

Immune Reconstitution Inflammatory Syndrome (IRIS): The Price of Progress

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Objectives

- 1. Recognize IRIS in HIV-infected patients in order to initiate timely treatment
- 2. Appropriately manage a patient presenting with IRIS

Case 1

- J.S is a 32 year old male newly diagnosed with HIV/AIDS with a CD4 count of 20/2% cells/mm³ and VL 900,000 copies/ml
- Pt is started on co-formulated emtracitabine, tenofovir, and efavirenz (Atripla)
- He returns to the clinic 4 weeks after starting his new regimen and has developed swelling of his neck.
- He denies pain, weight loss, night sweats, fever, or chills
- His repeat CD4 count is 100/7% cells/mm³ and his HIV Virus load is 900 copies/ml

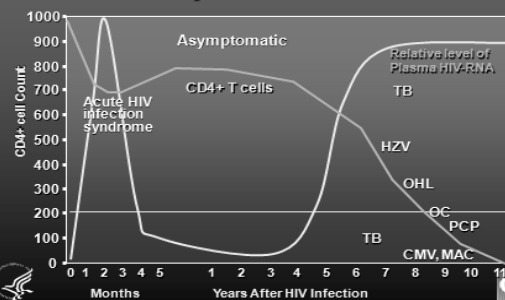
Case 1



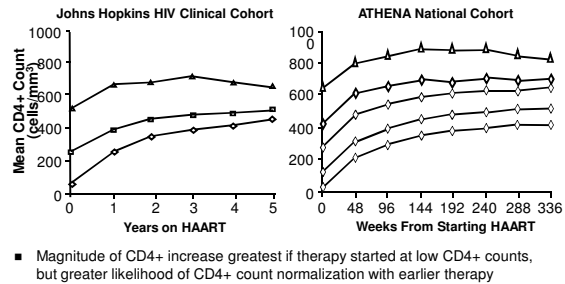
Question

- What is the most likely diagnosis?
- A. Lymphoma (NHL or Hodgkins)
 - B. MAC lymphadenitis
 - C. Kaposi's Sarcoma
 - D. Other

Natural Course of HIV Infection and Common Complications



CD4+ Count Response Based on Baseline CD4+ Count



Keruly J, et al. CROI 2006. Abstract 529. Gras L, et al. CROI 2006. Abstract 530.

Immune Reconstitution Disease

- **Case Definition:**
 - A paradoxical deterioration in clinical status after initiating highly active antiretroviral therapy (HAART) attributable to the recovery of the immune response to latent or subclinical infectious or non-infectious processes
- **Other Nomenclature**
 - Immune reconstitution inflammatory syndrome (IRIS)
 - Immune restoration/restition/recovery disease
 - Immune rebound illness
 - HAART attacks

Two Distinct Scenarios

- **1. Unmasking IRIS**-improving immune system interacts with occult, viable organisms already present resulting in clinical deterioration
 - Patients with advanced disease prior to ART are unable to mount an effective immune response against pathogens that are present → ART → improved immune function → evoke an immune response → inflammatory response
 - **Unmasking**-transition from subclinical to symptomatic infection

Two Distinct Scenarios

- **2. Paradoxical IRIS**-active infection is not present
 - Recrudescence of a successfully treated infection
 - Caused by activation of the immune system against persistent antigens present as debris or dead organisms
 - Typically, sterile cultures

Consensus Case Definition of IRIS

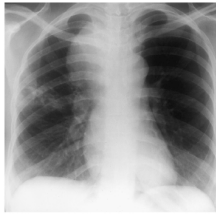
- Evidence of a clinical response to ART with:
 - a) virologic response with $> 1 \log_{10}$ copies/ml decrease in HIV RNA
- Infectious or inflammatory condition temporally related to the initiation of ART
- Symptoms cannot be explained by:
 - a) an alternate infection or neoplasm
 - b) treatment failure of an opportunistic infection
 - c) adverse drug reaction
 - d) non-compliance

