WHO의 MDR-TB 최신 치료지침 국내 적용의 문제점

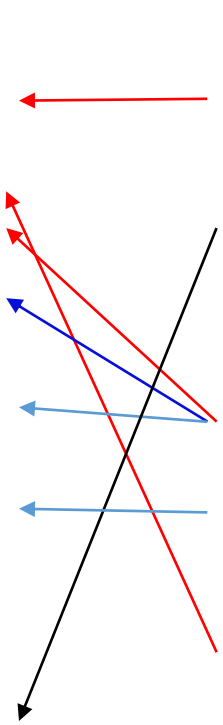
2018-11-09

연세대학교 의과대학 내과학교실

강영애

WHO Re-grouping of medicines

GROUP	MEDICINE	Abbreviation
Group A: Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: Add both medicines (unless they cannot be used)	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[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS



Group A. Fluoroquinolones[b]		Levofloxacin Moxifloxacin Gatifloxacin
Group B. Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)[c]
Group C. Other core second-line agents[b]		Ethionamide / prothionamide Cycloserine / terizidone Linezolid Clofazimine
Group 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[d] Meropenem[d] Amoxicillin-clavulanate[d] (Thioacetazone)[e]

WHO rapid communication 2018

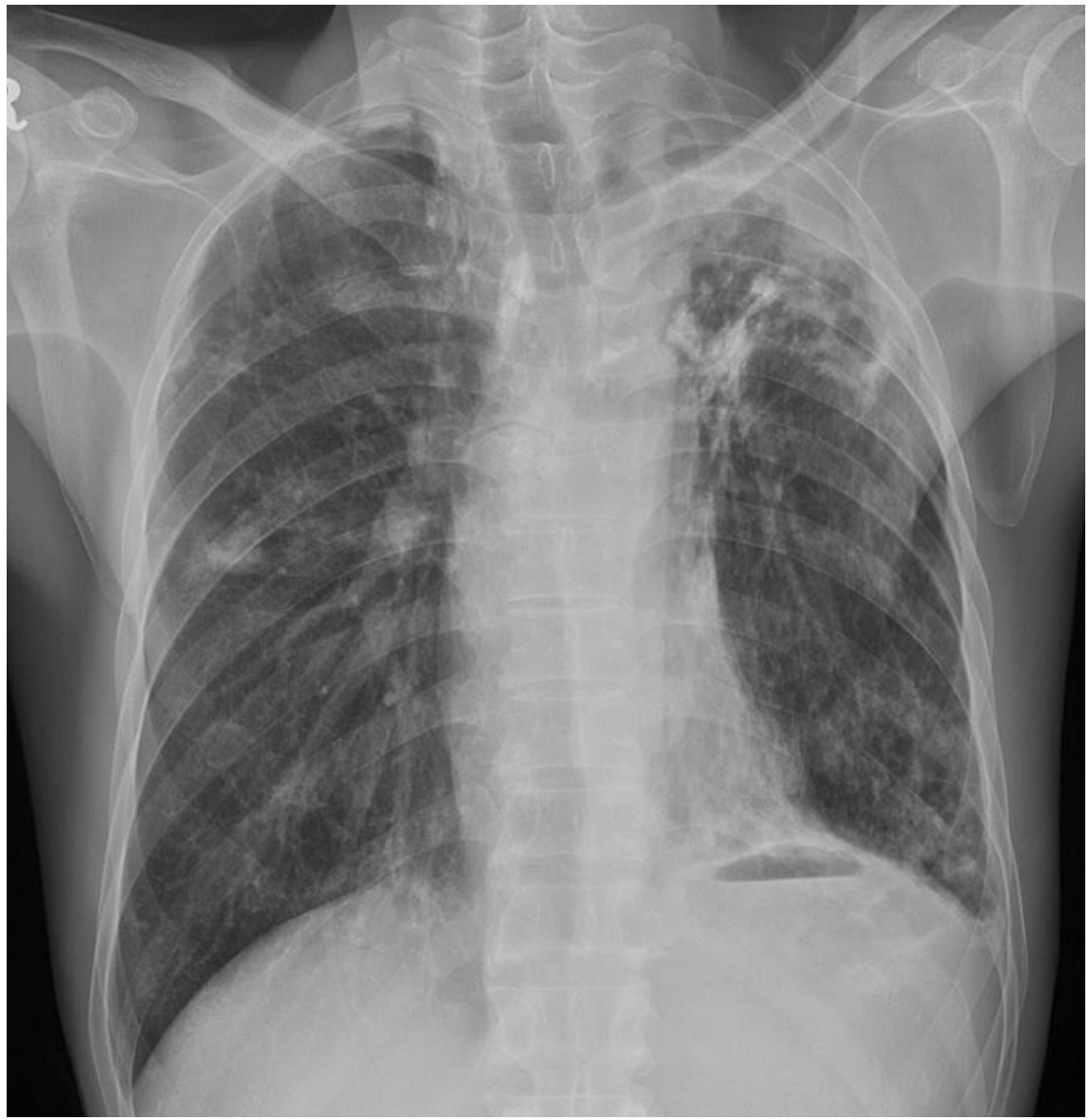
WHO 2018 rapid communication

- Evidence on the safety and effectiveness of BDQ beyond 6 months was insufficient.
- Optimal duration of use of Lzd is not established.
- Use for at least 6 months was shown to be highly effective, although toxicity may limit its use.
- The position of DLM will be re-assessed once individual patient data from trial 213 has been reviewed.
- Evidence on the safety and effectiveness of DLM beyond 6 months was insufficient.
- Evidence on concurrent use of BDQ and DLM was insufficient for review.
- Z is only counted as an effective agent when DST results confirm susceptibility.
- Amoxicillin-Clavulanic acid is administered with every dose of Imp-Cln or Mpm but is not counted as a separate agent and should not be used as a separate agent.
- Am and SM are only to be considered if DST results confirm susceptibility and high-quality audiology monitoring for hearing loss can be ensured. SM is to be considered only if Am cannot be used and if DST results confirm susceptibility (SM resistance is not detectable with 2nd line molecular line probe assays and phenotypic DST is required).

M/55

- 기침 , 가래 3개월
- 내원 일주일 전 객혈
- 20년전 결핵 치료력
- 20 PY smoker
- 자영업

- Sputum AFB smear 1+
- Xpert/MTB RIF : PCR +/Rif resistance +



Step 1 : Group A for all MDR TB_FQ

- Levofloxacin : Susceptible ?

- 7 University affiliated hospital
  Busan, Ulsan, Gyeongsangnam-do
- Jan 2010-Dec 2014
- 378 MDR TB (6.8%) / 5,599 culture positive TB

Drugs	No. (%) of resistant of patients				*P*	*P* for trend
	New	First-line drugs	Second-line drugs	Total		
Total No.	216	125	37	378		
RFB	146 (67.6)	90 (72.0)	28 (75.7)	264 (69.8)	0.513	0.242
EMB	146 (67.6)	73 (58.4)	22 (59.5)	241 (63.8)	0.196	0.128
PZA	68 (31.5)	45 (36.0)	22 (59.5)	135 (35.7)	0.004	0.005
SM	78 (36.1)	33 (26.4)	11 (29.7)	122 (32.3)	0.174	0.139
KM	34 (15.7)	22 (17.6)	12 (32.4)	68 (18.0)	0.050	0.045
CM	27 (12.5)	18 (14.4)	8 (21.6)	53 (14.0)	0.334	0.184
AMK	30 (13.9)	17 (13.6)	9 (24.3)	56 (14.8)	0.244	0.234
OFX	39 (18.1)	33 (26.4)	24 (64.9)	96 (25.4)	< 0.001	< 0.001
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MFX	30 (13.9)	24 (19.2)	22 (59.5)	76 (20.1)	< 0.001	< 0.001
PTH	27 (12.5)	23 (18.4)	16 (43.2)	66 (17.5)	< 0.001	< 0.001
CS	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
≥ 1 FQ	41 (19.0)	33 (26.4)	25 (67.6)	99 (26.2)	< 0.001	< 0.001
≥ 1 SLID	36 (16.7)	24 (19.2)	13 (35.1)	73 (19.3)	0.031	0.024
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

J Korean Med Sci 2017; 32: 636-641

Step 1 : Group A for all MDR TB_FQ

- Drug resistance patterns of MDR and XDR TB in Korea, 2009

Table 1. Drug resistance in multidrug-resistant tuberculosis patients by patient group (n=1,341)

Drugs	PHC new (n=154)	PHC retreatment (n=63)	Private sector (n=895)	DBC clinics (n=229)	*P* value*
	R% (95% CI)	R% (95% CI)	R% (95% CI)	R% (95% CI)	
Isoniazid†	75.3 (68.5, 82.1)	71.4 (60.3, 82.6)	81.5 (78.9, 84.0)	78.2 (72.8, 83.5)	0.379
Rifabutin	71.4 (64.3, 78.6)	84.1 (75.1, 93.2)	70.2 (67.2, 73.2)	72.1 (66.2, 77.9)	0.085
Streptomycin	34.4 (26.9, 41.9)	20.6 (10.6, 30.6)	32.6 (29.6, 35.7)	32.8 (26.7, 38.8)	0.121
Ethambutol	58.4 (50.7, 66.2)	55.6 (43.3, 67.8)	68.2 (65.1, 71.2)	68.1 (62.1, 74.2)	0.14
Pyrazinamide	42.2 (34.4, 50.0)	39.7 (27.6, 51.8)	51.3 (48.0, 54.6)	70.7 (64.8, 76.6)	<0.001
Kanamycin	10.4 (5.6, 15.2)	12.7 (5.5, 25.0)	17.7 (15.2, 20.2)	19.7 (14.5, 24.8)	0.227
Amikacin	9.1 (4.6, 13.6)	9.5 (3.5, 20.7)	14.9 (12.5, 17.2)	16.2 (11.4, 20.9)	0.299
Capreomycin	7.1 (3.1, 11.2)	6.3 (1.7, 16.3)	13.1 (10.9, 15.3)	16.6 (11.8, 21.4)	0.057
Ofloxacin	15.6 (9.9, 21.3)	14.3 (6.5, 27.1)	35.2 (32.1, 38.3)	61.1 (54.8, 67.4)	<0.001
Ethionamide	15.6 (9.9, 21.3)	15.9 (6.8, 24.9)	28.0 (25.1, 31.0)	43.7 (37.2, 50.1)	<0.001
Cycloserine	3.2 (1.1, 7.6)	4.8 (1.0, 13.9)	15.5 (13.2, 17.9)	26.6 (20.9, 32.4)	<0.001
PAS	14.9 (9.3, 20.6)	15.9 (6.8, 24.9)	27.2 (24.2, 30.1)	33.2 (27.1, 39.3)	0.004

