TB-IRIS

Graeme Meintjes

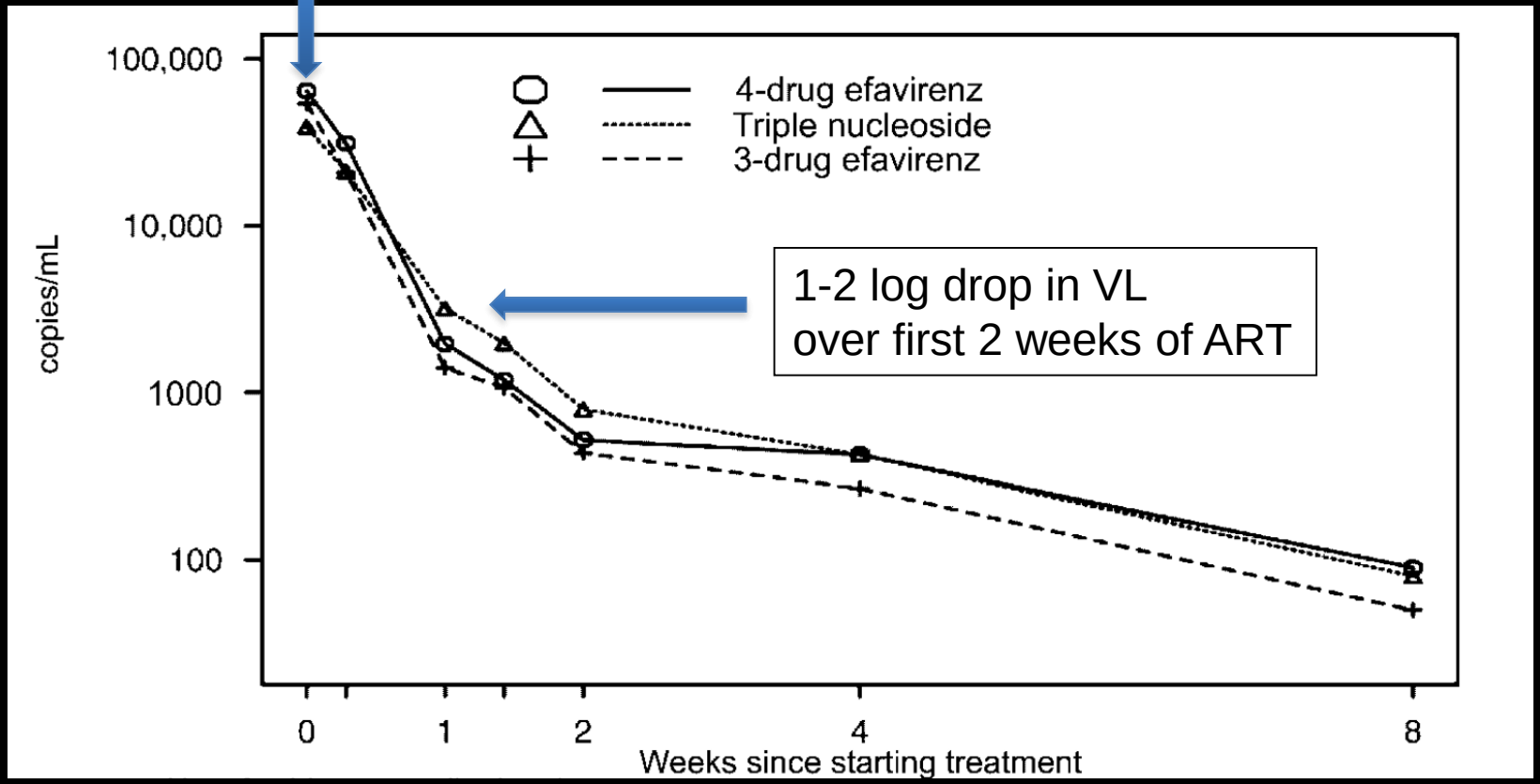
University of Cape Town

IDM
INSTITUTE OF INFECTIOUS DISEASE AND MOLECULAR MEDICINE

SPES BONA

CIDRI
CLINICAL INFECTIOUS DISEASES RESEARCH INITIATIVE

HIV viral load response to ART



Kuritzkes, JID 2007

Suppression of HIV replication on ART

↓

Early reversal of immune suppression
(systemically and at tissue level)

