TB & HIV: The Terrible Twins

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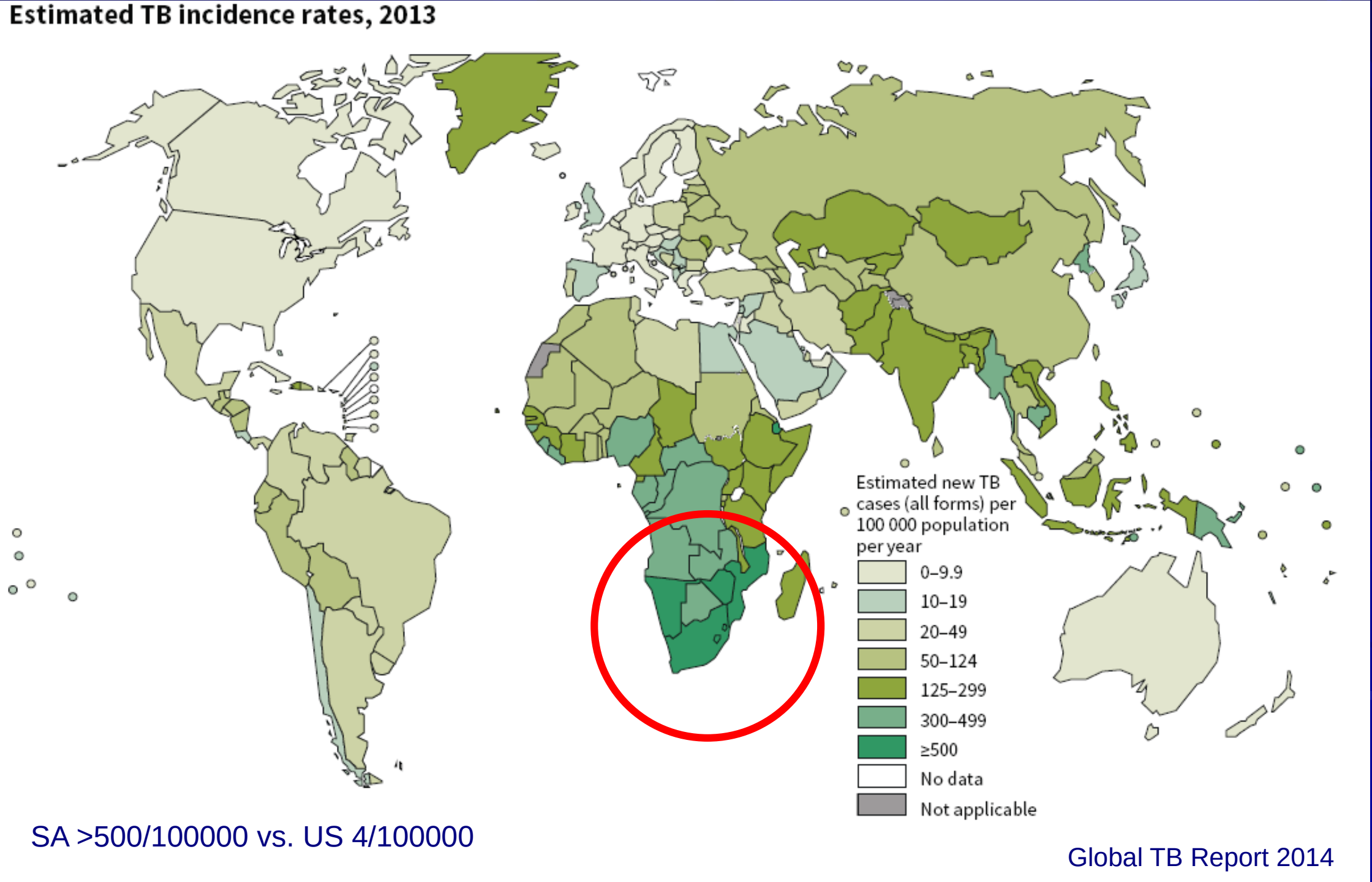
Epidemiology of HIV-Related Tuberculosis

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

World Health Organization. WHO Report 2011: Global Tuberculosis Control. 2011



SA >500/100000 vs. US 4/100000

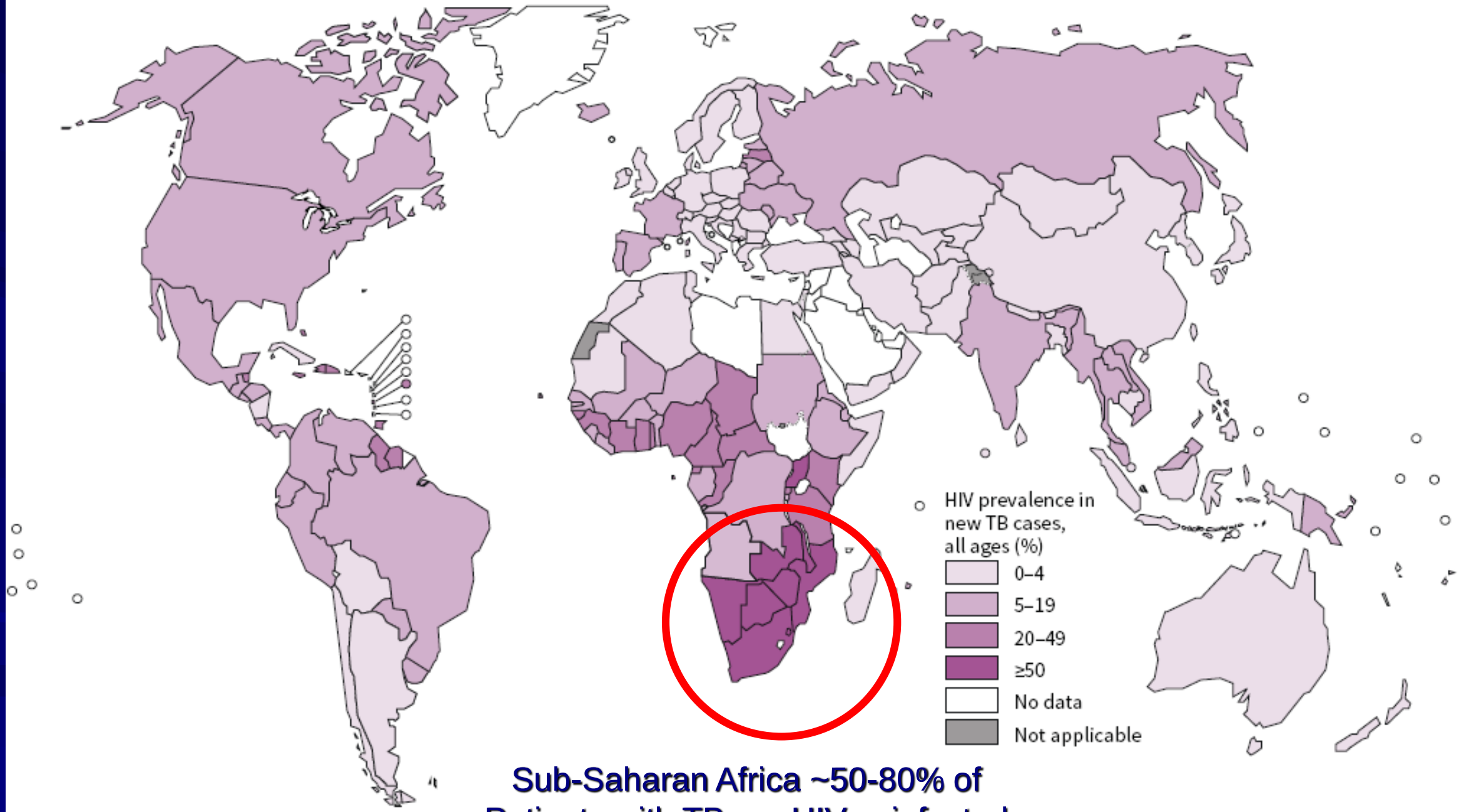
Global TB Report 2014

Epidemiology of HIV-Related Tuberculosis

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

JAMA;273:220-226, Trans R Soc Trop Med Hyg.;101(9):893-8.

Estimated HIV prevalence in new and relapse TB cases, 2013



Sub-Saharan Africa ~50-80% of Patients with TB are HIV coinfected

Global TB Report 2014

TB and HIV

- TB is essentially an Immunologic disease with host tissue damage occurring during immune response to MTB
- HIV by “interfering” with the immune system alters the response to TB and fuels TB
- Converts TB into an “new” disease almost unrecognizable by clinicians familiar with TB in the pre-HIV era.
- Understanding the interactions between TB and HIV is critical to the management of both HIV and TB

Outline of Presentation

- Impact of TB on HIV
- Impact of HIV on TB

- **Presentation** of TB in coinfected
- **Diagnosing** TB in the coinfected
- **Treatment** of TB in the coinfected

- Timing of ART in TB
- Immune Reconstitution Inflammatory Syndrome

Impact of TB on HIV

- TB increases risk of HIV progression and death esp. with untreated HIV disease
- Immune activation → increases expression of HIV co-receptors on CD4 cells -CCR5 and CXCR4- increase substrate for viral infection and virus production
- TB coinfection associated with higher HIV viral loads

