TB diagnosis and management among hospitalised patients with HIV:

Current issues

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Advanced Clinical Care (ACC)
Live Tutorial session

22 August 2024

Q1

In a patient with HIV and a current CD4 = 45, diagnosed with TB meningitis, and who had interrupted ART 2 years ago. When should the clinician restart ART in relation to starting TB treatment?

1. Restart ART on the same day as TB treatment

2. Restart ART 1-2 weeks after starting TB treatment

3. Restart ART 4-8 weeks after starting TB treatment

4. Wait 12 weeks after starting TB treatment and then restart ART

Q2

What is the correct dose of dolutegravir in adult patients being treated with TB treatment that contains rifampicin?

1. Dolutegravir 50mg daily
2. Dolutegravir 100mg daily
3. Dolutegravir 50mg twice daily
4. Dolutegravir 100mg twice daily

Q3

In a patient with HIV admitted to hospital, who has a 2-month history of weight loss, fatigue and night sweats, an abdominal ultrasound is performed as part of the diagnostic work-up. This shows several periportal abdominal lymph nodes 2cm in diameter. This finding can be interpreted to mean the following:

1. This patient definitely has TB and no further diagnostic work-up is required

2. The finding is suggestive of TB, but further work-up is required before starting TB treatment

3. The finding is suggestive of TB, TB treatment can be started, but further diagnostic tests to confirm the microbiological diagnosis of TB are required and the patient should be followed up to assess treatment response

4. The finding is more suggestive of lymphoma than TB and TB treatment should not be started

Q4

An Alere urine LAM assay is performed in a patient admitted to hospital with TB symptoms. The test is read at 25 minutes and the patient band shows a very faint line, less than 1+ in intensity on the reading card. This should be interpreted as:

1. A negative result

2. A trace positive result

3. A positive result

4. An invalid result

Q5

The Alere urine LAM assay has higher diagnostic sensitivity in:

1. HIV negative patients compared to people living with HIV
2. People with HIV with CD4 < 50 compared to those with higher CD4 counts
3. People with HIV with CD4 > 200 compared to those with lower CD4 counts
4. People with HIV with CD4 > 500 compared to those with lower CD4 counts

Overview

1. Epidemiology of HIV-associated TB

2. TB diagnostic challenges among patients with HIV in hospital

3. Studies of disseminated HIV-associated TB
   - Pathogenesis
   - Treatment

HIV

↑ TB disease risk up to 30-fold

Increased risk (2-fold) even in first year of HIV infection

Highest risk when CD4 < 200 and person not on ART (>30% per annum in Cape Town)
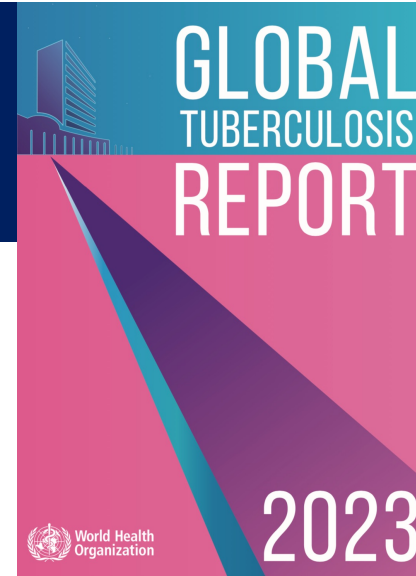
ART

ART reduces the risk of TB disease by 57-84%

Risk of TB on long term ART appears to remain elevated above background risk

Sonnenberg, J Infect Dis 2005
Boulle, unpublished
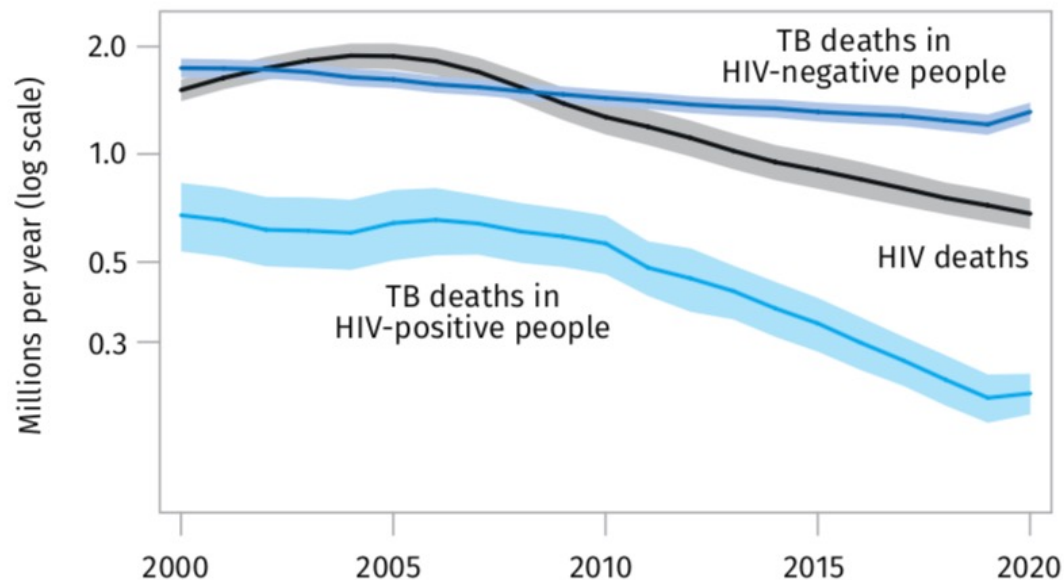Suthar, PLoS Medicine 2012
Gupta, PLoS ONE 2012

Global epidemiology of HIV-TB

FIG. 6

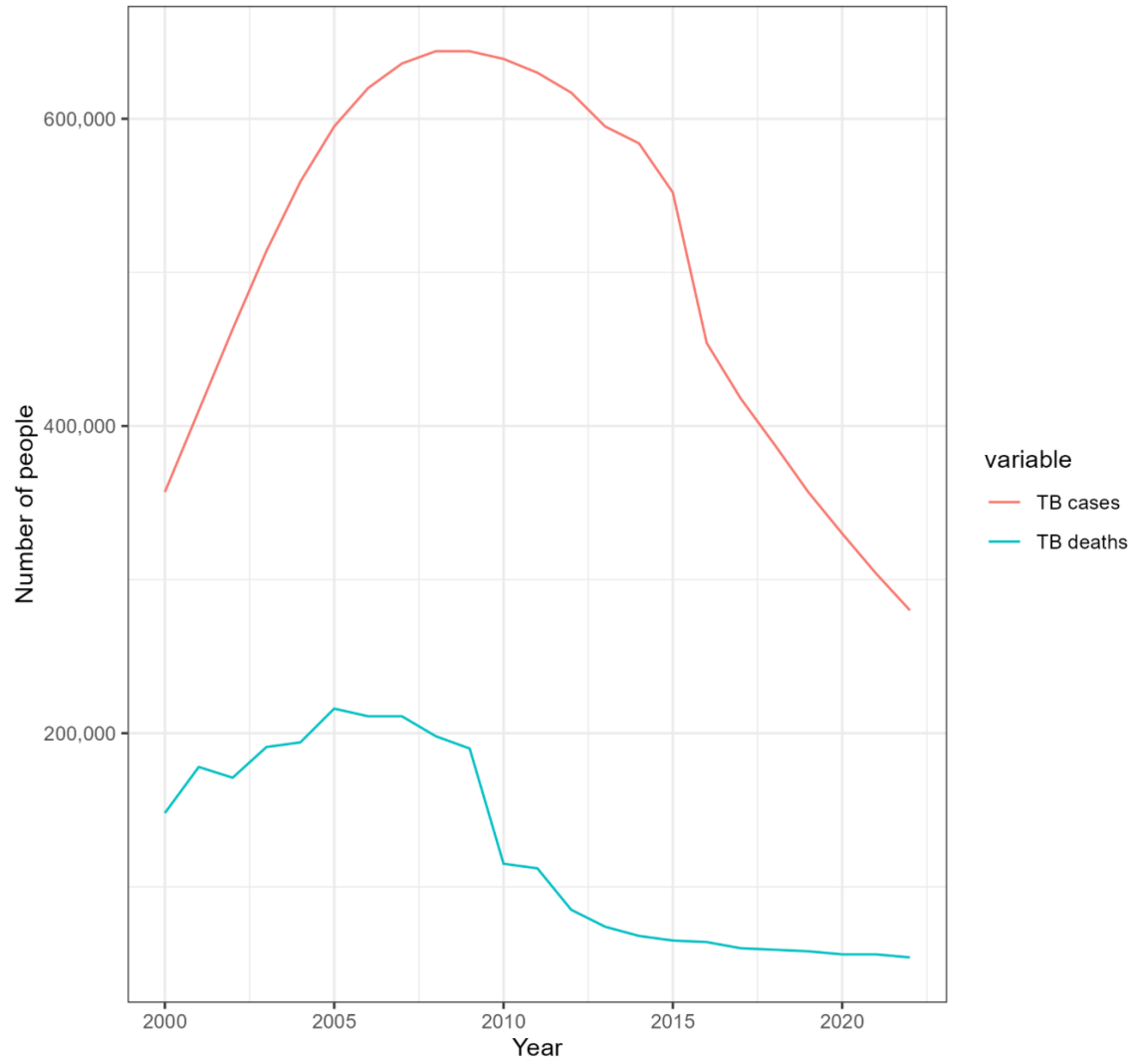**Global trends in the estimated number of deaths caused by TB and HIV, 2000–2020[a,b]**

Shaded areas represent uncertainty intervals.

In 2022:

- Out of 10.6 million globally
  - 671 000 (6.3%) PLWH

- 167,000 TB deaths in PLWH
  - More than 60% reduction from 2000

TB cases and TB deaths over time in SA

Graph by Spotlight. Data courtesy WHO.

Tuberculosis profile: South Africa

Population 2022: 60 million

Estimates of TB burden*, 2022

	Number	(Rate per 100 000 population)
Total TB incidence	280 000 (182 000-398 000)	468 (304-665)
HIV-positive TB incidence	152 000 (99 000-217 000)	255 (166-362)
MDR/RR-TB incidence**	11 000 (6 700-16 000)	19 (11-26)
HIV-negative TB mortality	23 000 (22 000-24 000)	39 (37-41)
HIV-positive TB mortality	31 000 (9 900-64 000)	52 (17-107)

54% of people falling ill with TB are living with HIV
57% of those dying with TB have HIV infection

Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis
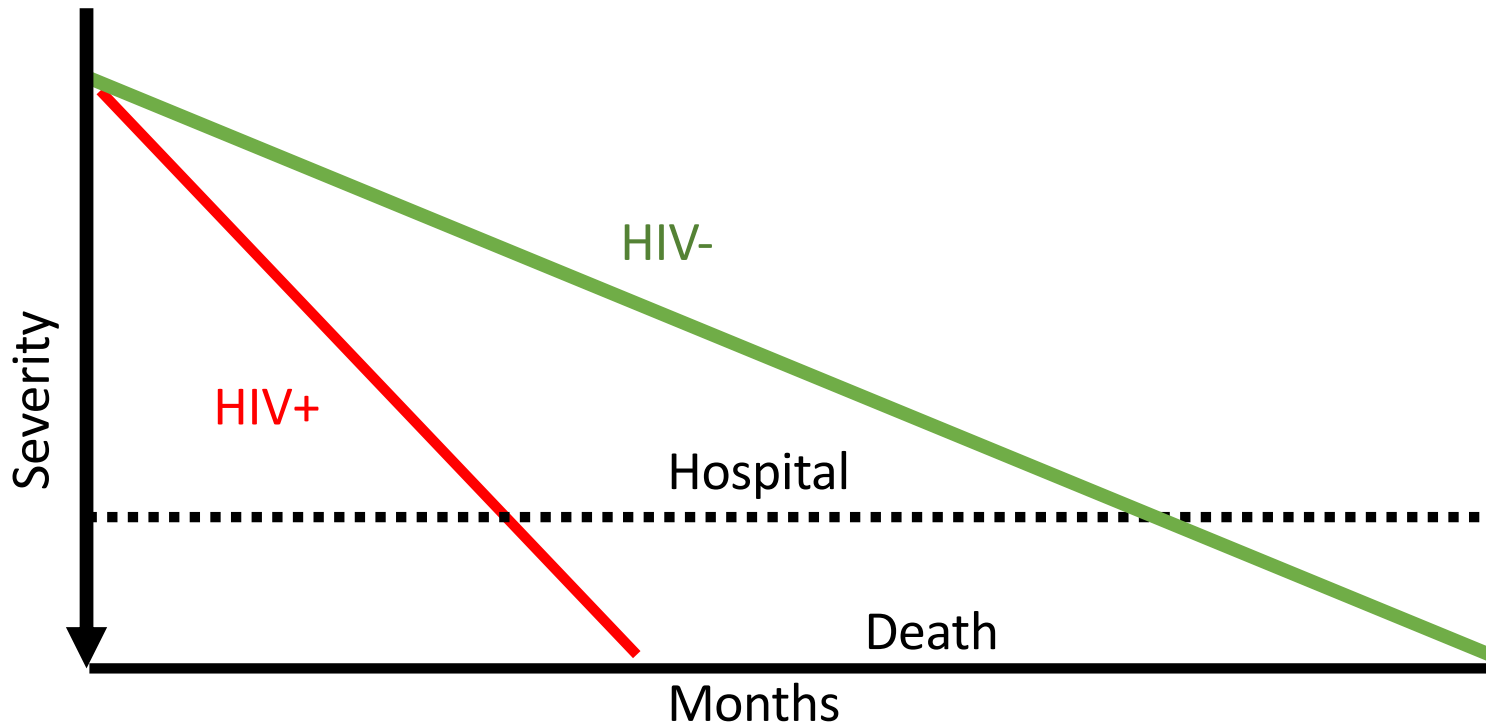
Rishi K. Gupta[a], Sebastian B. Lucas[b], Katherine L. Fielding[c] and Stephen D. Lawn[d,e]

