Later Generation Fluoroquinolones in treatment of XDR Tuberculosis

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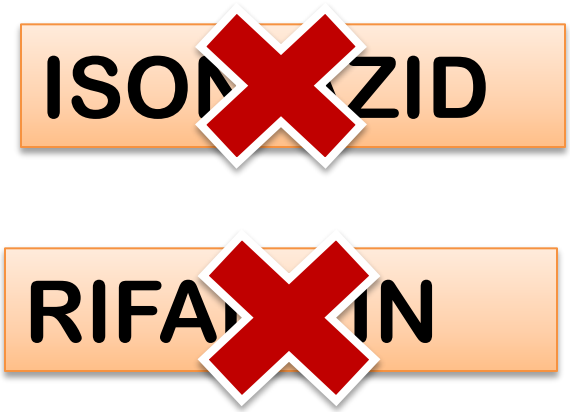
October 27, 2012

Standard TB Therapy

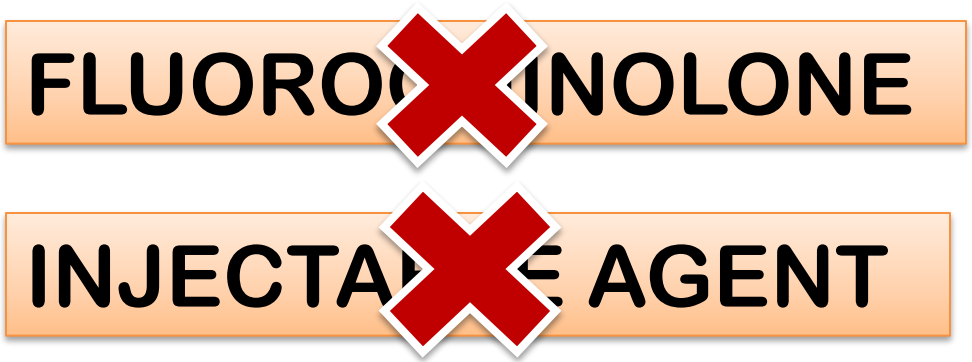


MDR

PYRAZINAMIDE

ETHAMBUTOL

MDR Tuberculosis Therapy



PYRAZINAMIDE

ETHIONAMIDE

CYCLOSERINE or PAS

± ETHAMBUTOL

XDR

WHO guidelines programmatic management drug-resistant tuberculosis: 2011 update

Tugela Ferry, KwaZulu-Natal, South Africa

- First described 2006
- 53 patients, all co-infected with HIV and XDR TB
- Survived median 16 days
- Mortality 98%

Gandhi NR et al. Lancet 2006;368:1575-80

Fluoroquinolones

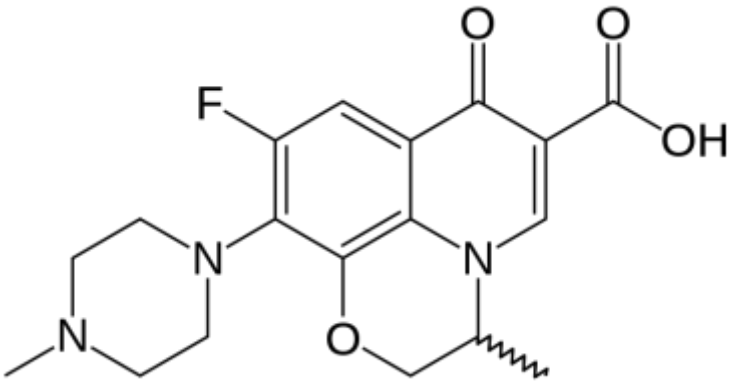
Early Generation	**Later Generation**
Ciprofloxacin	Gatifloxacin
Ofloxacin	Levofloxacin
	Moxifloxacin
	Sparfloxacin

Fluoroquinolone Mechanism

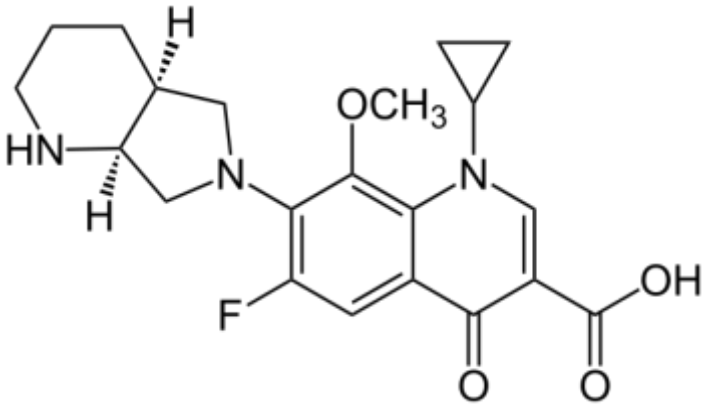
- Kill bacteria by altering DNA gyrase and topoisomerase IV
- DNA gyrase: 2 A and 2 B subunits encoded by *gyrA* and *gyrB* genes
- Quinolone resistance determining region (QRDR)
- Also shown in lab strains: efflux pumps and DNA mimicry

