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Scientific Updates in Tuberculosis

Presented at the Joint Australasian Sexual Health and HIV&AIDS Conferences, Perth 19 September 2019

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UNAIDS CAPRISA is the UNAIDS Collaborating Centre for HIV Research and Policy

CAPRISA hosts a DST-NRF Centre of Excellence in HIV Prevention

CAPRISA hosts a MRC HIV-TB Pathogenesis and Treatment Research Unit

COLUMBIA UNIVERSITY MAILMAN SCHOOL of PUBLIC HEALTH

UNIVERSITY OF KWAZULU-NATAL INYUVESI YAKWAZULU-NATALI

Outline

- Global TB Epidemic
- New TB drugs: latest updates from TB trials
- TB prevention updates
- TB Vaccine Developments
- TB diagnostic Developments

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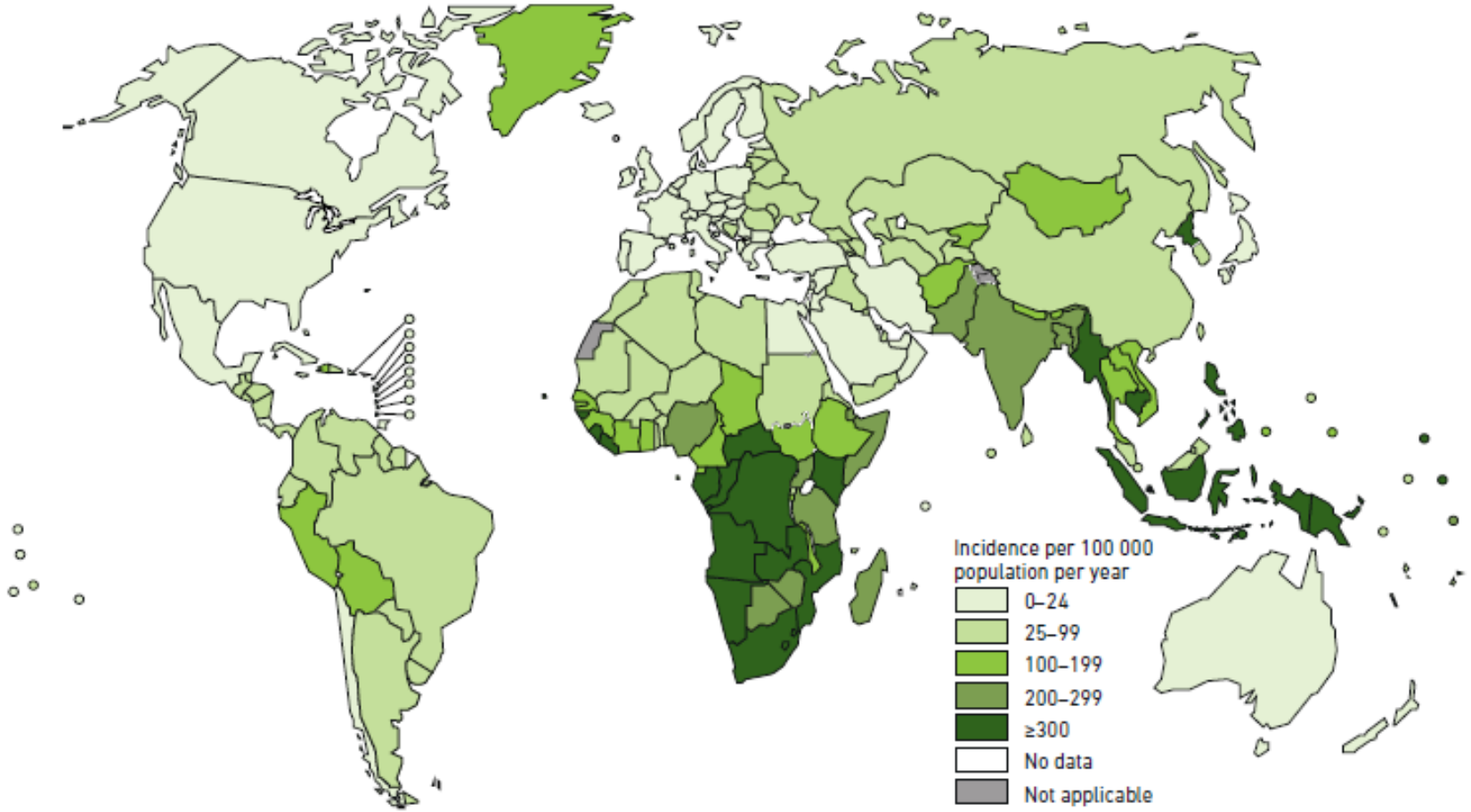
Global TB Epidemic – 2017 TB Incidence