International Network for the Study of HIV related IRIS

Case 2

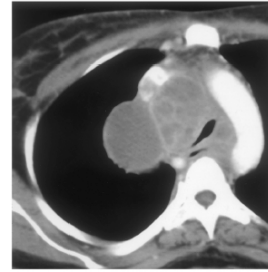


Commenced on anti-TB Tx + HAART



2-months later

Symptoms:
- Stridor



6 x 7 cm nodal mass
Displacement/compression of trachea

Case 3



Initiation of HAART



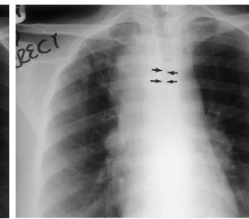
10 days later

Symptoms:
Fever, dyspnea,
pleural effusion

Case 4

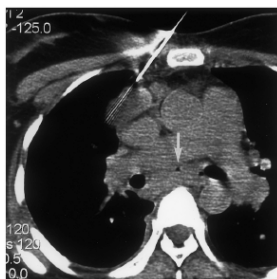


Baseline



7 months later

Symptoms:
Fever, lymphadenopathy



CT Scan
Significant lymphadenopathy

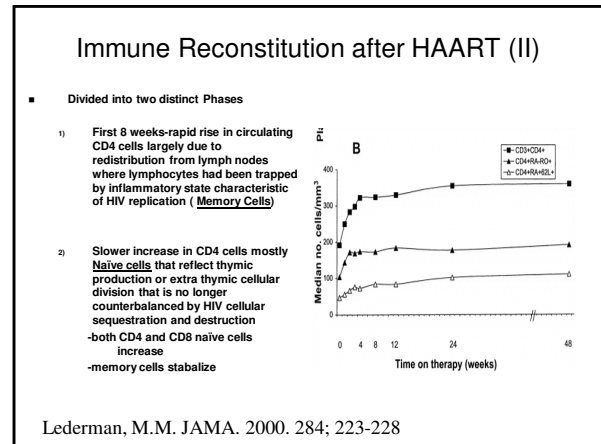
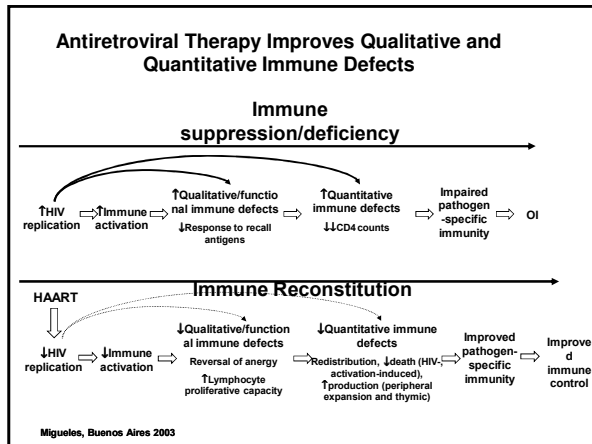
Immune Reconstitution Syndromes

■ Infectious

- Mycobacterium avium complex
- Mycobacterium tuberculosis
- Cryptococcus neoformans
- Human herpes viruses
 - Cytomegalovirus
 - VZV
 - HSV
 - HHV-8 (Castleman disease and Kaposi sarcoma)
 - EBV
- Pneumocystis jirovecii
- Histoplasma capsulatum
- Hepatitis B and C
- JC virus (PML)
- Bartonella henselae
- Microsporidiosis
- Toxoplasma gondii
- Leishmania major
- Mycobacterium leprae (BT)
- HPV-condyloma acuminata

■ Malignancies/Non-Infectious

- Lymphoma
- Sarcoidosis
- Graves disease
- Systemic Lupus Erythematosus
- Rheumatoid arthritis
- Polymyositis
- Reiter's syndrome
- Alopecia universalis
- Vasculitis
- Guillain-Barre' syndrome
- Gastrointestinal inflammation
 - Appendicitis
 - Cholecystitis
 - Splenitis
- Dermatoses
 - Eosinophilic folliculitis
 - Hyperergic/allergic reactions



Case 1

Case

- The patient is referred for a biopsy
- The pathology shows non-caseating granulomas
- AFB blood cultures isolate MAC after 23 days

Question

- What is your approach to treatment?
- A. Stop ART, no anti-MAC therapy
- B. Continue ART, no anti-MAC therapy
- C. Continue ART, start anti-MAC therapy
- D. Stop ART, start anti-MAC therapy

•IRIS secondary to MAC

- MAC infection presents in advanced disease and is characterized by disseminated disease with either positive blood cultures or bone marrow cultures
- MAC related IRIS-biphasic presentation
 - A. early-several weeks
 - Local lymphadenitis
 - B. later-as long as 25 months
 - Focal involvement of deep organ or soft tissue structures

Changes in OIs Manifestations with HAART

(Tantisriwat W et al : AIDS Reader 122-30,1999)