Mean Inhibitory Concentrations and Structure

- Ofloxacin ≥ 2.0 ug/ml
- Moxifloxacin ≥ 0.25-0.5 ug/ml



Ofloxacin



Moxifloxacin

Aims

- Assess XDR TB treatment outcomes
- Identify therapeutic approaches associated with favorable treatment outcomes

XDR TB treatment outcomes

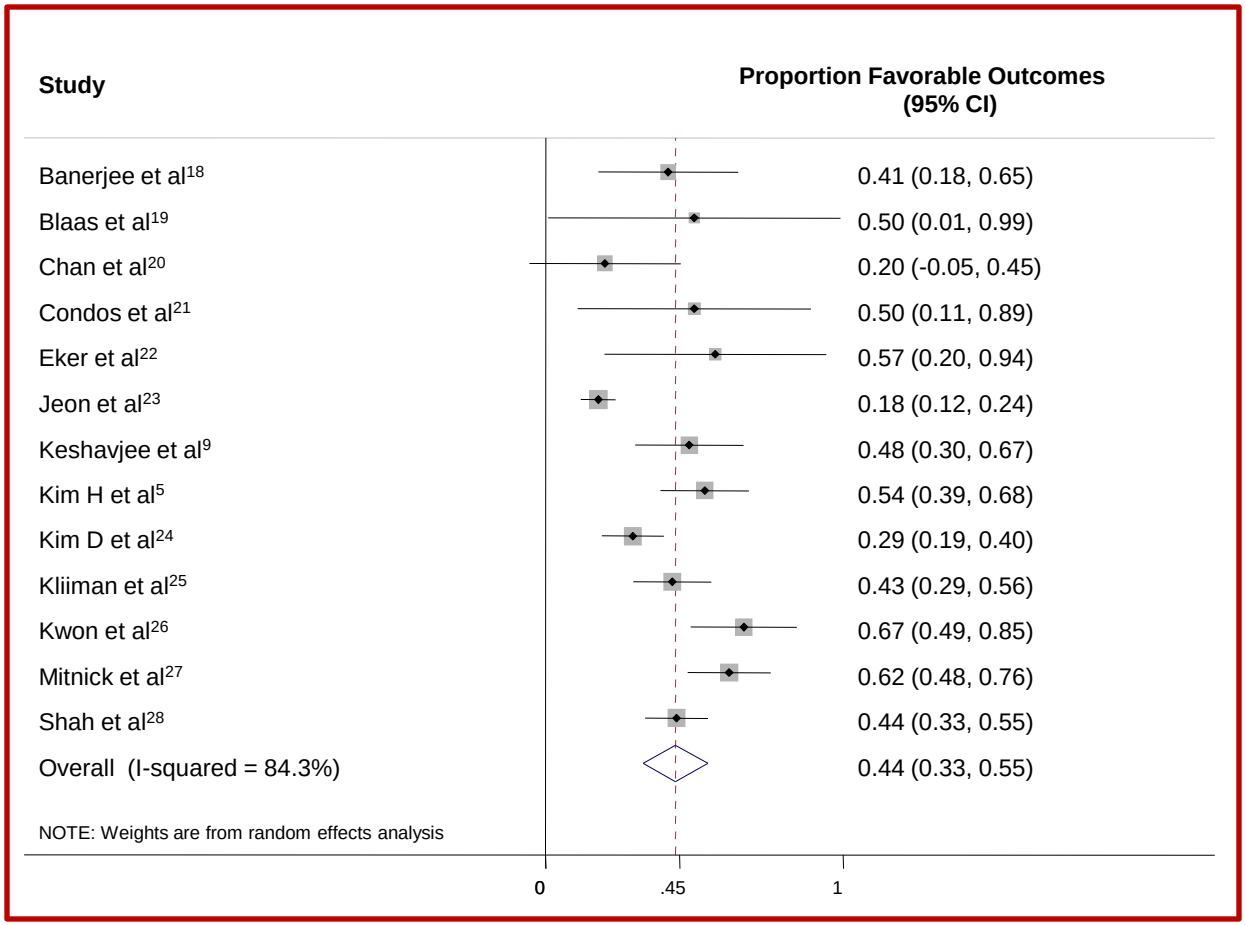
CID 2010:51 (1 July)

Treatment Outcomes among Patients with Extensively Drug-Resistant Tuberculosis: Systematic Review and Meta-Analysis

