Immune Reconstitution Inflammatory Syndrome (IRIS): How to Prevent, Recognize, and Treat It

William R. Short, MD, MPH, AAHIVS
Associate Professor of Medicine
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA
Disclosures

• No disclosures related to this presentation
• Very little discussion of TB-IRIS
Objectives

• Upon completion of this educational activity, participants should be better able to:
  – Recognize risk factors for immune reconstitution inflammatory syndrome (IRIS).
  – Identify key strategies for the clinical management and treatment of IRIS.
Case 1

- A 20 year old male presents for a new patient appointment (11/20/15)
- Diagnosed about 1 year prior to his first appointment
- Born and raised in Philadelphia, no recent travel, no incarceration
- Exam-oral candidiasis, prurigo nodularis
- CD4 count-8/2% cells/mm3
- HIV RNA-277,240 copies/ml
- HIV-1 Genotype-wild type (no integrase mutations)
- HLA-B*5701-negative
- Quantiferon TB Gold-negative
- Serum Cryptococcal antigen-negative
- Started on Lamivudine/Abacavir/Dolutegravir as well as PCP and MAI prophylaxis
CD4 level and Risk of Opportunistic Infections (OIs)

http://courses.inmed.us/self-paced_courses/international_hiv_medicine/opportunistic_diseases_1p.asp
Outpatient Course

• 11/24/15 (2 weeks)
  – CD4-283/24%
  – HIV RNA-2000 copies/ml

• 12/22/15 (4 weeks)
  – HIV RNA-343 copies/ml

• 2/2/16 (3 months)
  – CD4-237/22%
  – HIV RNA-88 copies/ml
3 month visit
Case 1 (continued)

- He went to radiology to get a CT scan
- While waiting for approval from the insurance company, he decided to leave and go to ED
- CT scan-grossly enlarged rim-enhancing lymph nodes with internal necrosis/suppuration L>R
- CXR-clear
- Needle aspirate by IR-acute inflammation/necrosis/negative for malignancy
  - few AFB by acid fast stain
  - No fungal elements
Question

• While waiting for the AFB culture, what is your next step?
  • A. Start treatment with a Macrolide and Ethambutol
  • B. Start treatment with Macrolide, Ethambutol, and Rifabutin
  • C. Start empiric TB treatment with RIPE
  • D. Hold all treatment pending cultures
  • E. Something else
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/sp-obb5y6
IRIS: definition

• IRIS is:
  – An illness occurring in an HIV+ person with temporal relationship to ART initiation
  – Associated with a decline in HIV RNA and a rise in CD4 count
  – Presentation with an unusual inflammatory course
  – Exclusion of alternate causes (progression of an opportunistic infection, drug toxicity, etc)

IRIS: two types

• **Paradoxical**: IRIS occurring when an opportunistic infection, responding to treatment before ART, deteriorates after starting ART

• **Unmasking**: disease that was cryptic prior to starting ART and now presents with inflammatory symptoms
  – Unmasking of a previously untreated infection
  – Our case

Historical Picture of IRIS

- Paradoxic reactions among HIV-negative patients treated for Mycobacterium Tuberculosis infection
- Inflammatory reactions occurring in patients on treatment for *Mycobacterium leprae*
- Recovery of immune cells following bone marrow transplantation or chemotherapy
- Atypical, localized MAC Inflammatory responses in patients when they were treated with AZT monotherapy
IRIS: Pathogenesis

**Chronic HIV infection and subsequent complex immunodeficiency**
- Favour opportunistic infections, leading to high antigenic exposure
- Create a pro-inflammatory environment due to chronic immune activation and tissular damage

**Antiretroviral therapy**

**ART-induced immune recovery**
- Lymphopenia-induced proliferation of pathogen-specific memory T cells
- Recovery of innate immune functions

**Effector-memory CD4 and CD8 T cells could represent a common thread of IRIS**
- While other effector mechanisms may depend on the underlying pathogen:
  - Activated IFNγ+ effector-memory CD4 T cells are dominant during TB-IRIS (and C. neoformans-IRIS)
  - CD8 T cells in virus-related IRIS
  - Macrophages, TCRγδ T cells and NK cells have been implicated in TB-IRIS

**Immune-mediated inflammatory tissue damage**

*Martin-Blondel, Curr Opin Infect Dis, 2012*
Onset of IRIS

Fig. 1. Time to diagnosis of IRIS after starting HAART. IRIS, immune reconstitution inflammatory syndrome; HAART, highly active antiretroviral therapy.

