Treatment of MDR-TB
An Update on New (Shorter) Regimens

2006 2008 2011 2013 2014 2016

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Global Drug-resistant TB Initiative
Accelerating the response

National Jewish Health
Science Transforming Life

Conflict of Interest Disclosure

- Otsuka
  - Chair, Data Monitoring Committee for delamanid MDR-TB trials (closed)
  - Member, Safety Monitoring Committee for delamanid pediatric MDR-TB trials (open)
- Novartis
  - Chair, Data Monitoring Committee for clofazimine MDR-TB trial (closed)
- Johnson and Johnson
  - Member, Advisory Board, NTM

Treatment of MDR-TB
An Update on New Regimens

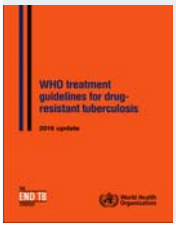
- Current WHO Treatment Recommendations

- Short(er) Course Regimens

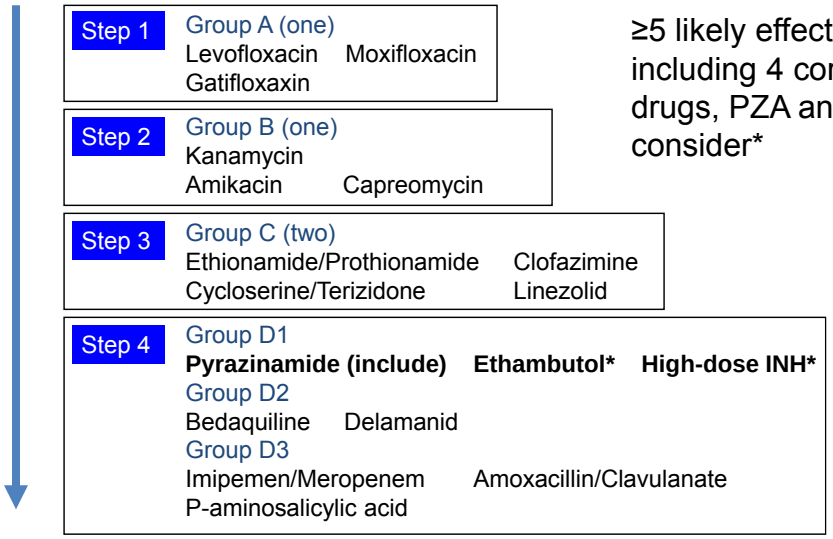
- Injectable Free Regimens

New Grouping of MDR-TB Drugs

Group A	Group B	Group C	Group D
Fluoroquinolone	**Second-line injectable**	**Other Core Second-line**	**Add-on agents**
Levofloxacin Moxifloxacin Gatifloxacin	Amikacin Capreomycin Kanamycin (Streptomycin)	Ethionamide/ Prothionamide Cycloserine/ Terizidone Clofazimine Linezolid	D1: Pyrazinamide Ethambutol High-dose INH D2: Bedaquiline Delamanid D3: P-aminosalicylic acid Imipenem/meropenem Amoxacillin/Clavulanate (Thioacetazone)



Building a Treatment Regimen with 2016 Update

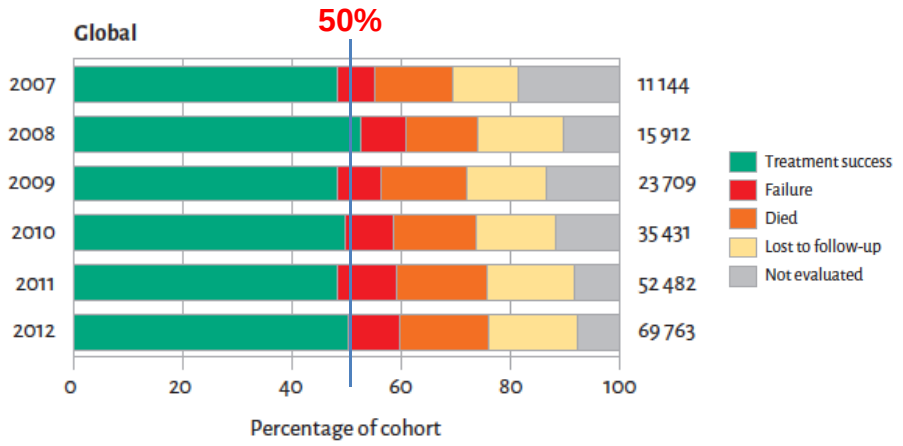


Treatment of MDR-TB
Duration of Therapy

- An intensive phase of **at least 8 mon**ths' duration is recommended
  (conditional recommendation, very low quality of evidence)
- A total treatment duration of **at least 20 months** is recommended in patients without any previous MDR-TB treatment
  (conditional recommendation, very low quality of evidence)

