Diagnosis of HIV-associated tuberculosis

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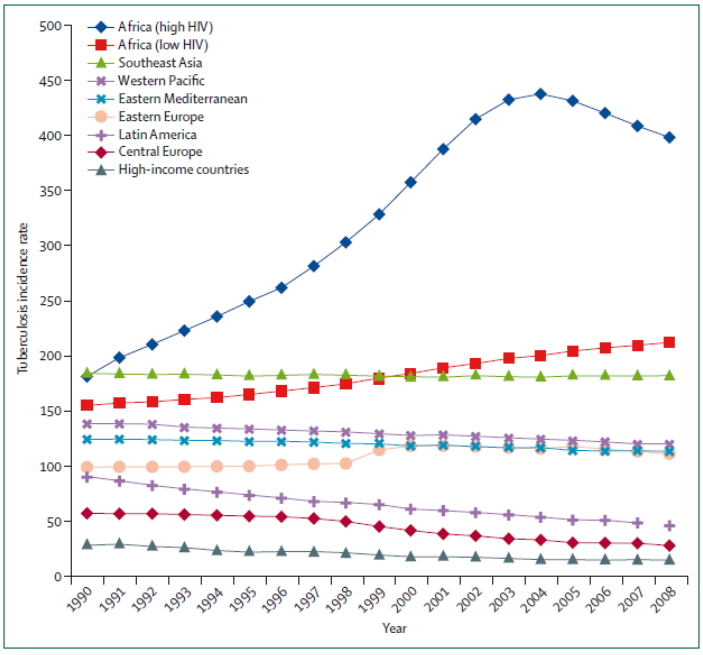
masithandane

wellcome trust

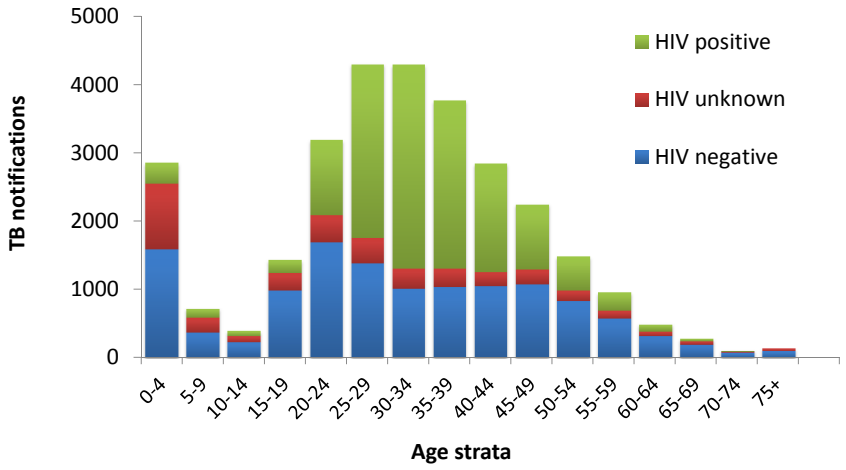
1899 1999
contributing to health worldwide

NO CONFLICTS OF INTEREST TO DECLARE



Lawn & Zumla. Lancet 2011

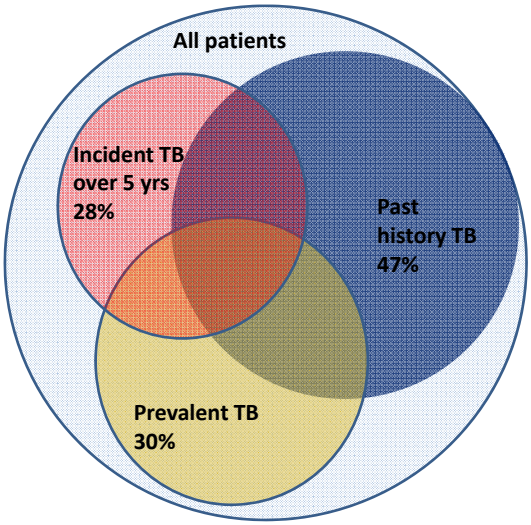
TB in Cape Town 2009 (n=29,478)



