Best Practices in the Care of People with Drug-Resistant TB that has Expanded Resistance: An Overview

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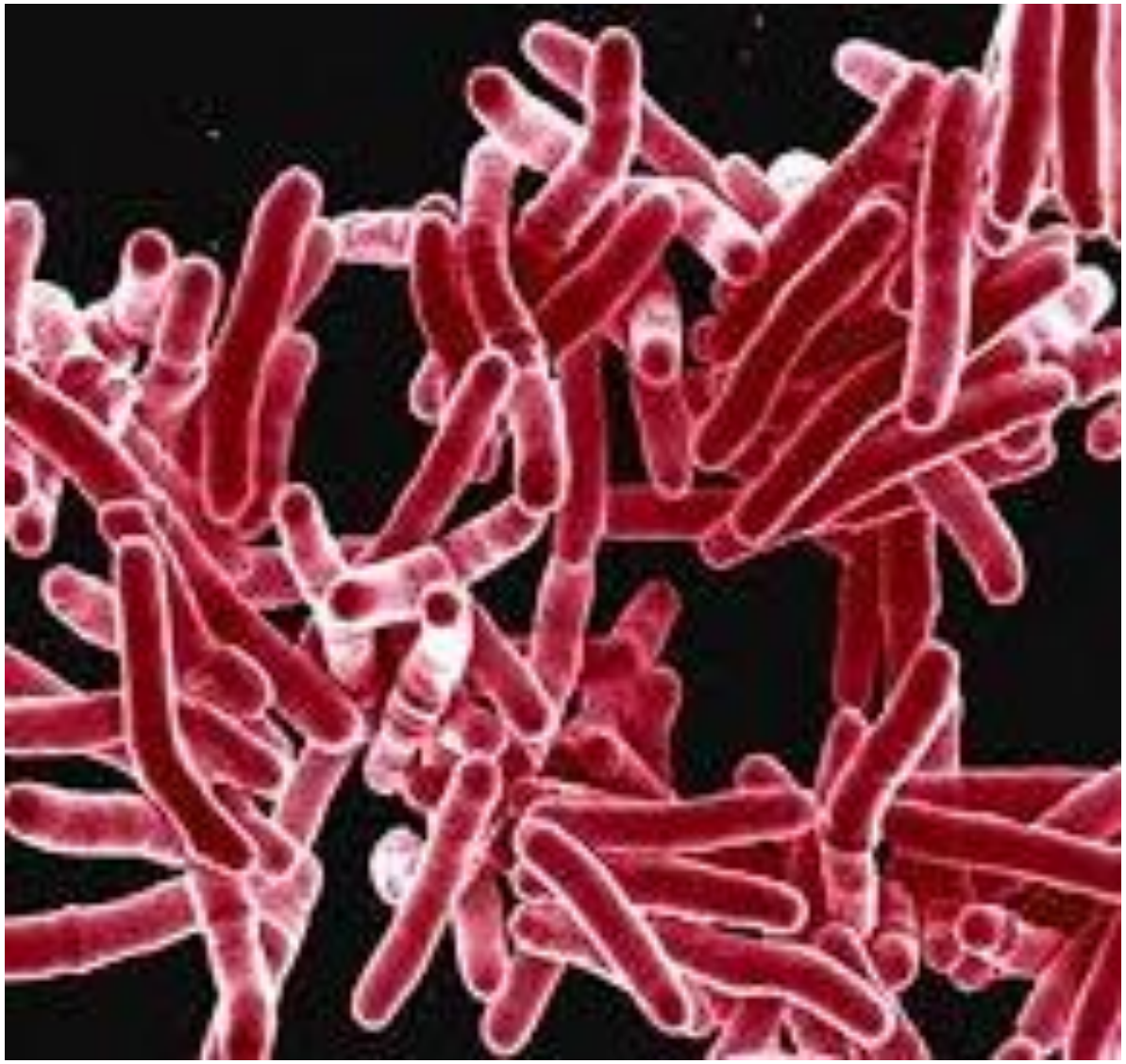
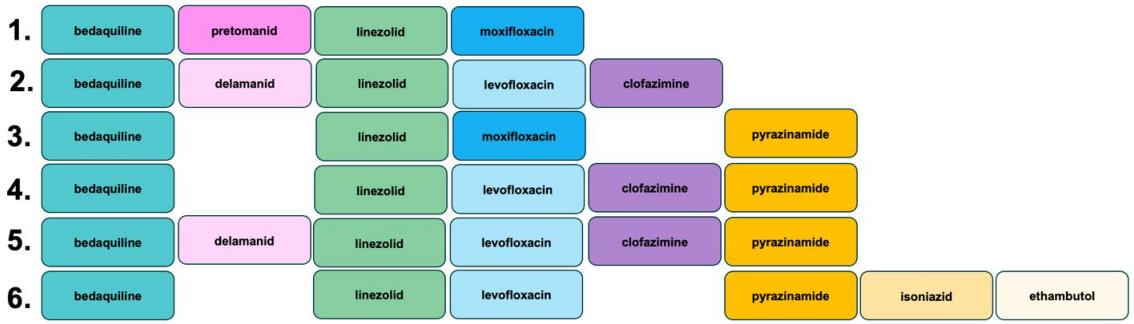


Objectives

- To present approaches to the care of people with complex drug resistance patterns, including diagnosis, management, and use of newer compounds



Individualized approaches still needed for some populations

- “Real-world” performance always less successful than that seen in trials;
- Toxicity and drug discontinuation must be managed by programs and clinicians;
- Drug resistance always exists and may be selected for during sub-optimal treatment;
- Lack of systematic baseline resistance testing can further amplify drug resistance;
- Ongoing transmission of drug-resistant strains is a well-documented occurrence with DR-TB.

