NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Opportunistic Infections II

Shireesha Dhanireddy, MD
Associate Director, Madison Clinic
Assistant Professor of Medicine (Infectious Disease), University of Washington

Presentation Prepared by:
Christian B. Ramers, MD, MPH; Shireesha Dhanireddy, MD
Last Updated: April 6, 2012

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Outline

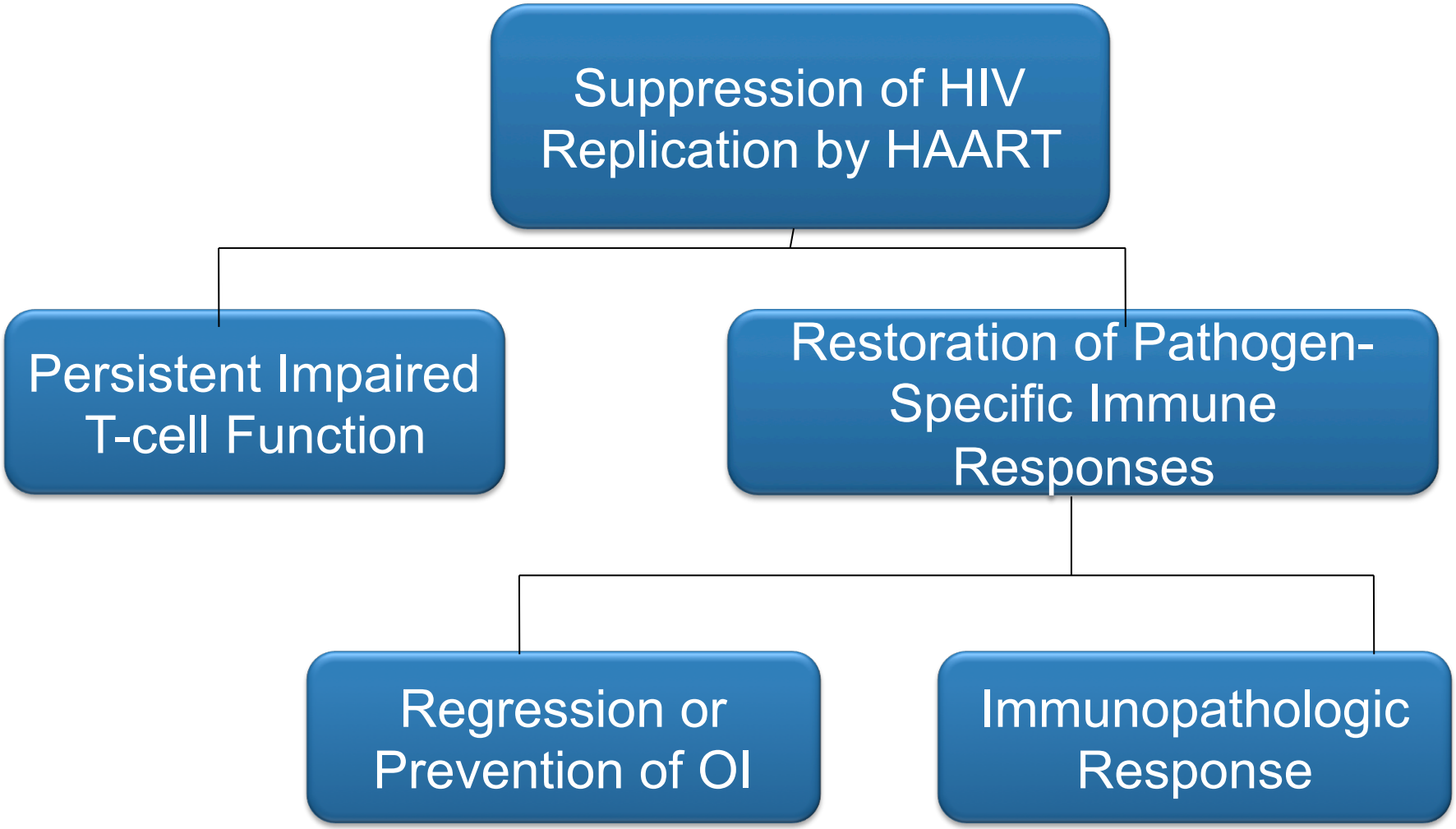
- **Opportunistic Infections I** – April 5, 2012
  - General Principles and Epidemiology
  - OI prevention and prophylaxis
  - Diagnosis and management of *Pneumocystis jiroveci* Pneumonia
- **Opportunistic Infections II** – April 12, 2012
  - Immune Reconstitution Inflammatory Syndrome
  - HAART in setting of acute OI's – ACTG 5164
  - Diagnosis and Management of MAC, Histoplasma, Candida

