



APPROACH TO MANAGEMENT OF TB IN PLWHA

SAHIVSOC CONFERENCE

24/09/14

CAPE TOWN

OUTLINE

- ▶ EARLY DIAGNOSIS – PTB and EPTB
- ▶ PROMPT TREATMENT
- ▶ REDUCING EARLY MORTALITY FROM HIV/TB
- ▶ MANAGING DRUG TOXICITY AND INTERACTIONS IN HIV/TB
- ▶ DEFINING VARIOUS TREATMENT OUTCOMES



▶ A normal CRP is useful to rule out TB in ambulant patients

▶ 1.True


▶ 2.False

Clinical Presentation

- ▶ Symptoms
- ▶ Signs
- ▶ Investigations:
 - CXR
 - Ancillary investigations
 - CRP-useful in ambulatory patients
 - Hb
 - Albumin

Cardinal symptoms of TB

- ▶ Fever $\times >2/52$
- ▶ Night sweats $\times >2/52$
- ▶ Weight loss $>2.5\%$ over 1/12
- ▶ Cough $\times >2/52$.

- 
- ▶ SYMPTOM SCREEN FOR PTB IS 100 % SENSITIVE FOR AT LEAST 2 SYMPTOMS
 - ▶ 1.TRUE
 - ▶ 2.FALSE

Diagnosis -PTB

- ▶ Absence of symptoms exclude TB
- ▶ 1.TRUE
- ▶ 2.FALSE

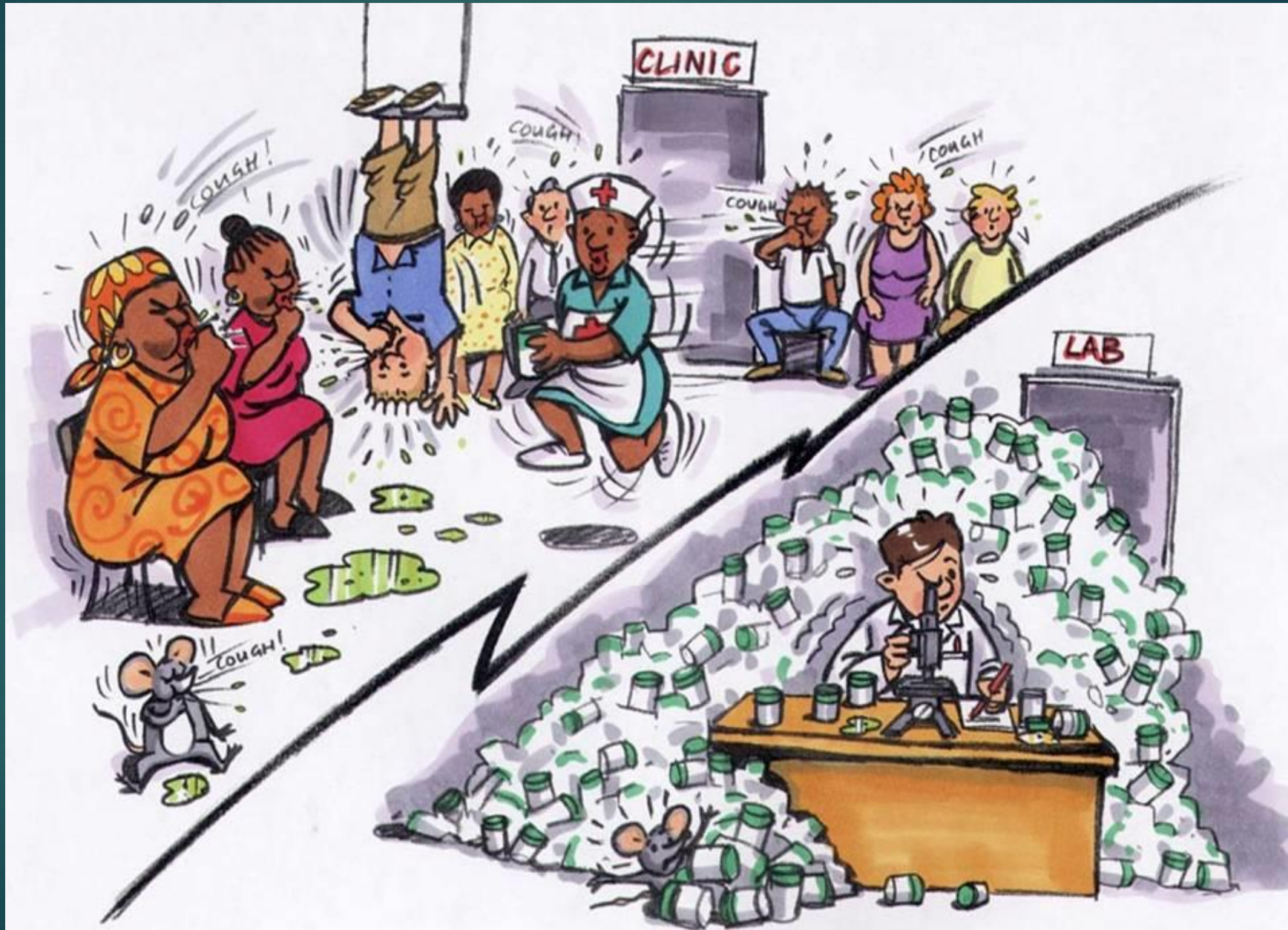
Diagnosis PTB

- ▶ In HIV positive patients the sensitivity of 2-3 sputum smears is
- ▶ 1.60-70%
- ▶ 2.40-50%
- ▶ 3.30-40%
- ▶ 4.>70 %


Reliability of Symptoms

- ▶ The presence of any 2 symptoms:
- ▶ **Sensitivity** - ~100% (all pts with TB have symptoms)
- ▶ **Specificity** - 88% (12% that don't have TB had symptoms)
- ▶ **PPV** - 44% (of pts with symptoms 56% falsely diagnosed with TB)
- ▶ **NPV** - ~100% (absence of symptoms excludes TB)
- ▶ CXR not sensitive at excluding TB.
- ▶ **Absent symptoms reliably excludes TB.**

BIGGER CHALLENGES



GeneXpert

- ▶ Smear-positive Sn: TB 98.2%
 - ▶ Smear-negative TB:
 - 1 sample Sn: 72.5%
 - 2 samples Sn: 85%
 - 3 samples Sn: 90.2%
 - ▶ Sp: 99.2%
- 

Definitive Diagnosis

- Smear
 - ▶ HIV negative- sensitivity of 2-3 smears » 50-70%
 - ▶ HIV positive sensitivity of 2-3 smears » 30-40%
- Culture (MGIT, MODS)
- Nucleic acid amplification
- Ag detection in urine (LAM)

Response to ATT at 8/52 to Diagnosis TB

- ▶ Response to ATT is an effective way to diagnose HIV-associated SNTB
- ▶ Clinical criteria to monitor @ 8/52:
 - Wt gain of $\geq 5\%$
 - Hb increase $\geq 1g\%$
 - Reduction in CRP by $>60\%$
 - Increase in KPS
 - Improvement in $\geq 50\%$ of initial symptoms.

Response to ATT at 8/52 to Diagnosis TB

- ▶ ≥ 2 response criteria at 8/52 has 97.5% sensitivity for confirmed TB.
- ▶ Patients with suspected SNTB who do not meet this criteria are unlikely to have TB:
 - TB treatment should be discontinued
 - Referred to the next level of care for diagnostic evaluation.

WHO Recommendation

- ▶ Best approach to reduce time to Rx of SNTB is to use a clinical approach, based on case definitions.
- ▶ Imposes evaluation over time
- ▶ HCW is expected to be a clinician, think and use discretion.

Classify Clinical State: Based on Danger Signs

Danger signs: The adult patient will be classified as seriously ill if one or more of the following danger signs are present:

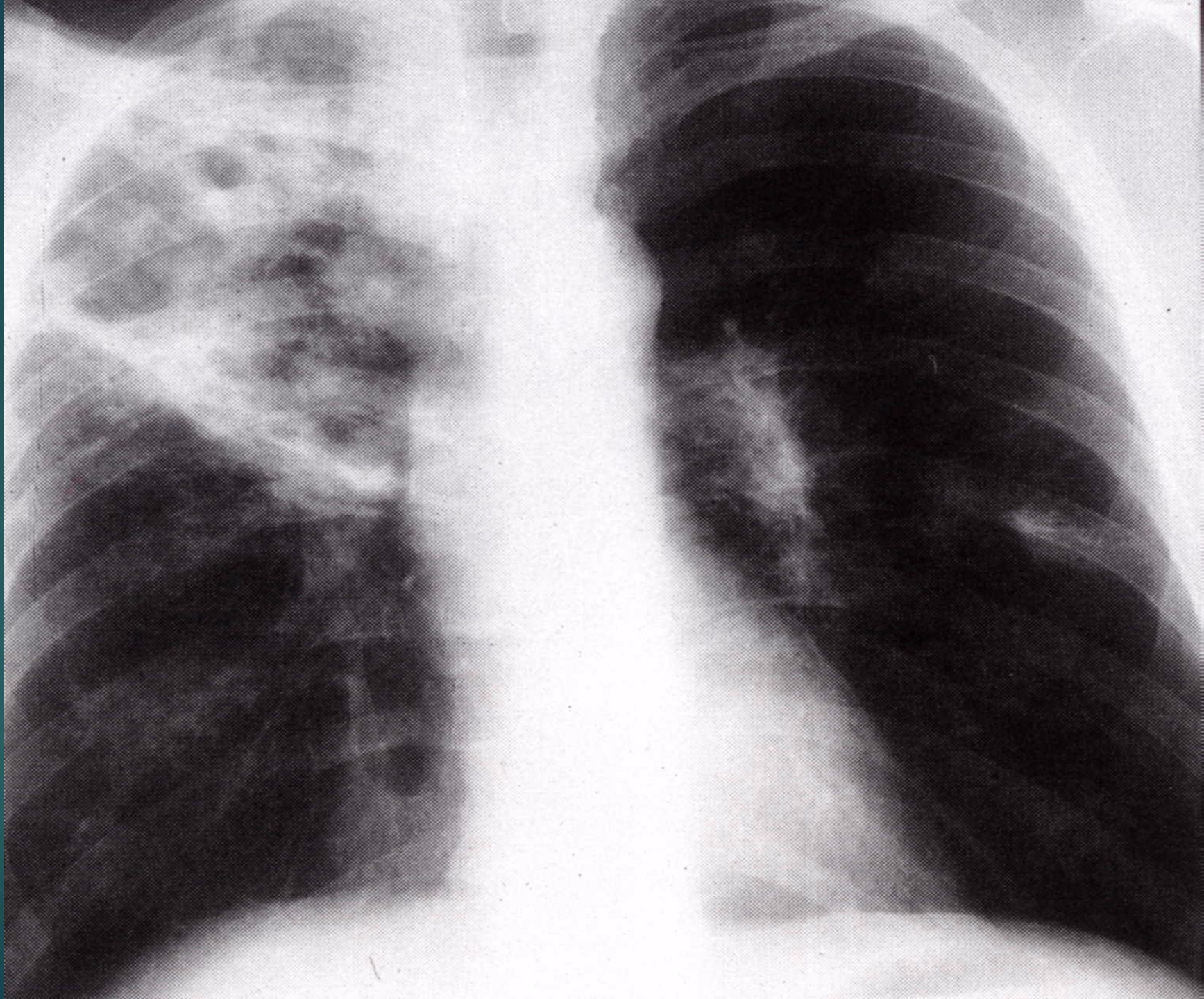
- unable to walk unaided
- respiratory rate over 30 per minute
- fever of more than 39 °C
- pulse rate of over 120 per minute.

