抗結核治療新趨勢

衛生福利部彰化醫院
黃伊文部長

2018.07.31

Chief of Acute Critical Care Department CHHW
Deputy commander of Central Region Communicable Disease Control Medical Network
Director Of Taiwan Society of Tuberculosis and Lung Disease
A/Professor , institute of Medicine , Chung Shan Medical University, Taichung

Outline

1. TB的現況

國際結核病發生情況

台灣結核病發生情況

2. 抗結核藥物的發展

3. 新藥的研究

4. 案例分享

前瞻、健康、品質、清新、熱情、勇氣
主動關懷、愛心、誠心、真心、盡心盡力、全心全意

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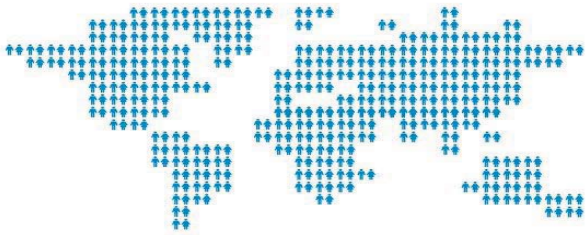
TB IS THE TOP INFECTIOUS DISEASE KILLER IN THE WORLD

IN 2016

1.7 MILLION PEOPLE DIED FROM TB
INCLUDING NEARLY 400 000 PEOPLE WITH HIV-ASSOCIATED TB

10.4 MILLION PEOPLE FELL ILL FROM TB

TB IS THE MAIN CAUSE OF DEATHS RELATED TO ANTIMICROBIAL RESISTANCE AND THE LEADING KILLER OF PEOPLE WITH HIV



EACH DAY -
4700 PEOPLE LOSE THEIR LIVES AND
28,500 PEOPLE FALL ILL DUE TO TB

World Health Organization

Reference: WHO Global Tuberculosis Control Report 2017 (WHO/HTM/TB/2017.23)
https://pbs.twimg.com/media/DNeJ6F3VwAAr9dt.jpg

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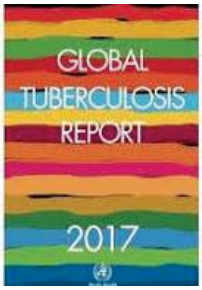

	Estimated number of cases, 2016	Estimated number of deaths, 2016
All forms of TB	10.4 million (100 cases per 100,000 population)	1.3milliion* (13 cases per 100,000 population)
HIV-associated TB	476,774	374,000
Multidrug-resistant TB	490, 000 (9% had XDR-TB)	240, 000

* Excluding deaths attributed to HIV/TB

Reference: WHO Global Tuberculosis Control Report 2017 (WHO/HTM/TB/2017.23)
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台灣結核病年度監測表

年別	新案數	新案發生率＊	死亡數	死亡率＊	MDR-TB確診個案數
2008	14,265	62.0	762	3.3	159
2009	13,336	57.8	748	3.2	176
2010	13,237	57.2	654	2.8	156
2011	12,634	54.5	638	2.8	154
2012	12,338	53	626	2.7	126
2013	11,528	49.4	609	2.6	129
2014	11,326	48.4	591	2.5	112
2015	10,711	45.7	571	2.4	117
2016	10,328	43.9	547	2.3	112

*單位為每10萬人口

Reference:2017台灣結核病防治年報，衛生福利部疾病管制署。

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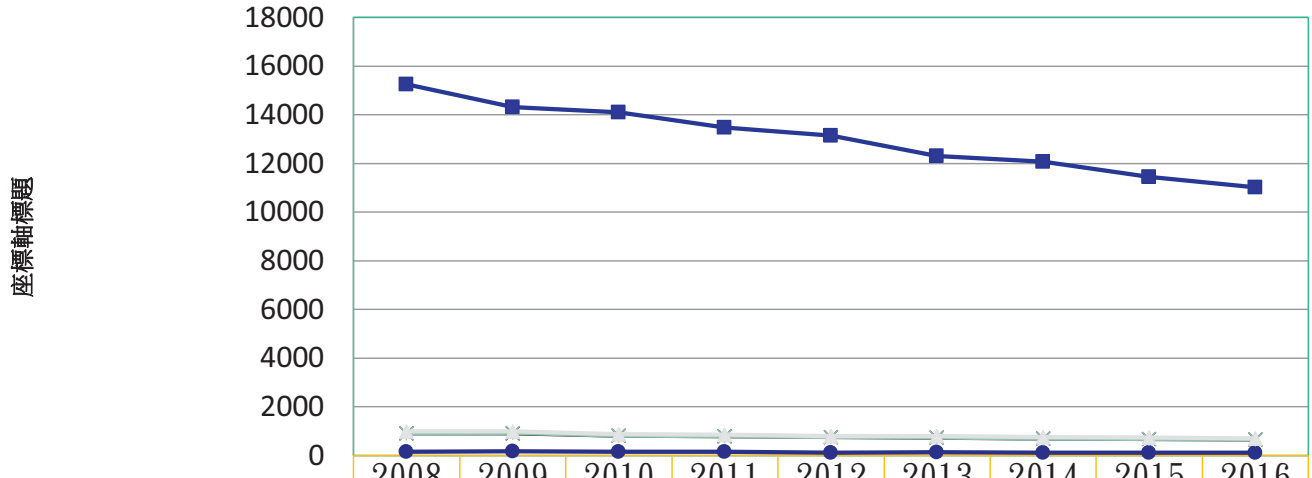
台灣結核病年度監測表



	2008	2009	2010	2011	2012	2013	2014	2015	2016
新案數	14,265	13,336	13,237	12,634	12,338	11,528	11,326	10,711	10,328
新案發生率＊	62	57.8	57.2	54.5	53	49.4	48.4	45.7	43.9
死亡率＊	3.3	3.2	2.8	2.8	2.7	2.6	2.5	2.4	2.3
死亡數	762	748	654	638	626	609	591	571	547
MDR-TB確診個案數	159	176	156	154	126	129	112	117	112

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抗結核藥物的發展

年份	藥品	縮寫
1943	Streptomycin	SM
1944	para-amino salicylic	PAS
1952	Isoniazid	INH
1954	Pyrazinamide	PZA
1961	Ethambutol	EMB
1965	Rifampicin	RIF

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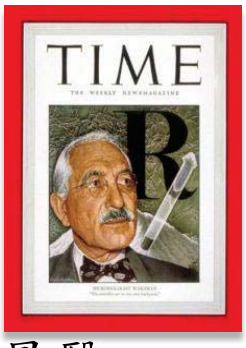
Streptomycin (SM)



1943年10月19日由Albert Schatz, 瓦克斯曼醫師的博士研究生分離出來。瓦克斯曼醫師隨即與Mayo Clinic的醫生合作首先將SM用於治療肺結核病人。

當時**第一個**有效治療肺結核的藥物。SM的應用大大地減少了死於肺結核的人數。

缺點：易復發，復發後結核菌有抗藥性。

Reference: Comroe JH Jr (1978). "Pay dirt: the story of streptomycin. Part I: from Waksman to Waksman". American Review of Respiratory Disease. **117** (4): 773-784.

抗結核藥物的發展

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Reference: Iseman M.D. Tuberculosis therapy: past, present and future. Eur Respir J, 2002;20:Suppl,36,87s-94s.

para-amino salicylic (PAS)

繼SM之後發現的第二種能夠治療結核病的藥物。瑞典化學家Jörgen Lehmann在研究結核桿菌對水楊酸的快速代謝時發現的。研究顯示這種藥物沒有耳毒性，且細菌不易對其產生抗藥性。

在1948年，英國醫學研究委員會的研究者證實氨基水楊酸與鏈黴素的**聯合療法**比它們單用的效果要更好。此後，結核病的治療均採用多種藥物的聯合。

缺點：與SM一樣有強烈副作用且容易造成抗藥性。

Reference: Mitchison DA. Role of individual drugs in the chemotherapy of tuberculosis Role of individual drugs in the chemotherapy of tuberculosis. Int J Tuberc Lung Dis. 2000, 4(9): 796–806. Fox, W.; Ellard, G. A.; Mitchison, D. A. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946-1986, with relevant subsequent publications. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 1999, 3(10 Suppl 2): S231–S279.

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Reference: Iseman M.D. Tuberculosis therapy: past, present and future. Eur Respir J, 2002;20:Suppl,36,87s-94s.

Isoniazid (INH)

- 毒性小，易吸收，穿透性強
- 用於各種類型的結核病
- 單用容易產生抗藥性
- The revelation of triple therapy：
  SM + PAS +INH for 24 month

缺點：治療時間太長 poor adherence

Reference: Iseman M.D. Tuberculosis therapy: past, present and future. Eur Respir J, 2002;20:Suppl,36,87s-94s.

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Ethambutol EMB

- Better tolerated than PAS
- Replacement of PAS in 1960s
- Allows reduction in the duration of treatment to 18 months

Reference: Iseman M.D. Tuberculosis therapy: past, present and future. Eur Respir J, 2002;20:Suppl,36,87s-94s.

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Pyrazinamide (PZA)

- Against tubercle bacilli in the acidic debris in pulmonary cavity walls
- INH + RIF + PZA

>95% cure rate in 6 months

Reference: Iseman M.D. Tuberculosis therapy: past, present and future. Eur Respir J, 2002;20:Suppl,36,87s-94s.

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Rifampicin (RIF)

- "Sterilizing effect"

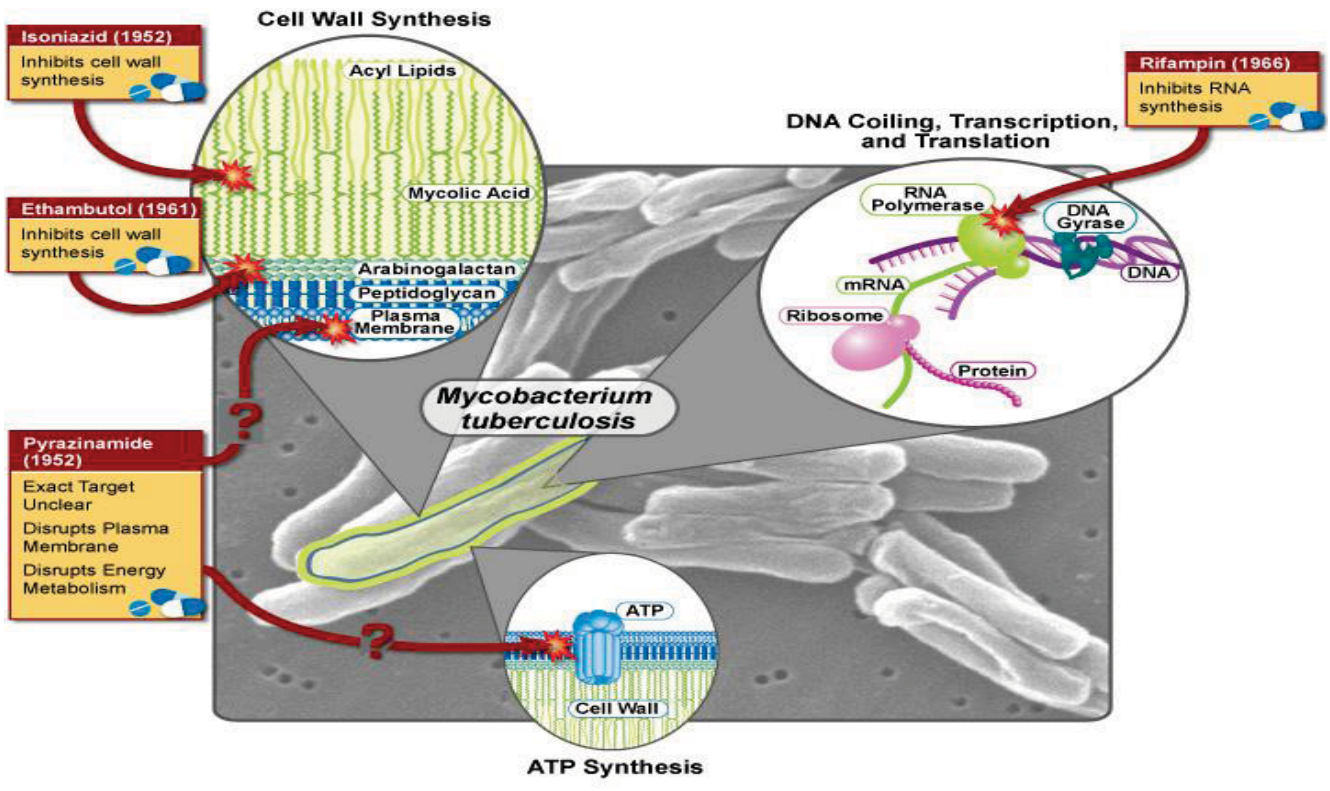
Kill mycobacteria undergoing sporadic metabolism

- INH+SM+EMB+RIF

cures in >95% cases in 8-9 months

Reference: Iseman M.D. Tuberculosis therapy: past, present and future. Eur Respir J, 2002;20:Suppl,36,87s-94s.