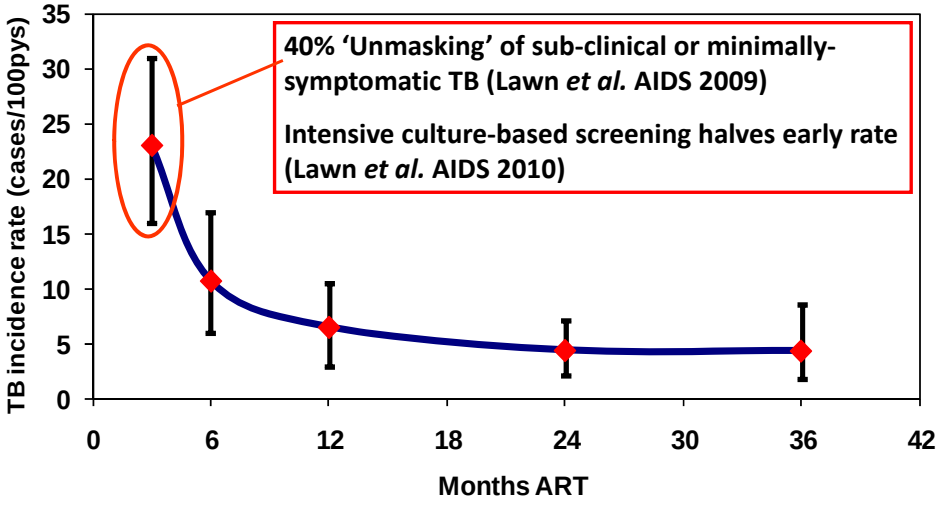
Wood, Lawn, et al. PLoS ONE 2011

The Burden of TB in an ART Clinic in Cape Town, South Africa

Burden of TB Among Patients (n=1544) Starting ART in Gugulethu ART Clinic

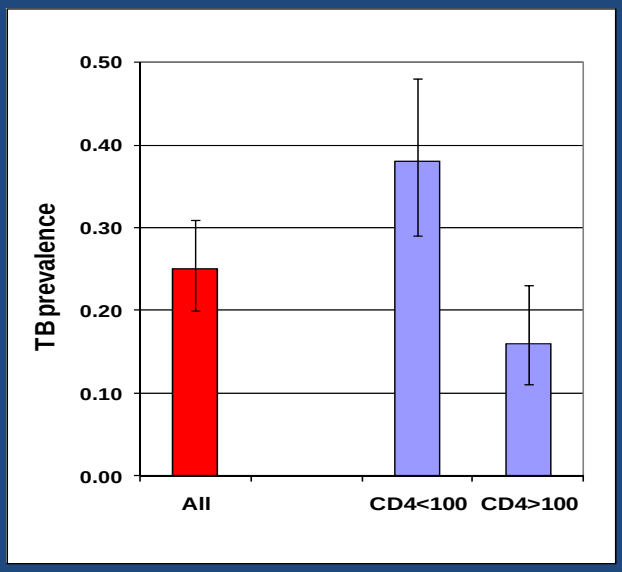


Incident TB During ART



Lawn et al AIDS 2006 & AIDS 2009

Prevalent Undiagnosed Sputum Culture-Positive TB at Baseline



Lawn et al AIDS 2009

Prevalence of Culture+ TB on ICF

	All patients	CD4 <100	CD4 >100
Lawn et al 2009	25%	38%	16%
Bassett et al 2010	19%	-	-
Lawn et al 2011	18%	28%	14%

How to best screen and diagnose??

Symptom Screening

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

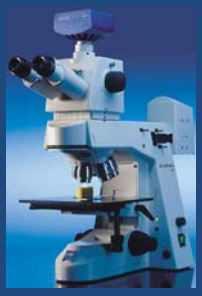
Haileyesus Getahun[1]*, Wanitchaya Kittikraisak[2], Charles M. Heilig[3], Elizabeth L. Corbett[4], Helen Ayles[4,5], Kevin P. Cain[3], Alison D. Grant[4], Gavin J. Churchyard[6], Michael Kimerling[7], Sarita Shah[8], Stephen D. Lawn[4,9], Robin Wood[9], Gary Maartens[10], Reuben Granich[1], Anand A. Date[3], Jay K. Varma[2,3]

Screen for presence of ≥1 of the following symptoms:

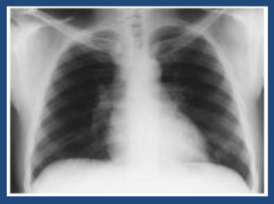
1. Current cough
2. Fever
3. Night sweats
4. Weight loss

Sensitivity: 78.9%
Specificity: 49.6%

Diagnostic Tools



Fluorescence microscopy
Sensitivity 15%-30%



Up to 30% cases normal CXR

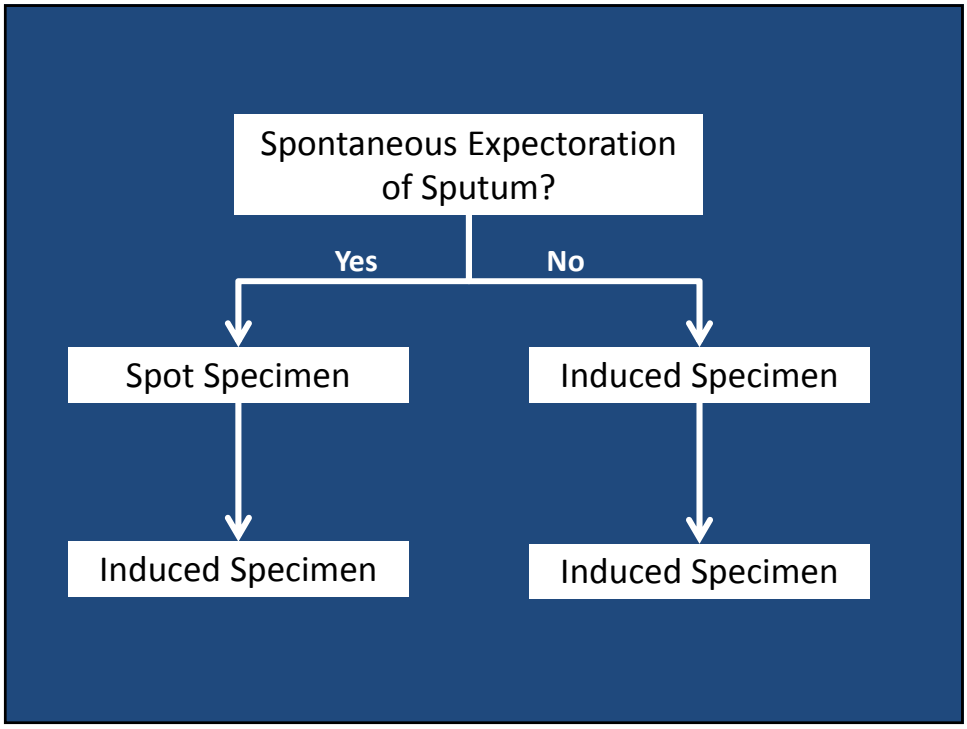
MGIT culture
Time to positivity:
>3 weeks for smear-neg samples