Immune Reconstitution Syndromes

Paradoxical worsening of an existing opportunistic infection or the emergence of a new infection after the initiation of antiretroviral therapy

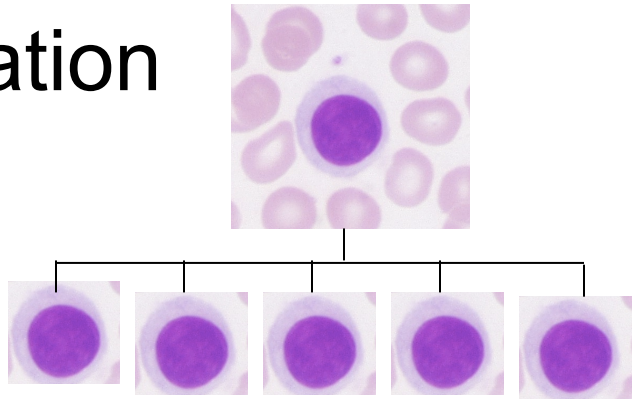
Novak RM et al. AIDS 2012 PMID 22233655

IRIS


Suppression of HIV Replication by HAART
Persistent Impaired T-cell Function
Restoration of Pathogen-Specific Immune Responses
Regression or Prevention of OI
Immunopathologic Response

IRIS Pathogenesis

Increased lymphocyte proliferation



Increased immune activation

CYTOKINES

Pathogen-specific effector T-cell response
(Type IV immune response)

Infections Associated with IRIS

Mycobacteria
- MAC
- MTB
- *M. leprae*

Fungi
- *Cryptococcus*
- *Pneumocystis jiroveci*
- *Histoplasma*
- *Candida*

Viruses
- CMV (vitritis)
- JC virus (PML)
- Hepatitis B and C
- HHV-8 (Castleman's Disease)
- VZV

Viruses
- Molluscum
- HSV
- Parvovirus B19

Protozoa
- Toxoplasma
- Microsporidia
- Leishmania
- Cryptosporiosis

Bacteria
- Bartonella

Worms
- Schistosoma
- Strongyloides

Novak RM et al. AIDS 2012 PMID 22233655

IRIS

Infection	Incidence	Timing relative to ARVs	Clinical	Rx & Outcomes
TB	15.7%	Within 2 months	Fever, new infiltrates, suppurative adenitis	NSAIDs, steroids: up to 3.2% death rate
MAC	3.5%	Within 2 months	Fever and suppurative adenitis	NSAIDs, steroids: rare IRIS death
Crypto	19.5%	Usually 1 month but up to 12?	Increased IC pressure	Steroids, up to 20.8% death rate
PCP	common	Early – days to weeks	Fever, worsening infiltrates, hypoxia	Steroids: Good
CMV	37.7%	Within 2 mo, but can be later	Vitritis	Steroids: poor visual outcomes
KS	6.4%	Within 2 mo, can be 1 yr	New or expanding lesions	Steroids: death rate up to 25%
PML	16.7%	Usually within 2 months	Progressive neurological findings	Steroids; variable

IRIS Diagnostic Criteria

- Low pre-ART nadir (usually < 100 cell/mm^3)
- Good virologic & immunologic response to ART
- Temporal association
- Absence of other explanation – i.e. progressive disease from OI, new OI, drug toxicity

