Photo: Shehzad Noorani/Stop TB Partnership

New Drugs and DRTB Management

詹珮君醫師

Outline

- Pediatric FDC 3 (RHZ) & 2(RH)
- Rifapentine
- Bedaquiline
- Delamanid
- DRTB WHO Guidelines Update

Pediatric FDC 3 (RHZ) & 2(RH)

New fixed-dose combinations for the treatment of TB in children

QUICK FACTS

- **At least 1 million children become ill with tuberculosis (TB) each year. Children represent about 10-11% of all TB cases.**
- **In 2014, 81 000 children died of TB, and there were an additional 55 000 TB deaths among children who were HIV-positive.**
- **TB in children can be treated. Most children tolerate treatment very well.**
- **Preventive therapy is highly effective in children exposed to TB.**
- **Simple, child-friendly fixed-dose formulations are easy to administer and match WHO dosage recommendations for first line treatment.**

NEW HOPE FOR CHILDREN WITH TB

SIMPLE, CHILD-FRIENDLY TB TREATMENT NOW AVAILABLE

Until recently, there was no appropriate first-line TB treatment designed for children. However, after sustained advocacy and new investment, now child-friendly formulations that do not need to be cut or crushed to achieve an appropriate dose are available, offering the opportunity to simplify and improve treatment for children everywhere.

The formulations were developed in line with the revised dosing published in the 2014 WHO Guidance

ABOUT THE FIXED-DOSE COMBINATIONS FOR CHILDREN

The formulations now available are :

For the intensive phase of TB treatment:

Rifampicin 75 mg + Isoniazid 50 mg + Pyrazinamide 150mg

For the continuation phase of TB treatment:

Rifampicin 75mg + Isoniazid 50 mg

The following dosing table provides information on the number of daily tablets needed to reach the proper dosing, based on the child's weight:

Weight band	Numbers of tablets	
	Intensive phase: RHZ 75/50/150*	Continuation phase: RH 75/50
4-7 kg	1	1
8-11 kg	2	2
12-15 kg	3	3
16-24 kg	4	4
25+ kg	*Adult dosages recommended*	

*Ethambutol should be added in the intensive phase for children with extensive disease or living in settings where the prevalence of HIV or of isoniazid resistance is high

TREATING TB IN CHILDREN

All children treated for TB should be registered with the National TB programme.

The following dosages of first-line anti-TB medicines should be used daily for the treatment of TB in children:

Isoniazid (H)	10 mg/kg (range 7–15 mg/kg)
Rifampicin (R)	15 mg/kg (range 10–20 mg/kg)
Pyrazinamide (Z)	35 mg/kg (range 30–40 mg/kg)
Ethambutol (E)	20 mg/kg (range 15–25 mg/kg)
As children approach a body weight of 25 kg, adult dosages can be used	

兒童複方可溶錠

- 兒童友善
- 巴布紐亞幾內亞是地球上第一個使用此新劑型的國家
- 目前有27個國家在2016年底之前會拿到此藥物
- 供未滿25kg孩童使用
- 水果口味口感
- 方便運送攜帶

Stop TB Partnership Announcement
5 October 2016

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THE STOP TB PARTNERSHIP

Leading the fight against TB

Photo: Shehzad Noorani/Stop TB Partnership

Children with TB getting better treatment - rapid roll-out of the new child friendly medicines in 27 countries

The cost of medicines to treat one child for six months

小兒患者體重 (kg)	使用錠數	
	加強期 (Intensive Phase)	持續期 (Continuation Phase)
	RHZ 75/50/150 (mg)	RH 75/50 (mg)
4-7	1	1
8-11	2	2
12-15	3	3
16-24	4	4
25以上	請參考成人劑量開立處方	

RHZ及RH的使用注意事項

1.	藥品尚未取得我國藥證，故不符合申請藥害救濟的範圍 請各醫療院所在使用時，加強病人不良反應監測及通報 若經發現，請立即通知全國藥物不良反應通報中心，以保障病人權益。
2.	為確保病人監護人知情同意之權利，藥品在使用前應先向其清楚說明與告知，並取得病人同意書；惟若情況緊急，亦應註於病歷，以供查考。

Rifapentine

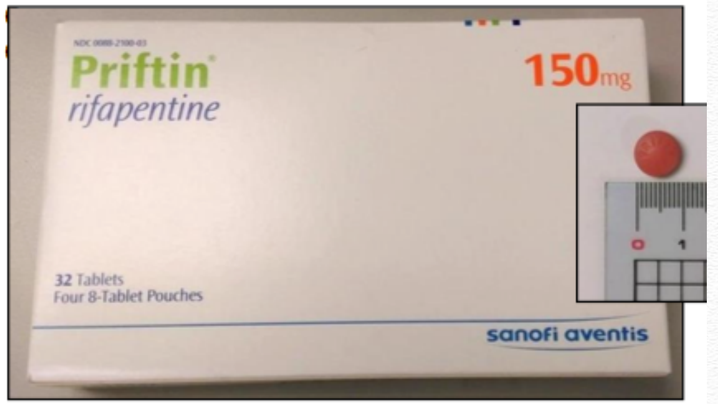
潛伏結核全都治計畫
2016年全面推行

增加短程治療處方之選擇
短程處方須以傳統都治方式執行

短程處方(3HP速克伏)

once weekly x 3 months =

only 12 doses



900mg Isoniazid (INH) +
900mg Rifapentine (RPT)

速克伏3HP短程處方建議劑量

Drug	Dose (>12 year-old)	Frequency	Duration
isoniazid (INH) **300mg 3#** 	**15 mg/kg rounded up to the nearest 50 or 100 mg;** 900 mg maximum (25 mg/kg for those 2-11 years)	Once weekly	3 months
rifapentine (RPT) **150mg 6#** 	**10.0–14.0 kg 300 mg** 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg **≥50.0 kg 900 mg** maximum	Once weekly	3 months

US CDC Latent Tuberculosis Infection: A Guide for Primary Health Care Providers
http://www.cdc.gov/tb/publications/ltbi/

潛伏結核全都治專區

https://goo.gl/dPwQye

使用速克伏需要做哪些監測？

- **肝硬化、慢性肝炎或肝病變、酒癮、靜脈毒癮者、HIV陽性病人、孕婦及產後3個月的婦女**、建議檢驗肝功能基礎值ALT(GPT)、total bilirubin，治療開始後的前2個月每月檢驗肝功能。**≧35歲以上者**，建議檢驗肝功能基礎值ALT(GPT)、total bilirubin 及HBsAg, anti-HCV Ab，HIV ELISA/Combo Ag+Ab，任一異常，則治療開始後的前2個月每月檢驗肝功能。
- 肝炎定義：
  - 治療前肝功能<正常值2X：ALT (GPT) >正常值5X或臨床有肝炎症狀且ALT (GPT) >正常值 3X或total bilirubin >3mg/dL
  - 治療前肝功能≧正常值2X：肝功能超過治療前基礎值的2X
- **有肝病或其他醫療考慮(貧血或血小板相關的疾病)時，建議驗CBC/DC的基礎值，再決定追蹤的頻率**
- 每月回診評估，視臨床情況進行抽血檢查

