HA Convention 2016 : Special Topic Session 3 May 2016

Diagnosis and Management of TB in Adults

Dr. Thomas Mok
COS(RMD), KH

Tuberculosis

- An airborne infectious disease caused by Mycobacterium tuberculosis (MTB)
- If the disease involves the lung, it is called pulmonary TB (PTB)(80% of cases)
- 15-20% of cases, TB affects other organs (extra-pulmonary TB)
- TB complex DNA was found in the spine of Egyptian mummy dating from 3000-2400 BC

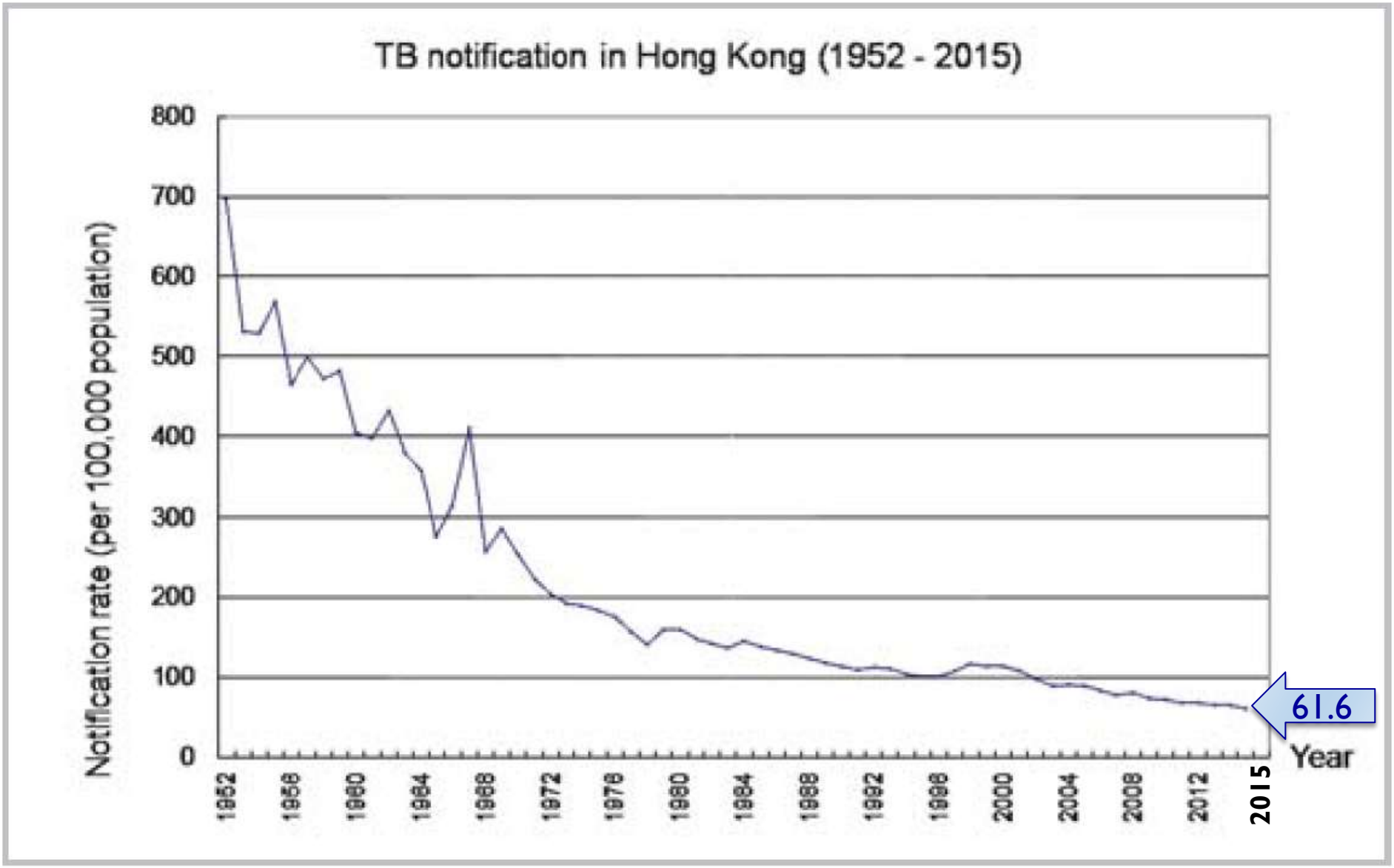


Figure 1 - TB notification rate in Hong Kong, 1952-2015.

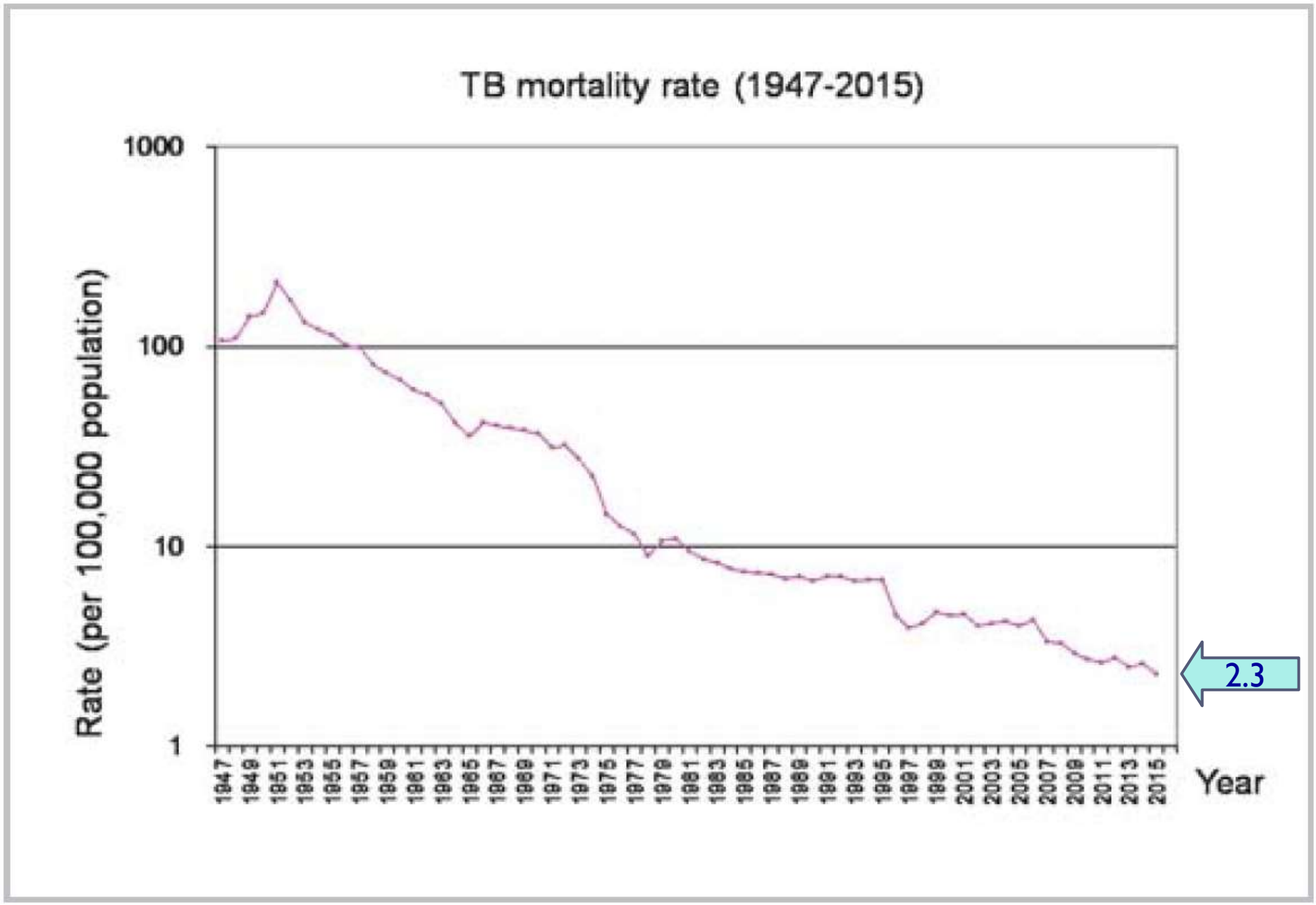


Figure 2 - TB mortality rate in Hong Kong, 1947-2015.

Global Scenarios

9.6 million people fell ill with TB in 2014

1.5 million men, women and children died from TB in 2014

1.2 million people living with HIV developed TB, with 0.4 million associated deaths in 2014

480 000 people developed MDR-TB (multidrug-resistant TB) in 2014, with 190 000 associated deaths

The End TB Strategy

Vision : A World Free of TB

(Zero deaths, disease, and suffering due to TB)

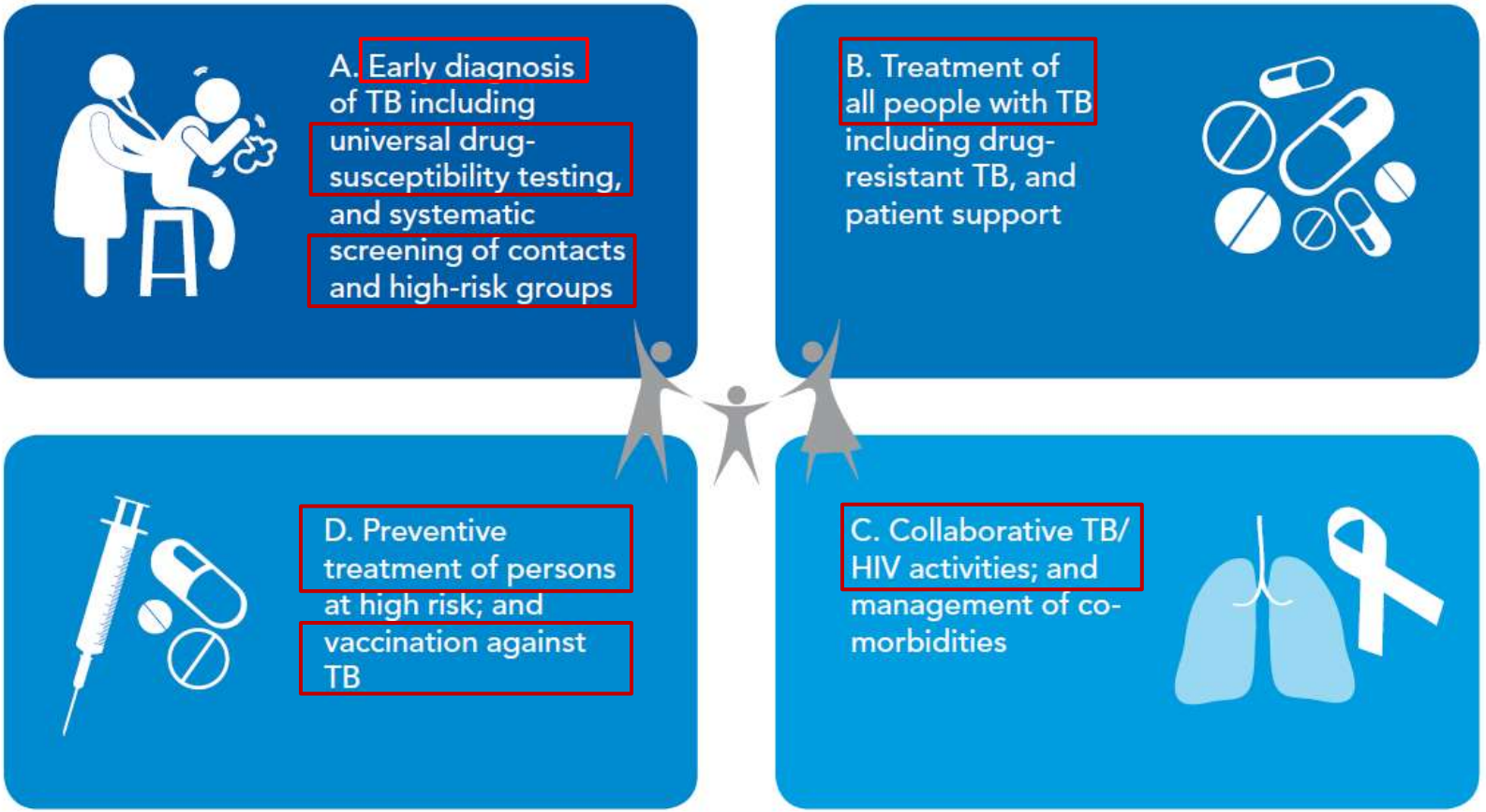
Goal : End the Global TB Epidemic

	MILESTONES		TARGETS	
			SDG*	END TB
	2020	2025	2030	2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20%	50%	80%	90%
TB-affected families facing catastrophic costs due to TB (%)	0%	0%	0%	0%

