MDRTB and TB/HIV

Dr. Ed Wilkins

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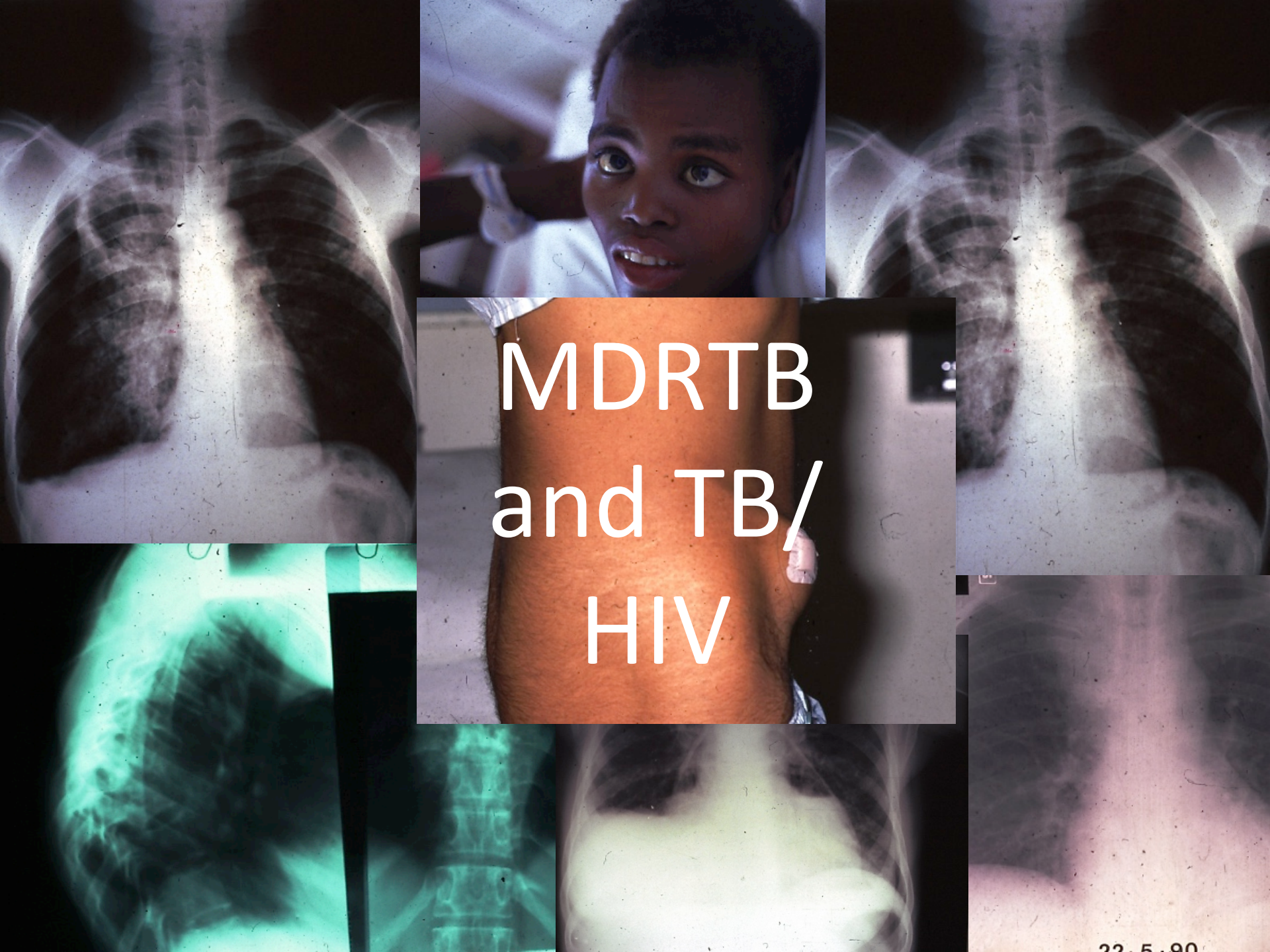
MDRTB
and TB/
HIV

Aims for today – 1

- What is MDRTB?
- The pitfalls in management:
  - Not suspecting and failing to make and early diagnosis
  - Failing to prevent hospital acquired infection
  - Not using an effective ant-TB regimen and not considering XDRTB

Aims for today – 2

- The pitfalls with TB/HIV:
  - Not testing for HIV!
  - Delaying HIV treatment and not considering overlapping toxicities
  - Not checking on drug-drug interactions
  - Missing IRIS
- Challenges:
  - TDRTB
  - Local planning

What is MDRTB?

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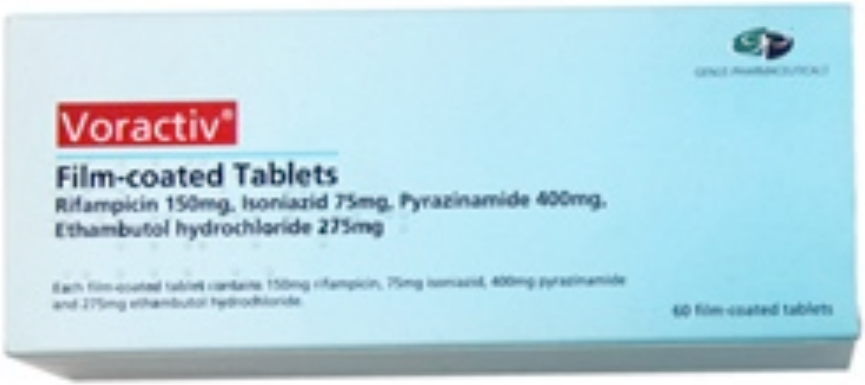
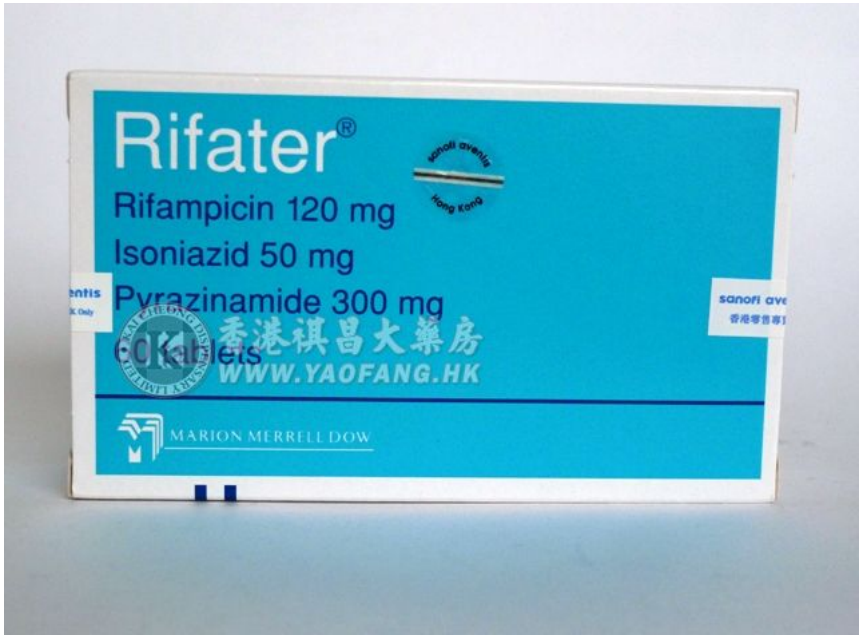
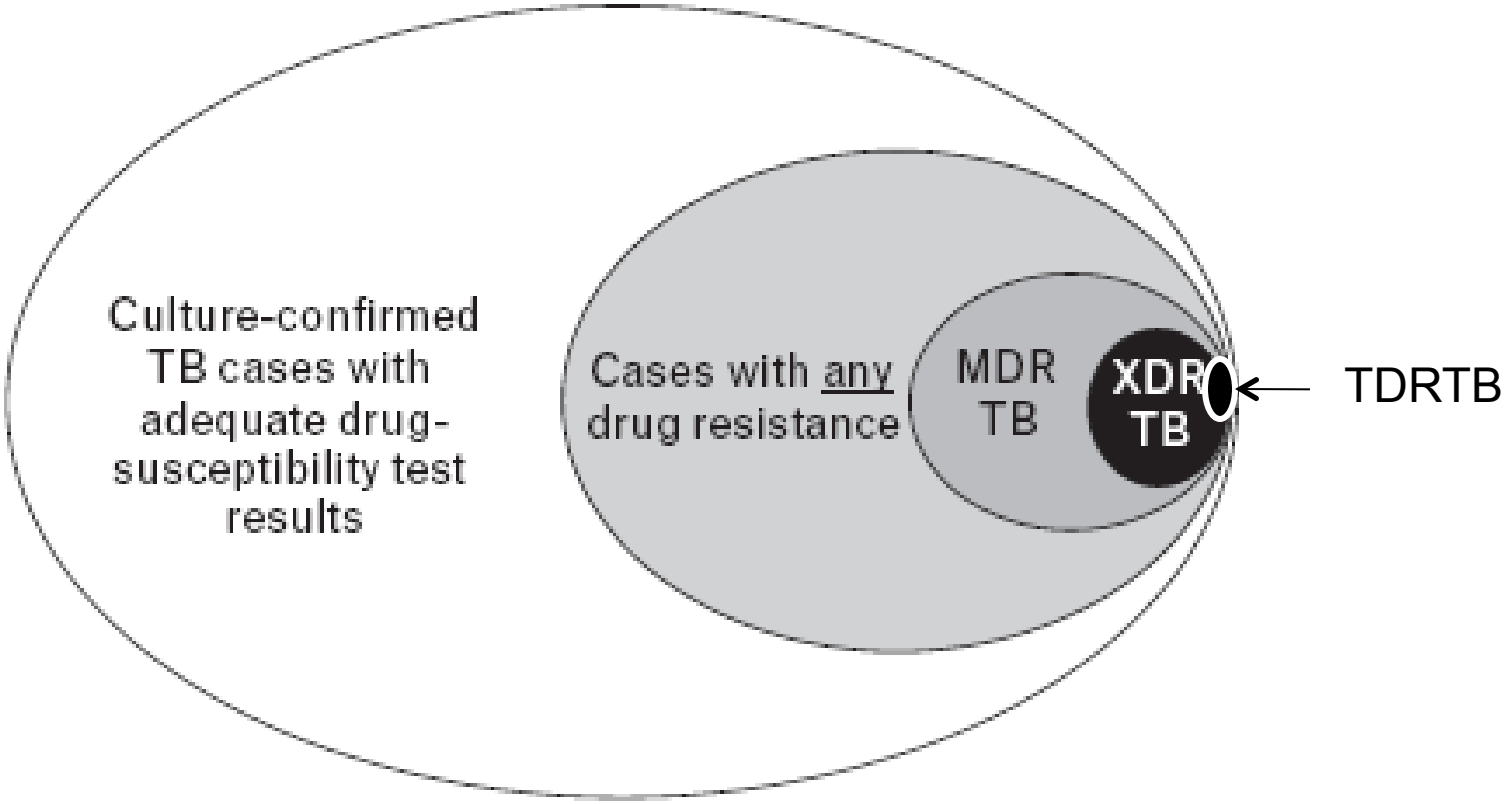
Normally straightforward





But over years sensitive TB has transitioned to MDRTB, XDRTB, & TDRTB

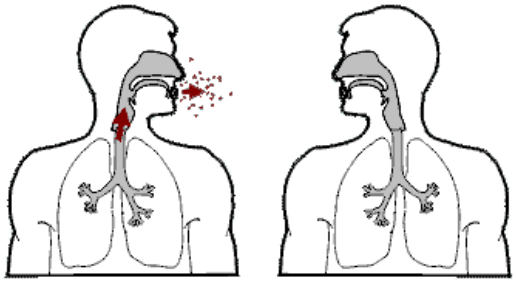


Definitions – drug resistance

- **Mono**: resistance to 1 first line drug (usually isoniazid) with susceptibility to the others
- **MDRTB**: resistance to **R (rifampicin)** and **H (isoniazid)**
- **XDRTB**: MDR plus:
  - Resistance to **any quinolone** AND
  - Resistance to **2nd line injectable (kanamycin, amikacin, capreomycin)**
- **TDRTB**: not clearly defined but resistance to **all 1st and 2nd line** drugs

Definitions: primary vs. acquired

- **Primary** drug resistance:
  - A person becomes infected with an organism that is already drug resistant



- **Acquired** drug resistance:
  - A person is infected with a drug susceptible organism and through drug pressure of inadequate treatment it becomes drug resistant

Pitfall 1
Not suspecting MDRTB

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TB is a major problem in Myanmar

	No. cases	Prevalence	%	Mortality	%
TB (All) -TBM	811 250	43.8 13.5		222 126	27 50
Anemia	191	10.3		4	2.1
GE	140	7.6		4	3
Crypto M	95	5.1		27	28.4
DILI	80	4.3		11	13.8
PJP	75	4		33	44.0
COL	50	2.7		18	36.0
Skin rash	44	2.4		3	6.8
Toxo	37	2		5	13.5
Renal toxicity	35	1.9		13	37
Penicilliosis	35	1.9		3	8.6
MAC	29	1.6		2	7
sepsis	26	1.4		16	61

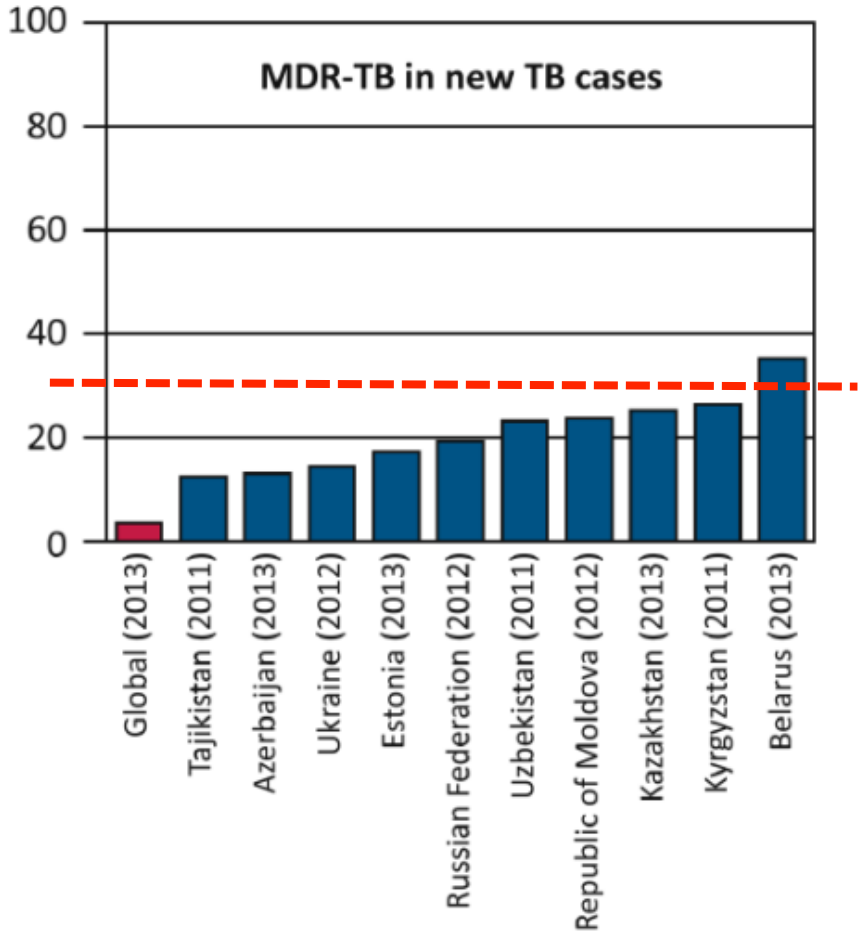
Pitfall 1: not suspecting resistant TB

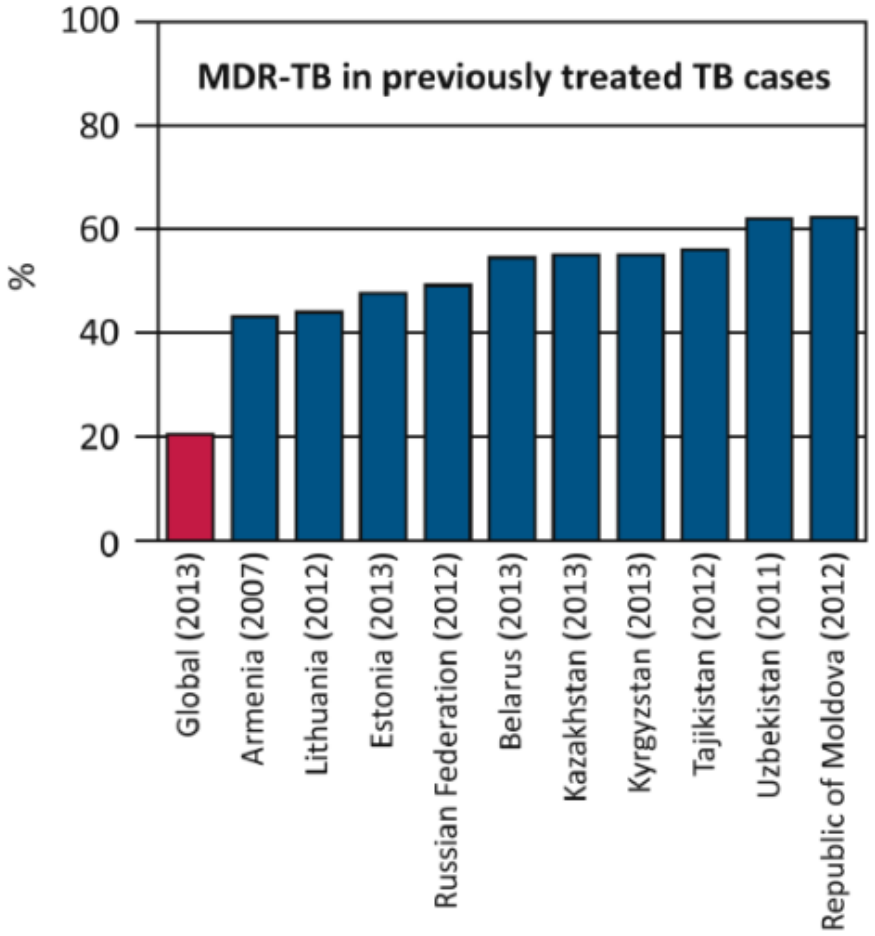
- Previous TB treatment
- History of poor adherence
- Contact with MDRTB/XDRTB
- Birth, travel or work in an area endemic for MDRTB