不適用「速克伏」者

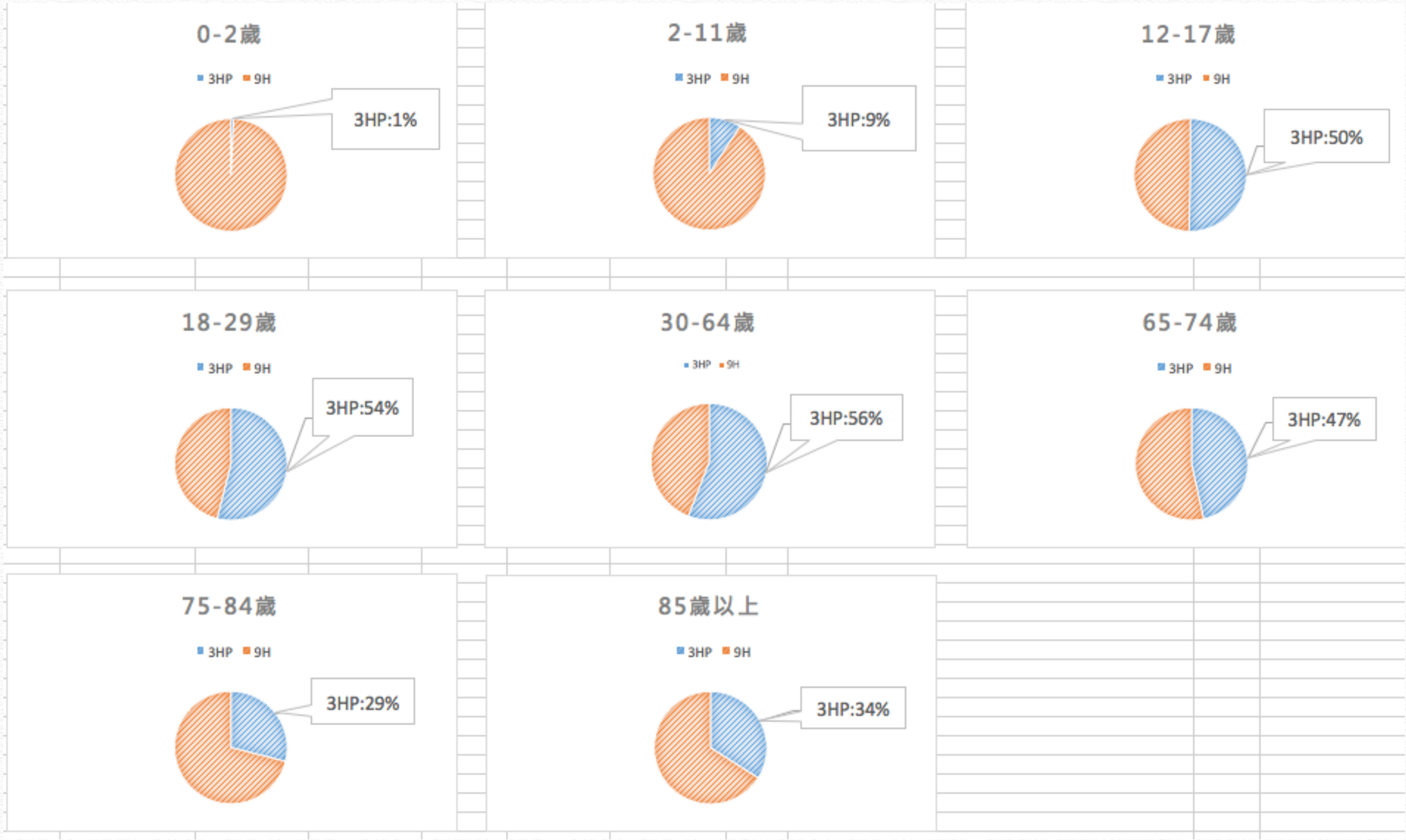
孕婦或準備懷孕的婦女	指標個案為INH或RMP抗藥	未滿2歲之兒童

- 接受ARTs治療之HIV感染者 **(protease inhibitors 的濃度會被影響)**
- 2-11歲兒童(建議處方為9H，欲使用3HP請參考劑量建議)
- **正在使用coumadin, methadone, phenytoin**

