Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV Infection: Beyond What Meets the Eye

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IRIS: beyond what meets the eye

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Learning Objectives

After attending this presentation, learners will be able to:

- Identify IRIS as a potential complication of immune restoration in HIV infection in patients with severe lymphopenia
- Describe how IRIS can present in HIV clinically and how best to approach it diagnostically (diagnosis of exclusion)
- Describe the basic pathophysiology of IRIS and strategies for management

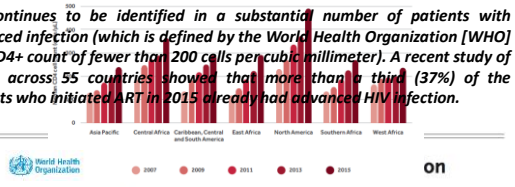
Slide 4 of 36

Outline

- IRIS in the ART era
  - Definition
  - Presentations
  - Pathogenesis
  - TB, MAC, Cryptococcus
  - Prevention and treatment considerations
- Case presentations
  - Questions

Late presentation of HIV: does it (still) exist?

HIV continues to be identified in a substantial number of patients with advanced infection (which is defined by the World Health Organization [WHO] as a CD4+ count of fewer than 200 cells per cubic millimeter). A recent study of trends across 55 countries showed that more than a third (37%) of the patients who initiated ART in 2015 already had advanced HIV infection.

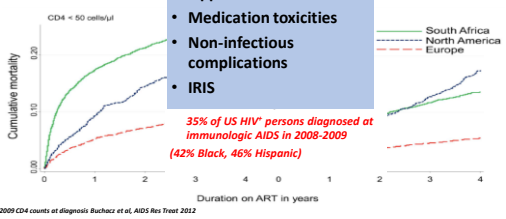


Source: Prepared for the IeDEA-WHO collaboration; global analysis of retention in care in initial HIV care and treatment program, on behalf of the IeDEA Consortium by Nathan Ford, M.P.H., Ph.D., and Meg Doherty, M.D., Ph.D.

Nathan Ford, M.P.H., Ph.D., and Meg Doherty, M.D., Ph.D.

Early morbidity and mortality after ART initiation in severe lymphopenia

- Opportunistic infections
- Medication toxicities
- Non-infectious complications
- IRIS



35% of US HIV+ persons diagnosed at immunologic AIDS in 2008-2009
(42% Black, 46% Hispanic)

HOPS 2000-2009 CD4 counts at diagnosis Buchacz et al, AIDS Res Treat 2012

Immunodeficiency at start of ART: the persistent problem of late presentation to care
Nathan Ford, Edward J. Mills, Matthias Egger, CID, Dec 2014

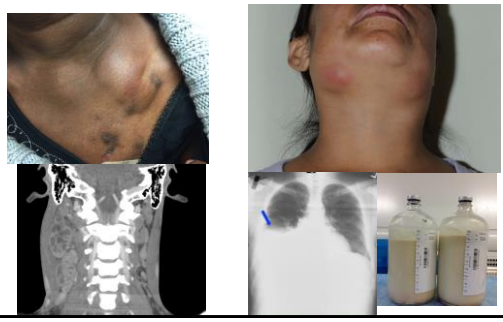
Boulle A et al. PLoS Med 2014 Sep 1;73(1):1-10.

Immune Reconstitution Inflammatory Syndrome (IRIS)

- Worsening of manifestations or abrupt/atypical presentation of infection when HIV patients start ART
- Paradoxical (pre-existing) or Unmasking (occult)
- Incidence ~3% to almost 50%
- Typically within 6 months of ART
- Successful HIV virologic suppression
- Successful microbiologic outcome (paradoxical)
- Three major clinical predictors:
  - ✓Severe CD4 lymphopenia at ART initiation
  - ✓Pre-existing OI (even if subclinical)
  - ✓Shorter treatment of OI pre-ART

IRIS

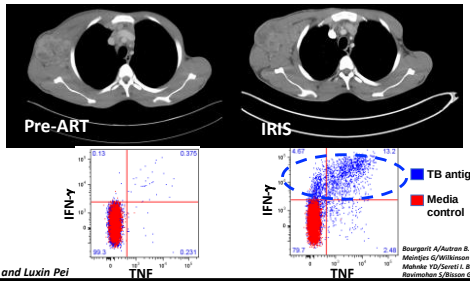
Chang et al, Curr HIV/AIDS Rep. 2014, Sereti et al, Curr Opin HIV AIDS. 2010, French et al CID 2009