RR, PR, T

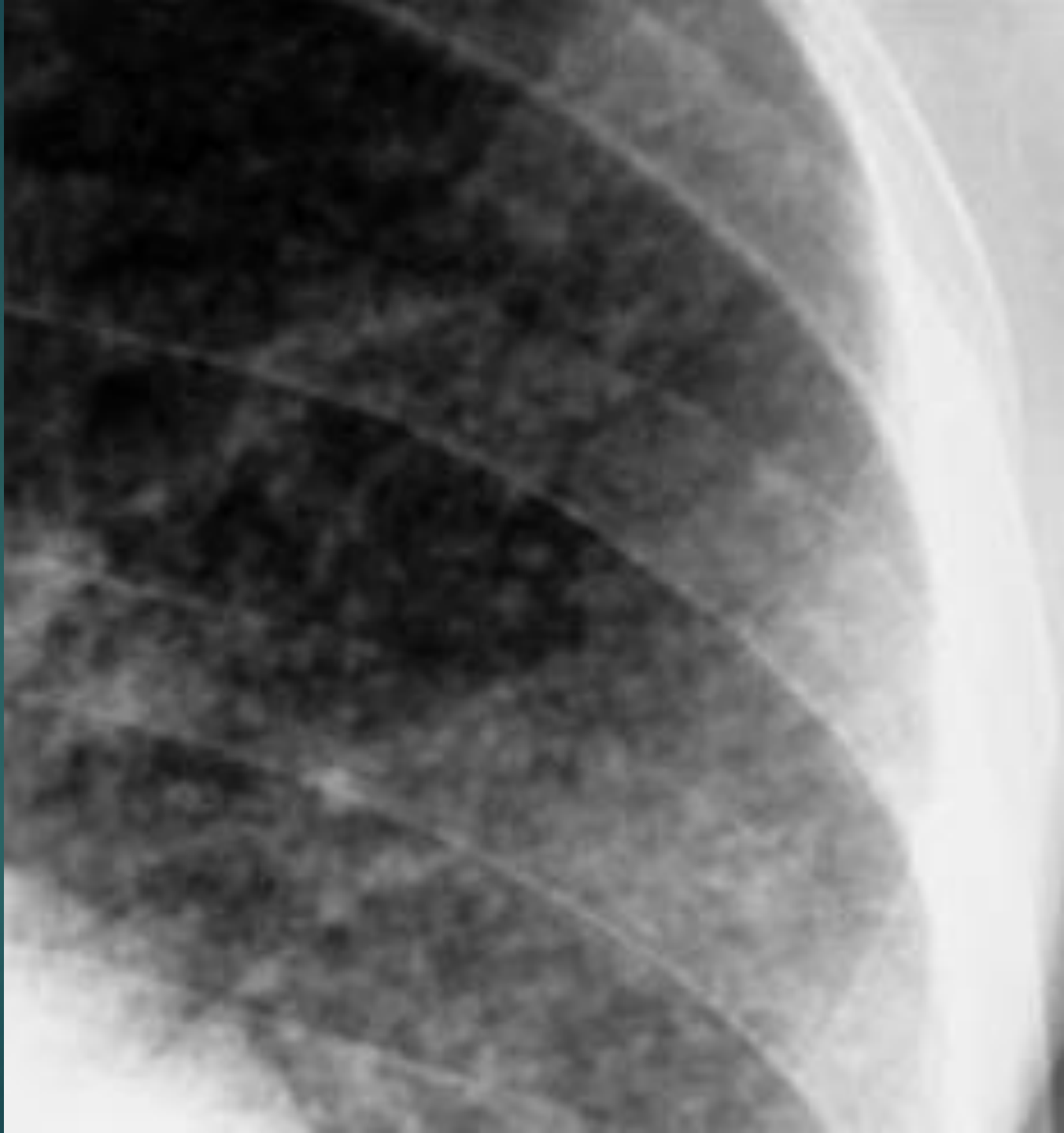
Chest X-ray

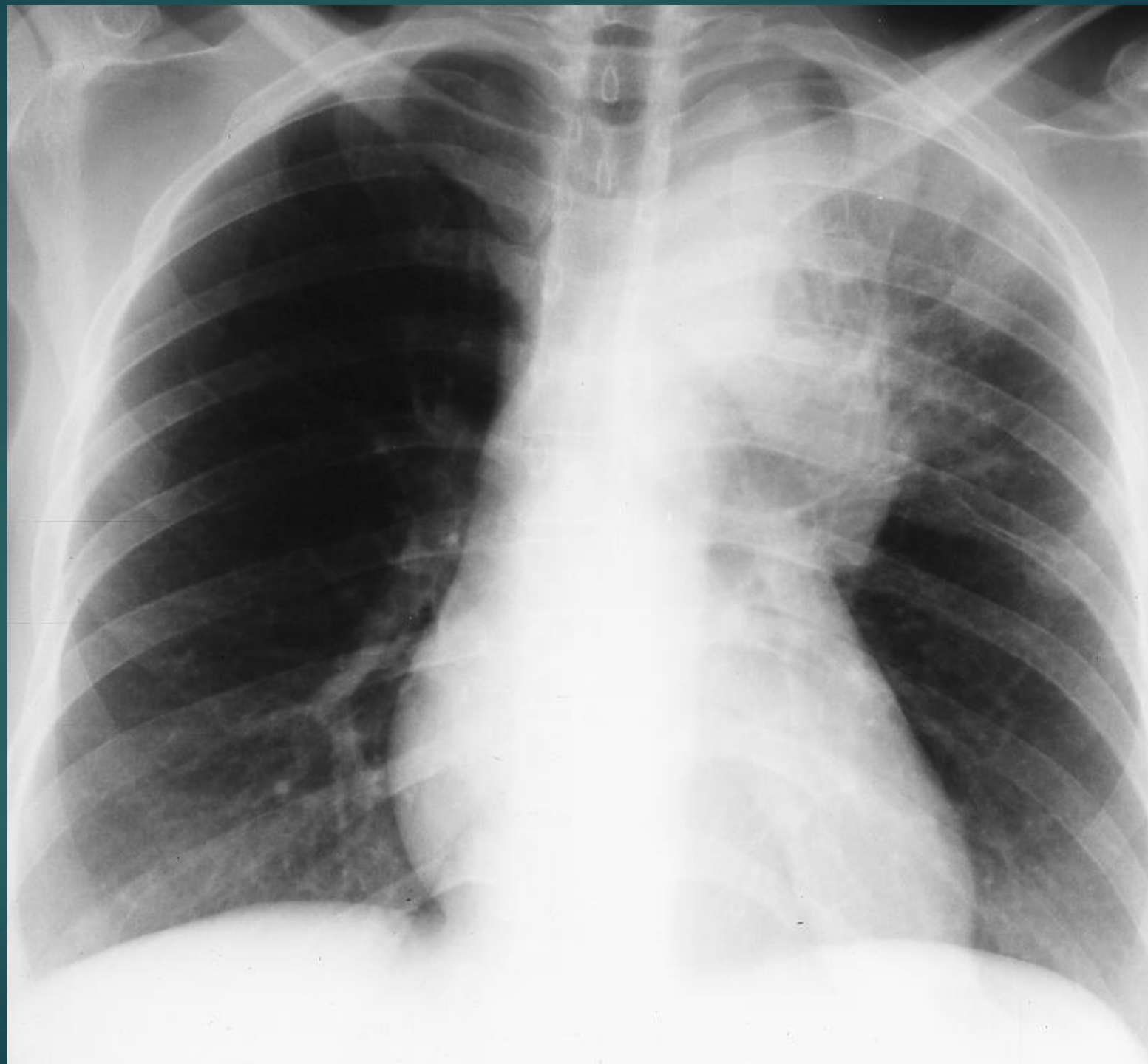
- Pattern recognition
- Distribution
- Characteristic pictures







