NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Meningitis in HIV

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NW AETC | echo

Susceptibility to CNS Opportunistic Infections

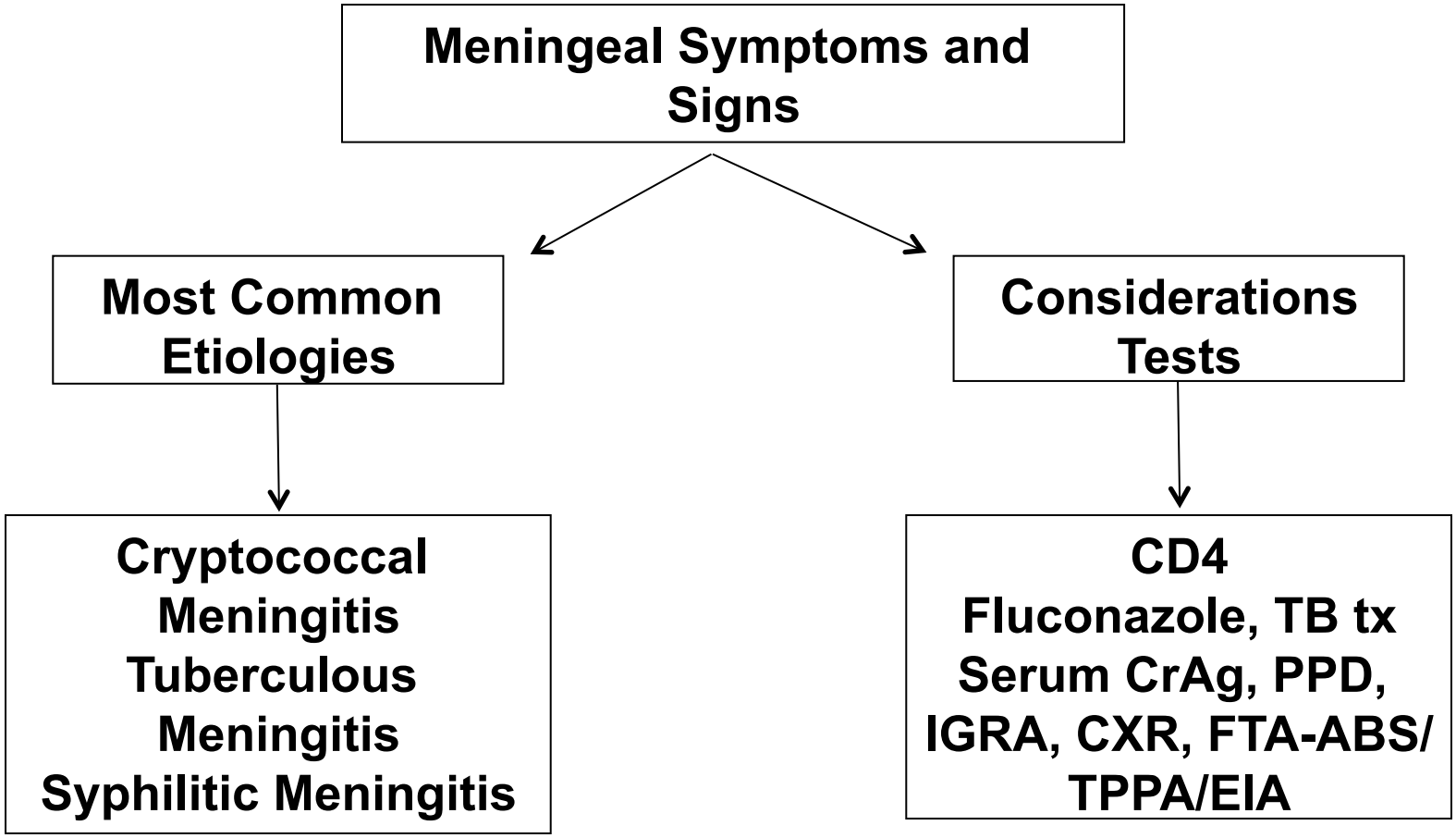
	CD4+ cells/ul		
	500-200	< 200	< 100
Neurosyphilis	X	X	X
TB	X	X	X
HIV Dementia		X	X
Crypto, Toxo		X	X
PCNSL, PML			X
CMVE			X

