AETC AIDS Education & Training Center Program Mountain West

Immune Reconstitution Syndrome (IRIS), 2023 Part 1 of 2

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Project ECHO®

Disclosures

Merck: Adjudicate cases for HIV diagnostic test development

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Data Considerations

Data in this presentation offer a limited perspective of how systemic, social, and economic factors impact health. We recognize that racism, not race, creates and perpetuates health disparities.

To Learn More:
https://www.cdc.gov/minorityhealth/racism-disparities

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Immune Reconstitution Inflammatory Syndrome

IRIS: Definition

An illness…

- Occurring in a person with HIV
- With a temporal relationship to ARV initiation
- Associated with a decline in plasma HIVRNA and a rise in CD4 count
- Presentation with an *unusual inflammatory course*
- Exclusion of alternative causes (e.g., progression of an OI, drug toxicity, development of a new OI, etc.)

French 2004, Shelburne 2006

IRIS: Definition

Two Versions

- Paradoxical: IRIS occurring when an OI, responding to treatment before ARV therapy, deteriorates after initiating ARVs
- Unmasking: disease that was cryptic prior to starting ARVs, presents after starting ARVs with florid, inflammatory symptoms

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IRIS: Epidemiology

Incidence

- Overall incidence 10-13%
- Paradoxical
  - CMV up to 38%
  - Cryptococcus 20% (range 4-49%)
  - Tuberculosis 17% (range 8-45%)
  - PML 17%
  - KS 7-31 %
- Unmasking
  - Tuberculosis 1-5%
  - Cryptococcus 1-2%

Haddow, PLoS One, 2012, Muller, Lancet Infectious Diseases 2010, Manzardo, Expert Rev, 2015, Novak 2012

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IRIS: Risk Factors

Advanced HIV	Low CD4 count High HIV RNA
High pathogen or antigen burden	Disseminated infection
Strong response to ARVs	Large drop in plasma HIVRNA Marked increase in CD4 count
Short interval between treatment of OI and initiation of ARVs	
Integrase inhibitors – some studies	
Other factors	Host genetics, ARV naïve, low hemoglobin, PI-based ARV

Martin-Blondel, Curr Opin Infec Dis, 2012, Dutertre 2017, Psichogiou 2017, Wijting 2019

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IRIS: Clinical Symptoms

- Timing: typically 4-8 weeks after ART but with a range of 4 days to 6 months
- Median CD4: 57 (Muller 2010)
- Mortality: 4.5% (Muller 2010, Novak 2012)
  - Higher with CNS involvement (13-75%) (Muller 2010 and Bahn 2013)

Grant (for ACTG 5164), JID, 2012, Muller 2010, McComsey 2012, Novak 2012, Bahn 2013, Manzardo, Expert Rev, 2015

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IRIS: Clinical Symptoms

Clinical symptom or illness	Possible etiologies
Meningitis	Cryptococcus, MTb
CNS mass	Cryptococcus, MTb, Toxo, PML, lymphoma
Encephalitis	HSV, VZV, CMV, HIV, Parvo B19
Retinitis	CMV, VZV, HSV
Uveitis	CMV, MTb, Histoplasma, Leishmania
Lymphadenitis	MTb, NTM, BCG, Histoplasma, Cryptococcus, Leishmania
Skin	HSV, VZV, KS, HPV, M. leprae, Crypto, Molluscum, Leishmania
Hepatitis	HBV, HCV, NTM, MTb, Histoplasma, Leishmania, KS
Peritonitis	MTb, NTM
Colitis	MTb, Histoplasma, CMV
Splenitis	MTb, Bartonella
Lung and pleural disease	MTb, NTM, PJP, Cryptococcus
Autoimmune IRIS	Thryroiditis, Sarcoid, SLE, Guillain-Barre, RA, PM

Grant (for ACTG 5164), JID, 2012, Achenbach, CID, 2012, Muller 2010, Manzardo, Expert Rev, 2015

