Immune Reconstitution Syndrome, 2023 – Part 2

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Disclosures

Merck: Adjudicate cases for HIV diagnostic test development

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Disclaimer

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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

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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: 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

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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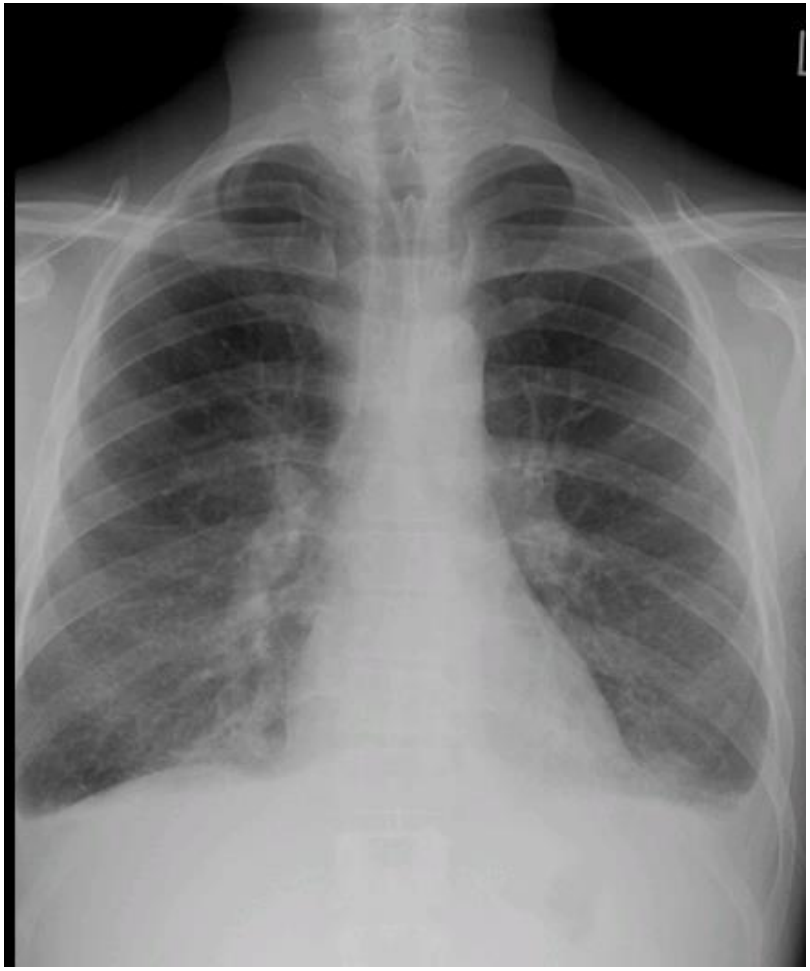
KS-IRS

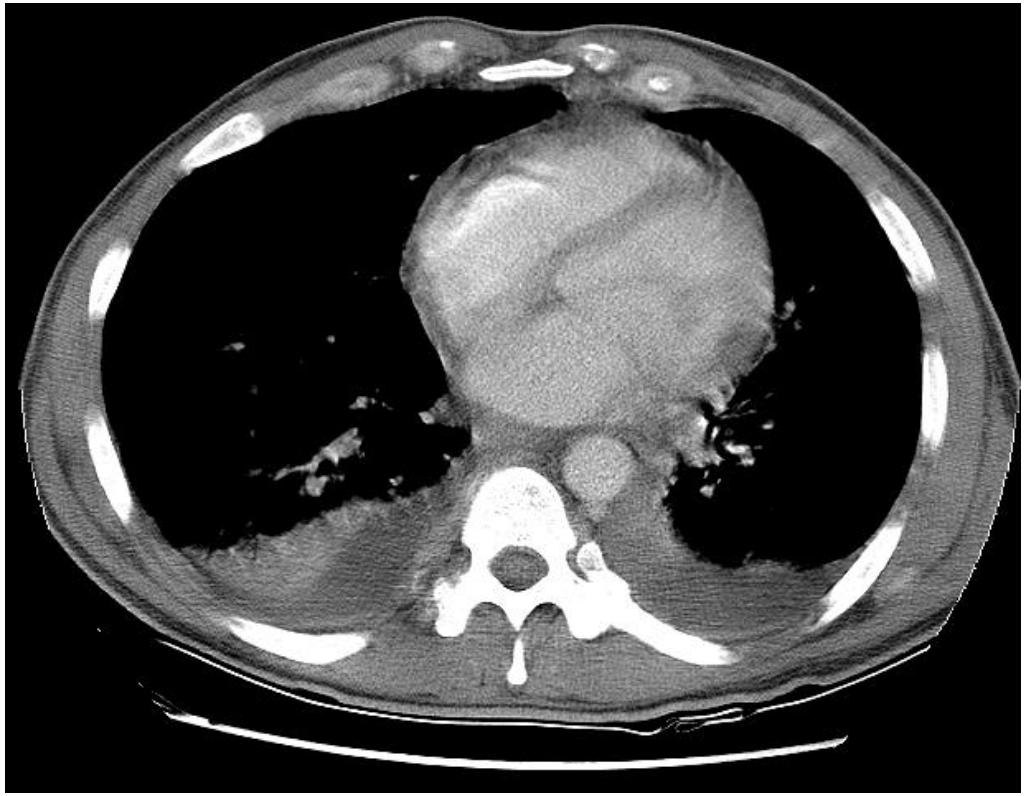
Case Presentation

- A 47 yo HIV+ man presented with fever, fatigue, and a dry cough 6 weeks after starting HAART. PE revealed T 39.3° C, BP 106/58, HR 135, RR 28, SO2 88% on RA.

