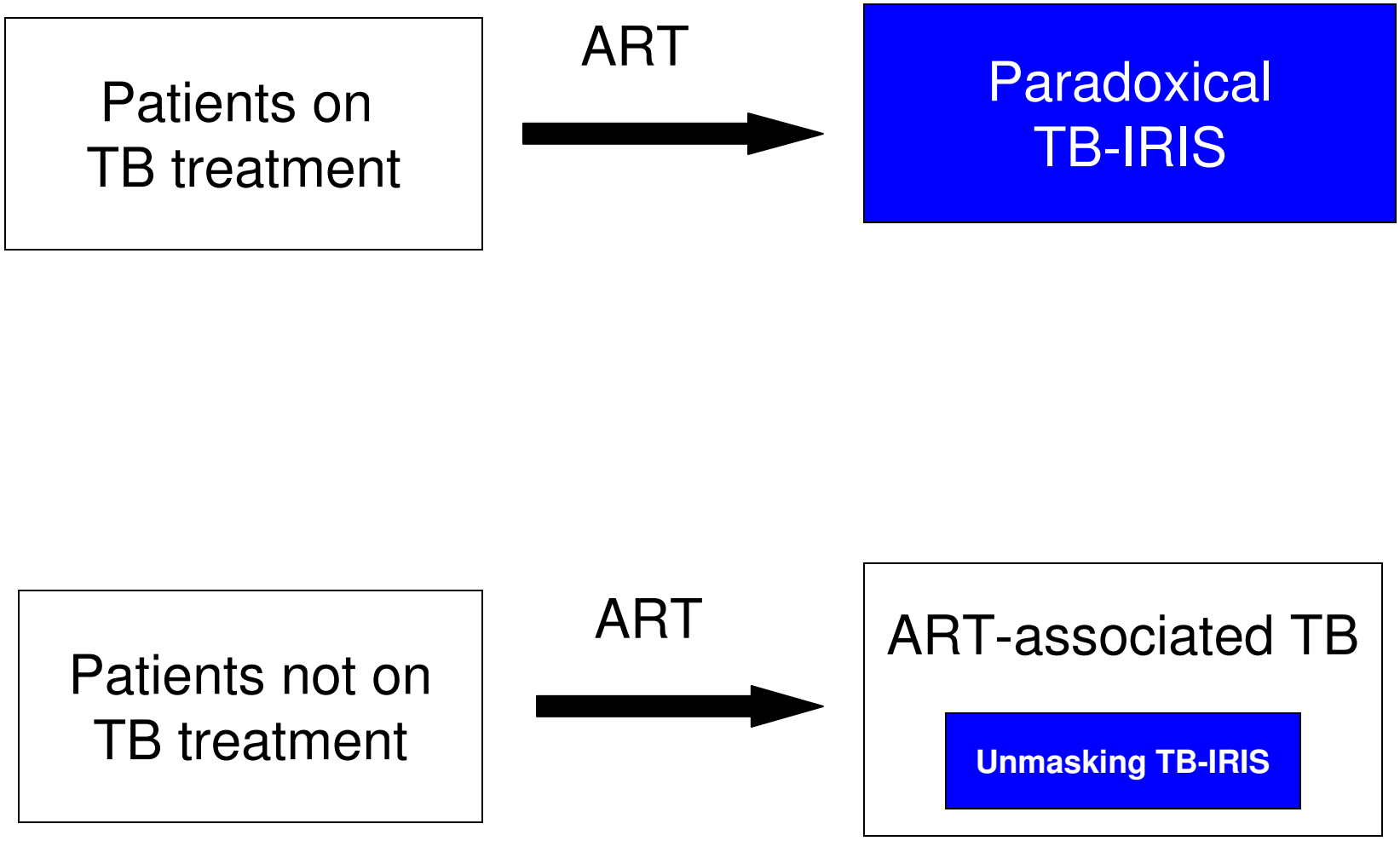
Latest developments in diagnosis and management of TB-IRIS

What are the gaps?

