Update on TB-IRIS

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Paradoxical TB-IRIS

Patient diagnosed with TB and started on TB treatment

↓

Typically improving on TB treatment then start ART

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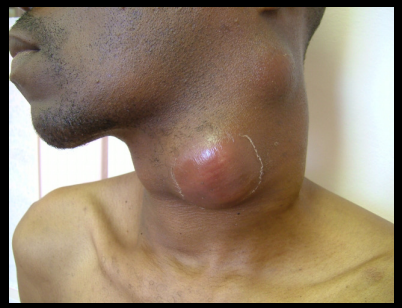
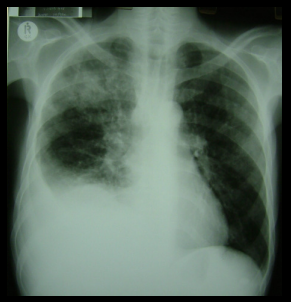
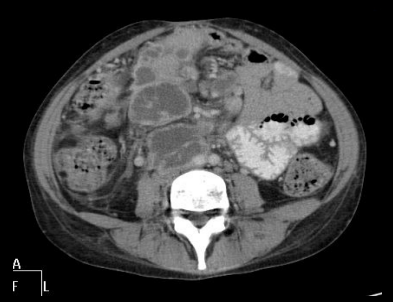
Recurrence of TB symptoms and new or recurrent clinical manifestations of TB

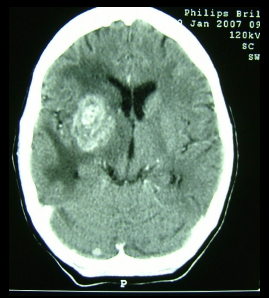
(Usually 1-3 weeks after starting ART)

8-43% of patients on TB treatment when starting ART develop paradoxical TB-IRIS









OUTLINE

- Neurological TB-IRIS
- Prolonged TB-IRIS
- Important differential diagnoses
- Corticosteroids
- Pathogenesis
- Risk factors and ART timing

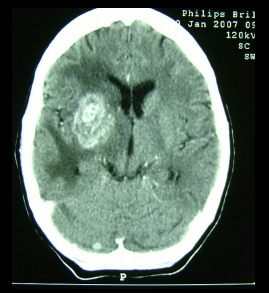
IRIS meta-analysis

Pooled cumulative incidences as % (95% credibility intervals)

	Incidence (%)	**Mortality (%)**
CMV retinitis	37.7 (26.6 - 49.4)	-
Cryptococcal meningitis	19.5 (6.7 - 44.8)	20.8 (5.0 - 52.7)
Tuberculosis	15.7 (9.7 - 24.5)	3.2 (0.7 - 9.2)
PML	16.7 (2.3 - 50.7)	-

Muller, Lancet Infect Dis 2010;10:251

Neurological TB-IRIS

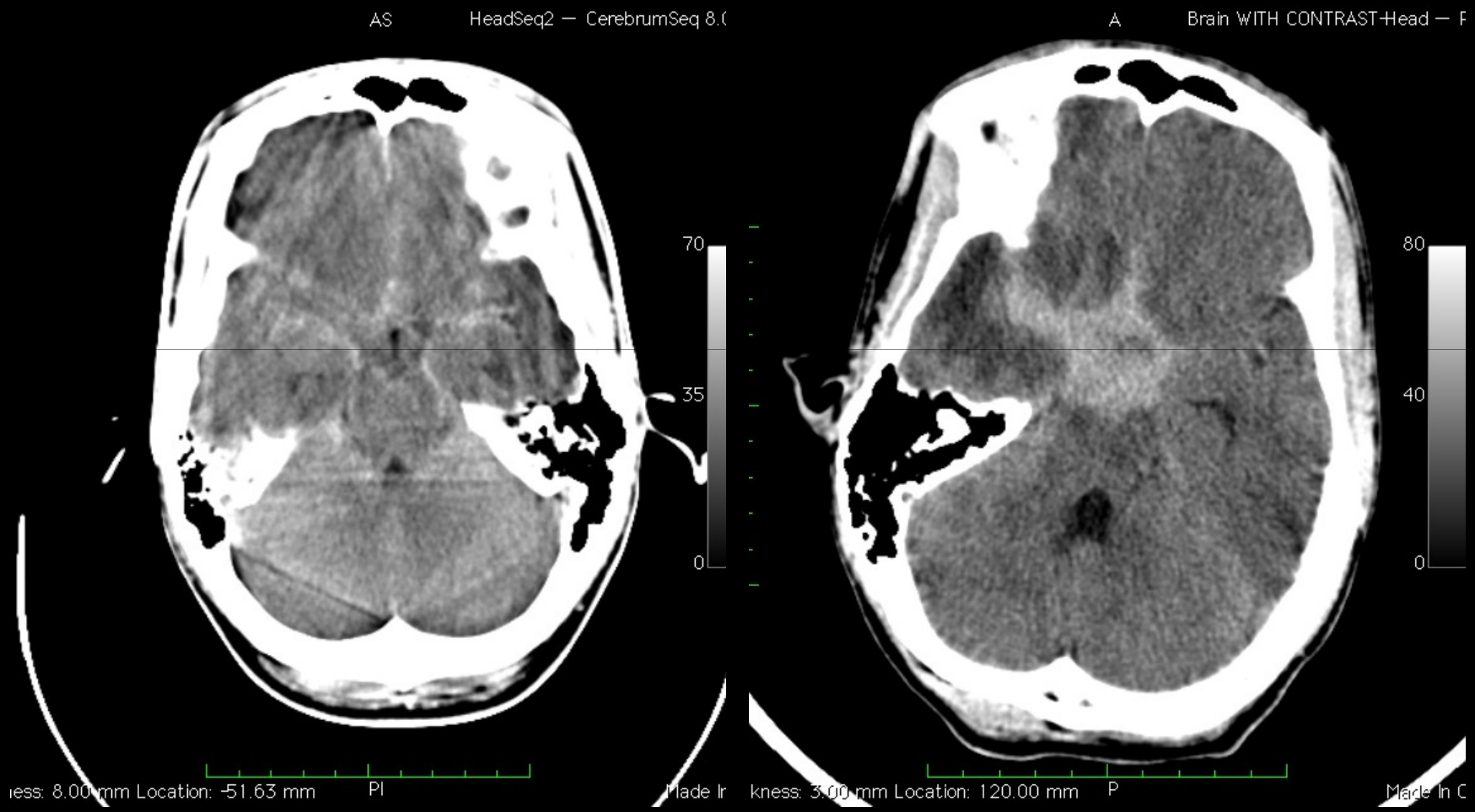


- 12% with paradoxical TB-IRIS have CNS involvement
- Up to 47% of TBM patients starting ART develop IRIS
- Features
  - Meningitis
  - Tuberculoma/s
  - Radiculomyelopathy
- Occurs in patients with or without CNS TB prior to ART
- Outcomes
  - 12% mortality and 18% loss to follow-up in one series
  - 25% mortality in another series
  - Neurological disability

