

An Update on TB and OI prophylaxis

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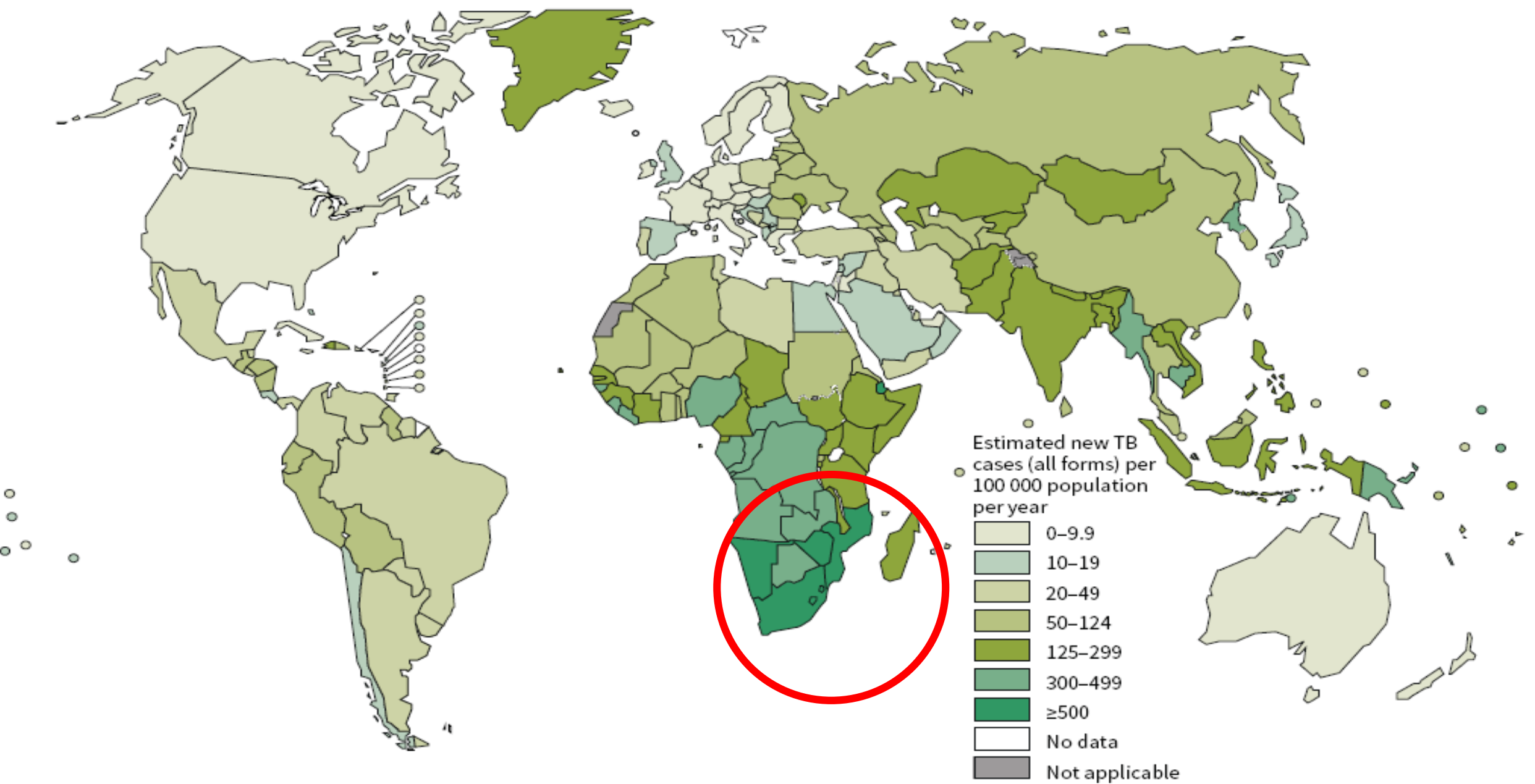
TB Infection

- ▶ Tuberculosis (TB) infection occurs when a susceptible person inhales droplet nuclei containing MTB
- ▶ Immune response limits multiplication of tubercle bacilli within 2 to 12 weeks
- ▶ Viable bacilli persist for years, a condition referred to as latent TB infection (LTBI).
- ▶ LTBI are asymptomatic and are not infectious
- ▶ TB disease can develop soon after exposure ,primary disease, or after reactivation of latent infection

Epidemiology of HIV-Related Tuberculosis

- ▶ One third of the world's population is infected with *MTB*
- ▶ ~ 9 million new cases of active TB in 2010

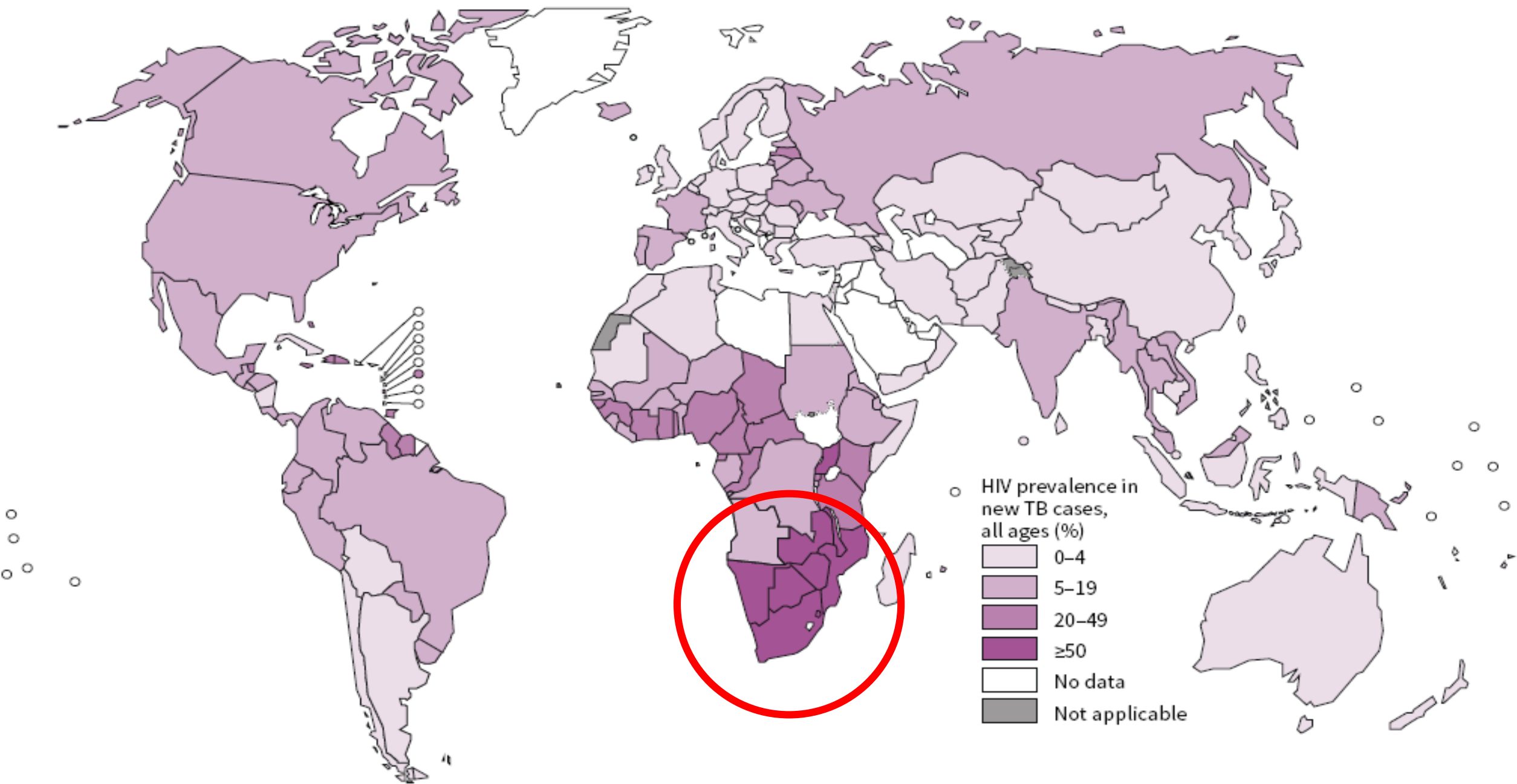
Estimated TB incidence rates, 2013



Epidemiology of HIV-Related Tuberculosis

- ▶ Worldwide, 14.8% of TB patients are co-infected with HIV
- ▶ TB is the most common cause of death among patients with AIDS accounting for about a third of AIDS deaths

Estimated HIV prevalence in new and relapse TB cases, 2013



TB and HIV

- ▶ TB **immunologic** disease with host tissue damage occurring during immune response to MTB
- ▶ HIV alters the response to TB and fuels TB by altering the immune response
- ▶ HIV converts TB into a “new” disease almost unrecognizable by clinicians familiar with TB in the pre-HIV era

Impact of TB on HIV

- ▶ Understanding interactions between TB and HIV critical to management of both HIV and TB
- ▶ TB increases risk of HIV progression and death in untreated HIV disease
- ▶ TB co-infection associated with higher HIV viral loads

Impact of HIV on TB

- ▶ Affects treatment: drug toxicity, drug interactions
- ▶ Response to treatment- paradoxical reactions
- ▶ Higher relapse of TB (~4 increased)
- ▶ Increased mortality (~4 fold)
- ▶ Impacts on response to treatment (regression of symptoms)

