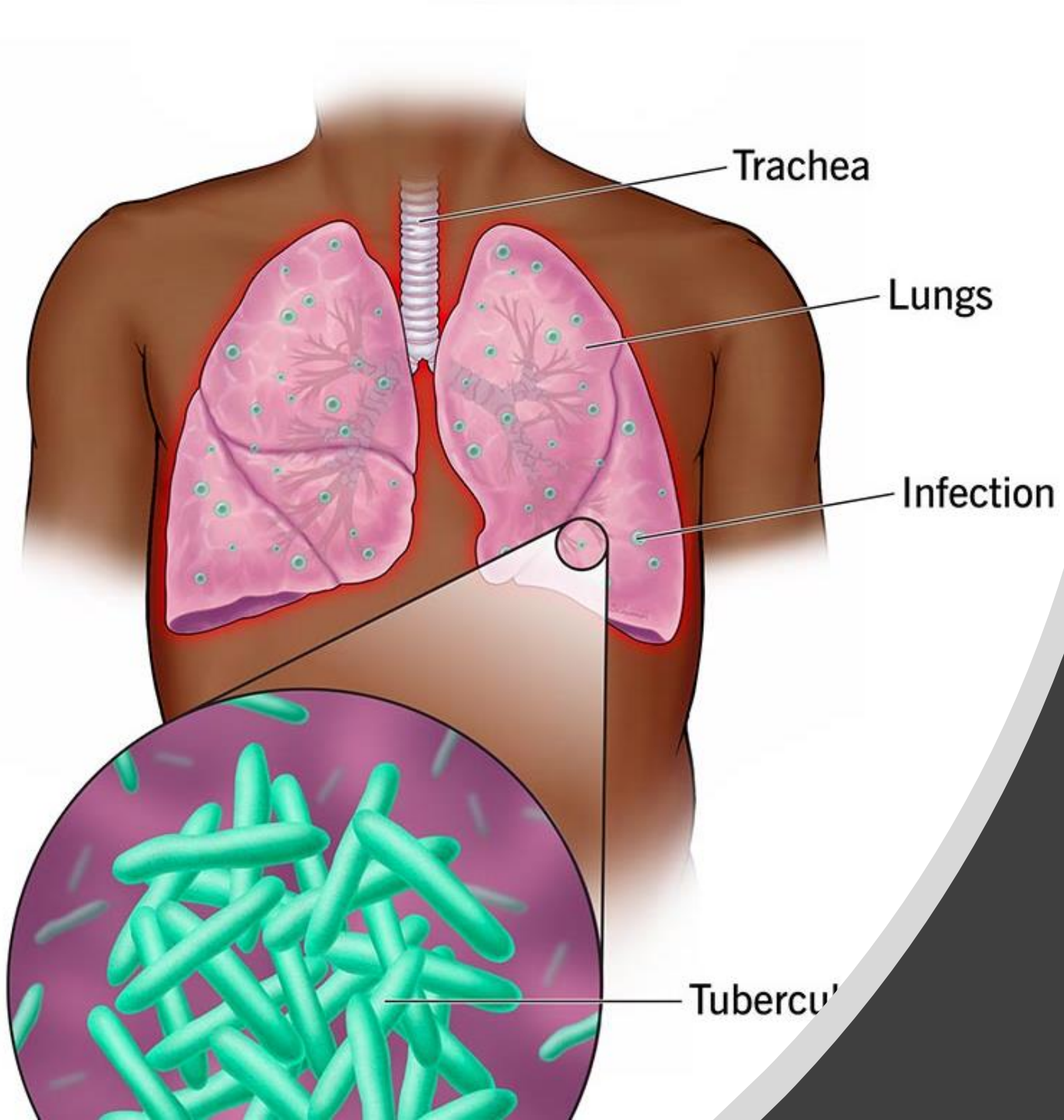

New drugs for treatment and prevention of tuberculosis

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Outlines

- New treatment regimens of MDR-TB
- Drugs interaction of anti-TB and ARV
- Tuberculosis preventive therapy (TPT) in HIV-infected patient

Definition of drug resistant TB (DR-TB)

- **INH mono-resistant TB (Hr-TB) : Resist to INH only.**
- **RMP mono-resistant TB (RR-TB) : Resist to RMP only.**
- **Poly-drug resistant TB : Any 2 anti-TB drugs – INH + SM, INH + EMB, INH + FQ, etc.**
- **Multidrug resistant TB (MDR-TB) : Resist to INH and RMP ± other drugs.**
- **Pre-extensively drug resistant TB (preXDR-TB) : Resist to INH and RMP and FQ ± other drugs or not.**
- **Extensively drug resistant TB (XDR-TB) : Resistant to INH and RMP and FQ and Bedaquiline or Linezolid.**

WHO 2022

WHO 2011		WHO 2016		WHO 2019 longer MDR-TB regimens	
Group 1 First-line oral drugs	Isoniazid Rifampicin Ethambutol Pyrazinamide	Group A	Levofloxacin Moxifloxacin Gatifloxacin	**Group A** Include all three medicines	Levofloxacin OR Moxifloxacin
					Bedaquilline
Group 2 Injectable drugs	Streptomycin Kanamycin Amikacin Capreomycin	Group B Second-line injectable drugs	Amikacin Capreomycin Kanamycin (Streptomycin)		***Linezolid***
				Group B Add one or both medicines	Clofazimine
Group 3	Levofloxacin Moxifloxacin Gatifloxacin Ofloxacin	**Group C** Other Core Second-line Agents	Ethionamide Prothionamide Cycloserine Terizidone ***Linezolid*** Clofazimine		Cycloserine OR Terizidone
				Group C Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol
					Delamanid
Group 4 Oral bacteriostatic second-line drugs	Ethionamide Prothionamide Cycloserine Terizidone PAS	Group D Add-on agents (not core MDR-TB regimen)	D1 Pyrazinamide Ethambutol High-dose INH		Pyrazinamide
					Imipenem OR Meropenem
Group 5	(Bedaquiline) (Delamanid) ***Linezolid*** Clofazimine		D2 Bedaquilline Delamanid		Amikacin (OR streptomycin)
			D3 PAS		Ethionamide OR Prothionamide

Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis

The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017; Nafees Ahmad, Shama D Ahuja, Onno W Akkerman, Jan-Willem C Alffenaar, Laura F Anderson, Parvaneh Baghaei, Didi Bang, Pennan M Barry, Mayara L Bastos, Digamber Behera, Andrea Benedetti, Gregory P Bisson, Martin J Boeree, Maryline Bonnet, Sarah K Brode, James C M Brust, Ying Cai, Eric Caumes, J Peter Cegielski, Rosella Ce… Gerard de… Medea Ge… Russell R… Charlotte… Eric Chun… Vladimir… Max R O'… Maria Roc… Ganzaya… Stalz Cha…

50 datasets from 25 countries – 12,030 MDR TB patients were analysed
99.1% were MDR, O.3 % RR TB and 0.7%- H status not known
High quality in 39 studies, moderate in 9 and low in 2

Summ…
Backgro… …et 2018; 392: 821–34
associat… …Comment pages 797 and 798
treatment with those drugs in patients with multidrug-resistant tuberculosis.

