WHO MDR-TB guideline, 2016 update

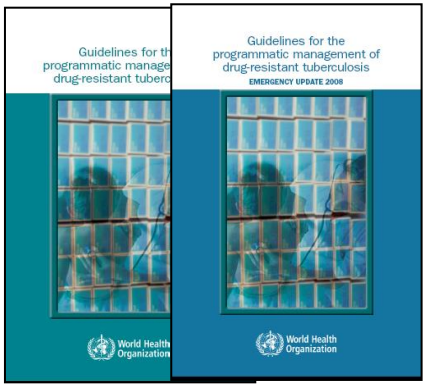
Pusan National University School of Medicine
Doosoo Jeon, M.D.

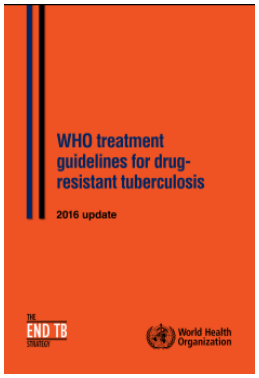




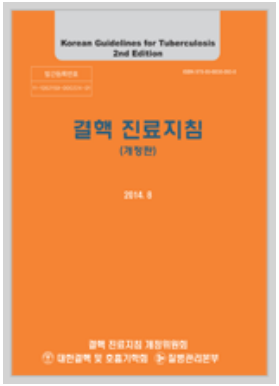
2006 2008 2011 2014 2016

WHO





Korea



2005 2011 2014

Brief summary of changes

Recommendation	2011	2016
Rapid diagnostics for rifampicin resistance	O	Updated
Composition of conventional MDR regimen	O	Updated
The shorter MDR regimen	X	New
Treatment of patients with RFP-R TB	X	New
Surgery as a part of MDR-TB treatment	X	New
Duration of conventional MDR regimen	O	No change
Role of new drug (BDQ, DLM)	O	No change

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New grouping of medicines recommended for the treatment of MDR-TB

A. Fluoroquinolones[2]		Levofloxacin Moxifloxacin Gatifloxacin
B. Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)[3]
C. Other core second-line agents[2]		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine
D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide Ethambutol High-dose isoniazid
	D2	Bedaquiline Delamanid
	D3	*p*-aminosalicylic acid Imipenem-cilastatin[4] Meropenem[4] Amoxicillin-clavulanate[4] (Thioacetazone)[5]

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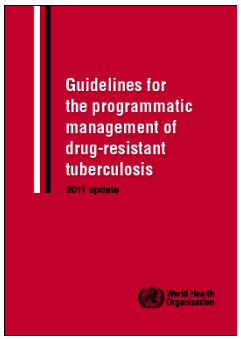
MDR-TB 치료 처방의 구성 원칙

1. 몇 가지 약제를 사용할 것인가?

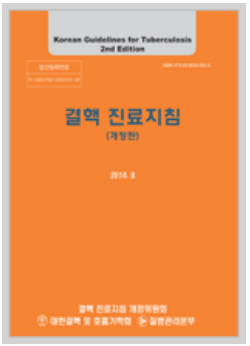
   집중 치료기 vs 유지 치료기

2. 어떤 순서로 약제를 선택할 것인가?

3. 치료 기간 : 주사제 사용 기간, 총 치료 기간



2011



2014

MDR-TB 진료 지침의 배경 연구

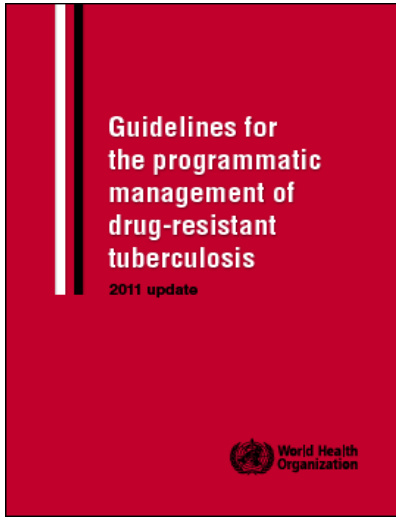
OPEN ACCESS Freely available online

PLOS | MEDICINE

Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9,153 Patients

the Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB*

Received September 27, 2011; **Accepted** July 17, 2012; **Published** August 28, 2012



- 3 systemic review
  - MDR-TB studies published after 1970
- 9153 individual patients from 23 countries

몇가지 약제를 사용할 것인가?

No of drugs, aOR for treatment success

	No prior history	Prior history
Intensive phase		
0-2	1.0	1.0
3	2.3	
4	**3.4**	1.4
5	2.6	**3.4**
6+	3.1	1.6
Continuation phase		
0-2	1.0	1.0
3	**5.5**	5.5
4	3.3	9.1
5+	4.6	**13.7**

개별 약제와 치료성공과의 관계

	aOR	95% CI
Group 1		
PZA	1.3	1.1 – 1.6
EMB	0.8	0.7 – 0.9
Group 3		
Later FQs		
vs no FQs	2.5	1.0 – 5.9
vs Ofx	1.9	1.0 – 3.6
Group 4		
PTH	1.9	1.6 – 2.2
CS	1.5	1.0 – 2.3
PAS	1.0	1.0 – 1.4
Group 5		
Any 1 drugs	0.7	0.6 – 0.8

약제 선택의 우선 순위 변화

Use any available
Group 1: First-line agents

↓

Plus one of these
Group 2: Injectable agents

↓

Plus one of these
Group3: Fluoroquinolones

↓

Pick one or more of
Group 4: 2nd-line oral agents
(우선 순위 없음)

↓

Consider use of these
Group 5: unknown efficacy

Choose one of these
Group 2: Injectable agents

+

Choose one of these
Group3: Fluoroquinolones

↓

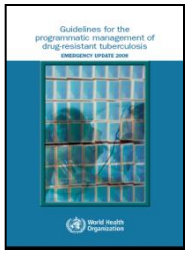
Add two or more of
Group 4: 2nd-line oral agents
(PTH > CS > PAS)