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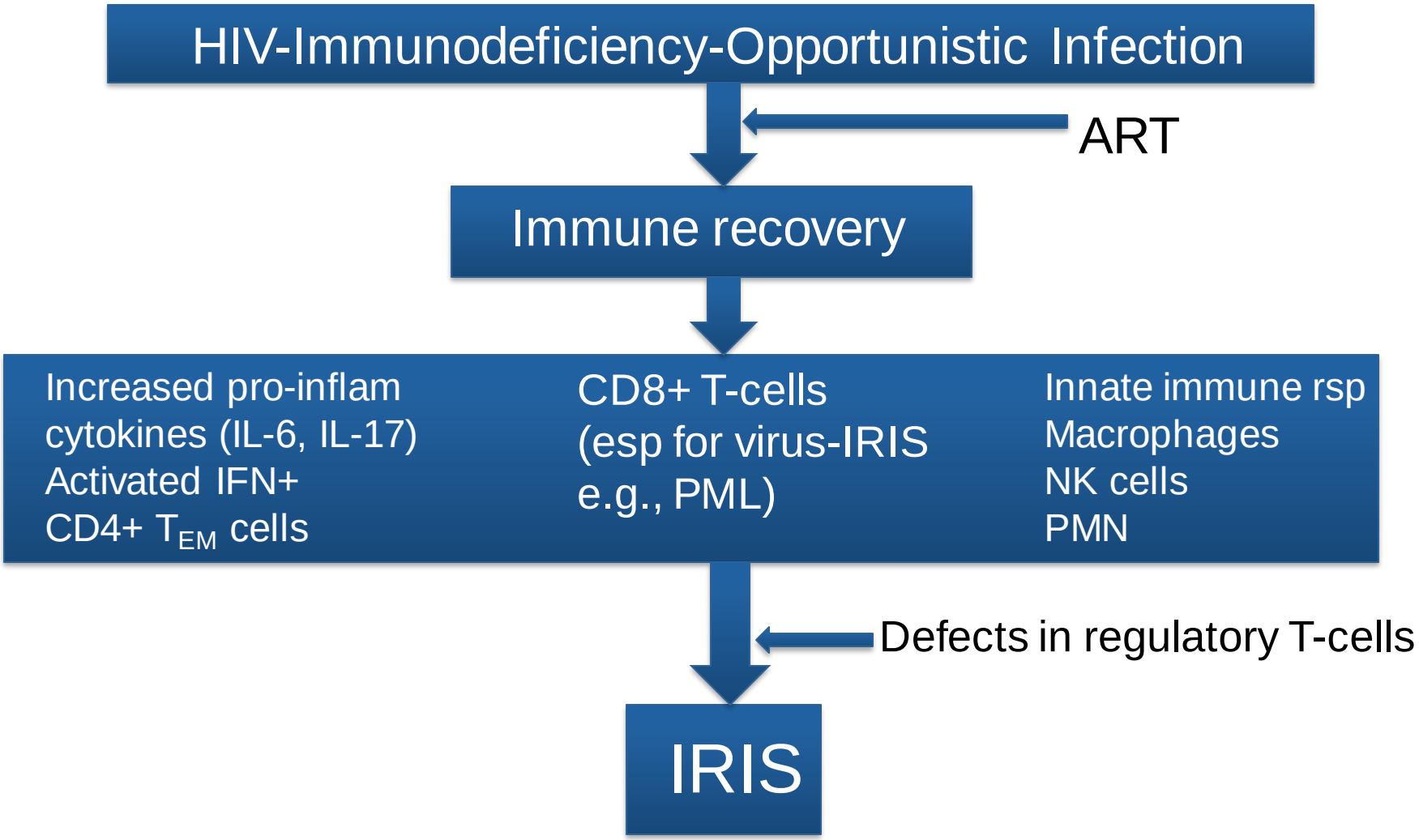
IRIS: Pathogenesis



Martin-Blondel, Curr Opin Infect Dis, 2012, Manzardo, Expert Rev, 2015

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TB-IRIS

Definition of TB IRIS

Paradoxical TB IRIS

- Diagnosed with TB and responding to treatment
- Clinical criteria: onset within 3 months of ART, Plus: 1 major or 2 minor
  - Major criteria
    - New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement
    - New or worsening radiological features of tuberculosis
    - New or worsening CNS tuberculosis
    - New or worsening serositis (pleural effusion, ascites, or pericardial effusion)
  - Minor criteria
    - New or worsening constitutional symptoms such as fever, night sweats or weight loss
    - New or worsening respiratory symptoms such as cough, dyspnea, or stridor
    - New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy
- No alternative explanation for symptoms

Meintjes, Lancet Infectious Diseases 2008

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Definition of TB IRIS

Unmasking TB IRIS

- Patient not on treatment for TB when ART started
- TB diagnosed within 3 months of starting ART
- Plus one of the following
  - Heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component to the presentation
  - Once established on tuberculosis treatment, a clinical course that is complicated by a paradoxical reaction

