NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Immune Reconstitution Syndrome, 2013

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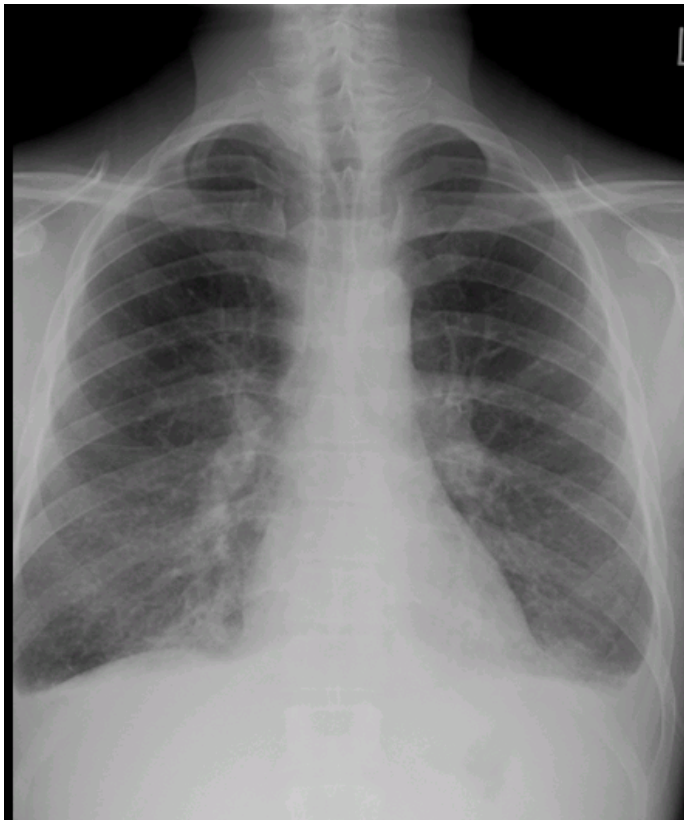
NW AETC | echo

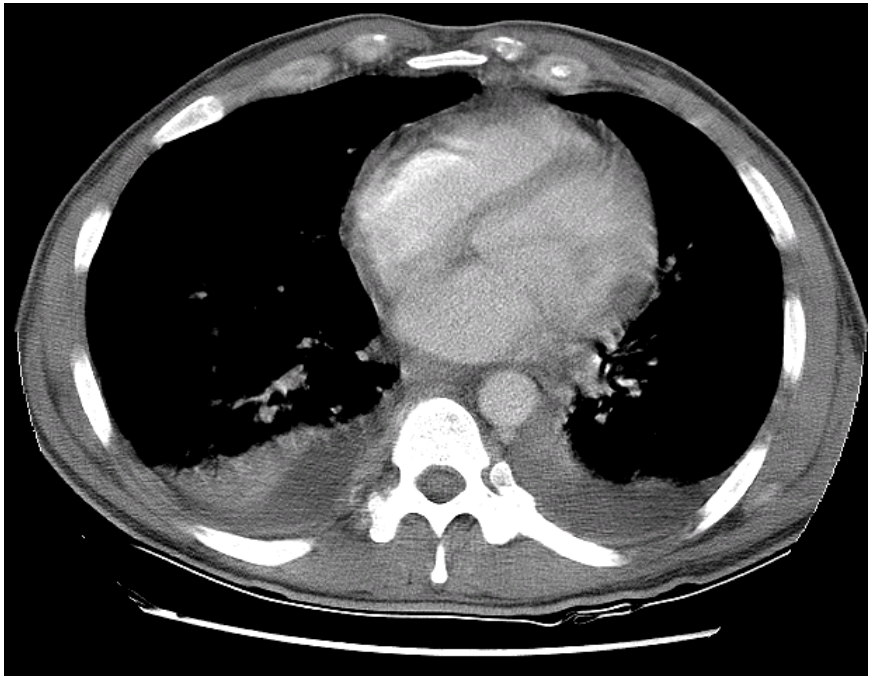
Case Presentation

- 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 PCP and CAP. CMV Ag was detected in blood. Ganciclovir, ethambutol, clarithromycin, and corticosteroids were added for possible CMV, MAC, or immune reconstitution
- 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

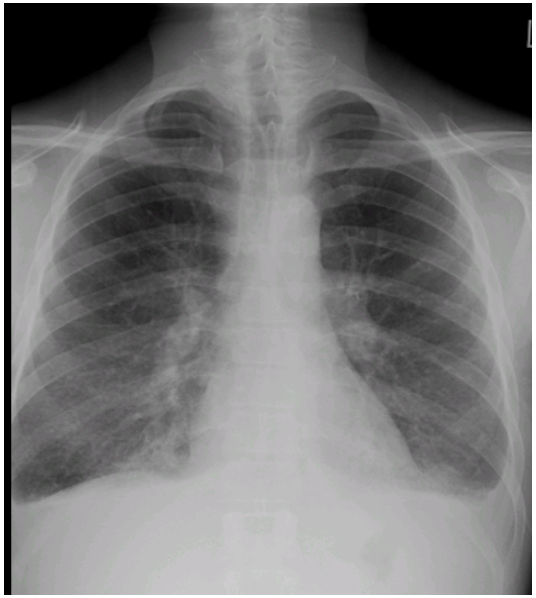
Case Presentation

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

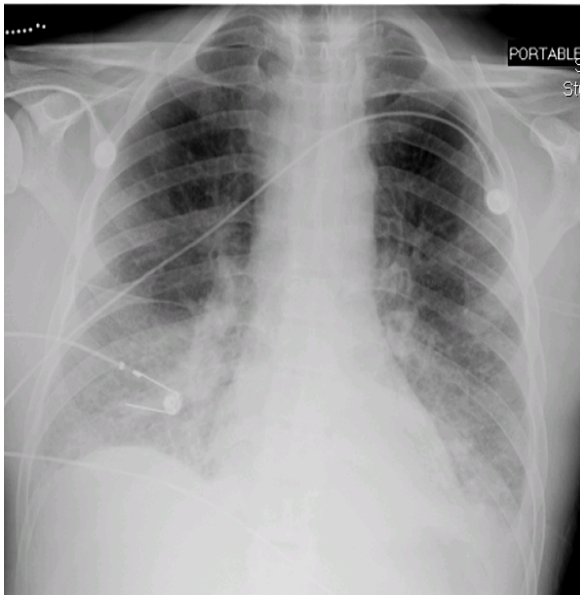
- The following day he developed a consumptive coagulopathy, ARF, and ARDS requiring intubation. Bronchoscopy was unrevealing.