≅20% of cases diagnosed are relapsed in Myanmar

	New	%	Relapse	%	total	%
S(+)PTB	196		74		270	19
Clinical PTB	485		106		591	41
					0	0
Clinical EP	453		114		567	40
	1134	79.4	294	20.6	1428	

Where MDRTB is prevalent, risk of primary TB being MDRTB is high





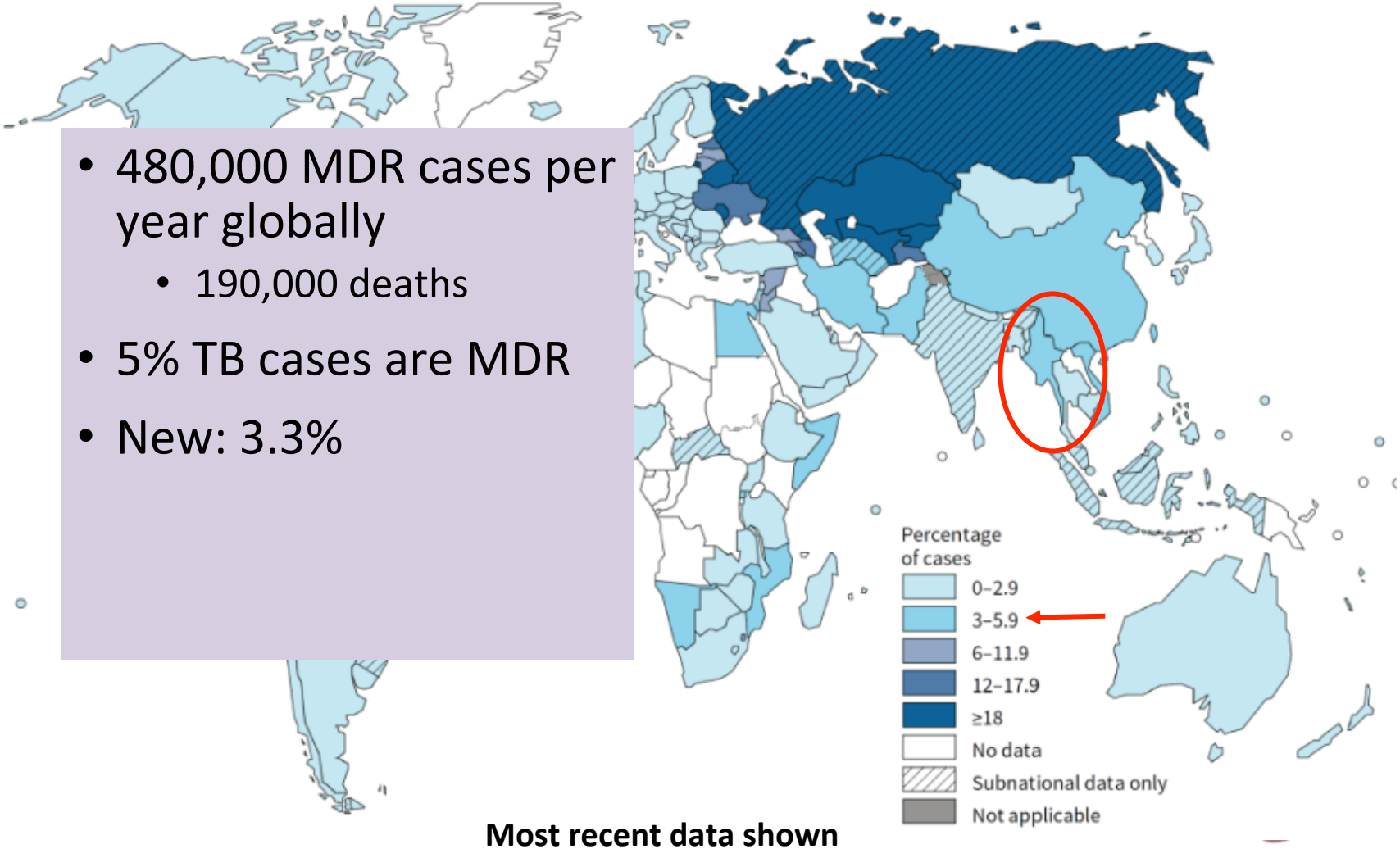
Pitfall 1: not suspecting resistant TB

- Previous TB treatment
- History of poor adherence
- Contact with MDRTB/XDRTB
- Birth, travel or work in an area endemic for MDRTB

- No clinical improvement on standard therapy and/or sputum positive after 2m
- Specific at-risk groups

Percentage of new cases with MDRTB 2014

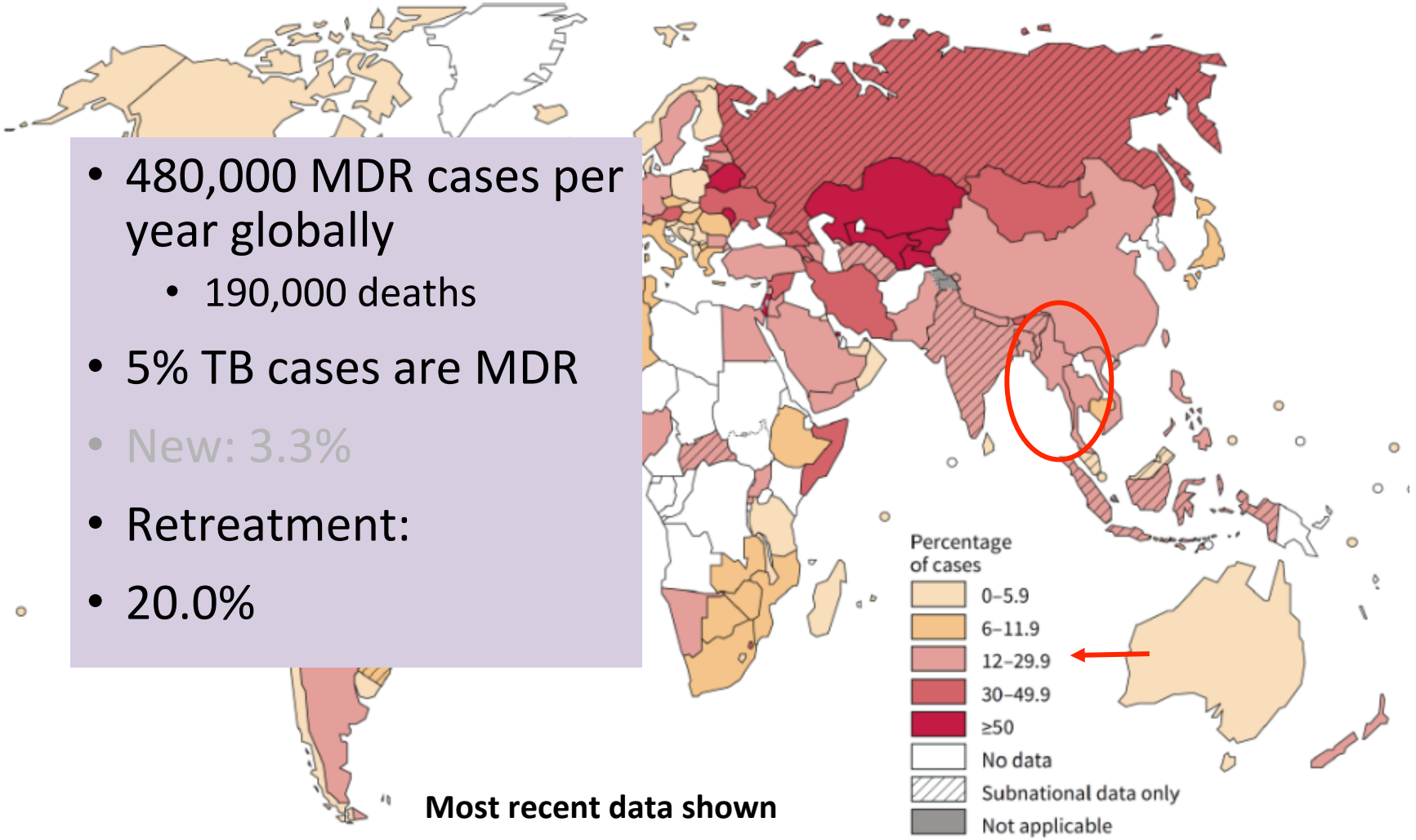
- 480,000 MDR cases per year globally
  - 190,000 deaths
- 5% TB cases are MDR
- New: 3.3%



Most recent data shown

Percentage of previously treated TB cases with MDRTB 2014

- 480,000 MDR cases per year globally
  - 190,000 deaths
- 5% TB cases are MDR
- New: 3.3%
- Retreatment:
- 20.0%



Pitfall 2
Failing to make an early diagnosis

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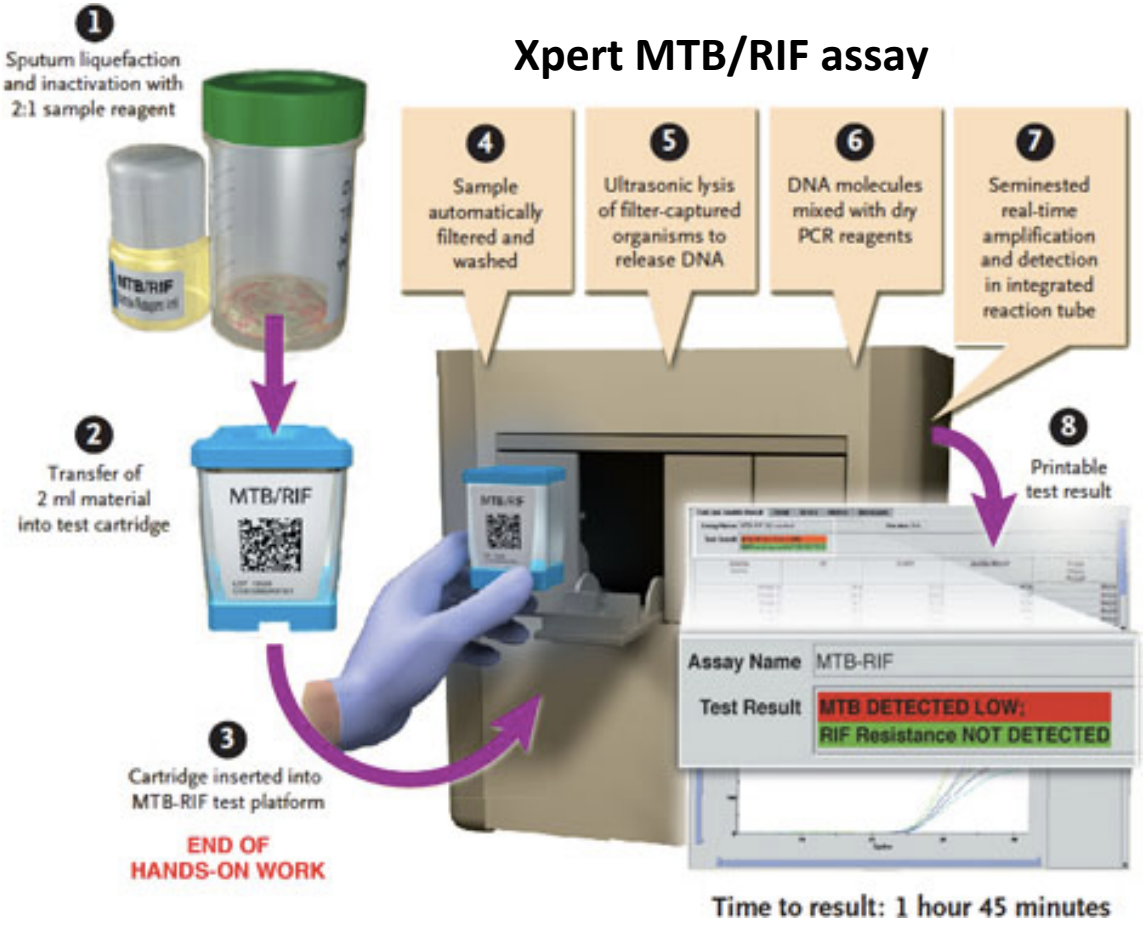
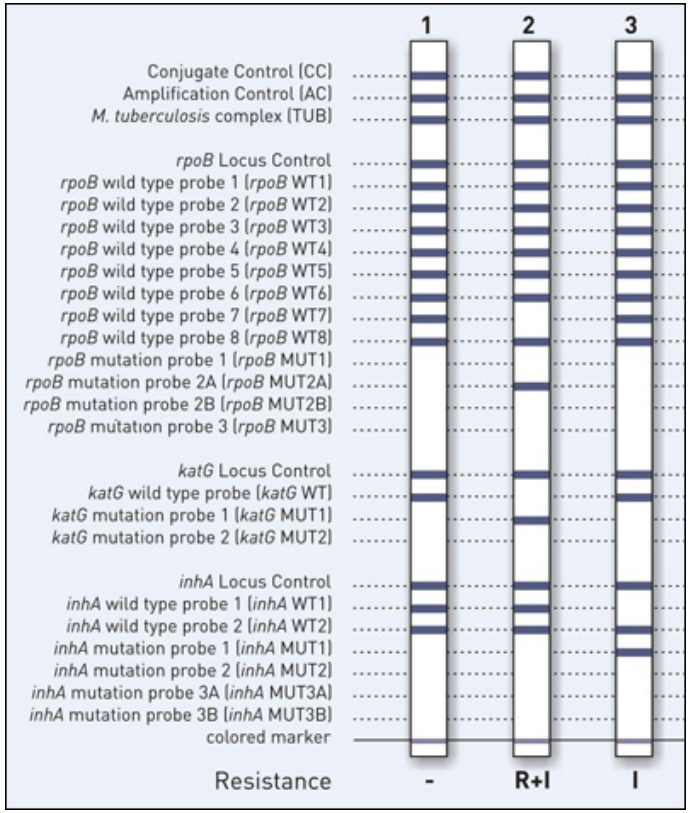
Pitfall 2: Early diagnosis essential

Xpert MTB/RIF assay



GenoType MTBDRplus



Gene-based assays associated with RIF and INH resistance

Drug	Gene
Rifampicin	**rpo B**
Isoniazid	**Kat G, Inh A**
Ethambutol	emb B
Streptomycin	rps L
Pyrazinamide	pnc A
Fluoroquinolones	gyr A

GeneXpert testing in Myanmar: CSF data

	Total	Indian Ink	%	GeneXpert	%
2011	182	34	19		
2012	250	50	20		
2013					
2014	225	35	16		
2015	225	28	12	8/110	7

World Health Organization

TUBERCULOSIS DIAGNOSTICS

Xpert MTB/RIF Test

ABOUT THE XPERT MTB/RIF TEST

The rapid TB test – known as Xpert MTB/RIF- is a fully-automated diagnostic molecular test. It has the potential to revolutionize and transform TB care and control. The test:

- simultaneously detects TB and rifampicin drug resistance
- provides accurate results in less than two hours so that patients can be offered proper treatment on the same day
- has minimal bio-safety requirements and training needs, and can be housed in non-conventional laboratories.

UPDATED WHO RECOMMENDATIONS

AS OF OCTOBER 2013

Strong recommendation:

- Xpert MTB/RIF should be used as the initial diagnostic test in adults and children presumed to have MDR-TB or HIV-associated TB

World Health Organization

No molecular tests performed

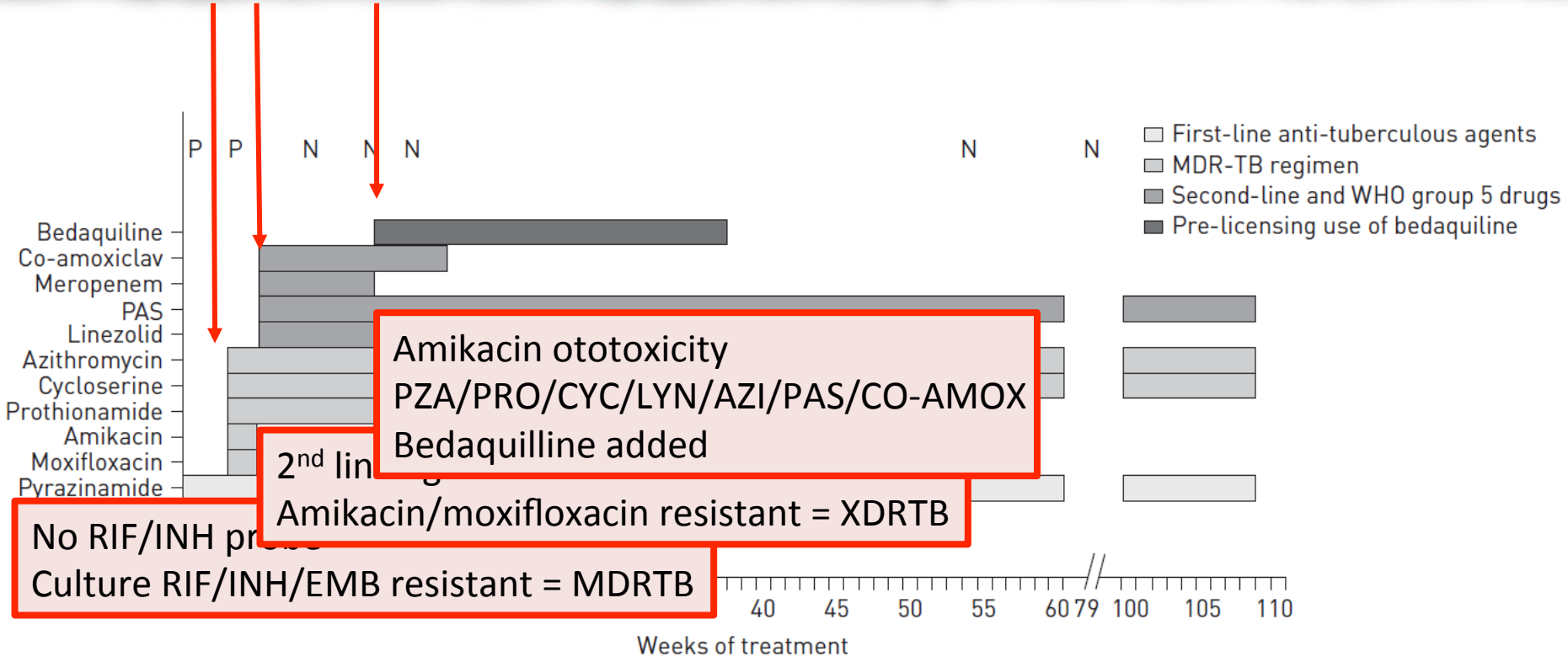


FIGURE 1 Schematic diagram showing the treatment course in this case of extensively drug-resistant tuberculosis. MDR-TB: multidrug-resistant tuberculosis; WHO: World Health Organization; PAS: para-amino salicylic acid; P: positive sputum culture; N: negative sputum culture.