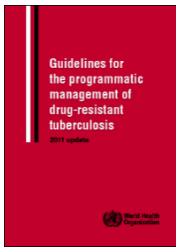
↓

Add if,
Group 1: First-line agents

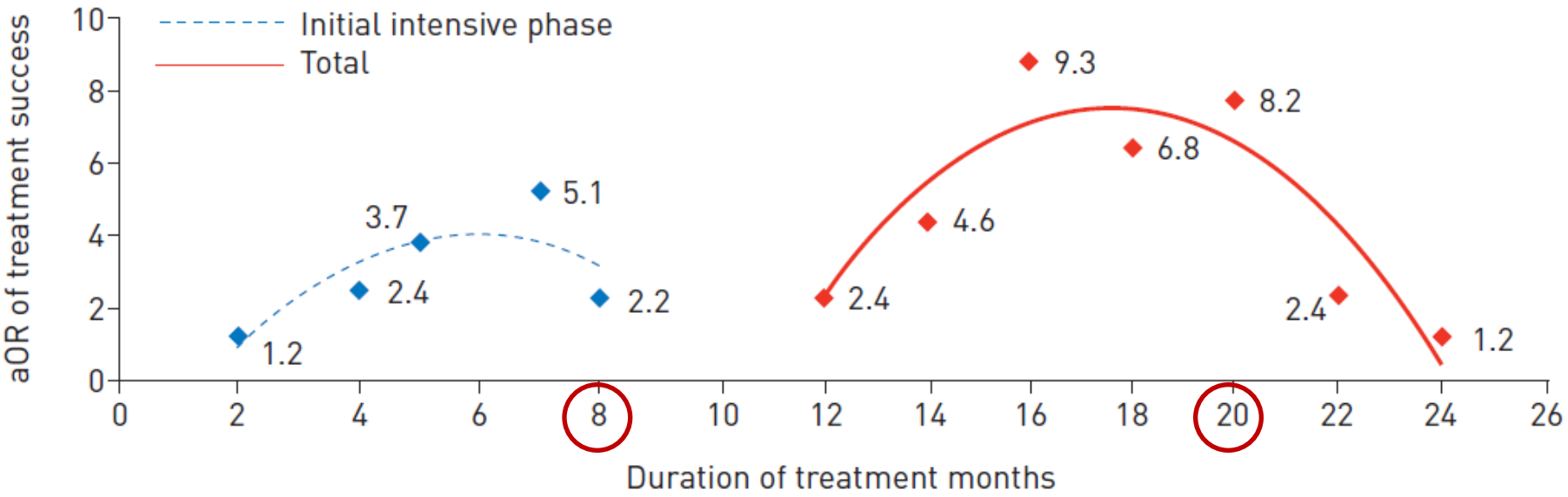
↓

Consider adding of these
Group 5: unknown efficacy





치료 기간 : 주사제, 총치료


aOR of treatment success
Initial intensive phase
Total
1.2
3.7
2.4
5.1
2.2
2.4
4.6
9.3
6.8
8.2
2.4
1.2
0
2
4
6
8
10
12
14
16
18
20
22
24
26
Duration of treatment months

WHO 2011, 국내 지침 2014

치료 처방 구성

집중치료기 : **효과적인 2차항결핵제**(주사제포함) **4가지**와 **피라진아미드**를 사용한다.

피라진아미드, 퀴놀론 1가지, 주사제 1가지, 프로치오나미드, 시클로세린으로 구성하며, 파스는 시클로세린을 사용할 수 없을 때 대체하여 사용할 수 있다.

치료 기간

최소 8개월간의 집중치료기를 권고한다.

과거 다제내성결핵 치료력이 없는 환자에서 총 치료기간은 최소 20개월을 권고한다.

- 집중 치료기: 4가지 약제면 충분한가?
- PZA 내성 : 처방에 포함하는 것이 타당한가?
  다른 약제를 추가해야 하는가?
- 약제를 선택하는 순서는 유효한가?

Recommendation 1

Conventional MDR regimen for adults and children

2a) In patients with rifampicin-resistant or multidrug-resistant TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second line TB medicines - one chosen from group A, one from group B, and at least two from group C2. *If the minimum of effective TB medicines cannot be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total to five.*

2b) In patients with rifampicin-resistant or multidrug-resistant TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol.

WHO. WHO Treatment guidelines for DR-TB 2016 Update

PZA 사용에 대한 권고

WHO 2011	Korea 2014
The intensive phase of MDR-TB treatment should consist of at least four second-line anti-TB drugs that are likely to be effective, as well as pyrazinamide	
DST to pyrazinamide is not reliable and for this reason it is considered an acceptable practice to use pyrazinamide in a regimen even when a laboratory result demonstrates resistance.	약제감수성검사 결과에 관계없이 피라진아미드 사용을 권고하는 타당성에 대해선 추후 연구를 통한 재평가가 필요하다.
Pyrazinamide is routinely added to MDR regimens unless there is a reasonable clinical contraindication for its use (hepatotoxicity or other serious adverse effect).	

PZA 내성: 유병률, 신뢰도

- Systemic review & meta-analysis
- Prevalence of PZA resistance

  MDR-TB: 51% (31-89), nonMDR-TB: 5% (0-9)

	N of R	N of S	Sens	Spec	*p* value*
pncA mutation	715	877	92%	93%	0.07
Pyrazinamidase	912	1,802	91%	97%	0.03

Reference assay: phenotypic DST using MGIT or BACTEC
*; Funnel plot asymmetry

Chang KC, et al. Antimicrob Agents Chemother 2011;55:4499

PZA 내성: impact on outcome

- Individual Patient Data Meta-analysis (n=8,955)
- aOR of treatment success, if susceptible to the drug used

Drug Used	Adjusted OR (95% CI)[a]
Pyrazinamide	**1.9 (1.3–2.9)**
Ethambutol	**1.7 (1.2–2.4)**
Streptomycin[b]	**1.7 (1.0–3.0)**
Kanamycin or amikacin[b]	**3.4 (1.7–6.9)**
Capreomycin[b]	**2.4 (1.4–4.0)**
Ofloxacin[b]	**4.6 (2.7–8.0)**
Levofloxacin and other later-generation quinolones[b]	**3.2 (1.6–6.7)**
Ethionamide or prothionamide	**2.3 (1.8–3.0)**
Cycloserine	**2.2 (1.5–3.3)**
PAS	**2.0 (1.3–3.1)**

Bastos ML et al. Clin Infect Dis 2014; 59:1364

4가지 약제면 충분한가?