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

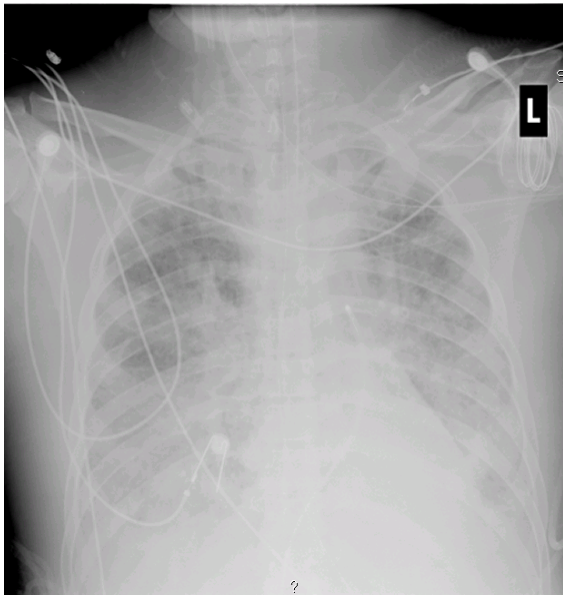
Case Presentation



Initial admission



Readmission



2 days later

Case Presentation

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

Immune Reconstitution Inflammatory Syndrome

IRIS: Definition

An illness…

- Occurring in an HIV + person
- 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, etc)

IRIS: Definition

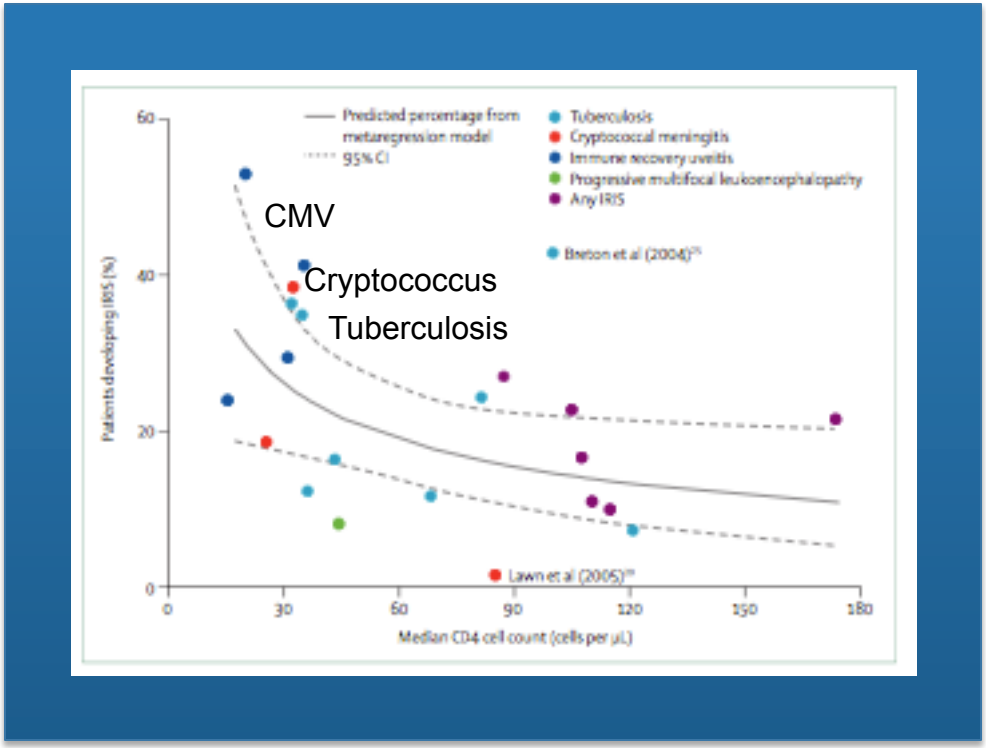
Two Versions

- 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

IRIS: Epidemiology

- Paradoxical
  - Tuberculosis 17% (range 8-45%)
  - Cryptococcus 20% (range 4-49%)
  - PML 17%
  - KS 7-31 %
- Unmasking
  - Tuberculosis 1-5%
  - Cryptococcus 1-2%



Haddow, PLoS One, 2012 and Muller, Lancet Infectious Diseases 2010

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	
Other factors	Host genetics, ARV naïve, low hemoglobin, PI-based ARV