Pepper et al, Clin Infect Dis 2009
Marais et al, Clin Infect Dis 2012

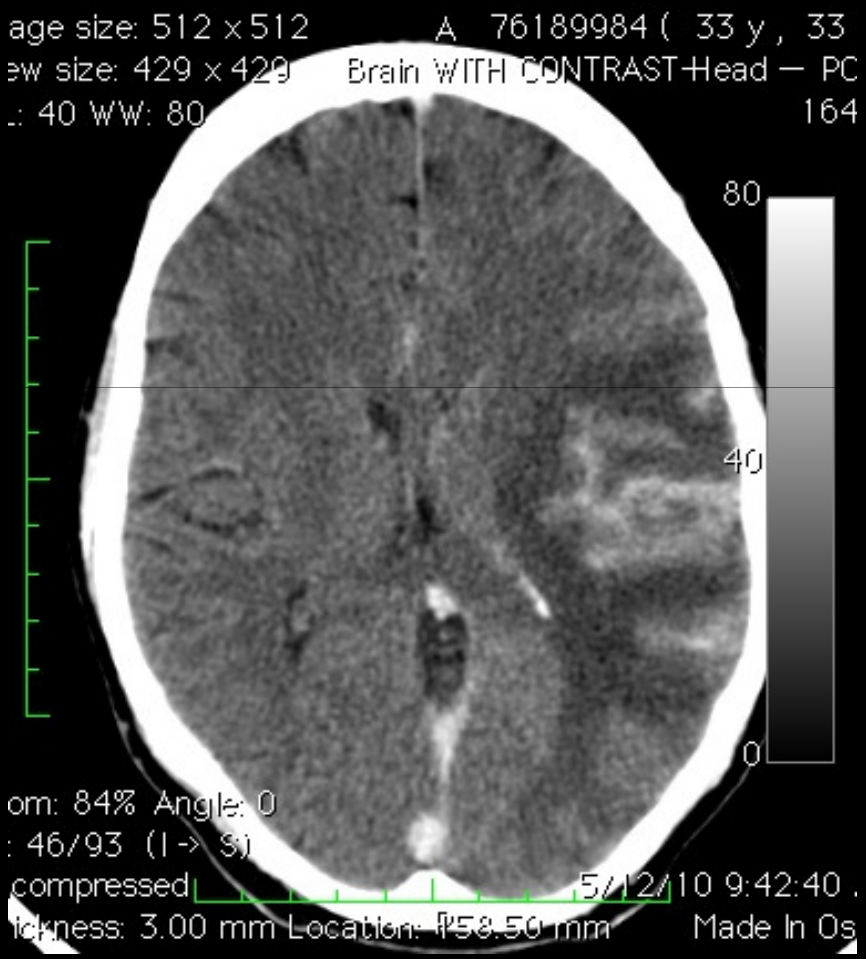
TBM diagnosis

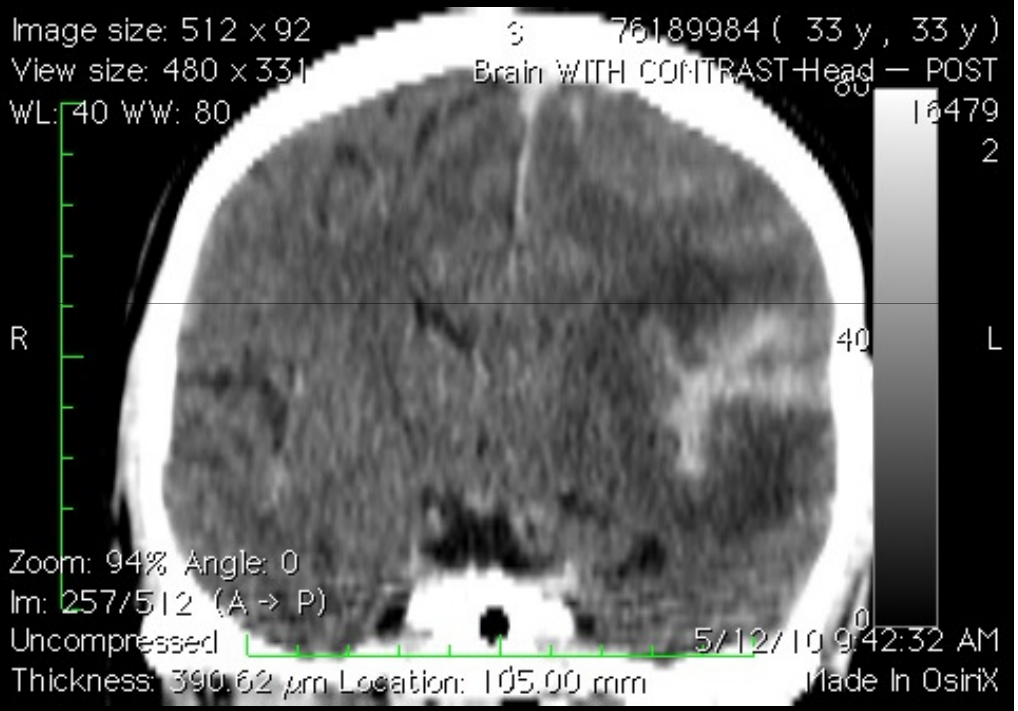
TBM-IRIS



Slide courtesy Suzaan Marais

TBM-IRIS with expressive aphasia





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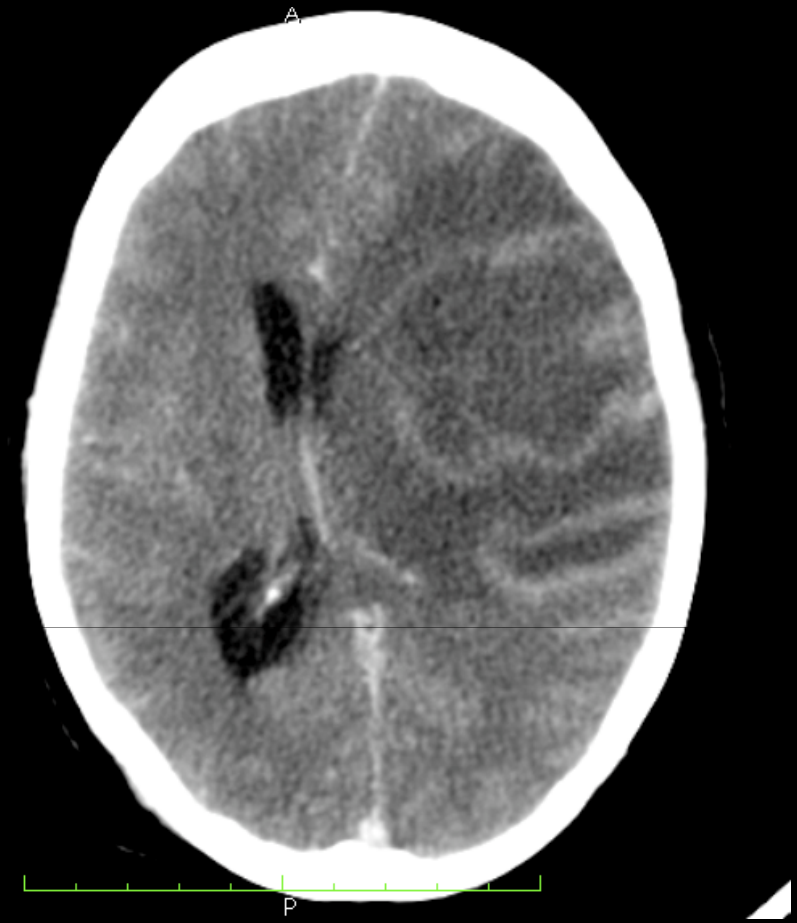
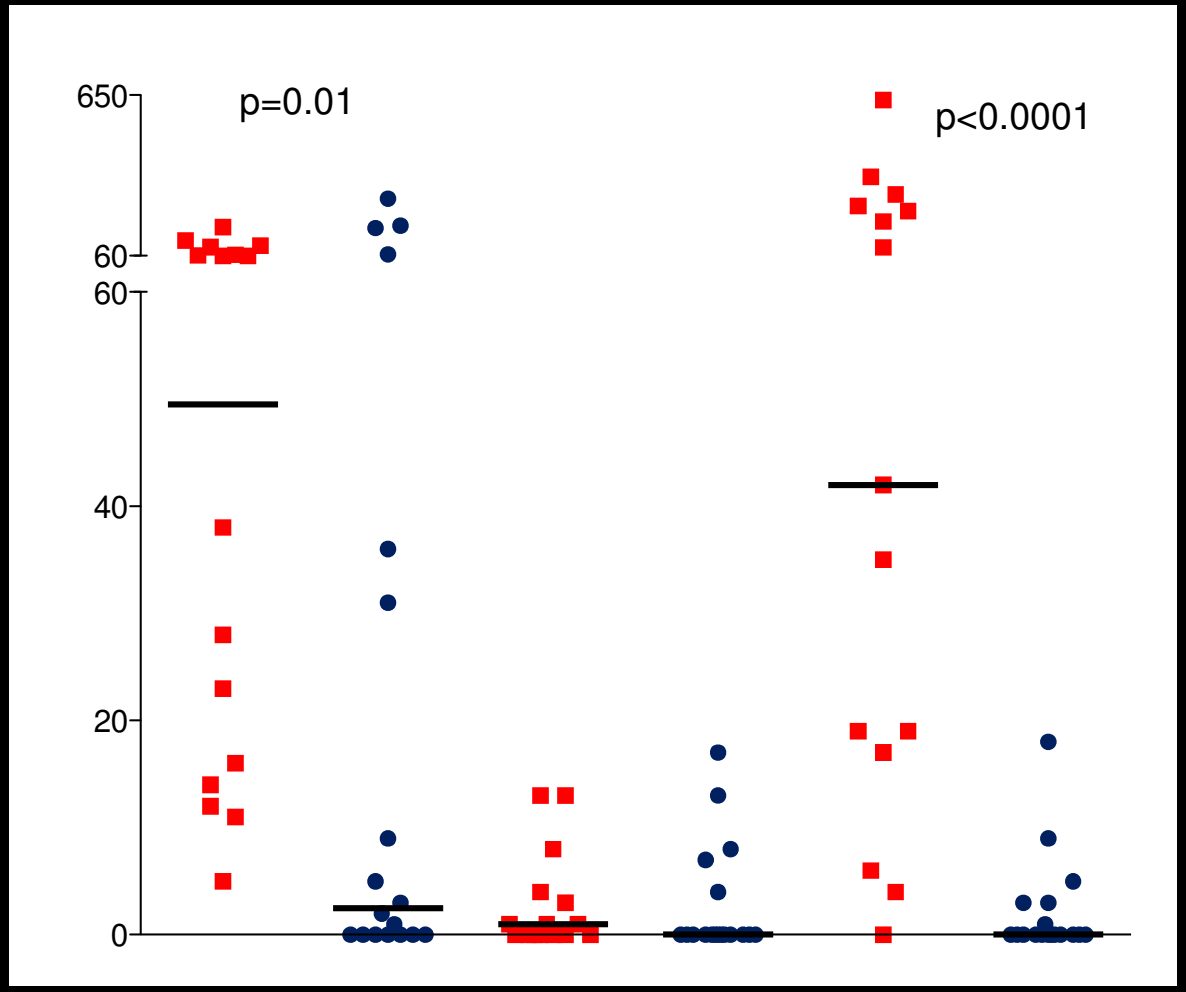