WHO 2011 Update

Treatment Outcomes in Patients with MDR-TB, 2007-2012 Cohorts



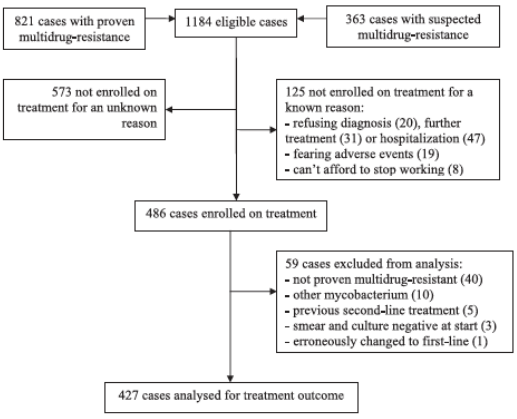
WHO, Global Tuberculosis Report 2015

Barriers to Implementation of Conventional MDR-TB

- Long duration of therapy
- Frequent drug-related adverse reactions
- Significant health resource burden
- High costs
- Suboptimal treatment outcomes with high default rates

Shorter Course Regimen
"Bangladesh Regimen"

- Observational study
- Previously untreated with SLD
- Serial introduction of regimens aimed at improving treatment success



Van Deun, et al. Am J Respir Crit Care Med 2010;182:684-692

Short Course Standardized Regimen for MDR-TB

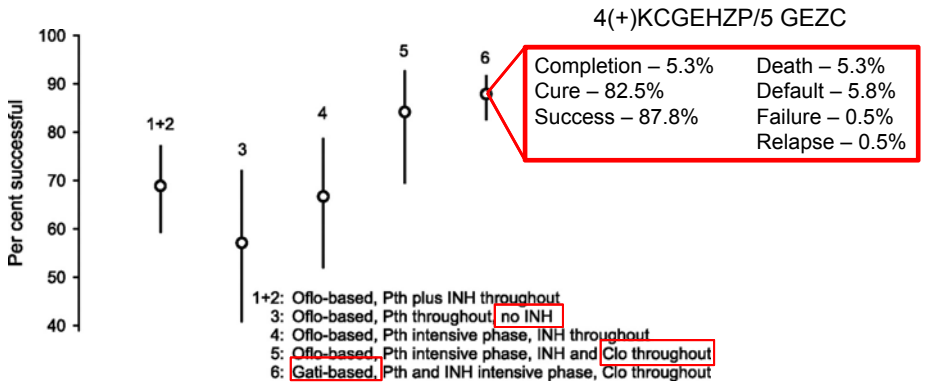
Regimen	Intensive	Continuation	Number	Cum. %	Treatment Success %
1	3KCOEHZP	12 OEHZP	59	13.8	68.9
2	3(+)KCOEHZP	12 OEHZP	44	10.3	
3	3(4)KCOEZP	12 OEZP	35	8.2	57.1
4	3(+)KCOEHZP	12 OHEZ	45	10.5	66.7
5	3(+)KCOEHZP	12 OHEZC	38	8.9	84.2
6	4(+)KCGEHZP	5 GEZC	206	48.2	87.8
			427	100.00	

C = clofazimine, E = ethambutol, G = gatifloxacin, H = isoniazid, K = kanamycin, O = ofloxacin, P = prothionamide, Z = pyrazinamide

3(4) = minimum of 3 mos, prolonged to 4 months if no conversion by end of 3 mos
3(+) = minimum of 3 mos, prolonged until conversion achieved
4(+) = minimum of 4 mos, prolonged until conversion achieved

Van Deun, et al. Am J Respir Crit Care Med 2010;182:684-692

Short Course Standardized Regimen for MDR-TB



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Shorter Course Treatment Regimen: A meta-analysis

