Treatment for MDR-TB – A Moving Target

C. Robert Horsburgh, Jr.
Boston University School of Public Health

Objectives

- Review history of MDR-TB treatment
- Review treatment tolerability and outcomes of recent MDR trials
- Discuss ongoing clinical trials of MDR treatment
- Look at new drugs in development

History of “MDR-TB”

- First defined - 1979
- Early reports suggested it was less transmissible - 1982
- Hospital outbreaks of MDR-TB among AIDS patients - 1992
- Global surveillance for tuberculosis drug resistance initiated – 1995
- Primary spread of MDR-TB - 2000
- “XDR-TB” in South Africa - 2006

WHO Calls Tuberculosis a Global Emergency

April 24, 1993 | Reuters

LONDON — The World Health Organization on Friday declared tuberculosis a global emergency, saying the disease will claim more than 30 million lives in the next decade unless action is taken now.

"Tuberculosis today is humanity's greatest killer, and it is out of control in many parts of the world," said Arati Kochi, manager of WHO's tuberculosis program, at a news conference announcing a plan to combat what has been dubbed the "forgotten epidemic."

"The disease, preventable and treatable, has been grossly neglected and no country is immune to it."

Once believed to be under control, TB, as tuberculosis is often called, is spreading worldwide because of the emergence of drug-resistant strains, changing research priorities and a link between TB and AIDS.

Early Treatment Regimens

"Second-line" drugs; 4-6 drugs for 20-24 months

- Based on "Expert Opinion"

- Ciprofloxacin/Ofloxacin/Levofloxacin/Moxifloxacin
- Kanamycin/Amikacin
- Ethionamide
- Cycloserine/Terazadone
- Thiacetazone
- Para-aminosalicylic Acid (PAS)
- Capreomycin

Results with Early MDR-TB Regimens

- 50-60% cures
- 10-20% mortality
- High rates of loss-to-follow-up
- Substantial ototoxicity

Reduced Prices of 2nd Line TB Drugs 1996-2000

Drug	*Formulation*	*1996 Price*	*2000 price*	*% Decline*
Amikacin	1 gm vial	$9.00	$0.90	90
Cycloserine	250 mg tab	$3.99	$0.13	97
Ethionamide	250 mg tab	$0.90	$0.14	84
Kanamycin	1 gm vial	$2.50	$0.39	84
Capreomycin	1 gm vial	$29.90	$0.90	97
Ofloxacin	200 mg tab	$2.00	$0.05	98

Global TB Drug Facility - 2001

Criteria for consideration:

- Estimated incidence of at least 100 TB cases per 100,000 population (all cases)
- Estimated GNP per capita equal to or less than US $1,000 per year
- NGO's eligible to apply as national consortium
- Countries may be able to purchase from GDF suppliers at same low prices
- *Green Light Committee* provides funding

