)	-2.2 (-6.3, 1.9)	0.301	
Baseline CD4 cell count, cells/ul					0.063
<100	133 (35.7)	107 (28.8)	-7.1 (-13.7, -0.4)	0.036	
>100	131 (14.6)	127 (14.0)	0.1 (-3.3, 3.1)	0.963	
Baseline haemoglobin, g/dl					0.056
<8	116 (38.9)	86 (29.8)	-9.0 (-16.6, -1.3)	0.021	
≥8	156 (15.8)	148 (15.0)	0.0 (-4.1, 2.8)	0.686	
TB clinically suspected at admission					0.111
Yes	136 (27.5)	106 (21.2)	-5.7 (-11.0, -0.5)	0.033	
No	136 (17.2)	128 (16.4)	-0.8 (-4.4, 2.9)	0.682	

* adjusted by site (except for sub-group analysis by site). 29 patients missing CD4 cell counts, 5 patients missing haemoglobin, 9 patients missing clinical TB suspect at baseline data.

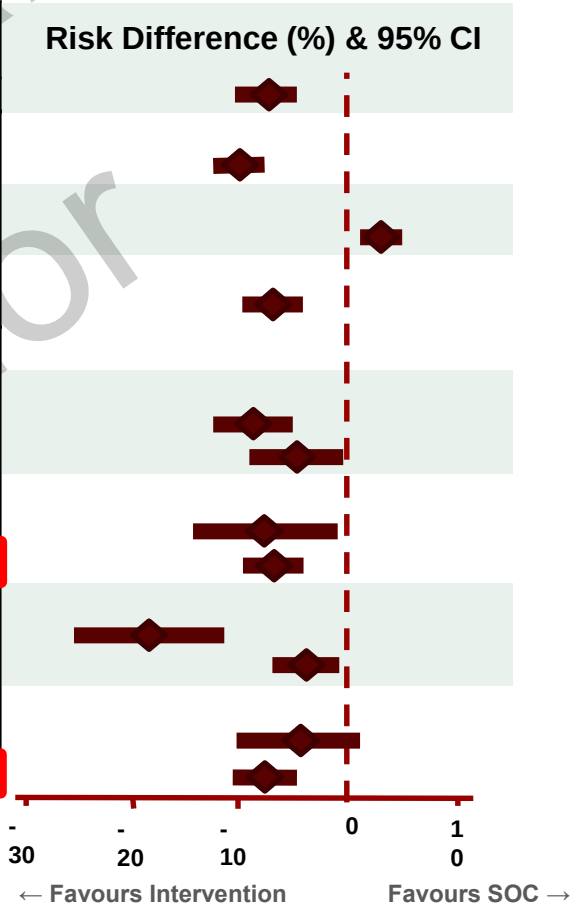


Slide courtesy of Liz Corbett

Secondary outcome: inpatient TB diagnosis

	SOC n (%)	Intervention n (%)	Risk Difference* % (95% CI)	p-value	Interaction p-value
Diagnosed with TB	192 (14.9)	282 (21.9)	7.3 (4.4, 10.2)	<0.001	
TB microbiologically confirmed	85 (6.6)	210 (16.3)	9.9 (7.5, 12.4)	<0.001	
TB clinically diagnosed (empirical)	107 (8.3)	72 (5.6)	-3.2 (-4.9, -1.4)	<0.001	
Treated for TB	182 (14.1)	268 (20.8)	7.0 (4.1, 9.8)	<0.001	
Subgroup analyses (all in-patient TB diagnoses):					
Site					0.193
Zomba, Malawi	68 (10.3)	126 (19.2)	8.9 (5.1, 12.7)	<.001	
Edendale, South Africa	124 (19.8)	156 (24.7)	5.0 (0.4, 9.5)	0.035	
Baseline CD4 cell count, cells/μL					0.876
<100	116 (31.1)	142 (38.3)	7.9 (1.1, 14.5)	0.021	
≥100	74 (8.2)	137 (15.2)	7.0 (4.1, 10.0)	<0.001	
Baseline haemoglobin, g/l					<0.001
<8	58 (19.5)	111 (38.4)	18.6 (11.5, 25.6)	<0.001	
≥8	133 (13.5)	171 (17.2)	4.1 (1.0, 7.2)	0.01	
TB clinically suspected at admission					0.323
Yes	143 (28.9)	170 (33.9)	4.7 (-1.1, 10.4)	0.11	
No	49 (6.2)	111 (14.2)	8.0 (5.0, 11.1)	<0.001	