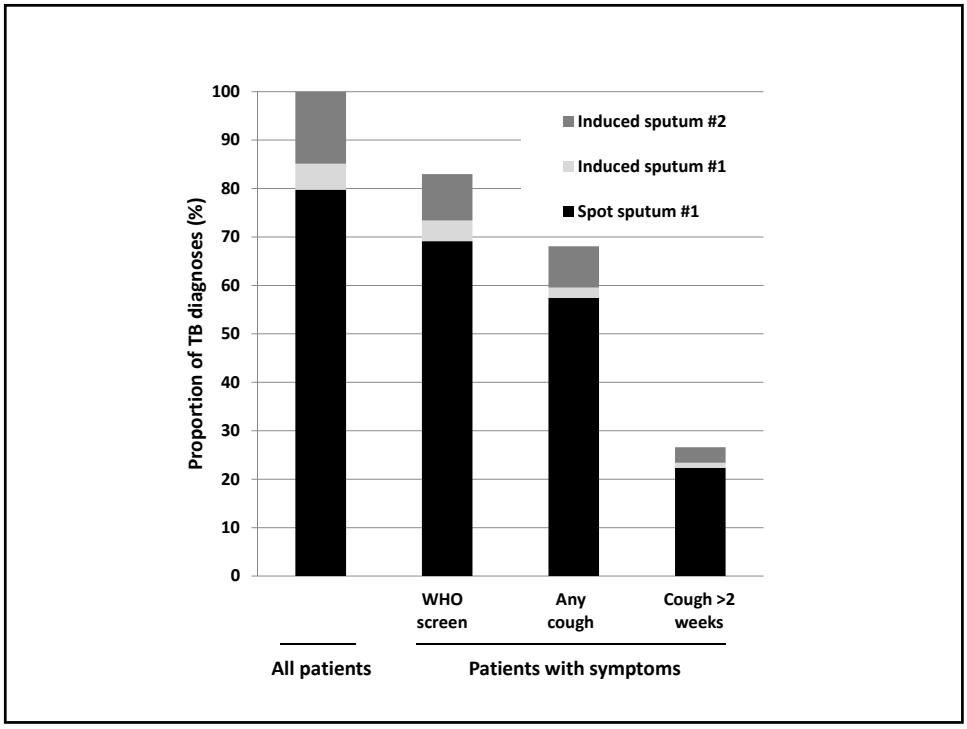
Rationale for ICF in ART Clinics

1. Morbidity
2. Mortality
3. Infection control
4. Prevent MDR-TB outbreaks

HAMSTRUNG BY POOR TB DIAGNOSTICS

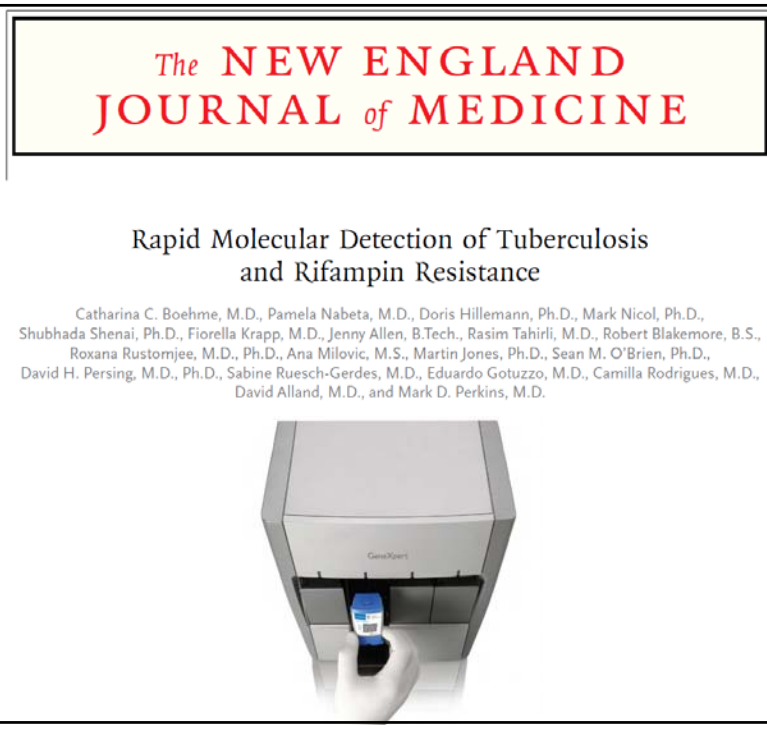
Incremental Yield of TB Using Sputum Induction During Screening Pre-ART


Spontaneous Expectoration of Sputum?
Yes
No
Spot Specimen
Induced Specimen
Induced Specimen
Induced Specimen


Proportion of TB diagnoses (%)
100
90
80
70
60
50
40
30
20
10
0
Induced sputum #2
Induced sputum #1
Spot sputum #1
WHO screen
Any cough
Cough >2 weeks
All patients
Patients with symptoms

