Can and should we get experimental drugs to patients with DR-TB?

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The Problem:
Difficult to treat and untreatable Drug-Resistant TB

Outcomes are very poor

Tugela Ferry examination of TB register 2005-2007:

→ One year mortality for XDR: 82%

→ One year mortality for MDR: 69%

→ One-year mortality for MDR dropped over time from 87% to 45%,

→ But no significant decrease for XDR.

Gandhi et al. IAS2009

Of 72 XDR patients in a Durban hospital enrolled in a study, less than half were alive and in care at six months.

O'Donnell et al. IAS2009

The Challenge:

If you had MDR TB, would you want to use an experimental drug?

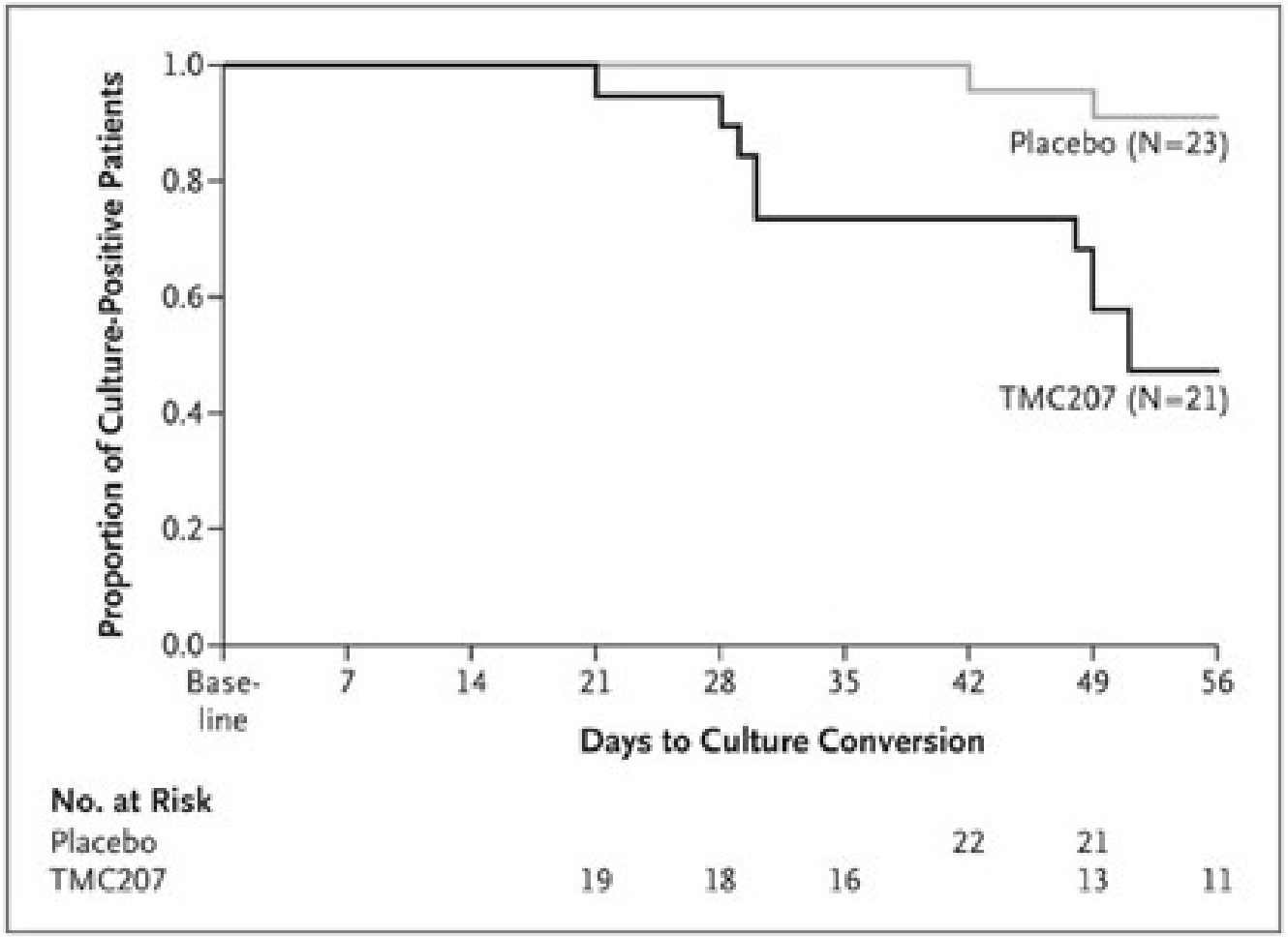
And if you had XDR TB?