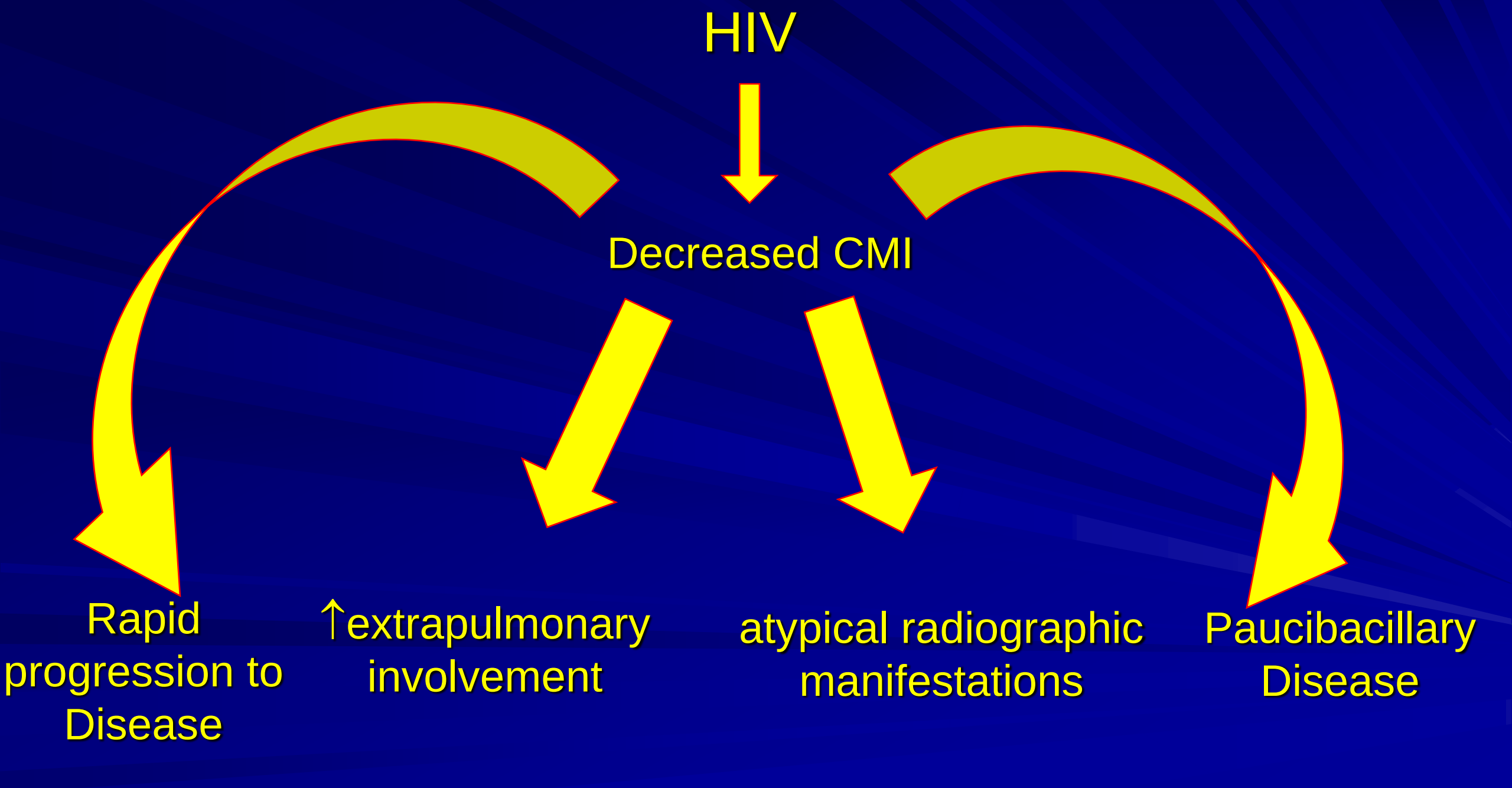
JAIDS;39(3):265-71, IJTLD;5(3):225-32, AJE;165(10):1134-42

Impact of HIV on TB

- HIV mimics TB.
- Alters pathogenesis of TB
- Causes rapid progression from infection to disease
- Alters clinical presentation.
- Alters radiological appearance.
- Affects diagnostic tests.
  - Smear, culture
  - Histology

< 50% of cases diagnosed ante mortem

- 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
↑extrapulmonary involvement
atypical radiographic manifestations
Paucibacillary Disease

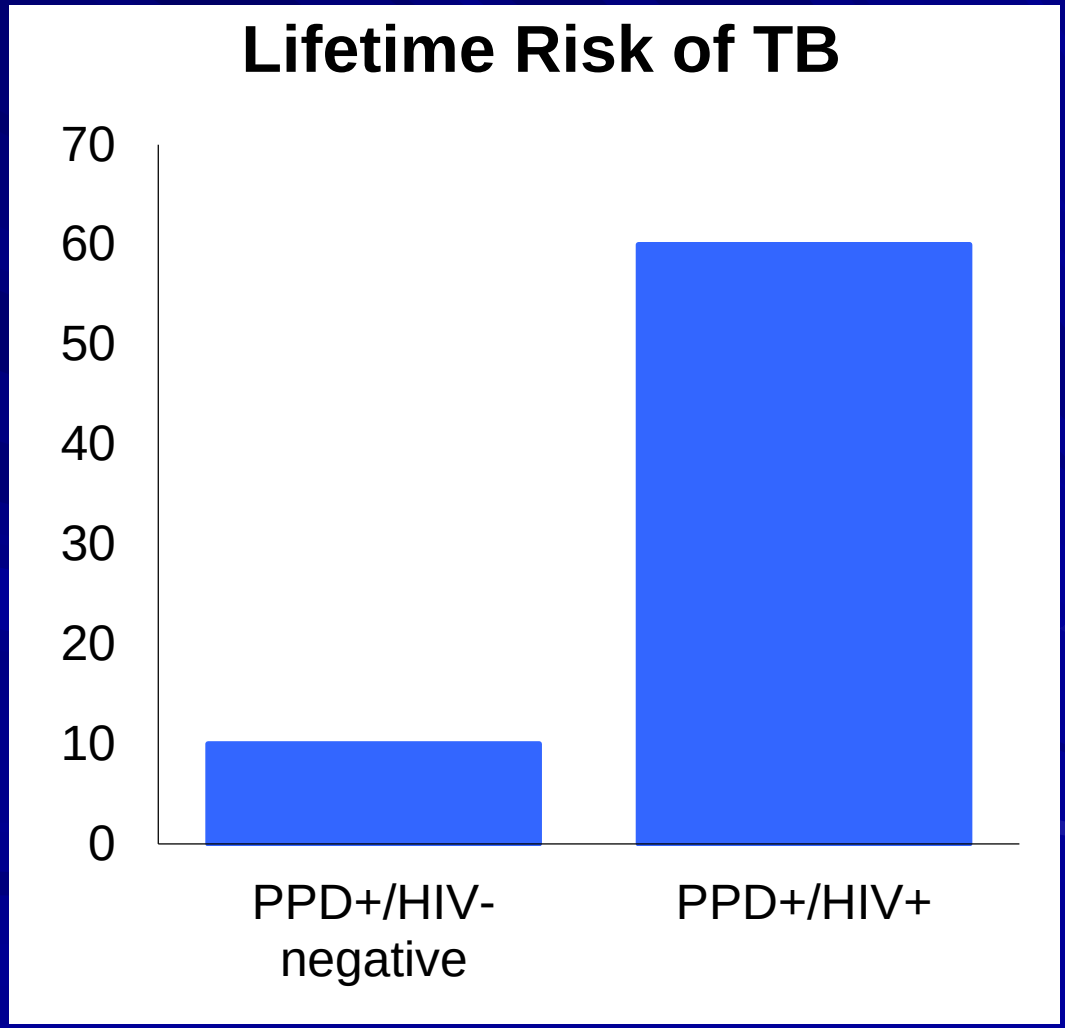
Risk of TB Disease

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 in the first year after HIV seroconversion
- Following effective immune reconstitution with ART the risk remains above the background risk of the general population.

J Infect Dis.191(2):150-8.

Symptoms of TB in HIV

- Cardinal symptoms are 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 OIs with similar symptoms

Symptoms of TB in HIV

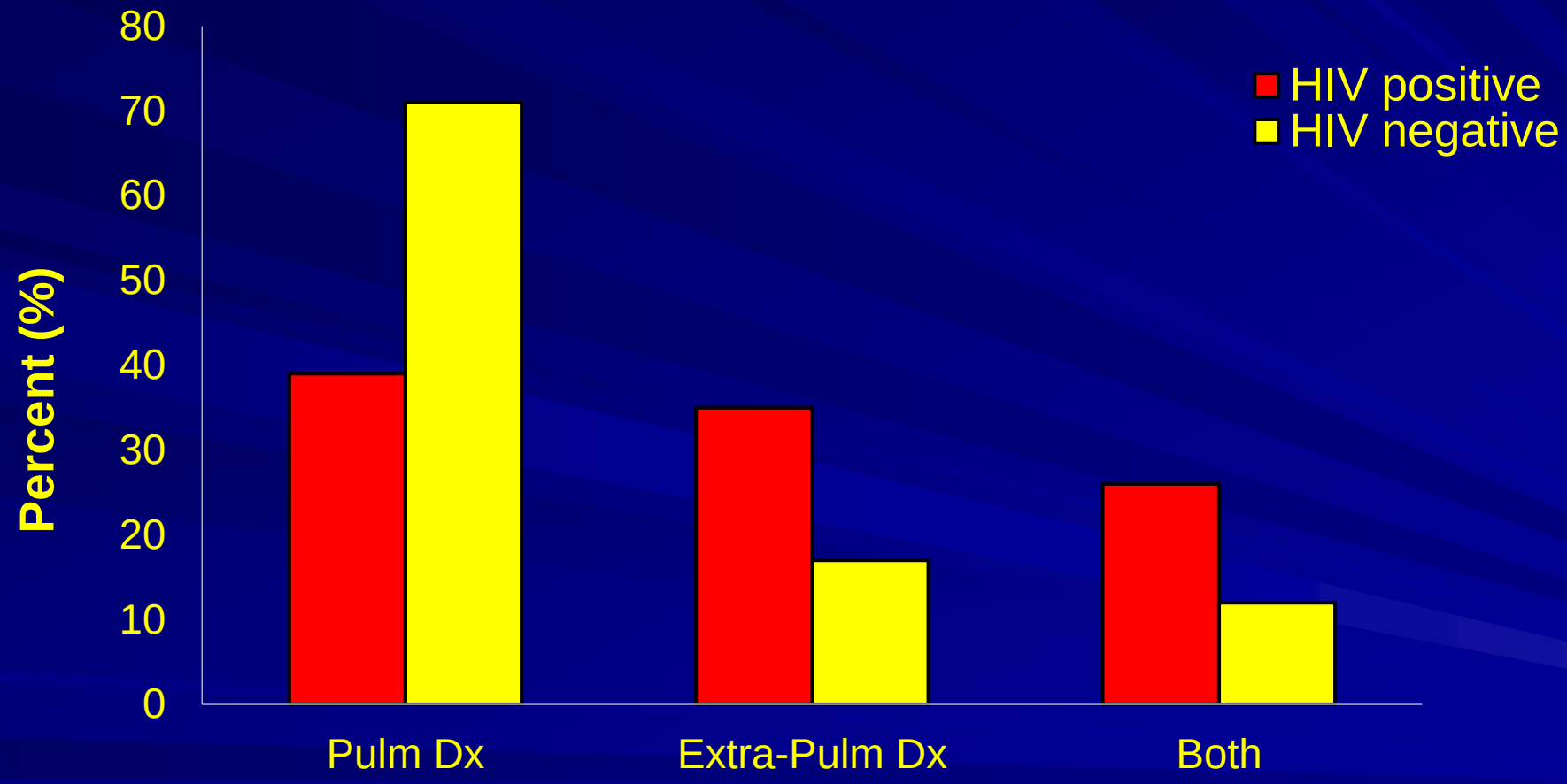
- How reliable is the absence of symptoms to exclude TB: Important to exclude TB prior to initiating ART or IPT
- Meta analysis of a symptom screening tool in HIV in RLS:
  - Prevalence 5% $\Rightarrow$ NPV 97.7%
  - Prevalence 20% $\Rightarrow$ NPV 90%
- Symptoms are usually due to an immune response
- Asymptomatic subclinical TB not uncommon in regions of high co-infection
- Active TB may be missed by symptom screen alone.