潛伏結核全都治專區

https://goo.gl/dPwQye

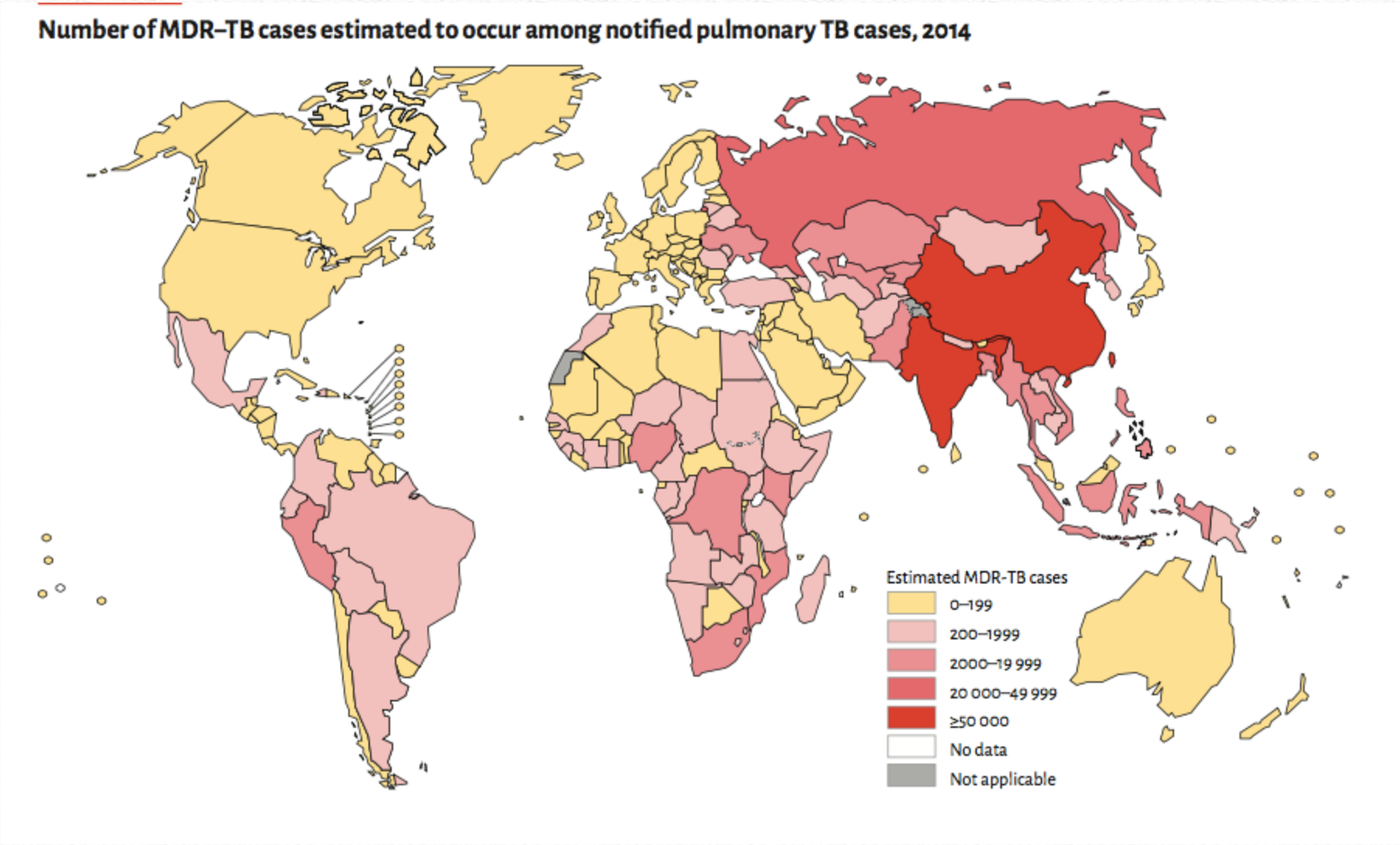
不同年齡層的3HP vs. 9H



不良反應

- 最常見的不良反應
- 永久停藥率
- 住院率
- 死亡率

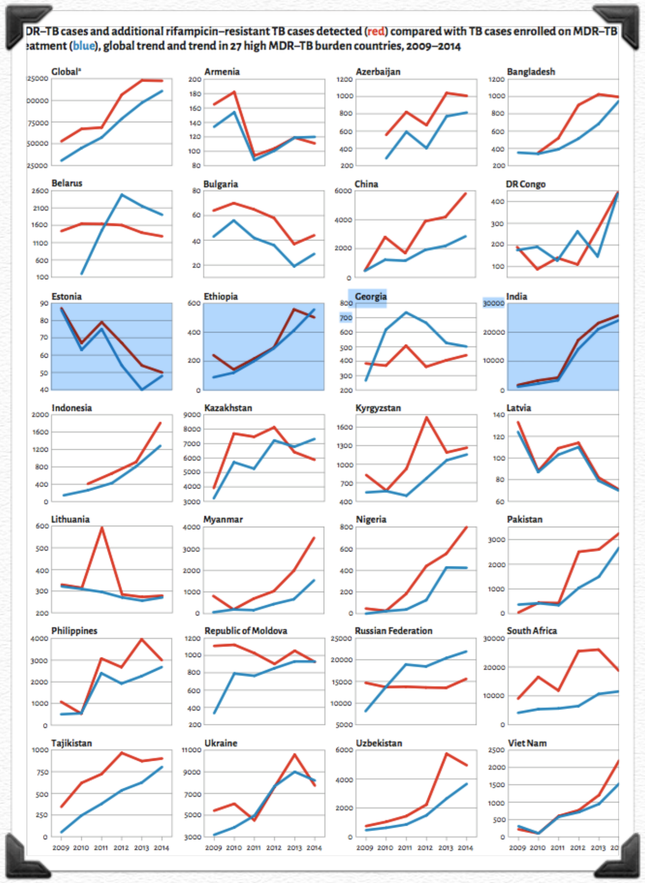
MDRTB Burden 2014



300,000 notified MDRTB , 62.5% of 480,000 MDRTB cases in the world (19-90%)

Low Treatment Rate

- 123,000 MDR/RR TB patients eligible for treatment
- 40% of the 300,000 notified MDRTB
- 26% of 480,000 MDRTB cases in the world



The development pipeline for new TB drugs, August 2015[a]

Lead optimization	Preclinical development	Good Laboratory Practice toxicity	Phase I	Phase II	Phase III
Cyclopeptides	TBI-166	PBTZ169	TBA-354	Sutezolid (PNU-100480)	Bedaquiline (TMC-207) with OBR[b] for MDR-TB
Diarylquinolines	CPZEN-45	Q203		SQ109	Delamanid (OPC-67683) with OBR[b] for MDR-TB
DprE Inhibitors	SQ609			Rifapentine for DS-TB	Rifapentine for LTBI
InhA Inhibitor, Indazoles	SQ641			AZD5847	Pretomanid-Moxifloxacin-Pyrazinamide Regimen
LeuRS Inhibitors, Ureas	DC-159a			Bedaquiline-Pretomanid-Pyrazinamide Regimen	
Macrolides, Azaindoles					
Mycobacterial Gyrase Inhibitors					
Pyrazinamide Analogs					
Ruthenium(II) Complexes					
Spectinamides SPR-113					
Translocase-1 Inhibitors					