HIV



**Decreased
CMI**

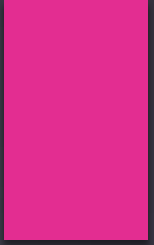


**Rapid
progression
to disease**

**↑Extra-pulmonary
involvement**

**Atypical
radiographic
manifestations**

**Pauci-bacillary
disease**



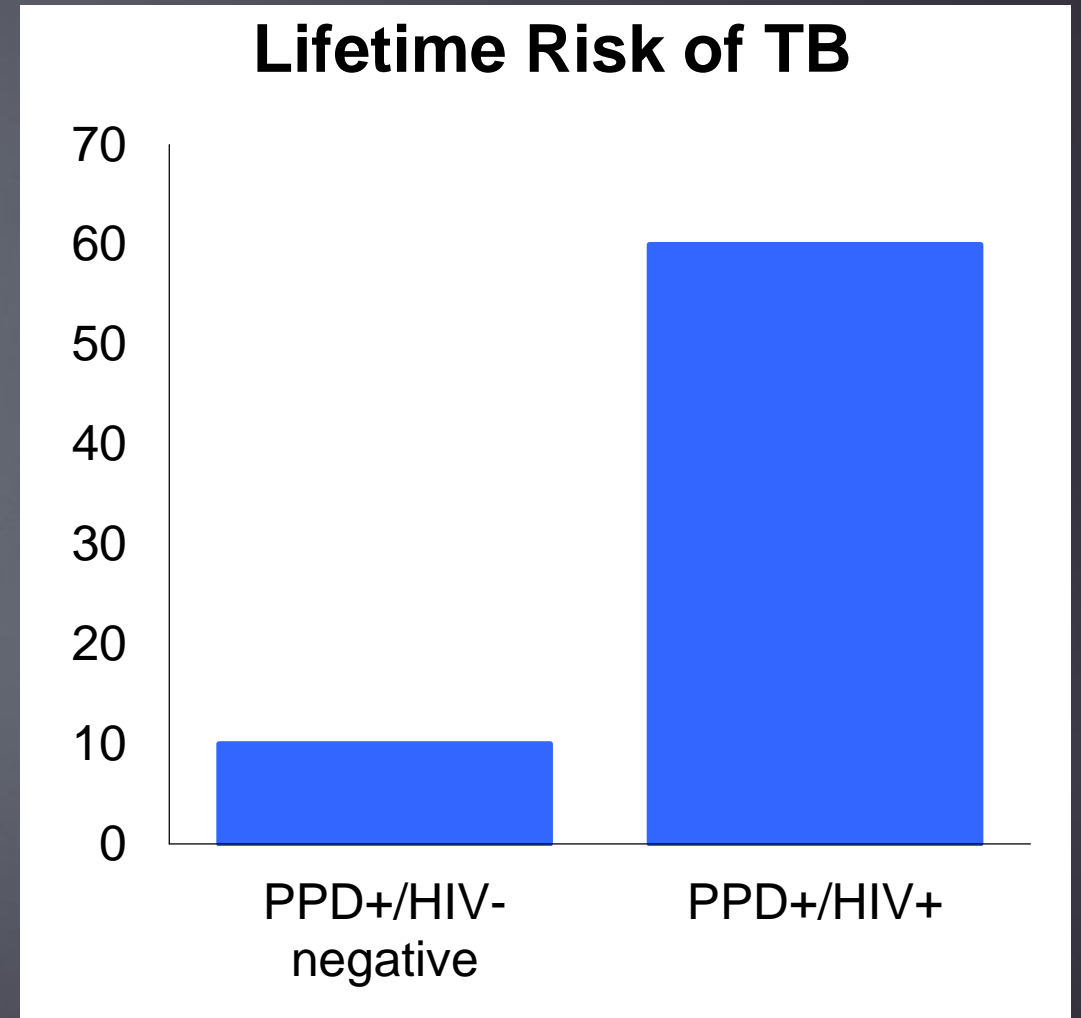
Risk of TB Disease

Risk Factor	Increase in risk of TB disease
HIV/AIDS	113-170
Diabetes	4.1
"old TB" on CXR	13.6
CRF	25
Other conditions	3-16

TB and AIDS

Without HIV lifetime risk of TB in infected person is ~ 10%

With HIV life time risk is 50%



Risk of TB is increased at **ALL** stages of HIV infection

- ▶ HIV affects CD₄ cells both **quantitatively** and **qualitatively**
- ▶ TB risk doubled first year after HIV seroconversion
- ▶ Following immune reconstitution with ART- risk remains above background risk of the general population

Symptoms of TB in HIV

- ▶ Cardinal symptoms are the same irrespective of HIV status

- ▶ Cough

- ▶ Fever

- ▶ Night sweats

- ▶ Weight loss

Sensitivity ~70-80% - 20% no symptoms but has TB

Specificity ~ 50%- 50% symptoms but no TB

- ▶ Low specificity due to other OI's with similar symptoms

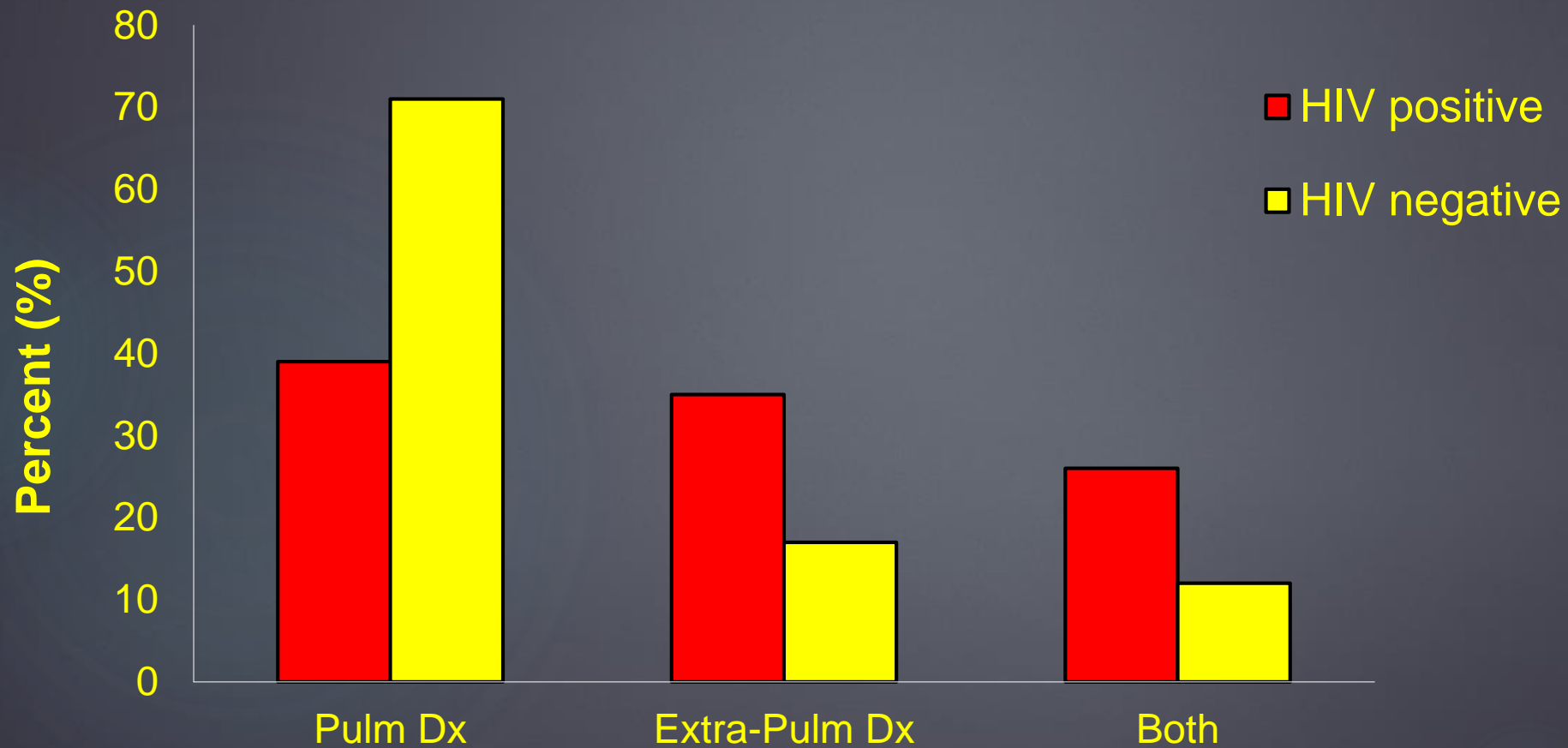
Symptoms of TB in HIV

- ▶ How reliable is the absence of symptoms to exclude TB?
 - ▶ Important to exclude TB prior to initiating ART or IPT
- ▶ Meta analysis of a symptom screening tool in HIV in RLS:
 - ▶ Prevalence 5% \Rightarrow NPV 97.7%
 - ▶ Prevalence 20% \Rightarrow NPV 90%
- ▶ Asymptomatic sub-clinical TB is not uncommon in regions of high co-infection
- ▶ **Active** TB may be missed by screening for symptoms alone

