Tuberculosis and IRIS

Brianna Norton, DO
Duke Infectious Diseases

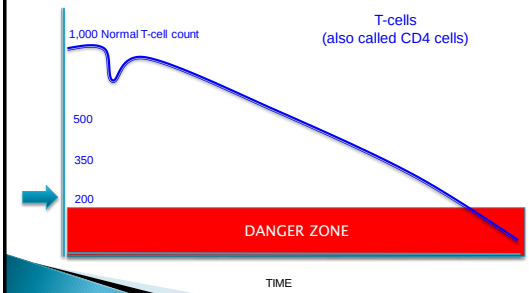
Immune Reconstitution Inflammatory Syndrome

- 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

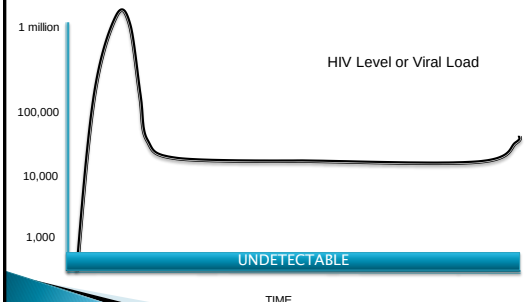
TB-Associated IRIS

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

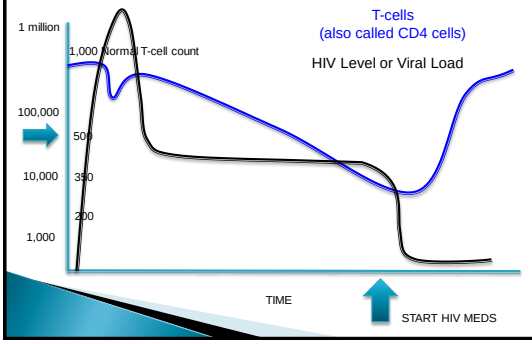
HIV and CD4 cell counts



HIV in a nutshell



HIV in a nutshell



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 CD4count <100
  - Exception is TUBERCULOSIS: CD4 can be >200
- A Positive Immune Response to ART
  - CD4 increase and HIV viral load decreases (1log)
- Temporal relationship to starting ART
  - Median of 48days (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

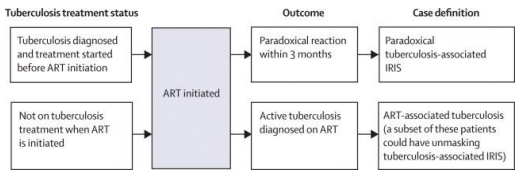
- Patient unknown to have TB at the start of HAART
- Patient on TB treatment before or at the start of HAART
- All HIV positive persons NEED a PPD

PPD RESULTS AND CD4+ COUNT IN HIV-INFECTED TB PATIENTS ON ANTIRETROVIRALS WHO HAD PARADOXICAL RESPONSES

Patient	PPD before ARV (*mm induration*)	PPD after ARV (*mm induration*)	Time to PPD Conversion after ARV (*wk*)	CD4+ Count before ARV (*/mm³*)	CD4+ Count Within a Month of PPD Conversion (*/mm³*)
A	0	30	20	12	96
B	0	20	4	80	67
C	0	0	—	27	—
D	15	Not done	—	91	—
E	0	10	2.5	2	32
F	0	67	9	35	350
G	0	20	8	75	30
H	0	7	5	133	110

Definition of abbreviation: ARV = combination antiretroviral therapy.

Types of Tuberculosis 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 Paradoxical TB-Associated IRIS (three components to case definition)

(A) Antecedent requirements

Both of the two following requirements must be met:

- Diagnosis of tuberculosis: made before starting ART and this should fulfill WHO criteria for diagnosis of smear-positive pulmonary tuberculosis, smear-negative pulmonary tuberculosis, or extrapulmonary tuberculosis
- 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, ≥1 major criterion or 2 minor clinical criteria 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 US, 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 with peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

(C) Alternative explanations for clinical deterioration must be excluded if possible[a]

- 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

INSHI = International Network for the Study of HIV-associated IRIS; ART = antiretroviral therapy; IRIS = immune reconstitution inflammatory syndrome.
[a]It might be difficult or impossible in resource-poor settings to confirm tuberculosis drug resistance and to exclude certain other infections or neoplasia. Cases where alternative diagnoses cannot be fully excluded because of limited diagnostic capacity should be regarded as "probable paradoxical tuberculosis-associated IRIS". In these probable cases, should resolution of clinical or radiological findings of the suspected IRIS episode occur without a change in tuberculosis treatment or ART having been made, they could then be reclassified as "paradoxical tuberculosis-associated IRIS" cases.