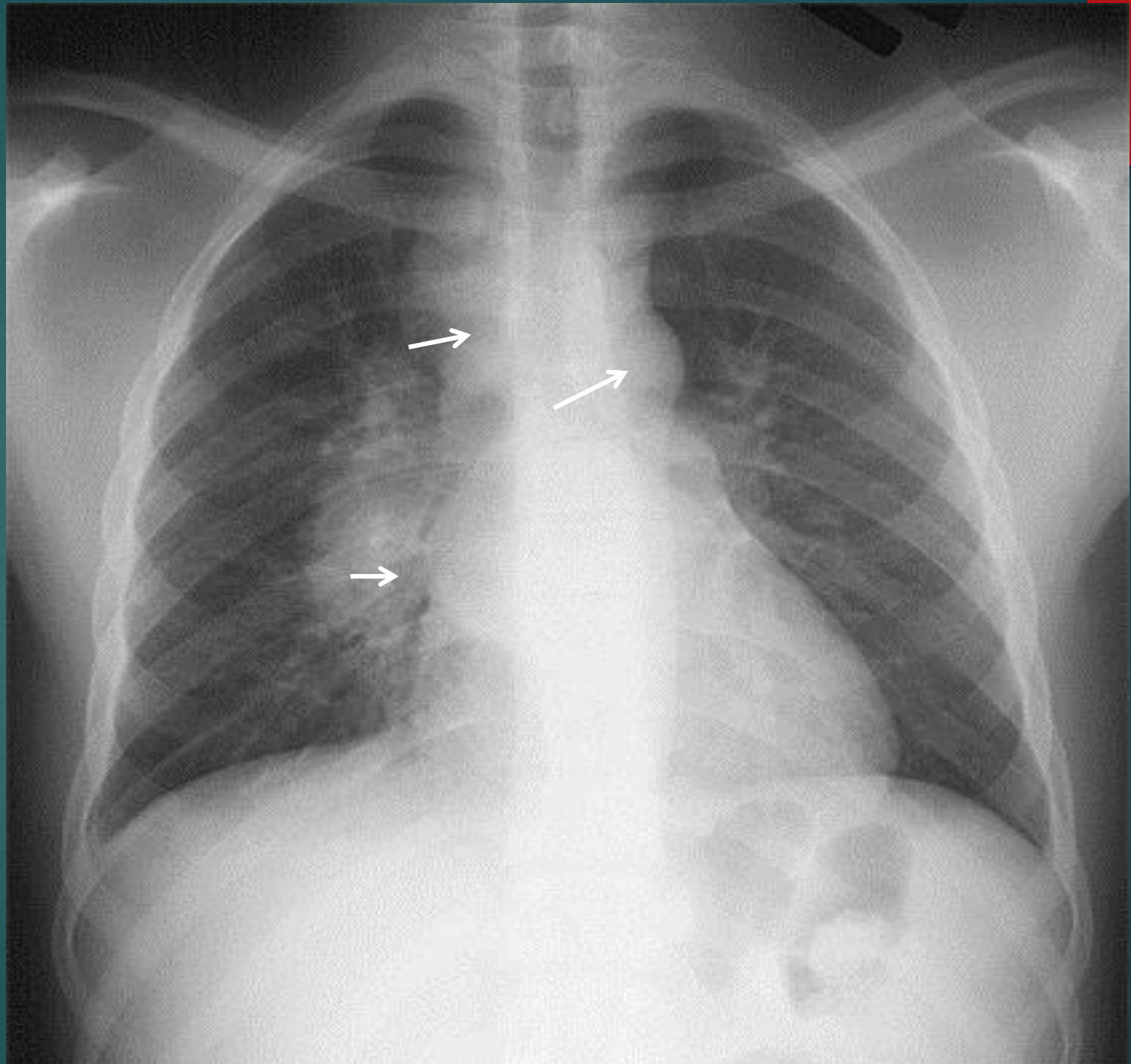


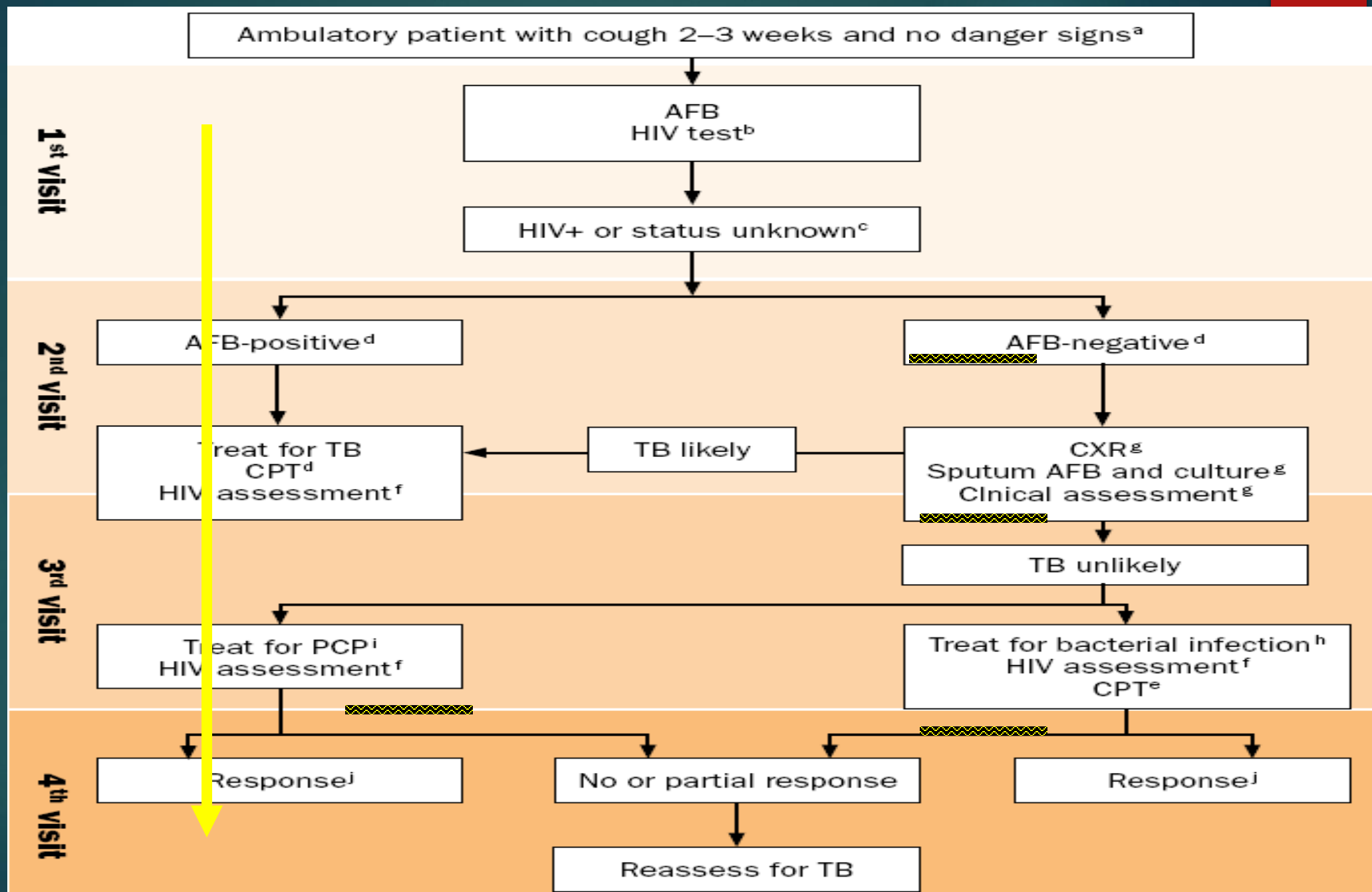




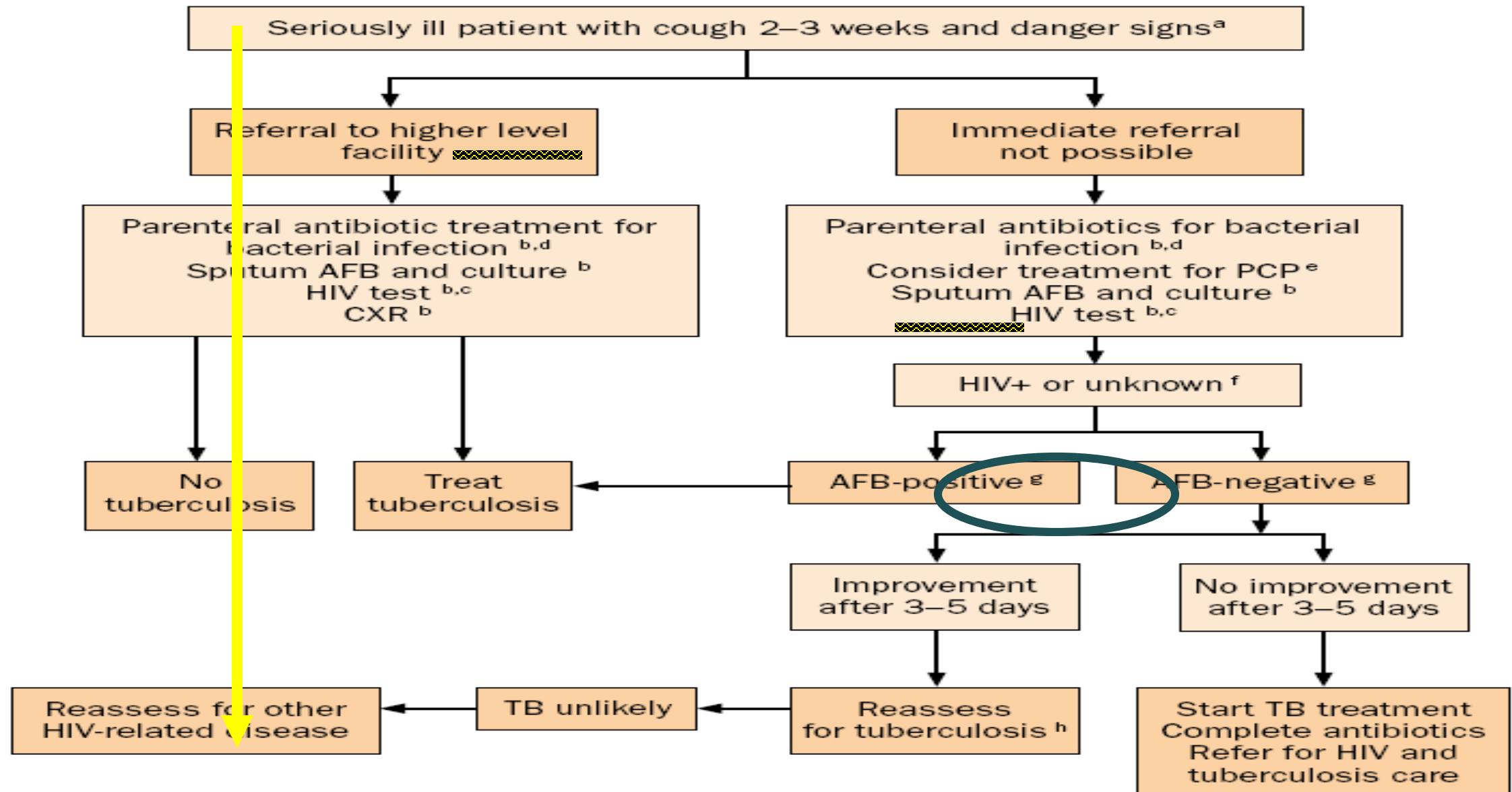


Bilateral hilar/
mediastinal LAN





Algorithm for the diagnosis of tuberculosis in seriously ill HIV-positive patient



Recent developments

1. Implementing the inpatient WHO SNTB algorithm for saves lives and gets patients home sooner
2. The outpatient WHO SNTB algorithm misses 20% of patients with culture-positive PTB
3. Compared to smear - the Xpert MTB-RIF assay rapidly diagnoses more (but not all) patients with culture-positive TB (at \$20 / test)

Use of a WHO-recommended algorithm to reduce mortality in seriously ill patients with HIV infection and smear-negative pulmonary tuberculosis in South Africa: an observational cohort study

Lancet Infect Dis 2011;
11: 533–40

Timothy H Holtz, Gaëtan Kabera, Thuli Mthiyane, Tainos Zingoni, Sidhambaram Nadesan, Douglas Ross, Jennifer Allen, Sekai Chideya, Henry Sunpath, Roxana Rustomjee

	Standard practice N = 338	WHO algorithm N= 187
On TB Rx	46%	100%
In hospital after 7 days	38%	27%
Alive after 8 weeks	68%	83%

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Clinical Presentation -EPTB

31

Tuberculosis *lymphadenitis* - most frequent form and typically multifocal in HIV-infected hosts.

Dx -An abdominal ultrasound and contrast-enhanced CT showing lymph nodes with central low attenuation suggests the diagnosis of mesenteric and para-aortic extrapulmonary TB.

CXR- Hilar adenopathy characteristic of mediastinal TB.

FNA- TB lymphadenitis (scrofula), fine-needle aspiration may be helpful in the diagnosis, as acid-fast staining and culture is often positive in HIV-infected hosts.

TB Pericarditis and pleural effusions

Tuberculosis pericarditis - usually due to contiguous spread, may be with hematogenous spread. Often have coexistent pleural effusion which may be aspirated to establish a diagnosis.

Dx-Pericardiocentesis

► **TB pleurisy,**

Dx- Pleural fluid aspirate -typical features include a high cell count with a lymphocytic predominance, a high protein and a low glucose count. Aid-fast bacilli are not frequently seen and culture is often negative.

Pleural needle biopsy may be helpful in diagnosis and may reveal granuloma formation or possibly culture positively for TB.

Skeletal TB

(Pott's disease) typically presents with back pain or stiffness in the absence of other symptoms, and sometimes develops into weakness or paralysis of the lower extremities (Pott's paraplegia) if diagnosis is delayed. The diagnosis of skeletal TB is difficult, given that bacilli are sparse and the culture of pus or tissue rarely positive. Tuberculosis vertebral osteomyelitis (Pott's disease) characteristically shows contiguous destructive vertebrae and paraspinal masses

Asymptomatic renal involvement

may occur in all forms of TB,

Patients typically have
concomitant extragenitourinary
disease.

Sterile pyuria is the most frequent
presentation of genitourinary TB.

Abdominal TB

- ▶ **Bowel involvement** is not commonly seen in HIV-associated TB,
- ▶ **Visceral abscesses** (including hepatic, splenic and pancreatic)
- ▶ **TB peritonitis** may be seen.