- Retrospective cohort study, 1999–2002, Peru, n=623
- Regimen composition and time to death

Regimen	aHR
5 likely effective drug (± PZA-likely effective)	reference
4 likely effective drug (PZA- not likely effective)	2.76 (0.92-8.27)
4 likely effective drug	2.87 (1.35-6.09)
< 4 likely effective drug	3.36 (1.43-7.85)
≥ 6 likely effective drug	1.20 (0.32-4.45)

Franke MF et al. Ann Am Thorac Soc 2015;12:674

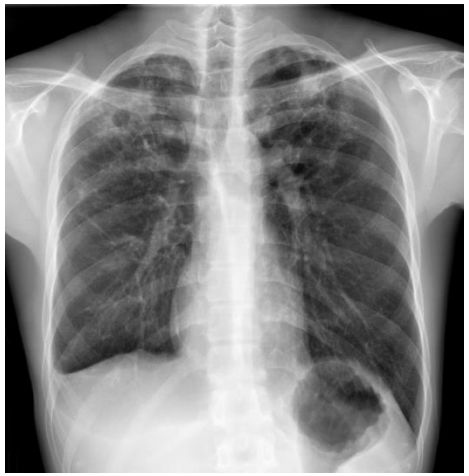
PZA 사용에 대한 권고 변화

WHO 2014	WHO 2016
The intensive phase of MDR-TB treatment should consist of at least four second-line anti-TB drugs that are likely to be effective, as well as pyrazinamide	A regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines
DST to pyrazinamide is not reliable and for this reason it is considered an acceptable practice to use pyrazinamide in a regimen even when a laboratory result demonstrates resistance.	Pyrazinamide is added routinely unless there is confirmed resistance from reliable DST, or well-founded reasons to believe that the strain is resistant, or risk of significant toxicity.
Pyrazinamide is routinely added to MDR regimens unless there is a reasonable clinical contraindication for its use (hepatotoxicity or other serious adverse effect).	If pyrazinamide is compromised or cannot be used, the regimen may be strengthened with an additional agent from group C or D (preferably D2, or if not possible, from D3).

집중 치료기 처방의 변화

WHO 2011	WHO 2016
▪ **4가지 2차 항결핵제 + PZA**	**5가지 효과적인 결핵약제** : 4 core 2nd-line agents + PZA
▪ 약제 선택 순서 주사제 – FQ – PTH - CS/PAS (추가) Group 5	FQ – 주사제 – PTH – CS – (LZD-CFZ) (추가) Group D2 (BDQ/DLM) -> D3
PZA 내성일 때 - 처방에 정규적으로 포함해야	- 처방에서 제외할 수 있음
PZA를 사용할 수 없을 경우 - 약제 추가에 대한 언급이 없음	- 약제를 추가한다. group C or D (D2 -> D3).

실제 처방 구성에서 어떤 변화가 있을까?



DST			
INH	**R**	**OFX**	**R**
RFP	**R**	**LFX**	**R**
EMB	**R**	**MFX**	**R**
PZA	**R**	PTH	S
SM	S	CS	S
KM	S	PAS	S

WHO 2011

KM-~~LFX(MFX)~~-PTH-CS-PZA

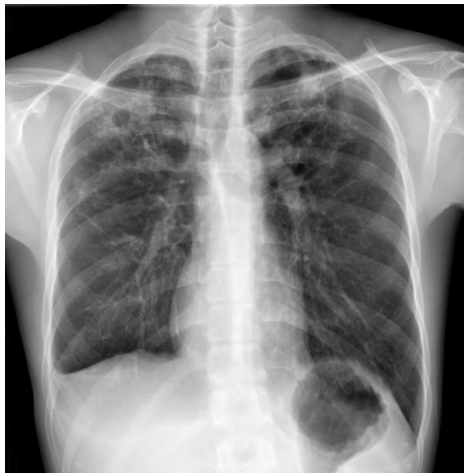
Add) PAS? BDQ/DLM? LZD?

WHO 2016

~~LFX(MFX)~~-KM-PTH-CS-~~PZA~~

Group C	LZD
	CFZ
Group D2	DLM/BDQ
Group D3	PAS
	IMP,MRP
	AMX/CLA

실제 처방 구성에서 어떤 변화가 있을까?



DST			
INH	**R**	OFX	S
RFP	**R**	LFX	S
EMB	**R**	MFX	S
PZA	**R**	PTH	S
SM	S	CS	S
KM	S	PAS	S

WHO 2011

KM-LFX(MFX)-PTH-CS-PZA

WHO 2016

LFX(MFX)-KM-PTH-CS-?

Group C	LZD
	CFZ
Group D2	DLM/BDQ
Group D3	PAS
	IMP,MRP
	AMX/CLA

Recommendation 2

Shorter MDR-TB regimen for adults & children

리팜핀 내성, 다제내성 결핵 환자 중

1) 과거 이차 항결핵제 치료력이 없고

2) 퀴놀론계 항생제와 주사제에 내성이 없는 환자에 대해

9-12개월의 shorter MDR-TB regimen을 conventional regimen 대신 사용할 수 있다. (conditional recommendation, very low certainty in the evidence).

