



TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Stakeholders Association Annual Meeting

The need for an increased pipeline Updates from the field

Andreas Diacon
Stellenbosch University
Task Applied Science
Cape Town, South Africa



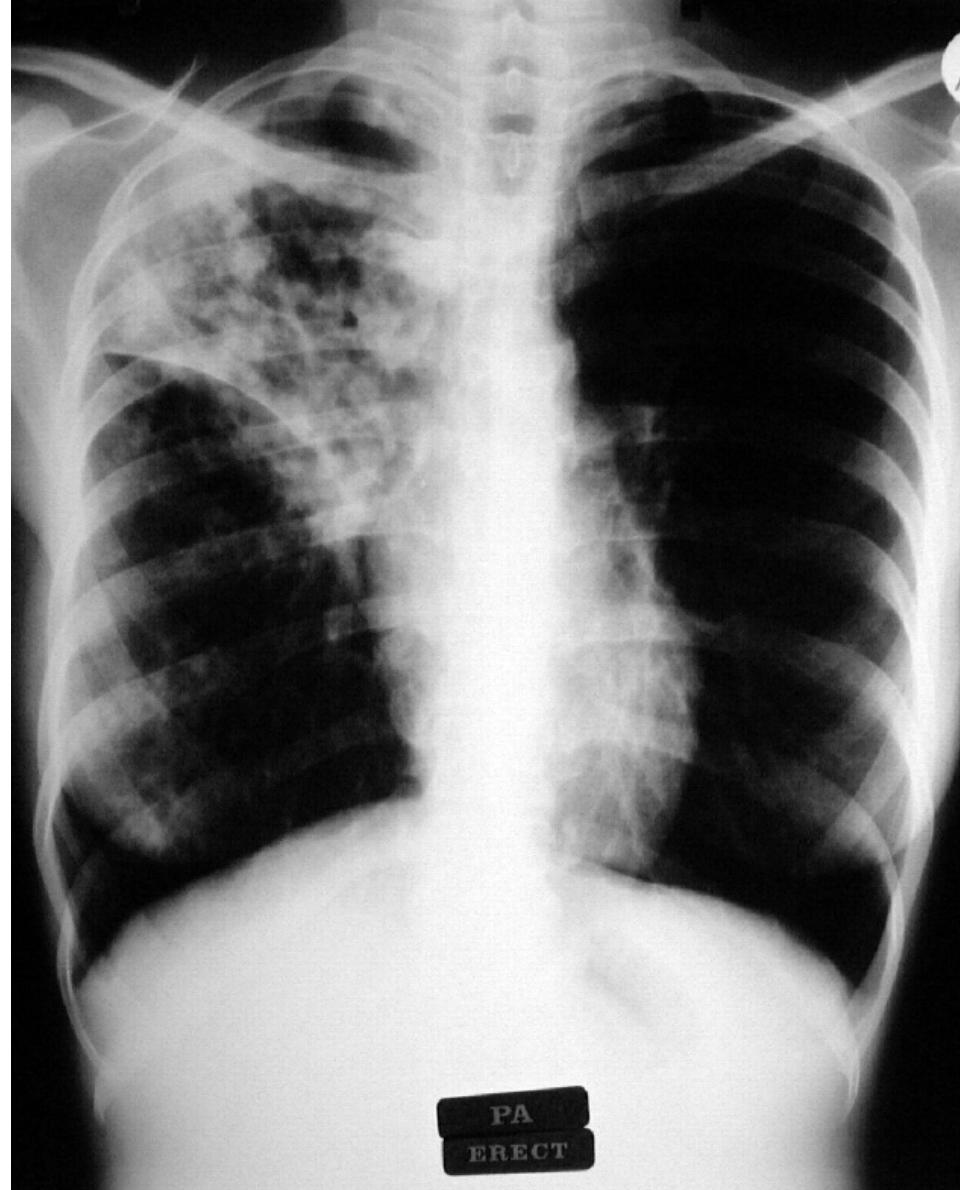


Ernst Ludwig Kirchner. Blick auf Davos. 1924. Bündner Kunstmuseum Chur, Switzerland