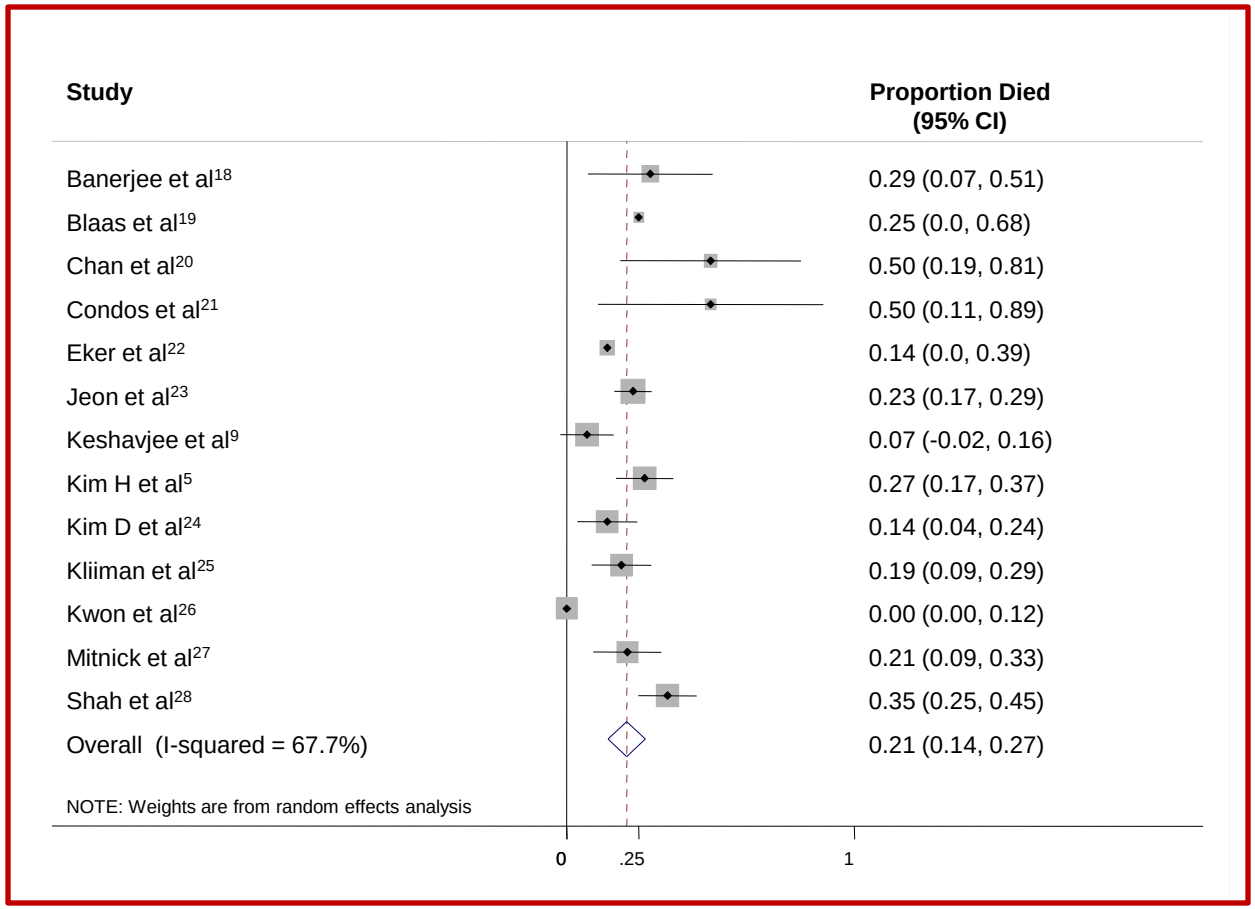
Karen R. Jacobson,[1] Dylan B. Tierney,[1] Christie Y. Jeon,[2] Carole D. Mitnick,[3,4] and Megan B. Murray[1,2,4]

- All XDR treatment outcome studies (13)