	Bangladesh	Cameroon	Niger	Uzbekistan	Swaziland
Years	2005-2011	2008-2011	2008-2010	2013-2015	2014-2016
Exclusion criteria:					
Prior SLD	Excluded	Excluded	Excluded	Excluded	
XDR-TB		Excluded	Excluded	Excluded	Excluded
FQN Resist				Excluded	Excluded if moxi resist.
SLI Resist.				Excluded if dual R	Excluded if dual R
DOT	Daily	Daily	Daily	Daily	Daily
Social support	Yes	Yes	Yes	Yes	Yes
Included HIV	No	Yes (20%)	Yes (2%)	No	Yes (67%)

Ahmad Khan F, et al. Eur Respir J 2017; 50: 1700061

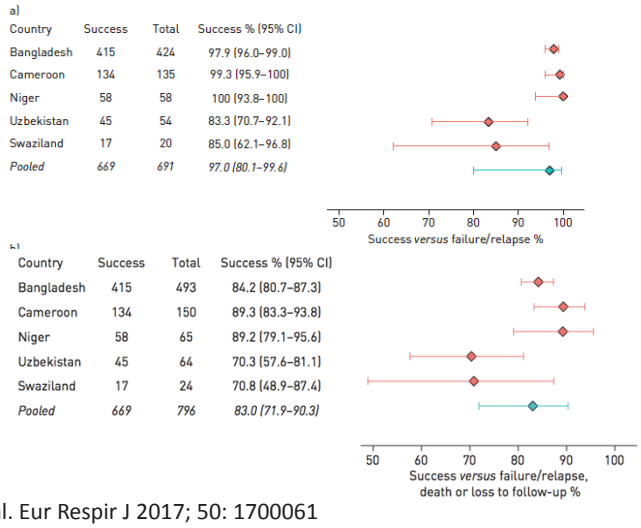
Shorter Course Treatment Regimen: A meta-analysis

	Bangladesh	Cameroon	Niger	Uzbekistan	Swaziland
Duration Intensive Continuation	 4(6) 5	 4(6) 8	 4(6) 8	 4(6) 5	 4(8) 5
SLD Inject	Kana	Kana	Kana	Capreo or Kana	Kana or amikacin
FQN used	Gati - high	Gati-usual	Gati-high	Moxi-usual	Moxi-usual
INH used	High	Usual	High	High	High
PTO	Intensive	Intensive	Intensive	Throughout	Throughout
Clofazimine	Throughout				

Ahmad Khan F, et al. Eur Respir J 2017; 50: 1700061

Treatment Outcomes

Success vs Failure/Relapse, Death, Lost to F/U



Ahmad Khan F, et al. Eur Respir J 2017; 50: 1700061

Risk Factors for Poor Treatment Outcomes

Risk Factor	OR (95% CI)
Failure/relapse vs success	
No culture conversion by 2 months	7 (3-20)
Use of moxi rather than gatifloxacin	9 (4-22)
Fluoroquinolone resistance	46 (8-273)
Pyrazinamide resistance	8 (2-38)
Death vs survival	
HIV infection	5 (2-17)
Lost to follow-up vs survival	
No culture conversion by 2 months	2 (1-5)

Ahmad Khan F, et al. Eur Respir J 2017; 50: 1700061

Treatment Success*
Shorter vs. Conventional Regimens

Resistance pattern	Shorter MDR-TB Regimen (N=1116)	Conventional MDR-TB Regimen (N = 5850)
All cases	**90.3%**	**78.3%**
PZA susceptible; FQN susceptible	96.8%	83.5%
PZA resistant; FQN susceptible	88.8%	81.4%
PZA susceptible; FQN resistant	80.0%	64.4%
PZA resistant; FQN resistant	67.9%	59.1%

Decreasing success

*Treatment success – cure or completed

WHO 2016 Update

PZA and Fluoroquinolone Resistance in Rifampin Resistant Strains

	Azerbaijan	Bangladesh	Belarus (Minsk)	Pakistan	South Africa (Gauteng)	South Africa (Kawazulu)
PZA	59.9	36.7	81.3	39.5	39.1	49.1
Ofloxacin (2.0 µg/ml)	25.0	16.0	30.7	21.8	12.3	18.3
Moxifloxacin (0.5 µg/ml)	17.9	12.2	26.8	13.8	8.4	12.2
Moxifloxacin (2.0 µg/ml)	2.0	3.2	9.2	1.4	3.8	0.0

