HIV and TB

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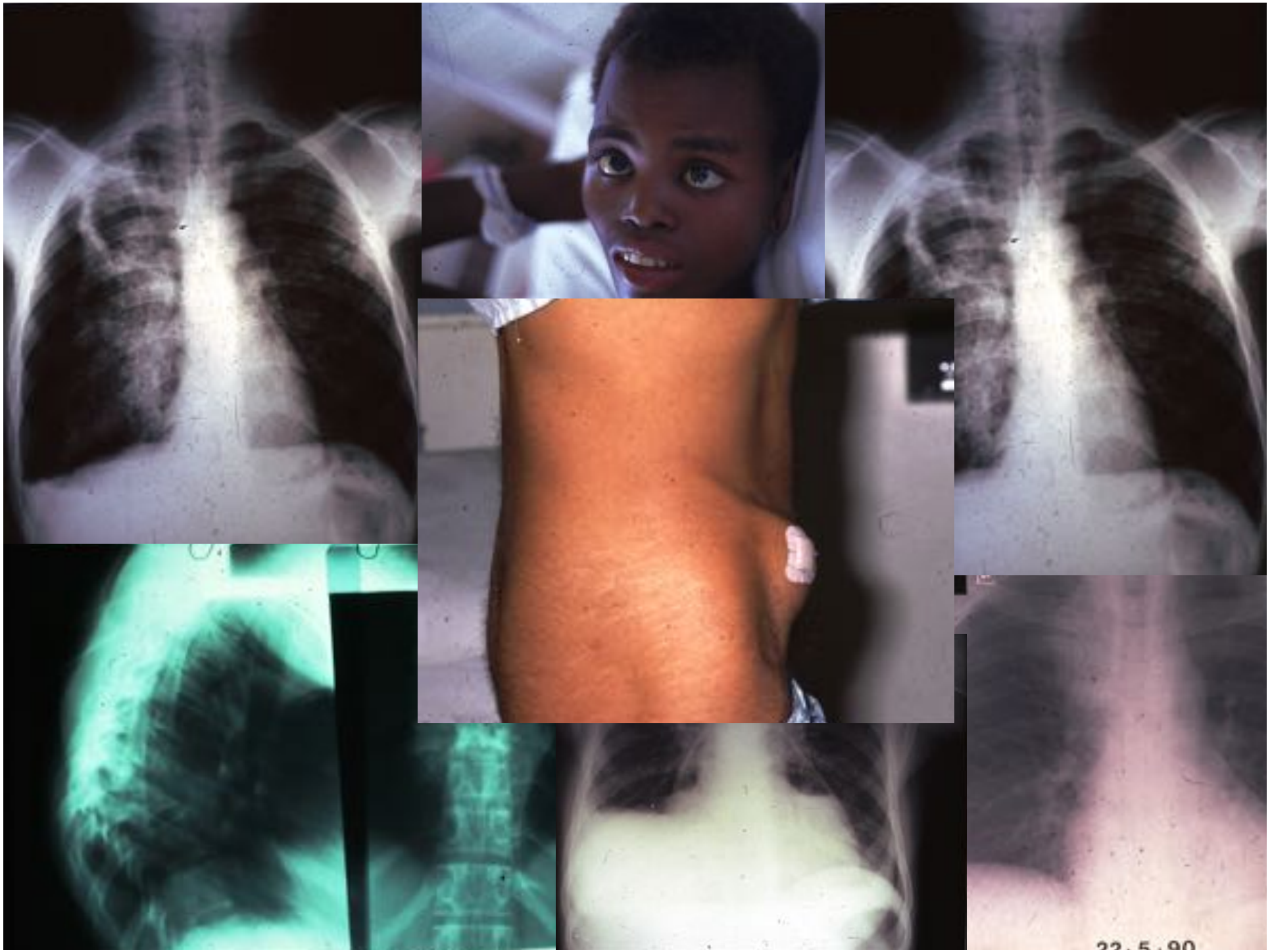
GreenShoots FOUNDATION

“Support needing populations through medical assistance and the transfer of knowledge to local medical practitioners.”

Our vision for the

Medical Assistance & Medical Education (MAME) Programs

GreenShoots FOUNDATION



Talks – brief!

- Epidemiology

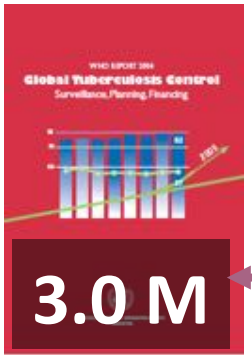
Some of the many challenges that remain

- **Epidemiology**

TB/HIV current situation: Testing for HIV in patients with TB

Number of countries reported to WHO

7/210



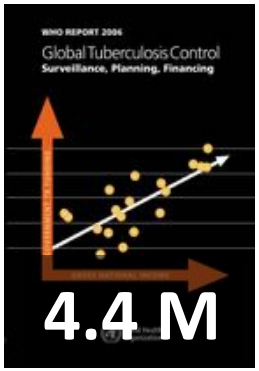
2002

Number of countries offering HIV testing for TB patients

62/199

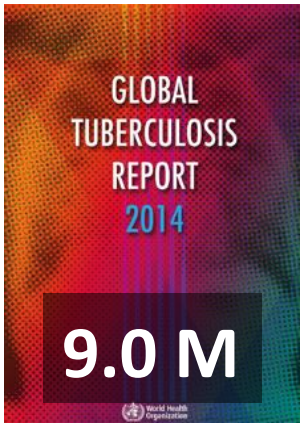
2003

69/200



2004

92/199



2014

Number of incident TB cases reported (millions)

Getahun H. *IAS* 2007;TUSY101.

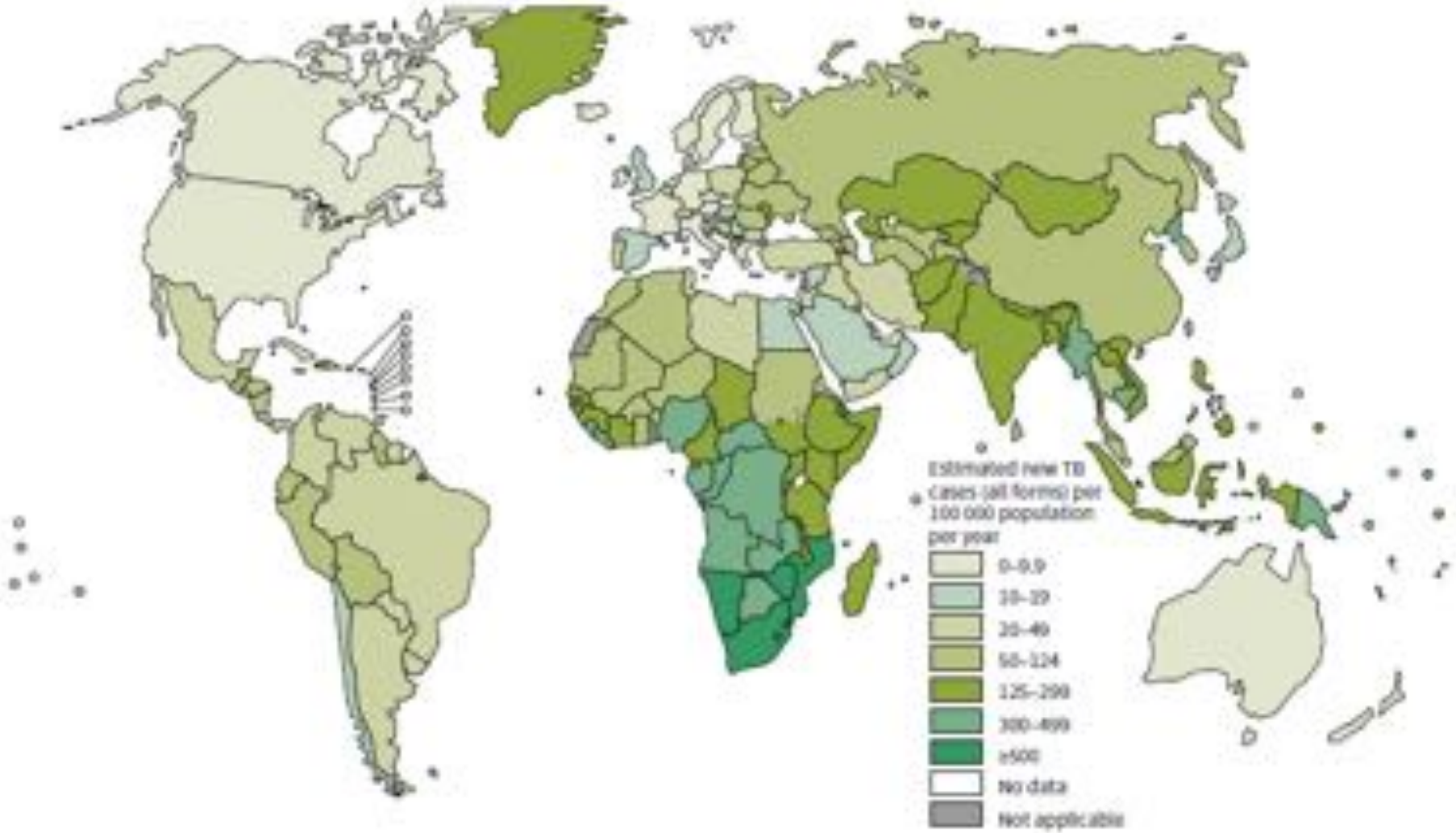
Epidemiology…

- In 2013, 6.1 million TB cases were reported to WHO
- Of the estimated 9 million people who developed TB in 2013, more than half (56%) were in the South-East Asia and Western Pacific Regions.
- An estimated 1.1 million (13%) of the 9 million people who developed TB in 2013 were HIV-positive
- Globally, the TB mortality rate fell by an estimated 45% between 1990 and 2013 and the TB prevalence rate fell by 41% during the same period.

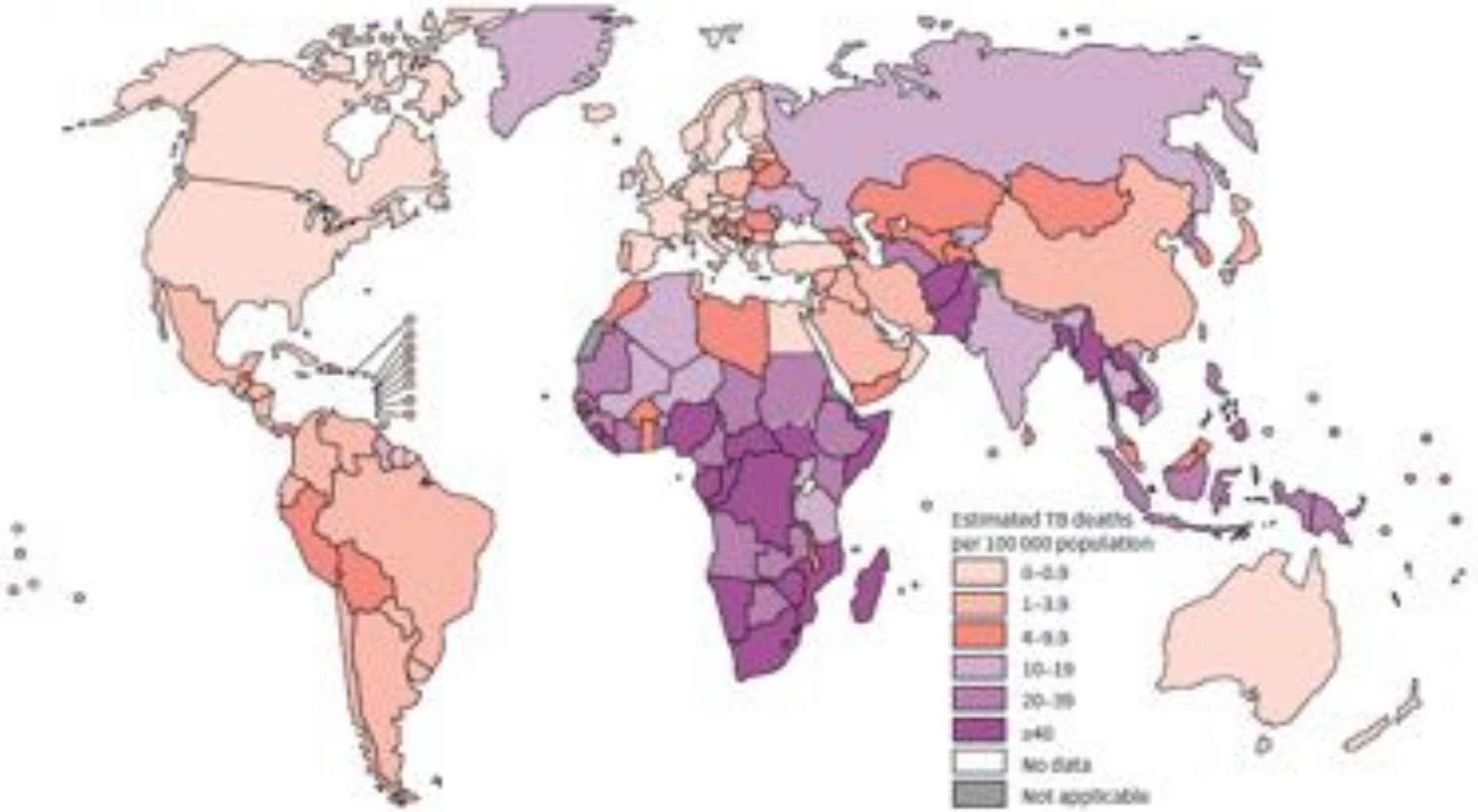
Epidemiology…

- 48% of TB patients globally had a documented HIV test result
- In 2013, 70% of TB patients known to be HIV-positive were on ART.
- In 2013, the treatment success rate continued to be high at 86% among all new TB cases.
- By June 2014, 108 countries had access to Xpert MTB/RIF at concessional prices

Estimated TB incidence 2013



TB mortality in HIV



Factors Increasing the Risk of Tuberculosis

- **HIV (800 x)**
- Silicosis
- Immunocompromise
- Malignancy [1]
- Insulin-dependent diabetes mellitus
- Chronic renal failure
- G-I disease associated with malnutrition [2]

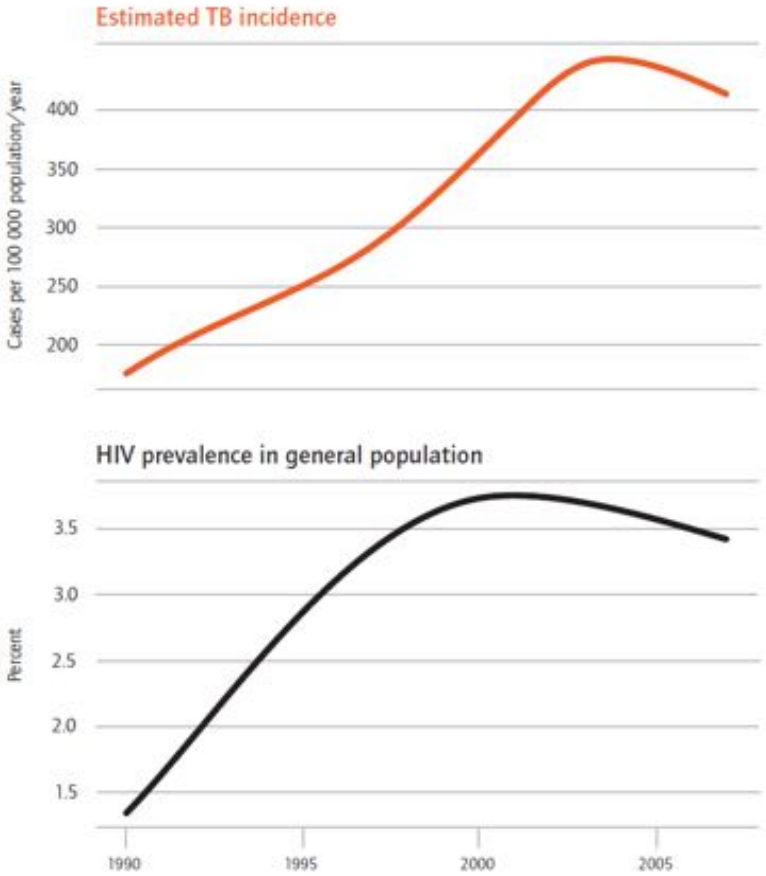
1. Especially lymphoma, leukaemia
2. Gastrectomy, jejunoileal bypass, Ca pancreas, malabsorption

- Age (children > young adults)
- First generation immigrants from high prevalence countries
- Close contacts of patients with smear-positive pulmonary tuberculosis
- CXR evidence of self-healed tuberculosis
- Primary infection < 1 year previously

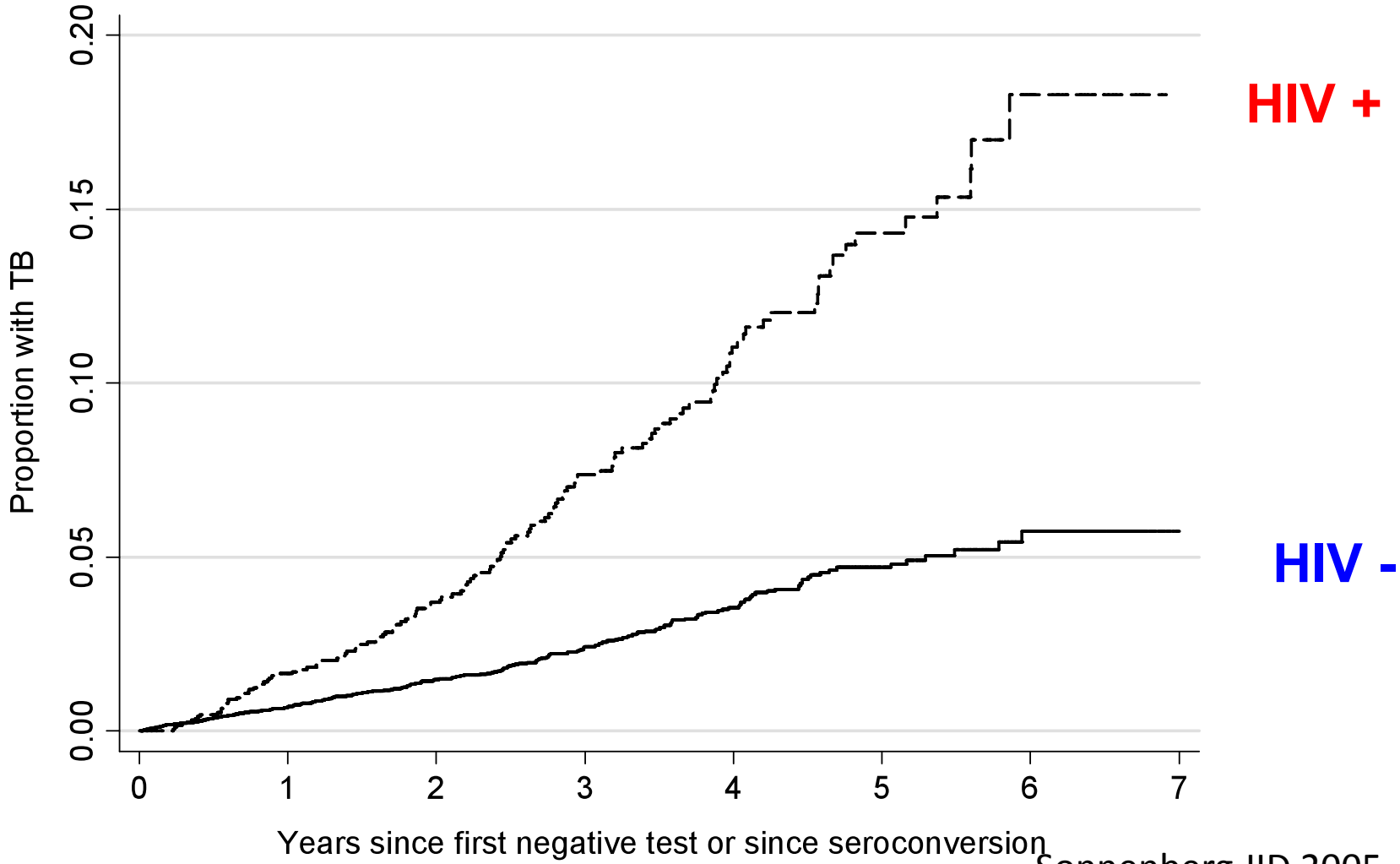
TB follows HIV

2006 - 709.000 co-infected
85% in Africa

FIGURE 1.7
Estimated incidence of TB and prevalence of HIV for the African subregion most affected by HIV (Africa high-HIV), 1990–2007

