IMMUNE RECONSTITUTION AND HIV

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AIDS Arms, Inc.

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Disclosures

- Bristol-Myers Squibb
  - Advisory board
- Gilead Sciences
  - Speakers bureau
- Abbvie
  - Speakers bureau
Overview

- Definition and Pathogenesis
- Risk factors
- Timing and Incidence
- IRIS syndromes and their management
  - MAC
  - TB
  - PML
  - CMV
  - Cryptococcus
  - KS
- Prevention
  - Timing of HAART initiation
What’s New

- No major guideline updates in the last 6 months
Case 1

- 51yo Ethiopian female, immigrated to the U.S. in August, 2013, admitted in October with cough, dyspnea, and weight loss, found to have a new diagnosis of HIV (CD4 21, VL 2 million c/mL) as well as pulmonary TB (culture-confirmed). HIV genotype was wild-type, and she was treatment naïve.
- She was started on RIPE, and ~two weeks later on Atripla. Discharged in stable condition.
- She returned to the hospital 8 days later with fever to 38.6°C, tachycardia, hypoxia, and worsening pleuritic chest pain and cough.
- CT chest showed increased cavitation of mediastinal lymph nodes and larger bilateral pleural effusions.
- HIV RNA had declined to 6684 c/mL, although she had to self-discontinue Atripla due to nausea. CD4 count unchanged.
IRIS/IRD

- Immune Reconstitution Inflammatory Syndrome (IRIS)
  - Also referred to as immune reconstitution disease (IRD)

- “Paradoxical” IRIS - Worsening of a recognized OI
- “Unmasking” IRIS – Symptoms from an unrecognized pre-existing OI that manifest in the setting of improving immunologic function.
Example: TB-IRIS

Patient on treatment for TB
(Worsening disease)
Paradoxical IRIS

Patient not known to have TB
(Symptoms of TB)
Unmasking IRIS
Pathogenesis

- Viral (CMV, JCV, HBV/HCV)
  - CD8 Response
- Mycobacterial/Fungal
  - CD4 TH1 Response

Genetic susceptibility

Antigenic burden

Immune recovery

Suppression of viremia
Figure 1. Postulated disease mechanisms in immune reconstitution disease

## Incidence

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelet, et al. AIDS. 1998</td>
<td>Retrospective</td>
<td>68%</td>
</tr>
<tr>
<td>Ratnam, et al. CID. 2006</td>
<td>Retrospective</td>
<td>23%</td>
</tr>
<tr>
<td>Murdoch, et al. AIDS. 2008</td>
<td>Prospective</td>
<td>10%</td>
</tr>
<tr>
<td>Grant, et al. PLoS One. 2010</td>
<td>Prospective</td>
<td>7.6%</td>
</tr>
<tr>
<td>Muller, et al. Lancet Infect Dis. 2010</td>
<td>Meta-analysis</td>
<td>13%</td>
</tr>
</tbody>
</table>

### Previously diagnosed OI

<table>
<thead>
<tr>
<th>Previously diagnosed OI</th>
<th>Incidence of IRIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi’s Sarcoma</td>
<td>6.4%</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>12.2%</td>
</tr>
<tr>
<td>TB</td>
<td>15.7%</td>
</tr>
<tr>
<td>PML</td>
<td>16.7%</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>19.5%</td>
</tr>
<tr>
<td>CMV retinitis</td>
<td>37.7%</td>
</tr>
</tbody>
</table>
Risk Factors:

- CD4 count < 100
- Disseminated infection (high antigenic burden)
- Shorter interval between initiating treatment for OI and starting HAART
- Younger age
- Rapidity and magnitude of virological response to ART
- Fungal infection (other than PJP)
Timing:

- Highly variable
- As little as 3 days after initiation of HAART, up to 3 months or longer
- IRD can occur early due to the immediate improvement in immune function that occurs with virologic suppression
- For the ID board exams – remember 2-4 weeks
Diagnosis:

- No strict diagnostic criteria, diagnosis based on degree of clinical suspicion
Case Definition (INSHI)

1. Response to anti-retroviral therapy by:
   ◦ a. receiving HIV anti-retroviral therapy and;
   ◦ b. virologic response with \( >1 \log_{10} \) copies/mL decrease in HIV RNA (if available).