PLoS Med 8(1): e1000391. doi:10.1371/journal.pmed.1000391

Clinical Presentation of TB

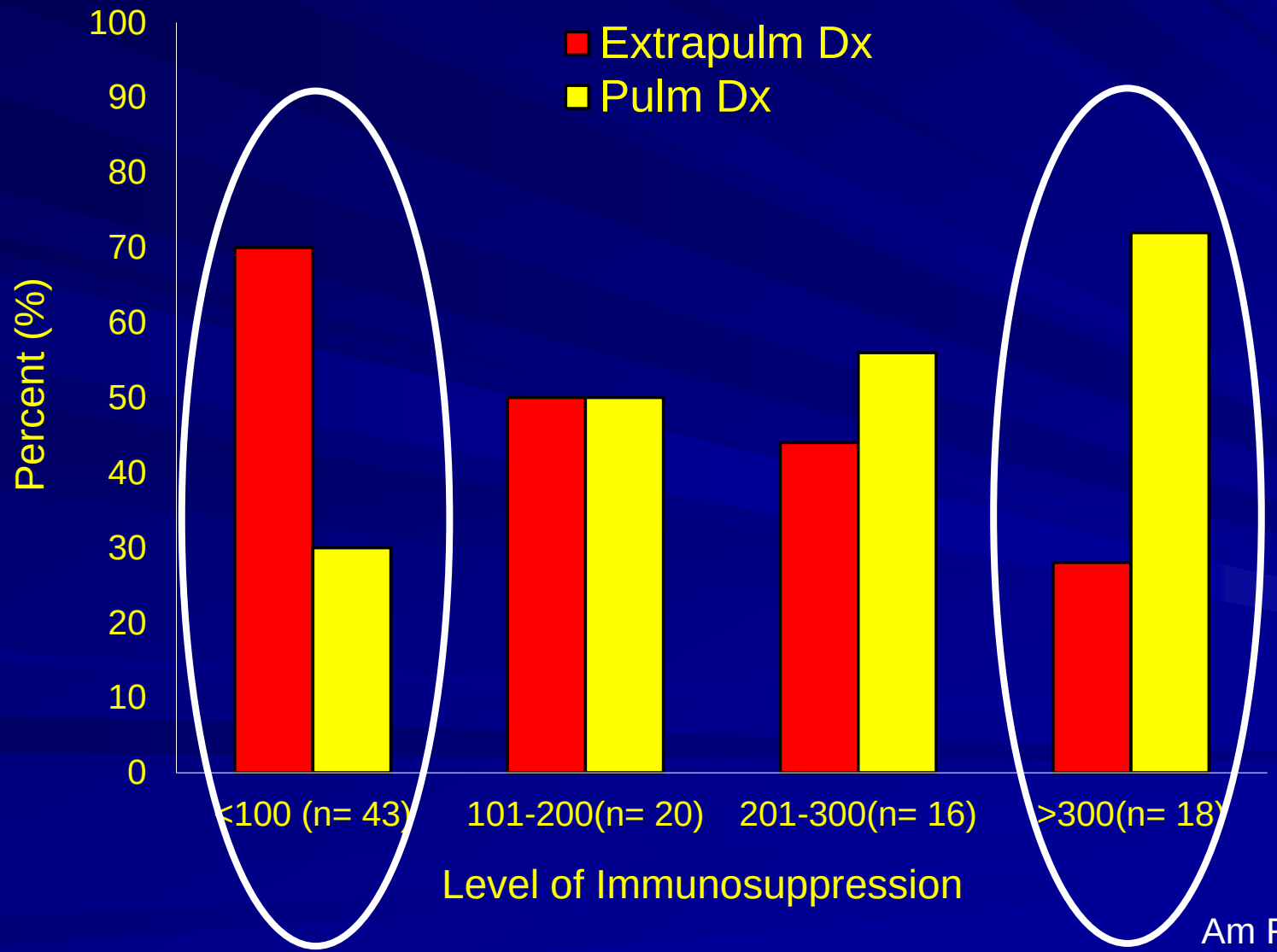
- Varies widely- generally similar to HIV uninfected
- Presentation often reflects level of immunosuppression
- Earlier in HIV $\rightarrow$ classic reactivation-disease
- Advanced immunosuppression similar to primary TB

Impact of HIV on Organ system involvement by TB



Trans R Soc Trop Med Hyg. 1995; 89(1):78.

Organ System involvement is related to level of immunosuppression



Am Rev Respir Dis. 1993;148(5):1292.

Common Sites of Extrapulmonary TB

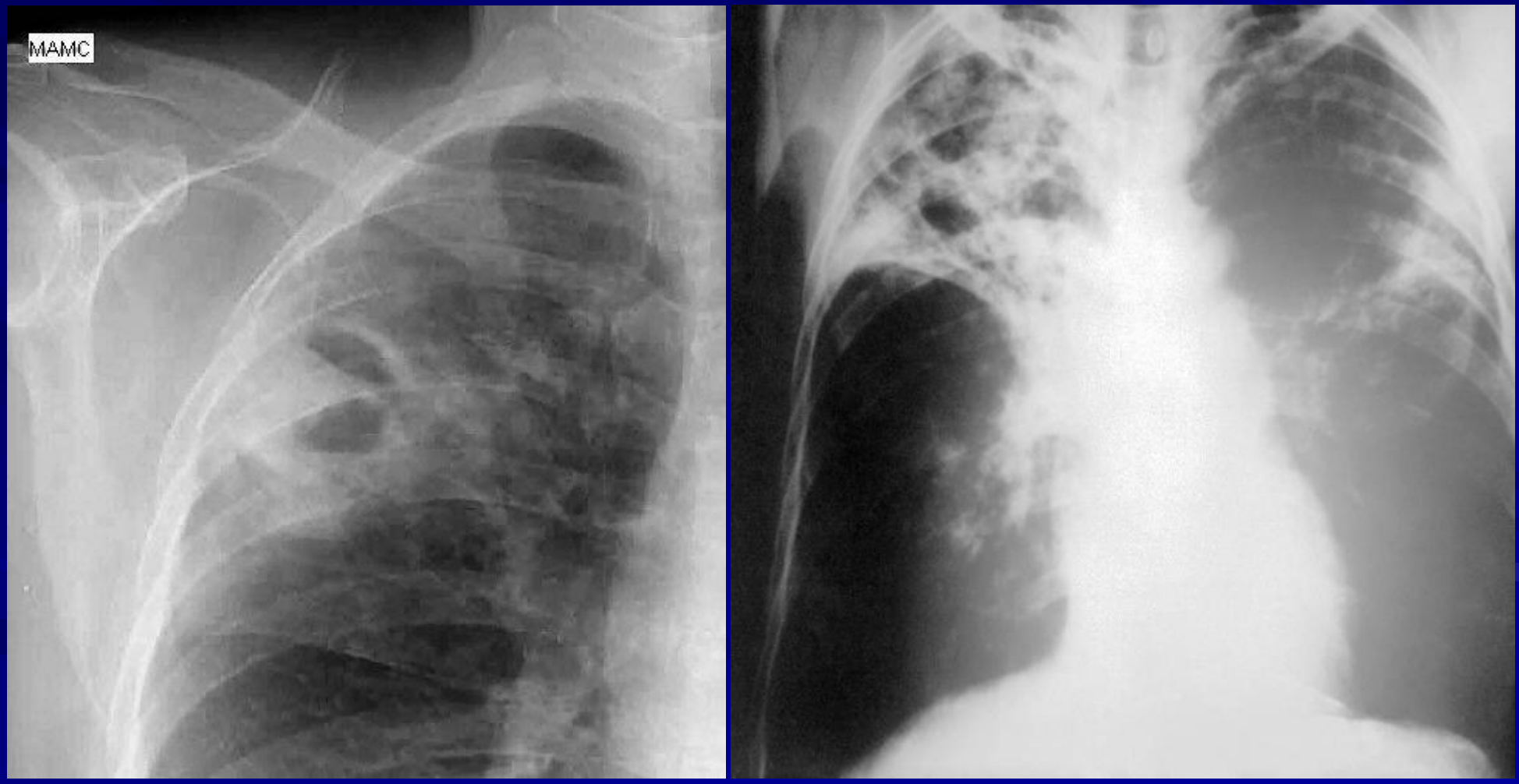
- Lymph node disease:
  - peripheral - cervical > axillary > inguinal
  - central - mediastinal > hilar, intra-abd.
- Disseminated disease
- Serositis- pleural, pericardial > ascites
- CNS- meningitis, tuberculoma
- Soft tissue abscesses