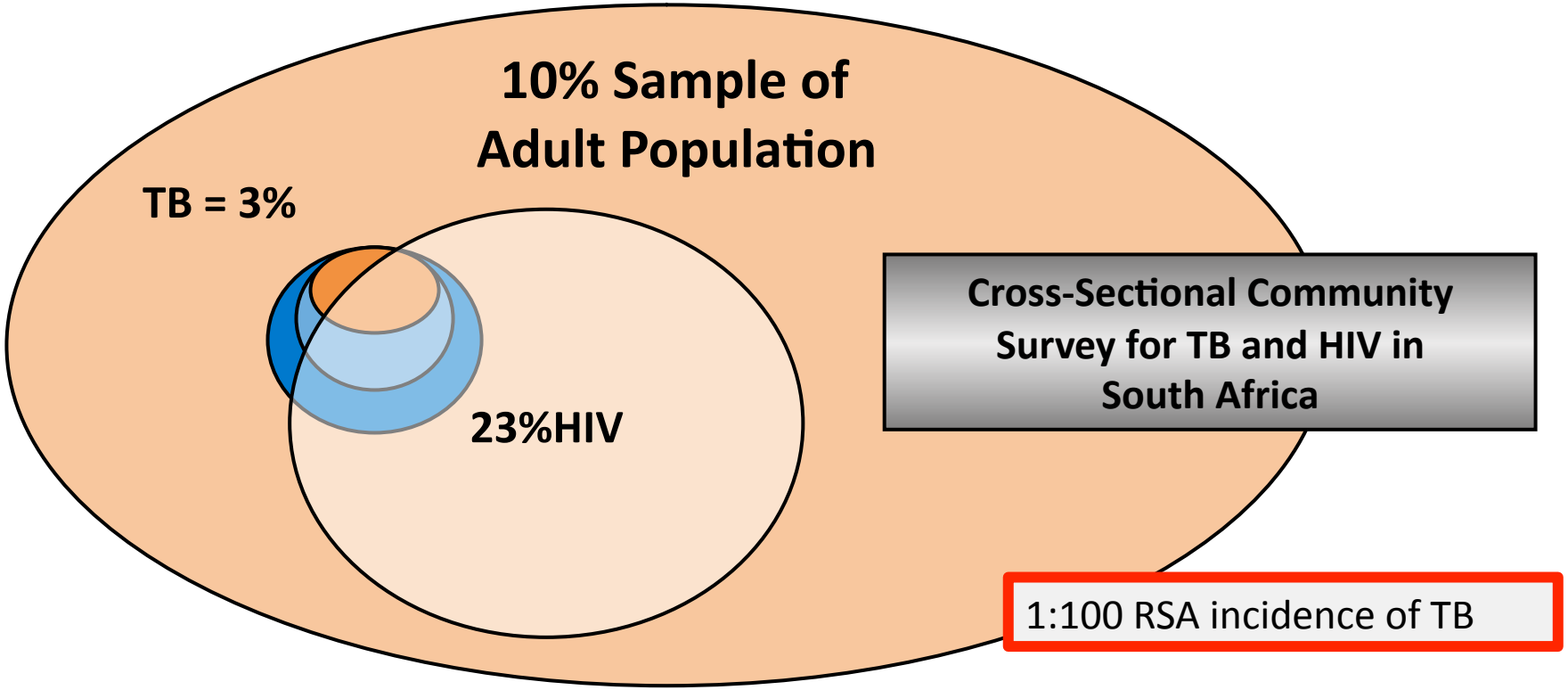


South African Miners Cohort – Cumulative hazard estimate of TB incidence by HIV status



Sonnenberg JID 2005

TB/HIV situation



Prevalent treated TB

Smear + PTB

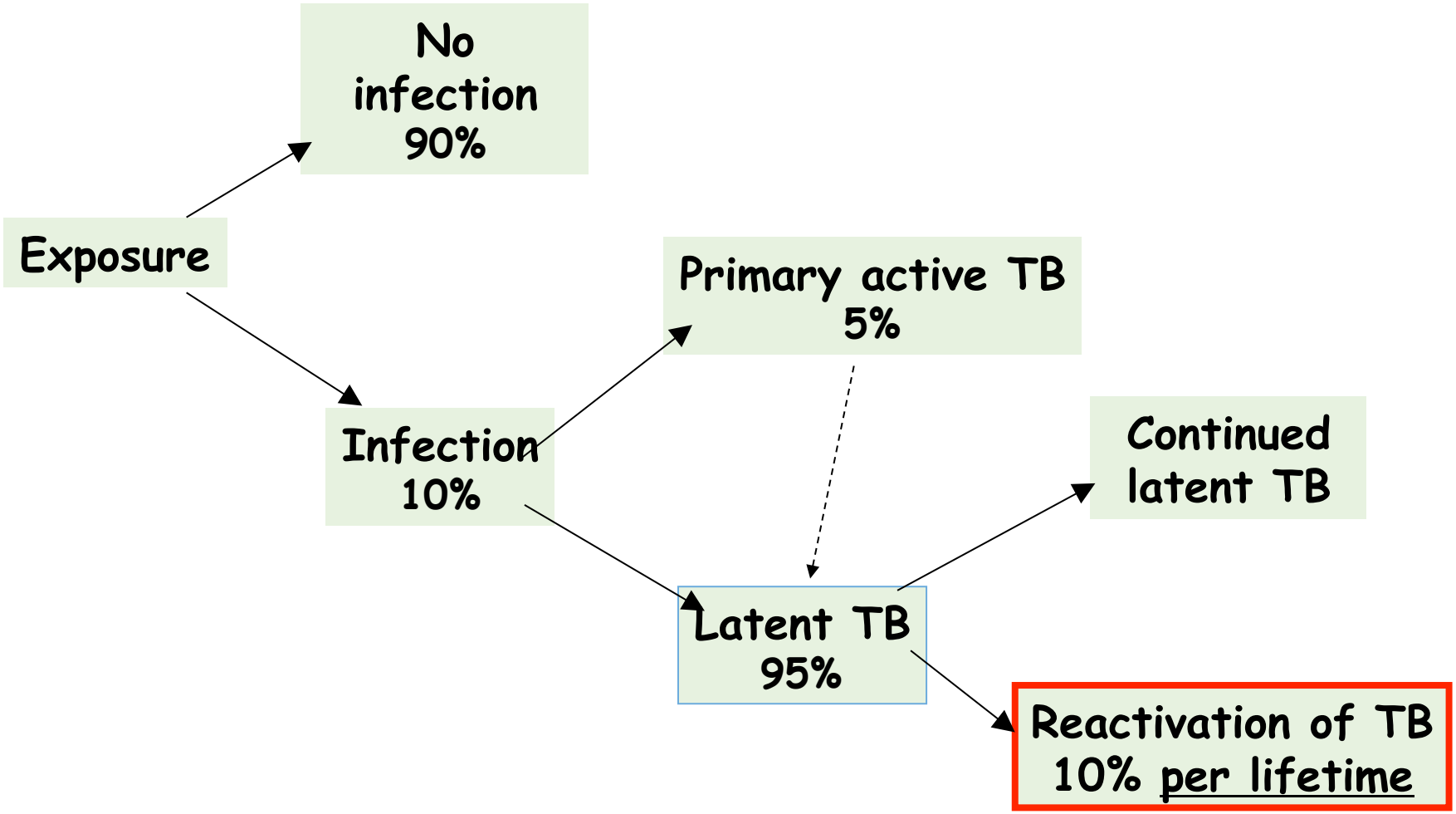
Culture + PTB

9% HIV-infected patients had PTB (5% undiagnosed)

Case finding proportions for HIV- TB = 0.67 and for HIV+ TB = 0.37

Lawn SD. *IAS* 2007;SUSA501.

Outcome of exposure to MTB – HIV negative

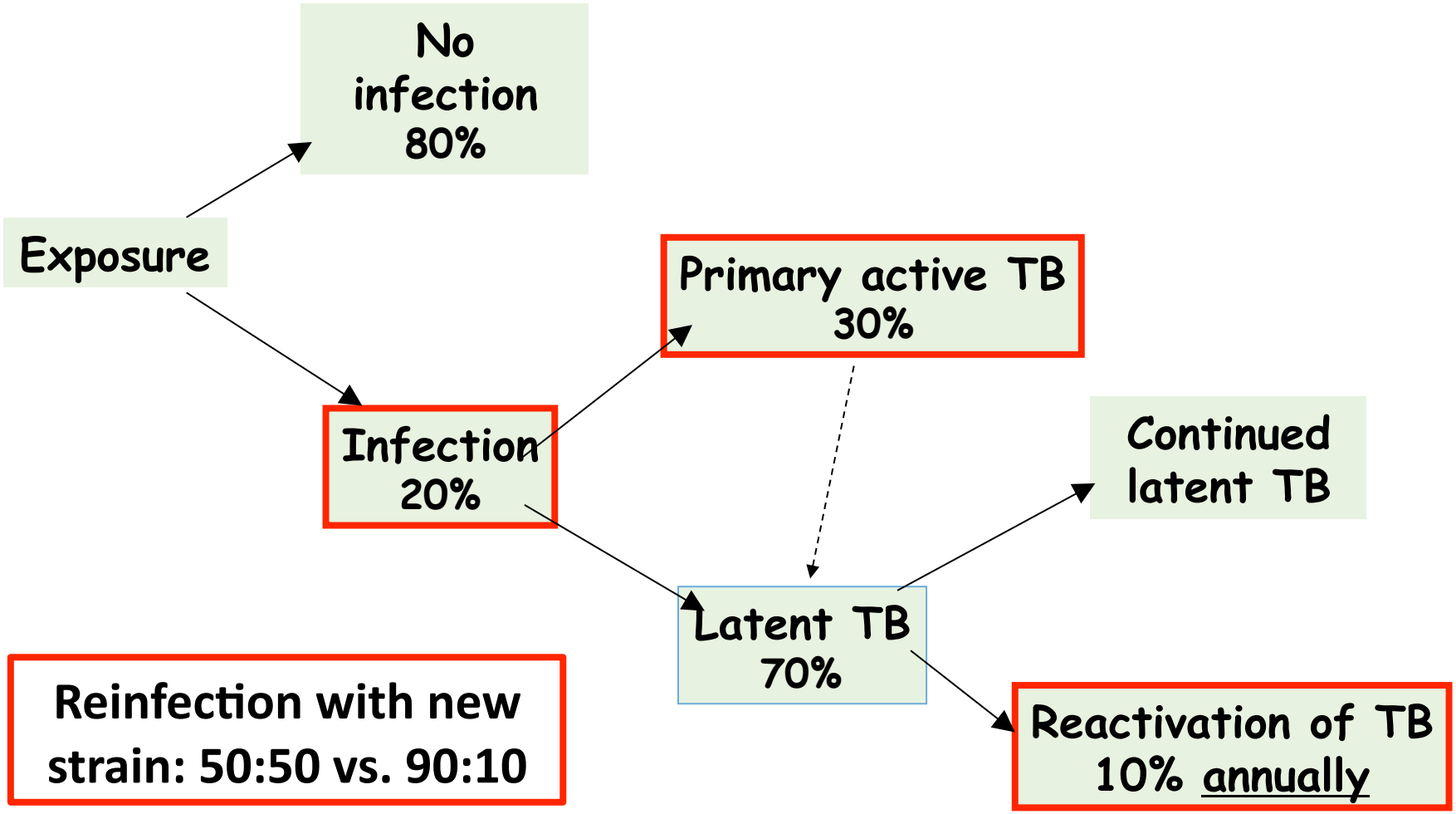


Timetable of primary tuberculosis

Time from infection	Manifestations
3-8 weeks	Primary complex, positive tuberculin skin test
3-6 months	Meningeal, miliary and pleural disease
Up to 3 years	Gastro-intestinal, bone and joint, lymph-node disease
Around 8 years	Renal tract disease
From 3 years onwards	Post-primary disease due to reactivation or re-infection

Adapted from Grange JM in Clinical Tuberculosis 1998. Editor PDO Davies

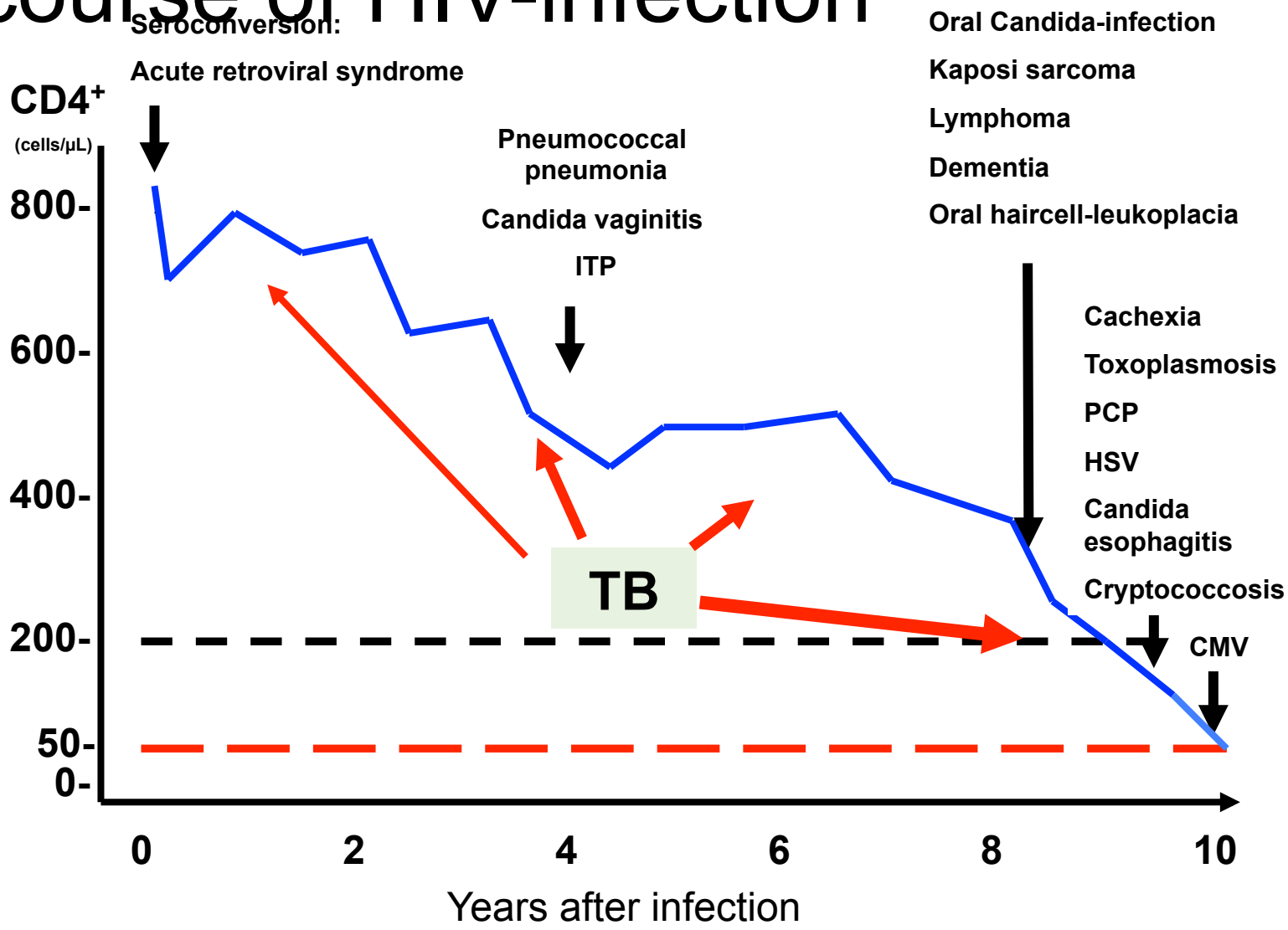
Outcome of exposure to MTB – HIV positive



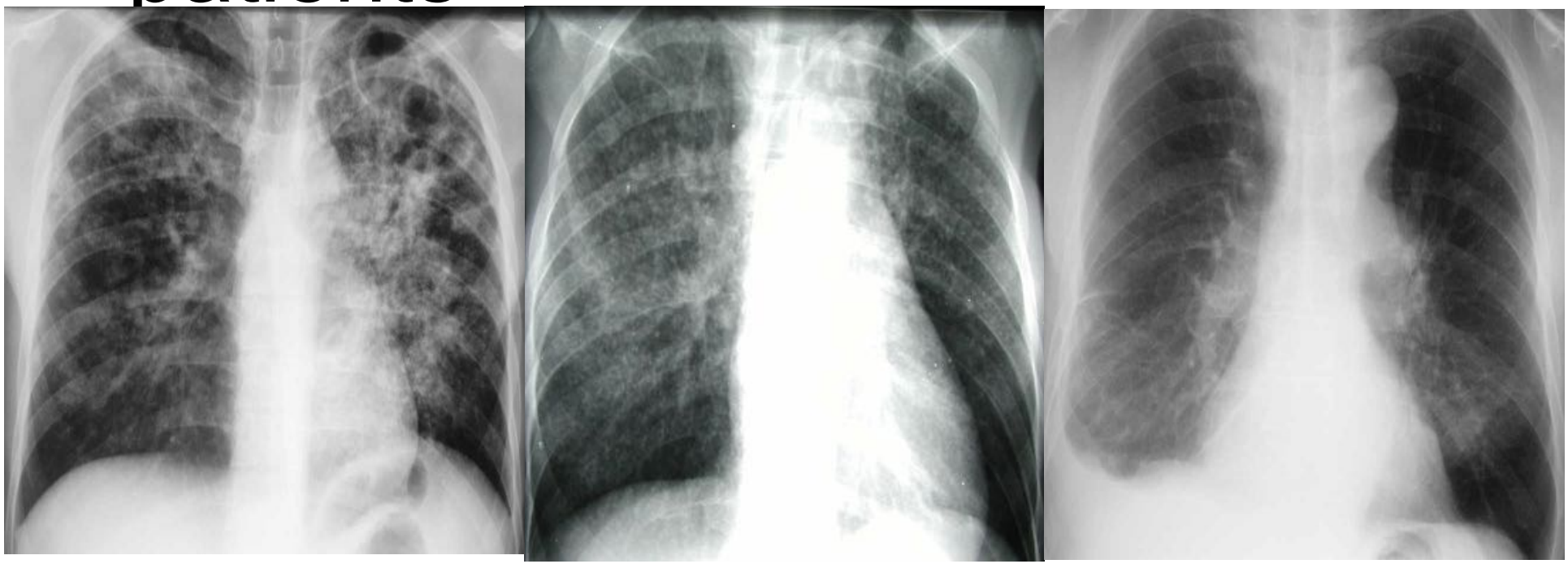
Also in PTB with lower CD4 ….