Immune Reconstitution Syndromes

Epidemiology

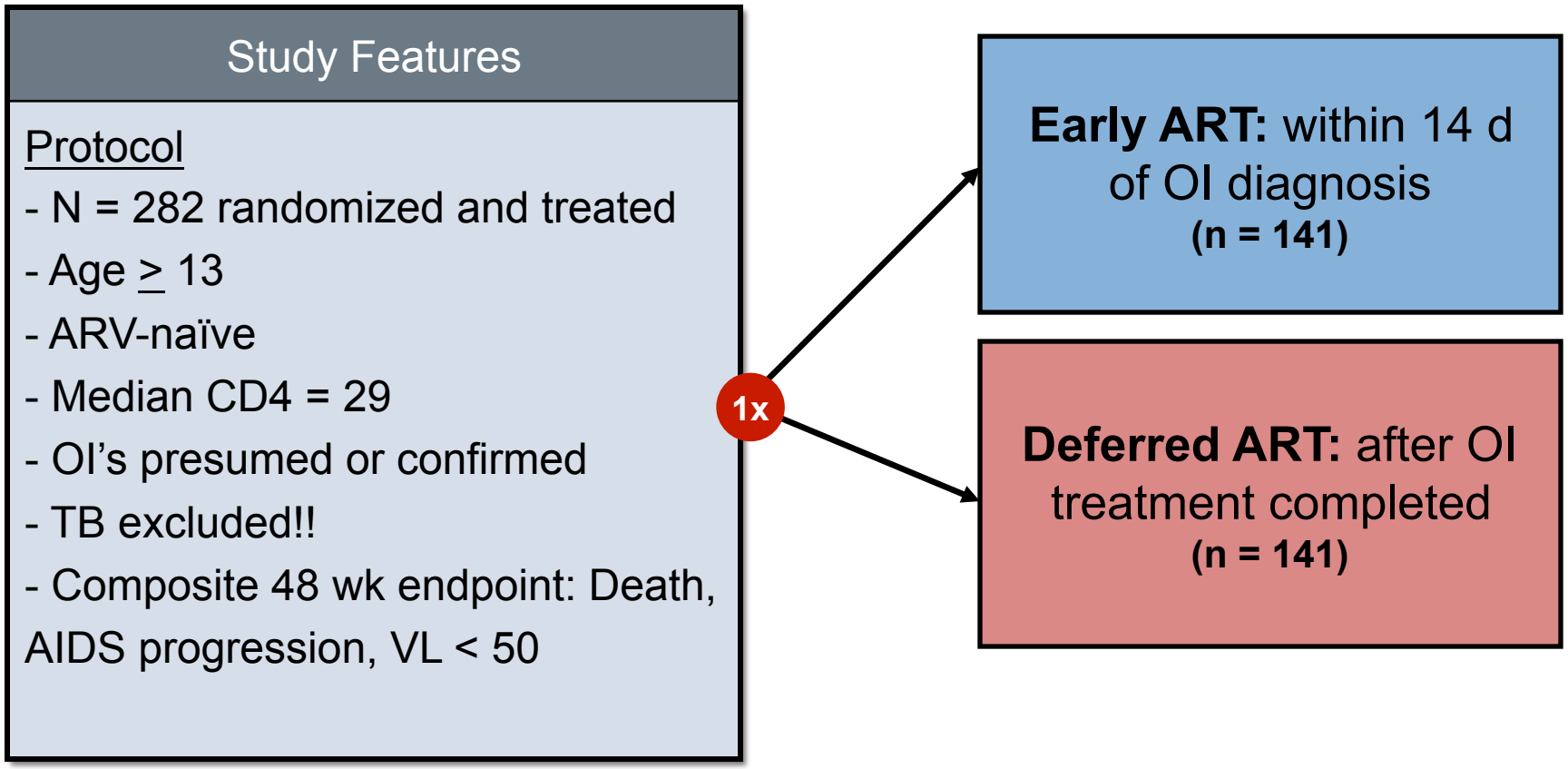
- 10-32% of patients staring ARVs

Risk factors

- Rapid decline in HIV RNA
- Low baseline CD4
- Initiation of ARVs soon after Rx for the OI
- Disseminated OI
- ARV naïve

Sharma, 2011, Indian J Med Res 134: 866-77
Novak RM et al. AIDS 2012 PMID 22233655

ACTG 5164 – HAART in setting of Acute OI



- Entry OI's: PJP (63%), Crypto (12%), Bacterial Infection (12%), Toxo (5%), Histo (4%), CMV (2%), MAC (2%), [Multiple 33%]