***Lancet* 2018**

Drug	Group	Efficacy	Safety (common or significant side effects)	Likelihood of susceptibility (DST assessment)	Overall ranking
Lfx	A	Excellent	Excellent	Excellent (rapid DST exists and low background resistance)	Excellent
Mfx	A	Excellent	Excellent (mild QT prolongation)	Excellent (rapid DST exists and low background resistance)	Excellent
Bdq	A	Excellent	V. Good (QT prolongation and hepatotoxicity)	Excellent (low background resistance)	Excellent
Lzd	A	Excellent	**Poor (peripheral neuropathy, myelosuppression)**	Excellent (low background resistance)	V. Good
Cfz	B	Good	Good (skin pigmentation, GI distress)	V. Good (low background resistance except in previously treated MDR-TB patients with shorter regimen or contacts)	Good
Cs	B	Good (bacteriostatic)	**Poor (psychosis, seizures, depression, peripheral neuropathy)**	Fair (background resistance not known, may be high in previously treated MDR-TB patients or contacts of an MDR-TB failure patient).	Fair
E	C	Good (bacteriostatic)	Very Good	**Poor (very high background resistance in MDR TB strains and no reliable DST)**	**Poor**
Dlm	C	Good (bactericidal, Phase 2 and 3 data support faster conversion)	Excellent	Excellent (low background resistance)	V. Good
Z	C	Excellent	Fair (hepatotoxicity)	Fair (moderate to high background resistance in MDR-TB strains and DST difficult to perform)	Fair

Rx MDR/RR regimens

Shorter regimen (9-12 mo.)

- 4–6 Amikacin-Lfx-Cfz-Z-E-Hh-Eto/ 5 Lfx-Cfz-Z-E

  (Old shorter regimen; Bangladesh regimen) ***(success rate > 80%)***
- 4–6 Bdq(6 m) -Lfx-Cfz-Z-E-Hh-Eto/ 5 Lfx-Cfz-Z-E

  (shorter all-oral BDQ-containing regimen) ***(success rate > 80%)***

Longer regimen (~ 18 mo)

- 18 Bdq (6 m)-Lfx-Lzd-Cfz

  (New longer regimen; all-oral longer)
- Amikacin (6 m)-Lfx-Cycloserine-Ethionamide/12 Lfx-Cycloserine-Ethionamide (Old longer regimen)

  (Success rate ~ 50%)

WHO 2020

All-oral Shorter RR/MDR Regimen or BDQ-based Shorter RR/MDR Regimen

เดือน	1	2	3	4	5	6	7	8	9
BDQ									
LVX									
CFZ									
EMB									
PZA									
PTA									
hINH									

BDQ=Bedaquiline, LVX=Levofloxacin, CFZ=Clofazimine, EMB=Ethambutol, PZA=Pyrazinamide, PTA=Prothionamide, hINH=high dose INH

ขอบคุณ อาจารย์ เจริญ

Patient exclusion (shorter regimen)

- Has been previously exposed to second line anti-tuberculosis drugs for ***more than one month***
- Pregnancy
- Severe form of extrapulmonary TB, Extensive disease

- QTcF interval **> 450 msec** (male), **> 470 msec** (female)
- Liver function enzyme; AST/ALT > 5 times of the upper normal limit
- Creatinine Clearance (CrCl)< 30 ml/min, calculated from Cockcroft-Gault equation

Extent of TB disease: bilateral cavitary disease, extensive parenchymal damage
Severe extrapulmonary TB: military TB, TB meningitis

WHO 2021

Treatment of drug-resistant tuberculosis

Rifampicin-susceptible and INH-resistant

6 (H) REZ-Lfx

Multi-drug or rifampicin-resistant

Not exposed second-line > 1 mo ***and*** **not resistance to fluoroquinolone**

Eligible

Shorter all-oral BDQ-containing regimen (9-12 mo)

4-6 Bdq*-Mfx(Lfx)-Pto (Eto)-Cfz-Z-$H_{high\text{-}dose}$-E/ 5 Mfx(Lfx)-Cfz-Z-E

Not eligible

All-oral longer regimens (15-17 mo after culture convert)

18 Bdq(6m)-Lfx/Mfx-Lzd-Cfz

Multi-drug resistant with additional fluoroquinolone resistance

BDQ, pretomanid and linezolid (BPaL) (6-9 mo) may be used under operational research

WHO 2020

Thai guideline 2020

ผลการรักษาผู้ป่วยวัณโรคดื้อยาหลายขนานหรือดื้อยา Rifampicin (MDR/RR TB) ด้วยสูตรยาระยะสั้น 9-11 เดือน (Shorter treatment regimen) ชนิดฉีดและรับประทานในประเทศไทย พ.ศ. 2560-2564

ประเภทผลการรักษา	สูตรยาระยะสั้น 9-11 เดือน (STR)			การทดสอบทางสถิติ	*P*-value
	Kanamycin จำนวน (ร้อยละ)	Amikacin จำนวน (ร้อยละ)	Bedaquiline จำนวน (ร้อยละ)		
รักษาสำเร็จ (Treatment success)	76 (69.1)	210 (82.7)	117 (88)	Fisher's exact test	0.017
ตาย (Died)	13 (11.8)	23 (9.1)	9 (6.8)		
ล้มเหลว (Treatment failed)	10 (9.1)	13 (5.1)	5 (3.8)		
ขาดยา (Lost to follow-up)	10 (9.1)	7 (2.8)	2 (1.5)		
โอนออก (Transferred out)	1 (0.9)	1 (0.4)	0 (0)		
รวม	**110 (100)**	**254 (100)**	**133 (100)**		

ผลวิเคราะห์การรักษาสาเร็จ (treatment success) จากผลถดถอยโลจิสติกส์(Logistic regression) เปรียบเทียบระหว่าง สูตรยา kanamycin, amikacin และ bedaquiline based STR

STR	รักษาสำเร็จ (Treatment success)	รักษาไม่สำเร็จ (Unsuccessful treatment)	OR	95% CI	P-value
Ref: Kanamycin	76 (69.1)	34 (30.9)	1		
Amikacin	210 (82.7)	44 (17.3)	2.1	1.3-3.6	<0.05
Bedaquiline	117 (88)	16 (12)	3.3	1.7-6.3	<0.001

จำนวนและร้อยละผู้ป่วยวัณโรคดื้อยาที่กลับเป็นซ้ำที่ใช้สูตรยาระยะสั้น 9- 11เดือน

ประเภท	จำนวนผู้ป่วยที่กลับเป็นซ้ำที่ใช้สูตรยาระยะสั้น 9-11 เดือน (STR)		
	Kanamycin (N=76) จำนวน (ร้อยละ)	Amikacin (N=210) จำนวน (ร้อยละ)	Bedaquiline (N=117) จำนวน (ร้อยละ)
ไม่กลับเป็นซ้ำ (No relapse)	75 (98.7)	207 (98.6)	117 (100)
กลับเป็นซ้ำ (Relapse)	1 (1.3)	3 (1.4)	0 (0)
ระยะเวลาของการกลับเป็นซ้ำ Time-to-relapse (Months)	16 เดือน	4, 5, 12 เดือน (เฉลี่ย 7 เดือน)	NA

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Bedaquiline and Linezolid improve anti-TB treatment outcome in drug-resistant TB patients with HIV: A systematic review and meta-analysis

Yaxin Wu [a,1], Yuening Zhang [c,1], Yingying Wang [a], Jiaqi Wei [a,b], Wenjing Wang [a], Wenshan Duan [a], Yakun Tian [a], Meixin Ren [a], Zhen Li [a,b], Wen Wang [a], Tong Zhang [a], Hao Wu [a], Xiaojie Huang [a,*]

Large sample size (n = 9279) from 40 cohorts from three continents and 10 cities (Uganda, Indonesia, Thailand, South Africa, Ukraine, Botswana, India, USA, The Republic of Belarus, Eswatini).