- Chest x-ray and CT showed interstitial thickening, small pleural effusions, splenomegaly, and diffuse adenopathy.

Case Presentation





Case Presentation

- Bronchoscopy, bone marrow aspiration and inguinal lymph node biopsies were unrevealing.

- He was treated with TMP-SMZ and levofloxacin for presumptive PJP and CAP. CMV Ag was detected in blood. Ganciclovir, ethambutol, clarithromycin, and corticosteroids were added for possible CMV, MAC, or IRIS.

- He improved promptly on prednisone and was discharged from the hospital on a prednisone taper.

- He returned to work, his CXR normalized and his CD4 cell count rose to 381 cells/mm^3.

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Case Presentation

- Three days after completing the steroid taper, the patient was readmitted with shortness of breath, fever, and edema.

- The following day he developed a consumptive coagulopathy, ARF, and ARDS requiring intubation. Bronchoscopy was unrevealing.

- Despite supportive measures, antibiotics, and high dose steroids, he expired 3 days after admission.

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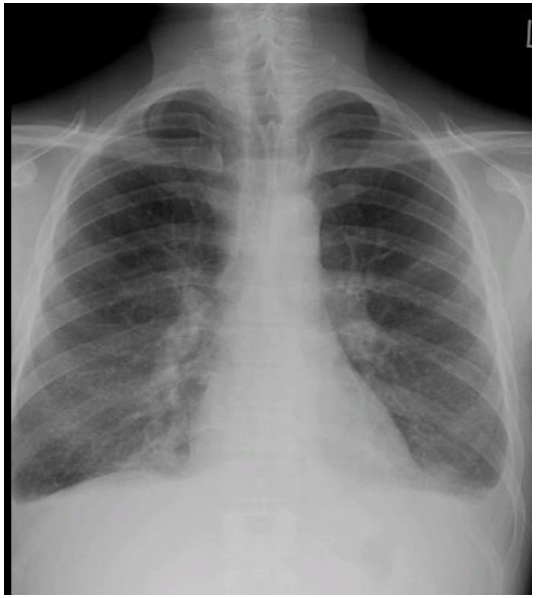
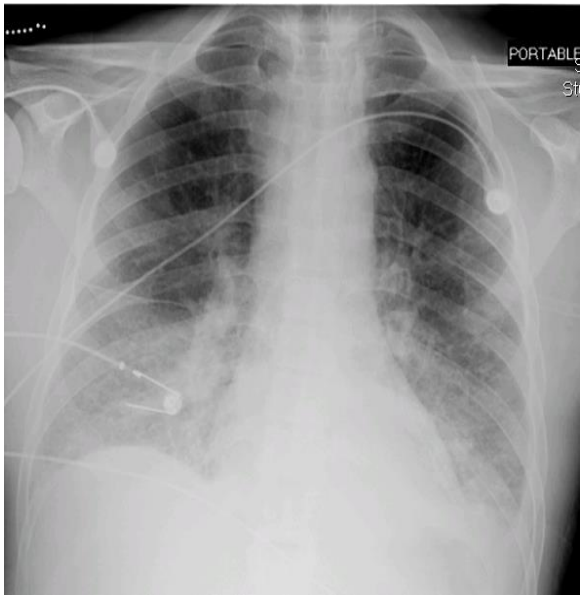
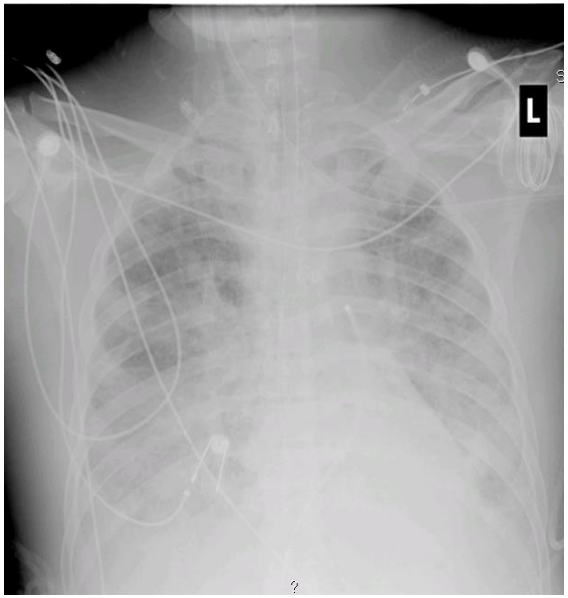
Case Presentation



Initial admission



Readmission



2 days later

Case Presentation

- Autopsy revealed extensive KS in both lungs with atypical lymphocytic infiltration