EUROPEAN RESPIRATORY JOURNAL
RESEARCH LETTER
R. PERUMAL ET AL.

Baseline and treatment-emergent bedaquiline resistance in drug-resistant tuberculosis: a systematic review and meta-analysis

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To the Editor:

Bedaquiline is a novel antimycobacterial agent for drug-resistant tuberculosis (TB) and is classified as a World Health Organization (WHO) group A drug due to its excellent clinical efficacy, high bactericidal activity, and potent sterilising effect [1]. The introduction of bedaquiline into treatment regimens has enabled short-course all-oral multidrug-resistant TB (MDR-TB) regimens and the shortening of drug-susceptible TB treatment [2, 3].

Bedaquiline targets F_1F_0-ATP synthase to impair *Mycobacterium tuberculosis* (*Mtb*) ATP synthesis and exerts other incompletely characterised bactericidal effects [4]. Variants in the target *atpE* and *atpB* genes and off-target mutations in *mmpR5*, *mmpL5* and *pepQ* have been associated with bedaquiline resistance [5, 6]. We performed a systematic review and meta-analysis to estimate the frequency of, and mutations associated with, baseline and acquired (treatment-emergent) bedaquiline resistance in clinical *Mtb* isolates.

The study protocol was registered in PROSPERO (CRD42022346547) and the PRISMA guidelines were followed for reporting of the review methods and findings. Systematic searches of MEDLINE/PubMed, Cochrane Central Register of Clinical Trials, and EMBASE were conducted through February 2023 for publications on phenotypic resistance of bedaquiline. We included studies which reported clinical *Mtb* isolates with bedaquiline resistance *via* minimum inhibitory concentration (MIC) values from patients with at least rifampicin-resistant TB. Given the suboptimal positive predictive value of resistance-associated variants for phenotypic resistance, our study only evaluated phenotypic resistance as defined by MIC thresholds. We excluded studies with MIC cut-offs inconsistent with WHO cut-offs, *in vitro Mtb* isolates not obtained from patients, or ⩽3 patients/isolates. Phenotypic bedaquiline resistance was defined by critical concentrations of 1 $\mu g \cdot mL^{-1}$ by MGIT method or 0.25 $\mu g \cdot mL^{-1}$ by broth microdilution or 7H11

Global Situation: Bedaquiline Resistance

- Baseline 2-3% among newly diagnosed people and as high as 7% in some settings;
- Emergence during treatment usually around 2-3% in general treatment cohorts;
- Rv0678 mutations most common but can see pepQ mutations as well;
- Not likely to have cartridge-based testing anytime soon;
- Cross-resistance with CFZ common (? universal?);
- In a population of patients on BDQ-containing regimens in Cape Town who still had a positive culture at 4 months, 8% had baseline BDQ resistance and 47% acquired BDQ resistance over time;
- Risk factors included baseline FLQ resistance, prior exposure to CFZ, and four or fewer effective drugs in the regimen.

Global Situation: Other Drugs

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LETTER

Linezolid resistance in patients with drug-resistant TB

Dear Editor,

Multidrug-resistant TB (MDR-TB) continues to be a global public health issue. Linezolid (LZD) has been shown to be one of the most effective drugs against MDR-TB.[1] A meta-analysis of 12,030 patients showed treatment success was positively associated with LZD use (adjusted risk difference 0.15, 95% confidence interval [CI] 0.11–0.18) compared to not using the drug.[2] New treatment regimens containing bedaquiline (BDQ), pretomanid, LZD with or without moxifloxacin (BPaLM/BPaL) have been recommended by the WHO for MDR-TB programmes.[3] Unfortunately, global resistance to LZD has been observed, especially in India, which has a high burden of MDR-TB.[4–6] Potential risk factors to acquired LZD resistance are addition of LZD to a failing or inadequate regimen, or interruption of LZD due to adverse events or loss to follow-up.[7] In a recent meta-analysis, pooled frequency of LZD resistance in clinical isolates of MDR-TB bacteria was reported to be 4.2%.[4] However, the majority of the studies included in this analysis were from China and Turkey, with only one carried out in India.[4] Here we report on the clinical/epidemiological profile and treatment outcome of patients with LZD resistance admitted to a Médecins Sans Frontières (MSF) clinic in Mumbai, India.