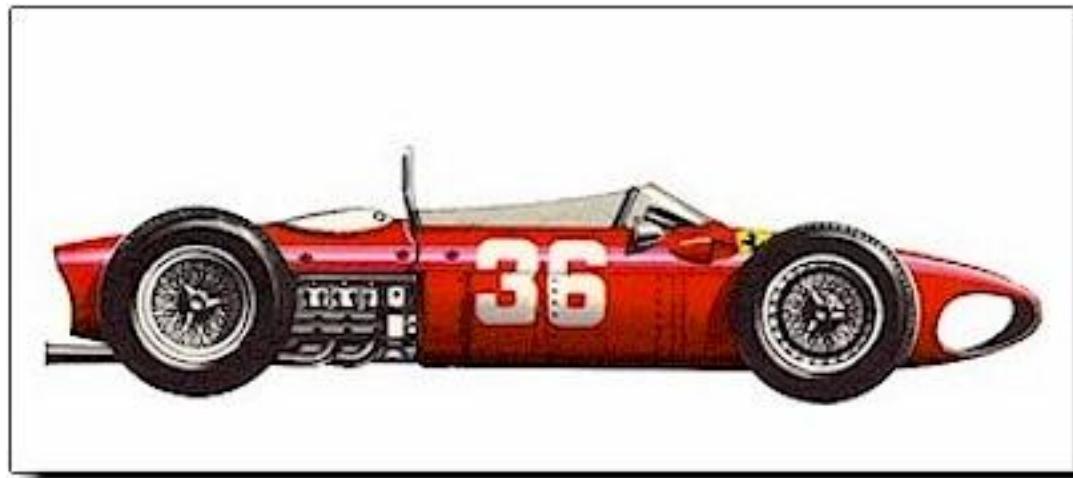
The Magic Mountain

- Sunlight
- Nutrition
- Supine



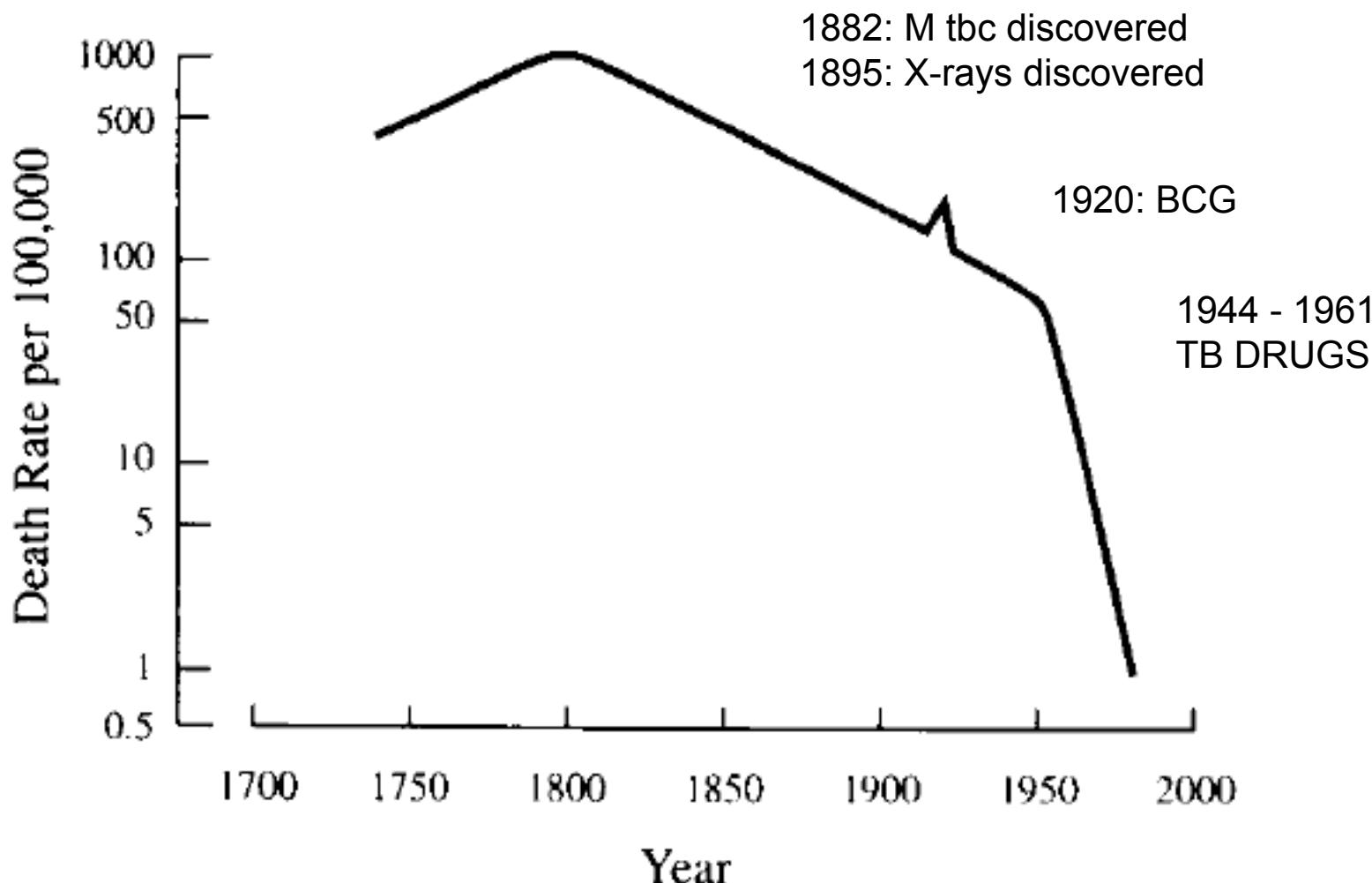
Ferrari 156 Sharknose

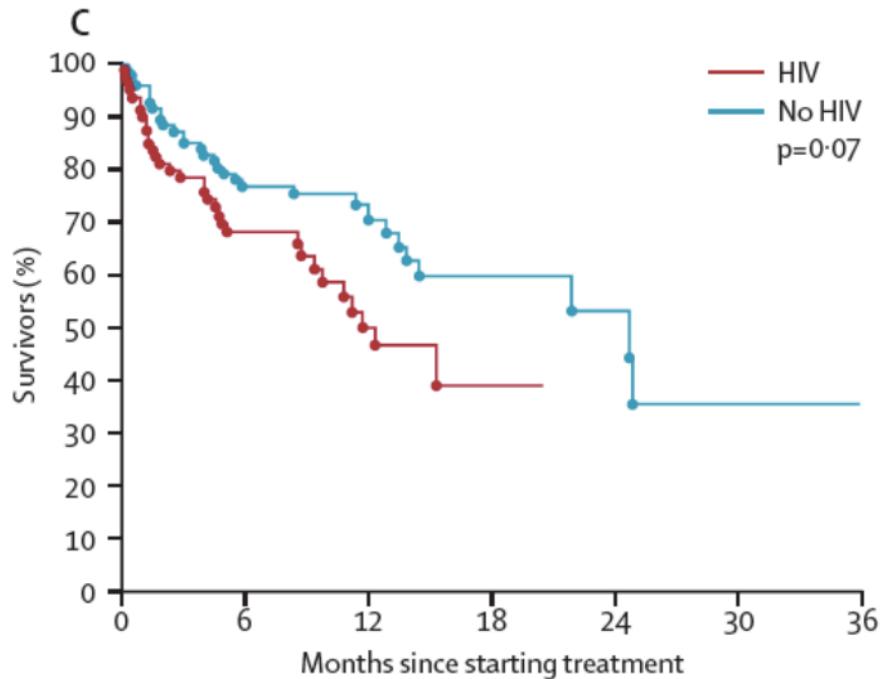
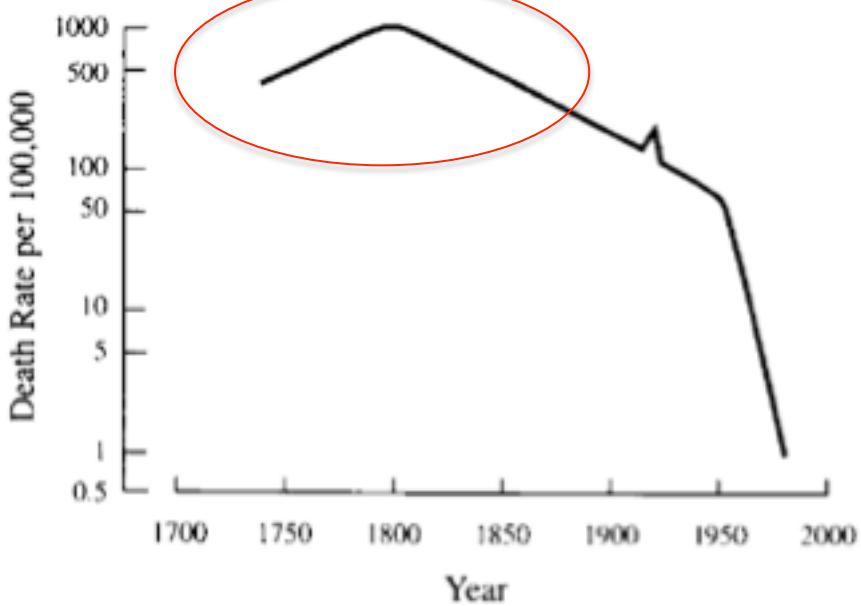
1961