* The United Nations Sustainable Development Goals (SDGs) include ending the TB epidemic by 2030 under Goal 3.

The End TB Strategy: Pillars

Pillar I : Integrated patient-centred TB care & prevention



Pillar II: Bold policies and supportive system

Pillar III: Intensified Research and innovation

Diagnosis of TB : goal is to diagnose as many patients and as early as possible

Systemic Screening

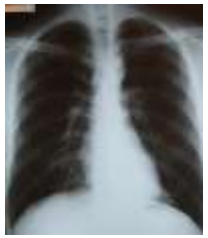
Line Probe Assay

Symptoms

TB Diagnosis

Xpert MTB/RIF

CXR



Microscopy

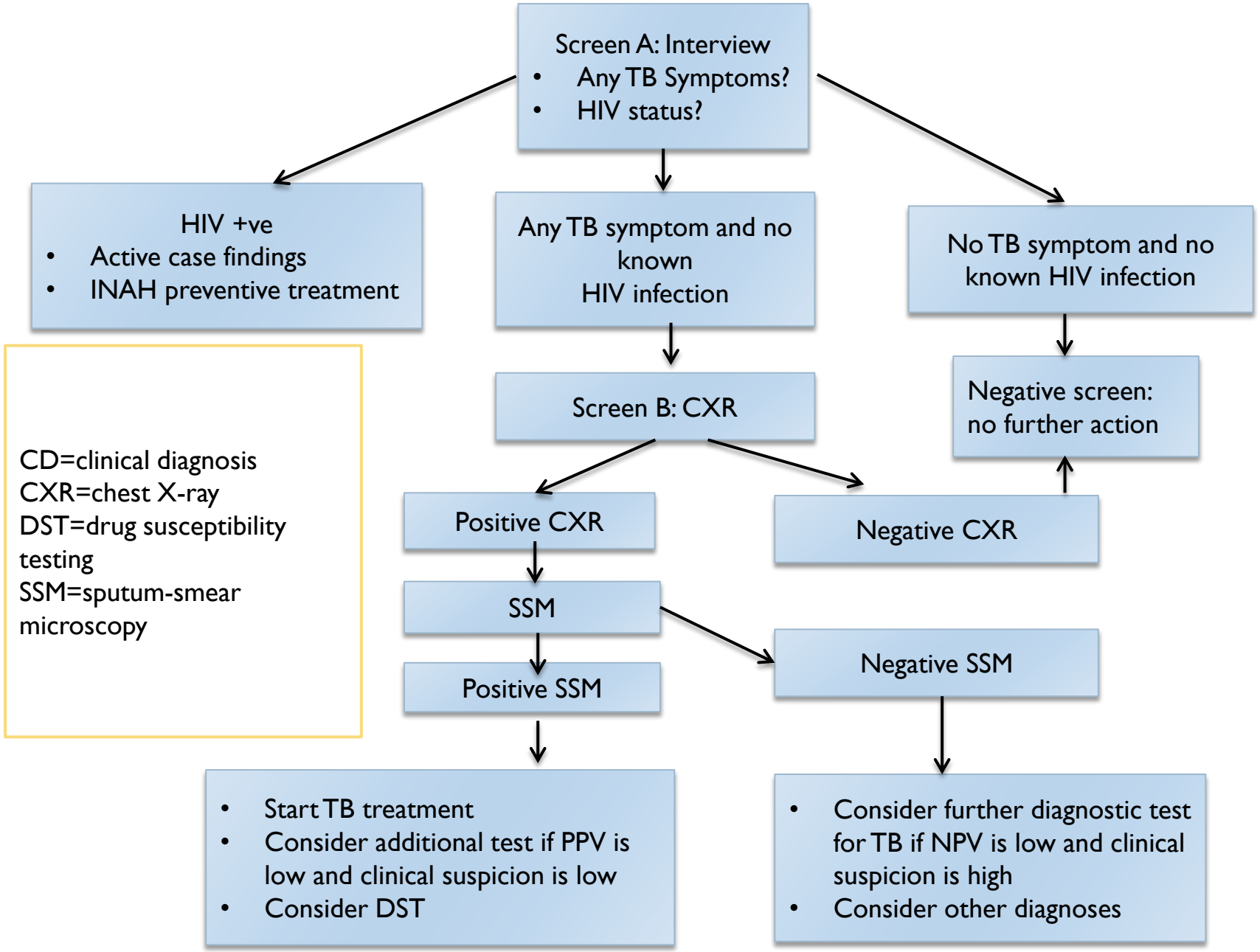
Bronchoscopy

Evaluation for TB

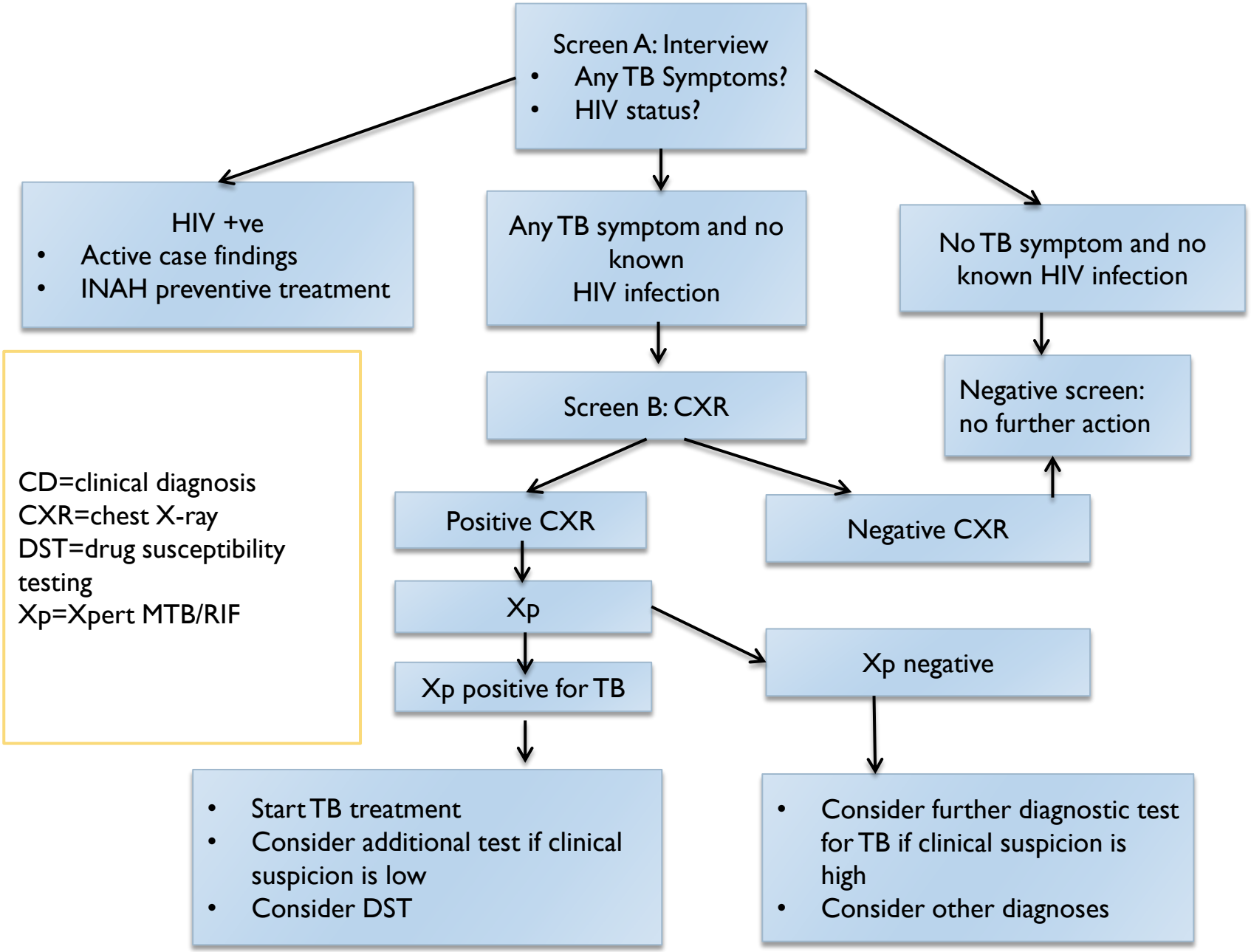
cough ≥2 weeks
or
cough of any duration
Fever, night sweats
or weight loss

Household contact and other close contact
+
HIV patients
+
workers with silica exposure