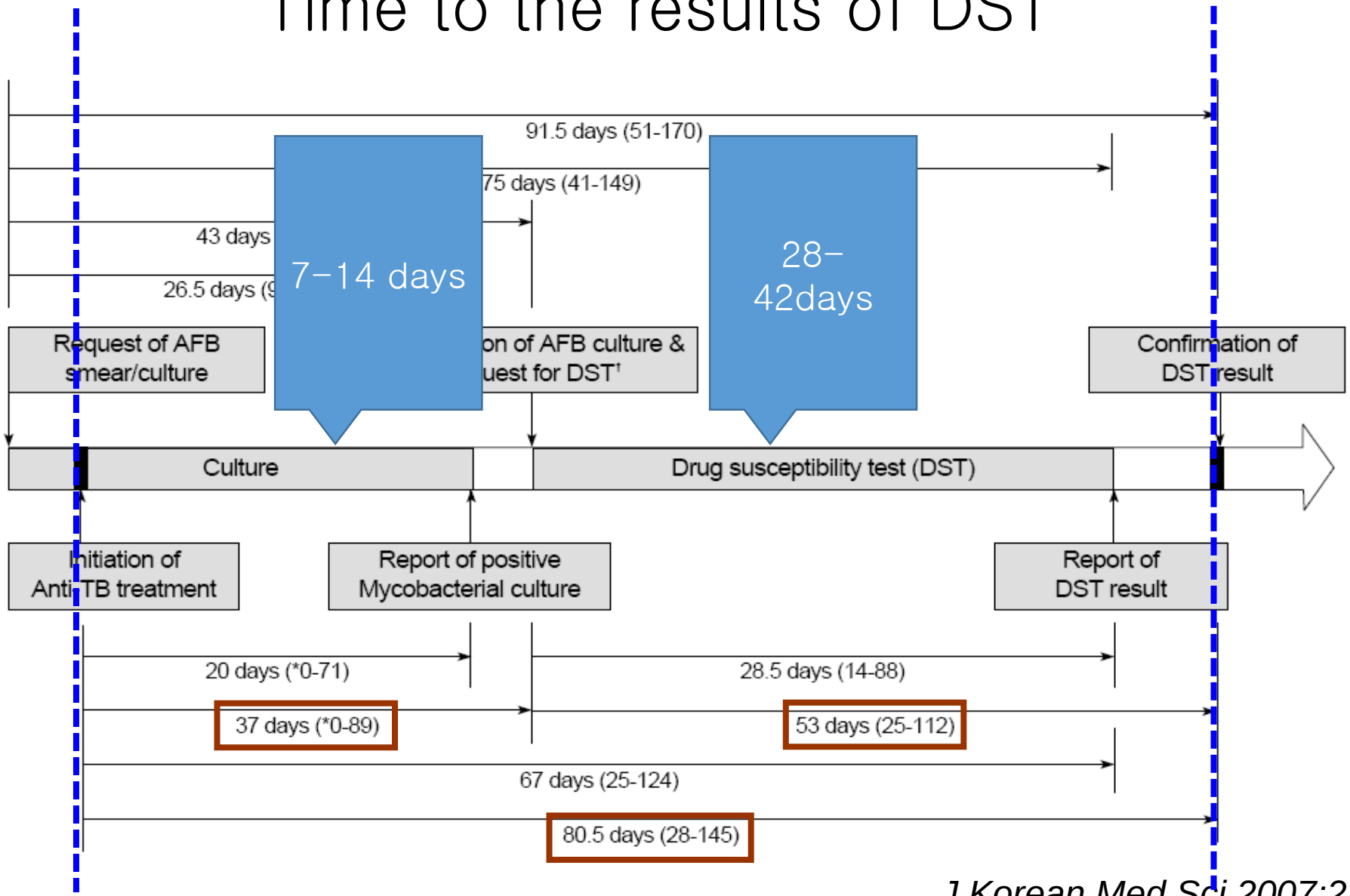
Ann Lab Med 2017;37:323

Choice of a MDR-TB regimen

- Treatment options for MDR-TB are increasingly becoming more individualised as a result of innovations in diagnostics and growing scientific understanding of the molecular basis for drug resistance and the pharmacokinetics and pharmacodynamics of TB medicines. Three signals are clear from the current scientific evidence assessment:
  - The feasibility of effective and **fully oral treatment regimens** for most patients;
  - The need to ensure that **drug resistance is excluded** (at least to the fluoroquinolones and injectables) before starting patients on treatment, especially for the shorter MDR-TB regimen;
  - The need for **close monitoring** of patient safety and treatment response and **a low threshold for switching non-responding patients or those experiencing drug intolerance** to alternative medicines and/or new regimens based on the regrouping of agents in Table 1.

WHO rapid communication 2018

Time to the results of DST



J Korean Med Sci 2007;22:26

Rapid diagnosis of resistance of FQ and SLID

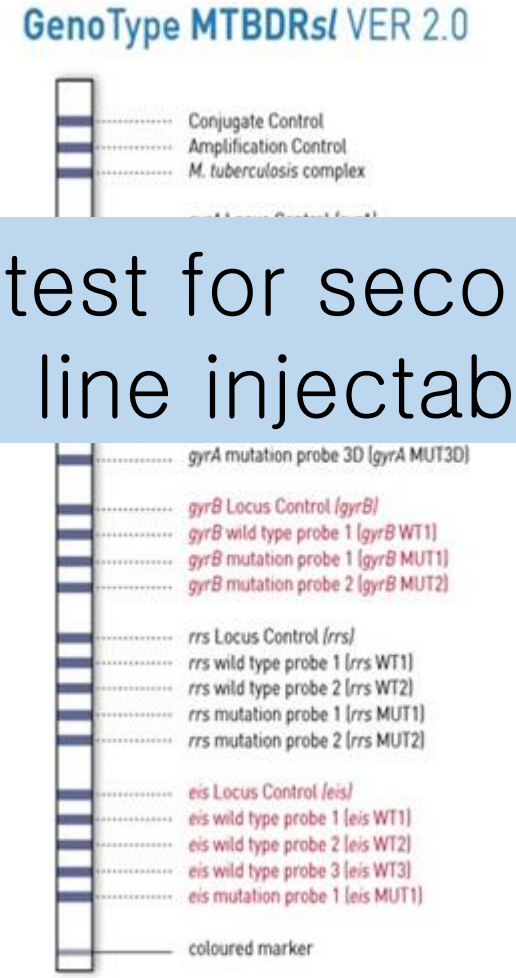
1) For patients with confirmed rifampicin-resistant TB or MDR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to fluoroquinolones

Rapid molecular drug susceptibility test for second drugs , fluoroquinolone and second line injectable drugs

2) For patients with confirmed rifampicin-resistant TB or MDR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to the second-line injectable drugs

- (Conditional recommendation; low certainty in the evidence for test accuracy for direct testing of sputum specimens; very low certainty in the evidence for test accuracy for indirect testing of *Mycobacterium tuberculosis* cultures).