First-Line Treatment of Tuberculosis (TB) for Drug-Sensitive TB



NIH: http://www.niaid.nih.gov/topics/tuberculosis/Understanding/WhatIsTB/ScientificIllustrations/Pages/firstLineIllustration.aspx

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抗結核處方之發展

The fundamental basis of TB treatment was defined based on the analysis of multiple randomized clinical trials (RCTs):

1) combining different effective drugs to avoid the selection of resistant M. tuberculosis strains; and
2) ensuring that treatment is long enough to sterilise the tissues infected with M. tuberculosis and, therefore, prevent relapse.

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1970到1980年間，British Medical Research Council 進行之大型研究結果顯示，使用isoniazid、ethambutol、rifampicin、pyrazinamide(HERZ)2個月，再合併HER 4個月的六個月短程治療療程(2HERZ/4HER)，可有效治療、減少復發，並防止抗藥性發生之結核病治療療程

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Why 6 month therapy?


Cochrane Library
Cochrane Database of Systematic Reviews

Regimens of less than six months for treating tuberculosis (Review)

Gelband H

Gelband H.
Regimens of less than six months for treating tuberculosis.
Cochrane Database of Systematic Reviews 1999, Issue 4. Art. No.: CD001362.
DOI: 10.1002/14651858.CD001362.

www.cochranelibrary.com

Regimens of less than six months for treating tuberculosis (Review)
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WILEY

- A comparison of <6 months vs. 6 months of treatment
- Success short course (3-5months) chemotherapy randomized trials between 1970sand 1980s
- 7 papers reviewed

Gellband, H. Regimens of less than six months for treating tuberculosis (review). Cochrane Database of Systematic Reviews, 1999, issue4. http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD001362/epdf

1. Agra 1981 :

3-month vs. 4.5-months regimen

2. Germany 1986:

3-month vs. 6-month

3.Hong Kong 1979:

2-month 、3-monthvs. 12-month

4.Hong Kong1989:

4-month vs. 6-month

3-month vs. 4-month

5.S. India 1983:

5-month vs. 7-month

6. S. India 1986:

3-month vs. 5-month

7.Singapore 1979:

4-month vs. 6-month

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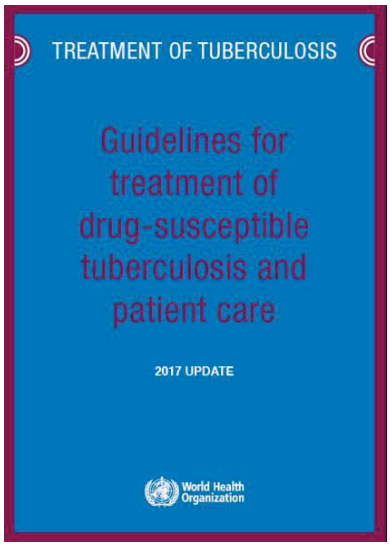
Conclusion

- Shorter regimen(2m,3m,4m,& 5m) than the standard 6 months are not as good as longer regimens at preventing relapse

Standard regimen recommended by WHO



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Regimen for drug-susceptible TB

Table A STANDARD REGIMEN AND DOSING FREQUENCY FOR NEW TB PATIENTS

Intensive phase	Continuation phase	Comments
2 months of HRZE[a]	4 months of HR	2HERZ/4HR
2 months of HRZE	4 months of HRE	Applies only in countries with high levels of isoniazid resistance in new TB patients, and where isoniazid drug susceptibility testing in new patients is not done (or results are unavailable) before the continuation phase begins

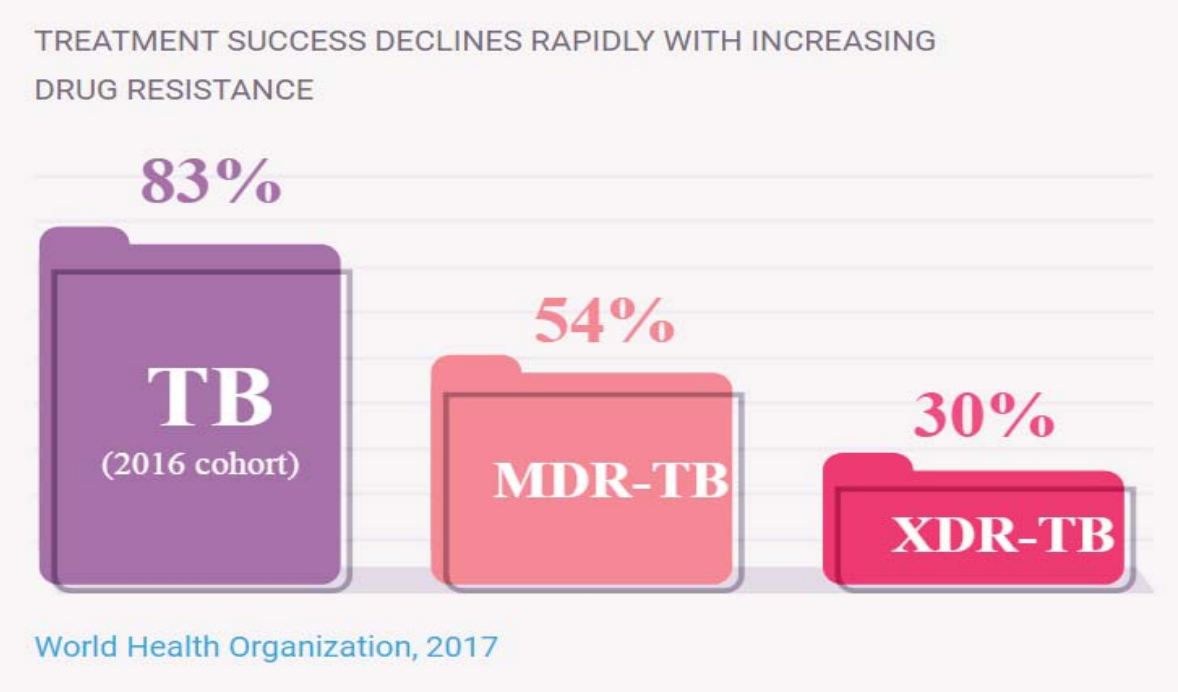
[a] WHO no longer recommends omission of ethambutol during the intensive phase of treatment for patients with non-cavitary, smear-negative pulmonary TB or extrapulmonary disease who are known to be HIV-negative.

Dosing frequency		Comments
Intensive phase	Continuation phase	
Daily	Daily	Optimal
Daily	3 times per week	Acceptable alternative for any new TB patient receiving directly observed therapy
3 times per week	3 times per week	Acceptable alternative provided that the patient is receiving directly observed therapy and is NOT living with HIV or living in an HIV-prevalent setting (see Chapter 5)

Note: Daily (rather than three times weekly) intensive-phase dosing may help to prevent acquired drug resistance in TB patients starting treatment with isoniazid resistance (see Annex 2).

Reference: Treatment of Tuberculosis guideline Fourth edition. 2017 WHO

TB治療成功率隨著抗藥性肺結核的增加而急速下降



Source: https://www.tballiance.org/why-new-tb-drugs/global-pandemic

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MDR-TB and XDR-TB

Multidrug-resistant TB 多重抗藥結核菌

Resistance to at least both INH and RMP

至少對isoniazid及rifampin。

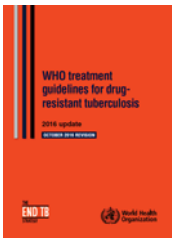
Extensively (Extremely) Drug-resistant TB 廣泛多重抗藥結核菌

Resistance to at least both INH and RMP (MDR-TB) in addition to resistance to any fluoroquinolone, and to at least one of three injectable 2nd-line anti-TB drugs (kanamycin, amikacin and capreomycin)

除了對 INH 和 RMP 抗藥之外，且對任一fluoroquinolone，及 任一種二線針劑(kanamycin, amikacin, capreomycin)也抗藥 。

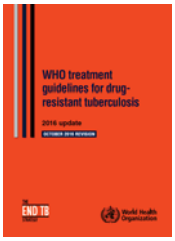
衛生福部疾病署結核病診治指引(第六版), 2017/12/14

Rifampicin-resistant TB and MDR-TB
WHO建議二線用藥



Group A. Fluoroquinolones[b]		Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
Group B. Second-line injectable agents		Amikacin	Am
		Capreomycin	Cm
		Kanamycin	Km
		(Streptomycin)[c]	(S)
Group C. Other core second-line agents[b]		Ethionamide / prothionamide	Eto / Pto
		Cycloserine / terizidone	Cs / Trd
		Linezolid	Lzd
		Clofazimine	Cfz
Group D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide	Z
		Ethambutol	E
		High-dose isoniazid	H[h]
	D2	Bedaquiline	Bdq
		Delamanid	Dlm
	D3	*p*-aminosalicylic acid	PAS
		Imipenem–cilastatin[d]	Ipm
		Meropenem[d]	Mpm
		Amoxicillin-clavulanate[d]	Amx-Clv
		(Thioacetazone)[e]	(T)

Reference: WHO treatment guidelines for drug-resistant tuberculosis –2016 update (WHO/HTM/TB/2016.04)



Group A Fluoroquinolones		**Levofloxacin**	**Lfx**
		Moxifloxacin	**Mfx**
		Gatifloxacin	**Gfx**
Group B Second-line injectable agents		Amicacin	Am
		Capreomycin	Cm
		Kanamycin	Km
		(Strptomycin)	sm
Group C Other core second-line agents		Ethionamide/protholonamide	Eto-Pto
		Cycloserin /terizidone	Cs/Trd
		Linezolid	Lzd
		Clofazimine	Cfz
Group D Add-on agents (not part of core MDR regimen)	D1	Pyraziramide	Z
		Ethambutol	E
		High-dose Isoniazid	H^h
	D2	Bedaquiline	Bdq
		Delamanid	Dlm
	D3	p-aminosalicylic acid	Pas
		Imipenem –Cilastatin	Ipm
		Meropenem	Mpm
		Amoxicillin-Clavulanate	Amx-Clv
		Thioacetazone	T

Reference: WHO treatment guidelines for drug-resistant tuberculosis –2016 update (WHO/HTM/TB/2016.04)

Fluoroquinolones

- MDR-TB regimen的關鍵成份
- Mfx more effective than EMB achieved sputum conversion at 8 weeks
- However…

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Chang Hua Hospital, Ministry of Health and Welfare

OPEN ACCESS Freely available online

PLOS ONE

Randomized Clinical Trial of Thrice-Weekly 4-Month Moxifloxacin or Gatifloxacin Containing Regimens in the Treatment of New Sputum Positive Pulmonary Tuberculosis Patients

Mohideen S. Jawahar[1]*, Vaithilingam V. Banurekha[1], Chinnampedu N. Paramasivan[1], Fathima Rahman[1], Rajeswari Ramachandran[1], Perumal Venkatesan[1], Rani Balasubramanian[1], Nagamiah Selvakumar[1], Chinnaiyan Ponnuraja[1], Allaudeen S. Iliayas[2], Navaneethapandian P. Gangadevi[2], Balambal Raman[1], Dhanaraj Baskaran[1], Santhanakrishnan R. Kumar[2], Marimuthu M. Kumar[2], Victor Mohan[2], Sudha Ganapathy[1], Vanaja Kumar[1], Geetha Shanmugam[1], Niruparani Charles[1], Murugesan R. Sakthivel[2], Kannivelu Jagannath[3], Chockalingam Chandrasekar[4], Ramavaram T. Parthasarathy[5], Paranji R. Narayanan[1]

A high relapse in the quinolone group compared with 6-month standard rifampin, isoniazid, pyrazinamide, and ethambutol .

Jawahar MS, et al. Randomized clinical trial of thrice-weekly 4-month moxi floxacin or gatifloxacin containing regimens in the treatment of new sputum posit ive pulmonary tuberculosis patients. PLoS One 2013;8:e67030.

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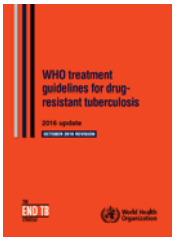
Moxifloxacin-containing Regimen Greatly Reduces Time to Culture Conversion in Murine Tuberculosis

Eric L. Nuermberger, Tetsuyuki Yoshimatsu, Sandeep Tyagi, Richard J. O'Brien, Andrew N. Vernon, Richard E. Chaisson, William R. Bishai, and Jacques H. Grosset

Center for Tuberculosis Research, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; and Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, Georgia

Moxifloxacin did not improve outcomes when added to rifampin, isoniazid, pyrazinamide, and ethambutol, but an earlier sputum conversion was founded when it was used instead of INH.

Nuermberger E L, Yoshimatsu T, T yagi S, O 'Brien RJ , Vernon AN, Chaisson RE, Bishai WR, Grosset JH. Moxifloxacin-containing regimen greatly reduces time to culture conversion in murine tuberculosis. Am J Respir Crit Care Med 2004;169 421–426.