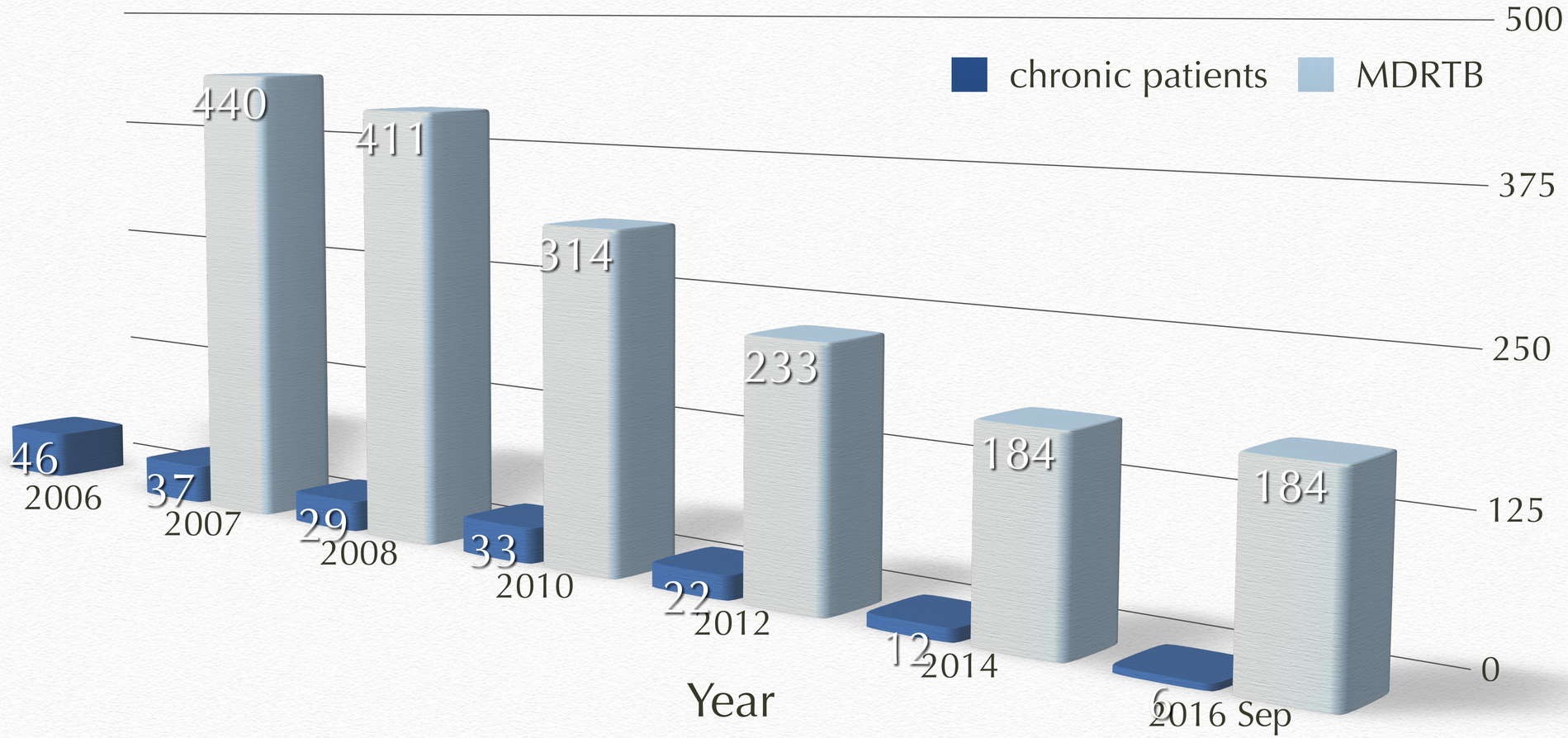
Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

[a] Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php

[b] OBR = Optimized Background Regimen

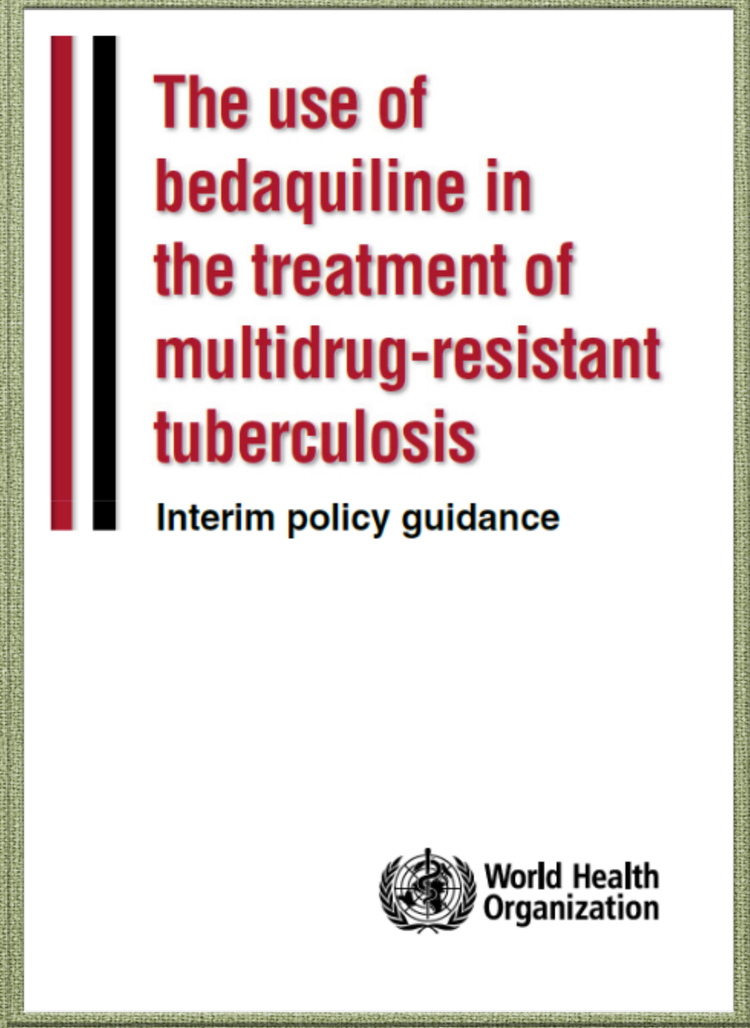
Source: Working Group on New TB Drugs, 2015 – www.newtbdrugs.org

Chronic Patients and MDR-TB



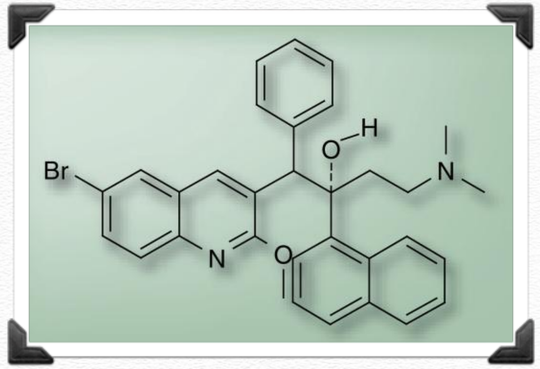
Bedaquiline

TMC 207



Compound of R207910

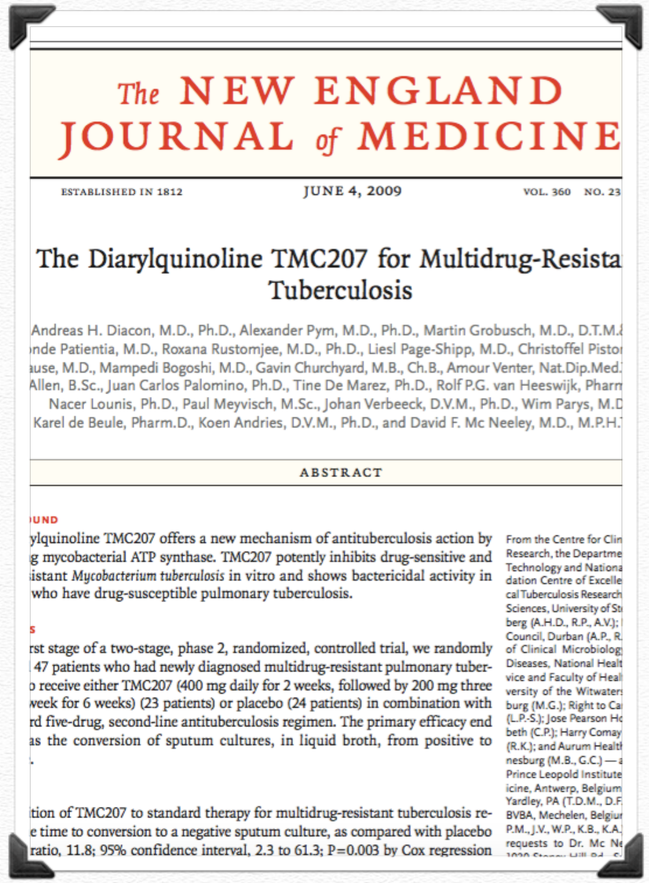
- Inhibition of the proton pump of mycobacterial ATP synthase.
- ATP synthase is a critical enzyme in the synthesis of ATP for M. tuberculosis.
- Binding of TMC207 to the oligomeric and proteolipic subunit c of mycobacterial ATP synthase leads to inhibition of ATP synthesis, which subsequently results in bacterial death.