PCNSL, primary CNS lymphoma; PML, progressive multifocal leukoencephalopathy; CMVE, CMV encephalitis

Other Susceptibility Considerations

- Exposures
  - Serum anti-*Toxoplasma* antibody
  - Serum treponemal tests
    - FTA-ABS, TPPA, EIA
- Prophylactic therapies
  - TMP/SMX (Bactrim)
  - Fluconazole

Approach to Diagnosis



CNS IRIS

- Clinical worsening or new disease after starting potent antiretroviral therapy (ART)
  - Paradoxical
    - Known disease
  - Unmasking
    - New onset after starting ART
    - No prior known disease

CNS IRIS

	Paradoxical	Unmasking
Toxoplasmosis	Very rare	5%
PML	10%	13%
Cryptococcal meningitis	8-49%	0.2-1.6%

PML, Progressive multifocal leukoencephalopathy

Martin-Blondel et al. JNNP 2011;82; Falcó et al. JAIDS 2008;49; Haddow et al. Lancet Infect Dis 2010;10.

CNS IRIS

- Can be difficult to distinguish from relapse or new infection
- Thorough diagnostic evaluation
- Start or intensify specific therapy
- Role of immunomodulators such as steroids is unproven in PML and cryptococcal meningitis

JH

- 29 year old man
  - CD4 15 cells/ul
  - Plasma HIV RNA 10,674 c/ml
- Headache, fever, nausea and vomiting
- Neurological examination normal