Zignol M, et al. Lancet 2016;16:1185-1192

Cross Resistance Among Fluoroquinolones

Fluoroquinolone	No. Resistant Strains	No. Susceptible Strains	% Resistant Strains
Ofloxacin (2.0 µg/ml)	282	0	100%
Levofloxacin (1.5 µg/ml)	245	37	87%
Moxifloxacin (0.5 µg/ml)	203	79	72%
Moxifloxacin (2.0 µg/ml)	19	263	7%
Gatifloxacin (2.0 µg/ml)	7	275	2%

Programs should be testing the drug used in the regimen

Zignol M, et al. Lancet 2016;16:1185-1192

Treatment Outcomes
Shorter Course vs. Conventional

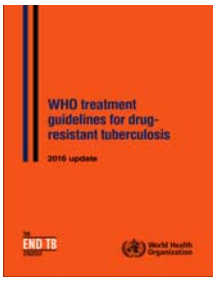
	Meta-analyses		
	Shorter regimens	Conventional regimens*	Programmatic data
Subjects, n	796	9153	86936
Treatment Success, %	83	54	52
Failure/relapse, %	3	8	9
Death, %	6	15	17
Lost to follow-up or no outcome data, %	5	23	22

*includes 603 patients treated with shorter course

Ahmad Khan F, et al. Eur Respir J 2017; 50: 1700061

WHO Policy Recommendation
Shorter Course MDR-TB Regimen

Recommendation:



In patients with RR or MDR-TB
- who have not been treated with second-line drugs *and*
- in whom resistance to FQNs and SLI agents has been excluded or is considered to be highly unlikely

a shorter MDR-TB regimen of 9-12 mos may be used instead of a conventional regimen

(conditional recommendation, very low certainty in the evidence)

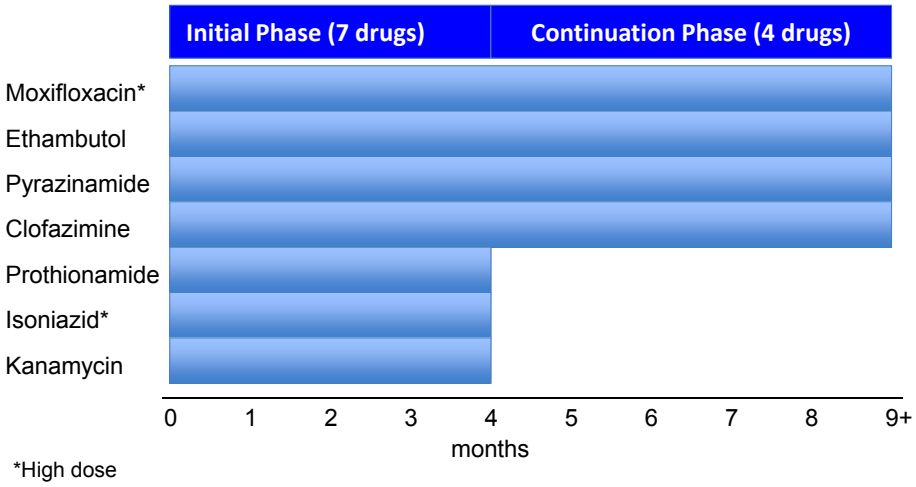
WHO 2016 Update

Choosing the MDR-TB Regimen

CRITERIA: Do any of the following apply ?

- ✓ Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- ✓ Exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for >1 month
- ✓ Intolerance to ≥1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- ✓ Pregnancy
- ✓ Extrapulmonary disease
- ✓ At least one medicine in the shorter MDR-TB regimen not available in the programme

Short(er) Course Regimen for MDR-TB



*High dose

Shorter Course MDR-TB Regimen
Implementation Considerations

- Patients should be tested for susceptibility to FQNs and SLI agents before starting the regimen
- WHO recommends that MTBDR*s*l be used as the initial direct test instead of phenotypic culture-based DST
- In settings in which laboratory capacity for DST to FQN and SLI agents is not yet available, treatment decisions would need to be based on likelihood of resistance
- Clofazimine and high-dose INH may be difficult to procure in some countries.
- Development of an active pharmacovigilance program