- Less often ‘chest’ presentation
- Reduced smear-positive rates: 40% vs. 70%
- Less cavitation
- Increased disseminated disease and extra-pulmonary infection : > 60% vs <20%
- More ‘covert/subclinical’ disease → IRS
- More reactions to all TB drugs
- More MDRTB and higher mortality rate

Opportunistic diseases in the course of HIV-infection



Radiological features of HIV^{+} patients



Cavitatory TB

CD4^{+} 510 (23%)

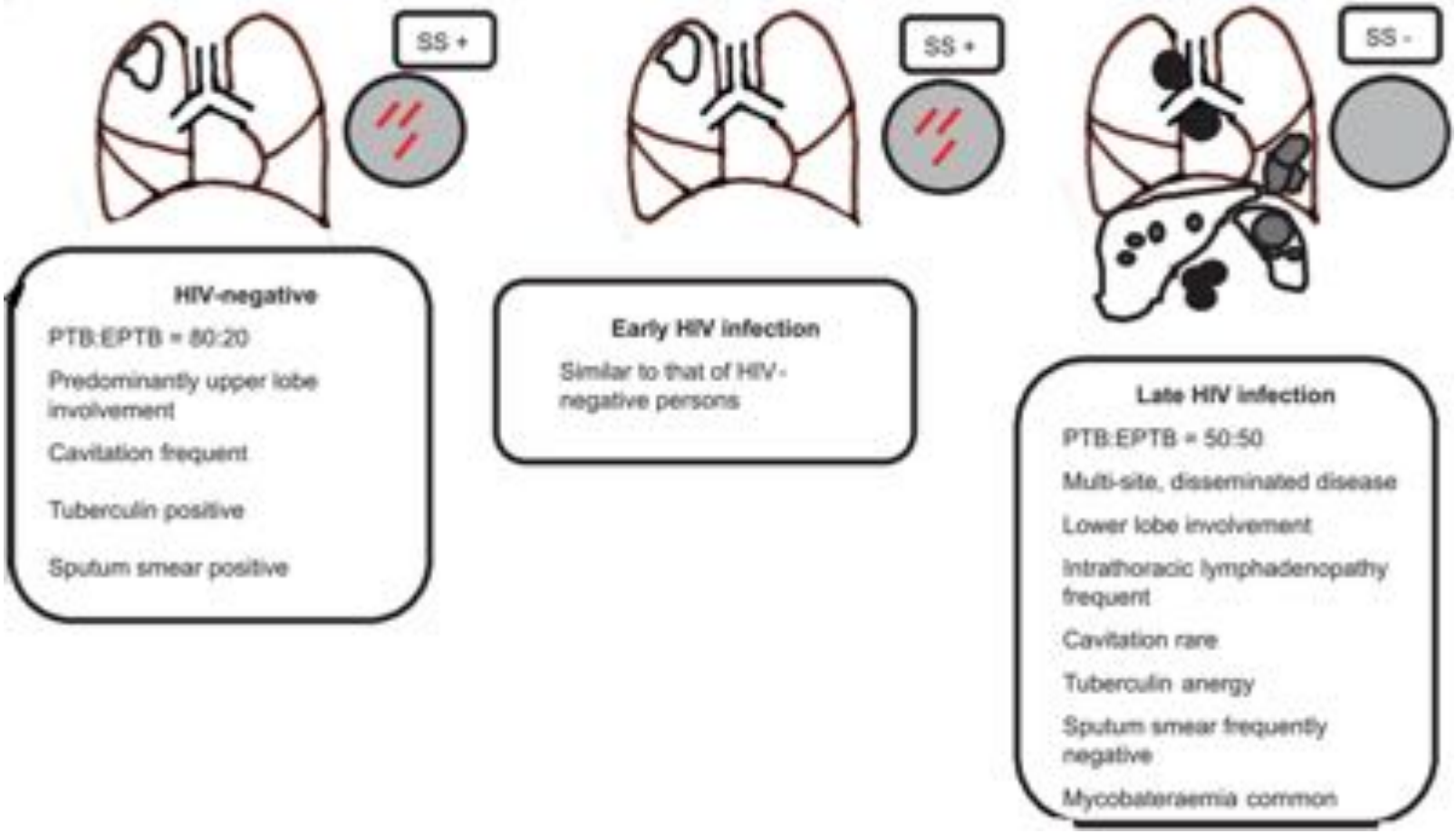
Miliary TB

CD4^{+} 194 (18%)

Disseminated TB

CD4^{+} 34 (8%)

Pulmonary vs extra-pulmonary TB: HIV^{+} vs HIV^{-}

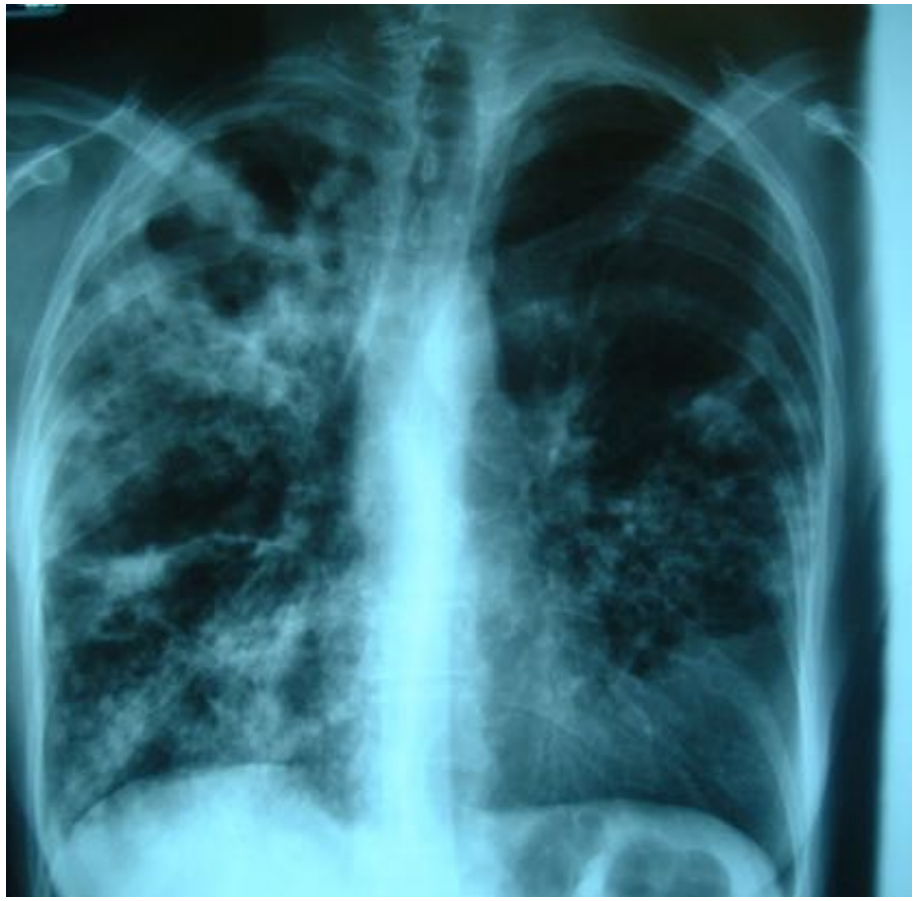


Patient AB – high CD4

- 43yr old heterosexual male; engineer contracted to Nigeria
- Several local partners: unsafe sex
- Admitted with fever, weight loss 6m, pain on swallowing and diarrhoea
- Increasing productive cough and breathlessness
- O/E: temp 38.5oC, cachectic, OCP, generalised lymphadenopathy, hepatosplenomegaly

Patient AB

- CXR:
- HIV +ve
- Induced sputum:
  - PCP –ve
  - AFB +ve
- Blood cultures –ve
- Absolute LC count 0.9
- CD4 320 cells/ml



Differential diagnosis

- **TB**

- Bacterial (staphylococcal/klebsiella)
- Atypical mycobacterium
  - MAI
  - Mycobacterium kansasii
- Rhodococcus equi
- Meliodosis
- Nocardiosis
- Cryptococcus
- Aspergillus

CXR manifestations of Pulmonary TB

Major

- Collapse/ Consolidation
- Cavitation
- Mediastinal lymphadenopathy
- Miliary
- Pleural effusion

Less Common

- Pneumothorax
- Loculated empyema
- ARDS
- Cor Pulmonale
- Localised emphysema

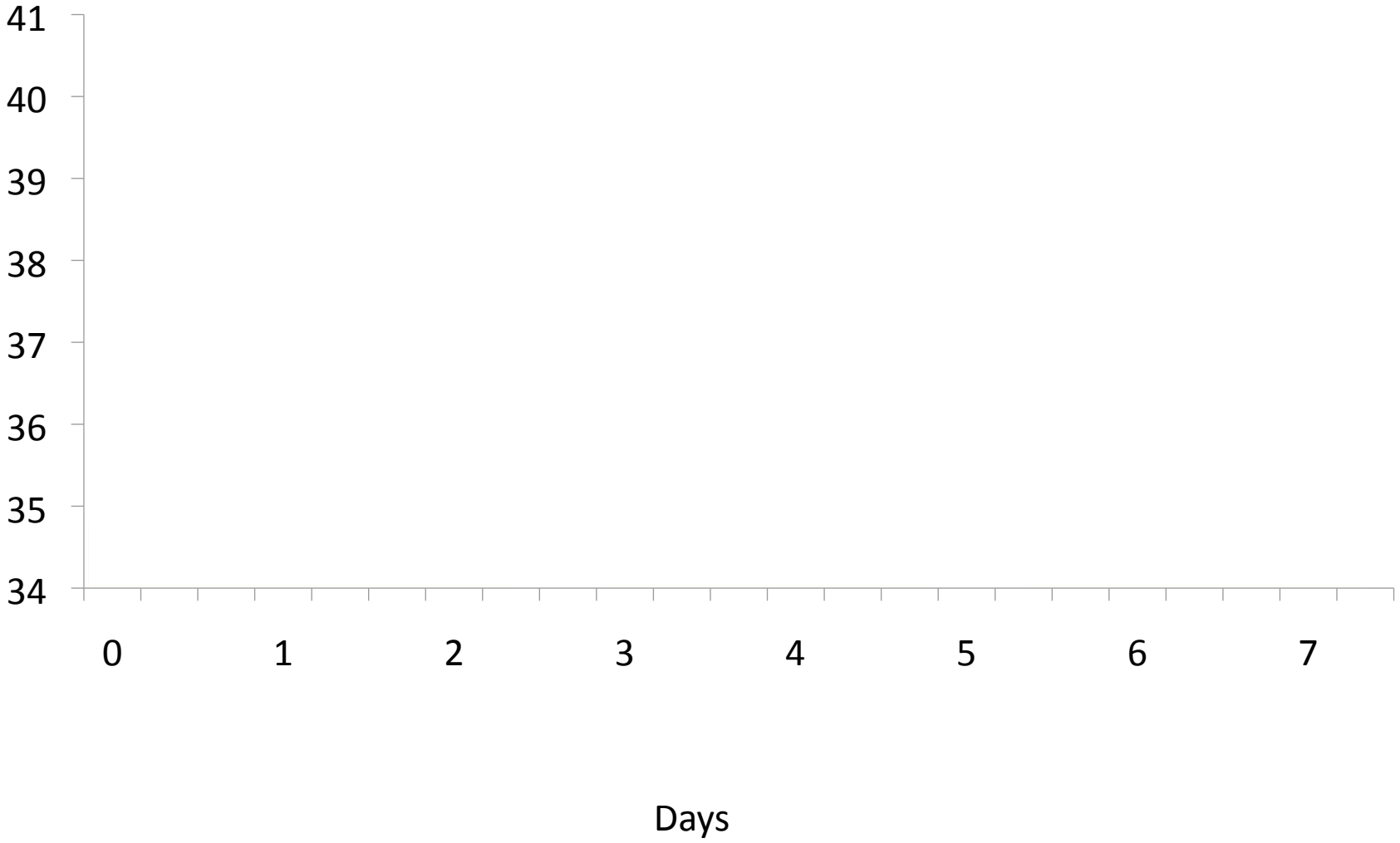
Differential Diagnosis Of TB - related Pulmonary Disease: Chest X-ray Findings

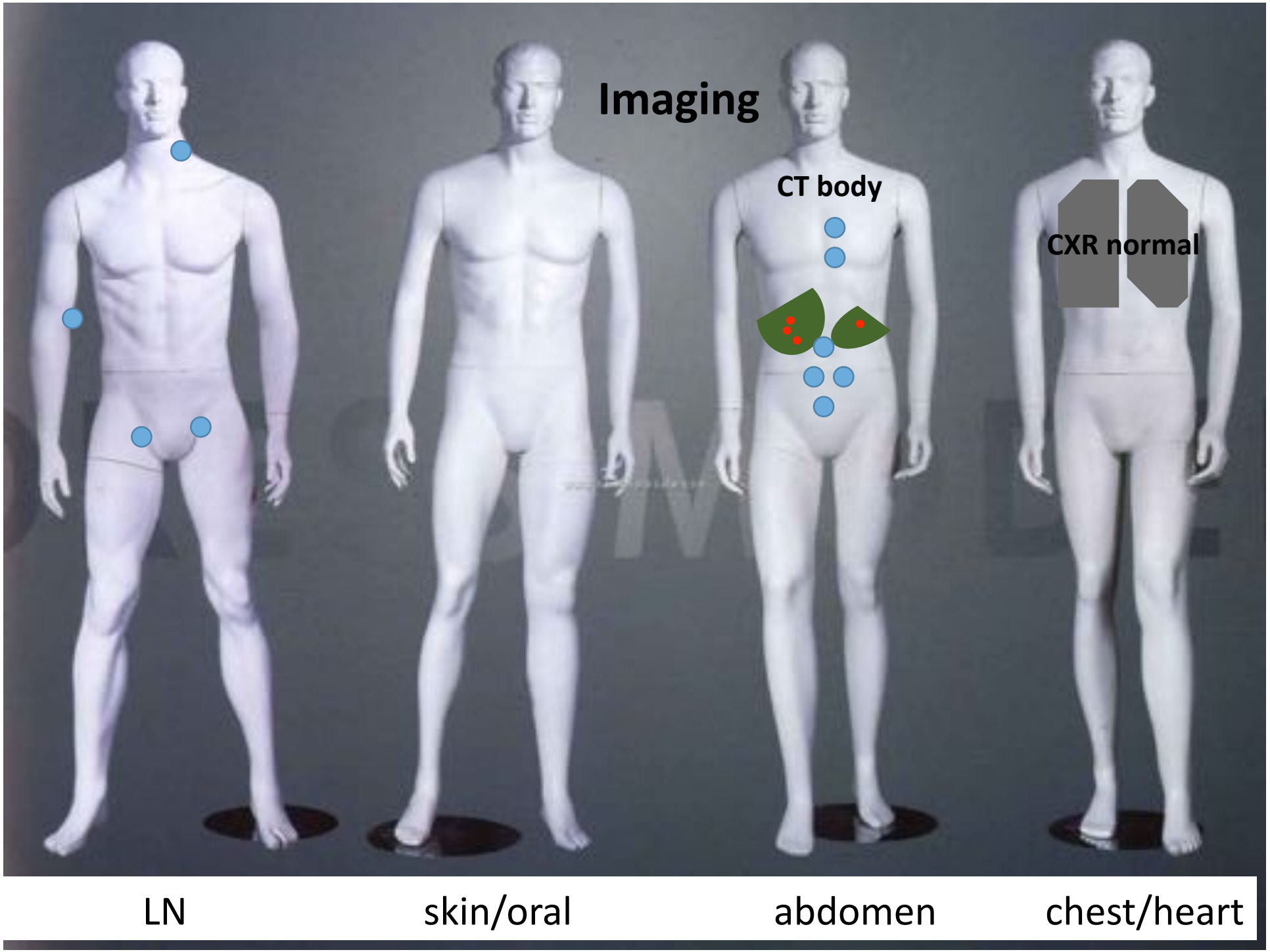
Appearance	Major causes
Diffuse infiltrate	*Pneumocystis jirovecii (carinii)* pneumonia, tuberculosis, Kaposi's sarcoma, non-Hodgkin lymphoma, atypical bacterial pneumonia, viral pneumonitis, lymphoid interstitial pneumonitis
Cavitations	TB, Nocardia, Rhodococcus, bacterial pneumonia, aspergillus
Nodules/focal consolidation	Tuberculosis, Kaposi's sarcoma, non-Hodgkin lymphoma *Cryptococcus, Histoplasma*
Hilar lymphadenopathy	Tuberculosis, Kaposi's sarcoma, non-Hodgkin lymphoma, *Cryptococcus, Histoplasma*
Pleural effusion	Kaposi's sarcoma, tuberculosis, pyogenic bacterial pneumonia, primary effusion lymphoma

Patient BC – low CD4

- 37y-old White French born ex-IDU for 8y
- Lived in Spain till 2005, travelled Asia/Europe ++
- PMH – pulmonary TB 1998, HCV +ve
- Presented with 6w history of fever, sweats, loss of weight
- HIV+ve, CD4 28 cells/mm3, VL 295,000 c/ml
- On methadone

Chronology of symptoms–




Imaging
CT body
CXR normal
LN
skin/oral
abdomen
chest/heart

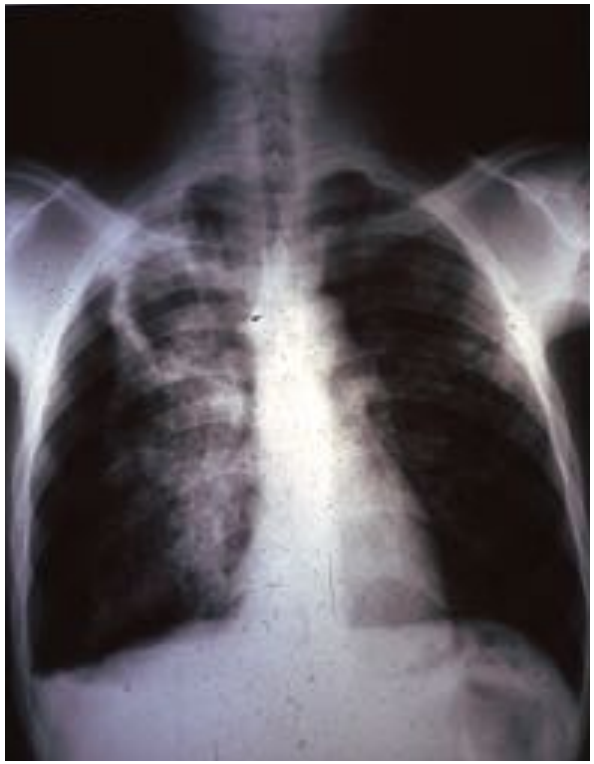
Causes of PUO in late stage HIV

- **Common:**
  - **TB**
  - **MAI**
  - **Lymphoma**
- **Less common:**
  - **PCP**
  - **Salmonellosis**
  - **Syphilis**
  - **CMV**
  - **Cryptococcus**
  - **IRIS**
- **Rare UK:**
  - **Histoplasmosis**
  - **Penicilliosis**
  - **Leishmaniasis**
  - **Bartonellosis**
  - **Coccidiodomycosis**
  - **Toxoplasmosis**
  - **Castleman's disease**
  - **Haemophagocytic syndrome**