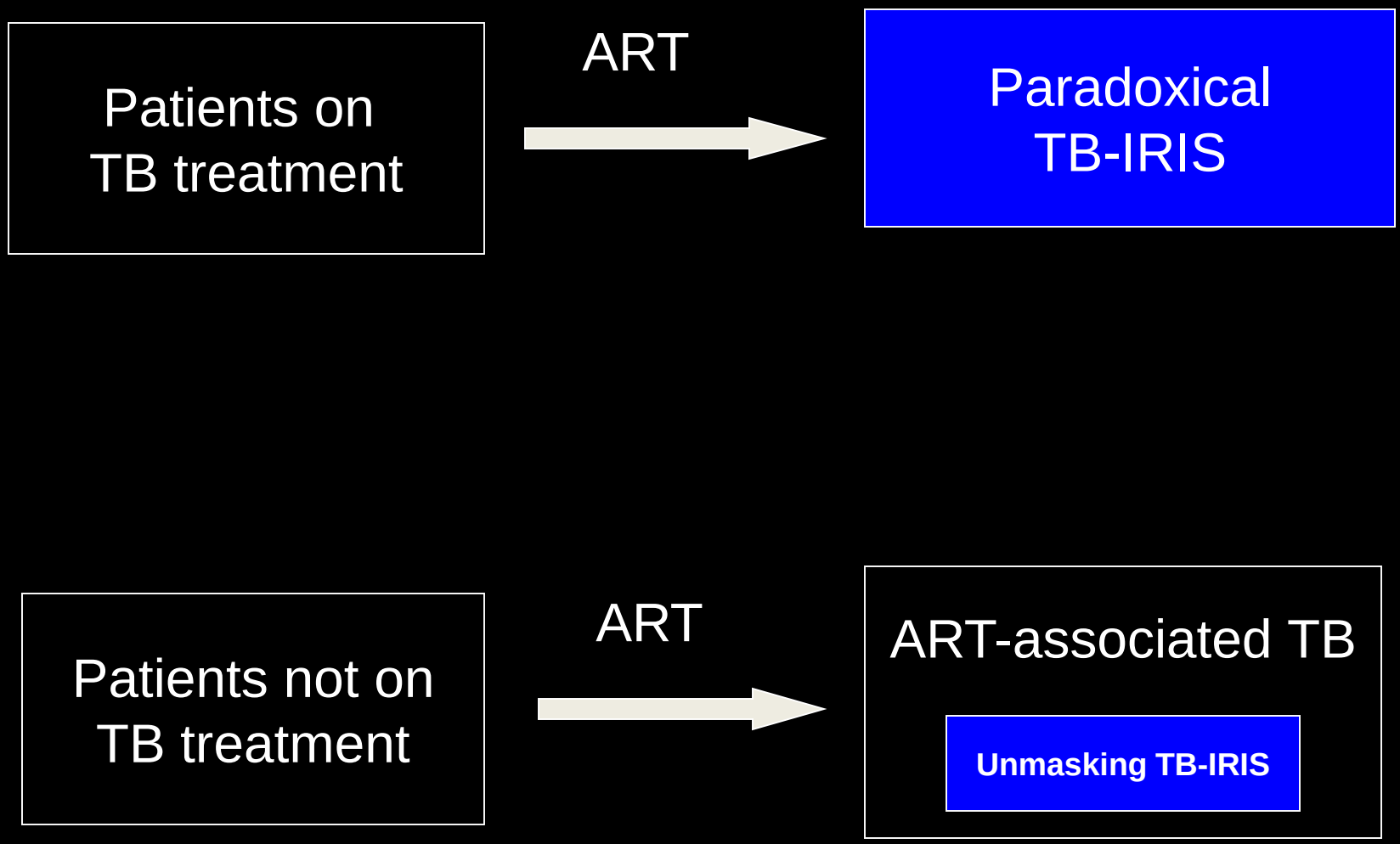
↓

Inflammatory reactions

↓

Targeted at TB antigens → Clinical deterioration with TB-IRIS

IRIS = Immune reconstitution inflammatory syndrome


Patients on TB treatment
ART
Paradoxical TB-IRIS
Patients not on TB treatment
ART
ART-associated TB
Unmasking TB-IRIS

Paradoxical TB-IRIS characteristics

- Incidence 8 – 54% (15.7% in meta-analysis)
- Onset of symptoms: Median 14 days from ART start
- Hospitalisation in up to 48%
- Median duration
  - 2-3 months in literature
  - 69 days (IQR = 38-106) in our cohort studies (n=217)
- Mortality infrequent
  - Meta-analysis 3.2% (CNS TB-IRIS = 25-75%)

Meintjes Lancet Infect Dis 2008;8:516, Muller Lancet Infect Dis 2010;10:251, Agarwal AIDS Res Ther 2012;9:17, Meintjes Clin Infect Dis 2009;48:667, Burman IJTLD 2007;11:1282, Bana unpublished

Key points in TB-IRIS diagnosis

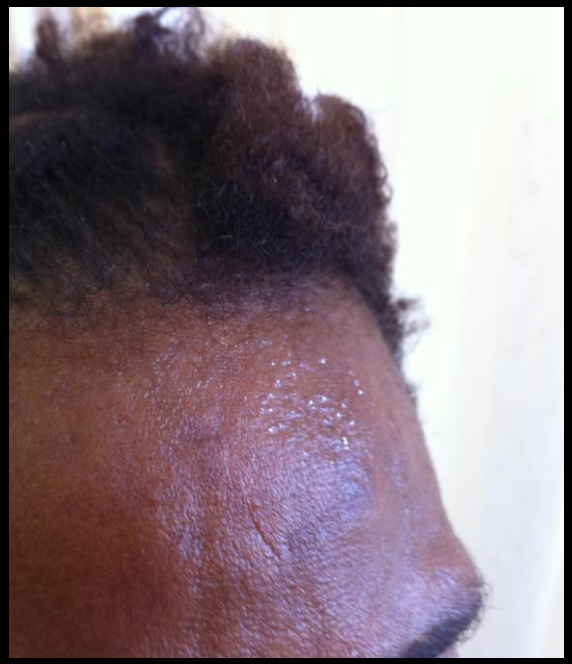
1. Diagnosis of TB confirmed or very likely?
2. Improvement on TB treatment prior to ART?
3. Symptom onset typically 1-4 weeks on ART
4. Deterioration with inflammatory features of TB
5. Consider and exclude differential diagnoses
6. Exclude drug-resistant TB

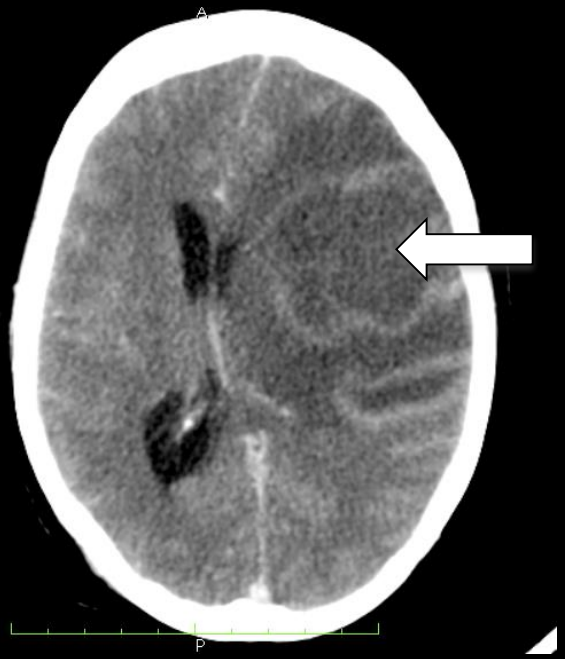
There is no confirmatory diagnostic test

Important differential diagnoses

Manifestation	Differential diagnoses
Lymph node enlargement	Kaposi's sarcoma Lymphoma
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