First Clinical Trials for MDR-TB

Goal: Shorten treatment from 20-24 months and improve upon~60% relapse-free cure

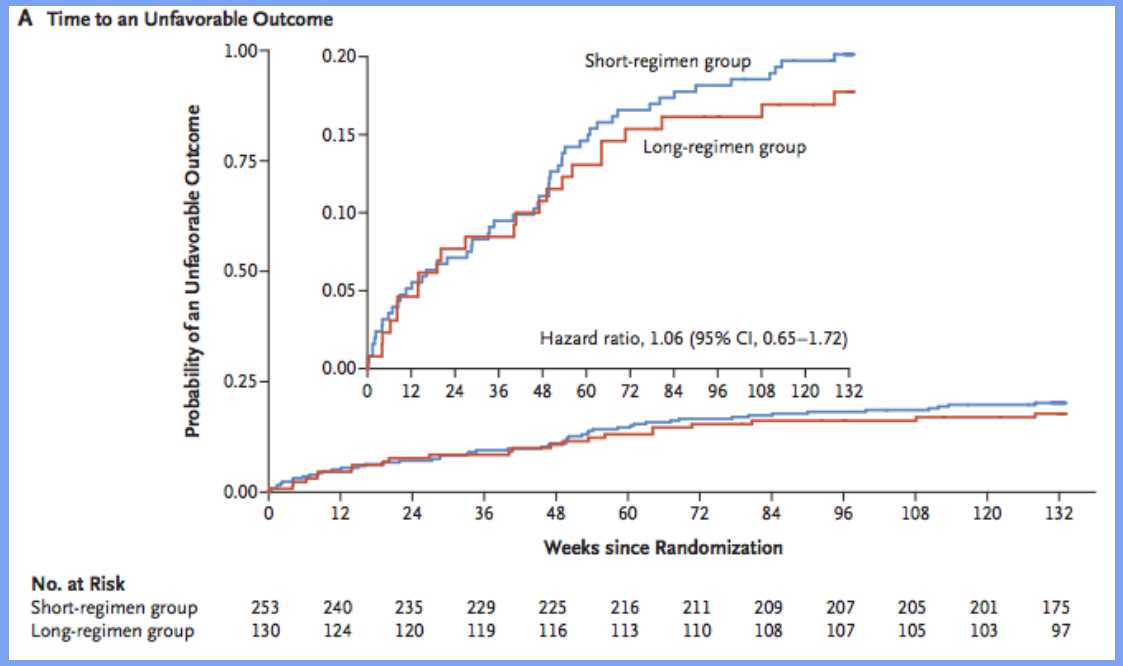
STREAM MDR-TB Treatment Trial

- **Arm 1**: 9-month regimen of 7 then 4 drugs:
  Kanamycin+Ethionamide+INH_{HD}+Cycloserine+PZA
  +$Moxifloxacin_{HD}$+Clofazimine+Ethambutol
- **Arm 2**: 20-24-month regimen of 5 then 4 drugs:
  Kanamycin+Levofloxacin+PZA+2 other drugs
- Target population: smear+, FQ-susceptible adults
- Outcome: Success vs failure/relapse/default/death
- Sites: Ethiopia, Mongolia, South Africa, Vietnam

NEJM 2019;380:1201-13

STREAM Trial: Results

- Success at 33 months: 78.8% vs 79.8%
- Difference: 1.0% (-7.5% to 9.5%); NI = 10%
- Grade 3-5 Adverse Event: 48.2% vs 45.4%
- Mortality: 8.5% vs 6.4%
- Acquired resistance to FQ: 3.3% vs 2.3%



NEJM 2019;380:1201-13

THE LANCET
Respiratory Medicine
Volume 6, Issue 9, September 2018, Pages 662-664

Comment

Time to act on injectable-free regimens for children with multidrug-resistant tuberculosis

James A Seddon [a, b] ✉, H Simon Schaaf [a], Ben J Marais [c], Lindsay McKenna [d], Anthony J Garcia-Prats [a], Anneke C Hesseling [a], Jennifer Hughes [a], Pauline Howell [e], Anne Detjen [f], Farhana Amanullah [g], Urvashi Singh [h], Iqbal Master [i], Carlos M Perez-Velez [j, k], Nirupa Misra [l], Mercedes C Becerra [l], Jennifer J Furin [l]

TOWARDS ZERO HEARING LOSS:

ACCESS TO NEW TB DRUGS AND THE HUMAN RIGHT TO ENJOY THE BENEFITS OF SCIENTIFIC PROGRESS

THURSDAY, 25 OCTOBER
4:00-5:30 PM
EVEREST 1&2

With the World Health Organization's newly released drug-resistant tuberculosis (DR-TB) treatment recommendations, this symposium will highlight strategies to end DR-TB amework of the right to enjoy the benefits of elated human rights.

Khayelitsha

t Advocate, The Economic Times
TAG)

Comment

Reducing harm in the treatment of multidrug-resistant tuberculosis

When describing the profound hearing loss she suffered as a result of her treatment for multidrug-resistant tuberculosis, the noted advocate Nandita Venkatesan said: "My world fell silent around me. I am in front of people, but I am not here."[1] In the context of India's National Tuberculosis Programme, she seems to be right: 8 years after she was clinically diagnosed, first

INT J TUBERC LUNG DIS 22(6):667–674

http://dx.doi.org/10.5588/ijtld.17.0830

Increased risk of aminoglycoside-induced hearing loss in MDR-TB patients with HIV coinfection

H. Hong,* C. Budhathoki,† J. E. Farley*‡

Departments of *Community-Public Health, †Acute and Chronic Care, and ‡REACH Initiative, Johns Hopkins University School of Nursing, Baltimore, Maryland, USA