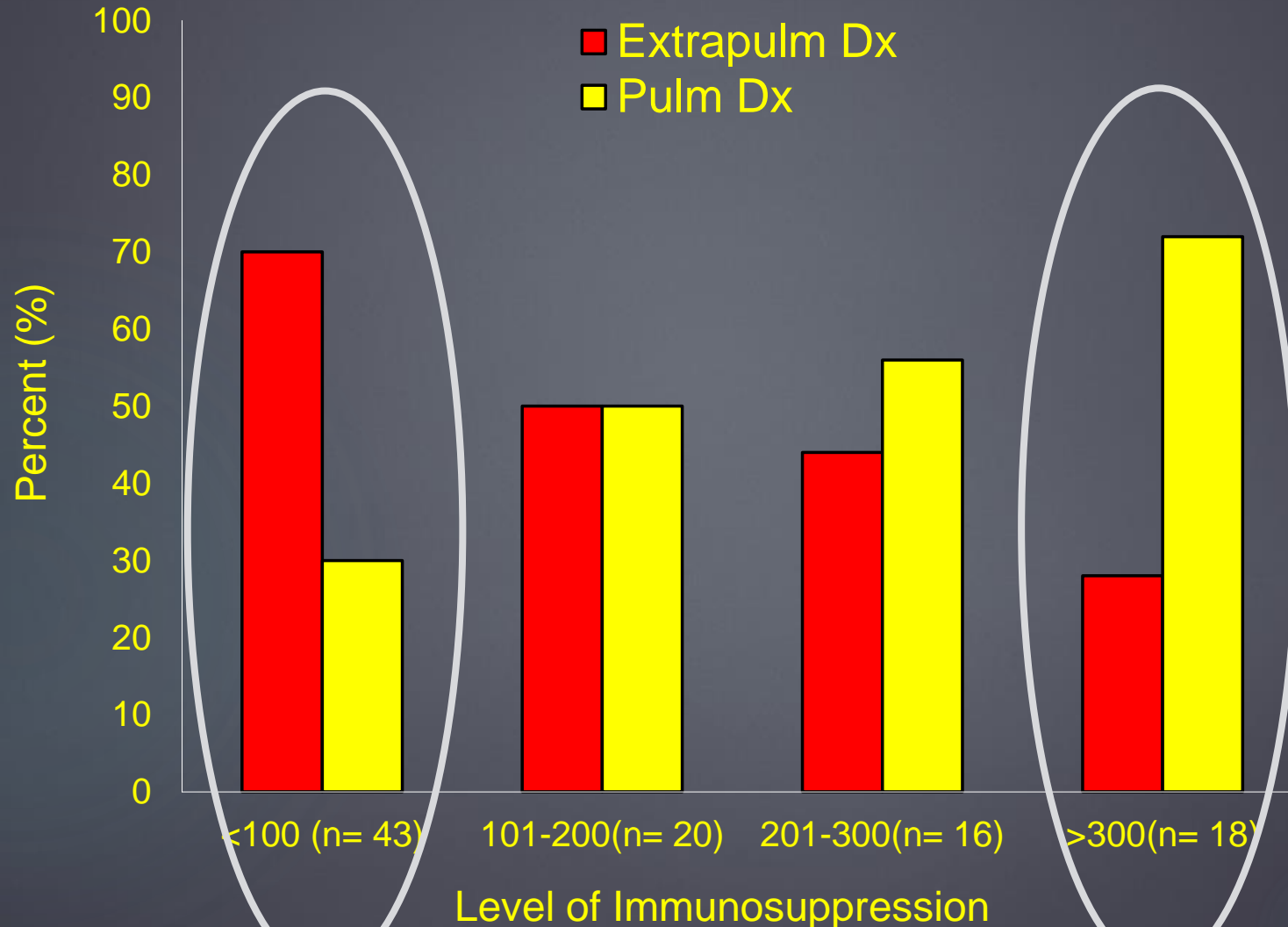
Clinical Presentation of TB

- ▶ Varies widely but is generally similar to HIV-uninfected
- ▶ Presentation often reflects the level of immunosuppression
- ▶ Earlier in HIV → classic reactivation-disease
- ▶ In advanced immunosuppression, may be similar to primary TB

Impact of HIV on organs involved by TB



Organ system involvement is related to the level of immunosuppression



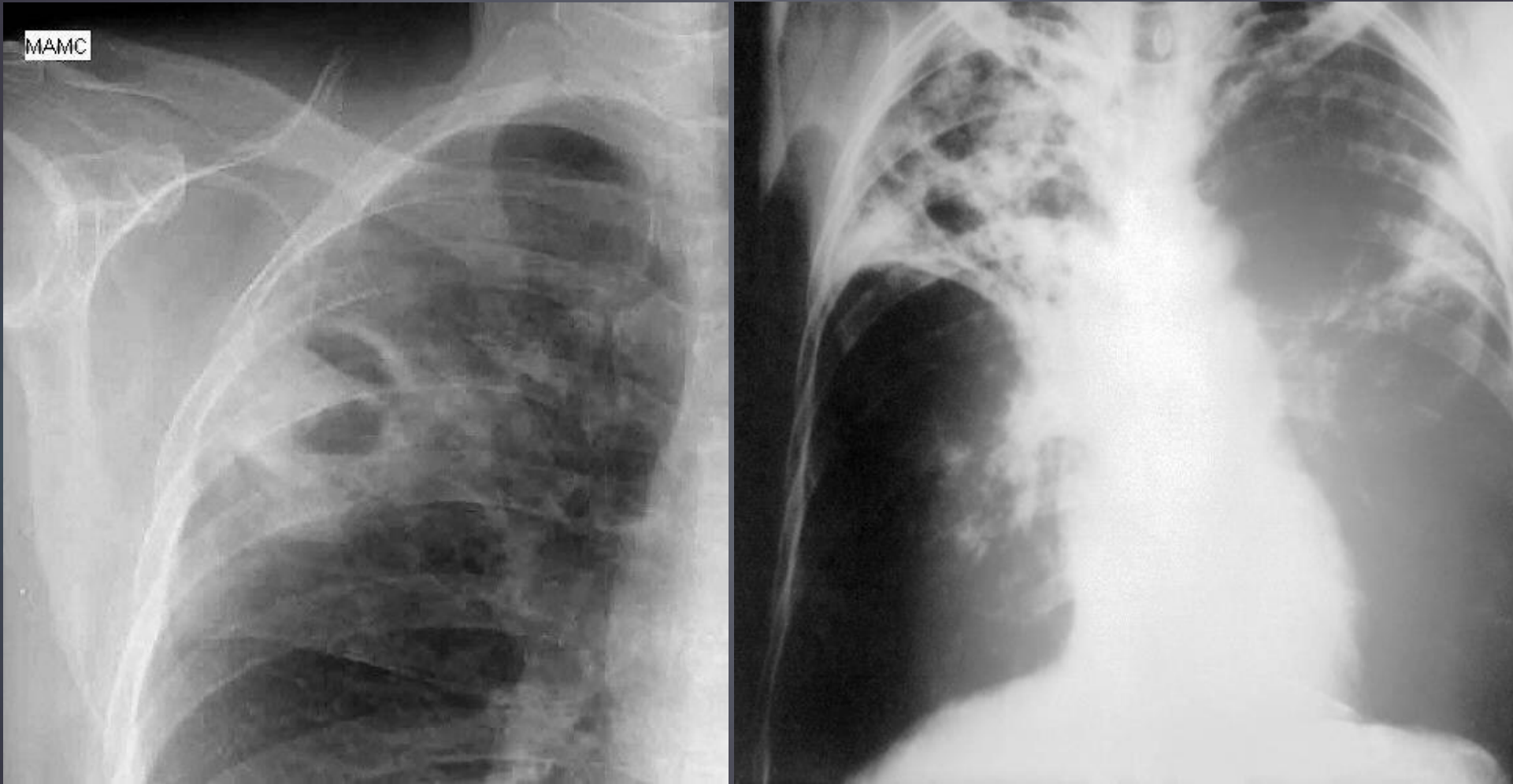
Common sites of extra-pulmonary TB

- ▶ Lymph node disease:
 - ▶ Peripheral - cervical > axillary > inguinal
 - ▶ Central - mediastinal > hilar, intra-abd
- ▶ Disseminated disease
- ▶ Serositis- pleural, pericardial > ascites
- ▶ CNS- meningitis, tuberculoma
- ▶ Soft tissue abscesses

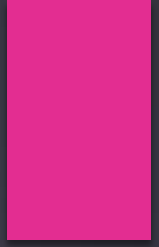
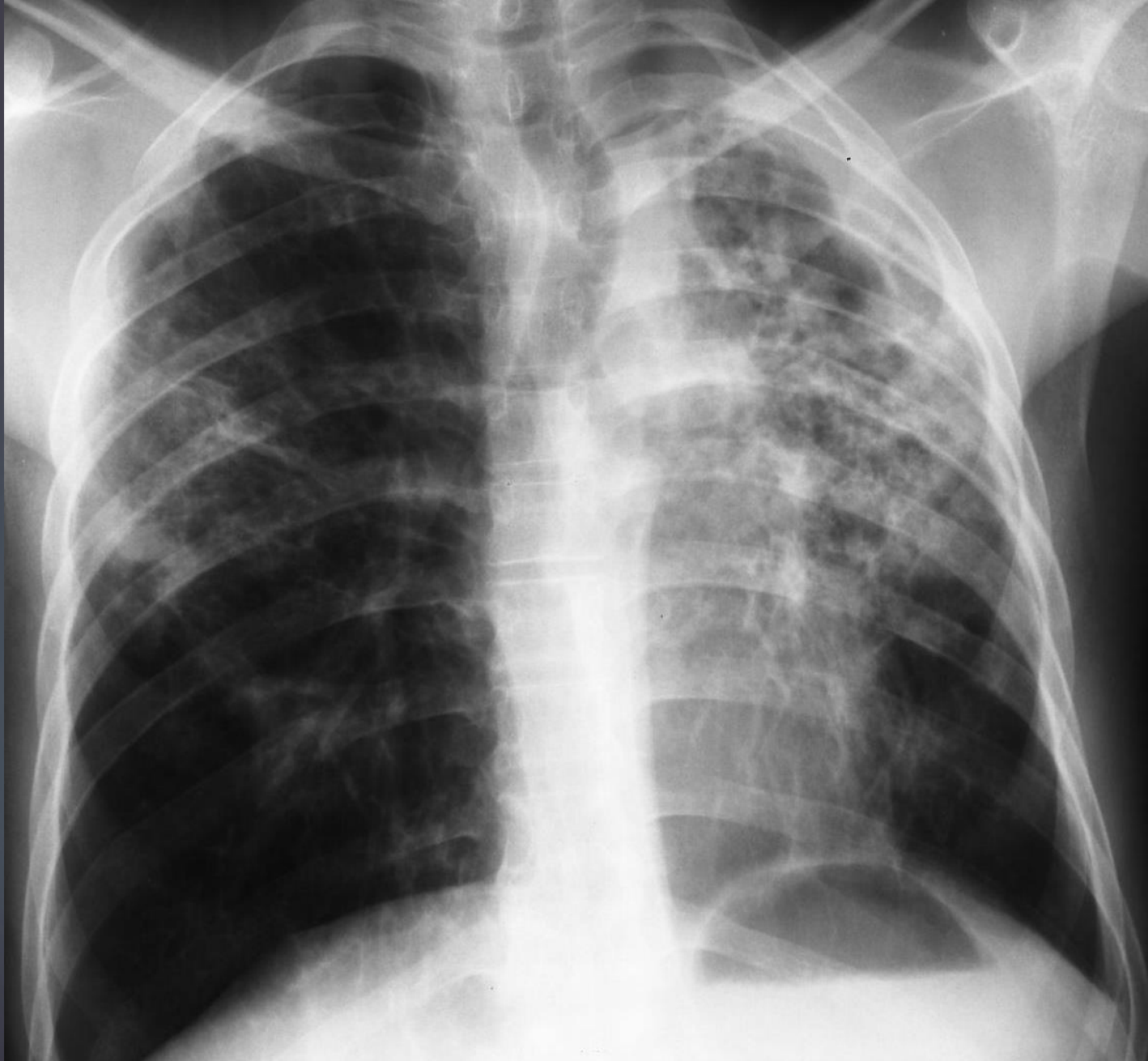
DIAGNOSING TB