- ▶ Dx-diagnosis of gastrointestinal TB is often made by **physical exam**, which may reveal ascites, peritonitis, or tender abdominal masses.
- ▶ **Abdominal ultrasound or CT** (if available) may reveal mesenteric lymphadenopathy as well as hepatic, splenic or pancreatic enlargement and/or abscesses, which may be aspirated for definitive diagnosis.
- ▶ If **peritoneal fluid** is present, it may be aspirated and examined for the typical findings: an exudative fluid with lymphocytic predominance, high protein, and low glucose.
- ▶ **Peritoneal biopsy** may also be obtained and tissue examined histologically.

Diagnosis -TBM

- ▶ 1.Many patients have evidence of TB elsewhere
- ▶ 2. 50% of adults have an abnormal CXR
- ▶ 3. Elevated protein
- ▶ 4. 43% of HIV+ patients had a normal protein
- ▶ 5. Moderate pleocytosis (usually 100-1000 cells/mm³) -Lymphocytic
-PMN predominance in 25% of cases, esp. in early phase
- ▶ 6. Low CSF sugar
- ▶ 7.CSF smears for AFB positive only in 50%
- ▶ 8.Culture of CSF gold standard

Imaging (continued)

- ▶ Basilar enhancement and thickening
- ▶ Hydrocephalus—ventricular enlargement
- ▶ Infarcts: basal ganglia
- ▶ Intracranial mass (tuberculoma)
 - ▶ May be more frequent in patients with HIV

Treatment

- ▶ Steroids if patients present with:
 - ▶ Mental status changes
 - ▶ Focal neurologic deficits
 - ▶ Significant cerebral edema
 - ▶ Spinal cord disease
- ▶ Dose: 8-12 mg/d of dexamethasone or 60-80 mg of prednisone tapered over 6-8 wks

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The current short-course treatment for active tuberculosis

Duration: 6 months

Antibiotics: rifampin (R), isoniazid (H), pyrazinamide (Z), ethambutol (E) for 2 months followed with RH for 4 months (2RHZE/4RH)

Efficacy: > 95% vs. drug-susceptible TB... if


- all drugs are available,
- appropriately prescribed,
- appropriately delivered,
- and actually taken by the patient for the entire treatment duration

Updated TB treatment guidelines-2013

Standardised treatment protocols with fixed dose combination medicines are used for TB treatment.

There are now three treatment regimens;

- ▶ **Regimen 1:** for new and previously treated adults and children >8yrs/ >30kg
- ▶ **Regimen 3A:** for children < 8yrs and <30kg with uncomplicated TB disease
- ▶ **Regimen 3B:** for children < 8yrs and <30kg with complicated TB disease



Updated 2013 guidelines for
retreatment of TB consists of

- ▶ 1. 3 months of intensive phase and 5 months of continuous phase
- ▶ 2. 2 months of intensive phase and 4 months of continuous phase.

Treatment for Extra pulmonary TB

Six months treatment is as effective in extra-pulmonary as in pulmonary disease.

In some instances of severe or complicated disease (meningitis, TB bones/joints, miliary TB) treatment may need to be extended to nine months.

The intensive phase remains two months and the continuation phase is prolonged to seven months – 2(RHZE)/ 7(HR).

REGIMEN 1: FOR ADULTS AND CHILDREN OLDER THAN 8 YEARS OR WEIGHING MORE THAN 30KG

Pre-treatment body weight	Intensive Phase 7 days a week for 2 months	Continuation phase 7 days a week for 4 months	
	RHZE (150,75, 400,275)	RH (150,75)	RH (300,150)
30-37 kg	2 tabs	2 tabs	
38-54 kg	3 tabs	3 tabs	
55-70 kg	4 tabs		2 tabs
>70kg	5 tabs		2 tabs

