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THE CHANGING LANDSCAPE OF TUBERCULOSIS TREATMENT:

NEW CHALLENGES FOR THE LABORATORY

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New treatments for TB: The landscape is changing.....

- Two significant breakthrough for TB treatment regimens
- Reduce the length of time for treating TB which has been a longstanding public health goal
- Lower number of drugs in the regimen (BpaL)
- Targeting an “all oral” treatment (pills vs injectable)

Treatment of pan-susceptible tuberculosis (TBCT 31/A5349)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

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ABSTRACT

BACKGROUND
Rifapentine-based regimens have potent antimycobacterial activity that may allow for a shorter course in patients with drug-susceptible pulmonary tuberculosis.

METHODS
In an open-label, phase 3, randomized, controlled trial involving persons with newly diagnosed pulmonary tuberculosis from 13 countries, we compared two 4-month rifapentine-based regimens with a standard 6-month regimen consisting of rifampin, isoniazid, pyrazinamide, and ethambutol (control) using a noninferiority margin of 6.6 percentage points. In one 4-month regimen, rifampin was replaced with rifapentine; in the other, rifampin was replaced with rifapentine and ethambutol with moxifloxacin. The primary efficacy outcome was survival free of tuberculosis at 12 months.

RESULTS
Among 2516 participants who had undergone randomization, 2345 had a culture positive for *Mycobacterium tuberculosis* that was not resistant to isoniazid, rifampin, or fluoroquinolones (microbiologically eligible population; 768 in the control group, 791 in the rifapentine–moxifloxacin group, and 784 in the rifapentine group), of whom 194 were coinfected with human immunodeficiency virus and 1703 had cavitation on chest radiography. A total of 2234 participants could be assessed for the primary outcome (assessable population; 726 in the control group, 756 in the rifapentine–moxifloxacin group, and 752 in the rifapentine group). Rifapentine with moxifloxacin was noninferior to the control in the microbiologically eligible population (15.5% vs. 14.6% had an unfavorable outcome; difference, 1.0 percentage point; 95% confidence interval [CI], −2.6 to 4.5) and in the assessable population (11.6% vs. 9.6%; difference, 2.0 percentage points; 95% CI, −1.1 to 5.1). Noninferiority was shown in the secondary and sensitivity analyses. Rifapentine without moxifloxacin was not shown to be noninferior to the control in either population (17.7% vs. 14.6% with an unfavorable outcome in the microbiologically eligible population; difference, 3.0 percentage points [95% CI, −0.6 to 6.6]; and 14.2% vs. 9.6% in the assessable population; difference, 4.4 percentage points [95% CI, 1.2 to 7.7]). Adverse events of grade 3 or higher occurred during the on-treatment period in 19.3% of participants in the control group, 18.8% in the rifapentine–moxifloxacin group, and 14.3% in the rifapentine group.

CONCLUSIONS
The efficacy of a 4-month rifapentine-based regimen containing moxifloxacin was noninferior to the standard 6-month regimen in the treatment of tuberculosis. (Funded by the Centers for Disease Control and Prevention and others; Study 31/A5349 ClinicalTrials.gov number, NCT02410772.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Nahid at the UCSF Center for Tuberculosis, University of California, San Francisco, 1001 Potrero Ave, 5K1, San Francisco, CA 94110, or at pnahid@ucsf.edu.

Drs. Dorman, Nahid, and Kurbatova contributed equally to this article.

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N ENGL J MED 384;18 NEJM.ORG MAY 6, 2021

1705

Why rifapentine?