Severity: wide spectrum





Recurrent fevers and night sweats

Fatal enlargement of cerebral tuberculoma complicated by cerebral oedema

Major TB-IRIS syndromes

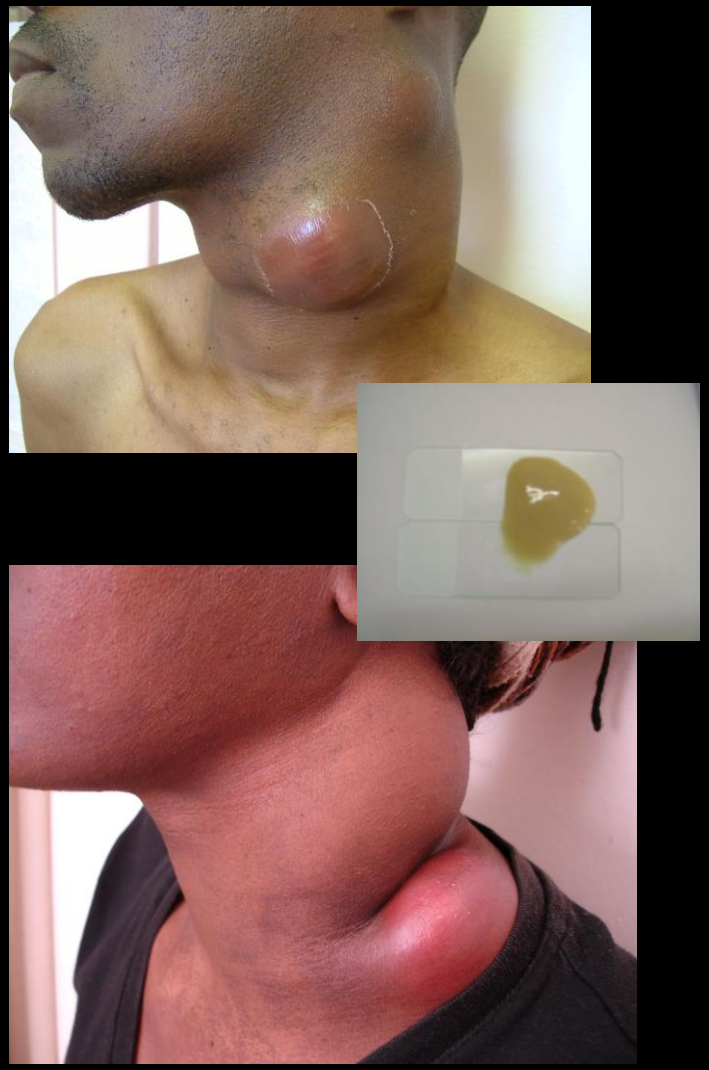
1. Lymphadenitis
2. Pulmonary
3. Neurological
4. Abdominal
5. Serositis (effusions)
6. Features of systemic inflammation

- High fevers, marked tachycardia, weight loss

83% multisystem manifestations in our cohort studies

Lymphadenitis

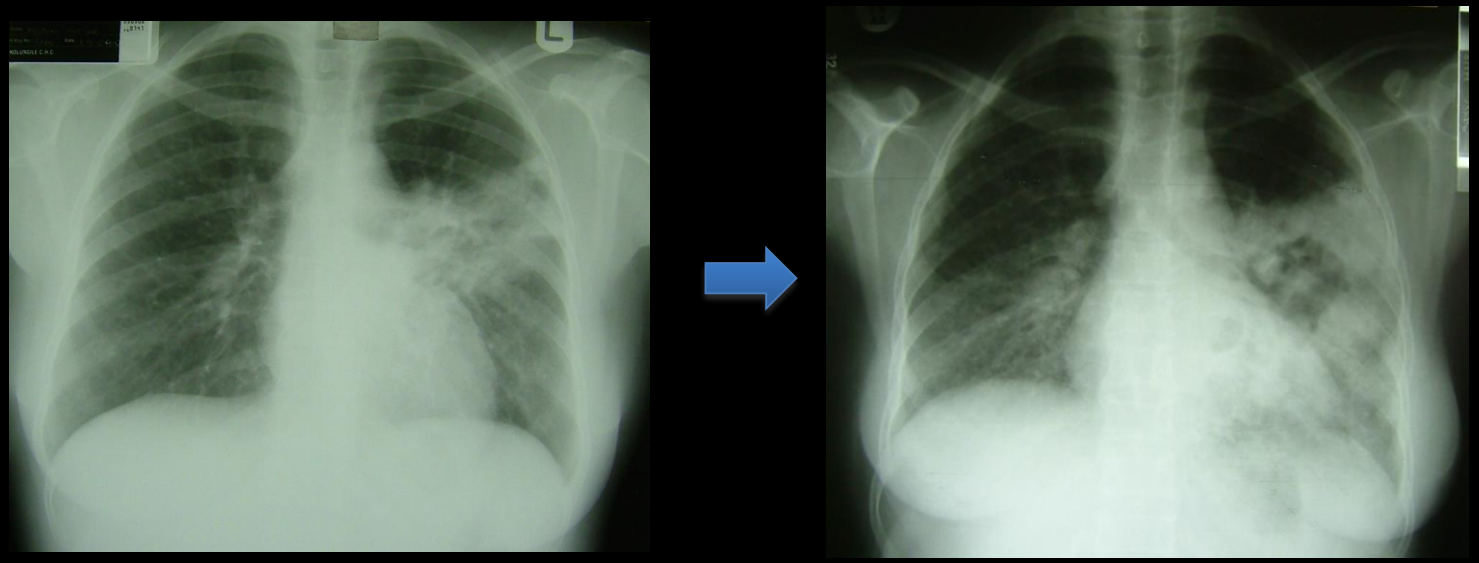
- 40% of TB-IRIS cases
- Prominent features of “acute inflammation”
- Typically suppurate within weeks
- Independent predictor of prolonged IRIS (>90 days)
  - aOR = 2.7 (95%CI = 1.3 -6.0)
- 6/217 patients in our cohort studies had IRIS > 365 days
  - typically suppurative lymphadenitis