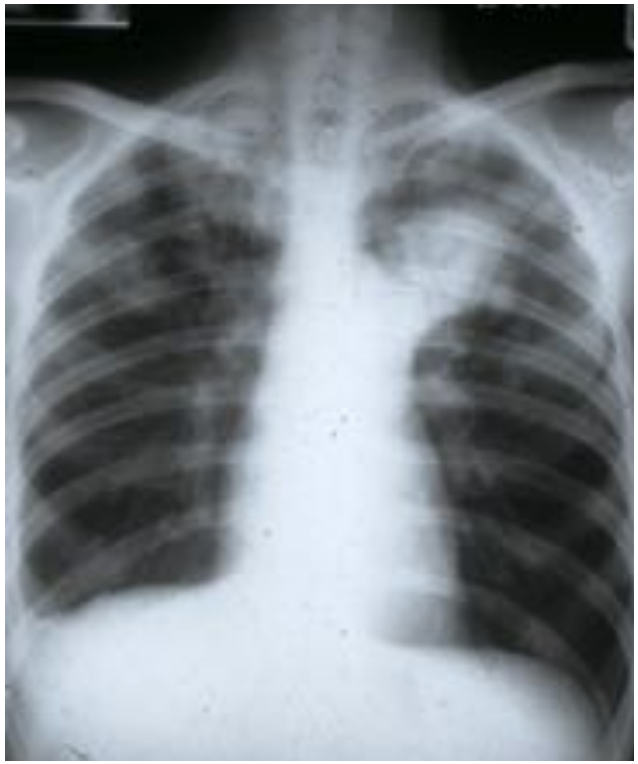
Patient BC

- AFB +ve:
  - Induced sputum
  - Lymph node biopsy
  - Bone marrow
- Covered for both MTB and MAI
- Mycobacteria isolated
  - Blood and tissues above
- TB identified – RIF probe -ve

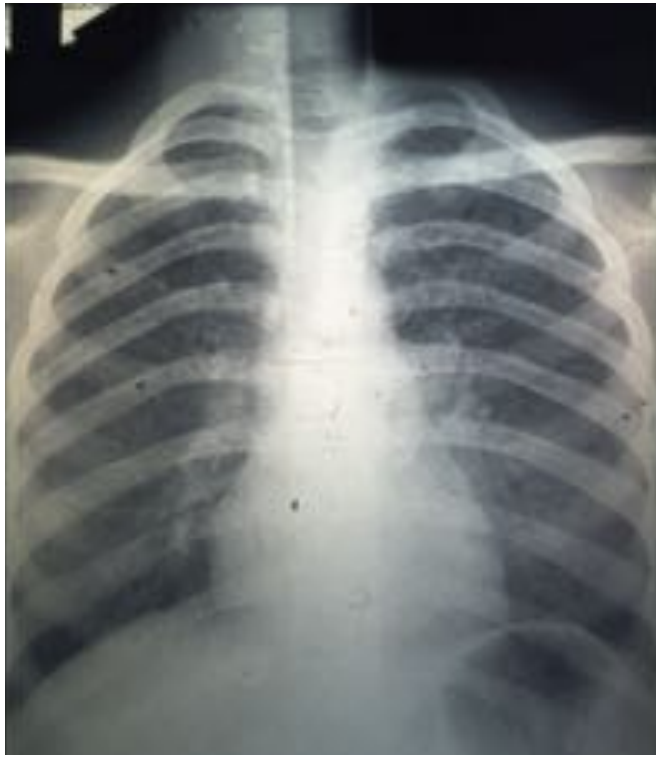
Pulmonary TB



HIV –ve
HIV +ve CD4 >500
AFB +++ve/culture +ve



HIV +ve
CD4 200-500
AFB scants/culture +ve



HIV +ve
CD4 <200
AFB –ve/culture +ve

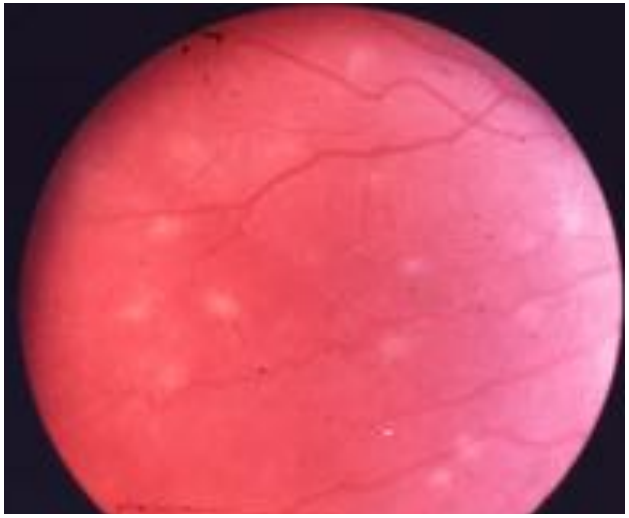
Identifying E-P and disseminated TB

No major differences between HIV+ve and HIV -ve

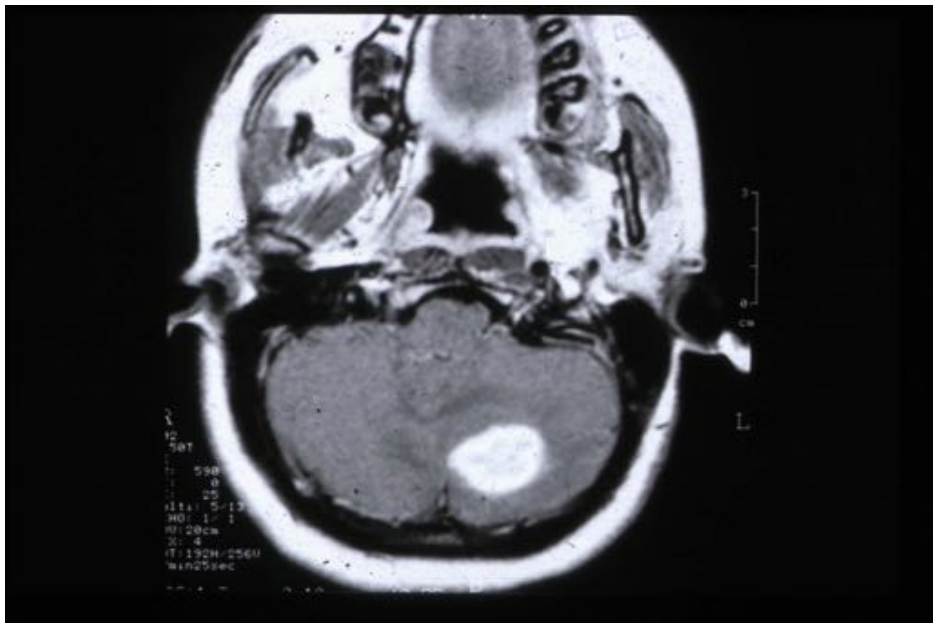
General rules

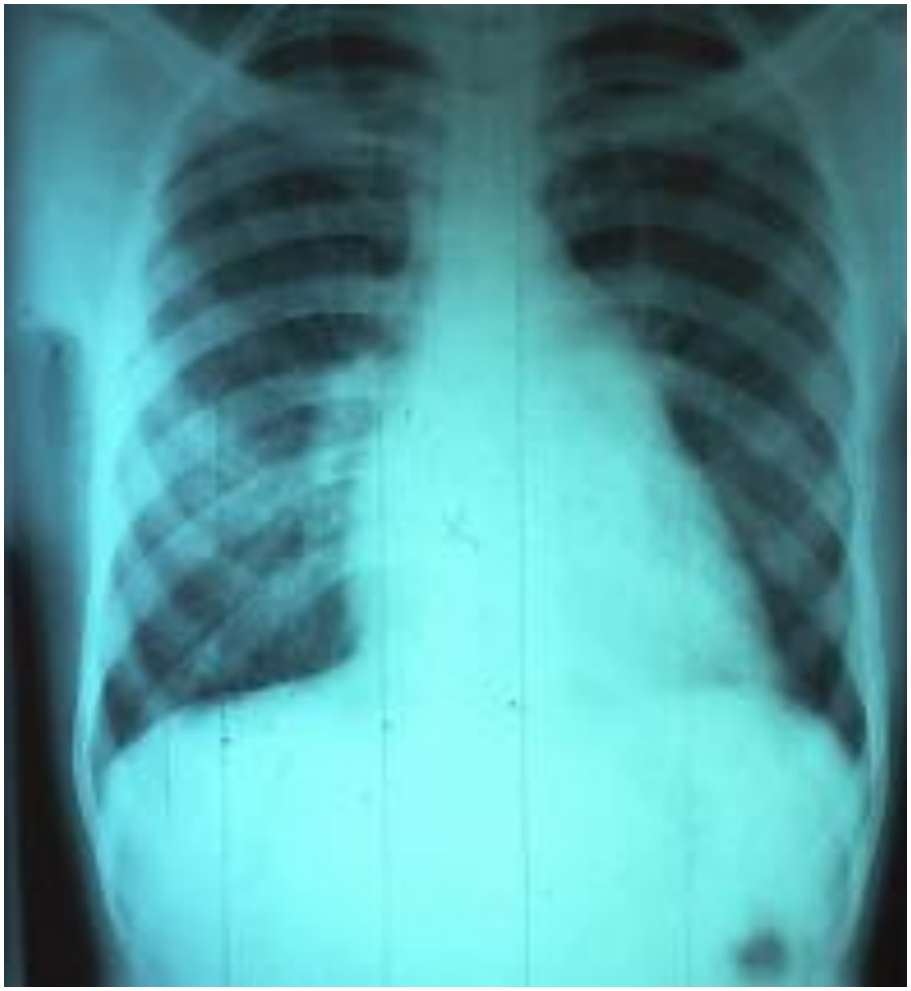
- In a patient with E-P TB HIV is more likely
- Occurs at younger age and often subclinical
- Often part of disseminated or multiple site disease or visceral disease
- If low CD4:
  - AFB +ve more common in biopsies
  - Mycobacteraemia more common
  - No granulomata / may present as IRS
- Often more difficult to manage

TB meningitis



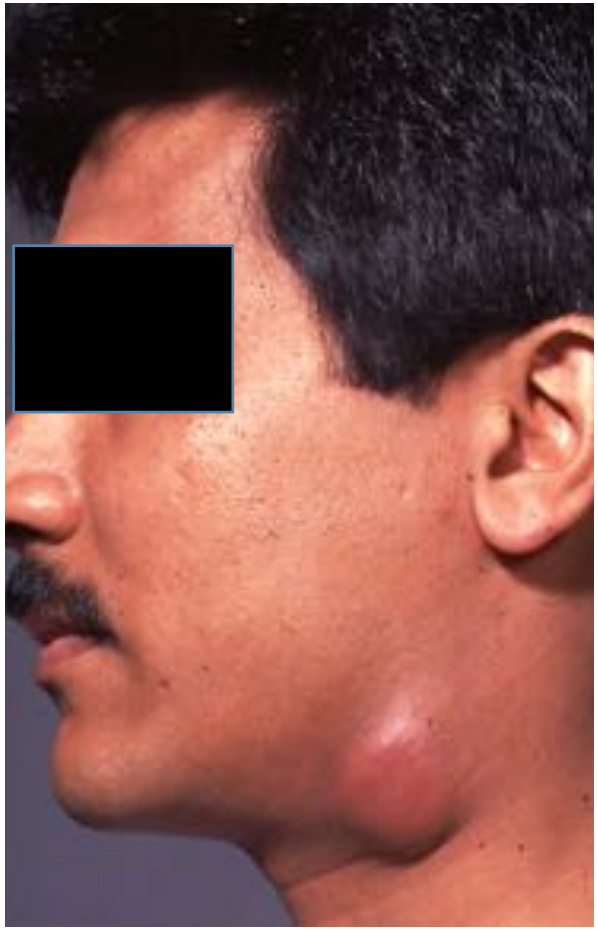
TB meningitis

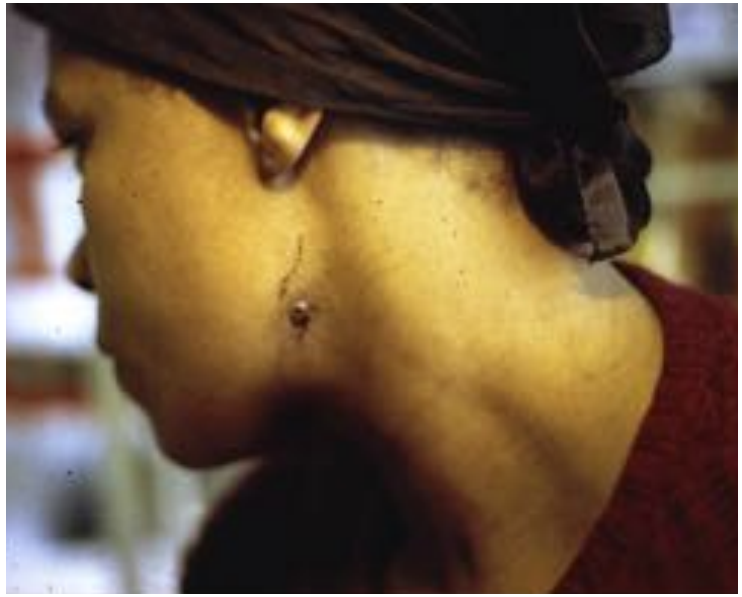


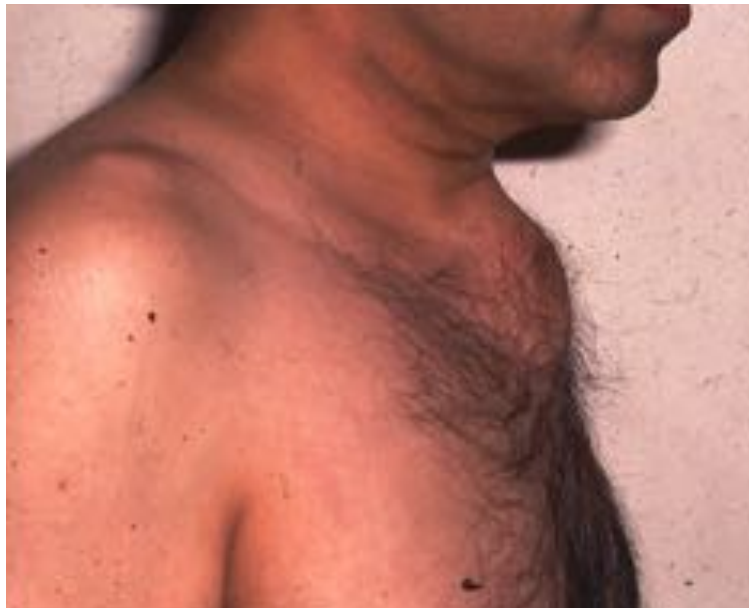


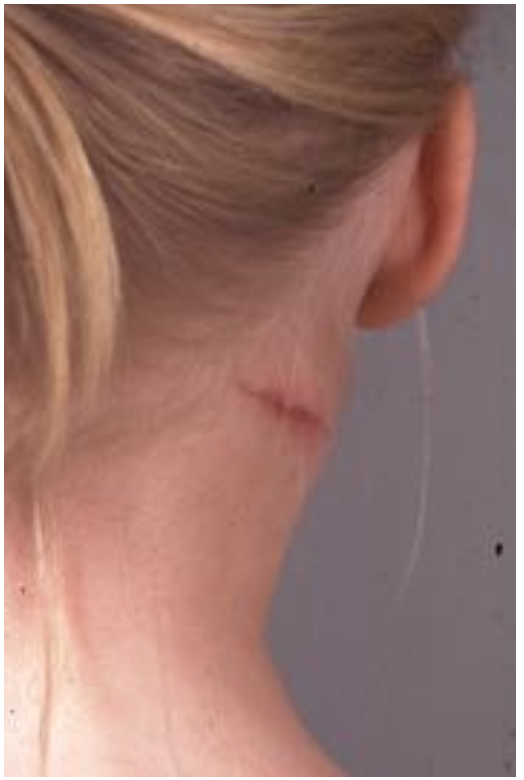
TBM: HIV +ve vs. HIV -ve

- No differences:
  - Clinical presentation
  - CSF findings
  - Blood parameters
  - Frequency of miliary picture
  - Neuroimaging abnormalities
- Significant difference:
  - Rate of AFB positivity CSF
  - Presence of extra-meningeal disease
  - Morbidity and mortality

