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

Jennifer Furin, MD., PhD

Harvard Medical School, Department of Global Health and Social Medicine

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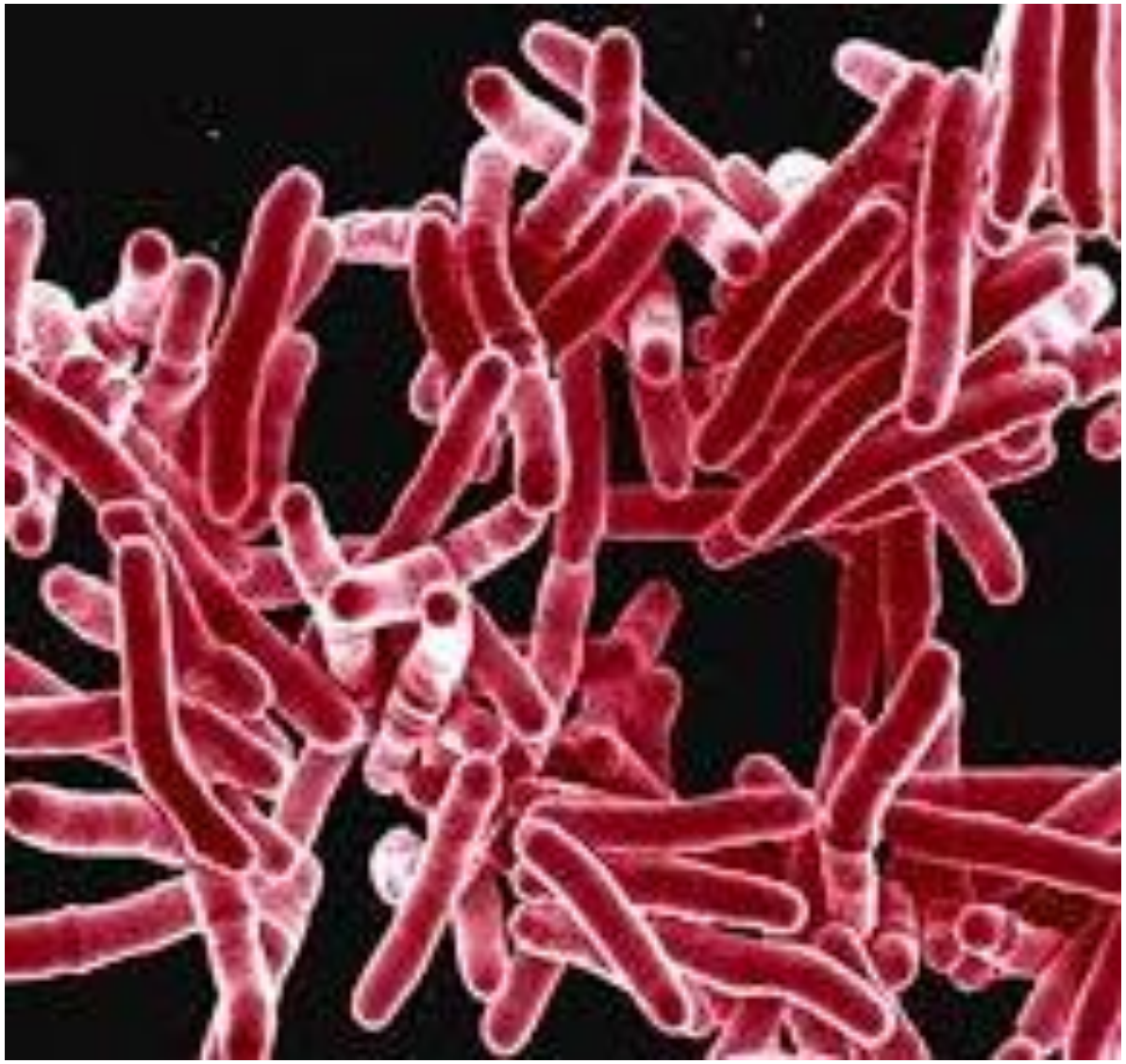
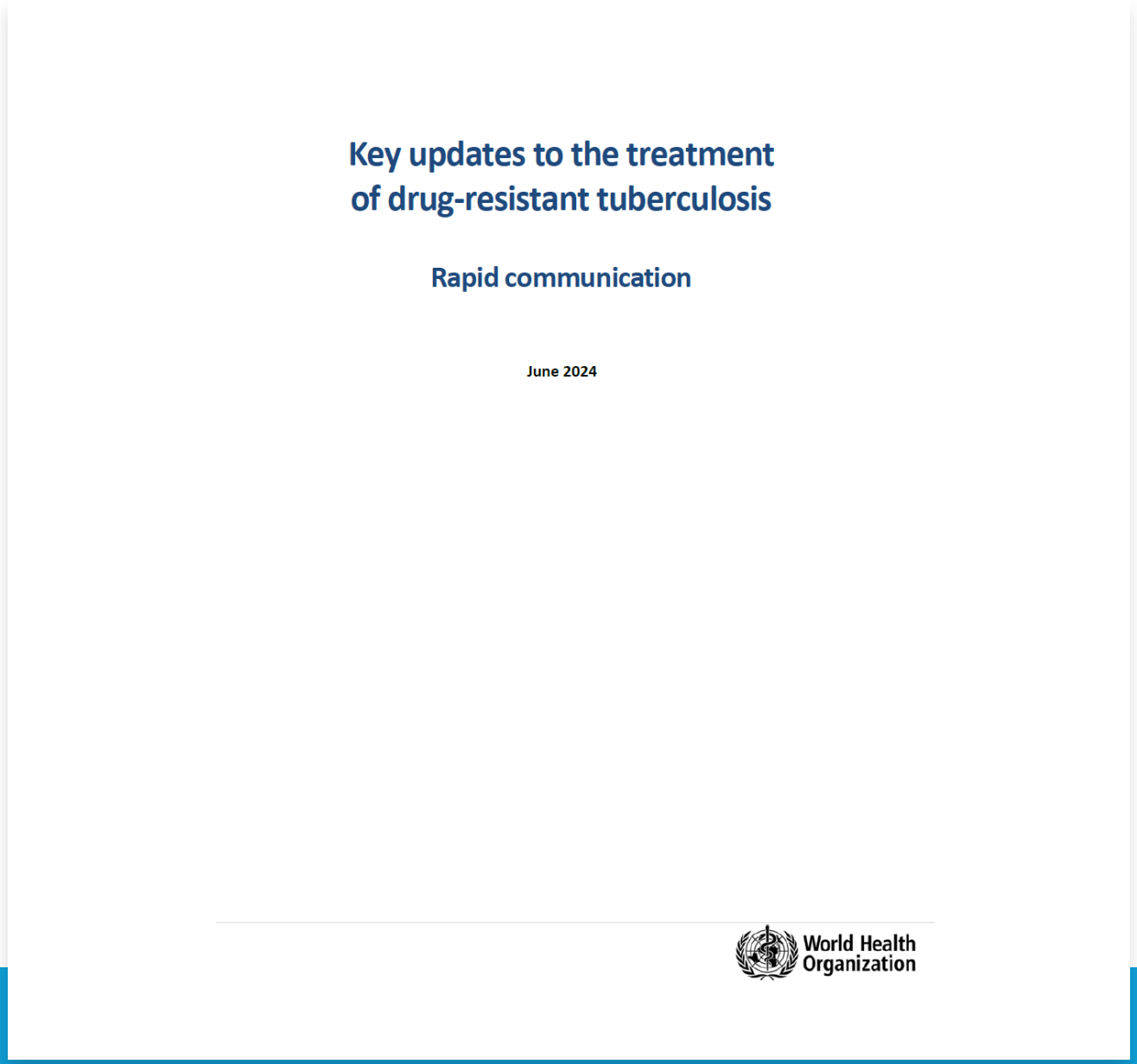


