# Development and deployment of new TB drugs



#### **Gerry Davies**

Reader in Infection Pharmacology

Institutes of Infection and Global Health & Translational Medicine

Malawi-Liverpool-Wellcome Research Unit



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Academic co-ordinator of the PreDiCT-TB consortium

Member of WHO Taskforce on Development of New Tuberculosis Drugs

Co-PI on HIRIF trial (NIH)

Steering committee member RIFAQUIN Trial

DSMB Chair RIFATOX trial







- A changing landscape
- Rifamycin optimisation
- Fluoroquinolones
- Bedaquiline
- Delaminid
- The (near) future



### A short history of Short Course Chemotherapy

THE LANCET, NOVEMBER 9, 1974

CONTROLLED CLINICAL TRIAL OF FOUR SHORT-COURSE (6-MONTH) REGIMENS OF CHEMOTHERAPY FOR TREATMENT OF PUMONARY TUBERCULOSIS

#### SECOND EAST AFRICAN / BRITISH MEDICAL RESEARCH COUNCIL STUDY

#### THE LANCET, AUGUST 12, 1978

CONTROLLED CLINICAL TRIAL OF FIVE SHORT-COURSE (4-MONTH) CHEMOTHERAPY REGIMENS IN PULMONARY TUBERCULOSIS

First Report of 4<sup>th</sup> Study

EAST AFRICAN AND BRITISH MEDICAL RESEARCH COUNCILS







## **The Challenge of Resistance**

Collaborative meta-analysis of 6724 patients on individualised regimens from 26 centres







### New anti-tuberculosis drugs



Rifapentine

Gatifloxacin

Bedaquiline (TMC-207)



## **Efficacy endpoints in TB trials**



Davies G Tuberculosis 2010 90:171-6





#### **Rifamycins : Phase II trials**







## **Rifamycins: Phase II Trials**







## **Rifamycins : PK and Safety**

- Saturable and non-linear PK observed for RIF
- Decreasing bioavailability with dose and food effect with RP
- Grade 3 transaminitis/hepatitis 2-4%
- No reports of immune-mediated syndromes
- HR1 MTD Study up to 40 mg/kg
- PanaCEA MAMS Study

## Fluoroquinolones : Phase II Trials



	Fluoroquinolone (F	0)	Basic red	imen		Risk Ratio	Risk Ratio
Study or Subgroup	Events T	otal	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.6.1 Ciprofloxacin vs rifampicin							
Mohanty 1993 Subtotal (95% CI)	27	30 <b>30</b>	25	30 <b>30</b>	11.9% <b>11.9%</b>	1.08 [0.88, 1.32] <b>1.08 [0.88, 1.32]</b>	
Total events Heterogeneity: Not an	27 nlicable		25				
Test for overall effect: Z = 0.76 (P = 0.45)							
1.6.2 Ciprofloxacin vs ethambutol plus pyrazinamide							
Kennedy 1993 Subtotal (95% CI)	6	9 9	11	11 <b>11</b>	3.0% 3.0%	0.68 [0.42, 1.09] 0.68 [0.42, 1.09]	
Total events Heterogeneity: Not ap	6 plicable		11				
Test for overall effect. $\angle = 1.62$ (P = 0.11)							
1.6.3 Ofloxacin versu	s ethambutol						
Kohno 1992	48	62	49	62	13.0%	0.98 [0.81, 1.18]	
Subtotal (95% CI)	28	53 115	32	112	5.7% 18.7%	0.83 [0.59, 1.15] 0.94 [0.80, 1.10]	-
Total events	76		81				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.87, df = 1 (P = 0.35); l <sup>2</sup> = 0% Test for overall effect: Z = 0.75 (P = 0.45)							
1.6.4 Lovoflovacin ad	dition						
FI-Sadr 1998	46	53	64	82	15.9%	1 11 0 95 1 301	+ <b>-</b> -
Subtotal (95% CI)		53		82	15.9%	1.11 [0.95, 1.30]	►
Total events	46		64				
Test for overall effect:	Z = 1.34 (P = 0.18)						
1.6.5 Gatifloxacin versus ethambutol							
Rustomjee 2008b	40	52	32	50	8.4%	1.20 [0.93, 1.55]	+
Subtotal (95% CI)	40	52	22	50	8.4%	1.20 [0.93, 1.55]	
Heterogeneity: Not ap	40 plicable		32				
Test for overall effect: Z = 1.41 (P = 0.16)							
1.6.6 Moxifloxacin vs ethambutol							
Burman 2006	99	169	98	167	13.6%	1.00 [0.83, 1.19]	-+
Conde 2009	59	85	45	85	9.0%	1.31 [1.03, 1.68]	
Rustomjee 2008b Subtotal (95% CI)	36	44 298	32	50 302	8.7%	1.28 [1.00, 1.64]	
Total events	194	200	175	302	51.270	1.11 [0.51, 1.41]	-
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 4.19, df = 2 (P = 0.12); l <sup>2</sup> = 52%							
Test for overall effect:	Z = 1.62 (P = 0.10)						
1.6.7 Moxifloxacin vs	isoniazid						
Dorman 2009 Subtotal (95% CI)	99	219 219	90	214 214	10.8% <b>10.8%</b>	1.07 [0.87, 1.33] 1.07 [0.87, 1.33]	
Total events	99		90				_
Heterogeneity: Not ap	plicable 7 = 0.66 (P = 0.51)						
	z = 0.00 (r = 0.01)						
Total (95% CI)	400	776	470	801	100.0%	1.07 [0.98, 1.17]	•
Lotar events	488 0.01: Chiz = 12.07 4	f = 0 /	4/8 P=0.16\	IZ = 21 ℃			
Test for overall effect $Z = 158$ (P = 0.11) - 0.5 0.7 1 - 1.5 2 - 0.5 0.7 1 - 1.5 2 - 0.5 0.7 1 - 1.5 2 - 0.5 0.7 1 - 0.5 0.5 0.7 1 - 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5							
Test for subgroup differences: Chi <sup>2</sup> = 7.94, df = 6 (P = 0.24), l <sup>2</sup> = 24.5%							

