Tuberculosis and IRIS

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Immune Reconstitution Inflammatory Syndrome

- Paradoxical worsening of pre-existing infectious processes after ART initiation
- The inflammation and pus produced during infection is due to fighting immune cells
- If you don’t HAVE ANY fighting immune cells—there is NO PUS, and you may not display obvious signs of infection
- If you start to GET immune cells, you might start making lots of pus

TB–Associated IRIS

- An invigorated inflammatory reaction against Mycobacterium tuberculosis antigens driven by antiretroviral therapy–induced reconstitution of the immune system

HIV and CD4 cell counts

DANGER ZONE

T-cells
(also called CD4 cells)

TIME
How do you know it’s IRIS and NOT something else?

- The presence of symptoms consistent with inflammation AND….

- Presence of AIDS with low treatment CD4 count < 100
  - Exception is TUBERCULOSIS: CD4 can be > 200
- A Positive Immune Response to ART
  - CD4 increase and HIV viral load decreases (1 log)
- Temporal relationship to starting ART
  - Median of 48 days (29–99 days)

Likelihood and Severity of IRIS

- 1. How LOW your CD4 cells are initially
- 2. The RAPIDITY of immune recovery after starting HIV medications
- 10–40% of patients with TB who start ART get TB-associated IRIS
Types of TB IRIS

- Patient unknown to have TB at the start of HAART
- Patient on TB treatment before or at the start of HAART
- All HIV positive persons NEED a PPD

Types of Tuberculosis IRIS

- Paradoxical TB-associated IRIS

Paradoxical TB–associated IRIS

- Patient KNOWN to have Tuberculosis
- On TB medications and doing well
- ART is started and THEN in 1–8 weeks later
  - Fever
  - Return of Cough
  - Lymph node enlargement
  - Abscesses
- Cultures often negative
**Case Definition for Antiretroviral Therapy-Associated Tuberculosis and Provisional Case Definition for Unmasking Tuberculosis-Associated IRIS**

**ART-Associated Tuberculosis**

- Active tuberculosis is diagnosed after initiation of ART.
- The diagnosis of tuberculosis should fulfill WHO criteria for smear-positive pulmonary tuberculosis, smear-negative pulmonary tuberculosis, or extrapolumonary tuberculosis.

**Unmasking Tuberculosis-Associated IRIS (provisional)**

- We propose that ART-associated tuberculosis (all cases of tuberculosis that are diagnosed during ART) should be defined as follows:
- Active tuberculosis is diagnosed after initiation of ART.
- The diagnosis of tuberculosis should fulfill WHO criteria for smear-positive pulmonary tuberculosis, smear-negative pulmonary tuberculosis, or extrapolumonary tuberculosis.

**Clinical Features of Tuberculosis-Associated IRIS**

- **FEVER!** Hectic fever.
- Malaise, weight loss, and worsening respiratory symptoms.
- New opacities on CXR.
- Thoracic and cervical lymph node enlargement.
- Can progress to ARDS.
Given that disseminated disease frequently develops in HIV–infected persons with active TB, TB–IRIS can present in diverse ways:

- New pleural effusions
- Worsening intracranial lesions
- Draining lymphadenitis
- Rarer but: Peritonitis, Epidydimitis, Bowel perforation, Granulomatous nephritis

Cervical Lymphadenitis in Patient with TB–IRIS

- Aspiration reveals purulence but no organisms
Differential—Don’t Miss Other Things

- Tuberculosis Treatment Failure!
  - Wrong Doses or Malabsorption or Poor Adherence
  - MDR TB
  - In a recent cohort study of South African patients, 10% of the patients with suspected TB-IRIS were found to have previously undiagnosed rifampicin-resistant TB
- Other Problems like PCP, or neoplasm
- Abacavir Hypersensitivity Reaction
- Other ART drug reactions

Management of TB-related IRIS

- Continue ART unless life-threatening symptoms
- Treat TB as you would normally with 4-drug therapy followed by continuous 2-drug phase
- Can use NSAIDS or steroids if inflammation
  - Prednisone 40–60mg daily with rapid taper over 10–14 days
- Exclude treatment failure
  - Ensure adequate treatment
  - Ensure adherence
  - Consider drug resistance

Prednisone for TB-IRIS?

Study Design
- N = 110 adults
- Randomized, double-blind, placebo-controlled
- Patients TB-Associated IRIS
- Excluded if IRIS immediately life-threatening
- Patients in South Africa
- Randomized to Placebo or Prednisone*
- Analysis at weeks 2 and 4
- Analysis of symptoms and chest radiographs

*Prednisone: 1.5 mg/kg x 2 weeks, then 0.75 mg/kg x 2 weeks

![Prednisone for TB-IRIS](image)

Week 2: Symptom Score

- Placebo Arm
  - Deteriorated: 43
  - No Change: 38
  - Improved or Resolved: 16

- Prednisone Arm
  - Deteriorated: 18
  - No Change: 7
  - Improved or Resolved: 76

*p<0.001
A recent meta-analysis involving more than 13,000 patients with TB-IRIS reported a case-fatality rate of 3.2% (not high, but not zero).

