



International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis (INTERTB)

The Story So Far

INTERTB Symposium 171117

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St. George's, University of London**

WHO Press release 27th February, 2017

- WHO publishes list of 12 bacteria for which new antibiotics are urgently needed
- “Tuberculosis – whose resistance to traditional treatment has been growing in recent years – was not included in the list because it is targeted by other, dedicated programmes.”

WHO Global Tuberculosis Report, 2016

- The TB epidemic is larger than previously estimated.
- In 2015, there were an estimated 10.4 million TB new (incident) cases worldwide, of which
 - 5.9 million (56%) were among men,
 - 3.5 million (34%) among women and
 - 1.0 million (10%) among children.
- Six countries accounted for 60% of the new cases: India, Indonesia, China, Nigeria, Pakistan and South Africa.
- People living with HIV accounted for 1.2 million (11%) of all new TB cases.

The Figures in 2015



- TB ranks as a leading cause of death worldwide.
- Estimated incidence is 10.4 million (1 million children and 12% HIV positive).
- Estimated 4.3 million undiagnosed.
- TB killed 1.8 million people (210,000 children).
- TB kills 4,900 people daily.
- Prevalence of MDR approximately 5% of which 10% are XDR

Global Tuberculosis Report 2016

- Despite some progress in the pipeline for new diagnostics, drugs and regimens, and vaccines, TB research and development remains severely underfunded.
- At least US\$ 2 billion per year is needed for TB research and development. Funding during the decade 2005–2014 never exceeded US\$ 0.7 billion per year.

Dr Bern-Thomas Nyang'wa is a TB specialist at Médecins Sans Frontières/Doctors Without Borders (MSF). June 1st, 2017

- Tuberculosis does not receive anywhere near the attention it deserves. Care, treatment and diagnostics remain woefully underfunded. Despite the fact that the number of new people being diagnosed with TB every year is decreasing, the overall number of people living with TB is at an all-time high as we fail to cure people already living with the disease.
- An estimated two in every five people who fall sick with the disease are left undiagnosed and untreated. Medicines to treat TB have barely improved in 50 years.

Treatment Action Group 2016

- 25 October 2016 – Liverpool, UK – Funding for research for appropriate TB prevention, diagnosis and treatment dropped by more than USD 53 million despite the disease killing 1.8 million people in 2015.
- The world spent USD 620.6 million on TB research and development (R&D) last year, the lowest level of funding since 2008. This marks the second straight year that funding for TB R&D has fallen, showing that very little is being really done to end TB by 2030.



TB R&D Funding by Product Type 2007 - 2015



G Finder Report 2016

Figure 7. TB R&D funding by product type 2007-2015 (Page 24)

<http://www.policycuresresearch.org/downloads/Y9%20GFINDER%20full%20report%20web.pdf>

Approvals for RIFAQUIN

NHRES

UWITS

BDRU

JRO

MCAZ

BHDRC

SA MCC

MRCZ

CDC IRB

SA DOH

BRTI

MISAU

UCT

UNZA

MOCEC

UKZN

ZPRA

MOREG

Passage through SA MCC

- Protocol submitted 12th March, 2007.
- Supplementary information requested by 25th September, 2007
- The protocol finally approved 22nd February, 2008.
- Recruitment began 15th August, 2008.

Analysis of time to regulatory and ethical approval of SATVI TB vaccine trials in South Africa

- Median approval time following first submission to the MCC was 122 days (IQR 112 - 168; range 71 - 350).

Approvals for RIFASHORT



Centre	Review Body	Submission date	Approval Date	Total days	Enrolment start
Botswana	UB IRB	16/10/2015	19/08/2016	245	01/02/2017
	CDCF	16/11/2015	15/07/2016	250	
Uganda	MUST	14/04/2016	11/10/2016	180	21/07/2017
	UNCST	01/11/2016	20/02/2017	111	
	NDA	25/01/2017	15/06/2017	144	
Peru	HNDM IRB	01/05/2016	18/08/2016	109	
	NIH	23/02/2017	28/06/2017	125	
Bolivia	Local IRB	24/10/2016			
	National IRB	24/10/2016	Rejected		
	MOH	24/10/2016	Rejected		
	NTP	24/10/2016			

Stop TB Partnership 27/04/2017

Globally, 4.3 million people with TB are unable to access good quality care each year. Addressing this gap is a global priority and of national importance in high TB burden countries. In order to address this, it is essential to know where the biggest numbers of “missed” people affected with TB are and what is the reason for them being missed by health systems.