- In LMIC, TB prevalence at autopsy in adults = 39.7% (36 studies)
  - TB was cause of death in > 90%
  - Undiagnosed at death in 45.8%

- In sub-Saharan Africa, TB prevalence at autopsy = 43.2% (9 studies)

- TB was disseminated in 87.9%
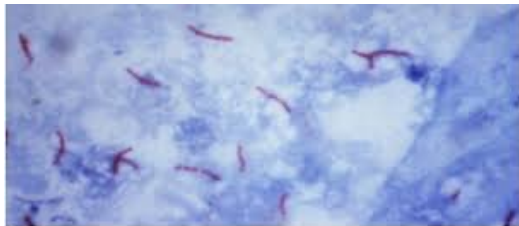 - Lung, liver, spleen and lymph nodes

Diagnostics for HIV-associated TB

Progress in diagnostics for TB

Sputum smear
Limited sensitivity (30-40%) in PLHIV

TB culture
Reference standard
Several weeks delay
Not widely available
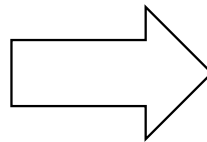
Xpert and now **Xpert Ultra MTB/RIF**
Automated PCR in cartridge
Takes 2 hours
Provides rifampicin susceptibility
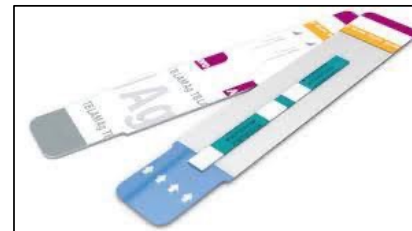
Urine LAM
Dipstick test with drop of urine
Takes 30 minutes

MacLean, Curr Opin HIV AIDS, 2018
Dorman, Lancet Infect Dis 2018;18:76
Bahr, Lancet Infect Dis 2018; 18:68
Shah, Cochrane Systematic Review, 2016

Sputum Xpert Ultra

- Meta-analysis (3 studies) among people with HIV:
  - Sensitivity: 87.6%
  - Specificity: 92.8% } Relative to sputum TB culture

    Zifodya, Cochrane Database Syst Rev 2021

- WHO (2021) recommended that certain molecular rapid diagnostics (including sputum Xpert Ultra) may be used for routine TB screening in settings with a high TB burden
  - Particular recommendation for systematic testing of inpatients with HIV in medical wards where TB prevalence > 10%

- Sputum sample can be difficult to obtain in inpatients
  - Only 38% - 81% produced in our studies
  - PCR testing of tongue swabs being investigated
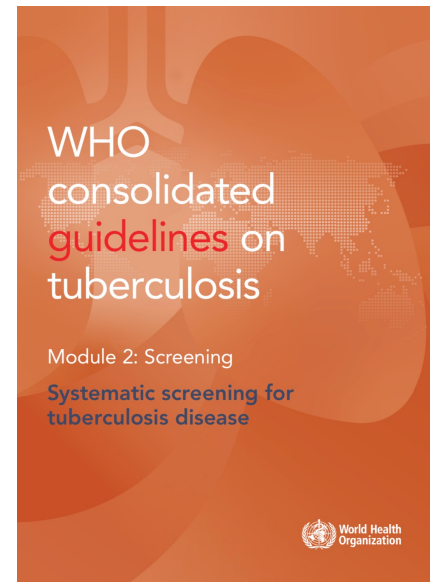
Alere urine lipoarabinomannan (LAM) test

- Always use Reference Scale Card
  - Very faint bands are negative
  - Only read as + if patient band:
    = or > intensity of 1+ band

- Read and discard after 25 minutes
  - Maximum 35 minutes

1+ band
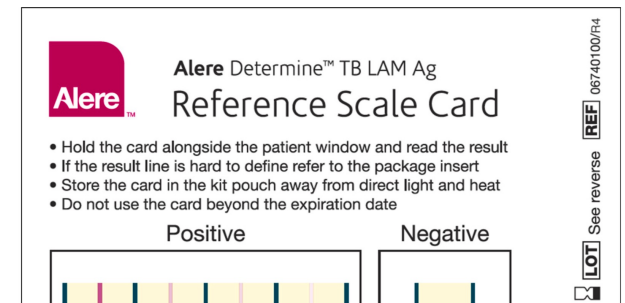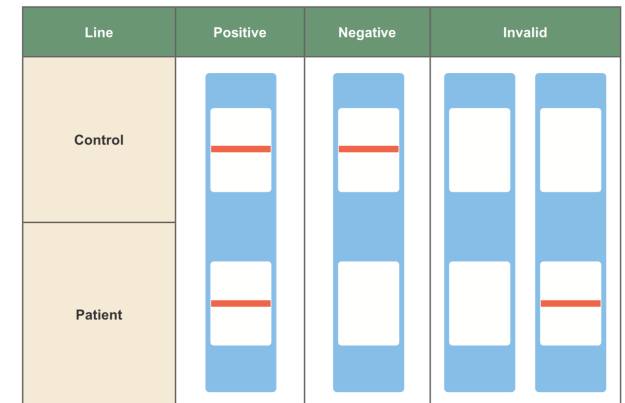
Urine Alere lipoarabinomannan (LAM) assay

In hospitalised patients with HIV, in meta-analysis:

- Sensitivity = 52%
- Specificity = 87%

→ Negative urine LAM does not exclude TB

- WHO recommends LAM in inpatients with TB signs/symptoms, if seriously ill, with WHO stage 3 or 4, or CD4 < 200 *(93% PWH inpatients)*

i) Glycophospholipid anchor
Myo-Inositol-Phosphate + Fatty acids

ii) Mannan core

iii) Arabinanan domain with variable side-chains and mannose capping
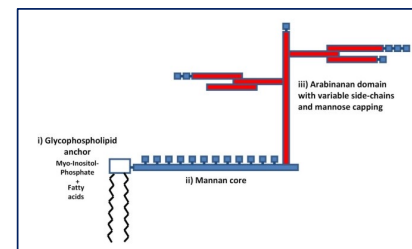
LAM = Mycobacterial cell wall component

Bjerrum, Cochrane Database Syst Rev 2019;10(10):CD011420
WHO Consolidated TB Guidelines 2021
Dhana, J Infect 2022;85:40

Urine Alere LAM assay

Diagnostic yield of urine LAM is much higher at low CD4 counts (reflecting high prevalence of dissemination in such patients)
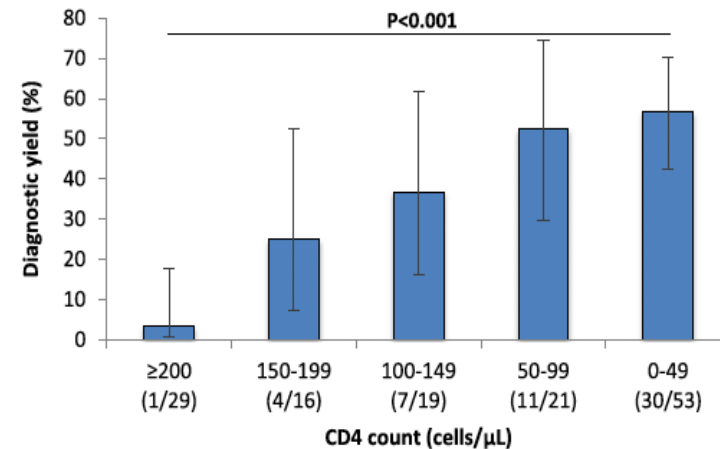
- Randomized trials in Southern Africa: mortality ↓ in hospitalized PWH
  - Deaths reduced from 25 to 21% in **TB NEAT: LAM RCT** (p=0.01)
  - Deaths reduced from 21 to 18% in **STAMP trial** (p=0.07) and from 36 to 29% in those with CD4 < 100 (p=0.036)
- Next generation LAM assays being evaluated

Lawn, BMC Medicine 2017;15:67
Peter, Lancet 2016;387:1187
Gupta-Wright, Lancet 2018;392:292

PWH admitted to medical wards in SA

- **Sputum Xpert Ultra and urine LAM test**

- Further testing if clinical concern for TB and sputum not obtained/ tests negative

GUIDANCE DOCUMENT

Guidance on the use of the Lateral flow urine lipoarabinomannan assay for the diagnosis of active tuberculosis in people living with HIV

POLICY UPDATE: APRIL 2021

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

NDP
2030

2021

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13. LF-LAM DIAGNOSTIC ALGORITHM

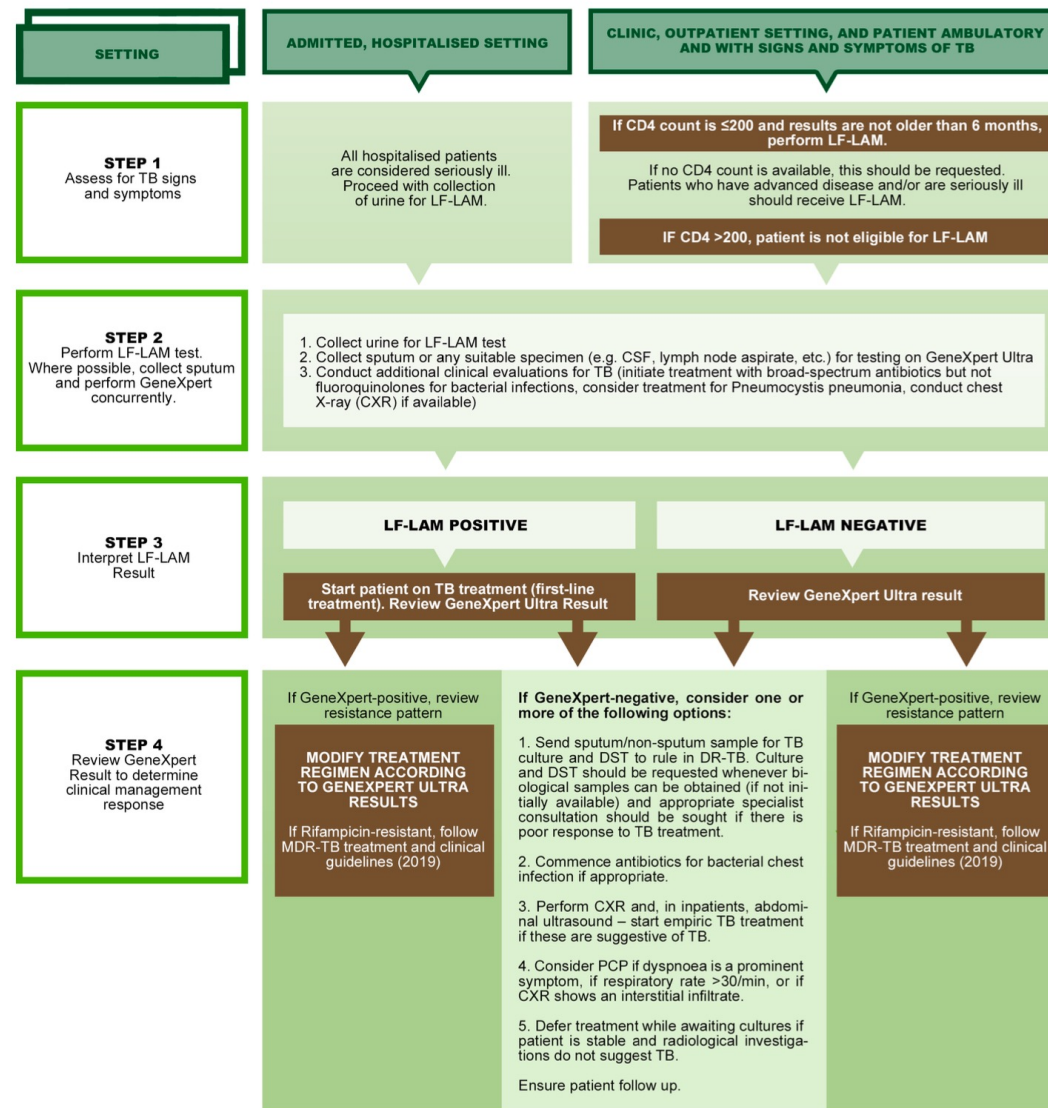| SETTING	ADMITTED, HOSPITALISED SETTING	CLINIC, OUTPATIENT SETTING, AND PATIENT AMBULATORY AND WITH SIGNS AND SYMPTOMS OF TB
STEP 1 Assess for TB signs and symptoms	All hospitalised patients are considered seriously ill. Proceed with collection of urine for LF-LAM.	**If CD4 count is ≤200 and results are not older than 6 months, perform LF-LAM.** If no CD4 count is available, this should be requested. Patients who have advanced disease and/or are seriously ill should receive LF-LAM. **IF CD4 >200, patient is not eligible for LF-LAM**

STEP 2
Perform LF-LAM test. Where possible, collect sputum and perform GeneXpert concurrently.