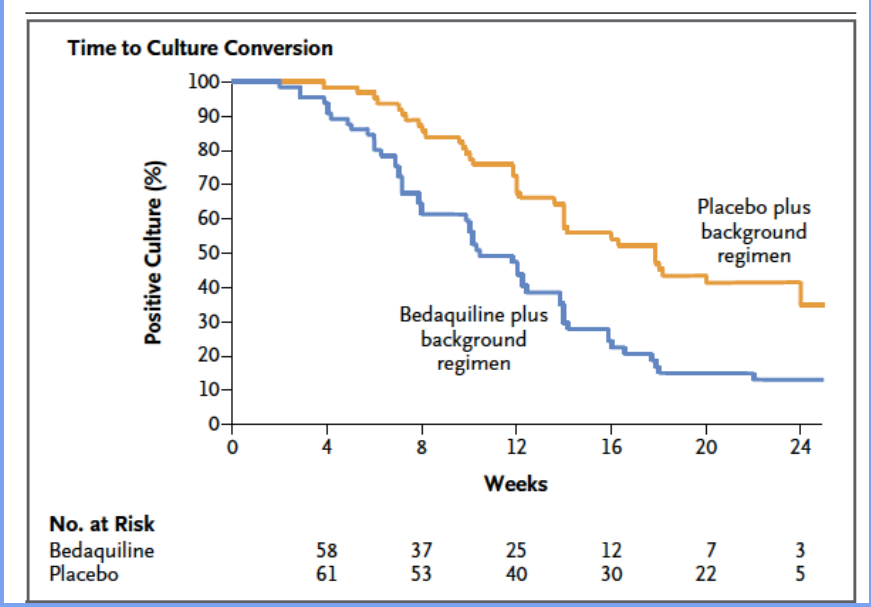
SUMMARY

First New TB Drug Classes in 40 years

- Diarylquinolone (Bedaquiline) Janssen, 2007-12
- Imidazooxazole (Delamanid) Otsuka, 2008-12
- Imidazooxazine (Pretomanid) GA, 2010-12
- Oxazolidinone (Linezolid) Pfizer, No trial
- Riminophenazine (Clofazimine) Novartis. No trial

Bedaquiline MDR-TB Clinical Trial

	Bedaquiline+OBT	Placebo+OBT
Number	79 patients	81 patients
Median Conversion	12 weeks	18 Weeks*
“Cure” at week 120	58%	32%*
Serious Adverse Events	23%	19%



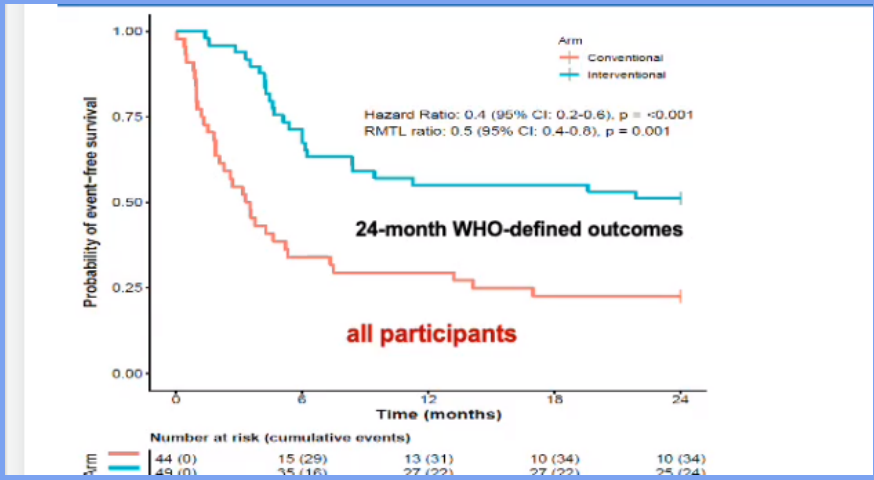
*p<0.01

N Engl J Med 2014; 371:723-732

NEJM 2014;371:723-32

NeXT Trial

- Phase 3 (2020)
- BDQ+LZD+LFX+ETA/INH_H+PZA (6-9 Mo)
- SOC Control arm: 9-month injectable-based
- Trial halted when BDQ came into use in SA
- Efficacy: 51% in BDQ arm, 27% in Control arm
- Toxicity: 66% in control arm, 37% in BDQ arm



2021 Union Meeting Oral Presentation

Delamanid+OBT vs. Placebo+OBT

- Population: Adults with pulmonary MDR-TB, CD4>350 if HIV+
- Outcome: Phase 2 trial showed improved sputum conversion at 8 weeks
- Subsequent Phase 3 trial failed to show superiority because control regimen improved