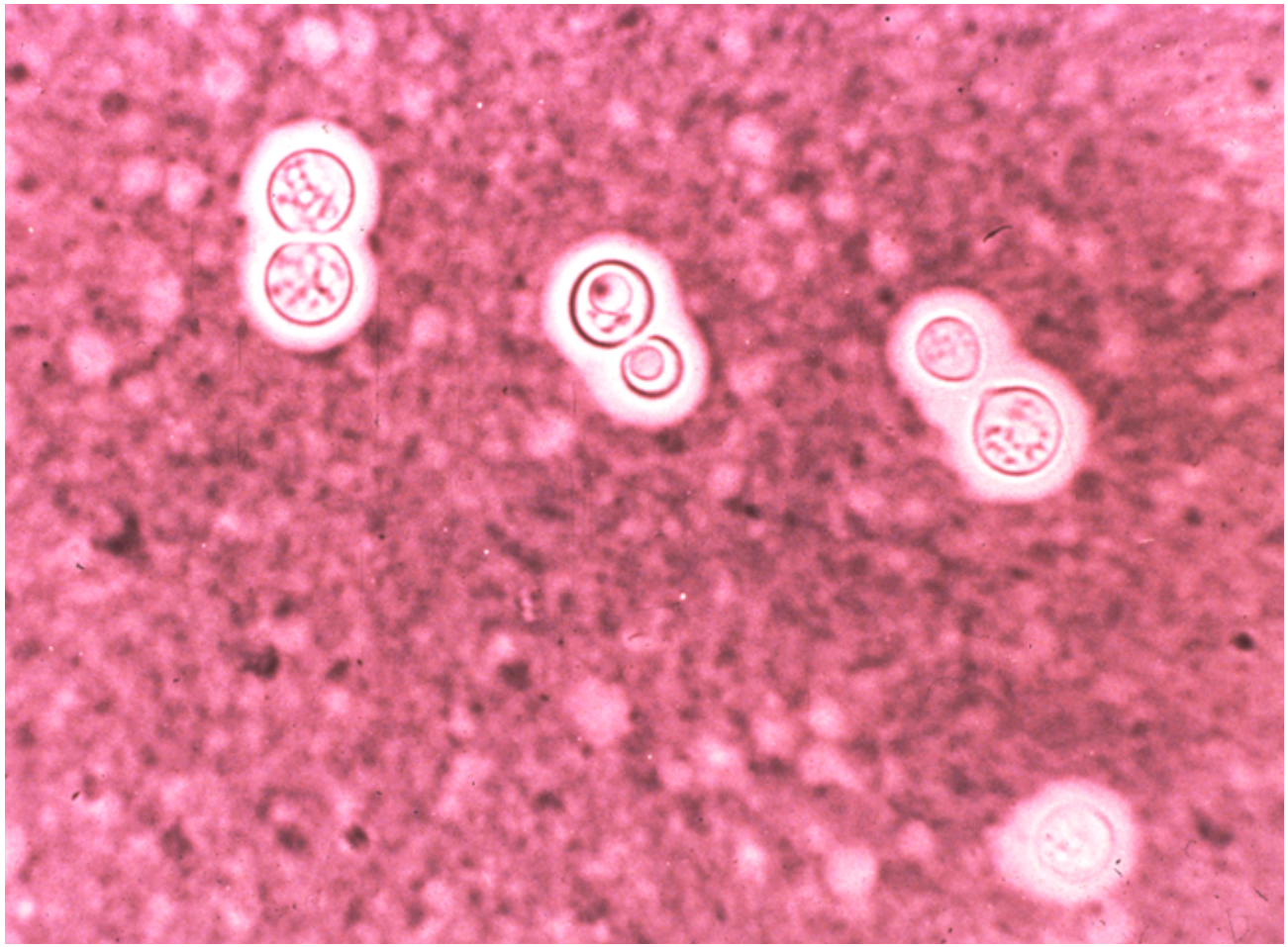
JH

- CT brain “microvascular disease”
- CSF
  - Opening pressure 290 mm H_20
  - WBC 69 cells/ul
  - Glucose 4 mg/dl
  - Protein 158 mg/dl
  - CSF CrAg 1:2048