“The chest radiograph the
cornerstone of diagnosis for
pulmonary TB”

Reactivation (Post-Primary/Secondary) TB

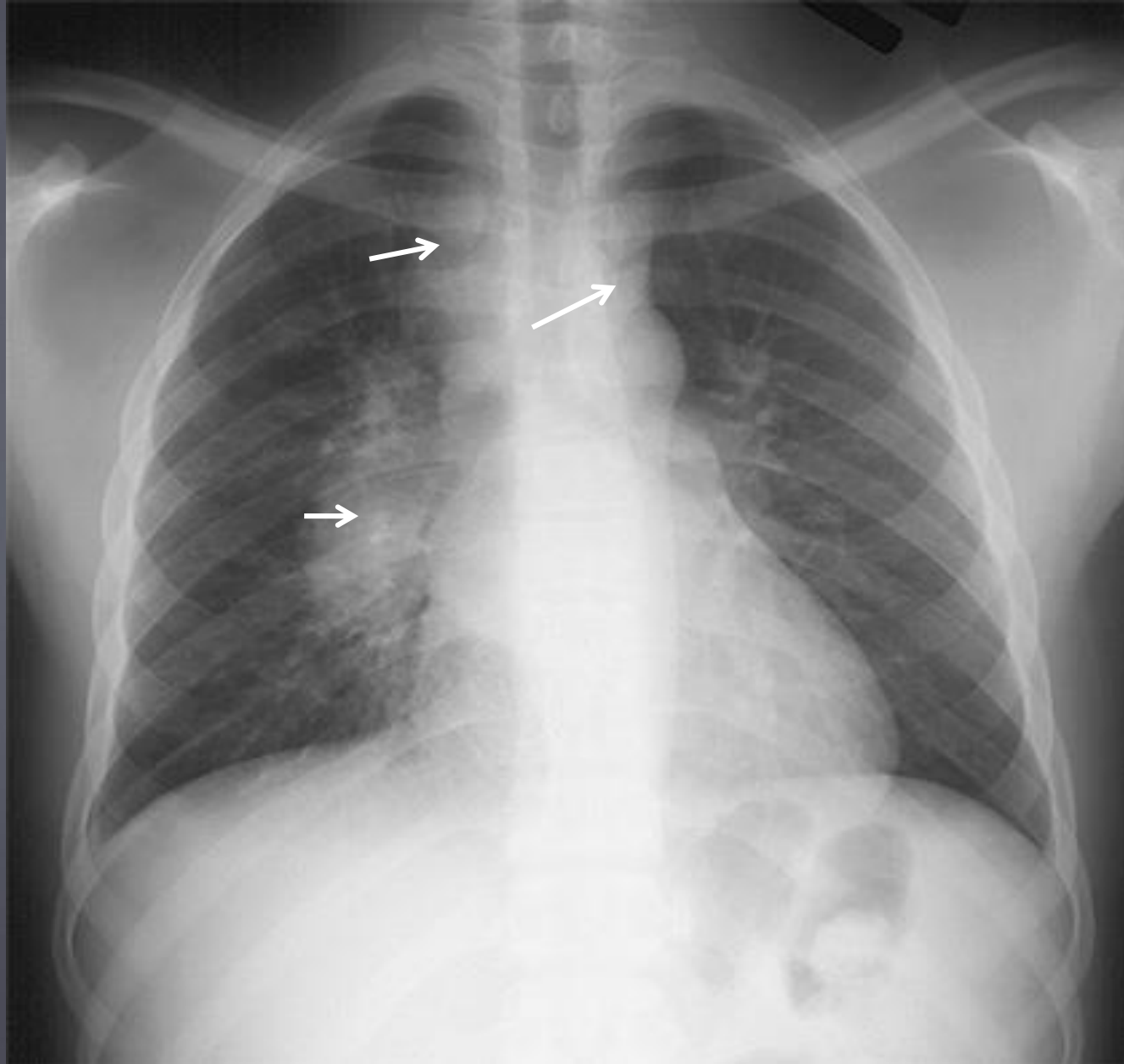


Reactivation (Post-Primary/Secondary) TB



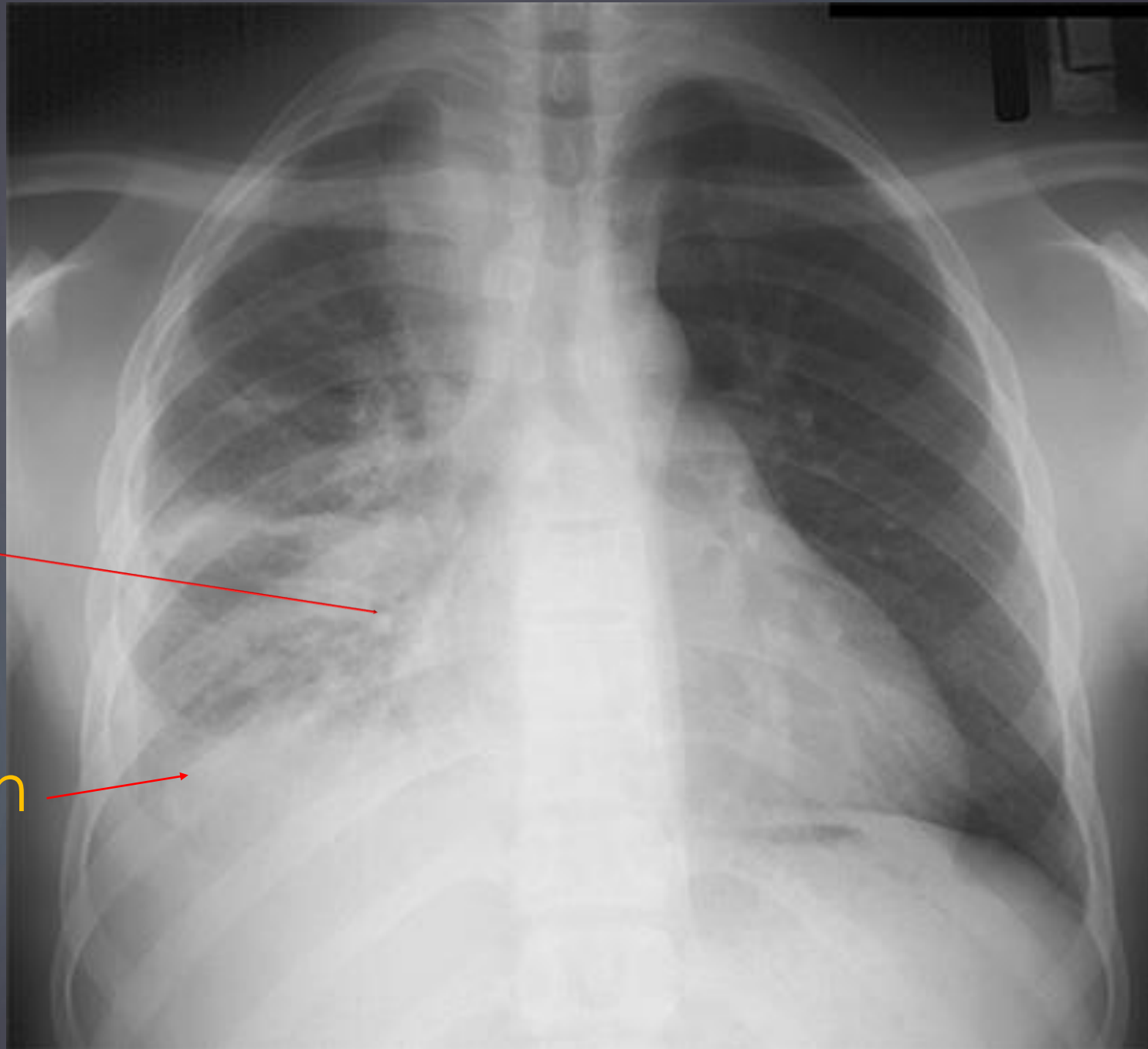
AIDS/TB Chest X-ray

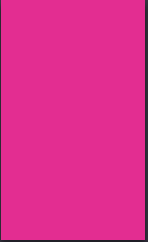
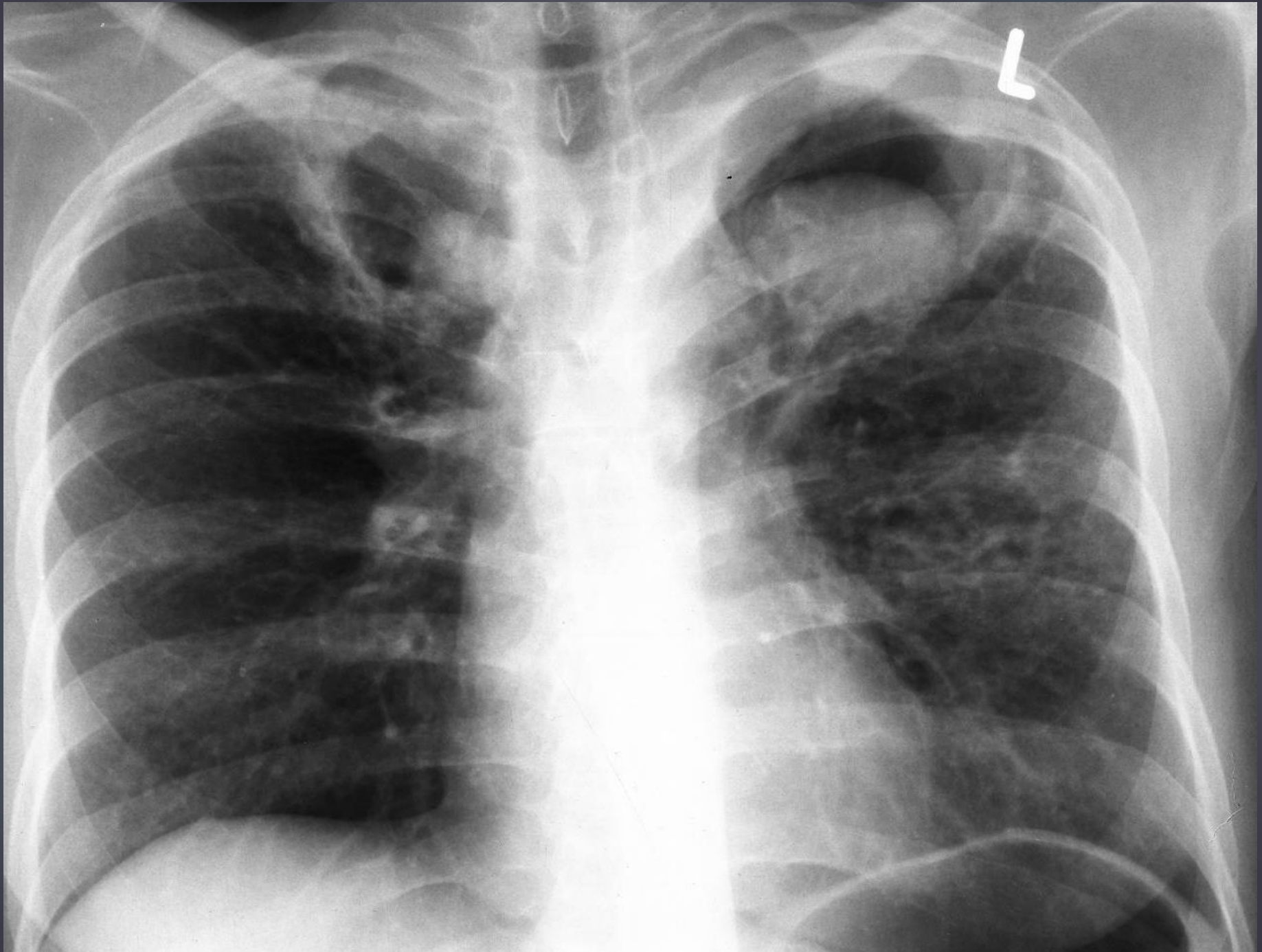
Bilateral hilar/
mediastinal LAD



RML Infiltrate

Pleural Effusion





The chest radiograph is **no** longer the
cornerstone for diagnosis of PTB

Chest radiographs may appear normal in up to
21% of culture-positive TB with CD4 <50

What is the role of the CXR in diagnosing TB

- ▶ Sensitive ~76%
 - ▶ Specificity ~68%
- } Risk of over-/ under-diagnosing

▶ **When should you do a CXR?**

- ▶ Complications: pneumothorax, effusion, haemoptysis
- ▶ Co-existent lung disease
- ▶ Smear negative patient with strong suspicion of TB

How to diagnose TB

▶ Symptoms

▶ Signs

▶ Ancillary Investigations:

■ CXR

■ Hb

■ Albumin

■ ESR

■ CRP

- Sensitive but not specific
- Unhelpful for diagnosis
- Helpful for monitoring response to Rx

Diagnosing TB: Detect organism or DNA

- ▶ Microscopy
- ▶ Culture
- ▶ PCR-based assays

AFB Smear- Microscopic examination for AFB

- Historically mainstay for the diagnosis of TB
- High specificity
- Rapid turn around time
- BUT low sensitivity- non-cavitatory disease with HIV (~35%)
- Require a minimum of 10,000 AFB/ml of sputum for smear to be positive

TB Culture

- ▶ Makes definitive diagnosis of TB
- ▶ Detects fewer AFB: limit 10-100 org/mL (100-1000x more sensitive than smear)
- ▶ Time to positivity depends on org. load- median time 3 weeks