van Halsema C, Humphreys S, Bonington A. *Eur Resp J* 2014

Pitfall 3
Failing to prevent hospital acquired infection

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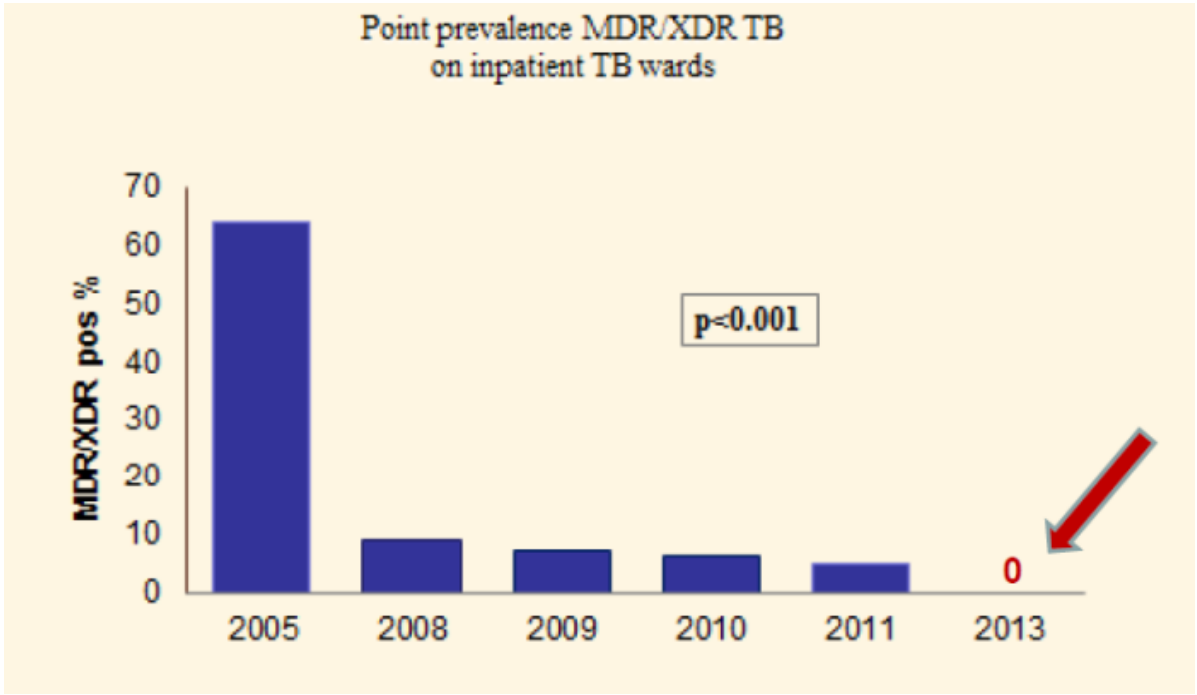
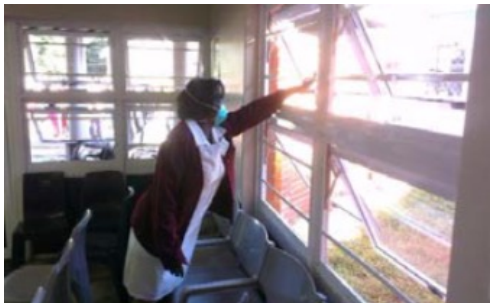
Pitfall 3: failure to prevent hospital acquired infection

Risk to patients and staff from hospital transmission

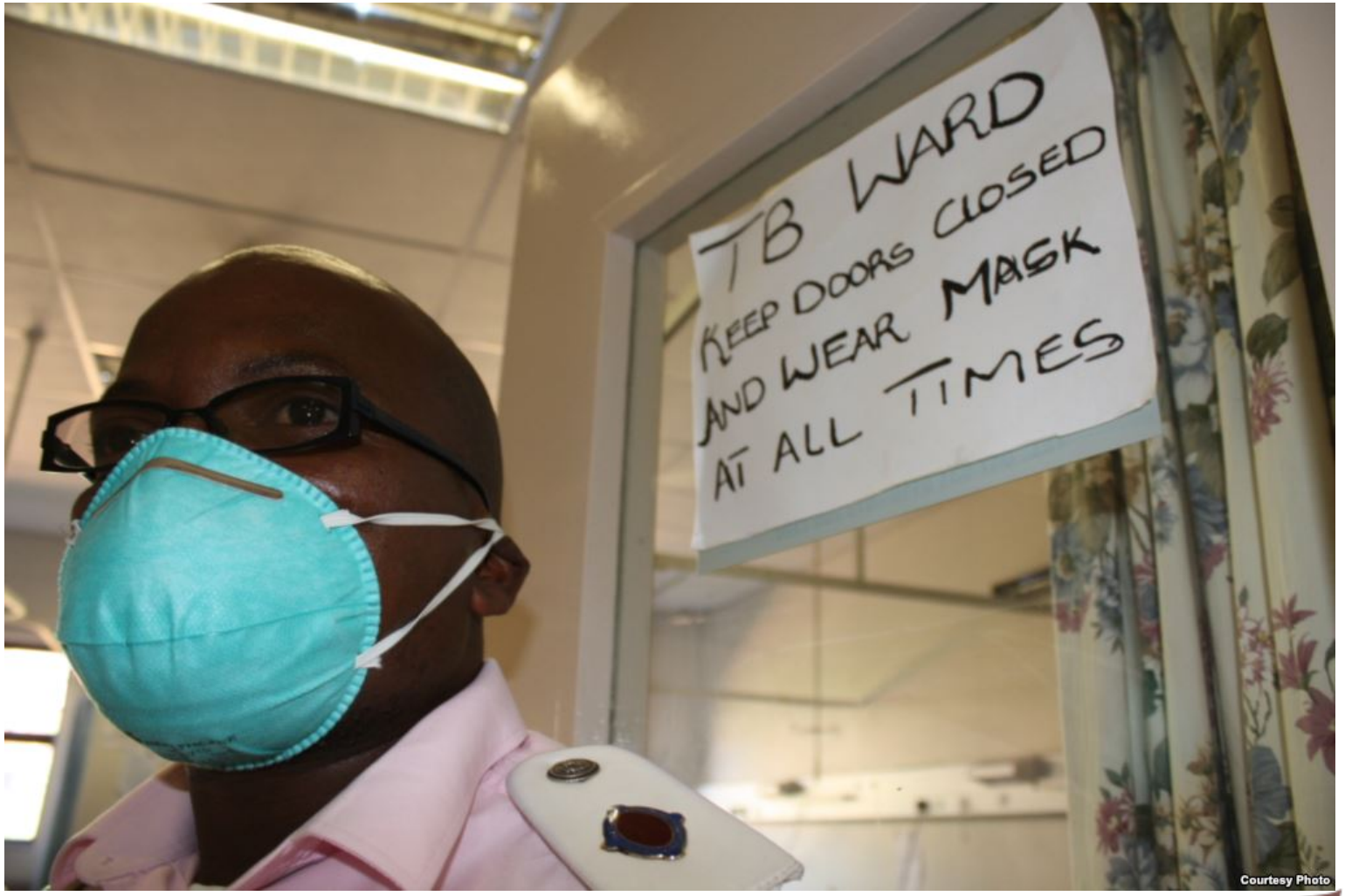
	HCW	General Population	Odds Ratio (95% C.I.)*
Annual DRTB Inc./100,00	70.5/100,000	11.7/100,000	5.84 (3.07-11.33)
Annual MDRTB Inc./100,000	63.2 /100,000	10.7/100,000	5.73 (2.93-11.50)
Annual XDRTB Inc./100,000	7.4/100,000	1.04/100,000	7.08 (4.55-10.91)

Establish good infection control practice





Isolation/FP2 mask



Pitfall 4
Not using an effective anti-TB treatment regimen

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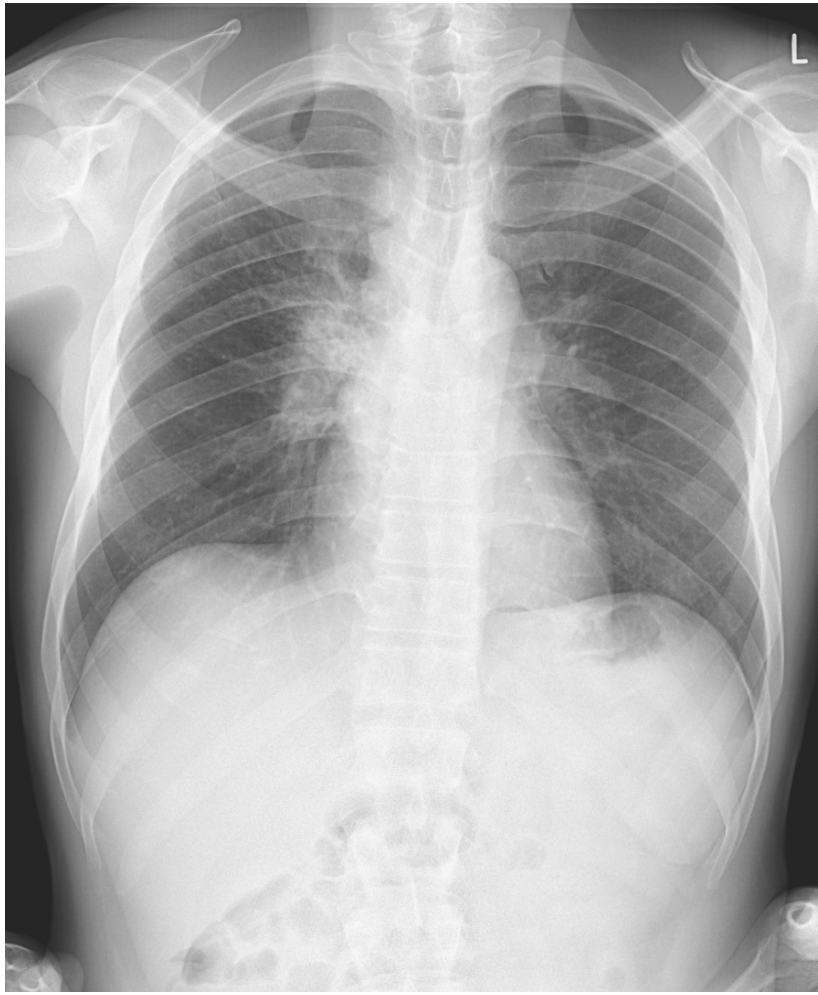
Not using an effective regimen

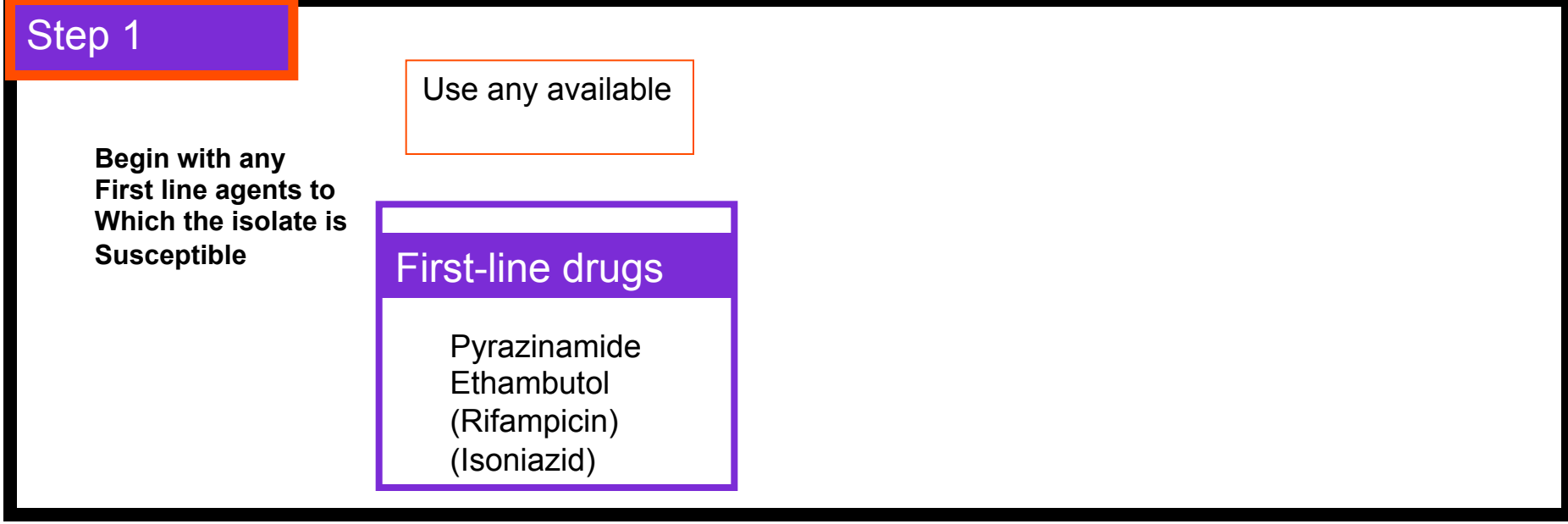
- The best current antituberculous drugs are rifampicin (R) and isoniazid (H)

- Second line treatment is less effective, more toxic, requires parenteral therapy and takes longer, compared with first line treatment.

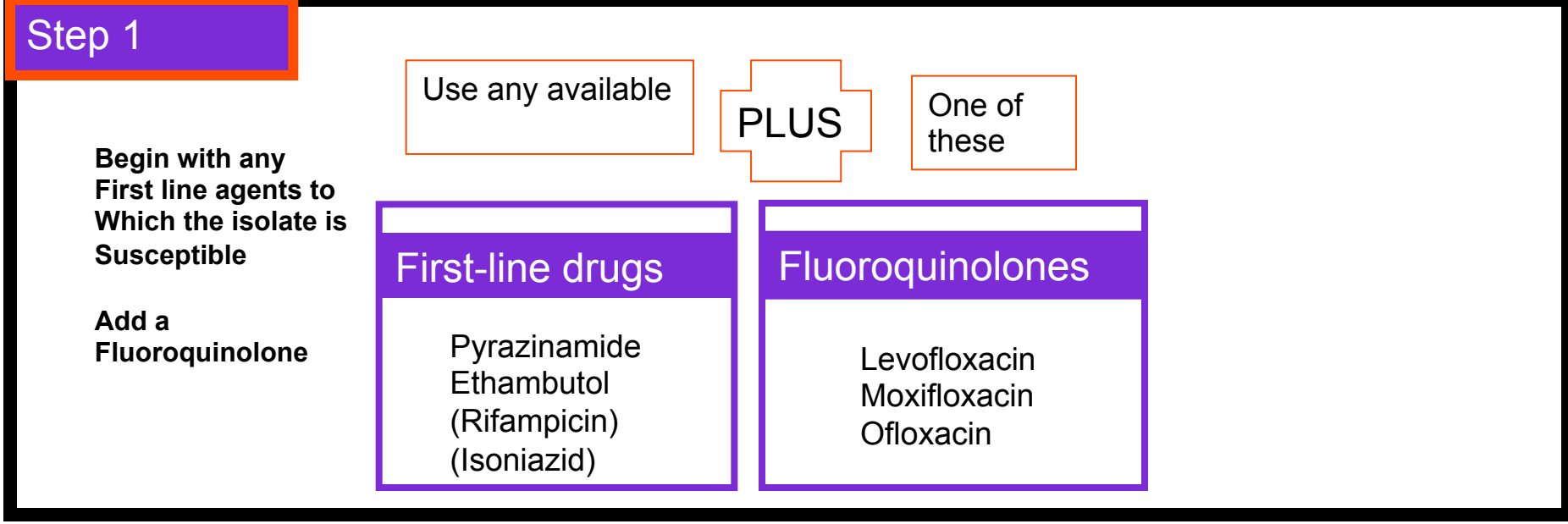


Principles of MDRTB treatment

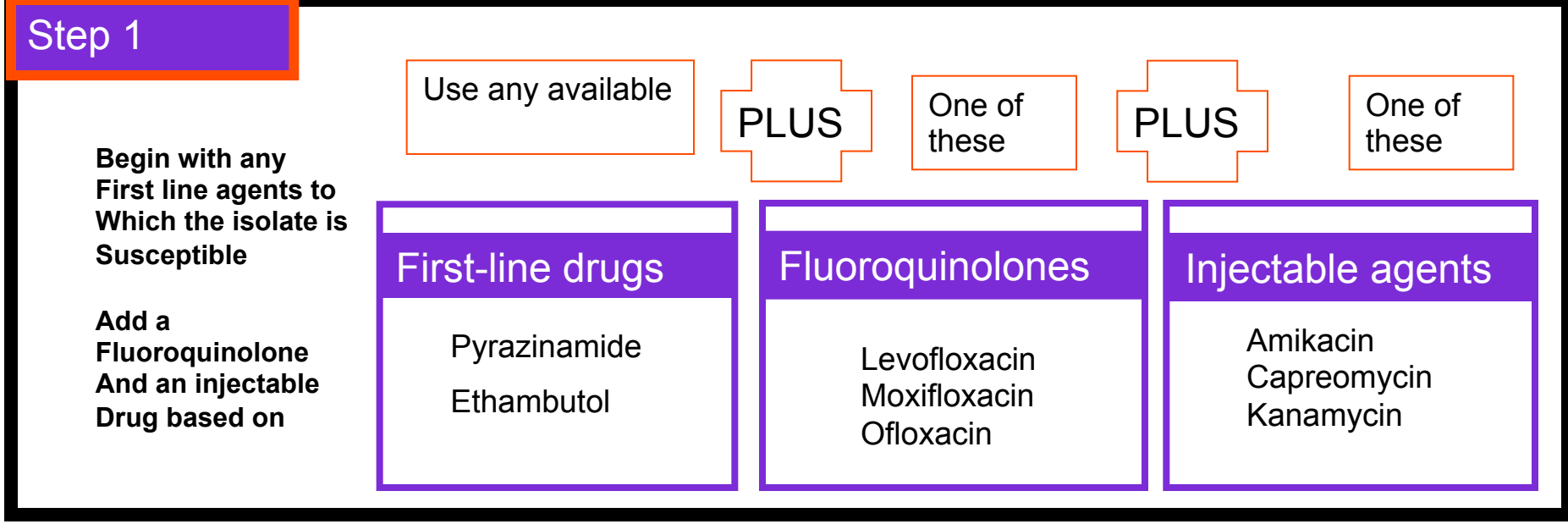
- Promptly suspect AND initiate appropriate therapy early
- Assume resistance if therapy given previously
- Resistance prevalence in country of birth/residence MUST be taken into consideration
- Tailor drugs to past treatment if available
- DO NOT rely on any drug being fully active
- Give AT LEAST 4 active drugs while awaiting sensitivities
- Drugs chosen in a stepwise manner