Lower MIC for TB

Longer half-life *in vivo* meaning that for the same dose, bacilli will be exposed longer to the drug than they would be with rifampin

Drawback: Poor distribution in lung cavities, therefore not recommended for cavitary disease

~~INH, PZA, RPT, EMB 2 months~~

INH, RPT 2months

INH, PZA, RPT MFX 2months

INH, RPT, MFX 2months

4 months rifapentine based regimen containing moxifloxacin is not inferior to the standard 6 months treatment regimen

Dorman et al., N Engl J Med 2021;384:1705-17018

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Treatment of MDR/XDR tuberculosis

TB Alliance

Patients with XDR-TB or Who Have Failed MDR-TB Treatment

N=109

Pretomanid 200 mg daily
26 weeks

Bedaquiline 400 mg daily for two weeks then 200mg 3 times a week for 24 weeks

Linezolid 1200 mg daily
26 weeks

BPaL regimen
Bedaquiline Pretomamid Linezolid

6 months of treatment

Additional 3 months if sputum culture positive at 4 months


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Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Cure at 6 months after end of therapy, with no clinical or bacteriologic evidence of TB

98 patients (90%) were found to have a favorable outcome, including 63 of 71 patients (89%) with XDR tuberculosis. Of the 38 patients with MDR tuberculosis who were enrolled in the study, 35 (92%) had favorable outcomes.
Outcome independent from the HIV status of the patient

Follow up for relapse-free cure over 24 months:
Thus far, only 1 relapse among the 47 patients who reached this milestone

Conradie et al., N Engl J Med 2020; 382: 893-902

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What are the new challenges for the laboratory?

https://www.fipp.com/news/coronavirus-media-challenges-opportunities/

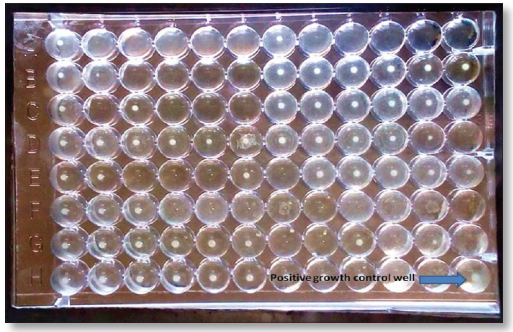
Drug susceptibility testing at Wadsworth

https://www.bd.com

Liquid culture – BACTEC MGIT 960

Rifampin, Isoniazid, Ethambutol, Pyrazinamide, Moxifloxacin, Bedaquiline, Clofazimine, Linezolid

Bhalla Gset al. J Health Res Rev 2018;5:93-7



Broth microdilution assay MIC (Sensititre)

1st and 2nd line drugs

https://www.currytbcenter.ucsf.edu

Agar proportion

All 1st line drugs + second line drugs including ethionamide, PAS, cycloserine, amikacin, rifabutin streptomycin and fluoroquinolones

https://www.qiagen.com

Pyrosequencing

Rifampin, Isoniazid, Fluoroquinolone

https://www.illumina.com

Whole Genome Sequencing

Rifampin, Isoniazid, Ethambutol, Pyrazinamide, Fluoroquinolone, Kanamycin/Amikacin, Ethionamide, Streptomycin

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Rifapentine

Phenotypic susceptibility testing: Very few studies available in the literature regarding *in vitro* susceptibility testing of rifapentine. Thus far, no guidelines/recommendations for critical concentrations in the different standard TB culture media. WHO recommends to still use rifampin as a surrogate for *in vitro* testing.

Minimal impact on the laboratory for rifapentine testing

Genotypic testing: Very scarce information about cross-resistance between rifampin and rifapentine for any given *rpoB* mutation. WHO recommends to use rifampin as a surrogate for genetic testing and assume total cross-resistance until further data become available.