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Group C Other core second-line agents		**Ethionamide/protholonamide**	**Eto-Pto**
		Cycloserin /terizidone	**Cs/Trd**
		Linezolid	**Lzd**
		Clofazimine	**Cfz**
Group D Add-on agents (not part of core MDR regimen)	D1	Pyraziramide	Z
		Ethambutol	E
		High-dose Isoniazid	H^h
	D2	Bedaquiline	Bdq
		Delamanid	Dlm
	D3	p-aminosalicylic acid	Pas
		Imipenem –Cilastatin	Ipm
		Meropenem	Mpm
		Amoxicillin-Clavulanate	Amx-Clv
		Thioacetazone	T

Reference: WHO treatment guidelines for drug-resistant tuberculosis –2016 update (WHO/HTM/TB/2016.04)

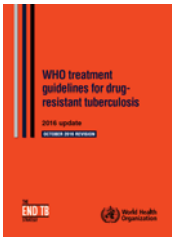
Linezolid

Eur Respir J 2012; 40: 1430–1442
DOI: 10.1183/09031936.00022912

Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis

- Limited to treatment of XDR
- High frequency of side effect- up to 59%
- The side effects are greater with higher dose and longer duration of treatment

Sotgiu G, et al.Efficacy, safety and tolerabili ty of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. EurRespir J 2012;40:1430–1442

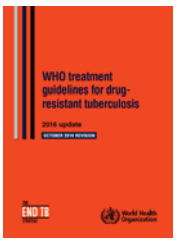


Group A Fluoroquinolones		Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
Group B Second-line injectable agents		Amicacin	Am
		Capreomycin	Cm
		Kanamycin	Km
		(Strptomycin)	sm
Group C Other core second-line agents		Ethionamide/protholonamide	Eto-Pto
		Cycloserin /terizidone	Cs/Trd
		Linezolid	Lzd
		Clofazimine	Cfz
Group D Add-on agents (not part of core MDR regimen)	D1	Pyraziramide	Z
		Ethambutol	E
		High-dose Isoniazid	H^h
	D2	**Bedaquiline**	**Bdq**
		Delamanid	**Dlm**
	D3	p-aminosalicylic acid	Pas
		Imipenem –Cilastatin	Ipm
		Meropenem	Mpm
		Amoxicillin-Clavulanate	Amx-Clv
		Thloacetazone	T

Reference: WHO treatme
(WHO/HTM/TB/2016.04)

CHHW

Rifampicin-resistant TB and MDR-TB
WHO建議二線用藥



GROUP A Fluoroquinolones		Levofloxacin Moxifloxacin Gatifloxacin
GROUP B Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)
GROUP C Other Core Second-line Agents		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine
GROUP D Add-on agents *(not core MDR-TB regimen components)*	**D1**	Pyrazinamide Ethambutol High-dose isoniazid
	D2	Bedaquiline Delamanid
	D3	*p*-aminosalicylic acid Imipenem-Cilastatin Meropenem Amoxicillin-Clavulanate (Thioacetazone)

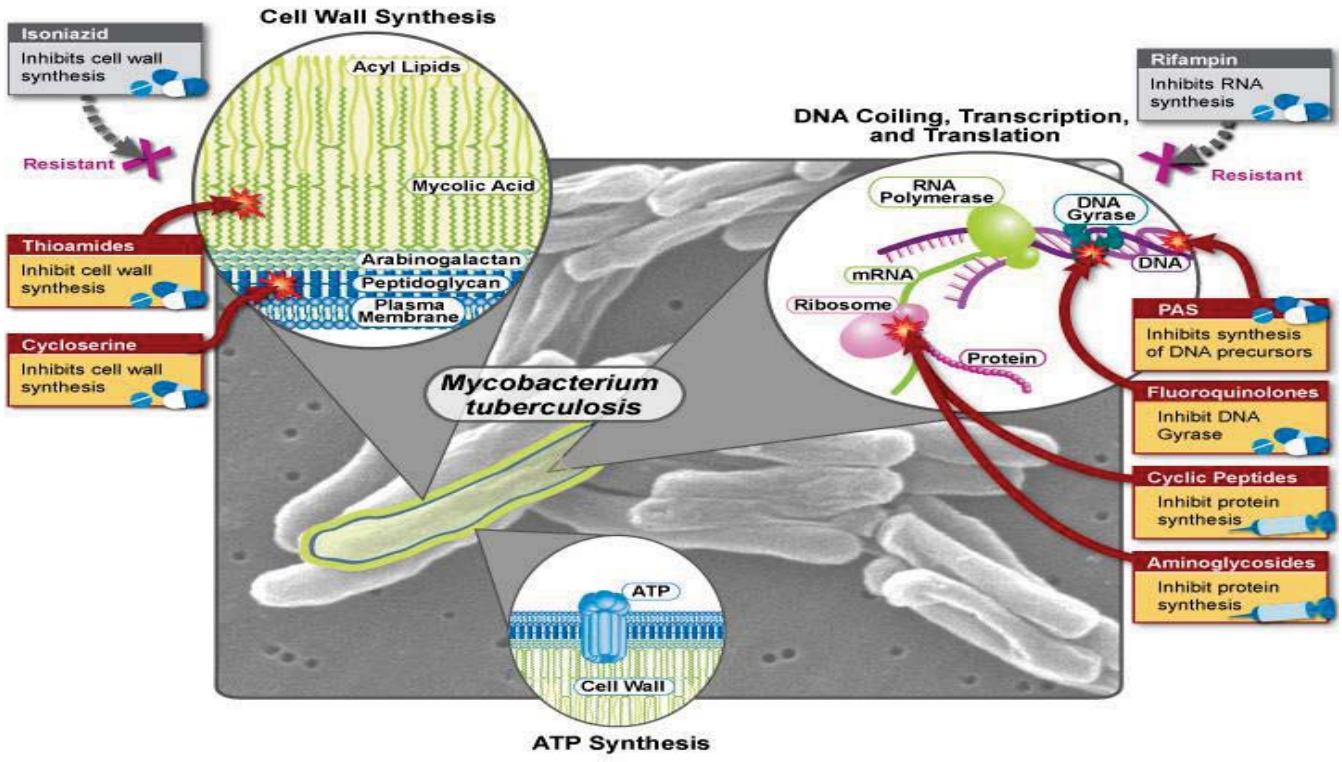
Reference: WHO treatment guidelines for drug-resistant tuberculosis –2016 update
(WHO/HTM/TB/2016.04)

第二線抗結核藥物

Second-line drugs	Target	Effect
Para-amino salicylic acid (1948)	Dihydropteroate synthase	Inhibits folate biosynthesis
Streptomycin (1944)	S12 and 16S rRNA components of 30S ribosomal subunit	Inhibits protein synthesis
Ethionamide (1961)	Enoyl-[acyl-carrier-protein] reductase	Inhibits mycolic acid biosynthesis
Ofloxacin (1980)	DNA gyrase and DNA topoisomerase	Inhibits DNA supercoiling
Capreomycin (1963)	Interbridge B2a between 30S and 50S ribosomal subunits	Inhibits protein synthesis
Kanamycin (1957)	30S ribosomal subunit	Inhibits protein synthesis
Amikacin (1972)	30S ribosomal subunit	Inhibits protein synthesis
Cycloserine (1955)	D-alanine racemase and ligase	Inhibits peptidoglycan synthesis

Nature Reviews Drug Discovery, 2013; 12:388-404
http://www.nature.com/nrd/journal/v12/n5/fig_tab/nrd4001_T1.html

Multidrug-Resistant Tuberculosis (MDR TB) and Possible Effective Treatments



Reference: NIH:
http://www.niaid.nih.gov/topics/tuberculosis/understanding/publications/Pages/multidrugResistantIllustration.aspx

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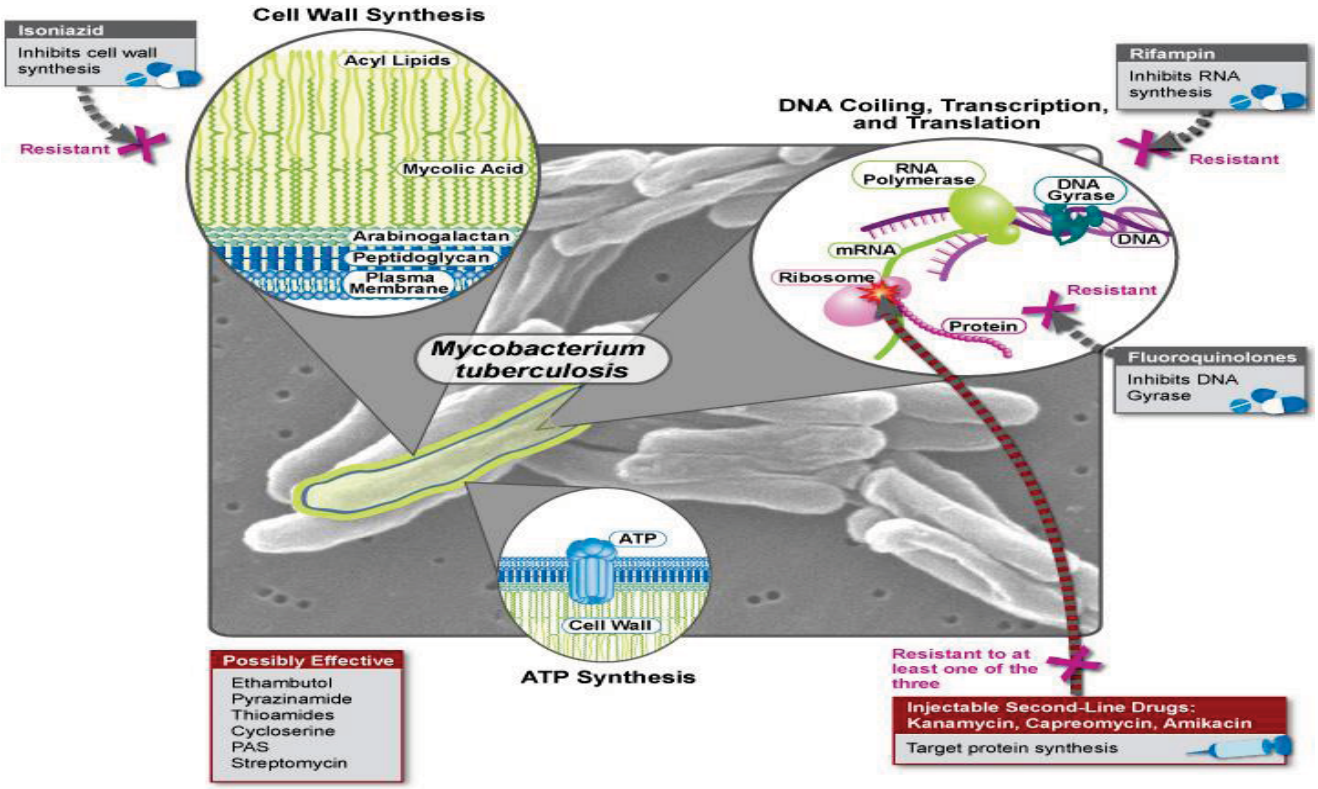
Extensively Drug-Resistant Tuberculosis (XDR TB)
Diminishing Options for Treatment



Reference: NIH: http://www.niaid.nih.gov/topics/tuberculosis/Illustrations/Pages/multidrugResistantIllustration.aspx

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Recommendation for longer MDR-TB treatment

In patients with rifampicin-resistant TB or MDR-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 C*	Group A = 1 levofloxacin; moxifloxacin; gatifloxacin Group B = 1 amikacin, capreomycin, kanamycin, (streptomycin) Group C = 2 ethionamide/ prothionamide, cycloserine/ terizidone, linezolid, clofazimine

Reference: WHO treatment guidelines for drug-resistant tuberculosis, 2016 update (WHO/HTM/TB/2016.04)

Recommendation for longer MDR-TB treatment

- If the minimum number of five effective TB medicines cannot be composed as given above, an *agent from Group D2 and other agents from Group D3 may be added to bring the total to five* - the regimen may be further strengthened with high-dose isoniazid and/or ethambutol	Group D2 bedaquiline, delamanid Group D3 *p*-aminosalicylic acid, imipenem–cilastatin, meropenem, amoxicillin–clavulanate, (thioacetazone)

Reference: WHO treatment guidelines for drug-resistant tuberculosis, 2016 update (WHO/HTM/TB/2016.04)

However...

Reference: The TB Alliance2018, https://www.tballiance.org/why-new-tb-drugs/inadequate-treatment, World Health Organization, Global Tuberculosis report 2016. Geneva: World Health Organization; 2016.

Why do we need new TB drugs?

