Urinary TB diagnostics in HIV

SAMRC UCT Eastern Cape
collaborative research symposium

20th October 2017
David Stead

Burden of tuberculosis at post mortem in inpatients at a tertiary referral centre in sub-Saharan Africa: a prospective descriptive autopsy study

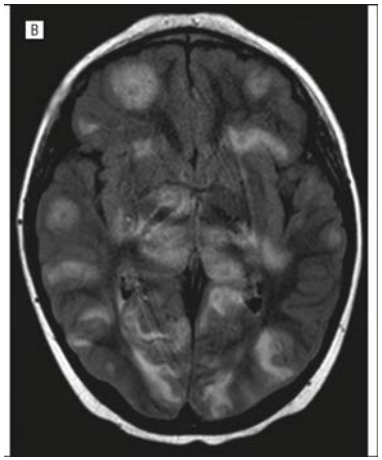
Matthew Bates, Victor Mudenda, Aaron Shibemba, Jonas Kaluwaji, John Tembo, Mwila Kabwe, Charles Chimoga, Lophina Chilukutu, Moses Chilufya, Nathan Kapata, Michael Hoelscher, Markus Maeurer, Peter Mwaba, Alimuddin Zumla

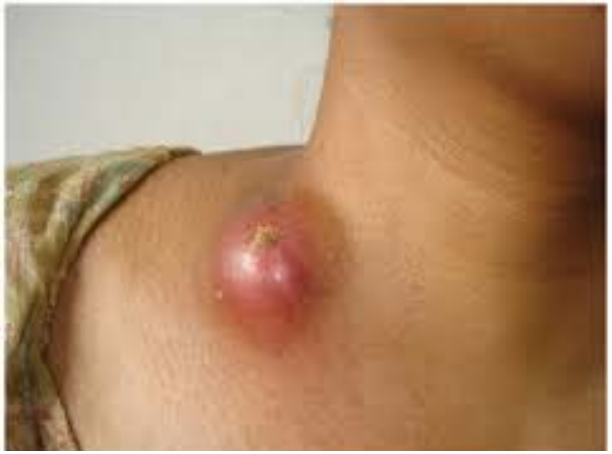
- Prospective PM study in Zambian tertiary hospital
  - All medical deaths over 1 year
  - 125 (9%) included
- 81% HIV-infected
- 62% diagnosed with TB, half of these had EPTB
- **A quarter of patients with TB not on treatment at time of death**

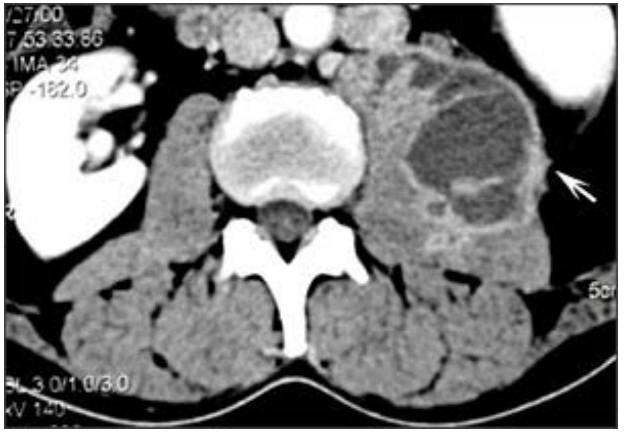
Lancet Infect Dis 2015;15: 544–51

HIV-associated TB difficult to diagnose

- Sputum paucibacillary
- EPTB more common
  - Limited access to extra-pulmonary diagnostics
    - Ultrasound
    - Biopsies
  - Tests less accurate