The chest radiograph the cornerstone of diagnosis for pulmonary TB

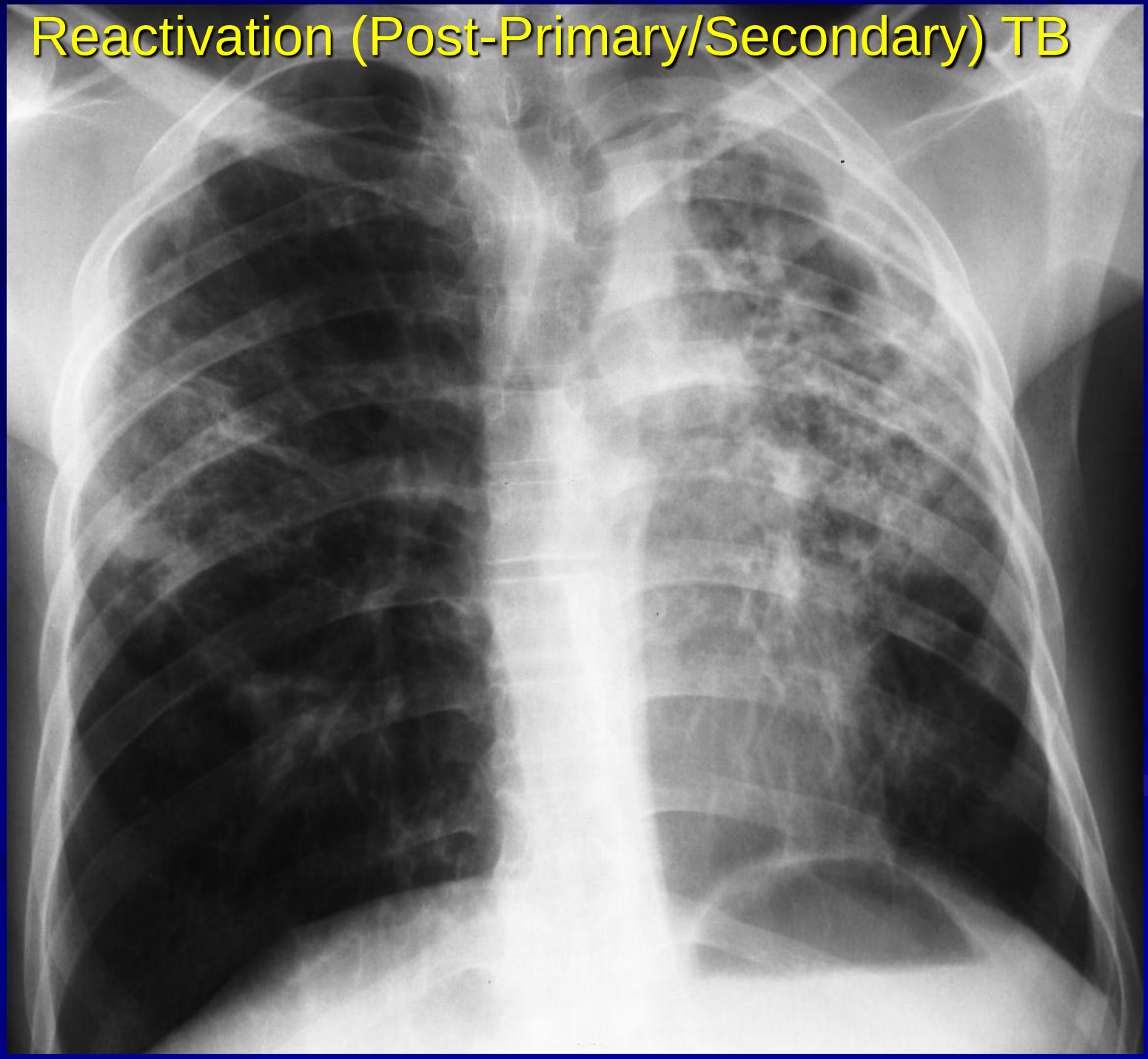
Upper-lobe infiltrates and cavities typical of reactivation TB is seen with higher CD4 counts (>350 cells/μL)

Tubercle and Lung Dis;76:518-21

Reactivation (Post-Primary/Secondary) TB



Reactivation (Post-Primary/Secondary) TB



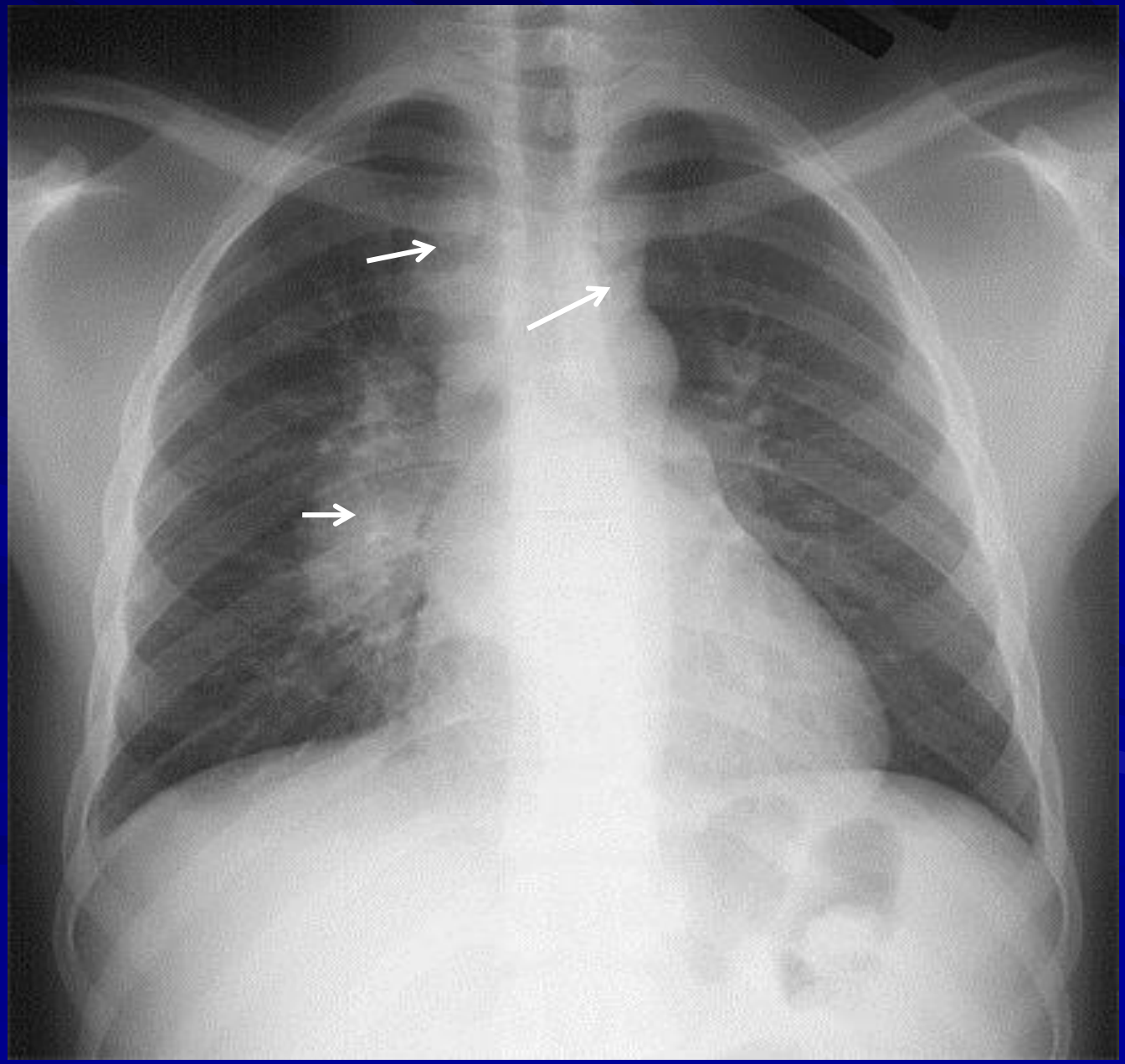
The chest radiograph the cornerstone of diagnosis for pulmonary TB

Primary disease characterized by intrathoracic lymphadenopathy & lower-lobe infiltrates is seen with more immunosuppression (CD4 <100)