clinic, patients' laboratory investigations and follow-up included GeneXpert testing (Cepheid, Sunnyvale, CA, USA), first-line and second-line line-probe assays, culture-based DST, chest radiographs (CXRs) and other relevant radiological examinations. Treatment lasted 20–22 months. A multidisciplinary team provided clinical and psychosocial support. Patients were followed up every month after enrolment and monthly sputum culture was done once treatment began. Treatment outcomes were defined according to national guidelines (cured, completed, failed, death, lost to follow-up).[9] Unfavourable outcomes were defined as treatment failure or died. Risk factors for unfavourable treatment outcome were tested using multivariable logistic regression; risk factors with $P < 0.2$. in univariate analysis were included in the model. Cumulative incidence of the unfavourable treatment outcome was estimated using the Kaplan–Meier method.

Between 2016 and 2020, 365 DR-TB patients were registered and LZD resistance was found in 19.7% (72/365). The median age of patients with LZD resistance was 28 years (interquartile range [IQR] 22–35); 53% (38/72) were male; 39% (28/72) were severely underweight (BMI-for-age Z-score of −3 for adolescents aged 11–17 years and a BMI of 16.5 kg/m^2 in adults), and 7% (5/72) had extrapulmonary TB.

- Meta-analysis showed pooled frequency of LZD resistance around 4.2%;
- High rates seen in some selected cohorts (i.e. 19.7% in MSF Mumbai);
- Delamanid and pretomanid with similar results: 1-4.4%;
- Higher pretomanid MICs in lineage 1 strains;
- Genetic mechanisms of resistance complex for all these drugs, limited phenotypic testing experience.

The BETTER Project

- Building Experience Treating Tuberculosis with Expanded Resistance;
- Volunteer group of front-line providers, impacted communities, TB programs, and civil society organizations;
- Goal is to share best practices and provide support to one another in how to best provide care for TB that has “expanded resistance”—community of practice;
- “Expanded resistance” includes resistance to BDQ, LZD, CFZ, or nitroimidazole

Issues Covered by BETTER

- Optimizing DST;
- Informed consent and shared decision making;
- Regimen design;
- Holistic packages of support;
- Special populations;
- Pre-approval access to novel compounds;
- Post-exposure management for household contacts;
- Toxicity monitoring and management;
- Operational research considerations.

Informed Consent and Shared Decision Making

Figure 1: Components of Shared Decision Making

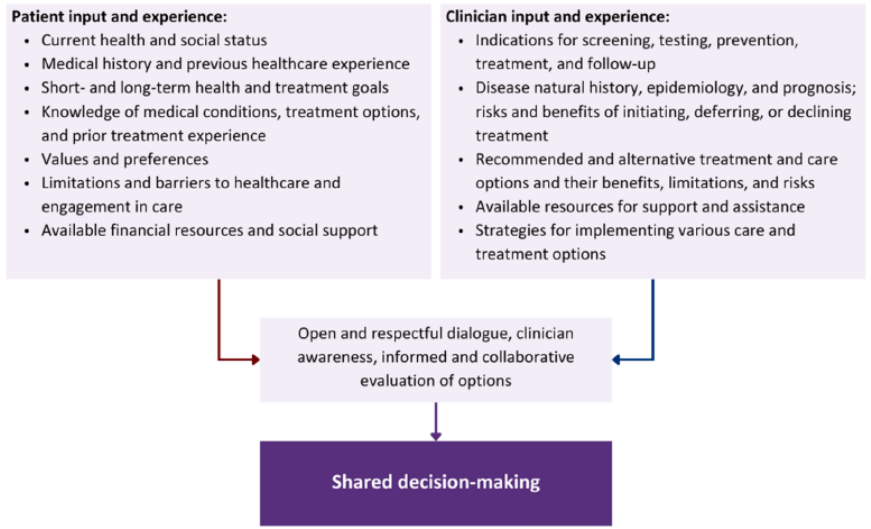
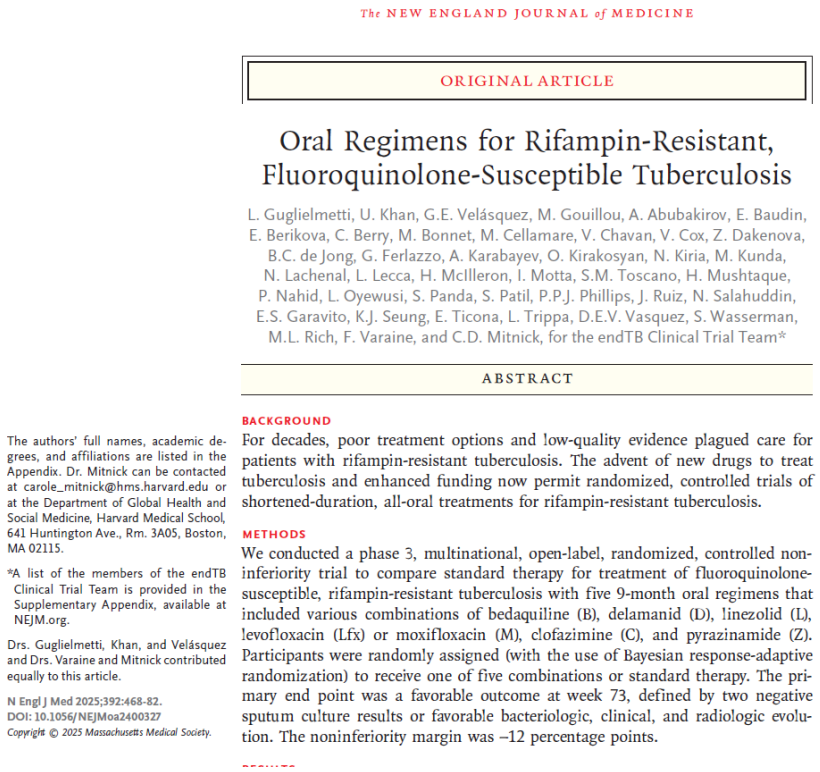