Martin-Blondel, Curr Opin Infec Dis, 2012

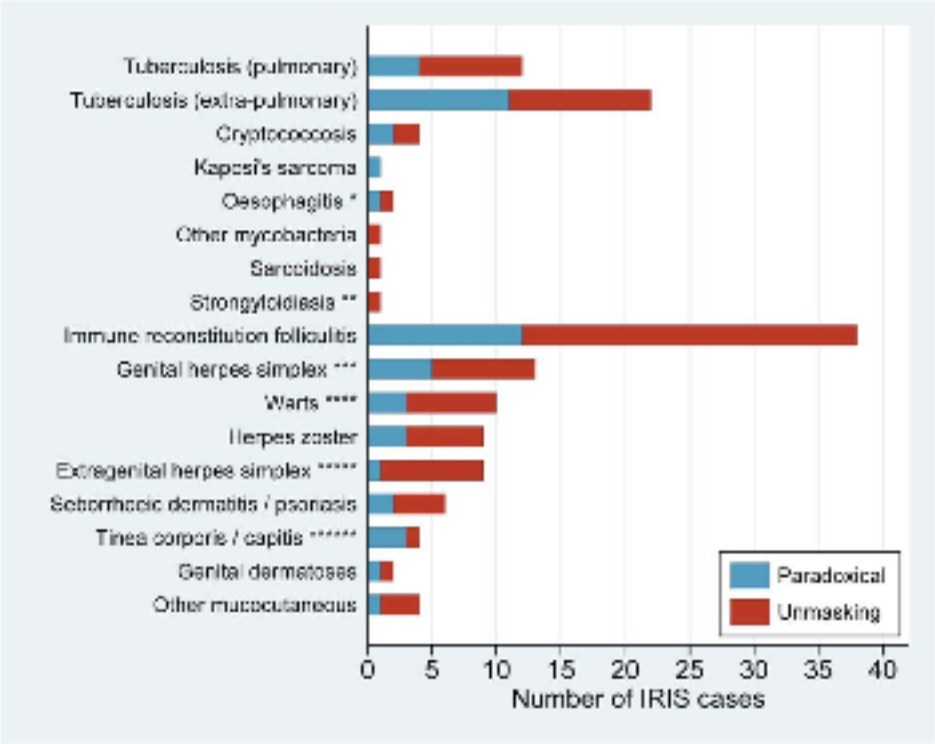
IRIS: Observational Study from South Africa

- Patients initiating ARVs in 2 clinics, followed for 24 weeks
- N = 498 patients, 620 events
- 139/620 IRIS events (22.4%)
- Non-IRIS events: new infections, pre-existing disease relapse or progression, drug toxicity, etc