Compatible findings on CXR



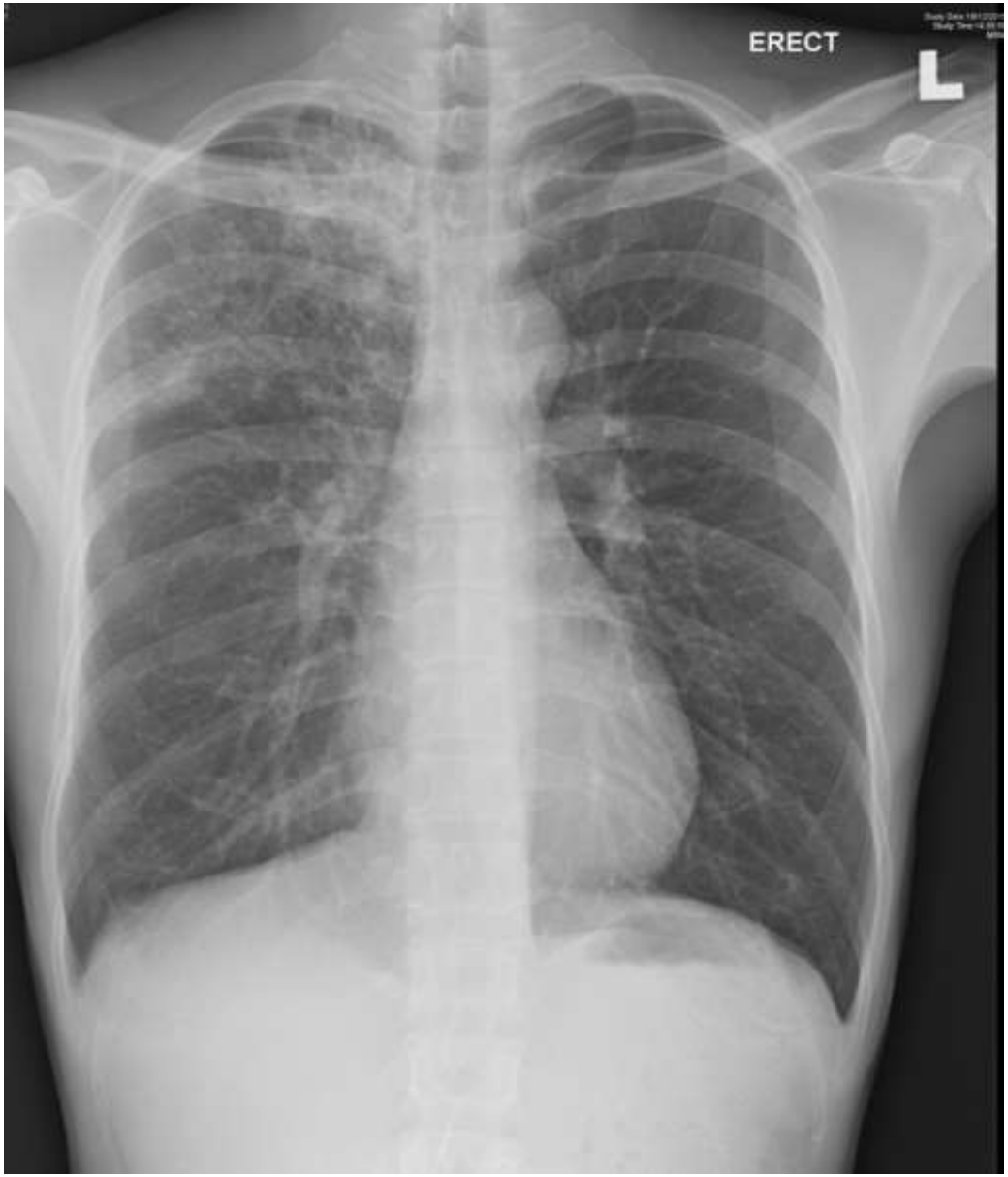
- WHO Systemic screening for active TB 2013



- WHO Systemic screening for active TB 2013

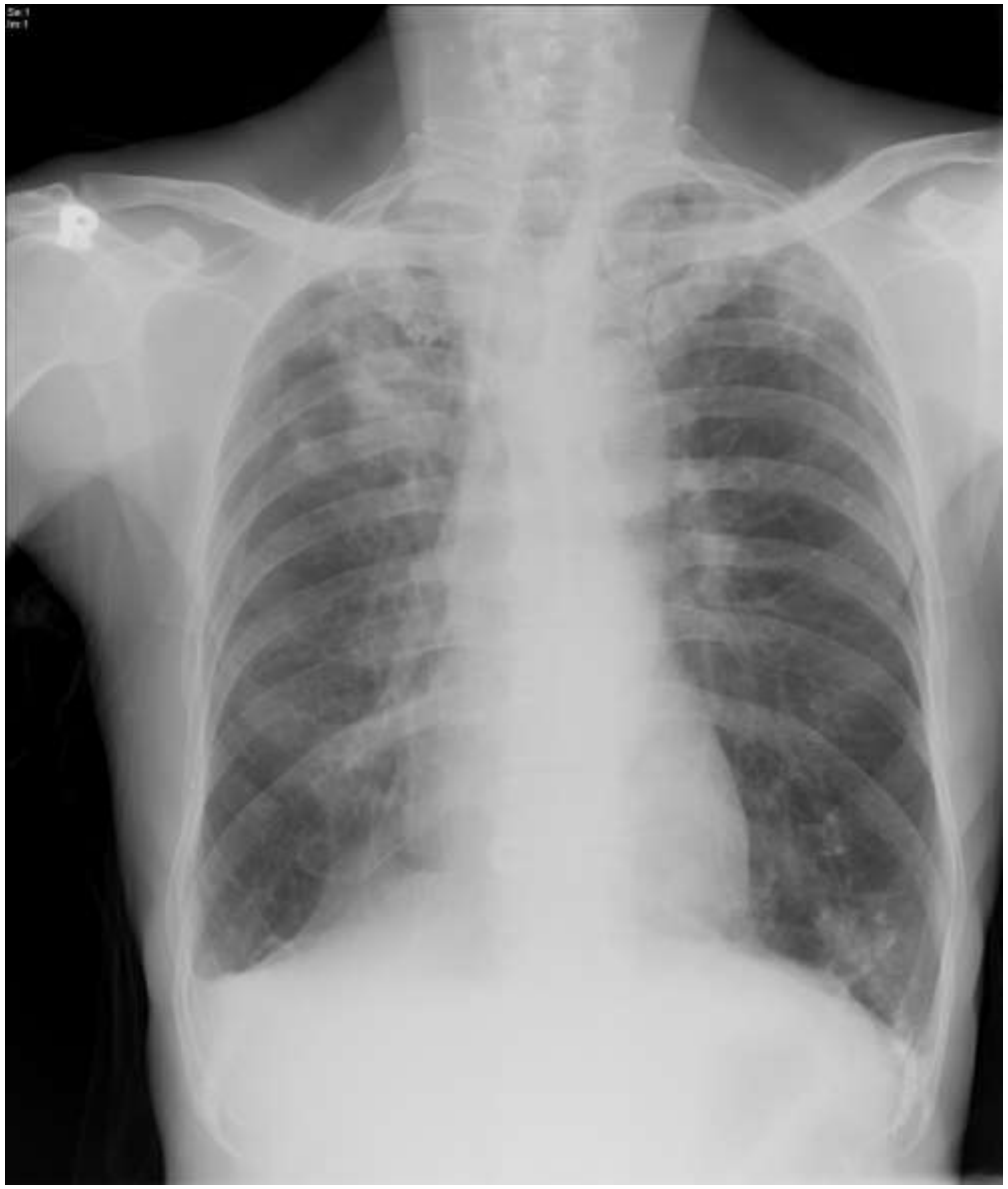
Sensitivity and specificity of diagnostic tests

	Sensitivity (%)	Specificity (%)
Any symptom	77	67
CXR (any abnormality compatible with TB)	98	75
Sputum smear microscopy (fluorescence microscopy)	64	98
Xpert MTB/RIF (1) Detect TB	88 (98 smear +ve 68 smear –ve)	98
(2) RIF resistance	94	98



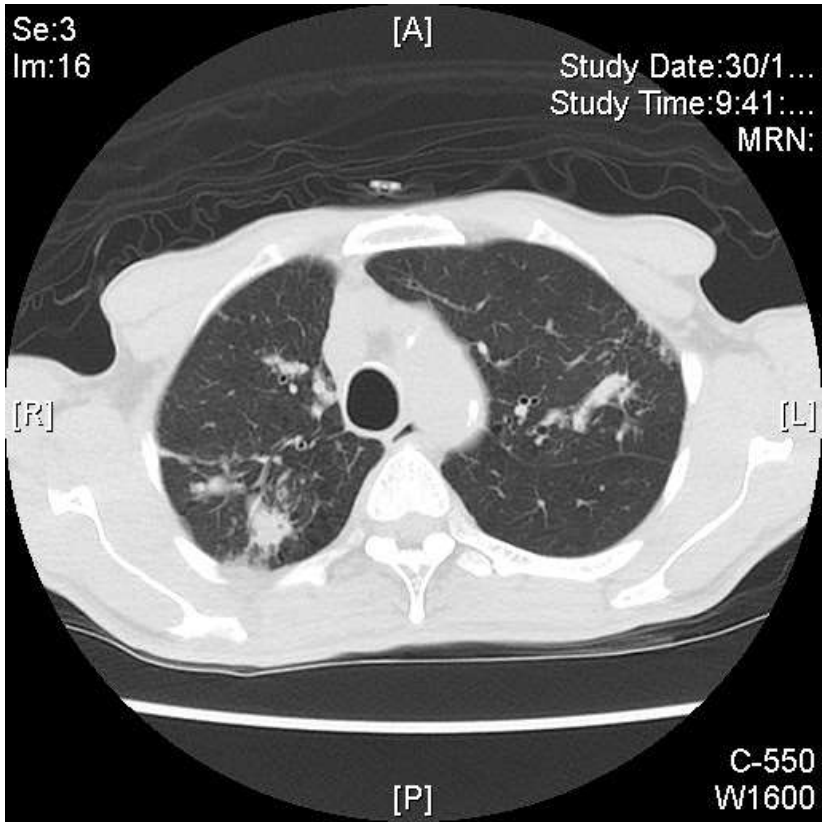
44-year-old chronic smoker complained of right-sided chest pain