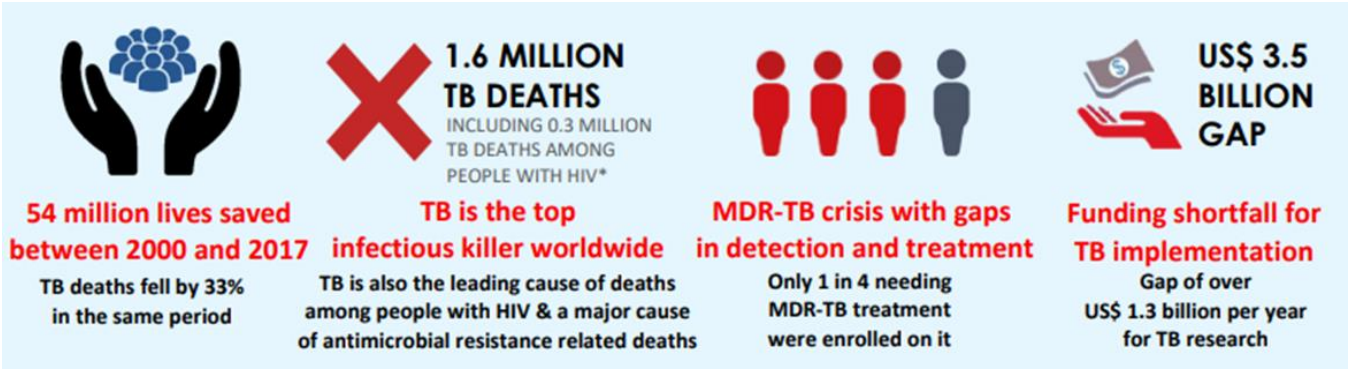
- 10 million new TB cases
- 10 % in PLWA

Source: WHO Global TB Report 2018

TB Burden Countries: 66% of New TB cases

HIV Rank (% Global PLWHA)	Country
3 (6)	India
12 (2)	China
-	Indonesia
-	Phillipines
-	Pakistan
2 (9)	Nigeria
-	Bangladesh
1 (18)	South Africa

66%



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Challenges in Treating Drug Resistant TB

- Multidrug-resistant TB and extensively drug-resistant TB are public health threats due to limited treatment options
- New drugs and treatment regimen are important to meet patient, national & global health needs
- Challenges in DR TB Regimen currently in use include:
  - Too long: up to 18 months to complete therapy
  - Too complicated: ≥ 5 drugs (IM/IV – no defined regimen)
  - High treatment limiting toxicity: deafness, renal impairment, psychosis
  - Suboptimal efficacy: DR TB cure rates about 20% in pre-BDQ era

Shorter Regimen for Rifampin-Resistant Tuberculosis (STREAM 1)

The NEW ENGLAND JOURNAL of MEDICINE

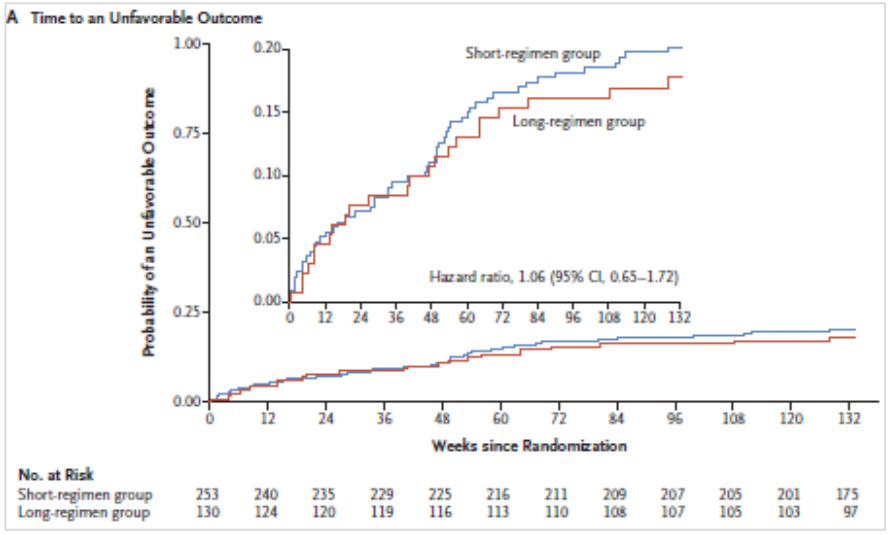
ESTABLISHED IN 1812 MARCH 28, 2019 VOL. 380 NO. 13