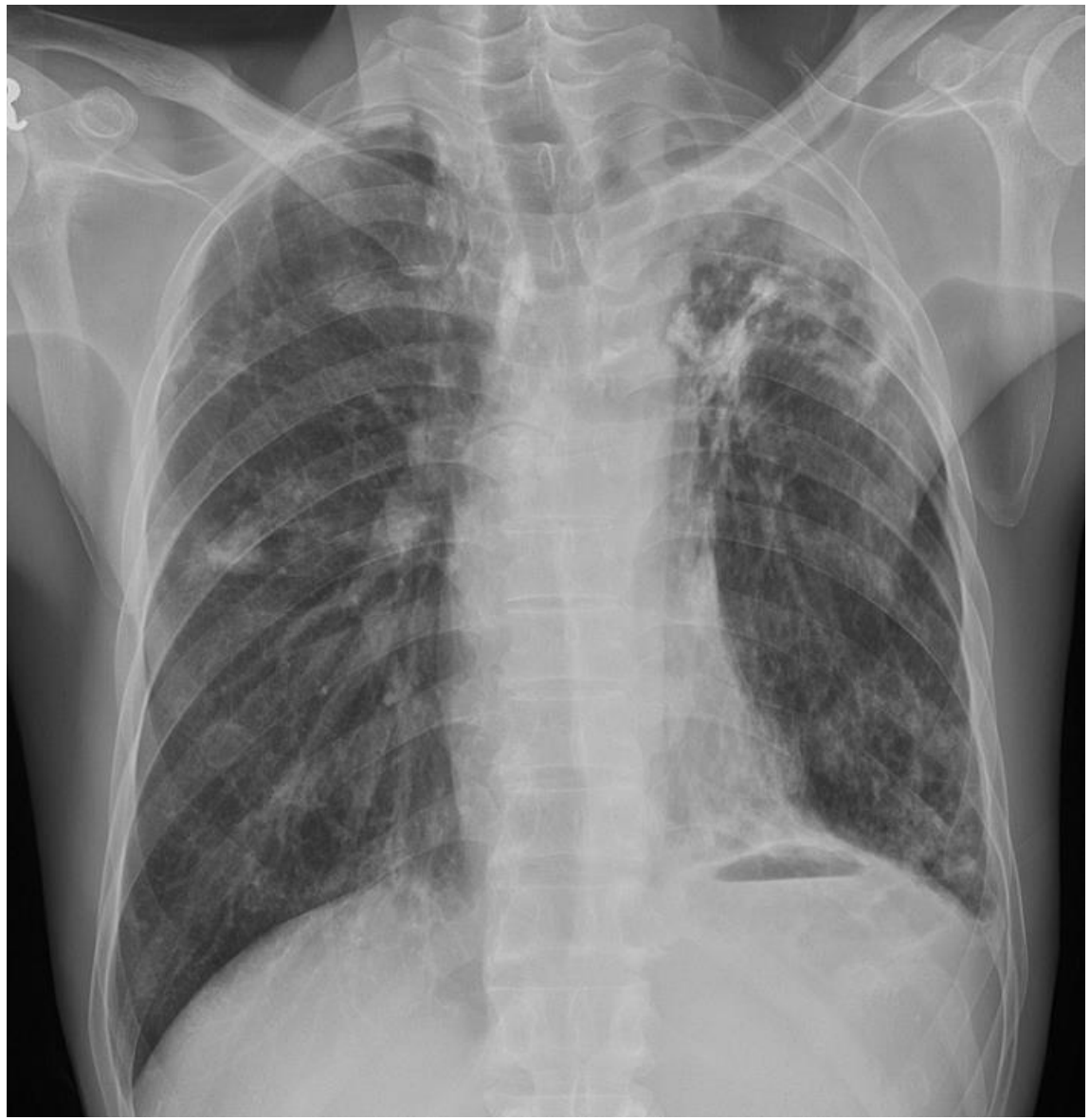
WHO Policy Guidance 2016



M/55

- Sputum AFB smear 1+
- Xpert/MTB RIF : PCR +/Rif resistance +

- Levofloxacin

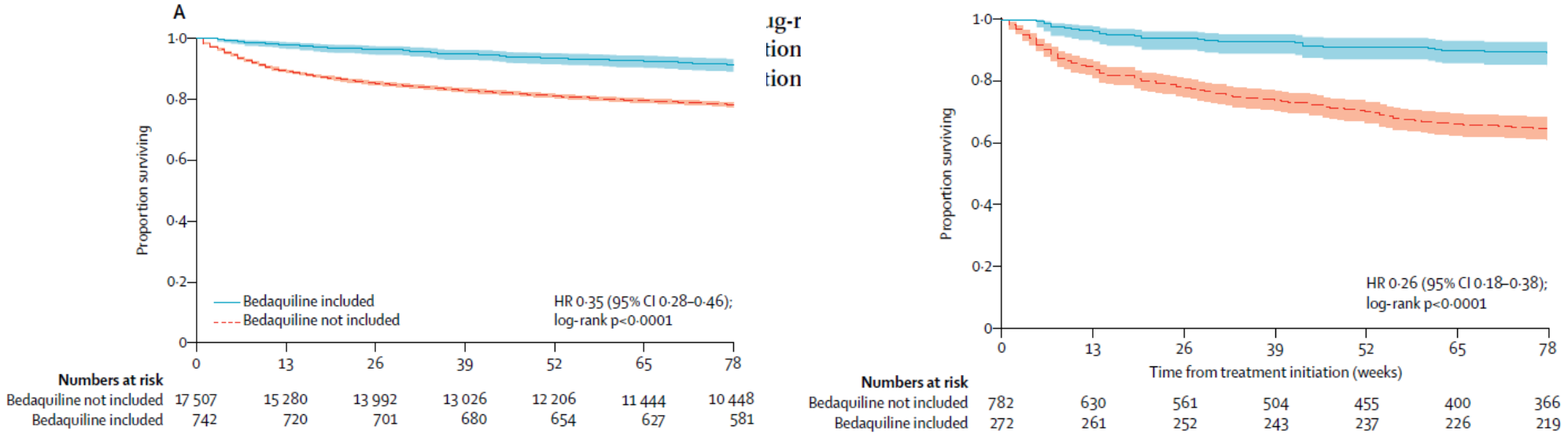


Step 1 : Group A for all MDR TB_Bedaquiline

Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study

Kathryn Schnippel, Norbert Ndjeka*, Gary Maartens, Graeme Meintjes, Iqbal Master, Nazir Ismail, Jennifer Hughes, Hannetjie Ferreira, Xavier Padanilam, Rodolfo Romero, Julian te Riele, Francesca Conradie*

Summary

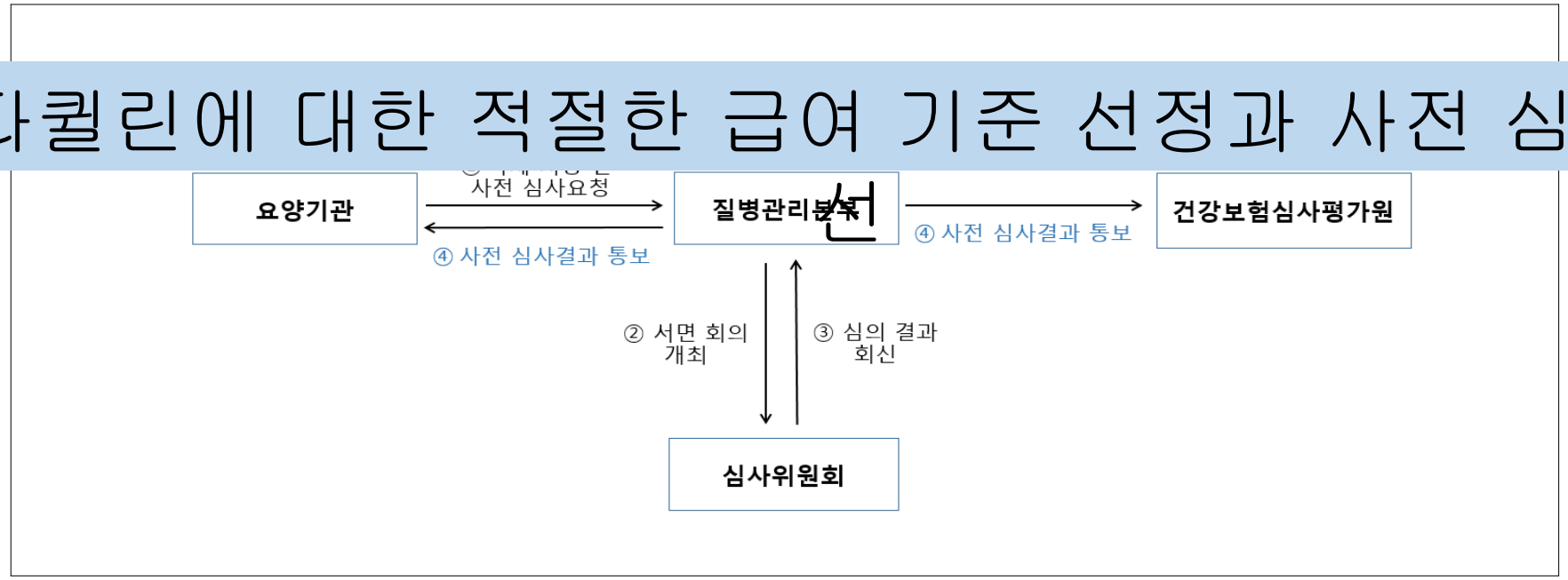


Lancet Respir Med 2018;6:699

Bedaquiline 사전 심의제

- When an effective treatment regimen containing four second-line drugs in addition to pyrazinamide according to WHO recommendations cannot be designed
- When there is documented evidence of resistance to any fluoroquinolone in addition to multidrug resistance