Zolopa A, *et al* PLoS One 2009; 4(5): 5575

ACTG 5164 – HAART in setting of Acute OI

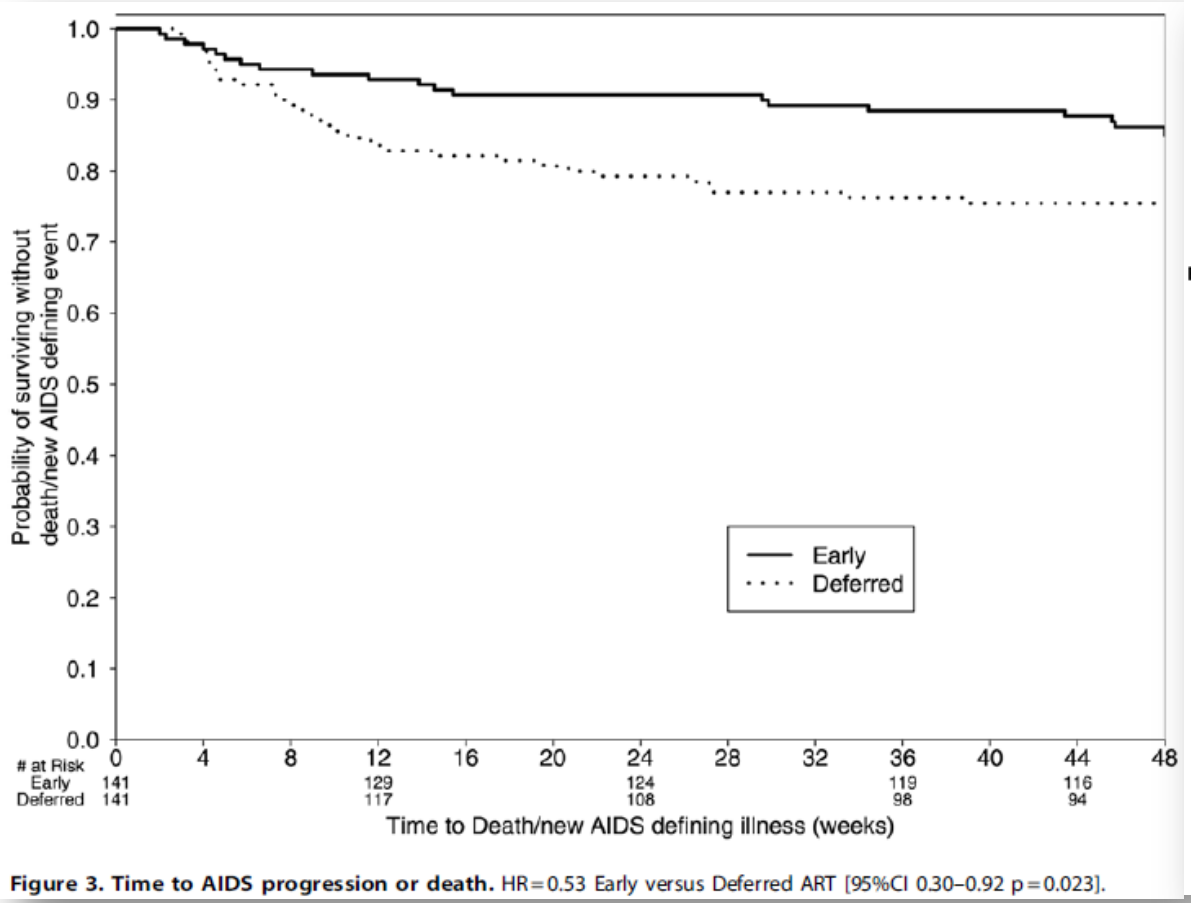
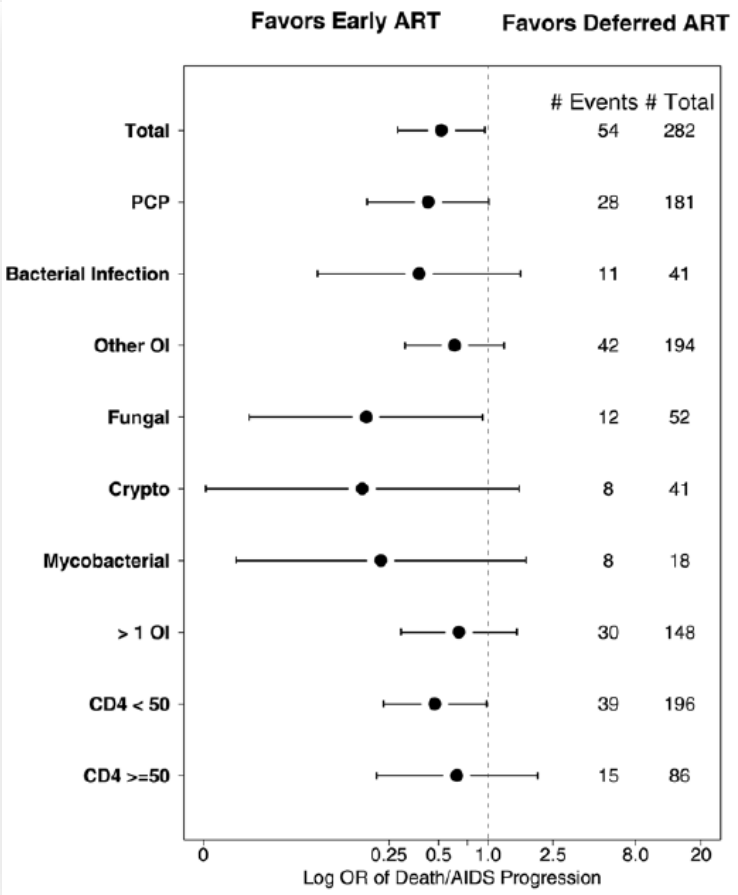


Figure 3. Time to AIDS progression or death. HR=0.53 Early versus Deferred ART [95%CI 0.30–0.92 p=0.023].