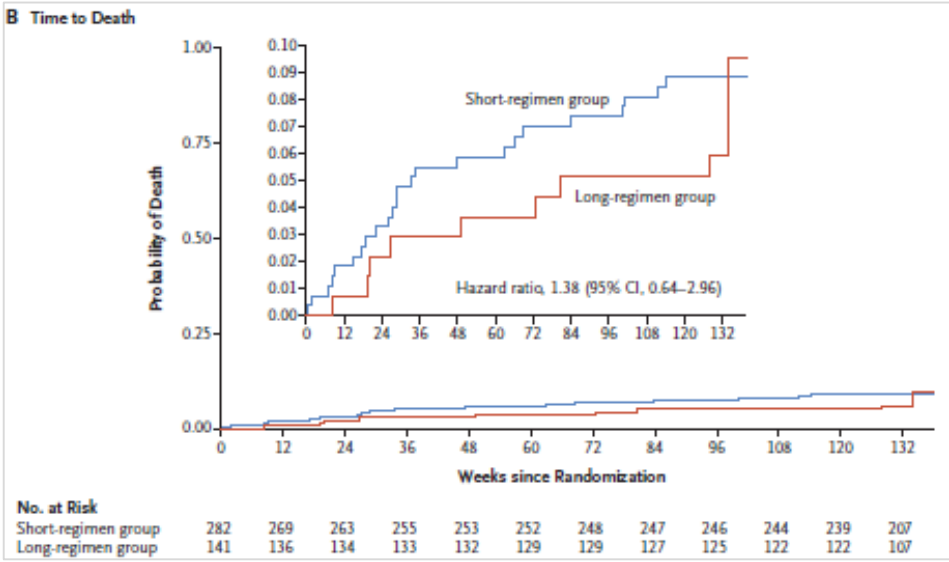
A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis

A.J. Nunn, P.P.J. Phillips, S.K. Meredith, C.-Y. Chiang, F. Conradie, D. Dalai, A. van Deun, P.-T. Dat, N. Lan, I. Master, T. Mebrahtu, D. Meressa, R. Moodliar, N. Ngubane, K. Sanders, S.B. Squire, G. Torrea, B. Tsogt, and I.D. Rusen, for the STREAM Study Collaborators*

March 2019

Non-Inferiority RCT: Short Regimen
4-6 Km-Mfx-Pto-Cfz-E-Hhigh dose-Z/ 5 Mfx-Cfz-E-Z
vs
SOC (20 month)





Short DR regimen non-inferior to long regimen with respect to safety and efficacy: 79.8% vs 78.8%

Shorter Regimen for XDR TB (NiX Study)

U.S FDA approves **Pretomanid** in combination with bedaquiline & linezolid for treatment of XDR-TB

- Novel 3-drug, all-oral, 6-month regimen: BPaL: bedaquiline (B) + pretomanid (Pa) + linezolid (L)
- Each drug has potent bactericidal & curative activity in both preclinical and clinical studies
- Minimal pre-existing resistance
- 95/107 patients converted to culture negative status: Median time of < 6 weeks
- All patients improved clinically
  - Reduction of TB symptoms
  - Overall improvement in patient-reported health status

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2019 Global TB Drug and Regimen Clinical Research

Ongoing Clinical Development Research: Strategy / Optimization / Regimen Development

Phase 2

OPC-167832*

Bedaquiline-Delamanid (ACTG 5343)

Bedaquiline-Pretomanid-Moxifloxacin-PZA (SimpliciTB Trial, NC-008)

Bedaquiline - Pretomanid – Moxifloxacin - Pyrazinamide (BPaMZ) (NC-005)

Levofloxacin with OBR for MDR-TB (OPTI-Q)

Linezolid Dose-Ranging

Beta-Lactams; Nitazoxanide

High Dose Rifampicin (PANACEA)