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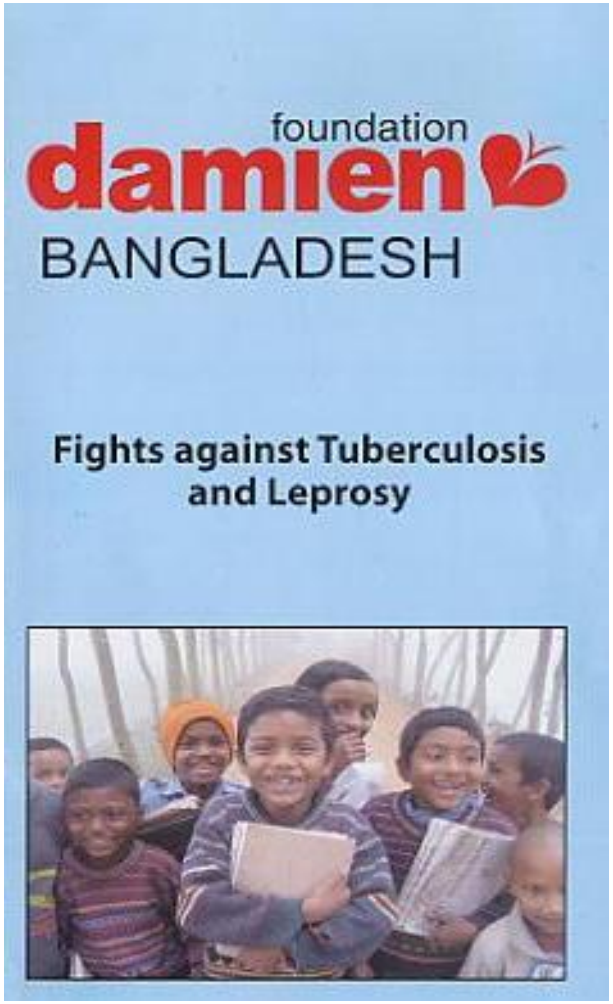
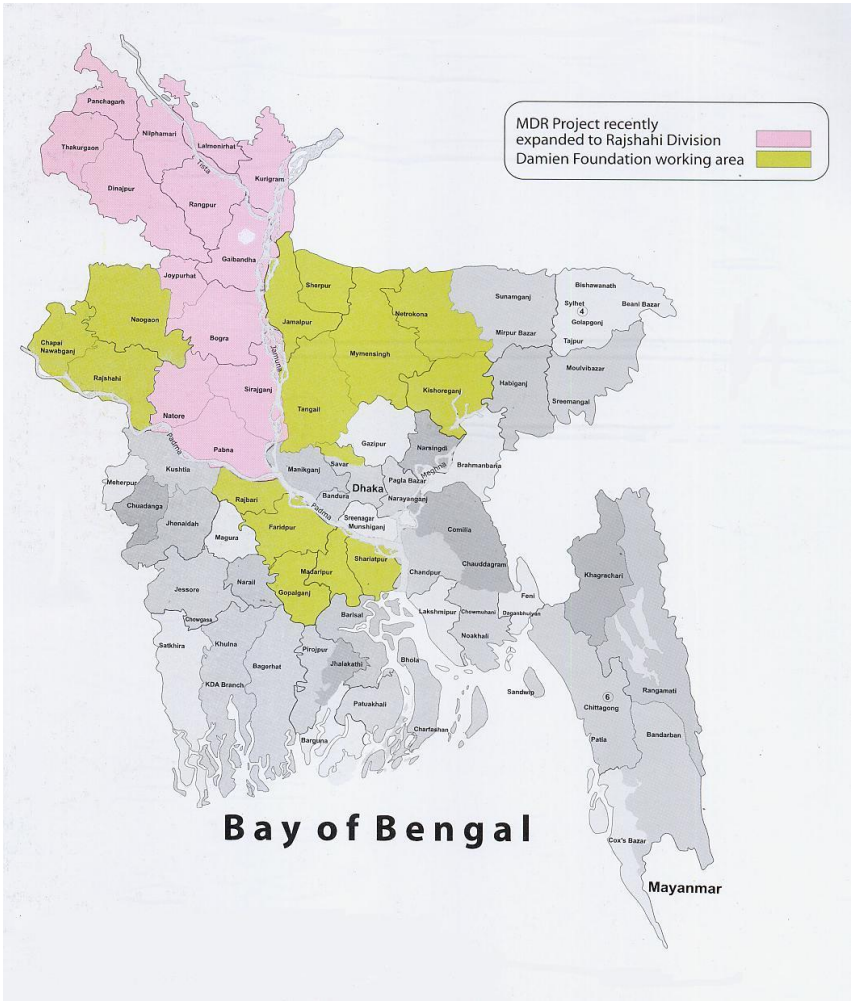
Story of the shorter regimen





Short, Highly Effective, and Inexpensive Standardized Treatment of Multidrug-resistant Tuberculosis

- Observational MDR-TB cohort study, Bangladesh, 1997-2007

Regimen	n	Intensive	Continuation	Success	Relapse
1	103	3 KCOEHZP	12 OEHZP	68.9%	0
2		3 KCOEHZP	12 OEHZP		
3	35	3 KCOEZP	12 OEZP	57.1%	0
4	45	3 KCOEHZP	12 OEHZ	66.7%	0
5	38	3 KCOEHZP	12 OEHZC	84.2%	0
6	206	4 KCGEHZP	5 GEZC	87.8%	0.5%

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

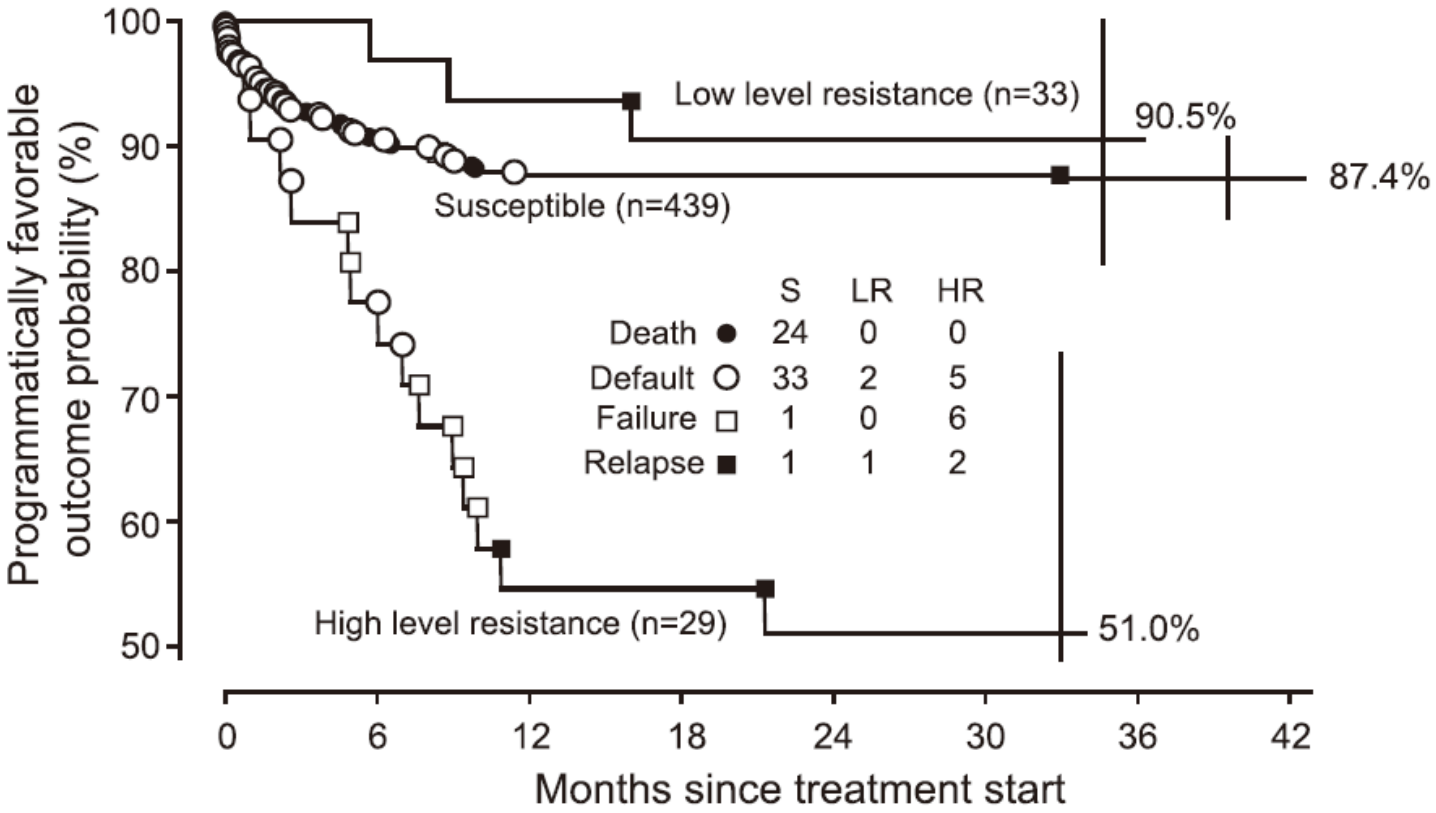
A parallel approach to assessing the effectiveness of the Bangladesh regimen