Tubercle and Lung Dis;76:518-21

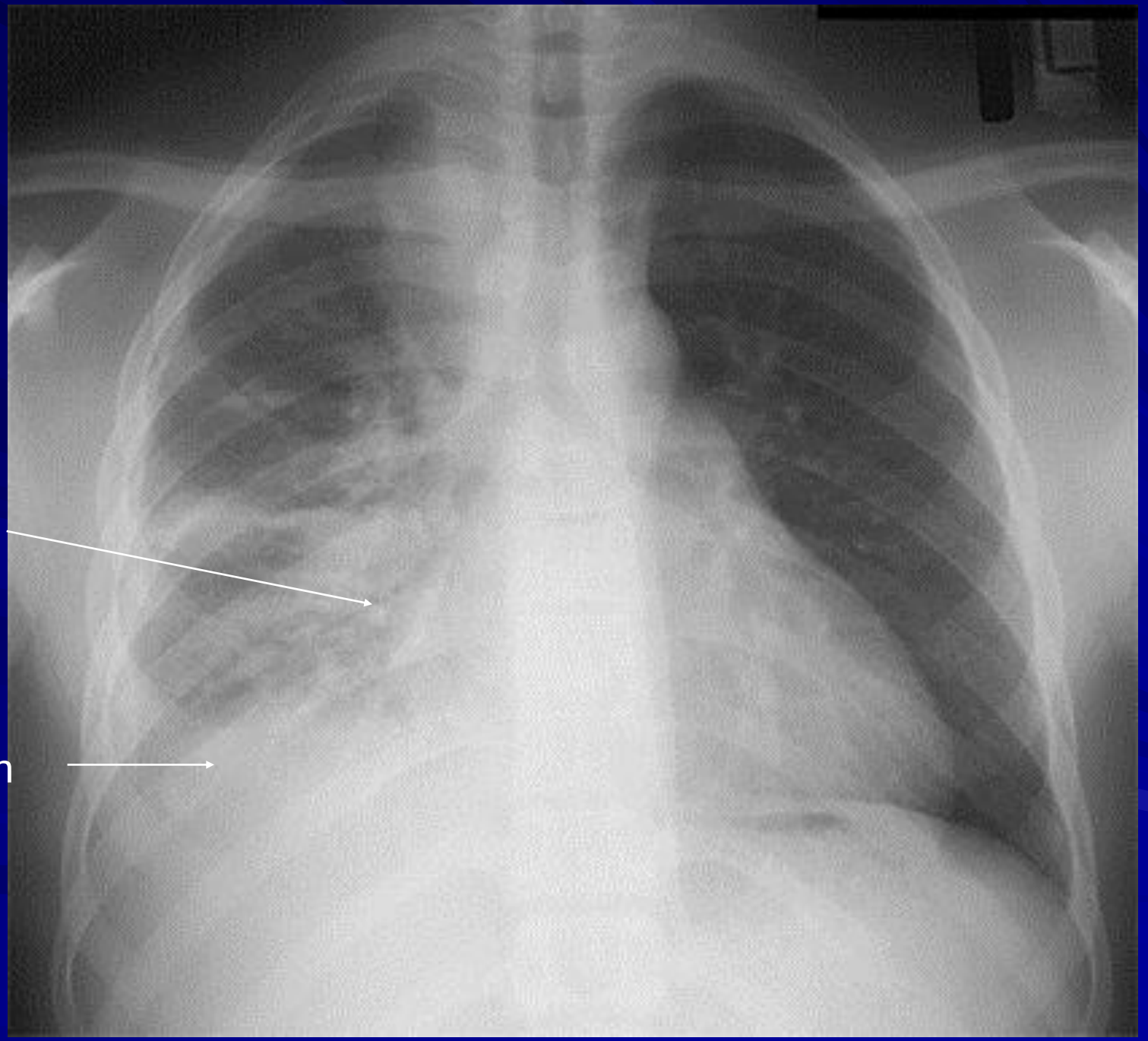
AIDS/TB Chest X-ray

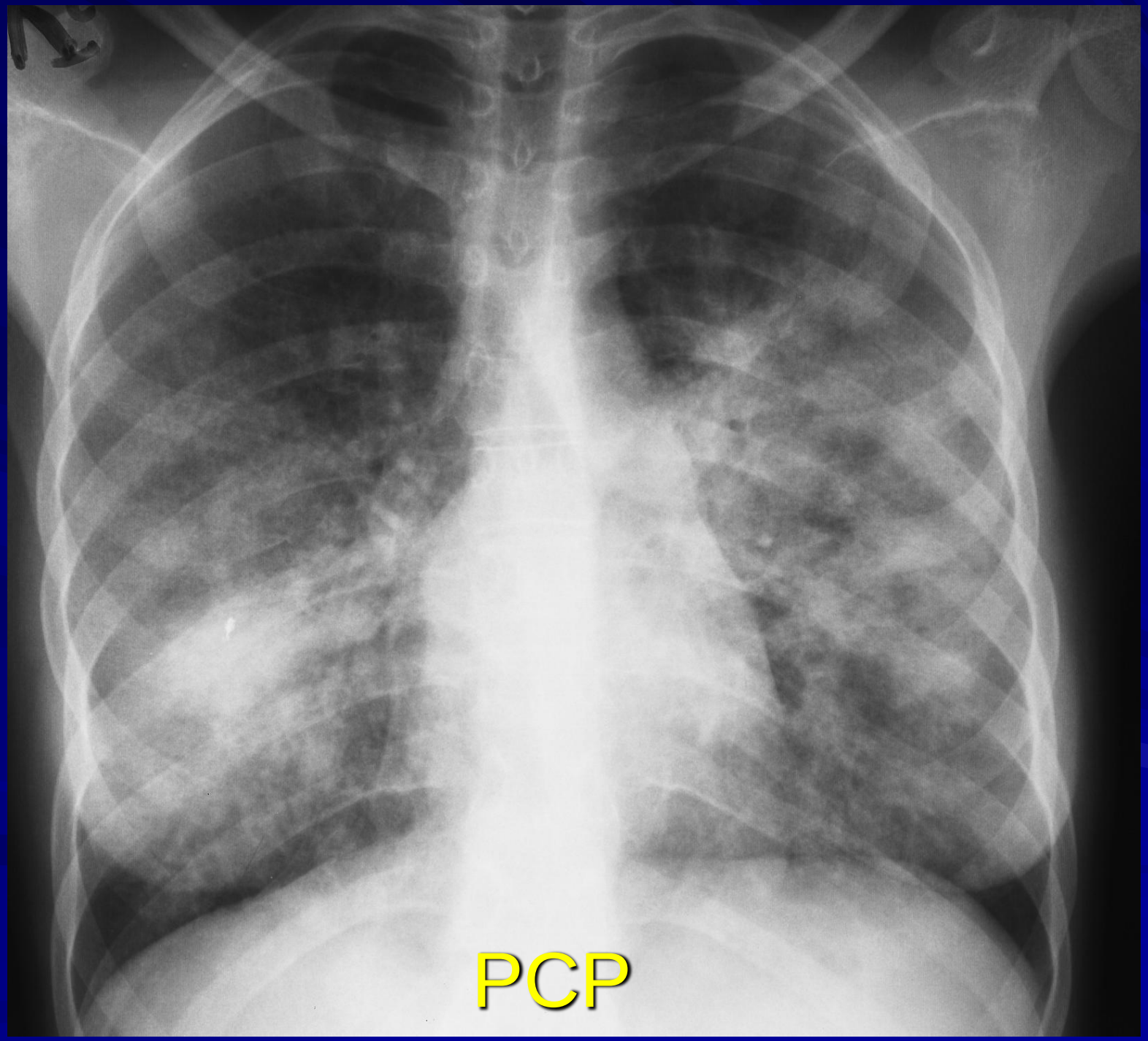
Bilateral hilar/ mediastinal LAN

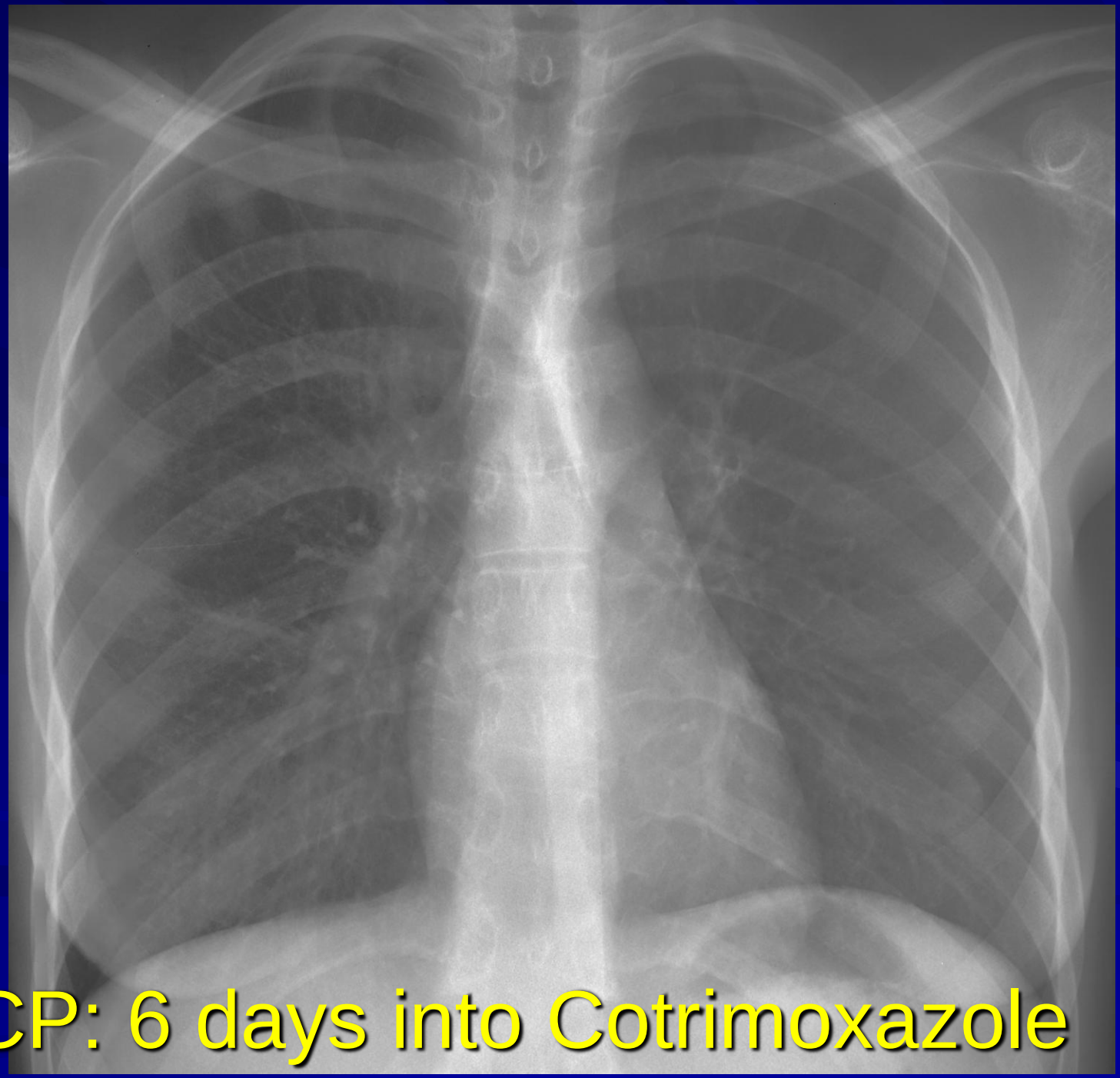


RML Infiltrate

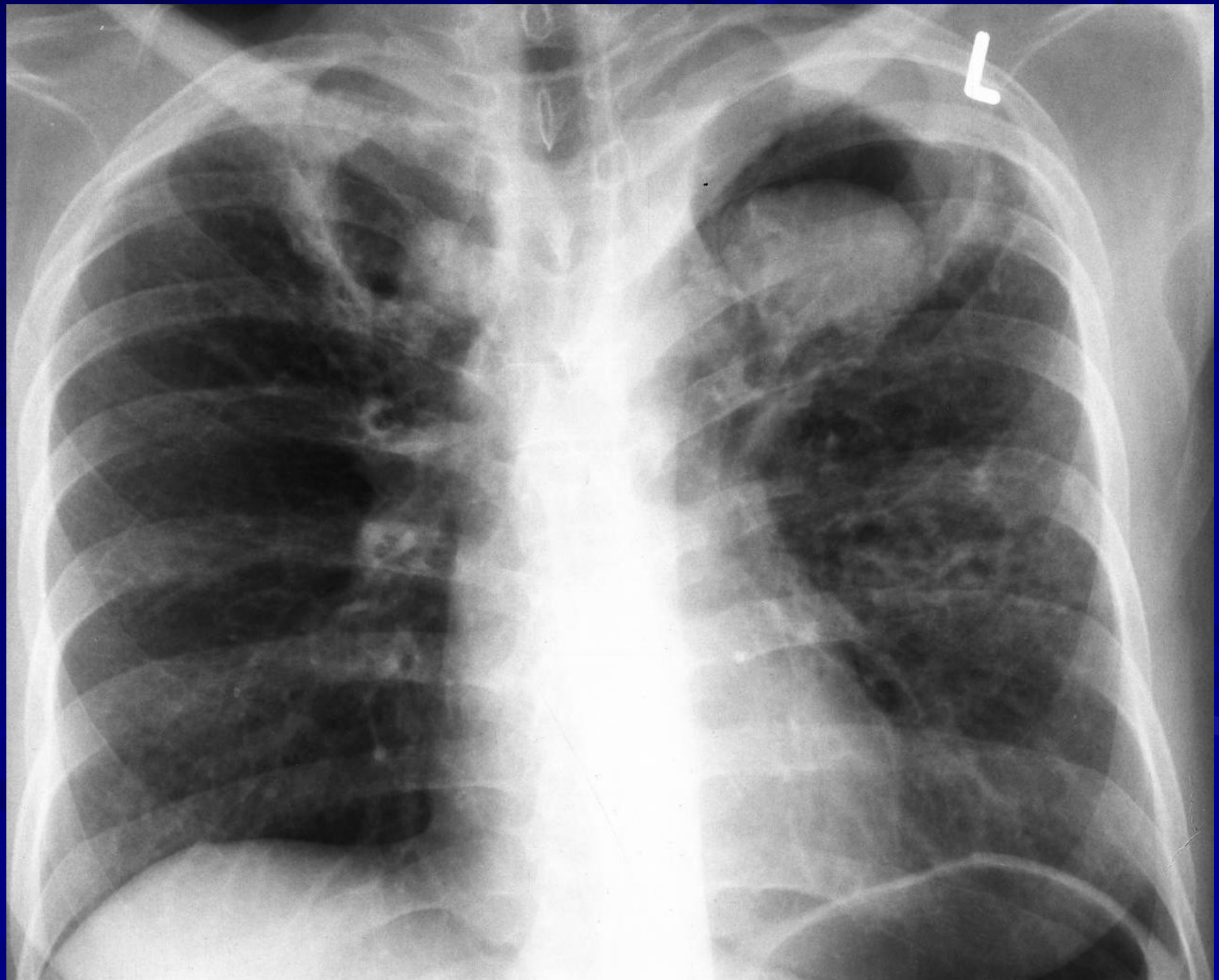