TB PRACTECAL - regimens with Bedaquiline-Pretomanid-Linezolid

Phase 3 Regimens

Bedaquiline-STREAM MDR-TB Trial Stage 2 with oral OBR (9 mo) or OBR with injectables (6 mo)

Bedaquiline-Pretomanid-Linezolid (NiX-TB)

Delamanid with OBR for MDR-TB

High Dose Rifampicin for DS-TB (RIFASHORT)

Rifapentine - Moxifloxacin for DS-TB (CDC TBTC 31, ACTG 5349)

Pretomanid-Moxifloxacin-Pyrazinamide (STAND)

Optimization/Post Market

Bedaquiline-Linezolid with OBR for MDR-TB (NExT Trial)

endTB 5-Regimen Trial for MDR TB

PredictTB – PET/CT, biomarkers DS-TB, 4 mo

TRUNCATE-TB Trial, 2 mo

Known chemical classes are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone , imidazopyridine amide, beta-lactam.

[1] Strategy trials, regimen development, open label, repurposed drug studies. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

[2] OBR = Optimized Background Regimen

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2019

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Prevention of TB in HIV

One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

S. Swindells, R. Ramchandani, A. Gupta, C.A. Benson, J. Leon-Cruz, N. Mwelase, M.A. Jean Juste, J.R. Lama, J. Valencia, A. Omoz-Oarhe, K. Supparatpinyo, G. Masheto, L. Mohapi, R.O. da Silva Escada, S. Mawlana, P. Banda, P. Severe, J. Hakim, C. Kanyama, D. Langat, L. Moran, J. Andersen, C.V. Fletcher, E. Nuermberger, and R.E. Chaisson, for the BRIEF TB/A5279 Study Team*

March 2019

- RCT: Efficacy and safety of 1-month daily rifapentine plus isoniazid (1-month group) with 9 months of isoniazid alone (9-month group)
- 3000 in HIV-infected patients from TB endemic settings, median follow up: 3.3 years, median CD4 470 cells/mm^3
- **1-month HP non-inferior to 9 months H**
- All patients on a non-DTG ART containing regimen

Prevention of TB in the DTG era

SAFETY & PK OF WEEKLY RIFAPENTINE/ISONIAZID (3HP) IN ADULTS WITH HIV ON DOLUTEGRAVIR CROI 2019

Author(s):
Kelly E. Dooley[1], Gavin Churchyard[2], Radojka M. Savic[3], Akshay Gupte[1], Mark A. Marzinke[1], Nan Zhang[3], Vinodh Edward[2], Lisa Wolf[1], Modulakgotla Sebe[2], Morongwe Likoti[2], Mark Fyvie[4], Innocent Shibambo[4], Trevor Beattie[2], Richard E. Chaisson[1]

- 60 patient study – DOLPHIN Trial
- 12 once-weekly high dose rifapentine/isoniazid doses (3HP) given to virally suppressed HIV infected patients
- Co-administration of DTG and HP was well-tolerated, with no HP-related Grade >3 AEs
- DTG AUC was reduced by 29% at weeks 3 and 8, however DTG levels sufficient, & viral load suppression <40 copies/mL was maintained throughout 3HP/DTG treatment
- DTG may be co-administered with 3HP without dose adjustment

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TB Vaccine Development – 1
Prevention of Latent TB infection

Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination

E. Nemes, H. Geldenhuys, V. Rozot, K.T. Rutkowski, F. Ratangee, N. Bilek, S. Mabwe, L. Makhethe, M. Erasmus, A. Toefy, H. Mulenga, W.A. Hanekom, S.G. Self, L.-G. Bekker, R. Ryall,* S. Gurunathan, C.A. DiazGranados, P. Andersen, I. Kromann, T. Evans, R.D. Ellis, B. Landry, D.A. Hokey, R. Hopkins, A.M. Ginsberg, T.J. Scriba, and M. Hatherill, for the C-040-404 Study Team†

July 2018

- 990 adolescents previously received BCG vaccination at birth
- Randomly assigned to receive
  - H4:IC31 vaccine
  - BCG revaccination
  - Placebo
- All participants negative HIV & negative for TB infection on the QuantiFERON-TB Gold In-tube assay (QFT)
- **Outcome: reduced sustained QFT conversion reflecting reduced sustained MTB infection**