ART-associated Tuberculosis or Unmasking TB-associated IRIS

- Patient UNKNOWN to have TB
- Starts on ART
- Presents with typical Signs of Tuberculosis
  - ART-associated TB
- Presents with EXAGGERATED signs of TB
  - Unmasking TB-Associated IRIS
- Cultures usually positive

Case Definition for Antiretroviral Therapy-Associated Tuberculosis and Provisional Case Definition for Unmasking Tuberculosis-Associated IRIS

Antiretroviral Therapy (ART)-Associated Tuberculosis

We propose that ART-associated tuberculosis (all cases of tuberculosis that are diagnosed during ART) should be defined as follows:

- Patient is not receiving treatment for tuberculosis when ART is initiated
- 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 extrapulmonary tuberculosis

Unmasking Tuberculosis-Associated IRIS (provisional)

We propose that the following could suggest a diagnosis of unmasking tuberculosis- associated IRIS:

- Patient is not receiving treatment for tuberculosis when ART is initiated and then presents with active tuberculosis within 3 months of starting ART

AND one of the following criteria must be met:

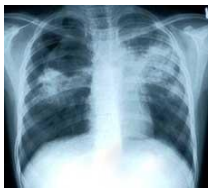
- Heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component to the presentation. Examples include tuberculosis lymphadenitis or tuberculosis abscesses with prominent acute inflammatory features, presentation with pulmonary tuberculosis that is complicated by respiratory failure due to adult respiratory distress syndrome, and those who present with a marked systemic inflammatory syndrome related to tuberculosis.
- Once established on tuberculosis treatment, a clinical course that is complicated by a paradoxical reaction

INSHI = International Network for the Study of HIV-associated IRIS
ART = antiretroviral therapy.
IRIS = immune reconstitution inflammatory syndrome.
Researchers in the field are encouraged not to regard all patients with ART-associated tuberculosis as having tuberculosis-associated IRIS, but only those that fit this provisional unmasking tuberculosis-associated-IRIS case definition. We suggest that the clinical manifestations of all patients developing ART-associated tuberculosis should be well characterised and reported in studies, which will assist with refinement of this case definition in the future. Studies of the immunological processes underlying the presentation of these cases are also likely to assist with refining this case definition.

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

TB-Associated IRIS

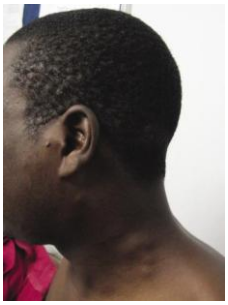


Extrapulmonary TB and IRIS

- 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



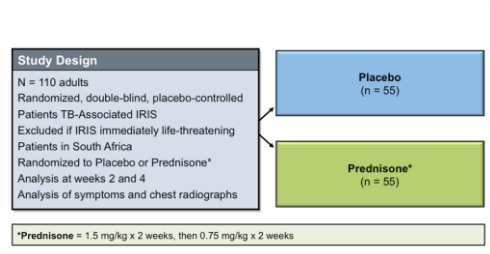
Differential–Don't Miss Other Things

- 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

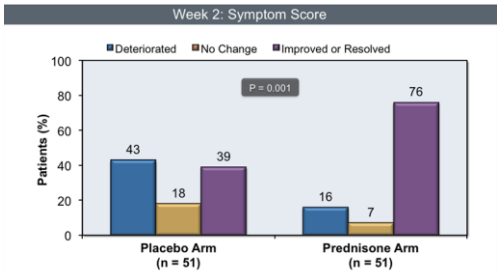
Management of TB-related IRIS

- 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

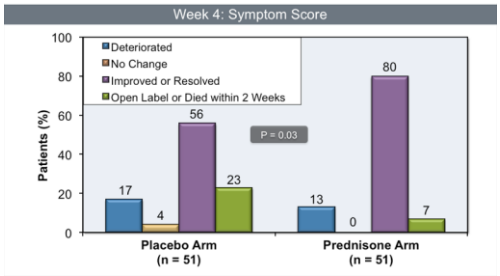
Prednisone for TB-IRIS?