Future Microbiol. 2010; 5 (6): 849–58.

Era of TMC207

- TMC-207 was described for the first time in 2004 at the ICAAC meeting, after the drug had been in development for over 7 years
- A Phase II trial of 47 patients, which showed that the drug was effective in reducing the time to TB-free sputum cultures.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 4, 2009 VOL. 360 NO. 23

The Diarylquinoline TMC207 for Multidrug-Resista Tuberculosis

Andreas H. Diacon, M.D., Ph.D., Alexander Pym, M.D., Ph.D., Martin Grobusch, M.D., D.T.M.
nde Patientia, M.D., Roxana Rustomjee, M.D., Ph.D., Liesl Page-Shipp, M.D., Christoffel Pisto
use, M.D., Mampedi Bogoshi, M.D., Gavin Churchyard, M.B., Ch.B., Amour Venter, Nat.Dip.Med.
Allen, B.Sc., Juan Carlos Palomino, Ph.D., Tine De Marez, Ph.D., Rolf P.G. van Heeswijk, Pharm
Nacer Lounis, Ph.D., Paul Meyvisch, M.Sc., Johan Verbeeck, D.V.M., Ph.D., Wim Parys, M.D
Karel de Beule, Pharm.D., Koen Andries, D.V.M., Ph.D., and David F. Mc Neeley, M.D., M.P.H.

ABSTRACT

UND

ylquinoline TMC207 offers a new mechanism of antituberculosis action by g mycobacterial ATP synthase. TMC207 potently inhibits drug-sensitive and istant *Mycobacterium tuberculosis* in vitro and shows bactericidal activity in who have drug-susceptible pulmonary tuberculosis.

S

rst stage of a two-stage, phase 2, randomized, controlled trial, we randomly 47 patients who had newly diagnosed multidrug-resistant pulmonary tuber- receive either TMC207 (400 mg daily for 2 weeks, followed by 200 mg three week for 6 weeks) (23 patients) or placebo (24 patients) in combination with rd five-drug, second-line antituberculosis regimen. The primary efficacy end as the conversion of sputum cultures, in liquid broth, from positive to

tion of TMC207 to standard therapy for multidrug-resistant tuberculosis re- e time to conversion to a negative sputum culture, as compared with placebo ratio, 11.8; 95% confidence interval, 2.3 to 61.3; P=0.003 by Cox regression

From the Centre for Clin Research, the Departme Technology and Nationa dation Centre of Excelle cal Tuberculosis Research Sciences, University of St berg (A.H.D., R.P., A.V.); Council, Durban (A.P., R. of Clinical Microbiolog Diseases, National Healt vice and Faculty of Heal versity of the Witwaters burg (M.G.); Right to Ca (L.P.-S.); Jose Pearson Ho beth (C.P.); Harry Comay (R.K.); and Aurum Health nesburg (M.B., G.C.) — Prince Leopold Institute icine, Antwerp, Belgium Yardley, PA (T.D.M., D.F. BVBA, Mechelen, Belgiu P.M., J.V., W.P., K.B., K.A. requests to Dr. Mc Ne

N. Engl. J. Med. 2009;360 (23): 2397–2405.

The Benefit–Risk Balance for Drug-Resistant Tuberculosis

- **Approved by the USFDA at the end of 2012 for the treatment of adults with pul MDR-TB for whom an effective treatment regimen is not otherwise available.**

- The phase 2 RCT of Bedaquiline sponsored by Tibotec and the TB Alliance revealed unexplained excessive mortality for patients in TMC-207 arm (2/81 vs. 10/79, 1 accident, 4 patients not related to TB disease itself)

- One of the deaths among bedaquiline-treated patients occurred during the 24-week trial period; the median time to death in the remaining 8 patients was 329 days after the patient last received bedaquiline.

Future Microbiol. 2010; 5 (6): 849–58. n engl j med 2014; 371;8


辦法、新的藥的時候，再


妞妞，一個17歲女孩

Compassionate Use

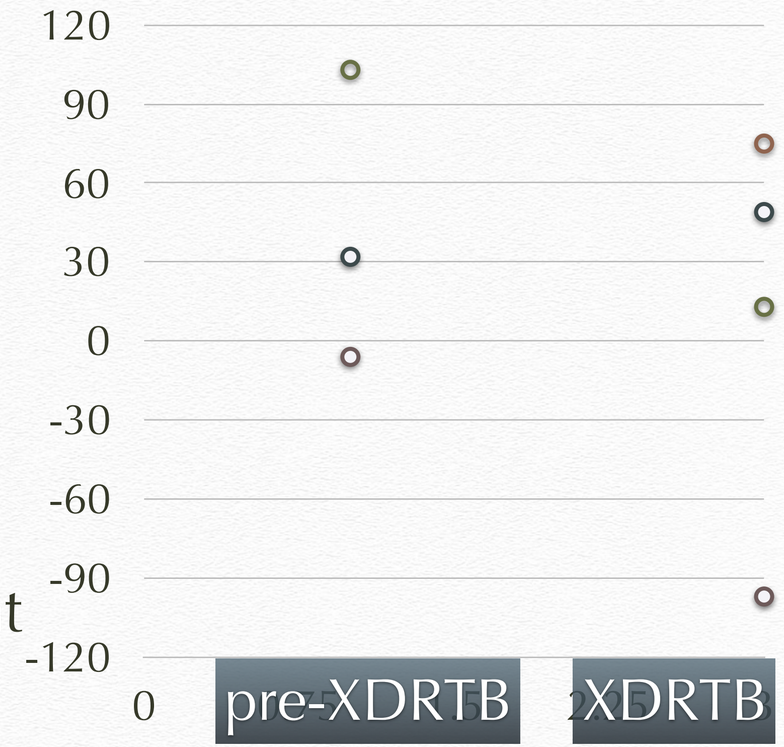
- From 2013/1 to 2014/10, 3 patients received TMC-207 from Janssen through this pathway
- Six months of TMC-207 were prescribed
- The 2 XDRTB & 1 pre-XDRTB, chronic patients all completed their TB case management 24 months after beginning of TMC-207