Source: AIDS 2005, Vol 19 No4 ;399-406, Samuel A. Shelburne et al
Risk Factors for HIV IRIS?
# IRIS: Risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced HIV</td>
<td>Low CD4 count</td>
</tr>
<tr>
<td></td>
<td>High HIV RNA</td>
</tr>
<tr>
<td>High pathogen or antigen burden</td>
<td>Disseminated infection</td>
</tr>
<tr>
<td>Strong response to ART</td>
<td>Large drop in plasma HIV RNA</td>
</tr>
<tr>
<td></td>
<td>Marked increase in CD4 count</td>
</tr>
<tr>
<td>Short interval between treatment of an OI and initiation of ART</td>
<td></td>
</tr>
<tr>
<td>Other factors</td>
<td>Host genetics</td>
</tr>
<tr>
<td></td>
<td>ART naïve</td>
</tr>
<tr>
<td></td>
<td>Low Hemoglobin</td>
</tr>
</tbody>
</table>
## Presentation of IRIS

<table>
<thead>
<tr>
<th>Major Presentations</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tuberculosis</strong></td>
<td>- Patients responding to TB treatment may have worsening of pulmonary symptoms or X-ray findings suggestive of worsening TB disease, enlarging lymph nodes, or meningeal symptoms - can also see hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td><strong>Mycobacterium avium complex</strong></td>
<td>- May present as localized lymphadenitis, pulmonary disease, or systemic inflammation that are indistinguishable from active MAC - usually not bacteremic</td>
<td></td>
</tr>
<tr>
<td><strong>Cryptococcus</strong></td>
<td>- worsening of meningitis symptoms</td>
<td></td>
</tr>
<tr>
<td><strong>Cytomegalovirus</strong></td>
<td>- presents as retinitis, vitritis, or uveitis - IRIS dies to CMV can cause rapid and permanent vision loss - time is variable, the median time was 20 weeks after initiation of ART</td>
<td></td>
</tr>
</tbody>
</table>
Presentation of IRIS

<table>
<thead>
<tr>
<th>Presentations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B or C</td>
<td>- Transient elevations in transaminases may occur after initiation of ART with IRIS and may be difficult to distinguish from drug-induced hepatitis - usually mild and self-limited - may result in decompensation in someone with preexisting cirrhosis</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>- Lesions may be unmasked or worsen</td>
</tr>
<tr>
<td>Varicella zoster or Herpes simplex virus</td>
<td>- These can reactivate after initiation of ART</td>
</tr>
<tr>
<td>Dermatologic conditions</td>
<td>- Number of conditions can occur such as folliculitis and oral and genital warts</td>
</tr>
</tbody>
</table>
Figure 1. Clinical spectrum of 139 IRIS events by mode of presentation (paradoxical or unmasking) and underlying diagnosis.

http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0040623
Case-Question

- Would you stop his ART?
- A. Yes
- B. No
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/spwwddg0
When to stop ART

• Published clinical experience suggests that it is reasonable to continue ART in the majority of cases.
• Mild to moderate symptoms may be tolerable and patients can be reassured that symptoms will resolve over time.
• ART should be discontinued and hospitalization may be required in patients who experience life-threatening IRIS or in whom localized symptoms threaten to cause permanent sequelae
  – Airway obstruction from an enlarging mass

Case-Question

• While waiting for the AFB culture, would you add steroids?
• A. Yes
• B. No
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/sp-lsapnx
What is the role of Steroids?