Pathogenesis of IRIS

The role of T cells, monocytes and metabolism

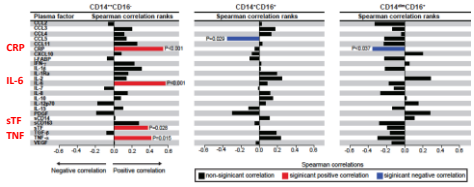
Rapid expansion of activated CD4+ T-cells during TB-IRIS



Bourgarit A/Autran B. AIDS. 2006
Meintjes G/Wilkinson RJ. AIRCCM 2008
Mahnke YD/Sereti I. Blood 2012
Ravimohan S/Bisson GR CID 2015

Denise Hsu and Luxin Pei

Inflammatory monocytes are strongly associated with CRP, IL-6 and TNF pre-ART in IRIS

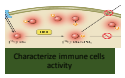


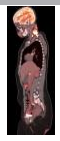
Increased inflammatory cytokines in IRIS incl TNF, IL-6 (CRP), IL18, IFNγ

Andrade et al, PLoS Pathog, 2014

In vivo imaging modalities: ^{18}F-FDG-PET

Positron emission tomography (PET): imaging technique that uses short-lived radioactive substances injected into patients to produce powerful images of the body using specialized scanners



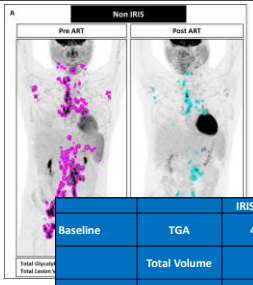


Standardized uptake value (SUV)

$$SUV = \frac{r}{(a'/w)}$$

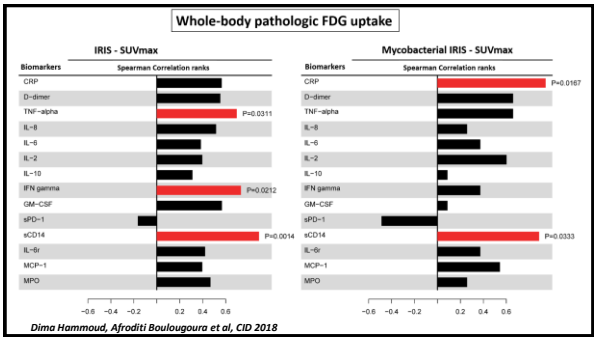
r = radioactivity conc in ROI as measured by scanner
a'= decay corrected injected radioactivity
w = patient's weight

Hammoud et al, Clinical Infectious Diseases, Volume 68, Issue 2, 15 January 2019



		IRIS (N=10)	Non-IRIS (N=20)	P-value
Baseline	TGA	404.7	106.4	0.017
	Total Volume	68.9	20.0	0.029
	SUVmax	20	12.1	0.010

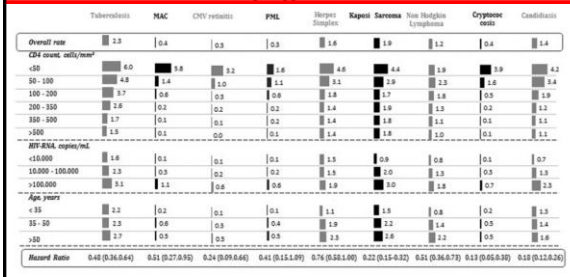
Dima Hammoud, Afroditi Boulougoura et al, CID 2018



Dima Hammoud, Afroditi Boulougoura et al, CID 2018

Diagnosis and Definitions

IRIS and underlying disease



Incidence rates of AIDS-defining events per 1000 person-year of follow-up, HIV-CAUSAL Collaboration 1996–2013

IRIS and Tuberculosis

- Incidence varies between 7-50%
  - Association with timing of ART in most reports
  - 2 to 6 weeks post-ART
  - Higher incidence in very low CD4 counts (<50 cells/uL)
- Spectrum includes:
  - Exacerbation of existing disease
  - Development of new manifestations or new site
  - Dissemination/death
- Delaying ART in pts with CD4<50 cells/µL can be associated with mortality & AIDS defining illnesses (SAPIT, STRIDE, CAMELIA)
  - Not the case with TB meningitis
- MDR TB in DDx but can also be accompanied by IRIS

Walker NF et al, Curr Opin HIV AIDS. 2018, Naidoo et al, Ann Intern Med 2012, Laureillard D et al, AIDS 2013, Luetkemeyer AF et al IAIDS 2014

