
Clinical challenges of diagnosing and treating TB in people Living with HIV: what next for research

Rapporteur- Dr Prudence Ive

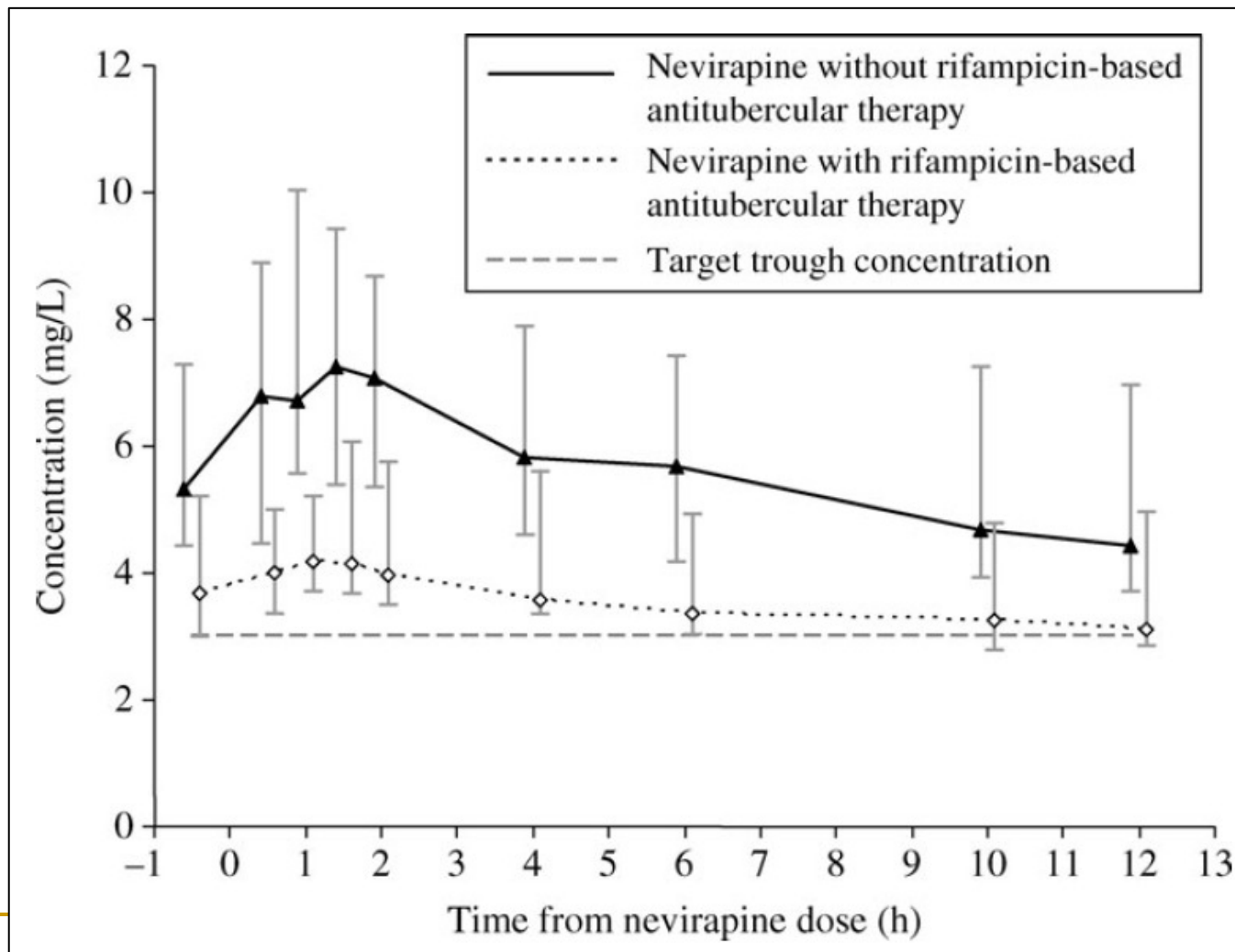
Strategies for co-treatment: first and second line ART and TB treatment