Pleural Effusion




PCP



PCP: 6 days into Cotrimoxazole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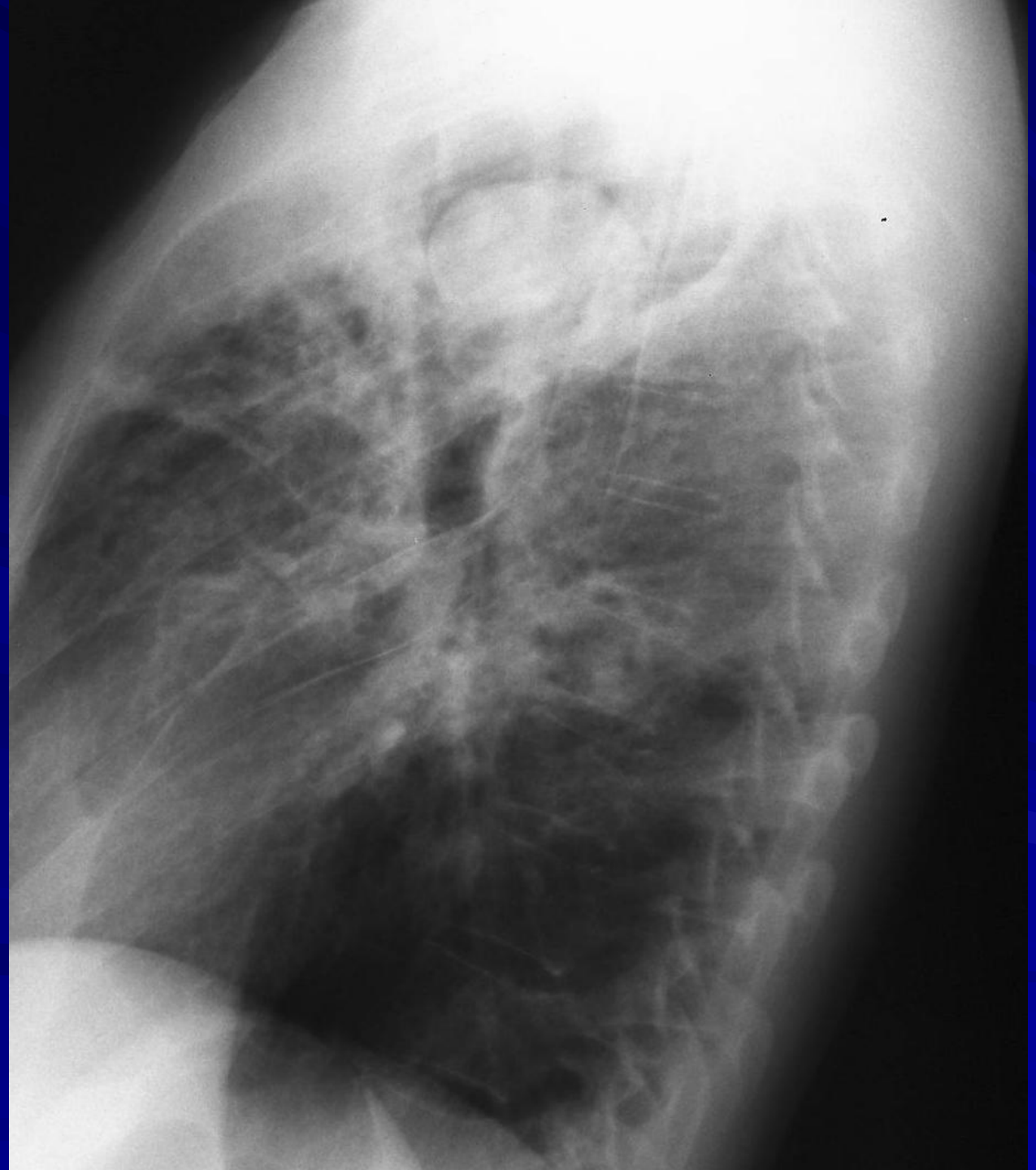
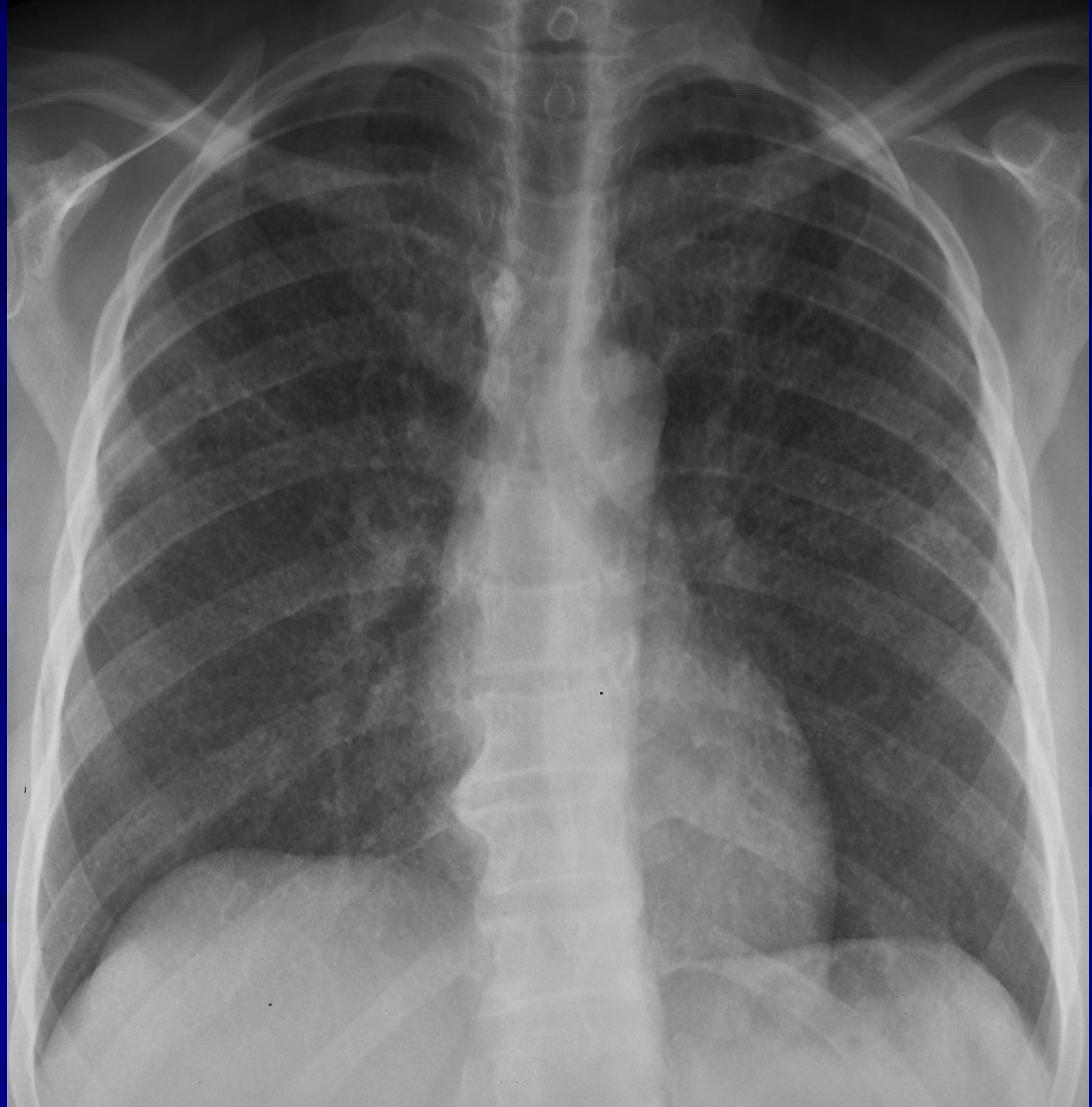
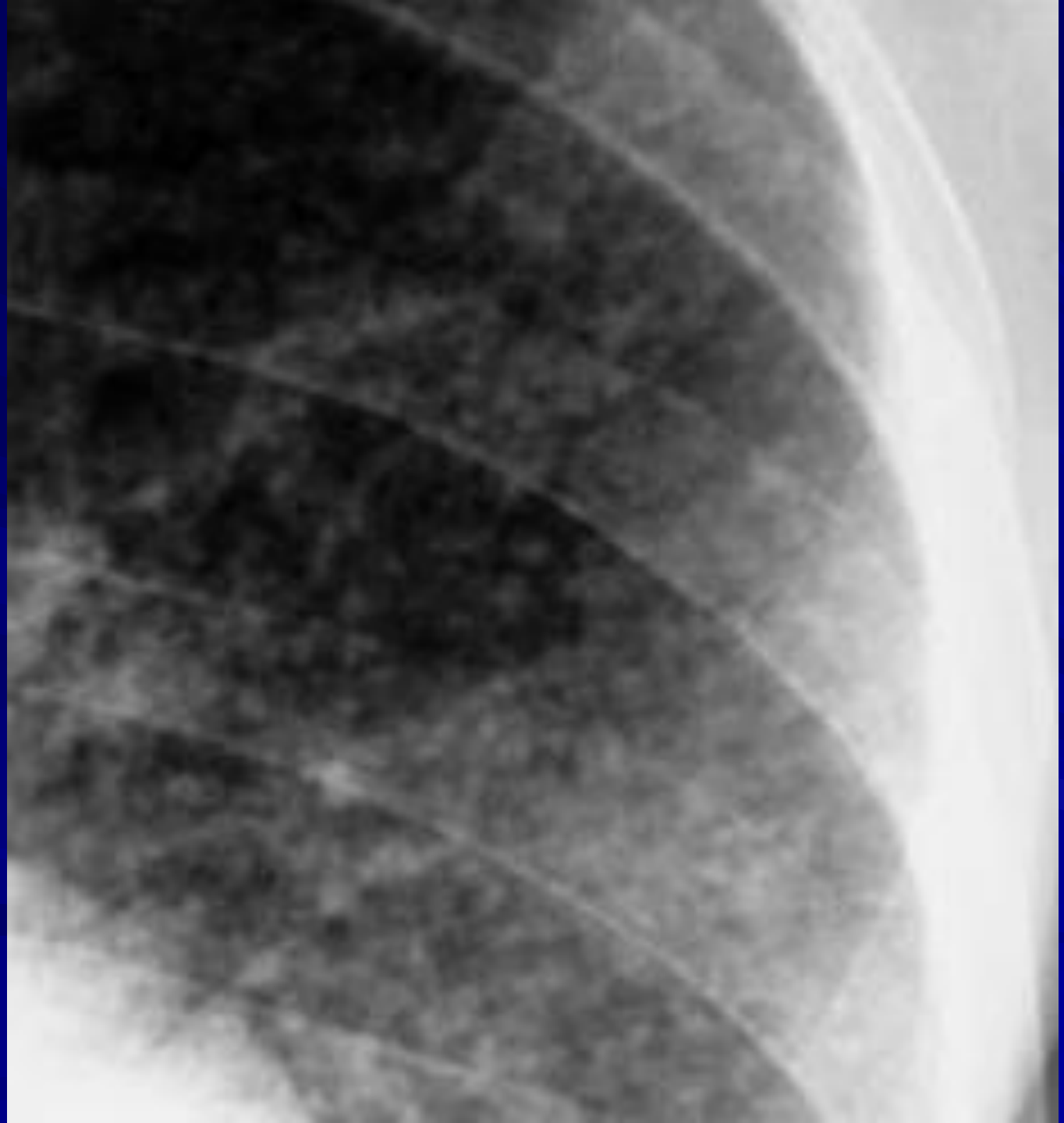