Objectives

- To review briefly global epidemiology of resistance to newer TB drugs;
- To present approaches to the care of people with complex drug resistance patterns, including diagnosis, management, and use of newer compounds



Exciting times in the care of DR-TB!

- All-oral shorter regimens can now treat the majority of people diagnosed with DR-TB in 6-9 months;
- Multiple options exist—not just BPaLM!
- Higher quality data support many of the regimens recommended by the WHO;
- Novel compounds being assessed in trials (although many directed toward treatment shortening for DS-TB or “universal regimens”).

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

- Most data about this new drug (compared with other newer agents) in clinical practice;
- Growing problem—both baseline and acquired during treatment;
- Rv0678 mutations most common but can see pepQ mutations as well;
- Not likely to have cartridge-based testing anytime soon
- Different clinical breakpoints and implications make determining resistance more challenging;
- Cross-resistance with CFZ common (? universal?);
- I491F mutation with FLQ susceptibility preserved in some regions (i.e. southern Africa);

Bedaquiline resistance in patients with drug-resistant tuberculosis in Cape Town, South Africa: a retrospective longitudinal cohort study

Brigitta Derendinger, Anzaan Dippenaar*, Margaretha de Vos*, Stella Huo, Rencia Alberts, Rebecca Tadokera, Jason Limberis, Frik Sirgel, Tania Dolby, Claudia Spies, Anja Reuter, Megan Folkerts, Christopher Allender, Darrin Lemmer, Annelies Van Rie, Sebastien Gagneux, Leen Rigouts, Julian te Riele, Keertan Dheda, David M Engelthaler, Robin Warren, John Metcalfe, Helen Cox, Grant Theron*

Summary

Background Bedaquiline is a life-saving tuberculosis drug undergoing global scale-up. People at risk of weak tuberculosis drug regimens are a priority for novel drug access despite the potential source of *Mycobacterium tuberculosis*-resistant strains. We aimed to characterise bedaquiline resistance in individuals who had sustained culture positivity during bedaquiline-based treatment.

Methods We did a retrospective longitudinal cohort study of adults (aged ≥18 years) with culture-positive pulmonary tuberculosis who received at least 4 months of a bedaquiline-containing regimen from 12 drug-resistant tuberculosis treatment facilities in Cape Town, South Africa, between Jan 20, 2016, and Nov 20, 2017. Sputum was programmatically collected at baseline (ie, before bedaquiline initiation) and each month to monitor treatment response per the national algorithm. The last available isolate from the sputum collected at or after 4 months of bedaquiline was designated the

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See Comment page e964

*Joint first authors

DSI-NRF Centre of Excellence for Biomedical Tuberculosis Research, SAMRC Centre for Tuberculosis Research, Division

How common is BDQ 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;
- 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: Linezolid Resistance