INSHI IRIS definition

Major clinical criteria

- New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement
- New or worsening radiological features of tuberculosis
- New or worsening central nervous system tuberculosis
- New or worsening serositis (pleural effusion, ascites, or pericardial effusion)

Minor clinical criteria: (>/=2 required)

- New or worsening constitutional symptoms
- New or worsening respiratory symptoms
- New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

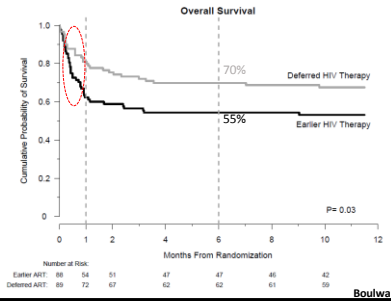
Meintjes G et al, Lancet ID 2008

Cryptococcal IRIS (INSHI)

- Antecedent criteria:
  - Cryptococcal infection, improved with antifungal treatment
  - ART
- Clinical criteria (clinical deterioration):
  - Within 12 months of ART
  - Meningitis, IC lesions, skin lesions, pulmonary nodules, LAN
- Exclusion of other diagnoses
  - Non-adherence
  - Other infection or malignancy

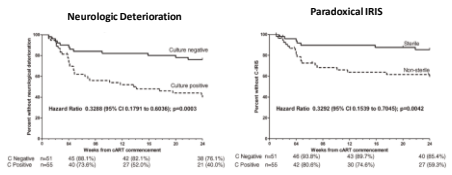
Haddow et al. Lancet ID 2010

Cryptococcal meningitis: COAT results



Boulware et al. *NEJM* 2014; 370:2487-98

Importance of CSF culture negativity in CM



Chang CC et al. AIDS 2013

Hepatic flares following ART

- Are associated with Hep B or C viral load
  - HBV: adjusted OR per log 1.36 (1.11-1.66), P=0.003
  - HCV: adjusted OR per log 1.30 (1.01-1.65), P=0.04
- Associations with IL-10, IL-18, CXCL10
- Fatalities have been reported
- *Can occur even in just HBcAb+*
- Incidence can be as high as 20%
- DDx with drug toxicity
- May lead to clearance of HbeAg or seroconversion

Current Opinion in HIV & AIDS, July 2008. Hepatitis virus immune restoration disease of the liver. Crane, Megan; Matthews, Gail; Lewin, Sharon/ Crane et al, JID 2010 , Andrede B et al, JID 2013

Most important concepts for Clinicians

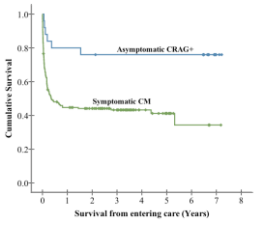
- Patients at high risk: very low CD4, disseminated disease (higher Ag load), lack of immune responses in CM, anemia
- Diagnosis of exclusion: do not start blindly corticosteroids, still immunocompromised
- High CD4 not necessary in contrast to decreasing VL
- ALL regimens can be associated with IRIS, not higher with INSTIs in prospective studies (Inspiring, Reflate and Reality)
- Occam's razor *lex parsimoniae* "law of parsimony" does not hold- could be IRIS++++
- Not HIV exclusive phenomenon

Clinical management of IRIS

- Observation or symptomatic relief in mild cases (fevers, rashes, LFT elevations)
- Pre-treat CM until CSF sterile (COAT trial)
- Non-steroid inflammatory drugs
- Corticosteroids
- Drainage of LN, lumbar drain (CM-IRIS)
- Only rarely d/c ART
- Prevention of unmasking
  - *CRAG screening*
  - *AFB screening*

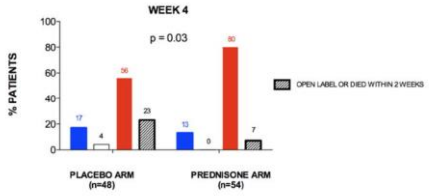
Expert Rev Anti Infect Ther. 2015, Hsu et al CID 2016, Meintjes G. Curr HIV/AIDS Rep. 2012, Lawn S et al, BMC Med. 2013Boulware D et al, NEJM 2016

Prevention of unmasking CM: 5-yr Survival after Cryptococcal meningitis in Uganda



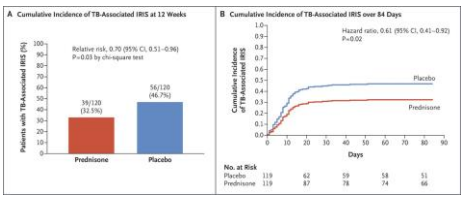
Butler EK, et al. PLoS One 2012

Prednisone early treatment in mild-mod TB-IRIS



Meintjes et al, AIDS 2010

Prophylactic prednisone prevents paradoxical TB-IRIS



G Meintjes et al. N Engl J Med 2018;379:1915-1925.