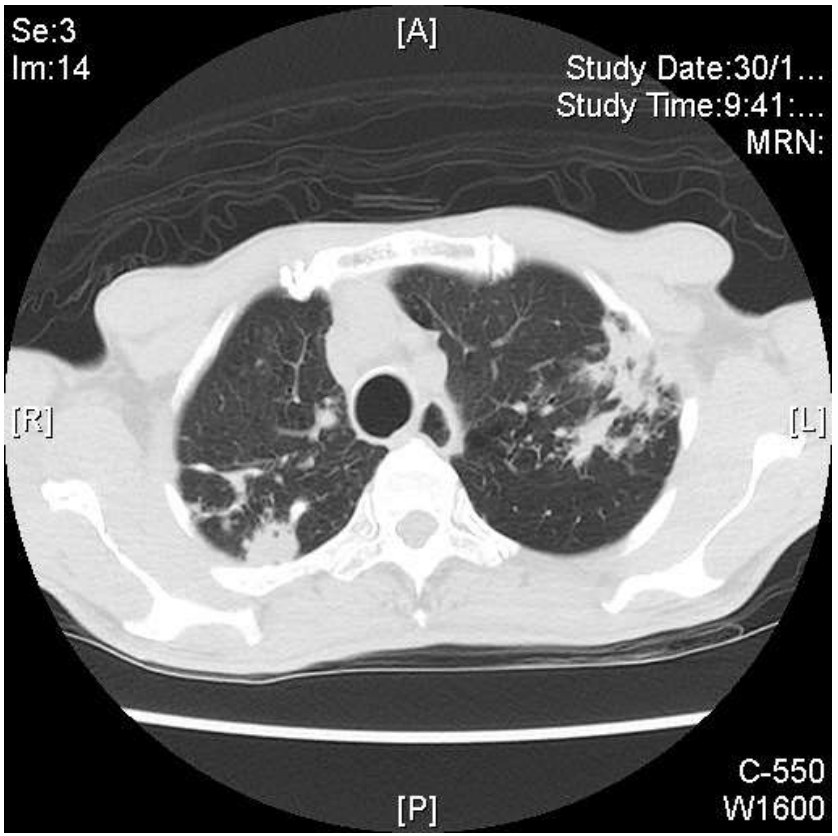
Microscopy : Direct smear +ve



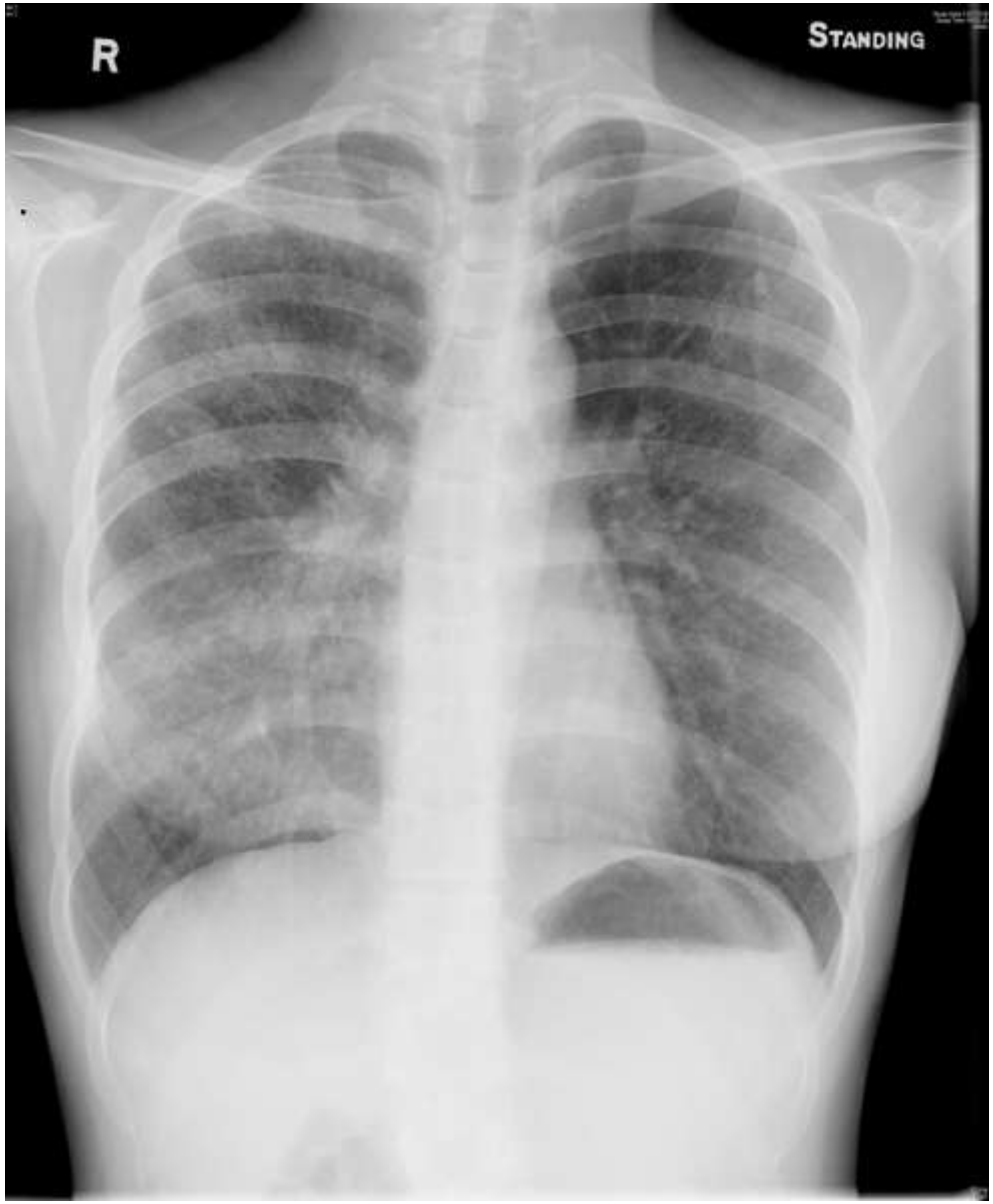
54-year-old had cough and sputum x 1 month and one episode of blood stained sputum

CT diagnosis : BOOP





Microscopy : Direct smear +ve



24-year old, born in Shenzhen and a U grad presented as haemoptysis

Microscopy : Direct smear -ve

Clinical Details: PATIENT CATEGORY 1

Date/time Collected: 21/01/2016 --:--
Date/time Registered: 21/01/2016 11:45
Specimen:- Sputum

This is an INTERIM REPORT.

AFB Smear: Negative (Concentrated method)

Culture for Mycobacteria :-

** To Follow **

Real Time Polymerase Chain Reaction (PCR) for
Mycobacterium tuberculosis complex DNA :

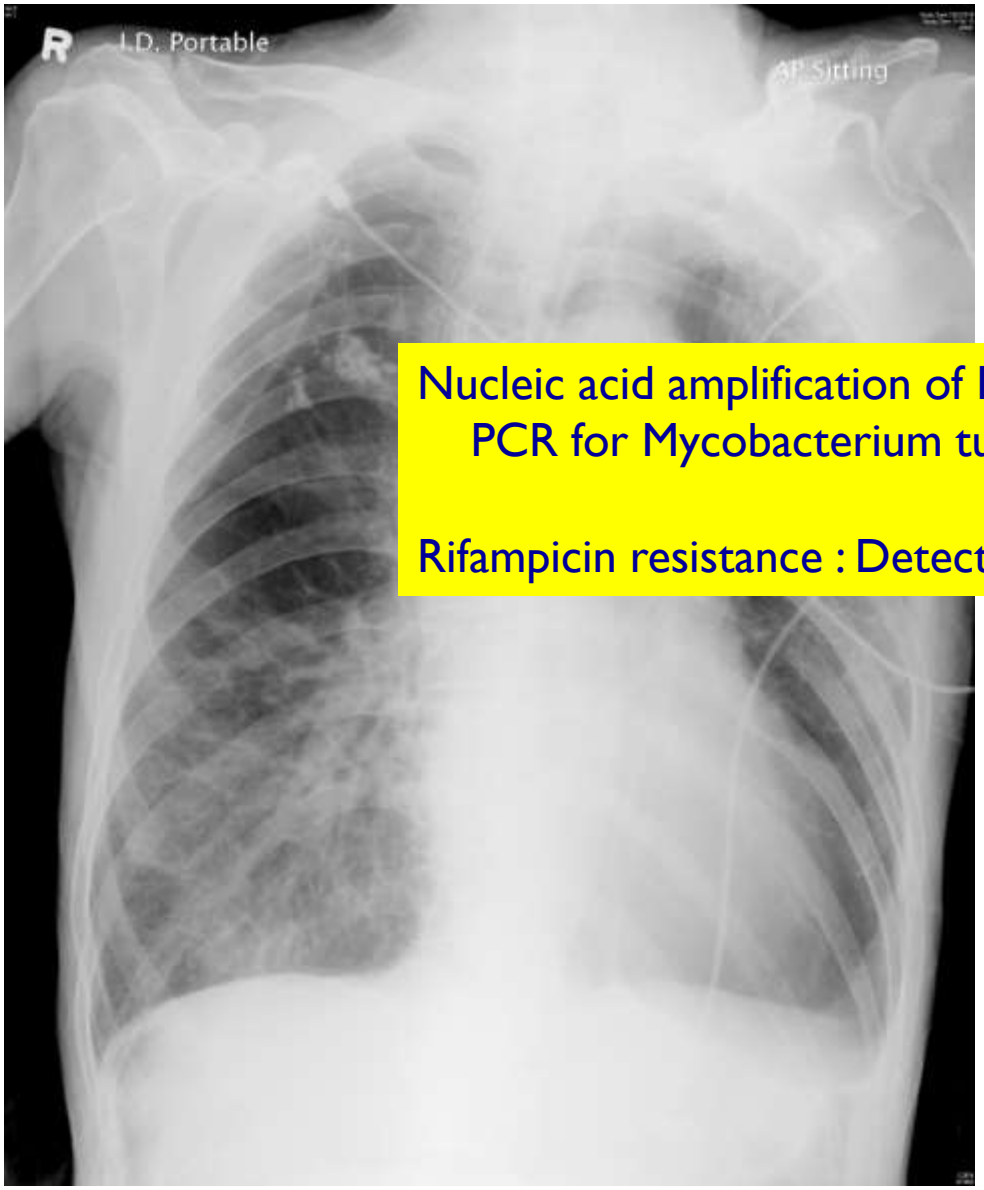
Detected in low level

Rifampicin resistance not detected

Comment:

1. Tuberculosis is a notifiable disease.

2.Polymerase Chain Reaction (PCR) is performed by GeneXpert system.



History of 80-year-old PTB, HT, AF COPD with 3 AE in 2015 c/o cough and purulent sputum

Nucleic acid amplification of MTB:
PCR for Mycobacterium tuberculosis complex : Positive

Rifampicin resistance : Detected

Clinical Details: PATIENT CATEGORY 2

Date/time Collected: 24/02/2016 --:--
Date/time Registered: 24/02/2016 16:46
Specimen:- Sputum

*This is

AFB Smear: Negative (Concentrated method)

Culture for Mycobacteria :-

** To Follow **

Real Time Polymerase Chain Reaction (PCR) for Mycobacterium tuberculosis complex DNA :

Detected in low level

Rifampicin resistance detected

Specimen arrival date: 26 FEB 2016 Report Date: 07 MAR 2016

DNA amplification assay for M. tuberculosis result:

☐ NEGATIVE ☑ POSITIVE Dr. W.C. Yam

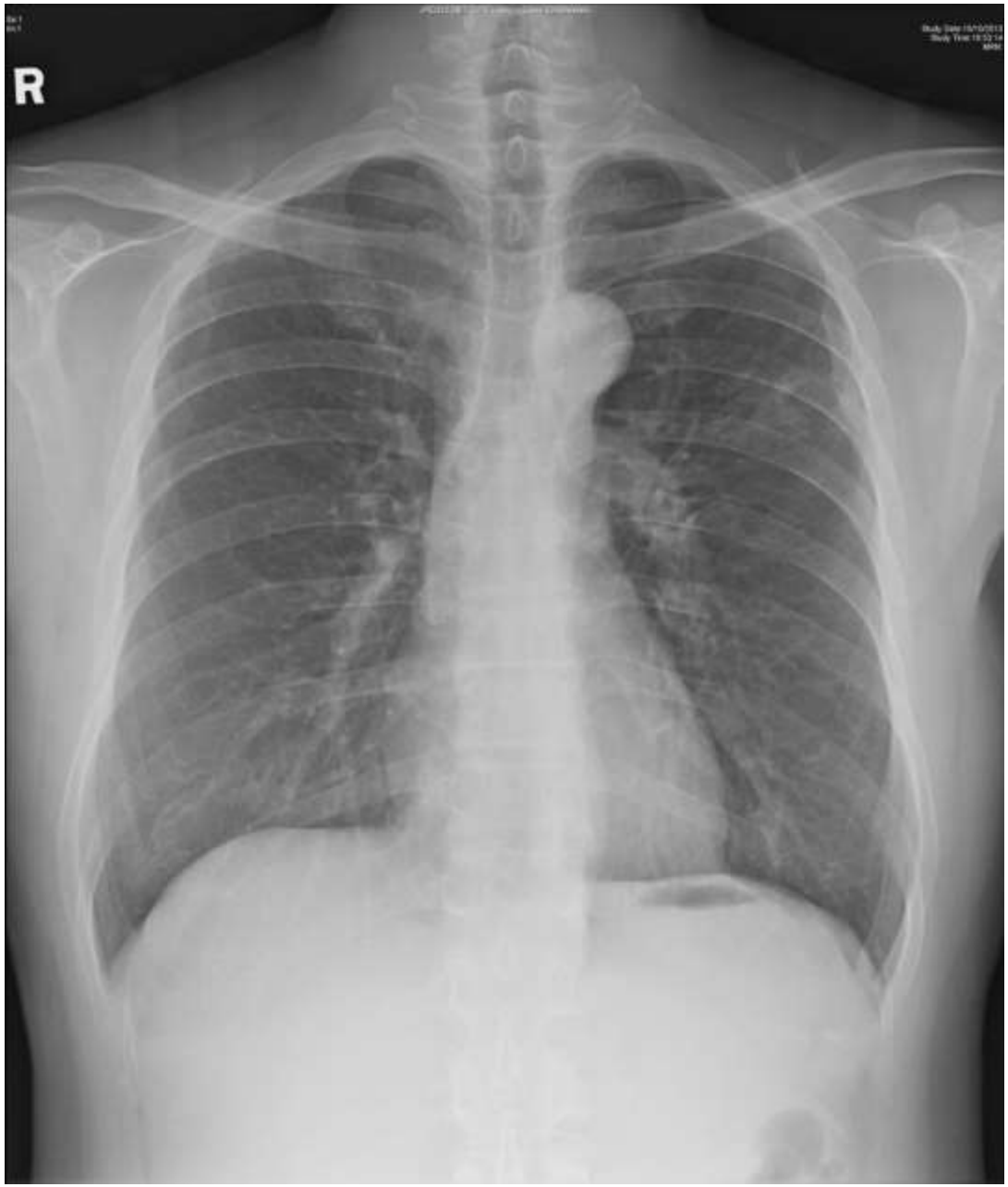
Hain Genotypic Drug Susceptibility results Report date: 07 MAR 2016

MTBDR*plus* Ver 2.0		MTBDR*sl* Ver 2.0		
Isoniazid	**Rifampicin**	**Aminoglycosides/ Cyclic Peptides**		**Fluoro-quinolones**
No mutation*	No mutation*	No mutation*		No mutation*
Resistant KatG S315T	Resistant S531L	Resistant C1402T	Kanamycin: High-level / Low-level	Resistant
			Amikacin	
			Capreomycin	
			Viomycin	
Indeterminate#	Indeterminate#	Indeterminate#		Indeterminate#

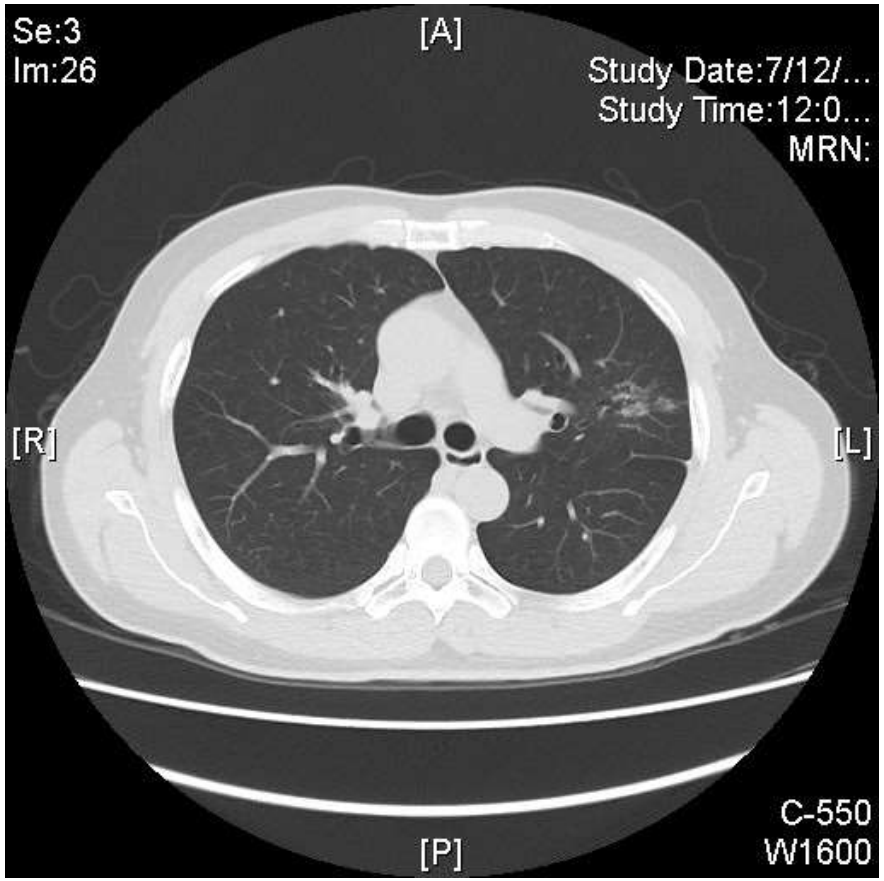
***No known mutation associated with drug resistance.**

#Genotyping failure due to insufficient DNA.

Dr. W.C. Yam



Asymptomatic 52 year-old pre-employment CXR abnormality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Im:26
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Study Date:7/12/...
Study Time:12:0...
MRN:
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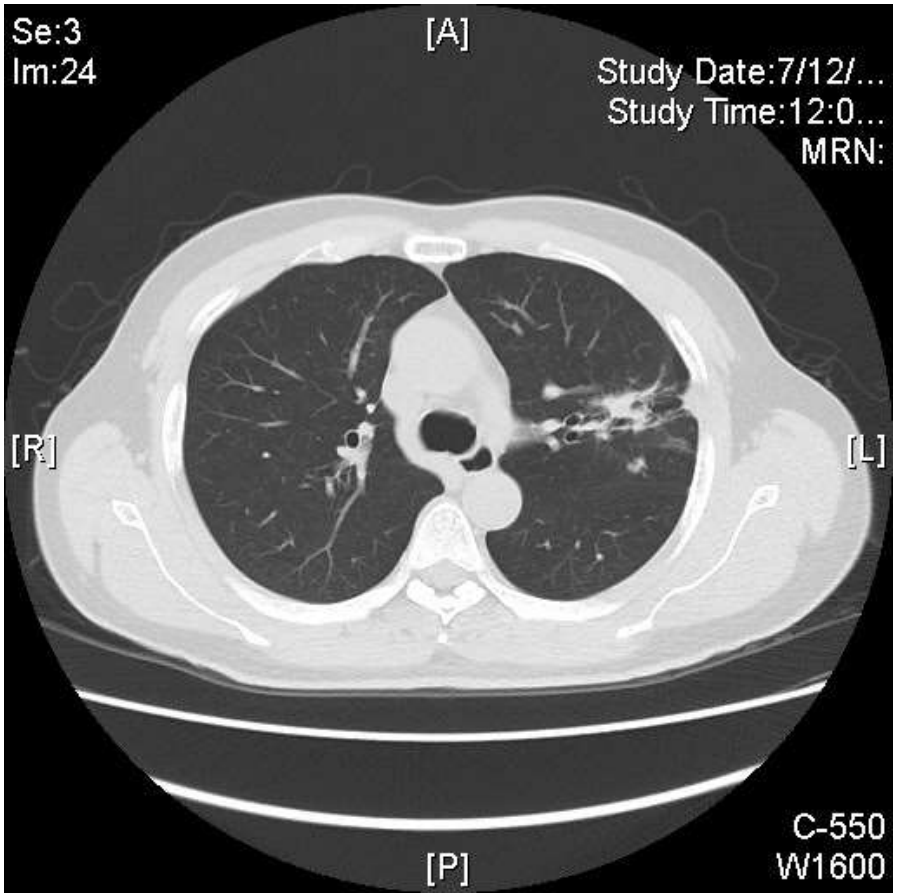
C-550
W1600


Se:3
Im:24
[A]
Study Date:7/12/...
Study Time:12:0...
MRN:
[R]
[L]
[P]
C-550
W1600

Clinical Details: PATIENT CATEGORY 1

Date/time Collected: 08/01/2016 09:15
Date/time Registered: 08/01/2016 16:54
Specimen:- Bronchial Aspirate

This is a FINAL REPORT.

AFB Smear: Negative (Concentrated method)

Real Time Polymerase Chain Reaction (PCR) for Mycobacterium tuberculosis complex DNA :

Not detected

Culture for Mycobacteria :-

No Mycobacterium

Comment:

1.Polymerase Chain Reaction (PCR) is performed by GeneXpert system.

2.The assay for Mycobacterium tuberculosis and Rifampin resistant gene polymerase chain reaction by GeneXpert system is not validated for Bronchial Aspirate sample, for reference only.

CLINICAL HISTORY:

LUL shadow. B'scopy: NAD.

GROSS EXAMINATION:

2 pieces of tissue were received. All embedded in 1 block.

MICROSCOPIC EXAMINATION:

Sections show 2 piece of bronchial mucosa. The subepithelial tissue shows a few small epithelioid granulomas, surrounded by chronic inflammatory infiltrate. No necrosis is present. There is no dysplasia or malignancy. Ziehl Neelsen and PASD show no acid fast bacillus or fungus. However, the possibility of infection, particularly mycobacterial infection, cannot be thus excluded.

DIAGNOSIS:

LUNG, transbronchial biopsy - GRANULOMATOUS INFLAMMATION.