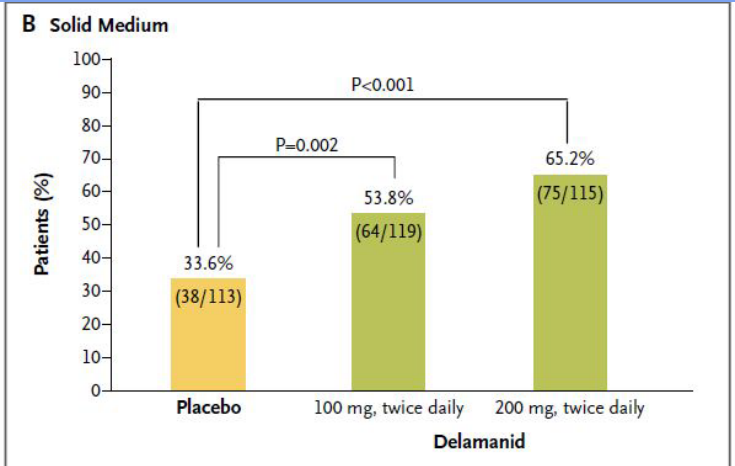


Figure 2. Proportion of Patients with Sputum-Culture Conversion by Day 57.

NEJM 2012;366:2158

Ongoing Trials of 9-month Oral Regimens

- MDR-END Trial – (2018)

  DEL+LZD+LFX+PZA vs. SOC

- STREAM Stage 2 Trial – (2017)

  BDQ+CFZ+EMB+LFX+PZA+4(INH_H+PTO)

  vs. SOC

- endTB Trial – (2017)

  Combinations of BDQ, DLM, LZD, FQ, PZA

  vs. SOC

Trials of 6-Month Regimens for MDR-TB

- NiX-TB Trial (2019)
- ZeNiX Trial (2020)
- TB-PRACTECAL (2020)

NiX-TB – Phase 2/3

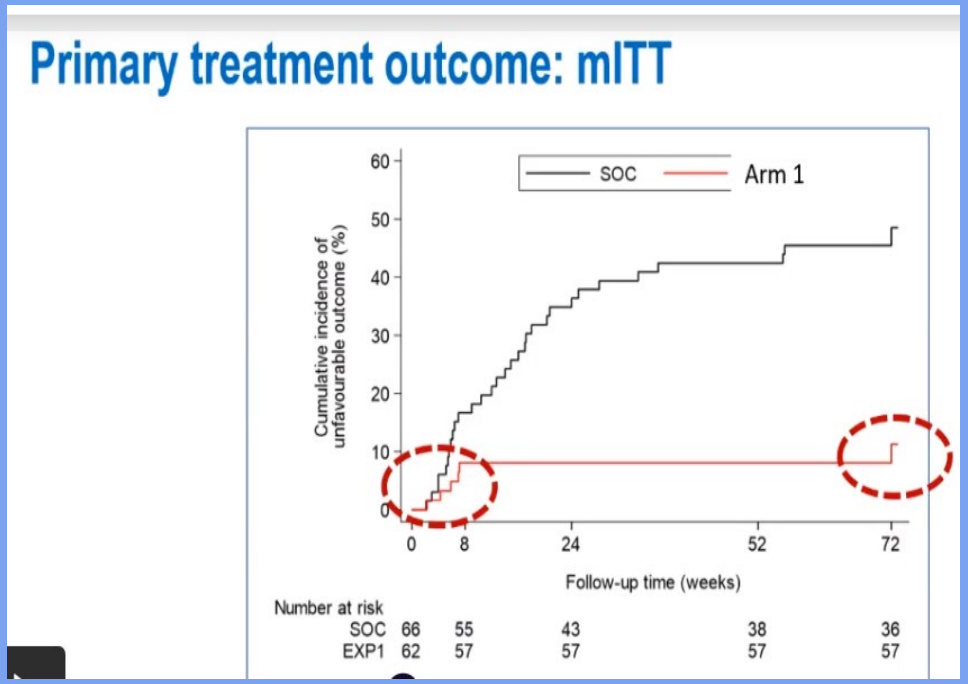
- Regimen: BDQ+PTM+LZD x 6 mos (no Control arm)
- Population: 109 adults with XDR-TB or “Pre-XDR-TB”
- Efficacy: 98/109 (90%, 83%-95%) had relapse-free cure
- Toxicity: 48% myelosuppression, 81% peripheral neuropathy
- Conclusion: Linezolid dose of 1200 mg per day had substantial toxicity and required careful monitoring with does interruptions and reductions in the majority of patients
- WHO recommends NiX Regimen for XDR-TB in December 2019 (as “operational research”)