2. Clinical deterioration of an infectious or inflammatory condition temporally related to ART initiation.

3. Symptoms cannot be explained by:
   ◦ a. expected clinical course of a previously recognized and successfully treated infection
   ◦ b. medication side effect or toxicity
   ◦ c. treatment failure
   ◦ d. complete non-adherence.
Challenges:

- Diagnosis is clinically challenging, one must differentiate from:
  - Progression of the initial OI
    - antimicrobial resistance
    - treatment failure for any reason, including poor adherence
  - Development of a new OI
  - Unrelated organ dysfunction
  - Drug toxicity
    - Allergic Reaction – Abacavir Hypersensitivity
IRIS SYNDROMES
Clinical Manifestations:

- Symptoms are diverse and have not been defined precisely
- Usually characterized by:
  - Fever
  - Worsening of the clinical manifestations of underlying OI.
Causes of IRIS:

- **Mycobacteria**
  - MAC
  - TB
- **Viruses**
  - PML
  - CMV
  - Herpes virus
    - VZV
    - HSV
  - HBV/HCV
- **Fungal**
  - Cryptococcus
  - Histoplasmosis
  - PJP
- **KS**
- **Toxoplasmosis**

- **Parvovirus B19**
- **Strongyloides stercoralis and other parasites**
- **Sinusitis**
- **Folliculitis**
- **Rheum/autoimmune**
  - RA, SLE
  - Graves disease
- **Sarcoid**
- **Tattoo ink**
- **AIDS-related lymphoma**
- **Guillain-Barre Syndrome**
Case 2

- 50 y/o man with HIV, CD4 initially 16, VL 2 million, PPD neg
- Started on HAART
- Returned to clinic with tender lump in axilla one month later
  - 1 x 2 cm, firm mass, almost cystic
  - No overlying cellulitis
  - CD4 up to 192, VL down to 4K
- Referred to FNA clinic, around which time it had started to drain
- Sample was sent for culture, AFB stain negative
- 2 months later culture found to be growing MAC.
**MAC-IRIS**

- Incidence ~ 3.5% among patients with CD4 < 100
- Median time to onset of *symptoms is 3 weeks after ART initiation
- Usually unmasking of subclinical disease (75% of cases)

<table>
<thead>
<tr>
<th><strong>Peripheral lymphadenitis</strong></th>
<th><strong>Pulmonary thoracic disease</strong></th>
<th><strong>Intra-abdominal disease</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Enlarged lymph node</td>
<td>- Fever</td>
<td>- Fever</td>
</tr>
<tr>
<td>- Draining sinus</td>
<td>- Night sweats</td>
<td>- Night sweats</td>
</tr>
<tr>
<td>- Less than half with fever</td>
<td>- Cough</td>
<td>- Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>- Dyspnea</td>
<td>- CT findings</td>
</tr>
<tr>
<td></td>
<td>- CT findings</td>
<td>- Intra-abdominal lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>- Mediastinal lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Parenchymal infiltrates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Cavitary lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Nodules</td>
<td></td>
</tr>
</tbody>
</table>

Phillips P, et al. CID. 2005
MAC-IRIS: Management

- Anti-mycobacterial therapy
  - Azithromycin + ethambutol (+/- rifabutin)

- For moderate-severe IRIS
  - Initial treatment with NSAIDs (CIII)
  - If no improvement, prednisone 20-40 mg daily for 4-8 weeks (CII)

- Relapse is common after stopping steroids

- Symptoms may persist up to 6 months
TB, HIV, and IRIS

- HIV and TB co-infection
  - Pulmonary disease
  - Lymphadenitis
  - Intracranial tuberculomas/meningitis
  - Cutaneous lesions
  - Peritonitis
  - Epididymitis/Prostatitis
  - Cystitis
  - Granulomatous nephritis/hepatitis
  - Osteomyelitis
TB-IRIS

- Can occur with treatment of TB in the absence of ART
  - Release of new antigen targets during mycobacterial killing
  - Restoration of TB-induced immunosuppression

- Incidence for patients started on ART is ~15%. Time to onset is typically 2-4 weeks
  - Resolution of symptoms in ~3 months
  - Generally paradoxical IRIS (except in developing countries where the diagnosis may be missed)

Worsening radiographic infiltrate (50% of patients starting ART)

Fever

Enlarging lymph node

Enlarging serous effusions


A) Time of diagnosis of TB
B) 3 weeks after ART initiation
TB-IRIS: Management

- Continue HAART and continue RIPE
- Prednisone 1.5 mg/kg/day x 2 weeks, followed by 0.75 mg/kg/day x 2 weeks
  - This steroid regimen was evaluated in a randomized, double-blind placebo-controlled trial
  - Decreases hospital days (p=0.04), and improves both symptoms and chest radiographs at 2 and 4 weeks