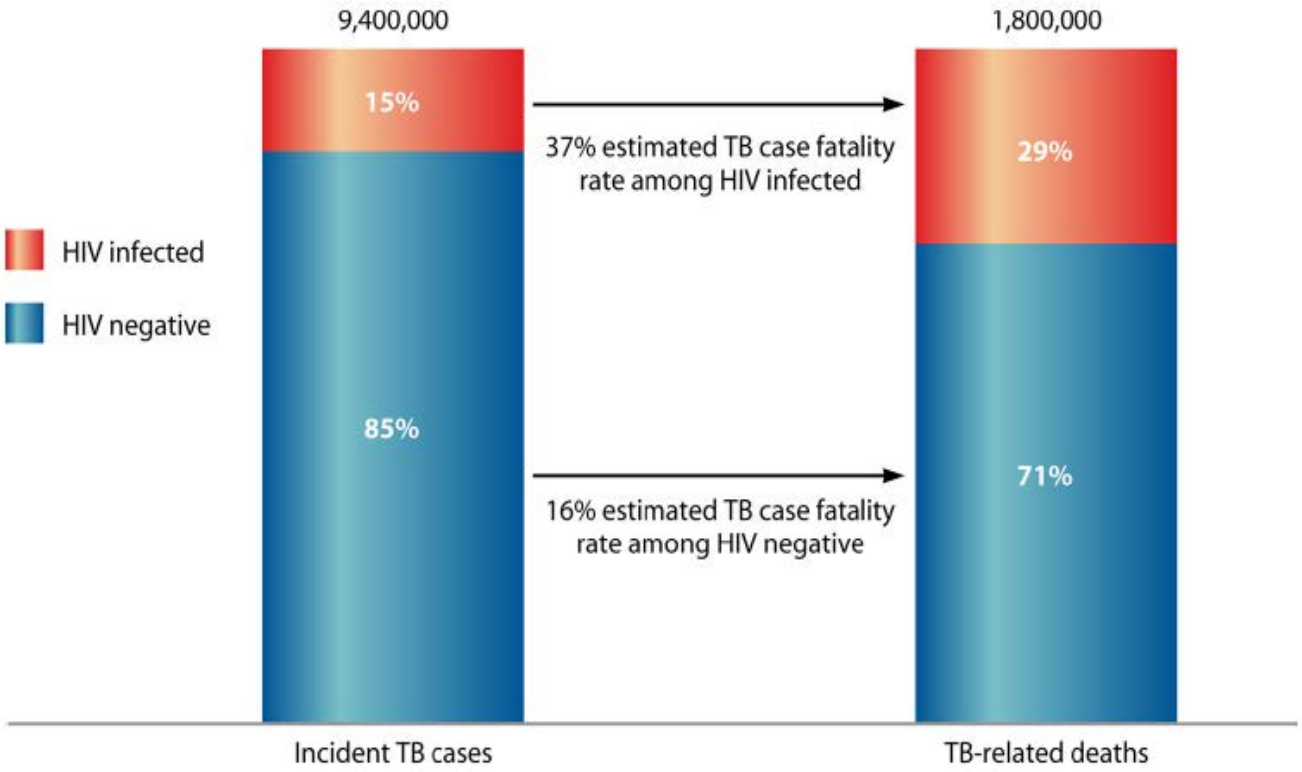






HIV related TB progresses more rapidly

- "HIV-positive patients with smear-negative tuberculosis are more likely to die during or before diagnosis"



Getahun 2007
Kwan 2011

Limitations of sputum Xpert

- Centralised
  - Delays in initiating Rx: median 9 days in one study
- Suboptimal sensitivity with single specimen
  - 72% after a negative smear
- Poor performance in patients unable to produce sputum
  - Variable yield on extra-pulmonary specimens

Lawn CID 2012
Steingart 2013
Friedrich 2013
Lawn PLoS Med 2011

Rapid microbiological screening for tuberculosis in HIV-positive patients on the first day of acute hospital admission by systematic testing of urine samples using Xpert MTB/RIF: a prospective cohort in South Africa

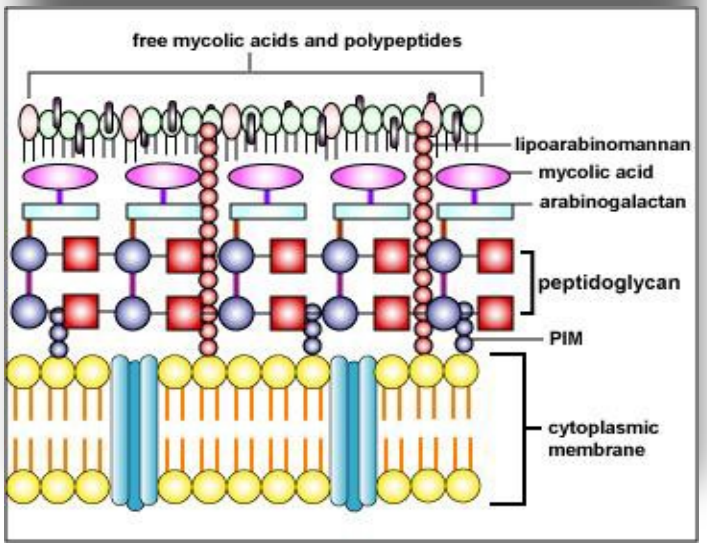
Stephen D. Lawn[1,2,3*], Andrew D. Kerkhoff[2,4,5], Rosie Burton[3,6,7], Charlotte Schutz[3,8], Gavin van Wyk[3,6], Monica Vogt[2], Pearl Pahlana[2], Mark P. Nicol[9,10] and Graeme Meintjes[3,8,11]