Graeme Meintjes
University of Cape Town
GF Jooste Hospital


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

Paradoxical TB-IRIS

Patient diagnosed with TB and started on TB treatment

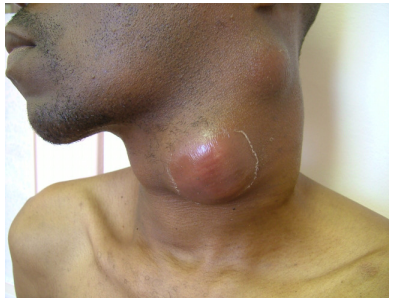
Improving on TB treatment then start ART

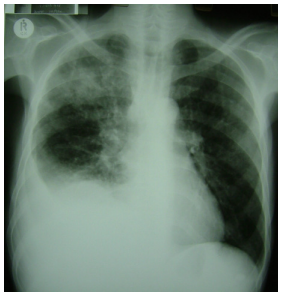
Recurrence of TB symptoms and new or recurrent clinical manifestations of TB

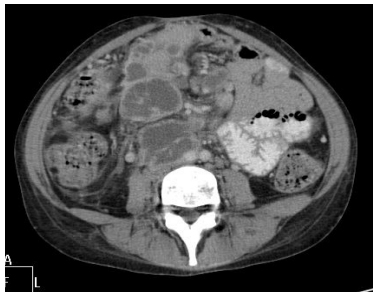
(Usually 1-4 weeks after starting ART)

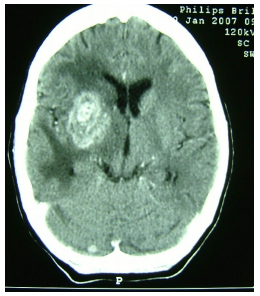
Up to 25% of patients starting ART in sub-Saharan Africa are on TB treatment

<u>Major risk factors:</u>
Low CD4 count
Disseminated TB
Short interval between TB treatment and ART









	Incidence	Duration	Mortality
Narita (US, 1998)	36 %	-	-
Breen (UK, 2004)	29 %	-	-
Breton (France, 2004)	43 %	-	-
Kumarasamy (India, 2004)	8 %	-	0 (0%)
Michailidis (UK, 2005)	32 %	Median 2.5 months	-
Manosuthi (Thailand, 2006)	13 %	-	2 (10%)
Lawn (South Africa, 2007)	12 %	-	2 (11%)
Burman (US, 2007)	17 %	Median 60 days	1 (5%)
Tansuphasawadikul (Thailand, 2007)	15 %	-	0 (0%)
Serra (Brazil, 2007)	12 %	Mean 91 days	0 (0%)
Baalwa (Uganda, 2008)	29 %	-	-

Clinical and programmatic impact

- Life threatening manifestations described
  - TBM and tuberculomas (12% mortality)
  - Cardiac tamponade
  - Respiratory failure
  - Splenic rupture
  - Acute renal failure
- Hospitalisation (21-48%)
- Diagnostic and therapeutic procedures
- Impacts on decision regarding when to start ART
  - This may indirectly impact on mortality

Pepper et al, Clin Infect Dis 2009
Lawn et al, AIDS 2007
Burman et al, IJTLD 2007

Diagnosis

- No diagnostic test
- Diagnosis relies on
  - Clinical deterioration with features of TB
  - Temporal relationship to ART initiation
  - Exclusion of alternative diagnoses
  - (Demonstration of response to ART)
- Difficult in resource-limited settings

International Network for the Study of HIV-associated IRIS (INSHI) Consensus Clinical Case Definition

***Panel 2:* Case definition for paradoxical tuberculosis-associated IRIS**

There are three components to this case definition:

(A) Antecedent requirements

Both of the two following requirements must be met:

- Diagnosis of tuberculosis: the tuberculosis diagnosis was made before starting ART and this should fulfil WHO criteria for diagnosis of smear-positive pulmonary tuberculosis, smear-negative pulmonary tuberculosis, or extrapulmonary tuberculosis[44]
- Initial response to tuberculosis treatment: the patient's condition should have stabilised or improved on appropriate tuberculosis treatment before ART initiation—eg, cessation of night sweats, fevers, cough, weight loss. (Note: this does not apply to patients starting ART within 2 weeks of starting tuberculosis treatment since insufficient time may have elapsed for a clinical response to be reported)

(B) Clinical criteria

The onset of tuberculosis-associated IRIS manifestations should be within 3 months of ART initiation, reinitiation, or regimen change because of treatment failure.