Cohort studies	Randomised trial
Cameroon Benin Niger Swaziland Afghanistan Uzbekistan	**STREAM stage 1** Sites: Ethiopia (2), South Africa (3), Vietnam and Mongolia 424 patients enrolled Enrolment closed: June 2015 Results expected: 2018

Cohort studies for the shorter treatment

	Bangladesh	Niger	Cameroon
	2005-11	2008-10	2008-11
No	515	65	150
Primary MDR	0.8%	1.5%	0.1%
HIV	0	1.8%	20%
Smear (+)	96.3%	83.1%	100%
R to PZA	41.3%	NA	NA
R to EMB	65.1%	69.2%	NA
outcomes			
Success	84.5%	89.2%	89.3%
Failure	1.4%	0	1%
Death	5.6%	10.3%	6.7%
Lost to FU	7.8%	1.5%	3.3%
Relapse	0.8% (n=4)	0	0

Predictor of poor outcome : FQ resistance



Aung KJ et al. Int J Tuberc Lung Dis 2014;18:1180

World Health Organization

THE SHORTER MDR-TB REGIMEN

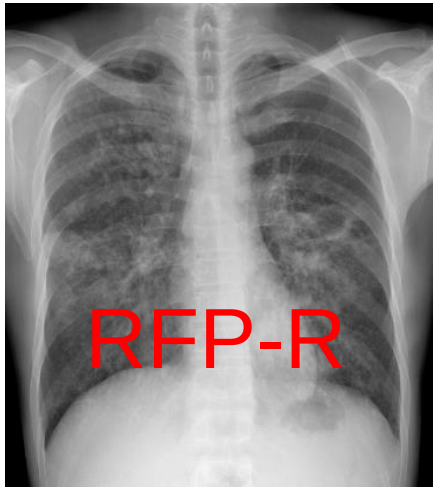
REGIMEN COMPOSITION

4-6 Km-Mfx-Pto-Cfz-Z-$H_{high\text{-}dose}$-E / 5 Mfx-Cfz-Z-E

Km=Kanamycin; Mfx=Moxifloxacin; Pto=Prothionamide;
Cfz=Clofazimine; Z=Pyrazinamide;
$H_{high\text{-}dose}$= high-dose Isoniazid; E=Ethambutol

#. Mfx : 800mg, > 50kg

How to choose the MDR-TB regimen?

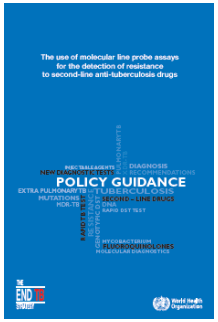


The shorter regimen

Uncomplicated MDR-TB
- FQ(S), SLID(S) ± PZA (S)
(X) 2nd-line drug therapy
(X) Pregnancy, EPTB