- 427 unselected HIV+ new admissions
- Intensively investigated for TB first 24 hrs
- 32% TB prevalence
- Overall 37% able to produce sputum
  - 79% of those with a cough
- Xpert sputum sensitivity: 28%

Lawn *et al. BMC Medicine* (2015) 13:192

Urinary LAM:
Principle of the test

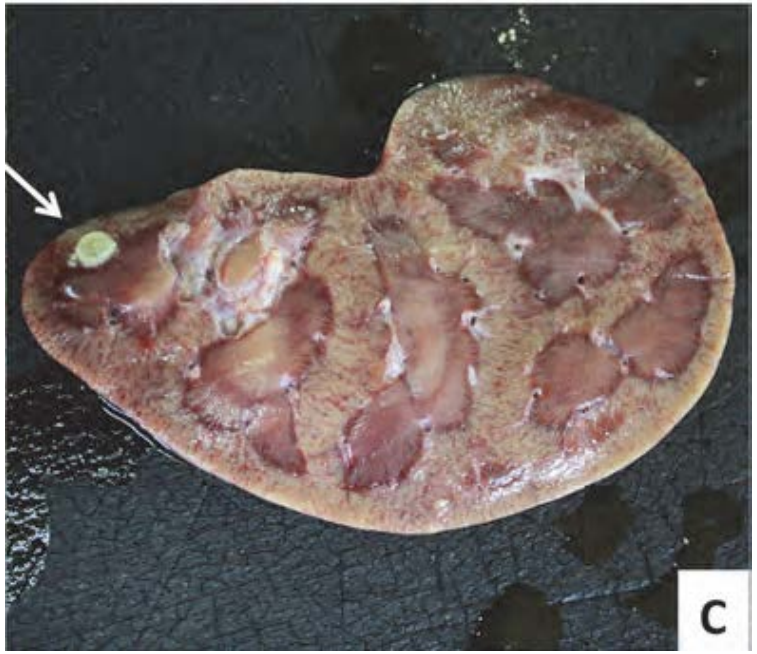
- Lateral flow assay that detects lipoarabinomannan (LAM) antigen of *Mycobacteria* in human urine
- LAM: 17.5 kD glycolipid found in the outer cell wall of mycobacterial species
- Immunogenic virulence factor released from metabolically active or degrading bacterial cells during TB infection
- LAM is heat stable, "filtered by the kidney" and detectable in the urine



Cell wall structure

How does LAM get into the urine?

- Free LAM is antibody bound thus unlikely to pass through glomerulus
- Correlation of LAM+ with TB blood culture+
- Renal TB at autopsy common in disseminated TB, and TB bacteraemia



(Stephen D. Lawn. Trans R Soc Trop Med Hyg 2016)

Where are we at in terms of the evidence?

- 2016 Cochrane review:

- Pooled sensitivity and specificity of LF-LAM:
  - CD4>100: 26% (16%-46%) and 92% (78%-97%)
  - CD4 <100: 56% (41% -70%) and 90% (81%- 95%)

WHO LF-LAM Policy 2015

LF-LAM may be used to assist in the diagnosis of TB in HIV positive **adult in-patients** with

- signs and symptoms of TB (pulmonary and/or extrapulmonary)
- who have a **CD4 cell count ≤ 100** cells/µL,
- Or who are **seriously ill** regardless of CD4