1. Collect urine for LF-LAM test
2. Collect sputum or any suitable specimen (e.g. CSF, lymph node aspirate, etc.) for testing on GeneXpert Ultra
3. Conduct additional clinical evaluations for TB (initiate treatment with broad-spectrum antibiotics but not fluoroquinolones for bacterial infections, consider treatment for Pneumocystis pneumonia, conduct chest X-ray (CXR) if available)

STEP 3
Interpret LF-LAM Result

LF-LAM POSITIVE

Start patient on TB treatment (first-line treatment). Review GeneXpert Ultra Result

LF-LAM NEGATIVE

Review GeneXpert Ultra result

STEP 4
Review GeneXpert Result to determine clinical management response

If GeneXpert-positive, review resistance pattern

MODIFY TREATMENT REGIMEN ACCORDING TO GENEXPERT ULTRA RESULTS

If Rifampicin-resistant, follow MDR-TB treatment and clinical guidelines (2019)

If GeneXpert-negative, consider one or more of the following options:

1. Send sputum/non-sputum sample for TB culture and DST to rule in DR-TB. Culture and DST should be requested whenever biological samples can be obtained (if not initially available) and appropriate specialist consultation should be sought if there is poor response to TB treatment.

2. Commence antibiotics for bacterial chest infection if appropriate.

3. Perform CXR and, in inpatients, abdominal ultrasound – start empiric TB treatment if these are suggestive of TB.

4. Consider PCP if dyspnoea is a prominent symptom, if respiratory rate >30/min, or if CXR shows an interstitial infiltrate.

5. Defer treatment while awaiting cultures if patient is stable and radiological investigations do not suggest TB.

Ensure patient follow up.

If GeneXpert-positive, review resistance pattern

MODIFY TREATMENT REGIMEN ACCORDING TO GENEXPERT ULTRA RESULTS

If Rifampicin-resistant, follow MDR-TB treatment and clinical guidelines (2019)

Lymph node aspiration

Other approaches to TB diagnosis

- Xpert Ultra (and TB culture) on extrapulmonary samples

| Sample type	Xpert Ultra sensitivity	Xpert Ultra specificity
CSF	89%	91%
Pleural fluid	75%	87%
Lymph node aspirate	70%	100%

- Imaging
  - Chest X-ray
  - Abdominal and cardiac ultrasound
- Empiric treatment justified if suggestive clinical and radiological picture
  - Must follow up to assess response

Kohli M, Cochrane Database Syst Rev 2021;1(1):CD012768

CXR to diagnose TB in inpatients with cough & WHO danger signs: radiologist blinded

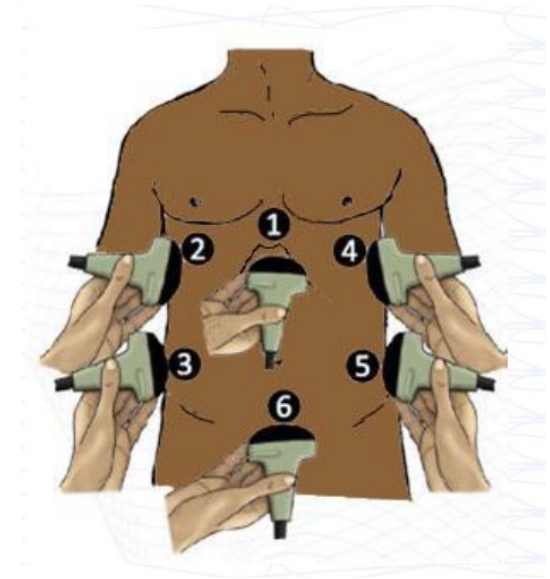| Feature	Odds ratio (95% CI)
Diffuse micronodular (miliary)	6.45 (2.20-18.87)
Hilar/mediastinal nodes	2.34 (1.58-3.47)
Nodularity >3 mm	2.21 (1.49-3.28)
Pleural effusion	1.24 (0.84-1.82)
Cavitation	1.01 (0.68-1.49)
Interstitial	0.92 (0.62-1.37)
Consolidation	0.86 (0.57-1.29)

48.8% prior TB

Griesel, Clin Infect Dis 2018;66:1419
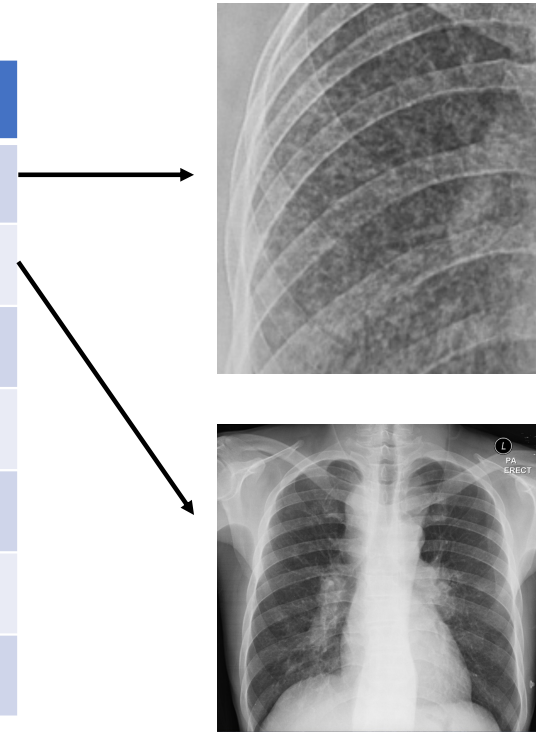
Ultrasound for TB diagnosis in HIV

Higher quality reference (bacterial confirmation)

- An abdominal ultrasound with any abnormal finding
- Pooled sensitivity of 63% (95% CI 43% to 79%)
- Pooled specificity of 68% (95% CI 42% to 87%)
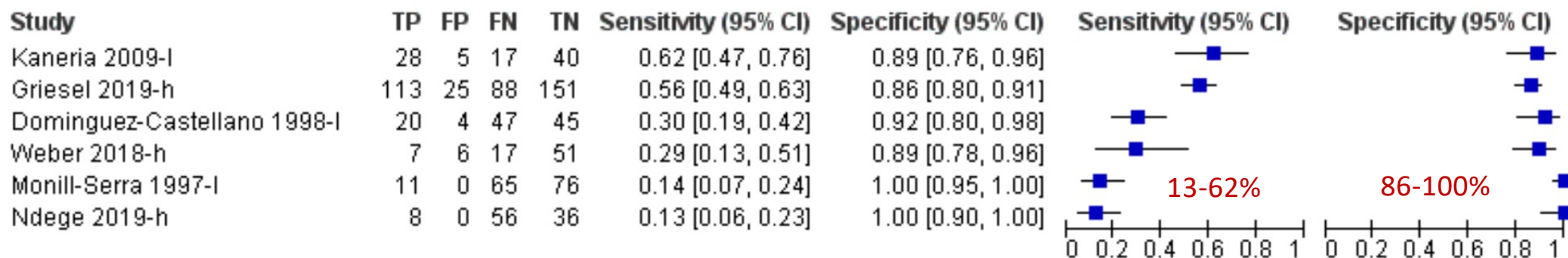
Supportive, not confirmatory
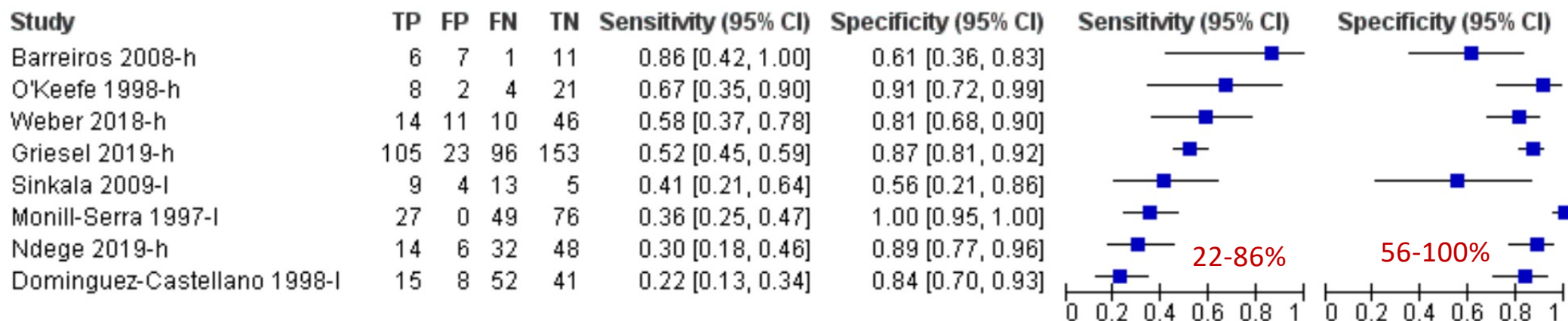
Lymphoma can mimic features

Splenic lesions

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kaneria 2009-I	28	5	17	40	0.62 [0.47, 0.76]	0.89 [0.76, 0.96]
Griesel 2019-h	113	25	88	151	0.56 [0.49, 0.63]	0.86 [0.80, 0.91]
Dominguez-Castellano 1998-I	20	4	47	45	0.30 [0.19, 0.42]	0.92 [0.80, 0.98]
Weber 2018-h	7	6	17	51	0.29 [0.13, 0.51]	0.89 [0.78, 0.96]
Monill-Serra 1997-I	11	0	65	76	0.14 [0.07, 0.24]	1.00 [0.95, 1.00]
Ndege 2019-h	8	0	56	36	0.13 [0.06, 0.23]	1.00 [0.90, 1.00]

13-62% 86-100%

Abdominal lymph nodes

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Barreiros 2008-h	6	7	1	11	0.86 [0.42, 1.00]	0.61 [0.36, 0.83]
O'Keefe 1998-h	8	2	4	21	0.67 [0.35, 0.90]	0.91 [0.72, 0.99]
Weber 2018-h	14	11	10	46	0.58 [0.37, 0.78]	0.81 [0.68, 0.90]
Griesel 2019-h	105	23	96	153	0.52 [0.45, 0.59]	0.87 [0.81, 0.92]
Sinkala 2009-I	9	4	13	5	0.41 [0.21, 0.64]	0.56 [0.21, 0.86]
Monill-Serra 1997-I	27	0	49	76	0.36 [0.25, 0.47]	1.00 [0.95, 1.00]
Ndege 2019-h	14	6	32	48	0.30 [0.18, 0.46]	0.89 [0.77, 0.96]
Dominguez-Castellano 1998-I	15	8	52	41	0.22 [0.13, 0.34]	0.84 [0.70, 0.93]

22-86% 56-100%

- Consider important differential diagnoses
  - Bacterial pneumonia
  - PCP
  - Cryptococcosis and other fungal infection
  - Disseminated NTM
  - Kaposi sarcoma
  - Lymphoma
  - Post-TB bronchiectasis
  - Gastro-intestinal pathogen

- In some patients and particularly those with suggestive CXR/USS and/or danger signs, empiric TB treatment is justified
  - Close follow-up for response required

*WHO danger signs
RR > 30
Temp >39°C
HR >120
Can't walk unaided

Urine Xpert Ultra

Centrifuge 15-40ml urine

Resuspend pellet & add sample reagent

Xpert Ultra performed on centrifuged urine

- 238 HIV+ patients admitted to hospital with TB symptoms
  - 2 hospitals in East London, South Africa
- 62 (26%) microbiologically confirmed TB
- All produced urine
- Only 37% spontaneous sputum
- **Diagnostic yield**
  - Sputum Xpert Ultra =34%
  - Urine LAM = 45%
  - Urine Xpert Ultra = 68%
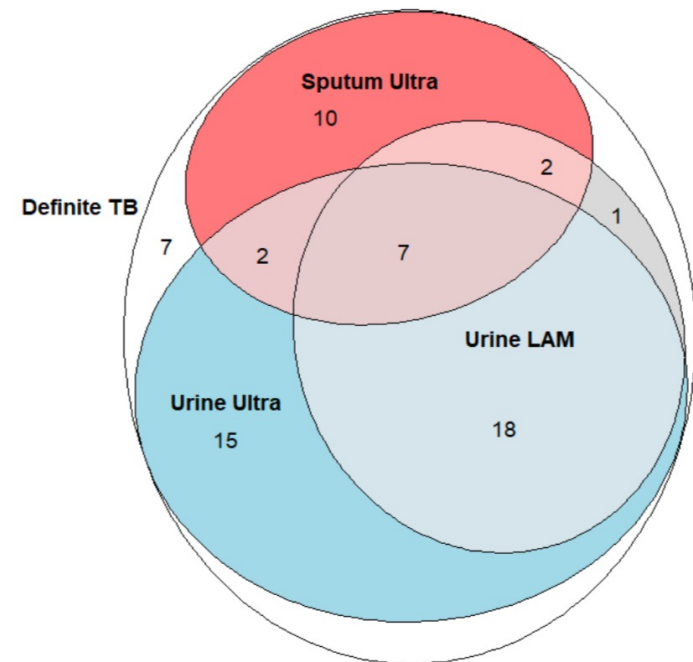
Stead, Poster abstract 761, CROI 2023