- Vaccines
- Diagnostics
- Treatments

1800s:
Improved socioeconomic conditions





HIV negative cases with active TB

Pre-chemotherapy era:

- 10-year fatality rate 70%

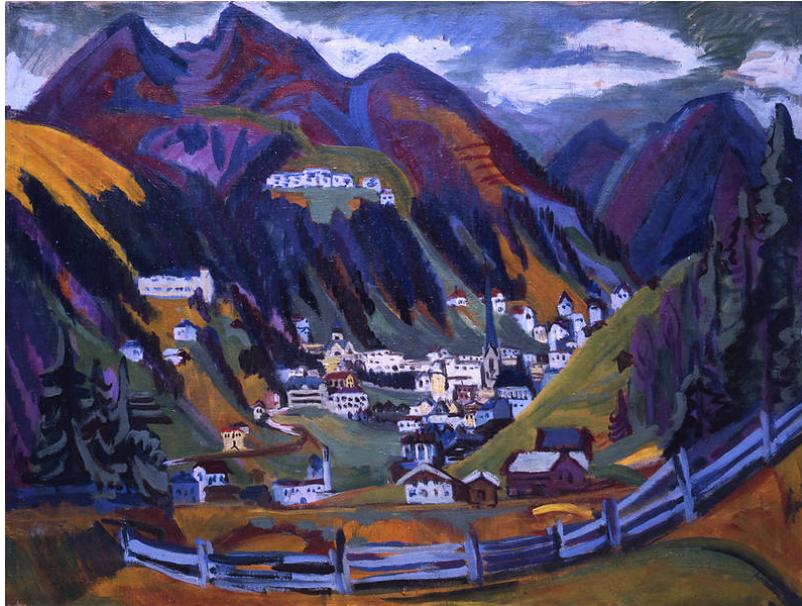
XDR TB Western Cape:

- 3-year fatality rate 60%

Tiemersma EW. 2011. PLoS ONE 6(4): e17601.

Dheda et al. Lancet 2010;375:1798–807

Tuberculosis today



Cape Town:

- >20,000 TB cases pa, 10% children <8y
- HIV prevalence in TB cases: 51%
- MDR >1,500/year, XDR >100/year
- Cost of drug resistance >50% of TB budget

WHO:

- XDR-TB in >50 countries
- >75% resistant TB in previously untreated patients

Drug resistance and poor compliance

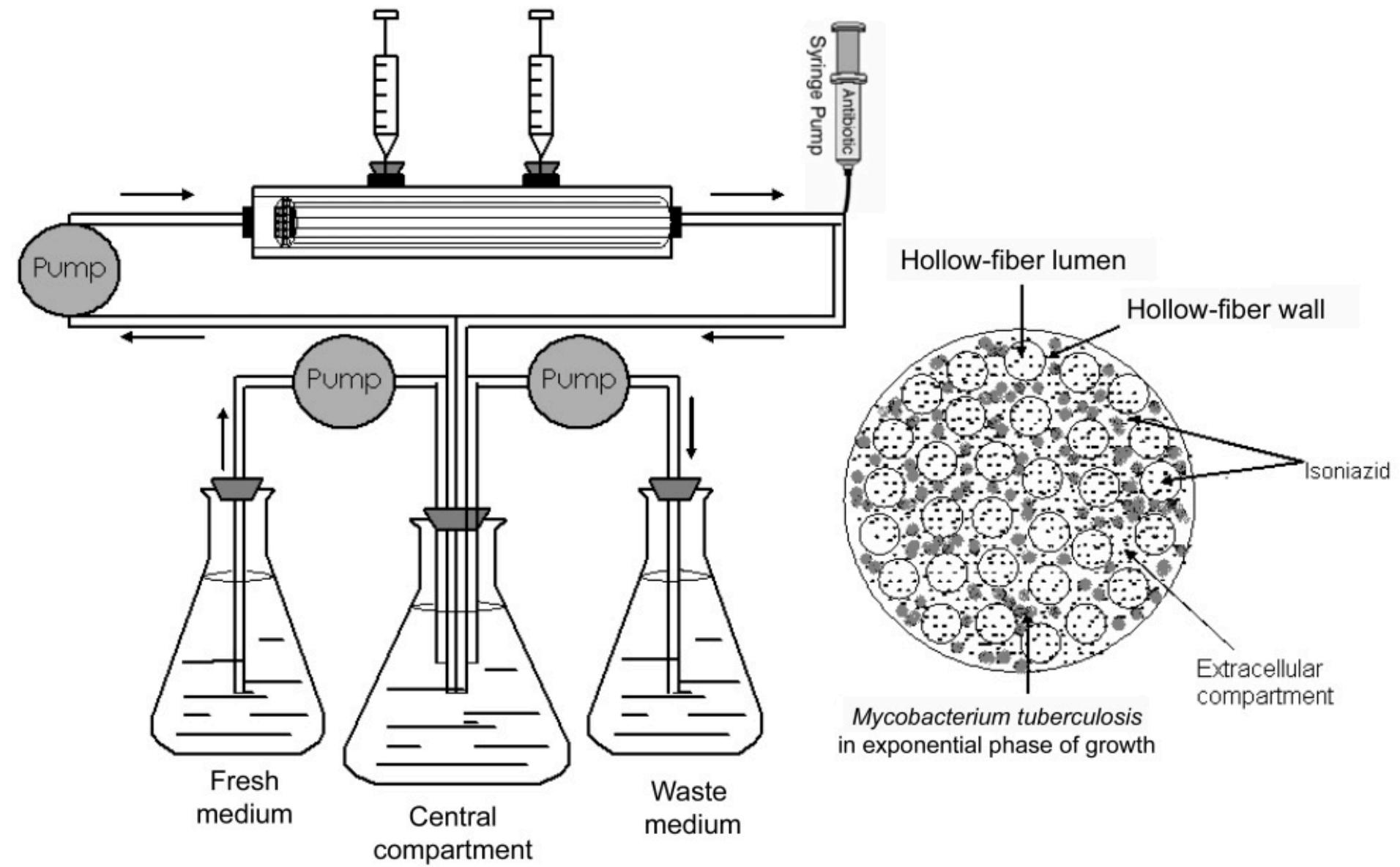


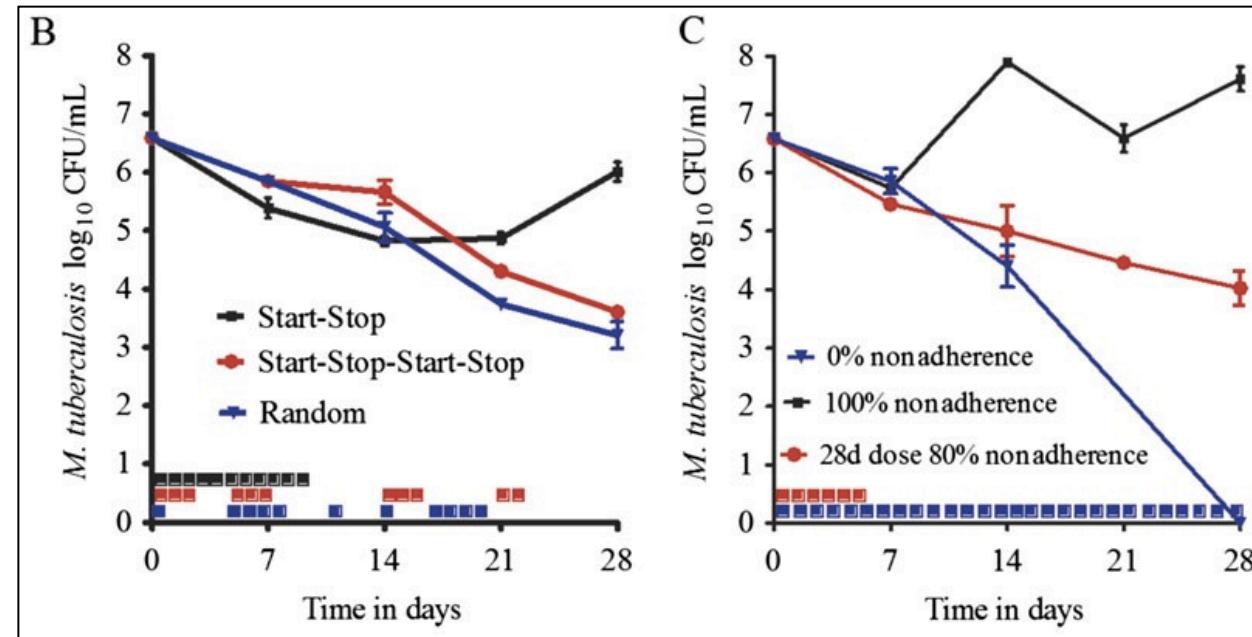
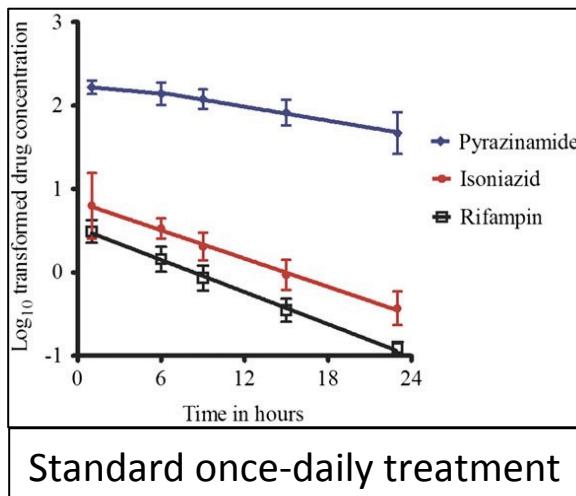
Hollow Fiber Model

Gumbo et al JID 2007:195;194-201

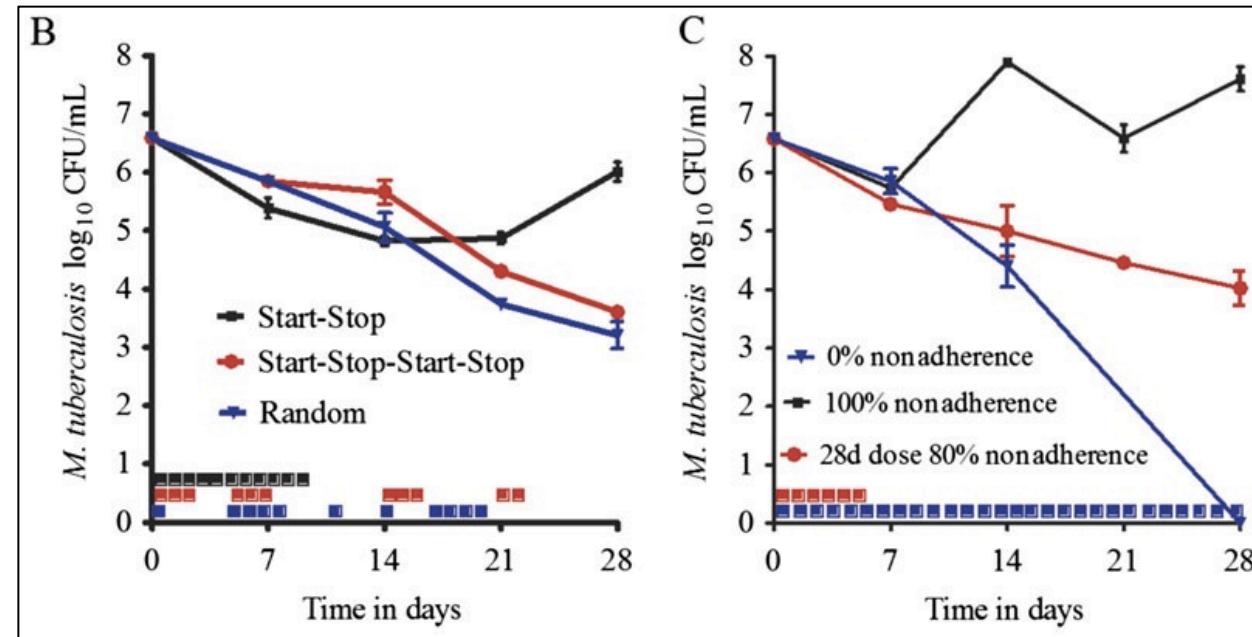
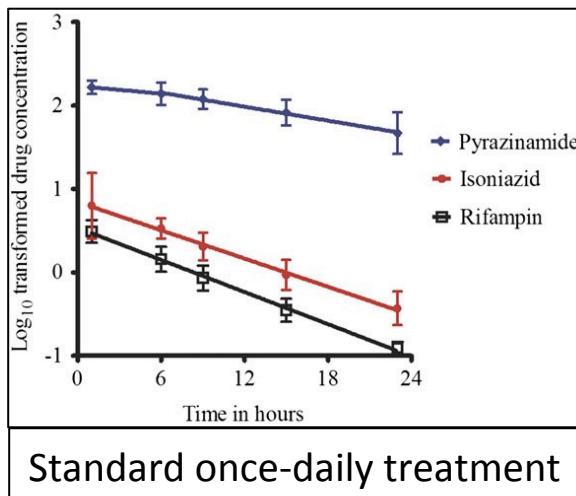
Srivastava et al JID 2011:204; 1951-9