TBM and PTB prior to ART
TB-IRIS with enlarging mass lesion/cerebral oedema
Patient died

IRIS

Non IRIS

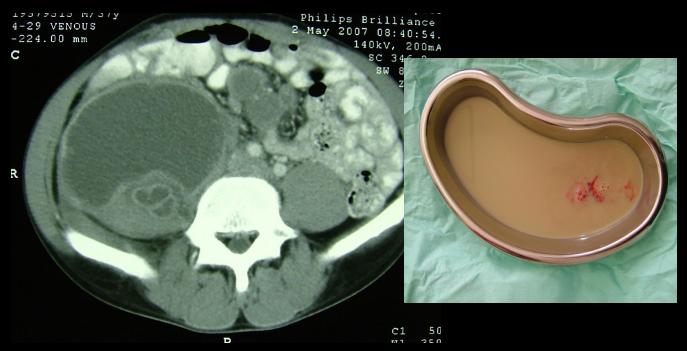
CSF Neutrophils and TBM-IRIS



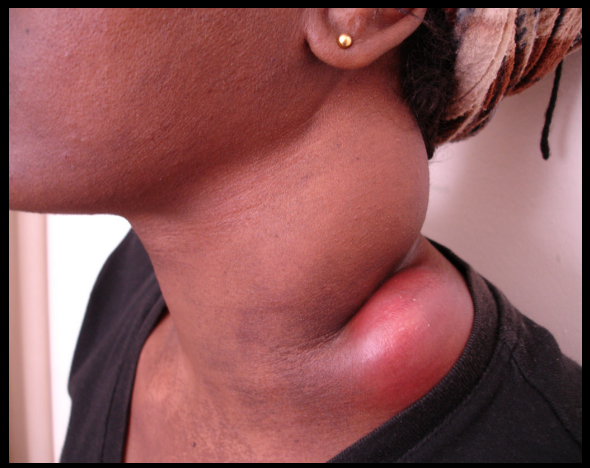
Marais
CID 2012

Prolonged TB-IRIS

- Typically suppurative lymphadenitis & abscesses
- Systemically well
- Tuberculomas & cerebral abscesses



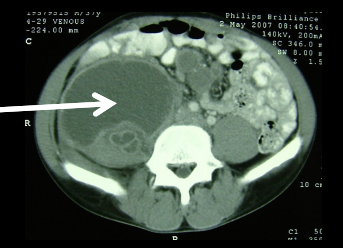
- <u>TB-IRIS duration (n = 176)</u>
  - Median: 70 days
  - IQR: 41-111 days
  - IRIS > 90 days: 36%



Bana, unpublished

Prolonged TB-IRIS: management

- Often repeated aspirations required
- Avoid surgical drainage
- Repeat TB culture (and DST if positive)
- Role of corticosteroids for more than 4 months questionable unless CNS involved
- Experimental therapies
  - Thalidomide and TNFa-blockers
- Consider prolonging TB treatment
  - How adequate is drug penetration?