Gary Maartens- Speaker 1

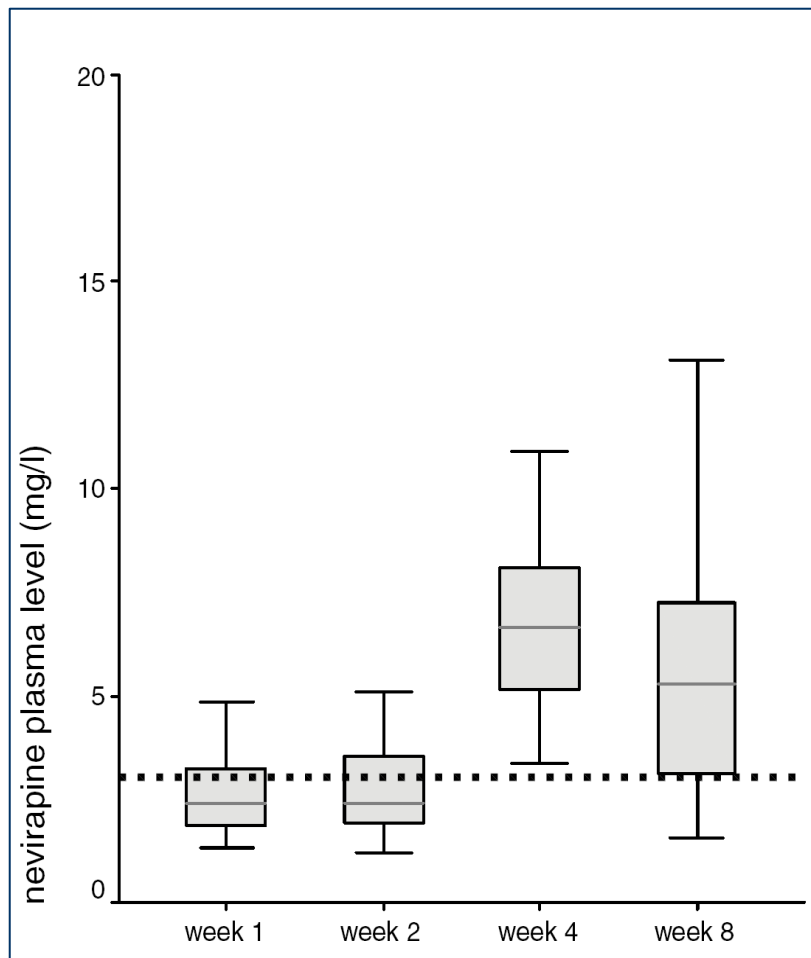
Rifampicin induction

Enzyme/transporter	ARV substrate
CYP3A4 CYP2B6	PIs, NVP EFV
P glycoprotein	PIs

Impact of rifampicin on nevirapine PK



Low NVP concentrations in Malawians on TB treatment during NVP lead-in dose phase



Thai study

High-dose (NVP 200 mg 12 hourly lead-in then 300 mg 12 hourly) vs standard doses with rifampicin.

Hypersensitivity reactions:

4/16 high vs 1/16 standard-dose

P=0.33

Rifampicin effect on EFV PK

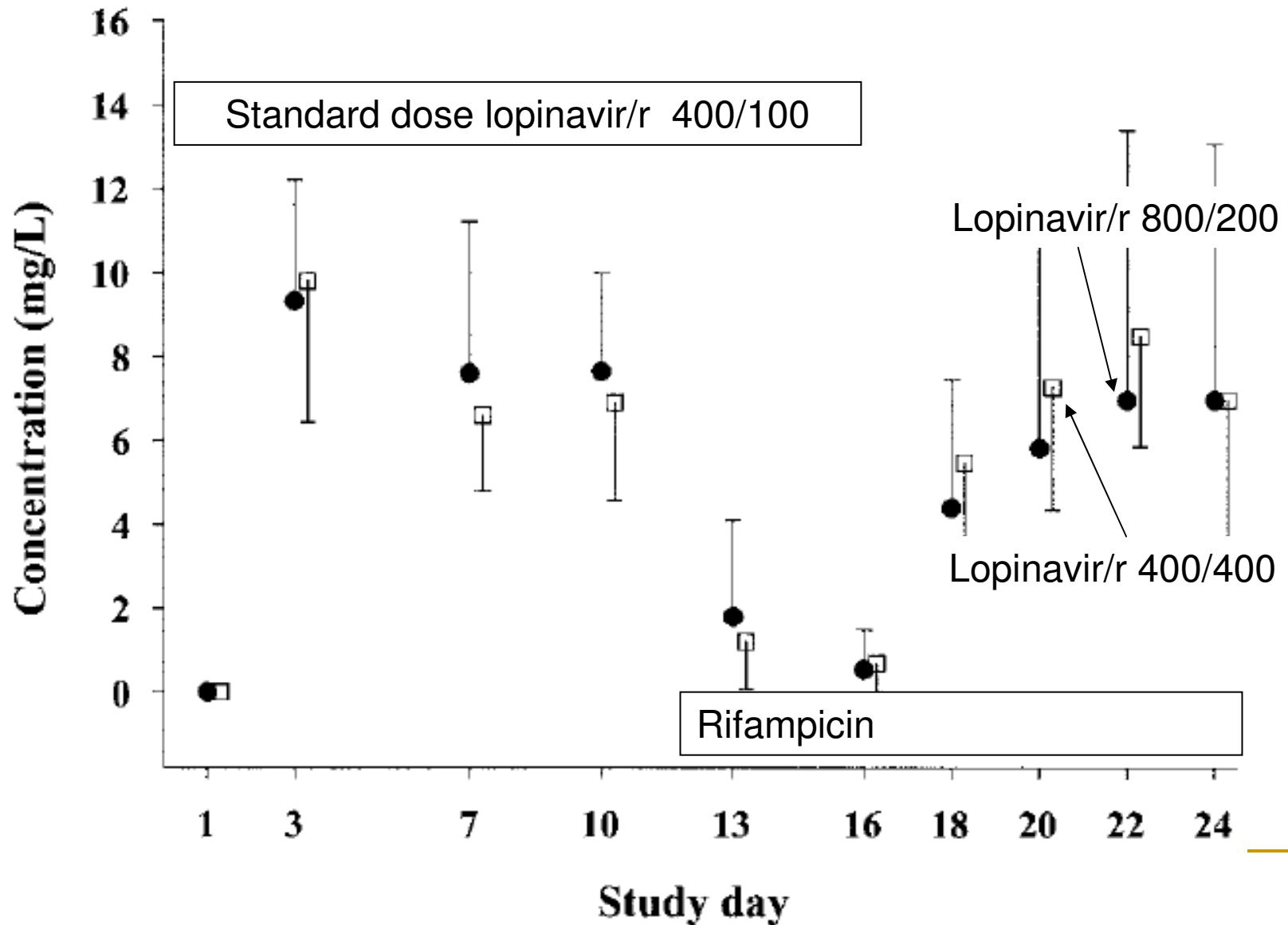
- PK studies in patients with TB show no significant effect:
 - Spain
 - South African adults (2 studies) & children
 - India
- Package insert says AUC reduced 26% (n=12, no P value given)
- Retrospective TDM database found significant reduction in EFV concentrations

Clin Pharmacokinet 2002;41:681
JAC 2006;58:1299
Cohen K Antivir Ther in press
JAIDS 2009;50:439
AAC 2009;53:863
Antivir Ther 2008;13:675

Research priorities: 1st line regimen

- Adequately powered RCT EFV vs NVP
- Effectiveness & PK studies in children
- Safety of omitting NVP lead-in dose, as when switching from EFV to NVP

“Super boosted” lopinavir/r & rifampicin



Double dose lopinavir/r in kids

- Median trough LPV concentrations:
 - TB 0.63 (IQR 0.11-1.62)
 - Controls 4.25 (IQR 3.42-8.1)
 - 60% of children with TB were sub-therapeutic
- Study stopped early by DSMB

Concerns with rifamycins and PI's

- Hepatitis with adjusted dose PIs & rifampicin in healthy volunteers, more commonly if rifampicin started first
 - Can we extrapolate data from healthy volunteers to HIV+
 - CDC 2008 recommends SQV:RTV 400:400 BD or double dose LPV/r or LPV/r + RTV: “Use with caution”
 - Rifabutin:
 - not enough efficacy data for Rifabutin in TB,
 - Rifabutin needs to be dose adjusted 150mg three times wkly
 - It is not part of FDC's for TB treatment.
 - Procurement and distribution
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Research Priorities: 2nd line regimen