KS-IRIS

- Incidence: 2.4-39%. Meta-analysis 6.4% (Paradoxical 6-11%, Unmasking 4-5%)
- Timing: days to 6 months after ART - most in the first 2 months
- Risk factors: usual RFs for IRIS + *steroid use*
- Risk factors for more severe disease and higher mortality:
  - CD4 < 200, visceral disease, + plasma HHV-8, platelets < 100K, no chemotherapy
- Clinical presentation:
  - Increased inflammation and edema of lesions, new lesions in any location (especially pulmonary, but can be any organ), pleural effusions, ascites (can be chylous)
- Prevention: Chemotherapy for KS does NOT decrease the risk of IRIS
- Treatment: Chemotherapy (doxorubicin or paclitaxel). NO STEROIDS

Poizont-Martin Cancers 2022, Fernandez-Sanchez 2016, Volkow 2017, Bowen 2009, Achenback 2012

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Cryptococcal-IRS

Definition of Cryptococcus IRIS

Paradoxical Cryptococcus IRIS

- Previously diagnosed with Cryptococcus and responding to treatment
- Clinical criteria:
  - Onset within 12 months of ART
  - Clinical deterioration with inflammatory features
    - Meningitis
    - Lymphadenopathy
    - Intracranial lesions
    - Multifocal disease
    - Cutaneous or soft tissue lesions
    - Pneumonitis or pulmonary nodules
  - No alternative explanation for symptoms

Haddow, Lancet Infectious Diseases 2010

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Definition of Cryptococcus IRIS

Unmasking Cryptococcus IRIS

- Clinical deterioration due to previously undiagnosed cryptococcus that develops after starting ART
- Clinical criteria:
  - Unusual, heightened or exaggerated symptoms, for example:
    - Meningitis with markedly elevated WBC (> 50) or opening pressure that is refractory to treatments
    - Painful or suppurating lymphadenopathy
    - Rapidly expanding intracranial lesions
    - Unusual focus of infection
    - Granulomatous inflammation on histology
    - Pneumonitis, particularly if cavitating
  - Typically occurs early after starting ART (within a month)
  - No alternative explanation for symptoms

Haddow, Lancet Infectious Diseases 2010

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Timing of ART: Early Vs Delayed ART in Patients with Cryptococcal Meningitis in Africa

- Open Label RCT
- Patients: Adults with HIV and Cryptococcal meningitis (CSF CrAg or India ink positive)
- All received Fluconazole 800 mg PO once daily x 10 wks + aggressive pressure management
- Followed by maintenance fluconazole 200 mg
- Intervention: d4T, 3TC, NVP
  - EARLY: Immediate start within 72 hours of diagnosis of Cryptococcal meningitis
  - DELAYED: Start after initial 10 wks of fluconazole
- Primary Outcome: Mortality after 2 years

Macadzange, CID, 2010;50:1532-38

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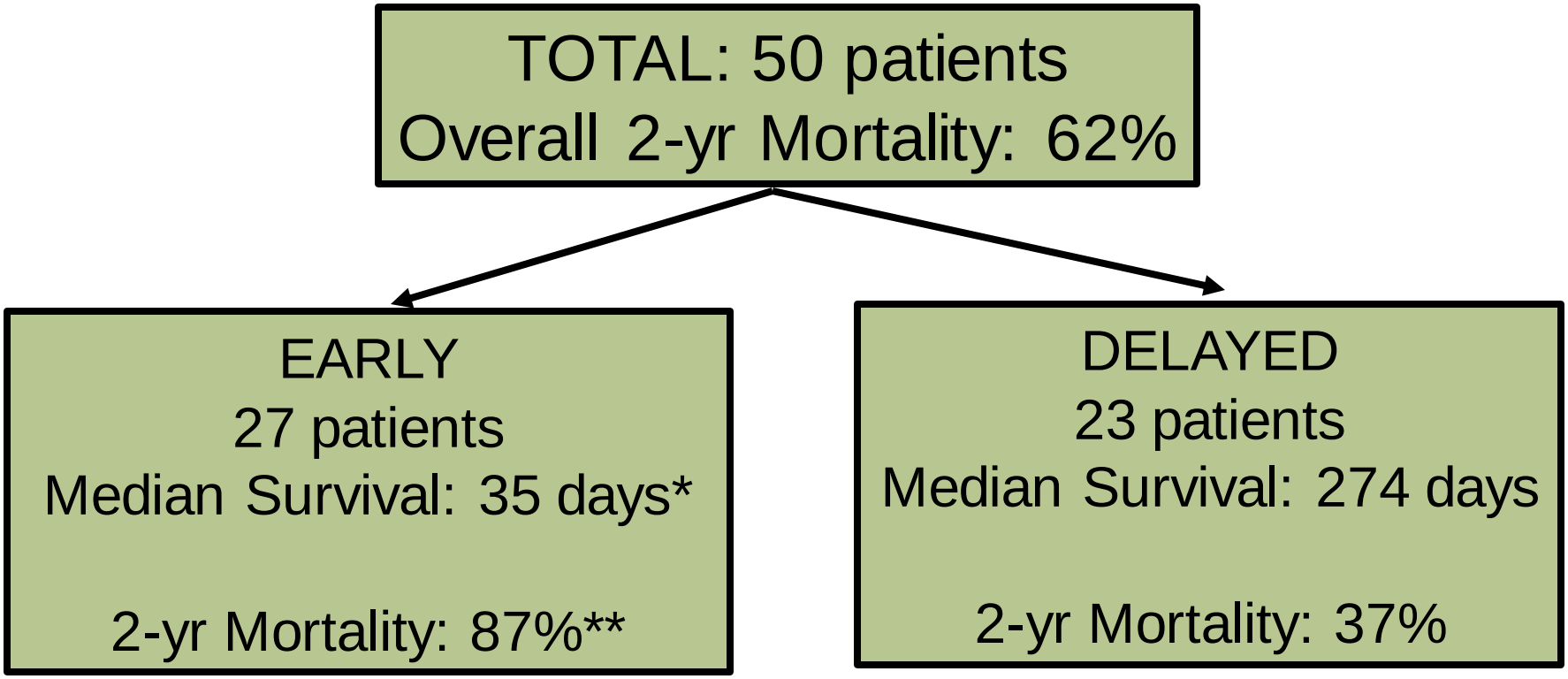
Early Vs Delayed HAART in Patients with Cryptococcal Meningitis in Africa