ZeNiX Trial Results

- NiX Arm (1200 mg LZD x 6mos): 93% cures, 38% neuropathy, 29% myelosuppression
- 600 mg LZD x 6mos: 91% cures, 24% neuropathy, 13% myelosuppression
- 1200 mg LZD x 2mos: 89% cures, 24% neuropathy, 15% myelosuppression
- 600 mg LZD x 2mos: 84% cures, 13% neuropathy, 16% myelosuppression

TB-PRACTECAL Trial

- BDQ+PTM+LZD+MFX vs. SOC; LZD 600 mg QDx 4mos then 300 mg QD x 2mos
- 301 adult patients, pulmonary MDR-TB
- Efficacy: 89% in BPaLM vs 52% in SOC
- Toxicity: not reported



2021 Union Conference Oral Presentation

Ongoing Trials of 6-month (and Shorter) Regimens

- SimpliciTB (2020) – BDQ+PTM+MFX+PZA x 6mos, no control
- BEAT-Tuberculosis (2021) – LZD 300/600 mg x 6mos BDQ+DLM+LZD+LFX/CF x 6mos, vs. SOC
- DRAMATIC Trial – (2022) LZD 1200 mg x 2mos BDQ+DLM+LZD_2+LFX+CF x 4, 5.5, 7, 8.5 mos, no control
- BEAT-TB (2021) – BDQ+DLM+LZD+CF vs. SOC
- TB-TRUST Trial – LFX+LZD_{600}+CS+PZA/CF vs. SOC

2021 Global New TB Drug Pipeline [1]

Discovery | Preclinical Development | Clinical Development

Lead Optimization	Early Stage Development	GMP / GLP Tox.	Phase 1	Phase 2	Phase 3	Regulatory Market Approvals
PanD inhibitors	JSF-3285*	FNDR-20081*	BVL-GSK098*	Delpazolid	Pretomanid* / Moxifloxacin / Bedaquiline*/ PZA (4-month regimen)	Bedaquiline*
Indazole sulfonamides	MPL-446, 447*	TB-47*	GSK-286*	Sutezolid	Truncate TB (2-month regimens)	Delamanid*
Diarylthiazoles	CPZEN-45*	GSK-839*	TBAJ-587	BTZ-043*	Rifapentine / Moxifloxacin / INH/PZA (4-month regimen)	Pretomanid*
DprE1 Inhibitors	NTB-3119*	OTB-658	TBAJ-876	TBA-7371*		
Direct InhA Inhibitors	TZY-5-84	Sanfetrinem	TBI-223	OPC-167832*		
Mtb energy metabolism	MBX-4888A (1810)*		Macozinone* (PBTZ-169)	GSK-656* (070)		
Macrolides	FNDR-10045*		Pyrifazimine (TBI-166)	SQ-109* Telacebec* SPR720* Macozinone*		
Mycobacterial Gyrase Inhibitors	FNDR-20364*					
Arylsulfonamides						
Inhibitors of MmpL3, Translocase-1, Clp, PKS13, F-ATP synthase						
Oxazolidinones						

Underline = updates since March 2021

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified: http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

Updated: October 2021

TB Drug Classes in Development

Class	Target	Mechanism
• Ethyl urea benzimidazole SPR720	Gyrase B	DNA synthesis
• Benzothiazinone BTZ043 Macozinone	DprE1	Cell wall synthesis
• 3,4-dihydrocarbostyril OPC167832	DprE1	Cell wall synthesis
• Imidazopyridine amide Telacebec	Cytbc1	Electron chain
• Oxaborole GSK070	Leucyl tRNA	Protein synthesis
• Oxazolidinones Sutezolid Tedazolid Dalpazolid	rRNA	Protein synthesis

Conclusions

- A broad spectrum of MDR-TB clinical trials are in the field or about to begin
- New and repurposed TB drug classes may increase MDR-TB treatment responses and shorten treatment duration
- Tolerability of a number of the new and repurposed agents remains to be defined, especially when used in combination
- Several new drug classes are on the horizon