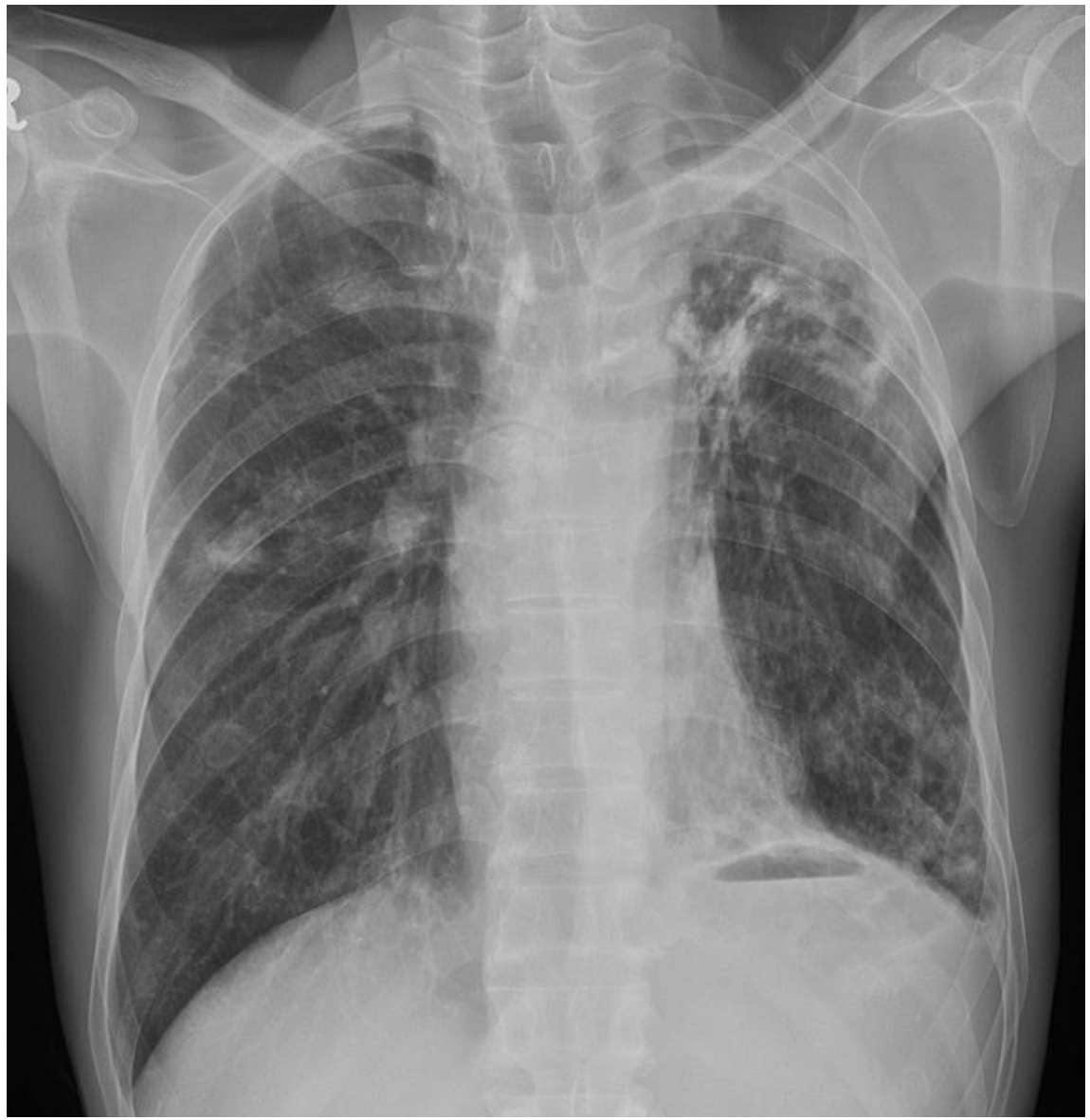
베다퀼린에 대한 적절한 급여 기준 선정과 사전 심의제 개



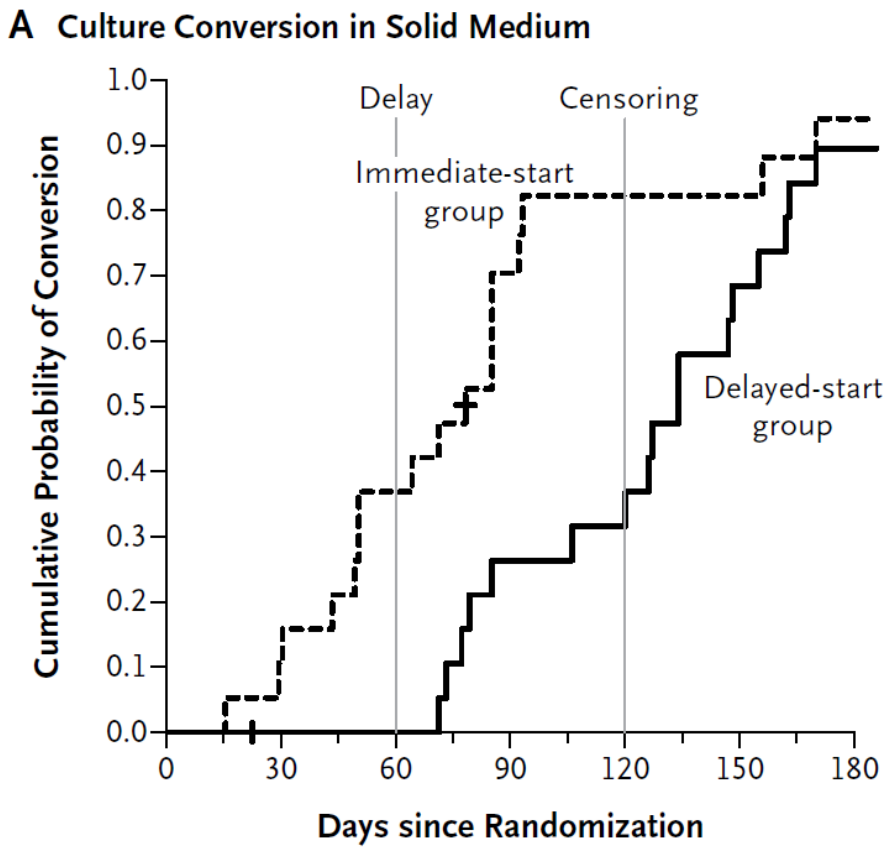
M/55

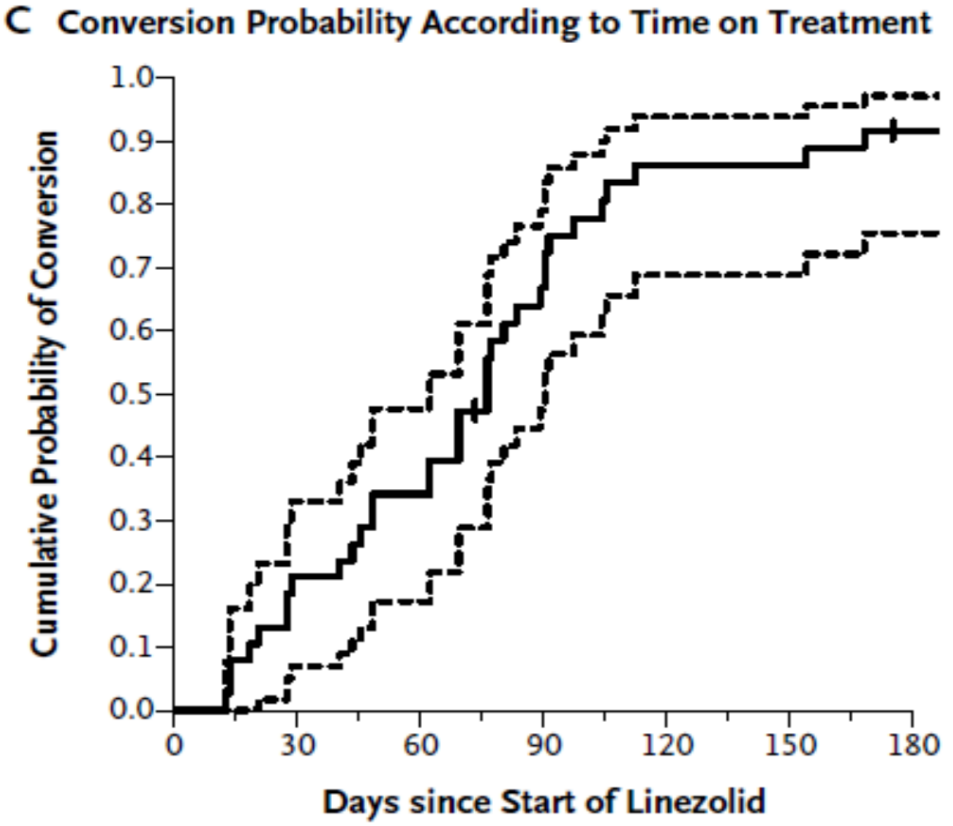
- Sputum AFB smear 1+
- Xpert/MTB RIF : PCR +/Rif resistance +

- Levofloxacin
- Bedaquiline



Step 1 : Group A for all MDR TB_Linezolid





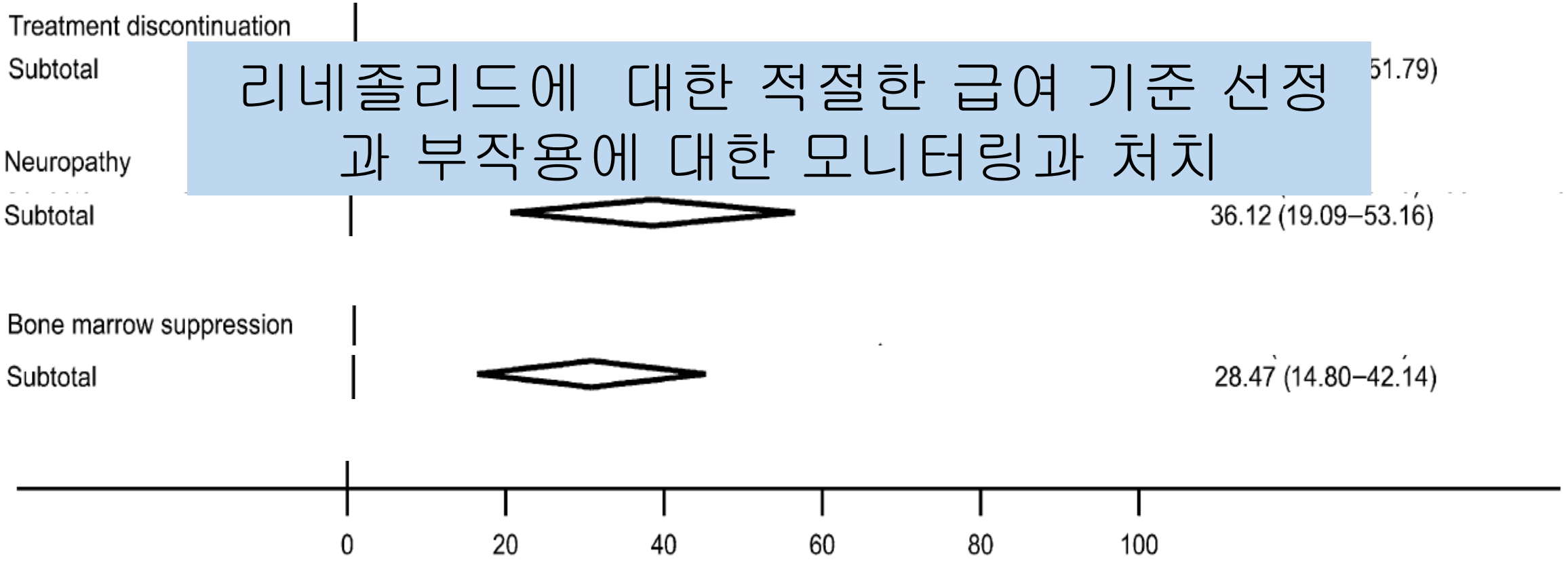
N Engl J Med 2012; 367: 1508

급여 기준 : 리네졸리드

- 2014년 WHO 지침 1-4군 약제로 충분한 약제를 구성할 수 없으면서
  - 광범위 약제 내성인 경우
  - 다제 내성 결핵 환자로 퀴놀론 또는 2차 주사제에 내성이거나 심각한 부작용으로 사용할 수 없는 경우
  - 다제 내성 결핵 환자로 PZA 를 사용 할 수 없는 경우
  - 다제 내성 결핵 환자로 prothionamide, cycloserine, PAS 중 2가지 이상을 사용할 수 없는 경우