**Comparison of median survival, p=0.03*
***Comparison of 2-yr Mortality, p=0.002*

Macadzange, CID, 2010;50:1532-38

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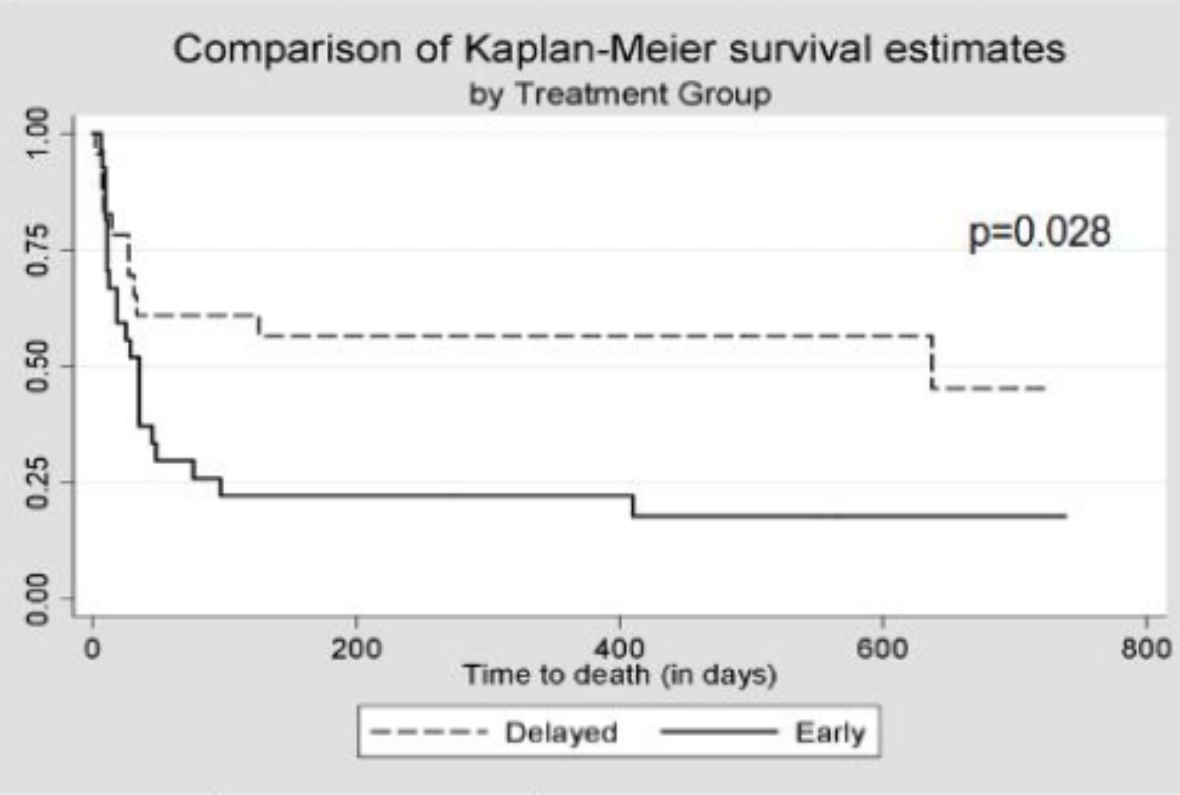
Early Vs Delayed HAART in Patients with Cryptococcal Meningitis in Africa

Survival



Macadzange, CID, 2010;50:1532-38

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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 800 mg.
  - Note – No 5-FC
- **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)]

