Immune Reconstitution Syndrome, 2023 – Part 2

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Disclosures

Merck: Adjudicate cases for HIV diagnostic test development
Disclaimer

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Data Considerations

Data in this presentation offer a limited perspective of how systemic, social, and economic factors impact health. We recognize that racism, not race, creates and perpetuates health disparities.

To Learn More:
https://www.cdc.gov/minorityhealth/racism-disparities
Immune Reconstitution Inflammatory Syndrome
IRIS: Definition

An illness...

• Occurring in a person with HIV

• With a temporal relationship to ARV initiation

• Associated with a decline in plasma HIV RNA and a rise in CD4 count

• Presentation with an unusual inflammatory course

• Exclusion of alternative causes (e.g., progression of an OI, drug toxicity, development of a new OI, etc.)
IRIS: Definition

Two Versions

• **Paradoxical**: IRIS occurring when an OI, responding to treatment before ARV therapy, deteriorates after initiating ARVs

• **Unmasking**: disease that was cryptic prior to starting ARVs, presents after starting ARVs with florid, inflammatory symptoms
IRIS: Clinical Symptoms

• Timing: typically 4-8 weeks after ART but with a range of 4 days to 6 months
• Median CD4: 57 (Muller 2010)
• Mortality: 4.5% (Muller 2010, Novak 2012)
  - Higher with CNS involvement (13-75%) (Muller 2010 and Bahn 2013)
## IRIS: Clinical Symptoms

<table>
<thead>
<tr>
<th>Clinical symptom or illness</th>
<th>Possible etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>Cryptococcus, MTb</td>
</tr>
<tr>
<td>CNS mass</td>
<td>Cryptococcus, MTb, Toxo, PML, lymphoma</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>HSV, VZV, CMV, HIV, Parvo B19</td>
</tr>
<tr>
<td>Retinitis</td>
<td>CMV, VZV, HSV</td>
</tr>
<tr>
<td>Uveitis</td>
<td>CMV, MTb, Histoplasma, Leishmania</td>
</tr>
<tr>
<td>Lymphadenitis</td>
<td>MTb, NTM, BCG, Histoplasma, Cryptococcus, Leishmania</td>
</tr>
<tr>
<td>Skin</td>
<td>HSV, VZV, KS, HPV, M. leprae, Crypto, Molluscum, Leishmania</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>HBV, HCV, NTM, MTb, Histoplasma, Leishmania, KS</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>MTb, NTM</td>
</tr>
<tr>
<td>Colitis</td>
<td>MTb, Histoplasma, CMV</td>
</tr>
<tr>
<td>Splenitis</td>
<td>MTb, Bartonella</td>
</tr>
<tr>
<td>Lung and pleural disease</td>
<td>MTb, NTM, PJP, Cryptococcus</td>
</tr>
<tr>
<td>Autoimmune IRIS</td>
<td>Thyroiditis, Sarcoid, SLE, Guillain-Barre, RA, PM</td>
</tr>
</tbody>
</table>
Case Presentation

• A 47 yo HIV+ man presented with fever, fatigue, and a dry cough 6 weeks after starting HAART. PE revealed T 39.3°C, BP 106/58, HR 135, RR 28, SO2 88% on RA.

• Chest x-ray and CT showed interstitial thickening, small pleural effusions, splenomegaly, and diffuse adenopathy.
Case Presentation
Case Presentation

- Bronchoscopy, bone marrow aspiration and inguinal lymph node biopsies were unrevealing.

- He was treated with TMP-SMZ and levofloxacin for presumptive PJP and CAP. CMV Ag was detected in blood. Ganciclovir, ethambutol, clarithromycin, and corticosteroids were added for possible CMV, MAC, or IRIS.

- He improved promptly on prednisone and was discharged from the hospital on a prednisone taper.

- He returned to work, his CXR normalized and his CD4 cell count rose to 381 cells/mm$^3$. 
Case Presentation

• Three days after completing the steroid taper, the patient was readmitted with shortness of breath, fever, and edema.

• The following day he developed a consumptive coagulopathy, ARF, and ARDS requiring intubation. Bronchoscopy was unrevealing.