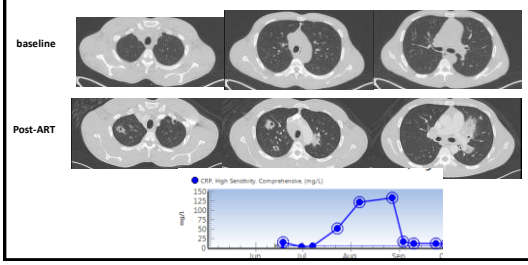
Conclusions

- Opportunistic infections remain a reality in regions with high prevalence of HIV
- IRIS is an inflammatory reaction that can be managed with maintenance of ART but may require immune suppression
- Management of immunosuppressed HIV patients should include screening for OI
- CM- important to sterilize CSF prior to ART
  - *Unmasking CM IRIS may increase with test and treat roll out in high prevalence areas*
- TB- prednisone for prevention or early treatment only in select patients

Case presentation 1: not your usual hiccups

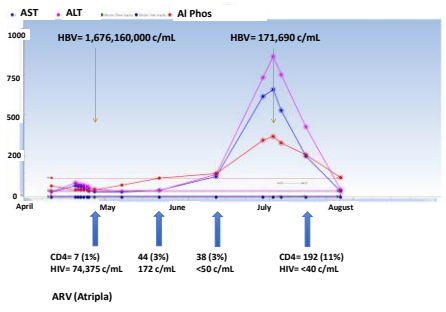
- 38 yo, - persistent hiccups, anemia, HIV+
- Thrush, weight loss, chills, fatigue, cough, CD4 10 cells/µL, VL 350,000c/mL
- BAL: +AFB, culture MAC, neg BCx--- azithromycin and EMB- improved
- ARVs (Stribild)
- *2 weeks later: worsening hiccups, CD4 63, VL 237, CRP 51 (from 14)*
- *4 weeks later: High fevers (40-41C), hiccups, CRP 120, CD4 163, Quantiferon neg (was indet)*
- Repeat chest CT

CT before and 1 month after ART



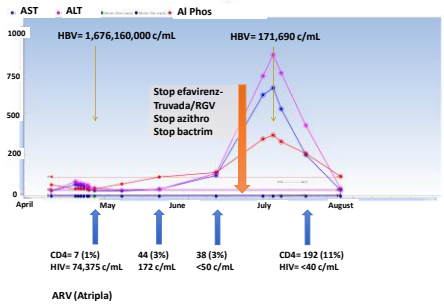
Case presentation 2: is it the drugs or the virus?

- 30 yo, AA, skin lesion– Kaposi Sarcoma
- HIV +, CD4 of 7 cells/µL
- HAV Ab neg, HCV Ab neg
- HBsAg+, anti-HBs Ab -, anti-HBcAb +, HBeAg+
- Atripla/ bactrim, azihromycin
- Hep A vaccine given



ARS Question 2:
Which of the following is <u>not true:</u>

1. It is unclear if this is IRIS/HBV flare as it could represent drug toxicity (bactrim, or efavirenz most likely)or a combination of the two
2. HBV flares during ART may be serious and even lead to hepatic failure
3. According to published studies, higher HBV viral load may have predisposed to this flare
4. HBV flares (IRIS) leads to lower rates of suppression and seroconversion
5. HCV viral load should be checked

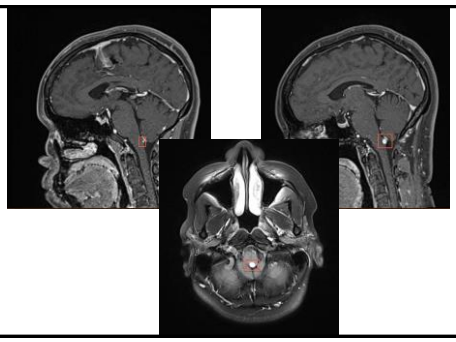


Case presentation 3: doing well but having trouble reading

- 33 yo, African woman with RUL infiltrate/mediastinal LAN--- TB
- HIV+, CD4 of 10 cells/µL, HIV RNA: 1.1 million c/mL, HBsAg+, HBV 165.000 c/mL
- Atripla, RIPE, bactrim
- DRESS from RIF
- INH, EBM and moxifloxacin
- Clinical improvement, CD4 84, VL <40
- Blurry vision