Meintjes, Lancet Infectious Diseases 2008

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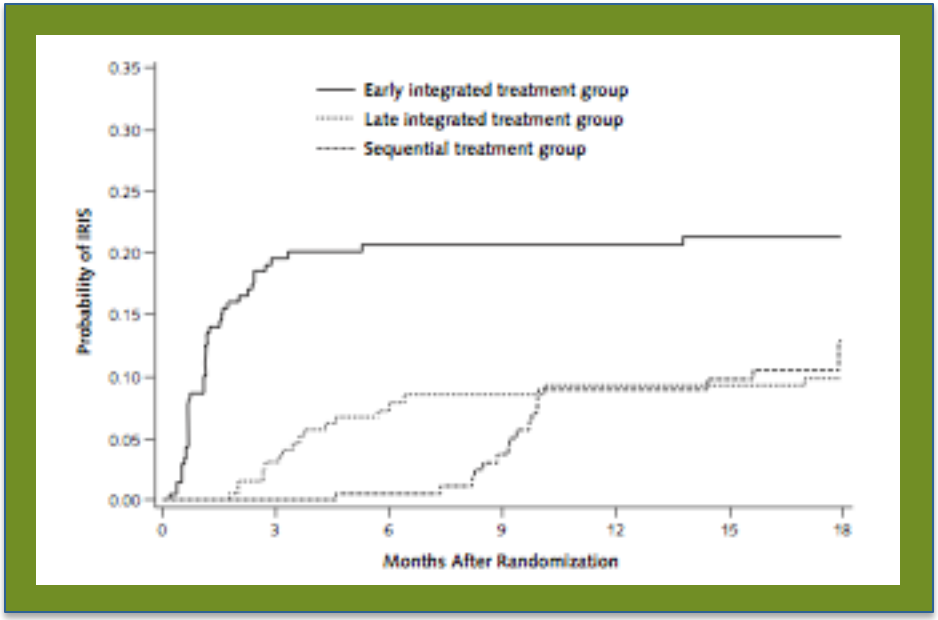
SAPiT Trial

- Starting ARV at Three Points in TB
  - Starting ARVs within 4 wks of TB Rx (group 1)
  - Starting ARVs within 4 wks of completing the intensive phase of TB Rx (group 2)
  - Starting ARVs within 4 wks of completion of TB Rx (group 3)
  - N = 642
  - TB IRIS = 85
    - Group 1 = 43
    - Group 2 = 18
    - Group 3 = 19