- 효과 적일 것으로 예상되는 항결핵제 (2014년 지침 1-5군 약제)가 최소 4가지 이상 병용이 가능한 경우

Adverse events with linezolid



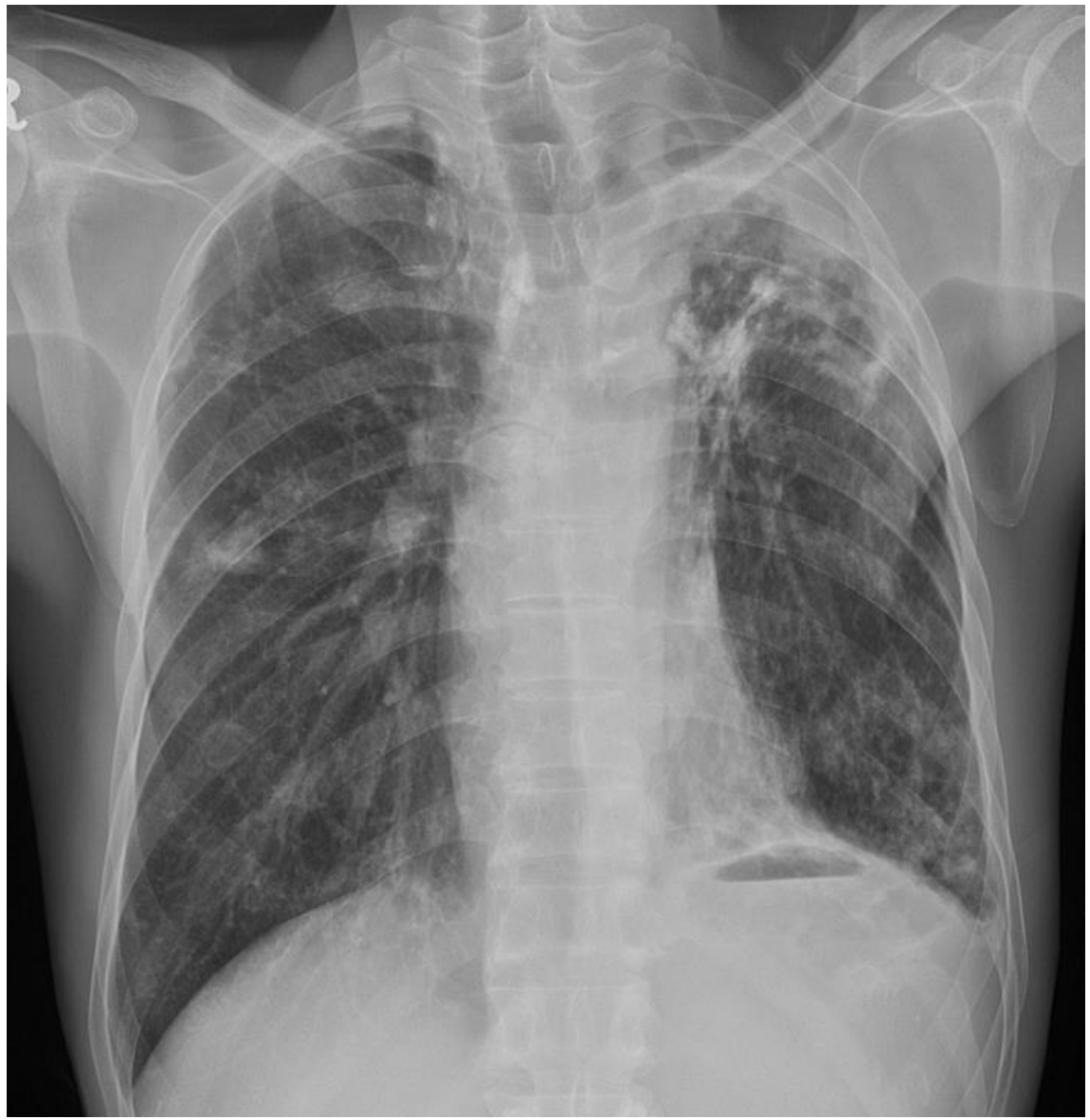
리네졸리드에 대한 적절한 급여 기준 선정과 부작용에 대한 모니터링과 처치

Int J Tuberc Lung Dis 2012;16:447

M/55

- Sputum AFB smear 1+
- Xpert/MTB RIF : PCR +/Rif resistance +

- Levofloxacin
- Bedaquiline
- linezolid



Group B : Clofazimine and Cycloserine

- Clofazimine RCT in China, 2010-2011
- 105 MDR patient : 53 vs 52

Treatment Outcomes	Cfz Group (n = 53), No. (%)	Control Group (n = 52), No. (%)	*P* Value
Treatment success	39 (73.6)	28 (53.8)	.04
Cure	27 (50.9)	20 (38.5)	.20
Treatment completion	12 (22.6)	8 (15.4)	.34
Poor treatment outcomes	14 (26.4)	24 (46.2)	.04
Death	4 (7.5)	4 (7.7)	1
Failure	6 (11.3)	15 (28.8)	.03
Default	4 (7.5)	5 (9.6)	.74

Background regimen :
PZA, Pto, FQ,PAS,CPM or AMK (76-79%)

- Clofazimine RCT in China, 2009-2010
- 49 XDR patients : 22 vs 27

Clinical outcome	No. of patients (%)		
	Experimental group	Control group	*P*
Favorable outcome			0.493
Cure	7 (31.8)	6 (22.2)	0.449
Treatment completion	1 (4.5)	6 (22.2)	0.178
Adverse outcome			0.493
Failure	7 (31.8)	8 (29.6)	0.869
Death	2 (9.1)	3 (11.1)	1.000
Default	5 (22.7)	4 (14.8)	0.733

Background regimen :
PZA, Pto, FQ,EMB, PAS (80-90%),
CPM or AMK (85%)

Clin Infec Dis 2015;60:1361
Antimicrob Agents Chemother 2018;27:62

Clofazimine

- Clofazimine RCT in China, 2010-2011
- 105 MDR patient : 53 vs 52
- Discontinuation trial: 3 (5.7%) vs 3 (5.8%)

Adverse Events	Cfz Group (n = 53), No. (%)	Control Group (n = 52), No. (%)	*P* Value
Anemia	1 (1.9)	1 (1.9)	1
Thrombocytopenia	2 (3.8)	2 (3.8)	1
Leukopenia	4 (7.5)	5 (9.6)	1
Nausea/vomiting	6 (11.3)	5 (9.6)	1
Peripheral neuropathy	2 (3.8)	1 (1.9)	1
Optic neuropathy	1 (1.9)	1 (1.9)	1
Liver injury	6 (11.3)	5 (9.6)	1
Tinnitus or hearing loss	2 (3.8)	3 (5.8)	.68
Rash or pruritus	2 (3.8)	2 (3.8)	1
Arrhythmia	3 (5.7)	3 (5.8)	1
Hypokalemia	3 (5.7)	4 (7.7)	.72
Pink to brownish-black discoloration of skin	50 (94.3)	0 (0)	0
Ichthyosis	25 (47.2)	0 (0)	0

Clin Infec Dis 2015;60:1361

- Retrospective observational cohort study, 2013-2015, N=42, Korea, single center, M.abscessus
- Discontinuation of clofazimine 18 (43%), after 24.4w
- Dose reduction of clofazimine 5 (12%), after 26w

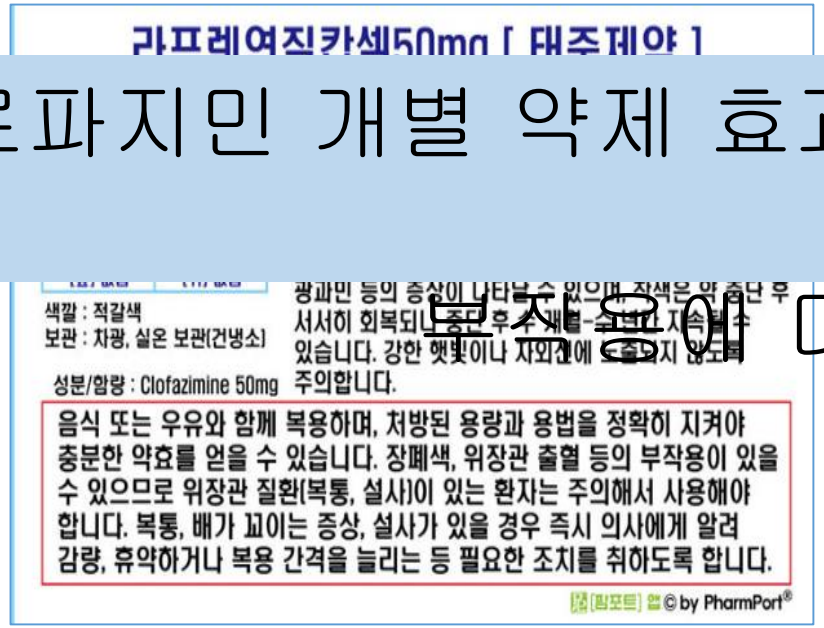
Adverse effect	No. (%) of patients Total (*n* = 23)
Gastrointestinal disturbance	12 (52)
Skin color change	9 (39)
Dizziness	1 (4)
Others	1 (4)