Zigansina L, Titarenko A, Davies GR. Cochrane Database of Systematic Reviews update 2013









## Fluoroquinolones: Phase III Trials

UNIVERSITY OF LIVERPOOL







## **Bedaquiline : pharmacology**

- Target atpE subunit of ATP synthase
- Bioavailability 2x with food
- Protein-binding >99%



- Metabolised by CYP3A4, AUC  $\downarrow$  50% RIF,  $\uparrow$  2-3x RTV
- Inactive monodesmethyl metabolite (M2)
- Complex PK/dosing with loading and terminal t<sub>1/2</sub> 5.5 months





### **Bedaquiline : Efficacy**





FDA NDA 204-384 Briefing package November 2012



## **Bedaquiline : Safety**

- 12.7% vs 2.5% mortality in C208 trial (p=0.017)
- QTcF prolongation in 26.4% vs 7.7% but no cardiac events
- Conditionally approved with a black-box warning
- WHO guidance recommended informed consent and active pharmacovigilance
- Stronger evidence for early use in MDR-TB then XDR-TB



The use of bedaquiline in the treatment of multidrug-resistant tuberculosis

> World Health Organization





## **Delamanid : pharmacology**

- Target mycolic acid synthesis
- Prodrug substrate for nitroreductases (Rv3547 and F<sub>420</sub> system)
- Bioavailability 4x with food
- Protein binding >99.5%
- Primary metabolism by albumin amino groups, 8 inactive metabolites
- Some CYP Interaction AUC ↓ 52% RIF, ↑ 20% RTV
- Twice daily dosing with terminal t<sub>1/2</sub> 32 hours





## **Delamanid : development programme**







#### **Delamanid : Efficacy**

**Trial 204** 

Trial 208

#### Sputum culture conversion in MGIT\* at 2 months



Mortality 8.3% versus 1% for <2 and >=6m (p<0.001)

EMA Public Assessment Report EMA/CHMP/125521/2013 December 2013



## The (Near) Future



- Effective roll-out of novel regimens to NTPs
- Continued efforts to reach an ultra-short regimen for DS-TB (TBTC Study 31)
- Treatment shortening to 9m for MDR-TB (STREAM)
- Completion of Phase III trials for BDQ and DLD (STREAM/ C210, Otsuka 213)
- Evaluation of new drugs in the DS-TB context (NC001-5)
- Promise of Phase III trials of universal regimens (STAND)