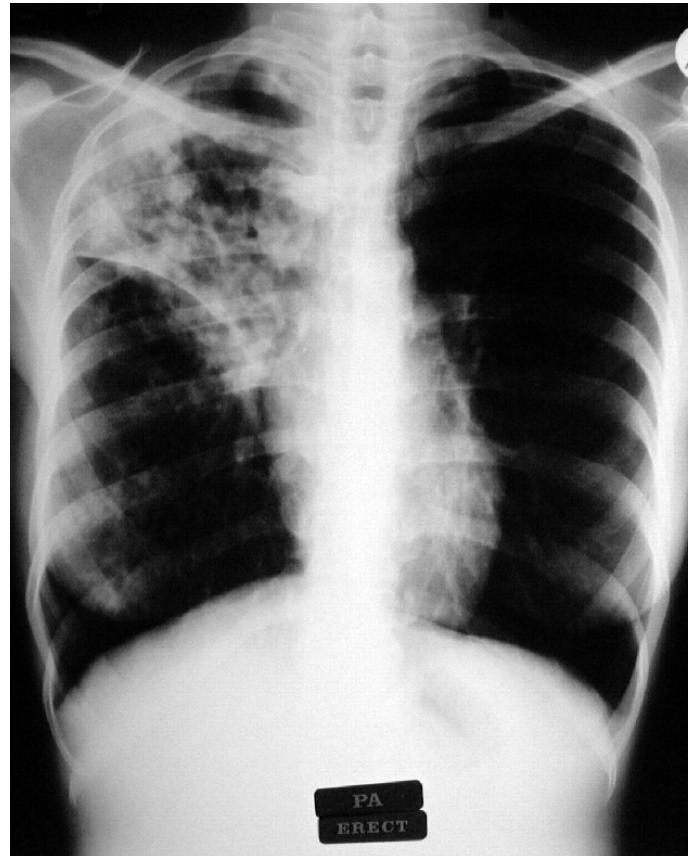
- Does non-compliance cause multidrug-resistant TB?
 - Fast and slow growing bacteria
 - 0.5% INH-resistant, 0.5% RIF-resistant
 - HRZ at human serum levels
 - Poor compliance patterns as seen in practice
- Augmentation of resistance?



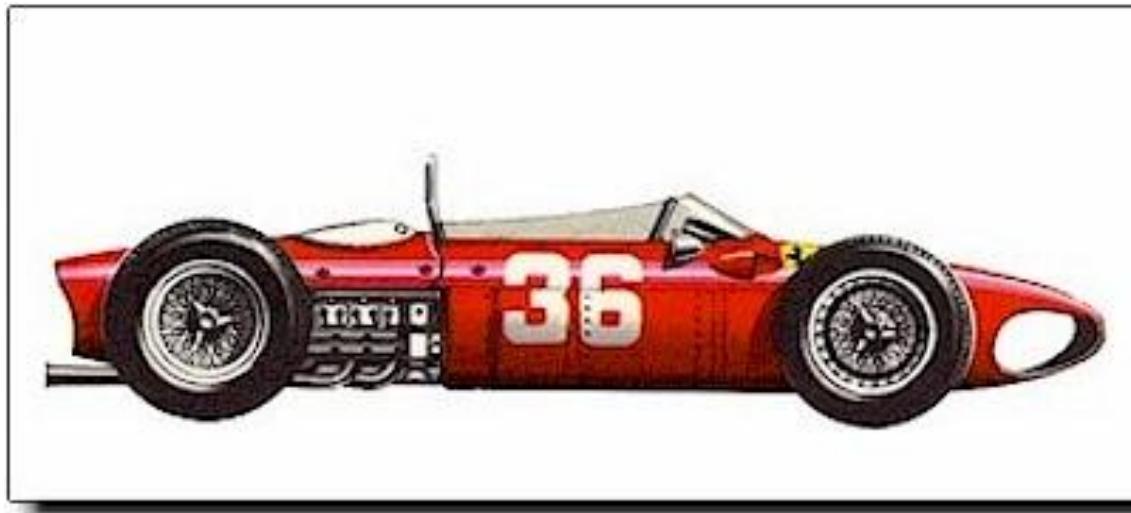
- Does non-compliance cause multidrug-resistant TB?
 - Fast and slow growing bacteria
 - 0.5% INH-resistant, 0.5% RIF-resistant
 - HRZ at human serum levels
 - Poor compliance patterns as seen in practice
- No increase in % resistance, no MDR TB

Underestimating the enemy

- Variability within a patient
 - Cavity walls, fibrosis
 - Bacterial subpopulations
- Between patient variability
 - Drug levels
 - Resistance levels



Innovation (at once, if not sooner)



1961



2013

www.ferrari.com

Ferrari F1 - 1950 to 2013

continuous process of innovation and testing (and failures too)