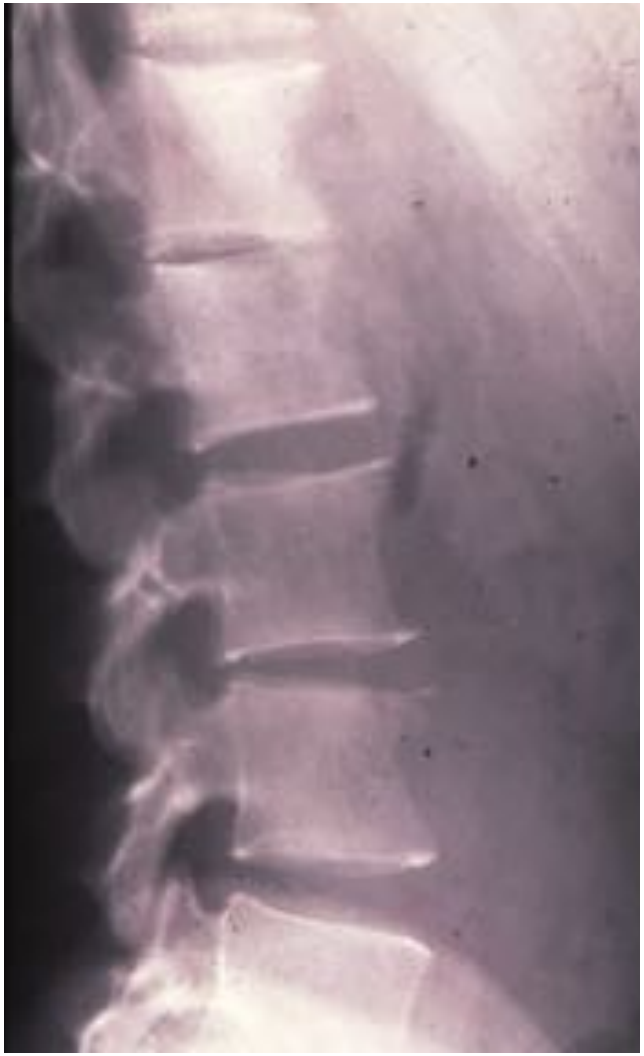


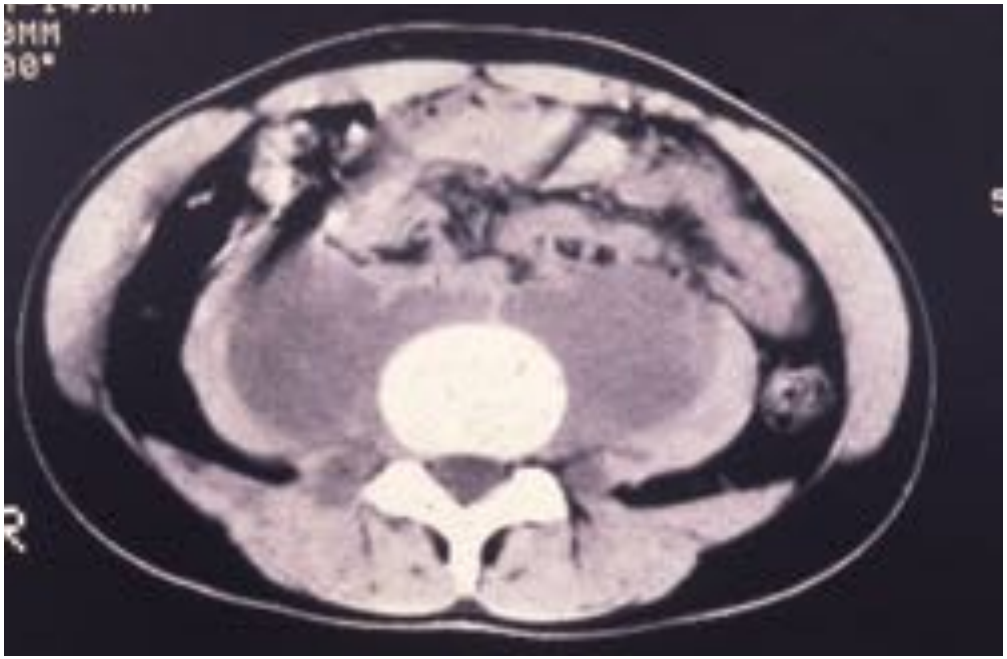


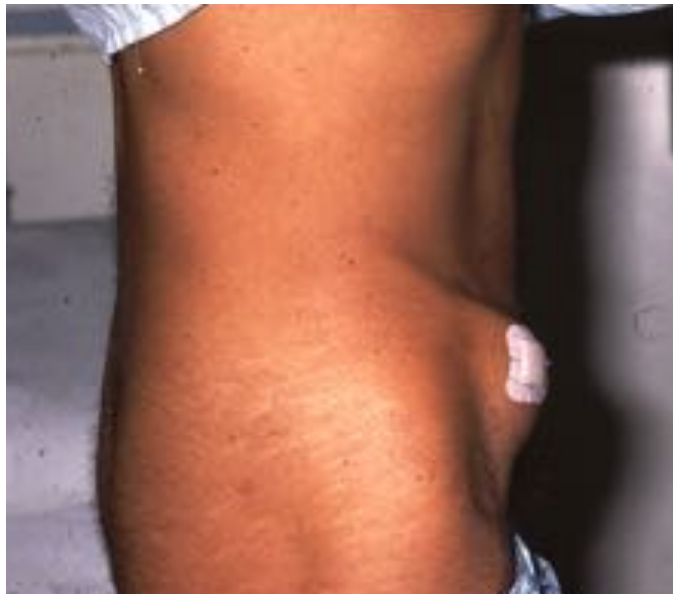




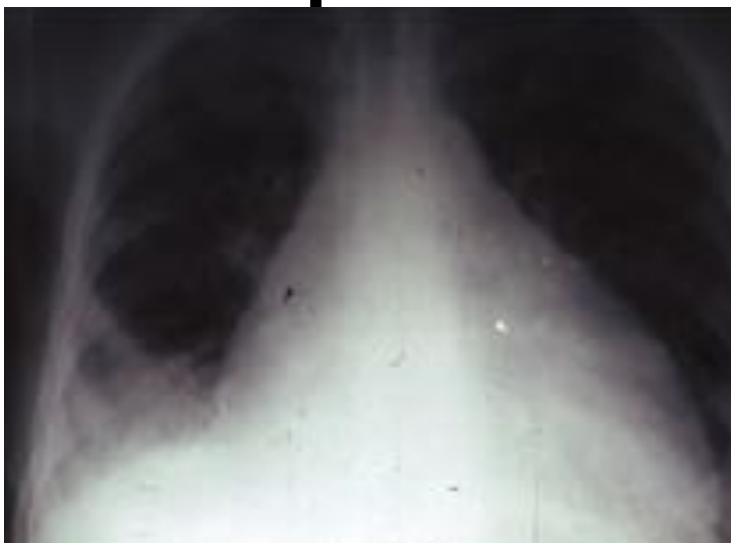
TB spine

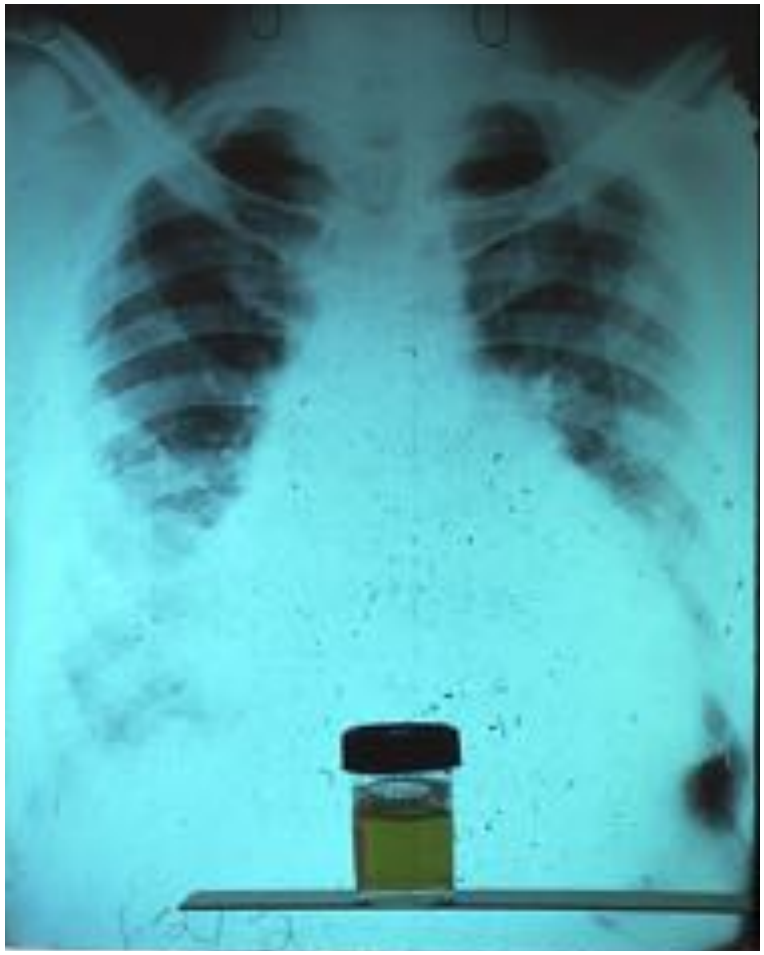




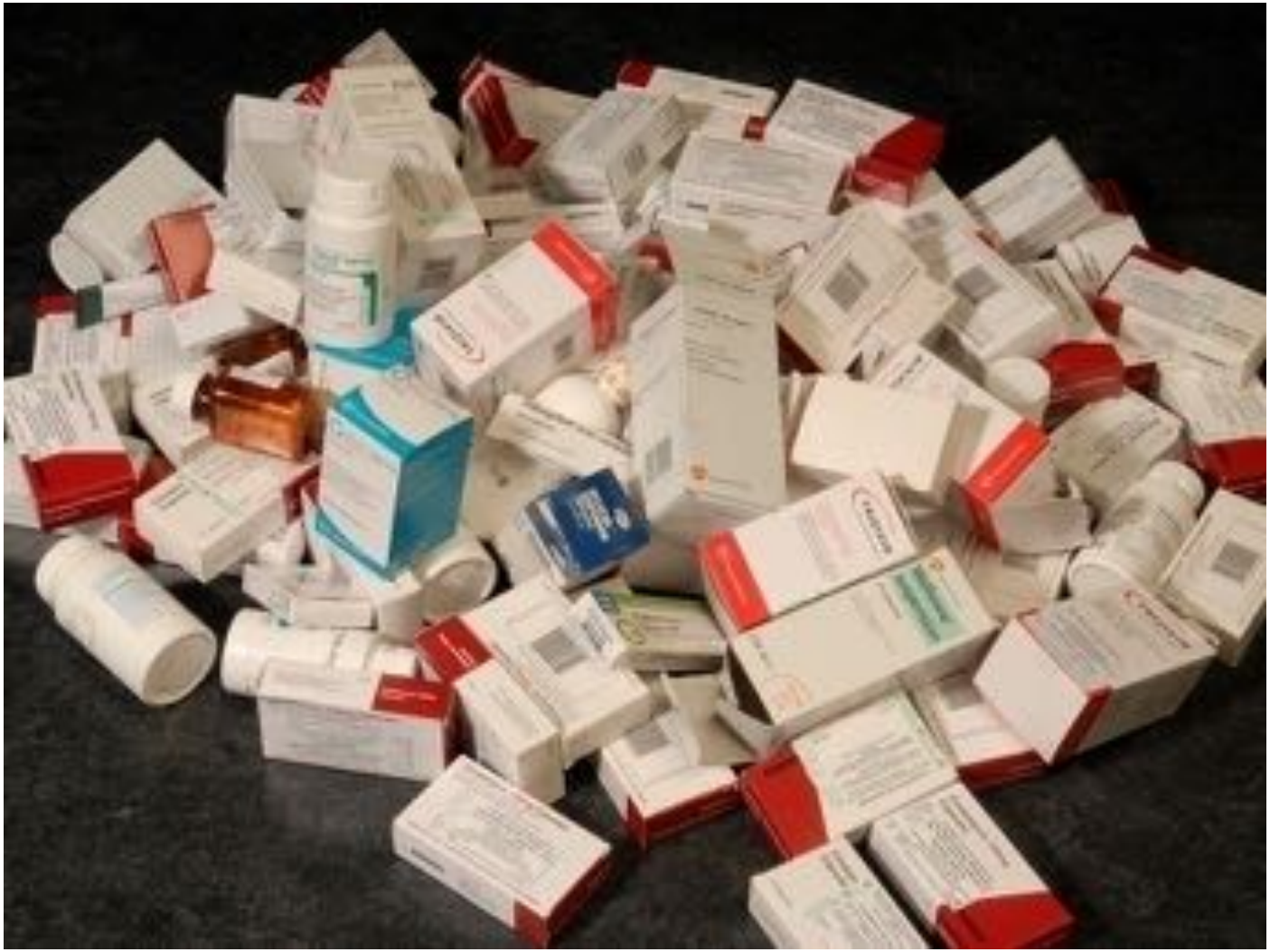


TB pericarditis

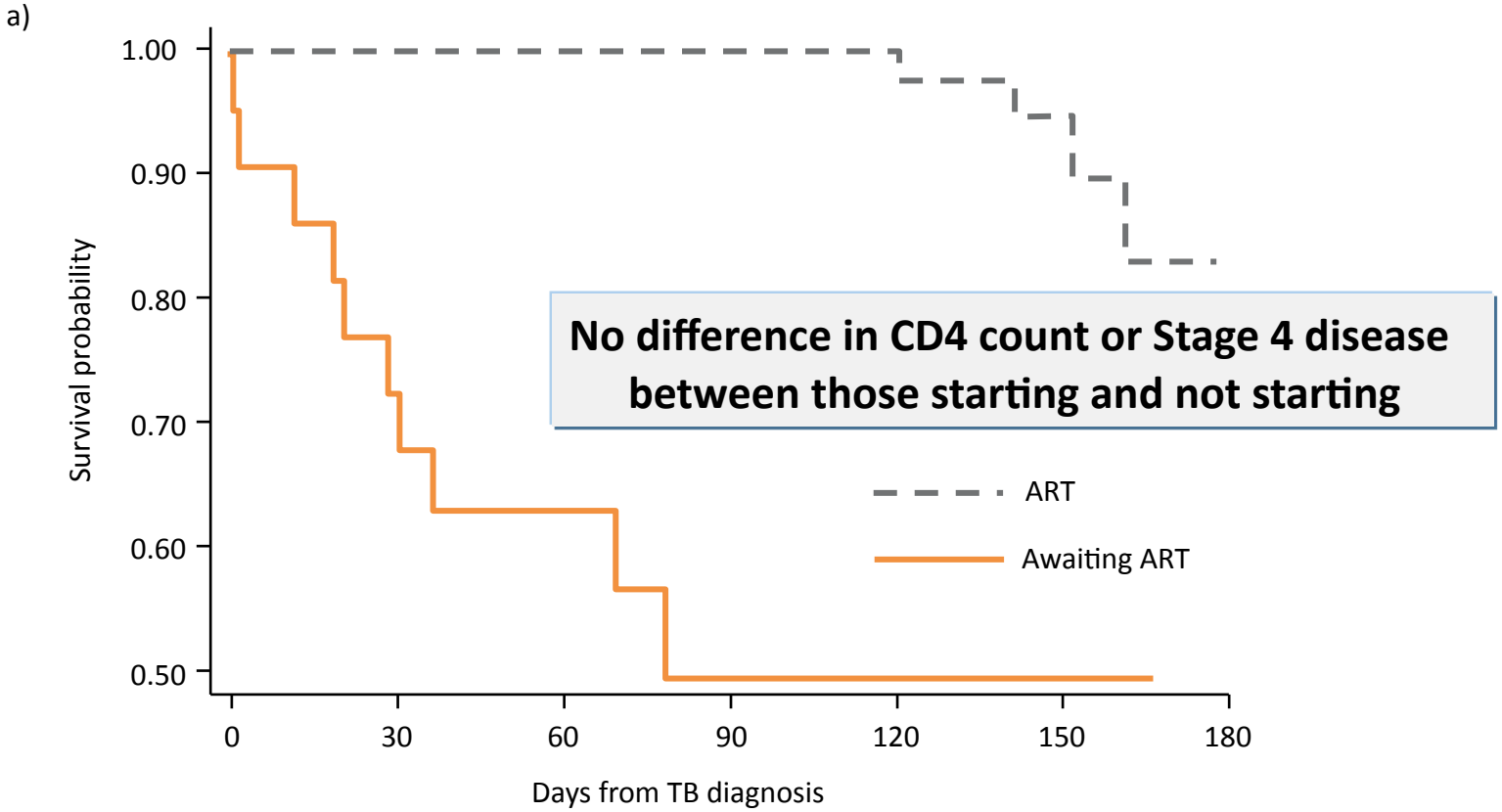




HAART is life saving in TB co-infected

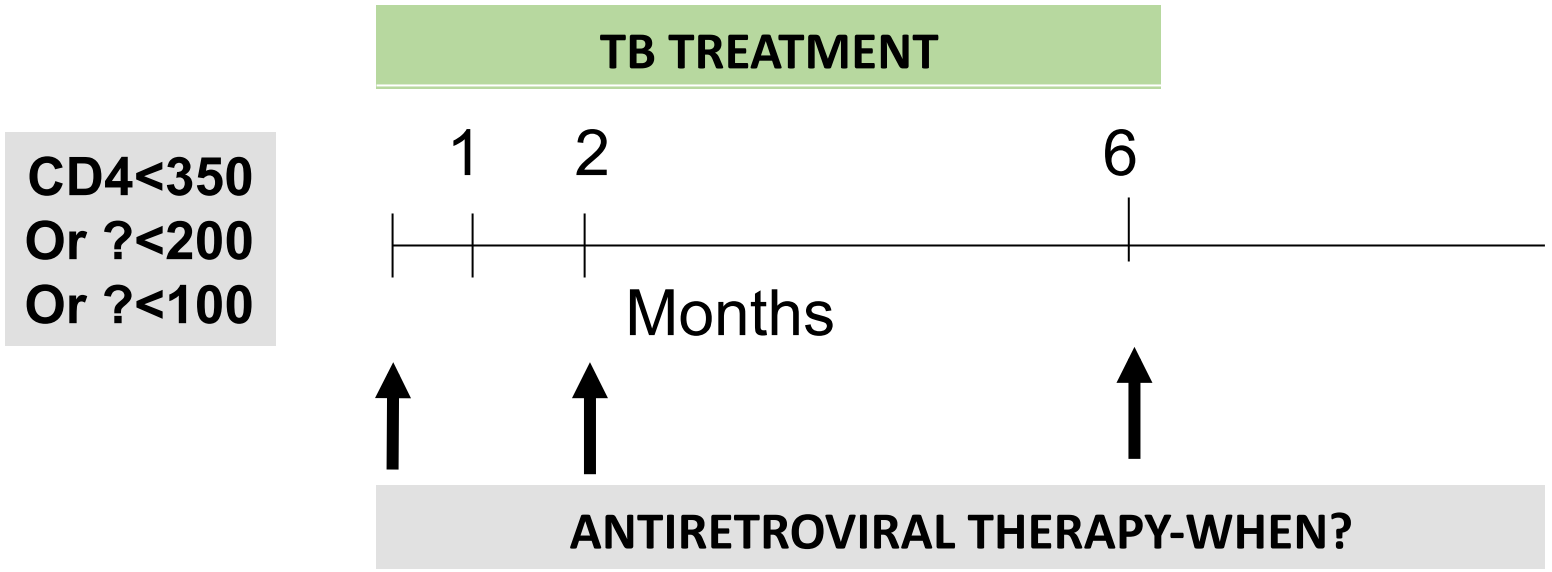


Mortality among patients with prevalent active TB (n=73) initiating ART



Lawn S et al. CROI 2007;Abstract 81

But do you need to / when to Start ART?