Pathology of Miliary TB

Lung

Spleen

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

IJTLD;14(10):1295-302, Radiology;193:115-119, Chest;99:123-127

Role of the CXR in diagnosing TB

- Sensitive ~76%
- Specificity ~68%

} Risk of over or under diagnosing

- When should do CXR:
  - Complications: pneumothorax, effusion, hemoptysis.
  - Coexistent lung disease.
  - Smear negative patient with strong suspicion of TB.

Diagnosing 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
- Hi specificity
- Rapid turn around time
- Low sensitivity- non-cavitary Dx & HIV (~ 35%)
- Require a minimum of 10,000 AFB/ml of sputum for smear to be positive

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 3/52
- 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.

Am J Respir Crit Care Med;180(9):903-8

Culture- Important diagnostic tool in paucibacilliary Disease

- When should you culture:
  - TB suspects with negative GeneXpert test
  - To confirm GeneXpert showing rifampicin resistant
  - To check susceptibility to other drugs
  - Patient failing treatment despite RIF susceptible- high suspicion of resistance to other drugs

2 different molecular based tests available

- The Gene Xpert (GXP)
- The Line Probe assay

Gene Xpert

- Automated PCR based
- Replaced sputum smear as rapid screening tool
- Allows for rapid diagnosis in SND 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 biospy)
- Instrument is a closed system $\rightarrow$ low risk for contamination, minimal expertise required, low risk for human error.
- Detects TB & RIF Ω

Gene Xpert

- Not a monitoring tool – high false positive in previously treated TB- 27% GXP positive after 6/12 ATT
- Cannot identify XDR TB
- Detects a minimum of ~130 org/ml sputum