Figure 1 taken from: New York State Department of Health. AIDS Institute HIV Guidelines. Shared Decision Making. August, 2023. Figure reprinted with express written permission from the New York State Department of Health.

Different Ways People Come into Care with “Expanded Resistance”

- Remote prior exposure to one or more agents;
- Currently on therapy and “not doing well”—how to define in terms of micro, clinical, and “interruptions”;
- Currently on therapy and doing well but results come that show resistance;
- Contacts of these individuals.

Regimen Design: Standardized Approaches?



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Regimens for Rifampin-Resistant, Fluoroquinolone-Susceptible Tuberculosis

L. Guglielmetti, U. Khan, G.E. Velásquez, M. Gouillou, A. Abubakirov, E. Baudin, E. Berikova, C. Berry, M. Bonnet, M. Cellamare, V. Chavan, V. Cox, Z. Dakenova, B.C. de Jong, G. Ferlazzo, A. Karabayev, O. Kirakosyan, N. Kiria, M. Kunda, N. Lachenal, L. Lecca, H. McIlleron, I. Motta, S.M. Toscano, H. Mushtaque, P. Nahid, L. Oyewusi, S. Panda, S. Patil, P.P.J. Phillips, J. Ruiz, N. Salahuddin, E.S. Garavito, K.J. Seung, E. Ticona, L. Trippa, D.E.V. Vasquez, S. Wasserman, M.L. Rich, F. Varaine, and C.D. Mitnick, for the endTB Clinical Trial Team*

ABSTRACT

BACKGROUND

For decades, poor treatment options and low-quality evidence plagued care for patients with rifampin-resistant tuberculosis. The advent of new drugs to treat tuberculosis and enhanced funding now permit randomized, controlled trials of shortened-duration, all-oral treatments for rifampin-resistant tuberculosis.

METHODS

We conducted a phase 3, multinational, open-label, randomized, controlled noninferiority trial to compare standard therapy for treatment of fluoroquinolone-susceptible, rifampin-resistant tuberculosis with five 9-month oral regimens that included various combinations of bedaquiline (B), delamanid (D), linezolid (L), levofloxacin (Lfx) or moxifloxacin (M), clofazimine (C), and pyrazinamide (Z). Participants were randomly assigned (with the use of Bayesian response-adaptive randomization) to receive one of five combinations or standard therapy. The primary end point was a favorable outcome at week 73, defined by two negative sputum culture results or favorable bacteriologic, clinical, and radiologic evolution. The noninferiority margin was –12 percentage points.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Mitnick can be contacted at carole_mitnick@hms.harvard.edu or at the Department of Global Health and Social Medicine, Harvard Medical School, 641 Huntington Ave., Rm. 3A05, Boston, MA 02115.

*A list of the members of the endTB Clinical Trial Team is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Guglielmetti, Khan, and Velásquez and Drs. Varaine and Mitnick contributed equally to this article.

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- Very few regimens do not contain BDQ (or CFZ), LZD, FLQ;
- ? endTB regimen 5: DLM-CFZ-MFX-PZA in people with non-severe disease (but CFZ and BDQ cross resistance);
- ? MDR-END: 9 DLM-LFX-LZD-PZA in people with non-severe disease;
- Be careful with BPaL!!

Individual Regimen Design: Principles

GROUPS & STEPS	MEDICINE	
Group A: Include all three medicines	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[2,3]	Bdq
	Linezolid[4]	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[3,5]	Dlm
	Pyrazinamide[6]	Z
	Imipenem-cilastatin OR Meropenem[7]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[8]	Am (S)
	Ethionamide OR Prothionamide[9]	Eto Pto
	p-aminosalicylic acid[9]	PAS

- Very similar to WHO principles for designing individual regimens;
- 4-5 “likely effective drugs”—although regimen may have more than 4-5 drugs (and 4 drugs really only for non-severe disease);
- Most regimens will contain cycloserine (terizidone)
- Older drugs such as PAS, ethionamide, amikacin;
- Duration 12-18 months after culture conversion;
- Often will involve injectable agents, drugs with higher rates of toxicity.