- **Drug resistant TB**
- **Challenges of current therapy**
- Prolonged duration/multiple drugs
- Tolerability, toxicities and drug interaction
- Adherence and treatment completion
- **Cost**

-adverse events, consequences of interruption or incomplete therapy

Required properties of new anti-TB drugs

What a new durg should do	Chracteristics required
Simplify treatment or reduce treatment duration	Strong (early) bactericidal and sterilizing activity Low pill count, fixed-dose combinations Allow for intermittent therapy
Have an acceptable toxicity profile	Low incidence of treatment-limiting adverse events No overlapping toxicity profile with other TB drugs
Be active against MDR/XDR TB	No cross-resistance with first-line drugs
Be useful in HIV-infected patients with TB	Minimal interactions with antiretroviral drugs No overlapping toxicity profile with antiretroviral drugs
Be active against latent TB	Activity against dormant bacilli Favorable toxicity profile

New drugs against tuberculosis: problems, progress, and evaluation of agents in clinical development. Antimicrob. Agents Chemother. 2009; 53(3):849-862.

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1)New anti-TB drugs

2)New uses of existing anti-Microbials

3)Immunomodulators

Drug-resistant Tuberculosis Clinical Trials Progress Report-1

Trial Name	Description	Status	Phase	Trial Registry Identifier (link)	Expected Study Completion Date
Janssen C211	Evaluate the PK, safety, tolerability and anti-mycobacterial activity of bedaquiline in combination with MDR-TB therapy for HIV uninfected children and adolescents	Open for participant enrollment	Phase 2	NCT02354014	2025
STREAM Stage 1	Comparison of standard WHO MDR-TB regimen with 9-month modified Bangladesh Regimen	Enrollment complete; follow up ongoing	Phase 3	ISRCTN78372190	2018
STREAM Stage 2	Comparison of 6 and 9 month bedaquiline-containing regimen against the WHO and Bangladesh regimen	Open for participant enrollment	Phase 3	NCT02409290	2021
NeXT	Open label RCT of a 6-9 month injection free regimen containing bedaquiline, linezolid, levofloxacin, ethionamide/high dose isoniazid, and pyrazinamide	Currently enrolling participants in South Africa	Phase 3	NCT02454205 PACTR201409000848428	2019
NiX-TB		Fully enrolled.	Phase 3	NCT02333799	2018
NC-005	Study of combinations of bedaquiline, moxifloxacin, pretomanid, and pyrazinamide for 8 weeks for DS-TB and MDR-TB patients, with one arm for MDR-TB patients adding moxifloxacin to bedaquiline, PA-824 and pyrazinamide	Fully enrolled	Phase 2	NCT02193776	2018
DELIBERATE (ACTG 5343)	Study of drug-drug interactions and combined QT effects of bedaquiline and delamanid	Open for participant enrollment	Phase 2	NCT02583048	2020
Otsuka 213	Safety and efficacy study of delamanid or placebo for 6 months in combination with optimized background therapy for 18-24 months	Results available here.	Phase 3	NCT01424670	2018
Otsuka 233	Safety, efficacy, and pharmacokinetic study of delamanid in pediatric patients with MDR-TB	Fully enrolled.	Phase 2	NCT01859923	2020
Otsuka 232	Pharmacokinetic and safety trial of delamanid to determine the appropriate dose for pediatric MDR-TB HIV- patients	Completed; analysis underway.	Phase 1	NCT01856634	2018

Bedaquiline 取代針劑

Reference: Resist-TB http://www.resisttb.org/?page_id=1602 Last updated Jun,6,2018

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Drug-resistant Tuberculosis Clinical Trials Progress Report-2

Trial Name	Description	Status	Phase	Trial Registry Identifier (link)	Expected Study Completion Date
ACTG 5312	Safety and efficacy study of different doses and generic variants of isoniazid resistant TB	Currently enrolling participants in South Africa	Phase 2	NCT01936831	2018
Opti-Q	Efficacy and safety study of increased doses of levofloxacin in combination with optimized background therapy	Follow up completed; anaylsis underway	Phase 2	NCT01918397	2018
V-QUIN	Evaluating 6 months daily levofloxacin vs. placebo as preventive therapy in contacts of MDR-TB. Enrolling Children, adolescents, infants HIV+/HIV- Household randomization	Currently enrolling participants in Vietnam	Phase 3	ACTRN12616000215426	2021
MDR-END	Comparing efficacy of treatment regimen including delamanid, linezolid, levofloxacin, and pyrazinamide for 9-12 months, with a control arm of the standard treatment regimen including injectables for 20-24 months for the treatment of quinolone sensitive MDR-TB	Currently enrolling participants in South Korea	Phase 2	NCT02619994	2019
TB-CHAMP	Randomized double blind placebo-controlled, superiority multicenter trial to evaluate the efficacy of levofloxacin vs. placebo for the prevention of MDR-TB in child and adolescent household contacts	Currently enrolling participants in South Africa	Phase 3	ISRCTN92634082	2020
Janssen Japan Trial	Open-label, single-arm, multi-ce…rial to explore safety, efficacy and PK of bedaquiline in Jap…icipants with pulmonary MDR-TB	Currently enrolling participants	Phase 2	NCT02365623	2020
endTB		Currently enrolling participants in Georgia, Peru, Kazakhstan, and Lesotho.	Phase 3	NCT02754765	2021
TB-PRACTECAL	Multi-centre, open label, multi-arm, randomized, controlled, phase II-III trial evaluating short treatment regimens containing bedaquiline and pretomanid in combination with existing and re-purposed anti-TB drugs for the treatment of biologically confirmed pulmonary MDR-TB	Currently enrolling participants in Uzbekistan, Kazakhstan, South Africa, and Belarus.	Phase 2-3	NCT02589782	2021

MDR-TB LTBI:1.V-QUIN & 2.TB-CHAMP

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2018 Global New TB Drug Pipeline [1]

Targets: Energy / QcrB / ATP Synthase

Preclinical Development | **Clinical Development**

Early Stage	GMP / GLP Tox.	Phase 1	Phase 2	Phase 3
Caprazene nucleoside CPZEN-45*	BTZ-043*	TBI-166	Delpazolid (LCB01-0371)	Bedaquiline (TMC-207)
Spectinamide 1810*	TBAJ-587	Macozinone* (PBTZ-169)	Sutezolid (PNU-100480)	Delamanid (OPC-67683)
Fluoroquinolone DC-159a	TBI-223	OPC-167832*	SQ-109*	Pretomanid (PA-824)
Gyrase inhibitor SPR-720 (pVXc-486)*	GSK-286*	Q203*	Macozinone* (PBTZ-169)	
Pyrazolopyridine carboxamide TB-47*		GSK-656*		
		Contezolid (MRX-4/MRX-1)		
		TBA-7371*		

New chemical class* Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical Ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org
Updated: March 2018

2018 Global New TB Drug Pipeline [1]

Targets: Protein Synthesis

Preclinical Development | Clinical Development

Early Stage	GMP / GLP Tox.	Phase 1	Phase 2	Phase 3
Caprazene nucleoside CPZEN-45*	BTZ-043*	TBI-166	Delpazolid (LCB01-0371)	Bedaquiline (TMC-207)
Spectinamide 1810*	TBAJ-587	Macozinone* (PBTZ-169)	Sutezolid (PNU-100480)	Delamanid (OPC-67683)
Fluoroquinolone DC-159a	TBI-223	OPC-167832*	SQ-109*	Pretomanid (PA-824)
Gyrase inhibitor SPR-720 (pVXc-486)*	GSK-286*	Q203*	Macozinone* (PBTZ-169)	
Pyrazolopyridine carboxamide TB-47*		GSK-656*		
		Contezolid MRX-4/MRX-1		
		TBA-7371*		

New chemical class* Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone , imidazopyridine amide.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

Updated: March 2018

2018 Global New TB Drug Pipeline [1]

Targets: Cell Wall DprE1

Preclinical Development | Clinical Development

Early Stage	GMP / GLP Tox.	Phase 1	Phase 2	Phase 3
Caprazene nucleoside CPZEN-45*	BTZ-043*	TBI-166	Delpazolid (LCB01-0371)	Bedaquiline (TMC-207)
Spectinamide 1810*	TBAJ-587	Macozinone* (PBTZ-169)	Sutezolid (PNU-100480)	Delamanid (OPC-67683)
Fluoroquinolone DC-159a	TBI-223	OPC-167832*	SQ-109*	Pretomanid (PA-824)
Gyrase inhibitor SPR-720 (pVXc-486)*	GSK-286*	Q203*	Macozinone* (PBTZ-169)	
Pyrazolopyridine carboxamide TB-47*		GSK-656*		
		Contezolid MRX-4/MRX-1		
		TBA-7371*		

New chemical class* Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone , imidazopyridine amide.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline/discovery

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www.newtbdrugs.org

Updated: March 2018

2018 Global New TB Drug Pipeline [1]

Targets: MmpL3

Preclinical Development | Clinical Development

Early Stage	GMP/ GLP Tox.	Phase 1	Phase 2	Phase 3
Caprazen nucleoside CPZEN-45*	BTZ-043*	TBI-166	Delpazolid (LCB01-0371)	SQ-109*
Spectinamide 1810*	TBAJ-587	Macozinone* (PBTZ-169)	Sutezolid (PNU100480)	Macozinone* (PBTZ-169)
Fluoroquinolone DC-159a	TBI-166	OPC-167832*		
Gyrase inhibitor SPR-720 (pVXc-486)*	TBI-223	Q203*		
Pyrazolopyridine carboxamide TB-47*	GSK-286*	GSK-656*		
		Contezolid (MRX-4/MRX-1)		
		TBA-7371*		

MmpL3 is a transporter of mycobacterial trehalose monomycolate (TMM) *MmpL3是分枝桿菌海藻糖單黴菌的轉運蛋白

New chemical class* Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline/discovery

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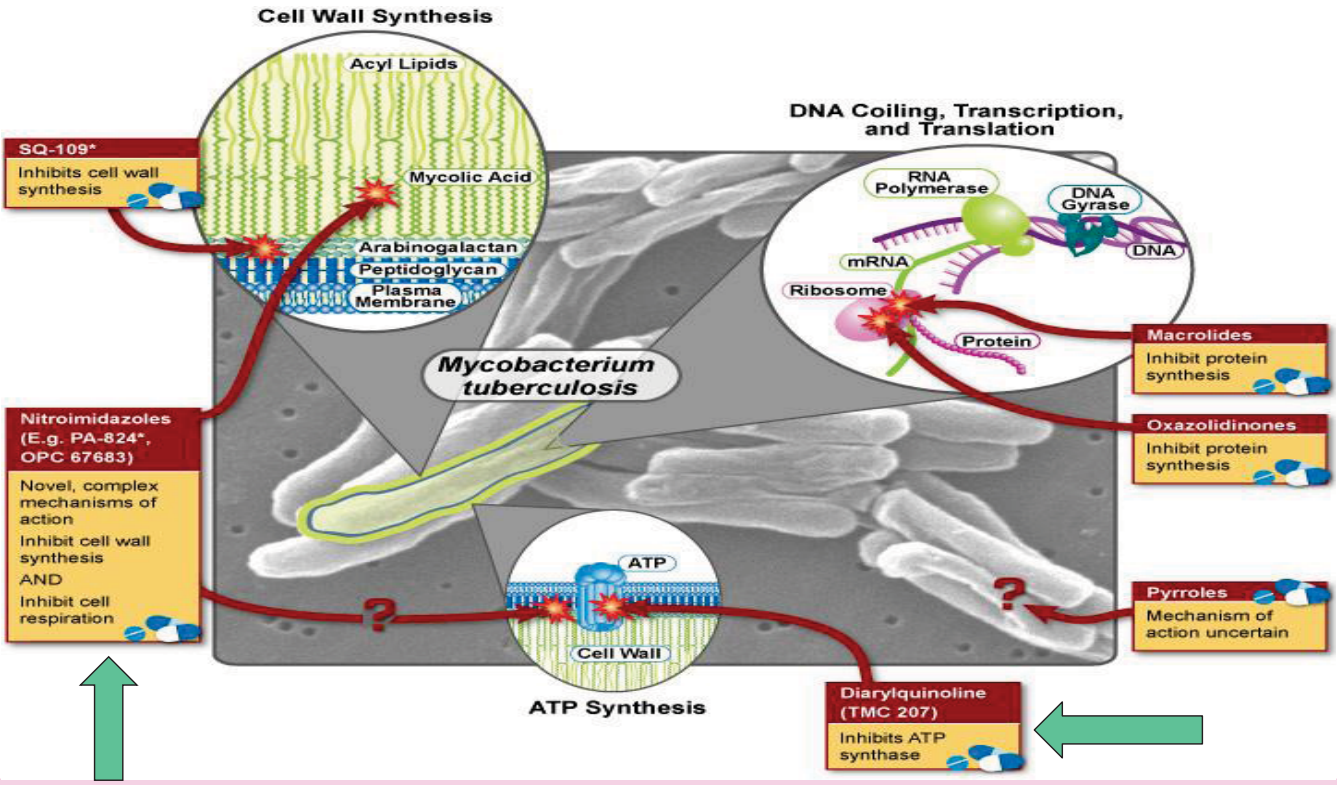
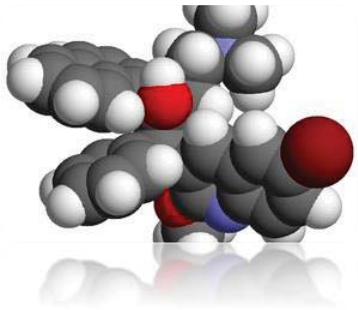
New Tuberculosis (TB) Drugs Under Development



Reference:
NIH:http://www.niaid.nih.gov/topics/tuberculosis/Understanding/WhatIsTB/Scientificillustrations/Pages/newTBdrugs.aspx

- Sirturo® bedaquline (TMC207)



Tbfacts.org. https://www.tbfacts.org/bedaquiline/

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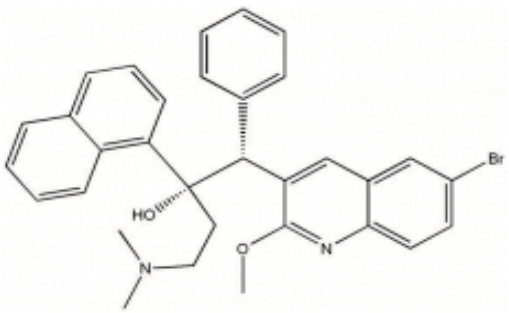
成分： Diarylquinoline

藥物名稱： Bedaquiline (TMC207)

商品名稱：Sirturo

劑型：tablet

劑量：100mg



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Bedaquiline

➢ Mechanism of action

- A member of the diarylquinoline group.
- Unique mechanism inhibits adenosine triphosphate (ATP) synthase enzyme of the TB mycobacteria.
- This enzyme is used by bacteria to generate energy.