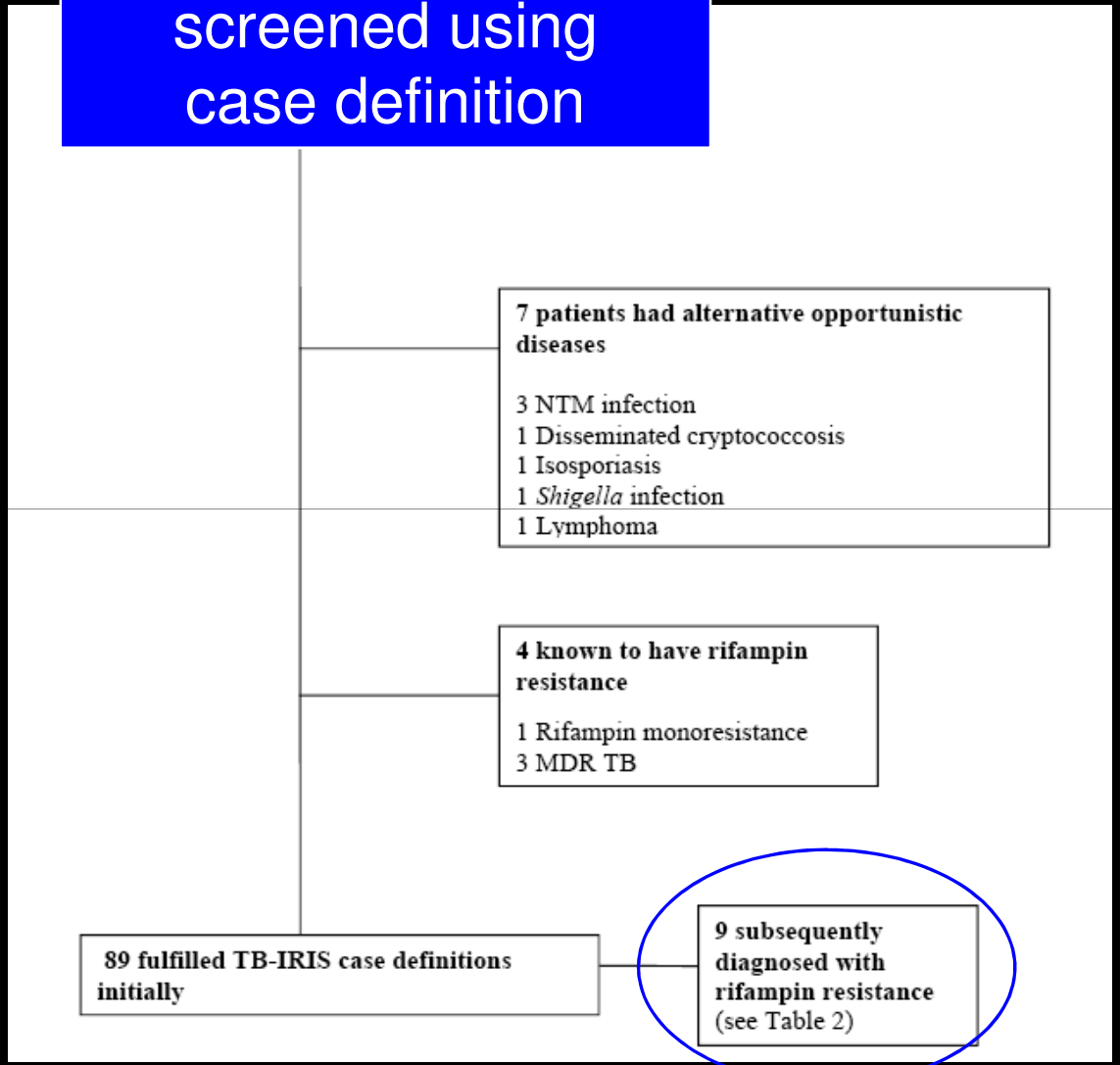


Key points in TB-IRIS diagnosis

1. Diagnosis of TB confirmed or very likely?
2. Improvement on TB treatment prior to ART?
3. Symptom onset typically 1-3 weeks on ART
4. Deterioration with inflammatory features of TB
5. Consider and exclude differential diagnoses
6. Exclude drug-resistant TB

No confirmatory diagnostic test

100 TB-IRIS suspects screened using case definition



KEY FINDING

Undiagnosed rifampicin resistance in **10.1%** of patients (95% CI 3.9-16.4%) presenting with TB-IRIS, after exclusion of known rifampicin resistance and alternative opportunistic diseases

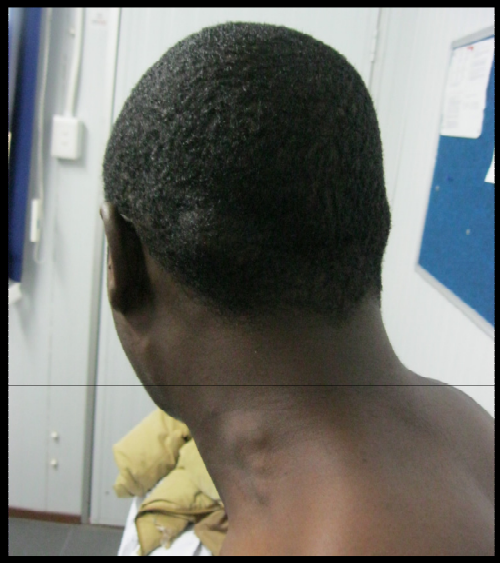
Lymph node enlargement

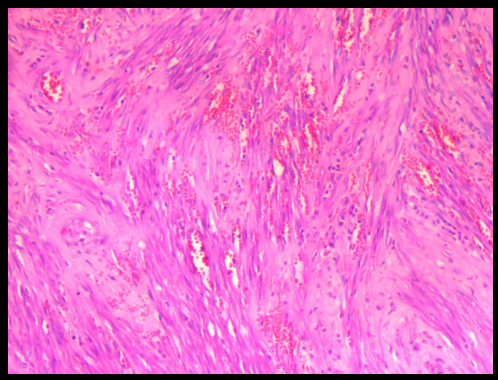
Differential diagnoses

- Lymphoma
- Kaposi's
- Castleman's disease

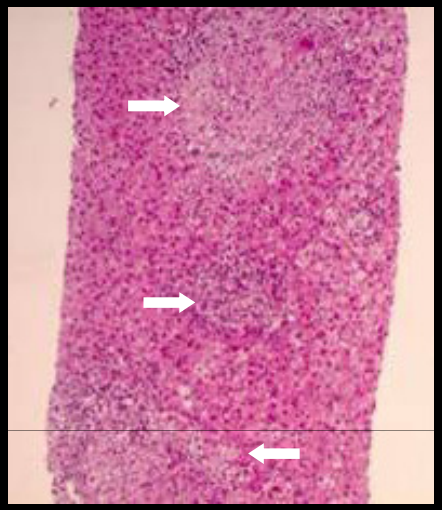
Consider malignancy particularly when LN remains firm

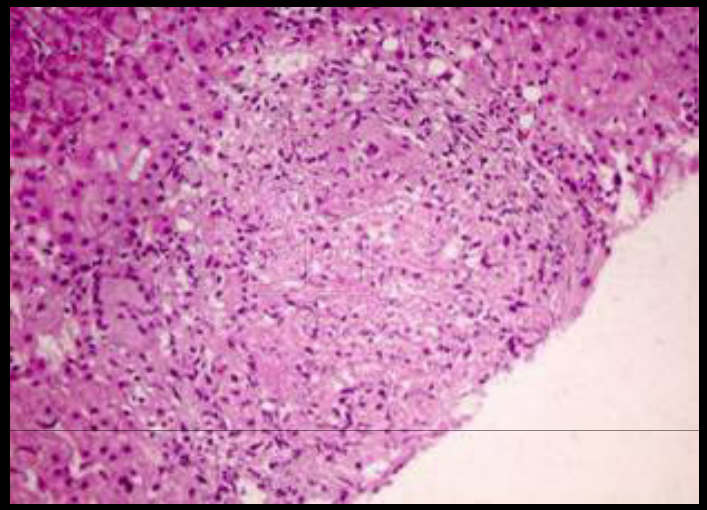
- NTM IRIS
- Cryptococcal IRIS

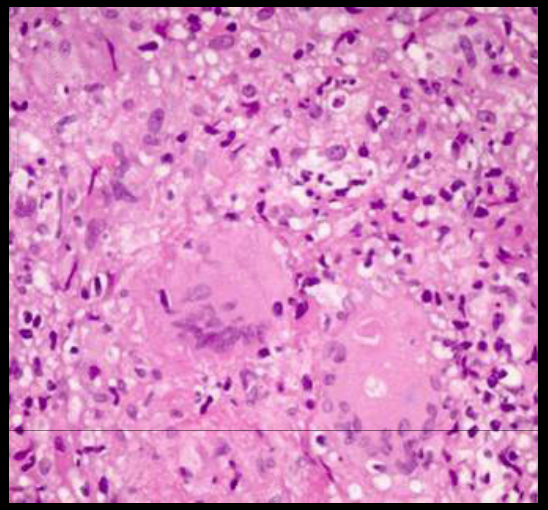




Hepatic TB-IRIS case







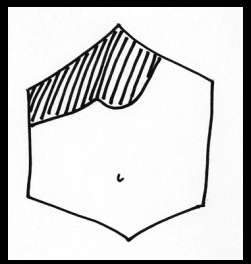
- 4 months treatment for drug-sensitive pericardial TB
- Clinically improved, then started ART
- 3 weeks later presented with fever and hepatomegaly
- LFT: Bil 52, CBil 31, Alk Phos 1081, GGT 1468, ALT 82, AST 88
- CD4 rise from 64 to 221
- Biopsy AFB- and TB culture -

Case courtesy of Mark Sonderup

Hepatic TB-IRIS vs DILI

Hepatic TB-IRIS

- RUQ pain, nausea and vomiting
- Tender hepatomegaly
- Cholestatic LFT derangement
- +/- mild jaundice
- Usually other TB-IRIS manifestations



Drug-induced liver injury

- Similar symptoms
- Typically not hepatomegaly
- Transaminitis +/- jaundice
- Absence of other TB-IRIS features

Patients may present with clinical picture between these two
- Biopsy or treat as DILI

Two conditions may co-exist

Other important differential diagnoses

Manifestation	Differential diagnoses
Pulmonary infiltrate	Bacterial pneumonia PCP Kaposi's sarcoma
Pleural effusion	Bacterial empyema Kaposi's sarcoma
Meningitis	Bacterial Cryptococcal
Space-occupying lesion	Toxoplasmosis Cryptococcoma Primary CNS lymphoma
Fever with general deterioration	Bacterial sepsis NTM Kaposi's or lymphoma