Disseminated HIV-associated TB

High mortality related to in-hospital TB diagnosis

Fig 4. Kaplan Meier survival curves for initial loss to follow up TB patients, Cape Town, South Africa, October 2018-March 2020, stratified by level of care of diagnosis and treatment initiation status. TB: tuberculosis.
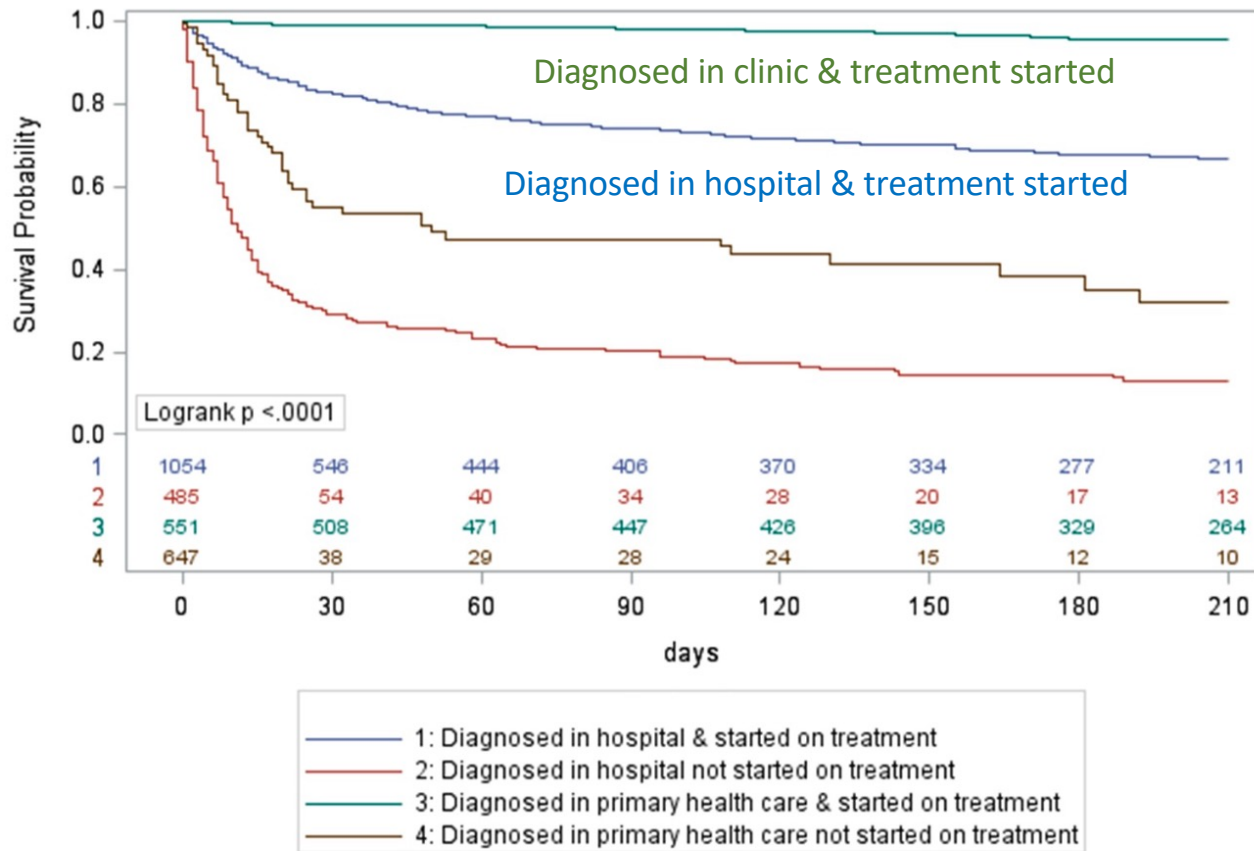
Cape Town, 2018-2020
n = 13,736
45% had HIV co-infection

**Diagnosed in hospital
OR for death = 7.4**

Osman, PLoS One 2021;16(6):e0252084

Case fatality in hospitalized HIV-TB patients

Cohort	Country	Mortality
Rural setting (Subbarao, JAIDS 2015)	South Africa	**32% at 8 weeks**
Urban setting (Meintjes, Medicine 2015)	South Africa	**11% at 90 days**
Urban setting (Agbor, PLoS ONE 2014)	Cameroon	**29% at 6 months**
STAMP clinical trial (Gupta-Wright, CID 2020)	South Africa Malawi	**26% at 8 weeks** **35% at 8 weeks**
Urban setting (Schutz, PLoS Medicine 2019)	South Africa	**22% at 12 weeks**

Upstream of hospitalization for HIV-TB

Many gaps and delays
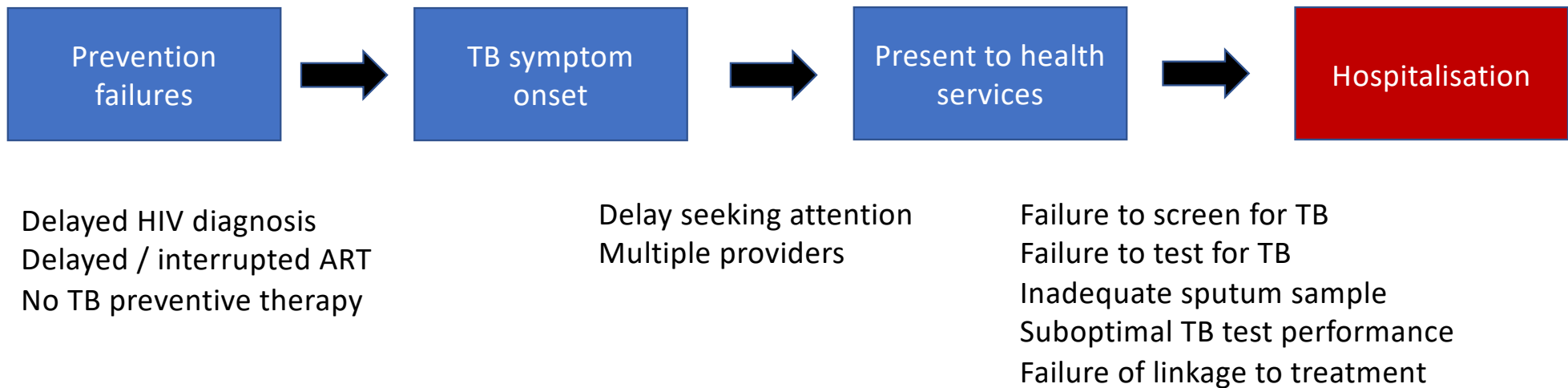
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┌──────────────┐      ┌──────────────┐      ┌──────────────┐      ┌──────────────┐
│  Prevention  │ ──▶  │  TB symptom  │ ──▶  │ Present to   │ ──▶  │Hospitalisation│
│   failures   │      │    onset     │      │   health     │      │              │
│              │      │              │      │   services   │      │              │
└──────────────┘      └──────────────┘      └──────────────┘      └──────────────┘
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Delayed HIV diagnosis
Delayed / interrupted ART
No TB preventive therapy

Delay seeking attention
Multiple providers

Failure to screen for TB
Failure to test for TB
Inadequate sputum sample
Suboptimal TB test performance
Failure of linkage to treatment

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[a], Sebastian B. Lucas[b], Katherine L. Fielding[c] and Stephen D. Lawn[d,e]

- In LMIC, TB prevalence at autopsy in adults = 39.7% (36 studies)
  - TB was cause of death in > 90%
  - Undiagnosed at death in 45.8%

- In sub-Saharan Africa, TB prevalence at autopsy = 43.2% (9 studies)

- TB was disseminated in 87.9%
  - Lung, liver, spleen and lymph nodes

Gupta, AIDS 2015;29:1987

In hospitalized patients with HIV-TB TB blood stream is common, associated with mortality, and delays in treatment appear to increase mortality

Mycobacterium tuberculosis **bloodstream infection prevalence, diagnosis, and mortality risk in seriously ill adults with HIV: a systematic review and meta-analysis of individual patient data**

David A Barr*, Joseph M Lewis*, Nicholas Feasey, Charlotte Schutz, Andrew D Kerkhoff, Shevin T Jacob, Ben Andrews, Paul Kelly, Shabir Lakhi, Levy Muchemwa, Helio A Bacha, David J Hadad, Richard Bedell, Monique van Lettow, Rony Zachariah, John A Crump, David Alland, Elizabeth L Corbett, Krishnamoorthy Gopinath, Sarman Singh, Rulan Griesel, Gary Maartens, Marc Mendelson, Amy M Ward, Christopher M Parry, Elizabeth A Talbot, Patricia Munseri, Susan E Dorman, Neil Martinson, Maunank Shah, Kevin Cain, Charles M Heilig, Jay K Varma, Anne von Gottberg, Leonard Sacks, Douglas Wilson, S Bertel Squire, David G Lalloo, Gerry Davies, Graeme Meintjes

Predicted probability of MTB BSI in hospital inpatients with HIV-TB, WHO danger signs, and CD4 count of 76 (the median for the cohort) was **45%** (95% CI 38–52).

Presence of MTB BSI compared with its absence in patients with HIV-TB increased **risk of death before 30 days: adjusted HR 2.48** (95% CI 2.05–3.08)

Propensity-score matched cohort analysis: mortality increased in those with MTB BSI who had **delay in TB treatment longer than 4 days: OR 3.15** (95% CI 1.16–8.84)

Barr, Lancet Infect Dis 2020;20:742

Research focus on hospitalized patients with HIV-TB

Two overarching questions in our current research programme:

- What are pathophysiological processes contributing to deaths?

- Can treatment strategies be improved to reduce mortality?

RESEARCH ARTICLE

Clinical, microbiologic, and immunologic determinants of mortality in hospitalized patients with HIV-associated tuberculosis: A prospective cohort study

Charlotte Schutz[1,2]*, David Barr[3], Bruno B. Andrade[1,4,5,6,7], Muki Shey[1,2], Amy Ward[1,2], Saskia Janssen[8], Rosie Burton[9], Katalin A. Wilkinson[1,2,10], Bianca Sossen[1,2], Kiyoshi F. Fukutani[4,5,11], Mark Nicol[12], Gary Maartens[13], Robert J. Wilkinson[1,2,10,14], Graeme Meintjes[1,2]

1 Wellcome Centre for Infectious Diseases Research in Africa (CIDRI-Africa), Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa, 2 Department of Medicine, University of Cape Town, Cape Town, South Africa, 3 Wellcome Trust Liverpool Glasgow Centre for Global Health Research, University of Liverpool, Liverpool, United Kingdom, 4 Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, Salvador, Brazil, 5 Multinational Organization Network Sponsoring Translational and Epidemiological Research (MONSTER) Initiative, Salvador, Brazil, 6 Division of Infectious Diseases, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America, 7 Universidade Salvador (UNIFACS), Laureate Universities, Salvador, Brazil, 8 Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands, 9 Khayelitsha Hospital, Department of Medicine, Cape Town, South Africa, 10 The Francis Crick Institute, London, United Kingdom, 11 Faculdade de Tecnologia e Ciências (FTC), Salvador, Brazil, 12 Division of Medical Microbiology, University of Cape Town and National Health Laboratory Services, Cape Town, South Africa, 13 Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa, 14 Department of Medicine, Imperial College, London, United Kingdom

* Charlotte.Schutz@uct.ac.za

Abstract

Background

In high-burden settings, case fatality rates are reported to be between 11% and 32% in hospitalized patients with HIV-associated tuberculosis, yet the underlying causes of mortality remain poorly characterized. Understanding causes of mortality could inform the development of novel management strategies to improve survival. We aimed to assess clinical and microbiologic determinants of mortality and to characterize the pathophysiological processes underlying death by evaluating host soluble inflammatory mediators and determined the relationship between these mediators and death as well as biomarkers of disseminated tuberculosis.