Higher Dose Options

- Clinical breakpoints show “low-dose” or “high-dose” options (i.e. FLQs, INH, ? BDQ):
- Theoretically done to “overcome” mechanisms of resistance;
- Could lead to better penetration or more time above the MICs (i.e. CFZ, LZD);
- Additional monitoring needed for toxicity;
- Should only be done if limited options available.

Drug	High-dose option	Monitoring on high-dose option	Comment
Bedaquiline	500mg loading dose for 14 days followed by 200 mg daily	More frequent monitoring of QTcF interval (i.e. every 14 days)	There are no clear microbiologic breakpoints indicating when higher dose Bdq might be effective. If there is detection of an *atpE* mutation, then do not use Bdq at any dose.
Clofazimine	300mg daily	More frequent QTcF monitoring, especially if used in combination with other QTcF prolonging drugs	
Isoniazid	10-15mg/kg/day or 15-20mg/kg/day if used in combination with Cs	Monthly monitoring for peripheral neuropathy	Should give with vitamin B6 (25-75mg daily) to prevent peripheral neuropathy. Do not use if there is a *katG* mutation detected.
Levofloxacin	20-30mg/kg/day	More frequent QTcF monitoring, especially if used in combination with other QTcF prolonging drugs	
Linezolid	1200mg daily	Complete blood count, visual accuity/color vision screening, and screening for peripheral neuropathy every 14 days	The toxicity of this dose of Lzd has been well established. It should only be used if there are no other options.
Moxifloxacin	12-15mg/kg/day	More frequent QTcF monitoring, especially if used in combination with other QTcF prolonging drugs	

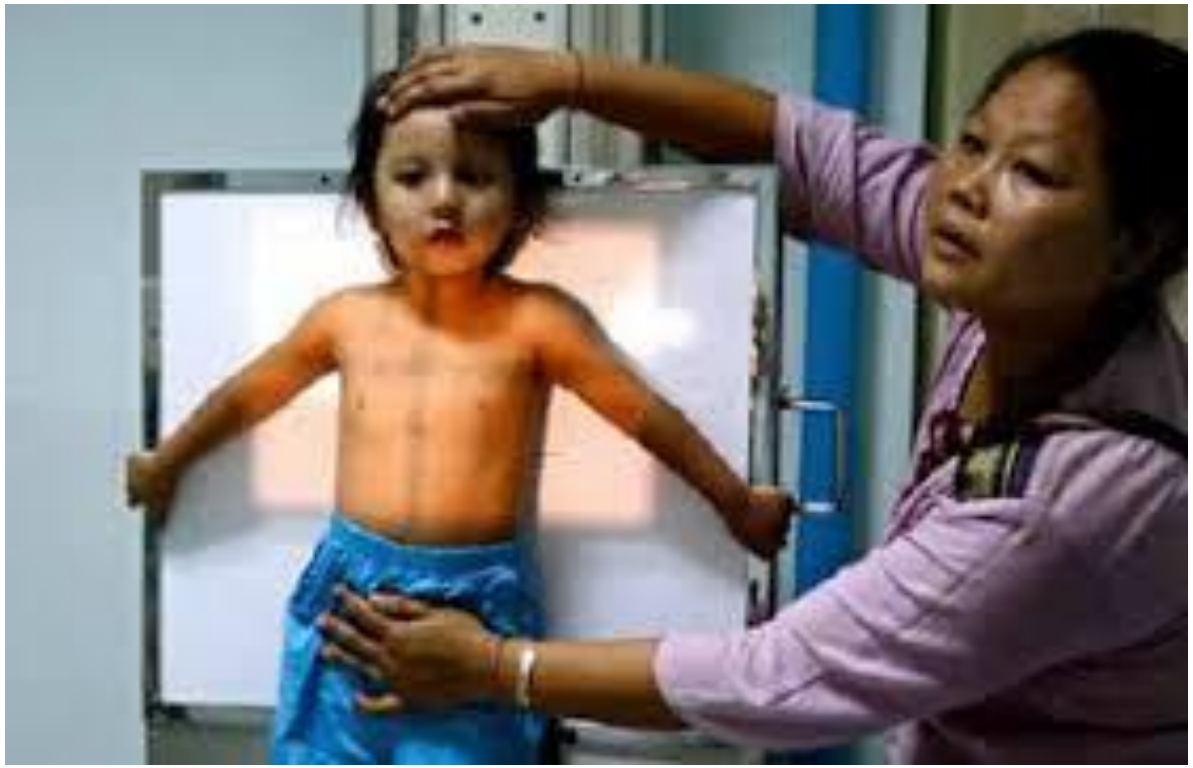
Verapamil Increases the Bactericidal Activity of Bedaquiline against Mycobacterium tuberculosis in a Mouse Model

Ancillary Medications

- Nutritional support;
- Corticosteroids for meningitis, pericarditis;
- ? Calcium channel blockers to block the efflux pump.