Moxifloxacin

- MGIT system FDA approved only for 1st line drugs. Requires *in house* validation for all second line drugs including fluoroquinolones
- Guidelines for critical concentrations are available from WHO
- Available data for genetic testing: *gyrA* and *gyrB* sequencing can predict susceptibility/resistance to fluoroquinolones with high accuracy (Sequencing, LPA)
- Different levels of resistance have been reported for moxifloxacin depending on the nature of *gyrA* mutation. Important to distinguish as low-level resistant strains can still be treated with higher doses of MFX

Moxifloxacin

- *In house* validation of *in vitro* MFX testing in liquid (MGIT) and solid medium (Agar proportion)

- Critical concentrations based on WHO recommendations:
  - 0.25 (CC) and 1.0 μg/ml (Clinical Breakpoint) for MGIT (7H9)
  - 0.5 (CC), 1.0 & 2.0 mg/ml (CB) for agar proportion (7H10)

- Diversity panel of clinical strains either wild-type *gyrA* or carrying different mutations in *gyrA* and/or *gyrB*

In house validation of MFX susceptibility testing

Accession #	*gyrA* mutation	*gyrB* mutation	Moxifloxacin agar proportion Result				MGIT	MGIT
			MOX 0.5	MOX 1.0	MOX 2.0		MOX 0.25ug/ml	MOX 1.0ug/ml
IDR1400013617	Asp94Phe		R	S	S		R	R
IDR1400013618	Ala90Val		R	S	S		R	S
IDR1400013619	wt		S	S	S		S	S
IDR1400035170	Ser91Pro		R	R	R		R	S
IDR1400036340	Asp94Gly		R	R	R		R	R
IDR1400036823	Asp94Gly		R	R	S		R	R
IDR1500006146	Asp94Gly		R	R	R		R	R
IDR1400005535	Asp94Asn		R	R	S		R	R
IDR1400005538	Asp94Asn		R	R	R		R	R
IDR1400005540	wt		S	S	S		S	S
IDR1400005541	wt		S	S	S		S	S
IDR1400005543	wt		S	S	S		S	N/A
IDR1400005542	wt		S	S	S		S	N/A
IDR1400005544	Asp94Gly		R	R	R		R	N/A
IDR1400005548	wt		S	S	S		S	S
IDR1400005549	wt		S	S	S		S	S
IDR1400005550	Asp94Gly and Arg489Lys		R	S	S		R	S
IDR1400007392	Asp94Gly		R	R	R		R	R
IDR1400007392	Ser91Pro		R	S	S		R	N/A
	wt							
IDR1500050365	wt		S	S	S		S	S
IDR1500067577	wt		S	S	S		S	N/A
IDR1500067579	Ser91Pro		R	R	R		R	N/A
IDR1500067576	Ala90Val		R	R	R		R	S
IDR1500067572	wt		S	S	S		S	S
IDR1500067578	wt		S	S	S		S	S
IDR1500045426	wt		S	S	S		S	S
IDR1500048074	wt		S	S	S		S	S
IDR1500045424	wt		S	S	S		S	N/A
IDR1500045428	wt		S	S	S		S	S
IDR1500045425	wt		S	S	S		S	N/A
IDR1500045426	wt		S	S	S		S	S
IDR1500052248	wt							S
IDR1400035169	Ala90Val		R	R	R			S
IDR1300019614	Asp94Gly	Asn499Thr	R	R	R			N/A
IDR1600032078	Asp94Asn (mixed)	Ser661Thr	R	R	R		R	
IDR1600040334	Gly247Ser	Asn499Val (mixed)	R	R	S		R	
IDR1700011881	Asp94Asn	Val488Ala	N/A	N/A	N/A		R	
IDR1700042147	Gly88Cys	Ile486Leu	R	R	R		R	
IDR1800008940	Asp94His (mixed)	Arg446Cys (mixed)	R	R	S		R	
IDR1800012088	Arg292Gly (mixed)	Arg446Cys (mixed), Asp461His (mixed)	R	R	R		R	
IDR1900007384	Ala90Val, Gly807Asp		R	R	R		R	
IDR1900007403	Asp94gly, Gly807Asp		R	R	R		R	
IDR1900042879	Gly88Cys (mixed)		R	R	R		R	R
IDR1900045557	Asp94Gly,Gly88Ala,Glu738Asp		R	R	R		INV	
IDR1900058856	Ala90Val (mixed), Gly247Ser	GIn9His	R	R	S		R	S
IDR1900063330	Pro472Ser	ASp461Asn	R	R	S		R	S
IDR2000172796		Arg446Cys					R	S
ATCC25177			S	S	S		S	S

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Treatment of MDR/XDR TB: BPaL

Why do we want to test for the new TB drugs?