*Consider and investigate for DR-TB in all scenarios

Randomised controlled trial of prednisone vs placebo

GF Jooste Hospital, Cape Town, 2005-8

- 110 participants
- Life-threatening TB-IRIS was an exclusion
- Prednisone (or placebo) dose
  - 1.5 mg/kg/d for 2 weeks then
  - 0.75 mg/kg/d for 2 weeks
- Open-label prednisone at physician discretion if clinical deterioration/relapse

Meintjes, AIDS 2010

Primary endpoint

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

	Placebo arm N = 55	Prednisone arm N = 55	P-value
Total days hospitalized	463	282	-
Total number outpatient procedures	28	24	-
Cumulative primary endpoint (median, IQR)	**3 (0-9)**	**0 (0-3)**	**0.04**

Secondary endpoints

- Consistent benefit, maximal in first 4 weeks, across a range of secondary outcome measures
  - Symptom score
  - Karnofsky performance score
  - MOS-HIV questionnaire (quality of life assessment)
  - Chest radiology score
  - C-reactive protein
- 10/55 in prednisone arm relapsed after completing study drug and required re-initiation of prednisone
  - 4 weeks appeared to be too short for these patients

Adverse events

	Placebo arm	**Prednisone arm**	**P-value**
Death on study	2 (4%)	3 (5%)	0.65
Corticosteroid side effects while on study drug*	3 (5%)	8 (15%)	0.11
Infections while on study drug	17 (31%)	27 (49%)	0.05
Severe infections**	4 (7%)	2 (4%)	0.40

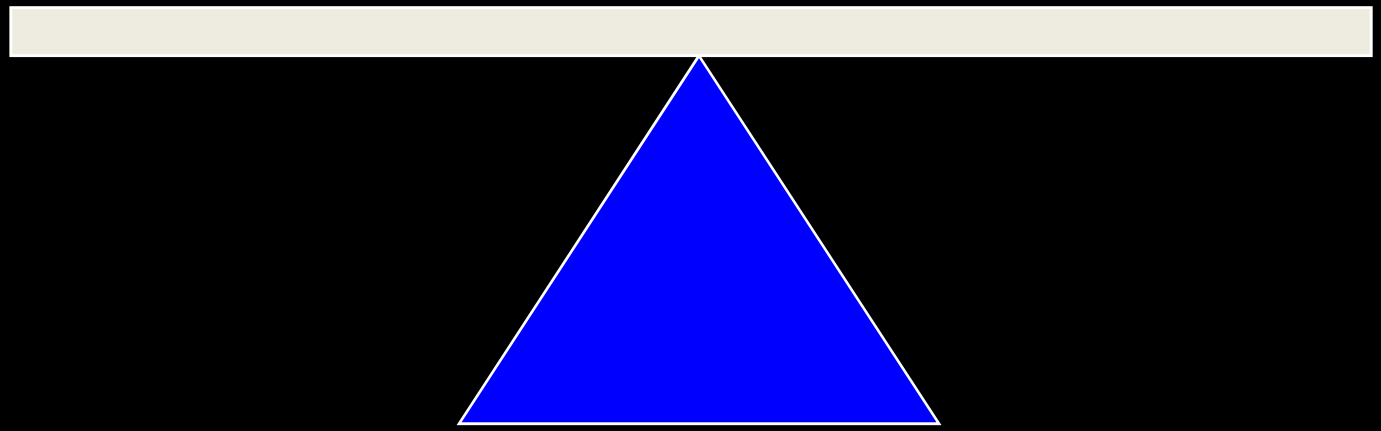
* Included BP > 140/90, oedema, hyperglycaemia, hypomania, acne, Cushingoid features, gastritis symptoms

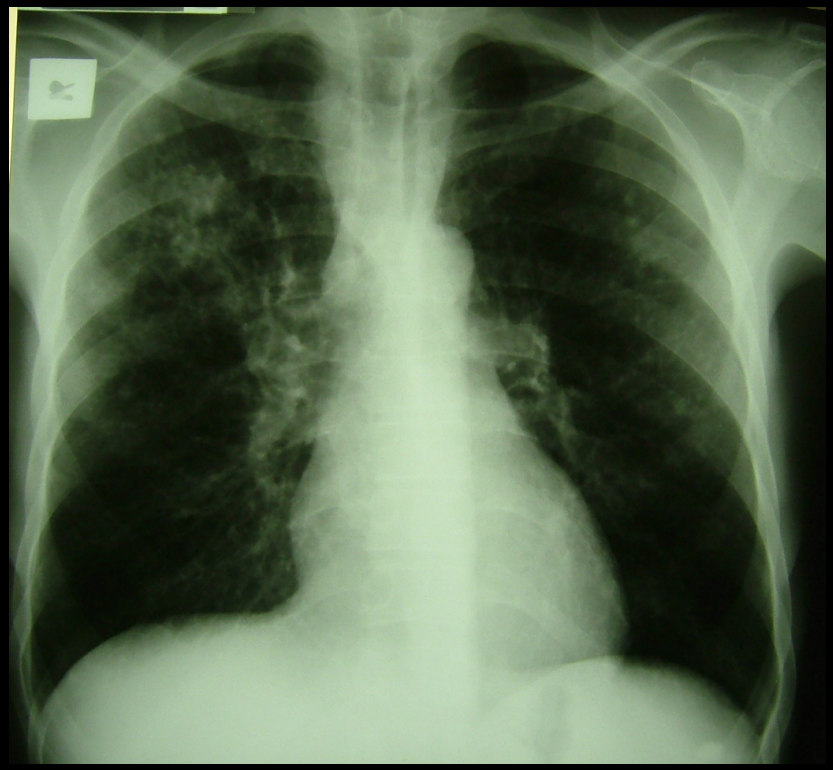
** WHO stage 4 or invasive bacterial infection

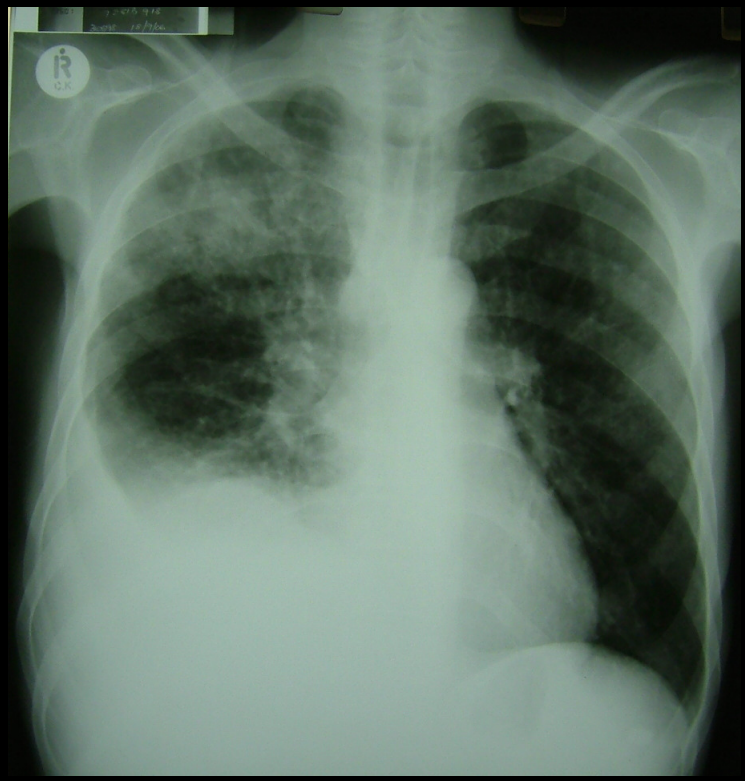
Corticosteroids for paradoxical TB-IRIS?