Of the following, at least one major criterion or two minor clinical criteria are required:

Major criteria

- New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement—eg, tuberculous arthritis
- New or worsening radiological features of tuberculosis (found by chest radiography, abdominal ultrasonography, CT, or MRI)
- New or worsening CNS tuberculosis (meningitis or focal neurological deficit—eg, caused by tuberculoma)
- New or worsening serositis (pleural effusion, ascites, or pericardial effusion)

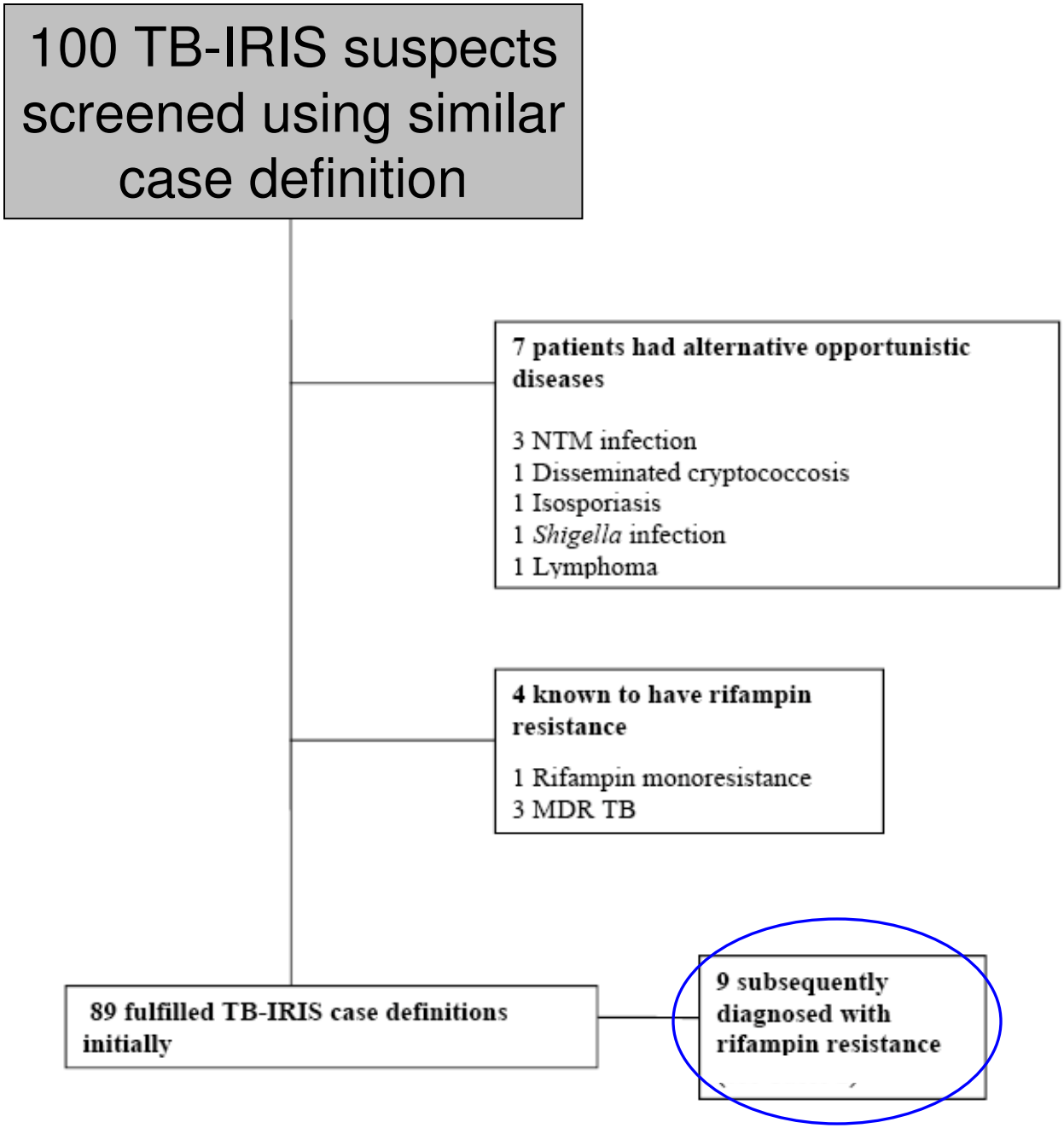
Minor criteria

- New or worsening constitutional symptoms such as fever, night sweats, or weight loss
- New or worsening respiratory symptoms such as cough, dyspnoea, or stridor
- New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