• Despite supportive measures, antibiotics, and high dose steroids, he expired 3 days after admission.
Case Presentation

Initial admission  Readmission  2 days later
Case Presentation

• Autopsy revealed extensive KS in both lungs with atypical lymphocytic infiltration
KS-IRIS

• Incidence: 2.4-39%. Meta-analysis 6.4% (Paradoxical 6-11%, Unmasking 4-5%)

• Timing: days to 6 months after ART - most in the first 2 months

• Risk factors: usual RFs for IRIS + **steroid use**

• Risk factors for more severe disease and higher mortality:
  - CD4 < 200, visceral disease, + plasma HHV-8, platelets < 100K, no chemotherapy

• Clinical presentation:
  - Increased inflammation and edema of lesions, new lesions in any location (especially pulmonary, but can be any organ), pleural effusions, ascites (can be chylous)

• Prevention: Chemotherapy for KS does NOT decrease the risk of IRIS

• Treatment: Chemotherapy (doxorubicin or paclitaxel). NO STEROIDS
Cryptococcal-IRS
Definition of Cryptococcus IRIS

Paradoxical Cryptococcus IRIS

- Previously diagnosed with Cryptococcus and responding to treatment

- Clinical criteria:
  - Onset within 12 months of ART
  - Clinical deterioration with inflammatory features
    - Meningitis
    - Lymphadenopathy
    - Intracranial lesions
    - Multifocal disease
    - Cutaneous or soft tissue lesions
    - Pneumonitis or pulmonary nodules
  - No alternative explanation for symptoms
Definition of Cryptococcus IRIS

Unmasking Cryptococcus IRIS

- Clinical deterioration due to previously undiagnosed cryptococcus that develops after starting ART

- Clinical criteria:
  - Unusual, heightened or exaggerated symptoms, for example:
    - Meningitis with markedly elevated WBC (> 50) or opening pressure that is refractory to treatments
    - Painful or suppurating lymphadenopathy
    - Rapidly expanding intracranial lesions
    - Unusual focus of infection
    - Granulomatous inflammation on histology
    - Pneumonitis, particularly if cavitating
  - Typically occurs early after starting ART (within a month)
  - No alternative explanation for symptoms

Haddow, Lancet Infectious Diseases 2010
Timing of ART: Early Vs Delayed ART in Patients with Cryptococcal Meningitis in Africa

- Open Label RCT
- Patients: Adults with HIV and Cryptococcal meningitis (CSF CrAg or India ink positive)
- All received Fluconazole 800 mg PO once daily x 10 wks + aggressive pressure management
- Followed by maintenance fluconazole 200 mg
- Intervention: d4T, 3TC, NVP
  - EARLY: Immediate start within 72 hours of diagnosis of Cryptococcal meningitis
  - DELAYED: Start after initial 10 wks of fluconazole
- Primary Outcome: Mortality after 2 years
Early Vs Delayed HAART in Patients with Cryptococcal Meningitis in Africa

TOTAL: 50 patients
Overall 2-yr Mortality: 62%

EARLY
27 patients
Median Survival: 35 days*
2-yr Mortality: 87%**

DELAYED
23 patients
Median Survival: 274 days
2-yr Mortality: 37%

*Comparison of median survival, p=0.03
**Comparison of 2-yr Mortality, p=0.002
Early Vs Delayed HAART in Patients with Cryptococcal Meningitis in Africa

Survival

Comparison of Kaplan-Meier survival estimates by Treatment Group

Time to death (in days)

- Delayed
- Early

p=0.028
COAT: Cryptococcal Optimal ART Timing

• Design:
  - Early ART (<14 days) vs. late (≥4 weeks)
  - Goal: 250 participants in each arm
  - Primary endpoint: 6-month survival
  - Stratified by MS (GCS 15 vs. <15) and CSF WBC (≥ or <5)
  - Induction: amphotericin 0.7-1 mg/kg/day + fluconazole 800 mg.
  - Note – No 5-FC

• Results:
  - Halted by DSMB after 177 randomized
  - 6-month survival: early ART- **48/88 (55%)**, delayed ART- **62/89 (70%)** [HR 1.7 (95% CI 1.1-2.8, p=0.03)]
COAT: Cryptococcal Optimal ART Timing