Meintjes, et al. AIDS. 2010
TB-IRIS: Management

- For some patients, 4 weeks is insufficient, and DHHS guidelines suggest that tapering steroids over 3 months may be considered (BIII)
- NSAIDs may be considered for mild TB-IRIS (CIII)
- Needle aspiration of effusions for symptomatic relief
Reminder: Steroids Up Front

• Patients with TB of the CNS or pericardium should receive adjunctive steroids at the time RIPE is initiated (A1)

CNS TB

• Dexamethasone 0.4 mg/kg/day × 4 weeks
• Taper 0.1 mg/kg/day per week × 4 weeks
• Taper 1 mg/day per week × 4 weeks

Pericardial TB

• Prednisone 60 mg daily, tapered by 10 mg every week × 6 weeks

Case 3

- 40 y/o man with HIV p/w word finding difficulty R hemiparesis and seizure. CD4 48.
- LP + JC Virus on PCR
- Started on HAART
- 2.5 months later presented with worsening aphasia and had repeat MRI. CD4 225, VL undetectable.
- HAART held x 2 wks, pt treated with dexamethasone.
- 2.5 yrs later, only mild residual word-finding deficit.

Case and images from Tan and Koralnik. Lancet Neurol. 2010
PML-IRIS

- HIV+ patients co-infected with JC virus with CD4 < 200 may develop Progressive multifocal leukoencephalopathy (PML)

- 10 – 20% of pts develop new or worsening neurologic symptoms following initiation of HAART.

Figure 2: Time to onset of PML-s-IRIS and PML-d-IRIS after initiation of combined antiretroviral therapy

IRIS = immune reconstitution inflammatory syndrome; PML = progressive multifocal leukoencephalopathy; PML-d-IRIS = worsening of preexisting PML; PML-s-IRIS = PML and IRIS simultaneously.

Classic PML

PML-IRIS

FLAIR sequence  T1 post-Gadolinium

Tan and Koralnik. Lancet Neurol. 2010
PML-IRIS

- Mediated by an influx of CD8$^{+}$ T-cells into existing lesions
  - JCV actually less likely to be detected in CSF

- IRIS with PML doesn’t seem to alter survival (1 yr survival rate 54% vs 49% in PML-IRIS vs PML without IRIS).

PML-IRIS: Management

- There are no effective anti-viral drugs for JCV
  - Continue HAART (AIII)

- Steroids are controversial, but recommended for patients with contrast-enhancing lesions on MRI (BIII).
  - Methylprednisolone 1 gm IV daily x 3 days
  - Prednisone 60 mg PO daily, tapered over 6 weeks

- Greatest benefit of steroids is seen when:
  - Started early after recognition of IRIS
  - Tapered over a prolonged course (6-12 weeks)

CMV and IRIS

- Immune reconstitution disease occurs in patients with inactive CMV retinitis who begin ART
  - Immune recovery uveitis (IRU)
    - Anterior uveitis
    - Vitritis
    - Cystoid macular edema
    - Epiretinal membranes
    - Retinal neovascularization

- The most common OI to result in immune reconstitution disease following ART initiation (~38% incidence)

- Symptoms:
  - Anterior chamber: ocular pain and photophobia
  - Posterior chamber: painless floaters and decreased visual acuity
Risk Factors for IRU

- CMV involving >30% retinal surface area at the highest risk
- Treatment of CMV retinitis with cidofovir compared to an alternative regimen
- Almost exclusively occurs in patients with immune recovery to CD4 > 100
  - Does not occur in patients with a virologic response but no immune recovery

Goldberg, et al. Retina. 2005
Management of IRU/IRV

- Corticosteroids and anti-CMV therapy (CIII)

- Anterior chamber: topical corticosteroids

- Posterior chamber: periocular or intravitreal corticosteroid injections

IRIS and Cryptococcus:

- ~20% of patients with cryptococcal meningitis and HIV develop IRIS after initiation of ART.