Treatment outcomes of DR-TB-HIV patients, by type of resistance

DR-TB-HIV treatment outcomes[a]	Number of cohorts	MDR/RR-TB-HIV	XDR-TB-HIV
Treatment success	40	59.0 % (54.3–63.6)	46.9 % (34.6–59.6)
Completion	21	13.1 % (8.5–19.6)	6.7 % (3.7–11.8)
Cure	21	39.9 % (32.2–48.1)	21.8 % (9.0–44.0)
Unfavorable	40	35.2 % (30.8–39.8)	50.6 % (38.3–62.8)
Failure	36	3.5 % (2.4–5.0)	10.5 % (6.6–17.6)
Default	36	9.4 % (7.4–12.0)	15.4 % (10.2–22.5)
Death	38	19.7 % (16.4–23.5)	29.1 % (19.5–41.0)

Pharmacological Research 2022

Characteristics associated with treatment success

Factors	No. of cohorts	Treatment success	P-value
CD4 (cell/mm3)			
< 200	8	43.6%	**0.019**
> 200	10	**63.1%**	
Type of drug resist			
MDR/RR	31	59%	0.079
XDR	9	46.9%	
BDQ use			
Yes	11	**70.3%**	**0.004**
No	29	52.0%	
BDQ and LZD use			
Yes	9	**72.9%**	**0.003**
No	31	52.5%	
Moxiflox or levoflox use			
Yes	26	58.6%	0.865
No	4	57.7%	
No. of group A drug use			
0-1	26	55%	**0.005**
2 or more	10	**73.3%**	

Conclusions

- BDQ and LZD based regimen, and ***≥ 2 Group A drugs were associated with a higher treatment success rate.***

- Besides, higher CD4 T-cell count at baseline was also correlated with higher treatment success rate, too

- ***BDQ and LZD based all-oral regimen and early ART could contribute to higher treatment success***, particularly among XDR-TB-HIV patients

Pharmacological Research 2022

New Rx regimen of Pre-XDR, XDR-TB

Madhukar Pai

FDA approved

FDA Approves New Treatment for Highly Drug-Resistant Forms of Tuberculosis

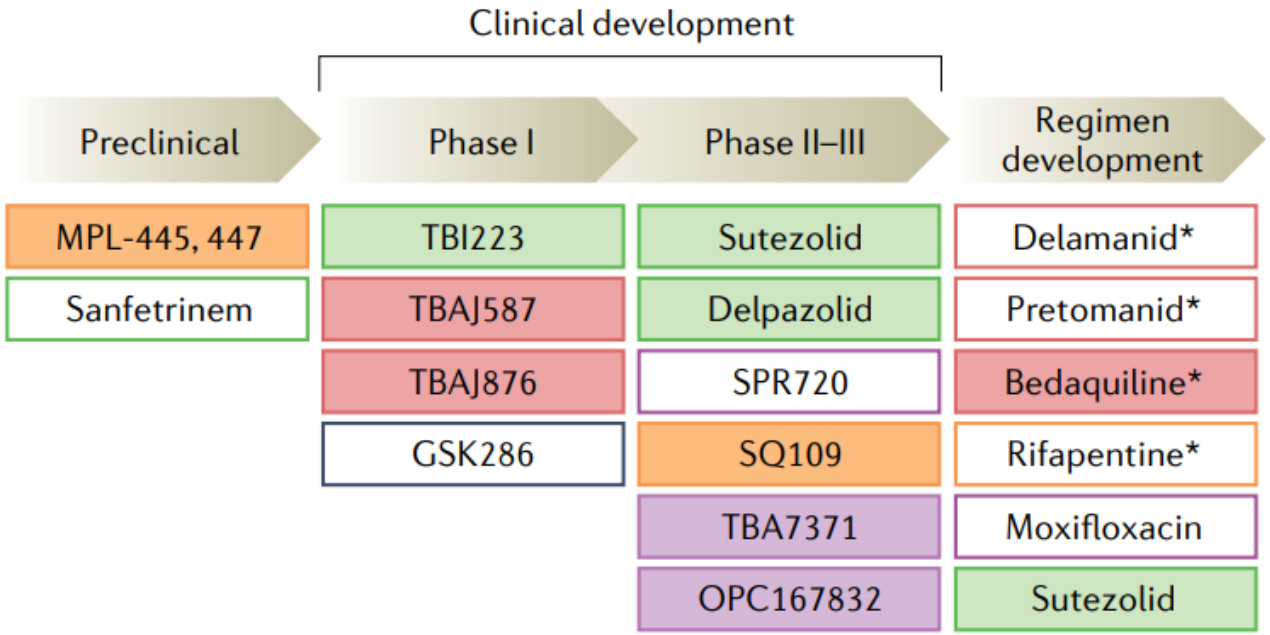
Pretomanid, developed by the non-profit TB Alliance, has received U.S. approval in combination regimen with bedaquiline and linezolid for people with XDR-TB or treatment-intolerant/non-responsive MDR-TB

August 14, 2019

Bedaquilline + Pretomanid + Linezolid for 6 mos.