• There are no controlled trials evaluating the role of corticosteroids or non-steroidal anti-inflammatory agents (NSAIDS) for non-TB IRIS

• There are multiple case reports and case series suggesting these agents may have efficacy in decreasing the inflammatory response associated with IRIS

• Must weigh the risks/benefits

• Prednisone 1mg/kg/day (max 60-80mg/d) with a rapid taper over 10-14 days (expert opinion)
Case 1 (continued)

- Started on Azithromycin, Ethambutol, and Rifabutin in the hospital without steroids
- Came back to the office, with no change in the size
- I started him on Prednisone 1mg/kg/day
- Within 2 weeks, the edema was significantly improved
- CD4-300/24% and HIV RNA 0
1 month after starting steroids
Case 2

• 34 year old male presents with fever, headache, dry cough, 20 pound weight loss, progressive DOE over the last 3 weeks.
• Never tested for HIV
• No past medical history
• He works as a travel agent.
• No Etoh/IDU/crack use
• Sexually active with men
• History of Gonococcal urethritis 6 years ago (treated)
Case 2 (continued)

- 4th generation HIV test Positive Ag/AB
  - Reactive on multispot for HIV-1
- CD4 count- 30 cells/mm³
- Viral Load-250,000 copies/ml
- Bronchoscopy performed and the silver stain is positive for PCP
Question

While on rounds, the resident ask you if you should start antiretroviral therapy on this patient?
A. Treat the OI first and start HAART within 2 weeks.
B. Defer HAART until the patient has been established in the office.
C. Call an ID consult.
D. Not sure.
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/phqs82z
Immediate vs. deferred ART in the setting of Acute Opportunistic Infection: ACTG 5164

- Randomized Phase IV strategy trial in US, South Africa
- Determine the optimal timing of ART in the setting of an acute OI or serious bacterial illness
- Comparison of immediate (2 weeks) vs. delayed (45 days) ART
- Included confirmed or probable diagnoses of OIs and bacterial infections for which antimicrobial therapy are available

ACTG 5164: Immediate vs. Delayed ART with an Acute OI

• 228 pts with a treatable OI
  • Most common OI: PCP (63%)
  • TB excluded
  • Small number cryptococcal meningitis, Toxoplasmosis

• AIDS progression/death: immediate rx (14%) vs. delayed rx (24%)

• No difference in safety/toxicity, IRIS, or week 48 responses

ACTG 5164: Summary and Recommendations

• Immediate ART compared to deferred
  – Results in less AIDS progression or death
  – More rapid CD4 cell increase
  – Equivalent virological response by 48 weeks
  – Requires somewhat more ART changes
  – No difference in safety
  – No difference in IRIS

• TB was not included. Small numbers of Cryptococcal meningitis, Toxoplasmosis

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 800mg

• **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

• **Secondary analyses:**
  – Mortality increased if change in mental status at presentation (GCS <15): HR 3.0
  – Mortality increased if CSF WBC <5/ul at presentation: HR 5.1
  – Trend toward increase IRIS in the early group: 13% vs. 10%

• **Recommendations:**
  – Anti-cryptococcal therapy should always come before ART
  – In general, start ART at 4 weeks
  – Consider a delay of ART until 5-6 weeks if change in mental status at presentation or if CSF WBC <5/ul

### Considerations in Starting ART during an Acute Opportunistic Infection

<table>
<thead>
<tr>
<th>Opportunistic Infection</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCP</td>
<td>Art should be initiated within 2 weeks of diagnosis of PCP.</td>
</tr>
<tr>
<td>Esophagitis (candida)</td>
<td>No data.</td>
</tr>
<tr>
<td>Disseminated mycobacterial infection</td>
<td>ART should be started as soon as possible after the first 2 weeks of starting MAC therapy.</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>No data: Most physicians would initiate ART within 2-3 weeks after a diagnosis of Toxoplasmosis.</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>Art should be initiated as soon as possible.</td>
</tr>
<tr>
<td>Cryptococcal Meningitis</td>
<td>Controversial</td>
</tr>
<tr>
<td></td>
<td>-the timing of ART administration should be considered between 2 and 10 weeks after the start of antifungal therapy with the precise starting dates based on individual conditions and local experience</td>
</tr>
</tbody>
</table>

Take Home Points

• IRIS is an inflammatory disease that occurs in the context of initiating ART and be classified as paradoxical or unmasking
• The clinical features of each individual case are highly variable
• There are no clear published guidelines to assist
• Management generally includes continuation of treatment of OI and ART plus supportive care +/- corticosteroids
• Outcomes are generally good with low mortality, exceptions being cryptococcal meningitis
ACTHIV 2016: A State-of-the-Science Conference for Frontline Health Professionals