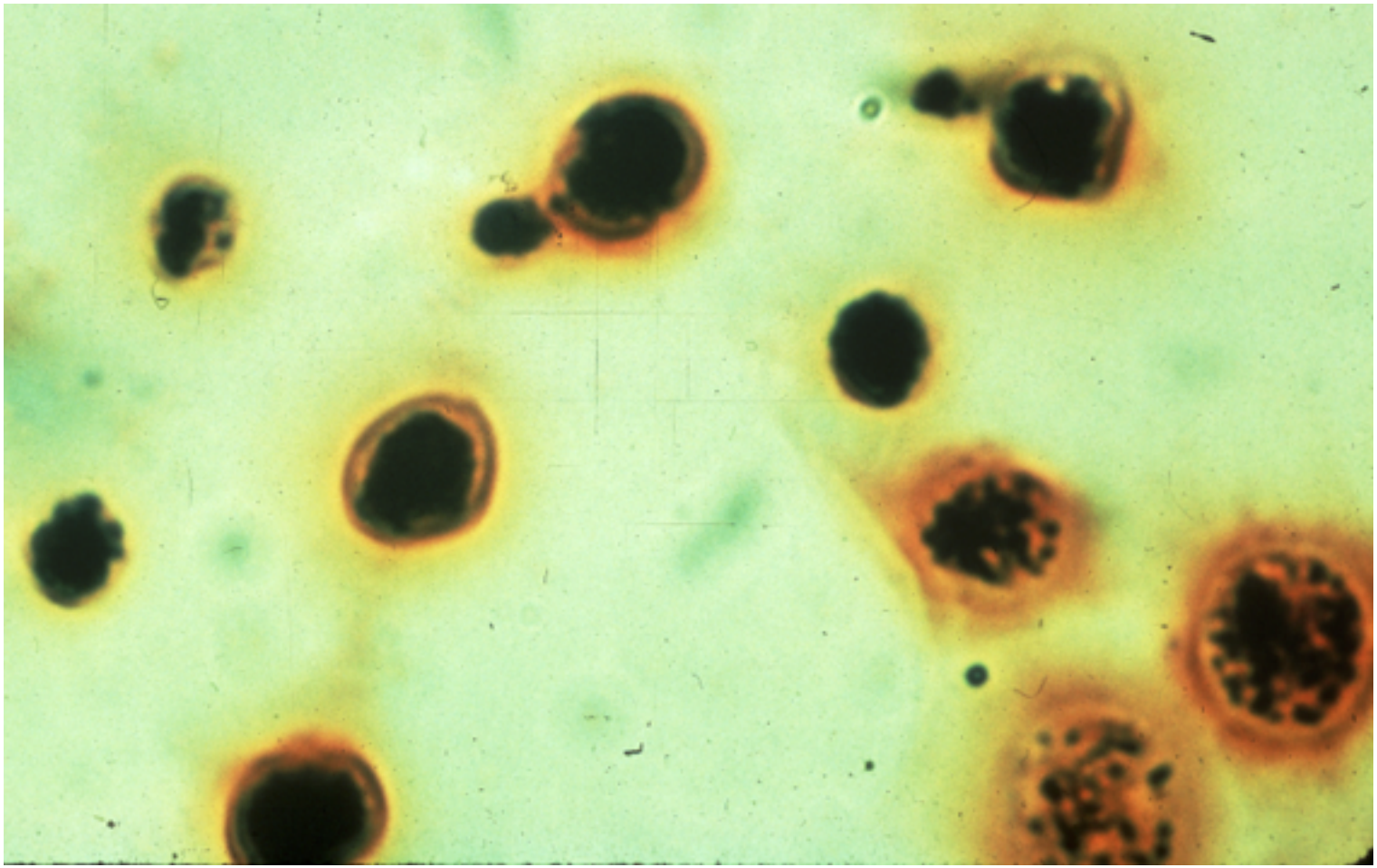
Cryptococcal Meningitis

- Most caused by *Cryptococcus neoformans* variant *grubii*
- Infection acquired from environment
  - Not person-to-person
- Meningitis likely due to reactivation

C. neoformans on India Ink



C. neoformans on Gram Stain



Risk for Cryptococcal Meningitis

- Peripheral blood CD4+ T cells < 100/ul
- Not receiving fluconazole
- Not on ART
- Detectable serum cryptococcal antigen (CrAg)

Poor Prognostic Factors

- Depressed level of consciousness
- CSF WBC < 20/ul
- CSF CrAg > 1:1024
- Elevated CSF opening pressure (OP)
  - OP > 350 mm H_2O associated with lower survival