- Most potent and best tolerated
- All MUST be used if MDRTB suspected but unconfirmed
- MUST not rely on and assume resistance is present and therefore add in additional drugs
- If RIF resistance then Rifabutin likely to be resistant
- If INH resistance then may be PRO/ETH resistant



- All patients should receive a quinolone unless resistance very likely.
- Ciprofloxacin should NO longer be used to treat TB
- Most potent: Moxifloxacin > Levofloxacin > Ofloxacin
- MOX/LEVO may have activity against CIP/OFL resistant strains
- GAT is associated with SERIOUS glucose imbalance and should NOT be used



- All patients with possible MDRTB MUST receive an injectable agent
- All patients SHOULD receive Amikacin or Kanamycin
- Streptomycin should not be used as likely resistance
- Hearing should be monitored with AMIK/KAN
- AMIK and KAN usually X-resistant
- If an isolate is resistant to AMIK/KAN, capreomycin should be used

Step 1

Begin with any First line agents to Which the isolate is Susceptible

Add a Fluoroquinolone And an injectable Drug based on susceptibilities

Use any available

PLUS

One of these

PLUS

One of these

First-line drugs

Pyrazinamide

Ethambutol

Fluoroquinolones

Levofloxacin
Moxifloxacin
Ofloxacin

Injectable agents

Amikacin
Capreomycin
Kanamycin

Step 2

Add 2nd line drugs until you have 4-6 drugs to which isolate is susceptible (which have not been used previously)

Pick one or more of these

Oral second line drugs

Cycloserine Ethionamide/ prothionamide PAS

- Generally more side effects & bacteriostatic
- Ethionamide = prothionamide for activity: ETH/PRO X-resistant
- ETH/PRO resistant then X-reactivity with INH resistance so also cannot rely on as fully active drug
- CYC + PRO or PAS common combination (check TSH)
- All neurotoxic – give high dose PYR

Myanmar MDR-TB Regimen

First-line | Second-line | Third-line

Group 1 First line oral
- Isoniazid
- Rifampicin
- Ethambutol
- Pyrazinamide

Group 2 Injectable
- Streptomycin
- Kanamycin
- Amikacin
- Capreomycin

Group 3 Quinolone
- Ciprofloxacin
- Ofloxacin
- Levofloxacin
- Moxifloxacin

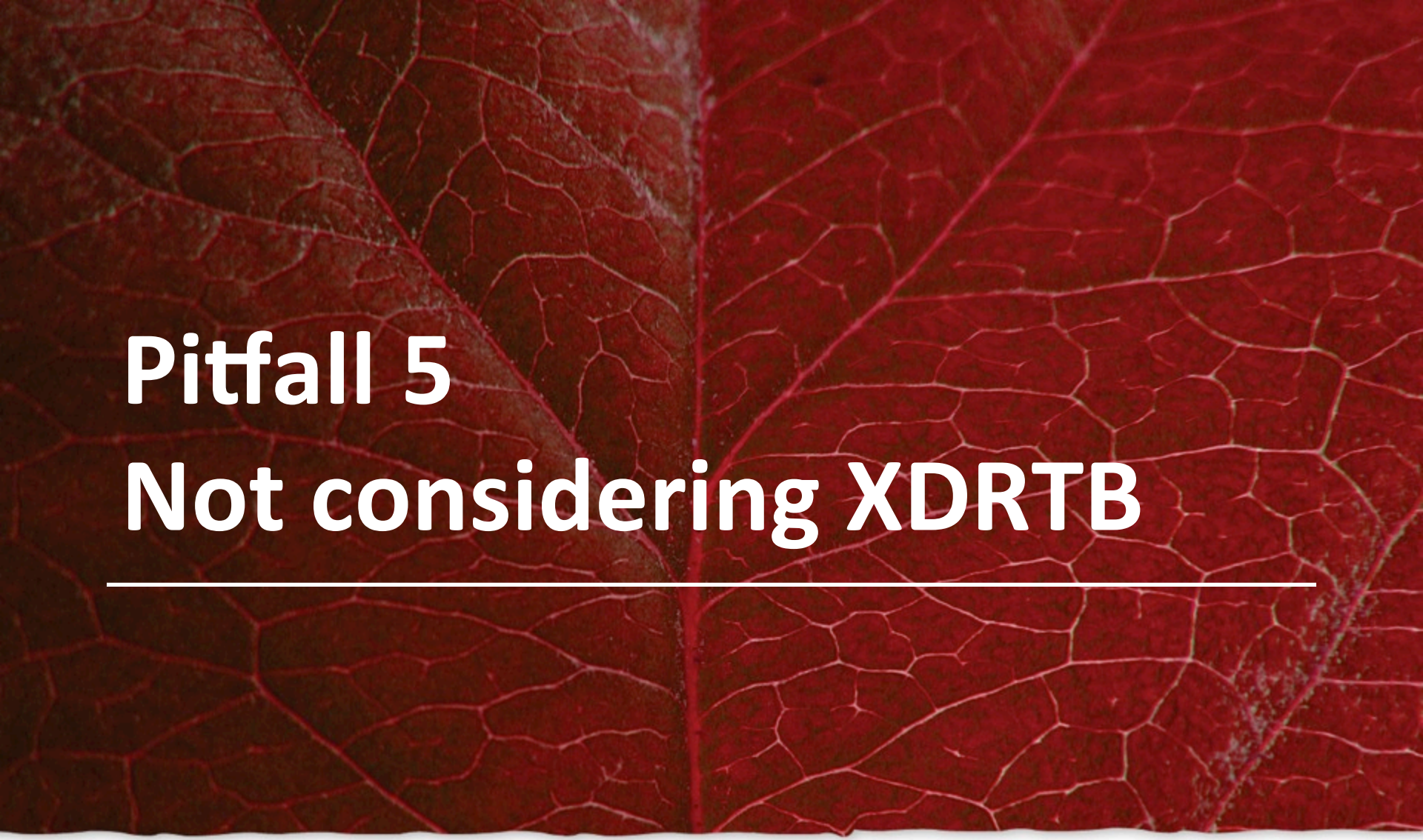
Group 4 Bacteriostatic 2nd-line drugs
- Ethionamide
- Cycloserine
- PAS

Group 5 Limited data of efficacy
- Clofazimine
- Linezolid
- AMX/CLV
- High dose INH

6 Am-Lfx-Eto-Cs-Z / 18 Lfx-Eto-Cs-Z

Principles of MDR+ treatment

- When possible, give pyrazinamide (PZA), ethambutol, and moxifloxacin once per day as thought high peaks may be more efficacious.
- Prothionamide, Cycloserine and PAS usually split because decreases side effects
- If you can monitor levels of Amikacin/Kanamycin/Cycloserine as may be needed for up to six months
- The minimum length of treatment for XDR-TB will be 18 months after culture conversion = usually 2y in total
- PZA can be used for full course of treatment
- Consider surgery if localised disease



Pitfall 5
Not considering XDRTB

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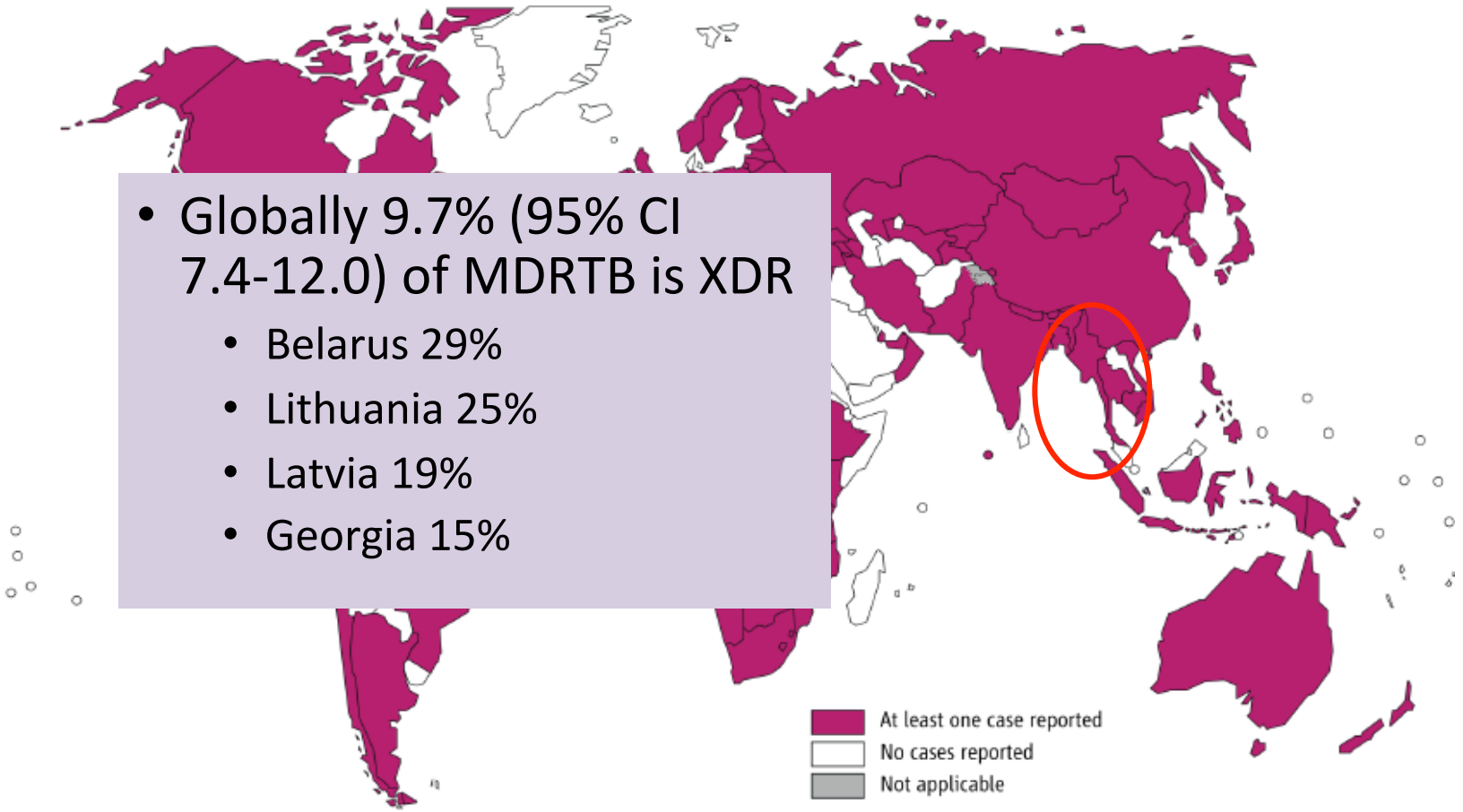
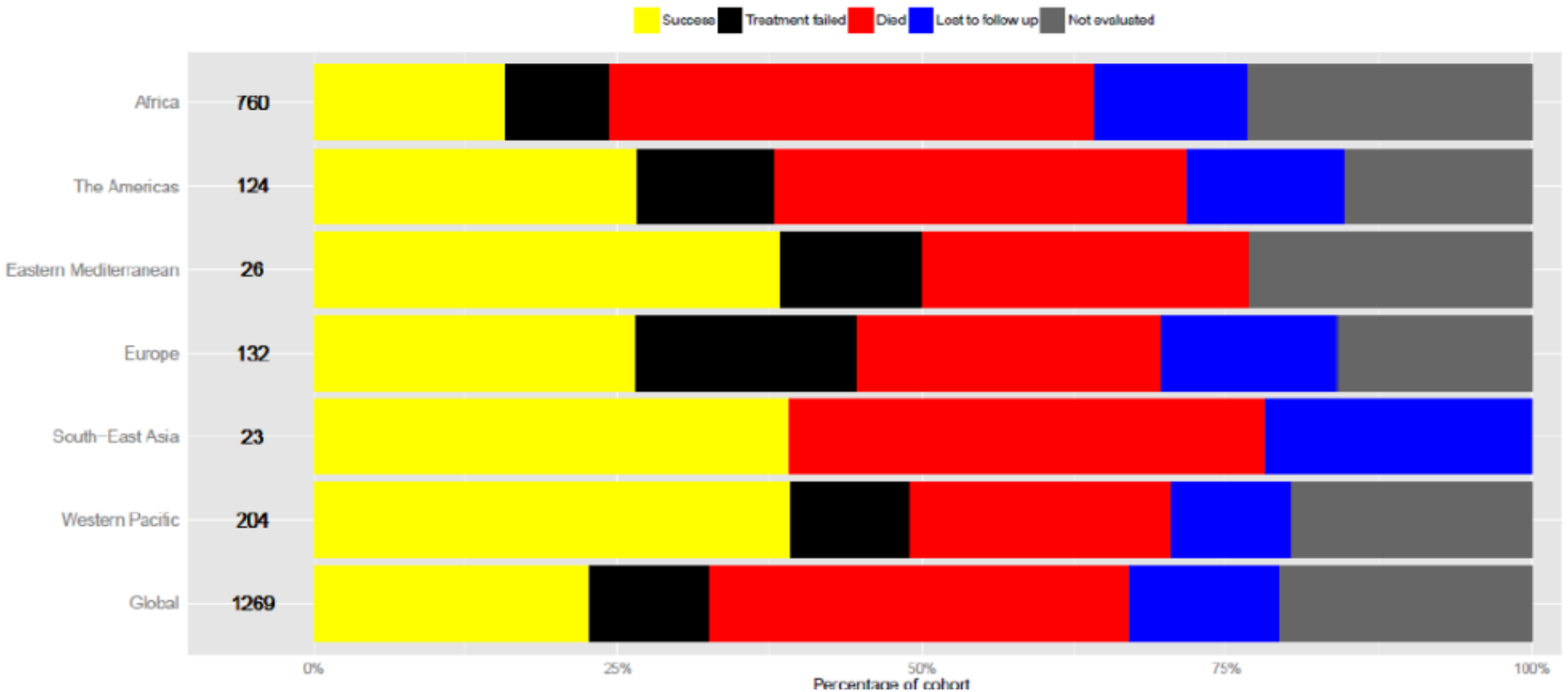
Countries reporting at least 1 case of XDRTB

- Globally 9.7% (95% CI 7.4-12.0) of MDRTB is XDR
  - Belarus 29%
  - Lithuania 25%
  - Latvia 19%
  - Georgia 15%



Outcome of XDRTB treatment 2011 worse: less than half cured



Step 1

Begin with any First line agents to Which the isolate is Susceptible

Add a Fluoroquinolone And an injectable Drug based on susceptibilities

Use any available

PLUS

One of these

PLUS

One of these

First-line drugs

Pyrazinamide

Ethambutol

Fluoroquinolones

Levofloxacin
Moxifloxacin
Ofloxacin

Injectable agents

Amikacin
Capreomycin
Kanamycin

Step 2

Add 2nd line drugs until you have 4-6 drugs to which isolate is susceptible (which have not been used previously)

Pick one or more of these

Oral second line drugs

Cycloserine
Ethionamide
PAS

PLUS

Step 3

If there are not 4-6 drugs available consider 3rd line

Consider use of these

Third line drugs

Imipenem **Linezolid** Macrolides
Amoxicillin/Clavulanic A High-dose INH
Meropenem Clofazimine Thiacetazone

BS

But these drugs..

- Efficacy often uncertain
  - Imipenem/Meropenem
  - Co-Amoxiclav
  - Linezolid
- Or weak and bacteriostatic
  - Clofazamine
  - Azithromycin/clarithromycin
  - Thioacetazone (NOT IN HIV)
- Expensive & may require IV admin
- High-dose INH can be considered if low level R

Step 3

If there are not 4-6 drugs available consider 3rd line

Consider use of these

Third line drugs

Imipenem Linezolid Macrolides
Amoxicillin/Clavulanic A High-dose INH
Meropenem Clofazimine Thiacetazone