Proportion of patients with favorable outcomes



Proportion of patients who died

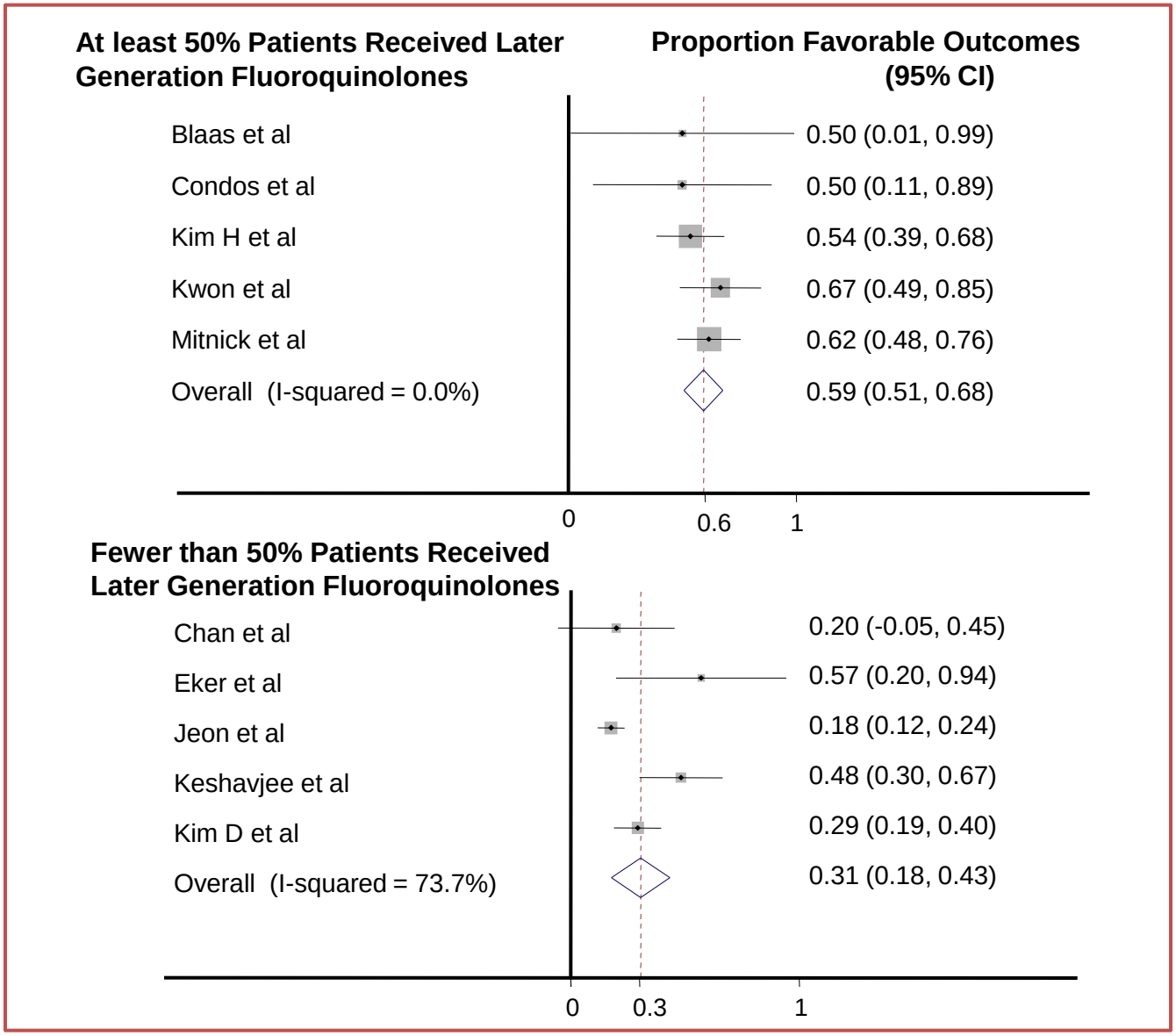


Univariate meta-regression of individual study characteristics

Study characteristics [number of studies reporting]	% Favorable outcomes improvements (95% CI)	*P* value
HIV % prevalence [13]*	0.27 (-6.6, 7.1)	0.93
Mean age (year) [13]*	-20 (-35, -3.8)	0.019
Gender, % female [12]*	2.5 (-3.7, 8.8)	0.39
Mean no. drugs in treatment regimen [10]	0.21 (-14.9, 15.3)	0.98
Mean no. "likely active drugs" in treatment regimen [8]	5.5 (-8.6, 20)	0.38
% received fluoroquinolones [10]*	3.7 (1.1, 6.4)	0.012
% received linezolid [10]*	1.2 (-3.9, 6.4)	0.55
% patients who had surgery [10]*	1.9 (-4.9, 8.7)	0.65

*per 10 unit change

Favorable outcomes, stratified on FQ use



Lancet 2010; 375: 1798–807

Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study

Keertan Dheda, Karen Shean*, Alimuddin Zumla*, Motasim Badri*, Elizabeth M Streicher, Liesl Page-Shipp, Paul Willcox, Melanie-Anne John, Gary Reubenson, Darshini Govindasamy, Michelle Wong, Xavier Padanilam, Alicia Dziwiecki, Paul D van Helden, Sweetness Siwendu, Julie Jarand, Colin N Menezes, Avril Burns, Thomas Victor, Robin Warren, Martin P Grobusch, Martie van der Walt*, Charlotte Kvasnovsky**