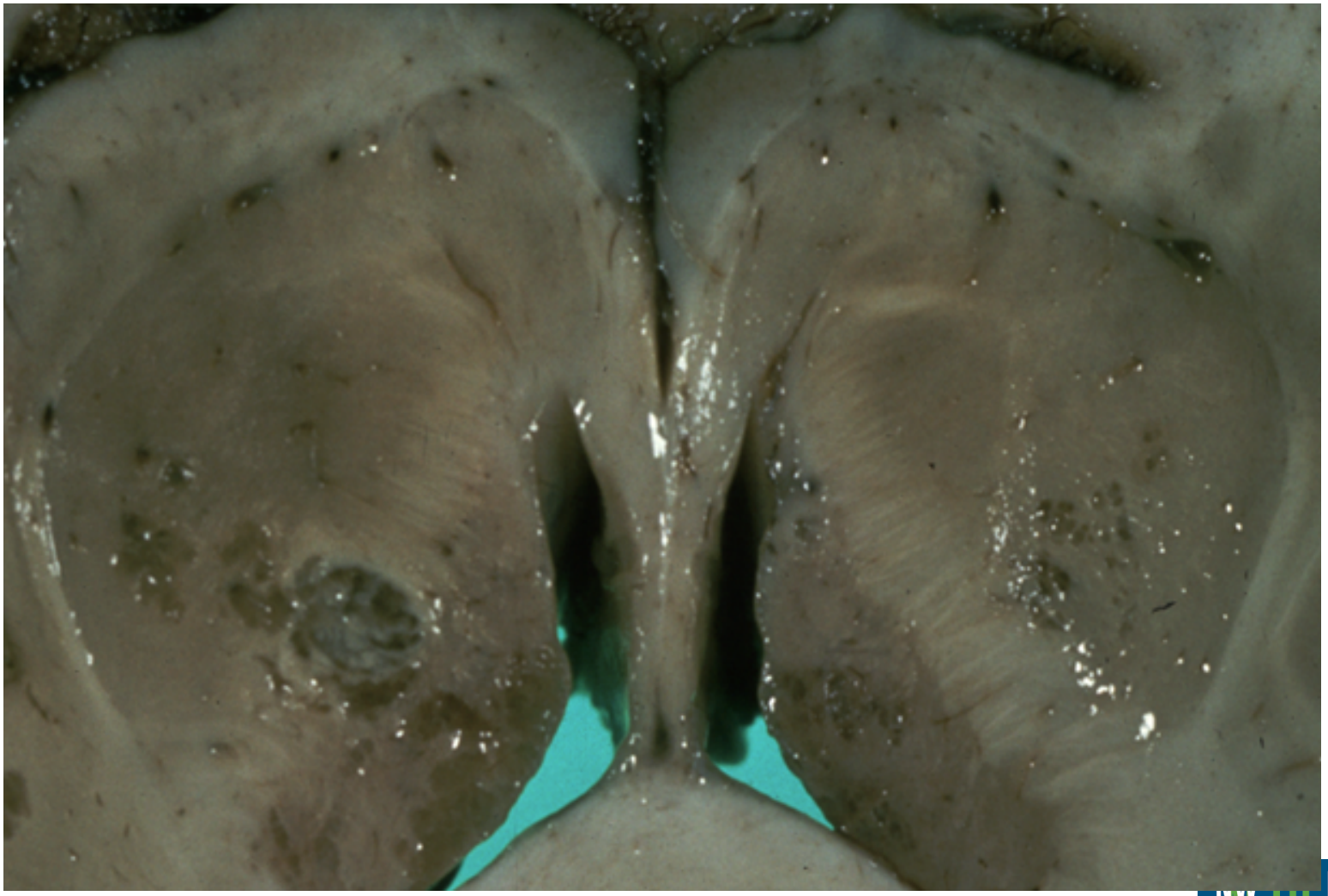
Cryptococcal Meningitis Clinical

- Fever
- Headache
- Nausea and vomiting
- Cognitive dysfunction
- Meningeal signs and photophobia less common than in HIV-uninfected
- Focal findings, seizures uncommon
- Chronic, insidious onset
  - Can be acute