Bana et al, unpublished

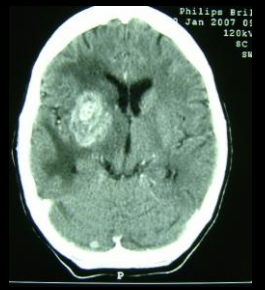
Pulmonary features

- 41% of TB-IRIS cases in our cohort studies



Recurrent cough, with worsening pulmonary infiltrate and cavitation

Neurological TB-IRIS

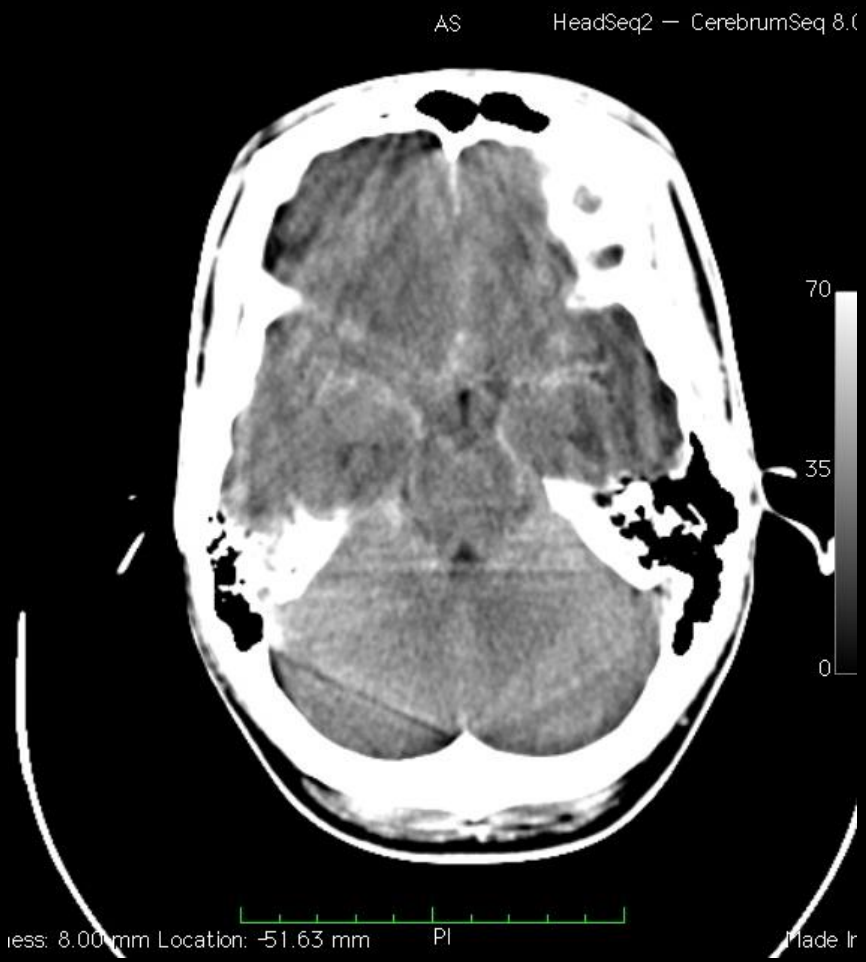


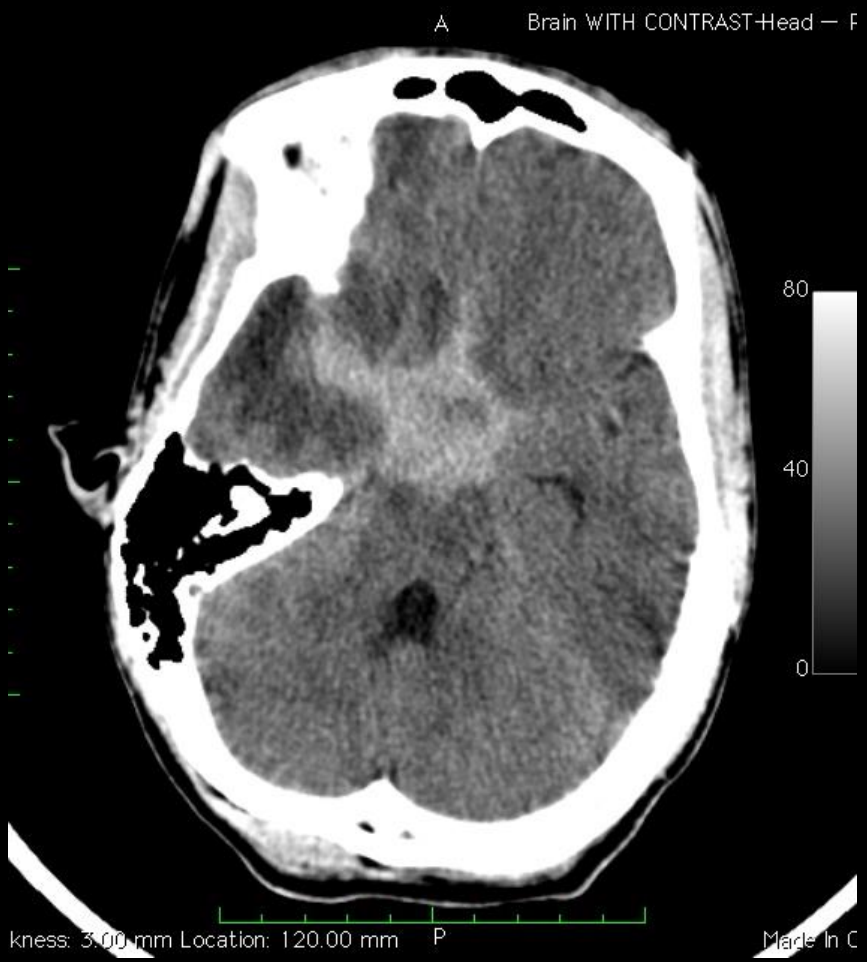
- 12% with paradoxical TB-IRIS have CNS involvement
- Up to 47% of TBM patients starting ART develop IRIS
- Features
  - Meningitis
  - Tuberculoma/s
  - Radiculomyelopathy
- Occurs in patients with or without CNS TB prior to ART
- Outcomes
  - 13% mortality and 18% loss to follow-up in one series
  - 25% and 75% mortality in other series
  - Neurological disability

Pepper et al, Clin Infect Dis 2009
Marais et al, Clin Infect Dis 2012
Agarwal et al, AIDS Res Ther 2012