Reference: review of available evidence on the use of bedaquiline for the treatment of multi-drug resistant tuberculosis: Data analysis report.

- **Delamanid (OPC-67683)**

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Delamanid (OPC-67683)

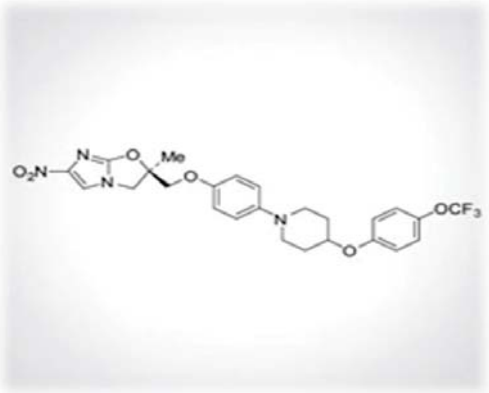
成分：Dihydroimidaze-oxazol

商品名稱： N/A

藥物名稱： DELAMANID
(OPC-67683)

劑型:tablet

劑量:50mg;2# bid for 6 months



- 是 nitroimidazopyrans 類藥物
- 研究顯示有效對抗抗藥性和非抗藥性結核之活性，有殺菌與滅菌之能力
- 可用於活動性或潛伏性的結核病，MDR/XDR-TB

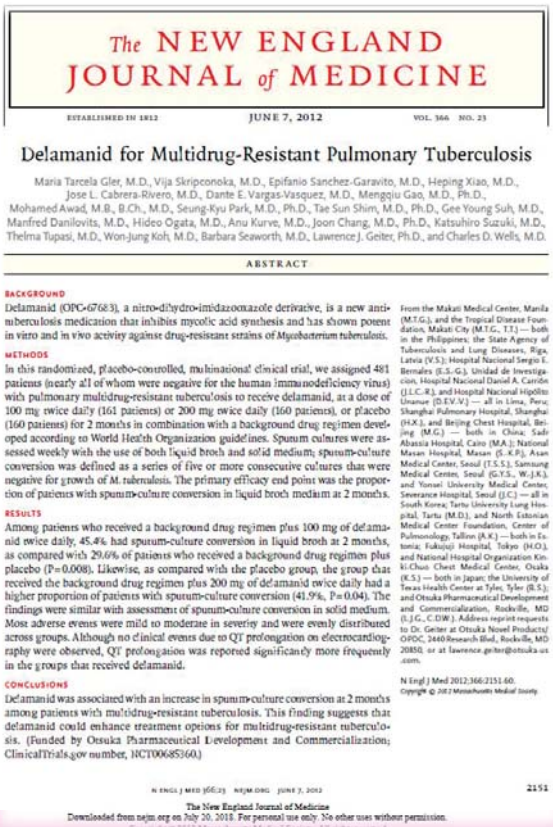
- Nitroimidazopyrans 是從bicyclic nitroimidazofurans 研發出來，一開始是用於治療癌症的化療藥物
- 但後來發現Nitroimidazopyrans 也可以抑制 actively growing 和dormant *M. tuberculosis*
  - 目前用於治療結核病的實驗
    - —PA-824 (a nitroimidazo-oxazine)
    - —OPC-67683 (a dihydroimidazo-oxazole)

New drugs against tuberculosis: problems, progress, and evaluation of agents in clinical development. Antimicrob Agents Chemother. 2009 Feb;53(2):465-79. doi: 10.1128/AAC.00777-08. Epub 2008 Nov 17.

- OPC-67683 showed sterilizing activity that was superior to that of isoniazid and equal to that of rifampin in an in vitro model of drug-tolerant *M. tuberculosis*, representing semidormant bacilli. No antagonism of OPC-67683 with rifampin, isoniazid, ethambutol, and streptomycin was shown in vitro.
- OPC-67683 in multiple doses up to 400 mg was tolerated well by healthy volunteers.

New drugs against tuberculosis: problems, progress, and evaluation of agents in clinical development. Antimicrob. Agents Chemother. 2009; 53(3):849-862.

Delamanid



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 7, 2012 VOL. 366 NO. 23

Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

Maria Tarcela Gler, M.D., Vija Skripconoka, M.D., Epifanio Sanchez-Garavito, M.D., Heping Xiao, M.D., Jose L. Cabrera-Rivero, M.D., Dante E. Vargas-Vasquez, M.D., Mengqiu Gao, M.D., Ph.D., Mohamed Awad, M.B., B.Ch., M.D., Seung-Kyu Park, M.D., Ph.D., Tae Sun Shim, M.D., Ph.D., Gee Young Suh, M.D., Manfred Danilovits, M.D., Hideo Ogata, M.D., Anu Kurve, M.D., Joon Chang, M.D., Ph.D., Katsuhiro Suzuki, M.D., Thelma Tupasi, M.D., Won-Jung Koh, M.D., Barbara Seaworth, M.D., Lawrence J. Geiter, Ph.D., and Charles D. Wells, M.D.

ABSTRACT

BACKGROUND
Delamanid (OPC-67683), a nitro-dihydro-imidazooxazole derivative, is a new antituberculosis medication that inhibits mycolic acid synthesis and has shown potent in vitro and in vivo activity against drug-resistant strains of *Mycobacterium tuberculosis*.

METHODS
In this randomized, placebo-controlled, multinational clinical trial, we assigned 481 patients (nearly all of whom were negative for the human immunodeficiency virus) with pulmonary multidrug-resistant tuberculosis to receive delamanid, at a dose of 100 mg twice daily (161 patients) or 200 mg twice daily (160 patients), or placebo (160 patients) for 2 months in combination with a background drug regimen developed according to World Health Organization guidelines. Sputum cultures were assessed weekly with the use of both liquid broth and solid medium; sputum-culture conversion was defined as a series of five or more consecutive cultures that were negative for growth of *M. tuberculosis*. The primary efficacy end point was the proportion of patients with sputum-culture conversion in liquid broth medium at 2 months.

RESULTS
Among patients who received a background drug regimen plus 100 mg of delamanid twice daily, 45.4% had sputum-culture conversion in liquid broth at 2 months, as compared with 29.6% of patients who received a background drug regimen plus placebo ($P=0.008$). Likewise, as compared with the placebo group, the group that received the background drug regimen plus 200 mg of delamanid twice daily had a higher proportion of patients with sputum-culture conversion (41.9%, $P=0.04$). The findings were similar with assessment of sputum-culture conversion in solid medium. Most adverse events were mild to moderate in severity and were evenly distributed across groups. Although no clinical events due to QT prolongation on electrocardiography were observed, QT prolongation was reported significantly more frequently in the groups that received delamanid.

CONCLUSIONS
Delamanid was associated with an increase in sputum-culture conversion at 2 months among patients with multidrug-resistant tuberculosis. This finding suggests that delamanid could enhance treatment options for multidrug-resistant tuberculosis. (Funded by Otsuka Pharmaceutical Development and Commercialization; ClinicalTrials.gov number, NCT00685360.)

From the Makati Medical Center, Manila (M.T.G.), and the Tropical Disease Foundation, Makati City (M.T.G., T.T.) — both in the Philippines; the State Agency of Tuberculosis and Lung Diseases, Riga, Latvia (V.S.); Hospital Nacional Sergio E. Bernales (E.S.-G.), Unidad de Investigación, Hospital Nacional Daniel A. Carrión (J.L.C.-R.), and Hospital Nacional Hipólito Unanue (D.E.V.-V.) — all in Lima, Peru; Shanghai Pulmonary Hospital, Shanghai (H.X.), and Beijing Chest Hospital, Beijing (M.G.) — both in China; Sadr Abassia Hospital, Cairo (M.A.); National Masan Hospital, Masan (S.-K.P.), Asan Medical Center, Seoul (T.S.S.), Samsung Medical Center, Seoul (G.Y.S., W.-J.K.), and Yonsei University Medical Center, Severance Hospital, Seoul (J.C.) — all in South Korea; Tartu University Lung Hospital, Tartu (M.D.), and North Estonian Medical Center Foundation, Center of Pulmonology, Tallinn (A.K.) — both in Estonia; Fukujuji Hospital, Tokyo (H.O.), and National Hospital Organization Kinki Chuo Chest Medical Center, Osaka (K.S.) — both in Japan; the University of Texas Health Center at Tyler, Tyler (B.S.), and Otsuka Pharmaceutical Development and Commercialization, Rockville, MD (L.J.G., C.D.W.). Address reprint requests to Dr. Geiter at Otsuka Novel Products/OPDC, 2440 Research Blvd., Rockville, MD 20850, or at lawrence.geiter@otsuka-us.com.

N Engl J Med 2012;366:2151-60.

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Background MDR-TB regimen +100mg Delamanid twice daily

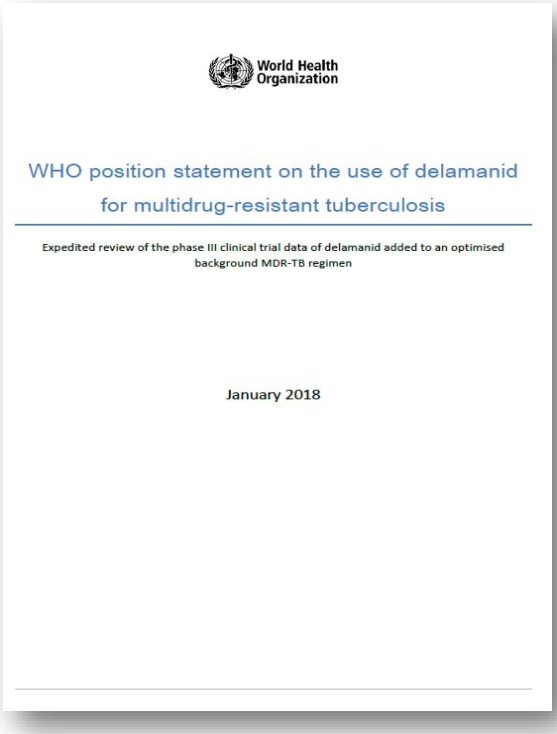
vs

Background MDR-TB regimen +placebo

Culture conversion improve significantly at **month 2** (45.4 vs 29.6%)

Gler, M. T. et al. Delamanid for multidrug-resistant pulmonary tuberculosis. *N. Engl. J. Med.* **366**, 2151–2160 (2012).

WHO position statement on the use of delamanid for MDR-TB


World Health Organization

WHO position statement on the use of delamanid for multidrug-resistant tuberculosis

Expedited review of the phase III clinical trial data of delamanid added to an optimised background MDR-TB regimen

January 2018

- The final *Trial 213* data were released by the manufacture to WHO in the late Nov,2017
- WHO response to the final data from trial 213

WHO position statement on the use of delamanid for multi-drug resistant tuberculosis WHO/CDS/TB/2018.1 2018 Jan
http://www.who.int/tb/publications/2018/WHO_position_statement_Delamanid_use.pdf?ua=1

Background

- WHO issued interim policy guidance on the use of delamanid in 2014
- The WHO interim policy was based on evidence available at the time from phase Ⅱb trial and an observational study conducted by the manufacture
- In 2016, the delamanid interim policy was extended to children aged 6-17 years following a review of data from a 6-month safety, efficacy, and pharmacokinetic trial of pediatric patients.