DIAGNOSTICS

- Xpert MTB/RIF(Cepheid)
- MinION- Portable, USB powered (NANOPORE)
- SmidgION- Smartphone sequencing (NANOPORE)
- QPOC hand held device (QUANTUMDx)

The Pipeline

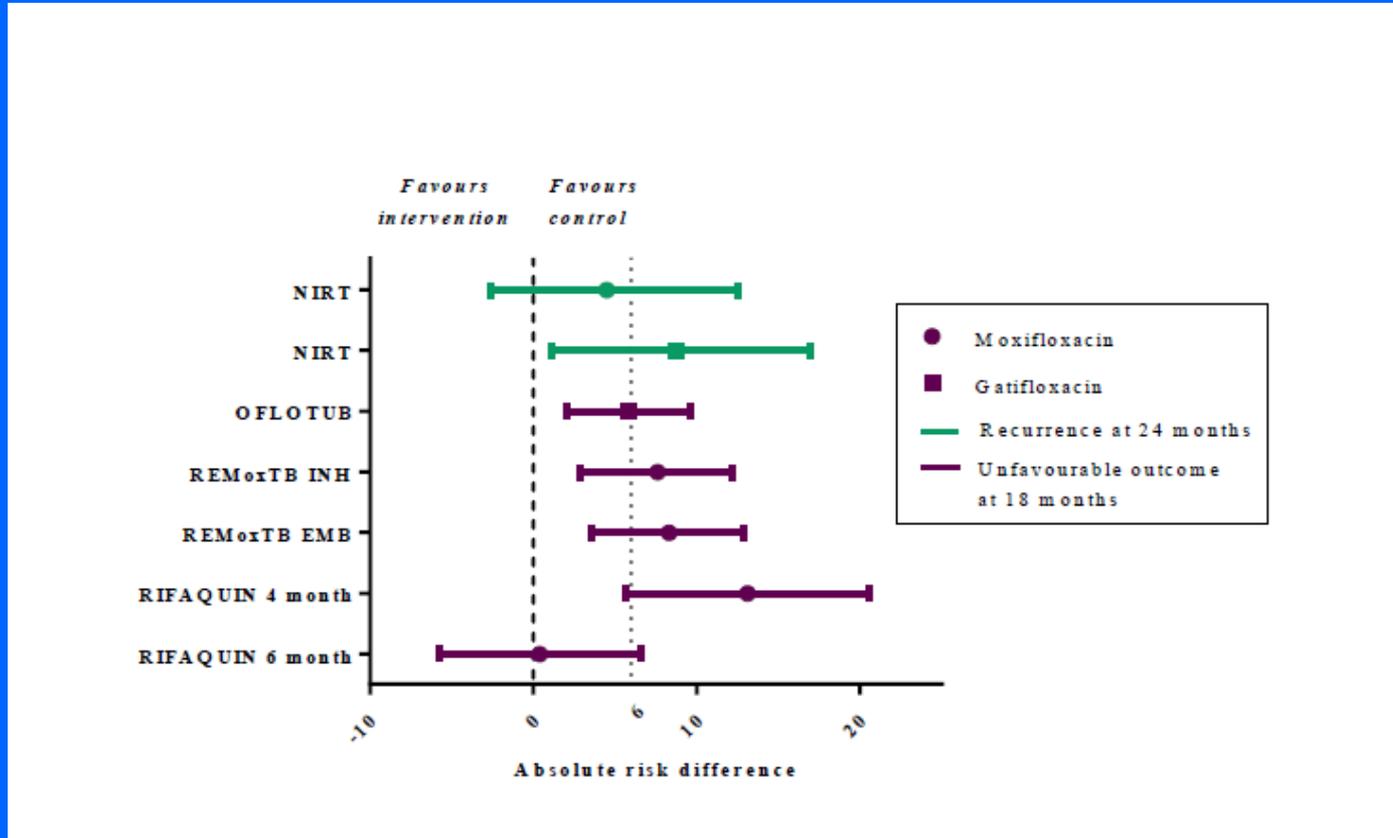
There are nine drugs in advanced phases of clinical trials for the treatment of drug-susceptible TB, drug-resistant TB or LTBI.