TBM diagnosis

TBM-IRIS



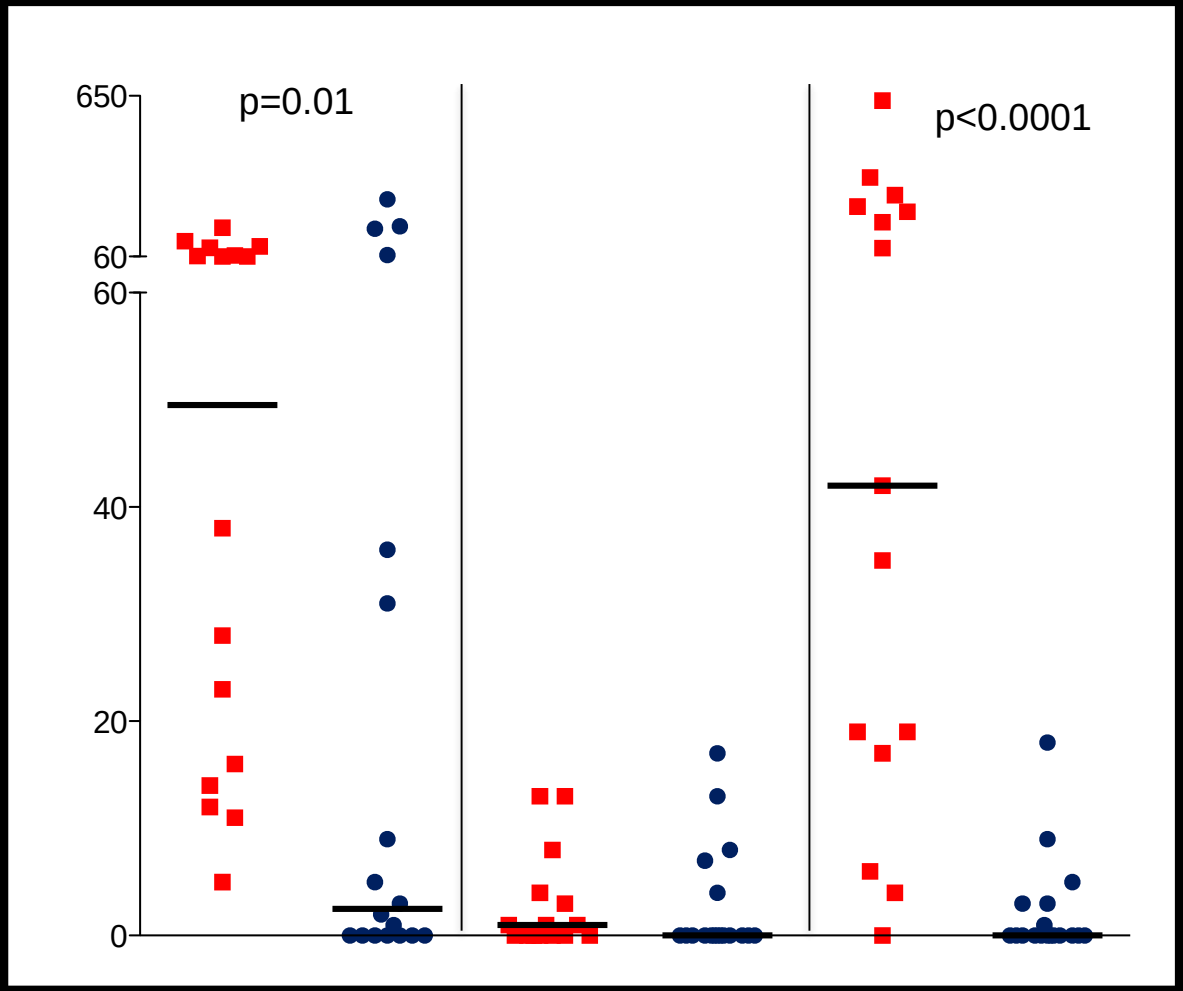


Slide courtesy Suzaan Marais

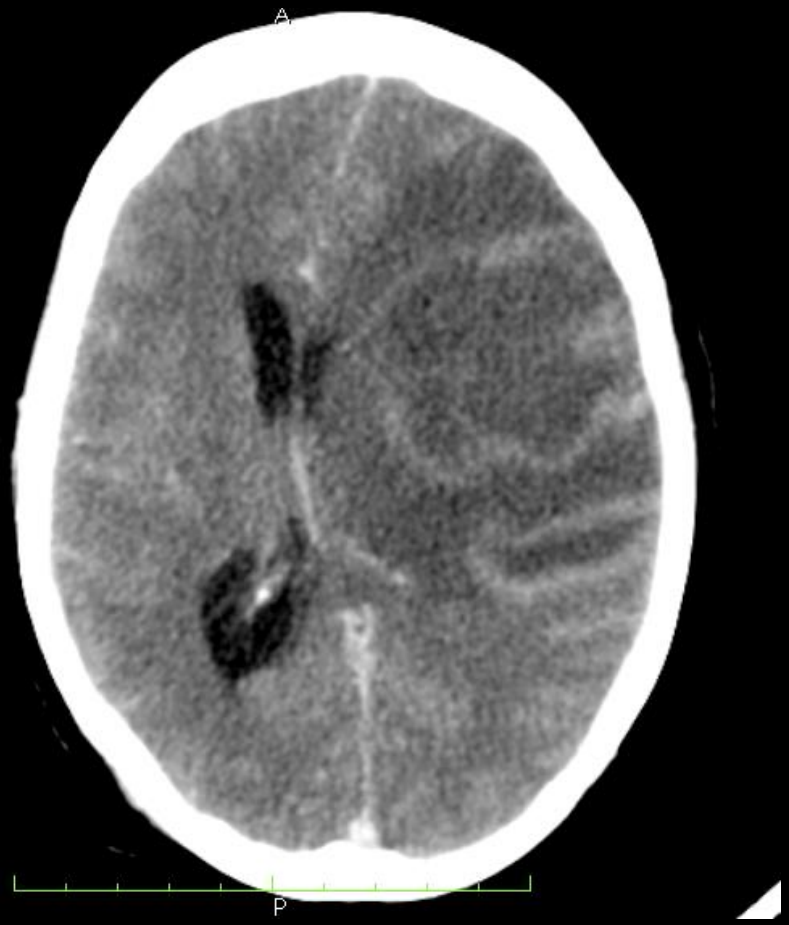
IRIS

Non IRIS

CSF Neutrophils and TBM-IRIS



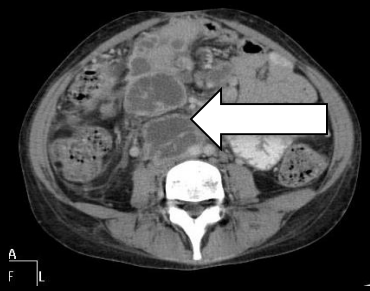
Marais
CID 2012

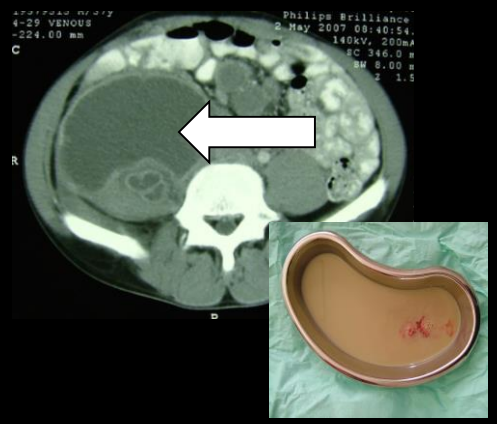


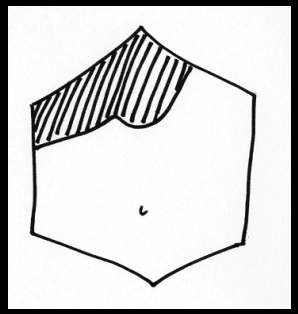
TBM and PTB prior to ART
TB-IRIS with enlarging mass lesion/cerebral oedema
Patient died