Haddow, PLoS one, 2012

IRIS: Observational Study from South Africa

Overall rate of IRIS – 22.4%



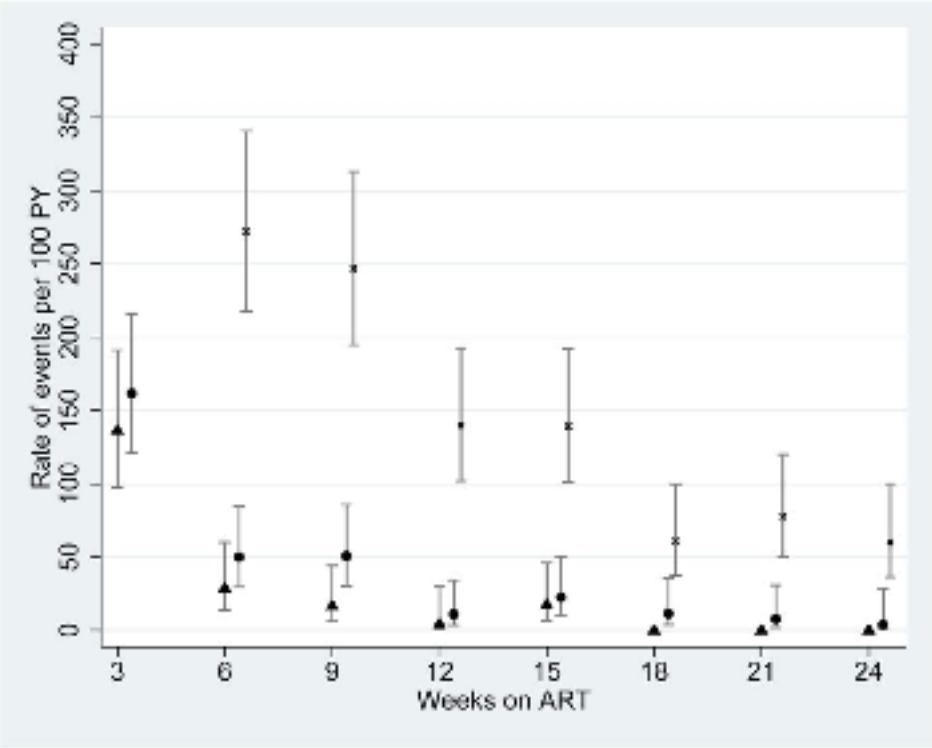
OIs

Mucocutaneous

Haddow, PLoS one, 2012

IRIS: Observational Study from South Africa

Timing of Disease



X - Non-IRIS events

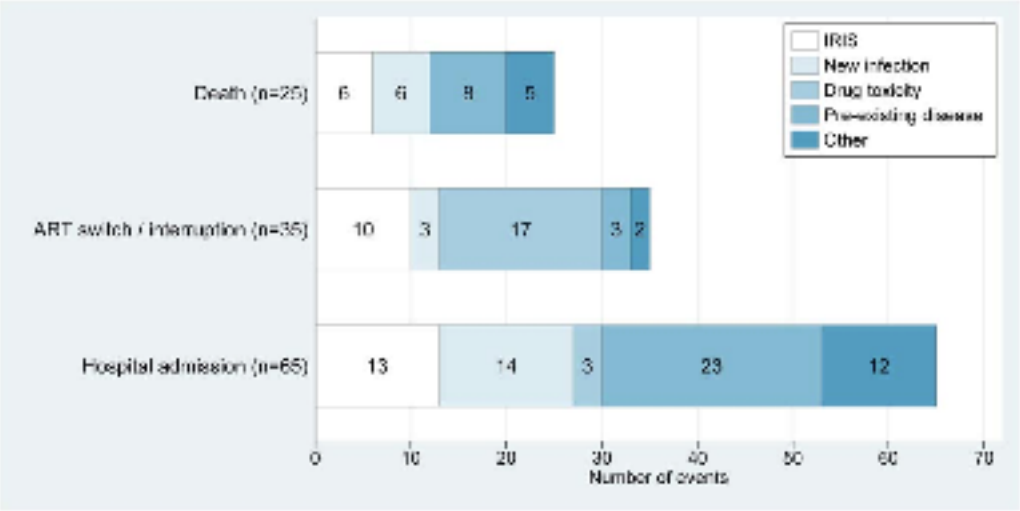
Δ IRIS-Paradoxical

O IRIS-Unmasking

Haddow, PLoS one, 2012

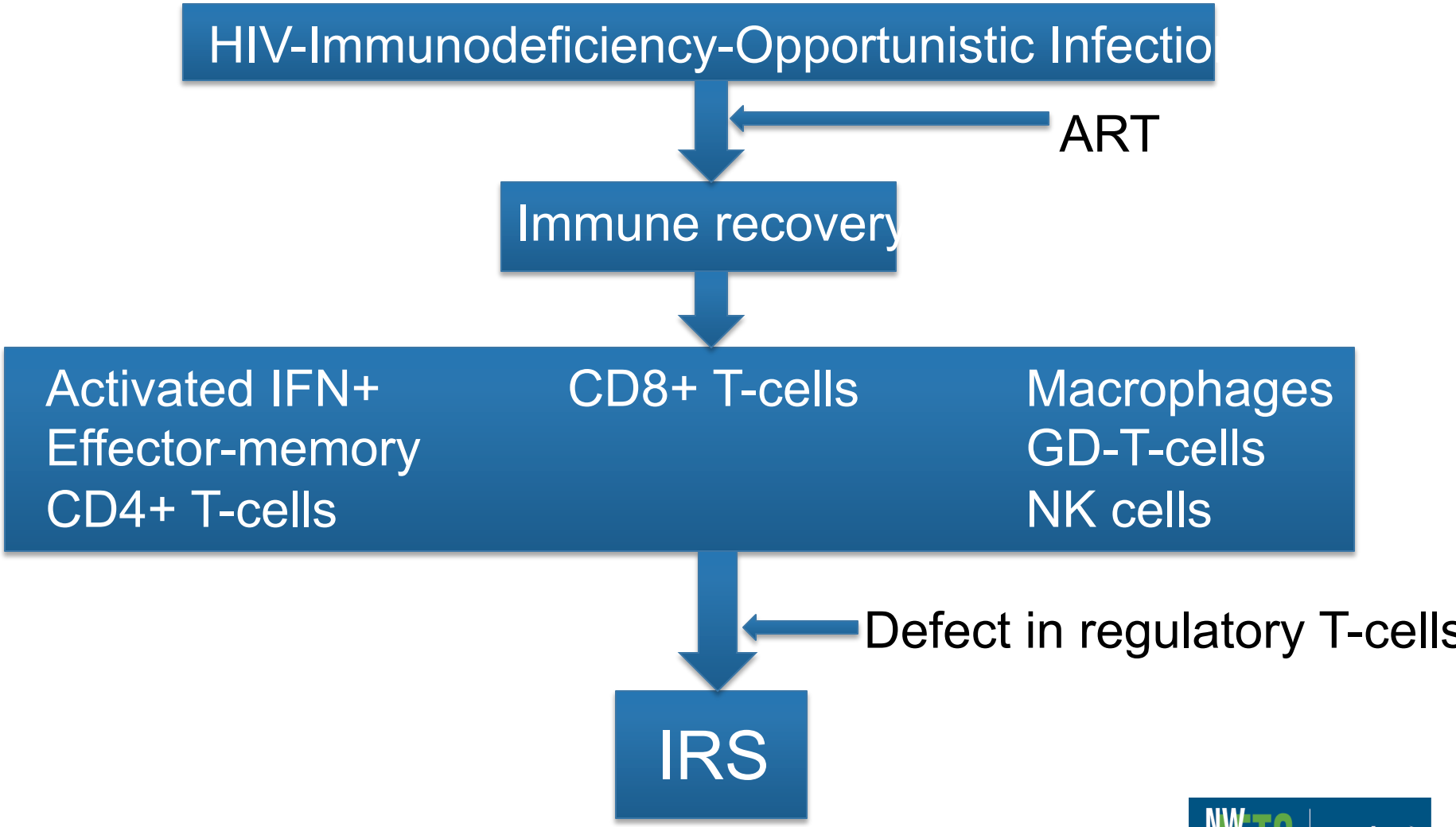
IRIS: Observational Study from South Africa

IRIS responsible for
24% of all deaths
28% of ARV changes
20% of hospital admissions



Haddow, PLoS one, 2012

IRIS: Pathogenesis



Martin-Blondel, Curr Opin Infect Dis, 2012

IRIS: Clinical Symptoms and Predicting Tests

- Symptoms
  - New or worsening adenopathy (TB, MAC, KS)
  - Hepatitis (HBC, HCV)
  - Pulmonary infiltrates (TB and fungi)
  - Vitritis (CMV)
  - Multi-organ symptoms (TB, MAC, fungi, KS)
  - CNS symptoms (JCV, Cryptococcus)
- Predicting Tests
  - Elevated plasma levels of IL-2, INF, TNF, IL-17, IL-8

