Immune reconstitution inflammatory syndromes in HIV-infected patients:

Does HAART hurt?

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(1) The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

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Immune Reconstitution Inflammatory Syndrome (IRIS)

- Definition
- Epidemiology
- Clinical presentation
- Risk factors and pathogenesis
- Management and outcomes
IRIS: Immune reconstitution inflammatory syndrome

- **Synonyms**
  - Immune restoration disease
  - Immune reconstitution syndrome

- **Occurs in non-HIV as well**
  - BMT, chemotherapy
  - *M. tuberculosis*, leprosy

- **1st described in HIV+ patients with atypical MAC after zidovudine**
IRIS
General definition

• Paradoxical clinical worsening related to recovery of the immune system following immunosuppresion

• Can be due to
  – Subclinical opportunistic pathogen
  – Previously known pathogen on treatment

• Controversial whether degree of response to HAART is part of definition

Types of IRIS

• “Unmasking”
  – Clinical worsening due to a previously undiagnosed subclinical opportunistic pathogen

• “Paradoxical”
  – Clinical worsening due to a previously known opportunistic pathogen responding to therapy

• Both require adequate response to HAART

Categories of IRIS

- Infectious
- Sarcoid-like
- Autoimmune
  - Polymyositis, lupus, rheumatoid arthritis, Grave’s disease, Guillan-Barre syndrome
- Other (case reports)
  - Tumor-related (Kaposi’s sarcoma)
  - Interstitial pneumonitis

Infectious causes of IRIS

- **Mycobacterial**
  - Tuberculosis, MAI

- **Fungal**
  - *P. jirovecii*, Cryptococcus, Histoplasma

- **Viral**
  - CMV (pneumonitis reported)
    - Hepatitis B+C
    - Herpes, PML

- **Parasitic: Rare reports**
Immune Reconstitution
Inflammatory Syndrome (IRIS)

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Incidence of IRIS

- Retrospective studies
- 15-25% of all patients on HAART
- 15-45% of patients with underlying OI

Proportion of patients with IRIS according to OI

Prospective incidence of IRIS

- 1st prospective study from South Africa
- 423 HAART-naïve patients
  - 6-month f/u after HAART initiation

- IRIS diagnosed in 10.4% of patients
  - 25.1 cases per 100 person-years
  - 80% attributed to “unmasking” IRIS
  - 20% attributed to “paradoxical” IRIS

IRIS diagnoses by disease

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Timing of IRIS

Early (<12 weeks) vs. Late (>12 weeks)

South Africa:
- Median onset of 48 days
- 75% of cases within 90 days of HAART
- Follow-up limited to 6 months

IRIS
*Mycobacterium tuberculosis*

- Majority with known antecedent TB
- Typical presentation
  - Fever
  - Thoracic, cervical lymphadenopathy (71%)
  - Pulmonary infiltrates (28%)
  - Worsening in areas of prior disease (50%) or new manifestations

IRIS
Mycobacterium tuberculosis

• Less commonly
  – Cerebritis
  – Pleural effusions
  – Hepatosplenomegaly
  – Hypercalcemia

• Time course
  – 1st 2 months, usually in 1st 2-3 weeks

• Histology
  – Tissue necrosis and granulomatous inflammation

IRIS
*Mycobacterium avium intracellulare*

- Majority without prior known infection
- Typical presentation
  - Fever, painful lymphadenitis (often cervical or abdominal)
- Pulmonary disease (19%)
  - Infiltrates or inflammatory masses, endobronchial lesions

IRIS
*Mycobacterium avium intracellulare*

- **Time course**
  - Usually within 12 weeks of HAART

- **Findings**
  - Granulomatous inflammation
  - Tissue cultures but not blood cultures usually positive for MAC (atypical)

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IRIS

Cryptococcus

• Presentation
  – Meningitis (most common), typically early
  – Lymphadenitis (~10% of cases), often later
  – Lung nodules, necrotizing pneumonia
  – Hypercalcemia may be seen

• Biopsy of nodes, tissue in later cases
  – Cryptococcus and granulomas
  – Cultures sterile

Shelburne et al. CID 2005:40;1049-52.
IRIS

*Pneumocystis jirovecii*

- Worsening respiratory failure in 5-30d
- 1 day to 5 weeks after HAART
- Findings
  - Fever, increasing hypoxia
  - CXR – alveolar opacities
  - Biopsy – non-specific inflammation, intense CD4+, CD8+ T-cell infiltration (n=1)
  - BAL – increased lymphocytes, high CD4/CD8 ratio

PCP and IRIS

Initial CXR

Follow-up CXR

PCP treatment for 18 days
5 days of HAART
Potential risk factors

- Stopping steroids prior to HAART
- Severe PCP on presentation (pO2 < 70)
- Marked decrease in HIV viral load
- Close proximity of HAART to PCP treatment

IRIS and sarcoid

• Sarcoidosis considered rare in HIV due to depletion of CD4+ T-cells

• Sarcoid or sarcoid-like disorder reported following start of HAART
  – May be delayed by months to years

• General presentation and findings similar in HIV+ as in HIV-

Foulon et al.  CID 2004;38:418-25.
Sarcoid in HIV: Late-phase IRIS?