Two New Diagnostics

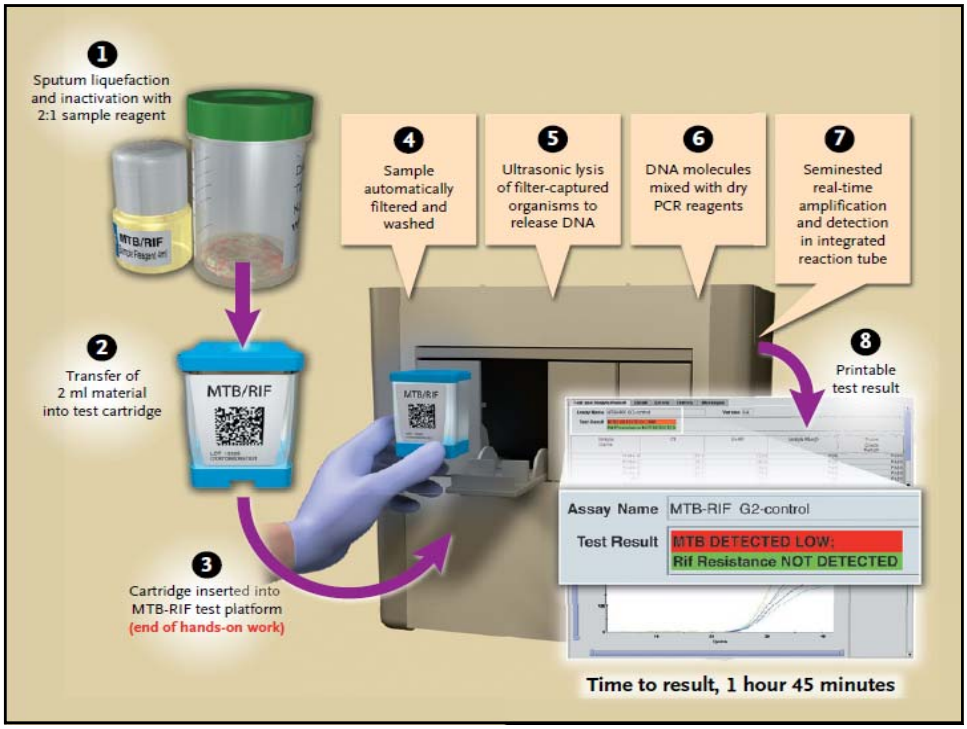
Xpert MTB/RIF **Determine TB-LAM Ag**

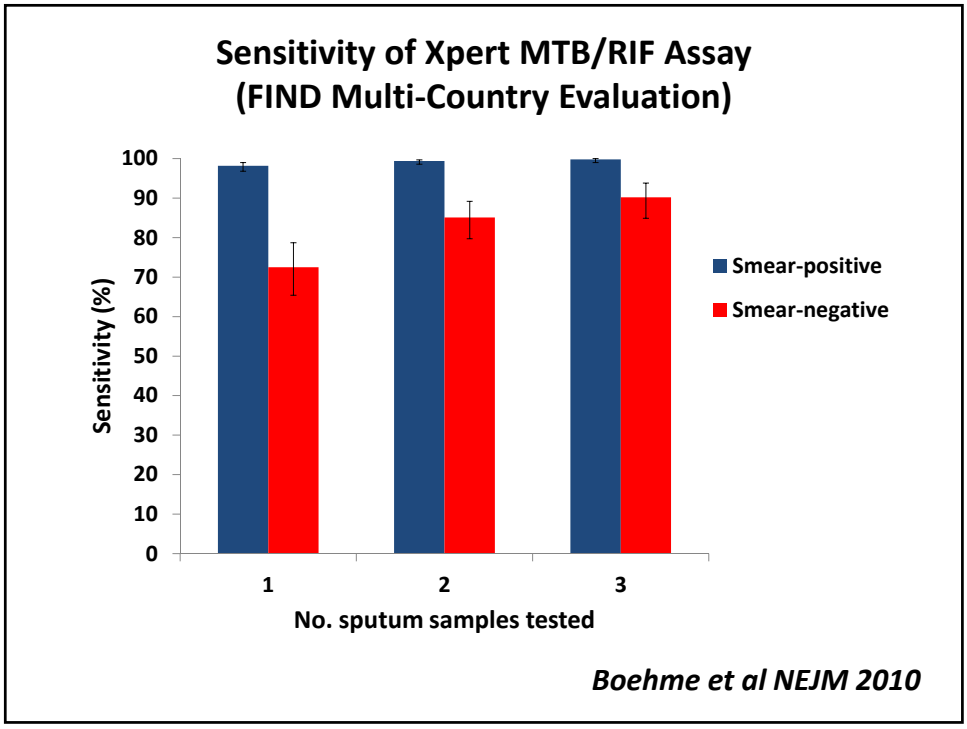


The NEW ENGLAND JOURNAL of MEDICINE

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillemann, Ph.D., Mark Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiorella Krapp, M.D., Jenny Allen, B.Tech., Rasim Tahirli, M.D., Robert Blakemore, B.S., Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.


1
Sputum liquefaction and inactivation with 2:1 sample reagent
2
Transfer of 2 ml material into test cartridge
MTB/RIF
3
Cartridge inserted into MTB-RIF test platform
(end of hands-on work)
4
Sample automatically filtered and washed
5
Ultrasonic lysis of filter-captured organisms to release DNA
6
DNA molecules mixed with dry PCR reagents
7
Seminested real-time amplification and detection in integrated reaction tube
8
Printable test result
Assay Name MTB-RIF G2-control
Test Result MTB DETECTED LOW;
Rif Resistance NOT DETECTED
Time to result, 1 hour 45 minutes

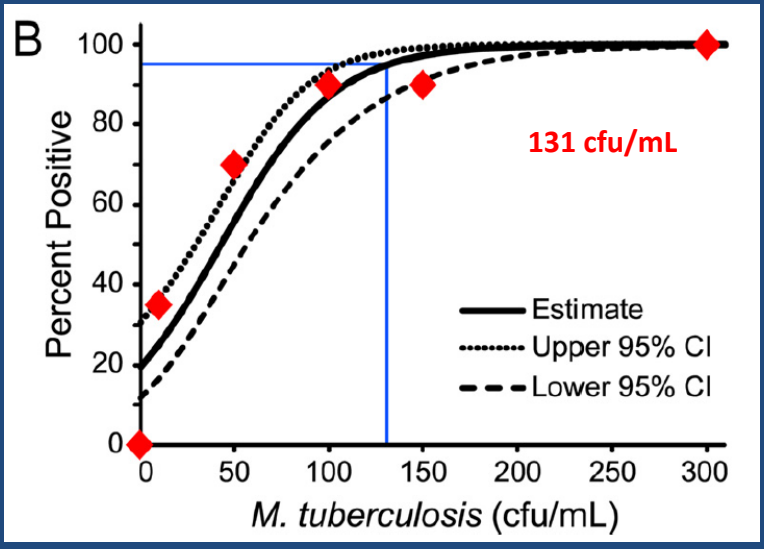

Sensitivity of Xpert MTB/RIF Assay
(FIND Multi-Country Evaluation)
Sensitivity (%)
100
90
80
70
60
50
40
30
20
10
0
1
2
3
No. sputum samples tested
Smear-positive
Smear-negative
Boehme et al NEJM 2010

Review of Studies

Type of TB	Sensitivity
Sputum smear-positive	99-100%
Sputum smear-negative	57-83%
Extrapulmonary (range of clinical samples)	53-95%

Lawn & Nicol. Future Microbiology 2011

Limit of Detection of *M. tuberculosis* spiked into sputum



Helb et al. J Clin Micro 2010

OPEN ACCESS Freely available online

PLoS MEDICINE

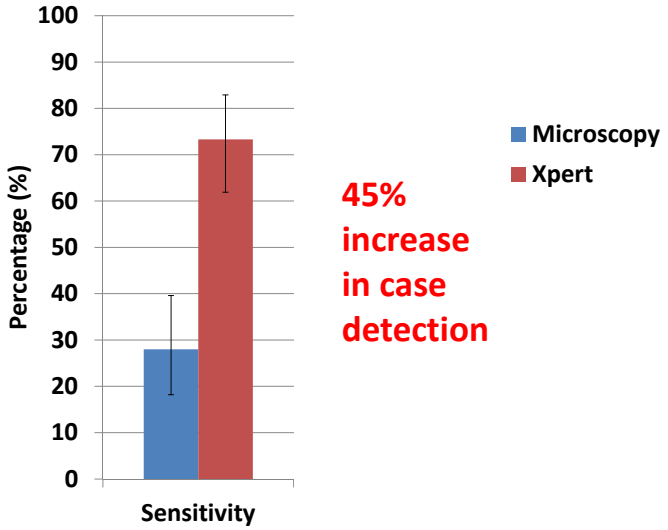
Screening for HIV-Associated Tuberculosis and Rifampicin Resistance before Antiretroviral Therapy Using the Xpert MTB/RIF Assay: A Prospective Study

Stephen D. Lawn[1,2*], Sophie V. Brooks[1], Katharina Kranzer[1,2], Mark P. Nicol[3,4], Andrew Whitelaw[3,4], Monica Vogt[1], Linda-Gail Bekker[1], Robin Wood[1,5]

PLoS Med 2011; 8: e1001067

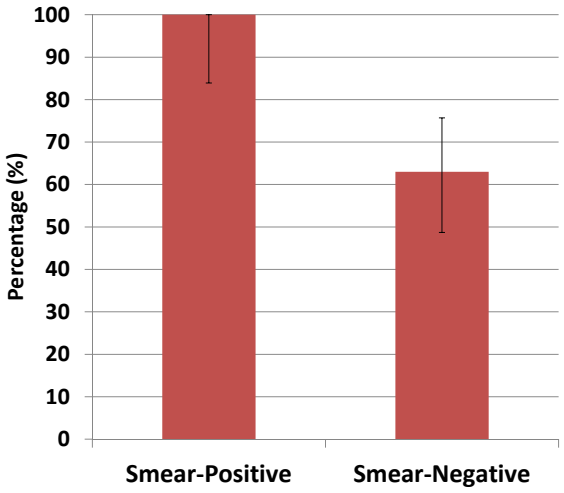
What is the diagnostic accuracy of Xpert MTB/RIF in this most challenging of clinical populations?