These are bedaquiline, delamanid, linezolid, PBTZ169, pretomanid, Q203, sutezolid, rifampicin (high-dose), and rifapentine.

Trials of quinolones

- REMoxTB
- OFLOTUB
- RIFAQUIN

Outcomes of the 3 Phase III Fluoroquinolone Trials



RIFAQUIN Trial



Randomisation

Test arm 1
2EMRZ/2(PM)₂

Test arm 2
2EMRZ/4(PM)₁

Control
2EHRZ/4RH

Rpe 15 mg/kg + Moxifloxacin 500 mg (TW)
Rpe 20/kg mg + Moxifloxacin 500 mg (OW)
Rifampicin 600 mg + INH 300 mg

Current Phase III Trials

- Alliance STAND Trial
- TBTC Study 31
- INTERTB RIFASHORT Trial

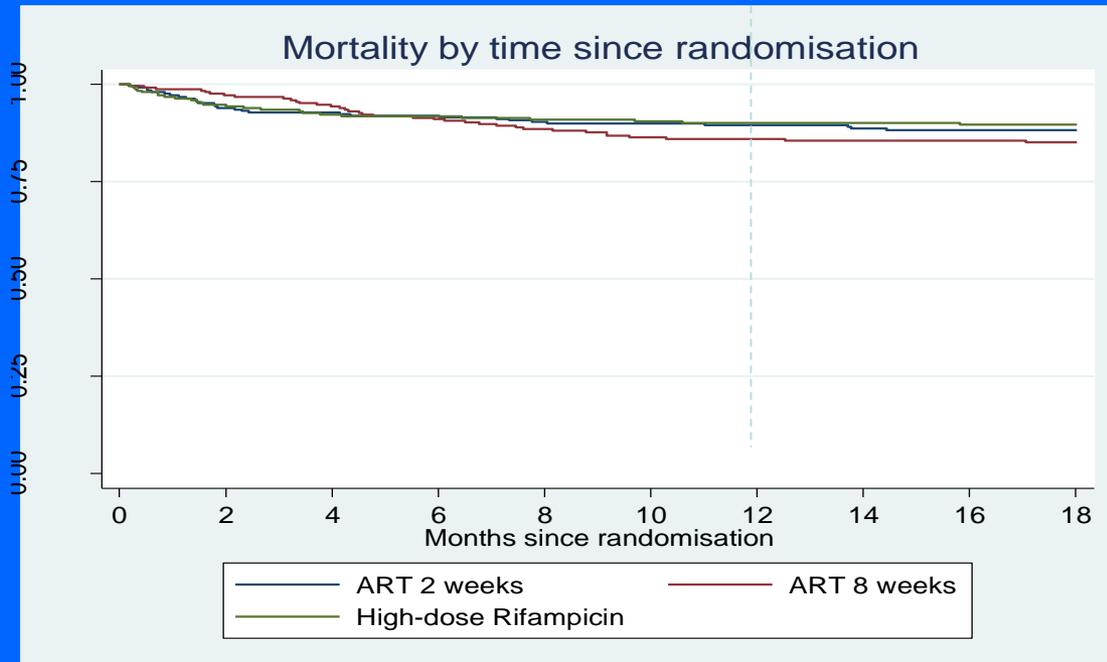
PLHIV

- HIV leading cause of death
- TB commonest opportunistic infection
- Globally 13% TB cases are co-infected
- In some African countries 40% co-infection

RIFAVIRENZ TRIAL

A pharmacokinetic study to evaluate the effect of high dose rifampicin on the blood levels of efaviranz

RAFA: Overall Mortality (n=747)