TB Drug Development

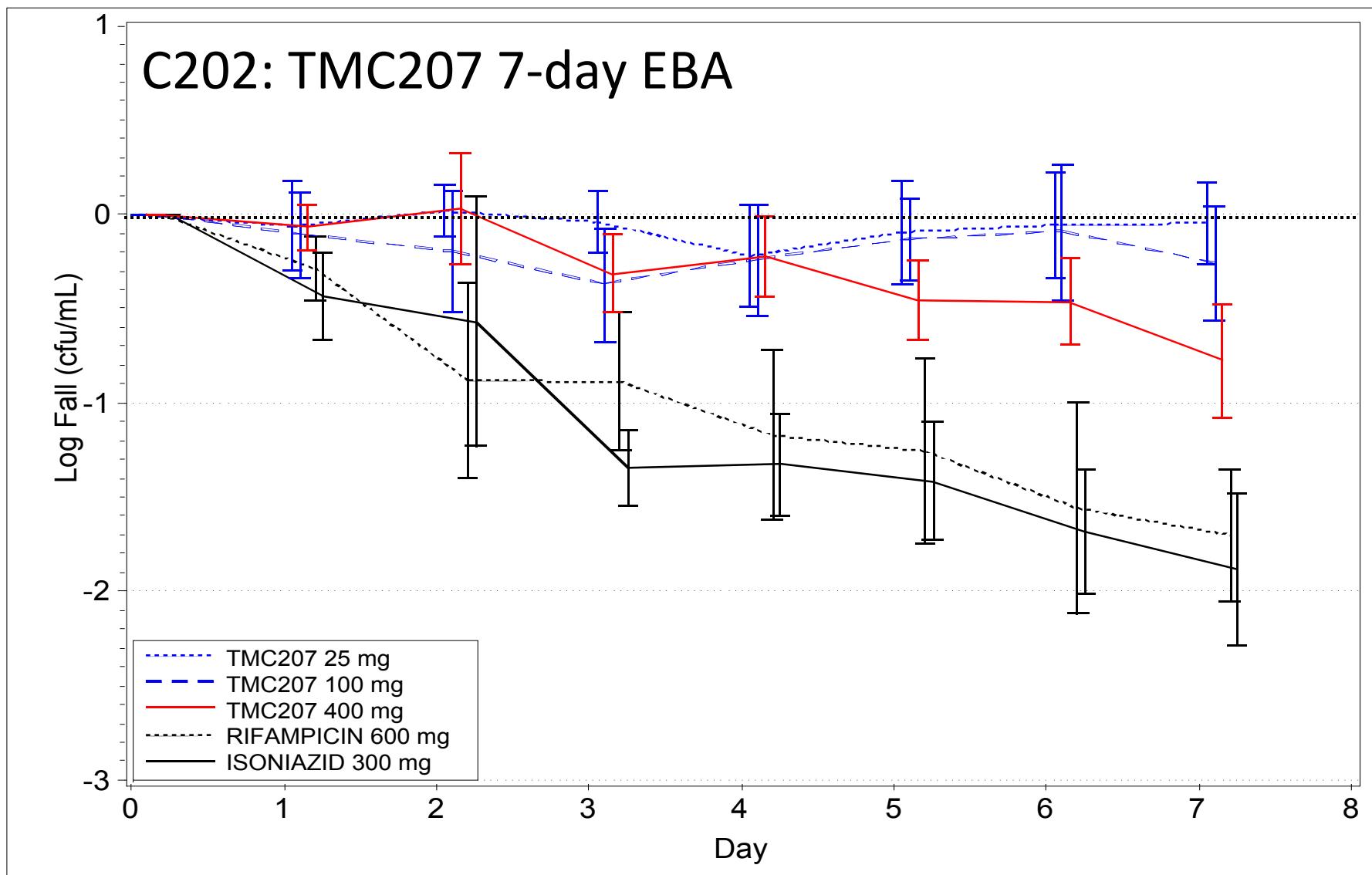
- Pathway for evaluation
 1. Mouse model
 2. 14-day EBA
 3. 8-week study
 4. Registration trial in MDR or DS TB