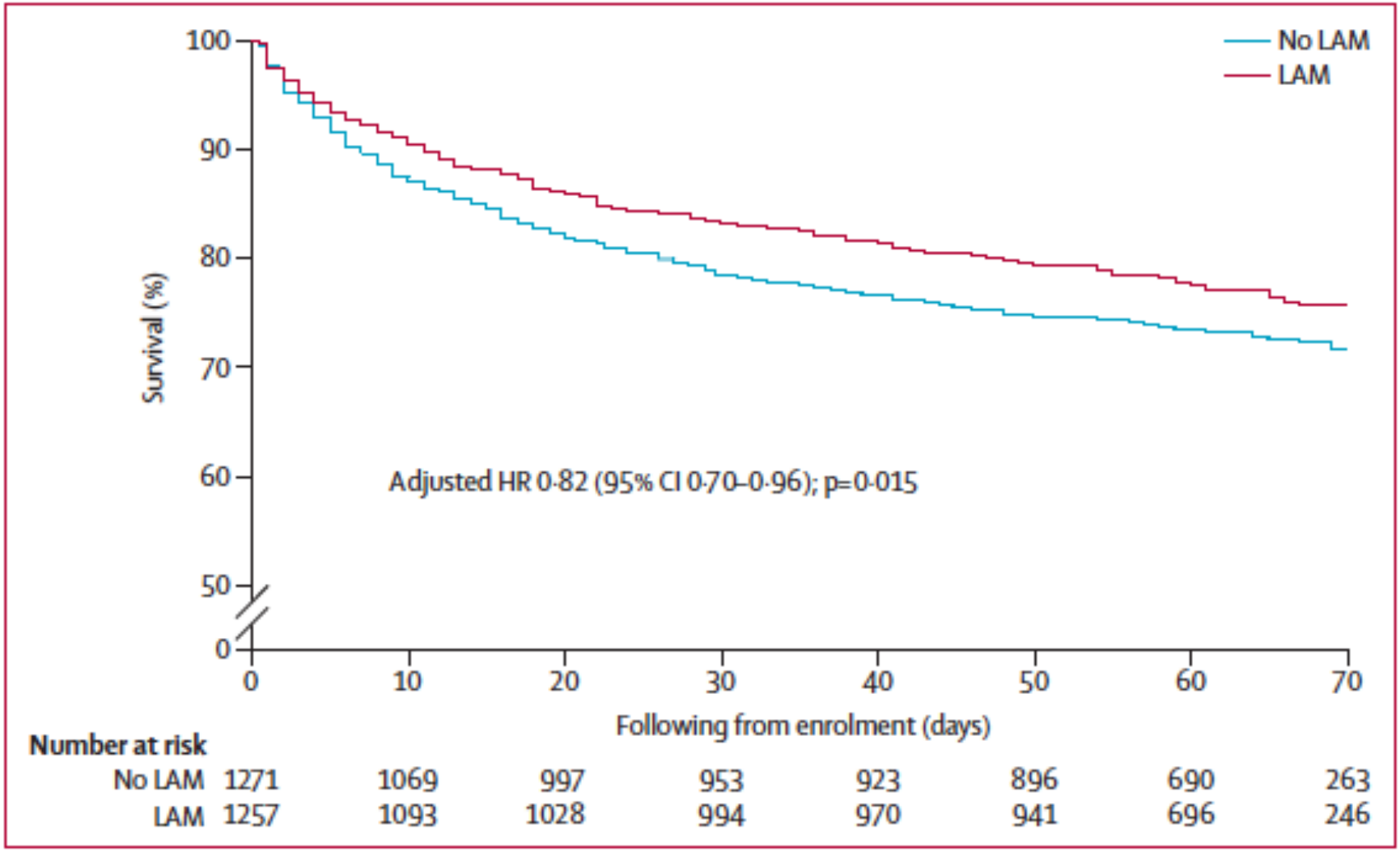
count or with unknown CD4 count

Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial

- 10 hospitals in SSA
- Inclusion: HIV+ adults, admitted to hospital with at least 1 TB symptom (cough, fever, night sweats, weight loss)
- Randomised to LAM or no LAM in addition to standard of care (Xpert, smear, culture)
- 2659 patients included
- Primary outcome: 8 week mortality

(Peter, J. Lancet 2016)