- ▶ Expensive, need skill technologists, infrastructure
- ▶ Estimated ~ 15% of reported TB cases are culture negative
 1. MGIT culture identifies 71% cases
 2. MGIT increase yield to 88% (17% increase)
 3. MGIT identifies 98% cases (10% more cases)

} Depends on the number of times the culture is repeated

When should you send for culture?

- ▶ Suspected TB with negative GeneXpert test
- ▶ To confirm GeneXpert showing Rifampicin resistance
- ▶ To check susceptibility to other drugs
- ▶ Patient failing treatment despite RIF susceptibility-
high suspicion of resistance to other drugs

Molecular tests

There are 2 different molecular based tests available:

1. GeneXpert (GXP)
2. Line Probe assay

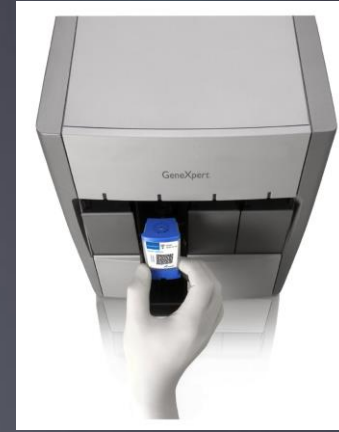
GeneXpert

- ▶ Automated PCR based
- ▶ Replaced sputum smear as rapid screening tool
- ▶ Allows rapid diagnosis AND processing time ~ 2hours
- ▶ Uses sputum - minimal pre-processing prior to loading instrument
- ▶ Validated for CSF, gastric aspirate, L/N aspirate and tissue (i.e. pleural biopsy)
- ▶ Instrument is a closed system → low risk for contamination, minimal expertise required, low risk for human error
- ▶ Detects TB & RIF Ω

GeneXpert

	Sensitivity	Specificity
Smear positive disease	98.2%	99.2%
Smear negative disease – one sample	72.5%	
Smear negative disease – 3 samples	90.2%	
Rifampicin Susceptibility	97.6%	
Rif resistance	98.1%	

Drawbacks to GeneXpert



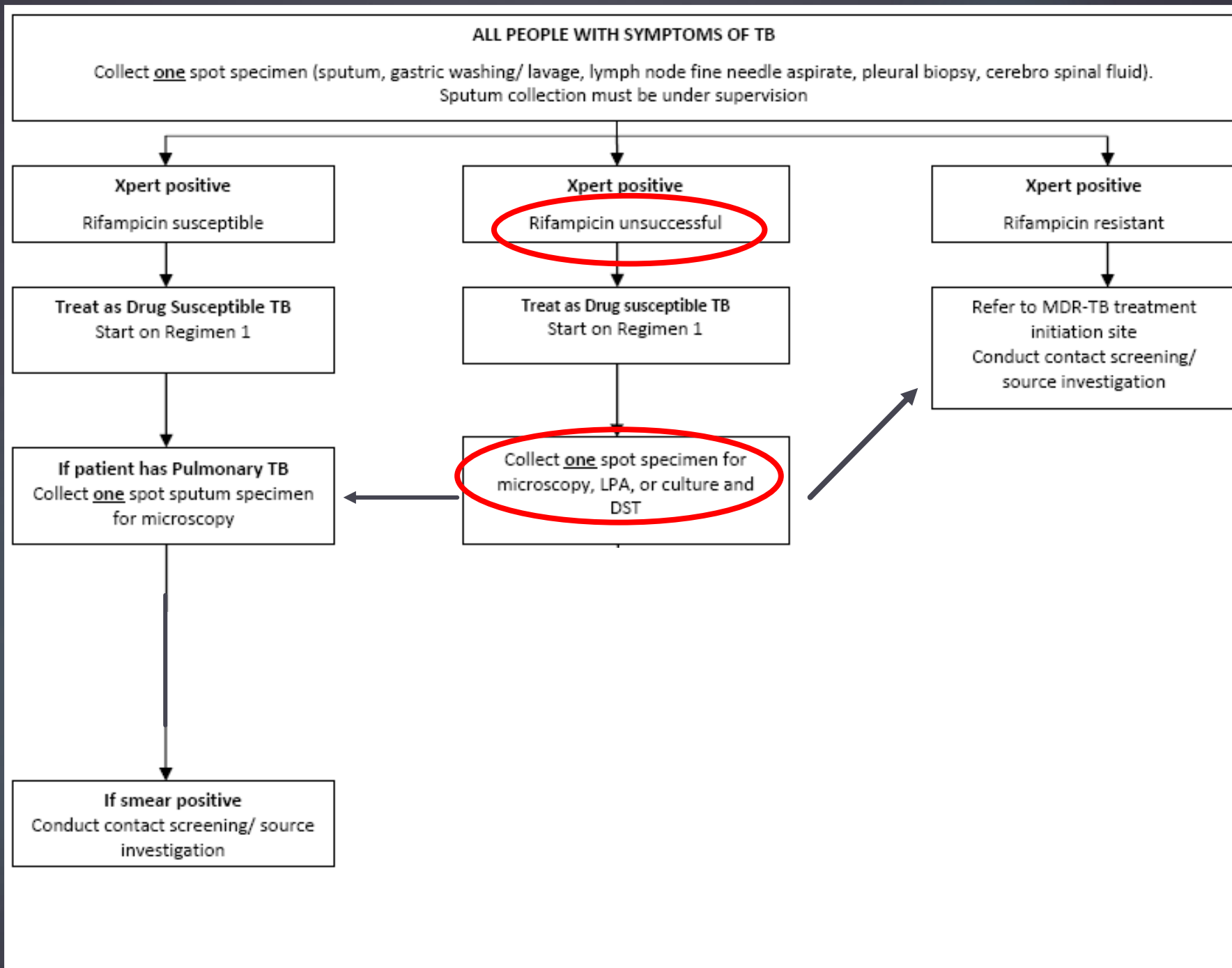
- ▶ **Not** a monitoring tool
 - ▶ High rate of false positivity in previously treated TB (27% GXP positive after 6/12 ATT)
- ▶ Cannot identify XDR TB
- ▶ Detects a minimum of ~130 org/ml sputum