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LETTER

Linezolid resistance in patients with drug-resistant TB

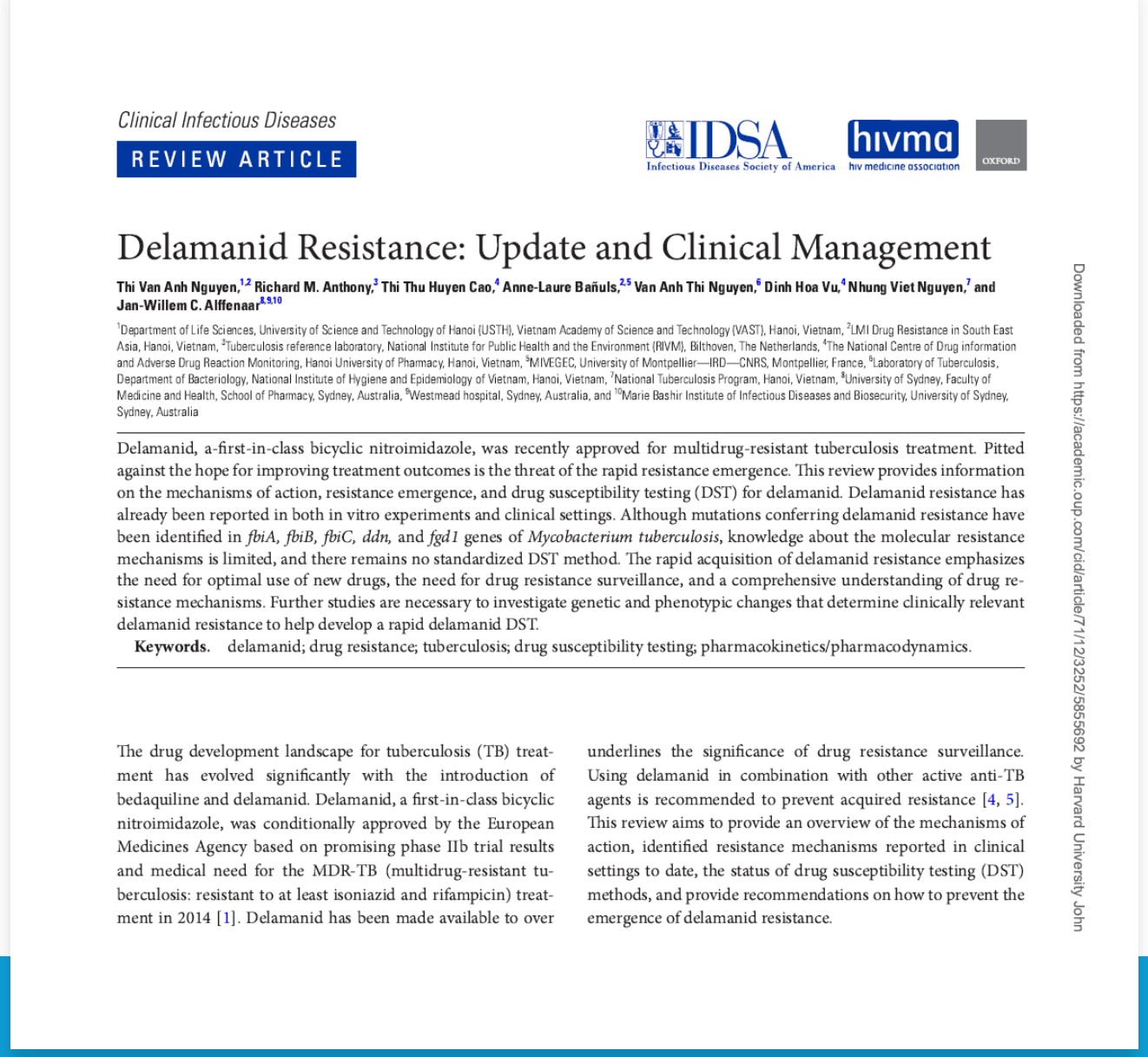
Dear Editor,

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.

- May develop later in course of therapy (?)—most resistance due to mutations in the ribosomes;
- 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)
- May be more common in setting with broad antibiotic access.



Clinical Infectious Diseases

REVIEW ARTICLE

Delamanid Resistance: Update and Clinical Management

Thi Van Anh Nguyen,[1,2] Richard M. Anthony,[3] Thi Thu Huyen Cao,[4] Anne-Laure Bañuls,[2,5] Van Anh Thi Nguyen,[6] Dinh Hoa Vu,[4] Nhung Viet Nguyen,[7] and Jan-Willem C. Alffenaar[8,9,10]

[1]Department of Life Sciences, University of Science and Technology of Hanoi (USTH), Vietnam Academy of Science and Technology (VAST), Hanoi, Vietnam, [2]LMI Drug Resistance in South East Asia, Hanoi, Vietnam, [3]Tuberculosis reference laboratory, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands, [4]The National Centre of Drug information and Adverse Drug Reaction Monitoring, Hanoi University of Pharmacy, Hanoi, Vietnam, [5]MIVEGEC, University of Montpellier—IRD—CNRS, Montpellier, France, [6]Laboratory of Tuberculosis, Department of Bacteriology, National Institute of Hygiene and Epidemiology of Vietnam, Hanoi, Vietnam, [7]National Tuberculosis Program, Hanoi, Vietnam, [8]University of Sydney, Faculty of Medicine and Health, School of Pharmacy, Sydney, Australia, [9]Westmead hospital, Sydney, Australia, and [10]Marie Bashir Institute of Infectious Diseases and Biosecurity, University of Sydney, Sydney, Australia

Delamanid, a-first-in-class bicyclic nitroimidazole, was recently approved for multidrug-resistant tuberculosis treatment. Pitted against the hope for improving treatment outcomes is the threat of the rapid resistance emergence. This review provides information on the mechanisms of action, resistance emergence, and drug susceptibility testing (DST) for delamanid. Delamanid resistance has already been reported in both in vitro experiments and clinical settings. Although mutations conferring delamanid resistance have been identified in *fbiA, fbiB, fbiC, ddn,* and *fgd1* genes of *Mycobacterium tuberculosis*, knowledge about the molecular resistance mechanisms is limited, and there remains no standardized DST method. The rapid acquisition of delamanid resistance emphasizes the need for optimal use of new drugs, the need for drug resistance surveillance, and a comprehensive understanding of drug resistance mechanisms. Further studies are necessary to investigate genetic and phenotypic changes that determine clinically relevant delamanid resistance to help develop a rapid delamanid DST.

Keywords. delamanid; drug resistance; tuberculosis; drug susceptibility testing; pharmacokinetics/pharmacodynamics.