ARS Question 3: What would you do first:

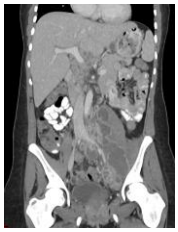
1. MRI
2. LP and repeat chest CT
3. EEG and call a neurologist
4. Call an ophthalmologist
5. Stop ethambutol immediately

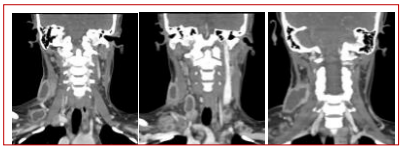


Case presentation 4: when something doesn't feel right, it usually isn't…

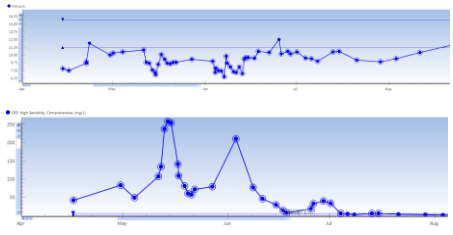
- 30 yo, African woman with neck swelling/LAN
- TB---HIV+, CD4 of 6 cells/µL, HIV RNA: 980.000 c/mL, KSHV PCR+
- Atripla, RIPE, bactrim
- Fevers, necrotizing tender LAN 1st week of ART
- CD4 70, VL 6700 c/mL
- Prednisone initiated for TB IRIS
- Persistent fevers and severe anemia despite high dose prednisone and large volume drainage

Further coalescence of necrotic lymphadenopathy



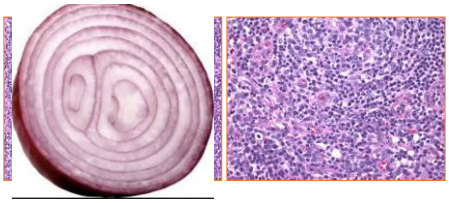


Hg and CRP during clinical course



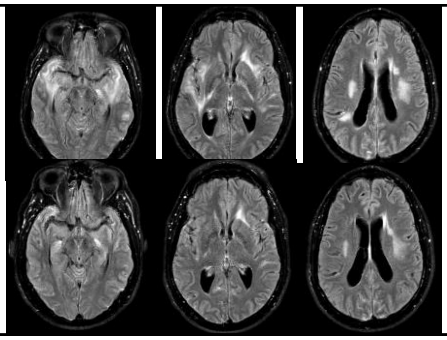
ARS Question 4: Which is least likely to help with diagnosis and management:

1. Repeat drainage with mycobacterial stains & cultures
2. Consider other diagnoses that are associated with severe anemia and LAN
3. Pursue a LN and/or BM biopsy to evaluate histology better
4. Fever and anemia could be a drug toxicity and bactrim should be stopped
5. Increased immunosuppression (higher doses of corticosteroids or other) should be started



Case presentation 5: can we consent him?

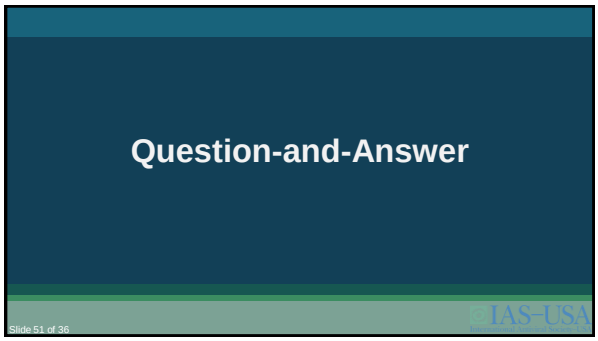
- 48 yo man HIV/AIDS on ART for 3 months (CD4 11)
- H/o cryptococcal disease (pulmonary + meningitis), treated with amphotericin + FC for 2 weeks and started on Atripla
- CD4 117, VL<40c/mL
- Acute onset fevers, headaches and MS changes
- Amphotericin restarted
- LP with OP 38, WBC 312, protein 285, Glc 18
- CSF culture no growth
- Chest CT: decreasing pulmonary nodule
- Encephalopathic, not responsive



ARS Question 5:
Next immediate step in management should be:

1. Brain biopsy
2. LP and initiation of corticosteroids
3. Initiation of sertraline for CM-IRIS
4. Initiation of Toxoplasma treatment and repeat MRI in 2 weeks
5. ART discontinuation

Immunocompromised patients:
Always more than meets the eye!


Question-and-Answer
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