A Overall Survival

Cumulative Probability of Survival

Deferred ART

Earlier ART

P=0.03

No. at Risk
Earlier ART 88 54 51 47 47 46 42
Deferred ART 89 72 67 62 62 61 59

Months since Randomization

B Survival in Those with CSF White-Cell Count ≥5 Cells per mm³ at Randomization

Cumulative Probability of Survival

Earlier ART

Deferred ART

P=0.71

No. at Risk
Earlier ART 42 29 26 24 24 23 21
Deferred ART 40 28 25 22 22 22 22

Months since Randomization

C Survival in Those with CSF White-Cell Count <5 Cells per mm³ at Randomization

Cumulative Probability of Survival

Deferred ART

Earlier ART

P=0.008

No. at Risk
Earlier ART 33 19 19 17 17 16 16
Deferred ART 31 28 27 26 26 26 24

Months since Randomization

Boulware D et al, NEJM, 2014
COAT: Cryptococcal Optimal ART Timing

• Secondary analyses:
  - Mortality ↑ if AMS at presentation (GCS<15): HR 3.0
  - Mortality ↑ if CSF WBC <5/μL at presentation: HR 5.1
  - Trend toward ↑ IRIS in early group: 13% vs. 10%

• Recommendations:
  - Anti-cryptococcal therapy should always come before ART
  - In general, start ART at 4 weeks
  - Consider delay of ART until 5-6 weeks if AMS at presentation or if CSF WBC <5/μL
Cryptococcal Meningitis and Early ART: Not a Good Idea

Ingle Abstract: 2014 CROI

- Cited in IAS guidelines as support for immediate ART
- Not published
- Used patients in 3 retrospective cohorts (1998-2009 - COHERE, NA-ACCORD and CNICS) to “mimic” the COAT study.
- Retrospective, observational! In fact, most deaths occurred in those patients who did not get ART at all.
- Equal number of deaths in those that did and those that did not get early ART.
  - But difference between groups was ART < 2 weeks or > 2 weeks: > 2 weeks not defined (might have been all at 2.5 weeks!).
  - 1998 – pretty bad ART so may not have been very effective, less immune reconstitution and therefore less of a deleterious effect of early ART
Cryptococcal Meningitis and Early ART: Not a Good Idea

• For persons with cryptococcal meningitis and with access to close monitoring and supportive care for adverse events, ART should be initiated 2 to 4 weeks after starting antifungal therapy (evidence rating: BII). The data supporting a delay in ART initiation for persons with cryptococcal meningitis were largely generated in resource-constrained settings where access to close monitoring and supportive care may not be as readily available and in persons who were not being treated with InSTI-based ART.

• A cohort study that did not show an increase in adverse outcomes with earlier initiation of ART (Ingle, CROI abstract 2014)
Cryptococcal Meningitis and Early ART: Not a Good Idea

• Boulware editorial from July 2023 CID: Comment on Ingle paper (same issue): that used a marginal structural model to mimic an RCT

• Why believe observational studies > RCTs?

• Large sampling bias in the Ingle paper: 630 with CM, 41% LTFU, 28% excluded for missing data – final analysis on 190 subjects:
  - These 190 subject were cloned and entered into 2 hypothetical arms who started ART < 2 weeks or > 2 weeks (post-ART)
  - Median time to ART was 0 days in the “early ART arm”
  - Many deaths in the delayed arm occurred between 2 and 4 week which would have been categorized in an “early group” in other RCTs
  - Those who never started ART were put in the late group so much of the comparison was “early ART” Vs ”no ART”
  - Many subjects were censored at day 14 in the early group so any deaths that happened after this time point were only considered in the late group

• Why believe observational studies > RCTs?
Cryptococcus IRIS

Prevention and Treatment

• Prevention:
  - Delay ART for 4-6 weeks after therapy for cryptococcus
  - In well-resourced settings consider starting ART sooner?

• Treatment
  - Manage increased ICP (serial taps, drains, shunts)
  - Enhance antifungal therapy while waiting to confirm that antifungal therapy is effective (sterilizing) by restarting L-amphotericin or increasing fluconazole
  - Some experts might recommend: A brief course of tapering steroids starting at 1.0 mg/kg/day
Case Presentation

• A 23 year old gay man not previously diagnosed with HIV presents with anorexia, dysphagia, a 25# weight loss over 6 months, night sweats, fatigue and diarrhea.

• On exam he is cachectic and apathetic. Temperature is 38.2, BP 90/60, HR 110, RR 14. He has obvious thrush, seborrheic dermatitis, indurated purple plaques on his face, feet and hard palate. His liver edge is 2 FB below his R costal margin.

• He tests + for HIV, his CD4 cell count measures 14 cells/uL and a plasma HIV RNA level is 454,000 copies/uL
• He declines hospitalization but receives several liters of IV fluids, is given fluconazole and TMP/SMX and goes home.