Microscopy vs Xpert vs Culture Gold Standard
(All patient samples)

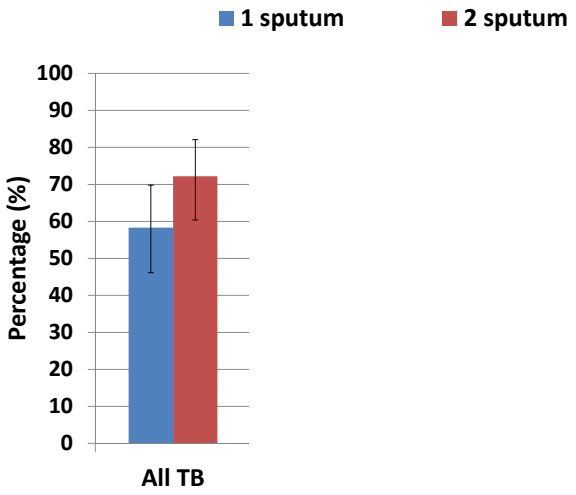


Xpert Sensitivity by Smear Status

(All patient samples)



Xpert Sensitivity: 1 vs 2 samples



How to Use in Diagnostic Algorithms??

Hypothetical cohort (n=1000) with TB prevalence of 20%

	Correct TB diagnoses	Missed TB cases	Xpert tests per TB case diagnosed
S-Sceen + microscopy	55.2	144.8	0
S-Screen + Xpert x1	101	99	6.9
Xpert x1 for all	120.2	79.8	8.3
Microscopy + Xpert x1	120.2	79.8	7.8
S-Screen + Xpert x2	121.2	78.8	11.1
Xpert x2	146.8	53.2	13.2

How to Implement in Screening Algorithms?

Xpert tests used per TB case diagnosed vs TB prevalence:

Diagnostic algorithm	20%	15%	10%	5%
S-Screen + Xpert x1	6.9	9.1	13.5	26.9
Xpert x1 for all	8.3	11.1	16.6	33.2
Microscopy + Xpert x1	7.8	10.6	16.1	32.7
S-Screen + Xpert x2	11.1	14.7	22.1	44.4
Xpert x2	13.2	17.8	26.8	54.1

Lawn et al PLoS Med 2011

Xpert MTB/RIF: A 'game-changer'?

- Pros include
  - Exceptional performance for TB diagnosis
  - Rapid Rif R screening
  - Near patient technology
- Some cons
  - Problems with RIF resistance specificity
  - Expense
    - 4 bay machine $17,000
    - 1 cartridge approx $17
  - Xpert-negative TB
  - Will it be used at point-of-care?

The cost-effectiveness of routine tuberculosis screening with Xpert MTB/RIF prior to initiation of antiretroviral therapy in South Africa: a model-based analysis

Jason R. Andrews[a,b,d,e], Stephen D. Lawn[f,g], Corina Rusu[c,d], Robin Wood[f], Farzad Noubary[c,d,e], Melissa A. Bender[h], C. Robert Horsburgh[i], Elena Losina[b,c,d,e,j,k], Kenneth A. Freedberg[a,b,c,d,e,i,l] and Rochelle P. Walensky[a,b,c,d,e]

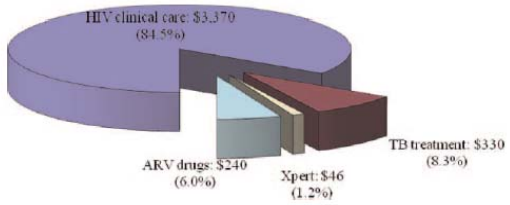


Fig. 1. Component costs of care for the first year after screening. Breakdown of the first year of health care costs for an individual initiating ART in South Africa in the Xpert-2-All strategy, a time frame which total costs may be compared for some budgetary purposes. Total per person costs were $3,990. TB: tuberculosis. ARV: antiretroviral.

MAJOR ARTICLE HIV/AIDS

Characteristics and Early Outcomes of Patients With Xpert MTB/RIF-Negative Pulmonary Tuberculosis Diagnosed During Screening Before Antiretroviral Therapy

Stephen D. Lawn,[1,4] Andrew D. Kerkhoff,[1,5] Monica Vogt,[1] Yonas Ghebrekristos,[3] Andrew Whitelaw,[2,3] and Robin Wood[1]

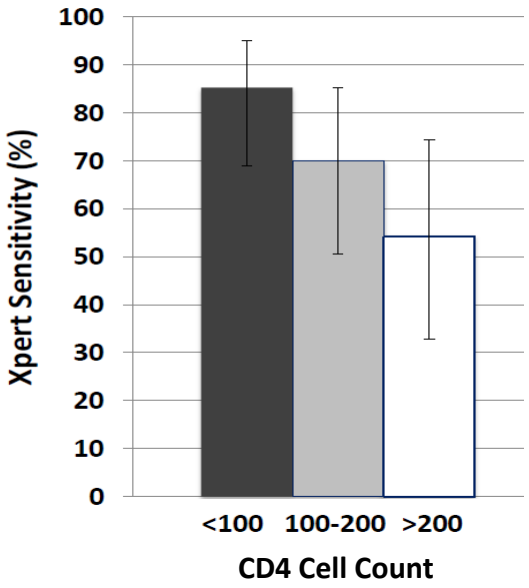
89 patients had *M. tuberculosis* culture-positive TB

- **1 x Xpert: 58% Xpert-positive + 42% Xpert-negative**
- **2 x Xpert: 72% Xpert-positive + 28% Xpert-negative**