- Presentation
  - Meningeal (73.7%)
  - Other CNS complications (11%)
  - Lymphadenopathy (11%)
  - Pneumonitis (4.5%)

- Timing: delayed compared to TB (1-10 months)

- The key CSF findings are elevated opening pressure and elevated CSF WBC, with sterile cultures

Risk factors for C-IRIS

- Fungal burden (initial CrAg titer)
- Lack of initial CSF inflammation (CSF WBC < 25 cells/µL and protein < 50 mg/dL)
- Early HAART initiation*
- Baseline HIV viral load and baseline CD4 do not appear to be risk factors

Sungkanuparph S, et al. CID. 2009
Bicanic T, et al. JAIDS. 2009
Boulware DR, et al. JID. 2010
C-IRIS: Management

- Continue ART
- Continue anti-fungal therapy
  - Re-induction with amphotericin B is unnecessary if CSF cultures are negative
- Reduce ICP with serial LP (AII)
- For severe symptoms, a brief course of corticosteroids may be considered (CIII)

- IRIS has been shown to increase mortality from cryptococcal meningitis, mainly in Africa
Kaposi’s Sarcoma and IRIS

- High-risk of IRIS with KS
  - Characterized by enlarging lesions and worsening peripheral edema
- Visceral KS-IRIS can have mortality up to 50%

Achenbach CJ, et al. CID. 2012
KS-IRIS: Management

- Continue HAART (AIII)
- Do not give steroids
  - Causes growth of the tumor
- Chemotherapy is indicated for visceral KS (AI) and can be considered for severe cutaneous KS (BIII)

Correspondence

*Clinical Effect of Glucocorticoids on Kaposi Sarcoma Related to the Acquired Immunodeficiency Syndrome (AIDS)*

Parkash S. Gill, MD; Carmen Loureiro, MD; Marjorie Bernstein-Singer, MD; Mark U. Rarick, MD; Fred Sattler, MD; and Alexandra M. Levine, MD


*Life-threatening exacerbation of Kaposi’s sarcoma after prednisone treatment for immune reconstitution inflammatory syndrome*
Preventing IRIS

- The strongest risk factor for developing IRIS is a baseline CD4 < 100
- The optimal time to initiate ART is before the patient develops advanced AIDS
Initiation of ART in the setting of Acute OI: Advantages

- For some OI’s, initiation of ART is the only effective treatment
  - Cryptosporidiosis
  - Microsporidiosis
  - Progressive multifocal leukoencephalopathy (PML)
  - KS

- Starting ART as secondary prevention: a second OI is less likely to occur if ART is started promptly rather than delaying initiation.
Initiation of ART in the setting of Acute OI: Disadvantages

- ART malabsorption → subtherapeutic serum levels → antiretroviral drug resistance

- ART toxicities vs. disease manifestations vs. OI drug toxicities

- Drug-drug interactions between ART and other antimicrobials

- Renal or hepatic dysfunction from acute OIs → complicated ART dosing

- IRIS
When to Start ART during Acute OI

Late

- Second OI
- ? Increased morbidity and mortality

Early

- Drug Interactions
- Toxicity
- IRIS
In a sub-study published the following year, early ART did not increase the risk of IRIS
What about TB and cryptococcal meningitis?
## TB: Five Randomized Controlled Trials

<table>
<thead>
<tr>
<th></th>
<th>SAPiT</th>
<th>ACTG 5221</th>
<th>CAMELIA</th>
<th>OXTREC 023-04</th>
<th>TB-HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB status</strong></td>
<td>Known</td>
<td>Known/suspected</td>
<td>Known</td>
<td>TB meningitis</td>
<td>Known</td>
</tr>
<tr>
<td><strong>Mean Age</strong></td>
<td>34</td>
<td>34</td>
<td>35</td>
<td>28.5</td>
<td>32</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>429</td>
<td>809</td>
<td>661</td>
<td>253</td>
<td>1675</td>
</tr>
<tr>
<td><strong>CD4 cutoff</strong></td>
<td>&lt;500</td>
<td>&lt;250</td>
<td>&lt;200</td>
<td>&lt;200</td>
<td>&gt;220</td>
</tr>
<tr>
<td><strong>Median CD4</strong></td>
<td>150</td>
<td>77</td>
<td>25</td>
<td>41</td>
<td>367</td>
</tr>
<tr>
<td><strong>Median VL</strong></td>
<td>5.21 log₁₀</td>
<td>5.43 log₁₀</td>
<td>5.64 log₁₀</td>
<td>5.4 log₁₀</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Early ART</strong></td>
<td>Within 4 weeks</td>
<td>Within 2 weeks</td>
<td>Within 2 weeks</td>
<td>Within 7 days</td>
<td>After 2 weeks</td>
</tr>
<tr>
<td><strong>Late ART</strong></td>
<td>Within 8 weeks</td>
<td>8-12 weeks</td>
<td>Within 8 weeks</td>
<td>After 8 weeks</td>
<td>After 6 months</td>
</tr>
<tr>
<td><strong>ART regimen</strong></td>
<td>DDI, 3TC, EFV</td>
<td>TDF, FTC, EFV</td>
<td>d4T, 3TC, EFV</td>
<td>AZT, 3TC, EFV</td>
<td>AZT, 3TC, EFV</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>South Africa</td>
<td>Africa, Asia, N/S America</td>
<td>Cambodia</td>
<td>Vietnam</td>
<td>South Africa, Tanzania, Uganda, Zambia</td>
</tr>
<tr>
<td><strong>Median follow up (months)</strong></td>
<td>17.7</td>
<td>25</td>
<td>25</td>
<td>12</td>
<td>24</td>
</tr>
</tbody>
</table>
## TB: Conclusions