Experimental Drugs for DR-TB

TMC207 (Tibotec)

OPC-67683 (Otsuko)

TMC207 is currently the most promising



Diacon et al. NEJM

Would you want to take this if I had MDR TB?

My personal answer:

TMC207: Yes

OPC-67683: Maybe

Would you want to take this if I had XDR TB?

My personal answer:

TMC207: Yes

OPC-67683: Probably

Another compelling reason for accelerated access

Health workers are at higher risk

MDR-TB incidence:

→ General Kwazulu-Natal population: 10.7/100,000 (OR: 5.53; 95%CI; 4.70-6.50)

→ Health workers: 58.9 per 100,000 people

O'Donnell et al. IAS2009

XDR-TB incidence:

→ General KZN population: 1.0/100,000 (OR: 3.89 95%CI: 2.02-7.11).

→ Health workers: 4.0/100,000

O'Donnell et al. IAS2009

There's a precedent: ARVs

- >35k people on DDI 1989 to 1991 before it was registered, which was important, but controversial.

- If it could be done for HIV, why not for TB?

There are risks

- About 9,000 people on adefovir as part of EAP, but it was never approved for HIV.
- DDI: fatal cases of pancreatitis
- We don't yet know if TMC207 et al. Work!
- Resistance
- Interactions with ARVs?
- Need people for clinical trials who prepared to risk taking placebo

So what are the barriers?

Clinical trials recruiting

Drug	Trial	Phase	Sites	Inclusion	Exclusion	Start	End	#
TMC207	NCT00910871 (C209)	II	33	MDR or XDR, AFB+		07/09	03/13	225
TMC207	NCT01012284 (C112)	I		Healthy	Latent TB	01/10	01/11	16
TMC207	NCT00449644 (C208)	II	18	SM+ MDR TB	CD4<350; XDR	05/07	02/12	200
TMC207	NCT00992069	I		Healthy, no TB, no HIV	Many	12/09	?	35
OPC-67683	NCT00685360	II	7	SM+ MDR TB	CD4<350	04/08	04/09	430
OPC-67683	NCT01131351	II	3	SM+ MDR TB	CD4<350	02/10	12/11	30
TOTAL (including placebo and healthy participants)								**936**

Compiled by doing a search for TMC207 and OPC-67683 on clinicaltrials.gov

Development just too slow

- Streptomycin discovered in 1943
  → 1947: Proven effective in MRC trial
  → Orwell using it by 1948

- Anti-HIV effects of AZT discovered in 1984.

  → Trial completed 3 years later.

- TMC207 discovered in 2003
  → Registration unlikely before 2012

Why?

- Money:
  - Not enough pharma investment.
  - Not enough public investment from NIH, South Africa, India, Brazil and China.
- Insufficient political will
- The regulatory process bureaucracy

What is the way forward? (1)

Meetings like this one have to produce a genuine commitment to accelerated access.

Even more importantly, we need faster development and more publicly funded TB drug research.

What is the way forward? (2)

Until registration, Tibotec, Otsuka and the Alliance need to:

1. Establish criteria for sites to qualify for accelerated access.

2. Make available the means to access the drugs for accelerated access urgently.

And medicine regulatory authorities need to co-operate. E.g. Section 21 Authorisation in South Africa

What is the way forward? (3)

We need an imaginative funding mechanism or incentive for TB drug and diagnostic research.

Perhaps a Global Fund for TB Research?