WHO recommended grouping of anti-TB drugs

GROUP NAME	ANTI-TB AGENT	ABBREVIATION
Group 1. First-line oral agents	Isoniazid Rifampicin Ethambutol Pyrazinamide Rifabutin Rifapentine	H R E Z Rfb Rpt
Group 2. Injectable anti-TB drugs (injectable agents or parental agents)	Streptomycin Kanamycin Amikacin Capreomycin	S Km Am Cm
Group 3. Fluroroquinolones (FQs)	Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx

WHO recommended grouping of anti-TB drugs

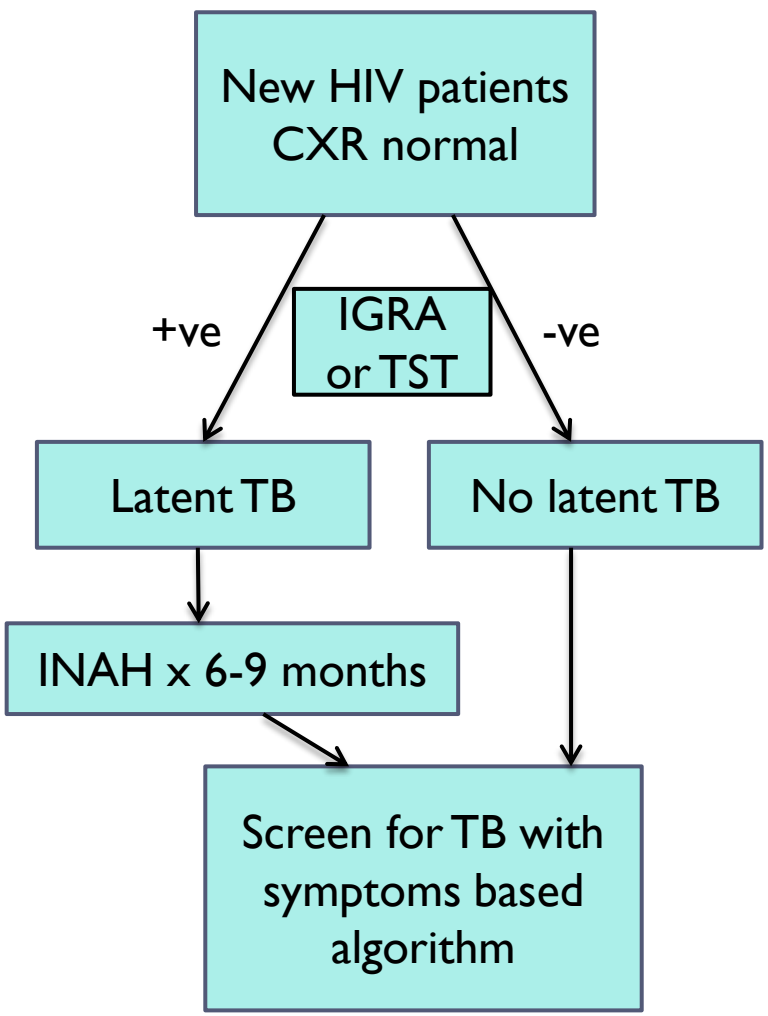
GROUP NAME	ANTI-TB AGENT	ABBREVIATION
Group 4. Oral bacteriostatic second line anti-TB drugs	Ethionamide Prothionamide Cycloserine Terizidone Para-aminosalicylic acid	Eto Pto Cs Trd PAS
Group 5. Anti-TB drugs with limited data on efficacy and/or long term safety in the treatment of drug-resistant TB (This group includes new anti-TB agents.)	Bedaquiline Delamanid Linezolid Clofazimine Amoxicillin / clavulanate Imipenem / cilastatin Meropenem High-dose isoniazid Thioacetazone Clarithromycin	Bdq Dlm Lzd Cfz Amx/Clv Ipm/Cln Mpm High dose H T Clr

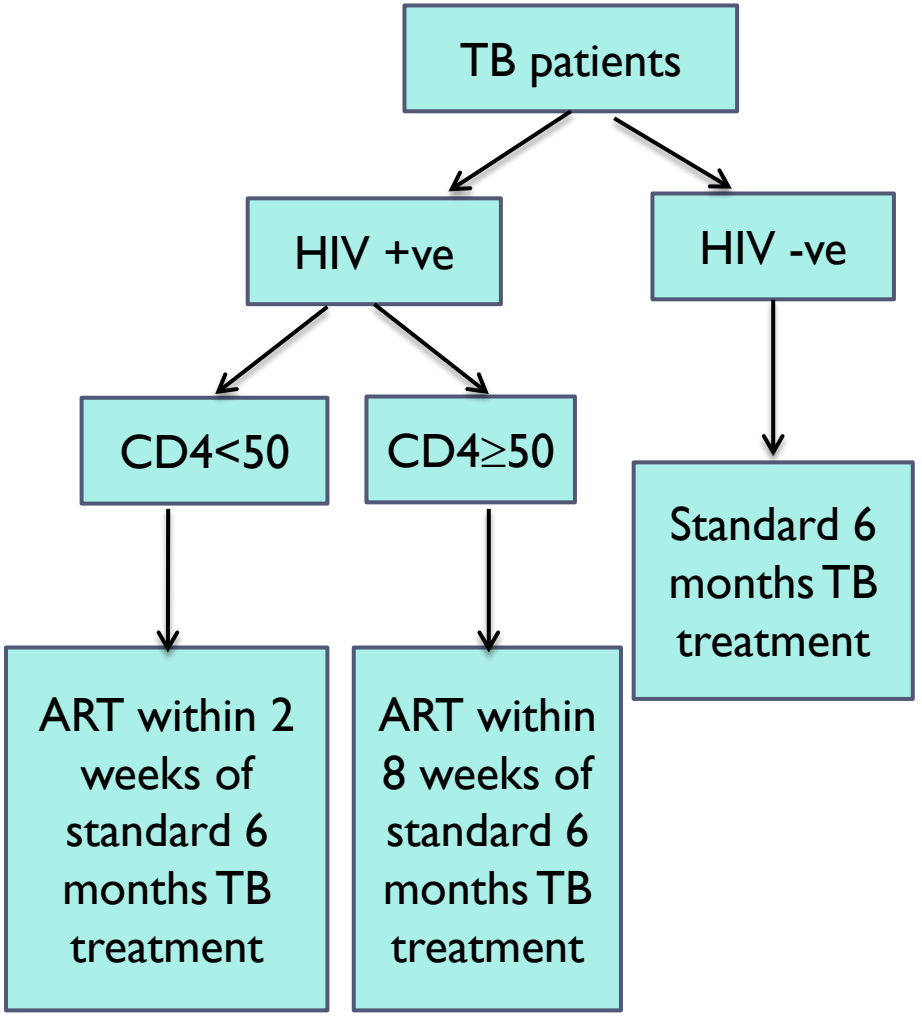
Treatment of TB

	Regimens
No previous treatment, no risk for drug resistance or no rifampicin resistance (RR) by Xpert MTB/RIF	2HRZE/4HR 2 (HRZE)/4(HR)3 2(HRZE)3/4(HR)3
Retreatment case	3(4)SHRZE/6(5)HR±E
Xpert MTB/RIF→RR Genotype MTBDR*plus* showed HR resistance	PZA + later generation FQs + an injectable + Pto/Eto + PAS or Cs for 8 months , then followed by PZA + 3 of the most potent SLD that are determined to be effective. A total treatment duration of 20 months.

A patient centred approach based on patient need and mutual respect

HIV & TB





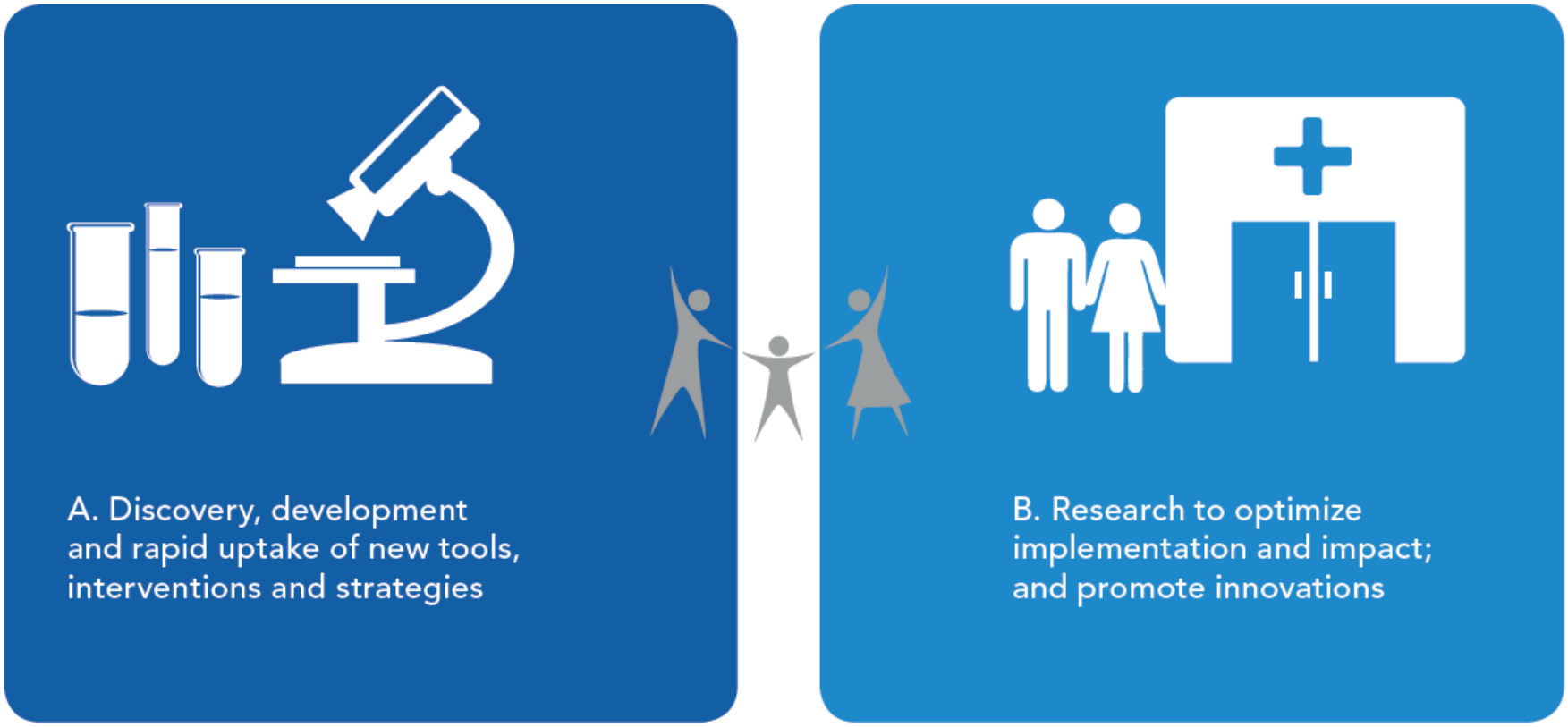
WHO Policy Collaborative TB/HIV activities 2012