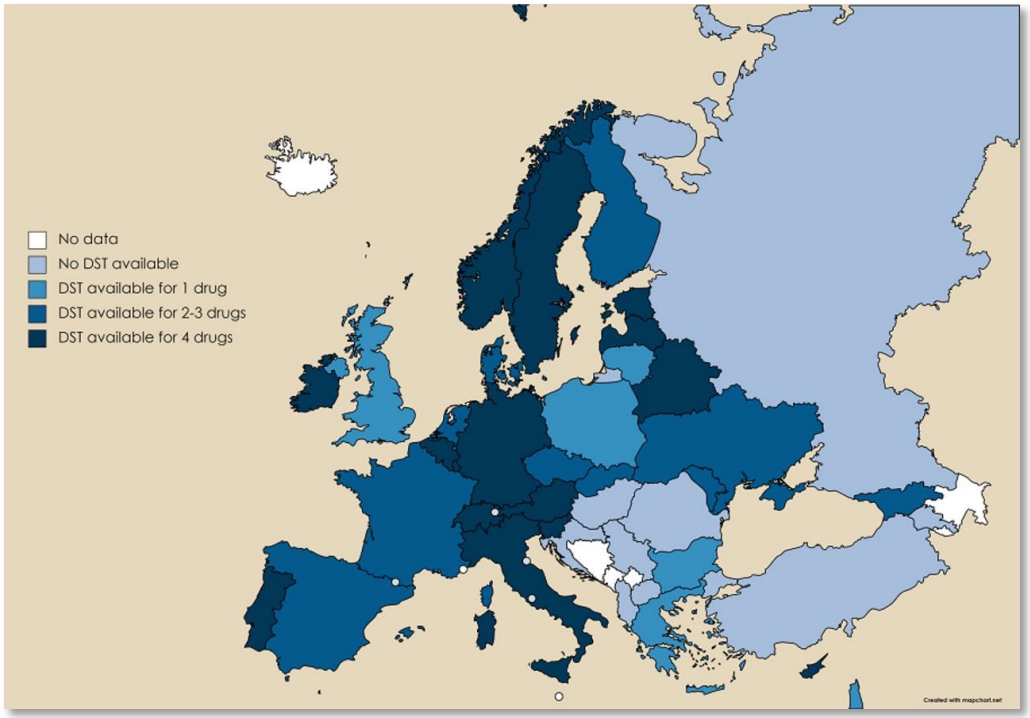
It is essential to establish susceptibility criteria for *Mycobacterium tuberculosis* (MTB) isolates for new and "off label" drugs, given their increasing relevance in the new WHO treatment recommendations, to ensure optimal regimen and prevent emergence of further resistance

With increasing use of BDQ, reports of clinical relapses associated with drug resistance and cross-resistance with clofazimine have emerged, tempering the early excitement. Therefore, more-stringent measures are required to control the emergence of BDQ resistance, including systematic rapid and reliable DST to personalize and optimize treatment regimen.

What are the hurdles?