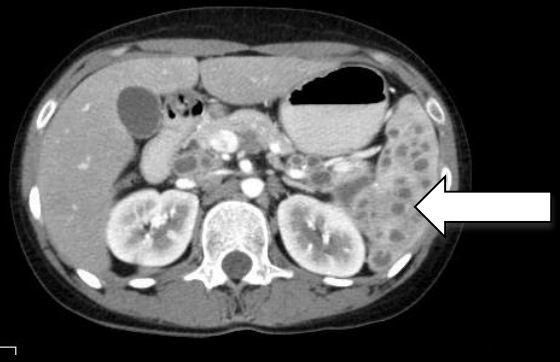
Abdominal features

- Lymph node enlargement
- Abscess formation
- Peritonitis and ascites
- Liver involvement
- Splenic involvement and rupture
- Intestinal involvement
- Renal involvement

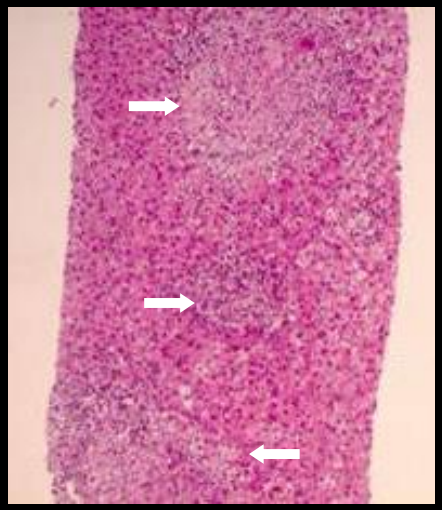


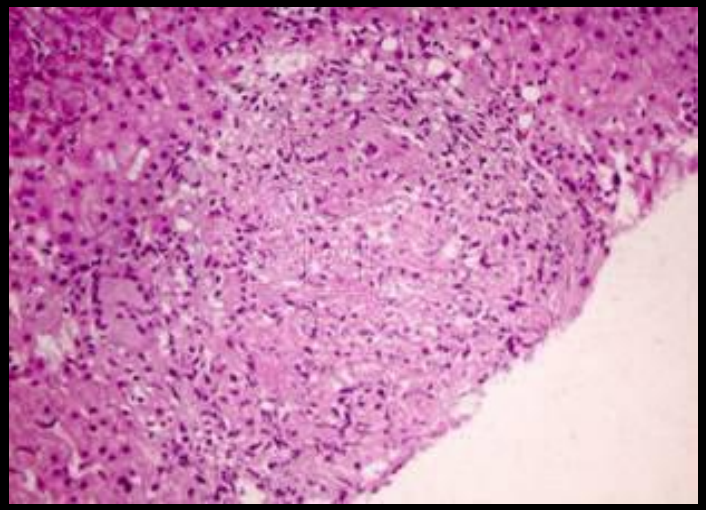


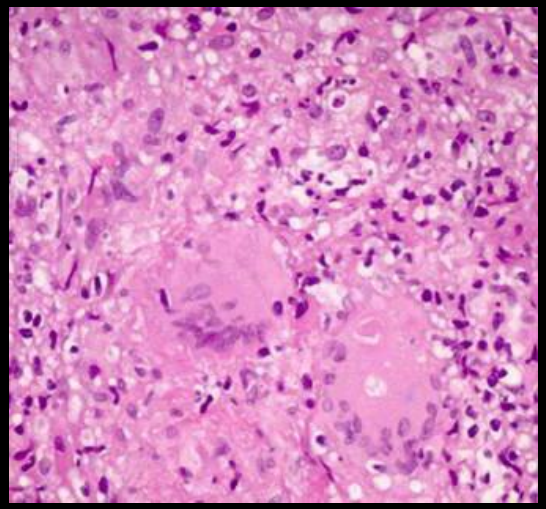




Hepatic TB-IRIS case







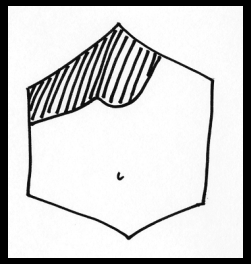
- 4 months treatment for drug-sensitive pericardial TB
- Clinically improved, then started ART
- 3 weeks later presented with fever and hepatomegaly
- LFT: Bil 52, CBil 31, Alk Phos 1081, GGT 1468, ALT 82, AST 88
- CD4 rise from 64 to 221
- Biopsy AFB- and TB culture -