(C) Alternative explanations for clinical deterioration must be excluded if possible*

- Failure of tuberculosis treatment because of tuberculosis drug resistance
- Poor adherence to tuberculosis treatment
- Another opportunistic infection or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis where the initial tuberculosis diagnosis has not been microbiologically confirmed)
- Drug toxicity or reaction

Meintjes et al, Lancet Infect Dis 2008



Meintjes et al
Clin Infect Dis 2009

Management

- Corticosteroids most frequently used with reported benefit, but potential risks
  - Kaposi's sarcoma
  - Herpes virus reactivations
  - Candidiasis
  - Strongyloides hyperinfection
  - If undiagnosed MDR-TB, may worsen condition
- Other treatments
  - NSAIDs and other immunomodulatory agents
  - Aspiration and surgical procedures

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 et al, Abstract 34, CROI 2009

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**

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

Secondary endpoints

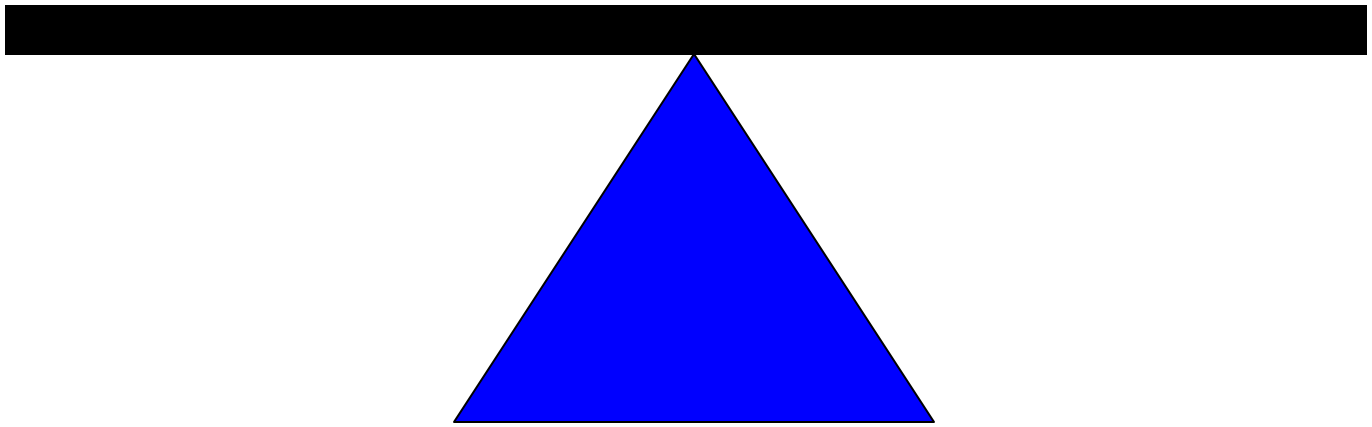
- Consistent benefit, maximal in first 4 weeks, across a range of secondary outcome measures
  - Symptom score
  - Karnofsky performance score
  - MOS-HIV questionnaire (quality of life assessment)
  - Chest radiology score
  - C-reactive protein

- 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

Corticosteroids for paradoxical TB-IRIS?

Symptom improvement
Reduced hospitalisation
? Survival benefit in life threatening cases

Potential adverse effects
Diagnostic uncertainty



Research “gaps”

- Assess performance of the consensus case definition
- Establish what the major differential diagnoses in different settings are and assess algorithms for exclusion of these
- Assess performance of rapid drug resistance assays in patients deteriorating rapidly with TB after starting ART
- Diagnostic immunological markers

Research “gaps”

- Larger multi-centre clinical trial
  - NSAIDs vs corticosteroids?

- Optimal management of life threatening TB-IRIS
  - ART interruption?
  - TNFα blockers or other immunomodulatory agents?