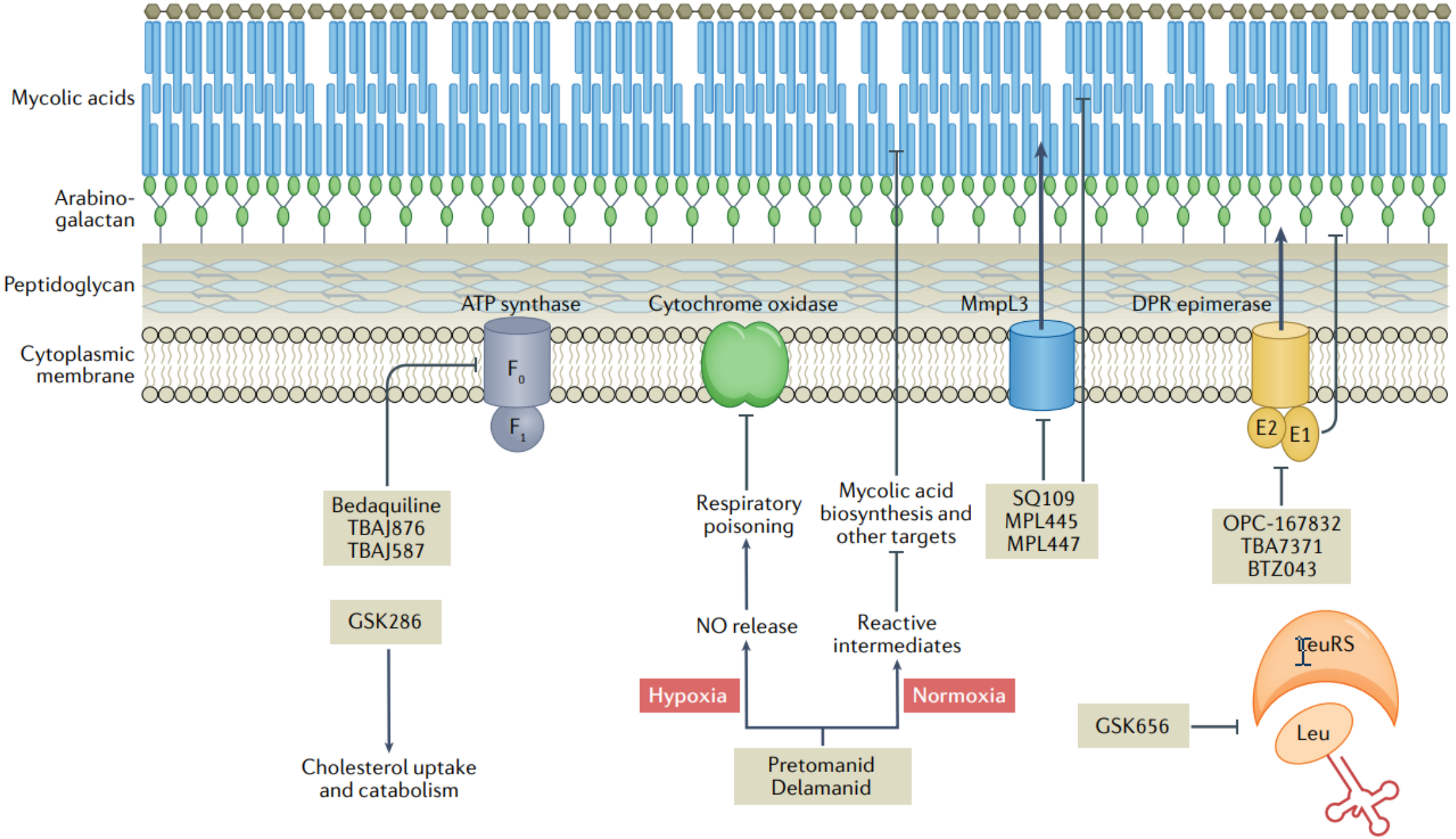
BPaL regimen

Anti-tuberculosis drug candidate pipeline and mechanism of drug action



Chemical class	Target
Nitroimidazole	Multiple
Diarylquinoline	ATP synthase
Oxazolidinone	Ribosome
Multiple	Cell wall (DprE1)
Fluoroquinolone benzimidazole	Gyrase
Multiple	Cell wall (MmpL3)
Oxaborole	Leu tRNA synthetase
Piperidinylpyrimidine	Cholesterol catabolism

NATURE REVIEWS | Microbiology 2022



NATURE REVIEWS | Microbiology 2022

The NEW ENGLAND JOURNAL of MEDICINE

Treatment of Highly Drug-Resistant Pulmonary TB

HIV-positiv

Linezolid 1,200 mg

- 17.3% completed Lzd 1,200 mg
- 36.5% completed with 600 mg
- 15.4 completed with 300 mg
- **30.7% stopped Lzd due to adverse event**

90% of all patients had favorable outcomes

Clinical resolution at 6 mo after therapy

89%
95% CI, 79–95

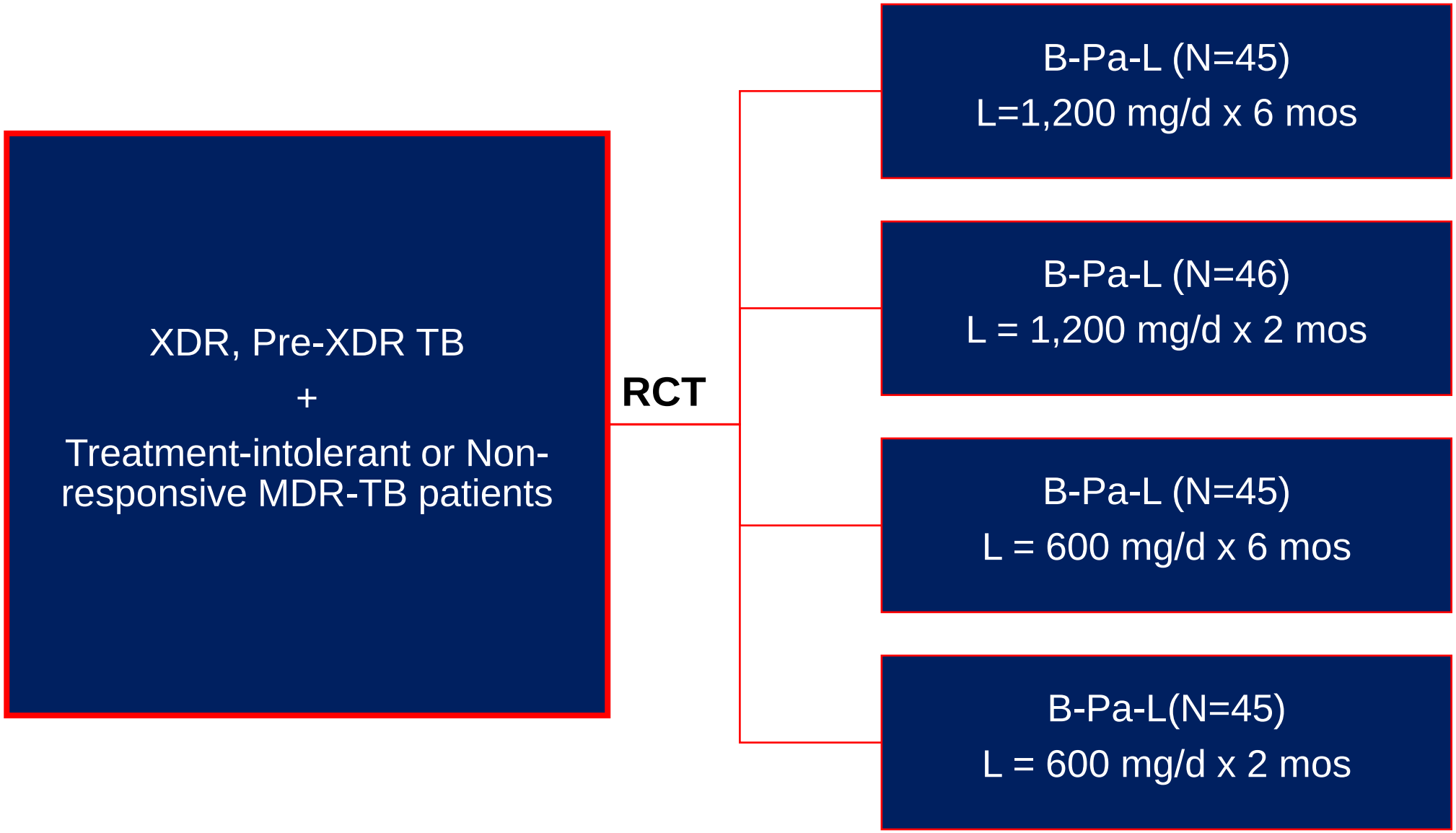
95% CI, 83–95

92%
95% CI, 79–98

Linezolid associated with peripheral neuropathy (81%) and myelosuppression (48%)

F. Conradie et al. 10.1056/NEJMoa1901814

The ZeNix study: Clinical design



BDQ dose = 200 mg x 8 wks, then 100 mg x 18 wks

Conradie, F. Presented at IAS 2021

The ZeNix study: primary efficacy analysis and side effects

	Linezolid 1,200 mg, 26 wks (N=45)	Linezolid 1,200 mg 9 wks (N=46)	Linezolid 600 mg, 26 wks (N=45)	Linezolid 600 mg, 9 wks (N=45)
Treatment emergent of AE of peripheral neuropathy	**17 (37.8%)**	11 (23.9%)	**11 (24.4%)**	6 (13.3%)
Treatment emergent of AE of optic neuropathy	**4 (8.8%)**	0 (0%)	**0 (0%)**	0 (0%)
Number of patients with worsening grade of anemia	**10 (22.2%)**	8 (17.4%)	**1 (2.2%)**	3 (6.7%)
Favorable treatment outcome	**41 (93.2%)**	40 (88.9%)	**40 (90.9%)**	37 (84.1%)

Conradie, F. Presented at IAS 2021

World Health Organization

2022

Rapid communication: Key changes to the treatment of drug-resistant tuberculosis

INT J TUBERC LUNG DIS 26(7):590–591

http://dx.doi.org/10.5588/ijtld.22.0263

EDITORIAL

WHO drug-resistant TB guidelines 2022: what is new?