Symptom improvement
Reduced hospitalisation
? Survival benefit in life threatening cases

Potential adverse effects
- Kaposi's
- Infections
- Metabolic
Diagnostic uncertainty



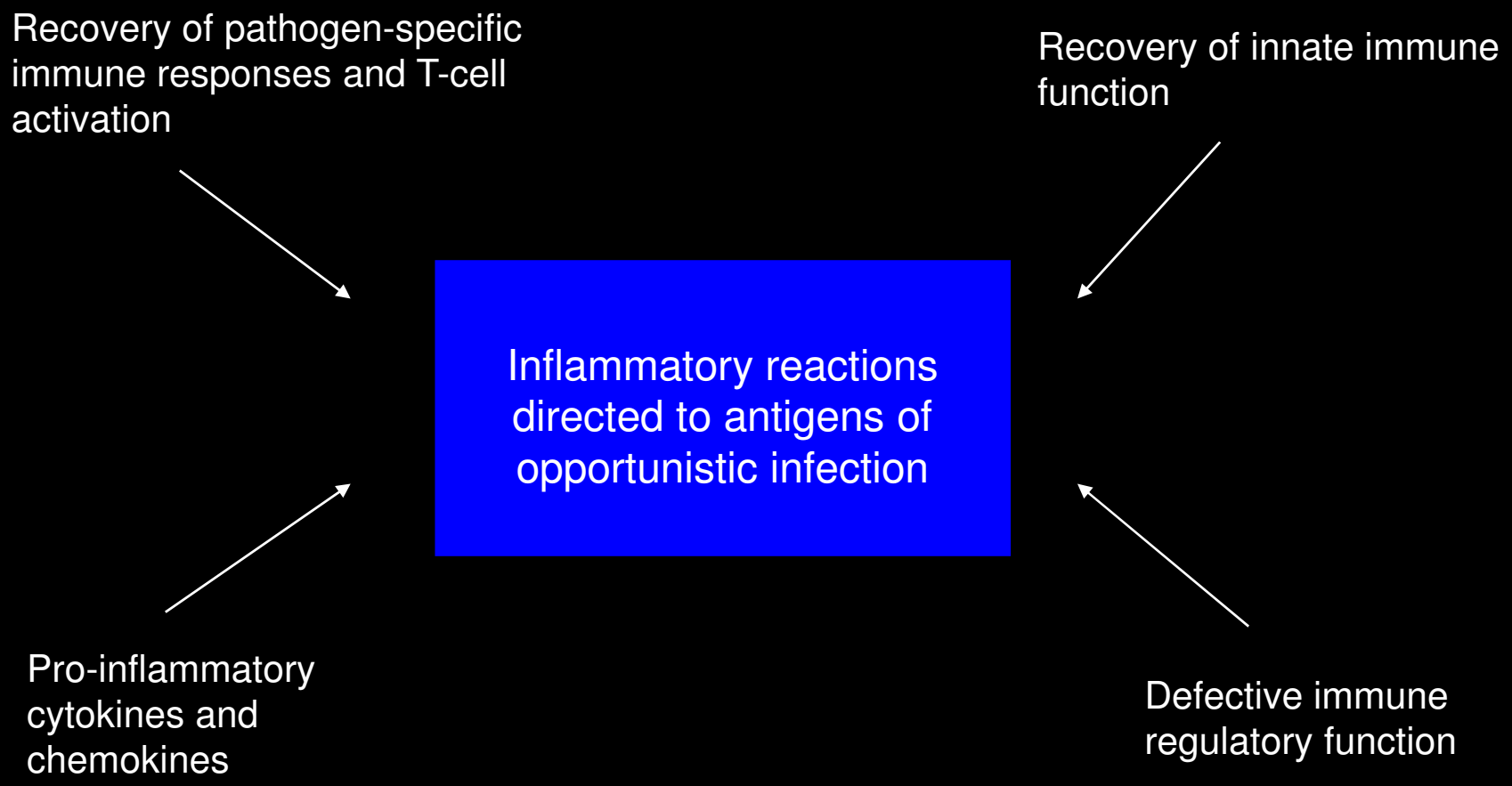




CASE: 49 year old HIV+ man with CD4=29, diagnosed with drug-susceptible PTB. Started ART 2 weeks after TB treatment. 2 weeks later developed recurrent TB symptoms, worsening of pulmonary infiltrate and new pleural effusion.

MANAGEMENT: Antibiotic, aspiration of pleural effusion, prednisone. TB cultures of sputum and effusion were negative at TB-IRIS.

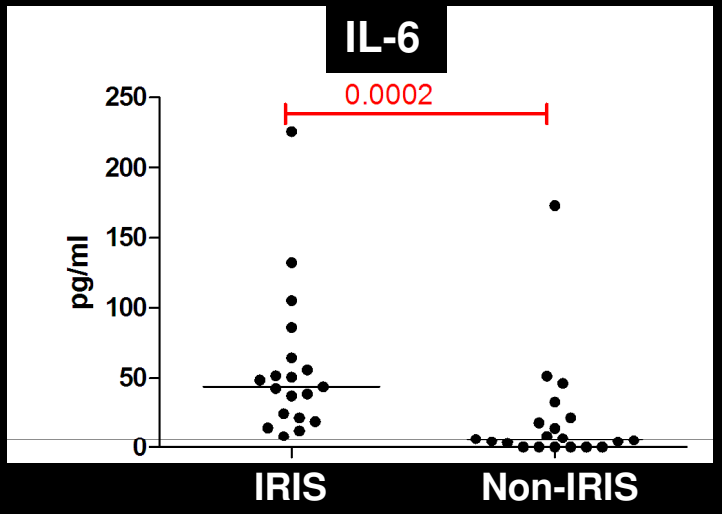
Pathogenesis of paradoxical IRIS

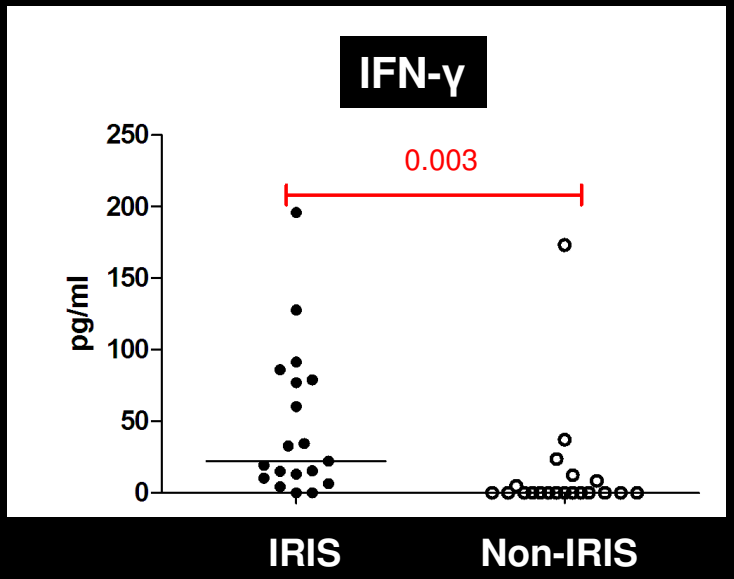


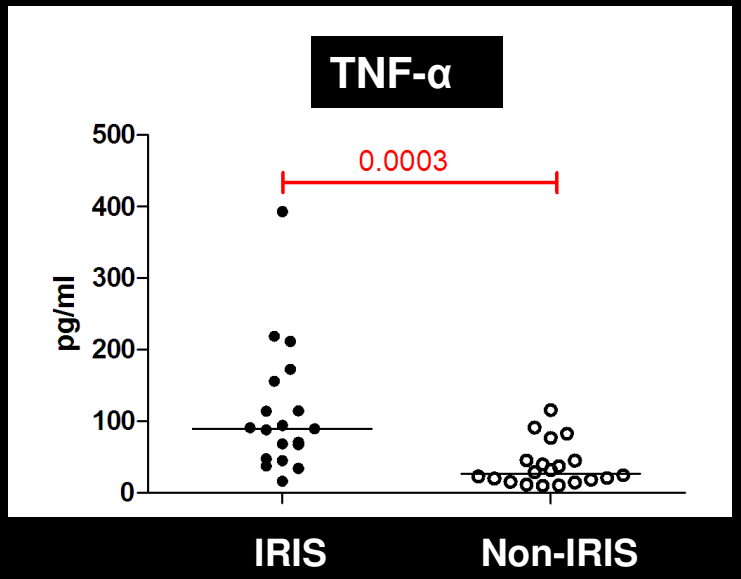
Hypercytokinaemia accompanies HIV-tuberculosis immune reconstitution inflammatory syndrome