Methods and findings

Adult patients with HIV hospitalized with a new diagnosis of HIV-associated tuberculosis were enrolled in Cape Town between 2014 and 2016. Detailed tuberculosis diagnostic testing was performed. Biomarkers of tuberculosis dissemination and host soluble inflammatory mediators at baseline were assessed. Of 682 enrolled participants, 576 with tuberculosis (487/576, 84.5% microbiologically confirmed) were included in analyses. The median age

Study design

January 2014 – October 2016

HIV+ patients
Age > 18
CD4 ≤ 350 cells/µl
TB diagnosed on admission*

Clinical care in government health services

Primary endpoint =
death by 12 weeks

Hospital visit at 12 weeks
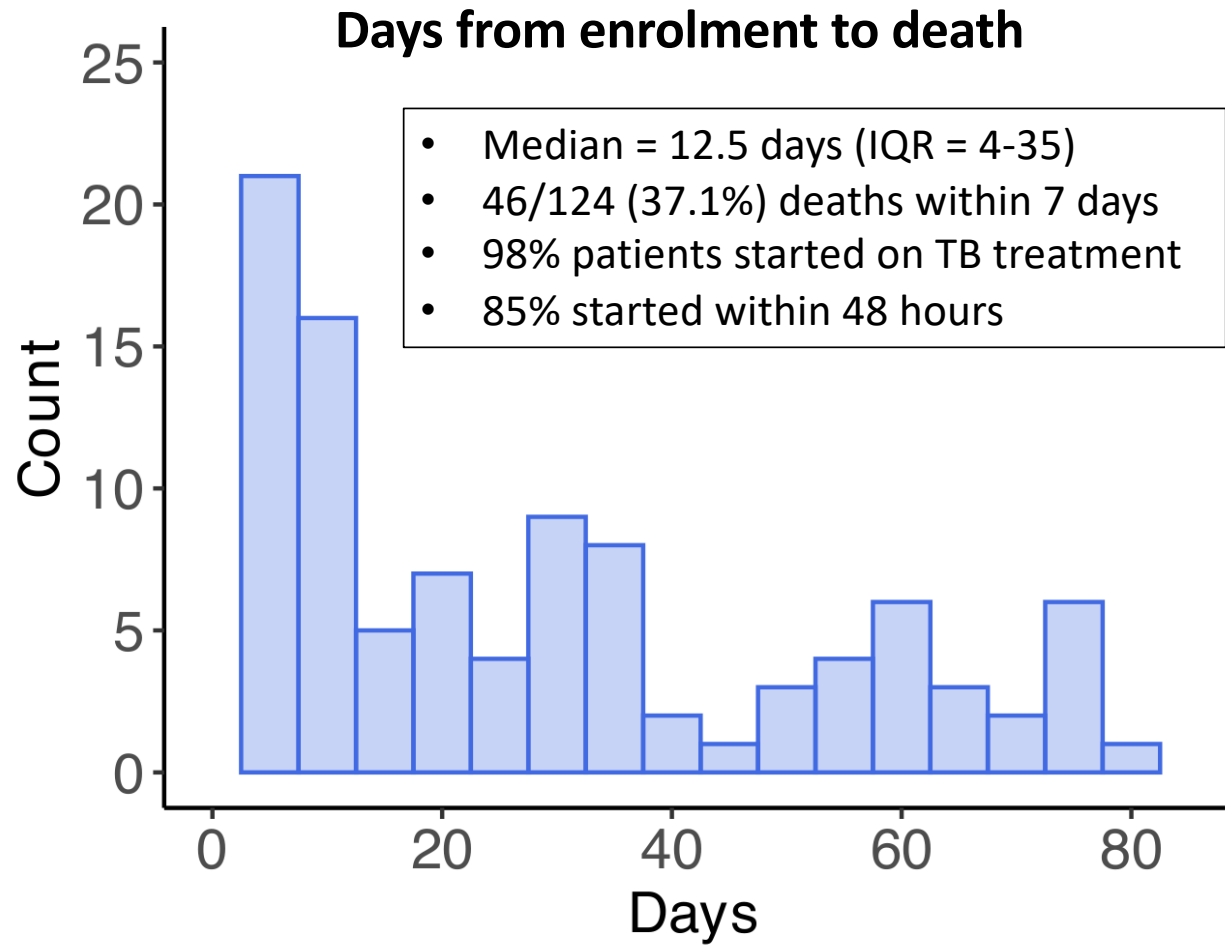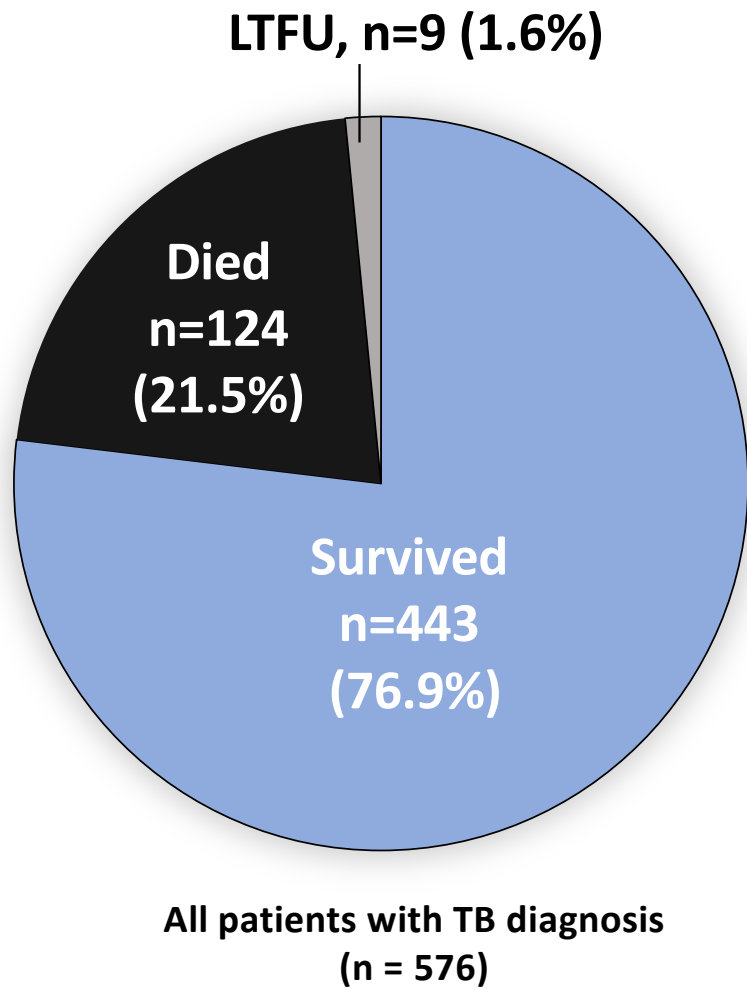(or vital status obtained from telephone contact, health service records or National Death Registry)

Enrolled and samples taken
Started TB treatment

Phone call
at 4 weeks

Visit at
12 weeks

***TB diagnosis:** Either microbiological confirmed or clinical diagnosis fulfilling WHO criteria
Exclusion criteria: Pregnant; 3 or more doses of TB treatment received; on TB treatment within last month

Schutz, PLoS Med 16(7): e1002840 38

Week 12 outcome

LTFU, n=9 (1.6%)

Died
n=124
(21.5%)

Survived
n=443
(76.9%)

All patients with TB diagnosis
(n = 576)

Days from enrolment to death

- Median = 12.5 days (IQR = 4-35)
- 46/124 (37.1%) deaths within 7 days
- 98% patients started on TB treatment
- 85% started within 48 hours

Count

Days

Patient characteristics

	Died (n=124)	Survived (n=443)	P-value
Female sex	56%	50%	0.3
Age (median)	39	35	<0.001
Current ART	36%	37%	0.3
Previous TB	46%	44%	0.7
CD4 count (median)	**40**	**63**	**0.002**
Haemoglobin (median)	8.0	8.8	0.005
Rifampicin resistant TB	17%	7%	0.003
Micro confirmed TB	87%	84%	0.3

Deaths associated with features of sepsis and organ dysfunction, but co-infections were not found to be a major contributor to mortality

Markers of sepsis elevated in those who died

	Died	Survived	P-value
Lactate (median)	2.3	1.7	<0.001
D-dimer (median)	2.4	1.2	<0.001
Creatinine (median)	101	77	<0.001

Lactate level

Percent survival

Normal range
Above normal

p <0.001

days

Lactate normal range: 0.5 - 2.2 mmol/l

Elevated creatinine (> 104 umol/L)

Survived   26%

Died   48%
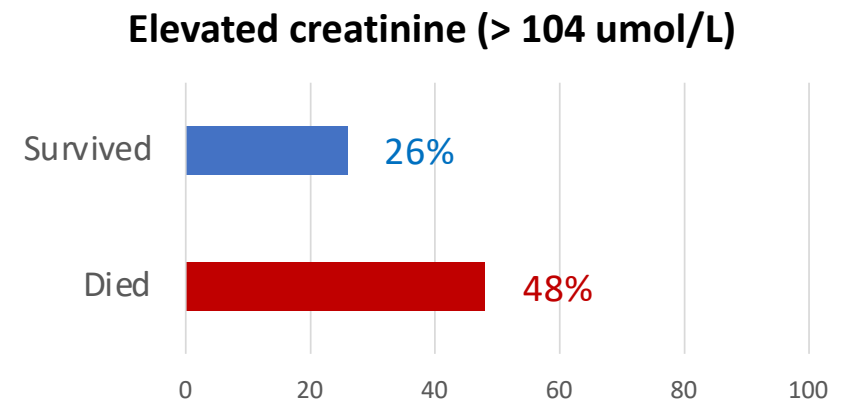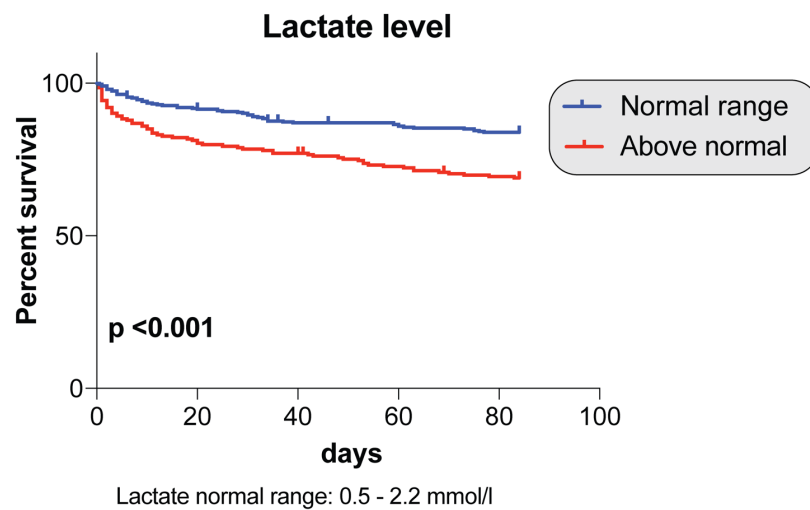
Rifampicin resistant TB and co-infections

- 5/296 (2%) cultured bacteria other than MTB on admission: 4 died
  - 1 Staphylococcus aureus, 4 gram-negative bacteria

- Serum CrAg+ in 19 patients: not associated with higher mortality

- CMV viral load detectable in 223/576 (39%): not independently associated with mortality in Cox model

- 21/124 (17%) who died had rifampicin resistance: ↑ mortality

Schutz, PLoS Med 16(7): e1002840

Dissemination of TB associated with mortality with a dose-response relationship

TB dissemination score
Khayelitsha Hospital TB study (n=519)

1. Urine Alere LAM assay
2. Urine Fuji LAM assay
3. Urine Xpert assay
4. Blood TB culture
5. Blood Xpert Ultra assay

Score	0	1	2	3	4	5
%	13%	19%	19%	14%	17%	18%

X−squared trend, p < 0.001
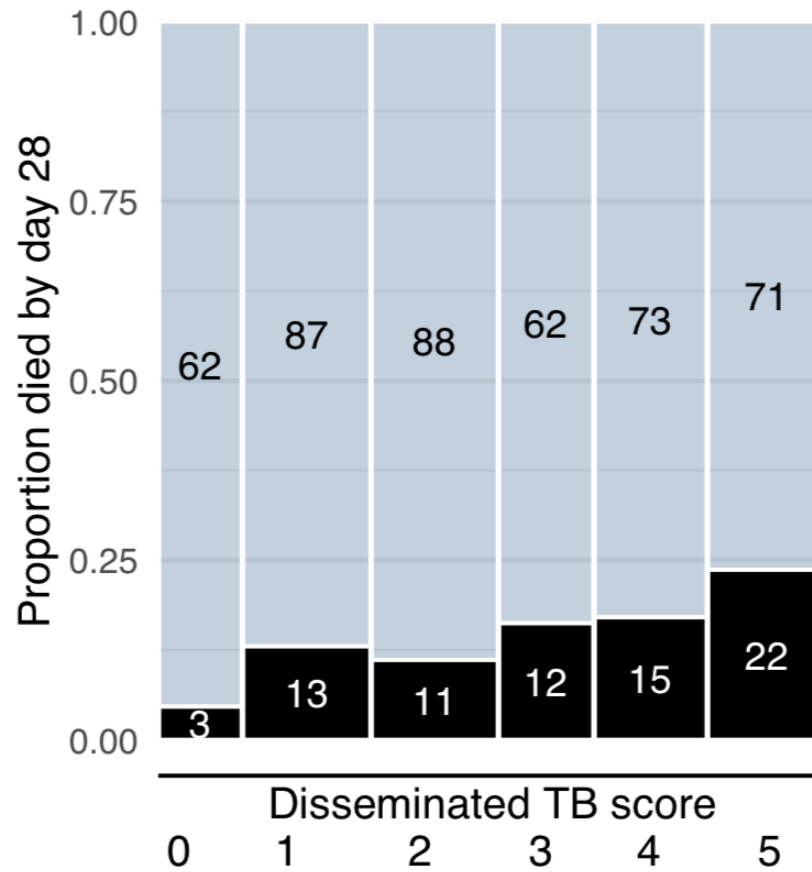
n = 519, with imputation missing values