Kaplan-Meier survival
8 week all cause mortality



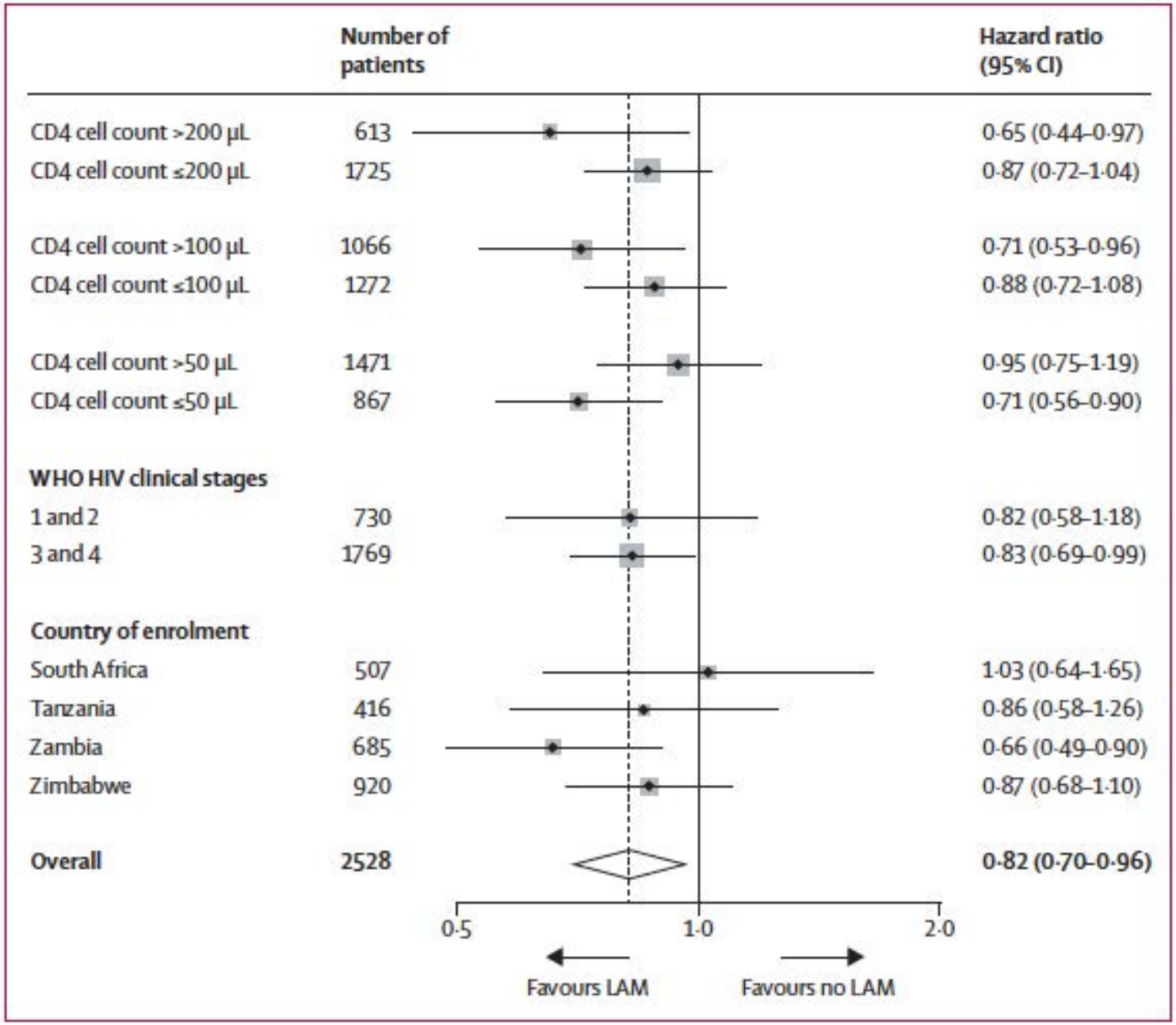
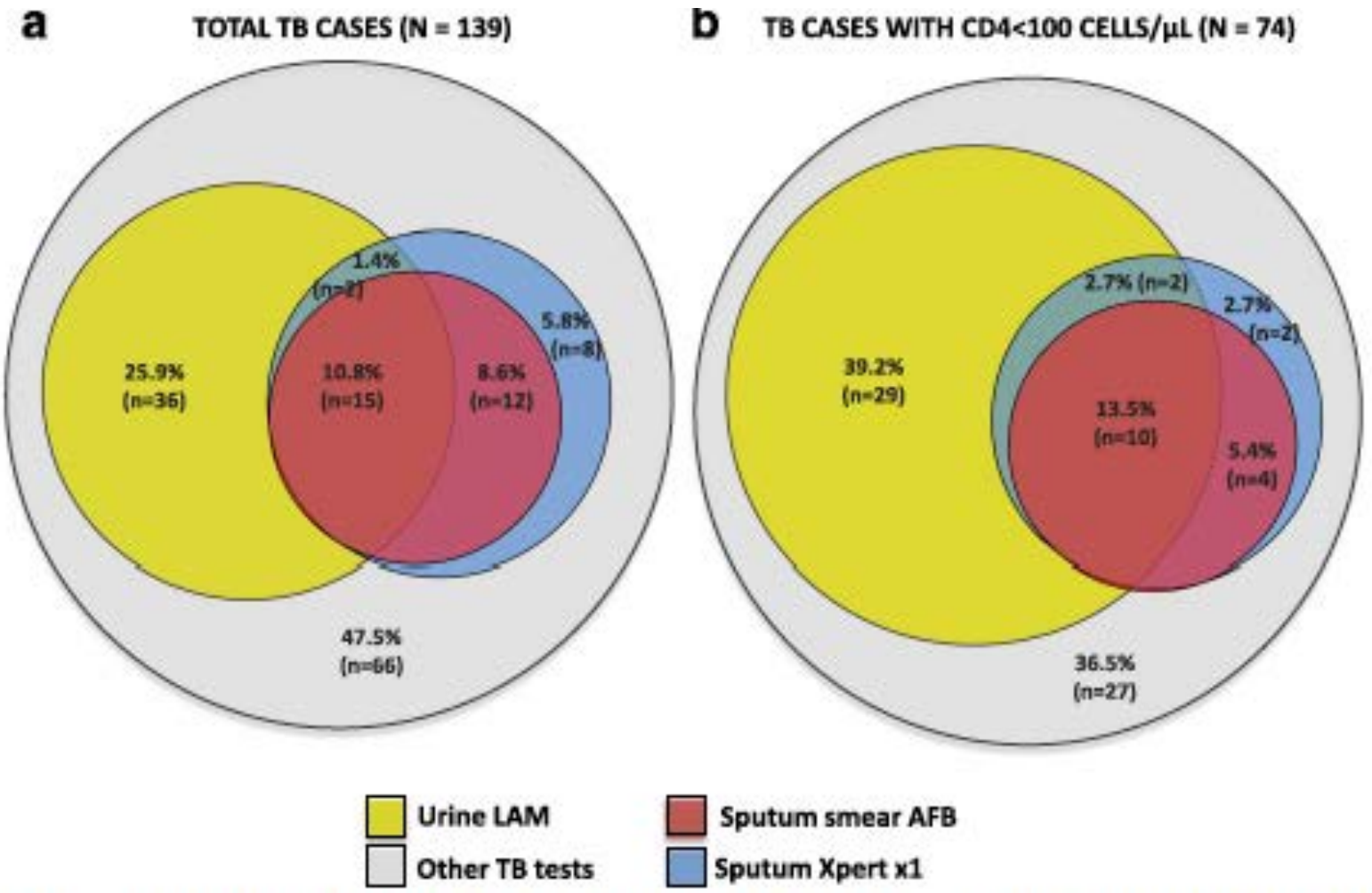