Difficulties with clinical trials

- Being certain of diagnosis, especially when diagnostic resources are limited

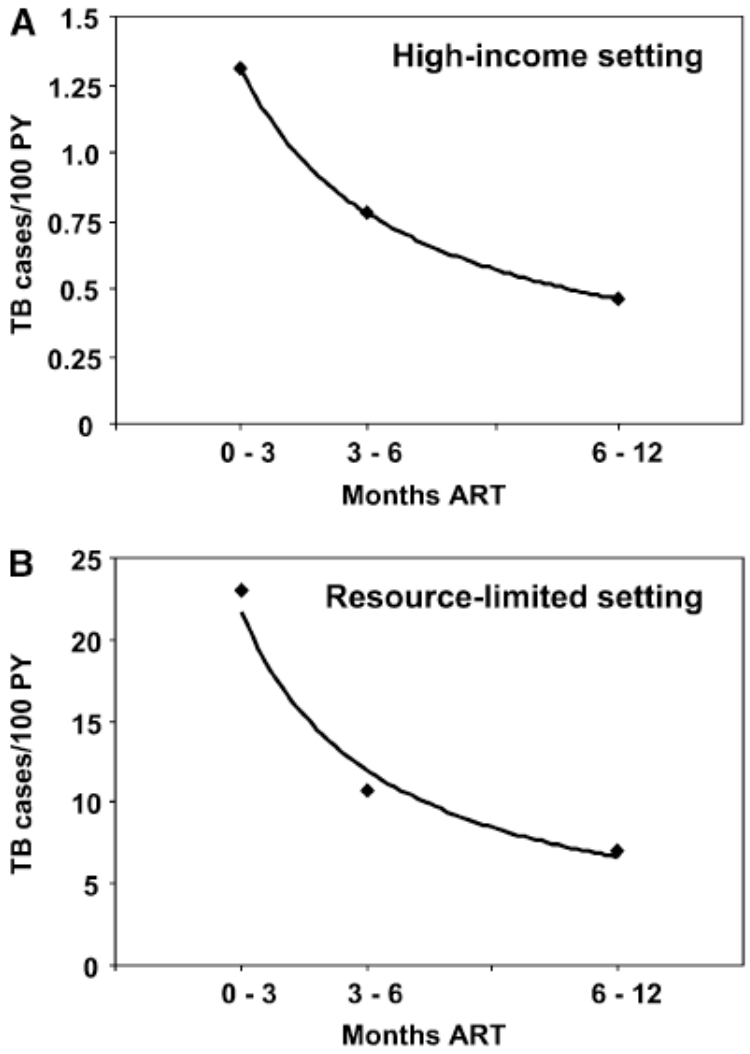
- Defining clinically meaningful and hard endpoints that hold across the spectrum of clinical manifestations

Unmasking TB-IRIS

TB incidence rates of
6 - 23 cases/100 person years documented in resource-limited countries in first 3 months of ART

8-26% mortality in first year of ART in sub-Saharan African programmes (up to 21% deaths ascribed to TB)

Moh et al, AIDS 2007
Brinkhof et al, Clin Infect Dis 2007
Lawn et al, AIDS 2006
Lawn et al, AIDS 2008