Clinical Infectious Diseases 2012

	Xpert-NEG (n=25)	Xpert-POS (n=64)	P value
Age	32.1 (28.3-40.4)	33.5 (26.8-40.7)	0.927
Female, n (%)	16 (64.0)	39 (60.9)	0.789
BMI	22.1 (20.6-28.5)	21.0 (18.8-23.8)	0.037
Hb (g/dL)	11.6 (10.4-13.1)	10.1 (8.5-11.7)	0.029
Neutrophils x10^9 cells/L	2.9 (2.0-3.9)	3.6 (2.5-6.5)	0.021
CD4 cell count	189 (137-215)	106 (37-185)	0.006
Viral load (log)	4.4 (4.2-4.7)	5.1 (4.7-5.5)	<0.001
WHO symptom screen, n (%)	18 (72.0)	55 (85.9)	0.124
Cough >2 weeks, n (%)	2 (8.0)	20 (31.3)	0.028

Sensitivity of Xpert by CD4 cell count



Comparison with other TB diagnostics

	Xpert-NEG (n=25)	Xpert-POS (n=64)	P value
Smear-positive	0	24 (37.5)	<0.001
Culture days to positivity, median (IQR)	21 (17-25)	13.5 (10-18)	<0.001
Urine LAM ELISA	2/25 (8.0)	21/59 (35.6)	0.031
Urine Xpert positive	2/25 (8.0)	15/60 (25.0)	0.084
Median zones CXR parenchymal abnormal	2 (1-4)	3 (2-5)	0.199

90-day ART Programme Outcomes

	Xpert-NEG (n=25)	Xpert-POS (n=64)	P value
Alive and in-programme	21 (84.0)	54 (84.4)	1.0
Dead	0	6 (9.4)	<0.179
LTFU	4 (16.0)	8 (12.5)	0.733
Transfer-out	0	1 (1.6)	1.0
Started TB Rx	17 (68)	49 (76.6)	0.4
Time to TB treatment	32 (26-48)	9 (6-18)	<0.001

Conclusions

- Xpert diagnoses the 'more important' TB cases
- Patients in whom a TB diagnosis is missed (Xpert-negative) have 'time on their side' for rescreening

90-day ART Programme Outcomes

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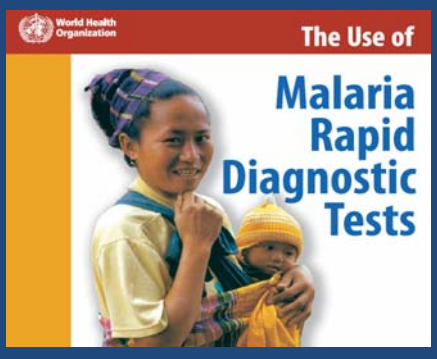
Time to TB treatment (median [IQR] days)	32 (26-48)	9 (6-18)	<0.001

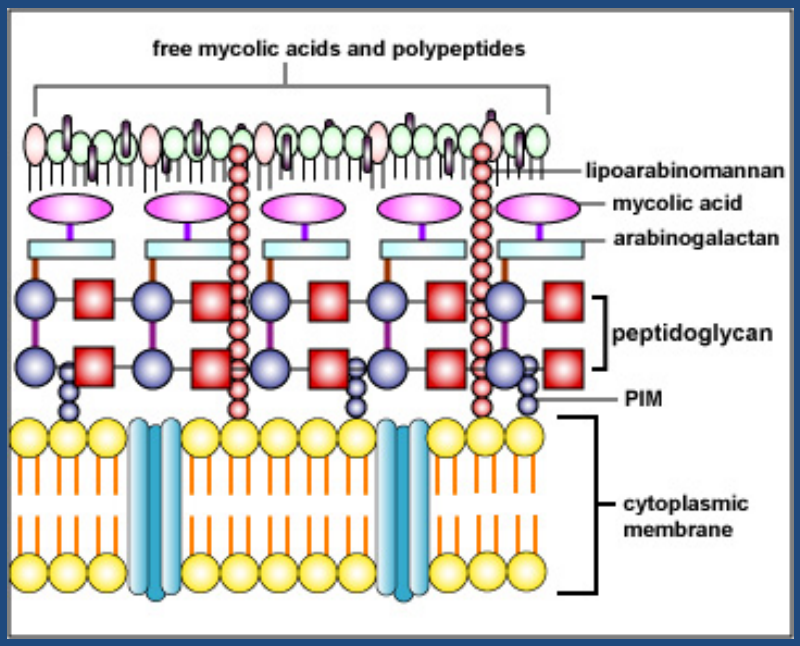
Living with HIV, dying of TB
We need a POC TB test!



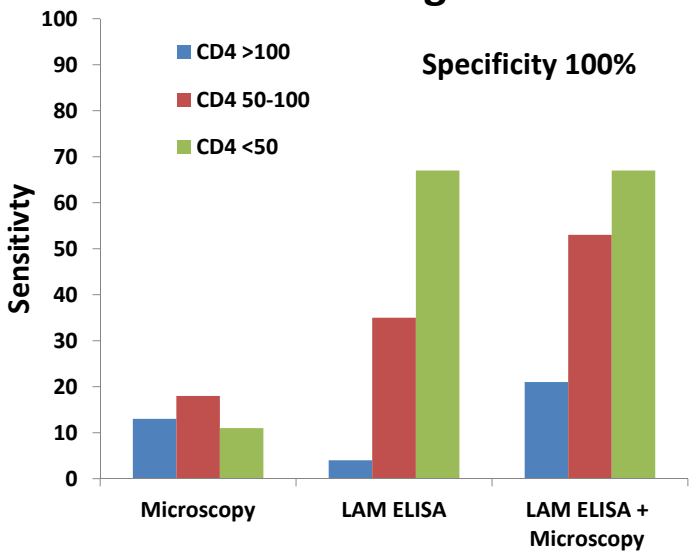
Urine lipoarabinomannan assay for tuberculosis screening prior to ART: diagnostic yield and association with immune reconstitution disease

Stephen D. Lawn[a,b], David J. Edwards[a], Katharina Kranzer[a,b], Monica Vogt[a], Linda-Gail Bekker[a] and Robin Wood[a]