WHO → new regimens

1. 6-month regimen base on Bedaquilline, pretomanid and linezolid in combination with moxifloxacin (BPaLM): **TB-PRACTICAL randomized clinical trial**

2. 6-month of BPaL with decreased exposure to linezolid (lower dosing (600 mg) or shorter duration): **ZeNix study**

3. The modified all-oral shorter regimens → 2 months of linezolid (at the daily dose of 600 mg) can replace 4 months of ethionamide: **NeXT trial**

INT J TUBERC LUNG DIS 2022.26(7):590–591

TB PRACTECAL Study (Uzbekistan, Belarus and South Africa)

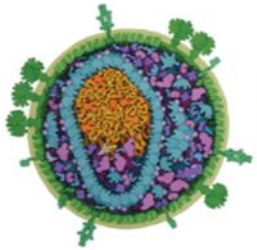
Stage I

Arm 1 : Bedaquiline + Pretomanid + Linezolid + Moxifloxacin 24 weeks

Arm 2 : Bedaquiline + Pretomanid + Linezolid + Clofazimine 24 weeks

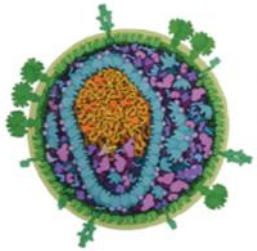
Arm 3 : Bedaquiline + Pretomanid + Linezolid 24 weeks

Linezolid: 600mg daily for 16 weeks then 300mg for 8 weeks



CROI
Conference on Retroviruses and Opportunistic Infections

TB PRACTECAL Study



CROI
Conference on Retroviruses and Opportunistic Infections

	Practecal Arm 1 (BPaLM)	Practecal Arm 2 (BPaLC)	Practecal Arm 3 (BPaL)
No. with culture conversion in liquid media at 8 weeks post randomization, n/N(%), [85% CI]	37/48 (77.1%) [66.4,85.6]	33/49 (67.3%) [56.2,77.2]	21/46 (45.7%) [34.4,57.3]
Unfavorable outcome	11.3%	18.8%	23.3%
Mean QTcF prolongation from baseline at 24 weeks	27.0 ms	40.2 ms	23.3 ms

TB PRACTECAL Study

24 MAR 21 This article is more than one year old

Drug-resistant TB clinical trial ends enrolment early after positive initial data

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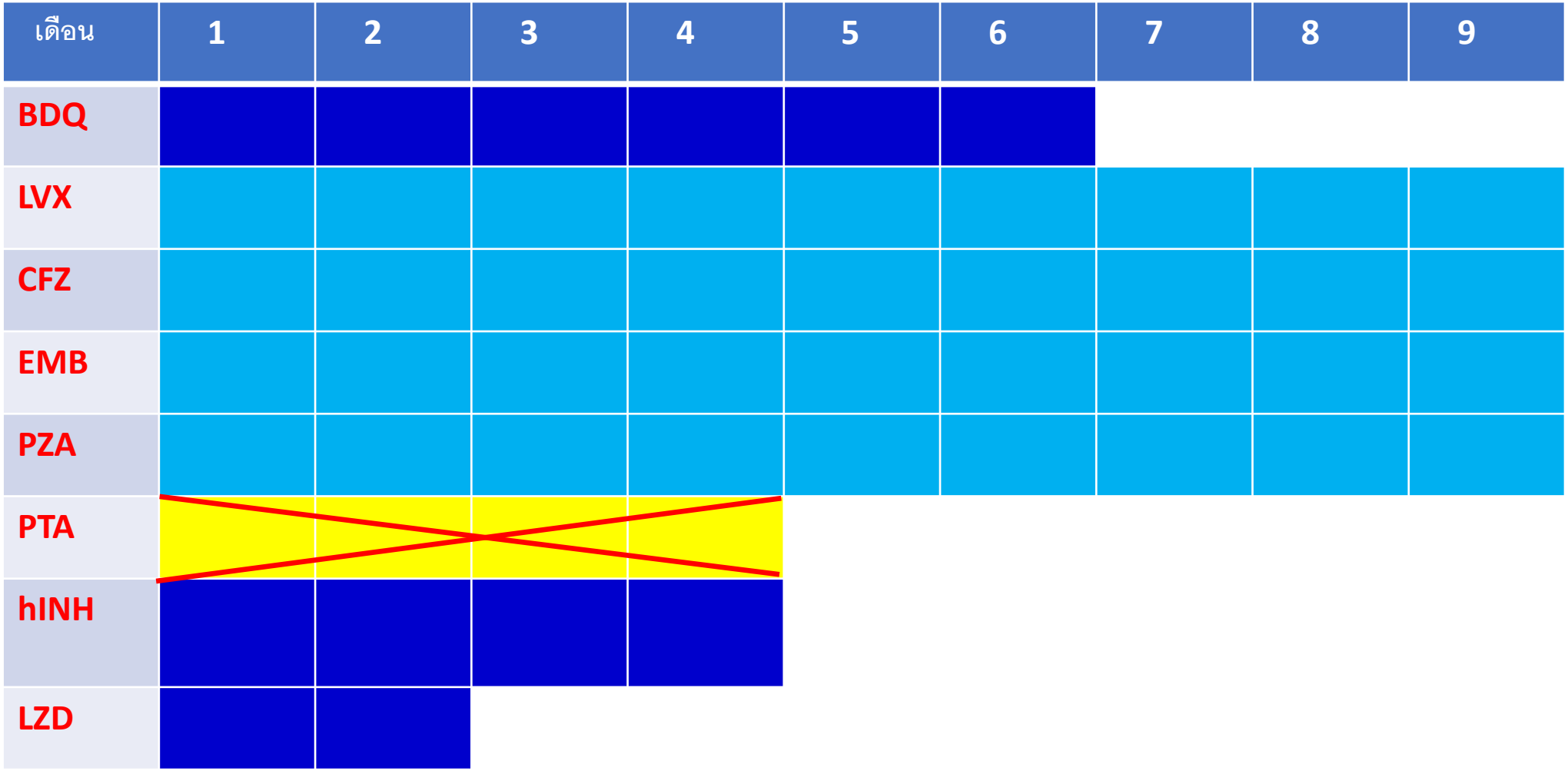
A trial aiming to find a better treatment for multidrug-resistant tuberculosis (MDR-TB) has stopped enrolling patients early after its independent data safety and monitoring board indicated that the regimen being studied is superior to current care, and more patient data was extremely unlikely to change the trial's outcome.

ขอบคุณ อาจารย์ เจริญ

New All-oral Shorter RR/MDR Regimen or BDQ-based Shorter RR/MDR Regimen 2022 (The NExT TB study)



BDQ=Bedaquiline, LVX=Levofloxacin, CFZ=Clofazimine, EMB=Ethambutol, PZA=Pyrazinamide, PTA=Prothionamide, hINH=high dose INH, LZD=Linezolid

ขอบคุณ อาจารย์ เจริญ

Core regimens to treat MDR/RR-TB

Regimen	Duration (months)	Indications	Contraindications
BPaLM (BDQ, pretomanid, linezolid, MFX) BPaL (without MFX)	6	MDR/RR-TB patients age 15 years or more; BPaL if documented resistance to FQs	Exposure to any of the drugs composing the regimen for ≥30 days
All-oral, BDQ-containing regimens **2 mo. of linezolid**	9	Adults and children with MDR/RR-TB	Previous exposure to second-line treatment (including BDQ), FQ resistance; extensive pulmonary TB disease; severe extrapulmonary TB
Individualised longer regimen	≥18	Patients with extensive forms of DR-TB (e.g., XDR-TB); or not eligible for the regimens described above or who previously failed shorter treatment regimens	