Grant (for ACTG 5164), JID, 2012, Achenbach, CID, 2012

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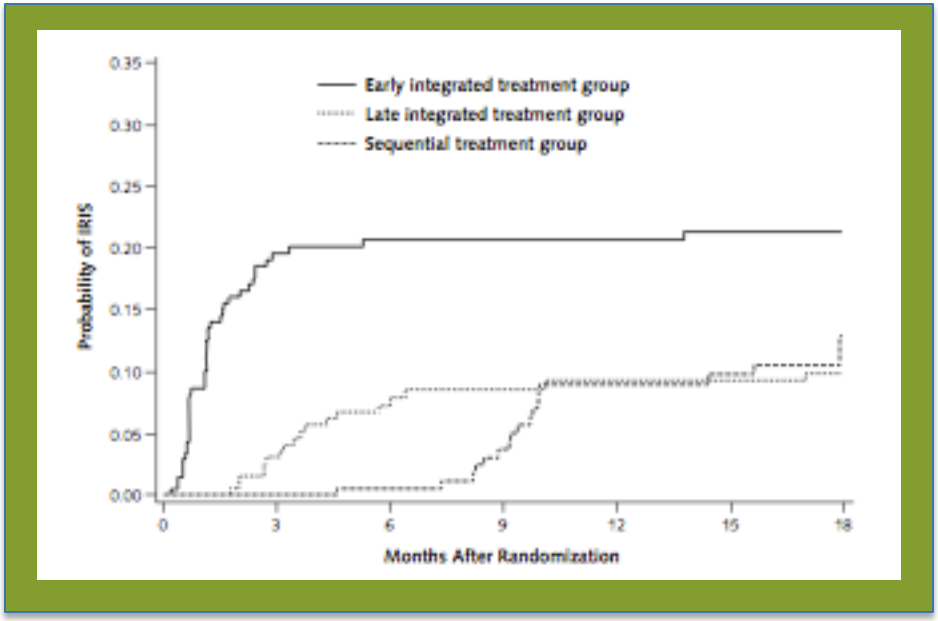
TB-IRS

SAPiT Trial

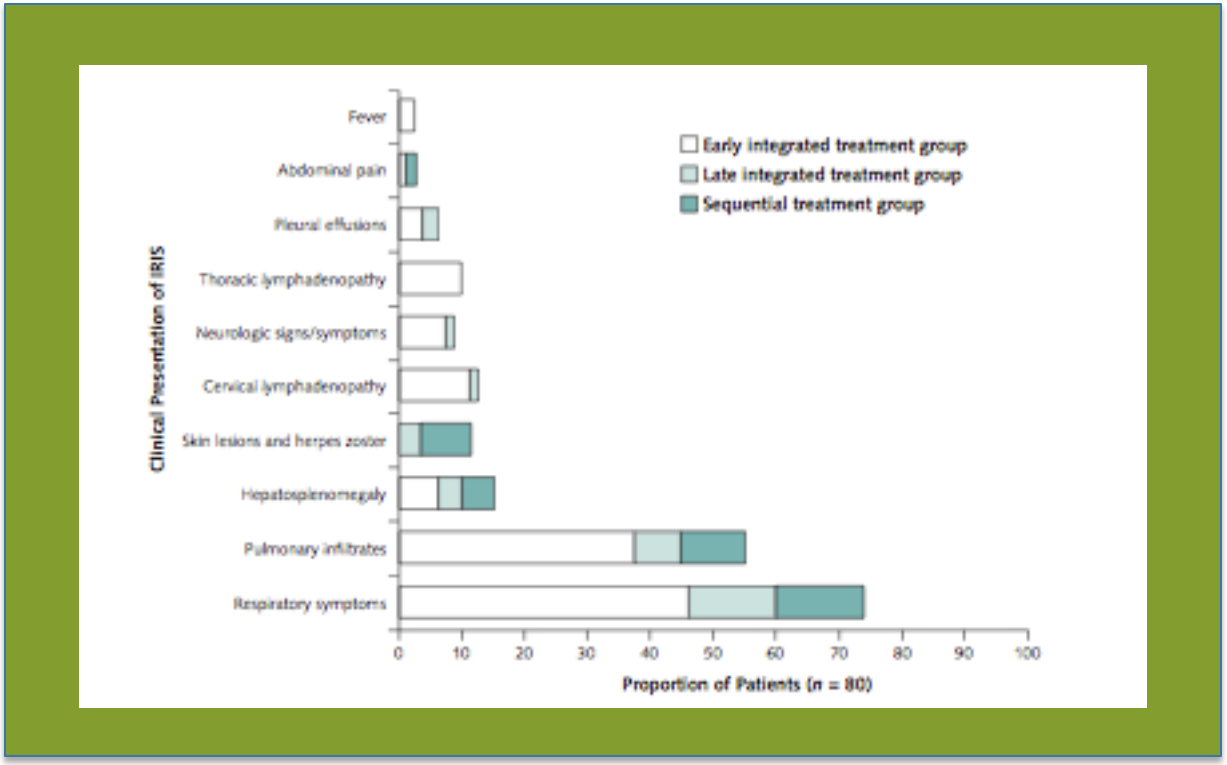
- Starting ARV at Three Points in TB
  - Starting ARVs within 4 wks of TB Rx (group 1)
  - Starting ARVs within 4 wks of completing the intensive phase of TB Rx (group 2)
  - Starting ARVs within 4 wks of completion of TB Rx (group 3)
  - N = 642
  - TB IRIS = 85
    - Group 1 = 43
    - Group 2 = 18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



(Naidoo, Ann Int Med, 2012)

SAPiT Trial

Symptoms of TB-IRIS



(Naidoo, Ann Int Med, 2012)

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)

Tuberculous Meningitis

- Prospective, observational study of 34 HIV+ patients with tuberculous meningitis (TBM)
- TBM-IRIS in 16/34
- TBM-IRIS associated with increased rate of culture + CSF (94% vs 33%)
- TBM-IRIS associated with higher median CSF WBC count (50 Vs 3)
- Combination of high CSF TNF and low IFN; predicted the development of TBM-IRIS