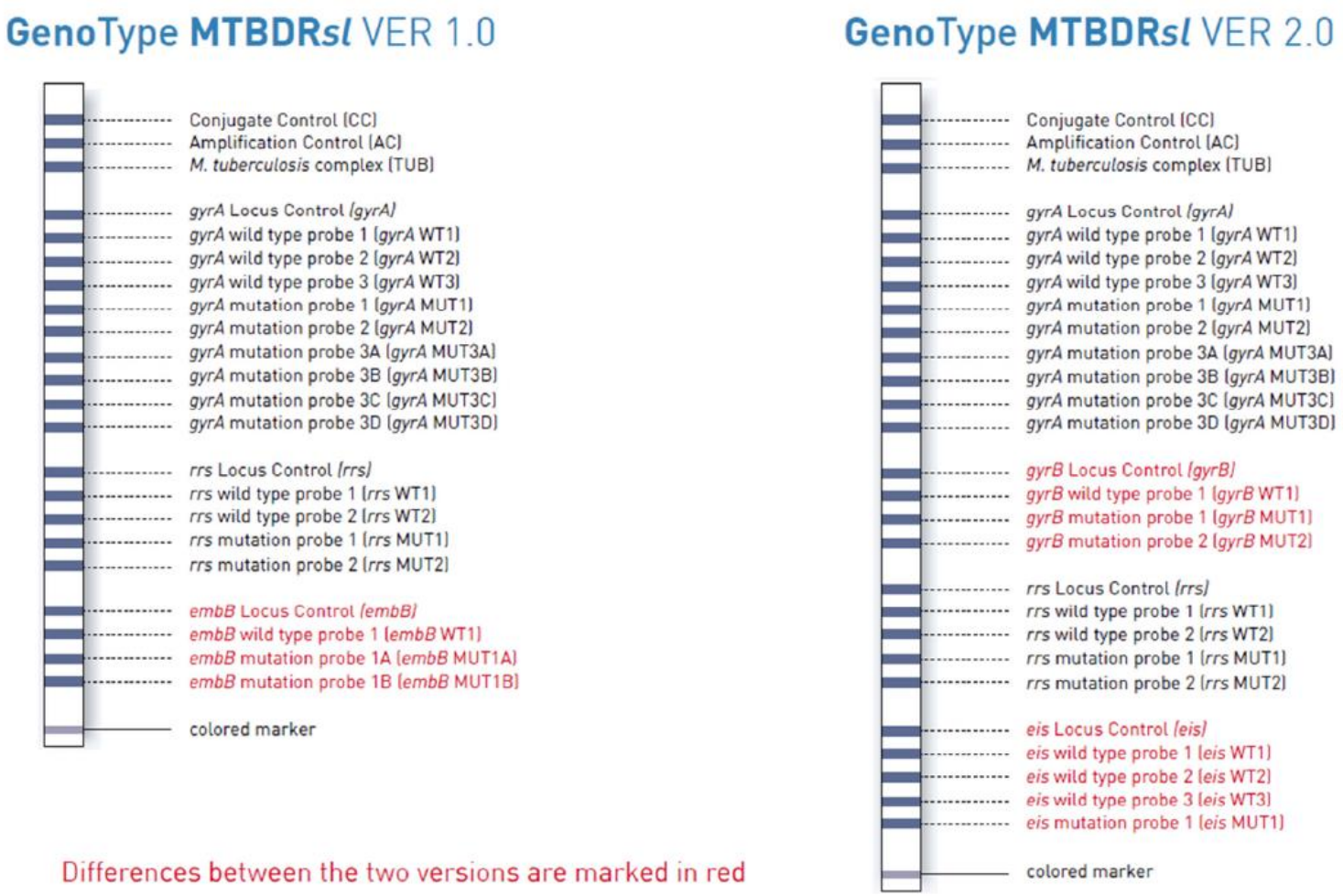
Conventional regimen

Uncomplicated MDR-TB
Pre-XDR/XDR TB



Genotype MTBDR*sl* assay

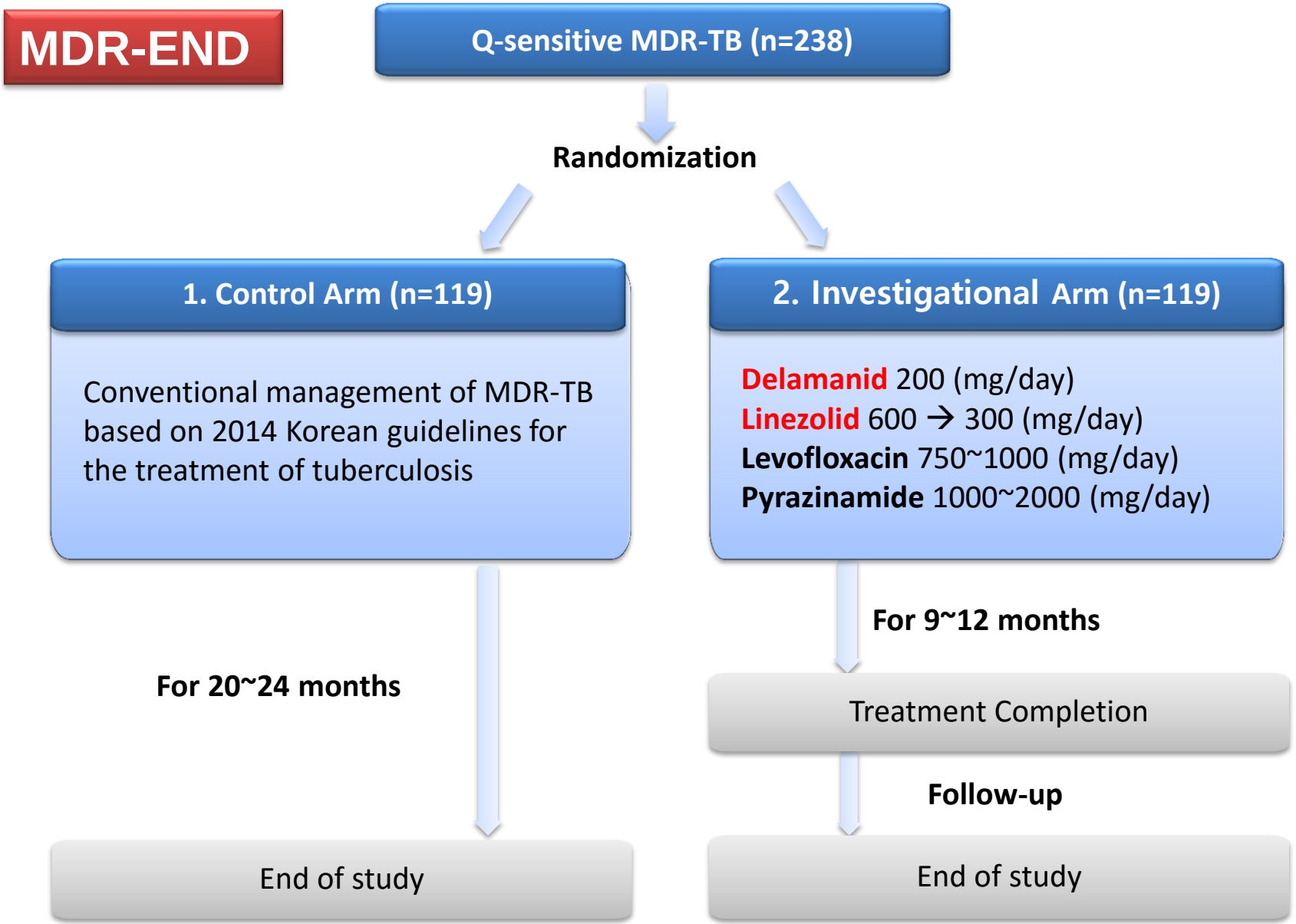
GenoType MTBDR*sl* assay



The shorter regimen in Korea
- feasibility and concern -

- High resistance to FQs and the injectable
- Safety & tolerability
- Adverse events of clofazimine
- Lack of DOT

23T+1Inj / day


MDR-END
Q-sensitive MDR-TB (n=238)
Randomization
1. Control Arm (n=119)
Conventional management of MDR-TB based on 2014 Korean guidelines for the treatment of tuberculosis
2. Investigational Arm (n=119)
Delamanid 200 (mg/day)
Linezolid 600 → 300 (mg/day)
Levofloxacin 750~1000 (mg/day)
Pyrazinamide 1000~2000 (mg/day)
For 20~24 months
For 9~12 months
Treatment Completion
Follow-up
End of study
End of study
Comparison of Treatment success rate at 24 months

Recommendation 3

The effect of time to start of treatment on treatment outcomes

Despite the absence of a discrete evidence base, it is reasonable to advise national programmes to adhere to the general standard of TB care which promotes an early start of appropriate therapy when RR-TB or MDR-TB are diagnosed or strongly suspected

Recommendation 4

The effect of surgical interventions on treatment outcomes

In patients with rifampicin-resistant or multidrug-resistant TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. (conditional recommendation, very low certainty in the evidence)