***Figure 3*: Effect sizes for 8-week all-cause mortality**

Back to the Jooste TB screening study…



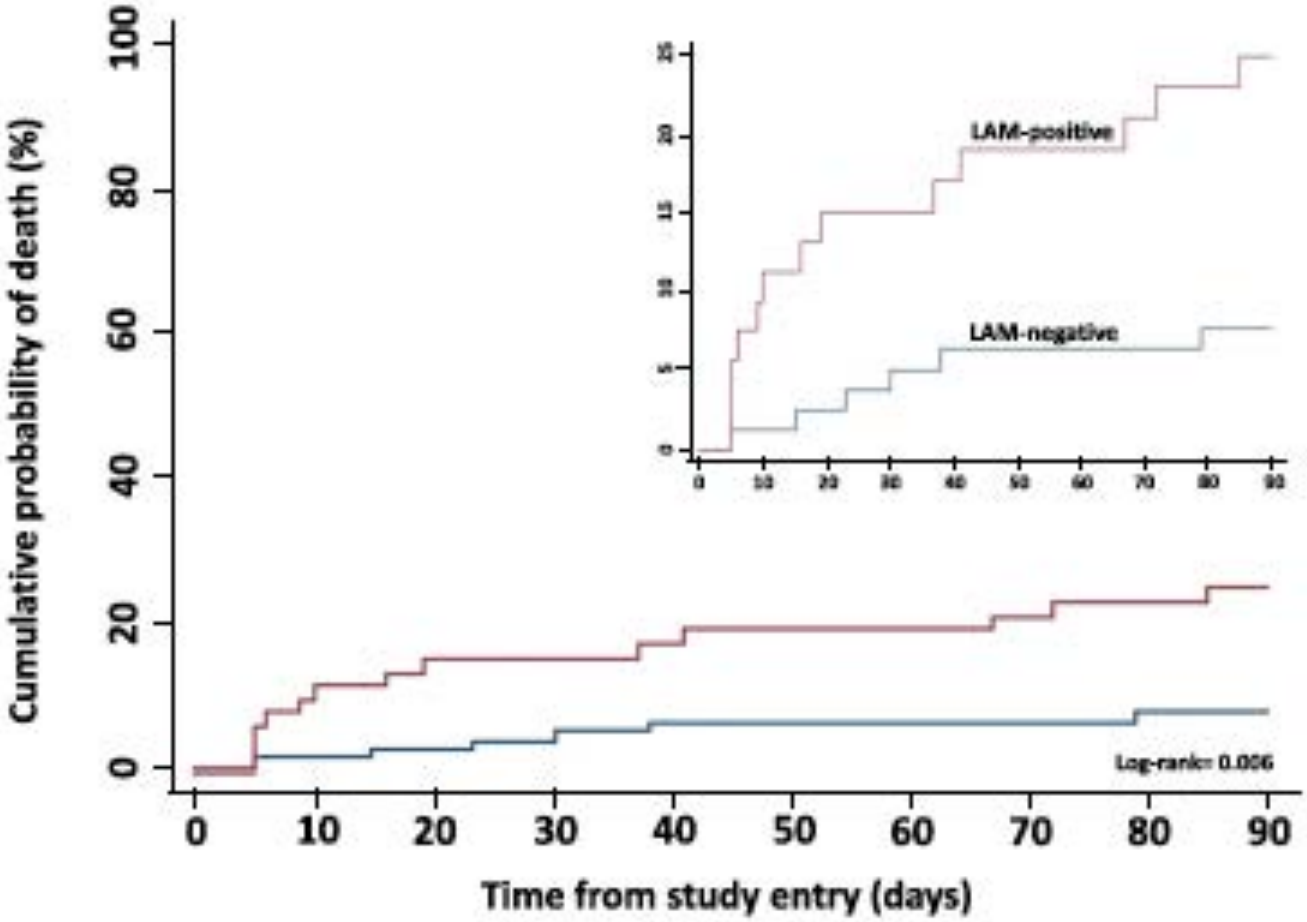
Lawn *et al. BMC Medicine* (2017) 15:67

Comparative diagnostic sensitivities

	All TB (n=137)	TB CD4<100 (n=74)
Sputum smear	19%	19%
Sputum Xpert	27%	24%
U-LAM	38%	55%
U-Xpert	64%	77%
U-LAM + sp Xpert	53%	64%
U-Xpert + sp Xpert	78%	83%

Lawn *et al. BMC Medicine* (2017) 15:67

LAM predicts 90 day mortality



AHR – 4.2 (1.5-11.7)