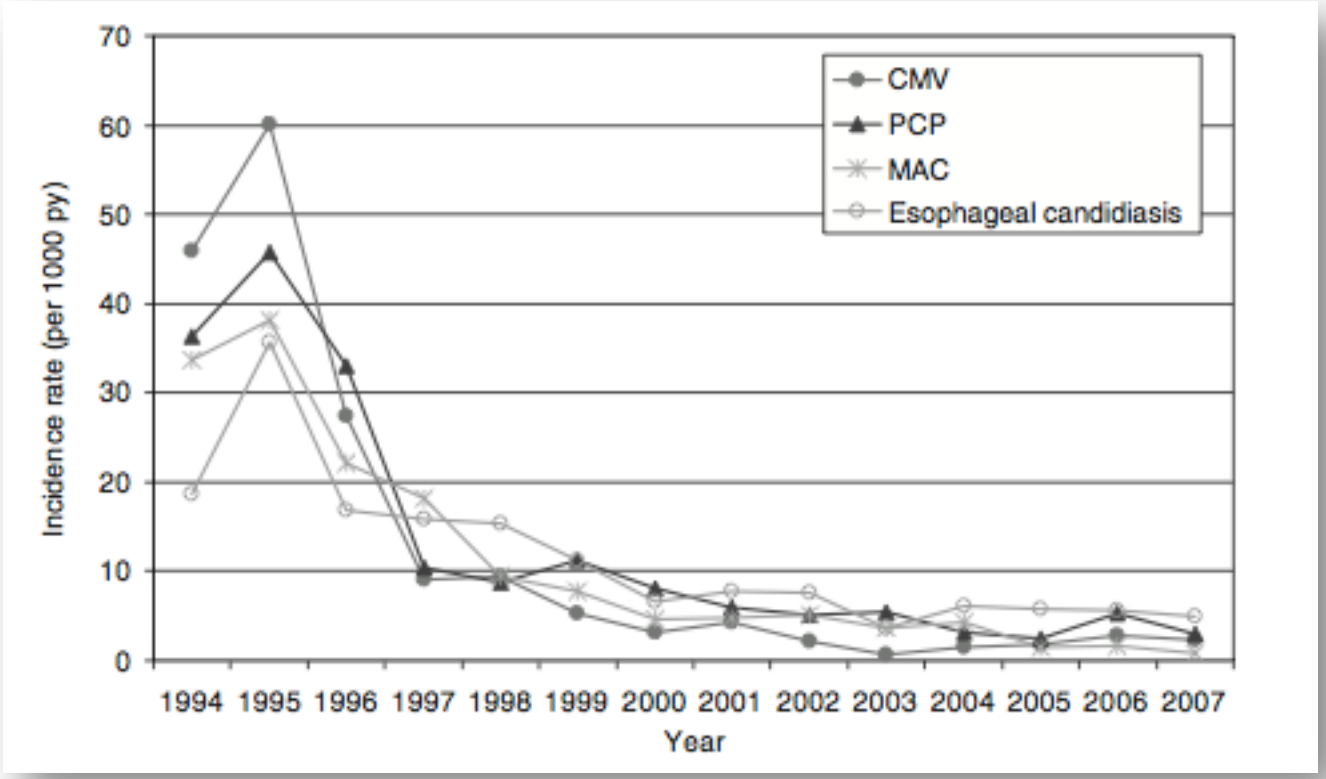
- HR 0.53 (95%CI 0.3-0.92) favoring early ART

Zolopa A, *et al* PLoS One 2009; 4(5): 5575

Mycobacterium Avium Complex (MAC)

Ubiquitous organism - water and soil

Patients with CD4 counts < 50 at risk



Buchacz K et al. AIDS 2010

MAC – Clinical Manifestations

Disseminated disease - usually seen in patients not on ART

- Diffuse LAD
- Fevers
- Diarrhea
- Pancytopenia
- Hepatomegaly, increased alk phos
- Asymptomatic

MAC – Clinical Manifestations

Localized disease

- Lymphadenitis
- Pneumonitis
- Osteomyelitis
- Skin/soft tissue infection
- CNS disease

MAC – Diagnosis and Treatment

Diagnosis

- Sensitivity of blood cultures - 100% for disseminated disease in one study
- Bone marrow biopsy
- Lymph node biopsy