• He returns to clinic a week later without thrush or dysphagia.

• He claims to be taking TMP/SMX but his diarrhea, fevers and sweats continue, and he now complains of abdominal fullness and pain.
Case Presentation

- CBC and chemistries: LDH 220, WBC 3.4, Hct 24, Plts 300K, ALT 54, AST 84, AP 480, TB 1.4, TP 9.0, Alb 2.1

- Stool O&P - negative

- Blood cultures for bacteria, mycobacteria, fungi – negative or pending

- Histoplasma urinary antigen negative

- PPD, IGRA – both negative
Case Presentation
Case Presentation

- Azithromycin and ethambutol result in a gradual reduction in temperature, sweats and diarrhea over the next weeks.

- He is then started on ART (dolutegravir-TDF-FTC) and 3 weeks later presents with recurrent fever, abdominal pain and a L sided abdominal mass.

- Imaging reveals……..
NTM IRIS: Observational cohort of 51 patients in British Columbia over a 10 year period ending 12/31/04

- Incidence: 3.5% of all patients starting ART with CD4 < 100
- Micro: *M. avium complex* (43), *M. genavense* (2), AFB stain + but did not grow (6)
- Clinically:
  - Peripheral adenopathy (17); draining sinuses (10)
  - Pulmonary-thoracic (15); infiltrates, nodules, cavities, tree-bud, collapse, pericardial effusion
  - Intra-abdominal (13); necrotic nodes, abscesses, ascites (chylous), obstruction, adrenal mass
MAC IRS

NTM IRIS: Observational cohort of 51 patients in British Columbia over a 10 year period ending 12/31/04

- Clinically:
  - Median CD4 at start of ART = 20
  - Median CD4 at IRIS dx = 120
  - Median time to IRIS symptoms post-ART = 3 weeks
  - Median time to IRIS diagnosis post-ART = 10 weeks

- Treatment
  - 41/51 received > 2 weeks of abx – duration of symptoms – 6 months
  - 10/51 received no or < 2 weeks of abx – duration of symptoms – 3 months
  - 8/9 who received steroids responded well
  - 10 patients died (MAC (2), other OI (5), non-HIV related (3)
MAC IRS

• Clinical presentation: fever, sweats, adenitis (cervical, inguinal, thoracic, abd/retroperitoneal)
  - Low CD4 (< 50): more severe illness; fevers, weight loss, leucocytosis, positive blood cultures
  - High CD4 (> 100-150): fewer systemic symptoms, more localized suppurative disease

• Treatment:
  - Continue ART
  - MAC therapy
  - NSAIDS
  - Steroids (prednisone 20-40 mg per day)

IRIS: Treatment

- Continue ART except in life-threatening situations
- Continue treatment of opportunistic infection or condition
- Mild disease: NSAIDs

Moderate to severe disease: steroids
- NOT in CNS cryptococcal infection (although some experts would do it!)
- Use carefully if KS present, consider concurrent KS therapy
- Do NOT use steroids to treat KS-IRIS
- Check for or just treat for Strongyloidiasis (ivermectin)

Alternatives to steroids
- Thalidomide
- Pentoxifylline
- Chloroquine
- TNF inhibitors: infliximab, adalimumab, etanercept
People with HIV on ART who develop moderate-to-severe symptoms typical of IRIS should receive initial treatment with non-steroidal, anti-inflammatory drugs (CIII). If IRIS symptoms do not improve, short-term (4 weeks–8 weeks) systemic corticosteroid therapy, in doses equivalent to 20 to 40 mg of oral prednisone daily, has been successful in reducing symptoms and morbidity (CII).\textsuperscript{29,74}
IRIS: Conclusions

- IRIS is an inflammatory disease that occurs in the context of initiating ARV therapy and can be classified as paradoxical or unmasking.

- The incidence varies greatly by geographic region and disease.

- Major risk factors include advanced HIV (low CD4), disseminated infections (high organism or Ag burden) and a short interval between the treatment of an OI and the initiation of ARVs.

- Management generally includes continuation of treatment of the OI/cancer and ARVs plus supportive care and the addition of anti-inflammatory therapy (NSAIDs, steroids (NOT for KS or Cryptococcus [with exceptions])).

- Outcomes are generally good but there can be significant mortality for some: cryptococcal meningitis, visceral KS, PML and HIV-CD8-encephalitis.
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