AIDS 2009

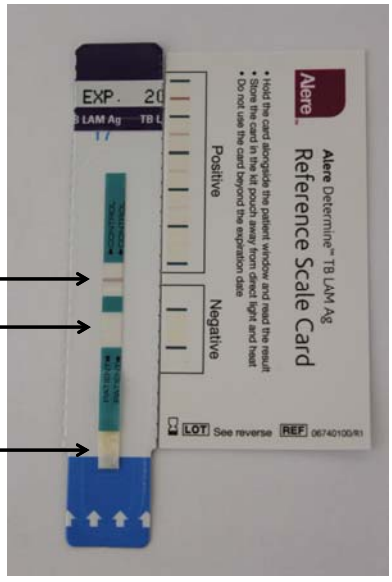


Sensitivity of LAM ELISA for TB Screening Pre-ART

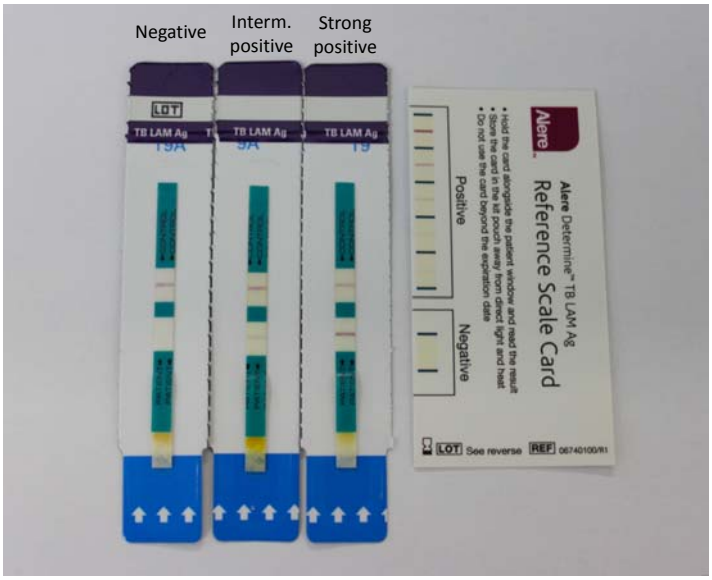


Lawn et al. AIDS 2009

Determine TB-LAM Ag



Determine TB-LAM Ag



Advantages of Urine Test Strip

- **Low-cost ($3.50 per test)**
- **Truly POC**
- **Urine easy to obtain and easier / safer / quicker than sputum expectoration or induction**
- **Hands-on time <5 mins / results in 25 mins**
- **Simple read-out - no hard-ware**
- **Rapid diagnosis in those who need quick management decisions**

Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study

Stephen D Lawn, Andrew D Kerkhoff, Monica Vogt, Robin Wood

Lancet Infectious Diseases 2011: epub ahead of print

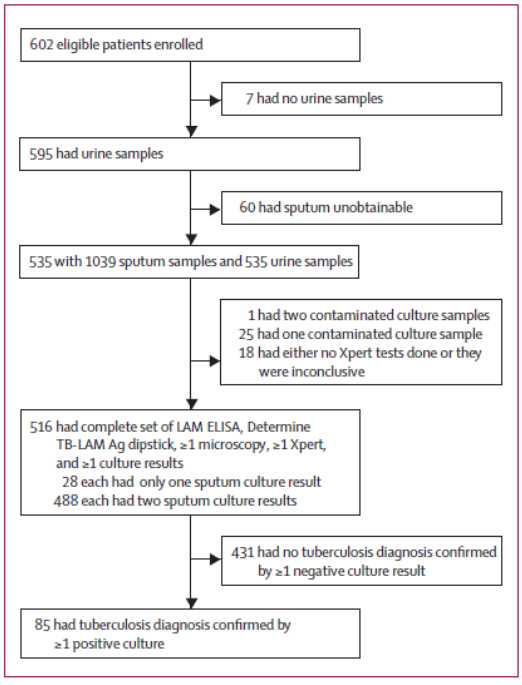
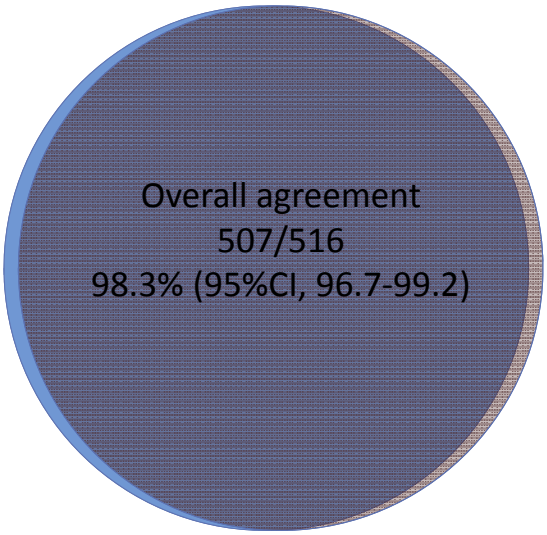


Figure 1: **Study profile**

Agreement between two readers?

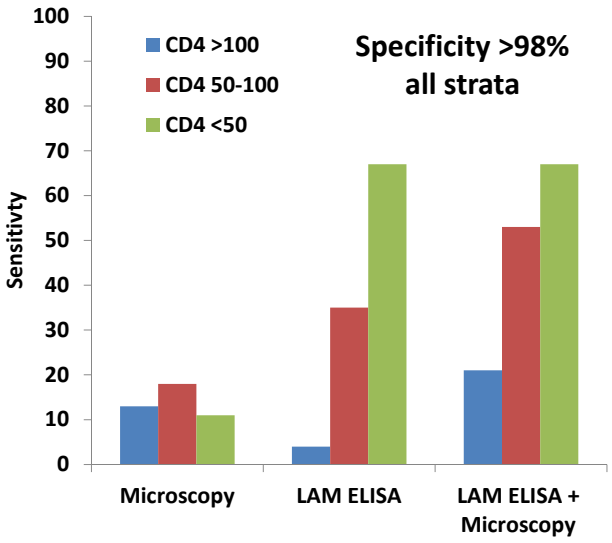
Kappa= 0.97
(95%CI, 0.88-0.99)

Agreement between TB-ELISA and Determine TB-LAM Strips?