IJTLD 18(7):876–878

Gene Xpert

	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%	

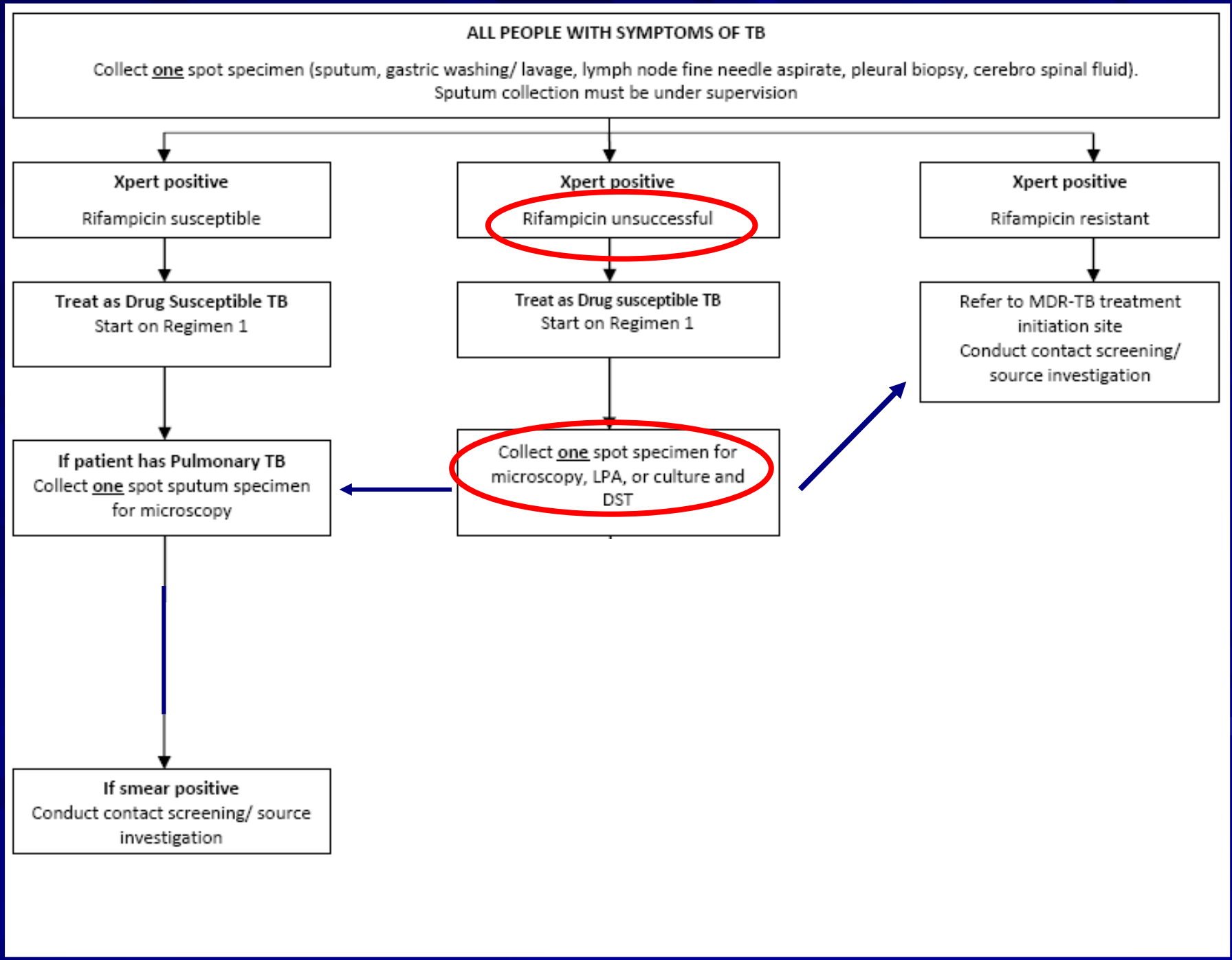
NEJM 2010; 363: 1005

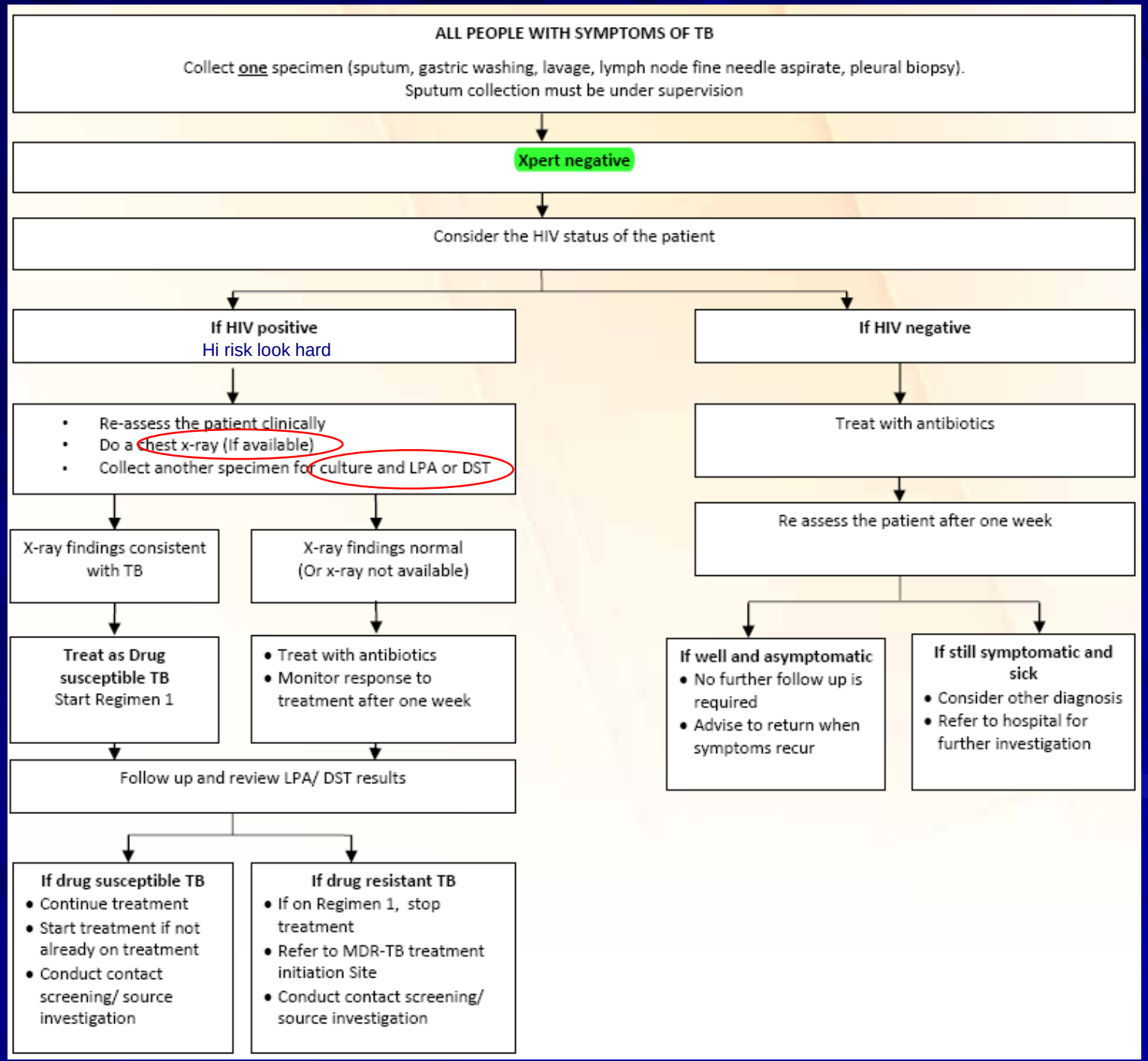
Line Probe Assay

- Approved for direct testing on smear positive specimens and isolates from solid and liquid culture for smear neg.
- PCR based – identifies MTB and specific mutations that confer RIF and INH resistance
- Results within 48 hours in the lab & 7 days in health facilities.
- Used as 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


ALL PEOPLE WITH SYMPTOMS OF TB
Collect one spot specimen (sputum, gastric washing/ lavage, lymph node fine needle aspirate, pleural biopsy, cerebro spinal fluid).
Sputum collection must be under supervision
Xpert positive
Rifampicin susceptible
Xpert positive
Rifampicin unsuccessful
Xpert positive
Rifampicin resistant
Treat as Drug Susceptible TB
Start on Regimen 1
Treat as Drug susceptible TB
Start on Regimen 1
Refer to MDR-TB treatment initiation site
Conduct contact screening/ source investigation
If patient has Pulmonary TB
Collect one spot sputum specimen for microscopy
Collect one spot specimen for microscopy, LPA, or culture and DST
If smear positive
Conduct contact screening/ source investigation


ALL PEOPLE WITH SYMPTOMS OF TB
Collect one specimen (sputum, gastric washing, lavage, lymph node fine needle aspirate, pleural biopsy).
Sputum collection must be under supervision
Xpert negative
Consider the HIV status of the patient
If HIV positive
Hi risk look hard
If HIV negative
Re-assess the patient clinically
Do a chest x-ray (If available)
Collect another specimen for culture and LPA or DST
Treat with antibiotics
Re assess the patient after one week
X-ray findings consistent with TB
X-ray findings normal (Or x-ray not available)
Treat as Drug susceptible TB
Start Regimen 1
Treat with antibiotics
Monitor response to treatment after one week
If well and asymptomatic
No further follow up is required
Advise to return when symptoms recur
If still symptomatic and sick
Consider other diagnosis
Refer to hospital for further investigation
Follow up and review LPA/ DST results
If drug susceptible TB
Continue treatment
Start treatment if not already on treatment
Conduct contact screening/ source investigation
If drug resistant TB
If on Regimen 1, stop treatment
Refer to MDR-TB treatment initiation Site
Conduct contact screening/ source investigation

Treatment

- 6/12 standard therapy 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.

CID;50(9):1288-99.

TB while on ART

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

Toxicities

- S/E twice as common in HIV coinfected (26 vs. 13%)
  - hepatotoxicity,
  - Peripheral Neuropathy
  - Vomiting
  - Arthralgia
  - Rash
- Peripheral neuropathy – INH, stavudine, didanosine
- DILI - INH, rifampin, pyrazinamide, NRTIs, NNRTIs, and PIs.

Int J STD AIDS. 20(5):339-45, CID;50(9):1288-99

Timing of ART in TB

- CD4 ≤ 50 -ART within 2wks of TB treatment
  - Reduced AIDS progression and mortality

NEJM 2011; 365:1482–1491., NEJM 2011;365:1471-81, CID 2011;52:1374–1383

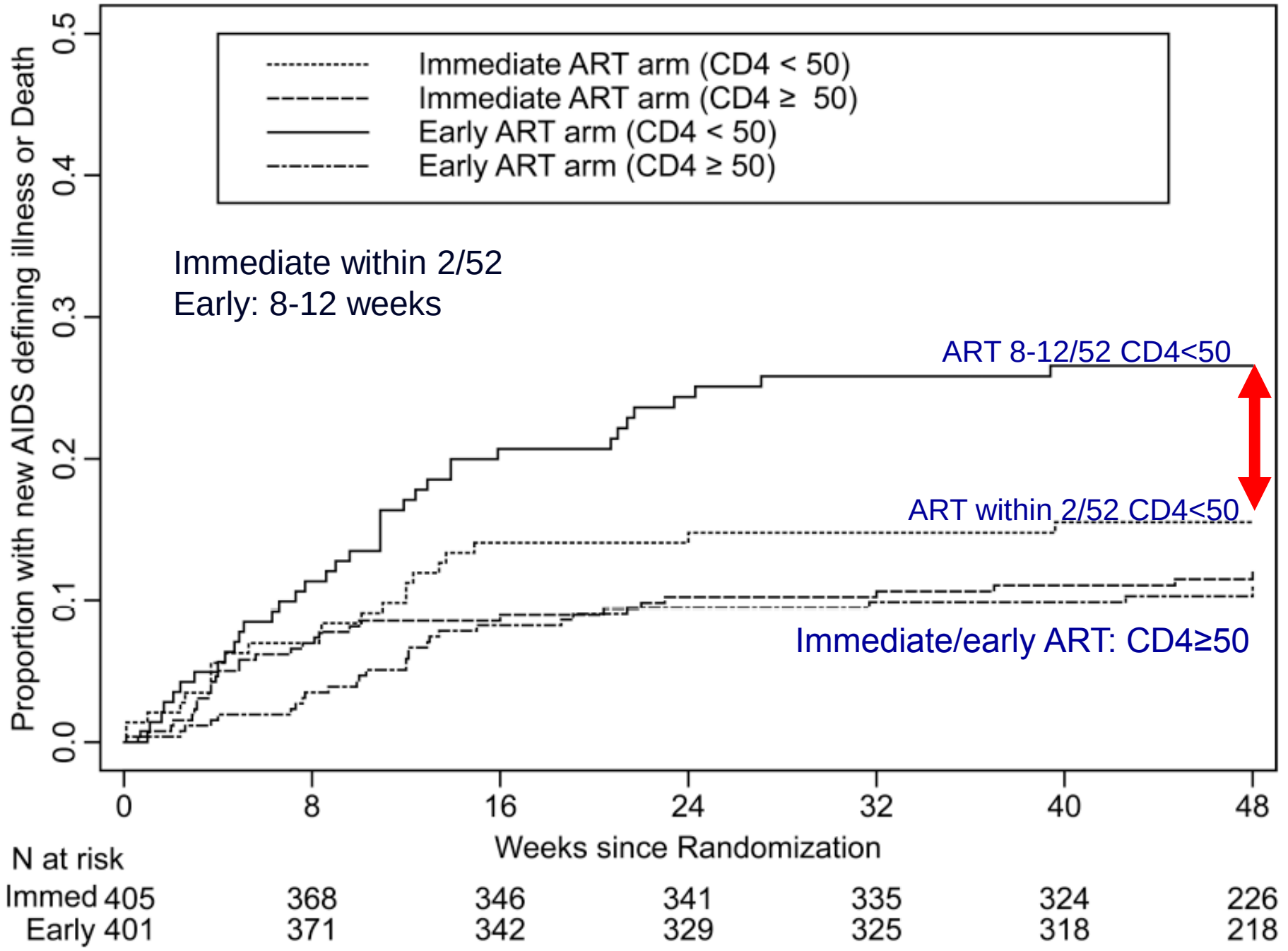


Figure 2. Time to New AIDS Defining Illness or Death

NEJM 2011; 365:1482–1491.

Timing of ART in TB

- CD4 >50 -ART after intensive phase of TB treatment.
  - Reduced overlapping toxicity, reduce risk of IRIS
- Early ART requires
  - Coordination between TB and HIV care
  - Vigilance for drug toxicities
  - Adherence to high pill burden
  - Vigilance for IRIS

NEJM 2011; 365:1482–1491., NEJM 2011;365:1471-81, CID 2011;52:1374–1383

What is IRIS?

- Aberrant manifestation of immune reconstitution → pathogen specific inflammatory response triggered by:
  - Initiation HAART
  - Re-initiation HAART
  - Change to more active HAART
- Two forms : Paradoxical, Unmasking

Paradoxical IRIS

- Clinical deterioration while on effective ATT
- Development of new or worsening clinical symptoms or signs of TB
  - Fever, night sweats, weight loss
  - Respiratory symptoms
  - Enlarged lymph nodes
  - Worsening radiologic features
  - New or worsening CNS manifestations

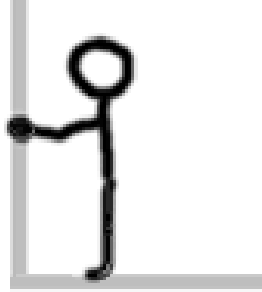
Paradoxical IRIS

- Associated with:
  - Low CD4
  - High viral load
  - Short interval bet TB Rx and ART initiation- 2-3 months of ART
- Diagnosis of exclusion: other O/Is, poor adherence, MDR
- Managed symptomatically, severe IRIS consider prednisone
- ART continued as far as possible.
- TB IRIS is seldom fatal

Unmasking IRIS

- New diagnosis of TB after initiation of ART in a patient who, prior to commencing HAART, had no features to suggest TB.
- Sub-clinical or unrecognised infections “unmasked” by the emergence of pathogen-specific immune responses.

Conclusion



- HIV has converted TB into a more complex disease
- Impacts virtually all aspects of the disease
- Diagnostic challenges →resort to molecular methods for rapid diagnosis
- Management complicated by drug interactions, overlapping toxicities
- Response to treatment confounded by IRIS
- Despite all, TB in the coinfected can be cured