Bedaquiline Under Programatic Use

- NTP Started to evaluate the potential patients among the list of chronic patients since Q1 of 2015
- July , 2015 Bedaquiline was imported by Taiwan CDC and provided to XDRTB patients whose physicians were willing to give them a try
- A total of eight patients passed the application process and 7 started to receive Bedaquiline (4 in 2015, 3 in 2016, two finished the standard tx and 2 prolonged their usage)

Surrogate Outcome of the Patients with Bedaquiline

- For the total of 10 patients started with Bedaquiline, 5 XDR-TB, 4 pre-XDR-TB and 1 MDR-TB (relapsed)
- Two not yet reached culture conversion (within 2 months after Bedaquiline), 1 had no culture proved for this episode
- Seven reached their culture conversion at different timing before or after beginning of Bedaquiline

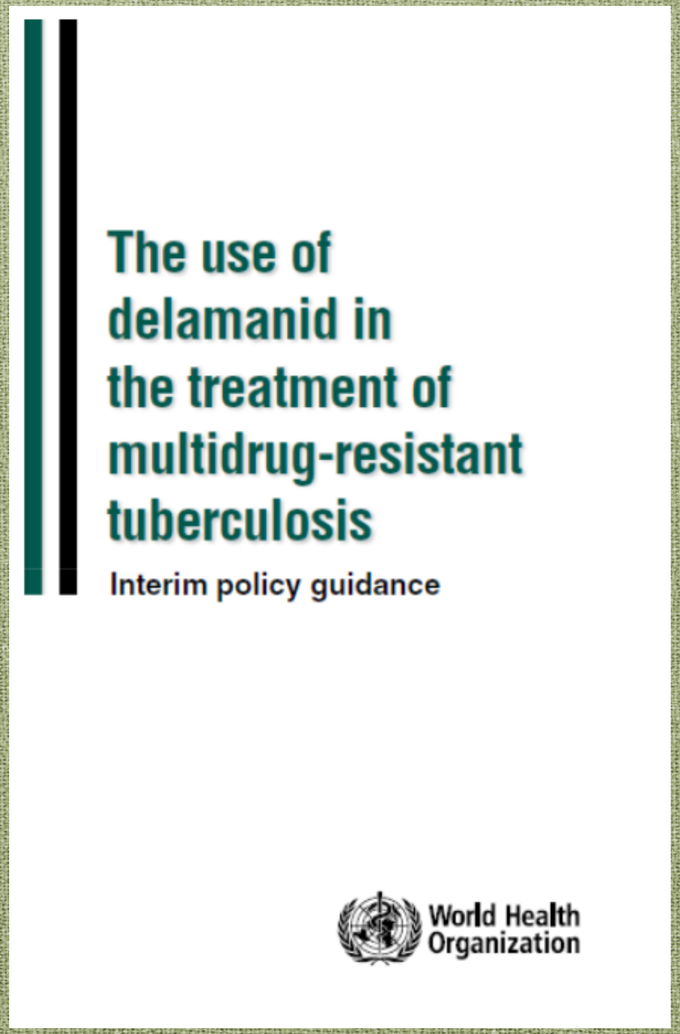


如何服用

- Bedaquiline 400mg daily for the first two weeks
- Followed by 200mg three times per week
- 建議處方24 weeks.
- Available data suggest better uptake of bedaquiline when administered with food.

Delamanid


DELTYBA 50 mg
delamanid

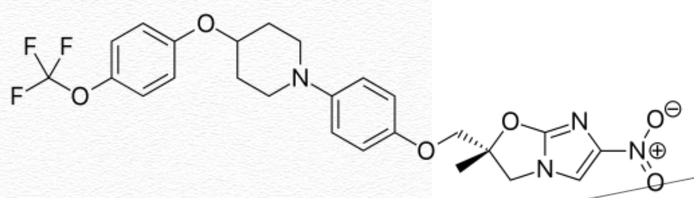

The use of delamanid in the treatment of multidrug-resistant tuberculosis
Interim policy guidance
World Health Organization

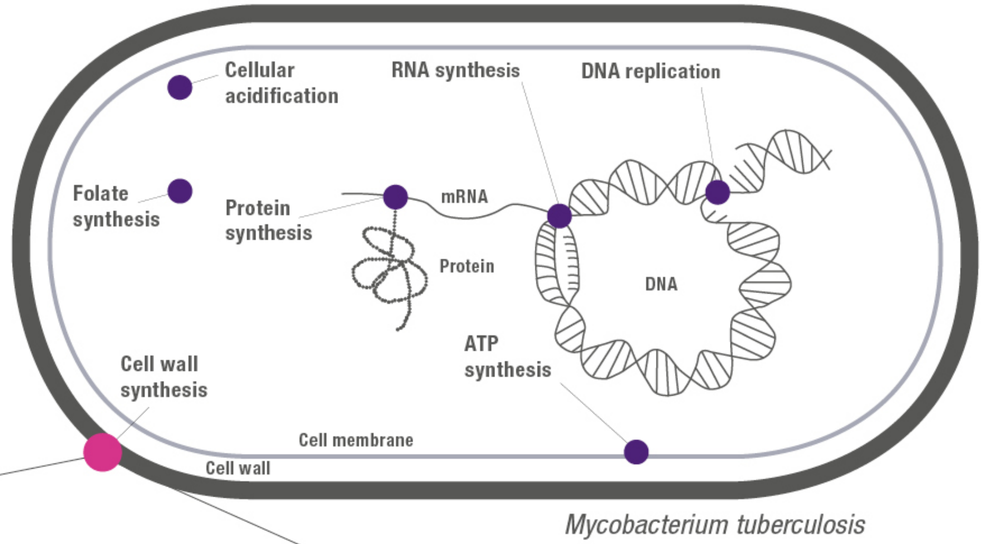
OPC-67683

- Delamanid is the first approved drug in the class of nitro-dihydro-imidazooxazoles for the treatment of MDR-TB
- Blocking the synthesis of mycolic acids in Mycobacterium tuberculosis,
- Deltyba® is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability
- Authorized for use in the European Union and Japan