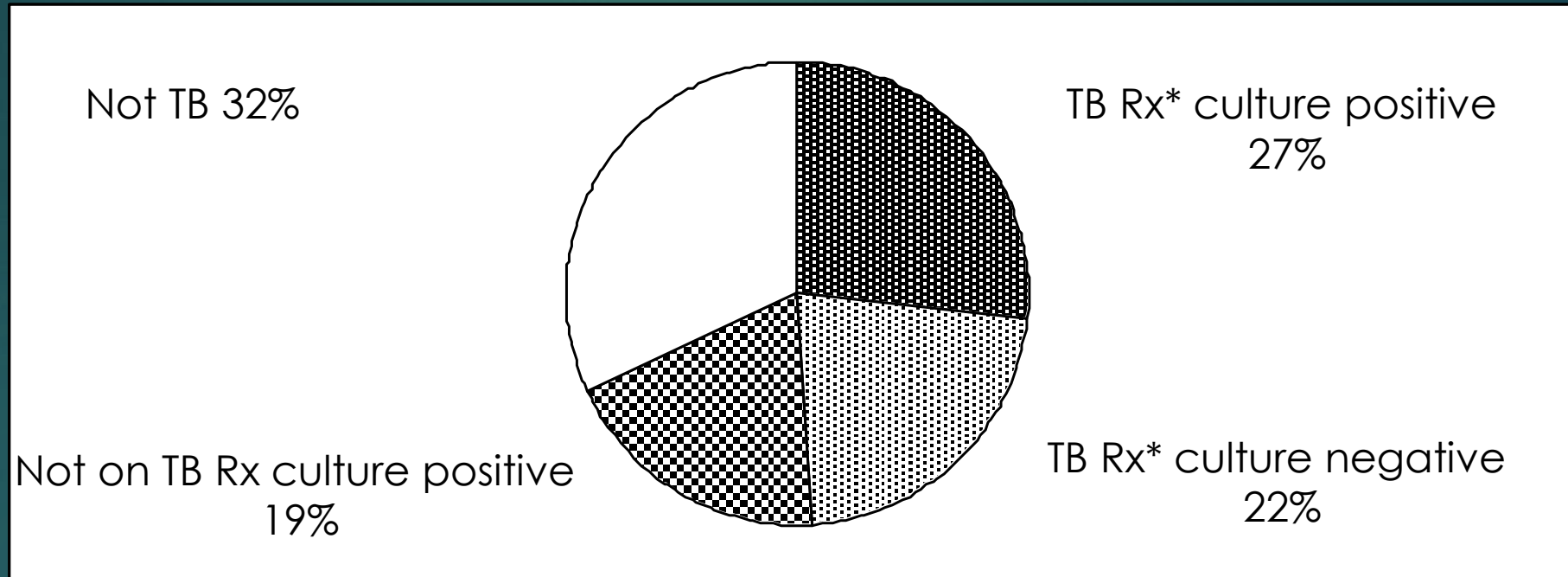
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SA Hospitals- Prevalence of OIs/Stage 4 conditions

- ▶ **Acute OI**— no. (90 %)
 - Pulmonary tuberculosis –39 %
 - Extrapulmonary tuberculosis (including meningitis)- 25%
 - Cryptococcal meningitis -10%
 - Chronic diarrhea (>14 days)-9%
 - Bacterial pneumonia -3%
 - Toxoplasmosis gondii* -2%
 - Pneumocystis jirovecii* pneumonia-1%
- ▶ **Others** (9%)
 - HIV related cardiomyopathy
 - Thrombocytopenia of various causes
 - PML
 - Viral encephalitis ?HSV
- ▶ **HIV-associated kidney disease** 1%

Edendale post mortem diagnosis by TB status [n = 240]



- Tuberculosis 68%
- *61% of TB cases on Rx diagnosed during final admission
- 14% of positive cultures MDRTB

Linkage into care from hospital

KwaZulu-Natal, South Africa (2006/7)

49 participants-
ART preparation

Median CD4 = 42

TB 76%

PCP 8 %

Chronic diarrhoea 8%

CM 6%

Toxoplasmosis 4%



27% died before ART

41% initiated ART

8% loss to follow-up

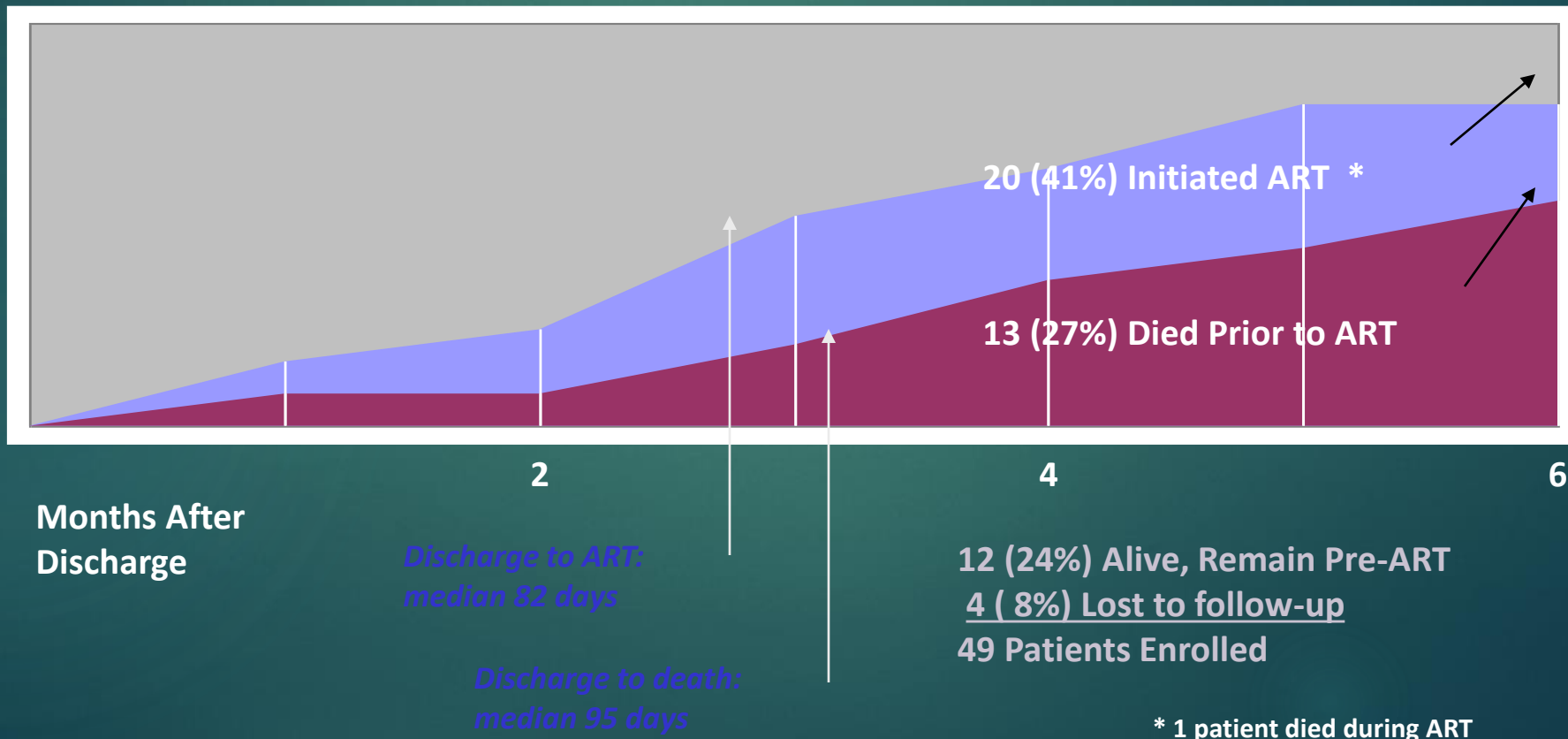
24% alive and still pre ART.

Low uptake of antiretroviral therapy after admission with human immunodeficiency virus and tuberculosis in KwaZulu-Natal, South Africa

Int J Tuberc Lung Dis 2009;14(7): 903-908. Murphy R.A., **Sunpath H**, Edwin C.et.al

Result -The patients with the most advanced disease (CD4 count <50/mm³) were least likely to initiate ART by 6 months.

Patient Trajectory After Discharge



Require fast track (ART initiation within 7 days of being eligible)

Patients with low CD4 <200

CNS infections including CCM, Toxoplasmosis ,PML

Lung infections –PCP, severe PTB, Bacterial pneumonias

Extrapulmonary and disseminated TB

HIV associated malignancies.

Persistent diarrhoea

Patients with TB/HIV co morbidity with CD4 count < 50

**Patients with poor general medical condition and high mortality
irrespective of CD4 count**

Renal failure

Cardiomyopathy

Dementia..... The South African Antiretroviral Treatment Guidelines March 2013. In: Department of
Health Republic of South Africa and South African National AIDS Council;

Operationalizing Early Inpatient ART during Hospitalization with Acute O

Sunpath H - Edwin C, Chelin N et al. *The International Journal Tuberculosis and Lung Diseases (TB Union Journal)*. Manuscript number : IJTLD-09-11-0651.R2, July 2012.

ART as part of inpatient care to pts with OI

- ▶ Median CD4 count -33 (12-78)
- ▶ 11/2006 to 8/2007- of 1126 pts admitted
- ▶ 382 prospectively enrolled
- ▶ Median time from admission to ART: 14 d (IQR 11- 18)
- ▶ TB –PTB (39%) EPTB including TBM (25%)
- ▶ CCM (9%); HIVAN (5%); CHR DIARRHOEA (3%); PNEUMONIA (2%)
- ▶ TOXO/PCP/OTHER

During 24 weeks of follow up

- ▶ Among patients who died, median days to death 33 days (IQR-9 -95)
- ▶ Longer interval between admission and ART initiation independently associated with mortality (≥ 21 d, OR 2.1 compared with < 21 d)
- ▶ **Mortality reduction by 50% among those initiated on ART within 3 weeks of admission**