- For newer and “off label” drugs, phenotypic DST is not yet fully standardized because of lack of epidemiological cutoff values
- Widely used BACTEC MGIT technology is not calibrated against a reference standard protocol and not FDA approved for second line drugs
- Issues with procuring pure compounds for testing.
- Availability of resistant isolates for validation studies
- Genomic DST lacks sensitivity and molecular mechanisms of resistance have not yet been fully established
- Natural resistance might vary depending on the MTB lineage

Still low accessibility to susceptibility testing for the new drugs

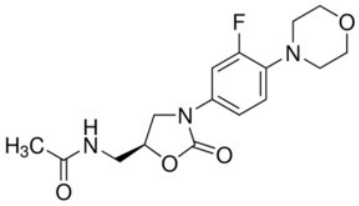


Phenotypic or genotypic DST was available for all four drugs in 38% of countries, and for none in 25%, mostly in Eastern Europe.
DST availability was lower for delamanid (45%), bedaquiline (50%), and clofazimine (55%), than for linezolid (68%).

Among countries with DST capacity, documented resistance was reported for linezolid by 52% of the countries and for bedaquiline by 38%. Most patients (83%) with phenotypic resistance started treatment.

Guglielmetti et al. , European Respiratory Journal 2021; 58: Suppl. 65, OA4202.

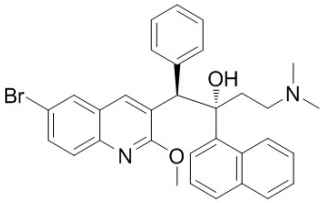
The BPaL Trio...



Linezolid

https://www.sigmaaldrich.com

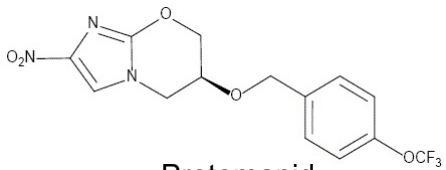
Approved by FDA in 2000 (Upjohn). Oxazolidinone class. Mainly used to treat drug resistant gram positive infections but has shown activity against *Mycobacterium tuberculosis.* Prevents the synthesis of bacterial proteins via binding to rRNA on both the 30S and 50S ribosomal subunits.



Bedaquiline

https://www.medchemexpress.com

Approved by FDA in 2012 (Johnson & Jonhson). First TB drug approved in 40 years. Diarylquinoline class. Inhibits *M. tuberculosis* adenosine triphosphate (ATP) synthase enzyme.



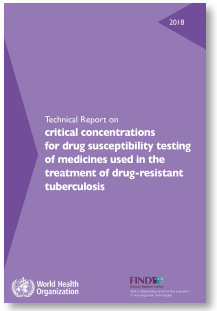
Pretomanid

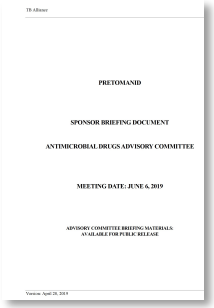
https://www.rxlist.com

Developed by TB Alliance. Nitromidazole class (as is Delamanid). Inhibits cell wall biosynthesis via blockage of the oxidation of hydroxy-mycolate to keto-mycolate. Under anaerobic conditions, causes respiratory poisoning by release of reactive nitrogen species during drug activation. Prodrug activated by a deazaflavin dependent nitroreductase (Ddn)

Validating MGIT DST for BPaL regimen drugs

Technical Report on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis. Geneva: World Health Organization;2018 (WHO/CDS/TB/2018.5). Licence: CC BY-NC-SA 3.0 IGO.





https://www.fda.gov/media/127593/download

- **Critical concentrations based on the recommendations from WHO and FDA**
- **If possible, include clinically resistant strains and different lineages in validation panel**
- **Analyze WGS data for presence of putative resistance mutations then reflex to phenotyping testing for confirmation (Linezolid and Bedaquiline),**

or

- **Use phenotypic data (MIC) from CRyPTIC (Comprehensive Resistance Prediction for Tuberculosis: an International Consortium project) and reflex to WGS data to identify putative resistance mutations (Pretomanid)**

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Linezolid

WHO recommended critical concentration for MGIT testing at 1μg/ml

Major resistance determinants have been characterized:

- Mutation in *rplC:* T460C resulting in a Cys154Arg substitution.