INT J TUBERC LUNG DIS 2022.26(7):590–591

Outlines

- New treatment regimens of MDR-TB
- **Drugs interaction of anti-TB and ARV**
- Tuberculosis preventive therapy (TPT) in HIV-infected patient

ARV and Rifampicin

Drugs	AUC	recommendation
Non-nucleoside RTI		
Efavirenz	No substantial change	No dose adjustment
Nevirapine	↓58%	Switch to rifabutin 300 mg
Rilpivirine	↓ 80%	Switch to rifabutin and double dose rilpivirine
Integrase inhibitors		
Raltegravir**	↓40%	Increase to 800 mg every 12 h
Dolutegravir	↓54%	Increase to 50 mg every 12 h
Bictegravir	↓75-80%	avoid

David Mhango. *Curr Opin Infect Dis* 2021 DHHS 2021 Graeme M. Lancet HIV 2019

ARV and Rifampicin

Drugs	AUC	recommendation
Nucleotide RTI		
Tenofovir alafenamide (TAF)	↓ 54%	Higher intracellular concentration
Protease inhibitors**		
Boosted atazanavir	↓ 72%	Switch to rifabutin 150 mg
Boosted darunavir	↓ 57%	Switch to rifabutin 150 mg
Boosted lopinavir	↓ 75%	Switch to rifabutin 150 mg

David Mhango. *Curr Opin Infect Dis* 2021

Graeme M. Lancet HIV 2019

Drug interaction of new anti-TB drugs vs antiretroviral agents

Drugs	Bedaquiline (BDQ) level
Rifampin	Reduced BDQ level ~ 79% (avoid)
Efavirenz	Reduced BDQ level ~ 50% (avoid)
Nevirapine	No interaction with BDQ
Lopinavir/ritonavir	Increase BDQ level ~ 22% (use with caution)
Integrase inhibitor	No significant interaction

Delamanid no interaction with EFV, NVP or boosted PI
Pretomanid: EFV reduced pretomanid concentrations by 30%

Overlap toxicity (anti-TB and HAART)

Side effects	Anti-TB	Anti-retroviral
Peripheral neuropathy	INH, Cycloserine, linezolid	D4T, DDI
Neuropsychiatric effects	Cycloserine, INH	Efavirenz, DTG
diarrhea	Eto/Pto, PAS	Protease inhibitors (PI)
Hepatitis	PZA, PAS, ethio	Nevirapine, EFV
Renal toxicity	Amikacin, Kanamycin	Tenofovir
Bone marrow suppression	Linezolid	AZT
Lactic acidosis	Lzd	D4T, DDI, AZT, 3TC
QT prolonged	Moxi, Levoflox, **BDQ**, Clofa	**Protease inhibitors** (**PI)**

F. Scano. *Int J Tuberc Lung Dis* 2008

HIV/AIDS - Research and Palliative Care 2020:12 9–31 Graeme M. Lancet HIV 2019

Clinical management of myelosuppression according to severity grading (Linezolid)

Severity grade	Mild	Moderate	Severe	Life threatening
Anemia	10.5-9.5 g/dL	9.4-8.0 g/dL	7.9-6.5 g/dL	< 6.5 g/dL
Platelets	99,999-75,000	74,999-50,000	49,999-20,000	< 20,000
WBC	3,000	< 3,000-2,000	**< 2,000-1,000**	< 1,000
ANC	1,500-1,000	999-750	**749-500**	< 500
Action	Monitor carefully	***Reduction of dose*** of Lzd (300 mg OD)	Stop Lzd immediately; restart at reduced dose once toxicity decrease to grade mild	

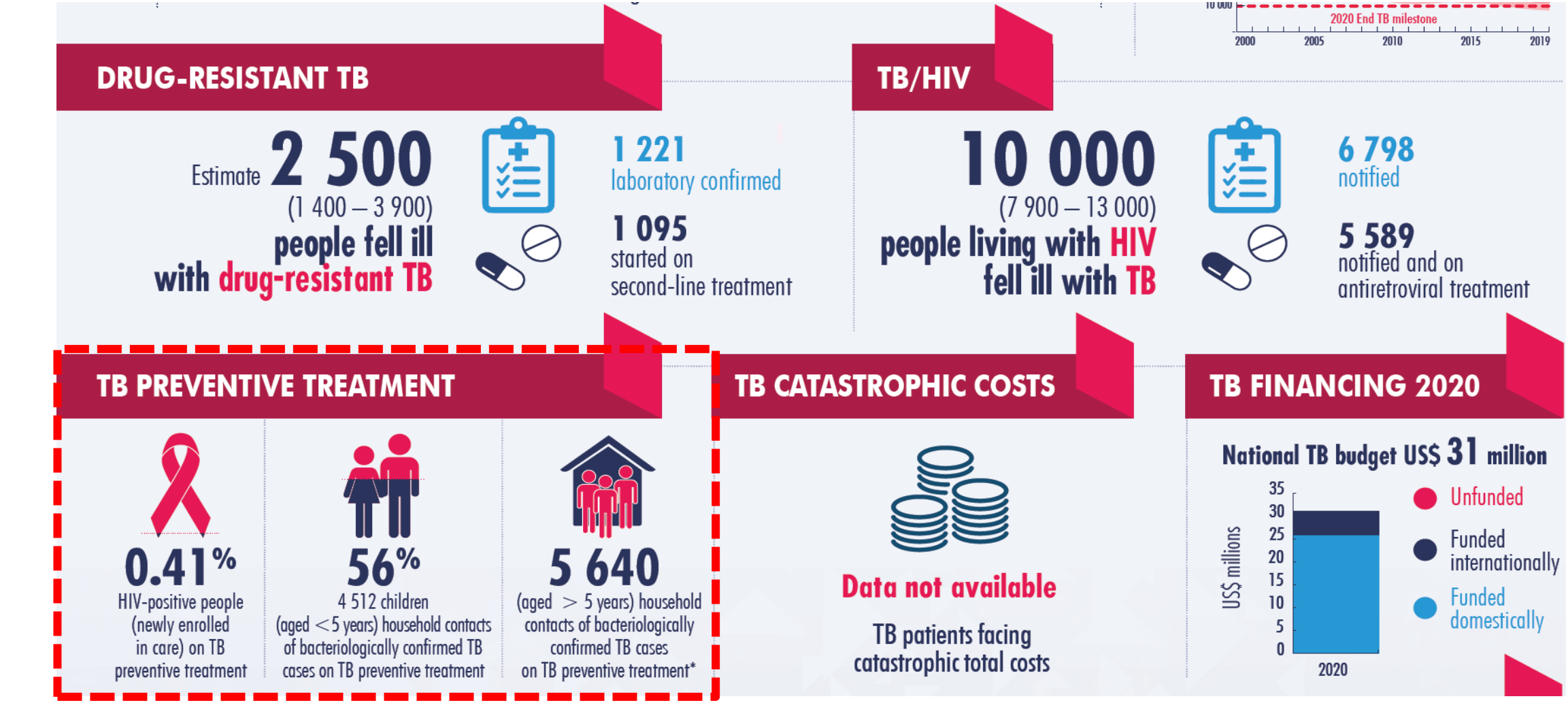
endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs. Version 4.0; 2018.