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p value*	Hazard ratio (95% CI)	p value
All patients (n=174)				
Isoniazid	0·20 (0·08–0·49)	<0·0001	0·76 (0·24–2·51)	0·68
Moxifloxacin	0·12 (0·02–0·89)	0·03	0·11 (0·01–0·82)	0·03
Ethambutol	1·87 (1·08–3·26)	0·03	1·49 (0·69–3·23)	0·31
Dapsone	2·19 (1·25–3·84)	0·006	1·79 (0·84–3·85)	0·13
Clofazamine	0·30 (0·11–0·82)	0·02	0·54 (0·14–2·08)	0·37
Clarithromycin	0·55 (0·32–0·94)	0·03	1·46 (0·61–3·52)	0·40
Terizidone	0·48 (0·27–0·84)	0·01	1·35 (0·71–2·55)	0·37
Number of drugs used	0·74 (0·61–0·88)	0·001	0·59 (0·45–0·78)	<0·0001
Previous treatment for multidrug-resistant tuberculosis	3·73 (1·69–8·22)	0·001	5·21 (1·93–14·1)	0·001
HIV-infected patients (n=82)				
Highly active antiretroviral therapy	0·31 (0·15–0·61)	0·001	0·38 (0·18–0·80)	0·01
Isoniazid	0·17 (0·05–0·56)	0·005	0·41 (0·06–2·96)	0·39
Moxifloxacin	13·00 (0·02–0·92)	0·006	0·08 (0·01–0·61)	0·02
Pyrazinamide	4·10 (1·00–17·50)	0·04	3·48 (0·74–16·50)	0·12
Clofazamine	0·21 (0·05–0·86)	0·03	1·37 (0·14–13·82)	0·79
Number of drugs used	0·74 (0·56–0·99)	0·04	0·87 (0·58–1·26)	0·43
Previous treatment for multidrug-resistant tuberculosis	7·46 (1·79–31·20)	0·006	4·50 (0·83–24·40)	0·08

*Wald test. Ofloxacin not included because it was significant in the χ^2 test (p=0·02), but not in the time-to-event analysis with Cox regression model (p>0·05).

Table 3: **Cox proportional hazards regression model of factors associated with risk of death in all patients given treatment for extensively drug-resistant tuberculosis, and in HIV-infected patients only**

Specific *gyrA* mutations

J Antimicrob Chemother 2012; **67**: 1088–1093
doi:10.1093/jac/dks033 Advance Access publication 22 February 2012

Journal of Antimicrobial Chemotherapy

gyrA mutations and phenotypic susceptibility levels to ofloxacin and moxifloxacin in clinical isolates of *Mycobacterium tuberculosis*

Frederick A. Sirgel[1]*, Robin M. Warren[1], Elizabeth M. Streicher[1], Thomas C. Victor[1], Paul D. van Helden[1] and Erik C. Böttger[2,3]

- Codons 94, 88 = higher level resistance
- Codons 90, 91, 89 = lower level resistance
- 96% of isolates with genetic alterations had MICs ≤ 2.0 ug/mL for moxifloxacin, within achievable serum levels

PLoS ONE | June 2012 | Volume 7 | Issue 6

New Insights into Fluoroquinolone Resistance in *Mycobacterium tuberculosis*: Functional Genetic Analysis of *gyrA* and *gyrB* Mutations

Seidu Malik[1], Melisa Willby[1], David Sikes[1], Oleg V. Tsodikov[2], James E. Posey[1]*

Table 2. MIC of *gyrA* transductants/mutants.