Antimicrob Agents Chemother 2017;61:e02052-16

쥐똥약

Clofazimine

- Availability



클로파지민 개별 약제 효과에 대한 평가와 안정적 약제 공급,
부작용에 대한 고려 및 대처

M/55

- Sputum AFB smear 1+
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- Levofloxacin
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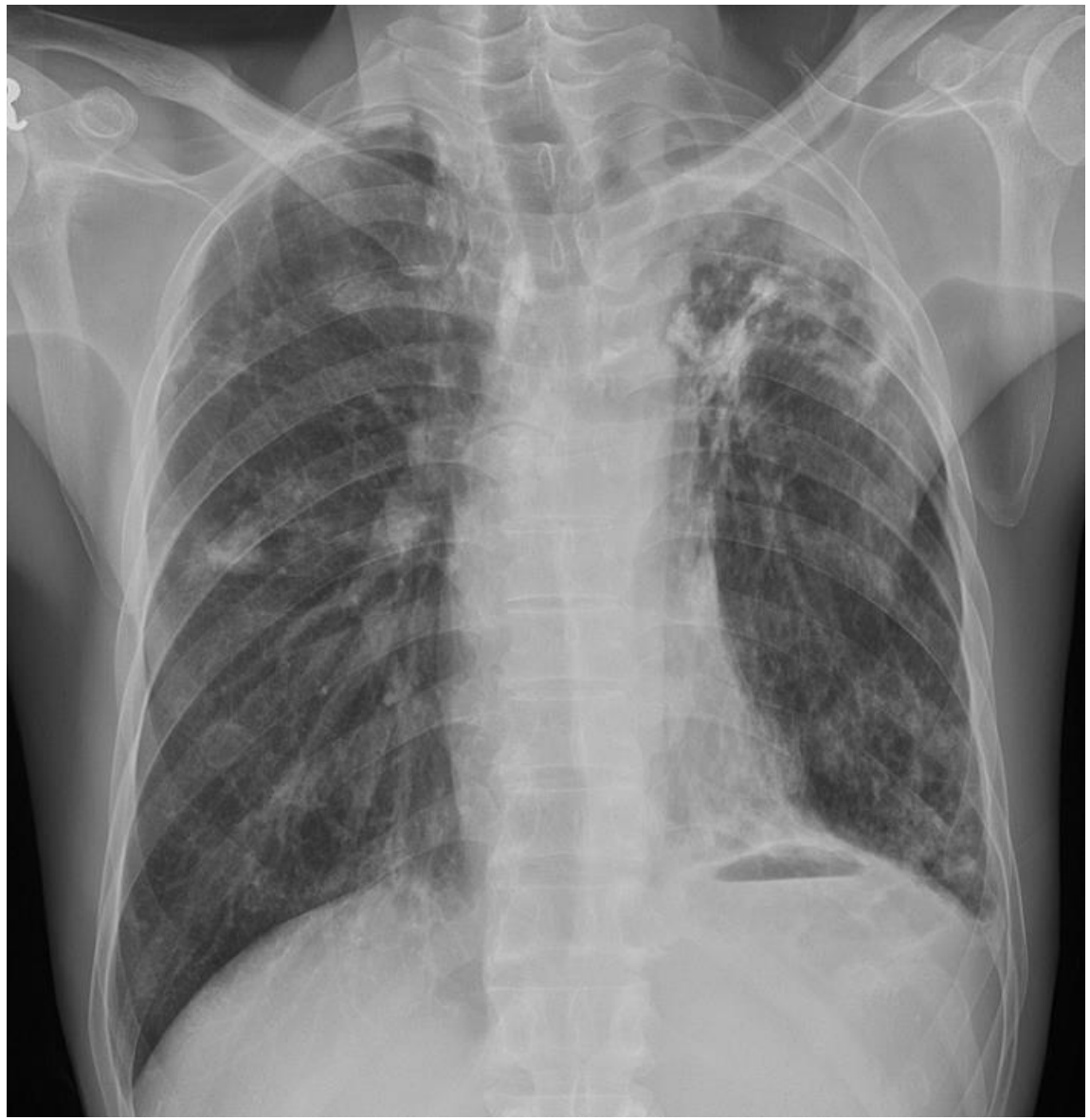

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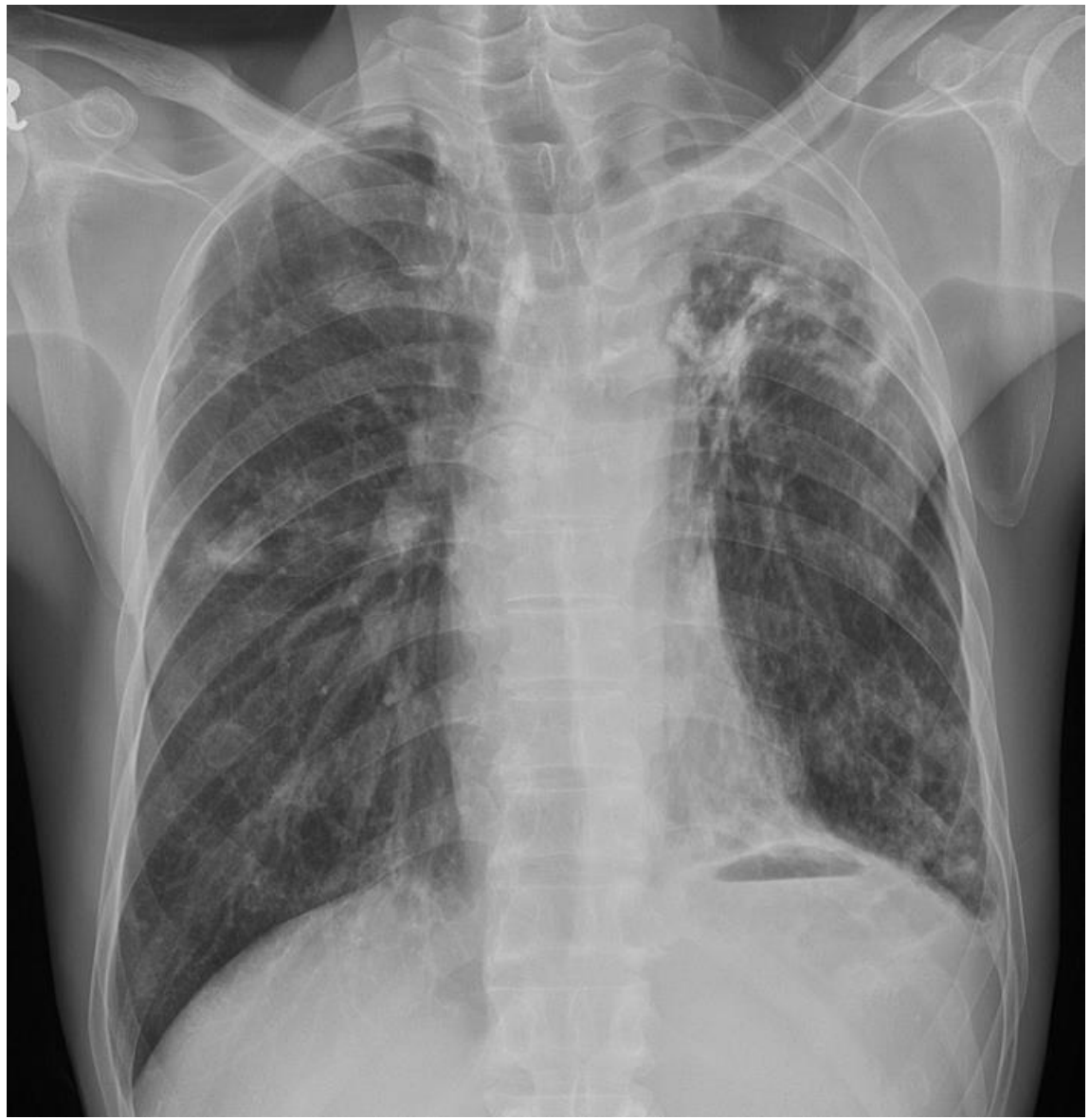
- 4개월째 방문하지 않음..??



High rate of default and transfer out in Korea

	XDR-TB (n=75)	Other MDR-TB (n=1332)	Total (n=1407)
Success (Cure and treatment completion)	22 (29.3%)	615 (46.2%)	637 (45.3%)
Failure	12 (16.0%)	53 (4.0%)	65 (4.6%)
Transfer out	9 (12.0%)	99 (7.4%)	108 (7.7%)
Default	12 (16.0%)	441 (33.1%)	453 (32.2%)
Death	20 (26.7%)	124 (9.3%)	144 (10.2%)
Relapse	3/22 (13.6%)	54/615 (8.8%)	57 (8.9%)

Am J Respir Crit Care Med 2008;178:1075

	N=151 2008 WHO	N=151 2013 WHO
Cure	108 (71.5)	122 (80.8)
Completion	19 (12.6)	2 (1.3)
Failure	5 (3.3)	9 (6.0)
Death	2 (1.3)	2 (1.3)
Default (2008)	11 (7.3)	
Lost to FU (2013)		10 (6.6)
Transfer out (2008)	6 (4.0)	
Not evaluated (2013)		6 (4.0)

Annals ATS 2016;13:364

High rate of drug resistance, community transmission

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CS	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
≥ 1 FQ	41 (19.0)	33 (26.4)	25 (67.6)	99 (26.2)	< 0.001	< 0.001
≥ 1 SLID	36 (16.7)	24 (19.2)	13 (35.1)	73 (19.3)	0.031	0.024
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

J Korean Med Sci 2017; 32: 636-641

Rapid emergence of BDQ resistance

- Patient 1, born in Pakistan, had no past history of TB. His strain was isolated before any TB treatment displayed BDQ resistance.
- Patient 2 was treated for MDR-TB in Romania and has never received BDQ nor CFZ. The strain isolated at that time displayed BDQ resistance.