Boulware D et al, NEJM, 2014

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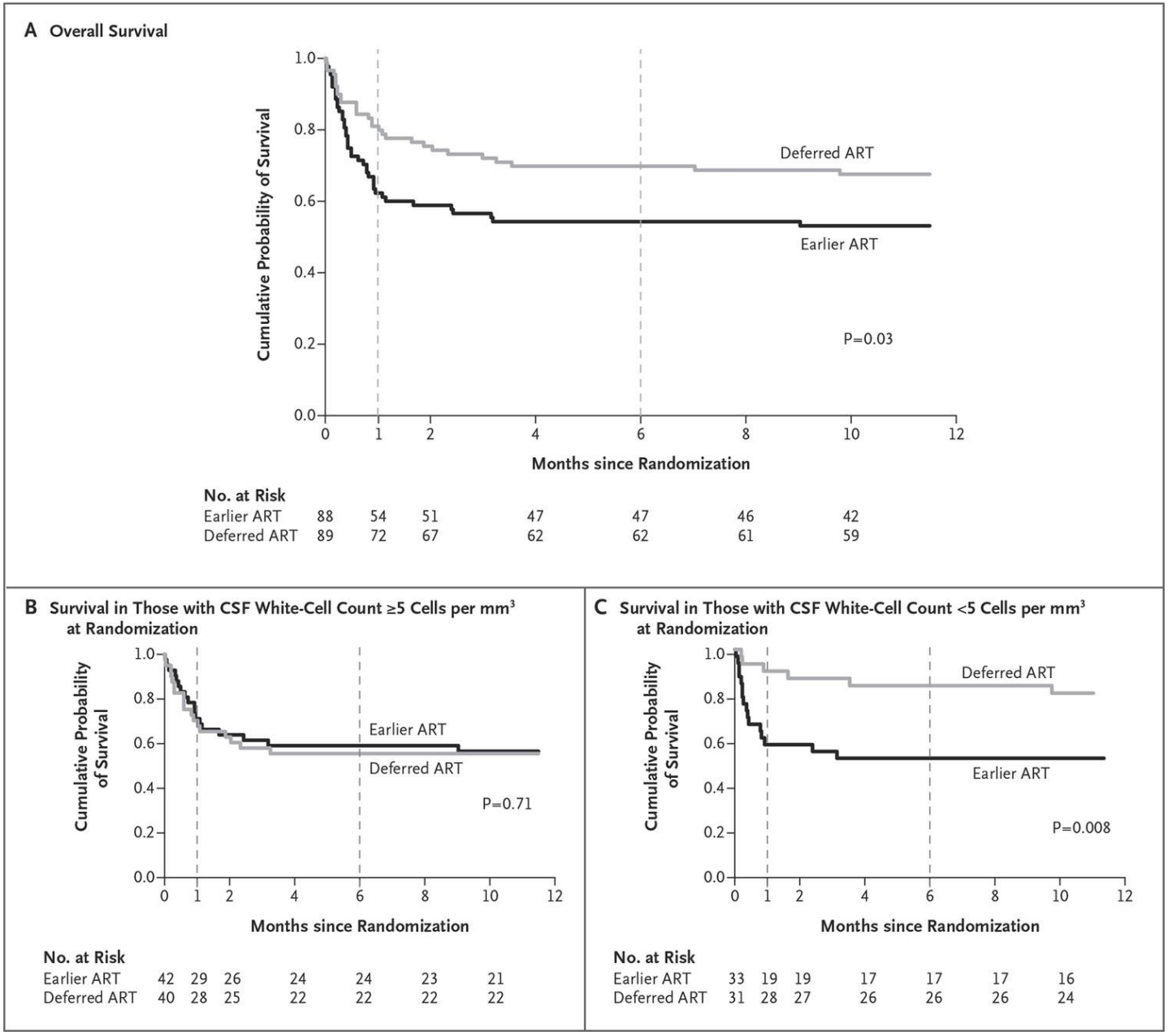
COAT: Cryptococcal Optimal ART Timing



Boulware D et al, NEJM, 2014

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COAT: Cryptococcal Optimal ART Timing

- **Secondary analyses:**
  - Mortality ↑ if AMS at presentation (GCS<15): HR 3.0
  - Mortality ↑ if CSF WBC <5/μL at presentation: HR 5.1
  - Trend toward ↑ IRIS in early group: 13% vs. 10%
- **Recommendations:**
  - Anti-cryptococcal therapy should always come before ART
  - In general, start ART at *4 weeks*
  - Consider delay of ART until *5-6 weeks* if AMS at presentation or if CSF WBC <5/μL

Boulware D et al, NEJM, 2014

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Cryptococcal Meningitis and Early ART: Not a Good Idea

Ingle Abstract: 2014 CROI

- Cited in IAS guidelines as support for immediate ART
- Not published
- Used patients in 3 retrospective cohorts (1998-2009 - COHERE, NA-ACCORD and CNICS) to "mimic" the COAT study.
- Retrospective, observational! In fact, most deaths occurred in those patients who did not get ART at all.
- Equal number of deaths in those that did and those that did not get early ART.
  - But difference between groups was ART < 2 weeks or > 2 weeks: > 2 weeks not defined (might have been all at 2.5 weeks!).
  - 1998 – pretty bad ART so may not have been very effective, less immune reconstitution and therefore less of a deleterious effect of early ART

Ingle, CROI 2014

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Cryptococcal Meningitis and Early ART: Not a Good Idea

- For persons with cryptococcal meningitis and with access to close monitoring and supportive care for adverse events, ART should be initiated 2 to 4 weeks after starting antifungal therapy (evidence rating: BII). The data supporting a delay in ART initiation for persons with cryptococcal meningitis were largely generated in resource-constrained settings where access to close monitoring and supportive care may not be as readily available and in persons who were not being treated with InSTI-based ART.
- A cohort study that did not show an increase in adverse outcomes with earlier initiation of ART (Ingle, CROI abstract 2014)

Gandhi, 2022 IAS ART Guidelines, Ingle, CROI 2014

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Cryptococcal Meningitis and Early ART: Not a Good Idea

- Boulware editorial from July 2023 CID: Comment on Ingle paper (same issue): that used a marginal structural model to mimic an RCT
- Why believe observational studies > RCTs?
- Large sampling bias in the Ingle paper: 630 with CM, 41% LTFU, 28% excluded for missing data – final analysis on 190 subjects:
  - These 190 subject were cloned and entered into 2 hypothetical arms who started ART < 2 weeks or > 2 weeks (post-ART)
  - Median time to ART was 0 days in the "early ART arm"
  - Many deaths in the delayed arm occurred between 2 and 4 week which would have been categorized in an "early group" in other RCTs
  - Those who never started ART were put in the late group so much of the comparison was "early ART" Vs "no ART"
  - Many subjects were censored at day 14 in the early group so any deaths that happened after this time point were only considered in the late group
- Why believe observational studies > RCTs?