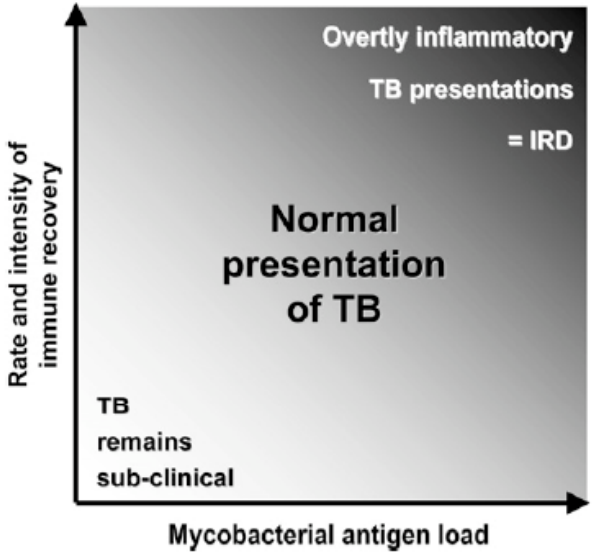


Lawn et al, AJRCCM 2008

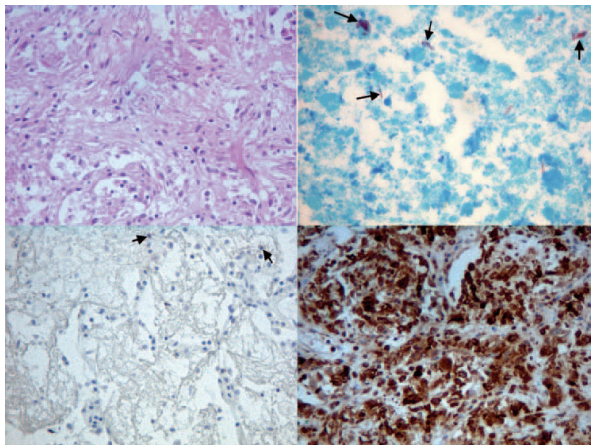
Many case reports of unmasking TB-IRIS

- Severe pulmonary TB
- Neurological presentations
- Tuberculous abscesses
- Systemic inflammatory response syndrome

John et al, AIDS 2005
Goldsack et al, Sex Transm Infect 2003
Lawn et al, AIDS 2009
Crump et al, Clin Infect Dis 1998
Meintjes et al, Lancet Infect Dis 2008
Chen et al, Am J Emerg Med 2009



Lawn et al, AJRCCM 2008



Lawn et al, AIDS 2009

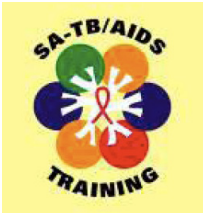
Research “gaps”

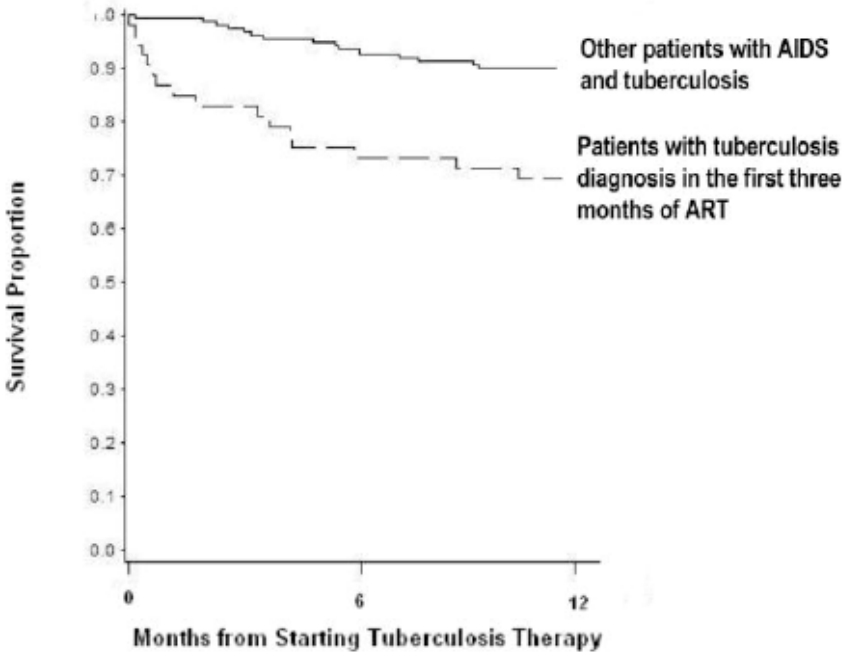
- Is a case definition possible?
- What proportion of TB in first 3 months of ART is unmasking TB-IRIS?
- Contribution to early ART mortality?
- Prospective clinical and immunological studies and postmortem studies
- Is any treatment additional to standard TB treatment required?

Acknowledgements

- Gary Maartens
- Robert Wilkinson
- Katalin Wilkinson
- Dominique Pepper
- Kevin Rebe
- Suzaan Marais
- Chelsea Morroni
- Molebogeng Rangaka
- Tolu Oni

- Bob Colebunders
- Stephen Lawn
- Other colleagues in the International Network for the Study of HIV-associated IRIS (INSHI)





Haiti

Koenig, Clin Infect Dis 2009

Uganda

TB associated with 35% of mortality on ART, but TB diagnosed in first 3 months was not associated with excess risk of mortality compared to later diagnoses

Moore, AIDS 2007