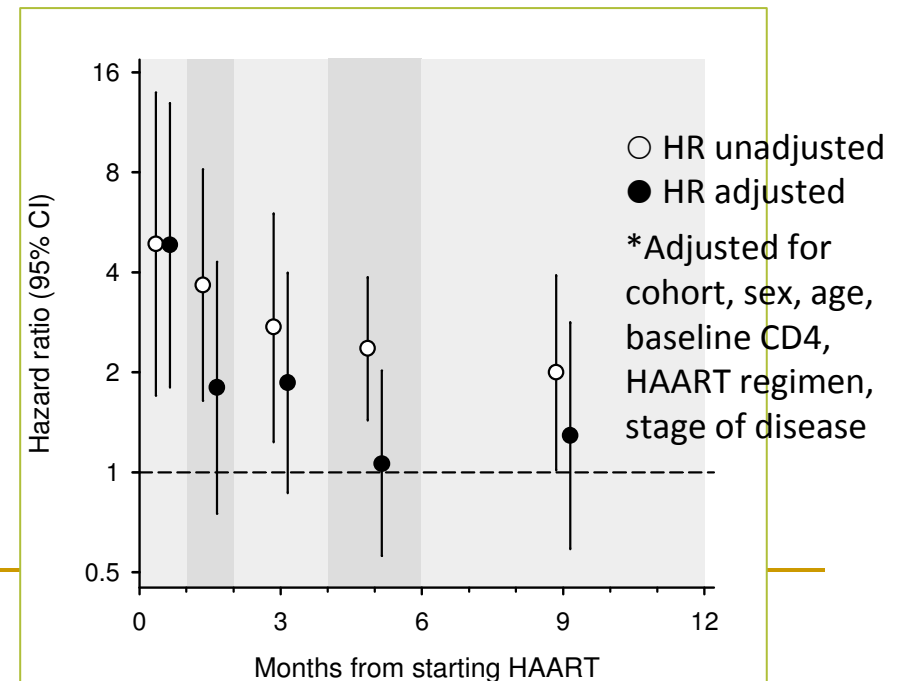
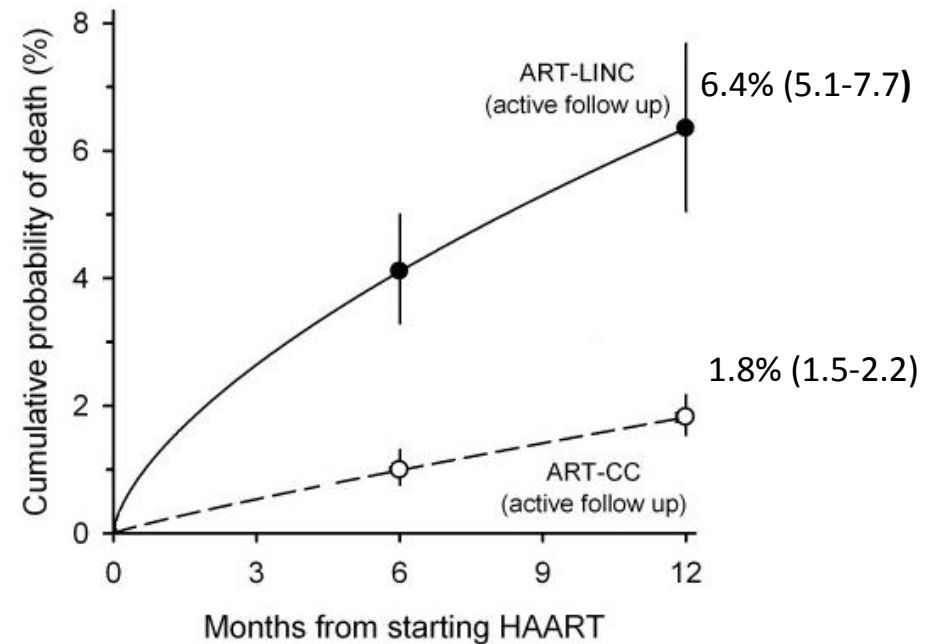
- Urgent need for data as more will inevitably move to 2nd line
 - Hepatotoxicity & PK of “super-boosted” PIs needs to be defined in adults with HIV-TB coinfection
 - Effectiveness studies in adults & children
 - Rifabutin not currently an option – need for more evidence of efficacy vs rifampicin in HIV-TB coinfection
 - Alternative regimens (triple NRTI, double dose raltegravir)
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Role of TB in early mortality of people living with HIV