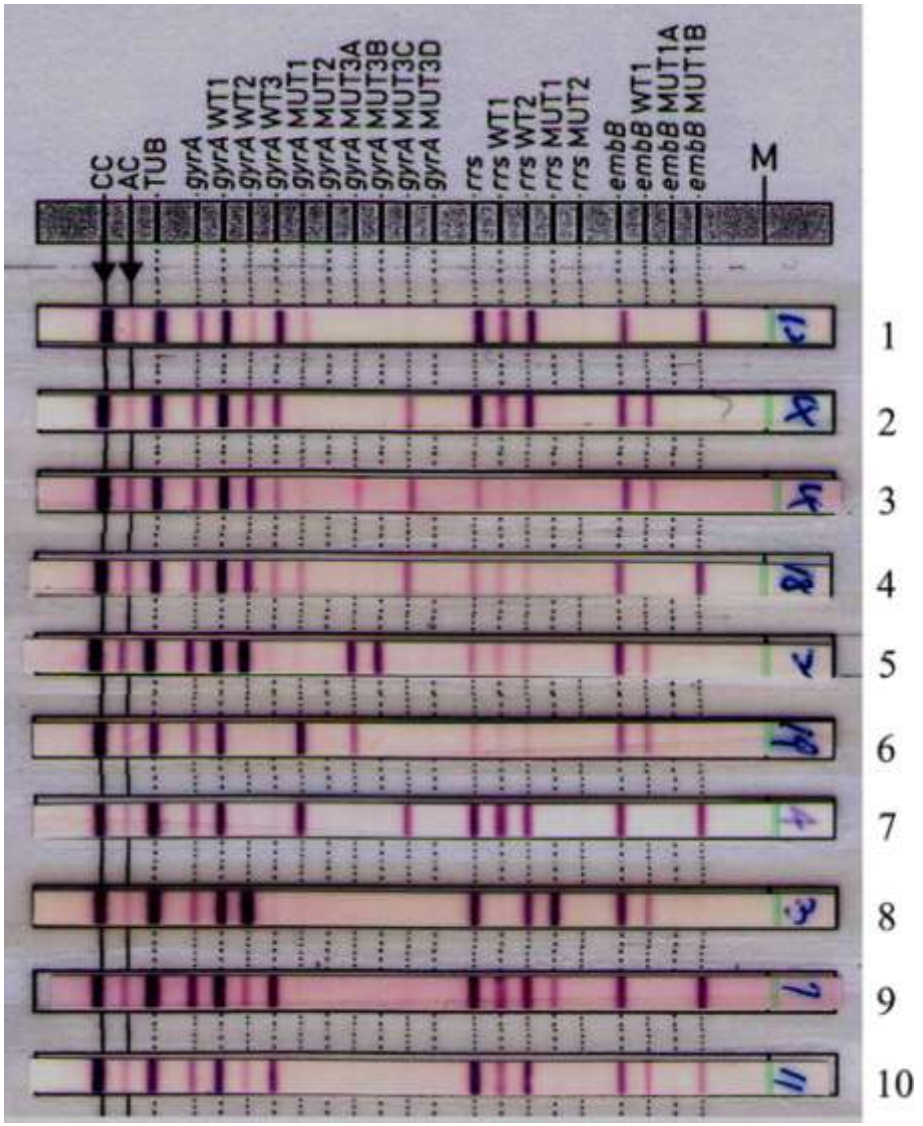
Strain	Background	Mutation	Range of MIC (μg/mL)			
			CIP	OFX	LVX	MXF
A1	H37Rv	WT	<0.25–0.5	0.5	<0.25	<0.25
A2	Erdman	WT	<0.25–0.5	0.5	<0.25	<0.25
A3	Erdman	A74S	1	1–2	1	0.5–**1**
A4	H37Rv	A74S+D94G	**16**	**16–32**	**16**	**4–16**
A5	H37Rv	T80A	0.5	<0.25	<0.25	<0.25
A6	Erdman	T80A	0.5	0.5	<0.25	<0.25
A7	H37Rv	T80A+A90G	<0.25	<0.25	<0.25	<0.25
A8	Erdman	T80A+A90G	<0.25	<0.25	<0.25	<0.25
A9	Erdman	A90G	<0.25	<0.25	<0.25	<0.25
A10	H37Rv	A90V	2–**4**	2–**4**	0.5–**2**	0.5–**1**
A11	Erdman	A90V	**4**	2–**8**	0.5–**4**	0.5–**1**
A12	CDC1551	D94G	**8**	**8**	**8**	**2**
A13	H37Rv	G247S	<0.25	0.5	<0.25	<0.25
A14	Erdman	G247S	0.5	0.5	<0.25	<0.25
A15	H37Rv	A384V	0.5	1	0.5	<0.25
A16	Erdman	A384V	1	1	0.5	<0.25

Table 3. MIC of *gyrB* transductants/mutants.