Naidoo, Ann Int Med, 2012

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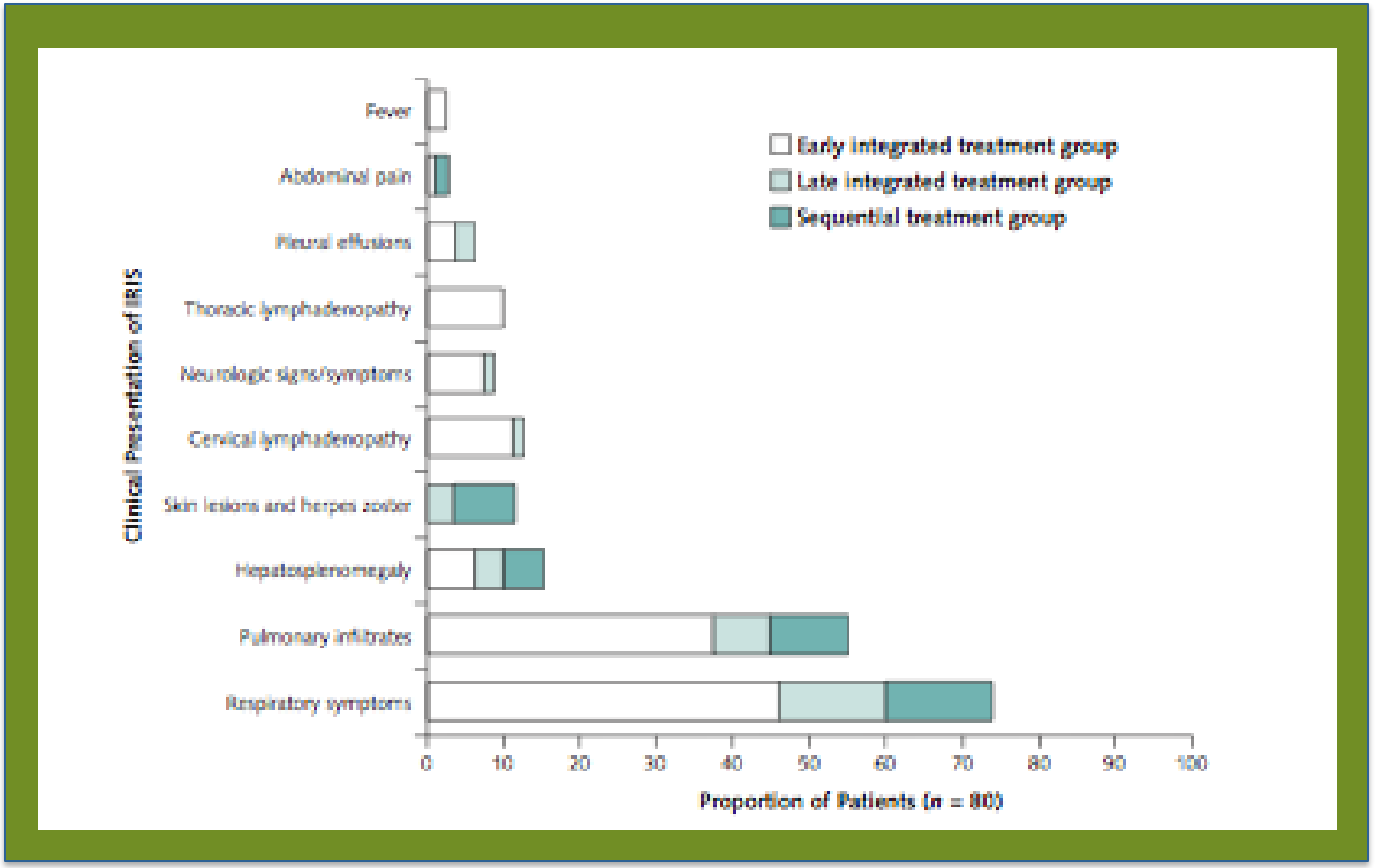
SAPiT Trial

Symptoms of TB-IRIS



Naidoo, Ann Int Med, 2012

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SAPiT Trial

Clinical Features and Outcomes

	Early ARV	Integrated ARV	Sequential ARV
Median time to IRIS from ART initiation (days)	17.5	17	28
Median time to IRIS resolution (days)	70.5	34	23.5
IRIS-associated death	2	0	0

Naidoo, Ann Int Med, 2012

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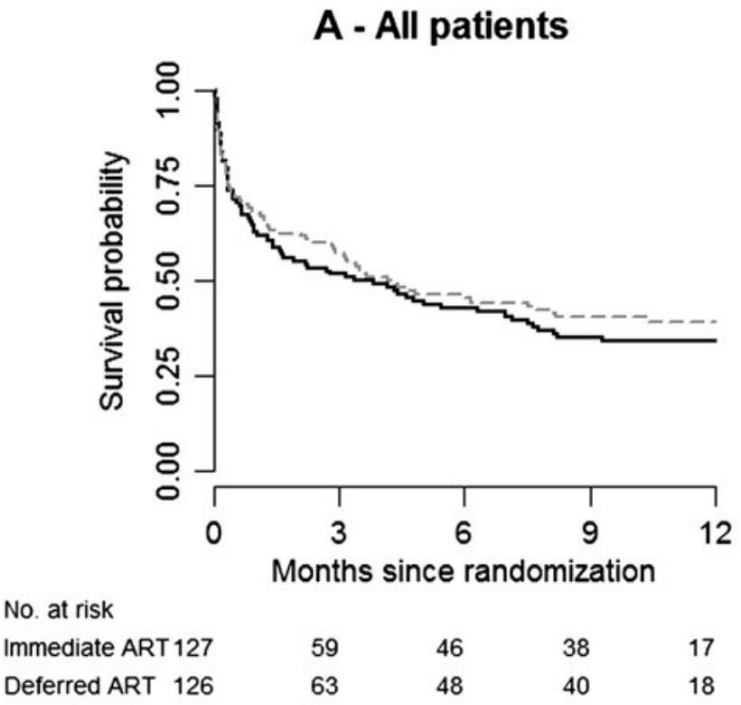
TB Meningitis and ART – Be Careful