Mina Hosseinipour-Speaker 2

Early Mortality

- Increased mortality on ART in resource poor settings
- Increased early mortality and specially in lower CD4 strata
- Risk factors: Low BMI, low CD4, WHO 3 and 4, low Hb.
- TB is the leading cause of death



Causes of Mortality

- 6 Cohort Studies (5 SSA, 1 Haiti)
 - TB was among the leading cause of death in 5/6 cohorts
 - TB likely under-reported due to difficulty in making diagnosis and LTFU rates

Causes of Mortality

- Tuberculosis (16-51%)
- Invasive Bacterial Infections (8-49%)
- Wasting (13-43%)
- Cryptococcal Meningitis
- Kaposi's Sarcoma

“Unknown” is the most common cause

Leading Question TB and Early Mortality

- Do community deaths have a similar pattern to inpatients death?
 - Can ART be optimized to reduce early mortality?
(simplified regimens, reduced toxicity, drug interactions)
 - Should we have aggressive screening for TB or empiric treatment for high risk patients?
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Sub-clinical TB among people
living with HIV: what does the
evidence say?

Haileyesus Getahun- Speaker 3

Is there a standard case definition for subclinical TB among PLHIV?

- Systematic literature review
 - Variety of case definitions
 - **Asymptomatic** – reliance on symptom screening will lead to missed TB cases
 - Sputum negative
 - Proven on culture
 - Including extrapulmonary in many articles
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Conclusion from literature review

- None of the studies specifically addressed subclinical TB as a primary objective.
 - The case definition of subclinical TB not standardised and varies from study to study.
 - Patient diagnosed with subclinical TB are not necessarily free of clinical signs and symptoms
 - Evidence is scarce to draw any meaningful conclusion on implications of sub-clinical TB
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Key Messages

- Needs to be defined to ensure that we recognize TB as a continuum of disease from infection through latency to active disease.
 - Asymptomatic TB in HIV contributes widely to the transmission and disease burden
 - Clinical symptoms alone will miss patients with TB
 - Undiagnosed TB has consequences for IPT and TB screening programs
 - Improved diagnostic tests required including non-sputum diagnostic approaches.
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Latest developments in diagnosis and management of TB IRIS: what are the gaps?

Graeme Meintjes- Speaker 4

Patients on
TB treatment

ART



Paradoxical
TB-IRIS

Patients not on
TB treatment

ART



ART-associated TB

Unmasking 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)

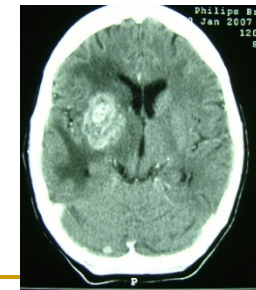
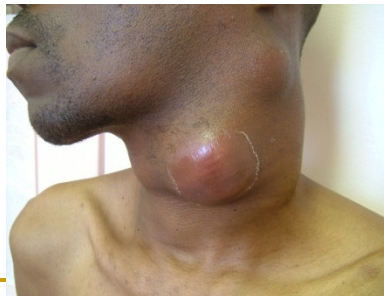
Up to 25% of patients starting ART in sub-Saharan Africa are on TB treatment

Major risk factors:

Low CD4 count

Disseminated TB

Short interval between TB treatment and ART



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 tuberculosis⁴⁴
- 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