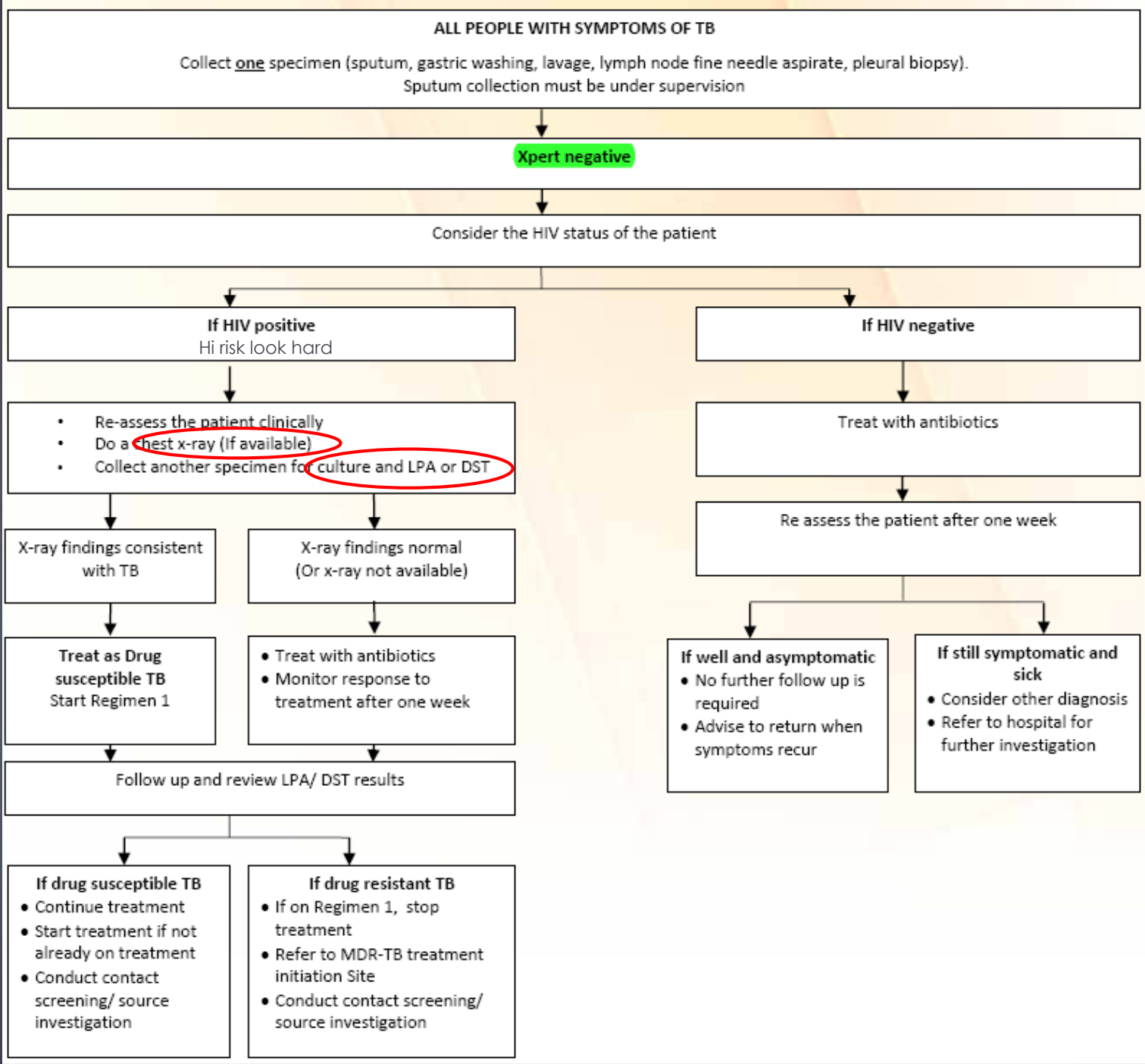
Line Probe Assay

- ▶ Direct testing on smear positive specimens and isolates from solid and liquid culture for smear negative
- ▶ PCR based – identifies MTB and specific mutations to RIF and INH resistance
- ▶ Results within 48 hours in lab- 7 days in health facilities
- ▶ Guide whilst awaiting phenotypic tests: 6-8wks
- ▶ Labour intensive, prone to contamination, human error, highly trained staff, special equipment & infrastructure

SA TB programme

Approach to the diagnosis of TB centered on GXP due to the high burden of HIV and MDR-TB





Treatment

- ▶ 6 months standard therapy is adequate
- ▶ Longer treatment may ↓ relapse – no RCT
- ▶ ART is recommended during TB therapy regardless of the CD4 cell count : ↓ mortality ↓ HIV progression
- ▶ Overlapping toxicities & drug-drug interactions with ARVs requiring dose modification, alternate regimens and alternate rifamycins

TB treatment on Anti-retrovirals

- Use standard first line treatment:
 - TDF/3TC/EFV
 - EFV is preferred over NVP
- On LPV/r second line ART:
 - Double dose LPV/r

Toxicity

- ▶ Side effects are twice as common in HIV co-infected (26 vs. 13%)
 - ▶ Hepatotoxicity
 - ▶ Peripheral Neuropathy
 - ▶ Vomiting
 - ▶ Arthralgia
 - ▶ Rash
- ▶ Peripheral neuropathy: INH, stavudine, didanosine
- ▶ DILI - INH, rifampin, pyrazinamide, NRTIs, NNRTIs, and PIs

Timing of ART with TB

- ▶ If $CD4 \leq 50$ start ART within 2wks of initiating anti-TB treatment
- ▶ This will reduce AIDS progression and mortality

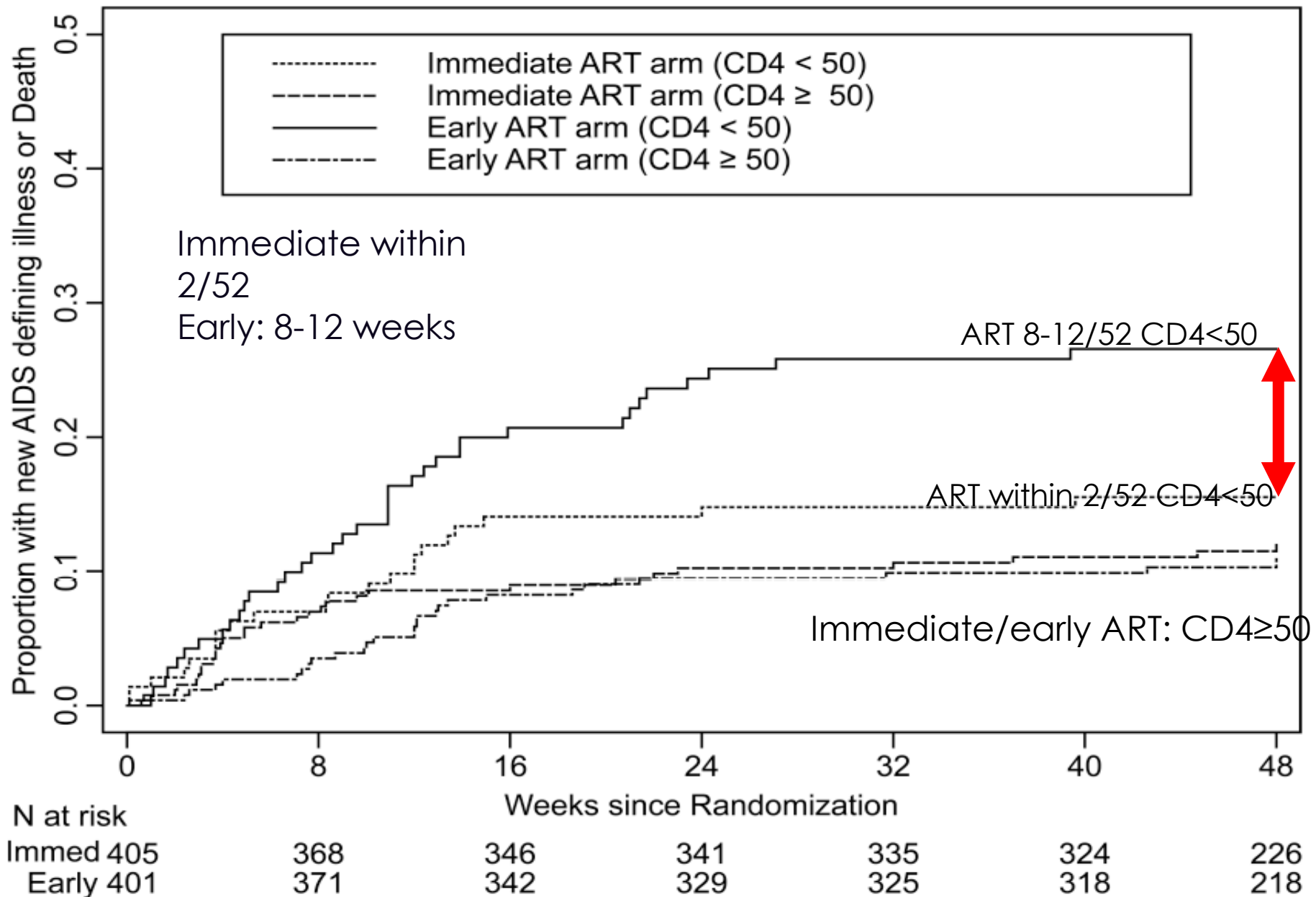


Figure 2. Time to New AIDS Defining Illness or Death

Timing of ART in TB

- ▶ If CD4 >50, start ART after intensive phase of TB treatment
 - ▶ Reduced overlapping toxicity, reduce the risk of IRIS
- ▶ Early ART requires:
 - ▶ Co-ordination between TB and HIV care
 - ▶ Vigilance for drug toxicities
 - ▶ Adherence to high pill burden
 - ▶ Vigilance for IRIS