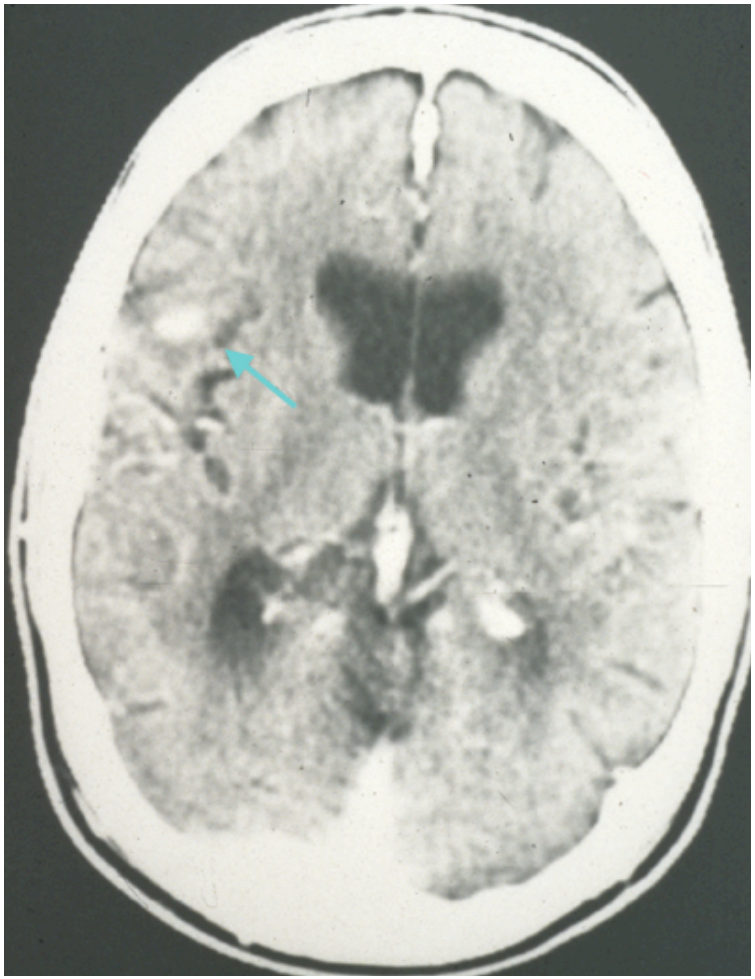
Cryptococcal Meningitis Diagnosis

- CSF examination
- Neuroimaging before lumbar puncture
- Always measure CSF opening pressure
- Diagnosis established by positive CSF culture or reactive CSF antigen test
- CSF cell count, glucose and protein may be normal

Cryptococcoma



Cryptococcoma



Cryptococcal Meningitis Treatment

Induction
2-3 wks

Consolidation
8 wks

Maintenance
≥ 1 yr

Cryptococcal Meningitis Treatment

- First 2 weeks induction tx
  - Amphotericin B deoxycholate 0.7-1.0 mg/kg/d IV
    - Liposomal AmB 3-6 mg/kg/d IV
    - AmB lipid complex 5 mg/kg/d IV
  - Flucytosine (5FC) 100 mg/kg/d PO in 4 divided doses
    - Check level 2 hours after dose at steady state
    - Target 30-80 ug/ml
  - Aggressive ICP management

Jackson A, van der Horst C. Current HIV/AIDS Reports 2012;9; Perfect JR et al. Clin Infect Dis 2010:50.

Management of Elevated ICP

- OP > 250 mm H_2O
- Daily lumbar punctures
  - Decrease closing pressure by 50% or to < 200 mm H_20, whichever higher
- Lumbar drain if very high pressures or frequent LPs
- VP shunt if above means don't work
- No role for steroids or acetazolamide

Cryptococcal Meningitis Treatment

- Perform LP at 2 weeks of induction tx
  - Ensure normal OP
  - Ensure culture negative
- Next 8 weeks consolidation tx
  - Fluconazole 400 mg/d PO

Cryptococcal Meningitis Treatment

- Maintenance therapy
  - Fluconazole 200 mg/d PO
  - Discontinue after 1 year when "immune reconstituted"
    - CD4 > 100/ul and plasma HIV RNA undetectable X 3 months

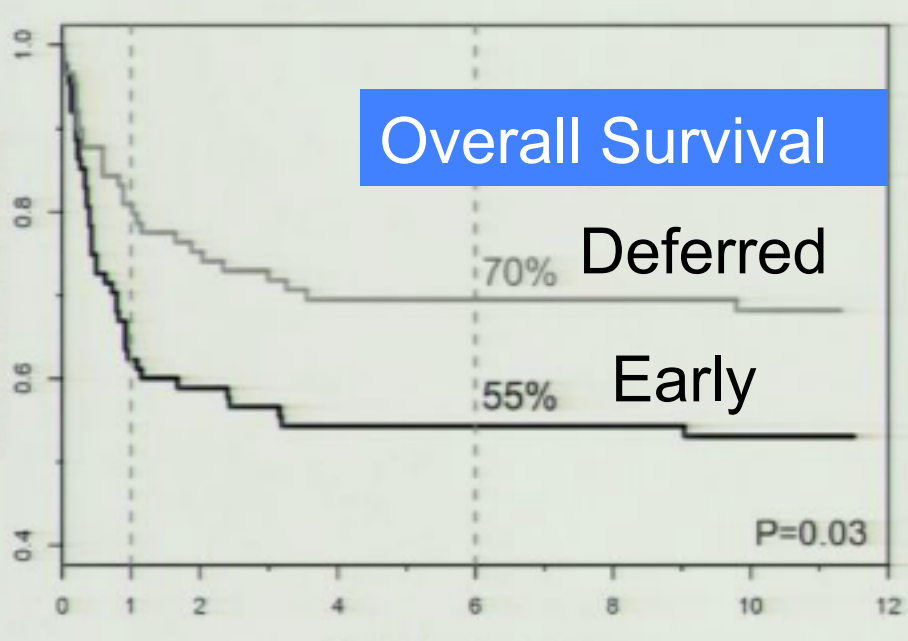
Cryptococcal Optimal ART Timing Trial: COAT