28 June 2005

First TMC207 dose to a TB patient



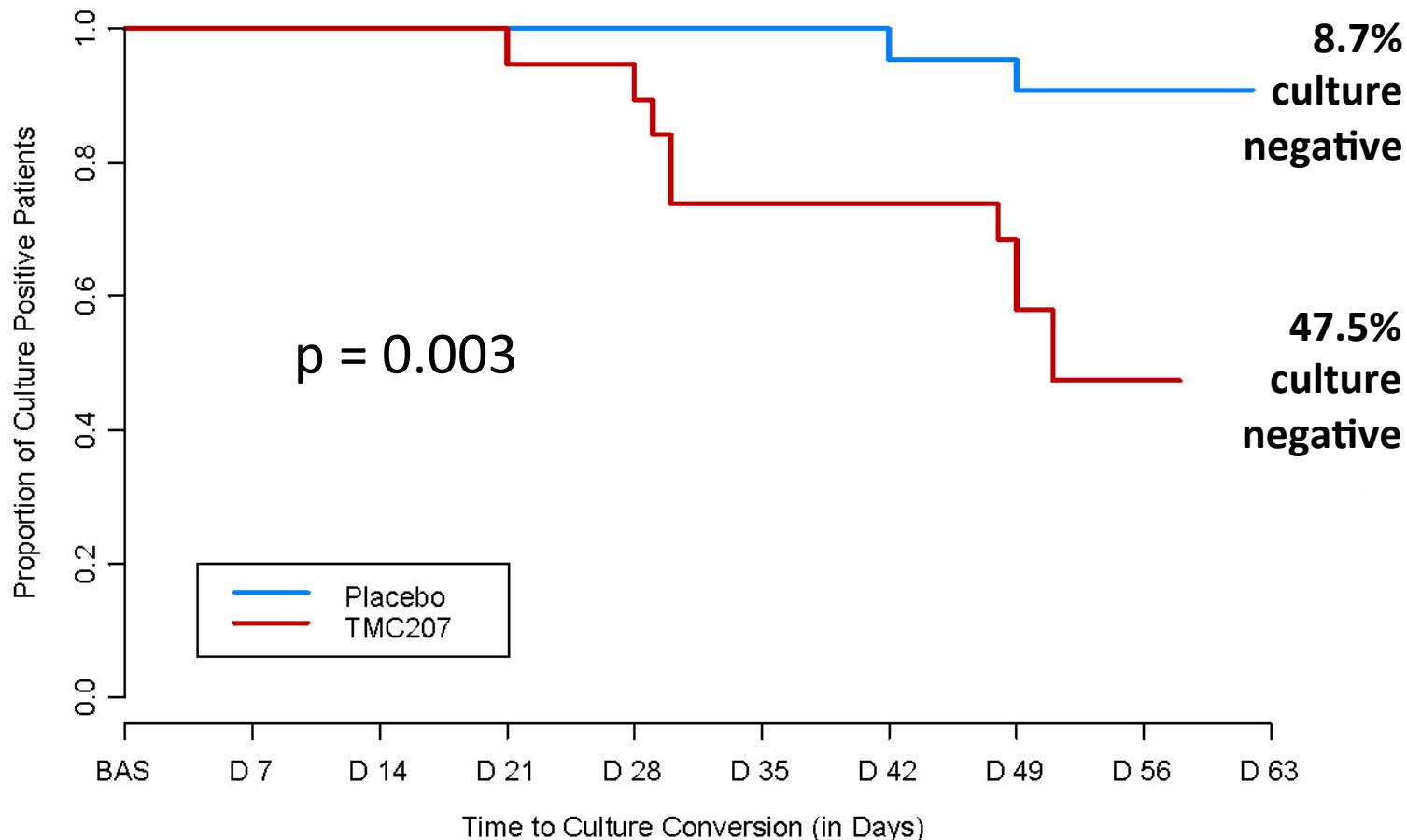
Proof of concept - activity



TMC207 400mg for 8 weeks

MDR regimen + placebo vs MDR regimen + TMC207

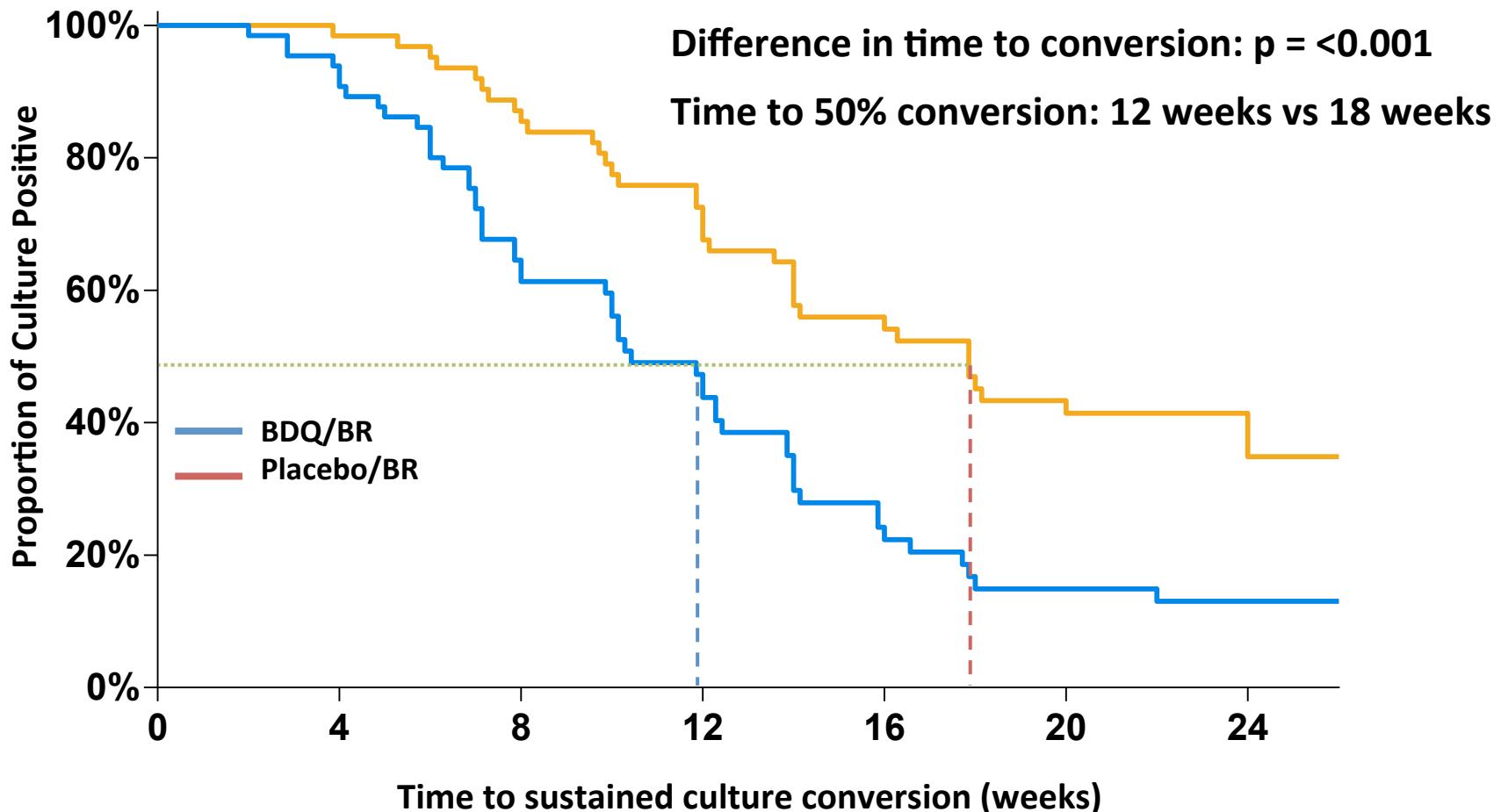
Sustained culture conversion in liquid media, n=44