Step 4

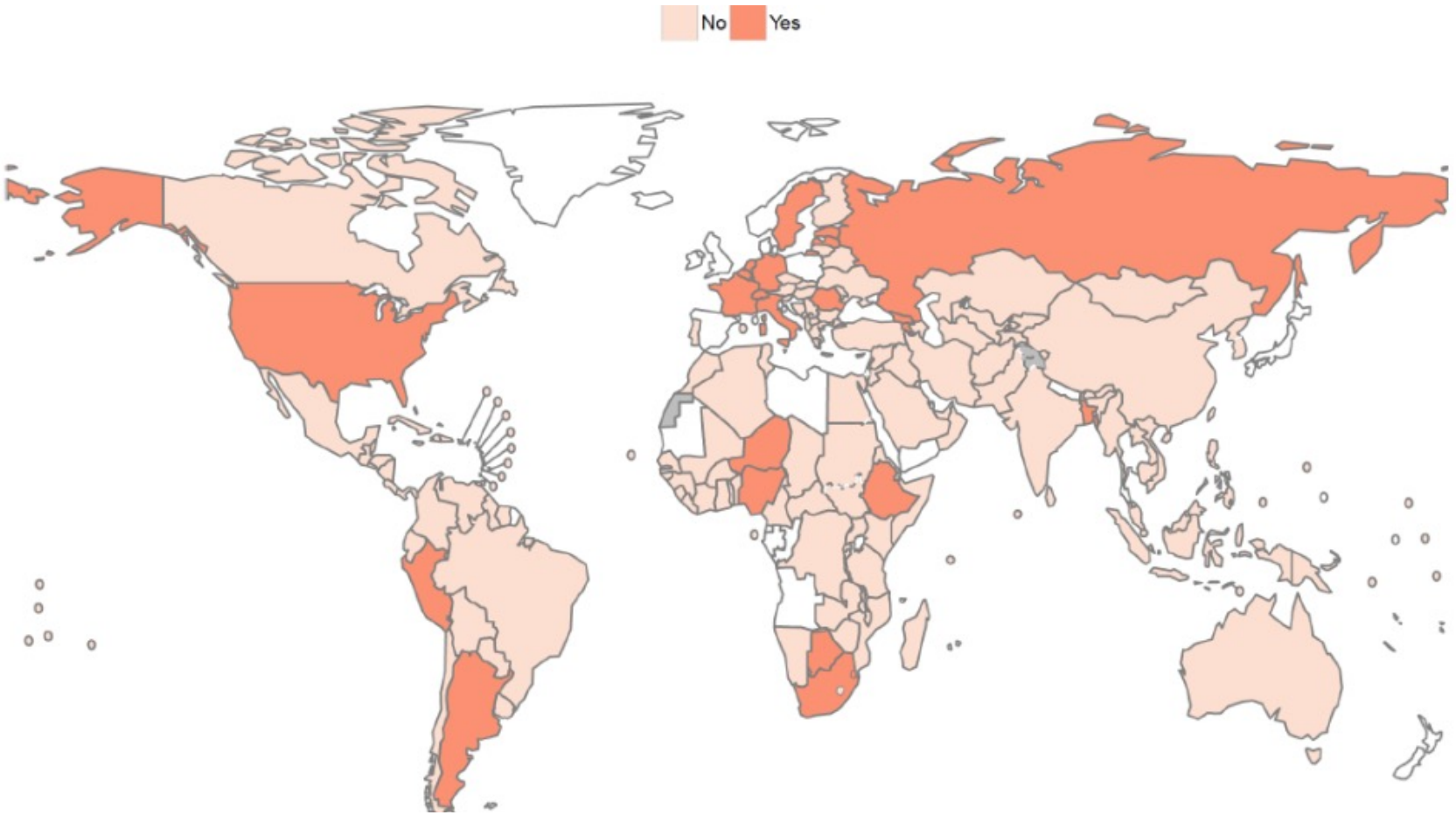
HELP

Consider use of these

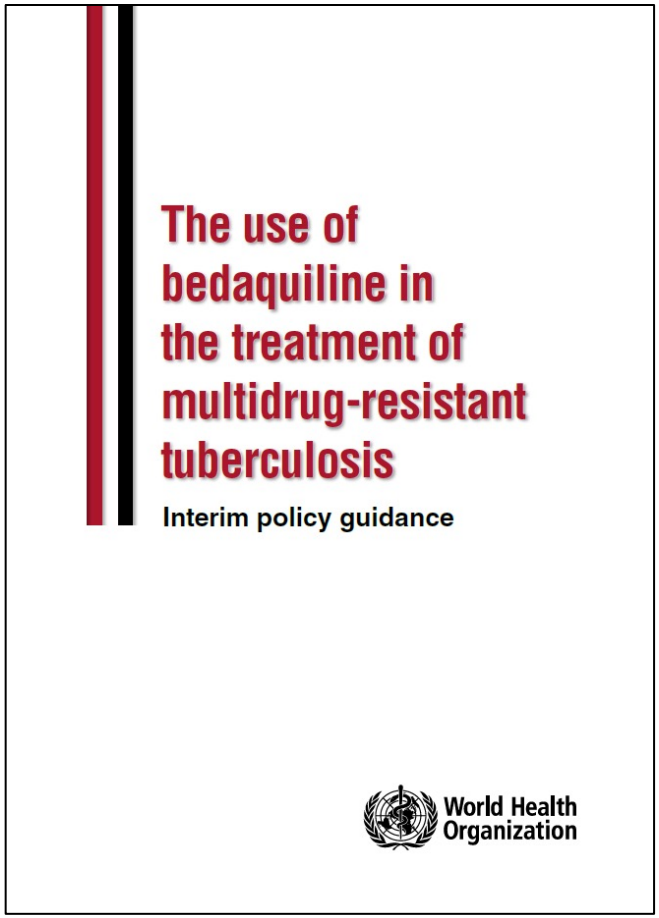
Expanded access drugs

Bedaquilline
Delamanid

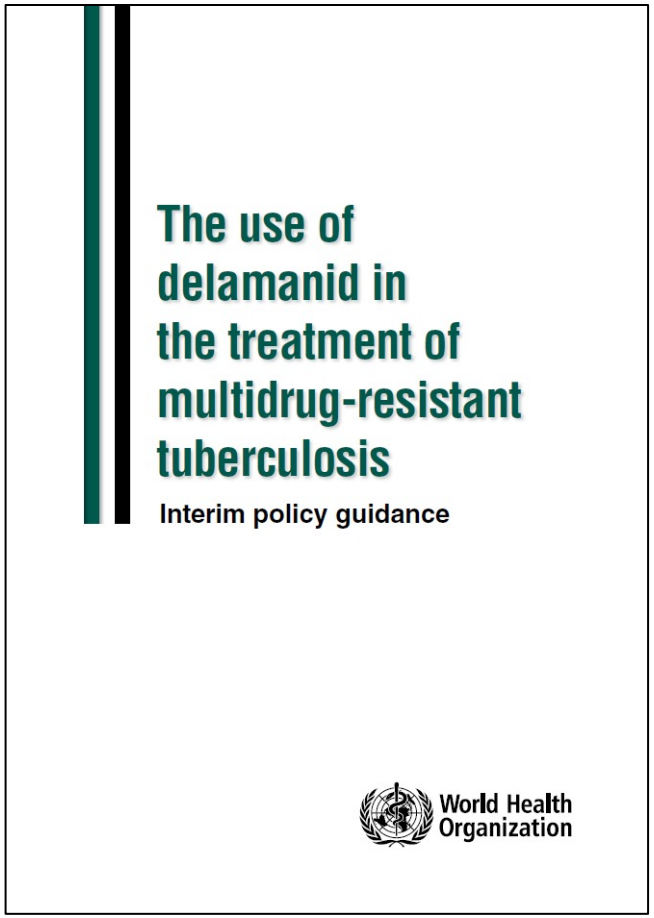
Countries that had used bedaquilline by 2014



WHO Policies available



2013



2014

Pitfall 6
Not testing for HIV

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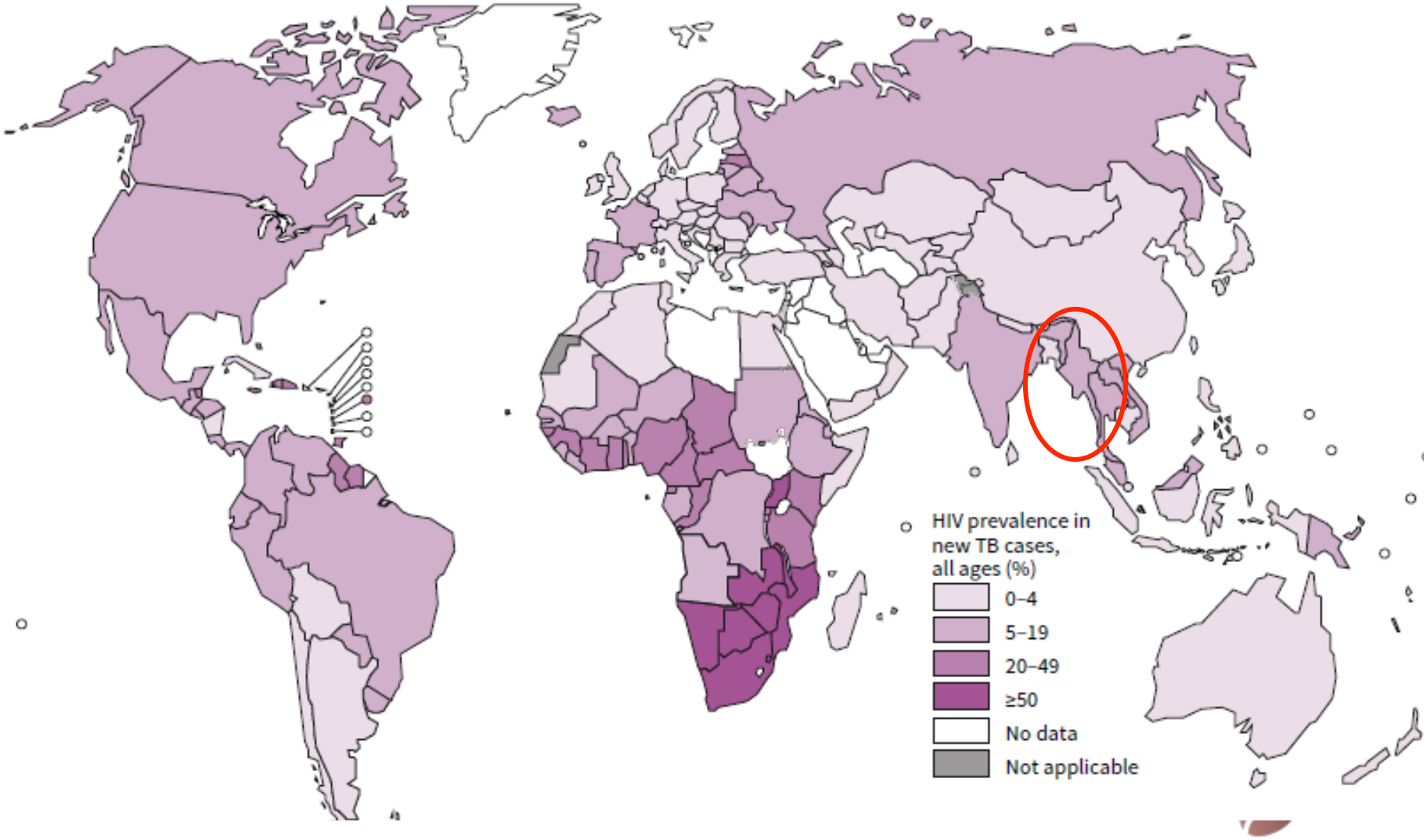
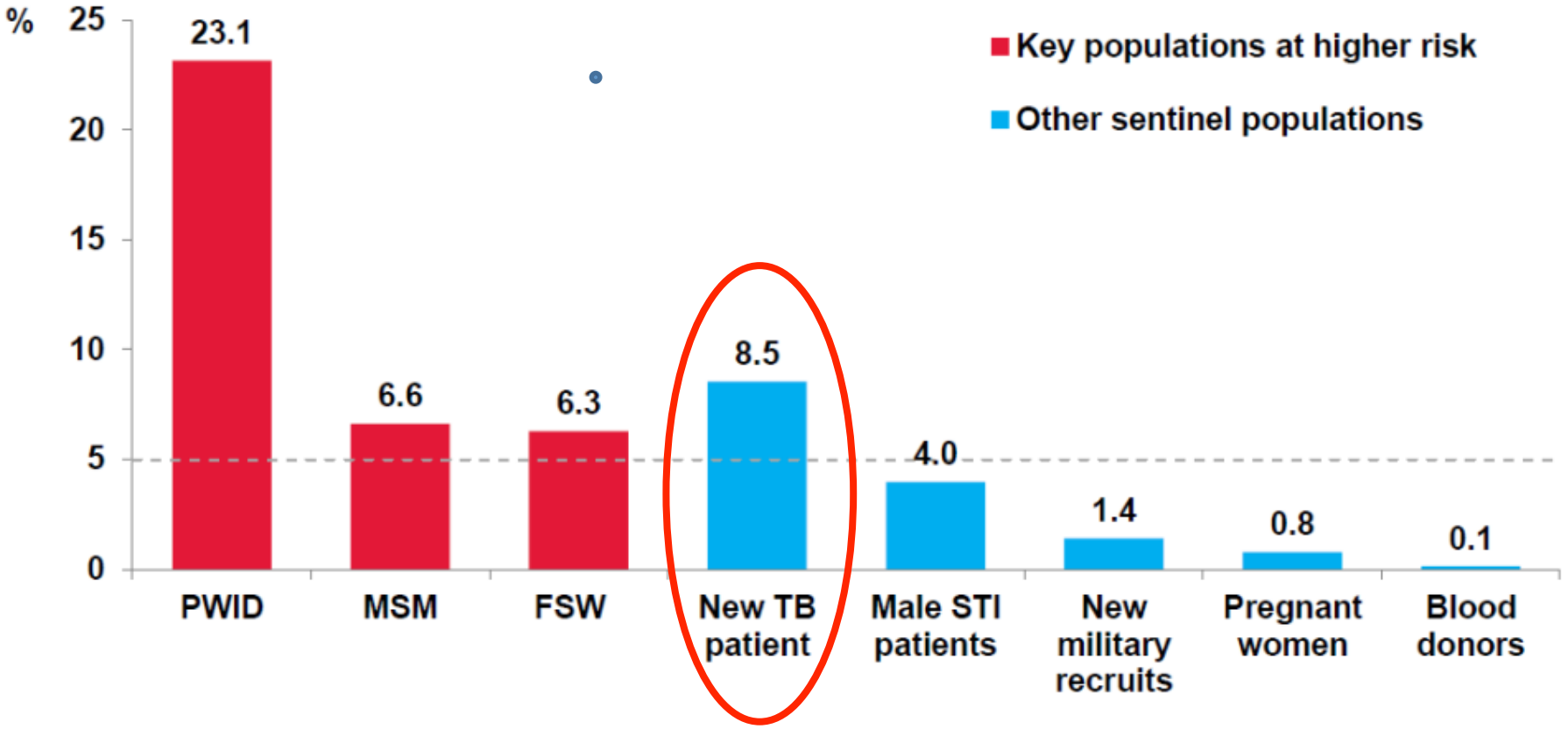
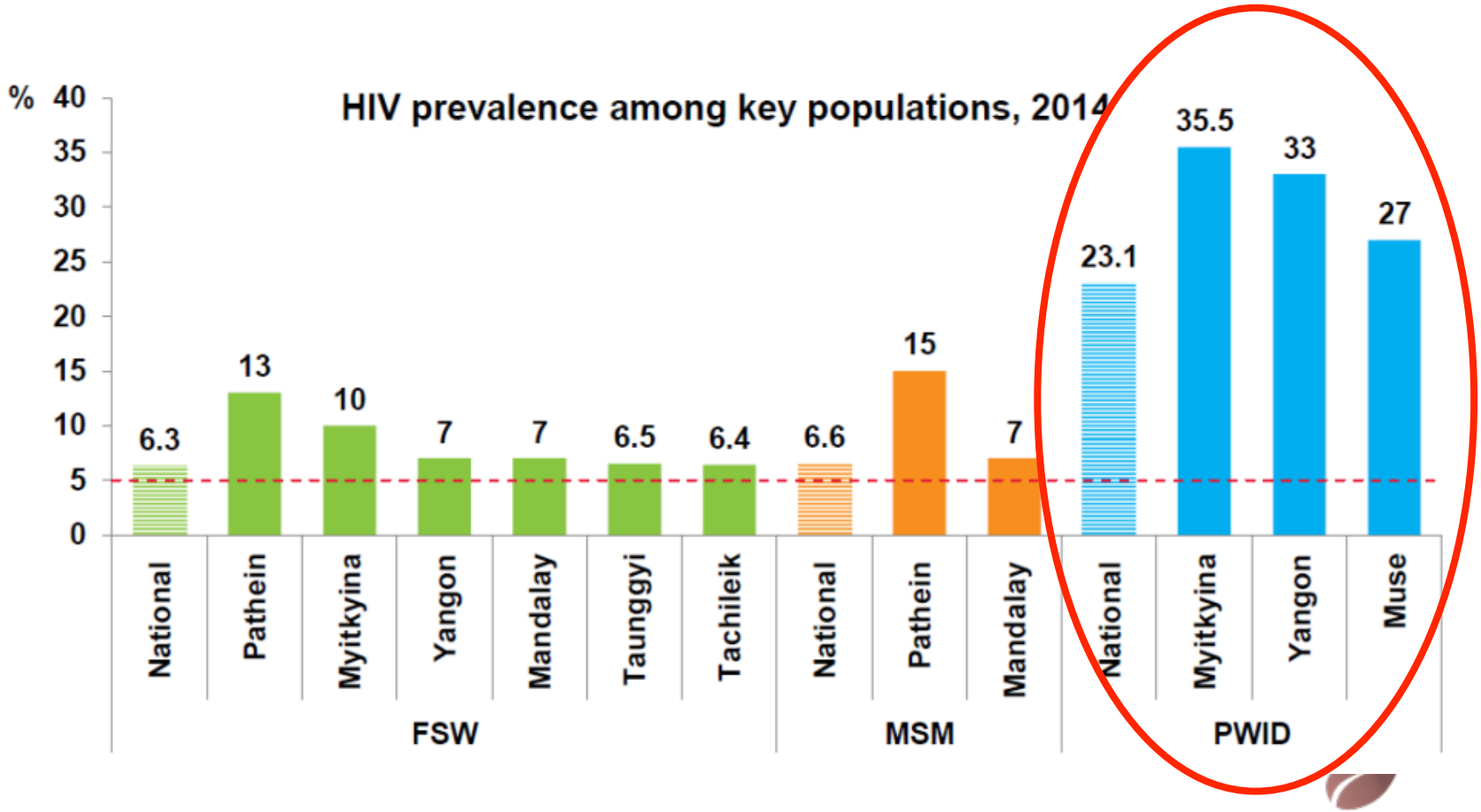
Not considering HIV: estimated HIV prevalence in TB



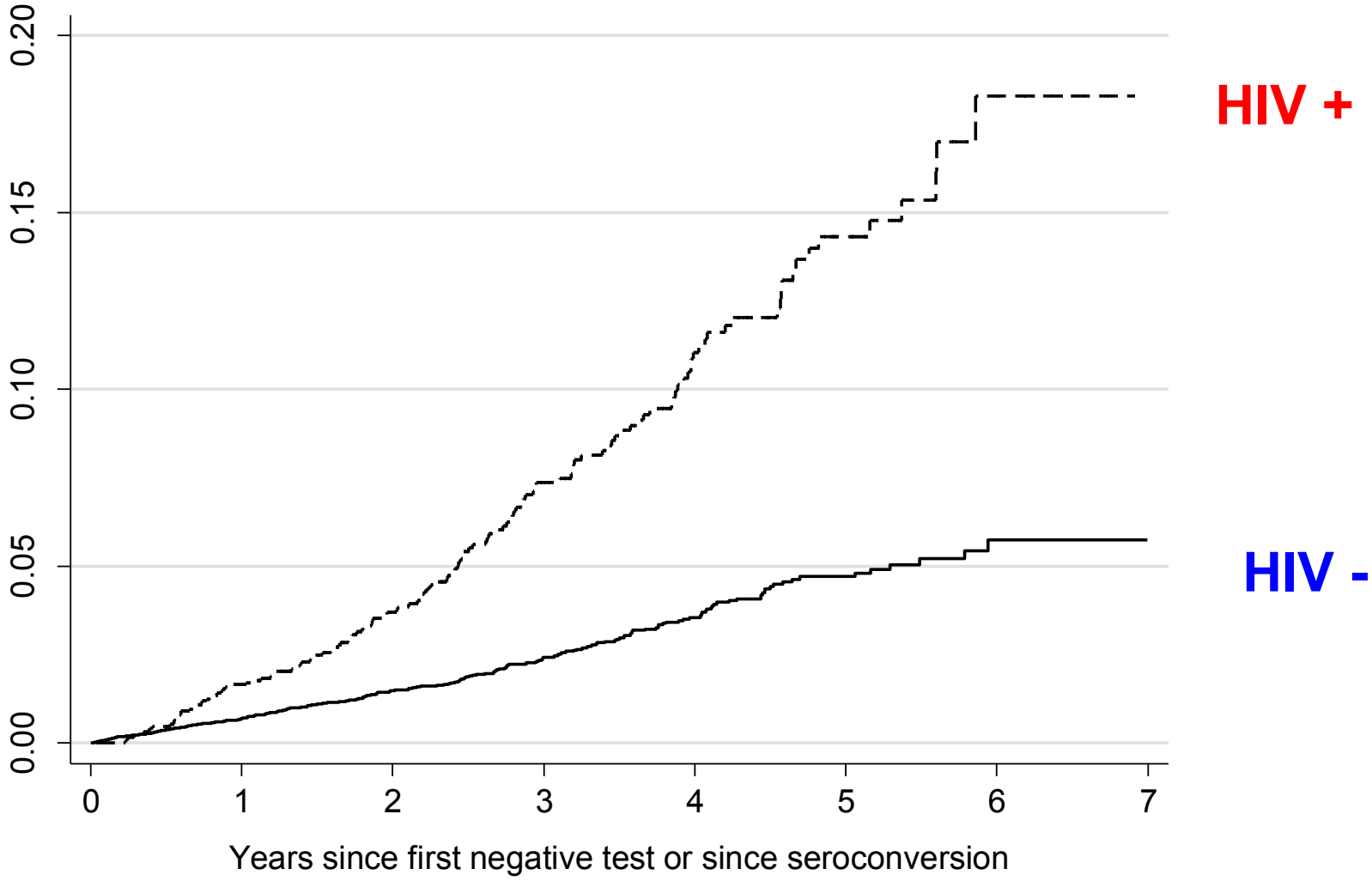
HIV prevalence in key populations: Myanmar 2014