Marquis, CID, 2013

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

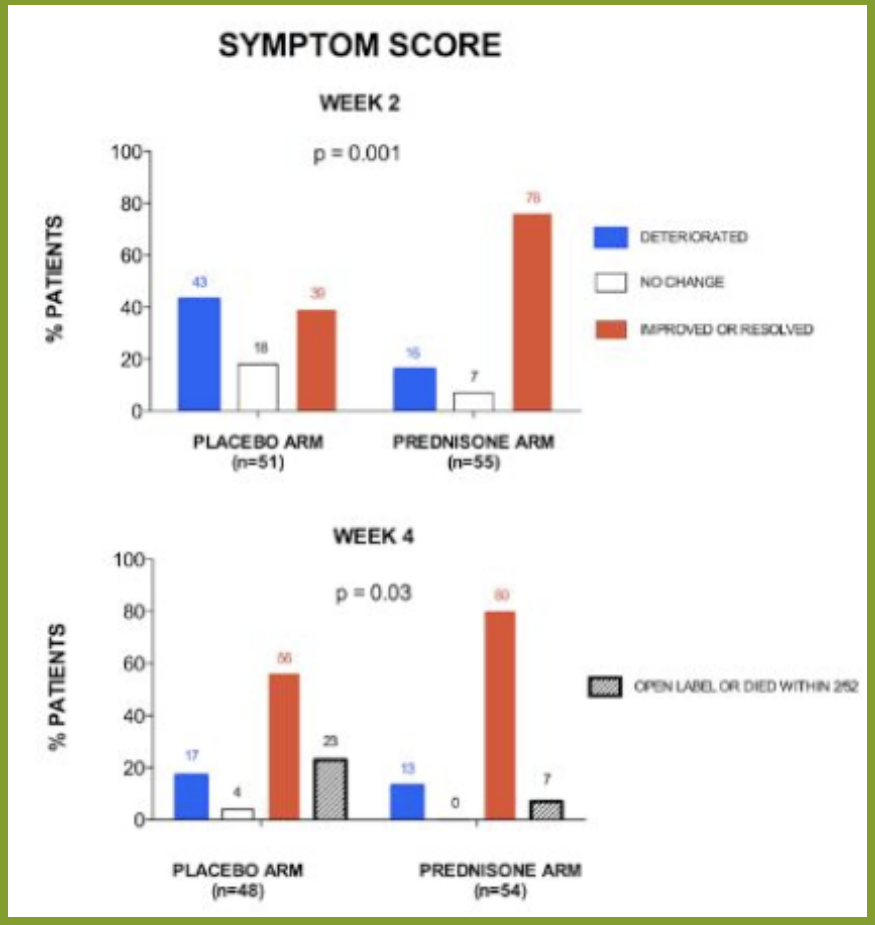
(Meintjes, AIDS, 2010)

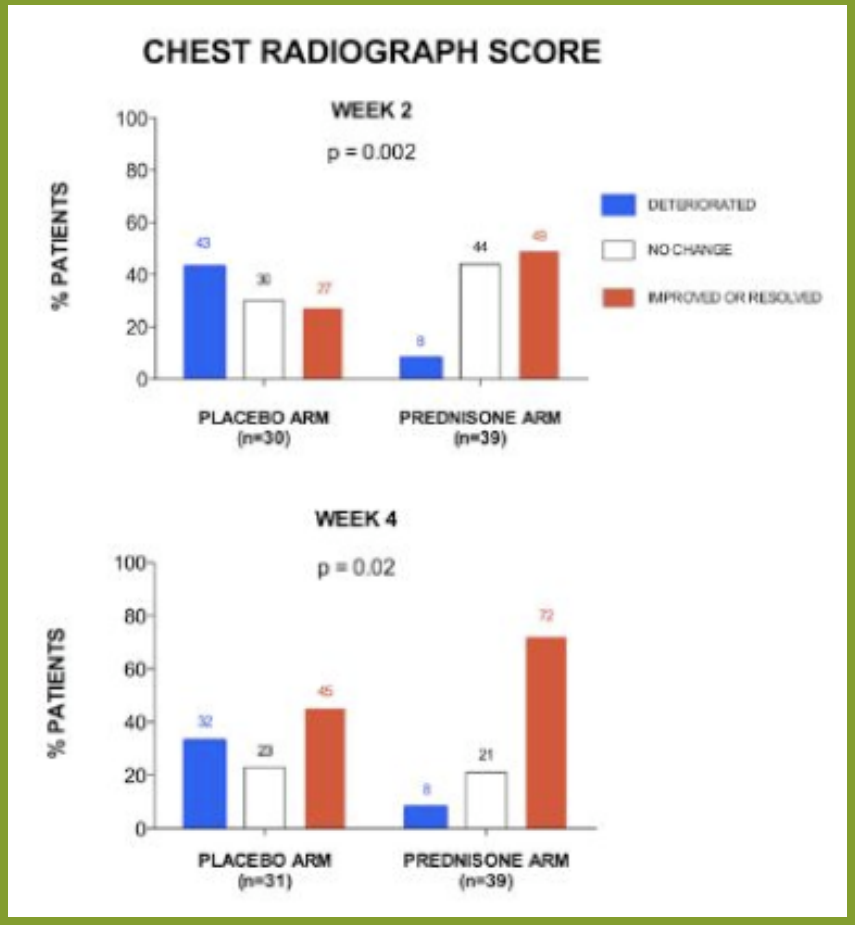
Randomized Placebo-Controlled Trial of Prednisone for TB-IRIS

	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 Outpatient procedures	282 27	463 31	
Median number of hospital days	1 (0-3)	3 (0-9)	0.046

(Meintjes, AIDS, 2010)

Randomized Placebo-Controlled Trial of Prednisone for TB-IRIS





(Meintjes, AIDS, 2010)

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)