- R, DB, PC trial of 253 pts with TB meningitis
- All received RIPE + Dexamethasone
- ART (3TC/AZT/EFV) was given either
  - Immediately (~ 1 week)
  - After 2 months of TB Rx
- Results
  - No difference in mortality or new AIDS dx between groups
  - More grade 4 AE in the immediate group
  - *No difference in neurological events between groups*

Survival



Torok, CID, 2011

Randomized Placebo-Controlled Trial of Prednisone for TB-IRIS

- Double-blind placebo controlled RCT
- Intervention: Prednisone 1.5 mg/kg (100 mg daily for 70 kg adult) for 2 weeks then 0.75 mg/kg (50 mg daily for 70 kg adult) for 2 weeks
- Assessments: 1, 2, 4, 8, and 12 weeks
- Could switch to open label prednisone at MD discretion if deterioration/relapse

Meintjes, AIDS, 2010

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Randomized Placebo-Controlled Trial of Prednisone for TB-IRIS

	Prednisone	Placebo	P value
Number	55	55	
Duration of TB RX before ART	66	43.5	0.02
Death	3 (5%)	2 (4%)	0.65
Severe infection	2 (4%)	4 (7%)	0.40
Infection	36 (65%)	30 (55%)	0.24
Steroid AE	8 (15%)	3 (5%)	0.11
Primary endpoint			
Total hospital days	282	463	
Outpatient procedures	27	31	
Median number of hospital days	1 (0-3)	3 (0-9)	0.046

Meintjes, AIDS, 2010

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Randomized Placebo-Controlled Trial of Prednisone for TB-IRIS

Conclusions

Prednisone reduced need for medical interventions (hospitalization and outpatient procedures)

Consistent benefit of symptoms and radiographic evaluations

Benefit despite cross over to open label

No excess steroid toxicity or infection

Optimal Duration? -- 4 weeks too short for some

Meintjes, AIDS, 2010

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Preventing TB-IRIS

PredART Study

- 240 patients had started on TB Rx within 30 days and were starting ART
- Randomized to prednisone 40mg/d x 2wk -> 20mg/d x 2wk
- Results
  - Prednisone decreased IRIS by 30% (33% Vs 47%) and decreased use of prednisone for IRIS (13% Vs 28%)
  - One death due to IRIS (placebo)
  - No increased AEs from prednisone