The drug development landscape for tuberculosis (TB) treatment has evolved significantly with the introduction of bedaquiline and delamanid. Delamanid, a first-in-class bicyclic nitroimidazole, was conditionally approved by the European Medicines Agency based on promising phase IIb trial results and medical need for the MDR-TB (multidrug-resistant tuberculosis: resistant to at least isoniazid and rifampicin) treatment in 2014 [1]. Delamanid has been made available to over underlines the significance of drug resistance surveillance. Using delamanid in combination with other active anti-TB agents is recommended to prevent acquired resistance [4, 5]. This review aims to provide an overview of the mechanisms of action, identified resistance mechanisms reported in clinical settings to date, the status of drug susceptibility testing (DST) methods, and provide recommendations on how to prevent the emergence of delamanid resistance.

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Global Situation: Delamanid Resistance

- Limited data and experience;
- Pro-drug so mutations in pathways that activate drug confer resistance;
- *In vitro* resistance rates similar to INH;
- 4.4% baseline resistance among isolates in China;
- Trials show baseline resistance < 1% and between 1-2% acquired during therapy, usually in regimens containing less than 4 active drugs;
- ? Cross resistance (loss-of-function mutations in the genes *ddn, fbi* A, *fbi* B, *fbi* C, *fbi* D and *fgd* 1) with other nitroimidazoles.

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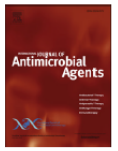

Review

Pretomanid resistance: An update on emergence, mechanisms and relevance for clinical practice

Thi Van Anh Nguyen[a,†], Quang Huy Nguyen[a,†], Tran Nam Tien Nguyen[b], Richard M. Anthony[c], Dinh Hoa Vu[b], Jan-Willem C. Alffenaar[d,e,f,*]

[a] LMI DRISA, University of Science and Technology of Hanoi, Vietnam Academy of Science and Technology, Hanoi, Vietnam
[b] National Centre of Drug information and Adverse Drug Reaction Monitoring, Hanoi University of Pharmacy, Hanoi, Vietnam
[c] National Institute for Public Health and the Environment, Bilthoven, The Netherlands
[d] School of Pharmacy, Faculty of Medicine and Health, University of Sydney, Sydney, Australia
[e] Westmead Hospital, Sydney, Australia
[f] Sydney Institute for Infectious Diseases, University of Sydney, Sydney, Australia

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ABSTRACT

Pretomanid (PA-824), a novel anti-tuberculosis (TB) nitroimidazoxazine, has been approved for multi-drug-resistant TB treatment for a few years. Pretomanid has been demonstrated to be highly active against *Mycobacterium tuberculosis* when combined with other anti-TB drugs. This review provides an update of the current knowledge on the modes of action, resistance mechanisms, emergence of drug resistance, and status of antimicrobial susceptibility testing for pretomanid and its relevance for clinical practice. Pretomanid resistance has been reported in in-vitro and animal models but not yet in clinical trials. Pretomanid-resistance-associated mutations have been reported in the *fbiA, fbiB, fbiC, fbiD, ddn* and *fgd1* genes. However, understanding of in-vivo molecular resistance mechanisms remains limited, and complicates the development of accurate antimicrobial susceptibility testing methods for pretomanid. As such, no reference method for antimicrobial susceptibility testing of pretomanid has been established to guide clinical use. Further studies linking specific mutations, in-vitro susceptibility, drug exposure and resistance mechanisms to treatment failure with pretomanid should be prioritized.

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Global Situation: Pretomanid Resistance

- Limited data and experience;
- Pro-drug as is delamanid;
- *In vitro* resistance rates similar to INH;
- 1% baseline resistance seen in ZeNix trial;
- Lineage 1 strains may have higher MICs and less intrinsic susceptibility to pretomanid;
- ? Cross resistance (loss-of-function mutations in the genes *ddn, fbi* A, *fbi* B, *fbi* C, *fbi* D and *fgd* 1) with other nitroimidazoles.

Clinical Approaches

- Poor clinical outcomes seen in people with strains of TB that have resistance to BDQ, LZD, or the FLQs—cohorts shows about 30-45% success rates;
- Limited access to DST for these drugs, and even when present, can take weeks for results;
- Patient populations presenting for care NOW;
- Presentations include: remote prior use; on treatment and not improving or “successfully treated”; contacts of these individuals.