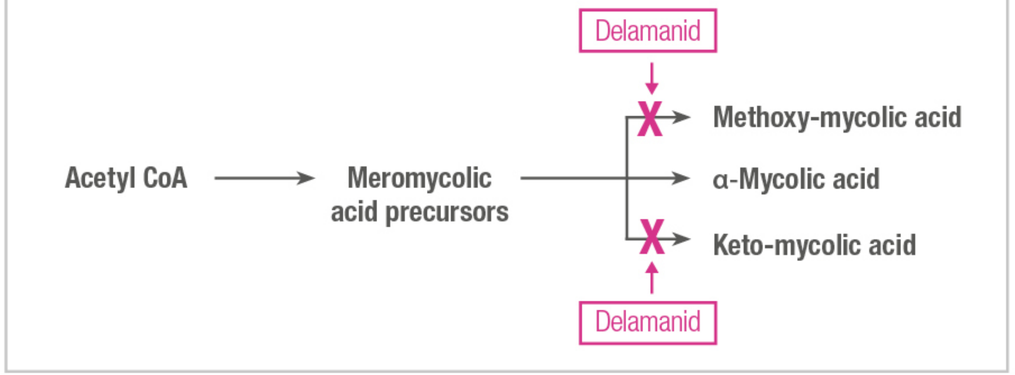
Hypothesised Mechanism of Action

Inhibition of the synthesis of mycolic acids in *M. tuberculosis*





Mycobacterium tuberculosis



如何服用

Film-coated tablets (50 mg delamanid)

Package of 48 tablets (6 blister strips of 8 tablets)

Oral use

Dose: 100 mg twice daily

2 tablets (50 mg) twice daily

Should be taken with food

It is recommended that delamanid is administered by directly observed therapy (DOT)

Duration of treatment: 24 weeks

心電圖上的QT

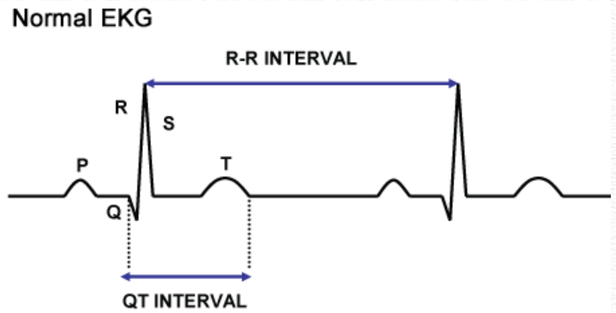


Figure 1

QTc延長

Bedaquiline plus delamanid for XDR tuberculosis

We read with interest the correspondence by Caitlin Reed and colleagues, reporting a patient with a severe case of extensively drug-resistant (XDR) tuberculosis who was treated with bedaquiline and subsequently denied delamanid because of concerns over additive cardiac toxic effects.[1] Here we report the case of a man with XDR tuberculosis who was treated with a regimen containing bedaquiline and delamanid in combination.

A 20-year-old man from Democratic Republic of the Congo was diagnosed with pulmonary tuberculosis in October, 2014. Sputum smears were positive. Cultures confirmed an XDR *Mycobacterium tuberculosis* strain. On the basis of genotypic and phenotypic drug susceptibility testing, an individualised combination of ethambutol, para-aminosalicylic acid, linezolid, cycloserine, ethionamide, and bedaquiline was initiated with directly observed treatment. After some initial improvement, the patient showed clinical and radiological worsening. In March, 2015, after the consilium organised by the French National Reference Center for Mycobacteria, a pulmonary lobectomy was radiological responses. No QT interval prolongation was observed. No other known adverse events were reported except nausea.

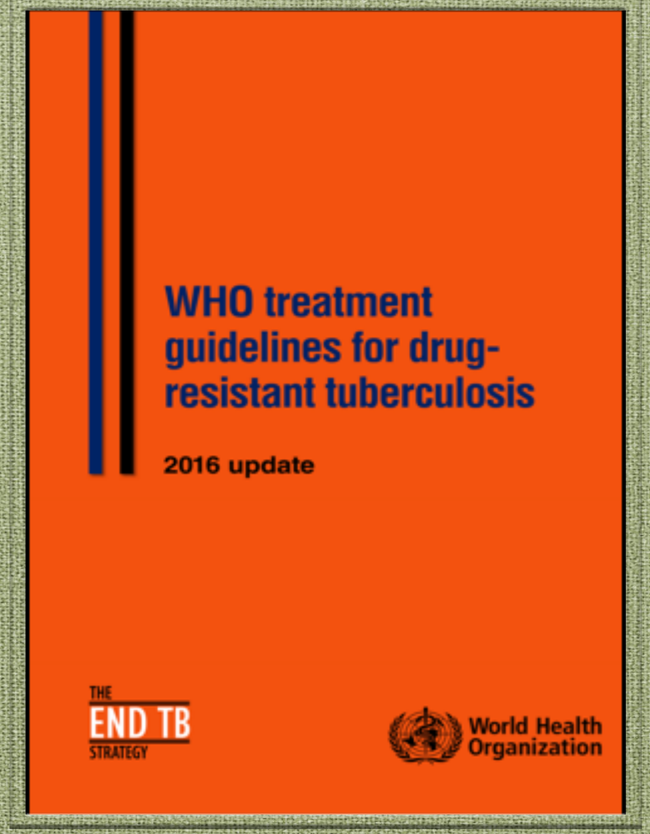
This is, to our knowledge, the first patient with XDR tuberculosis in whom a bedaquiline–delamanid combination has been initiated. The combination was initiated in a patient in whom an effective treatment cannot be designed, in the consideration that its potential life-saving benefits outweigh its unknown adverse event risks; in a department in which more than 100 tuberculosis cases a year are admitted to hospital, of which 14 cases are multidrug-resistant or XDR disease; after a multisciplinary consultation at the national level; and after patient's informed consent. Conditions for this combination use described by Alberto Matteelli and colleagues[2] were therefore fulfilled. Moreover, this combination was initiated under close cardiac monitoring and was well tolerated over a 6 month period. These data need to be confirmed in a larger number of patients and ideally in clinical trials. In the meantime, from an individual and societal perspective, compassionate use of these combinations should not be denied to specific patients if conditions such as those enumerated by Matteelli and colleagues[2] are respected.