High HIV prevalence in injection drug users – setting for TB

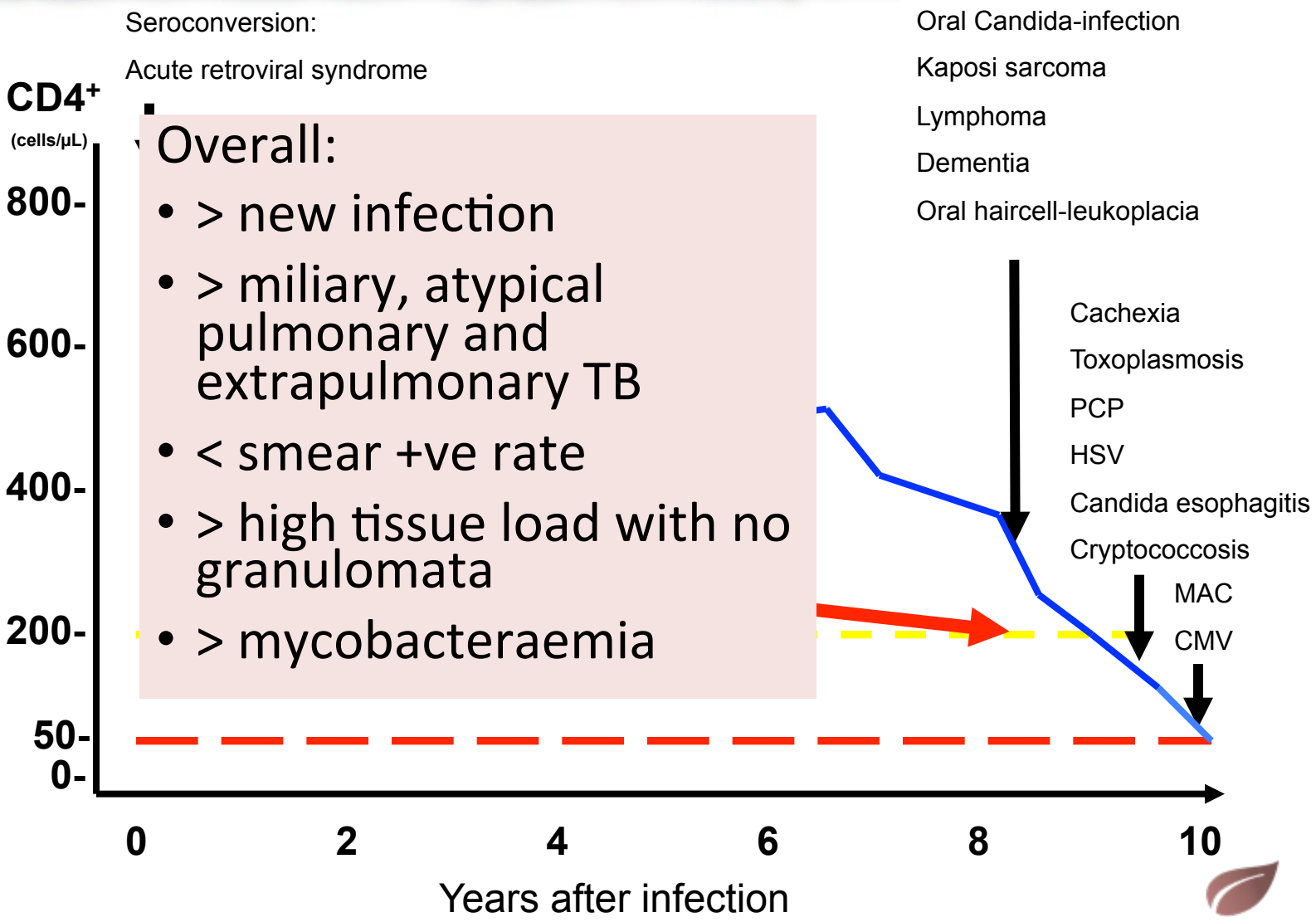


HIV patients more at risk of TB: South African Miners Cohort



Sonnenberg JID 2005

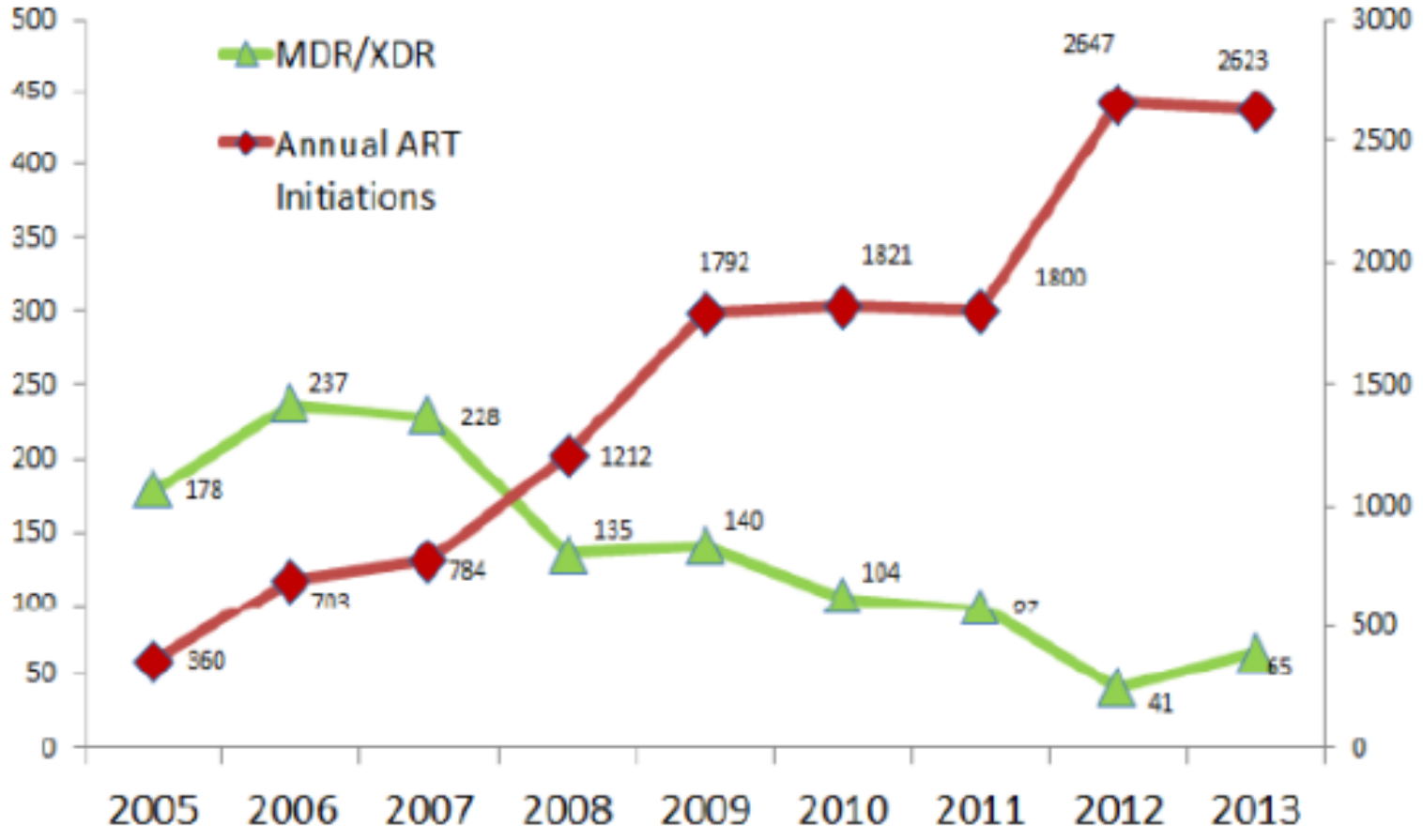
TB in the course of HIV-infection



Overall:

- > new infection
- > miliary, atypical pulmonary and extrapulmonary TB
- < smear +ve rate
- > high tissue load with no granulomata
- > mycobacteraemia

Initiating ARV therapy and reported cases of MDR/XDR TB 2005-13



Pitfall 7
Delaying HIV treatment

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TB cases starting ART is a common access into treatment

YEAR	Start ART	CD4 average	CD4 <200		Past ART		TB	
			N	%	N	%	N	%
2011	1165	136	852	73	130	11	430	37
2012	783	165	507	65	106	14	271	35
2013	1210	182	726	60	131	11	419	35
2014	1918	194	1107	58	213	11	707	37
2015	2191	208	1223	56	204	9	718	33

Delaying ART – competing risks

Immediate (< 2 wks)

Benefits:

- ↓ risk of other OI's
- ↓ risk of death <50

Risks:

- ↑ adverse effects
- ↑ incidence of IRIS

Mortality

Early (2 months)

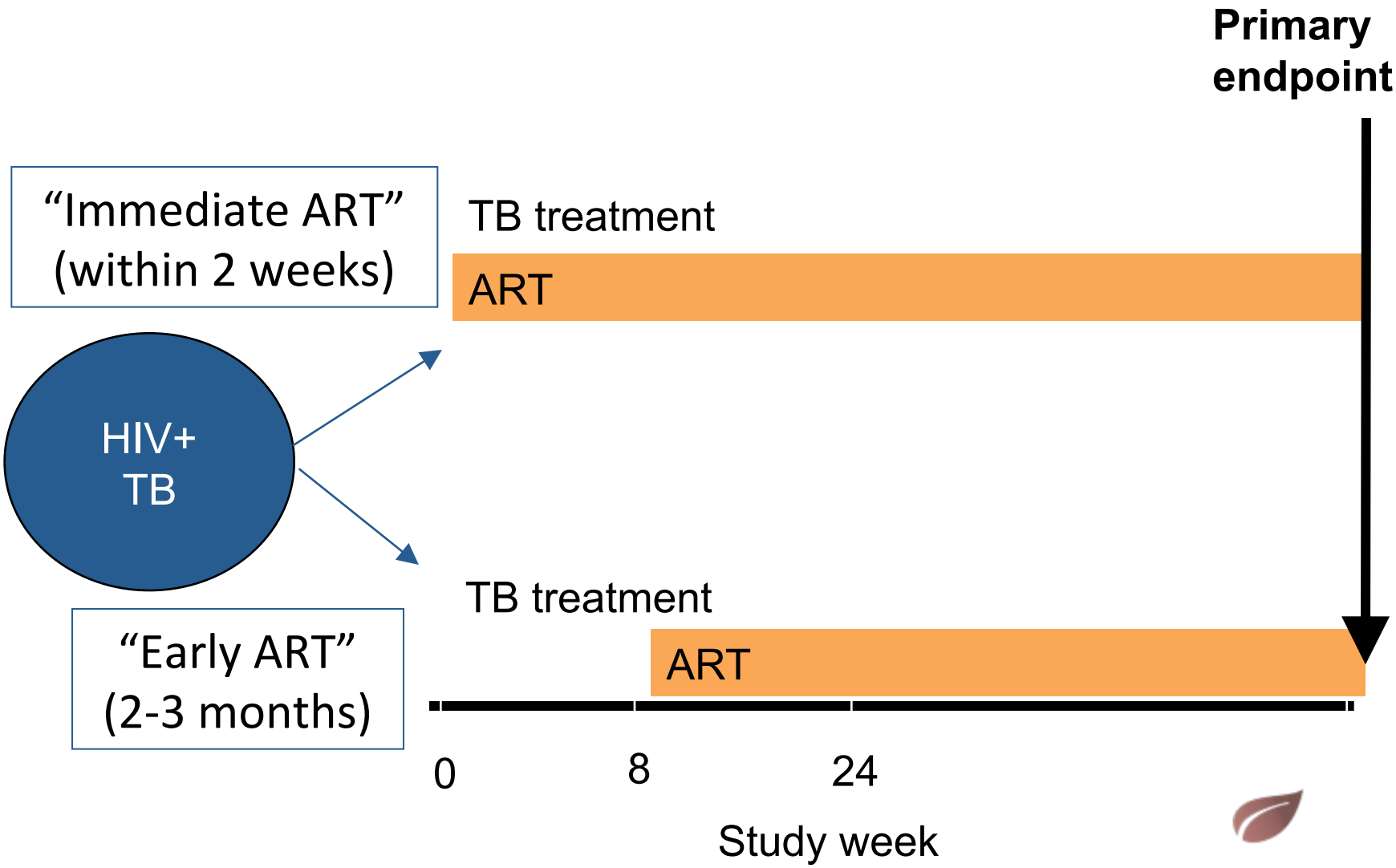
Benefits:

- ↓ risk of IRIS

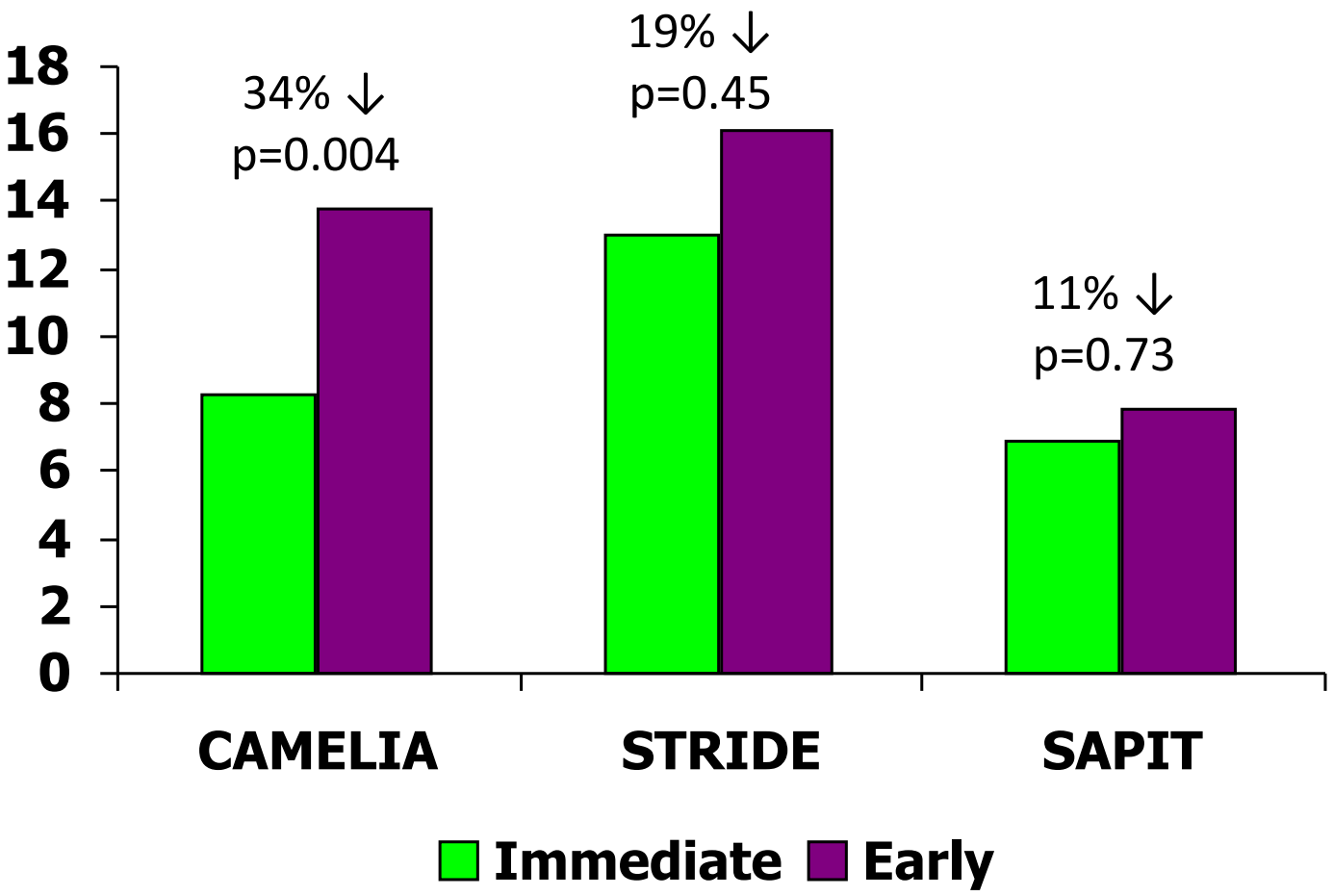
Risks:

- ↑ incidence of OIs
- ↑ risk of other death CD4 <50

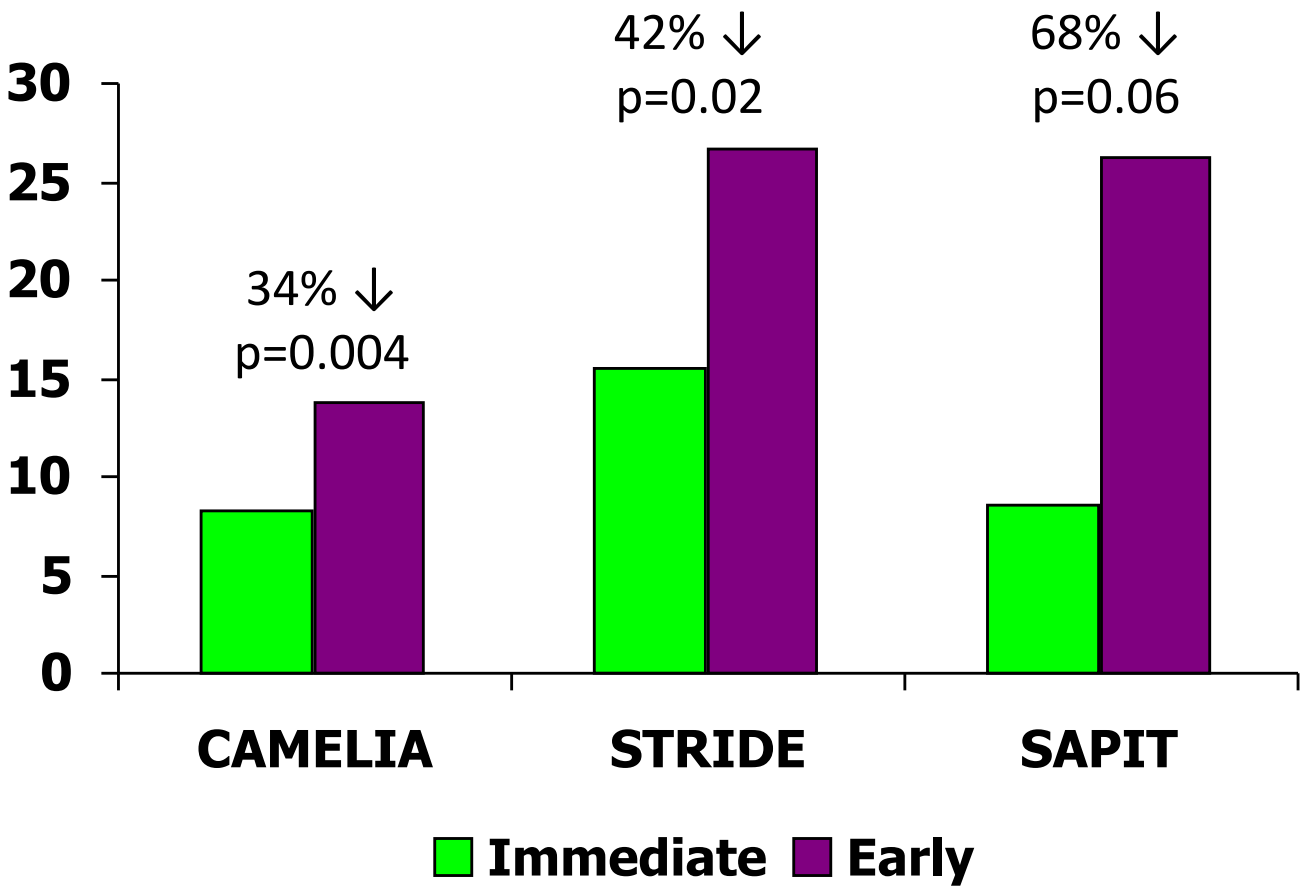
General schema for CAMELIA, STRIDE, and integrated arms of SAPIT



Effect of ART timing on death (CAMELIA) or death/AIDS (STRIDE, SAPIT)



Effect of ART timing on death (CAMELIA) or death/AIDS (STRIDE, SAPIT): CD4 <50



Pitfall 8
Potential drug interactions and overlapping toxicities

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Rifamycins & ART

	Rifampicin	Rifabutin
NRTIs	No problem	No problem
Efavirenz (EFV)	EFV AUC ↓ 26%	RFB AUC ↓ 38%
Nevirapine (NVP)	NVP AUC ↓ 40-60%	No problem
Etravirine/Rilpivirine	ETR/RPV ↓ 40-60%	NNRTI AUC ↓ 37%
PIs unboosted	PI AUC ↓ 80-90%	RFB AUC ↑ 200%
PIs boosted	PI AUC ↓ 60-75%	RFB AUC ↑ 300%
Raltegravir	Integrase AUC ↓ 40%	No problem
Dolutegravir	Integrase AUC ↓ 40%	No problem
Maraviroc	CCR5 AUC ↓ 60-70%	? No problem

Adapted from www.hiv-druginteractions.org with approximated AUC percentages displayed; Refer to individual SPCs for further details on drug interactions

NRTIs=nucleoside reverse transcriptase inhibitors; NNRTIs=non-nucleoside reverse transcriptase inhibitors; PIs=protease inhibitors; AUC=Area under curve; ABC=Abacavir; AZT=Zidovudine

AE problems - overlapping

Syndrome	Causes
Febrile, generally unwell	*IRIS, paradoxical reactions, MDR TB*
Abnormal LFTs	*TB drugs (RIF/INH/PZA), HIV drugs, paradoxical reactions, IRIS, hepatitis virus 'flares'*
Neuropathy	*d4T, ddI, 3TC, HIV, isoniazid, ethionamide, linezolid, cycloserine*
Eye problems	*Ethambutol, rifabutin, linezolid, ethionamide*
CNS	*Efavirenz, cycloserine, quinolones*
Cardiac	*PIs, quinolones*
Arthropathies	*HIV, pyrazinamide, quinolones, PAS*

Pitfall 9
Not identifying IRIS

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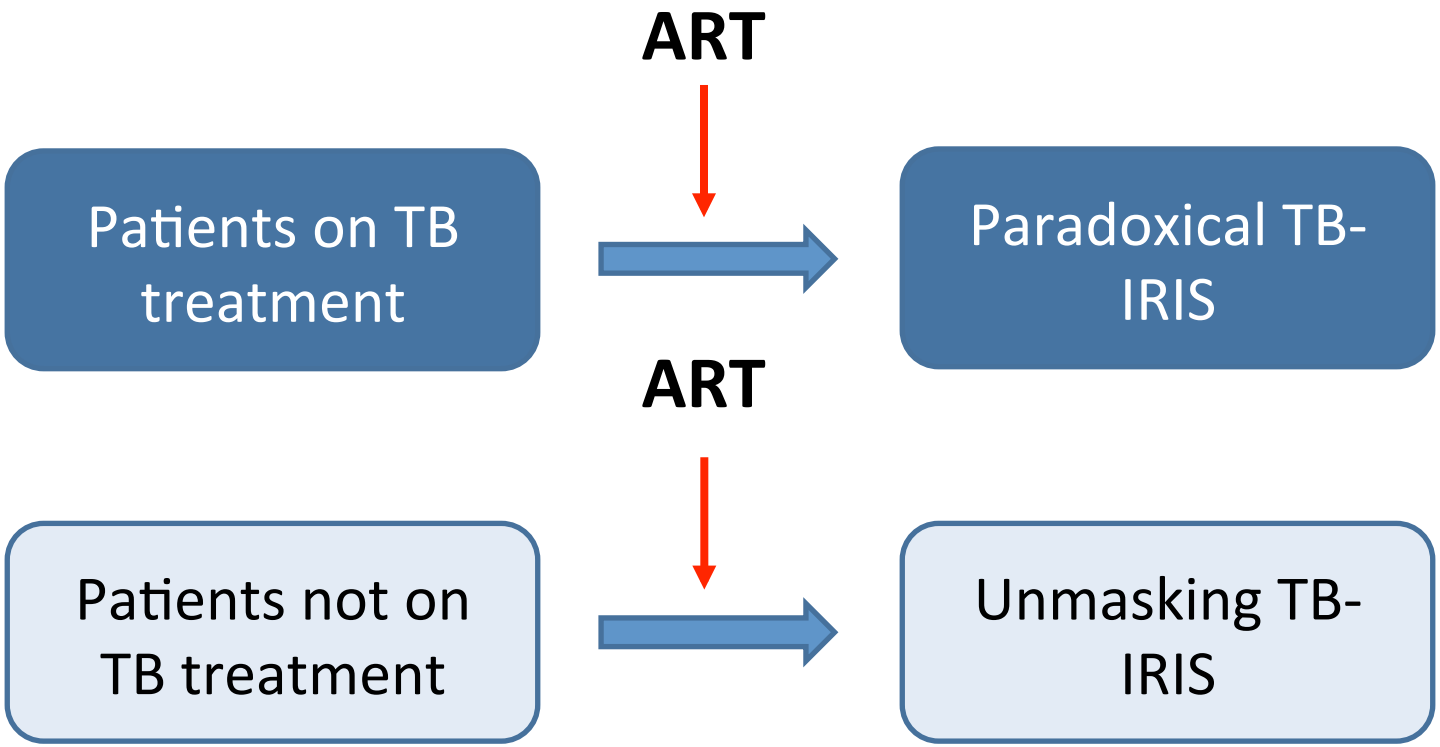
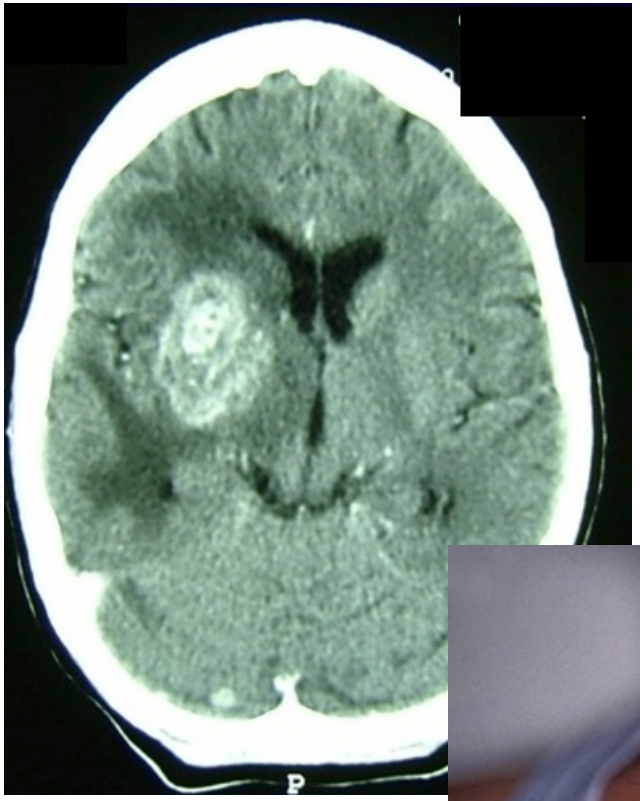
Not identifying IRIS

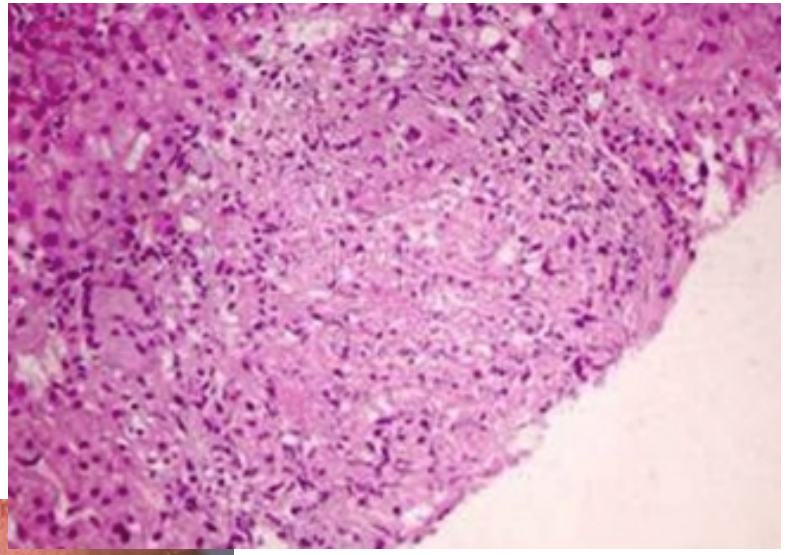


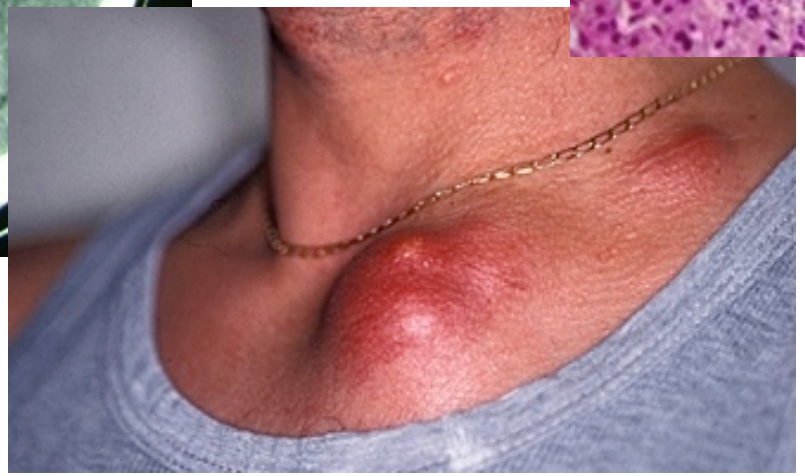
Paradoxical TB-IRIS

- Incidence 8-54% (15.7% in meta-analysis)
- Median 14d onset after starting ART
- Focal and often systemic features
- Hospitalisation in up to half
- Median duration 2-3 months but can be years
- Mortality infrequent
- Differential diagnosis wide

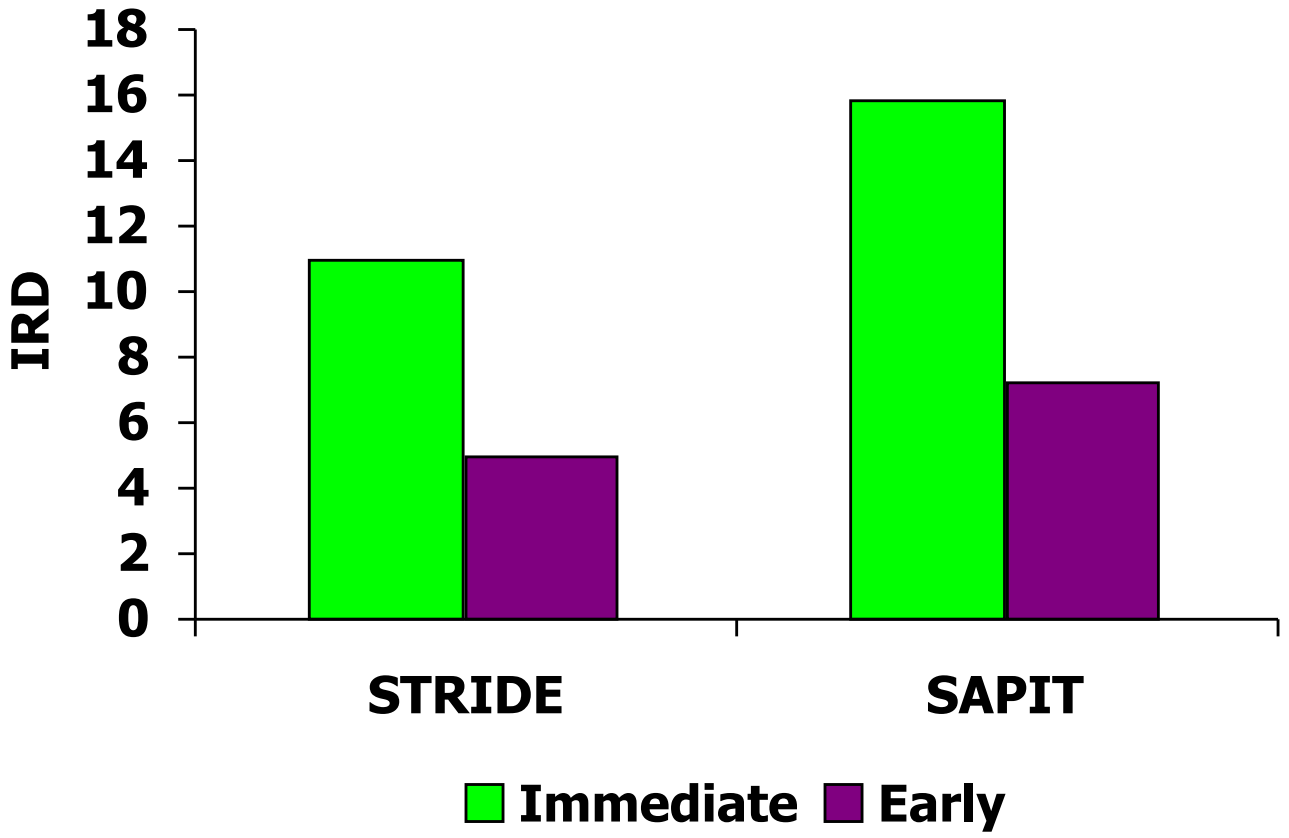
Lymph-node, lung, brain, and liver most common