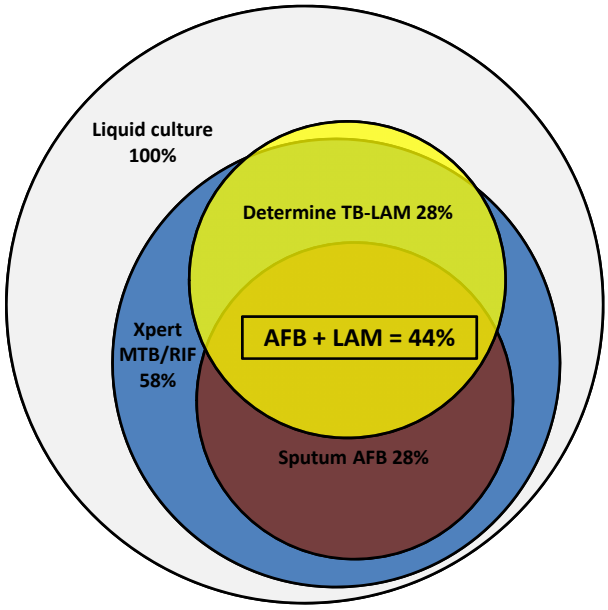


Kappa= 0.84
(95%CI, 0.72-0.92)

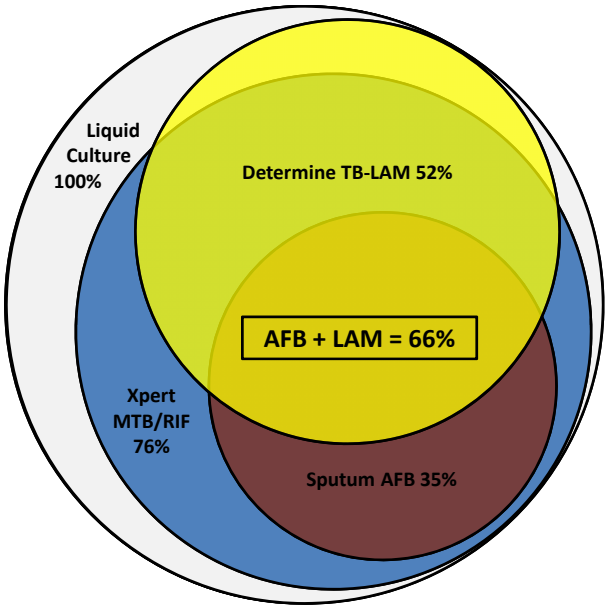
Sensitivity of LAM POC test



Sensitivity of TB diagnostic assays among all TB patients (n=85)



Sensitivity of TB diagnostics among patients with a CD4 <100 cells/µL



PPV and NPV

Patients	TB Prevalence (%)	PPV (%)	NPV (%)
All patients	16.5	84.1	89.8
CD4<50	28.1	92.9	90.0
CD4<100	22.7	95.0	90.7
CD4<150	20.5	93.1	90.3
CD4<200	18.2	88.6	90.3
CD4≥200	13.2	75.0	89.5
WHO stage 3/4	22.4	91.7	89.7
WHO symptom screen positive	19.7	87.2	88.6
CXR abnormal	26.4	90.3	83.7

Clinical Significance of LAM+ Disease?

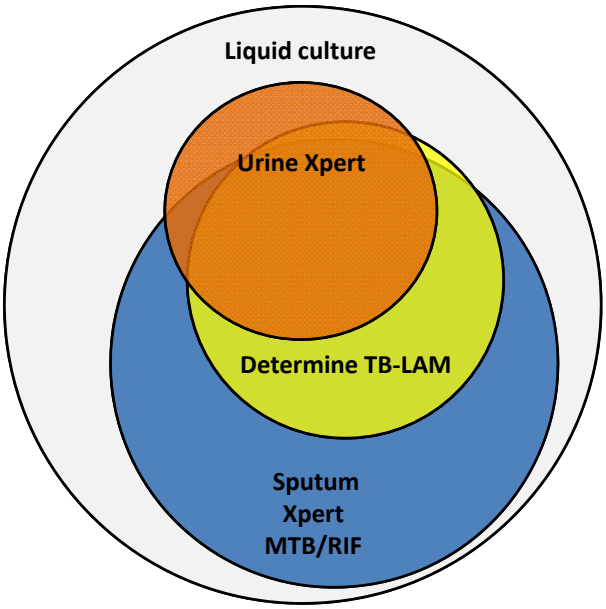
- Comparison LAM+ TB cases versus LAM- TB cases
- LAM+
  - More advanced HIV (lower CD4, higher VL)
  - Sicker (lower Hb, BMI, higher neutrophils, more symptoms)
  - Evidence of higher mycobacterial bacillary burden

    (smear+, time to culture positivity, sputum Xpert+, urine Xpert+)

Lawn et al AIDS 2012; submitted

- All 5 deaths within 90 days were LAM+
- i.e. LAM POC TEST DIAGNOSES THE SICKEST PATIENTS WITH HIGHEST MORTALITY RISK
- Use at POC could permit immediate TB Rx and might improve survival

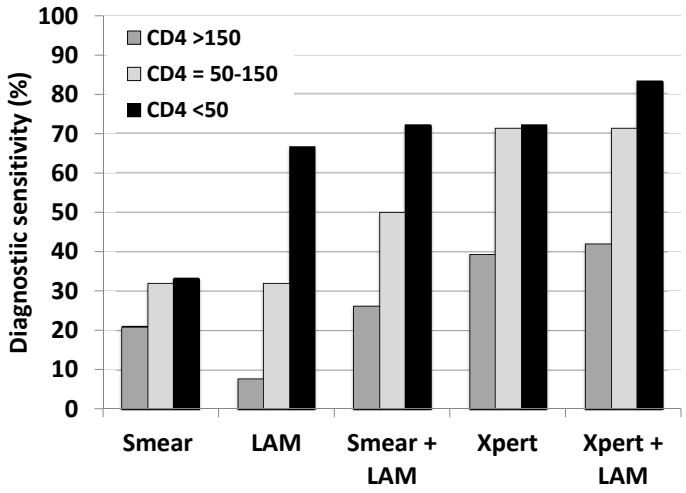
Identifying those with highest mortality risk



LAM Conclusions

- Advanced HIV+ with CD4 <150 cells/uL
- Rapid screening + Rx of sickest patients eg pre-ART or new in-patient admissions
- Not a stand-alone test: use in combination

Diagnostic sensitivity of LAM point-of-care assay used alone or in combination with other assays



Lawn SD. 2012 (submitted)

Combinations: advantages
Smear microscopy + LAM POC
CXR + LAM POC
Culture + LAM POC
Xpert + LAM POC

Overall Conclusions

- Xpert MTB/RIF and Determine TB-LAM Ag both have excellent utility for TB diagnosis among individuals with advanced immunodeficiency
- Sensitivity and specificity aren't everything:
  - What other information does the test give?
  - Ability to use at point-of-care is a MAJOR issue
- Need for impact studies

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