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Tiral 213

- The phase Ⅲ, multicentre, randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy to delamanid
- Comparing two regimens for treating adult MDR-TB patients

Tiral 213

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Trial 213

Control group	vs	Study group
The control regimen consisted of optimized Background regimen (OBR) + placebo for 6mos, followed by OBR for the remaining duration of therapy.(n=170)		An OBR consistent with WHO and National guideline + **delamanid 100mg BID for 2m**, followed by **200mg QD for 4m**; after 6m continued to receive OBR for a total treatment duration of 18-24m. (n=341)

Delamanid in treating MDR-TB is **challenging** due to …

1. didn't confirm the efficacy finding from Otsuka phase Ⅱ^{b} trials, which suggested statically significant reduction in mortality and increased culture conversion at 2mos

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Delamanid in treating MDR-TB is **challenging** due to …

2. The demonstrated benefit of delamanid *when added to an optimized background regimen* was small and limited to a modest reduction in time to culture conversion.

Delamanid in treating MDR-TB is **challenging** due to …

3. The exposure of many trial participants to multiple second-line medicines prior to randomization as well as the inclusion (probably by chance) of a disproportionate number of patients with both fluoroquinolone-resistant strains and bilateral cavitation in the delamanid arm of the MITT population may have masked a potentially stronger efficacy signal for delamanid.

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Delamanid in treating MDR-TB is **challenging** due to …

4. Trial 213 was not designed to indicate which MDR-TB patients would most likely benefit from delamanid, or whether delamanid can effectively replace or protect other medicines in composing MDR-TB regimens.

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- WHO advise only add delamanid to a longer MDR-TB regimen when it cannot be composed according to WHO recommendations.
- When an effective and well-tolerated longer MDR-TB regimen can be otherwise composed, the addition of delamanid may not be warranted.

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Shorter MDR-TB regimen

- Standardized regimen; limited modifications are possible
- 4-6 Km-Mfx-Pto-Cfz-Z-$H_{high\text{-}dose}$-E / 5 Mfx-Cfz-Z-E
- Recommendation applies to adults, children, PLHIV
- Ideally, patients are tested for resistance to fluoroquinolones and second-line injectable drugs; not recommended in case of 2nd line drug resistance, extrapulmonary disease and pregnancy

Reference: WHO treatment guideline for drug resistant tuberculosis: 2016update

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Short regimen for MDR-TB

Composition of the shorter regimen (known as the Bangladesh regimen) to treat multidrug-resistant tuberculosis, and the main contraindications suggesting prescription of the longer regimen[a]

Composition	
4–6 Km–Mfx–Pto–Cfz–Z–$H_{high\text{-}dose}$–E/5 Mfx–Cfz–Z–E: 4 to 6 months of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol, followed by 5 months of moxifloxacin, clofazimine, pyrazinamide, and ethambutol	
Contraindication	**Comments**
Confirmed resistance to or suspected ineffectiveness of a drug in the shorter MDR-TB regimen (except isoniazid resistance)	Evaluation of the drug resistance pattern of all patients with rapid diagnostic methods is recommended
Exposure to ≥1 second-line drugs in the shorter MDR-TB regimen for >1 month	
Intolerance to ≥1 drugs in the shorter MDR-TB regimen or risk of toxicity (e.g., drug–drug interactions)	Intolerance to a drug composing the regimen is, in practice, equivalent to resistance to the drug
At least one drug in the shorter MDR-TB regimen not available	
Pregnancy	Insufficient evidence available
Extrapulmonary disease	Insufficient evidence available

MDR-TB, multidrug-resistant tuberculosis.

[a] Note: The emergence of treatment failure, drug intolerance, return after an interruption >2 months, or emergence of any other exclusion criterion implies interruption of the shorter regimen and a move to the longer one.

Sotgiu G, Tiberi S, Centis R, D'Ambrosio L, Fuentes Z, Zumla A, Migliori GB. *Applicability of the shorter 'Bangladesh regimen' in high multidrug-resistant tuberculosis settings.* International Journal of Infectious Disease ,2017,53,190-193

In patients (adults and children) with

- rifampicin-resistant TB or MDR-TB,
- who have not been previously treated with second-line drugs and
- in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely

a shorter MDR-TB regimen of **9–12 months** may be used instead of a conventional regimen

- Conditional recommendation – very low quality of evidence

Reference: WHO treatment guideline for drug resistant tuberculosis: 2016update

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Shorter MDR-TB regimen "Bangladesh regimen"

Evidence available on the efficacy and safety of the shorter regimen (known as the Bangladesh regimen) to treat multidrug-resistant tuberculosis

Study (Ref.)	Setting/number of cases	Study results	Conclusions	Comments
Piubello et al. Int J Tuberc Lung Dis 2014 (26)	Niger National Tuberculosis Programme; 65 MDR-TB patients	Cure was achieved in 58 patients (89.2%, 95% CI 81.7–96.7); 6 died and 1 defaulted; all 49 patients assessed at the 24-month follow-up after cure remained smear- and culture-negative	Standardized 12-month treatment for MDR-TB was highly effective and well tolerated in patients not previously exposed to second-line anti-TB drugs in Niger	The main adverse events were vomiting (26.2%) and hearing impairment (20%), but no treatment had to be stopped; 1 patient HIV-infected (1.7%)
Van Deun et al. Am J Respir Crit Care Med 2010 (27)	Prospective observational study conducted over a 12-year period in this large TB control program in Bangladesh; 427 MDR-TB patients	206/427 (48.2%) patients received the most effective treatment regimen; a minimum of 9 months of treatment with GFX, CFZ, EMB, and PZA throughout the treatment period, supplemented by PTO, KM, and high-dose INH during an intensive phase of a minimum of 4 months, giving a relapse-free cure of 87.9% (95% CI 82.7–91.6)	Serial regimen formulation guided by overall treatment effectiveness resulted in treatment outcomes comparable to those obtained with first-line anti-TB treatment; confirmatory formal trials in populations with high levels of HIV co-infection and in populations with a higher initial prevalence of resistance to second-line anti-TB drugs are required	Major adverse drug reactions were infrequent and manageable Compared with the 221 patients treated with regimens based on OFX and commonly PTO throughout, the hazard ratio of any adverse outcome was 0.39 (95% CI 0.26–0.59)
Aung et al. Int J Tuberc Lung Dis 2014 (28)	Bangladesh National Tuberculosis Programme; prospective, observational study of a GFX-based directly observed regimen, mainly with initial hospitalization; 515 MDR-TB patients	515 patients were recruited from 2005 to 2011, 84.4% had a bacteriologically favourable outcome; due to extensive disease with delayed sputum conversion, only half of the patients completed treatment within 9 months; 95% completed treatment within 12 months; 11 patients failed or relapsed, and 93.1% of the 435 patients who were successfully treated completed at least 12 months of post-treatment follow-up	The excellent outcome of the Bangladesh regimen was largely maintained; bacteriological treatment failures and relapses were rare, except among patients with high-level GFX resistance, notably in the presence of PZA resistance	The strongest risk factor for a bacteriologically unfavourable outcome was high-level FQ resistance, particularly when compounded by initial PZA resistance Low-level FQ resistance had no unfavourable effect on treatment outcome Amplification of drug resistance occurred only once, in a patient strain that was initially only susceptible to KM and CFZ

CFZ, clofazimine; CI, confidence interval; EMB, ethambutol; FQ, fluoroquinolone; GFX, gatifloxacin; INH, isoniazid; KM, kanamycin; MDR-TB, multidrug-resistant tuberculosis; OFX, ofloxacin; PTO, prothionamide; PZA, pyrazinamide; TB, tuberculosis.

Sotgiu G, Tiberi S, Centis R, D'Ambrosio L, Fuentes Z, Zumla A, Migliori GB. *Applicability of the shorter 'Bangladesh regimen' in high multidrug-resistant tuberculosis settings.* International Journal of Infectious Disease ,2017,53,190-193

Treatment success in patients treated with a shorter MDR-TB regimen vs longer MDR-TB regimen

RESISTANCE PATTERN	SHORTER MDR-TB REGIMEN		LONGER MDR-TB REGIMEN	
	N	% (95% CL)	N	% (95% CL)
All cases regardless of pyrazinamide and fluoroquinolone susceptibility	1008/1116	90.3% *(87.8%– 92.4%)*	4033/5850	78.3% *(71.2%–84%)*
Pyrazinamide resistant; fluoroquinolone resistant	19/28	67.9% (47.6%–84.1%)	81/137	59.1% (50.6%–67.1%)
Pyrazinamide resistant; fluoroquinolone susceptible	90/100	88.8% (47.3%–98.6%)	840/1075	81.4% (71.6%–88.4%)
Pyrazinamide susceptible; fluoroquinolone resistant	12/15	80.0% (50.0%–94.1%)	72/120	64.4% (49.6%–76.9%)
Pyrazinamide susceptible; fluoroquinolone susceptible	121/125	96.8% (77.3%–99.6%)	890/1119	83.5% (75.7%–89.2%)

[a] Treatment success (cured or treatment completed *(10,15)*) versus treatment failure/relapse/death in patients not previously treated with second-line TB medications; percentages shown have been adjusted where possible (see also online Annex 4; Section 1 for more details).

Reference: WHO treatment guideline for drug resistant tuberculosis: 2016update

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Bedaquiline

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- 性　別 :男性
- 職　業: 鐵工廠員工/布農族
- 生　日 :59/04/18(48歲)
- 過去病史 :Bilateral THR S/P
- 初次通報日期：2014.9.22 體檢異常部豐通報
- 此次開始用藥日：2014.09.23
- 初次臨床症狀初次驗痰日期及結果：
  - 2014.09.26 M(+) C(+)鑑定TB(R:INH)
  - 2014.11.24 DST :H.E.R.S抗
- 2線藥開始用藥日：2015.02.12
- 入團隊日：2015.03.02

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Drug Susceptibility Test

Date	H	R	E	S	Z	Km	Am	Lfx	Mfx	Pto/ Eto	PAS	Cs	Ofx	CAP	Rifa butin	Fluno quinol oe
2014. 09.26	R	S	S	S												
2014. 11.24	R	R	R	R		R	R	R		S	S	S	R	R	R	
2015. 01.24	R	R	L:R H:S	R												
2015. 02.25	R	R	L:R H:S	R												
2015. 03.12	R	R	L:R H:S	R												

R = Resistance; S = Sensitivity

(H) = High in dosage ; (L) = Low in dosage

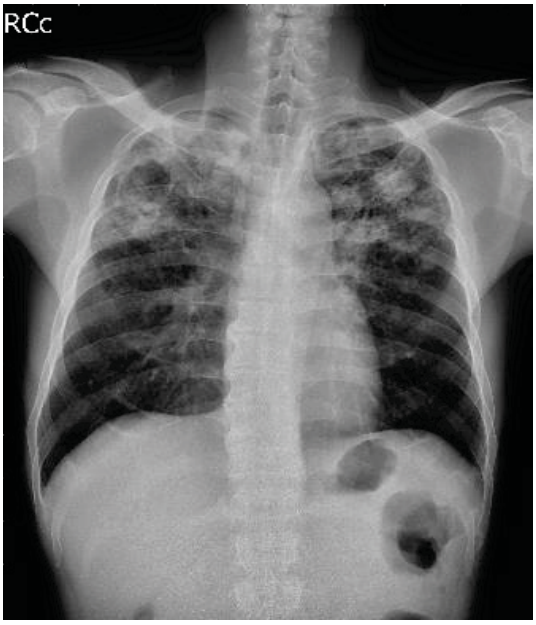
Date	Year	2014/9/19~	2015						
	Date	2015/2/11	2/12	2/26	3/26	3/29	4/16		
Regimen	RFT	5					Transferred to Chang-Hua Hospital hold		
	EMB	2							
	PZA 500mg		3	3	3	3			
	Moxi 400mg		1	1	1	1			
	CS 250mg		2	2	2	2			
	PASER 5gm			1#Bid	1#Bid	1#Bid			
	TBN 250mg		2	2	2	2			
	CM		850	850	R				
	Cfz 100mg		55 kg			2	50 kg		
Sputum	日期	9/25	1/24	2/25	3/12	3/25	4/16	5/18	6/18
	抹片	+*3	+*1	+*2	Scanty	-	-*2	Scanty	+*1
	培養	+*3	+*1	+*2	+	+	-*2	+	-*2
	ID	TB*3	TB*1	TB*2	TB	TB		NTM	
Lab	日期	9/19	2/12		3/26		4/16		
	AC / PC	AC 113					AC 123		
	GOT	43	21		80		0.39		
	GPT	12	13		20		11		
	T-bil	1.1	0.5				0.55		
	BUN						8		
	Cr	0.62	0.5		1.11		0.97		
	UA	7.9							
	WBC *10^3						4.1		
	RBC *10^6						4.25		
	Hb						13.4		
	Plat *10^3						103		