Effect of ART timing on IRIS (STRIDE, SAPIT): CD4 >50



Challenges in differential diagnosis of IRIS

ALTERNATIVE DAGNOSIS

Bacterial/fungal infections
NTM and PCP
Lymphoma
KS

DRUG RESISTANCE

14/141 suspected TB-ISIS had MDR or rifampicin resistance

DRUG REACTION

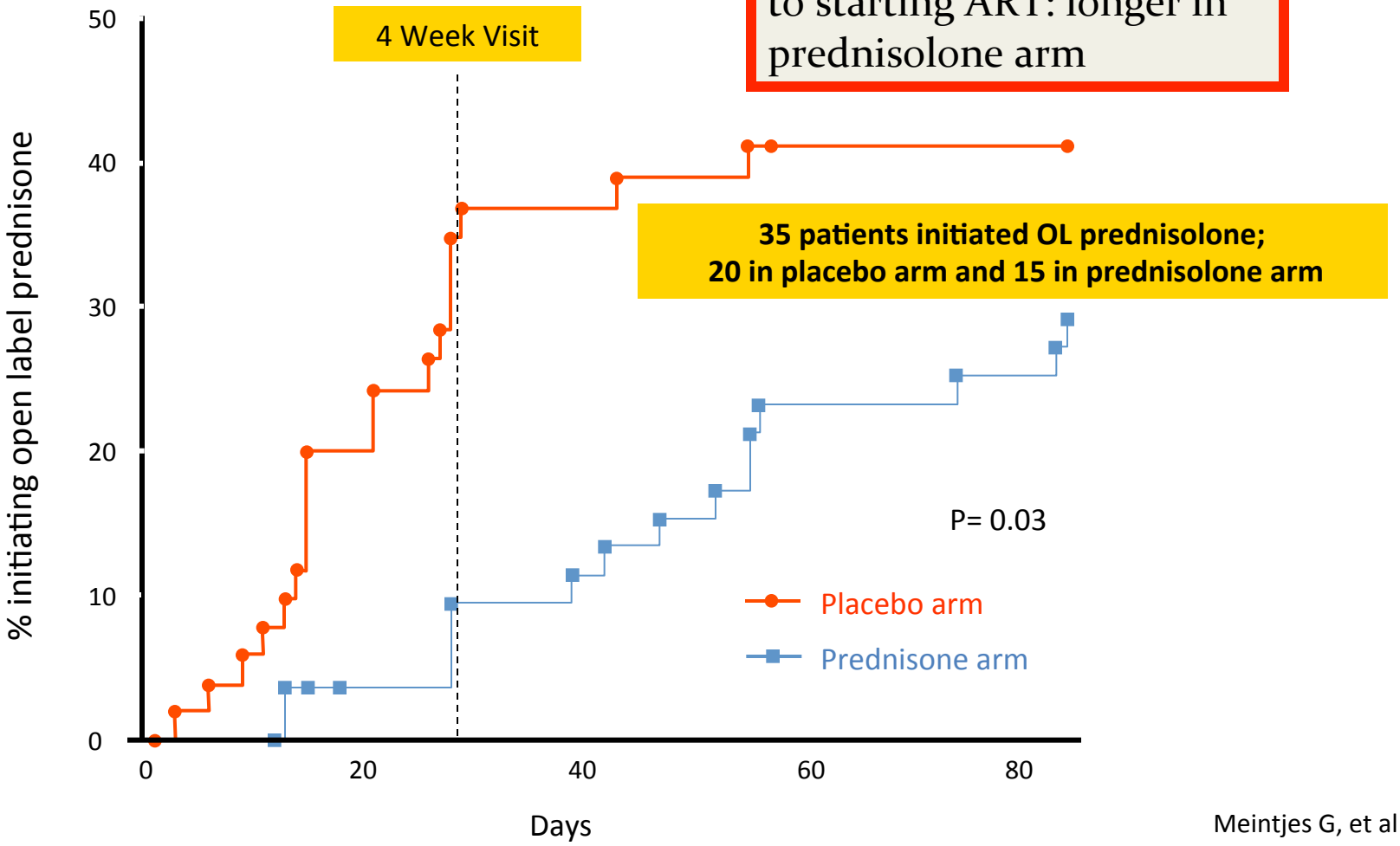
Especially if HEPATIC involvement

IRS management

- IRS treatment
  - **Continue TB and ARV treatment**
  - NSAID's then
  - Prednisolone (remember RIF induction) tapering off
  - Montelukast no harm
  - Thalidomide
  - Others

Time to initiation of open label prednisone

Matched groups at BL apart from length of time from starting TB treatment to starting ART: longer in prednisolone arm



Meintjes G, et al
Oral Abstract 34

Challenges

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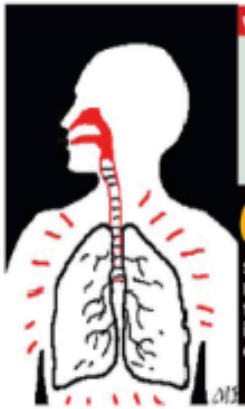
TDR-TB

Rich or poor, TDR-TB is a threat to everybody

Over 15.5 lakh people infected by TB in 2011, and 3 lakh have died so far

Soumita Majumdar
BANGALORE



WHAT IS TDR-TB?

Totally drug-resistant tuberculosis (TDR-TB) is a form of tuberculosis which is resistant to all currently-used drugs.

TDR-TB was first discovered in 2007 in Italy and later in 2009 among a small percentage of patients in a multi-drug-resistant tuberculosis outbreak in Iran.

"There are specific guidelines given by WHO, which requires to be followed strictly. The isolation period is usually two to three weeks and it takes the same time to turn the infection to a non-infectious disease.

– Dr Sumant Mantri, consultant pulmonology, Apollo Hospital

There has been an overall drop globally in the population of people infected by tuberculosis. Those infected by the disease worldwide fell to 8.9 million in 2011, as against 9 million in 2005.

But in India, over 15.5 lakh people have been infected by TB in 2011, and it took 3 lakh lives. Multi-drug resistant cases, which make up more than 2% of all new cases, have evoked concern lately.

As Karnataka State Tuberculosis Eradication Association has come up with the 'Anti-TB Week' from February 17-23, experts said children from well-to-do families from the city, too, are falling prey to it.

A TDR-TB case needs to be dealt separately, said Dr Sumant Mantri, consultant pulmonology, Apollo Hospital.

"There are specific guidelines given by WHO and they must be followed strictly. The isolation period is usually two to three weeks and it takes the same time to convert the disease non-infectious," he said.

While the doctor hasn't treated a single case of TDR-TB, he has dealt with several cases of Multi Drug Resistant (MDR) TB of late. There is no way to tackle TDR-TB once the diagnosis has been confirmed.

"Only if the TB is localised in a certain part/organ of the body, then surgical resection could be one of the options. The best way to tackle this problem is educating TB patients, who are undergoing the treatment. They should be told to complete the full course of treatment and not neglect or ignore the doctor's advice," said Dr Shantanu Rahman, founder and medical director, NationWide Primary Healthcare Services Pvt Ltd.

Ideally, a TB registry should be maintained and all patients undergoing treatment should have regular proactive follow-up from the treating physician, he added.

However, what is more worrying is that there are several instances of children falling prey to tuberculosis, despite having adequate nutrition.

TB is not a 'disease of poverty' any more. It is regularly found in the higher socio-economic population as well.

"There are no specific reasons for this phenomenon. One of the major reasons could be the Vitamin D deficiency, though there is no scientific study to support this hypothesis," said Dr Mantri.

While textbook signs of lung TB are persistent cough lasting for more than three weeks or cough with blood in the sputum, patients with weakness or fatigue, weight loss, loss of appetite, low-grade fever and night sweats should also be tested for TB, said Dr Rahman. Younger patients with history of poor immune status are more at risk of contracting TB, he added.

How can parents ensure that children don't get the disease? First, newborns should be administered with a BCG vaccine. Children should be given a diet that is rich in anti-oxidants.

Parents should ensure that children have at least four to five servings of fruit and vegetable daily.

Children should also have a good portion of protein in their diet. Parents should encourage children to exercise daily or participate in sports, added Dr Rahman.

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Nature of coverage: IN-DEPTH | Important for long descriptive questions in the Main Examination and also for Interviews.
Underlined words / sentences emphasize key information / concepts.

TB scourge acquires a new dimension: Emergence of Totally Drug-Resistant (TDR) Tuberculosis in India

TDR-TB

- Resistant to all 2nd line drugs
- Culture and smear remain +ve after 18m f 2nd line therapy
- Described mainly in India but also elsewhere

Now isolates reported resistant against new anti-TB agents 2015

Acquired Resistance to Bedaquiline and Delamanid in Therapy for Tuberculosis

TO THE EDITOR: Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are an increasing public health threat.[1] Bedaquiline and delamanid are two drugs that were recently approved by the Food and Drug Administration for treatment of MDR-TB and XDR-TB.[2] Here we describe the stepwise amplification of drug resistance in a patient who had emigrated from Tibet to Switzerland in December 2010 and who presented to a Swiss hospital with preextensively drug-resistant tuberculosis at that time.

Local management

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Myanmar: TB cases and deaths 1990-2014

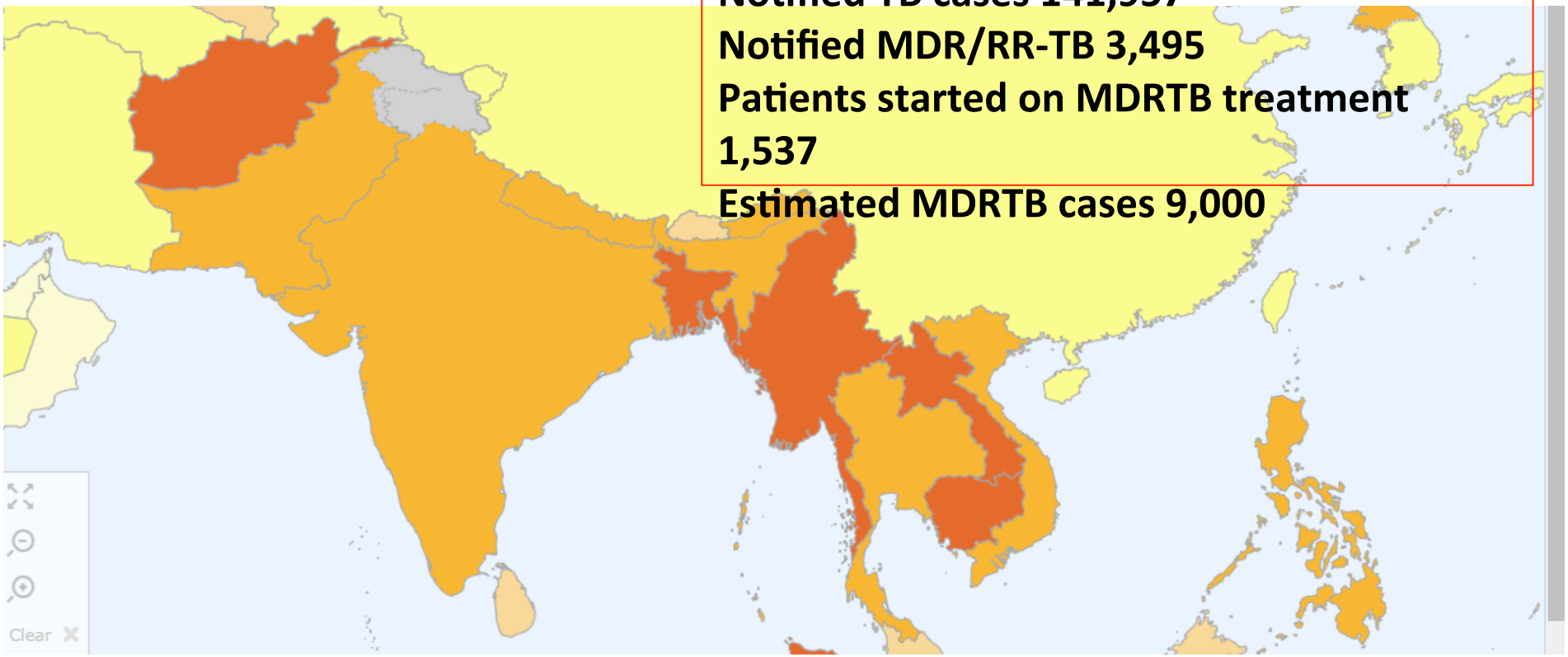
MYANMAR 2014

Notified TB cases 141,957

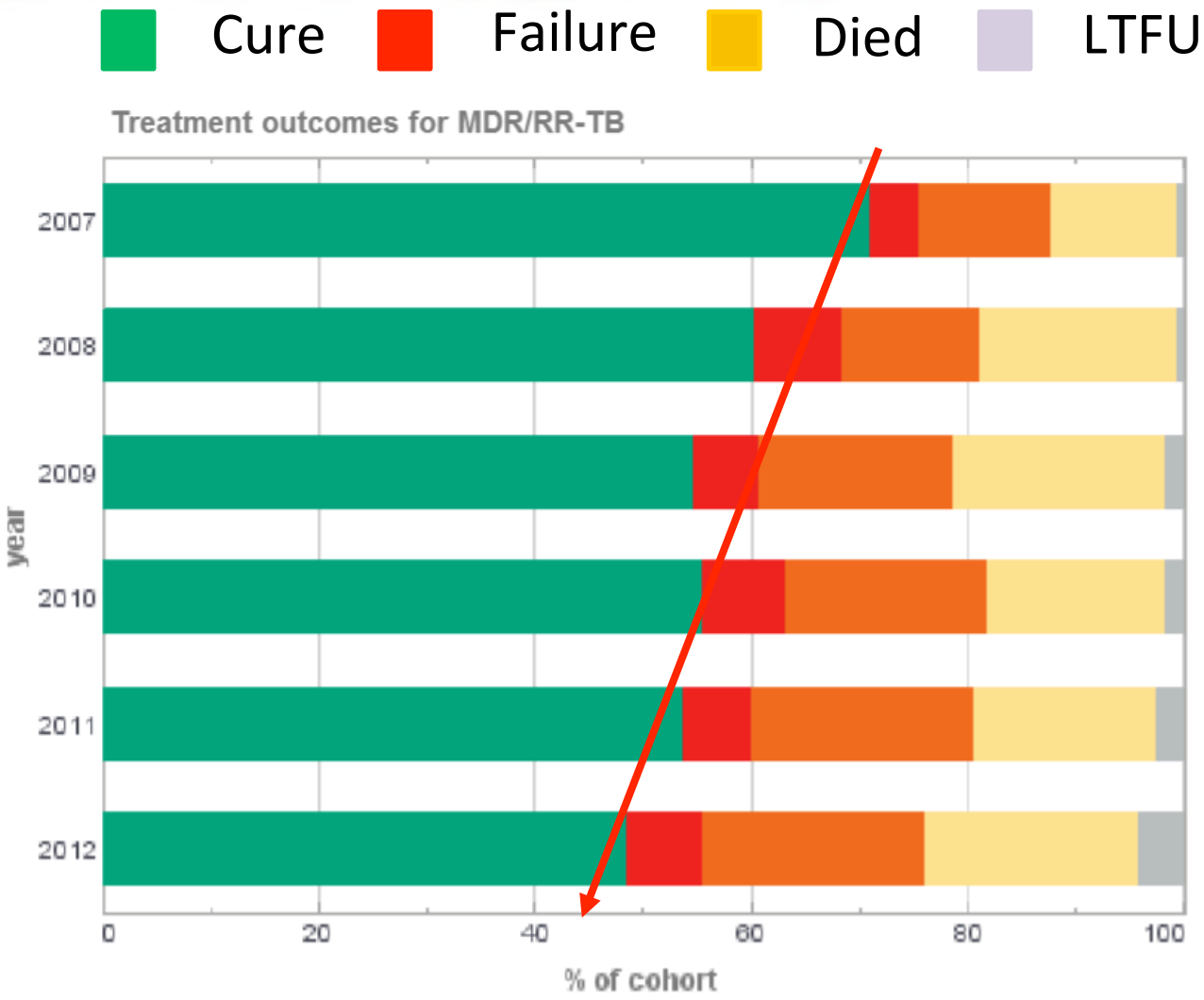
Notified MDR/RR-TB 3,495

Patients started on MDRTB treatment 1,537

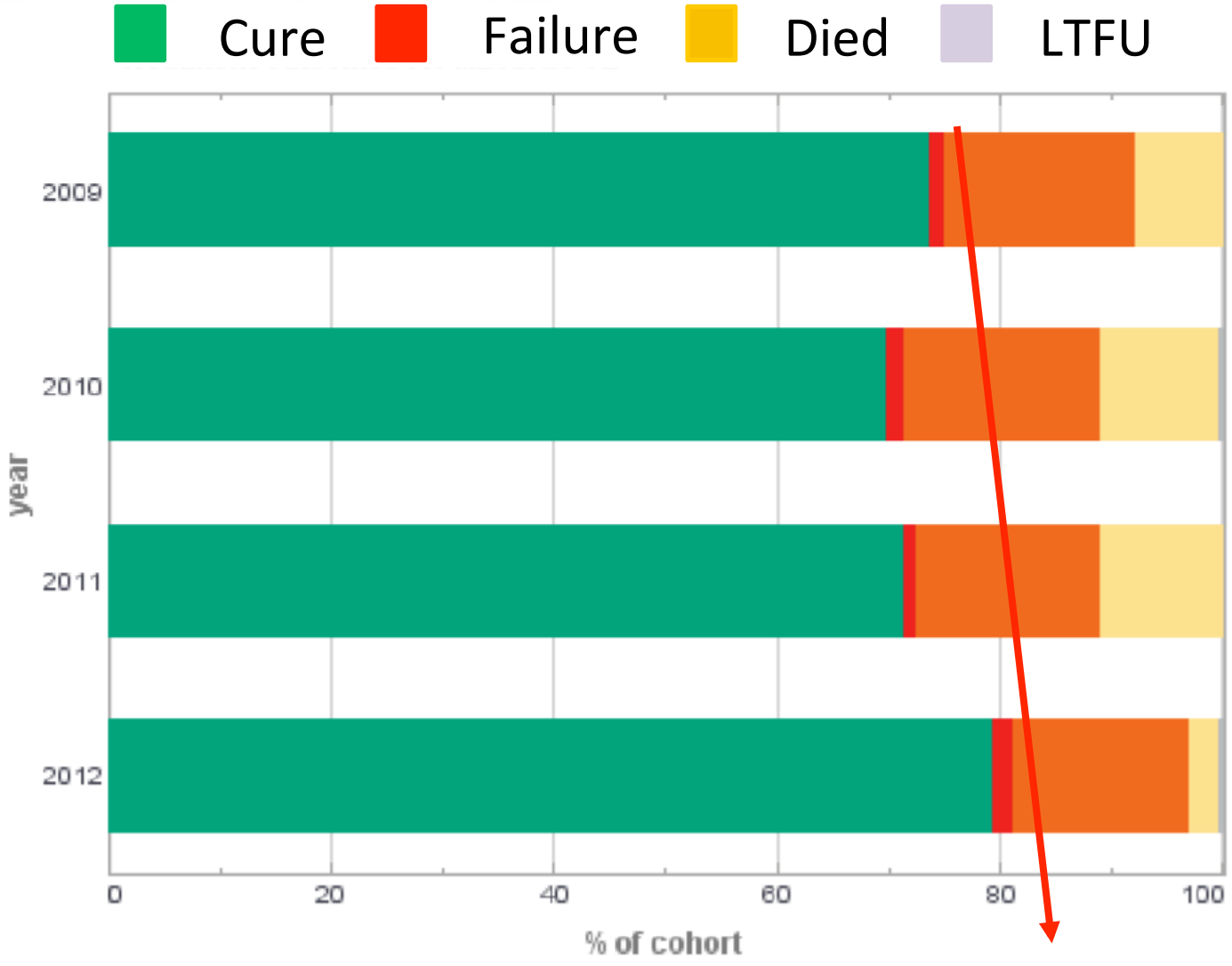
Estimated MDRTB cases 9,000



SE Asia: MDR/RR-TB outcome



Myanmar: MDR/R-RTB outcome



Aims for today

- What is MDRTB?
- The pitfalls in management:
  - Not suspecting and failing to make and early diagnosis
  - Failing to prevent hospital acquired infection
  - Not using an effective ant-TB regimen and not considering XDRTB
  - Not considering HIV