Prednisone for TB-IRIS?



Prednisone for TB-IRIS?



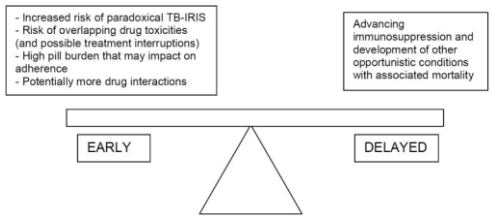
Mortality

- 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**

Recommendations to prevent or quickly address TB-associated IRIS

- 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

When should you start ART in patient with known TB?



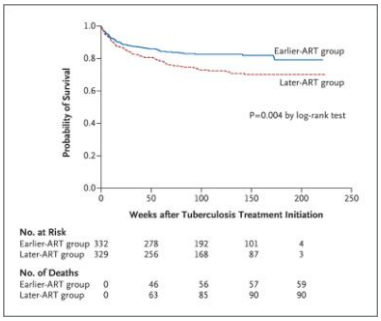
Kaplan–Meier Survival Estimates According to Study Group.

661 HIV+ patients

CD4 counts <200

2weeks after TB tx
vs.
8weeks after TB tx

DEATH more common if ART delayed



Blanc F et al. N Engl J Med 2011;365:1471-1481.

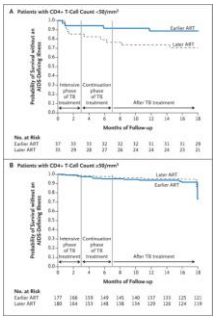
Kaplan–Meier Curves for Survival without an AIDS–Defining Illness.

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



Abdool Karim SS et al. N Engl J Med 2011;365:1492-1501.

DHHS Guidelines for starting ART in TB-infected patient

- CD4 count<200 cells should start ART therapy within 2-4weeks, 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.

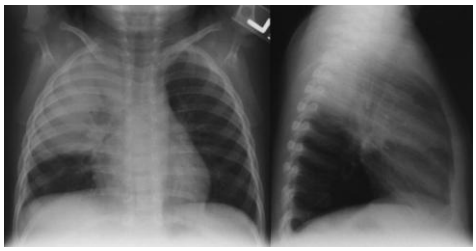
Case 1

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

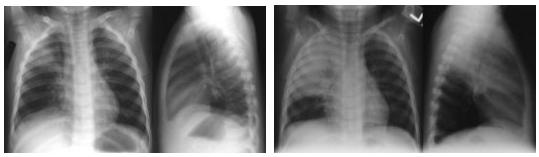
Chest Xray

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



Before ART	After ART

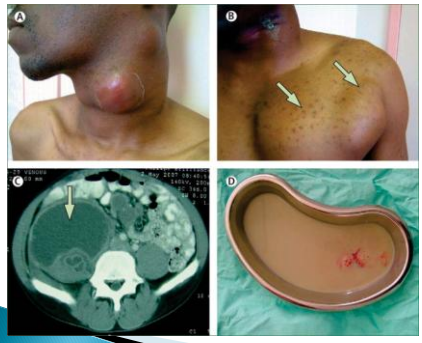
Case 1

- His CD4 had risen to 51 cells
- Repeat TB cultures from sputum and pleural aspirate were negative.
- Patient was monitored closely-no changes
- 6months 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



All aspirates were negative for organism

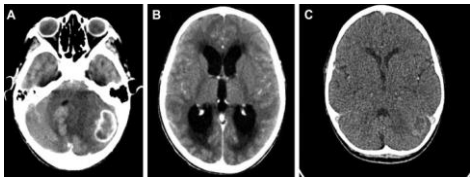
Case 2

- 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

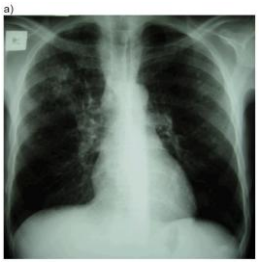
Case 3

- 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?