Date	Year	2015											
	Date	**7/3**	**7/6**	**7/17**	**8/9**	**8/20**	**8/24**	**9/5**	**9/9**	**9/11**	**9/16**	**9/27**	**10/7**
Regimen	Bedaquiline	4 QD	4 QD	2 QTW	2 QTW		2 QTW	2 QTW		2 QTW	2 QTW	2 QTW	
	Augmentin	1 /Tid	1 /Tid	1 /Tid	1 /Tid		1 /Tid	1 /Tid		1 /Tid	1 /Tid	1 /Tid	Hold
	Cfz	2	2	2	2		2	1		1	1	1	
	Linezolid	1	1	1	1		1	1		0.5	0.5	0.5	Ascites
	TBN	1 /Tid	1 /Tid	1 /Tid	1 /Tid	hold	1 /Tid	1 /Tid	hold	1 /Tid	1 /Tid	1 /Tid	
	CS	2	2	2	2		2	2		2	2	2	
	Meropenen	1gm Q12h	1gm Q12h	1gm Q12h	1gm Q12h		1gm Q12h	1gm Q12h		1gm Q12h	1gm Q12h	1gm Q12h	PRBL 2U
	PASER		5g /Bid	5g /Bid	5g /Bid		5g /Bid	5g /Bid		5g /Bid	5g /Bid	5g /Bid	
Sputum	Date			**7/17**	**8/2**			**9/2**					**10/3**
	Smear			Scanty* 2	+*1			-*2					-*2
	Culture			-*2	-*3			-*2					-*2
	Weight	60 kg		60	60		58.2	58.1		56.7			55.4
Lab	Date	**6/29**		**7/17**	**7/24**	**8/19**	**8/24**	**8/31**	**9/9**		**9/16**	**9/27**	**10/7**
	AC / PC										PRBL 2U	PRBL 2U	
	GOT	22		42	32	31		35	80				50
	GPT	16		22	16	12		13	21				15
	T-bil	0.84		0.55	0.54	0.8		1.32	1.15				2.84
	BUN	10		13	12	14		11	17				15
	Cr	0.68		0.75	0.73	0.87		0.83	1				0.84
	UA	7.1		4.4	4	4.1		5.4				**9/23**	3.4
	WBC *10^3	4.4		3.5	3.4	3.7	4.5	2.8	2.7		2.6	2.5	3.1
	RBC *10^6	3.94		4.05	4.05	3.63	2.73	3.02	2.85		2.22	2.38	2.44
	Hb	12.5		12.8	12.7	9.9	8.4	9.4	8.7		6.9	7.4	7.8
	Plat *10^3	174		109	90	79	95	132	70		72	108	94

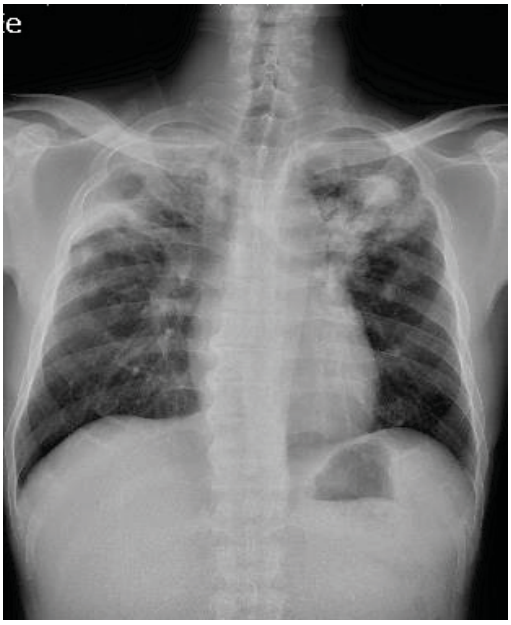
Date	Year	2015											
	date	**10/9**	**10/21**	**10/23**	**10/28**	**11/3**	**11/6**	**11/9**	**11/10**	**11/13**	**11/20**	**12/4**	**12/11**
Regimen	Bedaquiline	2 QTW		2 QTW	2 QTW	2 QTW	2 QTW	2 QTW	2 QTW	2 QTW	2 QTW	2 QTW	2 QTW
	Augmentin	1 /Tid	Hold	1 /Tid	1 /Tid	1 /Tid	1 /Tid	1 /Tid	1 /Tid	1 /Tid	1 /Tid	1 /Tid	1 /Tid
	Cfz	1		1	1	1	1	1	1	1	1	1	1
	Linezolid	0.5	Anemia	0.5	0.5	0.5	0.5	1 Q2D	1 Q2D	1 Q2D	1 Q2D	1	1
	TBN	DC											
	CS	2		2	2	2	2	2	2	2	2	2	2
	Meropenen	1 gm Q12h	PRBL 2U	1 gm Q12h	1 gm Q12h	1 gm Q12h	1 gm Q12h	1 gm Q12h	1 gm Q12h	1 gm Q12h	1 gm Q12h	1 gm Q12h	1 gm Q12h
	PASER	5g /Bid		5g /Bid	5g /Bid	5g /Bid	5g /Bid	5g /Bid	4g /Bid	4g /Bid	4g /Bid	4g /Bid	4g /Bid
Sputum	Date				**EPO**	**11/3**	**EPO**			**EPO**		**12/4**	
	Smear					-						-*2	
	Culture												
	ID	59.3				57		58.4	59.6			62.5	
Lab	Date	**10/13**	**10/21**		**10/28**		**11/6**			**11/13**	**11/20**	**12/4**	**12/11**
	AC / PC												
	GOT	52	52		39					47			
	GPT	15	14		13					10			
	T-bil	1.18	0.91		1.14					0.9			0.66
	BUN	12	10		10					12			11
	Cr	0.66	0.66		0.71					0.67			0.66
	UA									4.7			4.7
	WBC *10^3	3.5	2.7		2.6		2.8			3.6	3.1	3.3	3.4
	RBC *10^6	2.87	1.64		2.74		2.55			2.86	2.89	3.25	3.24
	Hb	9.1	5.5		9.1		8.9			10.4	10.3	11.8	11.8
	Plat *10^3	166	156		140		154			161	148	144	143

10/13
Albumin: 2.7

Chest X-Ray

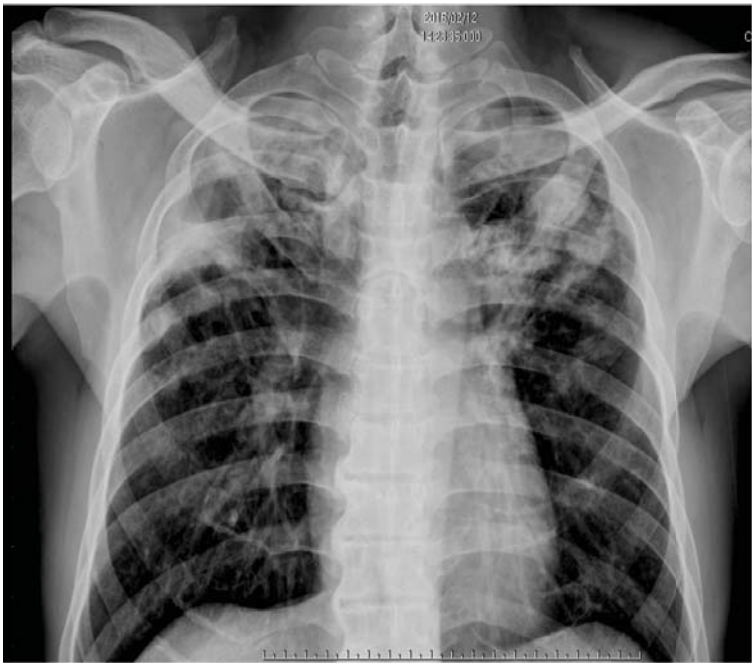


2014.09.19 at Feng Yuan Hospital



2014.12.19 at Feng Yuan Hospital

2015.02.12 at Taichung Hospital



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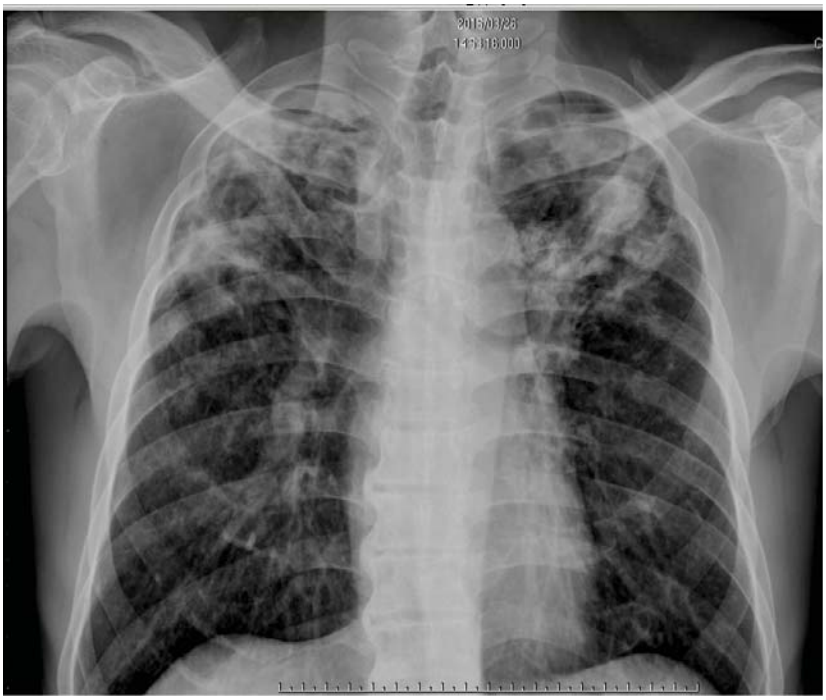
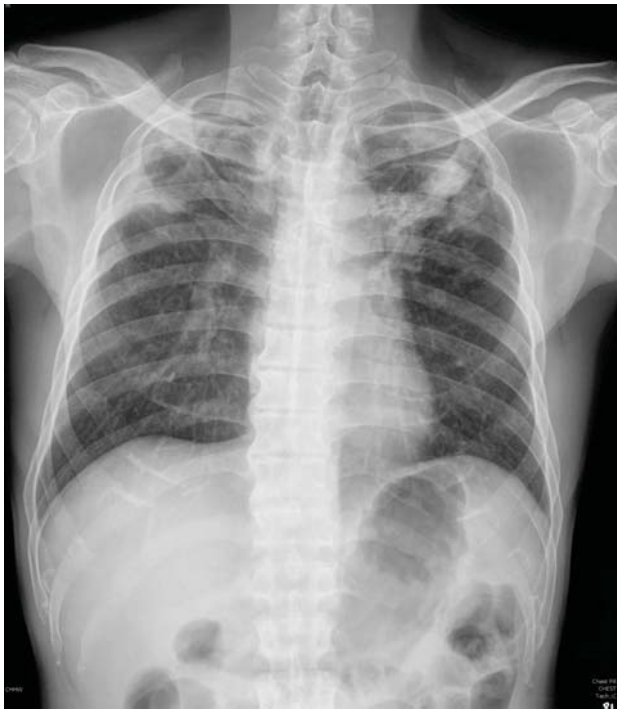
2015.03.26 at Taichung Hospital