Gandhi, 2022 IAS ART Guidelines, Ingle, CROI 2014

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Cryptococcus IRIS

Prevention and Treatment

- Prevention:
  - Delay ART for 4-6 weeks after therapy for cryptococcus
  - In well-resourced settings consider starting ART sooner?
- Treatment
  - Manage increased ICP (serial taps, drains, shunts)
  - Enhance antifungal therapy while waiting to confirm that antifungal therapy is effective (sterilizing) by restarting L-amphotericin or increasing fluconazole
  - Some experts might recommend: A brief course of tapering steroids starting at 1.0 mg/kg/day

MAC-IRS

Case Presentation

- A 23 year old gay man not previously diagnosed with HIV presents with anorexia, dysphagia, a 25# weight loss over 6 months, night sweats, fatigue and diarrhea.
- On exam he is cachectic and apathetic. Temperature is 38.2, BP 90/60, HR 110, RR 14. He has obvious thrush, seborrheic dermatitis, indurated purple plaques on his face, feet and hard palate. His liver edge is 2 FB below his R costal margin.
- He tests + for HIV, his CD4 cell count measures 14 cells/uL and a plasma HIV RNA level is 454,000 copies/uL

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Case Presentation

- He declines hospitalization but receives several liters of IV fluids, is given fluconazole and TMP/SMX and goes home.
- He returns to clinic a week later without thrush or dysphagia.
- He claims to be taking TMP/SMX but his diarrhea, fevers and sweats continue, and he now complains of abdominal fullness and pain.

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Case Presentation

- CBC and chemistries: LDH 220, WBC 3.4, Hct 24, Plts 300K, ALT 54, AST 84, AP 480, TB 1,4, TP 9.0, Alb 2.1
- Stool O&P - negative
- Blood cultures for bacteria, mycobacteria, fungi – negative or pending
- Histoplasma urinary antigen negative
- PPD, IGRA – both negative