The BETTER Project

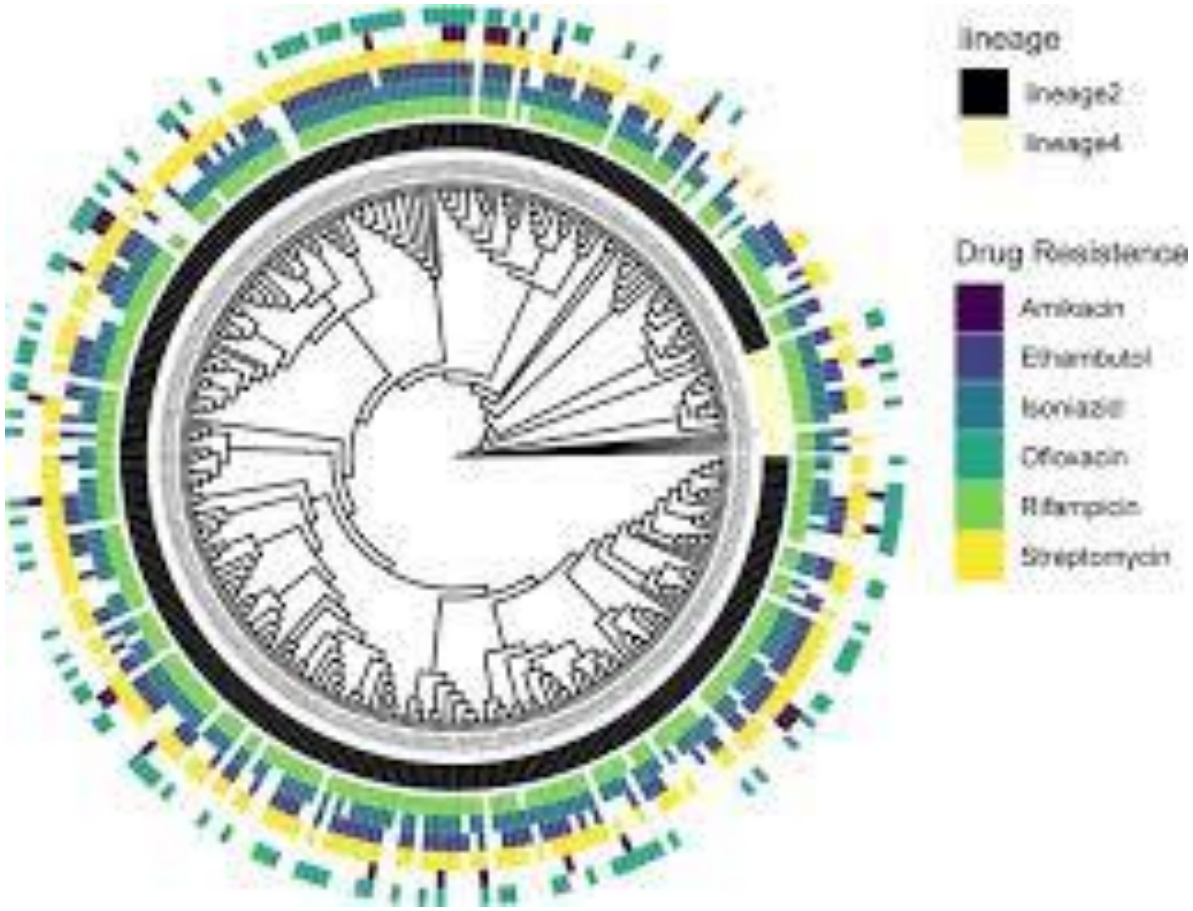
- Building Experience Treating Tuberculosis with Expanded Resistance;
- Volunteer group of front-line providers, impacted communities, TB programs, and civil society organizations;
- Goal is to share best practices and provide support to one another in how to best provide care for TB that has “expanded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

“Expanded Resistance”

- Strains of TB that are resistant to one or more of the following medications: BDQ, LZD, CFZ, or the nitroimidazoles;
- Reason for this term is that mono-resistance to any of these agents does not fit into current WHO definitions of pre-XDR or XDR.

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.



Optimizing DST

- Ideally, everyone would have rapid testing to all the drugs in the regimen they will receive;
- In reality, most people only have RIF results, with rapid access to FLQ for some;
- Advocacy for and investment in DST needs to happen (rather than wishing it away with universal regimen);
- In absence of this, risk groups should be: prior exposure to any second-line drug, positive culture at month 3 on treatment; treatment interruption, contacts of individuals in these groups, ? extensive disease.

Informed Consent and Shared Decision Making

Figure 1: Components of Shared Decision Making

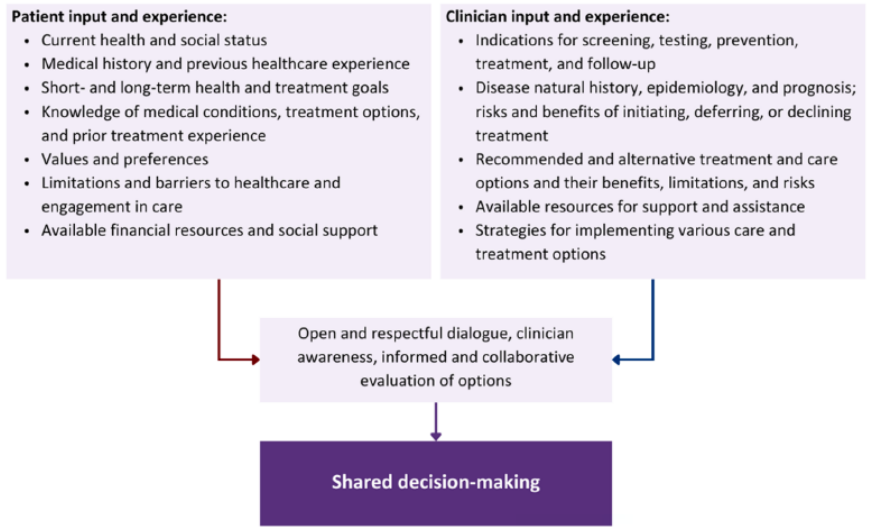
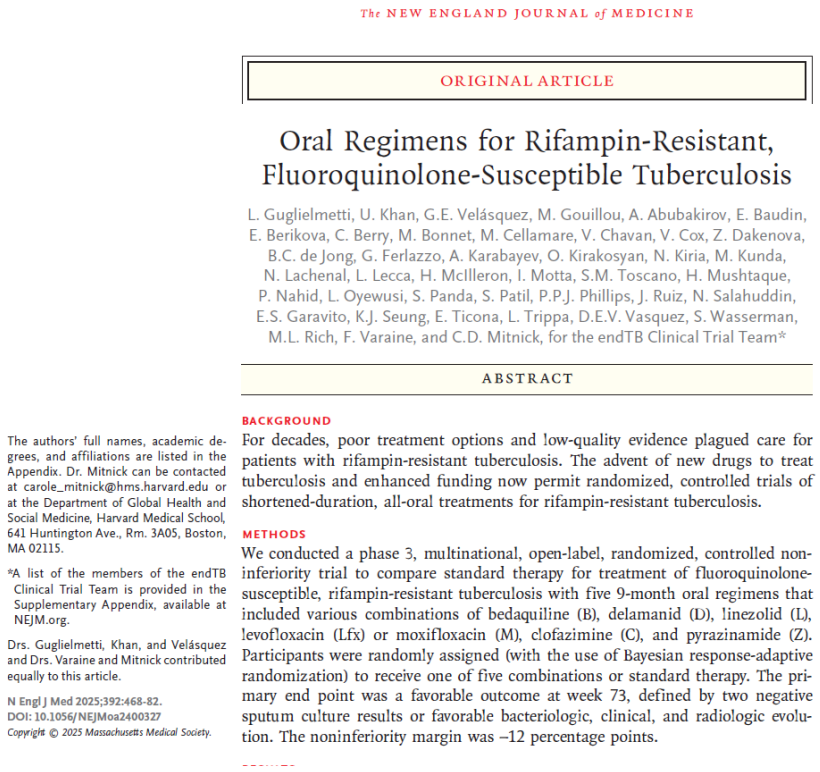


Figure 1 taken from: New York State Department of Health. AIDS Institute HIV Guidelines. Shared Decision Making. August, 2023. Figure reprinted with express written permission from the New York State Department of Health.