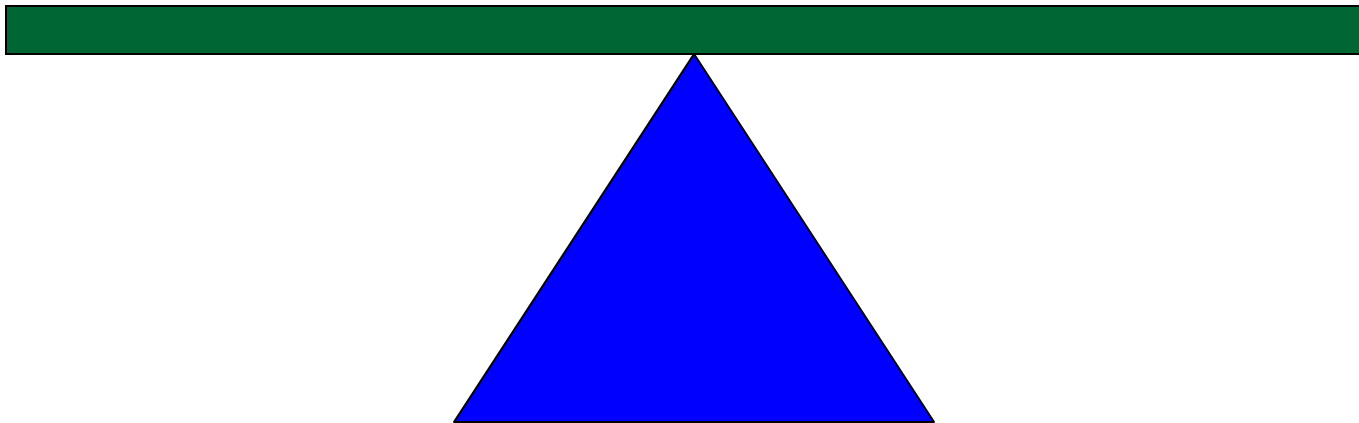
(C) Alternative explanations for clinical deterioration must be excluded if possible*

- 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

Corticosteroids for paradoxical TB-IRIS?

**Symptom improvement
Reduced hospitalisation
? Survival benefit in life
threatening cases**

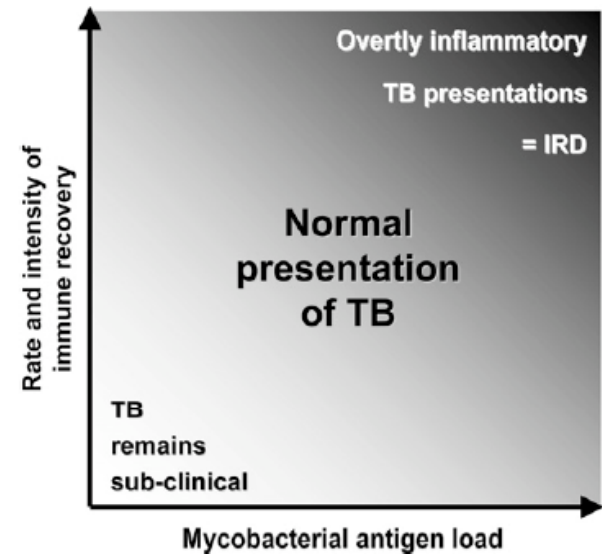
**Potential adverse effects
Diagnostic uncertainty**