Isoniazid Preventive Therapy (IPT)

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Exclude active TB

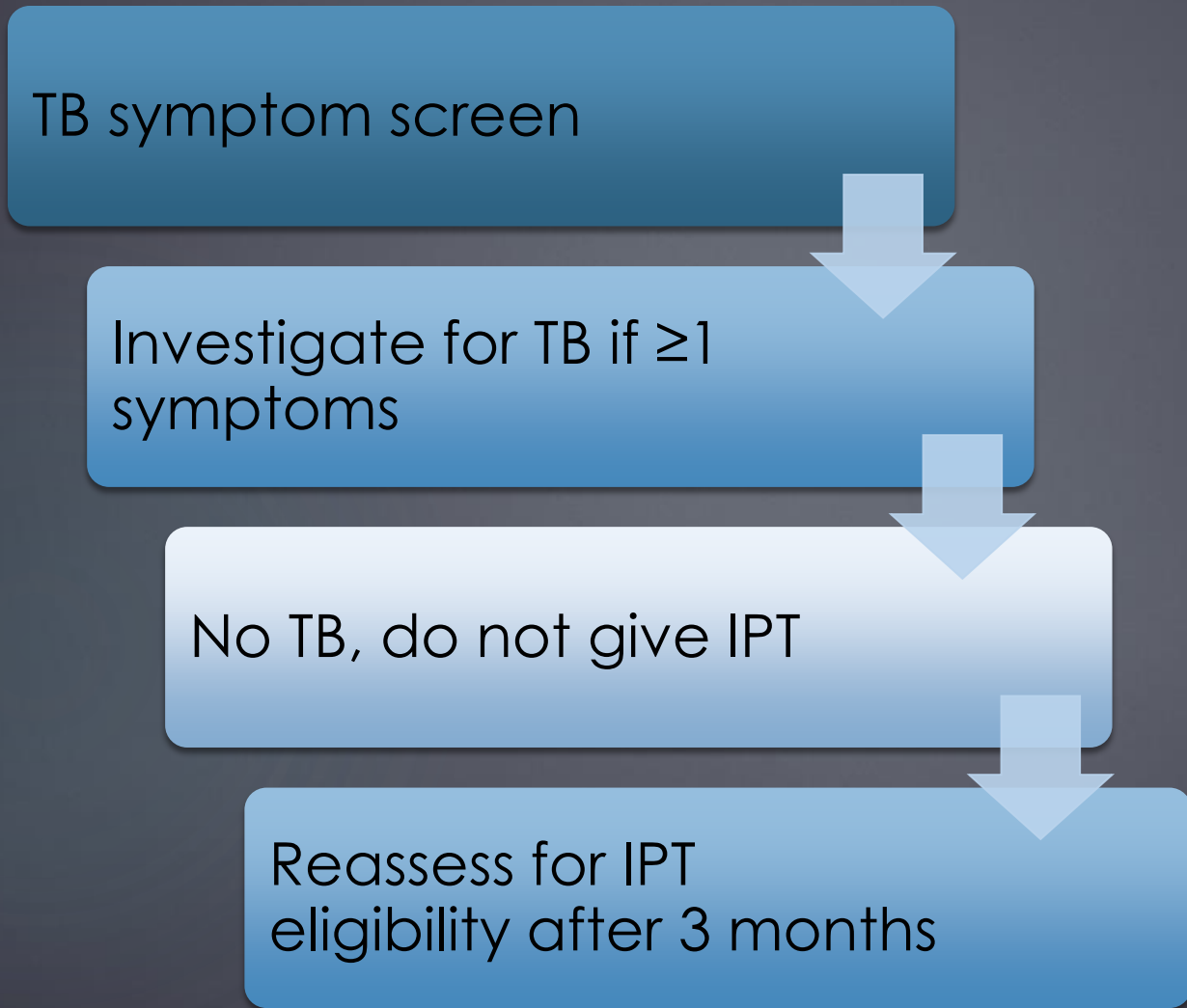
Confirm IPT eligibility

TST to determine duration

Start IPT and pyridoxine

Monitor adherence and SEs
Screen for TB at every visit

Exclude active TB



TB symptom screen
Current cough, any duration
Persistent fever >2 weeks
Unexplained weight loss
Drenching night sweats

IPT provision

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TST result	IPT duration	
	PreART	On ART
TST not available*	6 months	6 months [12]
TST negative	No IPT	12 months
TST positive	36 months	36 months

*Where TST not available at IPT initiation, must be performed as soon as possible after IPT initiation (within 1 month)

- ▶ TST relies on competent immune response
 - ▶ Severely immunocompromised may not have reactive TST despite TB exposure
- ▶ Mantoux is recommended test
 - ▶ Inject a known amount of PPD between layers of skin
 - ▶ Measure reaction at injection site 48-72 hours later
- ▶ If TST negative, re-assess annually until it becomes positive

Questions

The GeneXpert test will show resistance to which of these anti-TB drugs?

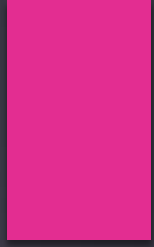
- A. Rifampicin
- B. Ethambutol
- C. Pyrazinamide
- D. Isoniazid
- E. All of the above

What adjustment needs to be made to 2nd line ARV treatment when treating drug-sensitive TB?

- A. Half the dose of Lop/rit
- B. Double the dose of Lop/rit
- C. Triple the dose of Lop/rit
- D. Double the dose of NRTI
- E. No adjustment is necessary

For patients with CD4 < 50 commenced on anti-TB treatment, after how long should ARVs be started?

- A. After 1 month
- B. After completion of intensive phase
- C. After 2 months
- D. Within 2 weeks
- E. Within 2 months



PCP

PCP

- ▶ *Pneumocystis jirovecii*
- ▶ Classified as a fungus but also shares biologic characteristics with protozoa
- ▶ Initial infection with *P. jirovecii* usually occurs in early childhood
- ▶ Disease occurs by new acquisition and by reactivation of latent infection
- ▶ Spreads by the airborne route
- ▶ Occurred in 70% to 80% of patients with AIDS- pre ART and prophylaxis

PCP

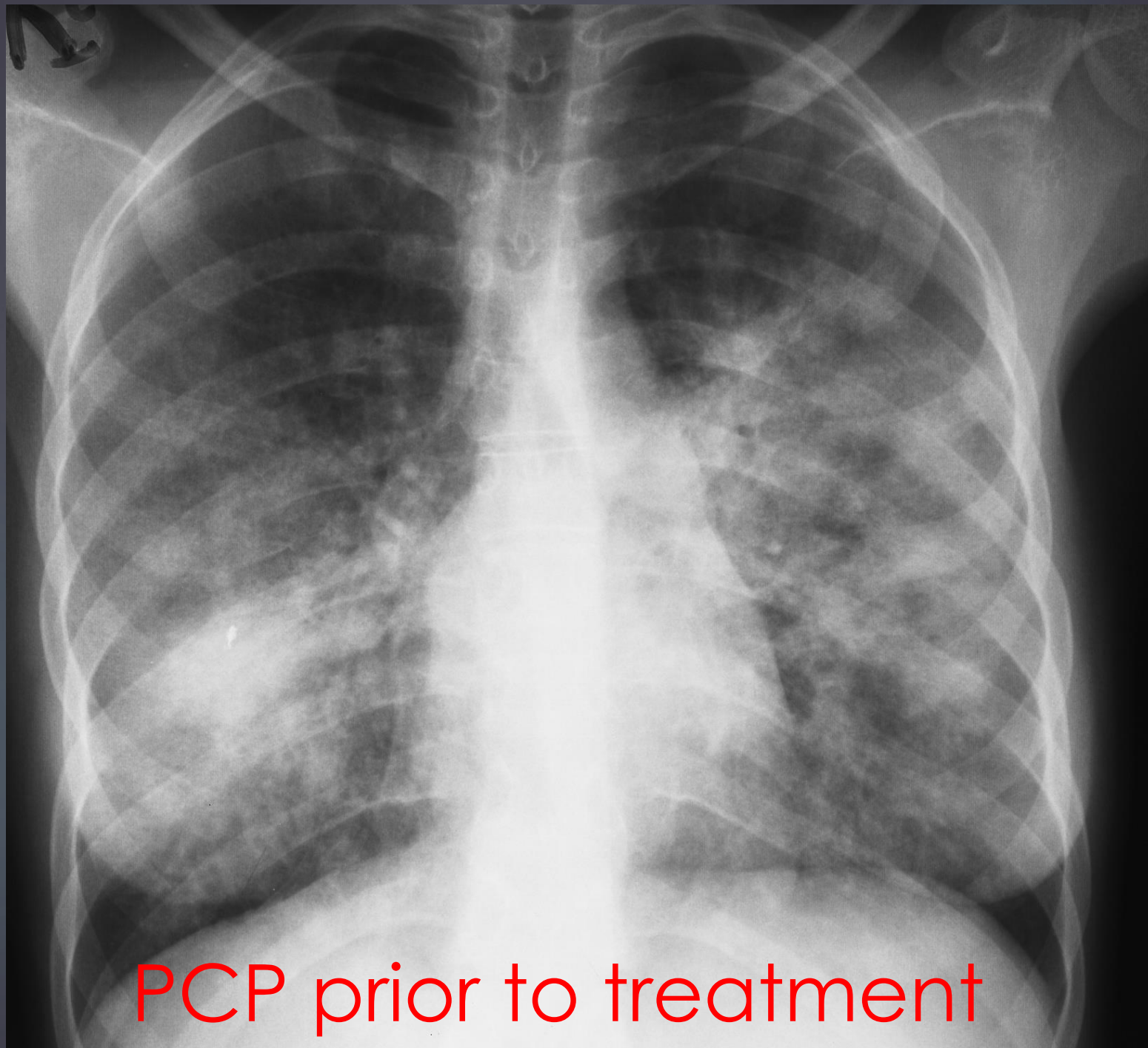
- ▶ 90% of PCP cases occur in patients with CD4 counts <200 cells/mm³
- ▶ Those at high risk
 1. CD4 cell percentage $<14\%$,
 2. Previous episodes of PCP
 3. Oral thrush
 4. Recurrent bacterial pneumonia
 5. Higher Viral Loads

PCP- Clinical presentation

- ▶ Subacute onset of progressive dyspnea
- ▶ Fever
- ▶ Non-productive cough
- ▶ Chest discomfort that worsens within days to weeks
- ▶ Pulmonary examination can be normal at rest
- ▶ With exertion, tachypnea, tachycardia, and diffuse crackle may be observed.