Potential Benefits and Risks of Starting ART Immediately With TB Treatment

Benefits

- Reduced morbidity[1,2]
- Reduced mortality[1,2]
- Improved TB outcome

Risks

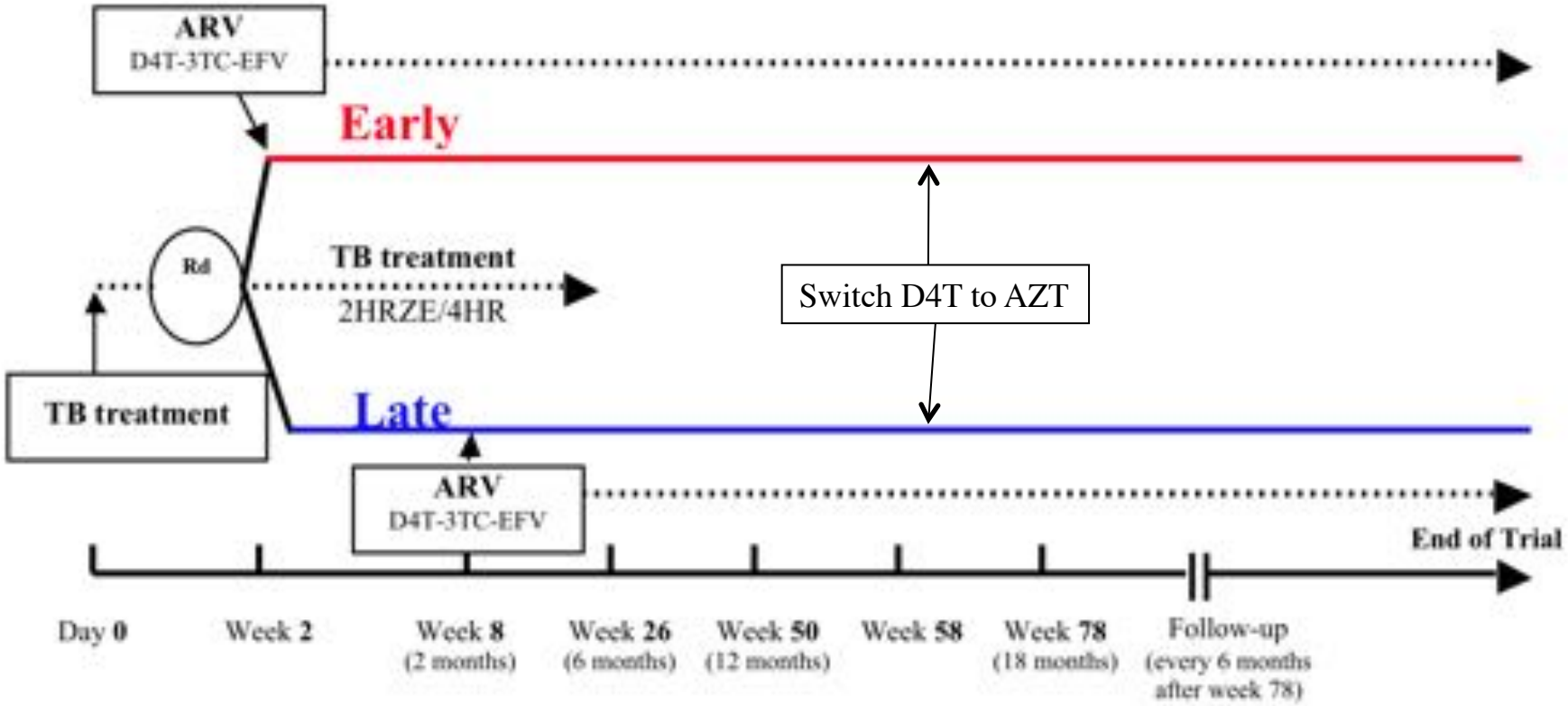
- Increased toxicity to TB and ART therapy[3]
- Drug interactions between HIV and TB medications[3]
- Pill burden
- Immune Reconstitution Syndromes (IRS)[4]

[1] Dean, AIDS, 2002; [2]Pedral-Sampaio,2004, Brazil JID; [3]Harries, Lancet, 2006;[4]Lawn, Lancet ID, 2005

4 key studies on TB

• CAMELIA	Cambodia	PTB <500
• SAPIT	South Africa	PTB <200
• STRIDE	4 Continents	PTB <250
• NCT00433719	Vietnam	TBM

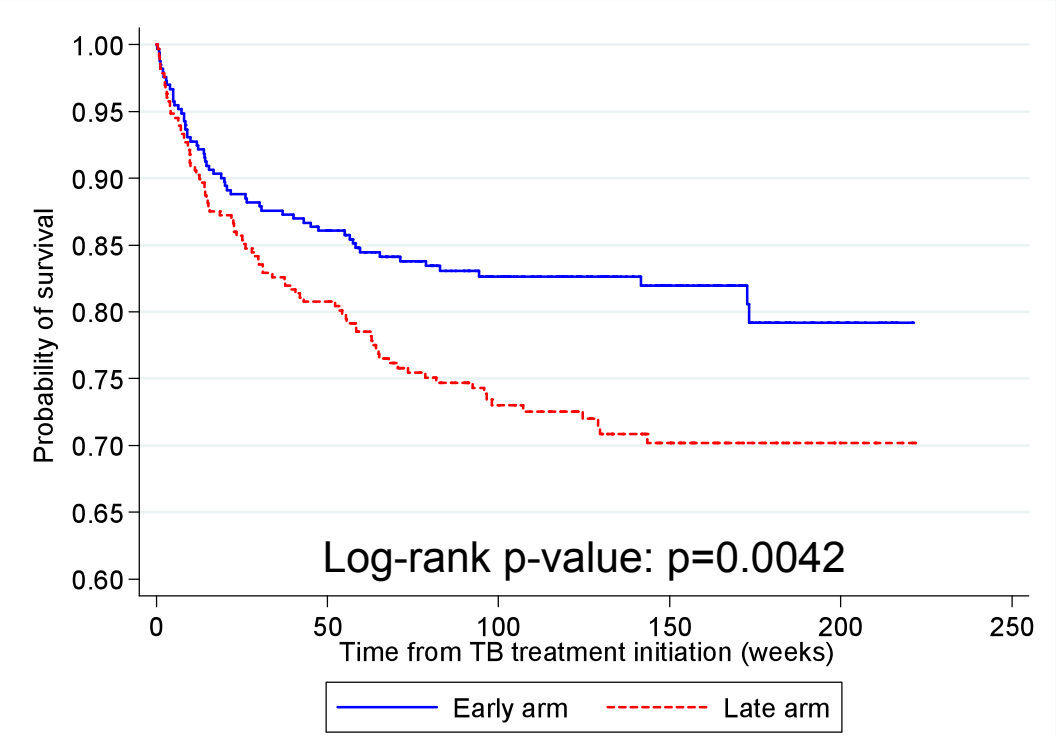
CAMELIA strategy: CD4 <200: 2w vs. 8w?



Rd : Randomization
H : isoniazid Z : pyrazinamide
R : rifampin E : ethambutol
D4T : stavudine
3TC : lamivudine
EFV : efavirenz

ANRS 1295/12160 - CIPRA KH001/10425 study

Kaplan-Meier survival curves

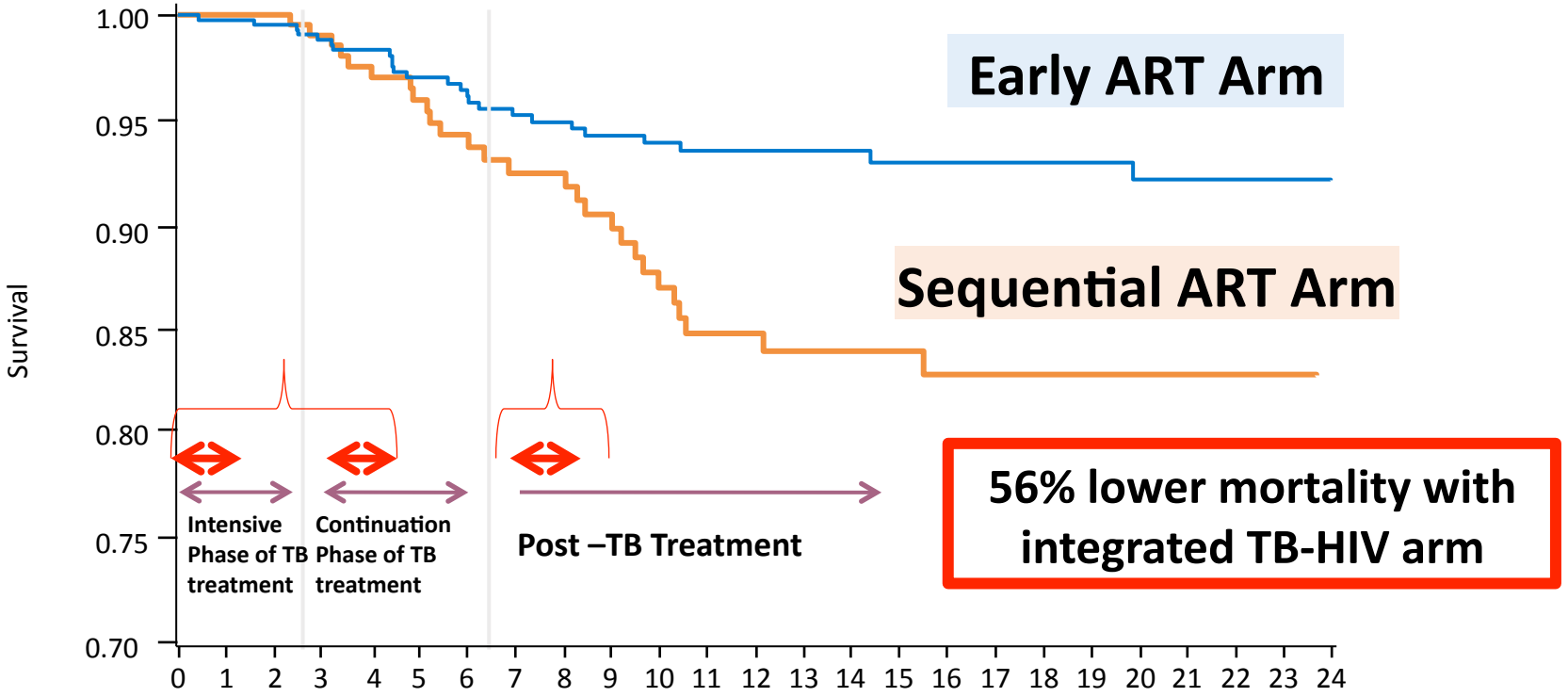


Survival probability (95% CI)	Early arm	Late arm	Log-rank *p*-value
Week 50	86.1 (81.8 – 89.4)	80.7 (76.0 – 84.6)	0.07
Week 100	82.6 (78.0 – 86.4)	73.0 (67.7 – 77.6)	0.006
Week150	82.0 (77.2 – 85.9)	70.2 (64.5 – 75.2)	0.002

ANRS 1295/12160 - CIPRA KH001/10425 study

SAPIT Study: Mortality in sequential arm occurred late

Sept 2008: DSMB arm of the SAPIT trial stopped



Reduction in mortality rates was present in patients with CD4 counts above and below 200 cells/mm3

Karim SA et al. CROI 2009. Abstract 36a.

SAPIT Study: Mortality in sequential arm occurred late

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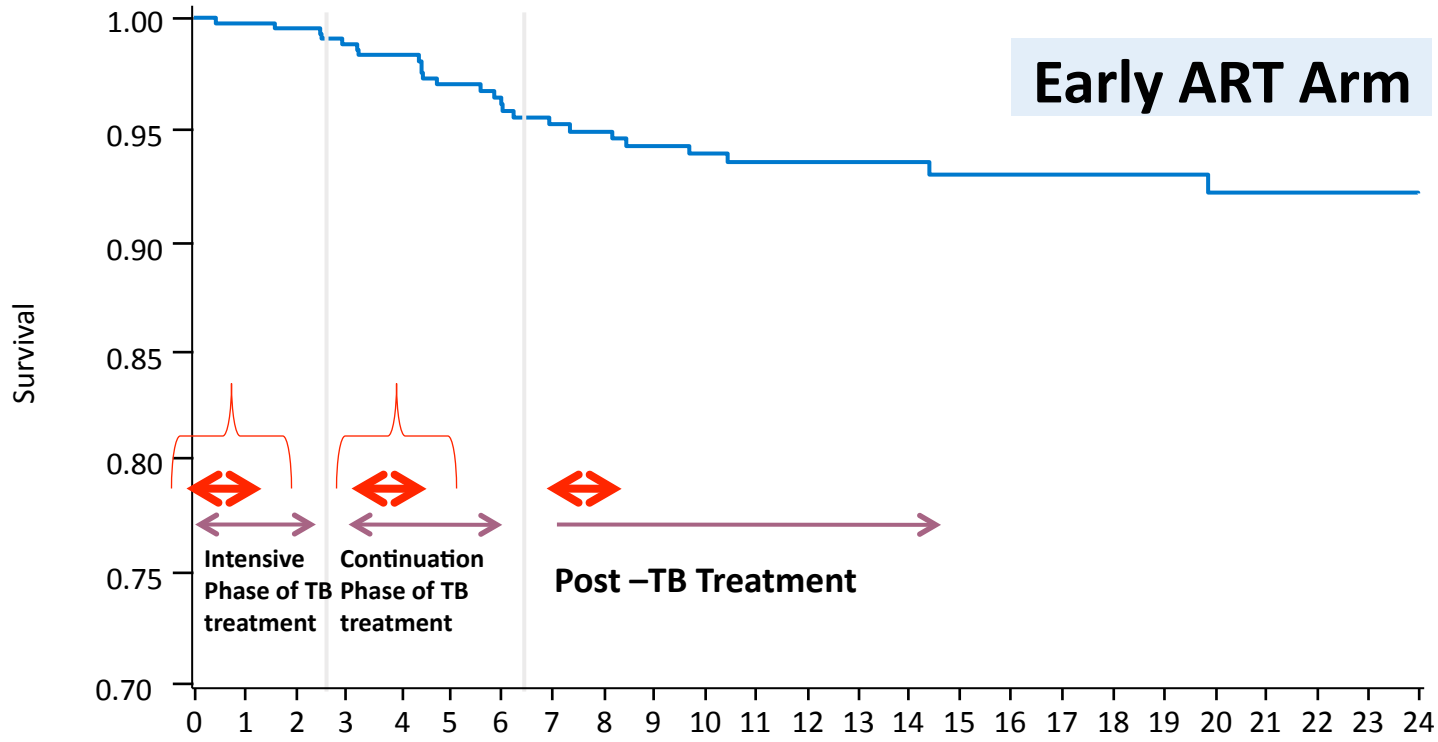
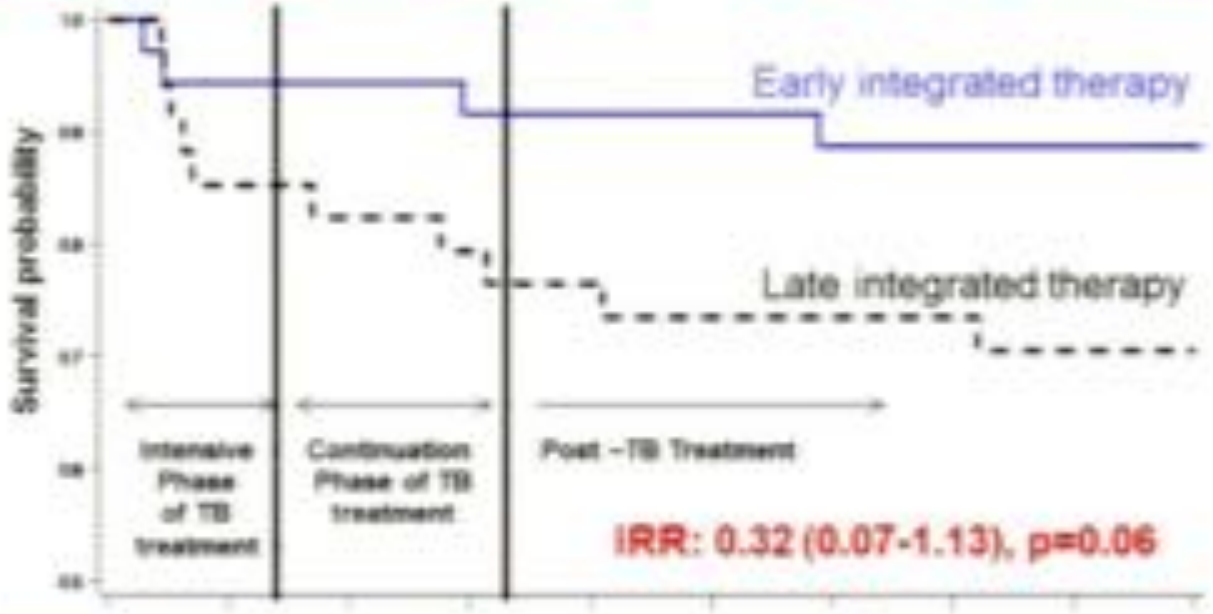


Karim SA et al. CROI 2009. Abstract 36a.

Kaplan-Meier curve for AIDS or death in patients with CD4 <50 cells/mm^3

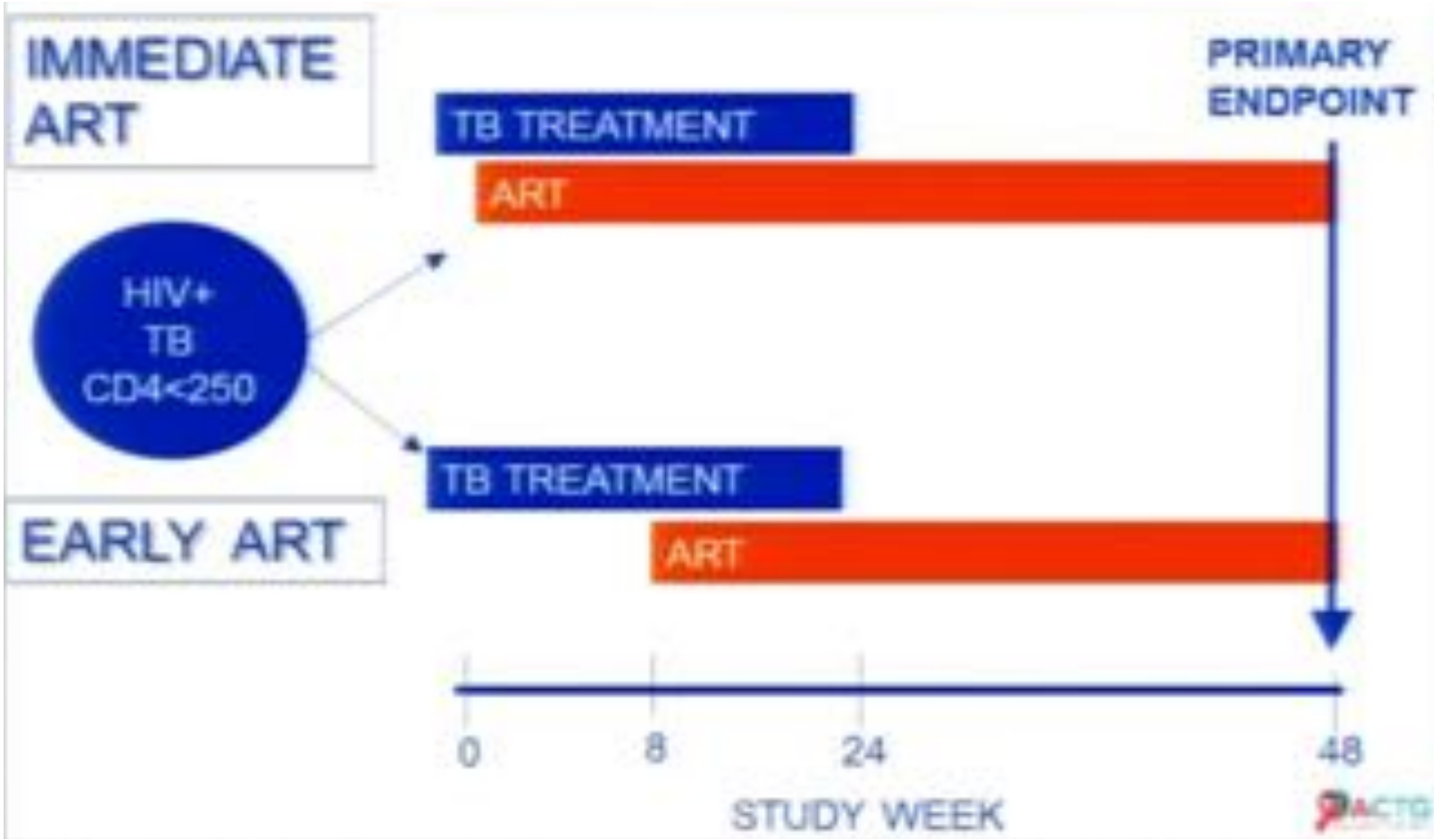


onths of follow-up	0	6	12	18
y – Events / # at risk	0/37	2/33	4/31	4/29
e – Events / # at risk	0/35	7/27	9/24	10/21

68% reduction of AIDS / death (p=0.06)

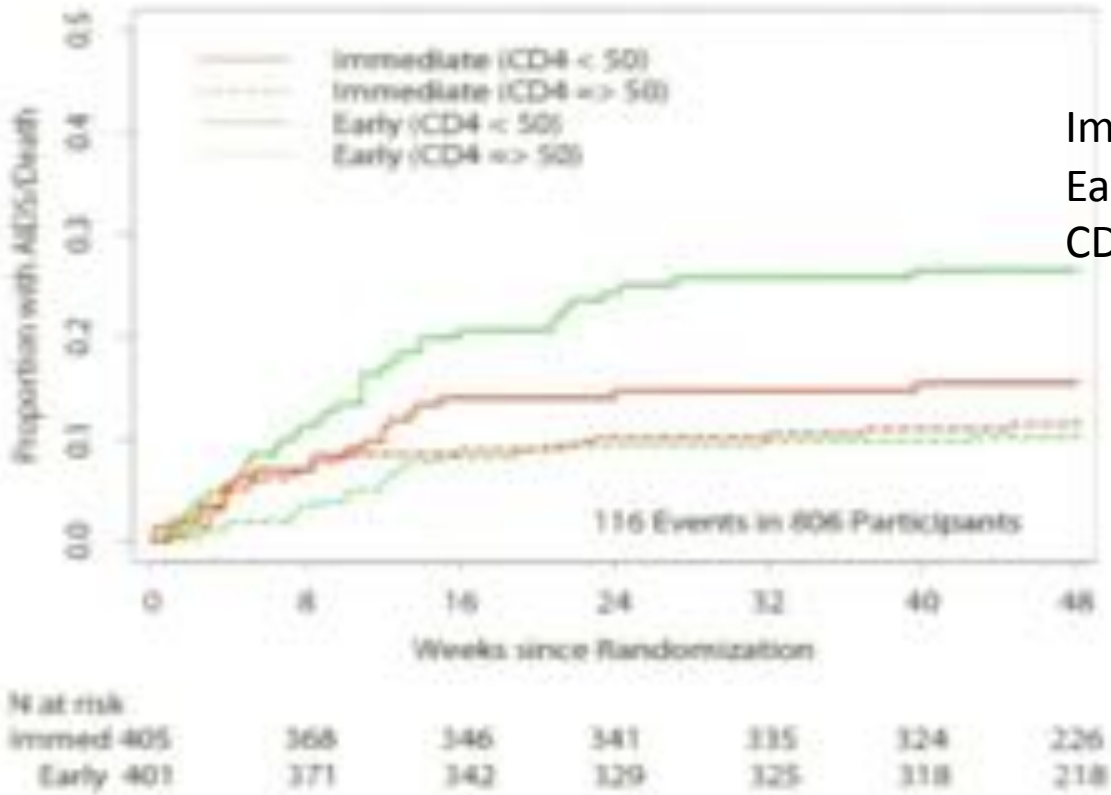
CAPRISA

A5221: STRIDE – study design



Presumed or confirmed TB; EFV TDF FTC: RIF based country approved regimen: <2w or 8-12w. 806 patients from 4 continents, Half had confirmed TB, Median CD4 77, Median 10d and 70d

Time-to-New AIDS-Defining Illness or Death by CD4 Stratum



Immediate

Early

CD4 > 50

More OI's and TB deaths in the early arm

When to start HAART (BHIVA 2009)

CD4 count	When to start
< 100	As soon as practical
100 - 350	As soon as practical, but can wait until 2 months of TB Rx, especially if difficulties with toxicity / adherence
> 350	At physician discretion

Is there enough evidence to give clear guidance on what level of CD4 and when into TB treatment one should start HAART?