Strain	Back-ground	Mutation	Range of MIC (μg/mL)			
			CIP	OFX	LVX	MXF
B1	H37Rv	WT	<0.25–0.5	0.5	<0.25	<0.25–0.5
B2	Erdman	WT	<0.25–0.5	0.5	<0.25	<0.25–0.5
B3	Erdman	M330I	<0.25	0.5	<0.25	<0.25
B4	H37Rv	V340L	0.5	0.5	<0.25	<0.25
B5	Erdman	V340L	0.5	1	0.5	<0.25
B6	H37Rv	R485C	1	1	1	<0.25
B7	Erdman	R485C	1	1	1	<0.25–0.5
B10	H37Rv	D500A	0.5	2	1	<0.25–0.5
B11	Erdman	D500A	0.5	2	1	<0.25–0.5
B16	H37Rv	D533A	<0.25	0.5	<0.25	<0.25
B17	Erdman	D533A	0.5	1	<0.25	<0.25
B34	H37Rv	A543T	1	0.5–2	1	<0.25–0.5
B35	Erdman	A543T	1	1	1	<0.25–0.5
B36	H37Rv	A543V	0.5–1	1	0.5–1	0.5
B37	Erdman	A543V	1	2	1	0.5–1
B38	H37Rv	T546M	<0.25	0.5	<0.25	<0.25
B39	Erdman	T546M	<0.25	0.5	<0.25	<0.25
B26	H37Rv	T539N	1	2	1	<0.25–0.5
B27	Erdman	T539N	2	2	1	1
B28	H37Rv	T539P	1	0.5–1	0.5–1	0.5–1
B29	Erdman	T539P	1	0.5–1	0.5–1	0.5–1
B24	H37Rv	N538T+T546M	2	0.5	0.5	0.5–1
B25	Erdman	N538T+T546M	2	0.5	0.5	<0.25–1
B30	H37Rv	E540D	0.5	0.5	0.5	2–4
B31	Erdman	E540D	0.5–1	0.5–1	0.5	2
B22	H37Rv	N538K	2	2	1	1–2
B23	Erdman	N538K	2	2	1	1–2
B12	H37Rv	D500H	1–2	4–8	2–4	<0.25–0.5
B13	Erdman	D500H	1	4–8	2–4	0.5
B14	H37Rv	D500N	1	4	2	<0.25–0.5
B15	Erdman	D500N	2	4	2	0.5
B32	H37Rv	E540V	2	4	1–2	0.5–1
B33	Erdman	E540V	2–4	4	2	1
B8	H37Rv	R485C+T539N	2	4–8	2–4	2
B9	Erdman	R485C+T539N	4	8	4	4
B18	H37Rv	N538D	4	4	2	1
B19	Erdman	N538D	4	4	2	1
B20	H37Rv	N538D+T546M	4	2	2	1
B21	Erdman	N538D+T546M	8	4	2	1–2

Genotype MTBDRsl

- Second-line and ethambutol testing
- GyrA codons A90V, S91P, D94A, D94N/Y, D94G, D94H

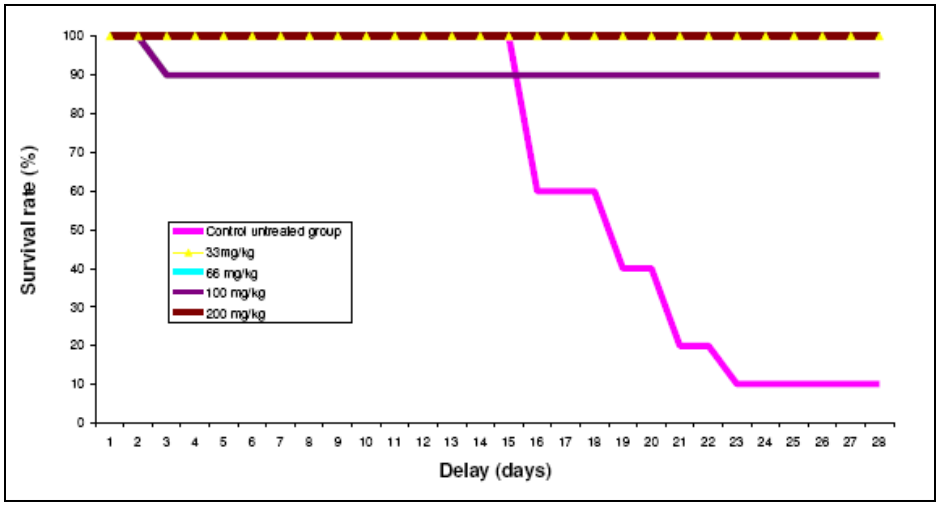


Murine model

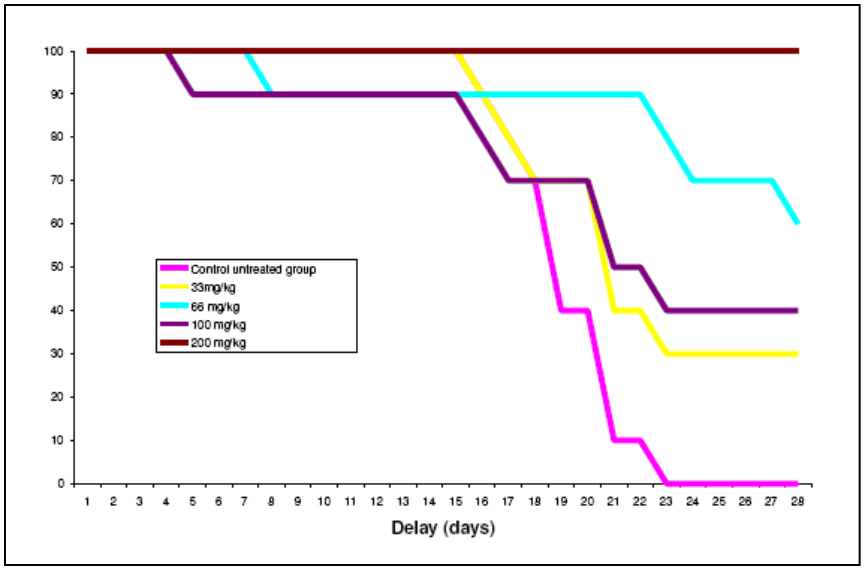
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2010, p. 4765–4771 Vol. 54, No. 11
0066-4804/10/$12.00 doi:10.1128/AAC.00968-10