Problems of TB treatment

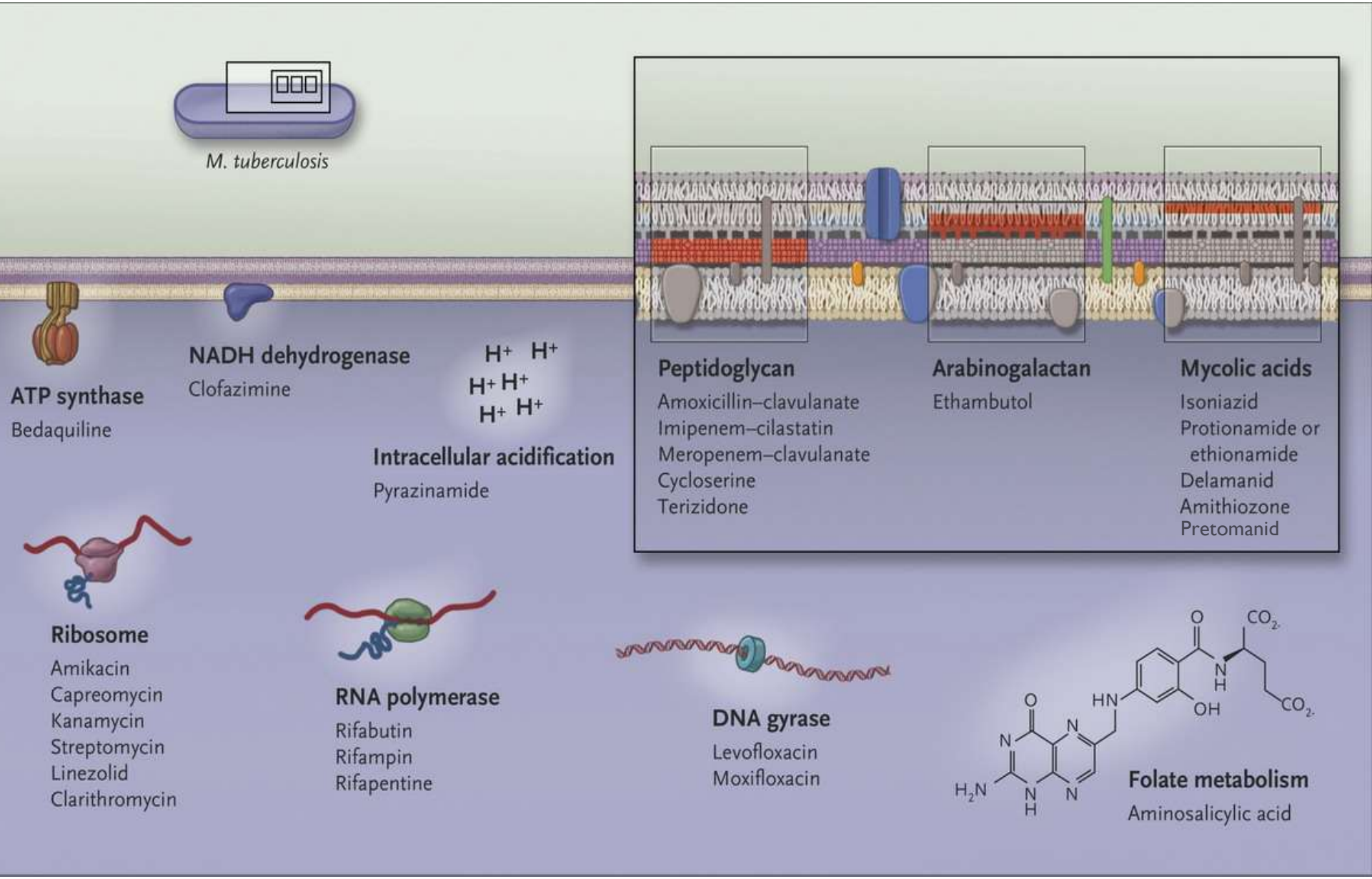
1. Long duration of treatment
   ➔low treatment success rate (cure + treatment completed): 67-95%
2. Low cure rate for MDR- & XDR-TB 60% & 40% respectively

INTENSIFIED RESEARCH AND INNOVATION

How pillar 3 works : Key actions



New drug & new regimen are required



NEJM 2015 Nov 26;373(22):2149-2159

Bedaquiline improves sputum culture conversion and cure rate for MDR-TB patients

Bedaquiline (Bedq); a diarylquinoline that inhibits mycobacterial ATP synthase

BR+Bedaquiline 400mg daily x 2 weeks, followed by 200mg 3x/week x 22 weeks

Trials	Design	No. of subjects	Sputum conversion rate at 120 weeks	Cure rate at 120 weeks	Mortality
TMC207-C208	RCT Bedq vs placebo (+BR)	160	Bedq 62% Placebo 44%	Bedq 58% Placebo 32%	Bedq 13% Placebo 2%
TMC207-C209	Open label single arm trial	233	MDR 72.2% preXDR 70.5% XDR-TB 62.2%		6.9%

NEJM 2014;371:723-32
ERJ 2016;47:394-402

Recommendation on the use of bedaquiline (1)

- When an effective treatment regimen containing 4 second-line drugs from the different classes of drugs according to WHO-recommendations cannot be designed;
- When there is documented evidence of resistance to any fluoroquinolone in addition to MDR.
- A duly informed decision making-process by patients should be followed;
- Bedaquiline should be used with caution in persons living with HIV infection, as well as in patients with co-morbidities (such as diabetes) or persons with drug or alcohol abuse, due to limited or no information;

WHO Expert Group Meeting Report 2013

Recommendation on the use of bedaquiline (2)

- Bedaquiline be used for a maximum duration of 6 months and at suggested dosing (400 mg daily for the first 2 weeks, followed by 200 mg three times per week for the remaining 22 weeks);
- Bedaquiline must not be added alone to a failing regimen;
- Baseline testing and monitoring for QT prolongation and development of arrhythmia is imperative;
- Spontaneous reporting of adverse drug reactions is reinforced

WHO Expert Group Meeting Report 2013

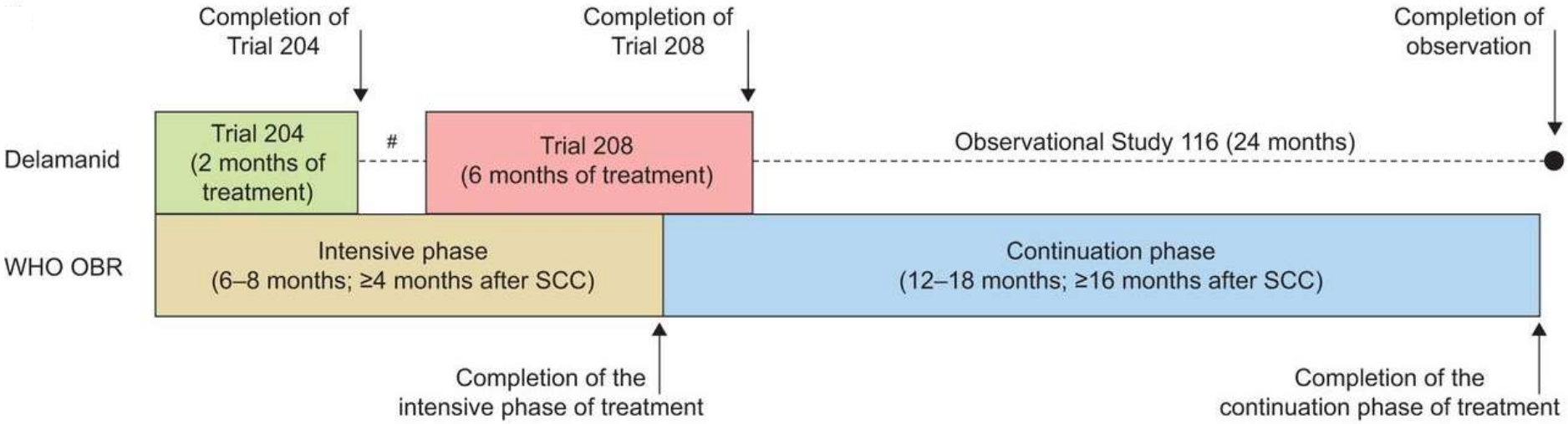
Delamanid improves sputum conversion and outcome and reduces mortality for MDR-TB patients

Delamanid : a nitro-dihydro-imidazooxazole which blocks mycolic acid synthesis

SCC at 2 months: 45% (Delamanid) vs 29.6% (P)

Favorable outcome : 55% (≤2 months Delamanid)
74% (≥6 months Delamanid)

Mortality : 2.9% (≥6 months Delamanid)
12% (≤2 months Delamanid)



ERJ 2013; 41:1393-1400
ERJ 2015; 45: 1-3

WHO interim policy recommendation (2014) on use of Delamanid

- Delamanid may be added to a WHO-recommended regimen in adults patients with pulmonary MDR-TB bringing a minimum of four drugs likely to be effective
- Dose of delamanid: 100mg twice a day for six months
- As delamanid prolongs QT interval (contraindicated if QTcF>500ms), caution is necessary when used with other drugs that also prolong QT interval. Concomitant use with bedaquiline not advised
- Delamanid should not be added to a failing regimen
- Monitoring of ECG and electrolysis imperative
- Patient informed consent should be obtained

Oxazolidinone : Linezolid

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis

Linezolid for at least 18 months after sputum conversion
At 6 months : SCC 87% (34/39)
At 36 months : cure rate 71% (27/38)
Side effects : 82% clinically significant adverse events

Sun Dae Song, M.D., Ph.D., Jong-Koo Lee, M.D., Dukhyoung Lee, M.D., Cheon Tae Kim, M.D., Veronique Dartois, Ph.D., Seung-Kyu Park, M.D., Sang-Nae Cho, D.V.M., Ph.D., and Clifton E. Barry III, Ph.D.

NEJM 2015 Jul 16 373:3

ABSTRACT

BACKGROUND

Linezolid has antimycobacterial activity in vitro and is increasingly used for patients with highly drug-resistant tuberculosis.

Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China

Shenjie Tang[1,2,8], Lan Yao[2,8], Xiaohui Hao[2,8], Xia Zhang[3], Gang Liu[4], Xin Liu[5], Meiying Wu[6], Linhai Zen[2], Hua Sun[7], Yidian Liu[2], Jin Gu[2], Feishen Lin[3], Xiafang Wang[6] and Zhanjun Zhang[2]

65 culture +ve XDR-TB patients treated x 2 years
At 24 months : SCC 78.8% (linezolid) vs 37.6% (placebo)
Treatment success rate : 69.7% (linezolid) vs 34% (placebo)
27/65 (82%) had clinically significant side effects

edical
chool of
[6]Souzhou Fifth People's Hospital, Souzhou, China.
[7]Shanghai Minhang Center for Disease Control and Prevention, Shanghai, China.
[8]Authors contributed equally.

Eur Respir J 2015; 45: 161–170

Correspondence: Shenjie Tang, Tuberculosis Multidisciplinary Center for Diagnosis and Treatment, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumor Research Institute, Machang NO.97, TongZhou district, Beijing, 101149, China. E-mail: tangsj1106@hotmail.com

ABSTRACT Linezolid may be effective in treating multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. We conducted a prospective, multicentre, randomised study to further evaluate the efficacy, safety and tolerability of linezolid in patients with extensively drug-resistant tuberculosis in China.

65 patients who had culture-positive sputum for extensively drug-resistant tuberculosis were randomly assigned to a linezolid therapy group or a control group. Patients in the two groups adopted a 2-year individually based chemotherapy regimen. The linezolid therapy group was given linezolid at a start dose of 1200 mg per day for a period of 4–6 weeks and this was then followed by a dose of 300–600 mg per day.

The proportion of sputum culture conversions in the linezolid therapy group was 78.8% by 24 months, significantly higher than that in the control group (37.6%, $p<0.001$). The treatment success rate in linezolid therapy group was 69.7%, significantly higher than that in the control group (34.4%, $p=0.004$). 27 (81.8%) patients had clinically significant adverse events in the linezolid group, of whom 25 (93%) patients had events that were possibly or probably related to linezolid. Most adverse events resolved after reducing

Other Oxazolidinone : Sutezolid & AZD5847

Sutezolid	:	• Higher bacteriocidal activity than linezolid in vitro and in mouse model. • Does not prolong QT interval or suppress bone marrow • Peripheral neuropathy and hepatotoxicity may occur
AZD5847	:	In vitro bactericidal activity is superior to that of linezolid, appears safe

Treatment outcomes observed in Bangladesh for MDR-TB cases treated with a 9-month regimen

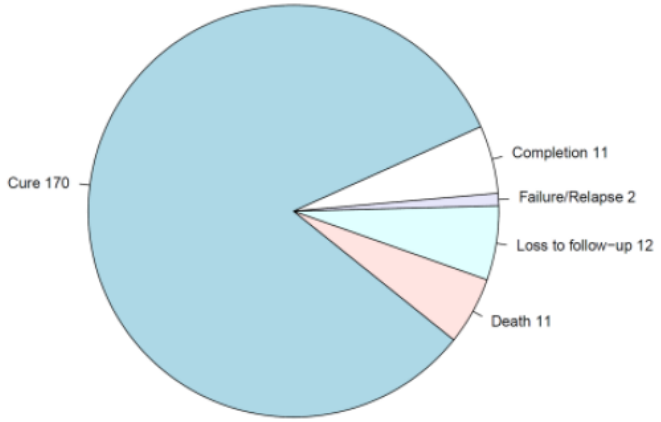
Standard MDR-TB regimen;

PZA+4 effective SLD in the intensive phase.