- HIV infection present for years
  - Average of 92 months
- HAART duration >1 year
- Most patients have higher CD4 and suppressed HIV viral load
  - CD4 >200 in 74% of cases reported
  - Median CD4 >400
  - Median HIV viral load 466 copies/mL

Foulon et al. CID 2004;38:418-25
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Potential risk factors for IRIS

• **Baseline factors**
  - Initial CD4 < 50 cells
  - Higher baseline HIV viral load
  - Active OI at time of initiating HAART
  - Initiation of HAART in close proximity to OI

• **Less consistently**
  - Decreased baseline CD4/CD8 cell ratio
  - Younger age

Potential risk factors for IRIS

• **Response to therapy**
  – Rapid fall in HIV viral load in 1st 12 weeks
  – Rapidity of rise in CD4 cell count
  – Magnitude of CD4 cell count increase

• **Not consistent in all studies**

Theories regarding pathogenesis

1. Normal response to high antigen burden
2. Exaggerated response by recovering immune system
3. Excessive pro-inflammatory cytokines
4. Deficiency in immune regulatory cytokines

Host and pathogen factors

- **Antigenic stimulus for IRIS**
  - Mycobacteria, viruses, parasites, tumors
  - Viable vs. nonviable organisms

- **Genetic predisposition** (cases of TB, HSV)
  - Polymorphisms in MHC complex and cytokine genes - clearance of organisms, dysregulated inflammatory responses

- **Duration since initiation of HAART**

CD4 cell recovery in HAART responders

Initial release of memory CD4 cells from lymphoid tissue

2nd phase: thymus-dependent expansion of naïve CD4 cells

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IRIS: A diagnosis of exclusion

Differential diagnosis

• Worsening of initial diagnosis
  – Drug resistance
  – Inadequate drug levels – malabsorption, wrong dosing, non-adherence

• Secondary process
  – Infectious vs. non-infectious
  – Drug reaction
Differentiating IRIS from OI

Early IRIS

- Initial clinical improvement from OI
- CD4 and virologic response to HAART
- Atypical manifestations of OI

Failure of HAART

- Poor CD4 and virologic response to HAART
- Typical manifestations of OI

Late IRIS

- CD4 and virologic response to HAART
- Atypical manifestations of OI

Failure of HAART

- Poor CD4 and virologic response to HAART
- Typical manifestations of OI

Incomplete immune recovery

- Persistent immune defects to specific OI’s

IRIS: Management

• In most cases HAART can be continued
• No randomized clinical trials to guide use of steroids, other anti-inflammatory agents
• OI guidelines
  – “…adding nonsteroidal anti-inflammatory agents or corticosteroids to alleviate the inflammatory reaction is appropriate”
• Particularly of concern in CNS disease or if lesions are life-threatening

IRIS Management

- Non-steroidal anti-inflammatory drugs
- Leukotriene inhibitors - case reports
  - “urticarial IRIS”
  - IRIS associated with TB and syphilis
  - Role of leukotrienes in pathogenesis

When should HAART be initiated?

- Risk of new OIs
- Morbidity
- Mortality

Delayed HAART

- Multiple toxic drugs
- Drug interactions
- Adherence
- IRIS

Early HAART
Timing of HAART

• TB: If CD4 <350, recommended to wait 4-8 wks on therapy prior to HAART
  – Decrease severity of paradoxical reactions
  – Improve adherence
  – Evaluate and manage side effects

• Await response to OI rx before HAART in MAC, PCP, cryptococcal meningitis

Benson et al. MMWR 2004;53:1-112
When should HAART be initiated?

O1 screening, such as sputum smears for TB; need to await culture results?

Prophylactic anti-inflammatorys?

Approach dependent on O1, region, genetic predisposition?

Delayed HAART  Early HAART
IRIS Outcomes

Deaths reported with IRIS from TB, cryptococcus
- CNS disease
- Disseminated disease

Park et al.  AIDS 2006;20:2390-2392.
IRIS
Outcomes

• Prospective study from S. Africa
• Most IRIS cases were mild
  – HAART discontinued in 3 patients (7%)
  – Corticosteroids in 4 patients (9%)
  – Hospitalization in 12 patients (27%)
  – 2 deaths attributed to IRIS

IRIS: Summary

• Diagnosis of exclusion
• Can occur days to months after HAART
• Infectious IRIS most common (TB)
  – Sarcoid, autoimmune diseases
• Potential risk factors:
  – Low baseline CD4, active OI
  – Initiation of HAART in close proximity to OI
  – Rapid response to HAART (viral load, CD4)
IRIS: Summary

• **Treatment**
  – Targeted at the underlying infection
  – Steroids, anti-inflammatory agents
  – Current recommendation to await response to OI treatment prior to HAART

• **Outcome generally good**
  – Limited morbidity
  – Rare mortality reported (CNS disease)