MAC	■ Localized lymphadenitis
M Kansasi	■ Mediastinal adinitis, osteomyelitis, arthritis
CMV	■ Vitritis, retinitis with ↑ CD4
Viral hepatitis (B,C)	■ Worsening hepatitis
TB	■ Paradoxical reaction
VZV	■ Acute retinal necrosis, ↑ shingles
Cryptococcus	■ Recurrent of meningitis, Pulmonary and cutaneous cryptococcosis

IRIS Treatment Strategies

Clinical Severity

- Mild
- Moderate
- Severe

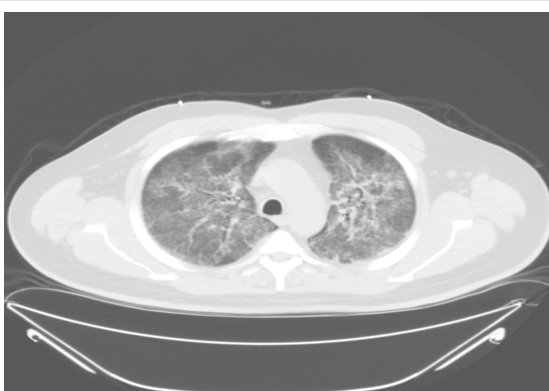
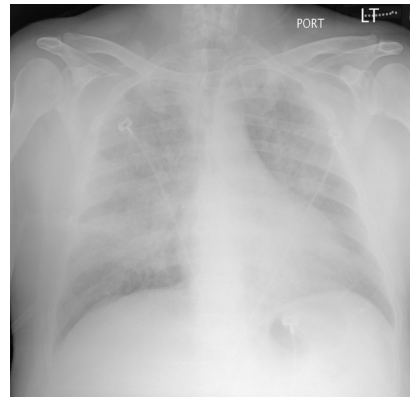
Treatment Options

- Observation
- NSAIDS
- Corticosteroids
- Temporary Cessation of ART
- Surgical debulking

No treatment has been prospectively studied!!

Case 5

- 52 year old AA gay white male presents to TJUH with a two week history of increasing SOB
- Last HIV test 10 years ago (negative)
- Rapid HIV test positive-later followed by positive western blot
- CD4 count 35 cells/mm³ and VL 200,000 copies/ml



Case Continued

- He is started on Trimethoprim-Sulfamethaxazole 5mg/kg IV every 6 hours, a fluoroquinolone, and methylprednisolone
- The resident calls you and wants to know if she should start the patient on ART.

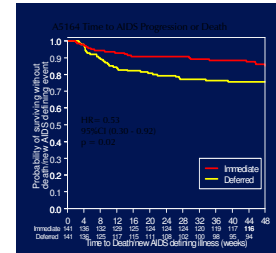


Question

- What is your response?
 - A. No wait 4-6 weeks post OI treatment
 - B. No. wait 8 weeks post OI treatment
 - C. yes start emtricitabine, tenofovir, and boosted protease inhibitor
 - D. not sure call Dr Kathleen Squires for a stat consult

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

- 228 pts with a treatable OI/bacterial infection diagnosed within 14 days randomized to start ART within 48 hours vs. after 4 weeks
- Most common OI: PCP (63%)
- Pt's with tuberculosis excluded
- AIDS progression/death: immediate rx (14%) vs. delayed rx (24%)
- No difference in safety/toxicity, IRIS, or week 48 responses



Zolopa CROI 2008, abstract #142

Acute Cryptococccal Meningitis

- Randomized clinical trial at Parinyenyatwa Hospital in Zimbabwe
- Study population: HIV + patients with CM treated with fluconazole (N=54)
- Study treatment: early ART (within 72 hours of diagnosis) or delayed ART (10 weeks after fluconazole)
- Results: 62% mortality rate overall
 - 82% (early ART) vs. 37% (late ART); HR of death 2.36 (95% CI 1.12, 4.97)
- Conclusion: early ART led to increased mortality

Makadzange CROI 2009 #36cLB

Conclusion

- IRIS is a recognized complication of ART
- The onset is variable
- The incidence of IRIS depends on the patient population, being higher in pt's with greater burden of infection and advanced disease
- The best approach to treatment of IRIS is unknown but anti-inflammatory agents such as NSAIDs or corticosteroids are anecdotal cornerstones of therapy
- The optimal time to start ART in the setting of an OI is changing

