HIV and the Brain: Opportunistic Conditions

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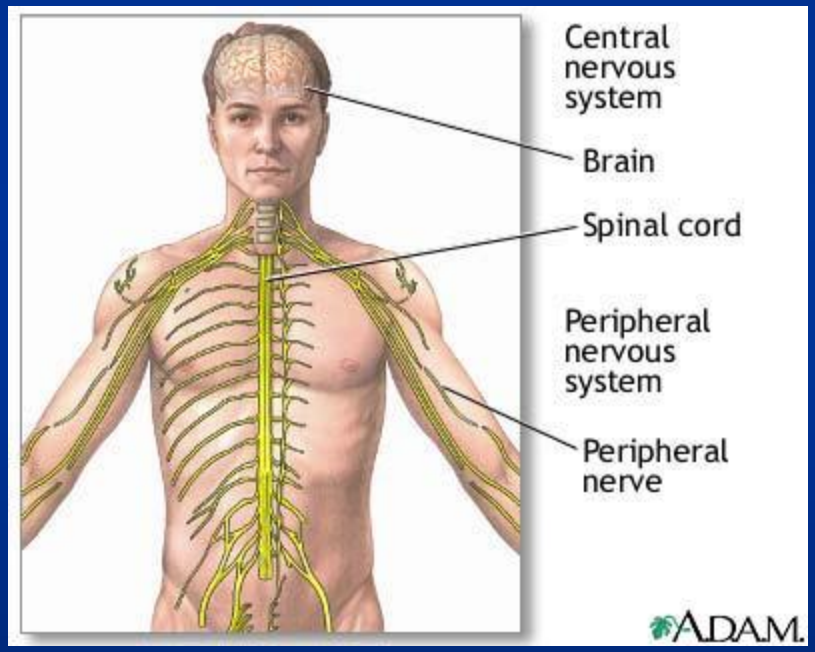
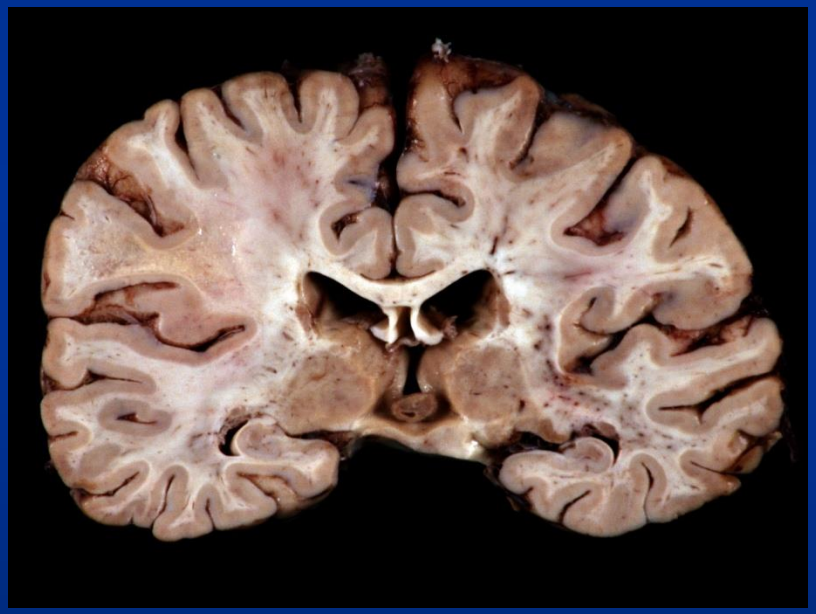
8th Regional Reaching Course in Sub-Saharan Africa
Maputo, Mozambique
November 10-12, 2016

HIV-1 Associated Neurologic Problems



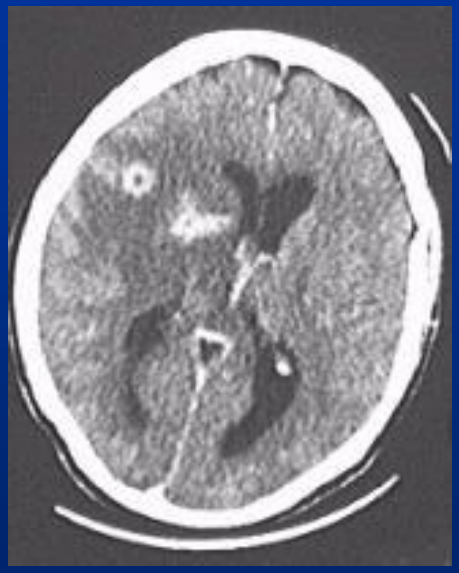
- Primary HIV-associated conditions
  - HIV-associated neurocognitive disorder and dementia
  - Myelopathy
  - Peripheral neuropathy
  - Myopathy

Selected Opportunistic Brain Complications of AIDS



- Toxoplasma encephalitis
- Cryptococcal meningitis
- CMV
- Primary CNS Lymphoma
- PML
- Syphilis