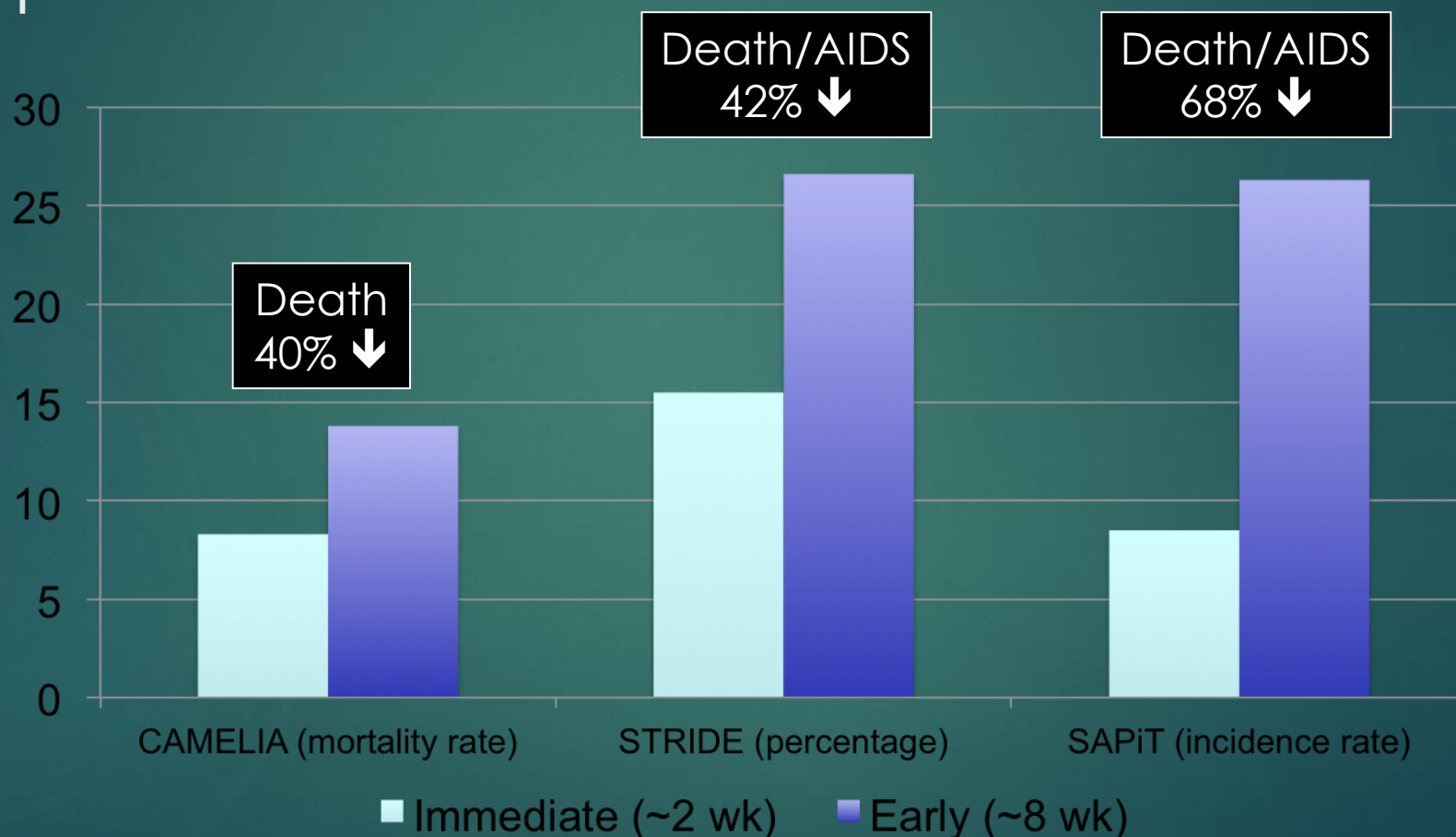
Reducing mortality from TB-HIV coinfection

▶ WHICH OF THE FOLLOWING STATEMENTS ARE FALSE

1. START TREATMENT FOR TB IN ILL PATIENTS ASAP BASED ON WHO ALGORITHM AND/OR CLINICAL SUSPICION
2. START ART AS AN INPATIENT ASAP OR LINK TO ART SITE UPON DISCHARGE
3. TB MENINGITIS –TREAT LONGER BEFORE ART
4. PATIENTS WITH CD4 COUNT<50 WILL HAVE THE GREATEST REDUCTION IN MORTALITY BY STARTING ART AT EIGHT WEEKS AFTER TB TREATMENT

TB

ART timing and major outcomes in patients with TB and CD4 < 50



* CAMELIA data represents all patients in trial, majority had CD4 < 50 (median CD4 =25)

SAHIVCS GUIDELINES-SEPT 2012

Starting ART in patients with TB

- ▶ CD4 count ≤ 50 cells/ μ l: - after 2 weeks of TB treatment when it is clear that the patient's TB symptoms are improving and that TB therapy is tolerated.
- ▶ CD4 count > 50 cells/ μ l: - delayed until after the intensive phase of TB treatment (2 months) unless the patient has other serious HIV-related conditions (e.g. Kaposi's sarcoma or HIV encephalopathy, persistent diarrhoea etc)
- ▶ TB meningitis (TBM) - Recommend starting ART 2 - 8 weeks after TBM diagnosis.
- ▶ Often patients with CD4 > 50 cells/ μ l have other compelling indications to start ART asap= so individualise the timing as long as one is able to follow up patients.

“New” potential drugs for TB

Which drug is stored in the lung tissue for a long time and can help reduce treatment to 2-4 months

- *1. the new diarylquinoline TMC207 or J
- *2. the metronidazole derivatives (Pa-824, OPC-67683)
- 3. Oxazolidinones
- 4. Benzothiazinones (BTZ)
- *5. Clofazimine

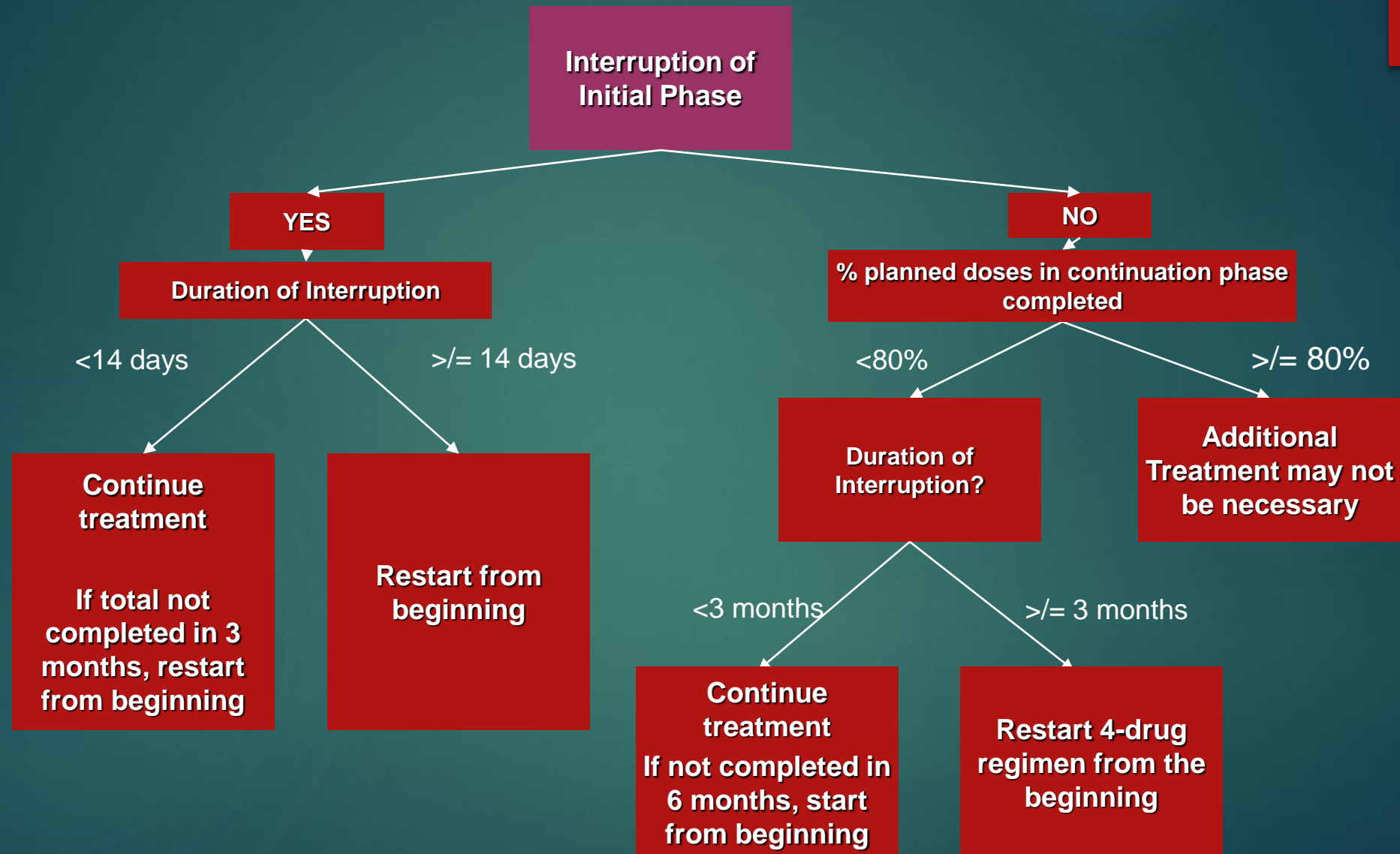
An ultra short-course regimen to test

- ▶ Rationale: Take advantage of both the potent bactericidal activity of RHZE and the Pk of clofazimine (long half life and accumulation in lung tissue)
- ▶ Protocol:
 1. Combine the most effective drug regimen (RHZE) with clofazimine for a relatively short period of time (2-4 months) to kill majority of bacilli, then stop treatment and let the “accumulated” clofazimine do the job of eliminating persisters
 2. Other possibilities: (i) Substitute the diarylquinoline TMC 207 for clofazimine; (ii) Substitute moxifloxacin for isoniazid after the first two days of treatment

Treatment Completion and Relapses

58

Treatment Outcomes	Definitions
Cure	Patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion
Treatment Completed	Patient who has completed treatment but who does not meet the criteria to be classified as a cure or a failure
Treatment failure	Patient who is sputum smear-positive at five months or later during treatment
Default	Patient whose treatment was interrupted for two consecutive months or more
Transfer out	Patient who has been transferred to another recording and reporting unit, and for whom the treatment outcome is not known
Died	Patient who dies for any reason during the course of the treatment



There is a role for trial of TB treatment

1.True

2.False

TRIAL OF TREATMENT

- Severely ill with possible TB
- Meningitis
- Haemoptysis
- Miliary TB
- Resp. failure
- Pneumothorax
- Persistent s/s suggestive of TB but where investigations are negative
- NB. Reassess other sites of organ involvement that may yield a diagnosis that was overlooked e.g. lymphnodes
- Ensure that relevant specimens for TB smears, culture, histology sent.