Higher mortality is seen with Cerebral TB-associated IRIS.

**Most cases of TB-IRIS have a self-limited course and will resolve with continuing treatment with little or no change in overall management**

Exclude TB before starting antiretroviral therapy.

Treat TB first! and start antiretroviral treatment only once the patient has clinically improved, and is tolerating TB treatment well.

Increase awareness about TB IRIS such that it is more rapidly diagnosed.

Recommendations to prevent or quickly address TB-associated IRIS

When should you start ART in patient with known TB?

- Increased risk of paradoxical TB-IRIS
- Risk of overlapping drug toxicities (and possible treatment interruptions)
- High pill burden that may impact on adherence
- Potentially more drug interactions

Advancing immune-suppression and development of other opportunistic conditions with associated mortality

EARLY DELAYED
**Kaplan-Meier Survival Estimates According to Study Group.**

- **661 HIV+ patients**
- **CD4 counts <200**
- **2 weeks after TB tx vs. 8 weeks after TB tx**
- **DEATH more common if ART delayed**

**Kaplan-Meier Curves for Survival without an AIDS-Defining Illness.**

- **642 HIV+ patients**
- **All with CD4 <500**
- **Start TB tx in 4 weeks vs. Start TB tx in 4 weeks after continuation phase**
- **People with CD4 <50 DIED more often if ART delayed**

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**Case 1**

- A 49 year-old man was diagnosed with pulmonary TB (sputum cultured *Mycobacterium tuberculosis* susceptible to rifampicin and isoniazid.)

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**DHHS Guidelines for starting ART in TB-infected patient**

- **CD4 count < 200 cells** should start ART therapy within 2–4 weeks, preferably 2 weeks, of starting TB treatment.
- **CD4 count of 200–500** should start ART within 2–4 weeks or by at most 8 weeks after starting TB treatment.
- **CD4 count > 500** should start ART within 8 weeks of starting tuberculosis treatment.

- If IRIS develops, patients should still continue both antiretroviral therapy and tuberculosis treatment.
Case 1

- His symptoms improved on TB treatment.
- His CD4 count was 29 cells and HIV viral load 191,000.
- He was started on antiretroviral therapy 2 weeks after TB treatment.
- 2 weeks later developed recurrent cough, night sweats and dyspnoea.

CXR

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<tr>
<th>Before ART</th>
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Case 1

- His CD4 had risen to 51 cells
- Repeat TB cultures from sputum and pleural aspirate were negative.
- Patient was monitored closely—no changes
- 6 months later patient viral load <50 and doing well

Case 2

- 36-year-old HIV-infected man was diagnosed with culture-positive pulmonary tuberculosis (sensitive to rifampicin and isoniazid) without evidence of extrapulmonary involvement.
- His CD4 count was 39 cells and HIV-1 viral load 1,300,000 copies per mL.
- Pt was started on appropriate TB therapy
- ART: stavudine, lamivudine, and efavirenz was started 7 weeks after initiating antituberculous therapy.
- One week later pt presents with fever and the following signs

Extrapulmonary TB-associated IRIS

The patient continued on TB treatment
- The patient continued on ART
- All abscesses were drained
- The patient was given prednisone for 4 weeks due to continued symptoms
- Pt was well at 6 months with undetectable HIV viral load and CD4 count 253
Case 3

- A 12 year old boy recently diagnosed with HIV infection (absolute CD4 count 274/μL) presented with culture negative TB meningitis.
- Initial response to anti-TB medication proved favorable and ART consisting of abacavir, lamivudine and efavirenz was introduced after 4 weeks of anti-TB therapy.
- 1 week later, the patient complained of headache, vomiting and drowsiness.

CT of Brain

Brain CT scan showed a large ring-enhancing lesion in the left cerebellar hemisphere with marked peri-lesional edema

Case 3

- The patient was taken off ART
- Dexamethasone was started
- Projectile vomiting continued
- Ventriculostomy was performed and patient improved
- Patient was given rest of TB treatment prior to ART initiation

Case 4

- 48-year-old HIV-infected man with a CD4 count of 10, and HIV VL of 600,000
- Examination was normal
- Pt started on ART
- 2 weeks later pt presents with fever, cough, and sputum production but feels ok
New RT Upper lobe Infiltrate

ART-associated TB
- Started on TB meds and did well

Thank you!
- Questions?