Lawn *et al. BMC Medicine* (2017) 15:67

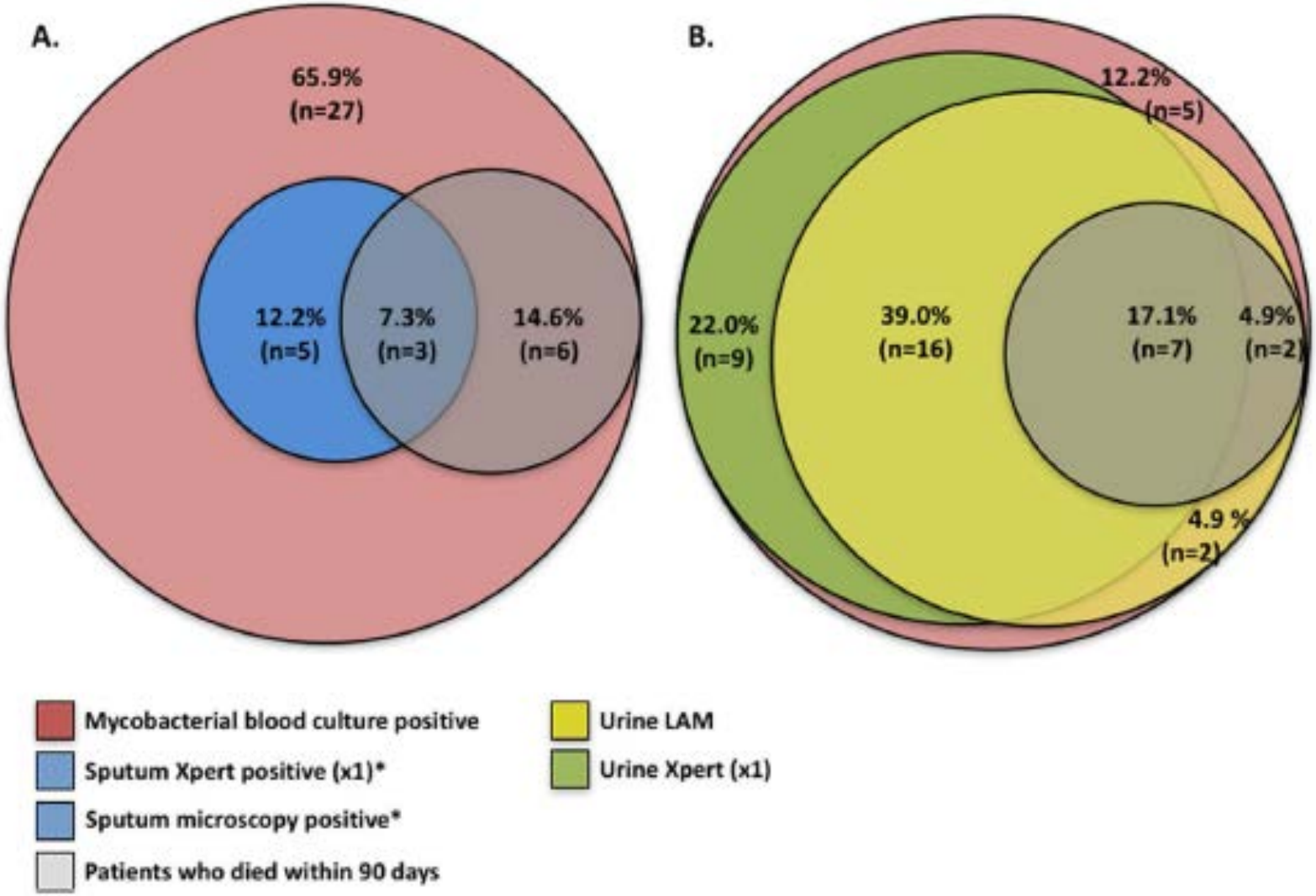


Figure 1. Venn diagram showing the proportions of *Mycobacterium tuberculosis* blood culture positive patients (n = 41) who had a TB diagnosis made by rapid microbiological tests. (A) Sputum-based diagnostics and (B). Urine-based diagnostics. Percentages represent the proportion of patients with positive

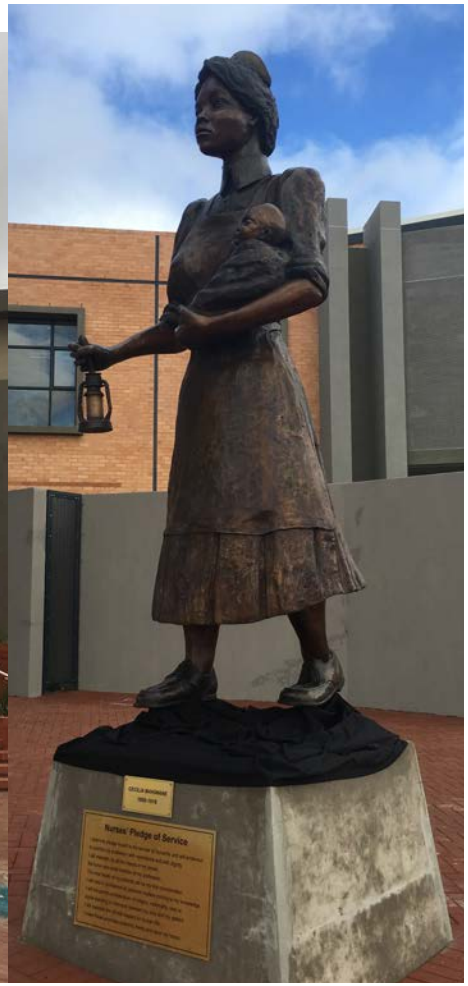
(Kerkhoff, A. Sci rep. 2017)

Xpert MTB/RIF Ultra

- Sensitivity close to culture
- Improved specificity for rifampicin resistance

(CROI abstract 91, 2015)

Proposed Cecilia Makiwane hospital urine TB diagnostics study:



Study design

- A comparative performance of LF-LAM and Xpert MTB/RIF ultra on urine
- Inclusion:
  - HIV+ adults admitted to CMH medicine with one or more TB symptom
  - Including all CD4 counts
- Exclusion:
  - On TB therapy, or within previous 60 days
- Routine TB blood cultures

Outcomes

- Primary:
  - Comparative sensitivity & specificity of the 2 urine tests
- Secondary:
  - U-LAM prevalence
  - Impact of a positive urine test on antibiotic exposure

Questions?

Limitations

- **Does Disseminated Nontuberculous Mycobacterial Disease cause False-positive Determine TB-LAM Lateral Flow Assay Results?**
- 26 patients with confirmed disseminated NTM
- 3 had proven TB-NTM co-infection
- 23/26 had LF-LAM performed:
  - Positive in 21/23 = (91.3%, 95% CI 73.2-97.6%)
  - Excluding proven TB co-infections:
    - Positive in 19/21 = (90.5%, 95% CI 71.1 – 97.4%)

(Nel j. Open forum Infectious diseases. 2017:4 (suppl. 1))