Treatment

- Macrolide (clarithro or azithro) + Ethambutol +/- Rifabutin

MAC - Treatment

Syndrome	Preferred	Alternative	Comments
Disseminated MAC	Clarithromycin 500 mg PO BID (AI), **PLUS**	Azithromycin 500-600 mg PO QD (AII), **PLUS**	3rd or 4th drug should be considered for CD4 < 50
	Ethambutol 15 mg/kg PO QD (AI)	Ethambutol 15 mg/kg PO QD (AI)	
	Rifabutin 300 mg PO QD may be considered (CI)	Amikacin 10-15 mg/kg IV Streptomycin 1 g IV/IM Ciprofloxacin 500-750 PO BID Levofloxacin 500 mg PO QD Moxifloxacin 400 mg PO QD	Dose adjustment of Rifabutin may be necessary based on drug-drug interactions
Chronic Maintenance (2o Proph)	Same as treatment regimens		Duration is lifelong (AII), unless sustained immune recovery on ART(BII)

MMWR 2009; 58 (RR4): 1-132

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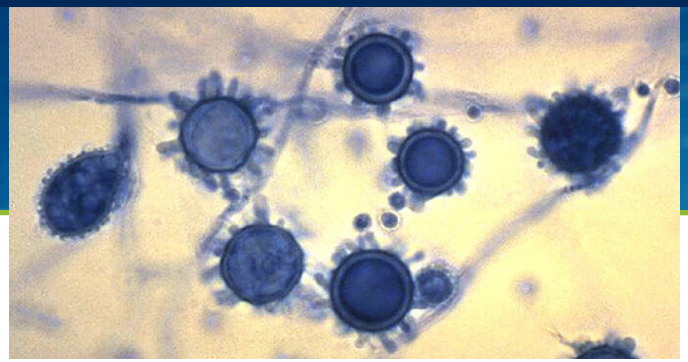
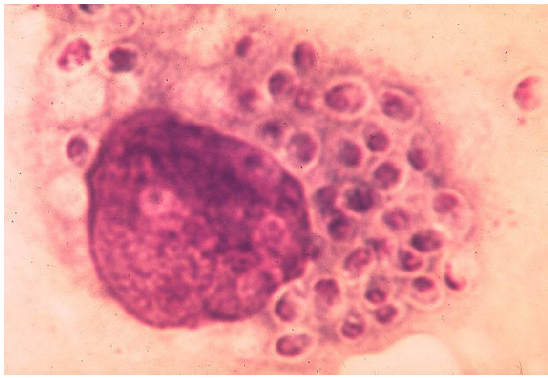
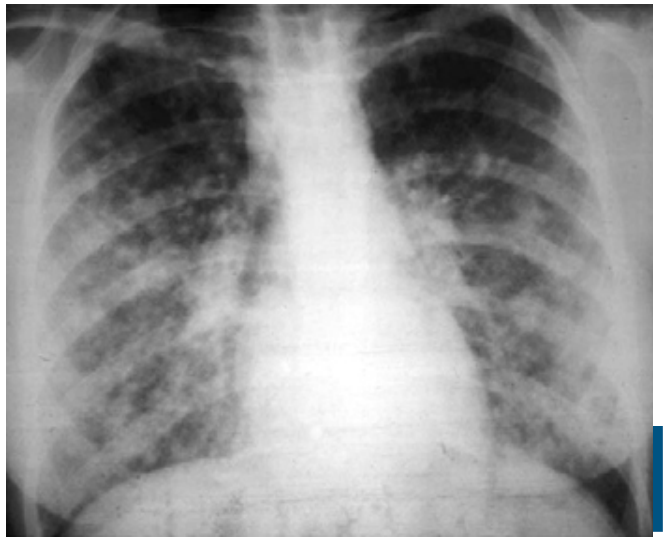
Histoplasmosis



- **Etiology:** *Histoplasma capsulatum*
- **Presentation:**
  - **Acute: febrile pulmonary infection**
  - **Reactivation: fever, chills, wt loss, bone marrow failure, anemia, high LFT's, may have evidence of old disease on CXR**
- **Pathophysiology:** Initially latent disease, with reactivation upon immunosuppresion
- **Diagnosis:** Direct visualization of fungus, culture, Serum or Urine Antigen test
- **Mortality:** low in immune competent; high in immunosuppressed.
  - **Risk Factors: dyspnea, plt < 100K, high LDH**