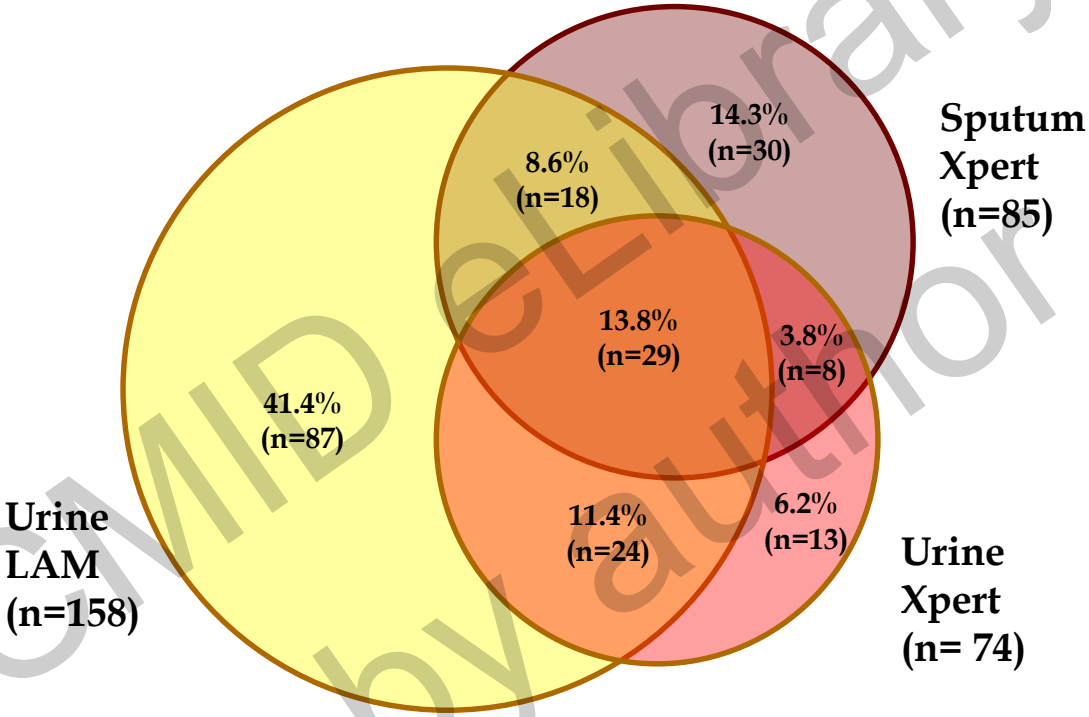
* adjusted by site (except for sub-group analysis by site). 29 patients missing CD4 cell counts, 5 patients missing haemoglobin, 9 patients missing clinical TB suspect at baseline data.



Slide courtesy of Liz Corbett

TB diagnostic yield

Microbiologically confirmed TB, intervention arm (n=210)



Note: 1 patient was negative on all Xpert and LAM tests but was sputum TB culture positive

Samples submitted for TB testing:

- 99.0% produced urine
- 56.9% produced sputum

Slide courtesy of Liz Corbett

Summary of LAM RCTs

In-patient LAM RCTs in PLHIV	Diagnostic: Peters 2016	Screening: STAMP Trial 2018
Country and size	2,569 clinically suspected TB S Africa, Tan, Zam, Zim	2,600 medical inpatients S Africa, Malawi
Intervention	Urine LAM vs SOC	Urine (LAM + Xpert) + Sputum Xpert vs Enhanced SOC (+ Sputum Xpert)
Outcomes	Mortality at 56-days TB score/ performance	Mortality at 56-days TB diagnosis and treatment
Median CD4 count	84	230
56-day mortality	**24.9% vs 20.8%** Absolute ↓4% (1-7), Relative ↓ 17% (4-28)	**21.1% vs 18.3%** Absolute ↓2.8% (-0.3 to 5.8), Relative ↓ 13% (0-27)
TB treatment	**52% vs 47%** Absolute ↑5% Relative ↑ 10%	**20.8% vs 14.1%** Absolute ↑7% Relative ↑ 50%

Support routine urine TB screening in HIV+ inpatients, irrespective of symptoms, CD4 count, or cause of medical admission

Slide: Courtesy of Liz Corbett

If you could choose one TB diagnostic test which would it be?

1. Induced sputum for Ultra
   - Good sensitivity, but delay and hazardous

2. Induced sputum for TB culture
   - High early mortality: can't delay diagnosis

3. Urinary LAM test
   - Best evidence

4. Xpert (or Ultra) test on a concentrated urine sample
   - Probably less benefit than LAM

5. Mycobacterial blood culture
   - Low yield

Conclusions

- Programmatic implementation of Ultra requires revision of diagnostic algorithms
  - Ensure acceptable PPV
  - Determine most cost-effective algorithm for test negative patients

- In high burden settings, urine-based TB testing should be used to supplement sputum-based testing for HIV-infected medical admissions regardless of TB symptoms

WHO recommendation on LAM

- **May be used** to assist the diagnosis of TB in:
  - HIV positive adult in-patients with signs and symptoms of TB and a CD4 cell count ≤ 100 cells/µL, and
  - people living with HIV who are "seriously ill", regardless of CD4 count or if the CD4 count is unknown.