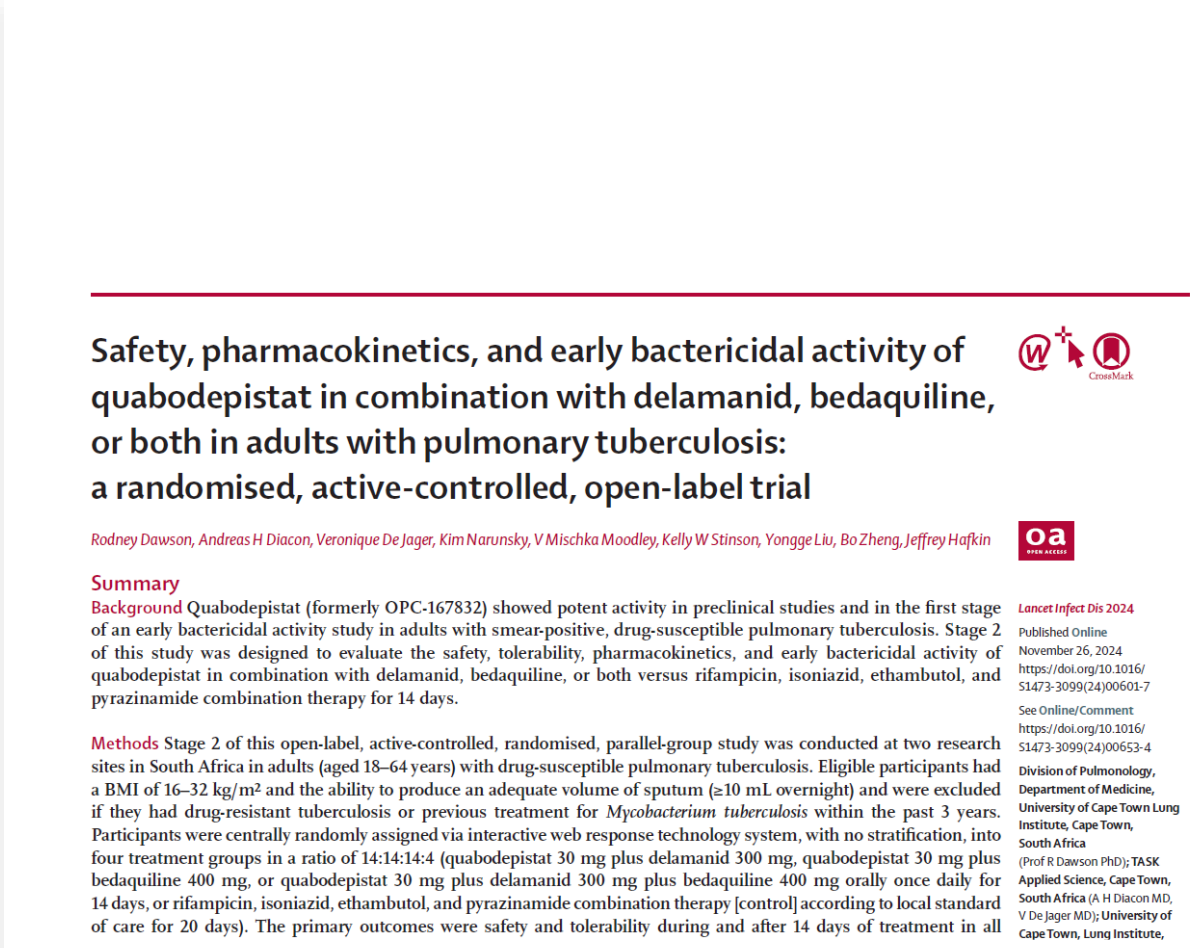
Holistic Packages of Support

- Location of care;
- Mental health services;
- Counseling;
- Nutritional support;
- Transport and finances;
- Transitions in care;
- Palliative care;
- Post-TB lung disease



Special Populations

- At increased risk for these forms of TB (i.e. congregate settings, co-morbidities);
- Issues that make dosing or access a challenge (children, pregnancy, substance use);
- Issues of drug penetration (EP-TB);
- Must be included in plans and treatment programs.



Safety, pharmacokinetics, and early bactericidal activity of quabodepistat in combination with delamanid, bedaquiline, or both in adults with pulmonary tuberculosis: a randomised, active-controlled, open-label trial

Rodney Dawson, Andreas H Diacon, Veronique De Jager, Kim Narunsky, V Mischka Moodley, Kelly W Stinson, Yongge Liu, Bo Zheng, Jeffrey Hafkin

Summary

Background Quabodepistat (formerly OPC-167832) showed potent activity in preclinical studies and in the first stage of an early bactericidal activity study in adults with smear-positive, drug-susceptible pulmonary tuberculosis. Stage 2 of this study was designed to evaluate the safety, tolerability, pharmacokinetics, and early bactericidal activity of quabodepistat in combination with delamanid, bedaquiline, or both versus rifampicin, isoniazid, ethambutol, and pyrazinamide combination therapy for 14 days.