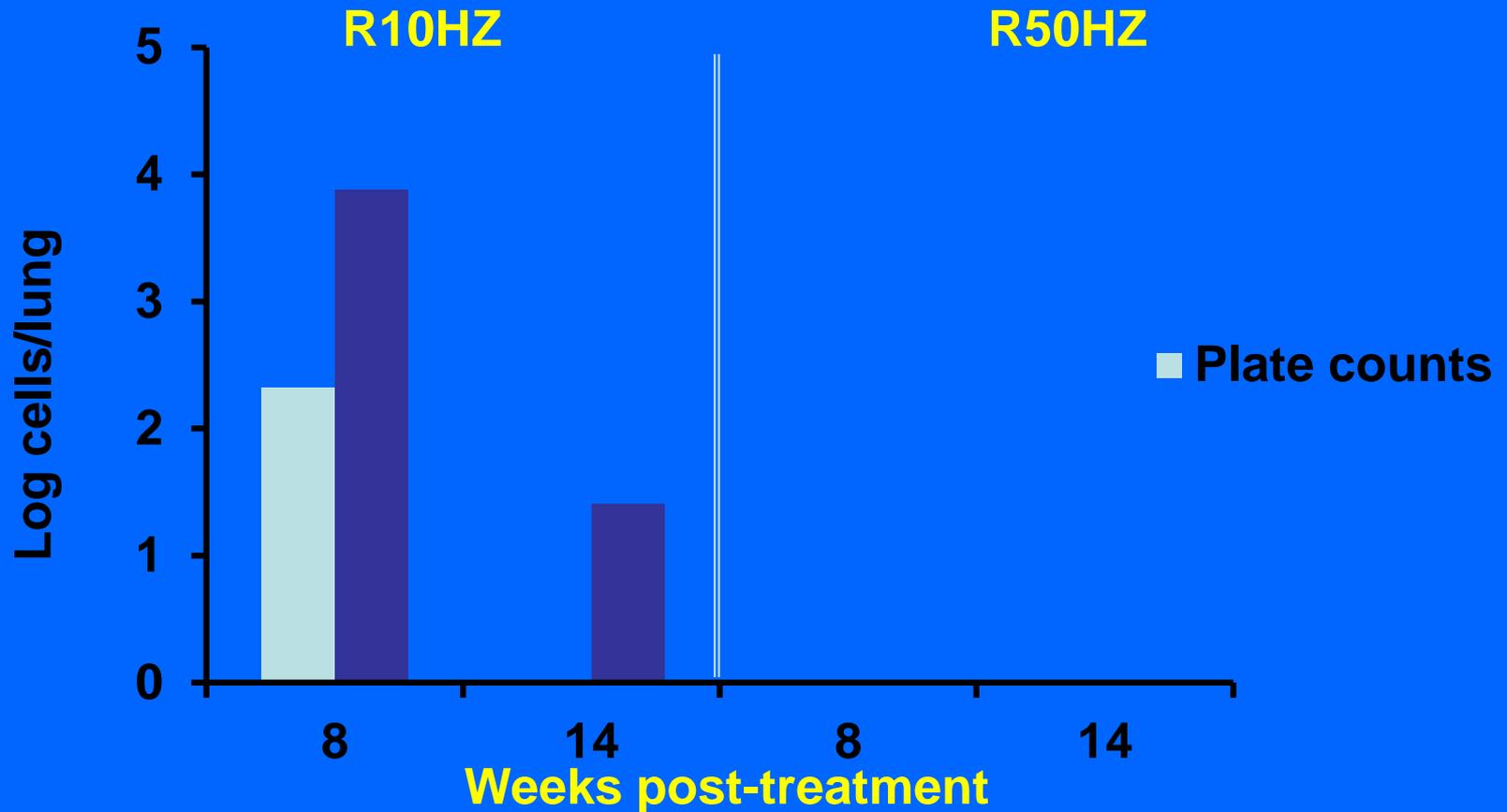
Interaction with
CD4 level
 $p = 0.0155$

CS Merle, S Floyd, A Ndiaye, T Galperine, A Furco, BC De Jong, H McIlleron, J Glynn, M Sarr, O Bah-sow, D Affolabi, 2016. High-dose rifampicin tuberculosis treatment regimen to reduce 12-month mortality of TB/HIV co-infected patients: The RAFA trial results. 21st International AIDS Conference (AIDS 2016)

Treatment arm	n	Survival 2 M	Survival 12 M	Survival 18 M	HR*	CI 95%
Arm A – ARV 2 Wks	251	0.94	0.89	0.88	0.77	0.46 – 1.28
Arm B – ARV 8 Wks	247	0.97	0.86	0.85	/	
Arm C – HD RIF	249	0.94	0.90	0.90	0.72	0.43 – 1.21

* Cox regression adjusted on country & interaction factor – B is the reference arm

No RPF-dependent persisters after treatment with high dose rifampicin regimen



Hu, Y., A. Liu, F. Ortega-Muro, L. Alameda-Martin, D. Mitchison & A. Coates, (2015) High-dose rifampicin kills persisters, shortens treatment duration, and reduces relapse rate in vitro and in vivo. *Front Microbiol* 6: 641.