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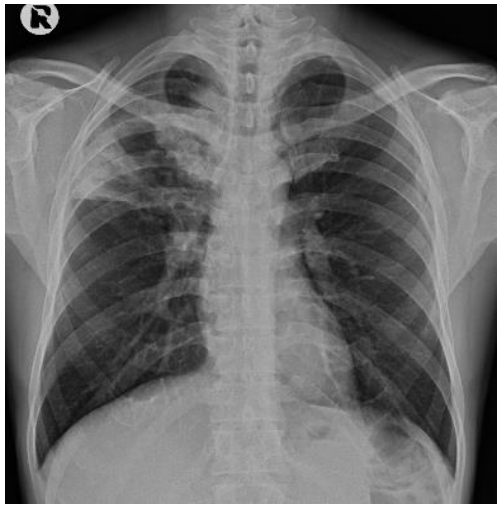
M/44. PTB (New case)

Initial

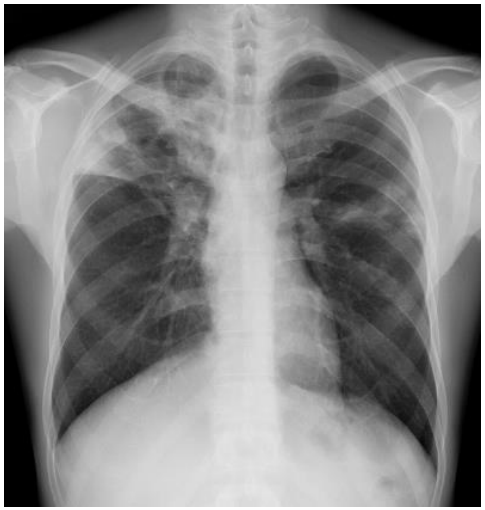


AFB 4+

HREZ

Rapid DST: HR에 내성

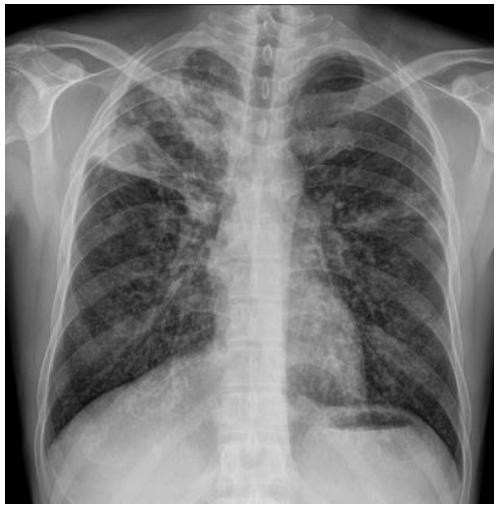
2 weeks



AFB 4+

Z-Amk-Mf-Pto-Cs

6 weeks



AFB 4+

DST			
INH	**R**	OFX	**R**
RFP	**R**	LFX	**R**
EMB	**R**	MFX	**R**
PZA	S	PTH	S
SM	S	CS	S
KM	**R**	PAS	**R**

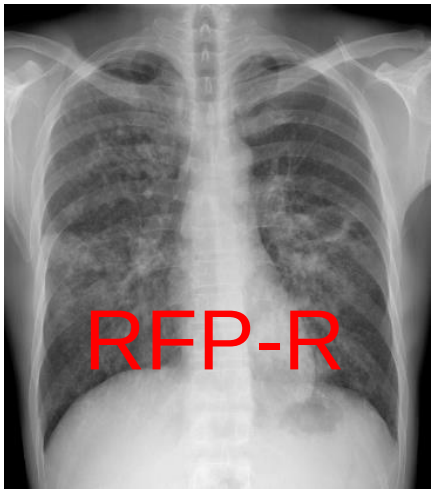
다제내성 결핵 환자의 약제 내성 패턴, 부울경, 2010-2014

	Resistance, n (%)				*p*	*P for trend*
	New	1st line	2nd line	Total		
no	216	125	37	378		
Ethambutol	146 (67.6)	73 (58.4)	22 (59.5)	241 (63.8)	0.196	0.128
Pyrazinamide	68 (31.5)	45 (36.0)	22 (59.5)	135 (35.7)	0.004	0.005
Streptomycin	78 (36.1)	33 (26.4)	11 (29.7)	122 (32.3)	0.174	0.139
Kanamycin	34 (15.7)	22 (17.6)	12 (32.4)	68 (18.0)	0.050	0.045
Amikacin	30 (13.9)	17 (13.6)	9 (24.3)	56 (14.8)	0.244	0.234
Ofloxacin	39 (18.1)	33 (26.4)	24 (64.9)	96 (25.4)	<0.001	<0.001
Levofloxacin	37 (17.1)	28 (22.4)	23 (62.2)	88 (23.3)	<0.001	<0.001
Moxifloxacin	30 (13.9)	24 (19.2)	22 (59.5)	76 (20.1)	<0.001	<0.001
Prothionamide	27 (12.5)	23 (18.4)	16 (43.2)	66 (17.5)	<0.001	<0.001
Cycloserine	10 (4.6)	12 (9.6)	5 (13.5)	27 (7.1)	0.050	0.024
PAS	70 (32.4)	35 (28.0)	14 (37.8)	119 (31.5)	0.489	1.000
Pre-XDR	37 (17.1)	21 (16.8)	20 (54.1)	78 (20.6)	<0.001	<0.001
XDR	20 (9.3)	18 (14.4)	9 (24.3)	47 (12.4)	0.031	0.010

- Unpublished data -

X-pert 검사만으로 충분한가?