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.

Individual Regimen Design: Combination of Bactericidal and Sterilizing Agents

- Need drugs that kill rapidly multiplying and more quiescent forms of TB;
- Bactericidal drugs more important in early part of therapy;
- Defining which drugs are working in which way can be complex;
- Many drugs have a combination of both properties.

Bactericidal/sterilizing utility	Drugs
Drugs used for both bactericidal and sterilizing activity	Bdq, Dlm, Lfx, Lzd, Mfx, Pa
Drugs used primarily for bactericidal activity	Am, Carbapenems-clavulanic acid, Cs, Emb, Eto, high-dose Inh (if no katG mutation)
Drugs used primarily for sterilizing activity	Cfz, PAS, Pza

Individual Regimen Design: Stepwise Approach

- Step 1: Choose as many core (Group A) drugs as you can;
- Step 2: Choose additional oral agents for bactericidal activity (nitroimidazole, CS);
- Step 3: Choose additional oral agents for sterilizing activity (PZA, CFZ);
- Step 4: Add amikacin if susceptible and able to monitor for hearing loss;

Individual Regimen Design: Stepwise Approach

- Step 5: Add carbapenem+ clavulanic acid;
- Step 6: Choose other “back up” oral drugs as needed to reach 5 total likely effective agents;
- Step 7: Consider pre-approval access/CU of novel compounds.

Individual Regimen Design: Keeping Drugs if Uncertainty

- Uncertainty could be due to mutation of unknown significance or because no DST done;
- Could consider this for drugs associated with improved outcomes/reduced mortality (BDQ, LZD, FLQ);
- Shared decision making important here.

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	

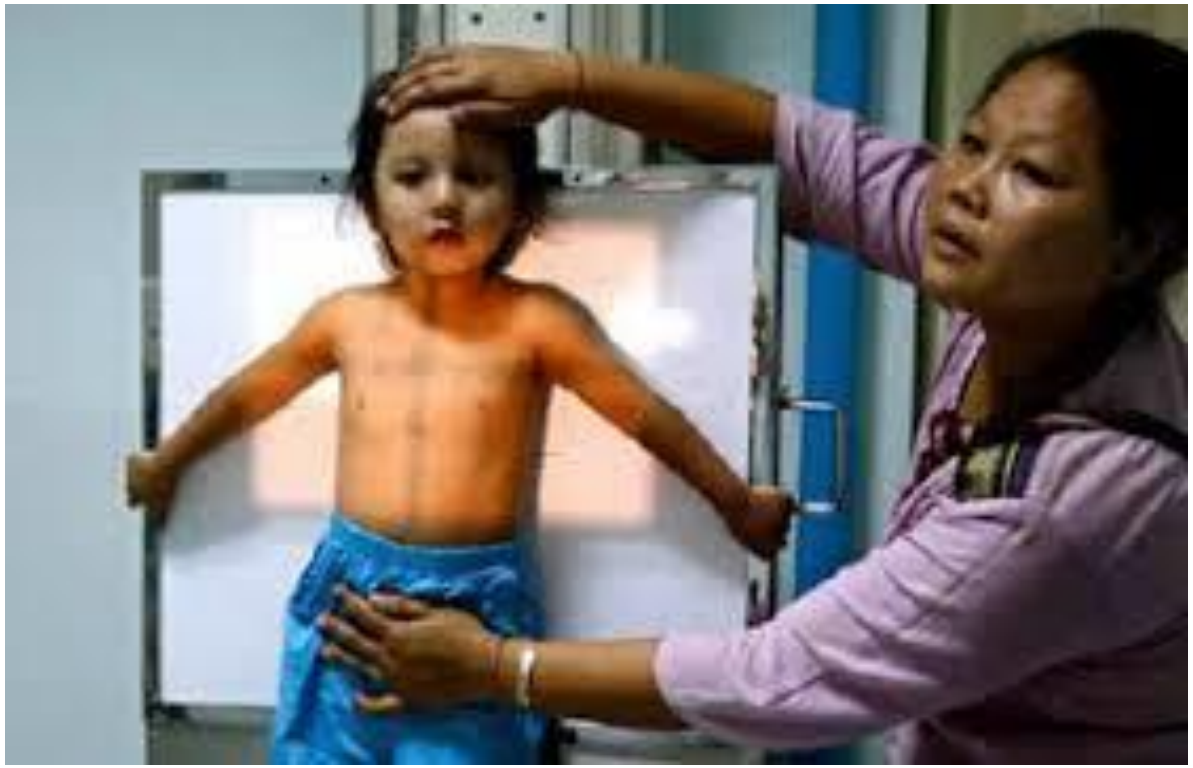
Verapamil Increases the Bactericidal Activity of Bedaquiline against *Mycobacterium tuberculosis* in a Mouse Model

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.