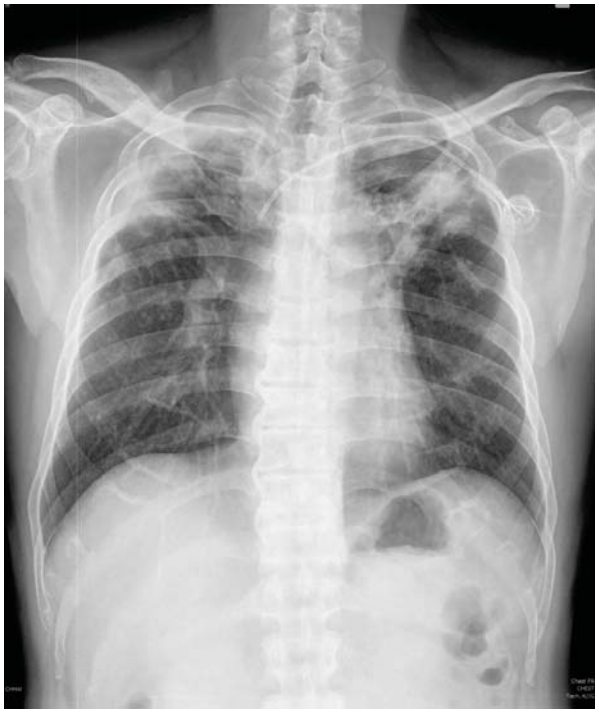


衛生福利部彰化醫院 CHHW

CXR at Chang-Hua Hospital

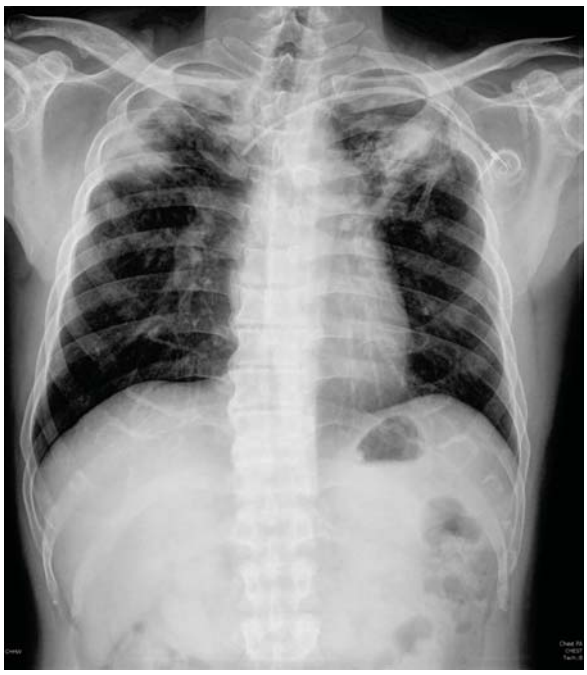


2015/04/18 Admitted to Chang-Hua Hospital

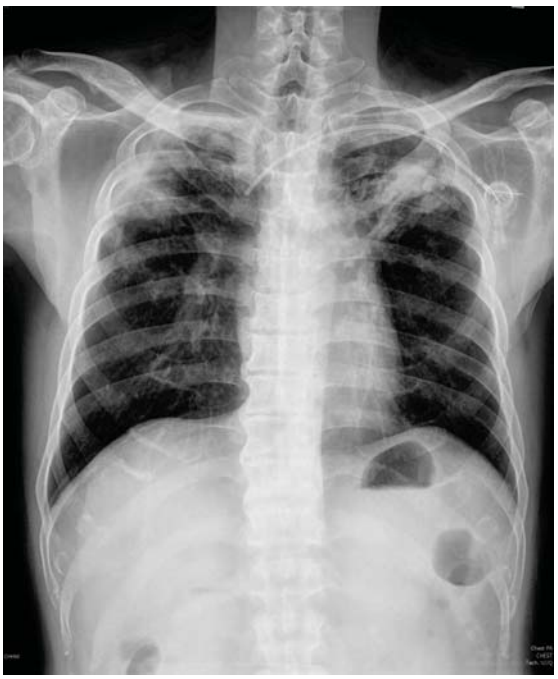


2015/07/17 two weeks after medication administration

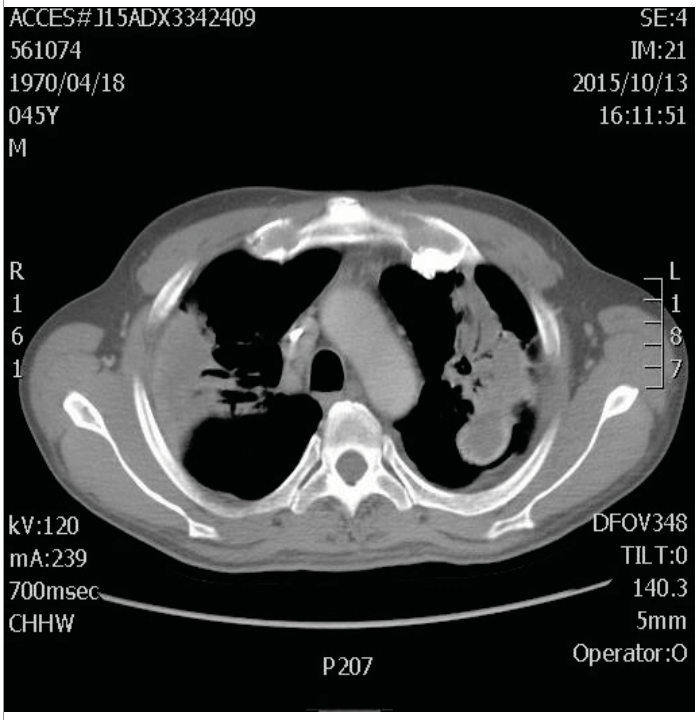
CXR at Chang-Hua Hospital

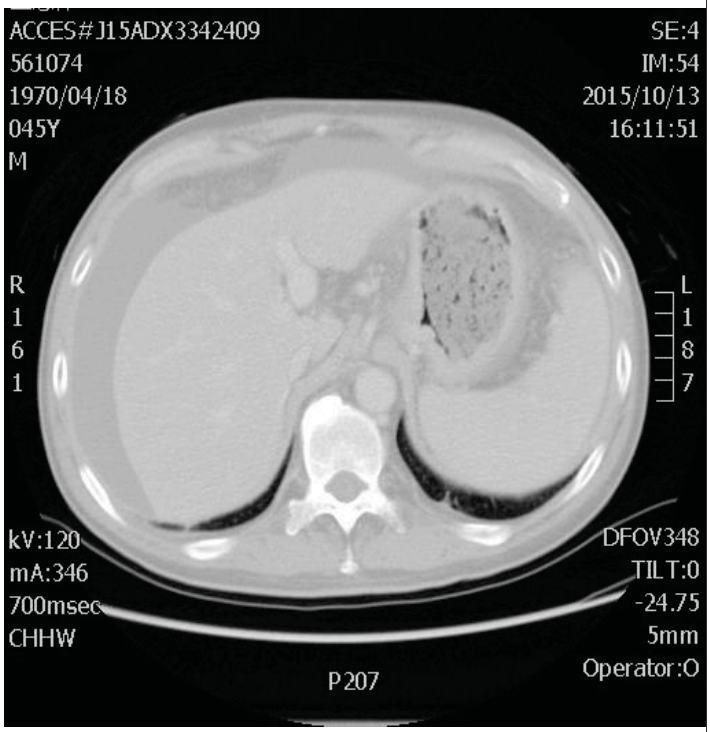


2015/08/17 One month after meds administration



2015/09/22 Two months after meds administration





前瞻、健康、品質、清新、熱情、勇氣
主動關懷、愛心、誠心、真心、盡心盡力、全心全意

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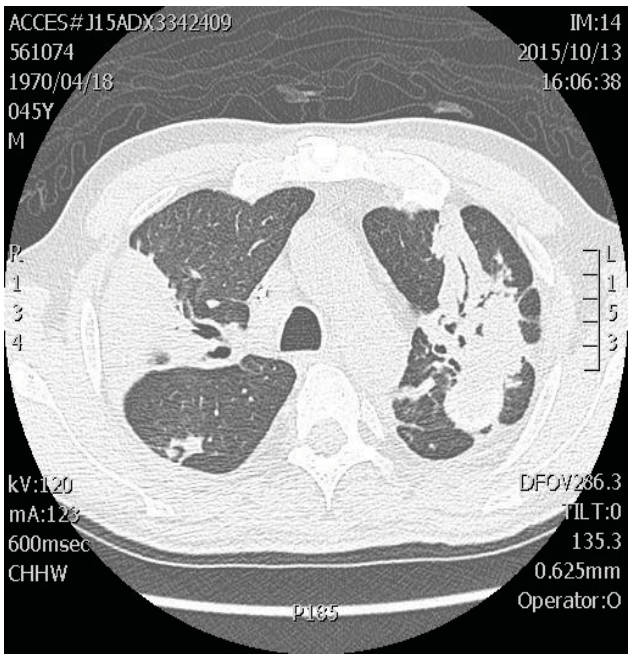
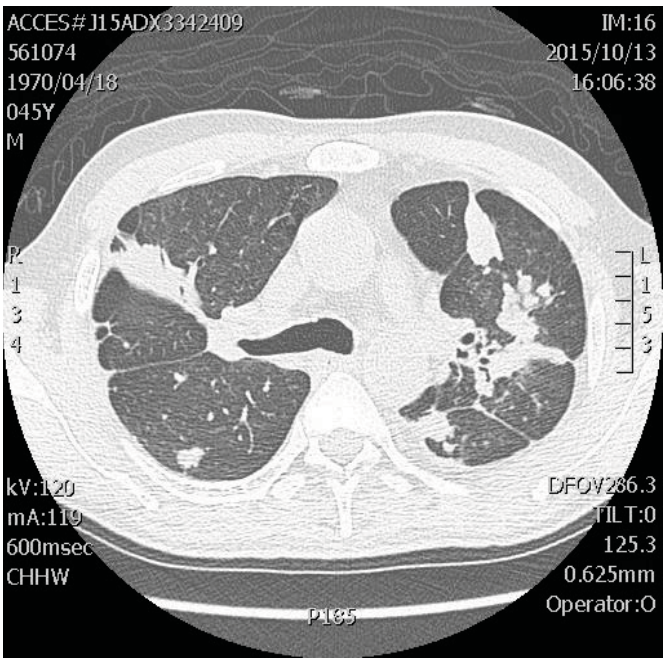
CHHW





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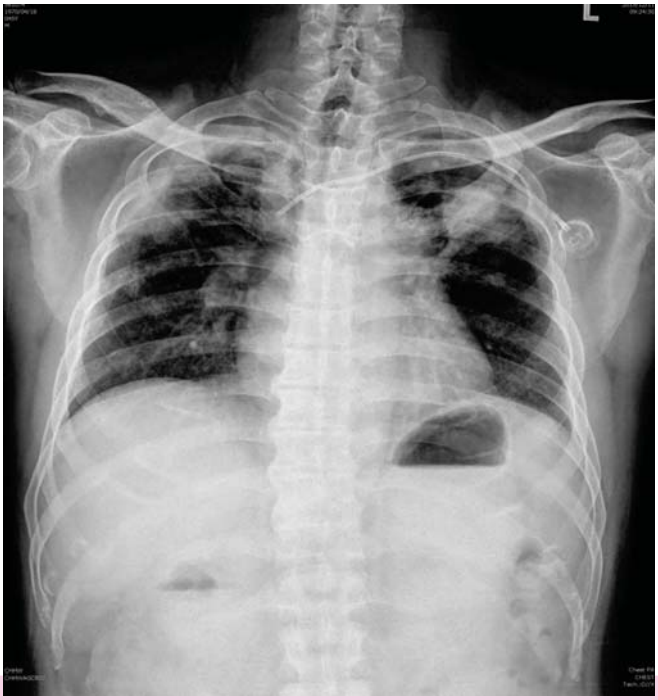
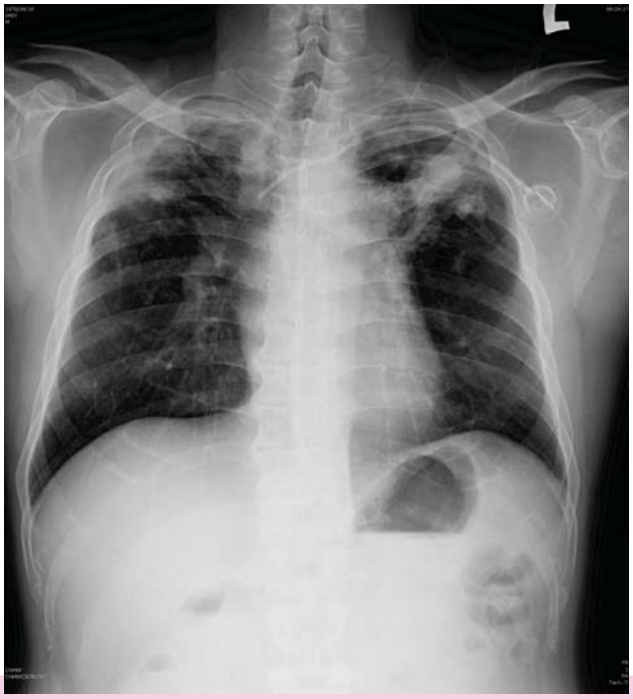
2015/12/11



2016/01/08



前瞻、健康、品質、清新、熱情、勇氣
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Anemia

※ Hemoglobin ↓ since 2015/08/19

Hb:5.5-9.1

Action:

1. Blood transfusion at 09/16、09/27、10/07、10/21
2. Erythropoietin injection at 10/28 、11/6、 11/13.

Result:

Hb11.8 at 12/08

*Discharged from Chang-Hua hospital and returned to his hometown at 10th of Jan, 2016.

*XDR treatment completed at July 2017.

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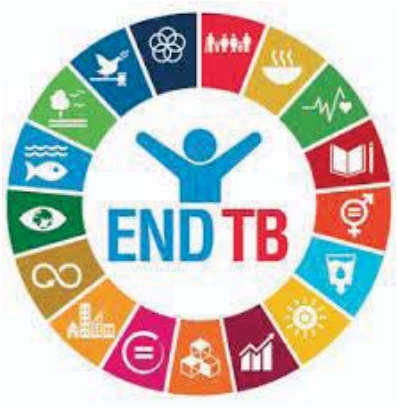
Thank you for your attention!



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