Shorter Course Regimen in 9 African Countries

- Prospective observational study in 9 African countries
- 1769 patients with RR-TB (316 not eligible, 426 did not start therapy) → 1027 (58%) enrolled
- Regimen:
  - Intensive phase – HD-INH, prothionamide, kanamycin, ND-moxifloxacin, ethambutol, pyrazinamide, clofazimine X 4(6) months
  - Continuation phase – ND-moxifloxacin, ethambutol, pyrazinamide, clofazimine X 5 months

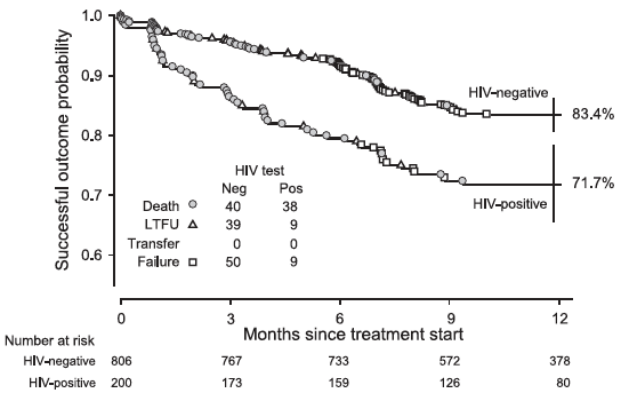
Trebucq A, et al. IUATLD 2018;22:17-25

Shorter Course Regimen in 9 African Countries: Treatment Outcomes

Treatment Outcomes	N (%)
Cured	728 (72.4%)
Completed	93 (9.2%)
Success (Cure + Completed)	81.6%
Failure	59 (5.9%)
Death	78 (7.8%)
Lost to follow-up	48 (4.8%)

Trebucq A, et al. IUATLD 2018;22:17-25

Treatment Success by HIV Status

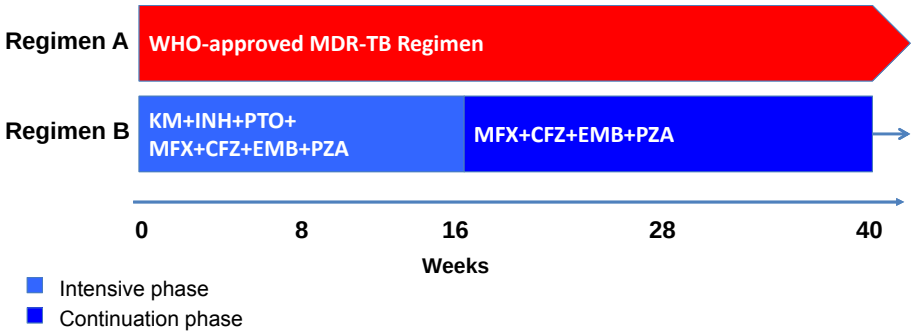


- Among those who survived, treatment success did not differ by HIV status (88.4 vs 88.9%)
- Proportion who died was similar whether or not they were on ART (18.6% vs. 19.0%)

Trebucq A, et al. IUATLD 2018;22:17-25

STREAM Trial

STREAM is a randomised controlled trial with a non-inferiority design



The 9-month Study Regimen

		Drug doses by weight group		
Drug	**Weeks**	**< 33 kg**	**33 - 50 kg**	**> 50 kg**
Kanamycin*	1 - 16	15 mg per kilogramme body weight		
Isoniazid (H)	1 - 16	300 mg	400 mg	600 mg
Prothionamide	1 - 16	250 mg	500 mg	750 mg
Clofazimine	1 - 40	50 mg	100 mg	100 mg
Moxifloxacin	1 - 40	400 mg	600 mg	800 mg
Ethambutol	1 - 40	800 mg	800 mg	1200 mg
Pyrazinamide	1 - 40	1000 mg	1500 mg	2000 mg