Methods Stage 2 of this open-label, active-controlled, randomised, parallel-group study was conducted at two research sites in South Africa in adults (aged 18–64 years) with drug-susceptible pulmonary tuberculosis. Eligible participants had a BMI of 16–32 kg/m² and the ability to produce an adequate volume of sputum (≥10 mL overnight) and were excluded if they had drug-resistant tuberculosis or previous treatment for *Mycobacterium tuberculosis* within the past 3 years. Participants were centrally randomly assigned via interactive web response technology system, with no stratification, into four treatment groups in a ratio of 14:14:14:4 (quabodepistat 30 mg plus delamanid 300 mg, quabodepistat 30 mg plus bedaquiline 400 mg, or quabodepistat 30 mg plus delamanid 300 mg plus bedaquiline 400 mg orally once daily for 14 days, or rifampicin, isoniazid, ethambutol, and pyrazinamide combination therapy [control] according to local standard of care for 20 days). The primary outcomes were safety and tolerability during and after 14 days of treatment in all

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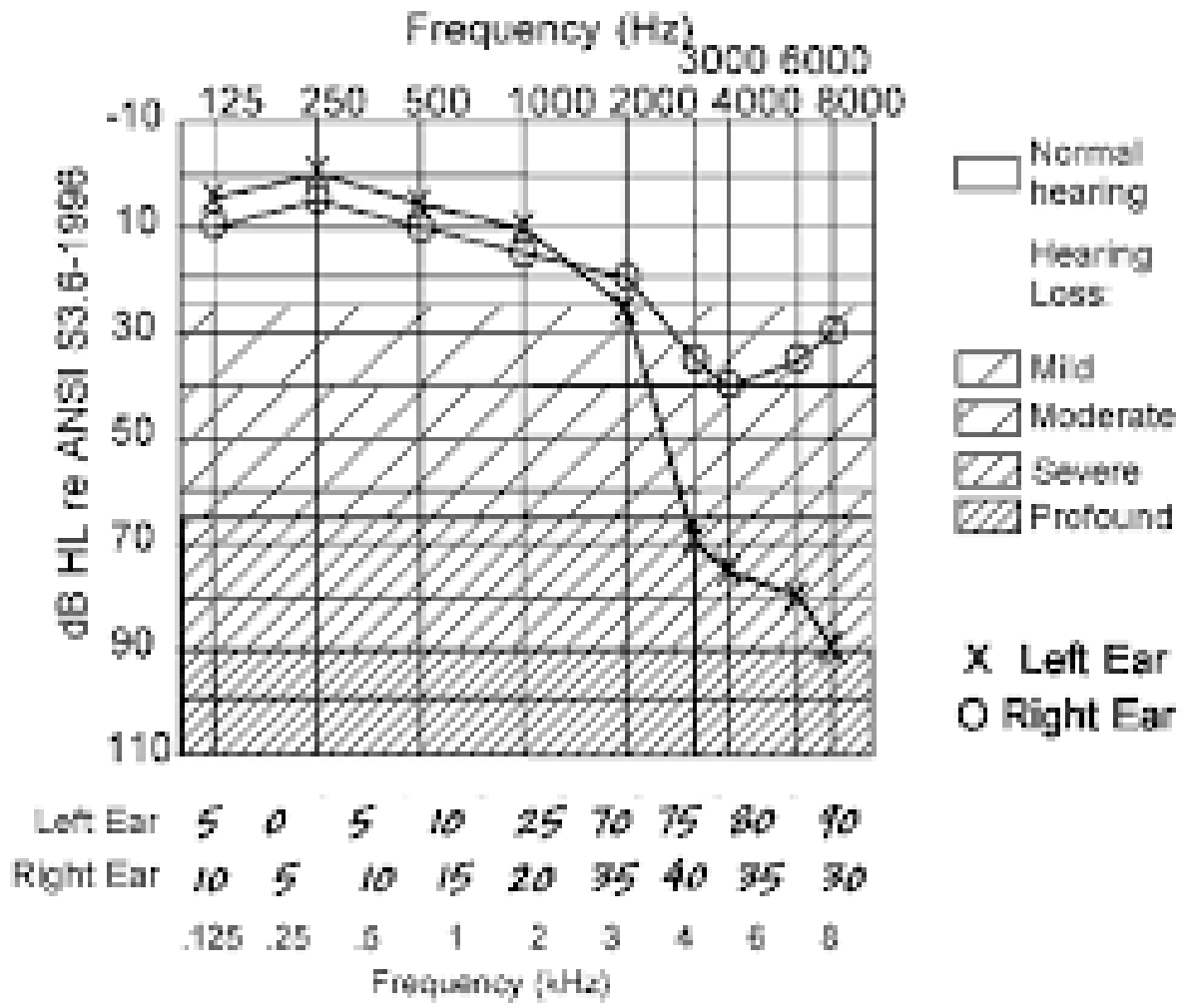
Division of Pulmonology, Department of Medicine, University of Cape Town Lung Institute, Cape Town, South Africa (Prof R Dawson PhD); **TASK Applied Science, Cape Town, South Africa** (A H Diacon MD, V De Jager MD); **University of Cape Town, Lung Institute,**

Pre-Approval Access

- Multiple novel compounds—although most being tested in treatment shortening trials for DS-TB;
- Quabodepistat furthest along, but also telacebec, ganefeborole, BTZ-043, TBAJ-876, TBAJ-587;
- Rocky history of pre-approval access in TB;
- Much of what we learned about BDQ, LZD, and DLM was through this kind of use.