Should Moxifloxacin Be Used for the Treatment of Extensively Drug-Resistant Tuberculosis? An Answer from a Murine Model▽

Julien Poissy,[1,4] Alexandra Aubry,[1,2,3] Christine Fernandez,[5] Marie-Catherine Lott,[5] Aurelie Chauffour,[1] Vincent Jarlier,[1,2,3] Robert Farinotti,[5] and Nicolas Veziris[1,2,3]*



GyrB D500N mutation

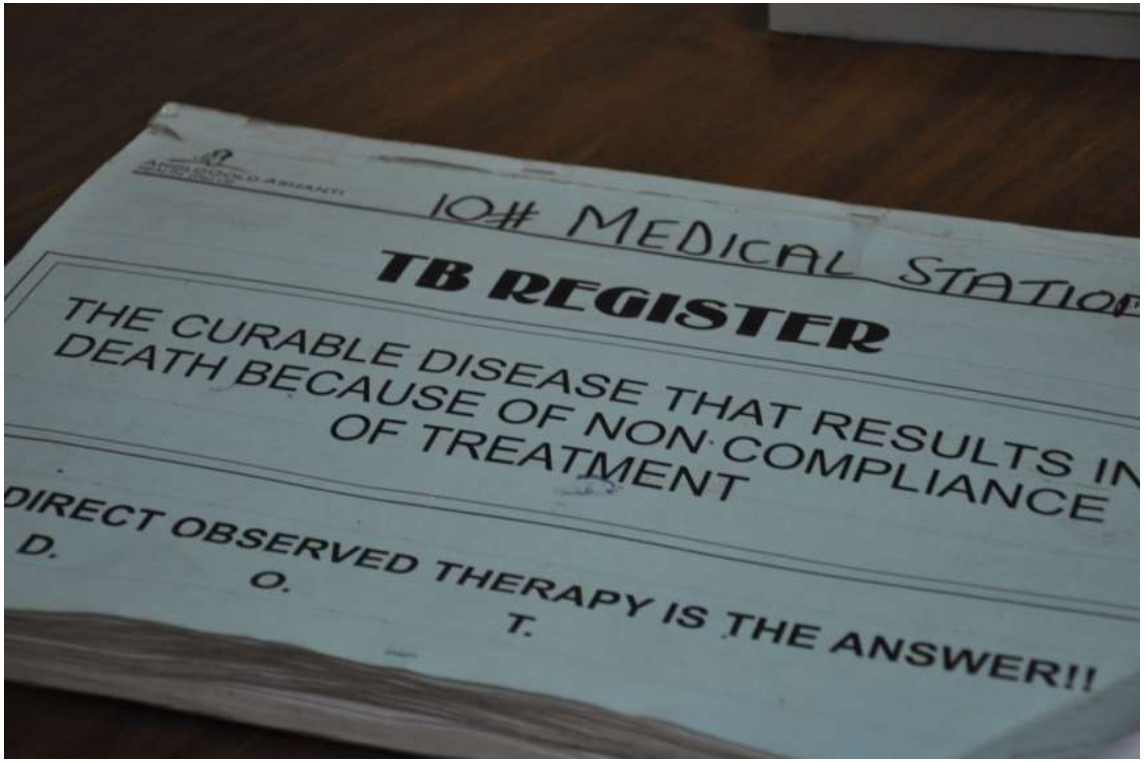


GyrA A90V mutation

Future

- Moxifloxacin in MDR and/or XDR regimens
- Should moxifloxacin doses be higher if MIC higher (current dose 400mg/day)
- Develop molecular test to diagnose fluoroquinolone resistance and distinguish early and later generation efficacy

Thank you


10# MEDICAL STATIO
TB REGISTER
THE CURABLE DISEASE THAT RESULTS IN
DEATH BECAUSE OF NON-COMPLIANCE
OF TREATMENT
DIRECT OBSERVED THERAPY IS THE ANSWER!!
D.
O.
T.