- Mutation in *rrl:* G2814T and G2270T

All the isolates predicted to be susceptible by WGS were confirmed with MGIT testing

Two isolates harbouring a rplC Cys154Arg mutation (thank you Florida!) were found resistant with MGIT testing

Bedaquiline

1) Identifying clinical strains carrying mutations in *atpE, pepQ* or *Rv0678* from WGS data

2) Testing susceptibility to Bedaquiline and Clofazimine in the MGIT system using critical concentrations suggested by WHO

	Bedaquiline (MGIT) 1 μg/ml	Clofazimine (MGIT) 1 μg/ml	Possible mutations associated with resistance
IDR1500049548*	Resistant	Resistant	*Rv0678* Arg50Gln
IDR1600001030	Resistant	Resistant	*Rv0678* Phe93Leu
IDR1700042139	Resistant	Susceptible	*Rv0678* Arg109Trp
IDR1700054211	Resistant	Resistant	*Rv0678* Trp42Arg
IDR1800001473	Resistant	Resistant	*Rv0678* Ala84Val
IDR1900007384**	Resistant	Resistant	*Rv0678* Leu40Ser
IDR1900007403**	Resistant	Resistant	*Rv0678* Frameshift Insertion (+G) at position 137
IDR2000205173	Resistant	Susceptible	*Rv0678* Ala59Val

* XDR-TB

** MDR-TB

Role of *Rv0678* in Bedaquiline resistance

Sample	Rv0678	MGIT BDQ (1.0 µg/ml)	MGIT CFZ (1.0 µg/ml)
IDR2100043848	100(TTC -> TTA,Phe -> Leu)	Resistant (x2)	Susceptible
IDR2100093147	101(GCG -> GTG,Ala -> Val)	Susceptible	Susceptible
IDR1700042139	109(CGG -> TGG,Arg -> Trp)	Resistant (x2)	Susceptible
IDR2100062392	115(CAG -> CCG,Gln -> Pro)	Resistant	Resistant/Susceptible
IDR1700050884	132(CGA -> GGA,Arg -> Gly)	Susceptible	Susceptible
IDR1900007403	137(Frameshift Insertion,+G)	Resistant (x3)	Resistant (x3)
IDR1900052071	157(TAC -> TGC,Tyr -> Cys)	Susceptible	Susceptible
IDR1600003528	162(GGA -> GAA,Gly -> Glu)	Susceptible	Susceptible
IDR1900060232	162(GGA -> GAA,Gly -> Glu)	Susceptible	Susceptible
IDR2100091381	162(GGA -> GAA,Gly -> Glu)	Susceptible	Susceptible
IDR1800038926	2(AGC -> AGA,Ser -> Arg)	Susceptible	Susceptible
IDR2200019606	21(GAA -> GGA,Glu -> Gly)	Susceptible	Susceptible
IDR1700022304	3(GTC -> ATC,Val -> Ile)	Susceptible	Susceptible
IDR1900007384	40(TTG -> TCG,Leu -> Ser)	Resistant (x3)	Resistant (x3)
IDR1500067578	417(Frameshift Insertion,+G)	Resistant (x3)	Susceptible (x3)
IDR1700011884	417(Frameshift Insertion,+G)	Resistant (x3)	Susceptible (x2)/Resistant (1x)
IDR1700043543	417(Frameshift Insertion,+G)	Resistant (x3)	Resistant (x2)/Susceptible (x1)
IDR1700054211	42(TGG -> CGG,Trp -> Arg)	Resistant (x3)	Resistant (x2)/Susceptible (x1)
IDR1500000665	50(CGG -> CAG,Arg -> Gln)	Resistant (x2)	Resistant (x2)/Susceptible (x1)
IDR1500049548	50(CGG -> CAG,Arg -> Gln)	Resistant (x3)	Susceptible (x2)/Resistant (1x)
IDR1600044262	50(CGG -> CAG,Arg -> Gln)	Resistant (x3)	Resistant (x3)
IDR1600052651	54(GAG -> GGG,Glu -> Gly)	Susceptible	Susceptible
IDR2000003988	55(GAA -> GAC,Glu -> Asp)	Susceptible	Susceptible
IDR1800031503	55(GAA -> GAC,Glu -> Asp)	Susceptible	Susceptible
IDR1800055080	55(GAA -> GAC,Glu -> Asp)	Susceptible	Susceptible
IDR1900056515	55(GAA -> GAC,Glu -> Asp)	Susceptible	Susceptible
IDR2000003988	55(GAA -> GAC,Glu -> Asp)	Susceptible	Susceptible
IDR2000205173	59(GCG -> GTG,Ala -> Val)	Resistant (x4)	Susceptible (x4)
IDR2100100721	64(AGC -> AGG,Ser -> Arg)	Susceptible	Susceptible
IDR2100019328	73(ATG -> ATA,Met -> Ile)	Susceptible (x2)	Susceptible (x2)
IDR1800001473	84(GCG -> GTG,Ala -> Val)	Resistant (x2)	Resistant (x3)
IDR1600001030	93(TTC -> TTG,Phe -> Leu)	Resistant (x3)	Susceptible (x3)