PCP Investigations

- ▶ Hypoxemia, the most characteristic laboratory abnormality
- ▶ Oxygen desaturation with exercise is often abnormal
- ▶ Elevated LDH- common but non specific



PCP prior to treatment



PCP Treatment

- ▶ TMP-SMX (Bactrim) treatment of choice
- ▶ Oral outpatient therapy with TMP-SMX is highly effective in patients with mild-to moderate disease
- ▶ Patients who have PCP despite TMP-SMX prophylaxis - can be treated effectively with standard doses of TMP-SMX
- ▶ Adjunctive corticosteroids indicated in moderate-to-severe disease within 72 hours after starting specific PCP therapy
- ▶ Severe defined by room air $pO_2 < 70$ mm Hg or Alveolar-arterial O_2 gradient ≥ 35 mm Hg
- ▶ Recommended duration of therapy for PCP is 21 days



PCP: 6 days into Cotrimoxazole

Cotrimoxazole preventive therapy

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When to start

CD4 count <200 cells/mm³
WHO stage 2, 3 and 4
HIV/TB coinfection

Reduces hospitalisation and morbidity
Protects against PCP, toxoplasmosis, malaria and bacterial infections

Benefit outweighs risk in pregnancy therefore continue in pregnant women

Maculopapular rash most common SE. Continue or stop and restart for mild rash

When to stop?

When to restart

CD4 drops <200
ART fails
New OI

160/800 mg daily
Monitor clinically at 3 monthly intervals

Safety of CPT

Neutropaenia is rare SE. Routine FBC monitoring not required

Can use dapsone 100 mg unless severe reaction (cross reactivity)
Less cover

Do not delay ART in favour of cotrimoxazole initiation

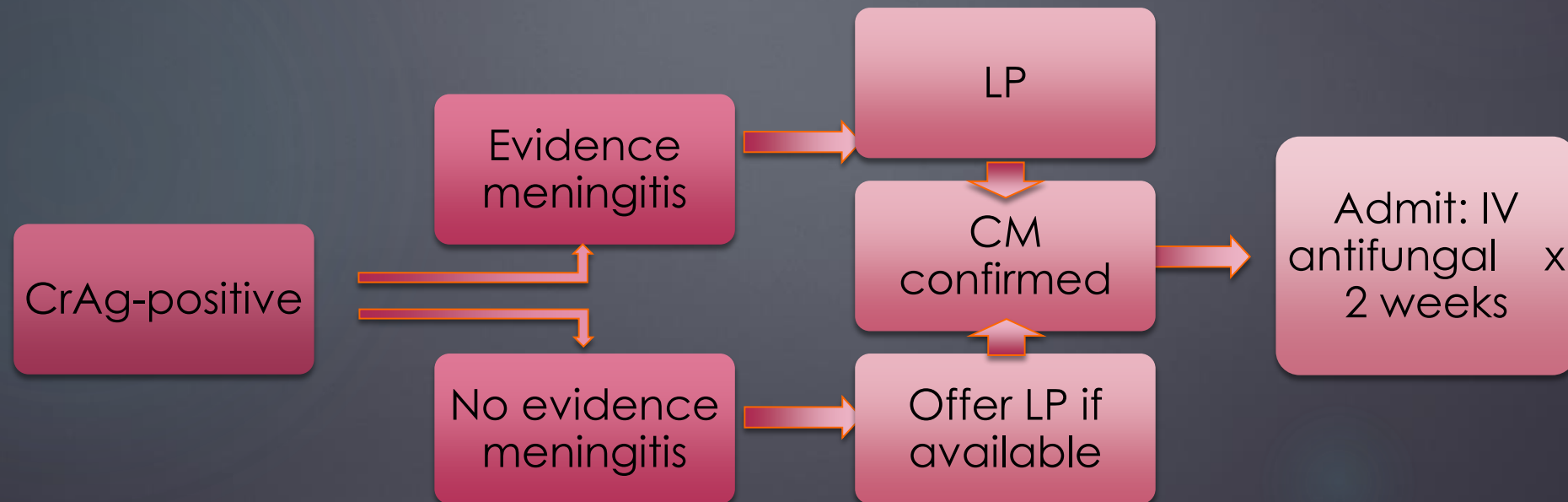
Cryptococcus infection

Cryptococcal infection

- Caused by *Cryptococcus neoformans* in South Africa
- Clinical presentation
 - Usually subacute meningitis or meningoencephalitis (CCM)
 - Symptoms of fever, malaise, and headache
 - Neck stiffness and photophobia in only 1/3 of patients
 - Other symptoms secondary to raised ICP

Cryptococcal infection

- ▶ Screen patients with CD4 count <100 cells/mm³ for cryptococcal disease BEFORE initiating ART (CrAg)
- ▶ CrAg-positive indicates disseminated cryptococcal disease
 - ▶ Evaluate for symptoms/signs of meningitis



CCM Diagnosis

- ▶ Common CSF findings
 - Elevated protein
 - Low-to normal glucose concentrations
 - Pleocytosis consisting mostly of lymphocytes
- ▶ Increased opening pressures ≥ 25 cm H₂O
- ▶ Gram's stain or India ink may demonstrate numerous yeast forms
- ▶ CrAg positive on CSF

CCM Treatment

- ▶ Induction therapy: **2 weeks** with Amphotericin B **and** Fluconazole 800mg daily
- ▶ Consolidation therapy: **8 weeks** with Fluconazole 400mg daily
- ▶ Maintenance/Continuation therapy: 200mg Fluconazole daily for at least **1 year**

Cryptococcosis

Summary recommendations		
Clinical picture	Antifungal treatment	ART
CrAg-positive but no evidence of meningitis	Oral fluconazole (800mg/day x 2 weeks; standard consolidation and maintenance antifungal treatment	Start after 2 weeks antifungal treatment
CrAg-positive with evidence of meningitis	IV antifungal treatment x 2 weeks; standard consolidation and maintenance antifungal treatment	Start after 4-6 weeks antifungal treatment

- **WOCBA: if CrAg-positive, do pregnancy test before starting fluconazole (teratogenic)**
- **All CrAg-positive PREGNANT women should be offered LP**
 - Discuss with expert before deciding management
- **Fluconazole may cause liver injury**
 - Monitor patients with evidence of liver disease carefully

When do we stop maintenance therapy?

Chronic antifungal maintenance therapy can be stopped if:

- CD4 counts are ≥ 200 cells/ μL , or
- CD ≥ 100 cells/ μL who have undetectable viral loads on ART for >3 months

Acute OIs and Timing of ART

- ▶ Early ART outweighs risk
 - ▶ Oesophageal candidiasis
 - ▶ Crypto/microsporidiosis
 - ▶ PML
 - ▶ KS
 - ▶ PCP
 - ▶ Serious bacterial infections
 - ▶ TB
- ▶ Early ART be beneficial or harmful
 - ▶ Toxoplasmosis
 - ▶ TB meningitis
- ▶ Early ART is harmful
 - ▶ Crypto meningitis

When to Start ART During Acute Opportunistic Infections: IAS–USA Recommendations 2012

- ▶ Start ART as soon as possible, preferably within the first two weeks (A1a) except for TB and cryptococcal meningitis as indicated below:
 - ▶ Patients with cryptococcal meningitis should be managed in consultation with experts (BIII)
 - ▶ Patients with TB should start TB treatment first; start ART as soon as possible but within the first 2 weeks for those with CD4 < 50 cells/ μ L
 - ▶ Within the first 2-8 weeks of TB treatment for those with TB meningitis
 - ▶ Within the first 8-12 weeks of TB treatment for others

Questions

What is the correct duration of treatment for *Pneumocystis jirovecii* pneumonia?

- A. 5 days
- B. 7 days
- C. 14 days
- D. 21 days
- E. 28 days

After a year of treatment, when is it appropriate to stop secondary Cryptococcal prophylaxis?

- A. Once CD4 > 500
- B. Once CD4 > 350
- C. Once CD4 > 200
- D. Keep on treatment lifelong
- E. Once CD4 > 50

References

- ▶ Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. Downloaded from <http://aidsinfo.nih.gov/guidelines/10/4/2016>
- ▶ “Tuberculosis and HIV” HIV InSite Knowledge Base Chapter, January 2013. Annie Luetkemeyer, MD, University of California San Francisco. Original chapter written by Lisa Goozé, MD, and Charles L. Daley, D, University of California San Francisco

Acknowledgements

- ▶ Prof MYS Moosa, Dept of Infectious diseases. UKZN
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MDR-TB BOOKING



***Toll Free Number**

0801 515 155

***Standard cellular rates apply to calls from cellphones**

or

send a "Please Call Me" to:

076 076 8803

- The helpline provides assistance for the inpatient/outpatient booking of MDR-TB patients to King Dinuzulu Hospital
- Available Monday to Fridays, 8:00 am to 3:30 pm
- Free from any Telkom landline in South Africa

Dept. of Infectious
diseases hotline:
0636825888