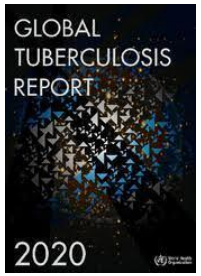
Outlines

- New treatment regimens of MDR-TB
- Drugs interaction of anti-TB and ARV
- **Tuberculosis preventive therapy (TPT) in HIV-infected patient**

	WHO 2018	WHO 2020	Thai guideline 2021/2022
HIV	Unknown or + TST TPT	Treated without tested	CD4 < 200 → Rx CD4 ≥ 200 → tested and Rx TST ≥ 5 mm or IGRA +
Household Contacts	HIV-negative < 5 years → Rx Low TB→ test and Rx High TB → up to	Regardless of HIV status children < 5 years → TPT ≥ 5 years, adults → national guideline	Children < 5 years → Rx adult → tested and Rx TST ≥ 15 mm or IGRA +
Anti-TNF Dialysis Transplant Silicosis	Tested and Rx (strong recommend)	Tested and Rx (strong recommend)	Tested and Rx TST ≥ 10 mm or IGRA +
Prisoner HCWs Homeless Immigrant	Tested and Rx (Conditional recommend)	same (Conditional recommend)	Not mentioned

สถานการณ์วัณโรคประเทศไทย





WHO 2020

ทำไม TPT ในผู้ป่วย HIV ในประเทศไทยถึงมีการให้อย่างไม่แพร่หลาย

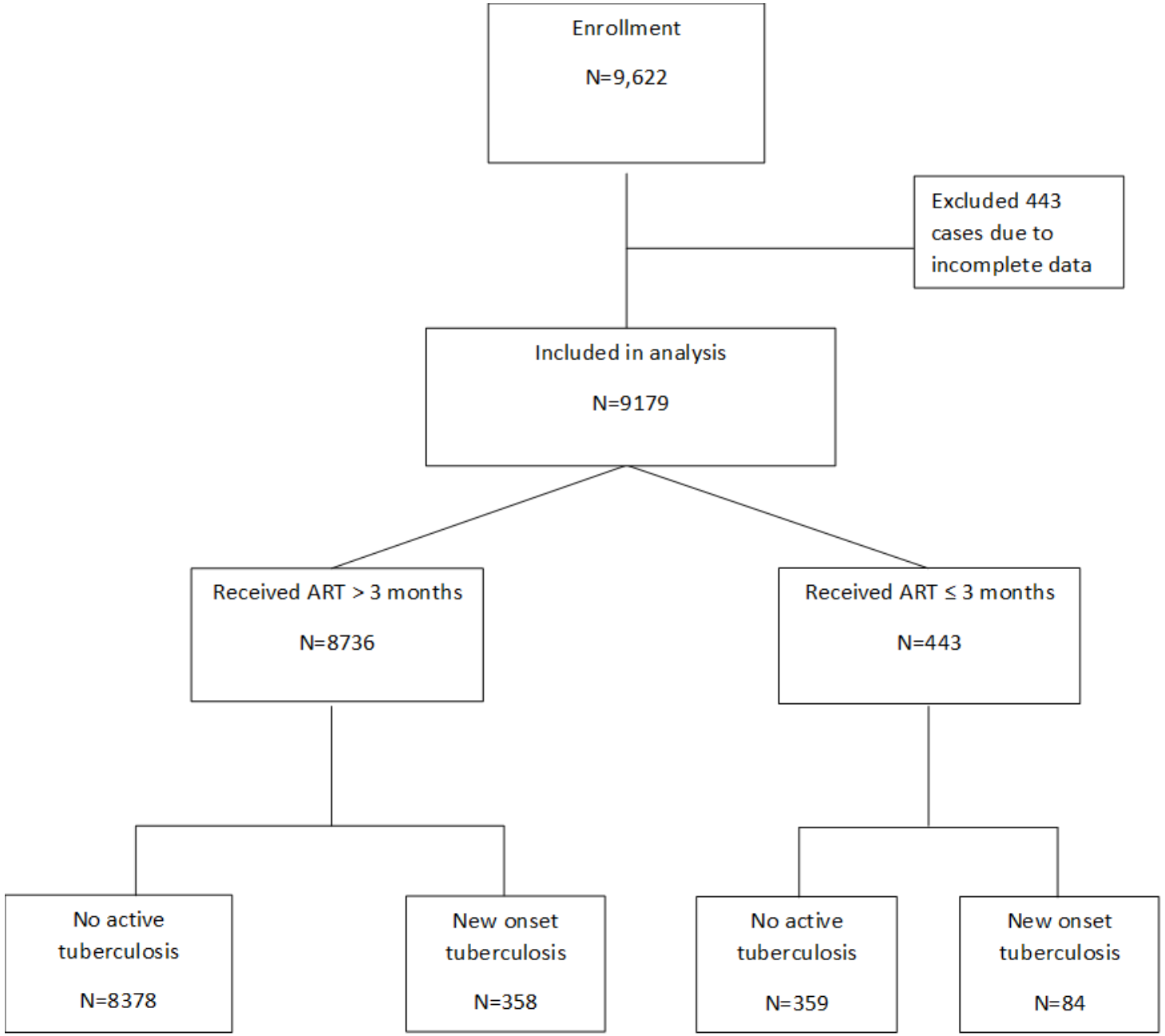
- Concern that TPT may **select resistant bacilli** when given to patients with ***undiagnosed TB***
- ***ART decreased the risk of TB***, physicians might priorities successful ART and ensure **immune recovery** as early as possible, rather than implement IPT
- **INH resistance > 15% in that country** → IPT may be not effective
- Concomitant **side effects**

Suwanpimolkul G et al. *Journal of the International AIDS Society* 2022, **25**:e25900
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25900/full | https://doi.org/10.1002/jia2.25900

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Incidence of active tuberculosis among people living with HIV receiving long-term antiretroviral therapy in high TB/HIV burden settings in Thailand: implication for tuberculosis preventive therapy



Incident of active tuberculosis among HIV-infected adults receiving long term antiretroviral therapy in high TB/HIV burden in Asia: Implication for tuberculosis preventive therapy

- We determined the incidence of active TB and mortality among ***9,179 adult PLHIV who attended and received ART from 15 hospitals*** across Thailand.

Suwanpimolkul G., Avihingsanon A, *Journal of the International AIDS Society* 2022

Incidence TB per 100,000/year follow-up by duration on antiretroviral therapy

Duration ART	person-year	TB new onset	incidence rate	95%CI	
≤ 3 months	48	84	175511	141720	217359
> 3 months to 6 months	119	32	26974	19075	38143
> 6 months - 1 year	310	39	12579	9190	17216
>1 years - 2 years	1350	58	4298	3323	5559
>2 years - 3 years	2335	39	1670	1220	2286
>3 years - 4 years	3476	34	978	699	1369
>4 years - 5 years	2527	30	1187	830	1698
>5 years - 6 years	3169	20	631	407	978
>6 years - 7 years	4039	18	446	281	707
>7 years - 8 years	3217	16	497	305	812
>8 years - 9 years	4211	10	237	128	441
>9 years - 10 years	5013	18	359	226	570
>10 years	29138	44	151	112	203

Suwanpimolkul G., Avihingsanon A, *Journal of the International AIDS Society* 2022

Incidence TB per 100,000/year follow-up by CD4 ***at time of antiretroviral initiation***

CD4 at initiate ART, cells/mm3	Person-year	TB new onset	Incidence rate	95%CI	
≤ 100	14652	169	1153	992	1341
101-200	10469	102	974	802	1183
201-350	15579	88	565	458	696
351-500	9160	33	360	256	507
>500	7113	31	436	306	620
Unknown	1978	19	960	613	1506
Total	58951	442	750	683	823

Suwanpimolkul G., Avihingsanon A, *Journal of the International AIDS Society* 2022

Incidence rate per 100,000 per Person-year follow up by HIV-RNA and CD4 *at TB diagnosis*

	Person-year	TB new onset	Incidence rate	95% CI	
HIV-RNA ≥ 50 copies/mL					
CD4 cell count at ART					
≤ 100	902	46	5100	3820	6809
101-200	427	25	5858	3958	8670
201-350	754	22	2919	1922	4434
351-500	443	8	1804	902	3607
>500	332	5	1505	627	3617
HIV-RNA< 50 copies/mL					
CD4 cell count at ART					
≤ 100	13038	105	805	665	975
101-200	9674	62	641	500	822
201-350	14125	62	439	342	563
351-500	8330	19	228	145	358
>500	6362	21	330	215	506

Suwanpimolkul G., Avihingsanon A, *Journal of the International AIDS Society* 2022

Conclusions

- Our findings also showed that PLHIV with ***VL suppression and CD4 > 500 cells/mm3*** the risk of active TB remained 2 times higher than general population

- Our findings further support ***rapid ART initiation and appropriated TPT*** to be a key intervention to tackle the TB epidemic and mortality rate among PLHIV in Asia.