Principles of Pre-Approval Access

Pre-Approval Access to Novel Compounds is an Urgent Priority to Treat People with Strains of Tuberculosis that are Resistant to Bedaquiline, Linezolid, Clofazimine, and/or the Nitroimidazoles

A Statement from The BETTER Project
Contact: Jennifer Furin (Jennifer_furin@hms.harvard.edu)

Background

Treatment regimens containing bedaquiline, linezolid, clofazimine, and the nitroimidazoles (delamanid or pretomanid) have revolutionized the care of people with rifampicin-resistant forms of tuberculosis (RR-TB), making cure possible for the majority in as short as six months. Strains of TB that have resistance to these newer medications are an emerging problem globally, leaving individuals sick with these forms of TB fighting for their lives with limited treatment options.

At the same time, there are more new TB drugs than ever before in stage 2b or later phases of clinical testing, with much of the development of these products subsidized by public agency and donor investments. These novel compounds need to be made available urgently to save the lives of people

Components of Equitable and Ethical Pre-Approval Access/Compassionate Use Programs:

1. **Free, equitable access to novel TB compounds** through **transparent mechanisms** prior to their regulatory approval but **as soon as early efficacy and safety data** have been demonstrated in the treatment of *M. tuberculosis* in phase 2b or later studies;

2. Access for people with strains of TB that have expanded resistance to these novel compounds **both as single agents and as part of regimens that combine multiple new drugs.** Single drugs cannot be used on their own in failing regimens, and some people with certain strains of expanded resistance may require access to more than one new drug to form an adequate regimen. Other people, however, may only need one new drug to construct an adequate treatment regimen if other approved TB drugs can be given in combination with the single novel medication. Drug sponsors, being private, public or product development partnerships, must collaborate with one another and with front-line providers and people needing treatment to ensure this range of options is available. When more than one novel compound is required to form an adequate regimen, the real risk of poor treatment outcome and/or death must outweigh potential risks stemming from absence of evidence to support concomitant use.

3. Access to these novel compounds must encompass **all drug-resistant forms of TB**, with the drug provided for the duration of therapy recommended by the treating clinicians. Although some new drugs are currently being assessed only for fully drug-susceptible TB as part of shorter regimens (i.e. lasting for 4 months or less), this does not preclude their use in people with drug-resistant TB for longer durations. The new drugs may be of greater benefit to people with drug-resistant forms of TB (compared with susceptible

Post-Exposure Management

- Close monitoring and assessment for active disease;
- Medication “treatment of infection” on an individualized level;
- Nutritional support based on the RATIONS study.

Nutritional supplementation to prevent tuberculosis incidence in household contacts of patients with pulmonary tuberculosis in India (RATIONS): a field-based, open-label, cluster-randomised, controlled trial

Anurag Bhargava, Madhavi Bhargava, Ajay Meher, Andrea Benedetti, Banurekha Velayutham, G Sai Teja, Basilea Watson, Ganesh Barik, Rajeev Ranjan Pathak, Ranjit Prasad, Rakesh Dayal, Adarsh Kibballi Madhukeshwar, Vineet Chadha, Madhukar Pai, Rajendra Joshi, Dick Menzies, Soumya Swaminathan

Summary

Background In India, tuberculosis and undernutrition are syndemics with a high burden of tuberculosis coexisting with a high burden of undernutrition in patients and in the population. The aim of this study was to determine the effect of nutritional supplementation on tuberculosis incidence in household contacts of adults with microbiologically

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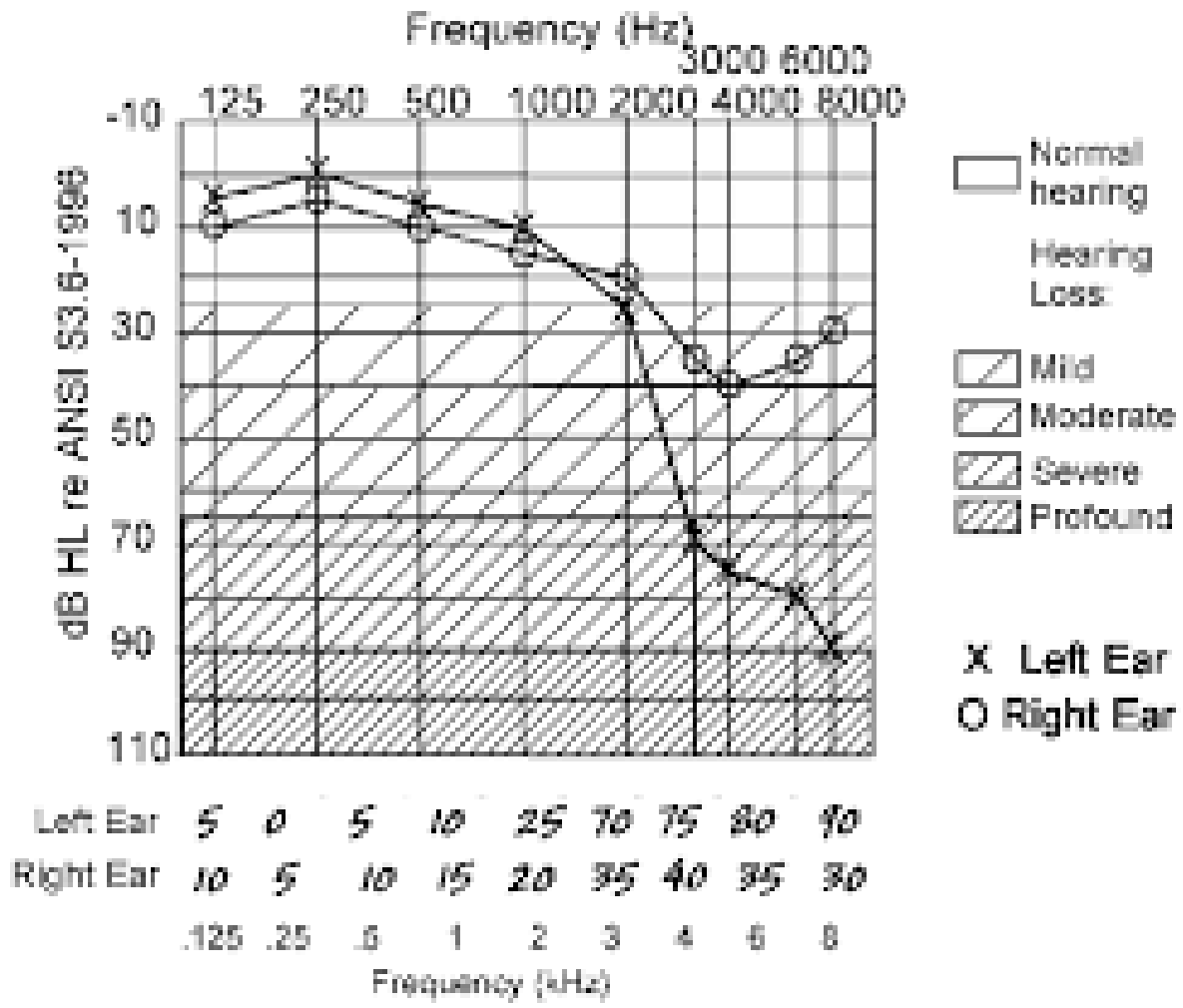