CRyPTIC Project

Using whole-genome sequencing (WGS) as a faster alternative to identify drug-resistant TB. Over 100,000 TB collected, many of which being MDR-TB, from across Africa, Asia, Europe and the Americas by teams at more than a dozen centers. Each site conducts drug-resistance testing on the samples in parallel with whole genome sequencing. Testing plates are provided to the testing sites by Oxford University and the Oxford team collects and assembles all the results into a single open-access database. These data will allow identification of specific mutations associated with resistance to TB drugs to accurately and quickly predict drug-resistance for new TB infections

Plate Code: **UKMYC5** Date: **6-Apr-16**

	1	2	3	4	5	6	7	8	9	10	11	12
A	BDQ	KAN	KAN	KAN	KAN	KAN	ETH	ETH	ETH	ETH	ETH	ETH
	2	16	8	4	2	1	8	4	2	1	0.5	0.25
B	BDQ	AMI	EMB	INH	LEVO	MXF	DLM	LZD	CFZ	RIF	RFB	PAS
	1	8	8	1.6	8	4	1	2	4	4	2	4
C	BDQ	AMI	EMB	INH	LEVO	MXF	DLM	LZD	CFZ	RIF	RFB	PAS
	0.5	4	4	0.8	4	2	0.5	1	2	2	1	2
D	BDQ	AMI	EMB	INH	LEVO	MXF	DLM	LZD	CFZ	RIF	RFB	PAS
	0.25	2	2	0.4	2	1	0.25	0.5	1	1	0.5	1
E	BDQ	AMI	EMB	INH	LEVO	MXF	DLM	LZD	CFZ	RIF	RFB	PAS
	0.12	1	1	0.2	1	0.5	0.12	0.25	0.5	0.5	0.25	0.5
F	BDQ	AMI	EMB	INH	LEVO	MXF	DLM	LZD	CFZ	RIF	RFB	PAS
	0.06	0.5	0.5	0.1	0.5	0.25	0.06	0.12	0.25	0.25	0.12	0.25
G	BDQ	AMI	EMB	INH	LEVO	MXF	DLM	LZD	CFZ	RIF	RFB	PAS
	0.03	0.25	0.25	0.05	0.25	0.12	0.03	0.06	0.12	0.12	0.06	0.12
H	BDQ	EMB	EMB	INH	LEVO	MXF	DLM	LZD	CFZ	RIF	POS	POS
	0.015	0.06	0.12	0.025	0.12	0.06	0.015	0.03	0.06	0.06		