Xpert Ultra on lysed whole blood

Blood Xpert-Ultra + in 165/427 (37%) with TB

Blood Xpert Ultra ordinal scale
- Negative
- Ct >32·1
- Ct 32·1–27·9
- Ct <27·9

Increasing Mtb DNA abundance in blood

Hazard ratio 1·5 (95% CI 1·3–1·7)
Likelihood ratio test p<0·0001

Linda Boloko

Boloko, Lancet Microbe 2022;3:e521
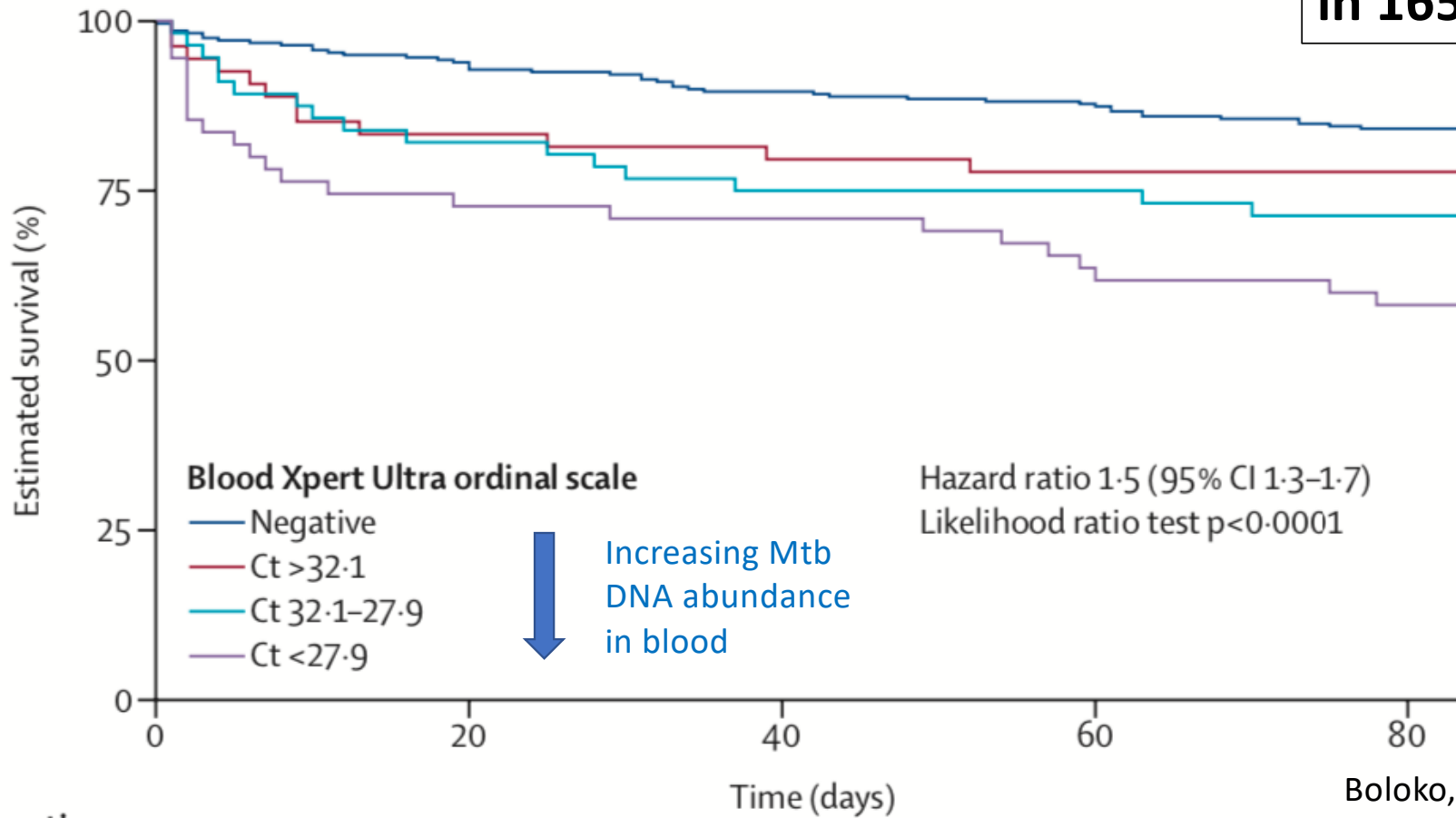
Suggestive evidence that viable TB persists in blood stream for several days on treatment
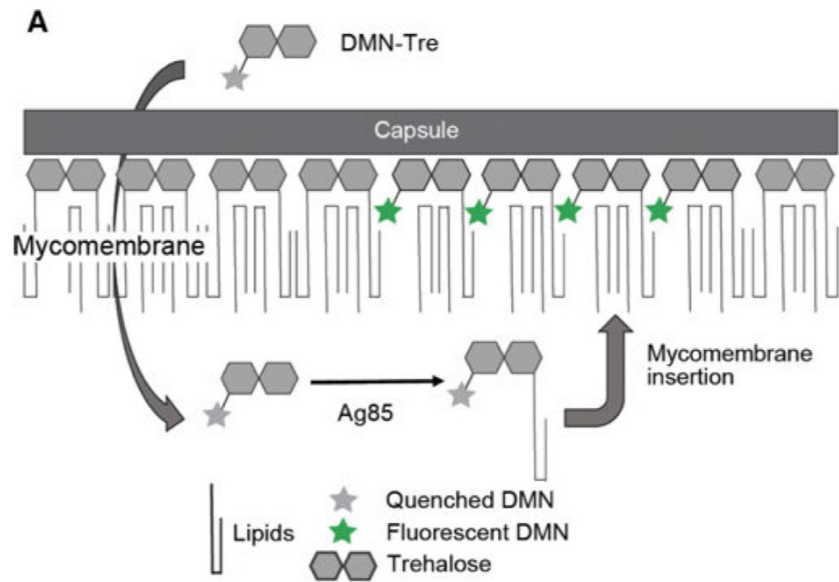
DMN-trehalose stain developed by Bertozzi group at Stanford optimized for use on lysed whole blood
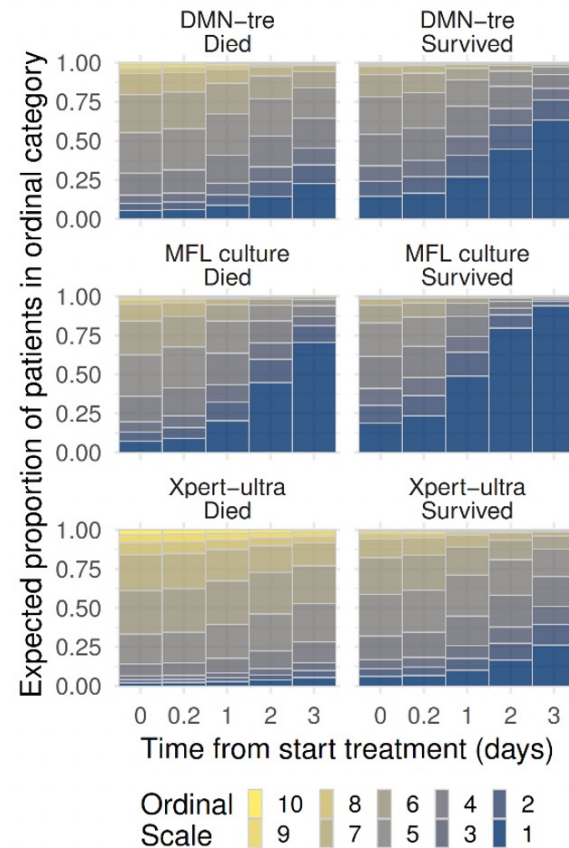
Kamariza, Sci Transl Med. 2018;10(430):eaam6310
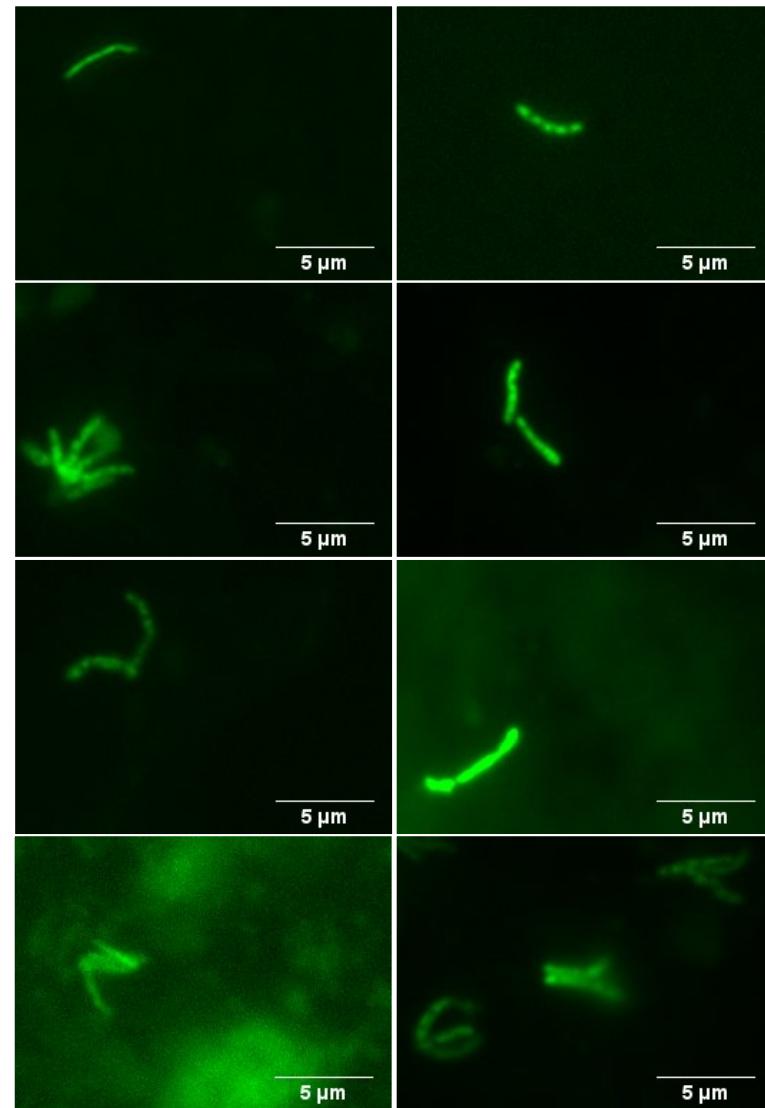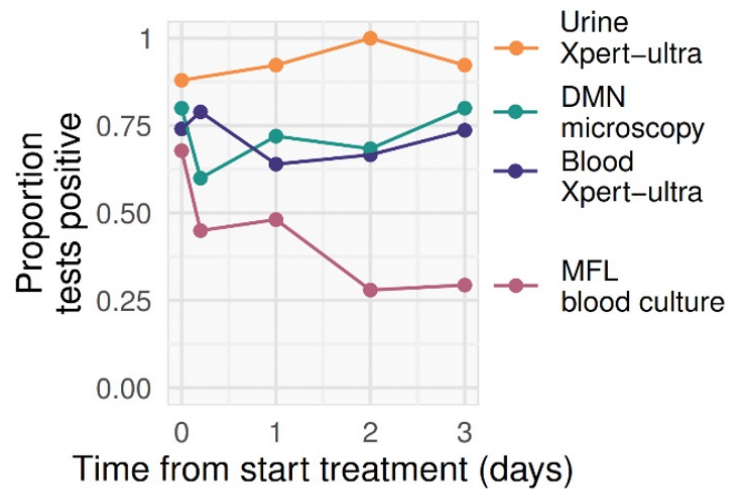
Three measures jointly modelled in an ordinal regression analysis:
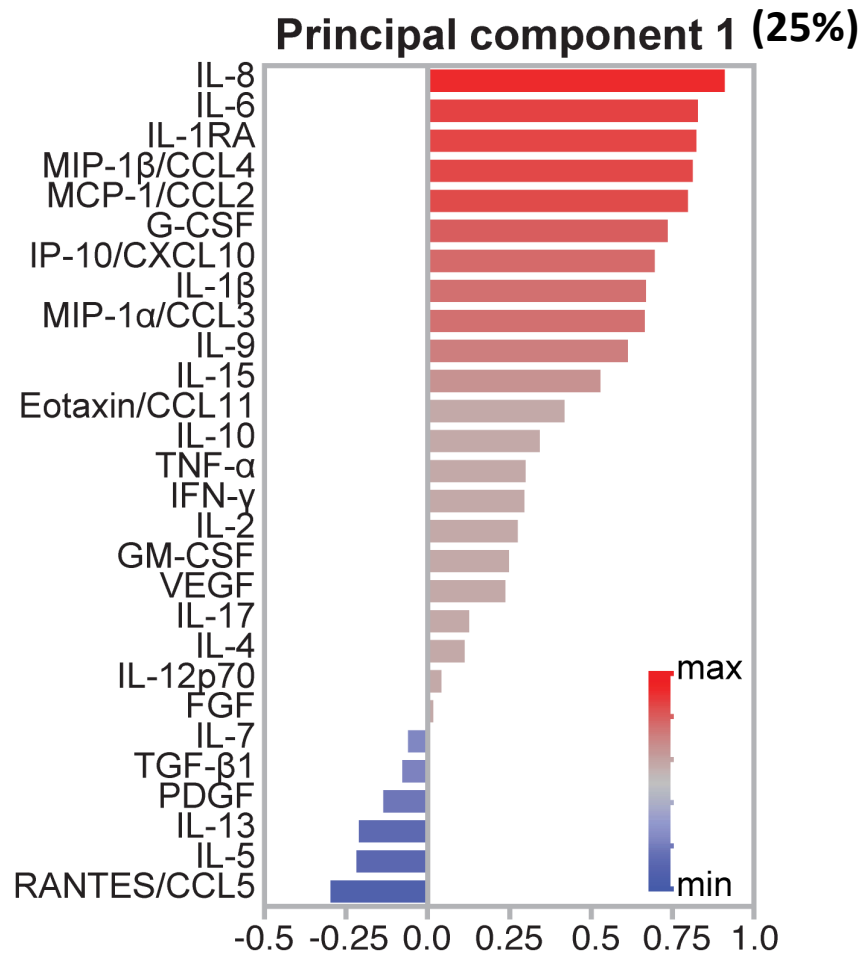>99% posterior probability of higher baseline MTB in those who died
88% posterior probability of less negative "slope" coefficient in those who died