Vaccines Development - 1

Table 2. Vaccine Efficacy.*

Outcome	QFT Conversion Threshold	H4:IC31 Group				BCG Group				Placebo Group
			Vaccine Efficacy				Vaccine Efficacy			
	IU/ml	*no./total no. (%)*	*point estimate (%)*	*80% CI (one-sided P value)†*	*95% CI (two-sided P value)‡*	*no./total no. (%)*	*point estimate (%)*	*80% CI (one-sided P value)†*	*95% CI (two-sided P value)‡*	*no./total no. (%)*
QFT conversion: primary outcome§	≥0.35	44/308 (14.3)	9.4¶	−18.3 to 30.6 (0.32)	−36.2 to 39.7 (0.63)	41/312 (13.1)	20.1¶	−4.8 to 39.1 (0.14)	−21.0 to 47.2 (0.29)	49/310 (15.8)
Sustained QFT conversion: secondary outcome‖	≥0.35	25/308 (8.1)	30.5¶	3.0 to 50.2 (0.08)	−15.8 to 58.3 (0.16)	21/312 (6.7)	45.4¶	22.3 to 61.6 (0.01)	6.4 to 68.1 (0.03)	36/310 (11.6)
Exploratory outcome										
Sustained QFT conversion**	<0.2 to >0.7	24/308 (7.8)	23.2¶	−8.8 to 45.8 (0.16)	−30.9 to 54.9 (0.33)	19/312 (6.1)	41.6¶	15.2 to 59.8 (0.03)	−3.3 to 67.0 (0.06)	31/310 (10.0)
End-of-trial sustained QFT conversion††	≥0.35	24/308 (7.8)	34.2¶	7.7 to 53.0 (0.05)	−10.4 to 60.7 (0.11)	20/312 (6.4)	48.2¶	25.9 to 63.8 (0.008)	10.5 to 70.0 (0.02)	36/310 (11.6)
QFT conversion‡‡	>4.0	22/308 (7.1)	34.5§§	6.8 to 54.2 (NA)	−12.1 to 62.3 (0.13)¶¶	19/312 (6.1)	45.1§§	20.5 to 62.2 (NA)	3.8 to 69.3 (0.04)¶¶	33/310 (10.6)
QFT conversion in ITT population‖‖	≥0.35	63/331 (19.0)	6.0¶	−17.7 to 24.9 (0.36)	−32.6 to 33.4 (0.72)	57/330 (17.3)	16.7¶	−4.9 to 33.9 (0.15)	−18.5 to 41.5 (0.30)	67/329 (20.4)

BCG revaccination reduced the rate of sustained QFT conversion
Efficacy of BCG 45.4% (P = 0.03) vs 30.5% in H4:IC31 vaccine vs 11.6% in placebo

Vaccine Development – 2
Prevention of progression of LTBI to TB disease

Phase 2b Controlled Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

O. Van Der Meeren, M. Hatherill, V. Nduba, R.J. Wilkinson, M. Muyoyeta, E. Van Brakel, H.M. Ayles, G. Henostroza, F. Thienemann, T.J. Scriba, A. Diacon, G.L. Blatner, M.-A. Demoitié, M. Tameris, M. Malahleha, J.C. Innes, E. Hellström, N. Martinson, T. Singh, E.J. Akite, A. Khatoon Azam, A. Bollaerts, A.M. Ginsberg, T.G. Evans, P. Gillard, and D.R. Tait

October 2018

- Randomized, phase 2b trial of M72/AS01E (GSK) tuberculosis vaccine in Kenya, South Africa, and Zambia
- HIV negative adults 18 to 50 years of age with latent M. tuberculosis infection (IGRA POSITIVE)
- 1786 participants received 2 doses of M72/AS01E and 1787 received placebo IMI AT Day 0, and Day 30
- Follow up for 2.3 years
- Endpoint: Bacteriologically confirmed active pulmonary Tuberculosis

54.0% vaccine efficacy: 0.3 vs. 0.6 cases per 100 person-years, (p=0.04)

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Meta-analysis of Sensitivity & Specificity of Xpert MTB/RIF in Pulmonary TB

- Meta-analysis of 27 unique studies with 9,558 participants
  - Initial diagnostic test replacing AFB smear: Pooled sensitivity 88%; specificity 99%
  - Add-on test following negative AFB smear: Pooled sensitivity 68%; specificity 99%
  - Detecting true RIF resistance: pooled sensitivity 95%; specificity 98%