Total duration 20 months in most cases

A regimen consisting of a minimum of 4 months of KmCfzGfxEHZPto, prolonged if necessary until conversion was achieved, followed by 5 months of GfxEZCfz, was reported to give high, relapse-free cure rate in MDR-TB patients [van Deun et al, 2010].

Completion 5.3%
Cure 82.5%
Death 5.35
Default 5.8%
Failure 0.5%
Relapse 0.5%

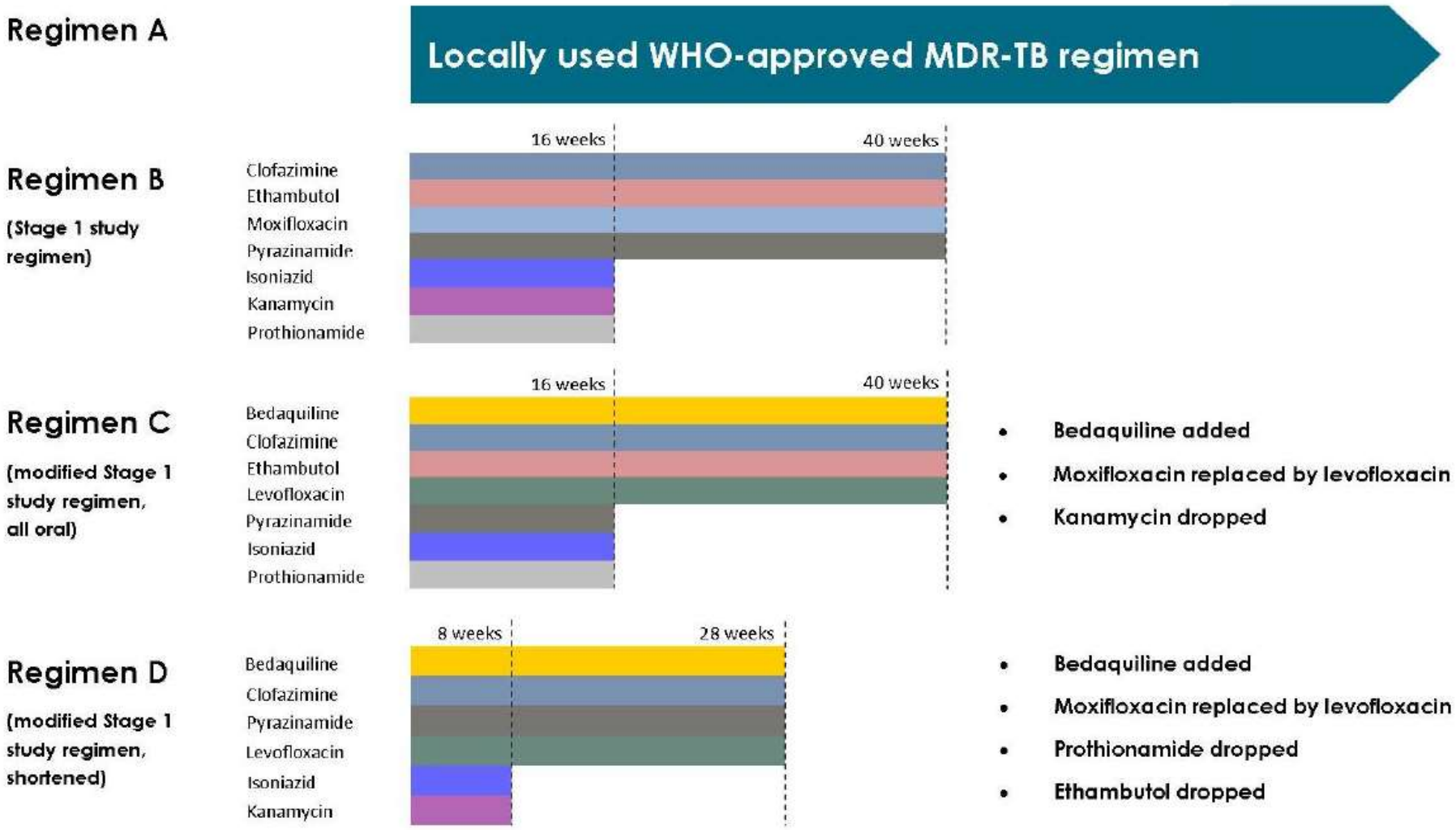


Km=kanamycin; Cfz=clofazimine; Gfx=gatifloxacin; E=ethambutol; H=high-dose isoniazid; Z=pyrazinamide; Pto=prothionamide

Source: van Deun A et al (2010); Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med 182(5):684–92.

WHO May 2013

STREAM (Evaluation of a **S**tandardised **T**reatment **RE**gimen of **A**nti-tuberculosis drugs for patients with **M**ulti-drug resistant tuberculosis



Regimen shortening studies : REMoxTB

A RCT phase 3 trial involving 1931 patients who had newly diagnosed, previously untreated drug sensitive MTB infection

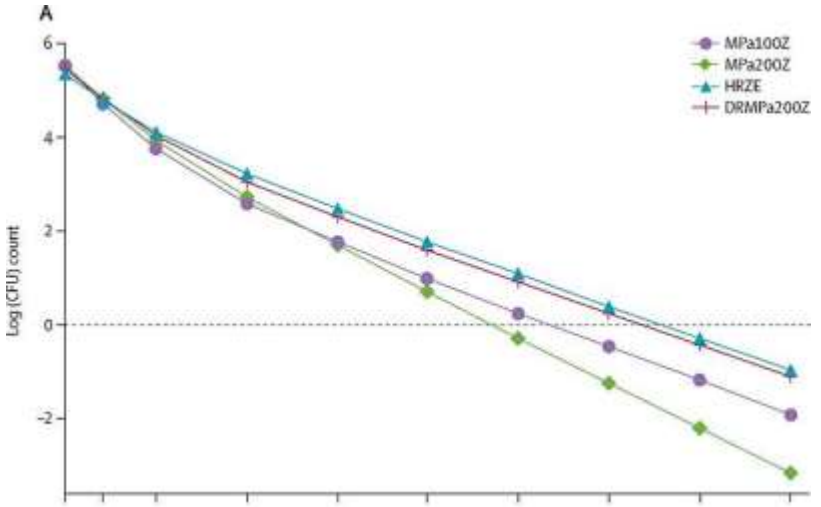
	Relapse within 18 months after randomization and after culture-negative status
HRZE x 8 weeks then HR x 18 weeks (6 months)	2%
HRZ Moxi x 18 weeks (4.2 months)	8%
RZE Moxi x 17 weeks (4 months)	12%

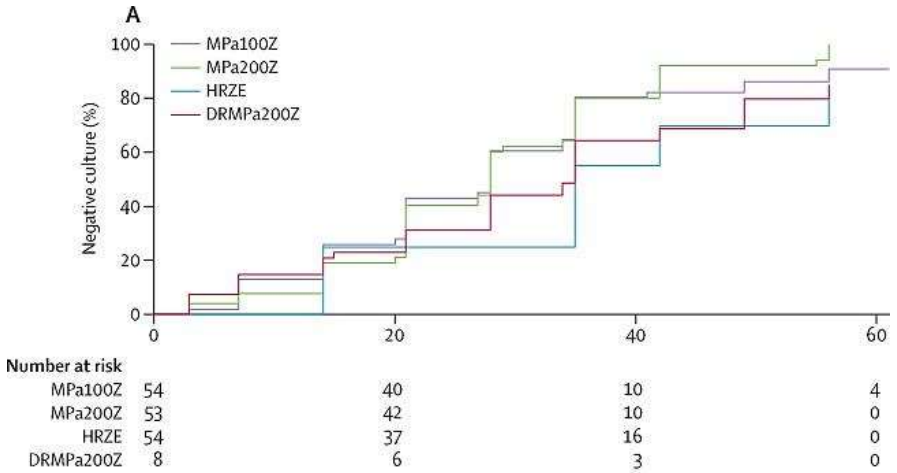
Moxifloxacin-containing 4 months anti-TB treatment is associated with a high relapse rate

NEJM 2014; 371:1577

8 weeks MfxPaZ has superior bacteriocidal activity than HRZE

- Pretomanid is a nitroimidazole
- Generates reactive nitrogen species→anaerobic killing
- Inhibit cell wall synthesis





- MPaZ has superior bacteriocidal activity during 1st 8 weeks of treatment compared with HRZE
- Probability of sputum culture conversion was higher for MPa200Z than for HRZE
- A phase 3 study will be performed for it treatment shortening capacity (STAND trial)

Lancet 2015; 385:1738

Daily Rifapentine increase rate of sputum sterilization

- Randomized partially blinded trial : increasing dose of Rifapentine instead of RIF were used during intensive phase (HRZE vs HRptZE) for 8 weeks

% of patients with negative cultures at completion of Intensive Phase Treatment

	Rifampin (n=85)	**Rifapentine 10 mg/kg (n=87)**	**Rifapentine 15 mg/kg (n=81)**	**Rifapentine 20 mg/kg (n=81)**
Solid culture medium				
% (n/n) with negative cultures	81.3 (52/64)	92.5 (62/67)	89.4 (59/66)	94.7 (54/57)
% difference vs. rifampin (95% CI)		11.3 (-1.7 to 24.3)	8.1 (-55 to 21.8)	13.5 (0.6 to 26.3)
P value		0.097	0.29	0.049
Liquid culture medium				
% (n/n) with negative cultures	56.3 (36/64)	74.6 (50/67)	69.7 (46/66)	82.5 (47/57)
% difference vs. rifampin (95% CI)		18.4 (0.8 to 35.9)	13.4 (-4.5 to 31.4)	26.2 (8.9 to 43.5)
P value		0.042	0.16	0.004

Definition of abbreviation: CI = confidence interval

When rifapentine AUC ≥ 324 ug • h/ml, the difference in culture –ve rate is 11-19%

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Diagnosis and Treatment of TB

- Early diagnosis of TB and drug resistance is made possible by advancement of rapid diagnosis including molecular test
- New classes of anti-tuberculous drugs have been developed in the past 15 years. Bedaquiline and delamanid received accelerated regulatory approval for treatment of MDR/XDR TB
- New drugs and new regimen have been designed and are being tested in phase II & III trials with the aims to improve cure rate of MDR/XDR TB and shorten duration of treatment for both sensitive and resistant TB

Thank you