Mortality associated with immune signature of innate immune cell activation & signalling
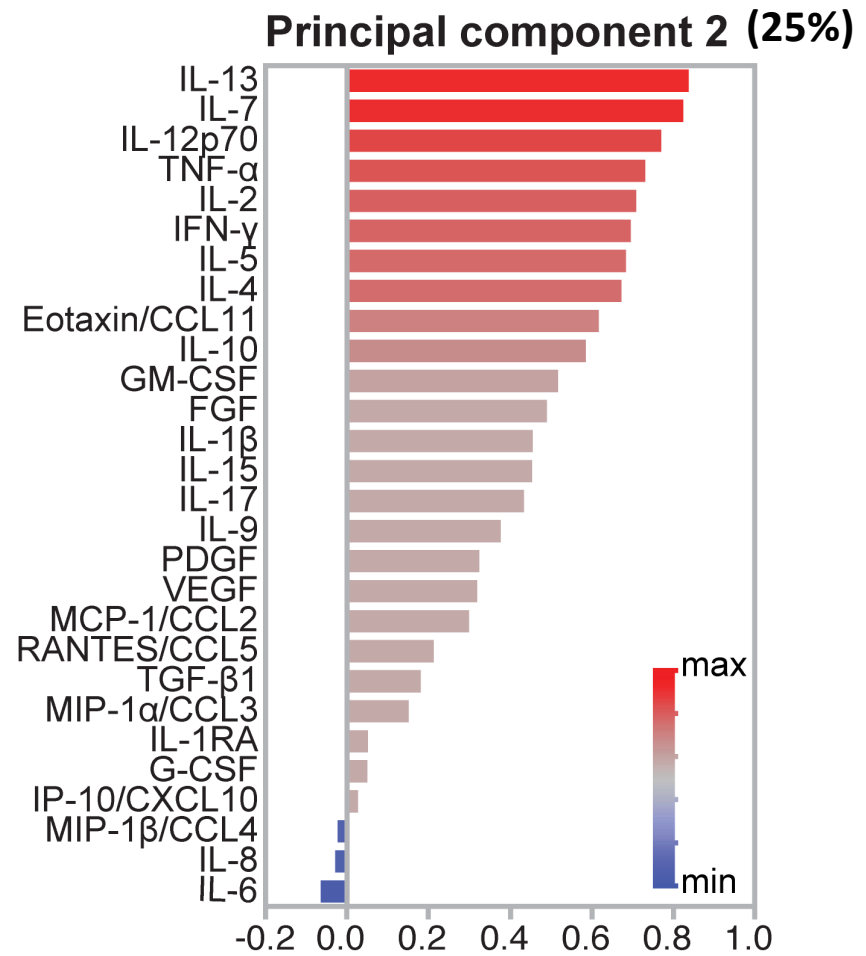
Soluble inflammatory mediators
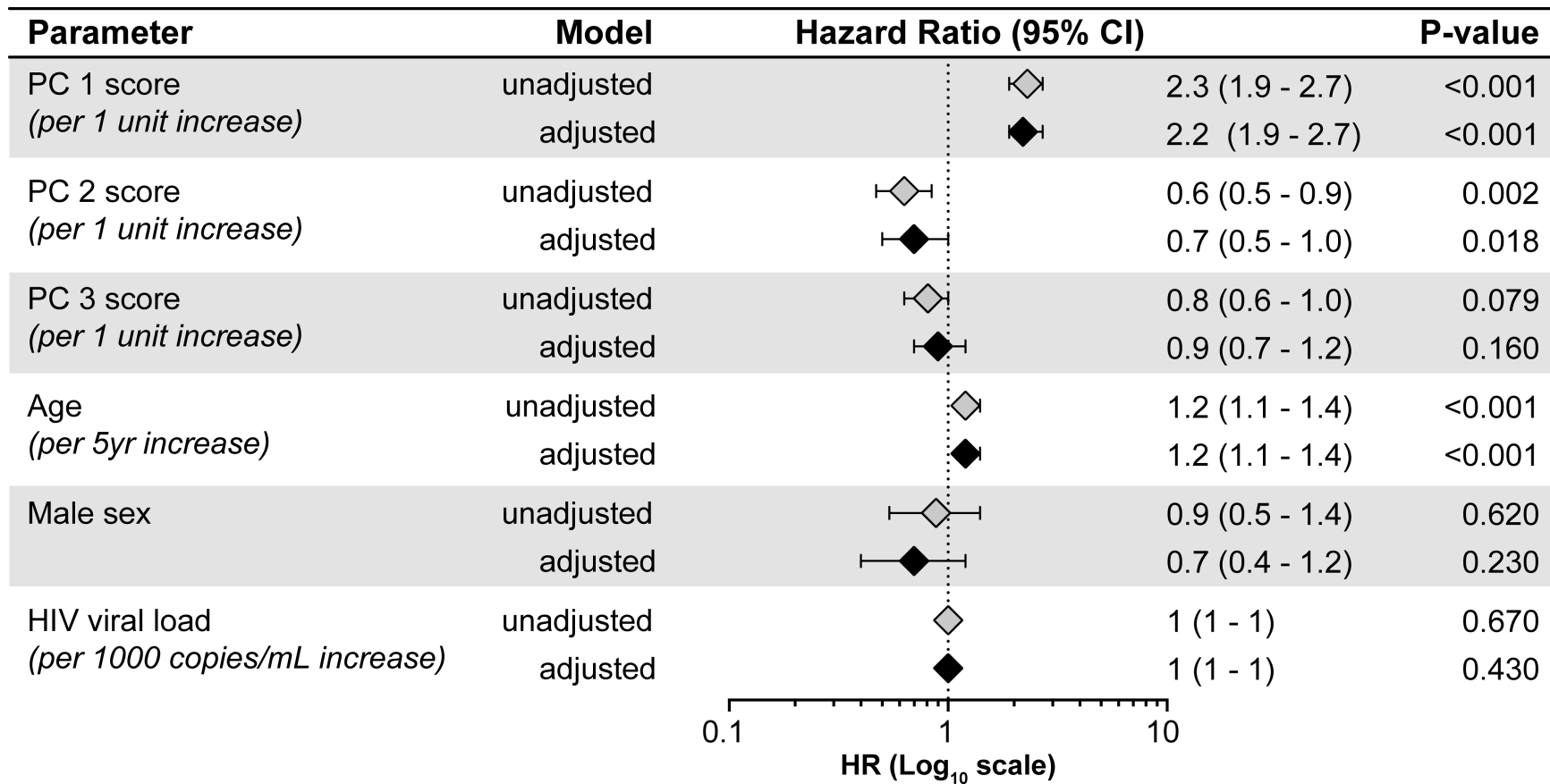
108 who died
391 who survived
Luminex/ELISA

Principal component 1 (25%)
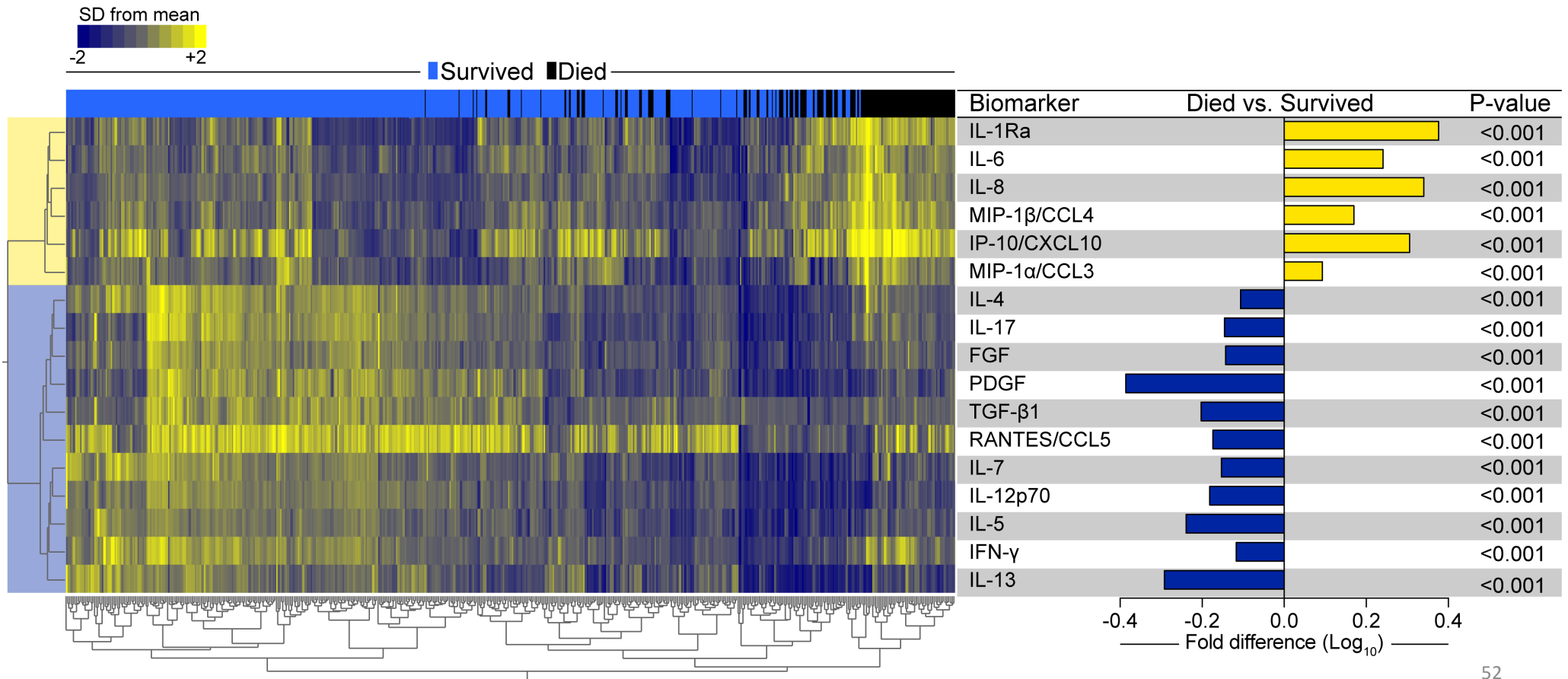
Dominated by:
IL-8, IL-6, IL-1Ra, MIP-1b, MCP-1

Principal component 2 (25%)

Dominated by:
IL-13, IL-7, IL-12, TNF, IL-2

53

PC1 associated with mortality and PC2 with survival

Parameter	Model	Hazard Ratio (95% CI)		P-value
PC 1 score (per 1 unit increase)	unadjusted		2.3 (1.9 - 2.7)	<0.001
	adjusted		2.2 (1.9 - 2.7)	<0.001
PC 2 score (per 1 unit increase)	unadjusted		0.6 (0.5 - 0.9)	0.002
	adjusted		0.7 (0.5 - 1.0)	0.018
PC 3 score (per 1 unit increase)	unadjusted		0.8 (0.6 - 1.0)	0.079
	adjusted		0.9 (0.7 - 1.2)	0.160
Age (per 5yr increase)	unadjusted		1.2 (1.1 - 1.4)	<0.001
	adjusted		1.2 (1.1 - 1.4)	<0.001
Male sex	unadjusted		0.9 (0.5 - 1.4)	0.620
	adjusted		0.7 (0.4 - 1.2)	0.230
HIV viral load (per 1000 copies/mL increase)	unadjusted		1 (1 - 1)	0.670
	adjusted		1 (1 - 1)	0.430