Parameter	Pooled Sensitivity	95% CrI
Smear (+)/Culture (+)	**98%**	**97-99%**
Smear (-)/Culture (+)	**68%**	**61-74%**
HIV (+)	**79%**	**70-86%**
HIV (-)	**86%**	**76-92%**

WHO Xpert MTB/RIF Policy Update-2014

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Meta-analysis of Sensitivity & Specificity of Xpert MTB/RIF in Extrapulmonary TB

66 unique studies evaluated 16 213 specimens (adult and children) for detection of EPTB and rifampicin resistance, 7% from LMIC

Specimen Type	Median Pooled Sensitivity (95% CrI)	Median Pooled Specificity (95% CrI)	False Positive (%)	False Negative (%)
CSF	71.1 (60.9 -80.4)	98.0 (97.0 -98.8)	20	3
Pleural Fluid	50.9 (39.7 -62.8)	99.2 (98.2 -99.7)	8	8
Urine	82.7 (69.6 -91.1)	98.7 (94.8 -99.7)	17	1
Rifampicin resistance	95.0 (89.7 -97.9)	98.7 (97.8 -99.4)	9	1

Finding TB in HIV co-infection: WHO Recommends Urine LAM

- Improved sensitivity for diagnosis of TB in HIV co-infected individuals
- Especially those with CD4 counts ≤ 100 cells/UL & signs & symptoms of TB
- Indications for LAM use:
- Hospitalised patients
    - Seriously ill, non-ambulatory patients, suspicion of TB, with or without a CD4 count, and any of the following signs:
        - respiratory rate> 30/min
        - Fever (temperature >39°C)
        - heart rate > 120/min
        - low BMI (< 18.5)/ severely underweight or wasted
- Out-patients (i) TB is suspected based on symptoms &/ or signs & (ii) CD4 count < 100 cells/ ml
- Sputum Xpert should be performed for all <u>presumptive TB cases</u>

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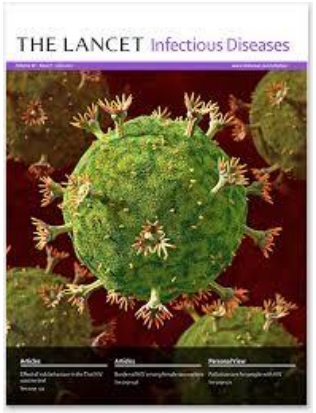
LAM: New Scientific Findings



Novel lipoarabinomannan point-of-care tuberculosis test for people with HIV: a diagnostic accuracy study

August 2019

Tobias Broger*, Bianca Sossen*, Elloise du Toit, Andrew D Kerkhoff, Charlotte Schutz, Elena Ivanova Reipold, Amy Ward, David A Barr, Aurélien Macé, Andre Trollip, Rosie Burton, Stefano Ongarello, Abraham Pinter, Todd L Lowary, Catharina Boehme, Mark P Nicol, Graeme Meintjes†, Claudia M Denkinger†

- Study compared Determine TB LAM Ag [AlereLAM] with novel Fujifilm SILVAMP TB LAM (FujiLAM)
- 968 stored urine samples from 3 cohorts of hospitalized HIV infected patient, 62% with microbiologically-confirmed tuberculosis
- Sensitivity of FujiLAM: 70.4% (95% CI 53 – 83.1) vs AlereLAM 42.3% (31.7 to 51.8) - difference 28.1%
- Specificity similar > 90% in both
- CD4 ≤100 cells per µL: FujiLAM sensitivity highest (84.2%), which was 26.9% higher than that with AlereLAM.
- Combined with sputum Xpert, FujiLAM could diagnose nearly three-quarters of microbiologically confirmed tuberculosis within 24 h of hospital admission.

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Summary

- TB remains the leading cause of morbidity and mortality in HIV infected patients
- Rigorous scientific evidence from several high impact studies –demonstrates strategies that could avert new TB cases, improve diagnosis, and reduce TB mortality and morbidity
- No room for complacency… need to ask the next set of high impact questions, and enhance TB program implementation

The world has made defeating AIDS a top priority…. But TB remains ignored. Today we are calling on the world to recognize that we can't fight AIDS unless we do much more to fight TB as well.

- Nelson Mandela

Bangkok, July 15, 2004

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