ANTIMICROBICS

BDQ	Bedaquiline
DLM	Delamanid
AMI	Amikacin
CFZ	Clofazimine
EMB	Ethambutol
ETH	Ethionamide
INH	Isoniazid
KAN	Kanamycin
LEVO	Levofloxacin
LZD	Linezolid
MXF	Moxifloxacin
PAS	Para-aminosalicylic acid
POS	Positive Control
RFB	Rifabutin
RIF	Rifampin

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Pretomanid

Select strains with elevated MIC for delaminid (ECOFF 0.12 μg/ml), test for susceptibility to pretomanid, look for possible mutations responsible for resistant phenotype

fbiA; fbiB; fbiC; fbiD; fgd1; ddn

	Delamanid MIC (mg/ml)	Susceptibility to Pretomanid MGIT (1 μg/ml)	Possible mutations associated with resistance
IDR1800010869	0.25	Resistant	*fgd1* Arg64Ser
IDR1800013967	0.25	Resistant	*fbiC* deletion (61 nt) at position 2563
IDR1800022302	0.25	Resistant	*fbiD* Glu100Glu* + *fbiA* Val5Val*
IDR1900000424	0.25	Resistant	none
IDR1900034591	0.5	Resistant	*fbiD* Glu100Glu* + *fbiA* Val5Val*
IDR1900032217	0.5	Resistant	*fbiC* frameshift –G at position 1329
IDR1800001482	0.25	Resistant	*fbiC* deletion (61 nt) at position 2563

* Possible phylogenetic SNP

Critical concentration for pretomanid might need to be revised as some lineages (L1) exhibit higher intrinsic MICs than other lineages

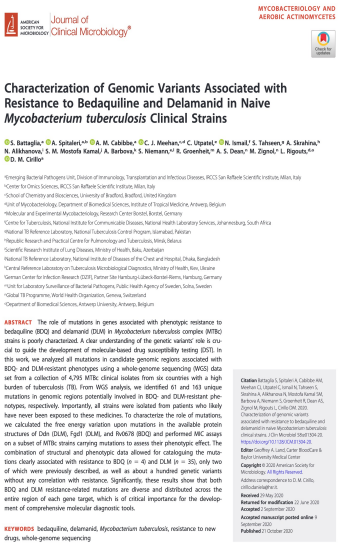
Bateson et al. (2021) J Antimicrob Chemother):1685-1693

One important lesson…….

Prevalence of “naïve” strains resistant to bedaquiline or pretomanid with no prior exposure to these drugs is alarming and further surveillance studies are needed


Articles

Genetic variants and their association with phenotypic resistance to bedaquiline in *Mycobacterium tuberculosis*: a systematic review and individual isolate data analysis


Journal of Clinical Microbiology

MYCOBACTERIOLOGY AND AEROBIC ACTINOMYCETES

Characterization of Genomic Variants Associated with Resistance to Bedaquiline and Delamanid in Naive *Mycobacterium tuberculosis* Clinical Strains


Journal of Antimicrobial Chemotherapy

Delamanid susceptibility testing of *Mycobacterium tuberculosis* using the resazurin microtitre assay and the BACTEC™ MGIT™ 960 system

- Battaglia et al. , J Clin Microbiol 2020; 58:e01304-e1320
- Ismail et al. Lancet Microbe 2021; : e604–e6162021;
- Schena et al. J Antimicrob Chemother 2016; 71:1532-1539

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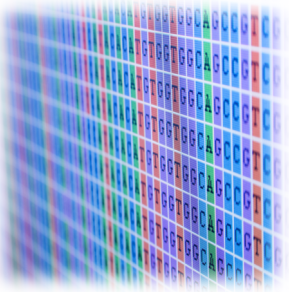
Consequently....

Prescription of these drugs in any MDR/XDR TB regimen should be preceded by drug susceptibility testing and/or mutational analysis

As emphasized by WHO and FDA, this demonstrates that these drugs should be used with caution under restricted conditions, only for extreme cases until mechanisms of resistance are better understood

Acknowledgements



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