NO – but don’t wait until it’s too late

Rifampicin

- The major problem is the use of rifampicin with HAART

- But it is an **essential** part of the solution for TB

TB-HIV drug interactions

	Rif	INH	PZA	Eth	Strep	RBT	RPT	Mox	Ethio	Cyclo	Capreo
SQV/r	●	◆	◆	◆	◆	■	■	◆	∇	◆	◆
RTV	■	◆	◆	◆	◆	■	■	◆	∇	◆	◆
IDV	●	◆	◆	◆	◆	■	■	◆	∇	◆	◆
NFV	●	◆	◆	◆	◆	■	■	◆	∇	◆	◆
FPV/r	●	◆	◆	◆	◆	■	■	◆	∇	◆	◆
LPV/r	●	◆	◆	◆	◆	■	■	◆	∇	◆	◆
ATV/r	●	◆	◆	◆	◆	■	■	◆	∇	◆	◆
TPV/r	●	◆	◆	◆	◆	■	■	◆	∇	◆	◆
DRV/r	●	◆	◆	◆	◆	■	■	◆	∇	◆	◆
NVP	●	◆	◆	◆	◆	■	■	◆	∇	◆	◆
EFV	■	◆	◆	◆	◆	■	■	◆	∇	◆	◆
ETR	●	◆	◆	◆	◆	■	●	◆	∇	◆	◆
ZDV	■	◆	◆	◆	◆	◆	∇	◆	∇	◆	◆
3TC	◆	◆	◆	◆	◆	◆	◆	◆	∇	◆	◆
ddI	◆	◆	◆	◆	◆	◆	◆	◆	∇	◆	◆
d4T	◆	■	◆	◆	◆	◆	◆	◆	∇	◆	◆
ABC	■	◆	◆	◆	◆	◆	∇	◆	∇	◆	◆
ddC	◆	◆	◆	◆	◆	◆	◆	◆	∇	◆	◆
FTC	◆	◆	◆	◆	◆	◆	◆	◆	∇	◆	◆
TDF	◆	◆	◆	◆	■	◆	◆	◆	∇	◆	■
ENF	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
MVC	■	◆	◆	◆	◆	■	■	◆	∇	◆	◆
RAL	■	◆	◆	◆	◆	◆	◆	◆	∇	◆	◆

www.hiv-druginteractions. org

Treatment of drug sensitive TB

- 90% of MTB dead in 2 days when regimen includes INH √
- 99% of MTB dead in 14 days when regimen also includes Rifampicin √
- If INH and RIF and PZA given in first 2 months then total course of TB treatment is 6 months √

- Debate whether HIV + should be treated for longer
- Debate whether use of quinolones could shorten to 4 months

Choices

- NNRTI's:
  - Nevirapine
  - Efavirenz
- PI/r
- 3NRTI
- New drugs:
  - Raltegravir
  - Maraviroc
  - Etravirine
  - T-20

Nevirapine and rifampicin

- Standard dose?
- Increased dose?
- Problems of Lead in

PK interactions between EFV and rifampicin in HIV patients with TB

- EFV peak, trough and AUC decreased 24%, 25% and 22% in the presence of rifampicin √
- Large inter patient variability observed, suggesting use of TDM √
- PK of EFV 800 mg plus rifampicin similar to those of EFV 600 mg without rifampicin √
- Rifampicin PK did not change substantially in the presence of efavirenz √

Lopez-Cortes et al. Clin Pharmacokinet. 2002;41:681-90

Body Weight Cutoff for EFV Dosing in Combination with Rifampicin

- 71 patients in Thailand taking anti-TB Rx, initiating HAART with EFV 600mg + d4T/3TC

- EFV concentrations at 12h after dosing at weeks 6 & 12
- High body weight associated with low C12 EFV at weeks 6 & 12
- C12 EFV of 1mg/l at mean weight of 57.5kg
- 60kg weight cutoff appropriate for EFV dose escalation 600 ➜ 800mg

NNRTIs with anti-TB drugs (BHIVA 2009)

	Rifampicin	Rifabutin	Clarithromycin
EFAVIRENZ	Efavirenz levels ↓ by 20–30% **Efavirenz increased to 800mg daily if weight >60kg** **Efavirenz at 600mg daily if weight <60kg** **Rifampicin at standard dose**	Rifabutin levels ↓ by 38%. **Rifabutin increased to 450mg daily** **Efavirenz at standard dose**	No significant interaction Use standard doses Reports of ↑ rates of rash: consider Azithromycin instead (no interaction)
NEVIRAPINE	Nevirapine levels ↓ 20–55% No change in rifampicin **Not recommended**	Use standard doses but little data so not recommended	No significant interaction Use standard doses
ETRAVIRINE	No data available but expected ↓↓↓ etravirine	Etravirine levels ↓ 37% Rifabutin 17%	Use with caution
RILPIVIRINE	TMC-278 levels ↓ 90% **Do not use**	TMC-278 levels ↓ 50% Double dose TMC-278	

Choices

- NNRTI's:
  - Nevirapine
  - Efavirenz
- PI/r
- 3NRTI
- New drugs:
  - Raltegravir
  - Maraviroc
  - Etravirine
  - T-20

Boosted PIs and Rifampicin Interaction

Lopinavir/rit

- Ritonavir 400 bid required
- GI toxicity and lipid perturbation
- High rates of elevated transaminase[1] (5/7 dropouts)[1]
- Plus recent PK study[2]
  -LFT problems

Saquinavir/rit

- Early studies from SA suggested could be used
- SQV 1000/rit100 BID[3]
- All patients in this arm experienced grade 4 transaminase elevations[3]

1. La Porte et al. AAC 2004;48(5):1553-1560
2. Nijland AIDS. 2008 May 11;22(8):931-5.
3. Schmitt C et al. Arch Drug Inf. 2009;2:8-16

TB Treatment Regimens: Rifabutin

HAART	Dose	TB therapy	Dose
NRTI	No change	RBT	No change
Boosted PI	No change	RBT	150? mg 2-3/7
nevirapine	200 mg bd	RBT	300 mg od
efavirenz	600 mg od	RBT	450 mg od

Anton Pozniak Personal Communication

Choices

- NNRTI's:
  - Nevirapine
  - Efavirenz
- PI/r
- 3NRTI
- New drugs:
  - Raltegravir
  - Maraviroc
  - Etravirine
  - T-20

Interactions with raltegravir

Rifabutin	Rifampicin
• No dose change required of either drug	• The co-administration of 800 mg q12hr RAL with 600 mg qd RIF resulted in a 53% decrease in RAL C12hr relative to 400 mg q12hr RAL alone

BHIVA TB Guidelines

Boosted PI

Rifampicin: Not recommended

Rifabutin: 150mg x 3 per week , boosted PI dosed as normal

Integrase inhibitors (raltegravir / elvitegravir)

Rifampicin: Do not use / not recommended

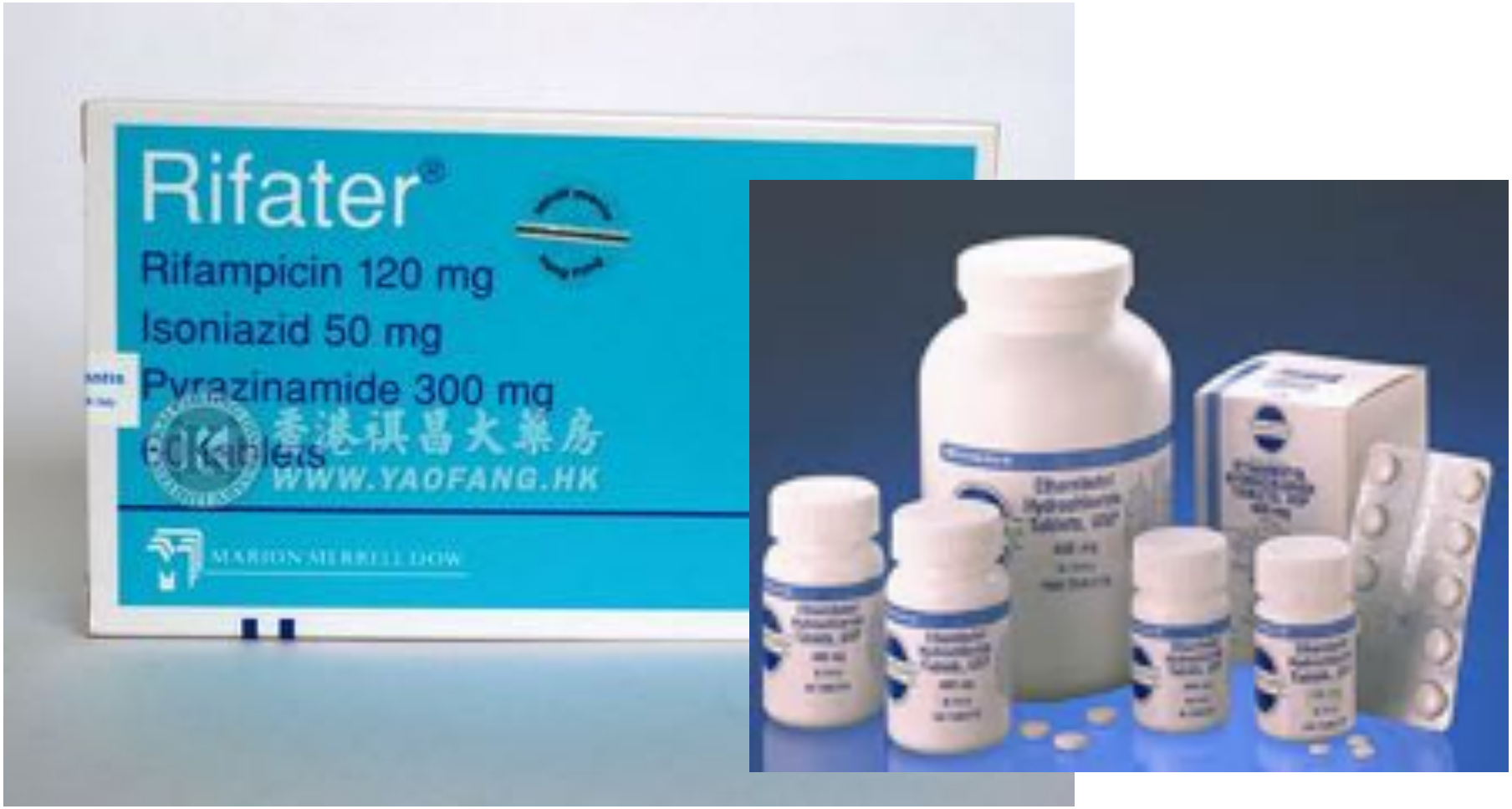
Rifabutin: Use with caution / not recommended

Entry Inhibitors (Maraviroc / T20)

Rifampicin: Not recommended / use standard doses

Rifabutin: Use standard doses

Treatment


Rifater®
Rifampicin 120 mg
Isoniazid 50 mg
Pyrazinamide 300 mg
WWW.YAOFANG.HK

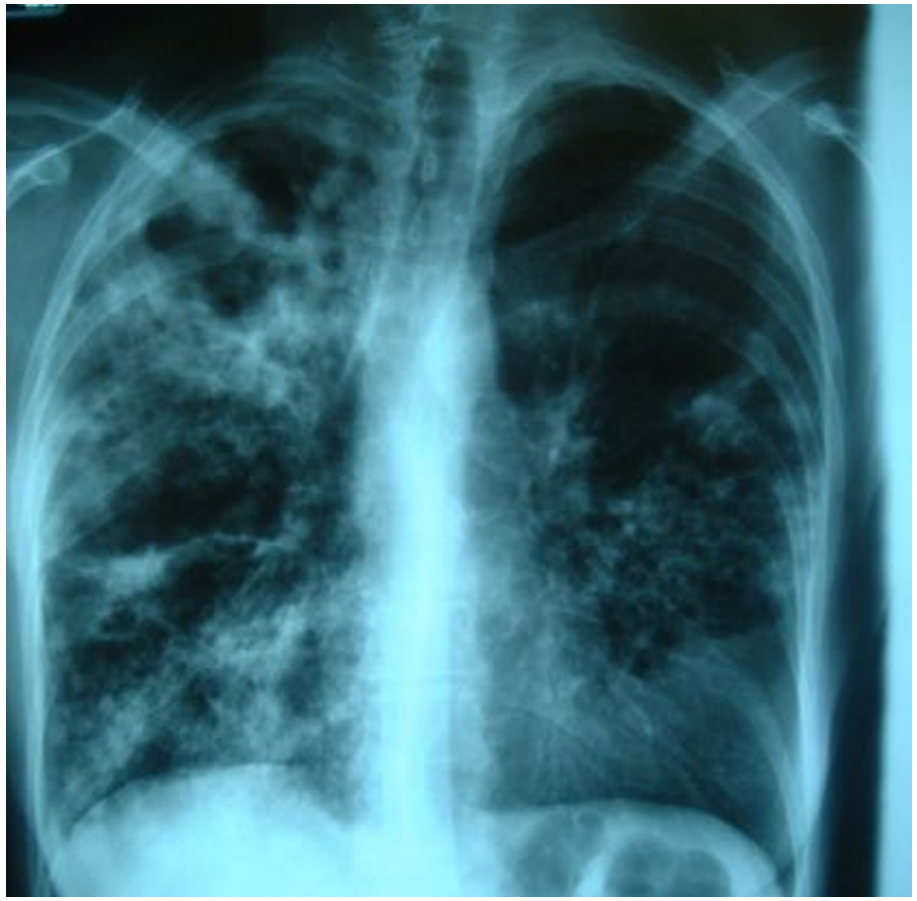
Drug therapy

- 1944 Streptomycin
- 1949 PAS
- 1952 Pyrazinamide
- 1954 Isoniazid
- 1955 Cycloserine
- 1962 Ethambutol
- 1963 Rifampicin

- Quadruple therapy:
  - rifampicin + isoniazide+ pyrazinamide+ ethambutol 2/12
  - Rifampicin + isoniazid 4/12

Patient AB

- CXR:
- HIV +ve
- Induced sputum:
  - PCP –ve
  - AFB +ve
- Blood cultures –ve
- Absolute LC count 0.9
- CD4 320 cells/ml



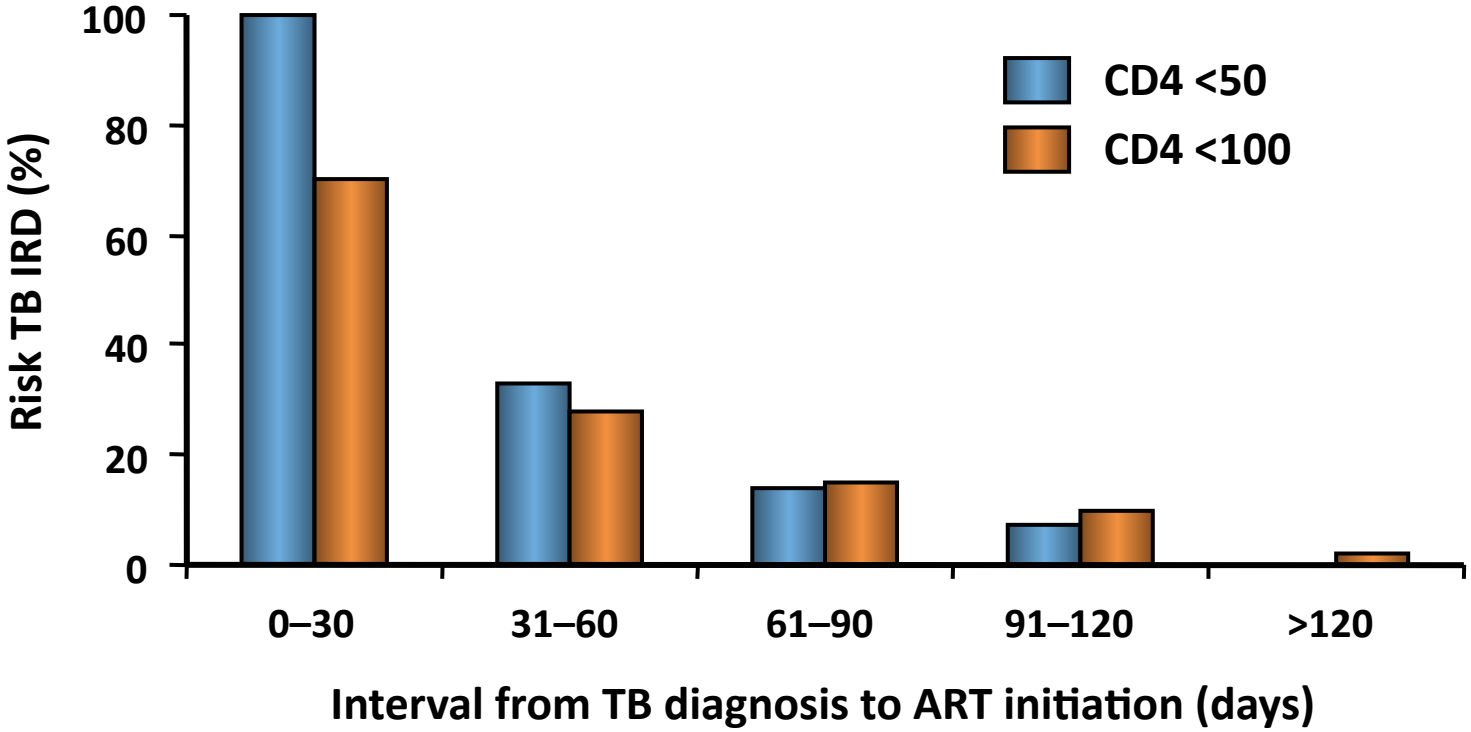
TB-associated Immune Reconstitution Disease (IRD)

- Retrospective cohort of incidence of IRD in TB patients in first 4 months of starting ARV in South Africa
- IRD developed in 19; 141 did not develop IRD
- IRD occurred in 32% of those who started ART within 2 months of TB diagnosis
- 84% had pulmonary and 37% intra-abdominal IRD

In multivariate analysis, risk of IRD strongly associated with early ARV initiation and CD4 count.