Histoplasma Distribution

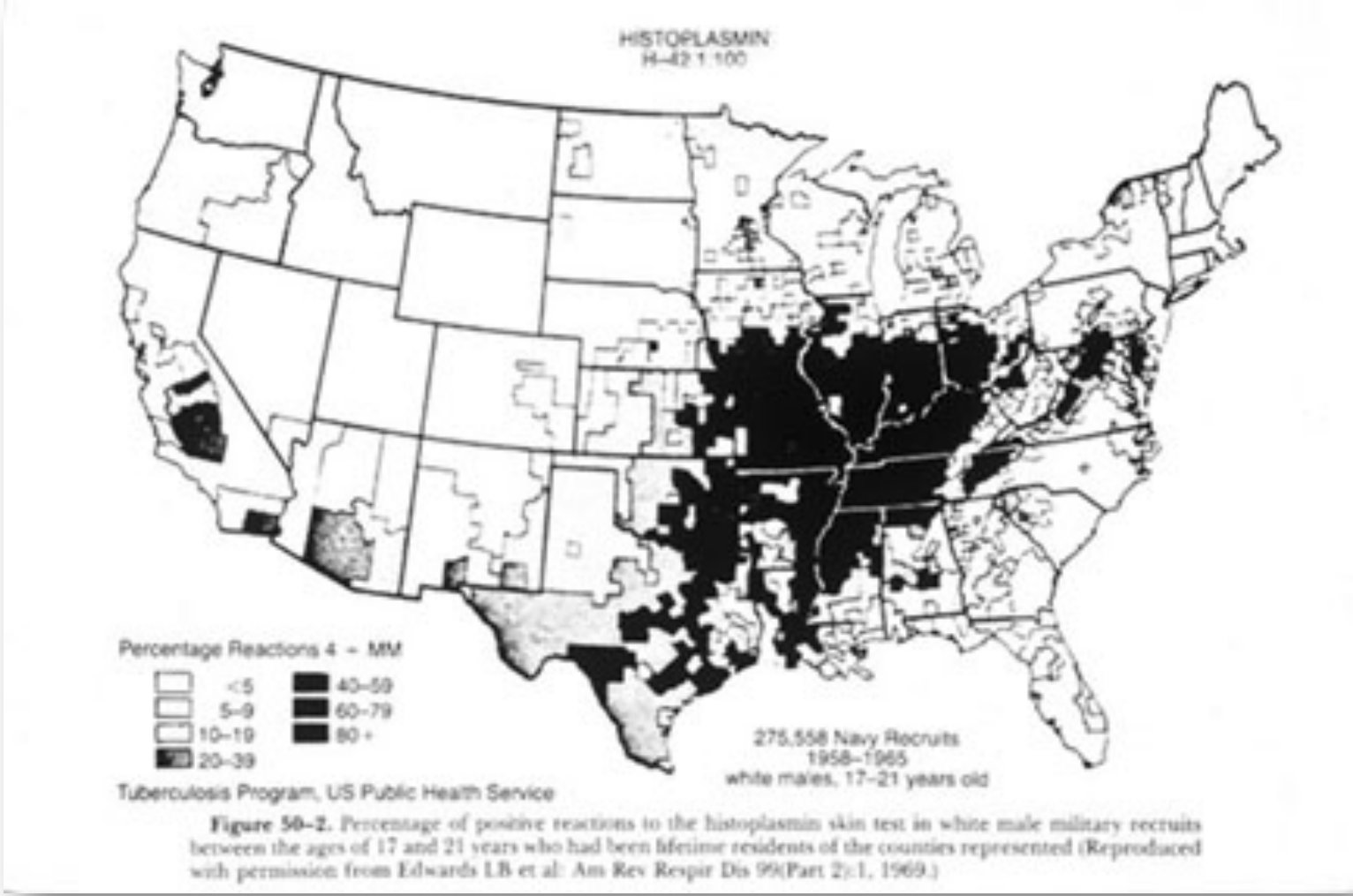


Figure 50–2. Percentage of positive reactions to the histoplasmin skin test in white male military recruits between the ages of 17 and 21 years who had been lifetime residents of the counties represented (Reproduced with permission from Edwards LB et al: Am Rev Respir Dis 99(Part 2):1, 1969.)