Meintjes, NEJM, 2018

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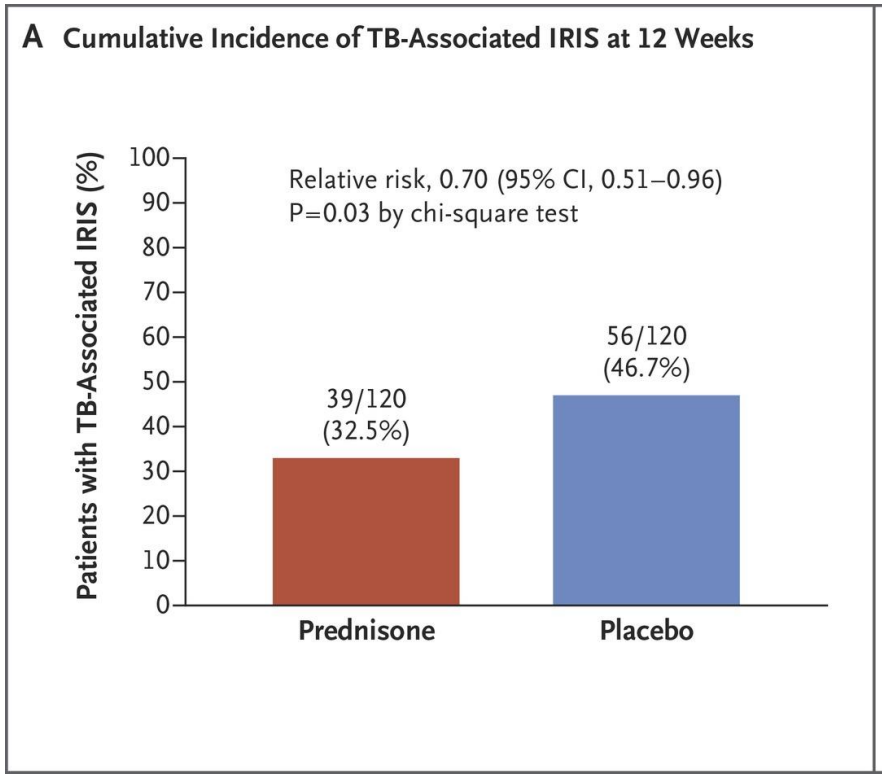
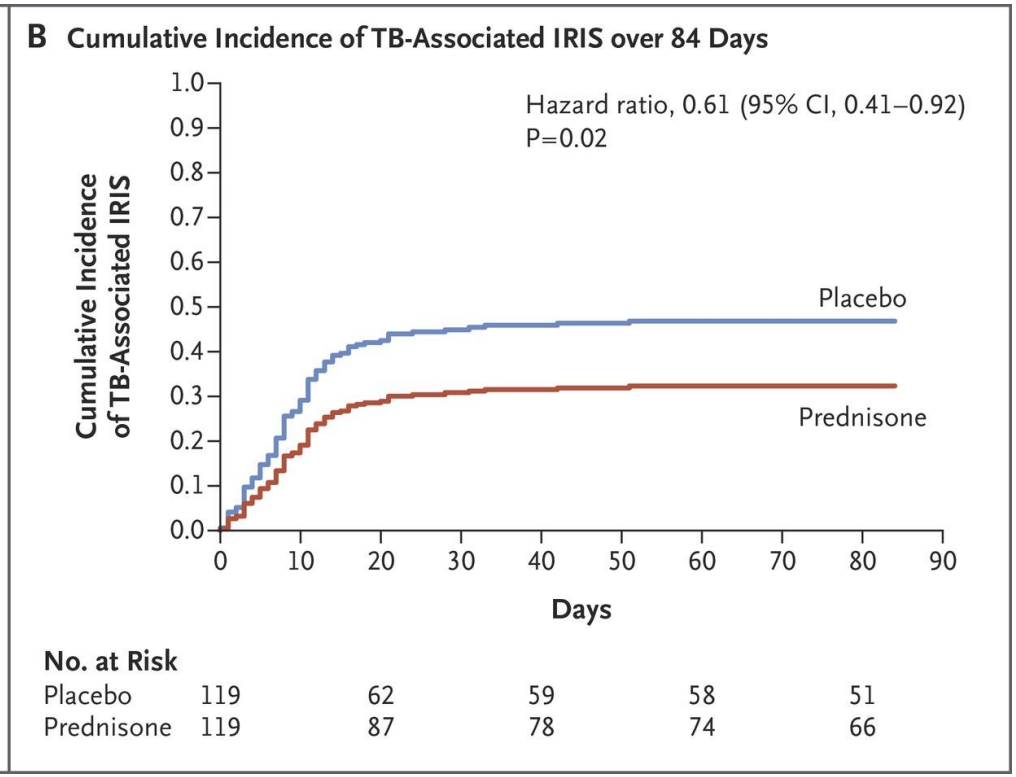
Preventing TB-IRIS

PredART Study





Meintjes, NEJM, 2018

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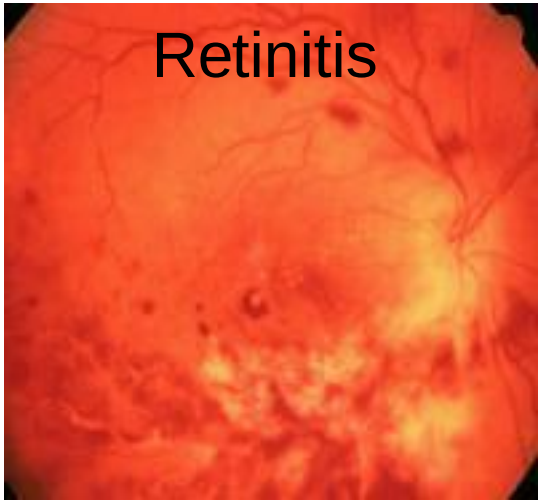
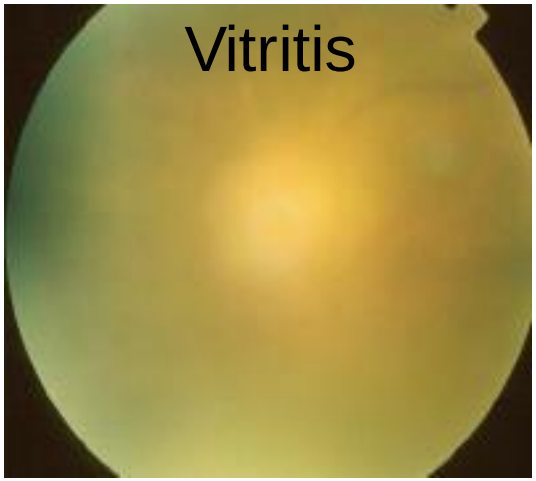
CMV-IRIS