Cryptococcal-IRS

Early Vs Delayed HAART in Patients with Cryptococcal Meningitis in Africa

- Open Label RCT
- Patients: Adults with HIV and *Crypto* 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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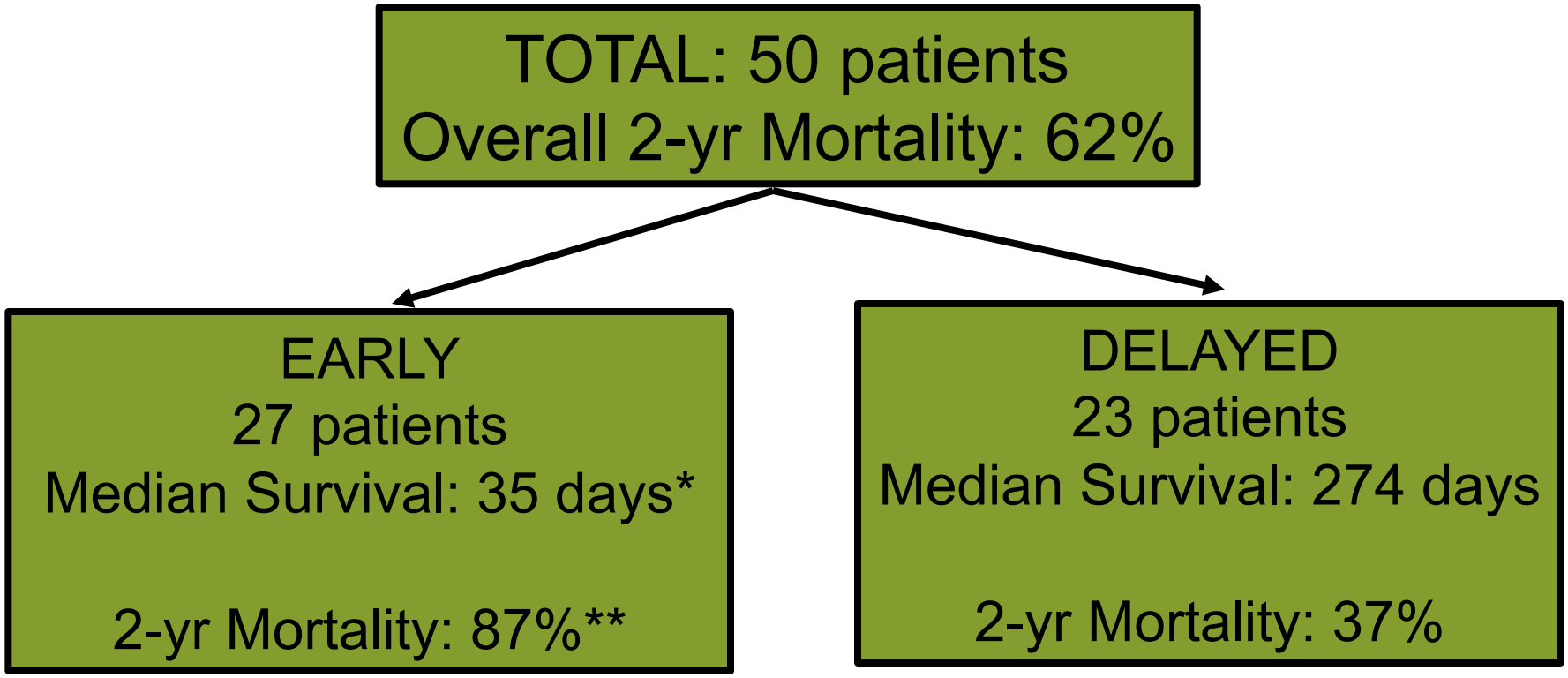
Early Vs Delayed HAART in Patients with Cryptococcal Meningitis in Africa

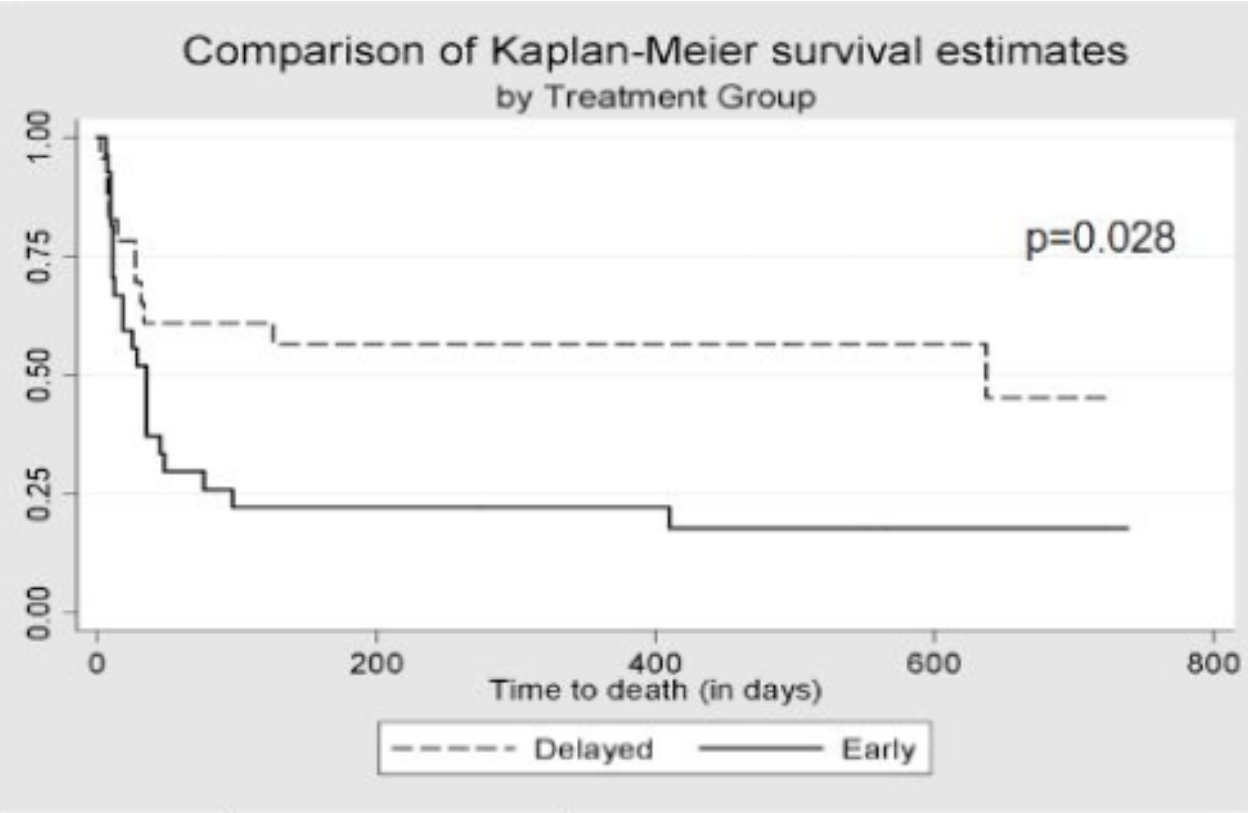


**Comparison of median survival, p=0.03*
***Comparison of 2-yr Mortality, p=0.002*

(Macadzange, CID, 2010;50:1532-38)