NV has received grants from Janssen, outside the submitted work. YY has received personal fees from

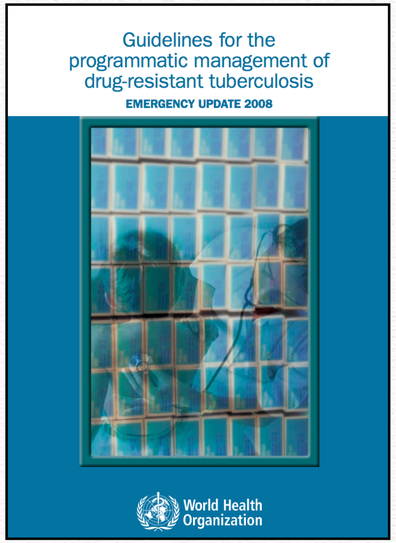
QTc延長 兩種藥共同的麻煩

- 一開始就必須要做心電圖, 接下來每月篩檢
- 哪些對象需要增加監視心電圖的頻率
  - use of strong CYP3A inhibitors,
  - fluoroquinolones,
  - known cardiac risk factors,
  - serum albumin <3.4 g/dL [34 g/L])
- QTcF > 500 ms observed -> 停止治療

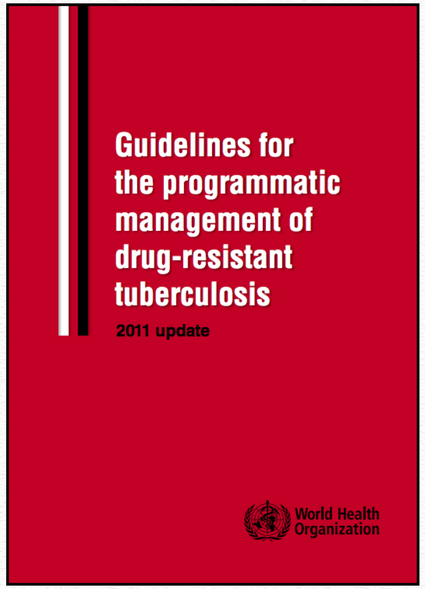
WHO treatment guidelines for drug-resistant TB 2016 update



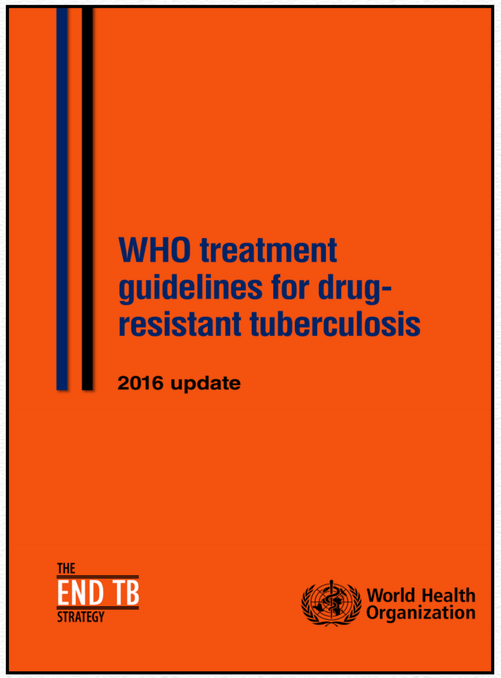
Evolution of WHO DR-TB treatment guidelines



2008



2011



2016

Treatment Guidelines for DR-TB WHO Vs. Taiwan

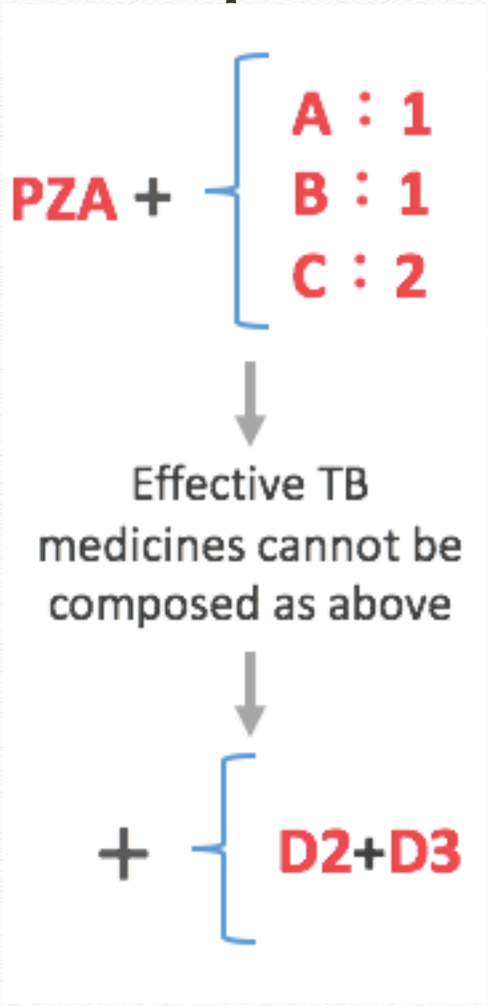
2016 WHO Guidelines	Taiwan Guidelines	
Use of a shorter MDR-TB Treatment regimen	√	Provide second-line rapid DST for RR TB. (Since 2014.01)
	√	The shorter regimen has been reimbursed in the TMTC program. (Since 2016)
Update the composition of conventional MDR-TB treatment regimens	√	Provide all agents of group A-D agents. (Bedaquiline has been provided since 2015)
	√	Delamanid (Scheduled to purchase)
Treatment RR TB with a recommended MDR-TB regimen	√	RR TB is required to refer to the TMTC.
	√	Treat RR TB with: 1.A shorter MDR-TB regimen. 2.MDR-TB conventional regimens (isoniazid should be added)
Use of surgery as part of MDR-TB treatment	√	Patient who is NOT culture conversion after 2 months of treatment is required to be reviewed in the TMTC quarterly for 1. Surgery plan. 2. Individual Treatment Plan.

Medicines recommended for the treatment of rifampicin- resistant and multidrug-resistant TB

A. Fluoroquinolones	Levofloxacin Moxifloxacin ~~Gatifloxacin~~
B. Second-line injectable agents	Amikacin Capreomycin Kanamycin (Streptomycin)
C. Other core second-line agents	Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine

* Medicines in Groups A and C are shown by decreasing order of usual preference for use

Medicines recommended for the treatment of rifampicin- resistant and multidrug-resistant TB



D. Add-on agents (not part of the core MDR-TB regimen)	1	Pyrazinamide Ethambutol High-dose isoniazid
	2	Bedaquiline Delamanid
	3	p-aminosalicylic acid Imipenem-Cilastatin Meropenem Amoxicillin-Clavulanate* (Thioacetazone)*

*Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin; HIV-status must be tested and confirmed to be negative before thioacetazone is started

Short Standardized Treatment of Multidrug- resistant Tuberculosis

Intensive phase: GEZC KHP 4 months, extended till sputum conversion	**Continuation phase: GEZC 5 months**
Kanamycin (K)	
Prothionamide (P)	
Isoniazid (H)*	
Gatifloxacin (G)*	Gatifloxacin (G)*
Clofazimine, C	Clofazimine, C
Ethambutol, E	Ethambutol, E
Pyrazinamide, P	Pyrazinamide, P

Deun A et al, AJRCCM 2010;182: 684-92

適合標準短程處方的對象

- 二線藥敏對FQ 和 二線針劑沒有抗藥
- WHO 因此建議使用 Genotype MTBDRs/ line probe assay 來快速偵測這兩種抗藥結果

Photo: Shehzad Noorani/Stop TB Partnership

Thanks for your listening