Toxicity Monitoring and Management

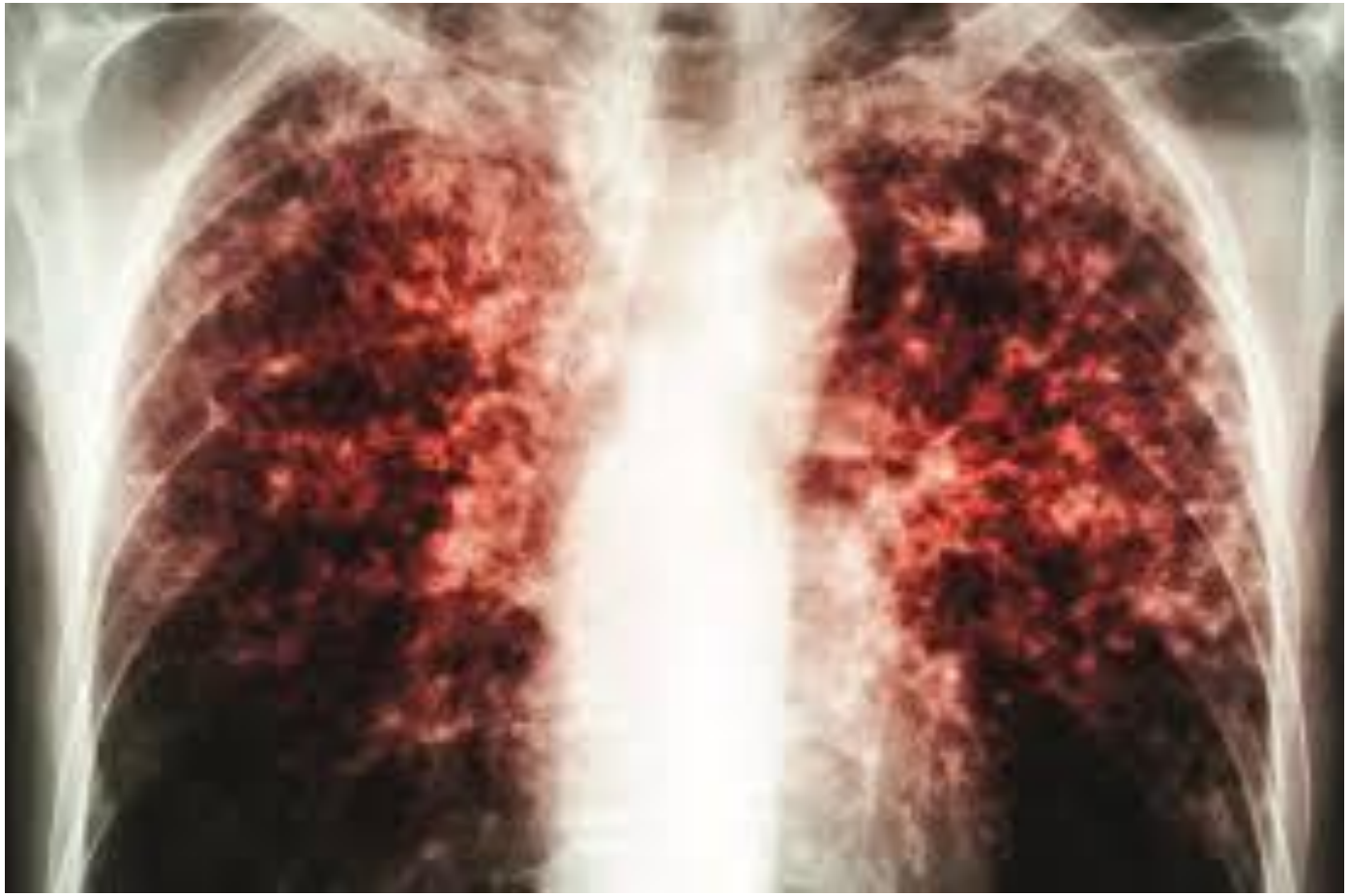
- Using many more toxic, second-line agents, including those that cause permanent disability (i.e. amikacin);
- Monitoring and management MUST be provided, including formal testing free of charge and ancillary medications;
- Shared decision making is essential.

Operational Research

- Common data elements are key to share experiences and generate data that can be used for guidelines even in the absence of RCTs;
- People with TB that has expanded resistance should be involved in setting priorities in this area;
- Should be funded and answer locally relevant questions.

BETTER: Future Work

- Continue to provide support as needed to people living with TB as well as countries/programs;
- As data emerge, practices can be defined;
- Clinical teams available for training and support;
- Advocacy!



Thank you!

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