CMV-IRIS

- The development of anterior chamber or vitreal inflammation in response to CMVr that occurs after ART
- Inflammation can lead to macular edema, epi-retinal membrane formation and retinal neo-vascularization





CMV-IRIS

Meta-analysis of ART associated IRIS: overall rate for CMV IRIS of 37.7% (highest of all OI)

Immediate ART in those with known or suspected CMVr = increased severity of IRIS

Risk factors

- Use of intra-vitreal cidofovir to treat CMVr
- Starting ART before completion of the induction phase of CMV Rx

Rx: steroids

Outcome: variable

Delay ART in those with known or suspected CMVr. Obtain dilated fundoscopic exam in all patients with CD4 <100 who are staring ART.

Muller, Lancet Infect Dis, 2010, Ortega-Larracea 2005

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PML-IRIS

PML-IRIS

- Review of 157 reported cases from 1998-2016. 46 cases meeting definition were reviewed.
- Definition:
  - HIV+
  - PML: neurological deficits, characteristic MRI, JCV in CSF or brain bx
  - PML-IRIS:
    - ART in the last 2 years, subacute onset of neurological symptoms that appeared with ART (unmasking PML-IRIS) or worsened in a patient with known PML (paradoxical PML-IRIS)
    - Decreased HIVRNA and increasing CD4
    - Evidence for inflammation in the brain by MRI (enhancement, edema or mass effect) or on biopsy (showing T-cell infiltration)

Fournier, Frontiers in Immunology, 2017

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PML-IRIS

- Timing (from onset of ART): 41d (unmasking), 38d (paradoxical)
- Clinical features: motor deficits, speech disorders, cognitive decline, ataxia, visual disturbances, seizures
- Imaging: enhancing lesions (87%), edema (30%), mass effect (24%)
- Median CD4 counts: before ART = 45 (0-301), at onset of PML-IRIS = 101 (20-610)
- CSF JCV PCR + in 84% (of 38 patients)
- Histopathology: + (T-cell infiltration) in 95% (of 20 patients)
- Treatment and outcome:
  - 29/46 (63%) received steroids (methylprednisilone, dexamethasone, prednisone)
  - At a median of 8 months follow-up: 31/43 (72%) improved or stabilized and 12 (28%) worsened and then died with 2 years – no difference b/n unmasking and paradoxical
  - No effect of steroids: 72% Vs 71% improved or stabilized

Fournier, Frontiers in Immunology, 2017

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HIV-CD8-Encephalitis

HIV-CD8-Encephalitis: IRIS?

- Collection of 53 cases (23 from the UK)
- Severe encephalitis caused by CD8 infiltration of the brain
- Clinically
  - Acute/sub-acute (3-28 days) decline in cognitive function, headache > vomiting, ataxia, cardiac arrest, seizures
  - Median CD4 at presentation 327
  - Of 16 who had CSF obtained: 11/16 (68%) were HIVRNA+
- Pathology
  - Perivascular and diffuse CD8 infiltration without little-to-no HIV detected (different than HIV associated encephalitis)