➔ Primary resistance to BDQ

- Patient 3 was treated in Georgia for 24 months for MDR-TB with ETH, PAS, CAP, CS, Amox, + PZA, BDQ. 1yr later, he was diagnosed in France with cavitary lung XDR-TB, with a BDQ-resistant strain.
- Patient 4 with 10-year history of TB treatment, started with PZA, AMK, ETH, PAS, Lzd, EMB, BDQ. 15mo later, BDQ resistance was diagnosed.

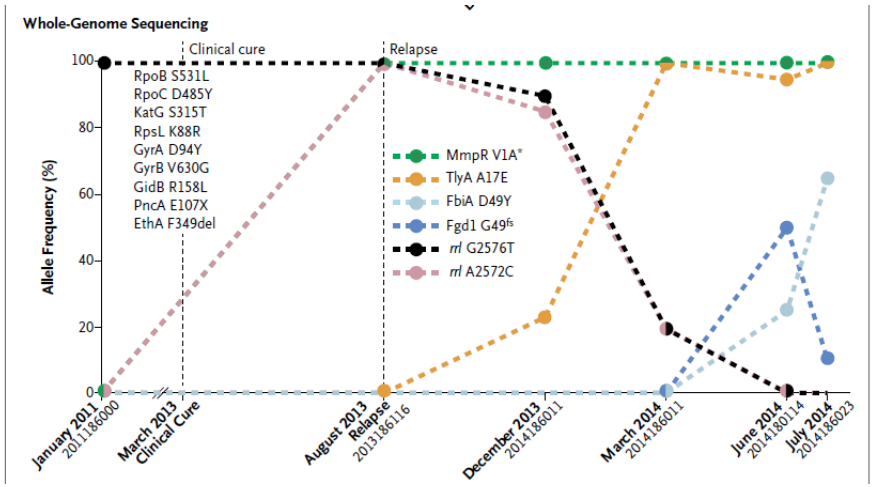
➔ Acquired resistance to BDQ

➔ Mutation : Rv0678, pepQ, atpE

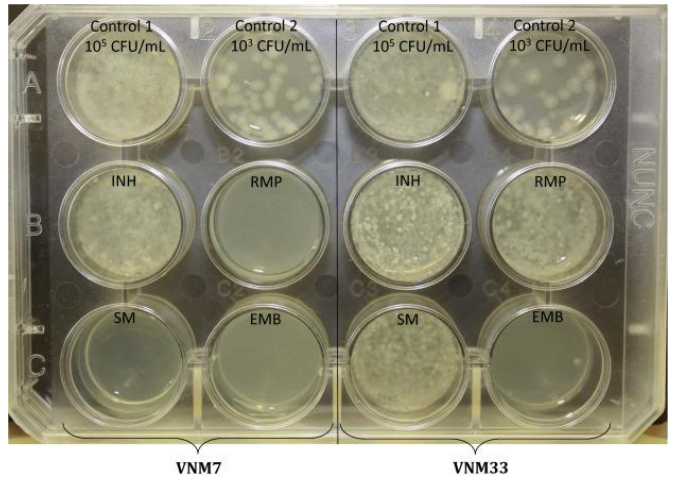
ERJ 2016, Clin Infec Dis 2018;66:1625

Rapid and reliable susceptibility testing

- Necessary for MDR TB treatment
- Drug susceptibility testing for all drugs in MDR-TB treatment
  - Individualized anti-TB treatment
  - Surveillance for new acquired resistance
- Molecular and phenotypic DST



New Eng J Med 2015;373:20

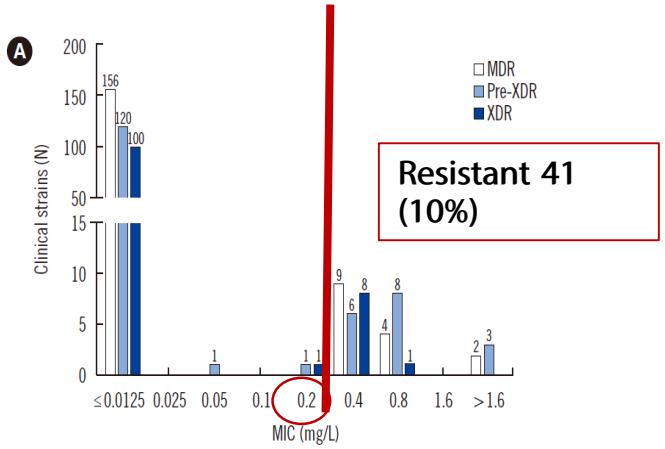


Clin Microbiol Inf 2015;21:1084

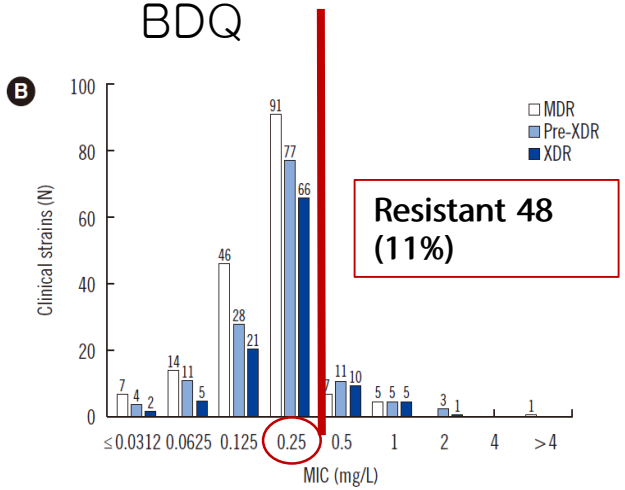
Drug susceptibility monitoring for new drugs

420
MDR
isolates
KIT

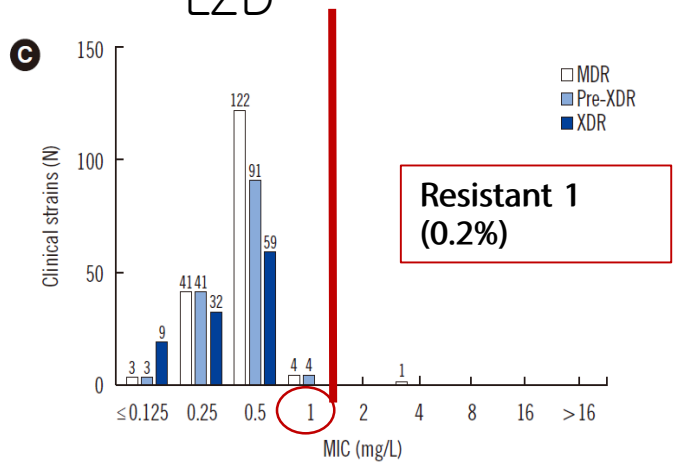
DLM



BDQ



LZD



90
XDR isolates
China

TABLE 2 MIC distribution of XDR-TB strains against MFX, GAT, LZD, CLO, BDQ, and DMD

Antimicrobial agent	No. of strains with MIC (mg/liter) of:											Breakpoint MIC for resistance (mg/liter)	No. (%) of resistant strains
	≤0.031	0.063	0.125	0.25	0.5	1	2	4	8	16	32		
MFX	0	0	2	1	5	13	27	29	10	3	0	0.5	82 (91.1)
GAT	0	0	2	2	10	19	34	19	4	0	0	0.5	76 (84.4)
LZD	0	0	6	35	40	4	0	1	1	2	1	1.0	5 (5.6)
CLO	0	13	28	34	7	3	4	1	0	0	0	1.0	5 (5.6)
BDQ	81	2	3	1	3	0	0	0	0	0	0	0.25	3 (3.3)
DMD	86	0	0	0	1	0	0	0	0	0	3	0.125	4 (4.4)

Ann Lab Med 2018;38:563
Antimicrob Agents Chemother 2017;61:e00900-17

DOT for patients with MDR-TB

- 2012 결핵 환자 DOT 시범사업
- 서울, 대구, 강원도, 충북, 경북, 제주
- 결핵 환자 541 명

1) DOT 요원 직접 방문, 보건소 방문에 의한 직접 복약 확인 (n= 235)

2) 디지털 복약기를 이용한 DDOT (Digital Directly Observed Therapy) (n=165)

3) 스마트폰 앱을 이용한 MDOT (Mobile Directly Observed Therapy) (n=141)

KNTA, TB 클리닉

Treatment Outcomes of Multidrug-Resistant Tuberculosis in Taiwan: Tackling Loss to Follow-up

Ming-Chih Yu,[1,2,3,a] Chen-Yuan Chiang,[1,3,4,b] Jen-[illegible] [illegible]u-Jui Lin,[7] Shih-Wei Lee,[7] Chih-Bin Lin,[5] Wen-Ta Yang,[8,9] Ying-Hsun Wu,[6] and Yi-Wen Huang[10,11,a]

Lost to FU 29.1%

Background. The proportion of treatment success among patients with multidrug-resistant tuberculosis (MDR-TB) enrolled between 1992 and 1996 was 51.2%, and that among patients enrolled between 2000 and April 2007 was 61%. To address the challenge of MDR-TB, the Taiwan MDR-TB Consortium (TMTC) was established in May 2007. To assess the performance of the TMTC, we analyzed the data of patients enrolled in its first 5 years.

Methods. Comprehensive care was provided at no cost to patients, who were usually hospitalized for 1 month initially. Treatment regimens consisted of 4–5 drugs and the duration of treatment was 18–24 months. A case manager and a directly observed therapy provider were assigned to each patient. Psychosocial support was provided to address emotional stress and stigma. Financial support was offered to avoid the financial hardship faced by patients and their families. We assessed treatment outcomes at 30 months using internationally recommended outcome definitions.