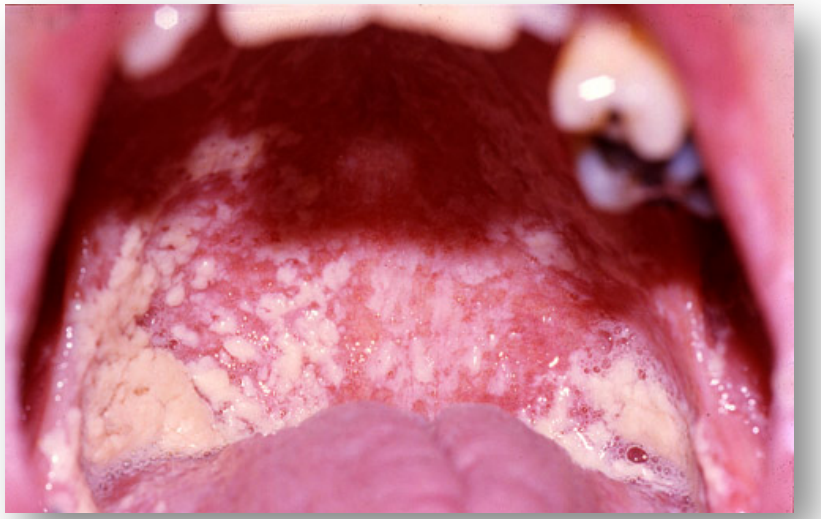
Edwards LB; *Am Rev Repir Dis.* 1969; 99(4):Suppl: 1-132

Histoplasmosis - Treatment

Syndrome	Preferred	Alternative	Comments
Severe Disseminated	Liposomal Ampho B 3 mg/kg x 14 d (AI)	Ampho B ABLC	
	Itraconazole 200 mg TID x 3d → BID (AII)		Levels should be obtained (AIII)
Less Severe Disseminated	Itraconazole 200 mg TID x 3 d → BID (AII)		Duration ≥ 12 mos
Meningitis	Liposomal Ampho B 5 mg/kg x 4-6 wks		
	Itraconazole 200 mg BID/TID x > 1 year		Treat until CSF normalizes
Long-term suppression	Itraconazole 200 mg QD		Recommended for CNS disease or any relapse

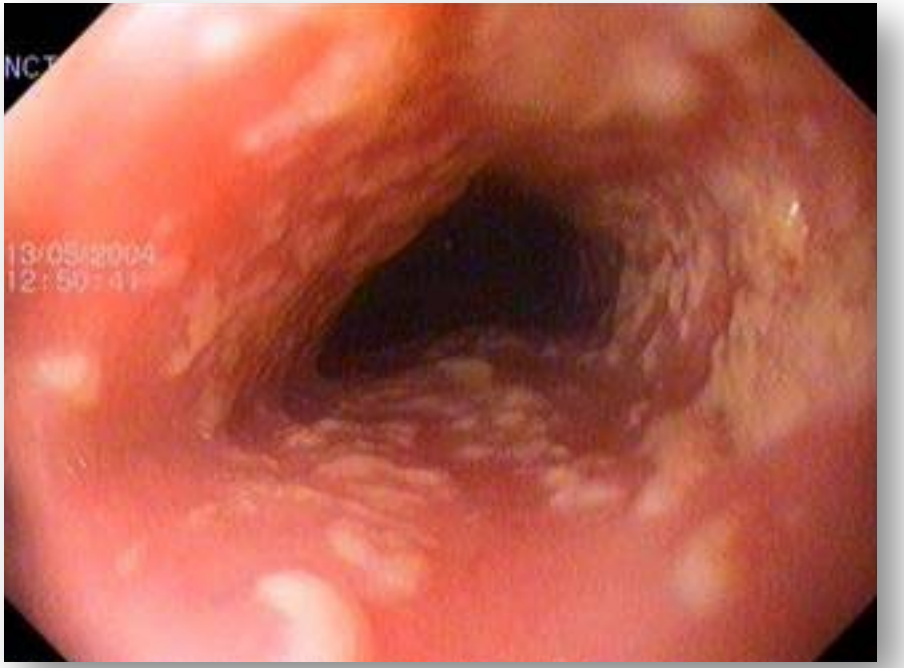
MMWR 2009; 58 (RR4): 1-132

Candidiasis



Oral Candidiasis, aka thrush

Esophageal Candidiasis



Candidiasis - Treatment

Infection	Preferred	Alternative	Comments
Oral	Fluconazole 100 mg QD (AI) **x 7-14 d**	Itraconazole 200 mg QD (BI)	Chronic Azoles may promote resistance
	Clotrimazole 10 mg troche 5X/day	Posaconazole 400 PO BID x 1→QD	Higher relapse w/ echinocandins
	Nystatin susp 5 mL QID (BII)		
	Miconazole QD (BII)		
Esophageal	Fluconazole 100-400 mg QD **x 14-21 d** (AI)	Echinocandin: Mica-, Caspo-, Anidulafungin (BI)	Suppressive therapy not recommended
	Itraconazole 200 mg QD x 14-21 d (AI)	Azole: Vori-, Posaconazole (BI)	
		Amphotericin B (BI)	

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Summary

- Opportunistic infections are predictable based on a patients immune status and environment
- The timing of HAART relative to OI therapy is controversial but should probably be early…..however, watch out for IRIS!