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► The drugs that caused do not cause hepatitis are

1. Isoniazid,
2. Pyrazinamide,
3. Rifampin
4. Ethambutol

ART hepatotoxicity (Htox)

▶ NRTI, esp. d-drugs

- ▶ Increased risk of hepatic steatosis
- ▶ May be related to inhibition of mitochondrial DNA pol- γ

McGovern et al, CID 43:365

▶ NNRTI, esp NVP

- ▶ Early NVP Htox (6-18 wks): Rash, systemic sx; Risk factors: female sex, CD4 count >250
- ▶ Late NVP HTox: no systemic sx; risk factor: viral hepatitis

▶ PIs: esp. TPV/rtv, RTV

Caution			
ddl	d4T	NVP	RTV*
		TPV	
AZT	EFV		
Safe			
ABV	TDF	APV	DRV
3TC	FTC	ATV	LPV
		SQV	NFV
			T20
NRTI	NNRTI	PI	Entry inhibitors

Soriano et al, AIDS (2008) 22:1

DILI due to antituberculous therapy (ATT)

- ▶ 40 patients (4.6%) developed severe hepatotoxicity after initiating ARVs : **TB treatment increased risk 8.5-fold**
- ▶ May occur with any of the 1st line drugs, particularly INH, rifampicin and

PZA

- ▶ Overall rate: 5-33%
- ▶ Risk factors:
 - ▶ Older age (>35 years)
 - ▶ Pregnancy
 - ▶ Elevated baseline LFTs
 - ▶ Malnutrition
 - ▶ HIV
 - ▶ Active Hepatitis B or C infection
 - ▶ Alcohol use
 - ▶ Concurrent use of other hepatotoxic medications
 - ▶ Allopurinol decreases PZA clearance, may increase its hepatotoxicity

Hepatotoxicity during ATT: Interventions

- ▶ Consider stopping medications if:
 - ▶ Serum transaminases are $> 5 \times \text{ULN}$ with or without symptoms (SA $\Rightarrow > 10 \times \text{ULN}$)
 - ▶ Transaminases are $> 3 \times \text{ULN}$ with jaundice or hepatitis symptoms ($> 5 \times \text{ULN}$)
- ▶ Rechallenge: Start with EMB and Strep imi
 - ▶ When ALT returns to $< 2 \times \text{ULN}$, rifampicin may be restarted
 - ▶ After 3-7 days, reintroduce INH, and subsequently check ALT
 - ▶ If symptoms recur or ALT increases, the last drug added should be stopped.

Saukkonen et al. Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy. Am J. Respir Crit Care Med 174:935 (2006)

LFT Abnormalities After Starting ARVs: Differential Diagnosis

- ▶ Drug-induced liver injury
 - ▶ ARV hepatotoxicity
 - ▶ Antituberculous therapy hepatotoxicity
 - ▶ Other: alcohol, traditional medications
- ▶ Immune Reconstitution Inflammatory Syndrome
 - ▶ TB
 - ▶ Opportunistic infections, e.g. MAC (granulomatous hepatitis)
- ▶ Superinfection
 - ▶ HAV, HCV, HDV, HEV, EBV, CMV
- ▶ Hepatitis B flare

TB IRIS

- ▶ TB IRIS is characterized by clinical worsening soon after initiation of ART
 - ▶ Occurs in 10-30% of patients commencing ART
 - ▶ Fever, adenopathy, worsening respiratory symptoms, increasing pulmonary infiltrates or effusions, intracranial tuberculomas, ascites, splenomegaly, psoas abscess, intra-abdominal adenopathy
- ▶ Two types:
 - ▶ Paradoxical TB IRIS
 - ▶ ART-associated TB/"Unmasking" TB IRIS

Meintjes et al. *Lancet ID* (2008). 8: 516.

TB IRIS of the Liver

- ▶ In 19 patients with TB-IRIS, 7 (37%) had intra-abdominal manifestations and 4 (21%) had hepatic involvement
- ▶ All 4 had hepatomegaly and elevated levels of biliary cannicular hepatic enzymes without evidence of biliary obstruction on U/S
 - ▶ Median AP 495, GGTP 338, ALT 66, AST 68.
- ▶ In all 4 cases, there was evidence of TB-IRIS at another anatomic site, e.g. intra-abdominal adenopathy, increased respiratory disease.

Lawn et al. AIDS 21:335. Lawn and Woods, AIDS 21: 2362. Verma S. AIDS Res Hum Retroviruses. 22:1052

Boosted PI-containing ART in patients with TB coinfection

The management of TB coinfection in patients receiving a PI is a challenge because rifampicin reduces the trough concentration of most PIs.

Rifampicin induces cytochrome 3A4 and p-glycoprotein resulting in a 90% reduction in lopinavir trough concentrations.

This reduction in lopinavir can be attenuated by using higher doses of RTV or higher doses of LPV.

South African recommendation for HIV/ TB patients receiving LPV/r-based 2nd line ART

2010 SA HIV Guidelines: “Patients receiving lopinavir/ritonavir (Aluvia) should have their dose doubled slowly over 2 weeks to 800/200 mg twice a day (4 tabs bd)”

The total ritonavir dose with the new recommendation is 400 mg/day (LPV/r 4 tabs bd contains 400 mg RTV) versus 800 mg/day with prior strategy.

What is the evidence?

PI-containing ART in TB:

Double dose LPV/r 800/200mg (4 tabs) bid?

Decloedt and Maartens *et al* (SA) study of patients receiving TB therapy:

- 11 patients received double dose LPV/r (4 tabs/bd)
- 9 received additional RTV (+300 mg RTV /bd)

Results: LPV concentrations remain above 1 mg/L in most patients

- 10/11 (91%) patients maintained an undetectable viral load

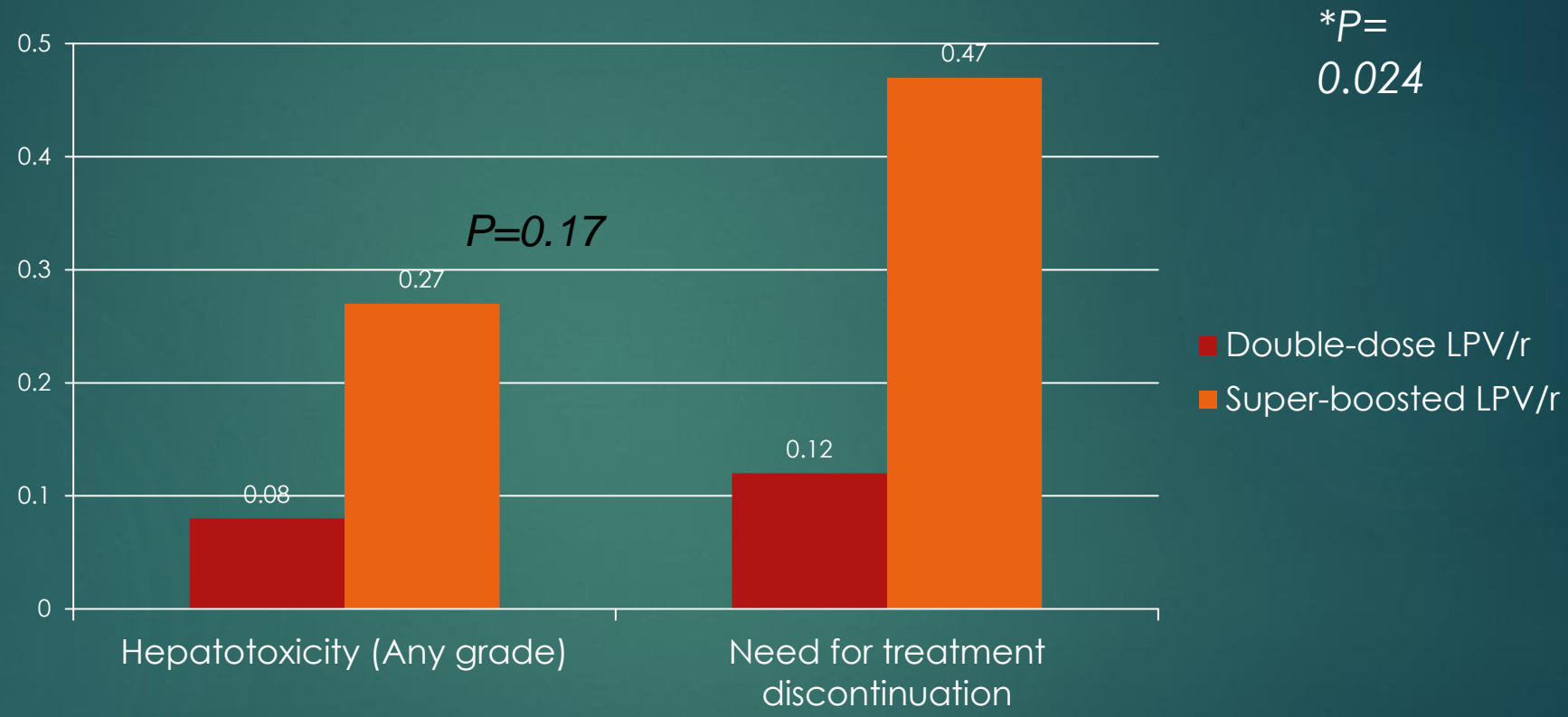
1/2 of patients developed at least one AE

- Grade 1 and 2 transaminitis common but no severe hepatotoxicity
- More patients in the additional RTV group developed AE vs double dose LPV/r group (5/7 compared to 5/11).
- 1 pt. defaulted additional RTV due to nausea , 1 pt. receiving double-dose LPV/r had “intolerable diarrhea” and LPV/r dose ↓ to 3 tabs bd

Authors recommend: Gradually increasing LPV/r to 4 tabs bd & monitor transaminases.