Results. Of the 692 MDR-TB patients, 570 (82.4%) were successfully treated, 84 (12.1%) died, 18 (2.6%) had treatment failure, and 20 (2.9%) were lost to follow-up. Age ≥65 years (adjusted odds ratio [aOR], 6.78 [95% confidence interval {CI}, 3.14–14.63]), cancer (aOR, 11.82 [95% CI, 5.55–25.18]), and chronic kidney disease (aOR, 3.62 [95% CI, 1.70–7.71]) were significantly associated with death. Resistance to fluoroquinolone (aOR, 10.89 [95% CI, 3.97–29.88]) was significantly associated with treatment failure.

Conclusions. The TMTC, which operates under a strong collaboration between the public health authority and clinical teams, has been a highly effective model of care in the management of MDR-TB.

CID 2018:67:202

as compared with self-administration of treatment [33]. Our experience shows that supportive DOT is crucial. The TMTC was led by senior clinicians who had substantial experience in TB control and clinical management of MDR-TB, thus ensuring that the regimens used were consistent with international

timely and effective manner. A unique aspect of TMTC is that the operation of the TMTC was mainly funded by the government. Using the sufficient financial resources provided to the TMTC, outreach teams were organized to provide patient-centered care and supportive DOT was provided at the location (in the community or at the home) that was most convenient to the patients. Additionally, financial hardship and psychosocial problems of patients during the whole treatment course were addressed and managed effectively. Our experience supports a previous report that monetary incentives may help enhance adherence to treatment of MDR-TB patients [34].

1) Supportive DOT
2) Monitoring of effective regimen and timely managed adverse reactions by experience

Patient-centered, supportive DOT for MDR-TB patients

4) Government funded sufficient financial resources – outreach team
5) Financial support for the patients
6) Psychosocial problems were addressed and managed effectively

CID 2018:67:202

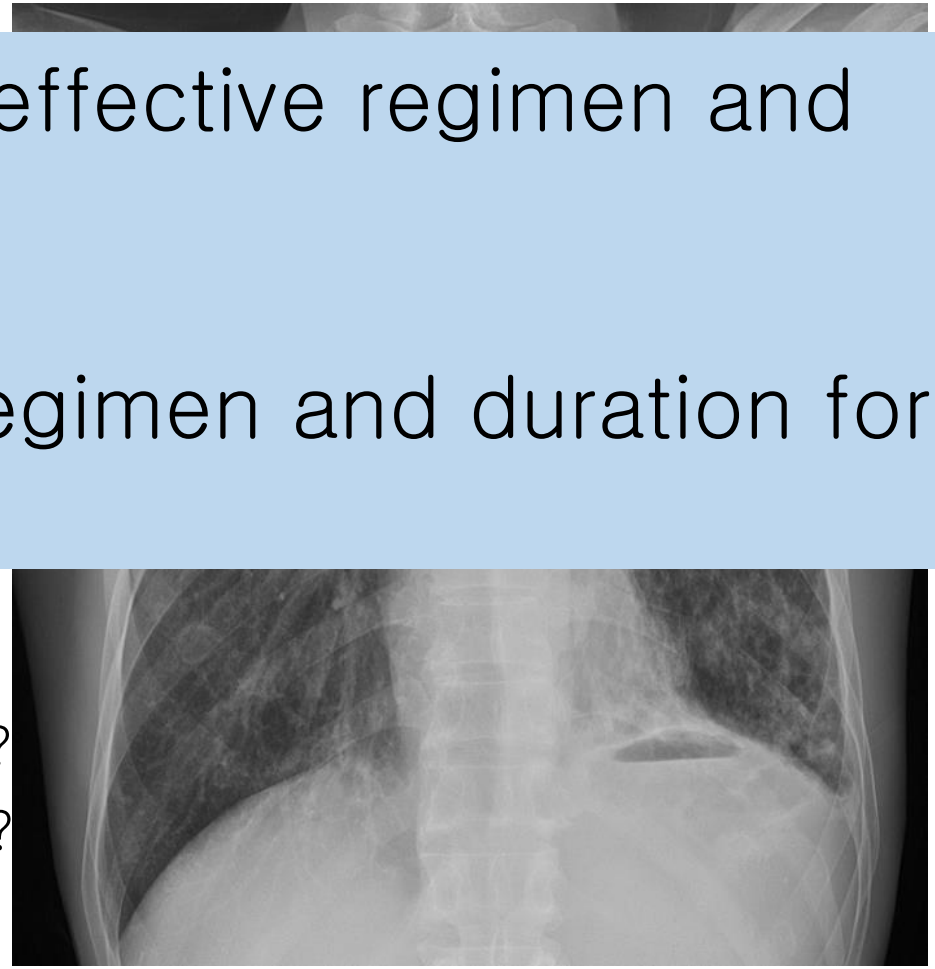
M/55, MDR-TB

1) Ensuring and monitoring of effective regimen and timely managed adverse events

2) Research for effective new regimen and duration for MDR-TB

- Linezolid 유지? Additional drug?

- Replacement of group A drug in intensive phase ?
- Replacement of group B drug in intensive phase ?
- How long for cure ?



Rapid communication_2018 WHO

Treatment principles

- **Ahead of enrolment on MDR-TB treatment, all patients should receive appropriate counselling to enable informed and participatory decision-making.**
- **Patient information material needs to reflect the new changes so that patients are appropriately informed about their treatment options.**
- **Social support to enable adherence to treatment is very important to ensure a patient-centred approach to the delivery of care.**
- **Active TB drug safety monitoring and management (aDSM) is essential for all patients enrolled on MDR-TB treatment.**

Key medicine changes

Longer MDR-TB regimens[ii]

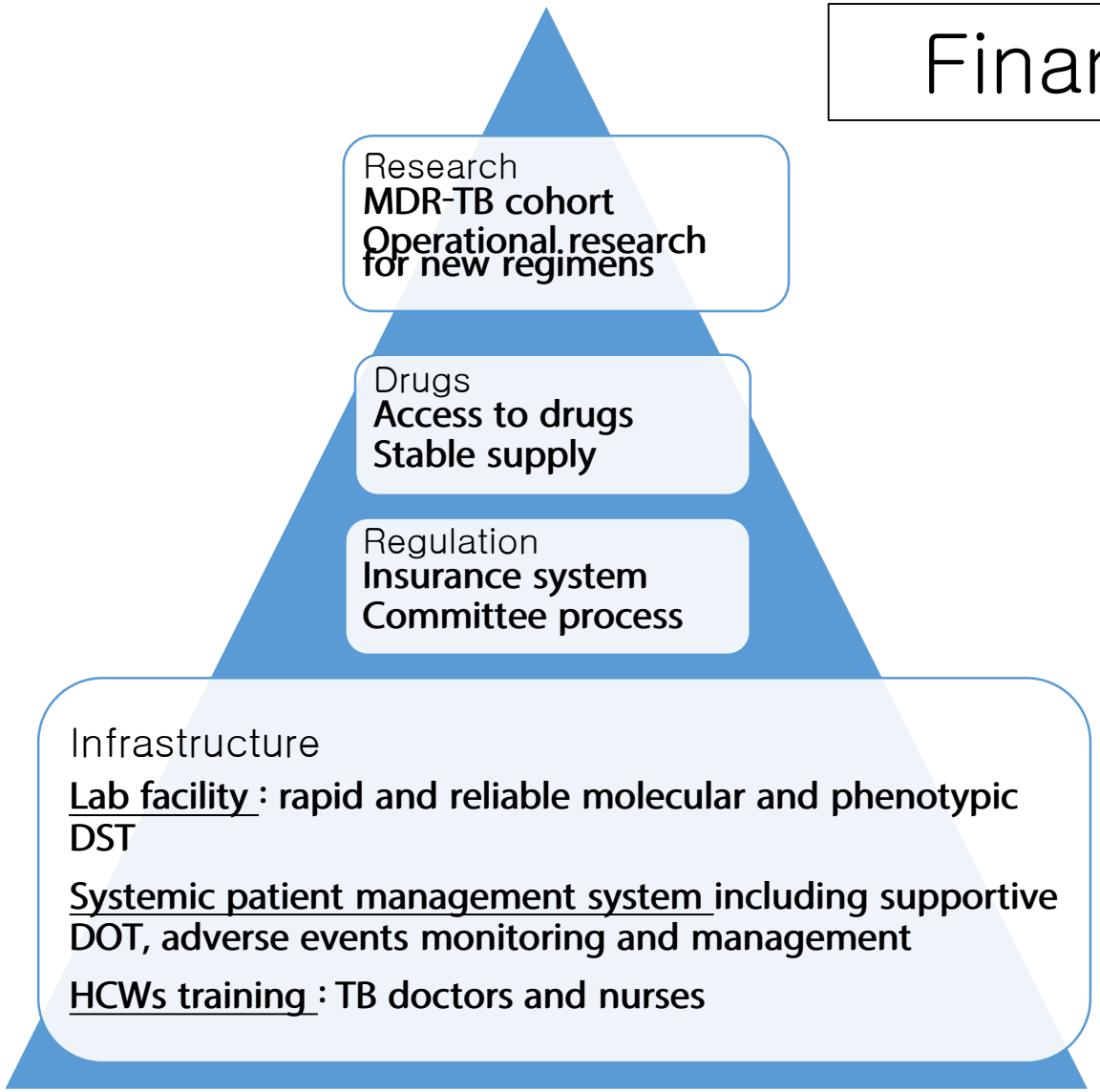
National TB program

- These changes also have implications for national TB programmes - on planning (several areas but especially in procurement and supply), human resources, financing, implementation and monitoring of the TB response.

- WHO advises countries to rapidly adjust their national treatment policies, drug procurement plans and monitoring system to quickly switch to the new priority regimens…

Rapid Communication: WHO 2018

Financing


Research
MDR-TB cohort
Operational research for new regimens
Drugs
Access to drugs
Stable supply
Regulation
Insurance system
Committee process
Infrastructure
Lab facility : rapid and reliable molecular and phenotypic DST
Systemic patient management system including supportive DOT, adverse events monitoring and management
HCWs training : TB doctors and nurses

감사합니다.