Lucas 2021, Frontiers in Neurology, 2021

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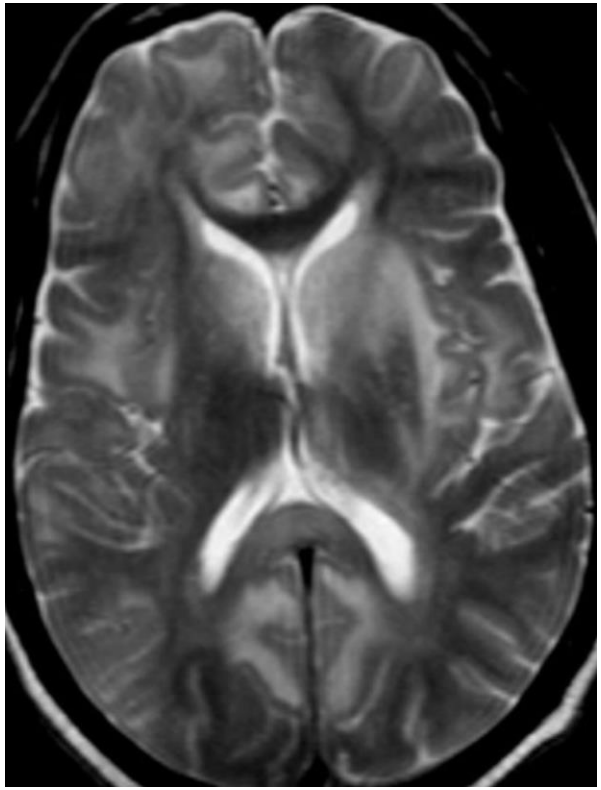
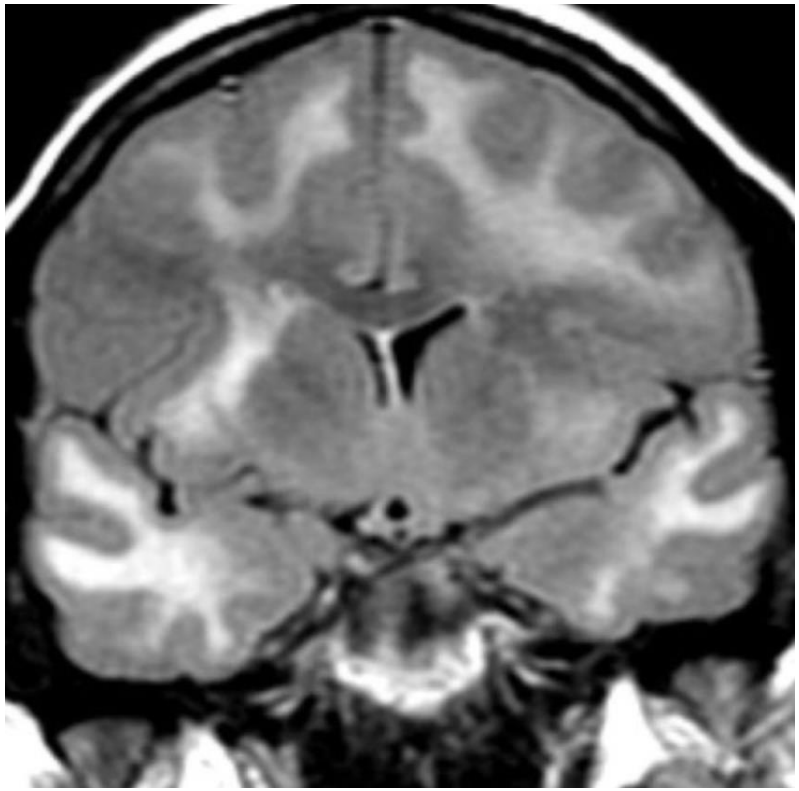
HIV-CD8-Encephalitis: IRIS?

- Imaging
  - Multiple, bilateral, confluent signal with edema throughout the white matter > cortical areas





Lucas 2021, Frontiers in Neurology, 2021

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HIV-CD8-Encephalitis: IRIS?

- Risk factors
  - Intercurrent infections (7/53)
  - ART interruption (14/53)
  - IRIS (14/53)
  - Black African ancestry (38/53)
- Treatment and mortality
  - 9/30 (30%) treated with steroids died
  - 16/23 (69%) of those not treated with steroids died

Lucas 2021, Frontiers in Neurology, 2021

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IRIS: Treatment

- Continue ART except in life-threatening situations
- Continue treatment of opportunistic infection or condition
- Mild disease: NSAIDs
- Moderate to severe disease: steroids
  - NOT in CNS cryptococcal infection (although some experts would do it!)
  - Use carefully if KS present, consider concurrent KS therapy
  - Do NOT use steroids to treat KS-IRIS
  - Check for or just treat for Stongyloidiasis (ivermectin)
- Alternatives to steroids
  - Thalidomide
  - Pentoxifylline
  - Chloroquine
  - TNF inhibitors: infliximab, adalimumab, etanercept

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IRIS: Conclusions

- IRIS is an inflammatory disease that occurs in the context of initiating ARV therapy and can be classified as paradoxical or unmasking
- The incidence varies greatly by geographic region and disease
- Major risk factors include advanced HIV (low CD4), disseminated infections (high organism or Ag burden) and a short interval between the treatment of an OI and the initiation of ARVs
- Management generally includes continuation of treatment of the OI/cancer and ARVs plus supportive care and the addition of anti-inflammatory therapy (NSAIDs, steroids (NOT for KS or Cryptococcus [with exceptions])
- Outcomes are generally good but there can be significant mortality for some: cryptococcal meningitis, visceral KS, PML and HIV-CD8-encephalitis

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