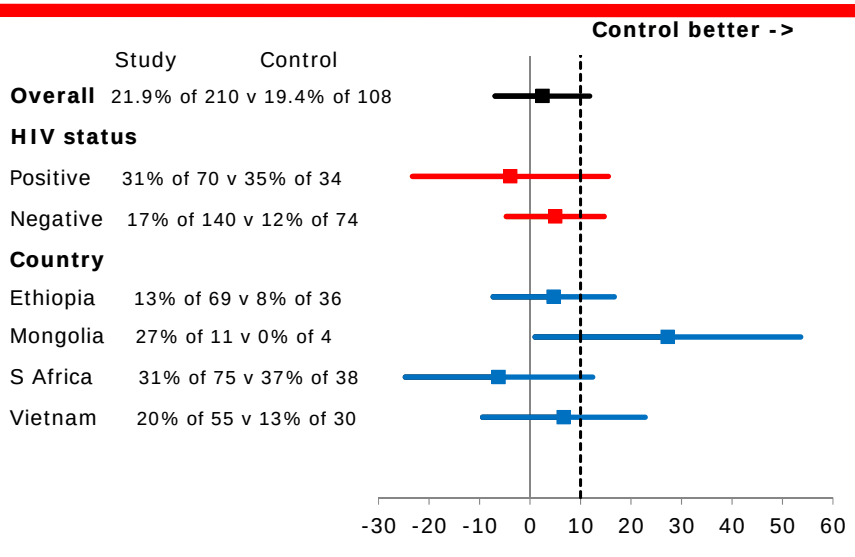
- Kanamycin 3 times/week after week 12

The intensive phase may be extended by 4 or 8 weeks if smear conversion has not occurred by 16 or 20 weeks

Primary Efficacy Result
Preliminary Results

	Study Arm		Control Arm	
	N	%	N	%
Total assessed	210	*100.0*	108	*100.0*
Favourable	164	*78.1*	87	*80.6*
Unfavourable	46	*21.9*	21	*19.4*
Difference in response (crude)	*2.5%*			
95% confidence interval	*-6.9%, 11.8%*			
Difference in response (standardised)	***2.1%***			
95% confidence interval	***-6.9%, 11.2%***			

Unfavourable Outcome by Subgroups
Preliminary Results



Summary and Conclusions: Efficacy

- Control regimen 80.6% favourable
- 9-month regimen 78.1% favourable
- Adjusted difference 2.1% (95% CI -6.9%, +11.2%), i.e. failed to formally demonstrate non-inferiority
- Control arm performed better than expected; likely to be due in part to choice of centers, patient selection and trial setting
- 9-month regimen performed well, similar to the cohorts, despite stricter criteria and longer follow-up

Why Use the Shorter Course Regimen?

- It is shorter duration!
  - 9-12 months vs. 20 months
- Good treatment outcomes
- Fewer lost to follow-up
  - 5% vs. 20%
- Less costly
  - $1000 USD vs. $2000 to $90,000 (drug costs)

How To Incorporate Underlying Drug Resistance in Shorter Course

Drug in Regimen	Resistance Present
INH	Use high dose
EMB	No correlation with outcome
PZA	Mixed findings
Moxi/Gati	Significantly lower success when high-level resistance
Prothionamide	No correlation with outcome
Clofazimine	Not studied
Kanamycin	No correlation but not enough resistant cases to date

Eligibility For Short-course Regimen for MDR-TB

Study	N	Sites	Eligible for Shorter Course Regimen
Lange C, 2016	612	Austria, France, Germany, Portugal, TBnet	8%
Dalcolmo M, 2017	6833	Brazil	≈ 50%
Balabanova Y, 2017	737	Latvia, Lithuania, Estonia, Bucharest city	4.0%
Sotgui G, 2017	348	8 European and 3 Latin American countries	4.0%
Van der Werf, 2017	1774	European Union	11%
Barry PM, 2017	180	California	15%

Adverse Events with Shorter Regimen

	No AE	Grade 1	Grade 2	Grade 3	Grade 4
Any type	11%	51%	28%	7%	4%
Gastrointestinal	43%	44%	13%	0%	0%
Hepatic	51%	34%	12%	3%	1%
Neurological	73%	21%	6%	0%	0%
Osteoarticular	82%	14%	4%	0%	0%
Renal	84%	13%	3%	0%	0%
Hearing loss	56%	30%	7%	5%	3%

Trebucq A, et al. Int J TB Lung Dis 2018;22:17-25

The devil we know: is the use of injectable agents for the treatment of MDR-TB justified?