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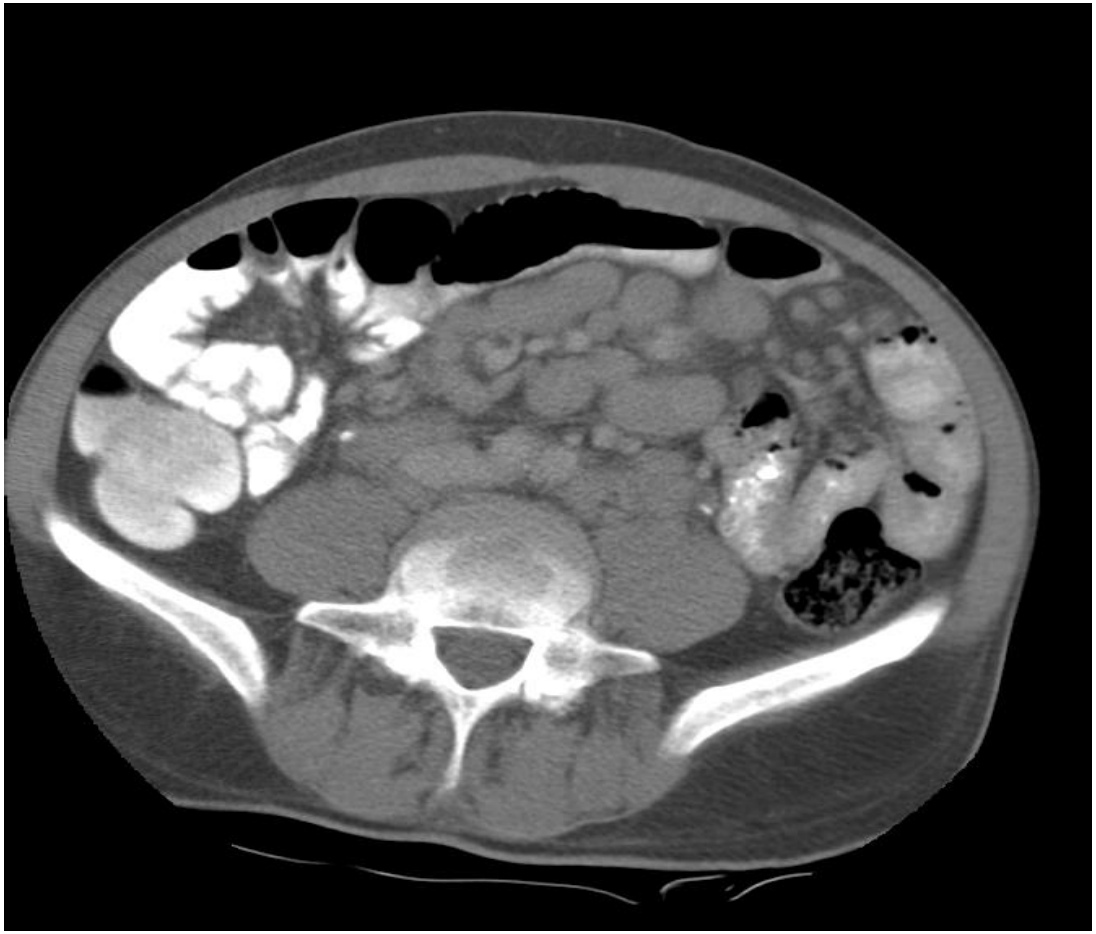
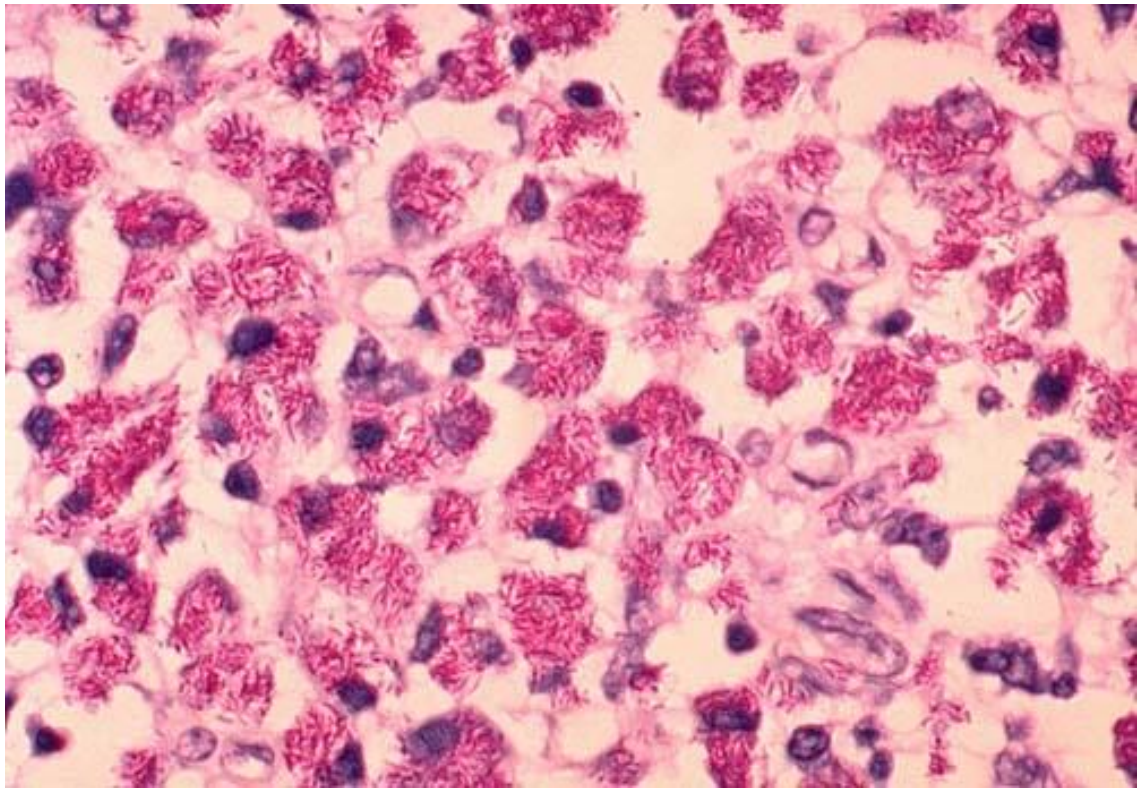
Case Presentation



Case Presentation



http://phil.cdc.gov/public/965.htm

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Case Presentation

- Azithromycin and ethambutol result in a gradual reduction in temperature, sweats and diarrhea over the next weeks.
- He is then started on ART (dolutegravir-TDF-FTC) and 3 weeks later presents with recurrent fever, abdominal pain and a L sided abdominal mass
- Imaging reveals……..