TMC207 400mg for 24 weeks

MDR regimen + placebo vs MDR regimen + TMC207

Sustained culture conversion in liquid media, n=132



3 Dec 2012 (7y, 5m, 5d later)

Experts at FDA hearing vote pro registration

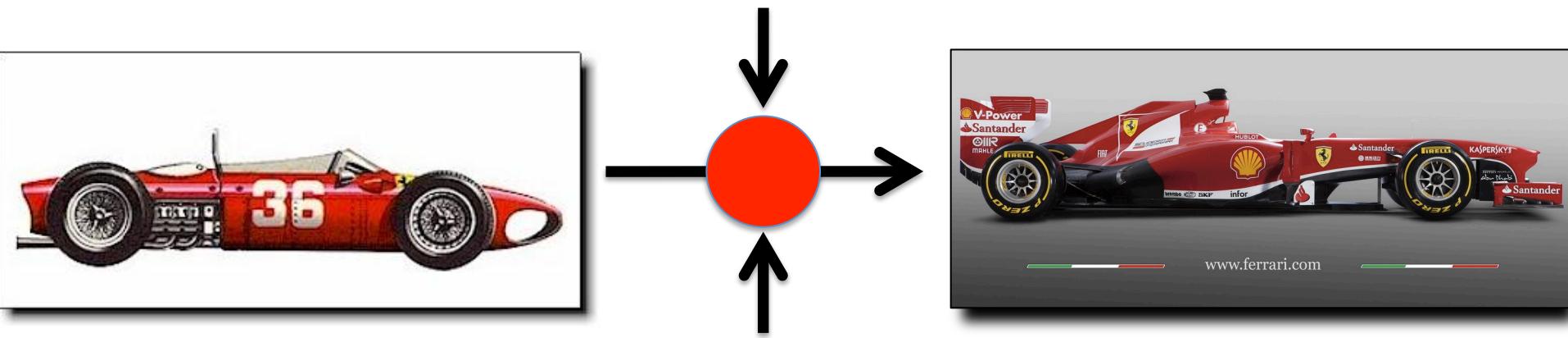


The Magic Bullet

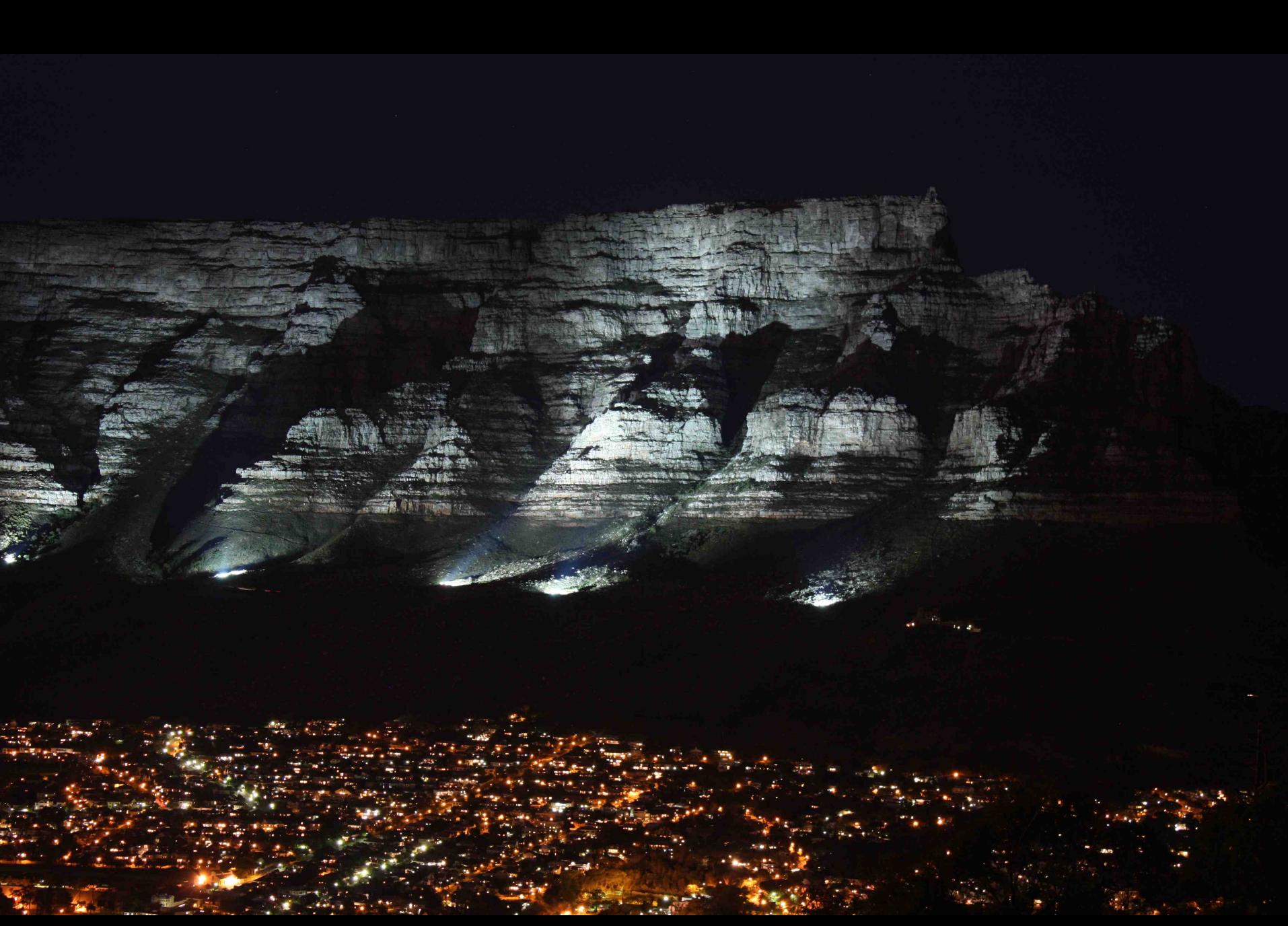
- 3 drugs from new classes
 - No resistance
 - All forms of TB



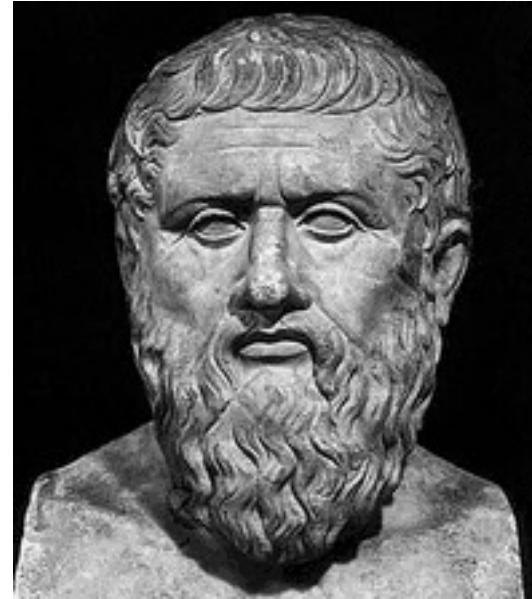
H, R, Z, E, S
AG, FQ, 2nd lines
PA, BDQ, DEL
LIN, β -lactams, CLO



Antiretroviral agents
Low market potential
Limited trial capacity
Urgency







Plato 428 – 348 BC

Never discourage anyone who continually makes progress, no matter how slow