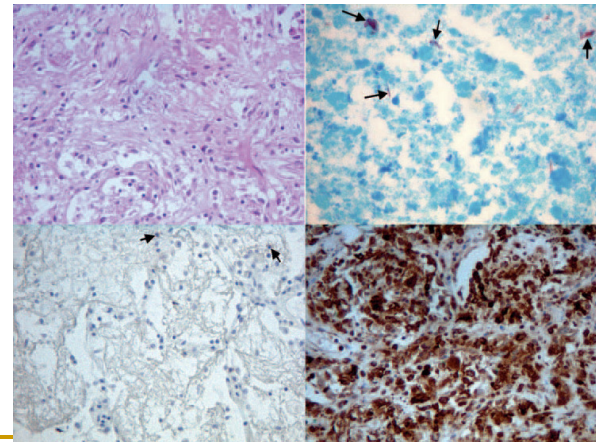
Many case reports of unmasking TB-IRIS

- 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



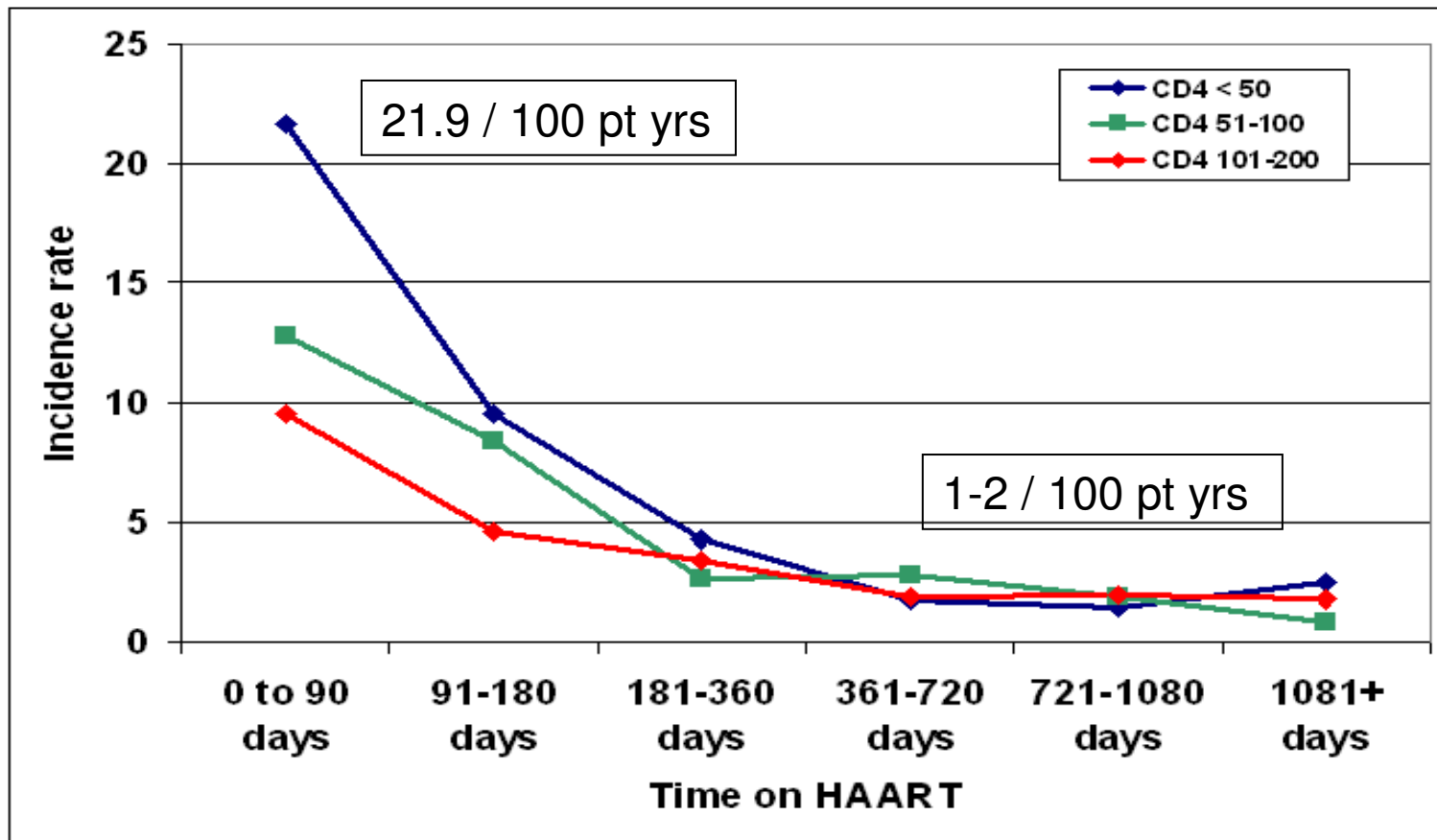
Lawn et al, AJRCCM 2008



Lawn et al, AIDS 2009

Incident TB by baseline CD4

(Number per 100 patient years)



Key Messages and Research Gaps

- No diagnostic test for IRIS – relies on clinical diagnosis and we need to assess the performance of the consensus case definition.
 - Corticosteroids have significant impact on morbidity
 - What proportion of TB in first 3 months of ART is unmasking TB-IRIS?
 - Prospective trial required:
 - TB treatment in patients with $CD4 < 50$ starting ART
 - Corticosteroids Vs NSAIDS
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Finale

- Thank you to all the contributors for an excellent session
 - TB/HIV integration in clinical practice remains a key priority
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