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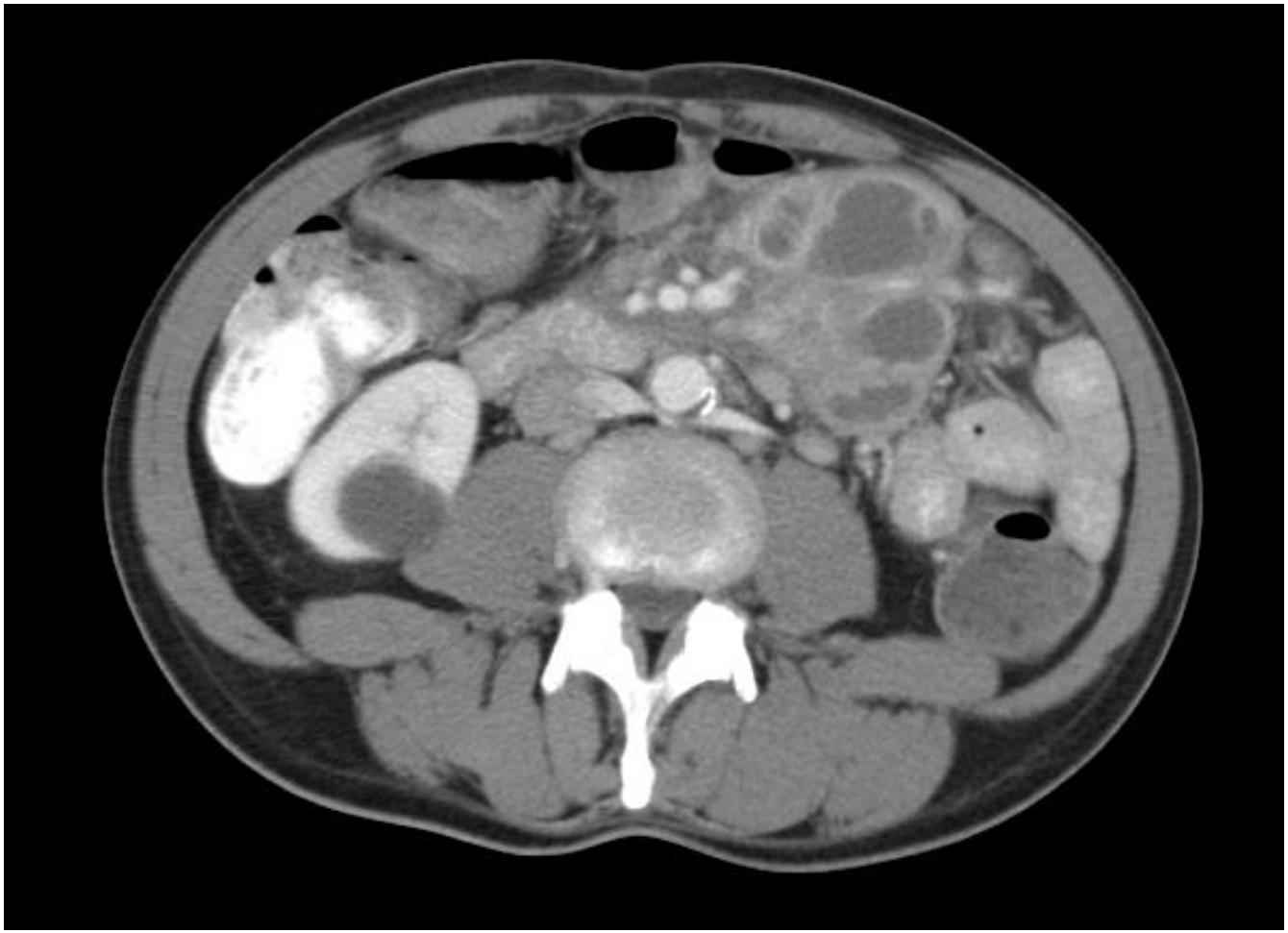
Case Presentation



Diagnosis?

MAC IRS

NTM IRIS: Observational cohort of 51 patients in British Columbia over a 10 year period ending 12/31/04

- Incidence: 3.5% of all patients starting ART with CD4 < 100
- Micro: *M. avium complex* (43), *M. genavense* (2), AFB stain + but did not grow (6)
- Clinically:
  - Peripheral adenopathy (17); draining sinuses (10)
  - Pulmonary-thoracic (15); infiltrates, nodules, cavities, tree-bud, collapse, pericardial effusion
  - Intra-abdominal (13); necrotic nodes, abscesses, ascites (chylous), obstruction, adrenal mass

Phillips, CID, 2005

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MAC IRS

NTM IRIS: Observational cohort of 51 patients in British Columbia over a 10 year period ending 12/31/04

- Clinically:
  - Median CD4 at start of ART = 20
  - Median CD4 at IRIS dx = 120
  - Median time to IRIS symptoms post-ART = 3 weeks
  - Median time to IRIS diagnosis post-ART = 10 weeks
- Treatment
  - 41/51 received > 2 weeks of abx – duration of symptoms – 6 months
  - 10/51 received no or < 2 weeks of abx – duration of symptoms – 3 months
  - 8/9 who received steroids responded well
  - 10 patients died (MAC (2), other OI (5), non-HIV related (3)

Phillips, CID, 2005

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MAC IRS

- Clinical presentation: fever, sweats, adenitis (cervical, inguinal, thoracic, abd/retroperitoneal)
  - Low CD4 (< 50): more severe illness; fevers, weight loss, leucocytosis, positive blood cultures
  - High CD4 (> 100-150): fewer systemic symptoms, more localized suppurative disease
- Treatment:
  - Continue ART
  - MAC therapy
  - NSAIDS
  - Steroids (prednisone 20-40 mg per day)

Race, Lancet, 1998, Phillips, JAIDS, 1998
Phillips, CID, 2005, Ratnam, CID, 2006, Lawn, AIDS, 2007

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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: Treatment

- People with HIV on ART who develop moderate-to-severe symptoms typical of IRIS should receive initial treatment with non-steroidal, anti-inflammatory drugs **(CIII).** If IRIS symptoms do not improve, short-term (4 weeks–8 weeks) systemic corticosteroid therapy, in doses equivalent to 20 to 40 mg of oral prednisone daily, has been successful in reducing symptoms and morbidity **(CII).**[29,74]

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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