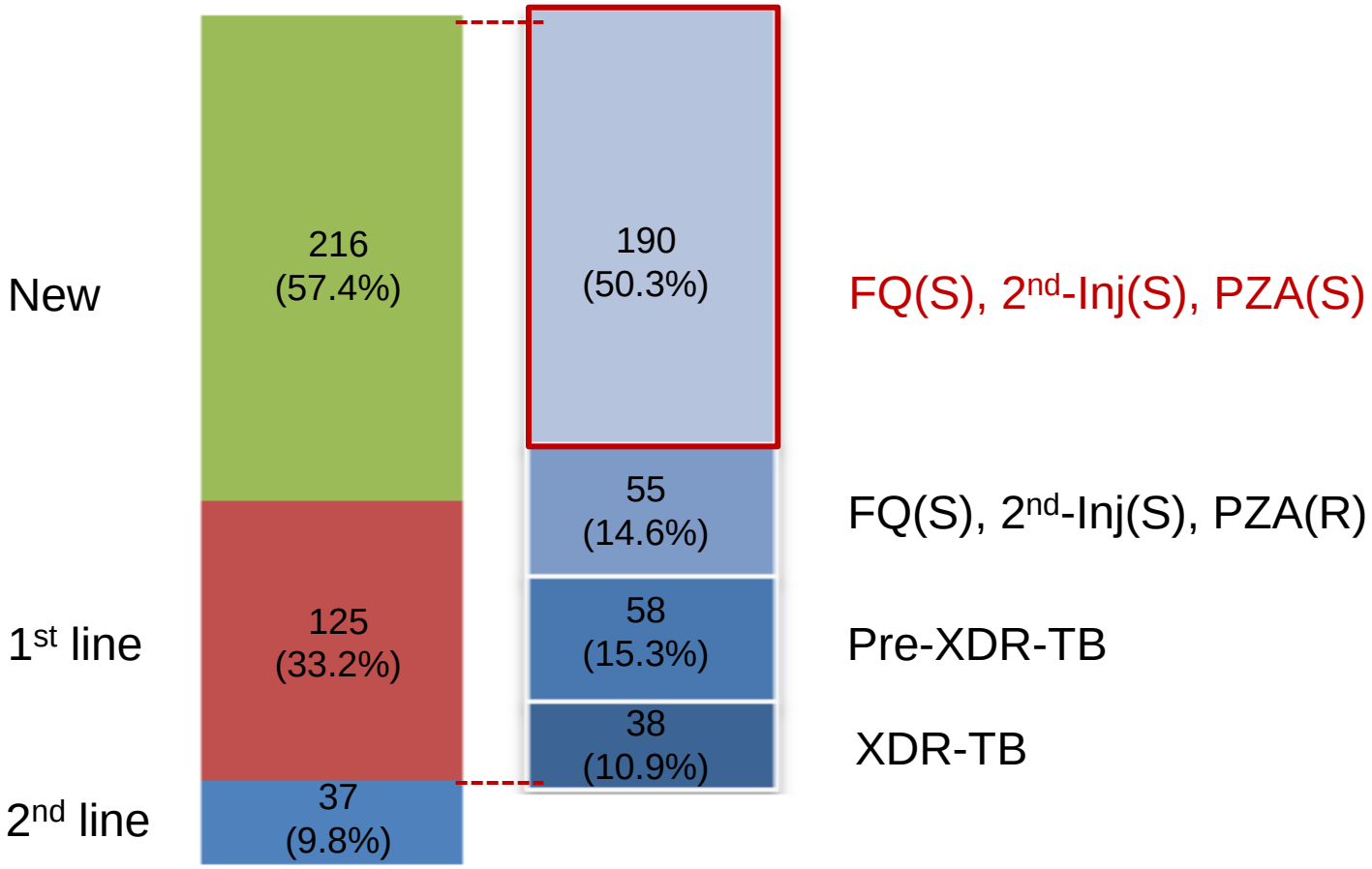
권고 처방: Km-Mf-Pto-Cs-PZA



Regimen composition	N (%)
5 likely effective	189 (50%)
4 likely effective	
R to PZA	52 (13.8%)
R to Pto/Cs	9 (2.4%)
Pre-XDR-TB	78 (20.6%)
R to FQ	52 (13.8%)
R to SLID	26 (6.9%)
XDR-TB	47 (12.4%)

- Unpublished data -

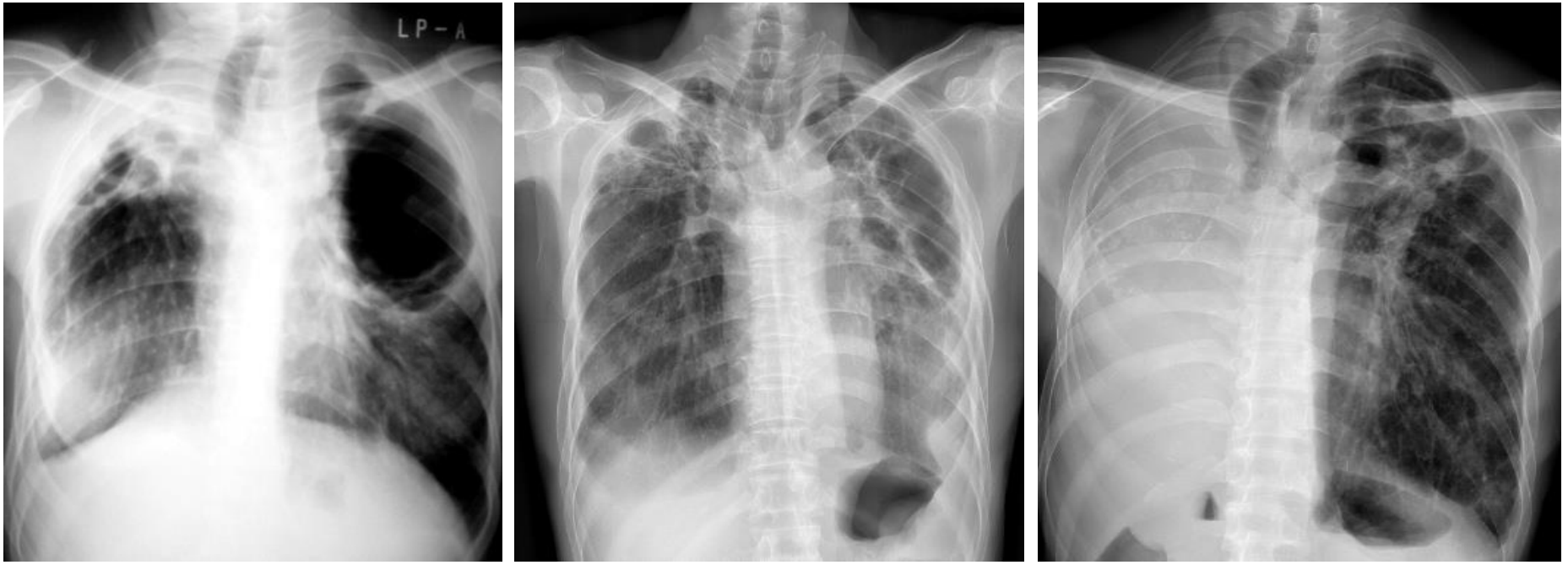
Shorter regimen은 가능한가?



Total 378 MDR-TB patients

- Unpublished data -

‘Cure’ 만으로 충분한가?



MDR-TB : 패러다임의 변화

- 신속한 진단
- 즉각적이고 효과적인 치료
- Repurposed drugs과 신약
- 개별화된 처방의 구성

완치, 그리고 삶의 질 개선