Suwanpimolkul G., Avihingsanon A, *Journal of the International AIDS Society* 2022

Tuberculosis Preventive Treatment in HIV

- DHHS guideline 2021 and WHO 2021
  - 3 months of once-weekly isoniazid plus rifapentine **(PREVENT TB study)**
    - **Treatment completion was *higher with 3HP (89%) than 9H (64%) (P < 0.001)***
  - 4 months of daily rifampin
  - 3 months of daily isoniazid plus rifampin
  - Also recommend 1 month of daily isoniazid with rifapentine **(BRIEF TB study):** 3,000 people with HIV → fewer adverse events and ***higher treatment completion rate (97% vs. 90%, P<0.001).***
  - Isoniazid daily for 6 or 9 months remains an alternative option, especially for patients in ***whom rifamycin cannot be used***

AIDS 2016, 30:1607–1615

N Engl J Med 2019;380:1001-11

TAKE HOME MESSAGES

- MDR-TB: ถ้าใช้ shorter BDQ-containing regimen ได้ ให้ใช้ถ้ามีข้อห้ามให้ใช้ all oral longer regimen
- BPaL and BPaLM regimen ในการรักษา MDR-TB/Pre-XDR TB: ประเทศไทยเริ่มมีการปรับนำมาใช้ใน guideline ที่กำลังปรับใหม่แล้ว แต่ยังใช้เป็น operational research อยู่เฉพาะบางโรงพยาบาลที่เข้าร่วมและมีความพร้อม
- Linezolid dose 1,200 → 600 mg
- BDQ ห้ามใช้คู่กับ EFV และ ต้องระวังถ้าจะใช้ร่วมกับ PI
- พิจารณาให้ IPT ในผู้ป่วย HIV ที่มี TST หรือ QFT เป็นบวก และไม่ได้เป็น active TB: จากข้อมูลการศึกษาในไทยพบว่าแม้ ได้ยาต้านไวรัสไปแล้ว อุบัติการณ์ของการเกิด active TB ยังสูงหลายเท่าเมื่อเทียบกับประชากรปกติ จะเท่ากับประชากรปกติได้จะต้อง ได้รับ HAART นานถึง 10 ปีไปแล้ว

ขอบคุณทุกท่านมากครับ

Drug-drug interaction between WHO group A and B drugs for rifampicin-resistant tuberculosis and antiretroviral drugs

Interacting antiretroviral drug	
Bedaquiline ***(with food)***	EFV ***(avoid coadministration);*** ↓ halves exposure Protease inhibitor *2-fold increase* (monitor EKG) Favor INSTI (DTG, RAL) → regular dose
Clofazimine	Additive QT effect with EFV, monitor EKG
Levofloxacin	No interaction
Linezolid	Avoid AZT (share bone marrow toxicity)
Moxifloxacin	EFV ***reduces AUC by 30%;*** clinical significant interaction need further study; consider using levofloxacin

Graeme M. Lancet HIV 2019

PK of Dolutegravir with 3HP: (the DOLPHIN trial)

60 African PLHIV with HIV RNA < 50 c/ml เปลี่ยนจาก EFV เป็น DTG

- In a phase 1/2 study of 60 adults with HIV and virologic suppression DOLPHIN study)
  - Adults (≥18 years) with HIV infection and undetectable viral load (<40 copies per mL) after at least 8 weeks of efavirenz-based or dolutegravir-based regimens were recruited
  - On once-daily dolutegravir-based ART and weekly rifapentine with isoniazid
  - ***DTG trough concentrations were reduced by 50% to 60%***
  - ***All but one participant's trough concentration remained above the DTG protein-adjusted IC90***
  - ***All HIV viral loads remained suppressed***

Lancet HIV 2020; 7: e401–09

- WHO 2020: Individual longer regimen (18 months) based on the drug grouping (A,B,C) is still consider

  - i) those with extensive forms of drug-resistant-TB (e.g., XDR-TB);
  - ii) those who are not eligible for the regimens described above, or
  - iii) those who have previously failed shorter treatment regimens.

INT J TUBERC LUNG DIS 2022.26(7):590–591

Guideline of LTBI among PLHIV in Thailand: 2021/2022

INH 300 mg+ RPT 450-600mg dailyx4 weeks (+B6)

BW<35 kg, RPT 300mg
BW 35-45 kg, RPT 450 mg
BW > 45 kg, RPT 600 mg

RPT + INH
300 mg/300 mg
Film-coated

Completion rate 97% (1HP) vs 90% (9H), p<0.001 (BRIEF study)[1]

INH 900 mg+ RPT 900 mg weekly x12 weeks (+B6)

BW > 50 kg, RPT900mg
BW 32-49.9 kg, RPT 750 mg
BW > 60 kg, INH 900 mg

Completion rates 82% (3HP) vs 69% (9H) (PREVENT study)

INH 15 mg/Kg

Alternative

INH 300 mg +B6 dailyx9 months

ผลข้างเคียงสำคัญ : **Elevated ALT : 1HP 2%, 3HP 0.4%, 9H 2.7-5%, Rifam 0%**
Hypersensitivity reaction : 3HP
systemic drug reaction : 3 HP (3.8%)vs. 9 H (0%);
Cutaneous reaction: 10.6% (3HP) vs 6.9%(9H)
Hypersomnia : 6.8% (3HP) vs 3.8% (9H)

ขอบคุณอาจารย์ อัญชลี

Risk factors associated with TB incidence after ART initiation

	Univariate		Multivariate	
	SHR (95% CI)	*p*-value	aSHR (95% CI)	*p*-value
At ART initiation				
Age (years)	0.94 (0.78–1.13)	0.55		
Male	1.35 (1.11–1.65)	<0.001	1.40 (1.11–1.78)	0.003
CD4 cell count, cells/mm^3				
• ≤100	2.79 (2.10–3.72)	<0.001	2.08 (1.47–2.92)	<0.001
• 101–200	2.54 (1.86–3.46)	<0.001	2.21 (1.54–3.16)	<0.001
• 201–350	1.48 (1.07–2.04)	0.02	1.59 (1.11–2.28)	0.01
• >350	Ref		Ref	
Weight <50 kg	1.38 (1.10–1.74)	0.005	1.52 (1.17–1.95)	0.001
Prior TB event	3.67 (2.97–3.58)	<0.001	3.50 (2.72–4.52)	<0.001
During follow-up				
Diabetes mellitus	0.71 (0.45–1.10)	0.13		
Chronic kidney disease	0.87 (0.59–1.27)	0.47		
Chronic liver disease	1.39 (1.05–1.84)	0.02	0.95 (0.67–1.35)	0.79

Suwanpimolkul G., Avihingsanon A, *Journal of the International AIDS Society* 2022