Toxicity Monitoring and Management

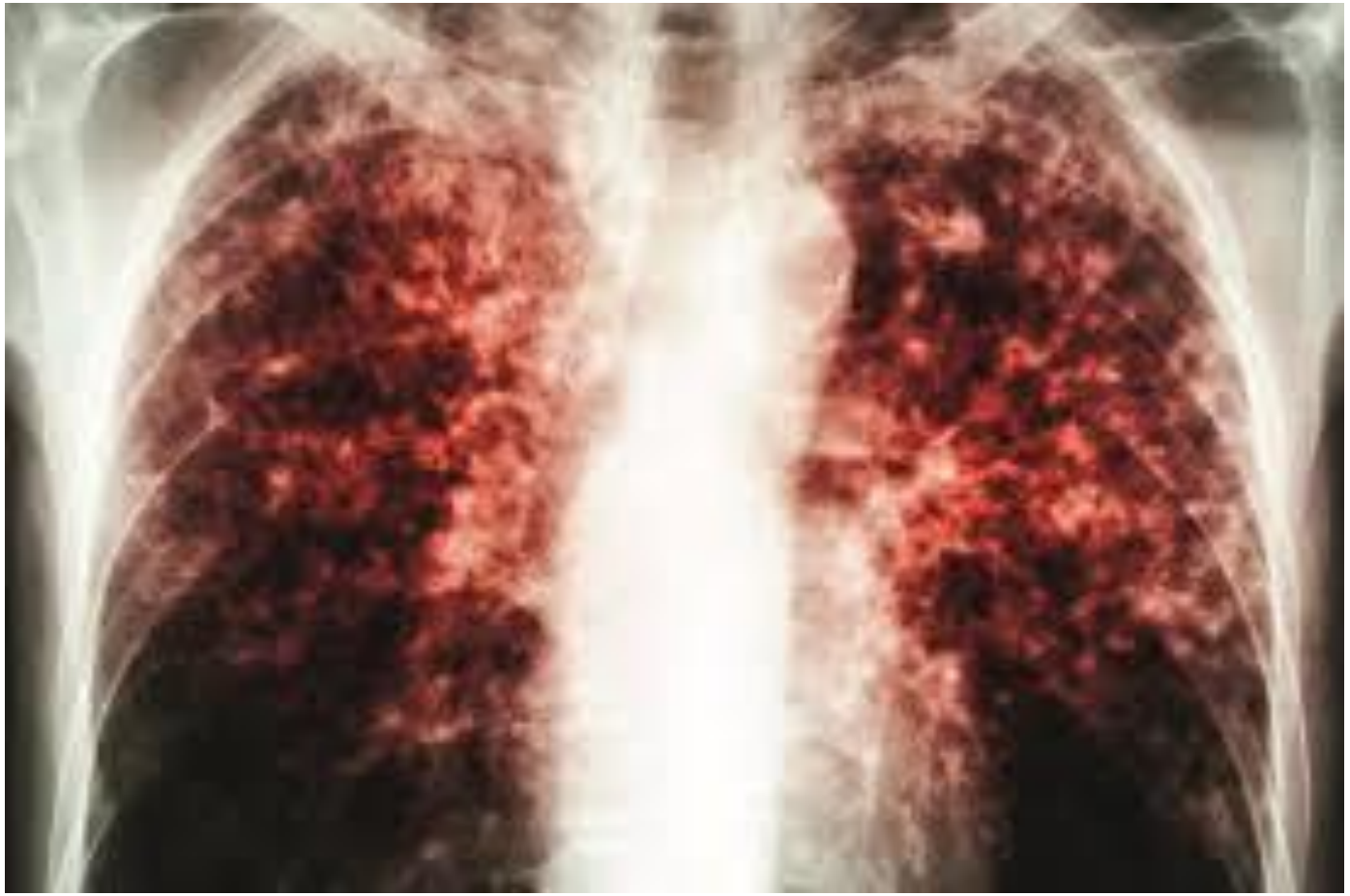
- Using many more toxic, second-line agents, including those that cause permanent disability (i.e. amikacin);
- Monitoring and management MUST be provided, includine formal testing free of charge and ancillary medications;
- Shared decision making is essential.

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!

jenniferfurin@gmail.com

VMC EURO/TB
Jennifer Furin
Askar Yedilbayev
Belinda Ameterra
Андрей Кутовой
Recording
RU
Sign in

Global Situation: Linezolid Resistance

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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.

- May develop later in course of therapy (?)—most resistance due to mutations in the ribosomes;
- 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)
- May be more common in setting with broad antibiotic access.

Unmute
Stop Video
Security
200
Participants
Share Screen
Stop Summary
AI Companion
Apps
Whiteboards
Notes
More
End