- Boulware D et al. 2013 CROI
  - ART naïve with cryptococcal meningitis
  - Study entry at day 7-11 of cryptococcal meningitis therapy
  - Early ART
    - < 48 hrs after entry, n=88
    - Median 8 d
  - Deferred ART
    - ≥ 4 weeks after entry, n=89
    - Median 35 d
  - Primary endpoint survival at 26 wks

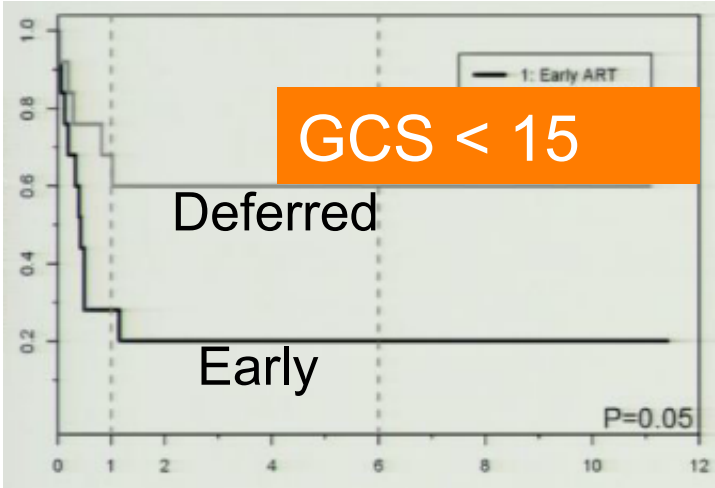
COAT

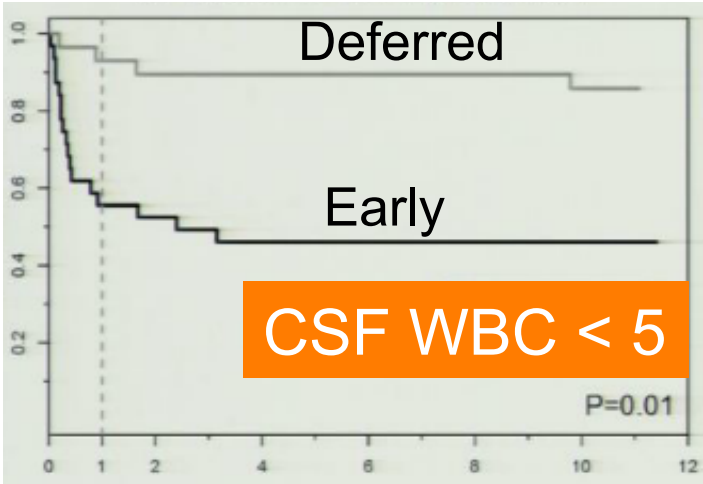
- Boulware D et al. 2013 CROI
  - IV ampho 0.7-1.0 mg/kg/d X 2 wks
  - Fluconazole 800 mg/d until CSF sterile
  - Fluconazole 400 mg/d X 8 wks
  - Fluconazole 200 mg/d
  - LP at dx, 7 and 14 d and prn high OP

COAT Outcome



IRIS incidence:
Deferred: 10%
Early: 16%





COAT Recommendations

- Treat meningitis first, optimally
- Verify CSF sterile before consolidation fluconazole or ART
- Start ART at ~4 wks
  - Most patients
- Start ART at ~5-6 wks
  - CSF WBC < 5/ul
  - AMS
  - Sepsis