Tadokera, Eur Resp J 2011;37:1248

22 TB-IRIS vs 22 controls
Controls were HIV-TB patients sampled at 2 weeks on ART

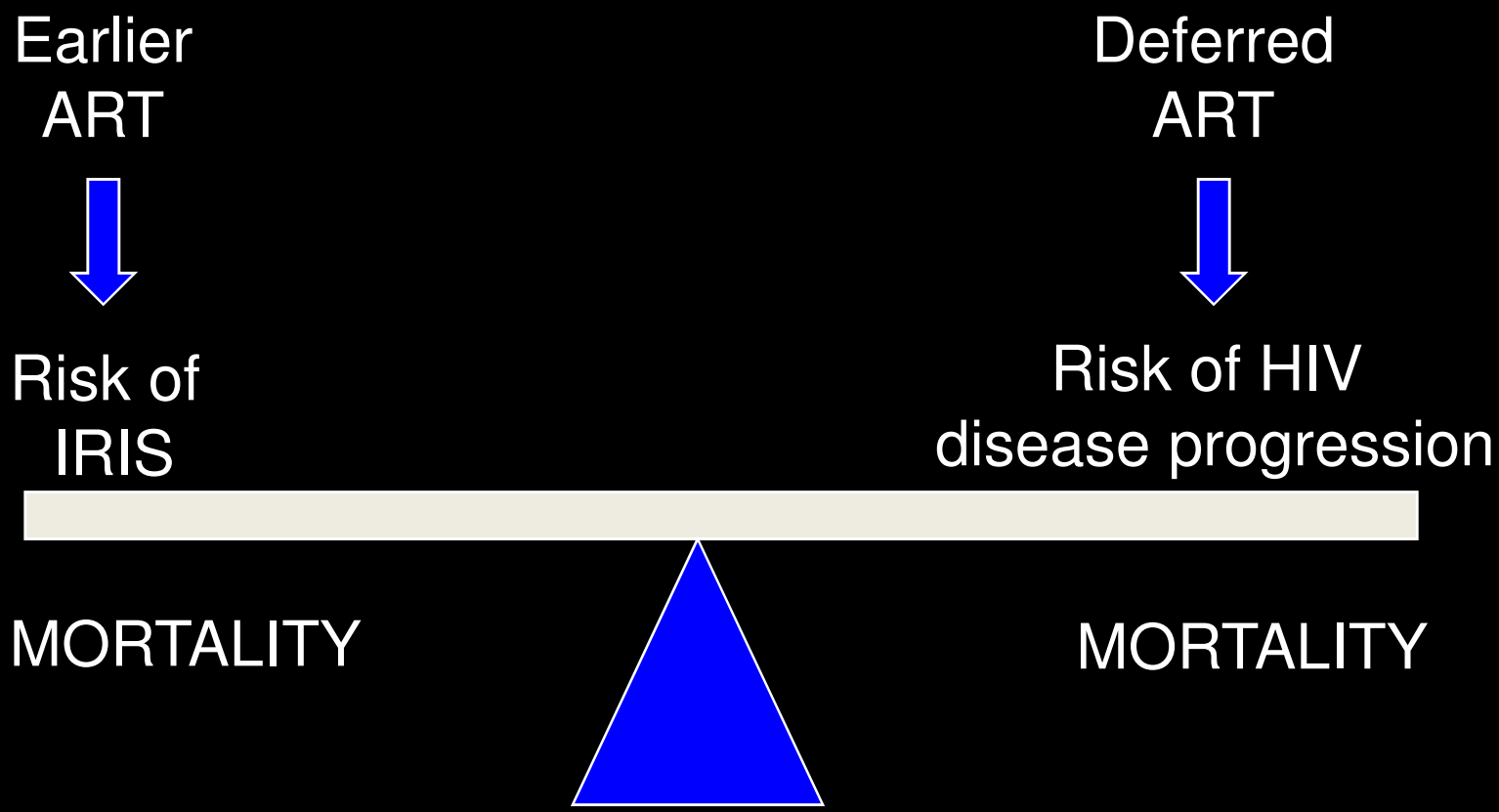






Major TB-IRIS risk factors

- Low CD4 count
- Short interval between TB treatment and ART
- Disseminated TB

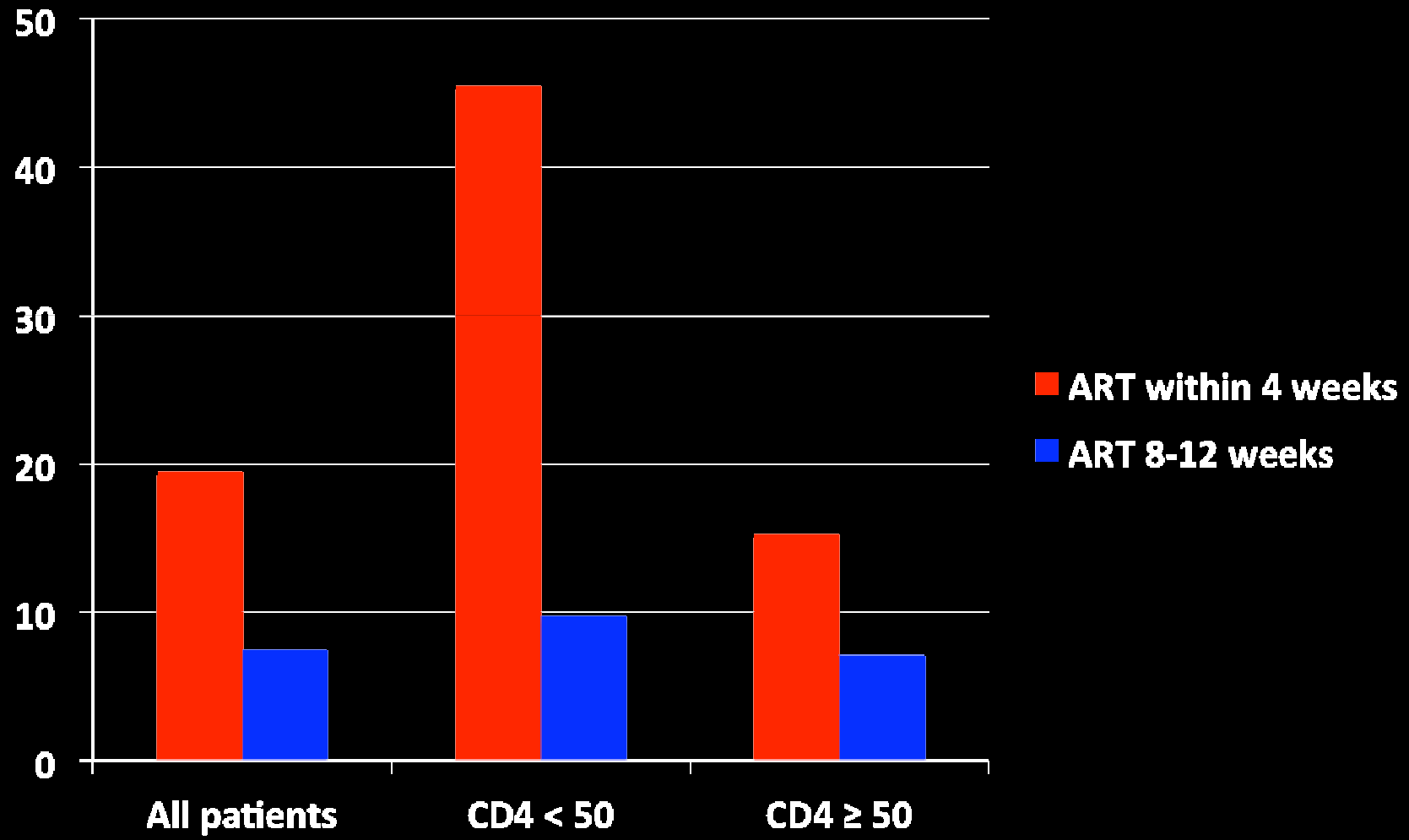


When to start ART after recent diagnosis of OI?