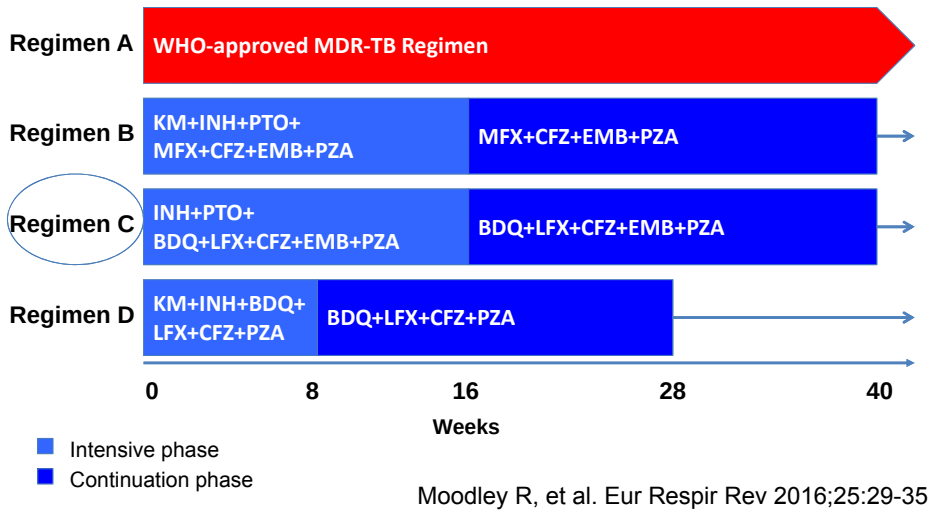
A. Reuter,* P. Tisile,† D. von Delft,† H. Cox,‡ V. Cox,§ L. Ditiu,¶ A. Garcia-Prats,# S. Koenig,** E. Lessem,†† R. Nathavitharana,‡‡ J. A. Seddon,§§ J. Stillo,¶¶ A. von Delft,†§ J. Furin**

- 2.6% to 61.5% of persons with MDR-TB treated with aminoglycosides have documented hearing loss
- Even with shorter course regimens (4 months of injectable), hearing loss as high as 44% has been reported
- Risk factors:
  - Most important is cumulative dose
  - Other possible RF include age, HIV infection, exposure to loud noises and genetic risks

We need injectable free regimens!

Reuter A, et al. IUATLD 2017;21:1114

STREAM Trial



Moodley R, et al. Eur Respir Rev 2016;25:29-35

Other Shorter Course Regimens

Injectable Free!

Clinical trial	Regimen	Completed
NiX-TB	Bdq, Pa, Lzd for 24-36 weeks	Yes
MDR END	Dlm, Lzd, Lfx, Z (36-52 weeks)	Ongoing
STREAM 2 regimen C	Bdq, Cfz, E, Z, Lfx, H, Pto (16 weeks); followed by Bdq, Cfz, E, Z, Lfx (24 weeks)	Ongoing
PRACTECAL regimen 1	Bdq, Pa, Lzd (36 weeks)	Ongoing
PRACTECAL regimen 2	Bdq, Pa, Lzd, Cfz (36 weeks)	Ongoing
PRACTECAL regimen 3	Bdq, Pa, Lzd, Mfx (36 weeks)	Ongoing
endTB regimen 1	Bdq, Lzd, Mfx, Z (36 weeks)	Ongoing
endTB regimen 2	Bdq, Cfz, Lzd, Lfx, Z (36 weeks)	Ongoing
endTB regimen 3	Bdq, Dlm, Lzd, Lfx, Z (36 weeks)	Ongoing
endTB regimen 4	Dlm, Cfz, Lzd, Lfx, Z (36 weeks)	Ongoing
endTB regimen 5	Dlm, Cfz, Mfx, Z (36 weeks)	Ongoing

Courtesy: KJ Seung

Summary

- The short(er) course regimen provides a novel means of treating MDR-TB at much lower cost
- Treatment outcomes are affected by baseline drug resistance patterns (FQN)
- Patients should be tested for susceptibility to FQNs and SLI agents before starting the regimen (?PZA)
- New drugs and drug regimens offer the promise of high cure rates in less time

Thank You!