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



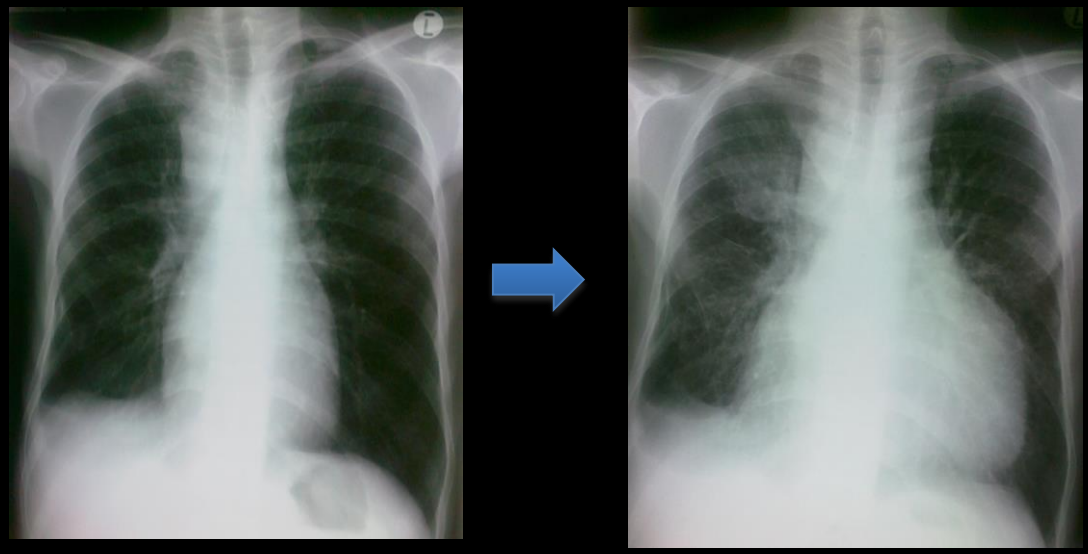
Drug-induced liver injury

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

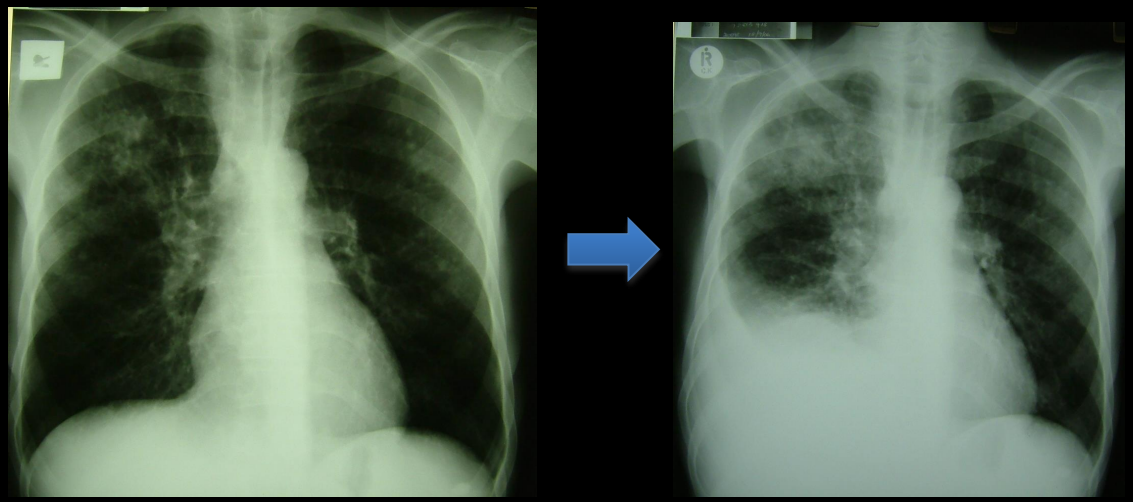
Patients may present with clinical picture between these two
- Biopsy or treat as DILI

Two conditions may co-exist

Pericardial effusion
with tamponade
(1 litre drained)



New right pleural effusion

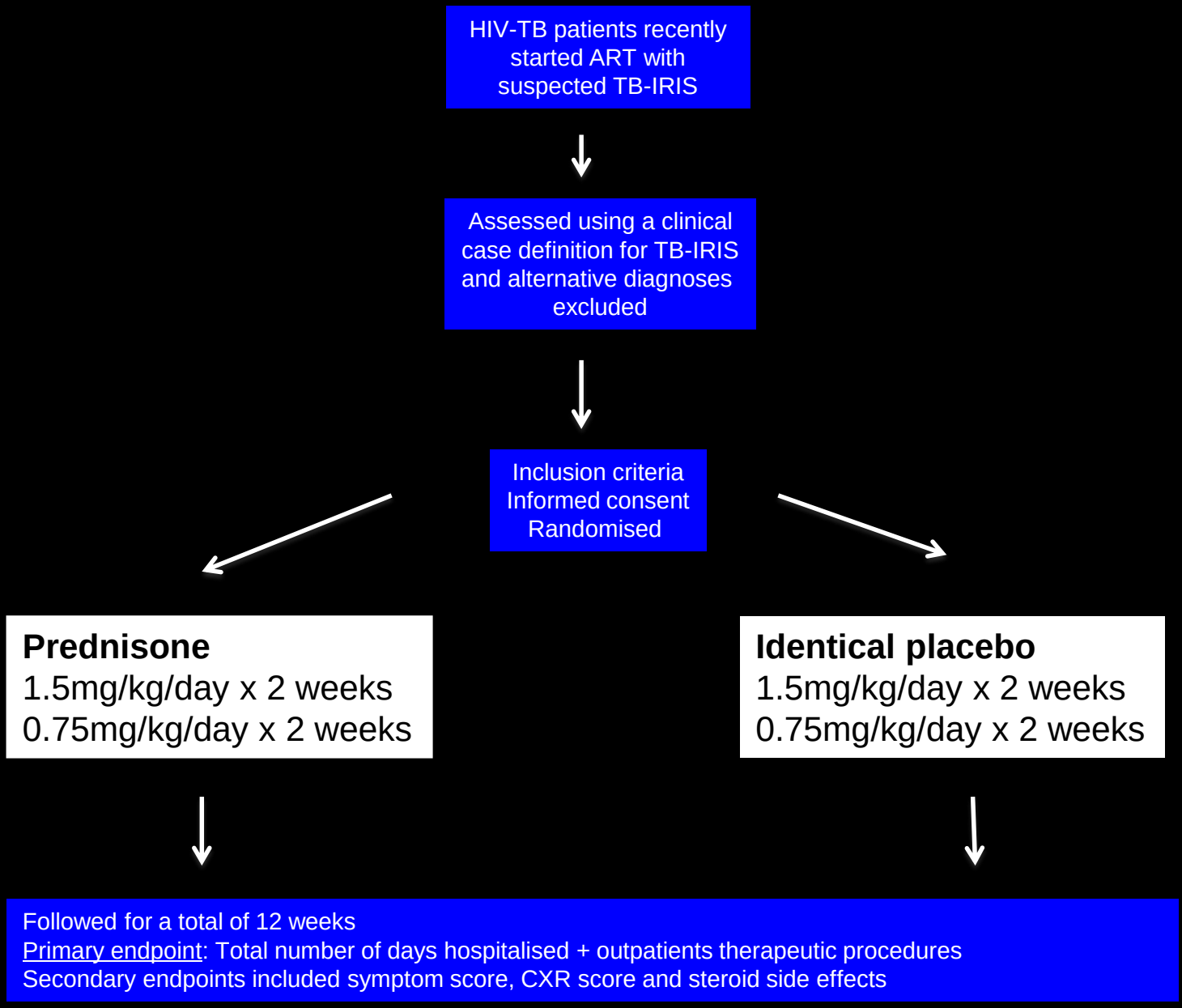


Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome

Graeme Meintjes[a,b,c], Robert J. Wilkinson[a,b,c,d,e], Chelsea Morroni[a,f], Dominique J. Pepper[a,b,c], Kevin Rebe[b,c], Molebogeng X. Rangaka[a], Tolu Oni[a,d] and Gary Maartens[a,g]