Early Vs Delayed HAART in Patients with Cryptococcal Meningitis in Africa

Survival



(Macadzange, CID, 2010;50:1532-38)

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
- **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, CROI 2013, Abstract 144

COAT: Cryptococcal Optimal ART Timing

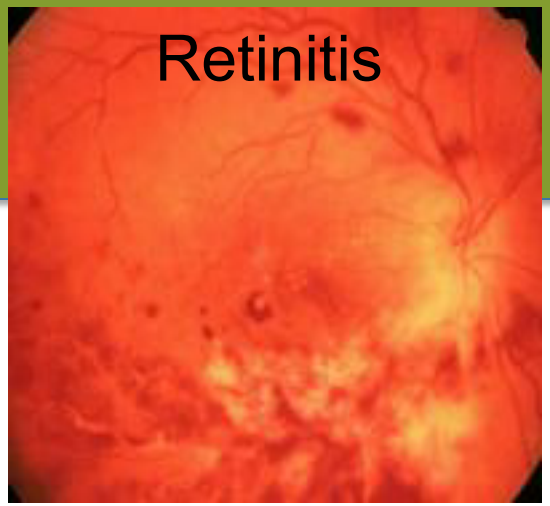
- **Secondary analyses:**
  - Mortality ↑ if AMS at presentation (GCS<15): HR 3.0
  - Mortality ↑ if CSF WBC <5/μL at presentation: HR 5.1
  - Trend toward ↑ IRIS in early group: 13% vs. 10%
- **Recommendations:**
  - Anti-cryptococcal therapy should always come before ART
  - In general, start ART at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

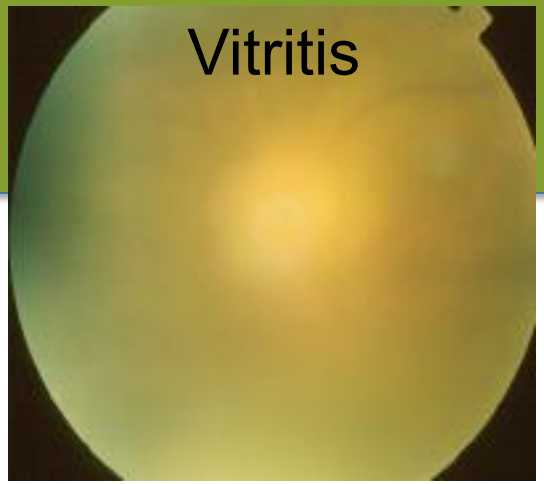
Boulware D et al, CROI 2013, Abstract 144

CMV-IRS

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

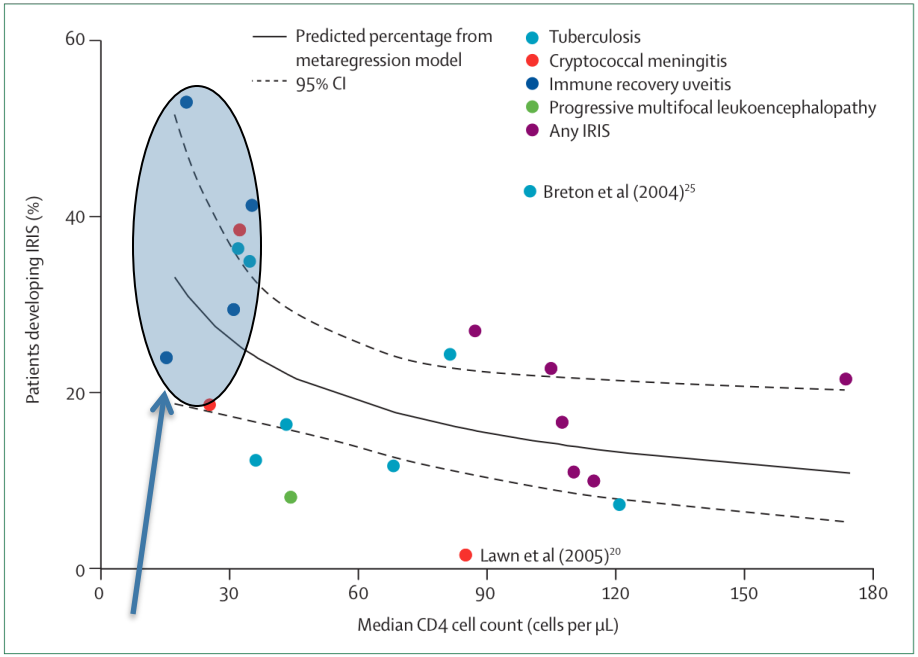




CMV-IRIS

- Meta-analysis of ART associated IRS: overall rate for CMV IRS of 37.7% (highest of all OI)
- Risk factors
  - Use of intravitreal cidofovir to treat CMVr
  - Starting ART before completion of the induction phase of CMV Rx
- Rx: steroids
- Outcome: variable

Proportion with IRIS



CMV

Muller, Lancet Infect Dis, 2010

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 and ARVs plus supportive care and the addition of anti-inflammatory therapy (NSAIDs, steroids, thalidomide)
- Outcomes are generally good with low mortality, exceptions being cryptococcal meningitis and visceral KS