Prospects for Advancing Tuberculosis Control Efforts through Novel Therapies

The introduction of new, shorter treatment regimens could dramatically accelerate the reductions in TB incidence and mortality that are expected under current regimens – with up to 2- or 3-fold increases in rates of decline if shorter regimens are accompanied by enhanced case detection.

J.A. Salomon, J.O. Lloyd-Smith, W.M. Getz, S. Resch, M.S. Sanchez, T.C. Porco, M.W. Borgdorff. PLOS Med Aug 2006, Volume 3, Issue 8.

Population-Level Impact of Short-Course Regimens for Tuberculosis: A Model-Based Analysis

These findings suggest that novel regimens that shorten treatment duration may have only a modest effect on TB transmission except in settings of very low treatment completion.

M.O. Fofana, G.M. Knight, G.B. Gomez, R.G. White, D.W. Dowdy.
PLOS One May 2014, Volume 9, Issue 5.

Cost Effectiveness



The introduction of a non-inferior 4-month first-line TB regimen into South Africa would have little impact on the TB burden. However, under several scenarios, it is likely that the averted societal costs would make such a regimen cost-effective in South Africa.

Knight GM, Gomez GB, Dodd OJ, Dowdy D, Zwerling A, Wells WA, Cobelens F, Vassall A, White RG.

The Impact and Cost-Effectiveness of a Four-Month Regimen for First-Line Treatment of Active Tuberculosis in South Africa.

PLoS One. 2015 Dec 30;10(12):e0145796. doi: 10.1371/journal.pone.0145796. eCollection 2015

Stop TB Partnership 31 October, 2015



The 2014 data shows the same trend of decline of TB incidence at 1.5 % year. The 2014 estimated incidence was 133/100,000 (from 126/100,000 in 2013) and this means that at the current rate, we will reach the 10/100 000 target of the End TB Strategy not in 2035 –
but in 2182.

Working Group for New TB Drugs

20 November 2015 – Geneva, Switzerland :

The world is losing its battle with tuberculosis (TB), which is now the biggest infectious killer globally, causing 1.5 million deaths every year. Without a clear investment plan and a complete overhaul in how this disease is tackled, TB is unlikely to be eliminated until the end of the 22nd century.

Estimated Annual Global Incidence

- 2002 : 8.7
- 2003 : 8.5
- 2005 : 8.8
- 2007 : 9.2
- 2008 : 8.8
- 2012 : 8.7
- 2013 : 8.6
- 2014 : 9.0
- 2015 : 10.4
- 2016 : 10.4





TB Alliance Report 2016



This is what one day of treatment can look like:

XDR-TB: 28% Survival Rate with Treatment

MDR-TB: 51% Survival Rate with Treatment

TB: 10.4 million become sick with TB each year

<http://www.tballiance.org/annualreport2016/assets/pdfs/epidemic.pdf>



TB Alliance Report 2016



Health Care Costs of Treating TB, per Patient, in South Africa

DS-TB: \$257

MDR-TB: \$6,772

XDR-TB: \$26,392

Source: World Health Organization, 2014

<http://www.tballiance.org/annualreport2016/assets/pdfs/epidemic.pdf>

HO, HO, HO TB!



- **Stop TB**
 - **End TB**
 - **Cap TB**
 - **TB ReFLECT**
 - **TB Alert**
 - **TB PACTS**
 - **Zero TB Cities**
 - **TB Alliance**
 - **Challenge TB**
 - **CRUSH TB**
 - **TB Research**
 - **INTERTB**
- PreDICT-TB**
 - CDC TBTC**
 - Louder Than TB**
 - TB PROOF**
 - FightTBack**
 - EMI-TB**
 - TB Free NYC**
 - TB REACH**
 - HALT TB**
 - Survivors Against TB**
 - TB-MAC**
 - World Without TB**
- TARGET TB**
 - Take That TB**
 - TB Forum**
 - TB Free India**
 - TB Europe Coalition**
 - TB Proof**
 - IMPACT TB**
 - TBNET**
 - CURETB**
 - Speak TB**
 - TBHaregaDeshJeetega**



RADA



<http://uk.virginmoneygiving.com/Rada.Savic>



CLAIRE



<http://uk.virginmoneygiving.com/claire85>



Next Meeting

Monday 22nd October, 2018