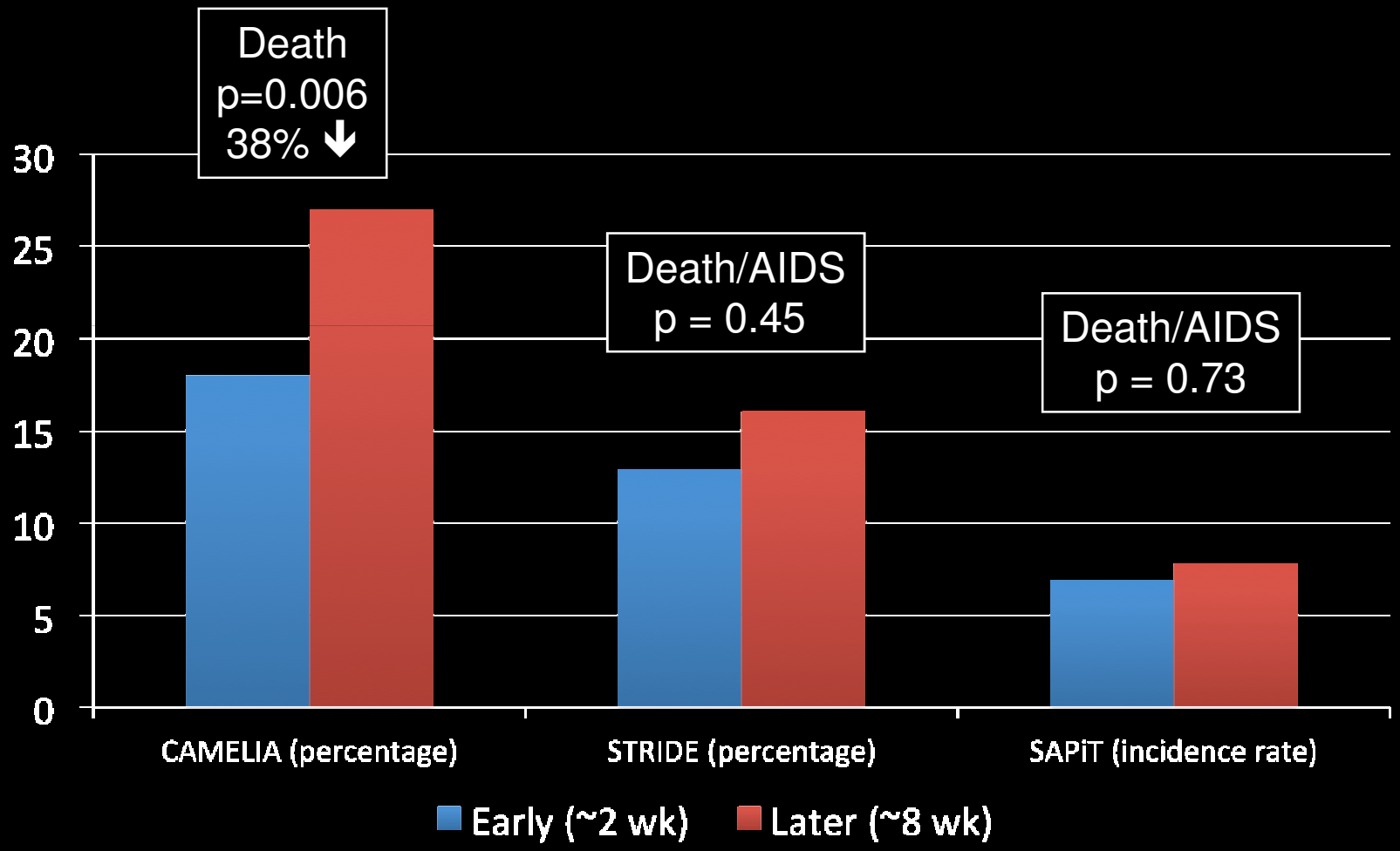
Several recent clinical trials

SAPiT IRIS incidence

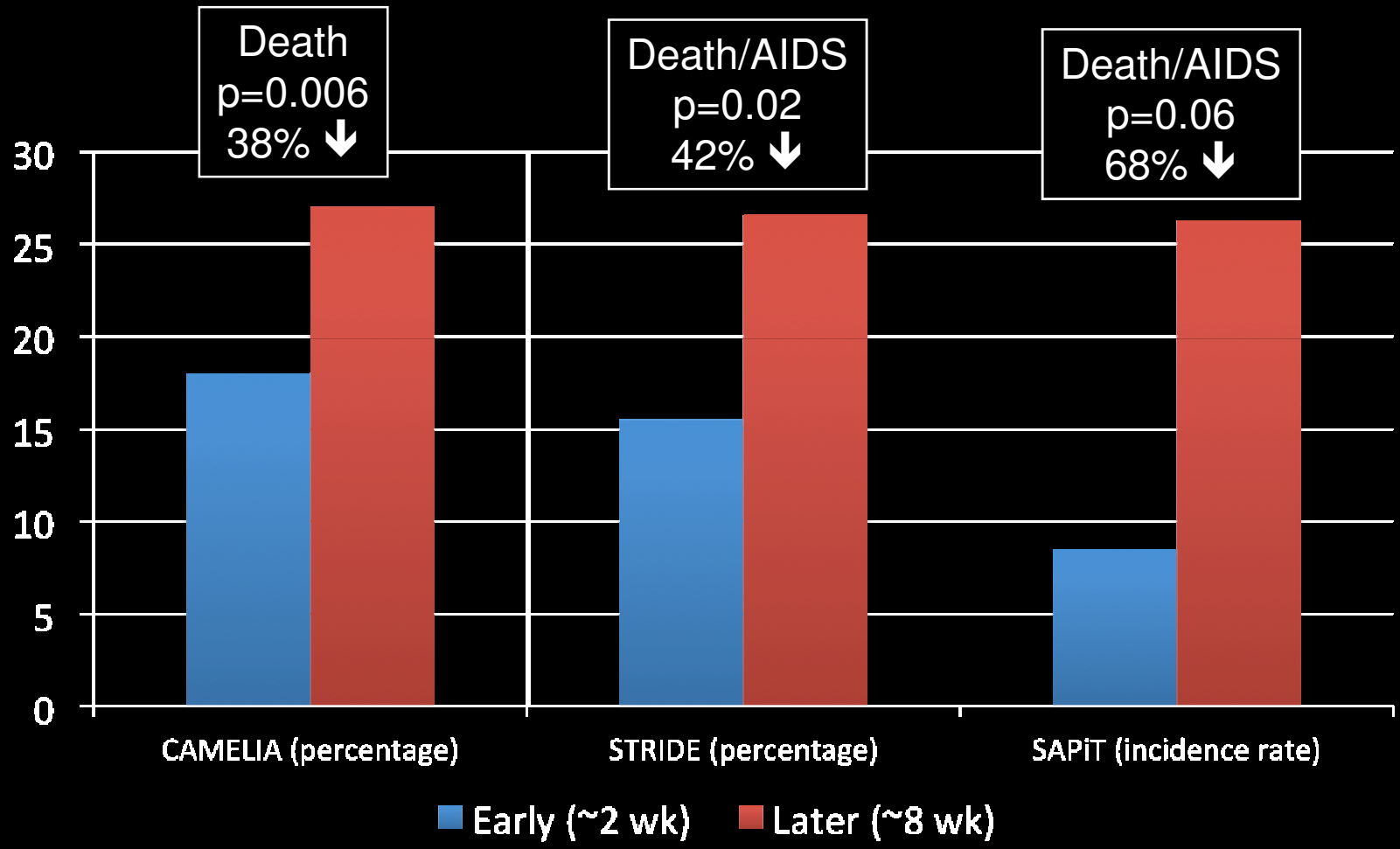
(IRIS cases/100 person years)



ART timing and primary endpoints



ART timing and primary endpoints in patients with CD4 < 50



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

Implications

- In patients with CD4 < 50 : start ART at 2 weeks
  - Even though more likely to develop IRIS with early ART
  - Benefit most from early ART in terms of survival and preventing AIDS events

- In patients with CD4 > 50
  - ART can be deferred ~ 8 weeks to reduce risk of IRIS
  - Except patients with severe clinical disease, organ system dysfunction, low performance score, low BMI or Hb as these are associated with higher mortality

Acknowledgements

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