HR (Log_{10} scale)

0.1   1   10

Management of inpatients with HIV-associated TB

- Avoid delays in diagnosis and initiating TB treatment
- Standard TB treatment:
  - Rifampicin/INH/PZA/Ethambutol for 2 months
  - Followed by Rifampicin/INH for 4-7 months
- Pyridoxine to prevent INH neuropathy
- Test for rifampicin resistance and modify treatment if present
  - WHO: bedaquline/pretomanid/linezolid/moxifloxacin 6 months (or longer regimen)
- Co-trimoxazole prophylaxis
- If patient not on ART, WHO recommends start (or restart) within 2 weeks
  - Can delay ART up to 8 weeks if CD4 > 50 (SA guidelines)
  - Should delay 4-8 weeks if TB meningitis
  - If CD4 < 100, consider prednisone for TB-IRIS prevention
- If CD4 < 200 cryptococcal antigen testing on serum/plasma
- Consider and investigate for other co-infections, eg. Pneumocystis pneumonia
- Appropriate counselling in relation to both HIV and TB
- TB screening and prophylaxis for household members

Treatment trials in inpatients with HIV- TB

- **NEW STRAT-TB** trial in Cape Town

- **DATURA** trial in West Africa and Asia

- Evaluating:
  - Intensified TB treatment
    - Higher dose rifampicin and higher dose INH in DATURA
    - Higher dose rifampicin and levofloxacin in NEW STRAT-TB
  - Corticosteroids in both trials

Current and planned TB meningitis trials

Title/Number	Phase	Interventions evaluated	Setting
HDH	3	High-dose INH (for NAT2 rapid acetylators)	China
HARVEST	3	High-dose Rifampicin	Indonesia, SA, Uganda
ALTER	2	High-dose Rifampicin and Linezolid	Uganda
SIMPLE	2	High-dose Rifampicin and Linezolid	Indonesia
IMAGINE-TBM	2	High-dose Rifampicin, high-dose INH and Linezolid	Multi-country ACTG trial
LAST ACT	3	LTA4H-stratified Dexamethasone	Vietnam
CTRI/2018/02/011722	NA	Indomethacin	India
TIMPANI	2	Adalimumab	Brazil, Mozambique, Zambia
INTENSE-TBM	3	High-dose Rifampicin and Linezolid and Aspirin	Cote d'Ivoire, Madagascar, SA, Uganda
SURE (Paediatric)	3	High-dose Rifampicin, high-dose INH, Levofloxacin and Aspirin	India, Uganda, Vietnam, Zambia, Zimbabwe

TB Rx (HDH, HARVEST, ALTER, SIMPLE, IMAGINE-TBM)

Adjunct (LAST ACT, CTRI/2018/02/011722, TIMPANI)

TB Rx + Adjunct (INTENSE-TBM, SURE)

Adapted and updated from Huynh, Lancet Neurol 2022; 21:450

Management of fluid status and anaemia

- KDH-TB observational study of HIV-TB inpatients:
  - Creatinine elevated in 31%
  - Anaemia in 94% (Hb < 8 in 42%)

Schutz, PLoS Med 16(7): e1002840

- RCT in Zambia (n=209) of early resuscitation protocol for sepsis with hypotension (IV fluids, vasopressors, transfusion)
  - 90% with HIV
  - 63% with suspected TB (21% TB on blood culture)
  - Sepsis protocol <u>increased</u> in-hospital mortality
    (48% vs 33%, p=0.03)

Andrews, JAMA 2017;318(13):1233

RESEARCH ARTICLE
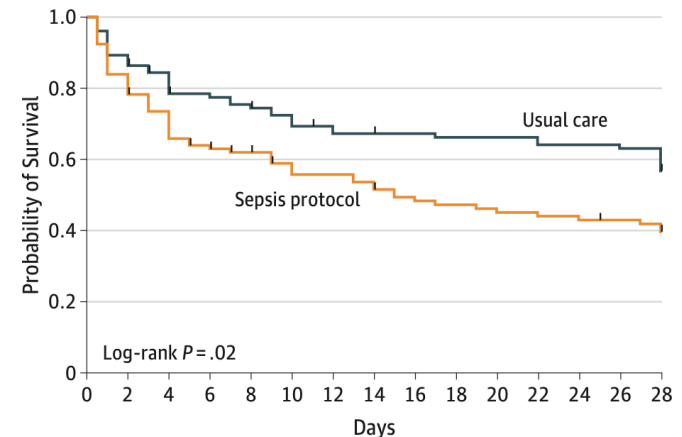
Early mortality in tuberculosis patients initially lost to follow up following diagnosis in provincial hospitals and primary health care facilities in Western Cape, South Africa

Muhammad Osman [1] *, **Sue-Ann Meehan** [1], **Arne von Delft**[2,3], **Karen Du Preez**[1], **Rory Dunbar**[1], **Florian M. Marx**[1,4], **Andrew Boulle**[2,3], **Alex Welte**[4], **Pren Naidoo**[1], **Anneke C. Hesseling**[1]
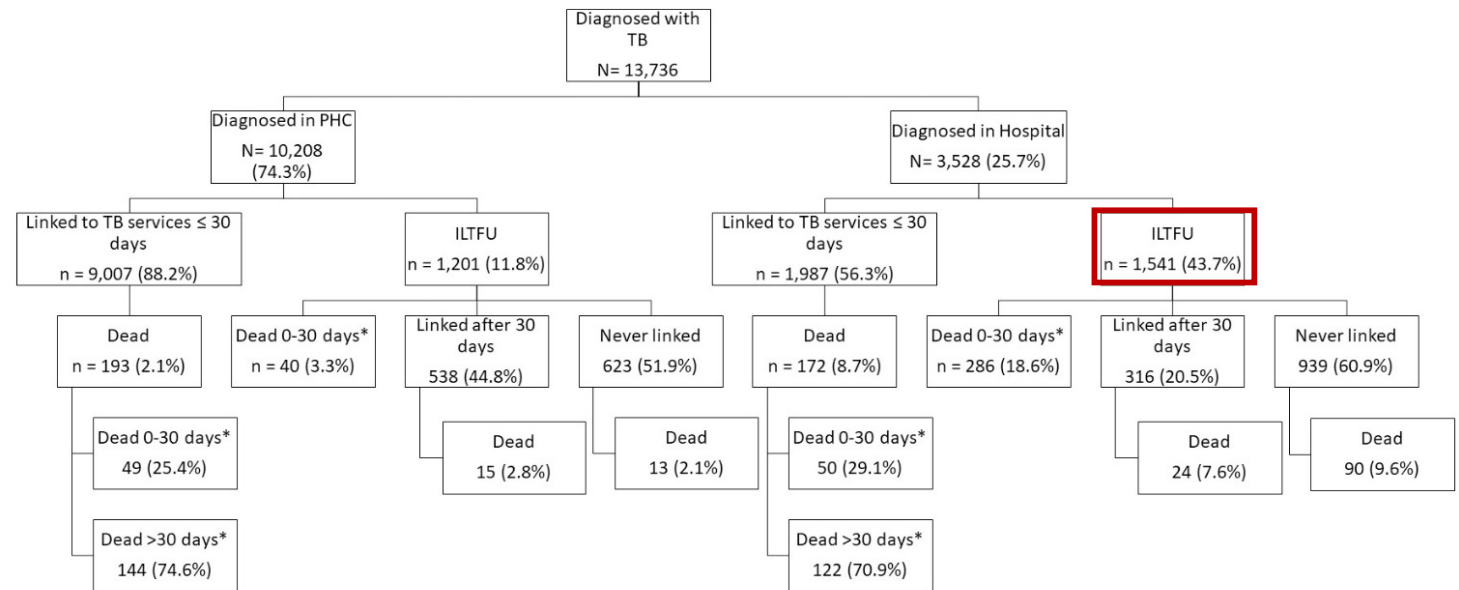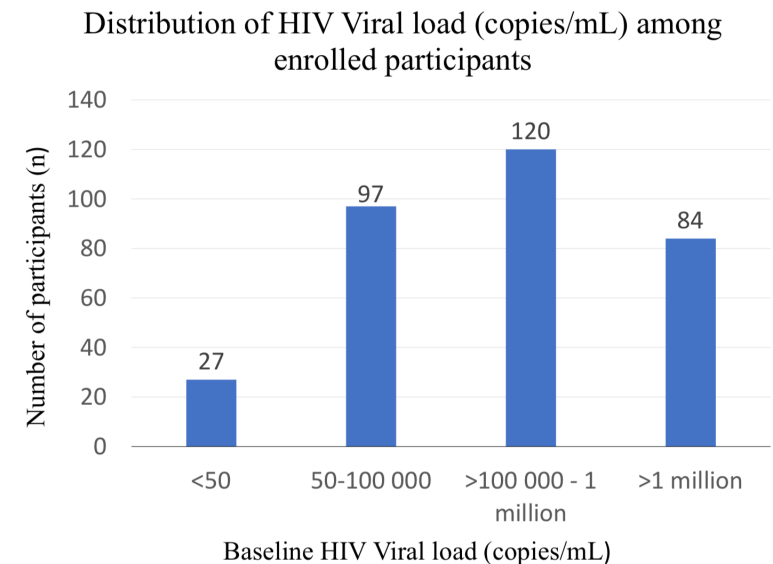
Need for strategies
to improve post-discharge
linkage to HIV-TB care

Fig 2. Overview of linkage to TB care and death of patients, stratified by level of care at which TB diagnosis was made, Cape Town, South Africa, October 2018-March 2020 (n = 13,736). *proportions do not denote a case fatality ratio but the proportion of the deaths to have occurred based on the timing of death. ILTFU: initial loss to follow up; PHC: primary health care.

NEW STRAT-TB: Most have unsuppressed VL

- Among first 335 participants
  - 8% had HIV VL less than 50
  - 90% had detectable VL, median = 5.6 log

- In those with detectable VL
  - 33% were ART naïve
  - 55% had interrupted ART
  - 12% reported being on ART at enrolment

- Disseminated HIV-associated TB (like cryptococcal meningitis) is an **indicator condition of gaps in HIV care cascade**

Distribution of HIV Viral load (copies/mL) among enrolled participants

Number of participants (n)

<50	50-100 000	>100 000 - 1 million	>1 million
27	97	120	84

Baseline HIV Viral load (copies/mL)

Vermeulen, SA HIV Conference 2023, Poster

Acknowledgements

Conclusions

- In patients hospitalised with HIV-TB:
  - Dissemination via the blood stream is frequent
  - Mortality high despite TB treatment (20 – 35%)
  - Disseminated Mtb load associated with mortality
- Important to make an early diagnosis and start TB treatment:
  - Sputum Xpert Ultra and urine LAM recommended by WHO
  - Urine Xpert Ultra shows promise
  - Other extrapulmonary samples can be tested with Xpert Ultra
  - May need to start empiric treatment based on clinical and radiological features
- Ongoing trials investigating novel treatment strategies

Q1

In a patient with HIV and a current CD4 = 45, diagnosed with TB meningitis, and who had interrupted ART 2 years ago. When should the clinician restart ART in relation to starting TB treatment?

1. Restart ART on the same day as TB treatment

2. Restart ART 1-2 weeks after starting TB treatment

3. Restart ART 4-8 weeks after starting TB treatment

4. Wait 12 weeks after starting TB treatment and then restart ART

Q2

What is the correct dose of dolutegravir in adult patients being treated with TB treatment that contains rifampicin?

1. Dolutegravir 50mg daily
2. Dolutegravir 100mg daily
3. Dolutegravir 50mg twice daily
4. Dolutegravir 100mg twice daily

Q3

In a patient with HIV admitted to hospital, who has a 2-month history of weight loss, fatigue and night sweats, an abdominal ultrasound is performed as part of the diagnostic work-up. This shows several periportal abdominal lymph nodes 2cm in diameter. This finding can be interpreted to mean the following:

1. This patient definitely has TB and no further diagnostic work-up is required

2. The finding is suggestive of TB, but further work-up is required before starting TB treatment

3. The finding is suggestive of TB, TB treatment can be started, but further diagnostic tests to confirm the microbiological diagnosis of TB are required and the patient should be followed up to assess treatment response

4. The finding is more suggestive of lymphoma than TB and TB treatment should not be started

Q4

An Alere urine LAM assay is performed in a patient admitted to hospital with TB symptoms. The test is read at 25 minutes and the patient band shows a very faint line, less than 1+ in intensity on the reading card. This should be interpreted as:

1. A negative result

2. A trace positive result

3. A positive result

4. An invalid result

Q5

The Alere urine LAM assay has higher diagnostic sensitivity in:

1. HIV negative patients compared to people living with HIV
2. People with HIV with CD4 < 50 compared to those with higher CD4 counts
3. People with HIV with CD4 > 200 compared to those with lower CD4 counts
4. People with HIV with CD4 > 500 compared to those with lower CD4 counts