- Rationale for steroid trial
  - Anecdotal reports of symptomatic response
  - Potential risks in patients with advanced HIV
- 110 participants (55 each arm)
- Life-threatening TB-IRIS was an exclusion
- Open-label prednisone at physician discretion if clinical deterioration/relapse

Meintjes et al, AIDS 2010;24:2381


HIV-TB patients recently started ART with suspected TB-IRIS
Assessed using a clinical case definition for TB-IRIS and alternative diagnoses excluded
Inclusion criteria
Informed consent
Randomised
Prednisone
1.5mg/kg/day x 2 weeks
0.75mg/kg/day x 2 weeks
Identical placebo
1.5mg/kg/day x 2 weeks
0.75mg/kg/day x 2 weeks
Followed for a total of 12 weeks
Primary endpoint: Total number of days hospitalised + outpatients therapeutic procedures
Secondary endpoints included symptom score, CXR score and steroid side effects

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**

Significant reduction in morbidity associated with prednisone treatment

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

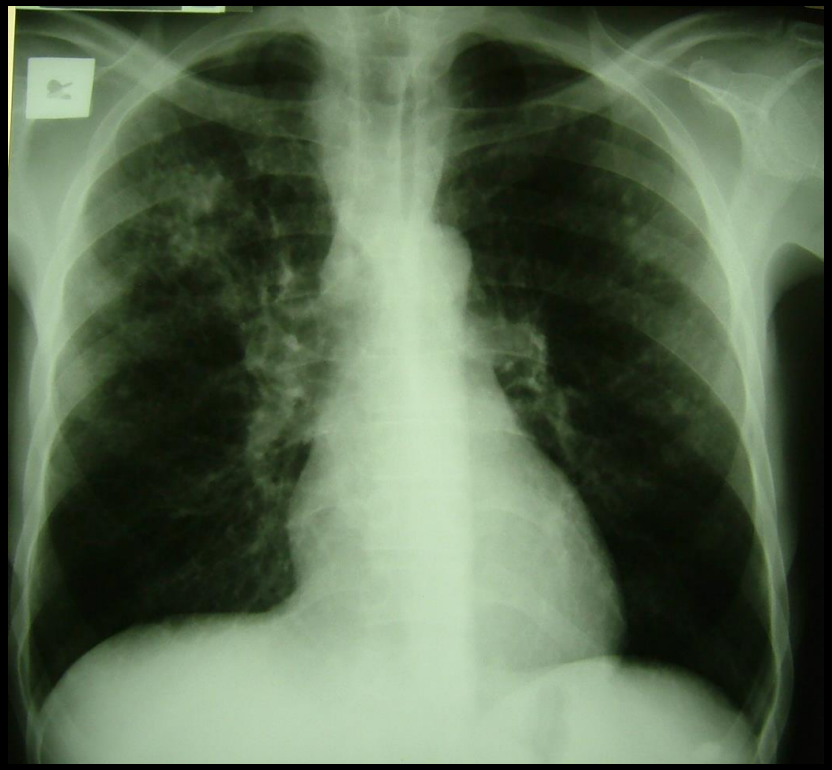
Prednisone treatment for TB-IRIS

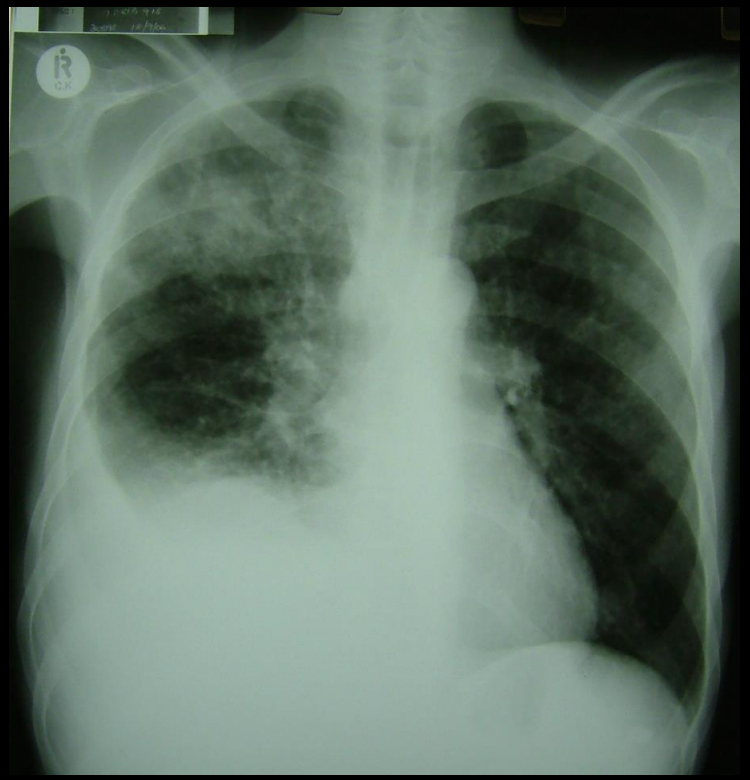
- No excess of severe infections or metabolic side effects with 4 week course of prednisone

- Based on these findings
  - If clinical diagnosis of TB-IRIS is made and other reasons for deterioration excluded
  - And symptoms are significant
  - Prednisone starting at 1.5mg/kg/d is indicated

Steroids for TB-IRIS: other points

- Effective for symptom control
- In most cases unlikely to have survival benefit
  - Apart from neurological TB-IRIS
- Reasonable to defer steroids until sure of diagnosis
  - Exclude or treat for other possibilities
- Average duration of TB-IRIS is 2-3 months, but many cases shorter





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.

Other management

- NSAID in milder cases
- Needle aspiration
  - Suppurative lymphadenitis/abscesses
  - Effusions
- ART interruption
  - CNS involvement with depressed level of consciousness

Acknowledgements

- Robert Wilkinson
- Gary Maartens
- Katalin Wilkinson
- Suzaan Marais
- Charlotte Schutz
- Tasnim Bana
- Maia Lesosky
- Molebogeng Rangaka
- Chelsea Morroni
- Tolu Oni
- Dominique Pepper
- Kevin Rebe
- Rene Goliath
- Helen van der Plas
- Marc Mendelson
- Priscilla Mouton
- Bob Colebunders
- Keira Skolimowska
- Kerryn Matthews
- Rebecca Tadokera
- Mark Sonderup

wellcome trust

NRF National Research Foundation

MRC SOUTH AFRICA

science & technology
Department: Science and Technology
REPUBLIC OF SOUTH AFRICA

EDCTP
European & Developing Countries Clinical Trials Partnership