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall mortality benefit for early ART?</th>
<th>Mortality benefit for patients with CD4 &lt; 50</th>
<th>Rates of IRIS increased for early ART?</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPiT</td>
<td>No</td>
<td>Yes</td>
<td>Yes (16% vs 7%)</td>
</tr>
<tr>
<td>ACTG 5221</td>
<td>No</td>
<td>Yes</td>
<td>Yes (11% vs 5%)</td>
</tr>
<tr>
<td>CAMELIA</td>
<td>Yes (but median CD4 25)</td>
<td>Yes</td>
<td>Yes (HR 2.5)</td>
</tr>
<tr>
<td>OXTREC</td>
<td>No</td>
<td>No</td>
<td>More grade 4 adverse events (p=0.04)</td>
</tr>
<tr>
<td>TB-HAART</td>
<td>No</td>
<td>N/A (CD4 &gt; 220 in all)</td>
<td>No (10% vs 10%)</td>
</tr>
</tbody>
</table>

1. ART is recommended for all HIV-infected patients with TB (AI)
2. ART should be started within 2 weeks of TB treatment for patients with a CD4 count < 50 (AI)
3. For all others ART may be delayed 8-12 weeks (AI)
4. ART should be delayed in patients with TB meningitis
Extremely Early ART with TB?

- TB-HAART (CD4 < 200)
  - Randomized to start ART at week 1, 4, or 8
  - No survival benefit to starting ART 1 week after TB therapy
  - Among patients who died during the trial: higher rate of TB treatment interruption due to hepatotoxicity in the week 1 group
## Crypto: Timing of ART

### Zimbabwe study (Makadzange, et al, 2010)

- Early initiation of ART (within 72 hours) versus delayed (>10 weeks) resulted in higher mortality (HR 2.85)
- Cryptococcal meningitis was treated with fluconazole 800 mg daily

### Botswana study (Bisson, et al, 2013)

- Early ART (within 7 days) versus delayed (> 28 days) did not improve the rate of fungal clearance from CSF
- Early ART resulted in a higher rate of IRIS (54% versus 0%)
- Cryptococcal meningitis was treated with amphotericin B 0.7 mg/kg x 14 days

### COAT study (Boulware, et al, 2014)

- Terminated early by the DSMB
- The patients randomized to early ART (1-2 weeks) versus delayed ART (5 weeks) had substantially higher mortality at 26 weeks (45% versus 30%, p=0.03)
- Cryptococcal meningitis was treated with amphotericin B 0.7 mg/kg + fluconazole 800 mg daily x 14 days
When to Start ART During Acute OIs

Early Treatment (< 2 wks):
- *Pneumocystis* pneumonia
- *Toxoplasma gondii* encephalitis
- *Mycobacterium avium* complex disease
- CMV disease
- Esophageal candidiasis
- Bacterial
- TB (CD4 < 50 cells/μL)

Delay Treatment:
- TB (CD4 > 50)
  - Delay 8-12 weeks
- TB meningitis
  - Delay 8-12 weeks
- Cryptococcal meningitis
  - Delay 2-10 weeks
Summary

- Incidence of IRIS ~10-15%.
- Know the risk factors for IRIS (CD4 < 100)
- Presentation varies depending on the OI
- Start HAART within 2 weeks of initiation of OI treatment.
  - TB – start within 2 weeks if CD4 < 50, otherwise delay 8-12 weeks
  - TB meningitis – delay 8-12 weeks regardless of CD4
  - Cryptococcal meningitis – delay 2-10 weeks
- Management of IRIS
  - NSAIDs and steroids
  - Continue HAART
- Prevention: initiate HAART before the development of advanced AIDS
Questions?