Lawn S *et al.* CROI 2007;Abstr. 863.

How common is IRIS? TB-associated IRD



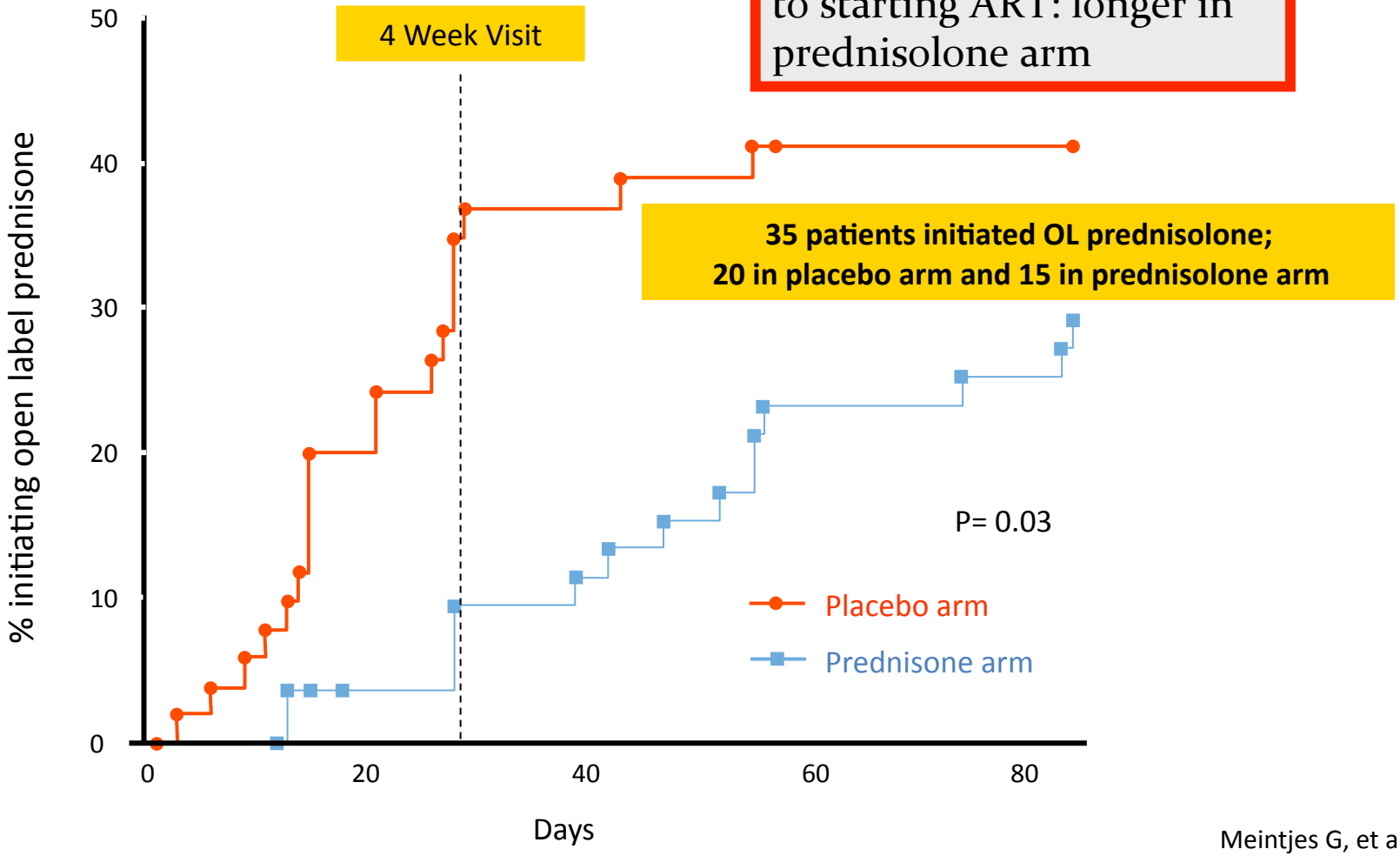
All patients with CD4 <50 cells/mm^3 developed IRD if ART initiated in first month

Low risk of death overall (1.3%): mostly self-limiting.

Lawn S *et al.* CROI 2007;Abstr. 863.

Time to initiation of open label prednisone

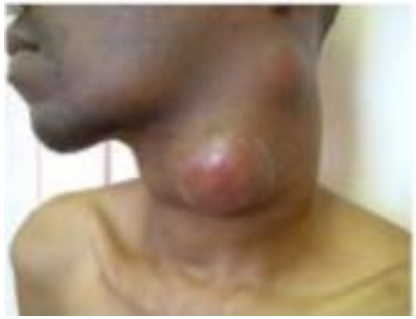
Matched groups at BL apart from length of time from starting TB treatment to starting ART: longer in prednisolone arm



Meintjes G, et al
Oral Abstract 34

How to manage TB-IRIS

- **Background:** occurs in 8-43%, anecdotal reports steroids beneficial but concerns may worsen KS/CMV
- **Hypothesis:** 4w prednisolone would reduce need for medical interventions, be safe and not ↑ infections
- **Design:**
  - Prednisolone or placebo, randomised double blind
  - 1.5mg/kg for 2 weeks then 0.75mg/kg for 2 weeks
  - Follow-up assessments: 1, 2, 4, 8, and 12 weeks
  - Open-label at physicians' discretion if clinical deterioration/relapse
- **Primary endpoint:**
  - Cumulative number of days and OPD therapeutic procedures (arbitrarily counted as 1 additional day), ITT analysis



Meintges et al. CROI 2009. Abstract 34

Case definition & enrolment

Case definition:

Prior to ART

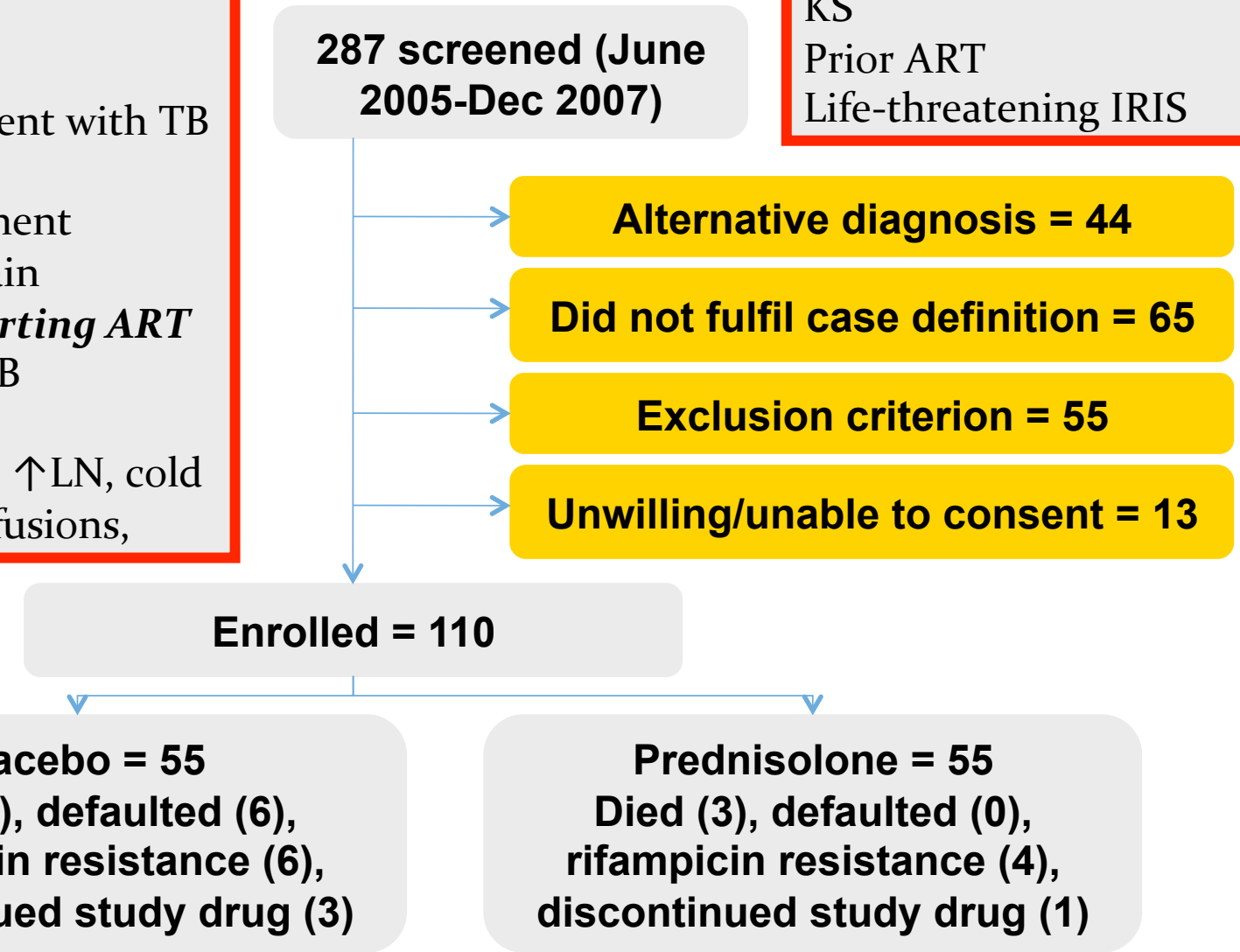
- Evidence of TB
- Initial improvement with TB treatment
- Still on TB treatment
- RIF-sensitive strain

Within 3m of starting ART

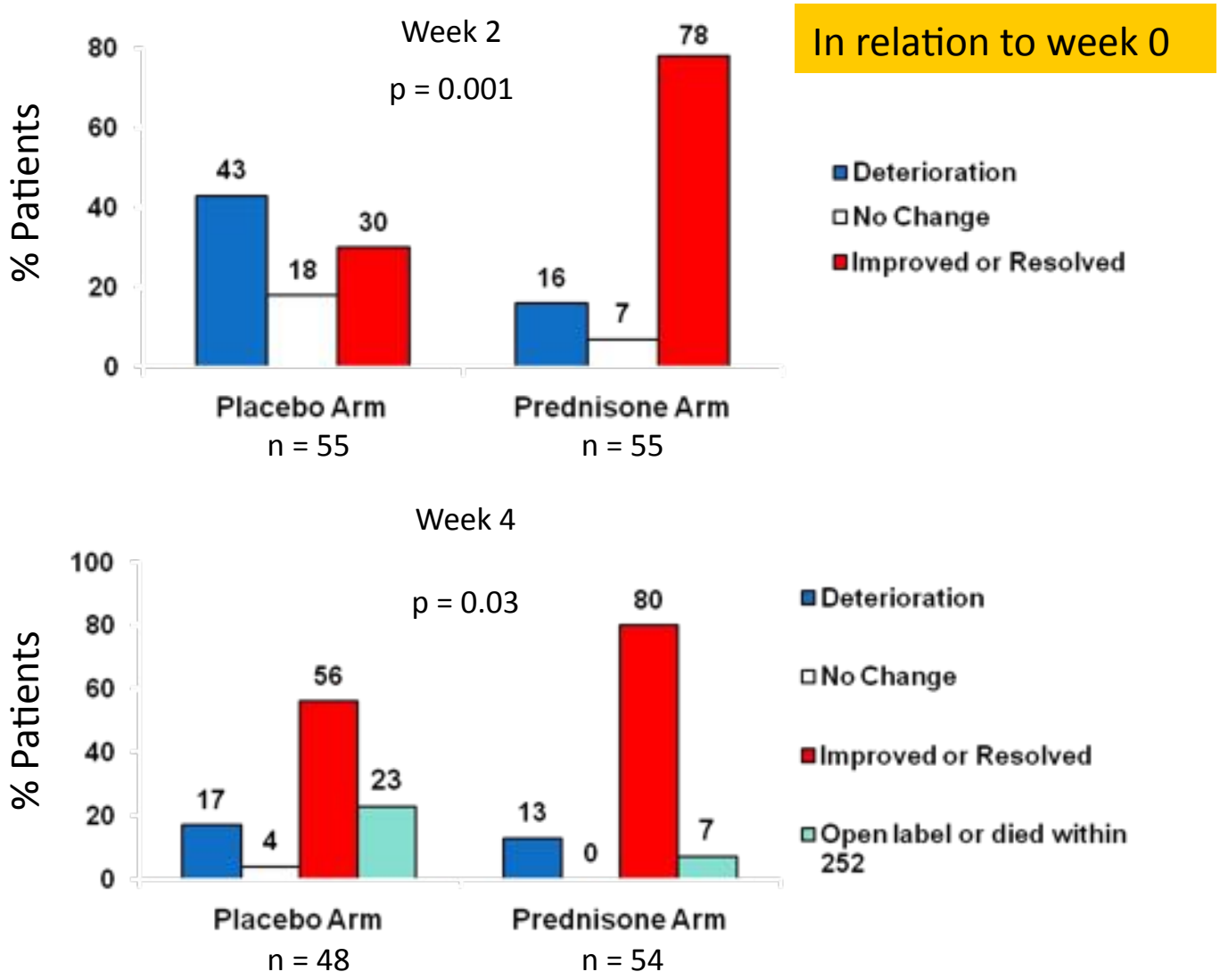
- New/recurrent TB symptoms
- Presence of ≥1 of: ↑LN, cold abscess, serous effusions, lung infiltrates

Exclusion criteria:

KS
Prior ART
Life-threatening IRIS

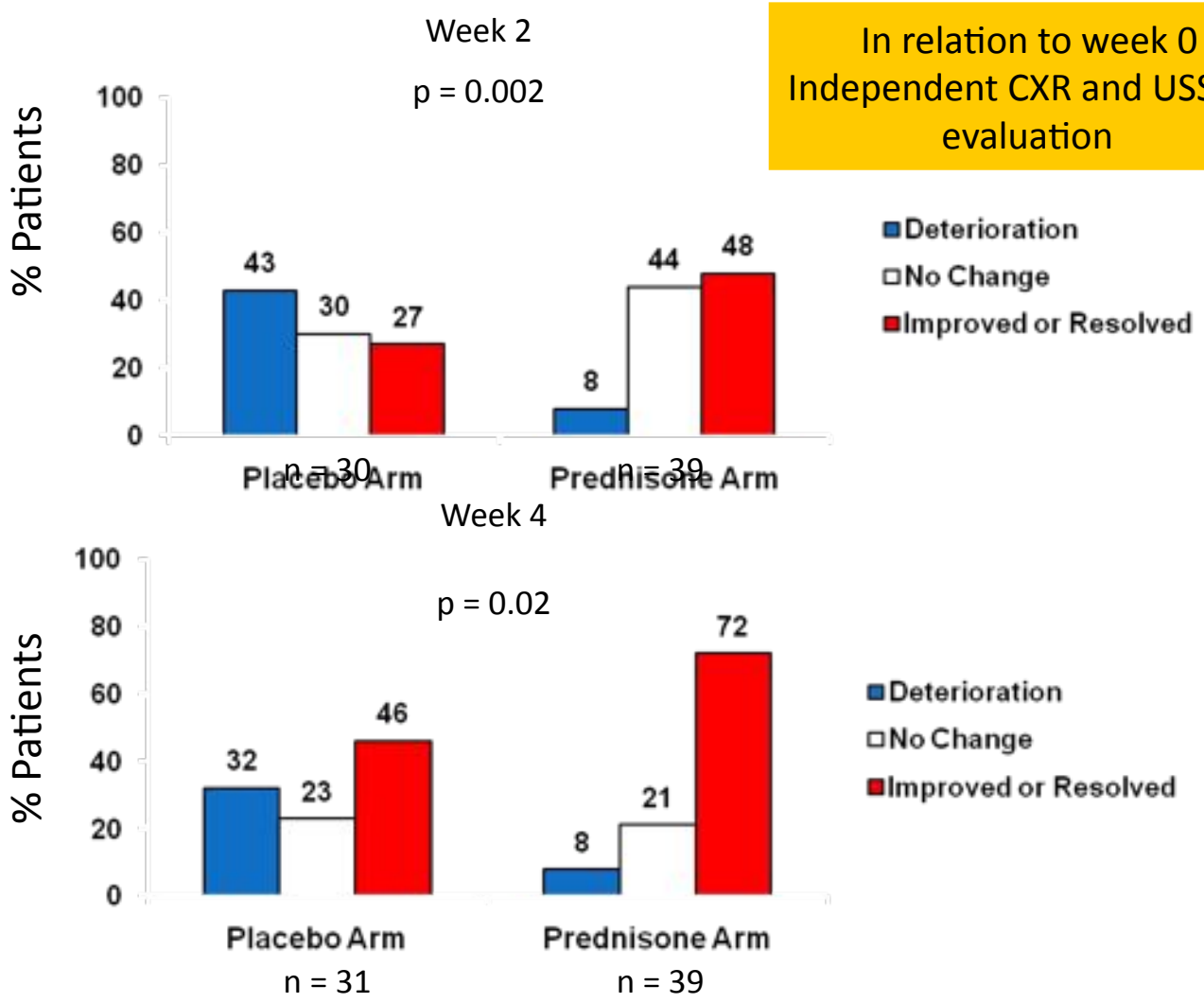


Symptom score



Meintges et al. CROI 2009. Abstract 34

Chest Radiograph score



In relation to week 0
Independent CXR and USS LN evaluation

Ultrasound score demonstrated no differences at week 2 or 4

Meintges et al. CROI 2009. Abstract 34

Primary endpoint/AE

Cumulative number of days and OPD therapeutic procedures (counted as 1 additional day), ITT analysis

	Placebo arm (n=55)	Prednisolone arm (n=55)	P-value
Total days hospitalised	463	282	
Total OPD procedures	31	27	
Cumulative 1º endpoint (median, IQR)	3 (0-9)	1 (0-3)	0.046

	Placebo Arm	Prednisone Arm	P-value
Death on Study	2 (4%)	3 (5%)	0.65
Corticosteroid side effects*	18 (33%)	12 (22%)	0.20
Corticosteroid side effectswhile on study drug	3 (5%)	8 (15%)	0.11
Infections	30 (55%)	36 (65%)	0.24
Severe Infections**	4 (7%)	2 (4%)	0.40

Meintges et al. CROI 2009. Abstract 34

Conclusions

- Prednisolone reduced need for medical interventions (days hospitalised and outpatients procedures combined)
- Consistent benefit maximal in 1st 4 weeks:
  - Symptom score, CRP, radiology score, Karnofsky score
- Benefits shown despite crossovers to OL prednisolone
- No excess of steroid complications
- 4 weeks may have been too short and tapering dose probably better

Meintges et al. CROI 2009. Abstract 34

Thank you

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