McCord Hospital - Using historical data, we compared adverse events and treatment discontinuation with two LPV/r (Aluvia) strategies used at McCord during TB therapy:

% experiencing



Murphy R, Ebrahim S, Sunpath H. Coadministration of lopinavir/ritonavir and Rifampicin in HIV and tuberculosis co-infected adults in" PLoS, August 2012.PONE-D-12-09610

Double dose LPV/r 800/200mg (4 tabs) bid?

The double-dose LPV/r strategy presents an additional advantage on a practical level:

- ▶ It does not require the use of ritonavir 100 mg soft-gel, a formulation which requires refrigeration and is difficult to store in the developing world where most tuberculosis coinfections occur.
- ▶ The double-dose LPV/r strategy only requires escalating the dose of heat-stable LPV/r tablets (Aluvia) which are widely available.

The use of double-dose lopinavir/ritonavir during rifampicin-based treatment appears to be a pragmatic interim strategy until more appropriate agents become available for HIV/TB coinfecting patients.

Since this is a new strategy, reporting of serious toxicities associated with this treatment strategy is critical.

Sunpath H, Winterheimer P, Cohen S, Tennant I, Chelin N, Gandhi R, Murphy. "Double-dose lopinavir/ritonavir in combination with rifampicin-based tuberculosis treatment in South Africa" (Original Article) R.Int J.TB and Lung Disease ..Sept 2013 ...i

Future options? Use of raltegravir in HIV/TB coinfection

Raltegravir 400 mg bid acceptable, maybe preferable

Prior data showed that when raltegravir is combined with rifampicin, trough RAL concentrations are reduced 61% and AUC drops 40%.

This effect partially compensated if RAL is increased to 800 mg bid.

But a randomized clinical trial showed that among patients who received rifampicin-based TB therapy followed after a median of 8 wks by TDF + 3TC + RAL 400 mg OR 800 mg BID the following 24 week outcomes were observed (n=~50 per group):

- RAL 400 mg bid: 24 wk suppression rate 76%, 0 AE with discontinuation
- RAL 800 mg bid: 24 wk suppression rate 78%, 3 AE with discontinuation (**2 with severe hepatotoxicity including 1 fulminant failure → liver tranpt.**)
 - Trend to ↑ integrase resistance in RAL 400 bid arm (4 pts.) vs 800 bid (1 pt.)
 - Suggestion of ↑ toxicity in the RAL 800 mg bid arm

Case 1

Sampson is a 47 year old man diagnosed with HIV approximately 5 years ago.

His presents with weight loss of 10kg over the course of 2 months and generally feels tired and unwell.

His temperature is 39°C.

You send off a CD4 count which is determined to be 37 cells/mm³.

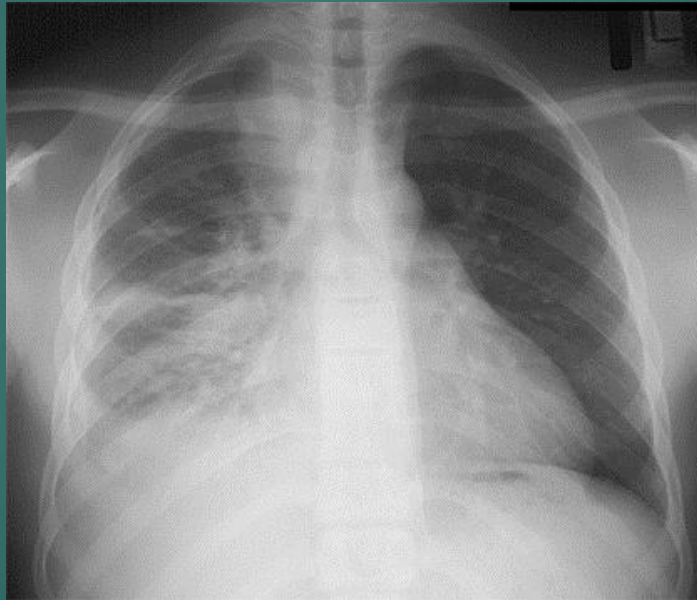
Case

- ▶ You send 2 sets of sputum for AFB and the results are negative
- ▶ You order a chest x-ray. What might you expect to see?
 - A. Pleural effusions
 - B. Intrathoracic lymphadenopathy
 - C. Diffuse infiltrates
 - D. Consolidations in the upper lobes
 - E. No abnormalities
 - F. **Any of the above**

Case

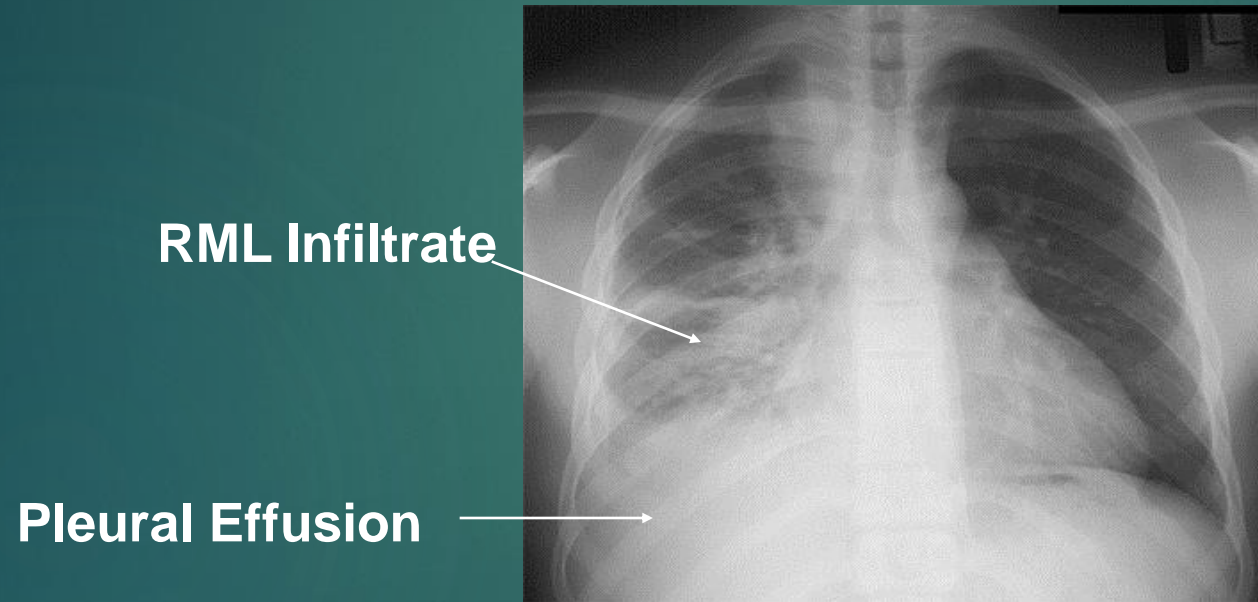
10 weeks ART initiation a pt presents to OPD with cough productive of brownish sputum, temp = 39.8⁰C, and retrosternal chest pain. You order a repeat chest-xray.

Repeat Chest Xray



What changes do you note in this chest x-ray?

Repeat Chest Xray



Case 3 Continued

New lymphadenopathy is noted on physical examination.



Case 3 Continued

- ▶ You obtain the following information
 - CD4 = 110
 - Viral Load = Undetectable
 - FNA of the lymph nodes = Multiple granulomas and signs of both acute and chronic inflammation

Case 3 Continued

- ▶ What's your differential?
 - Failure of TB treatment
 - MDR TB
 - PCP
 - Bacterial Pneumonia
 - Disseminated Fungal Infection
 - Mycobacterium Avium Complex
 - Paradoxical Worsening of TB on Treatment
 - Immune Reconstitution TB

What is Immune Reconstitution Syndrome? (IRS)

A Deterioration in Clinical Status
Due to Immune System Recovery
During Treatment with Antiretroviral Therapy

Final Quiz 1

- ▶ A 45 year old man who has never been tested for HIV presents with a 3 month history of productive cough and night sweats. A chest xray shows an upper lobe cavity and his sputum reveals AFBs. He is started on rifafour.
 - ▶ True or False
 - ▶ He should be offered an HIV test
 - ▶ His sputum should be sent for culture and sensitivity
 - ▶ He should have a TB blood culture
 - ▶ Close contacts in his home should be screened

Final Quiz 2

- ▶ The patient is counseled and tested for HIV. He is positive.
 - ▶ True or False
 - ▶ He should be started on cotrimoxazole prophylaxis immediately
 - ▶ His response to TB therapy is likely to be significantly poorer than an HIV-negative person's would be

- 
- ▶ TST IS MANDATORY BEFORE IPT IS GIVEN ACCORDING TO THE SA GUIUE DELINES
 - ▶ 1.TRUE
 - ▶ 2.FALSE

TB PREVENTION

▶ **Guidelines for Tuberculosis Preventive Therapy among HIV Infected Individuals in South Africa. (NDOH, 2010)**

- ✓ Isoniazid 300mg daily for 6 months for all persons living with HIV /AIDS.

- **Excluding persons:**

- ✓ who have TB symptoms (any of cough, night sweats, weight loss)

▶ **Including:**

- ✓ Persons on ART/ eligible for ART
- ✓ Pregnant women

NEW DEVELOPMENTS ON IPT POLICY

- ▶ Tuberculin Skin Test (TST) is recommended
 - ✓ HIV+ve no TST available 6/12 INH
 - ✓ HIV+ve TST-ve not on ARV: 6/12 INH
 - ✓ HIV+ve TST-ve on ARV 12/12 INH
 - ✓ HIV+ve TST+ ve INH 36/12

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