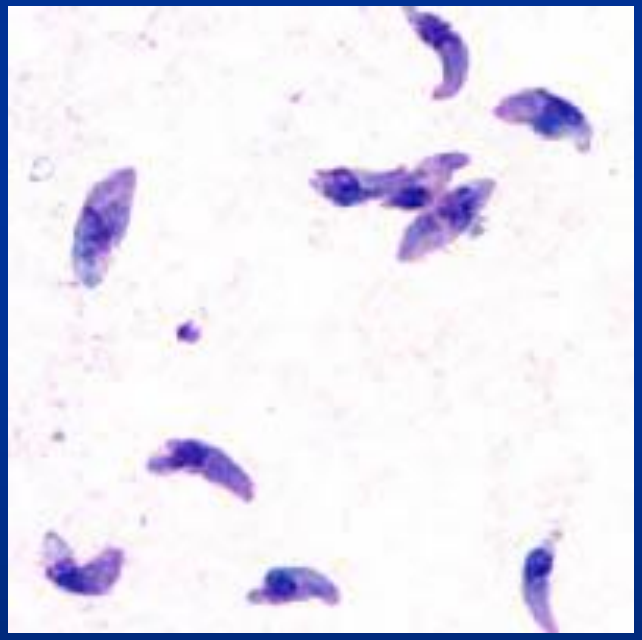
Toxoplasma Encephalitis



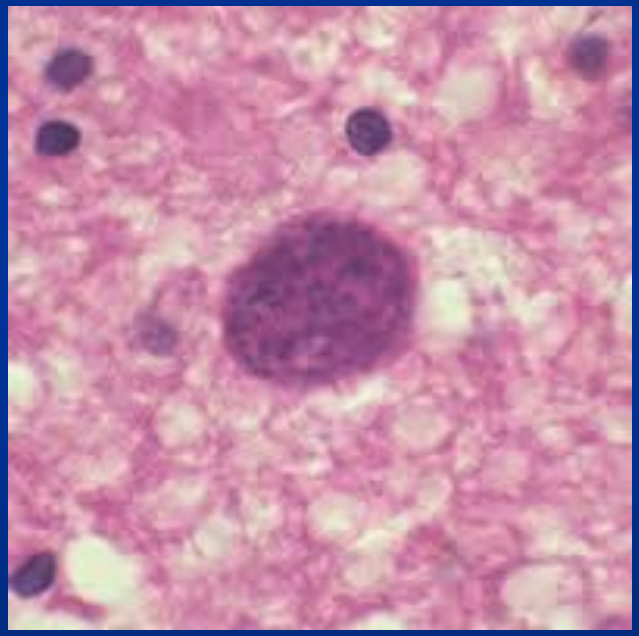
Life Cycle of Toxoplasma

- Obligate intracellular protozoan
  - Oocyte - felines
  - Tissue cysts (brain, muscle-skeletal and heart), retina, lung
  - Tachyzoites

Toxoplasma gondii



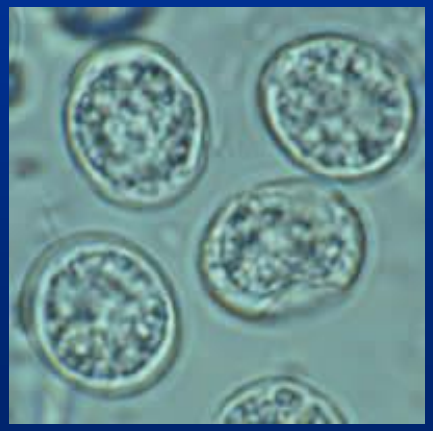
Tachyzoites

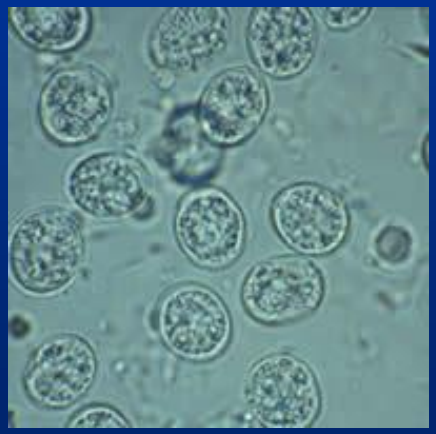


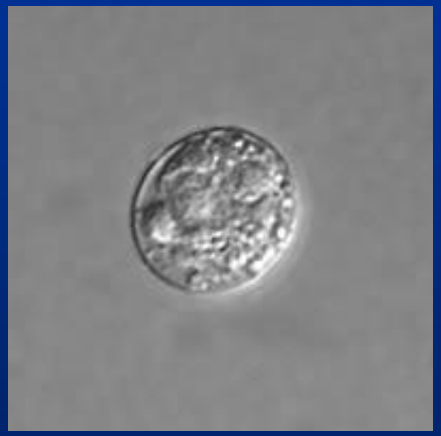
Cyst in brain tissue

Toxoplasma - oocysts

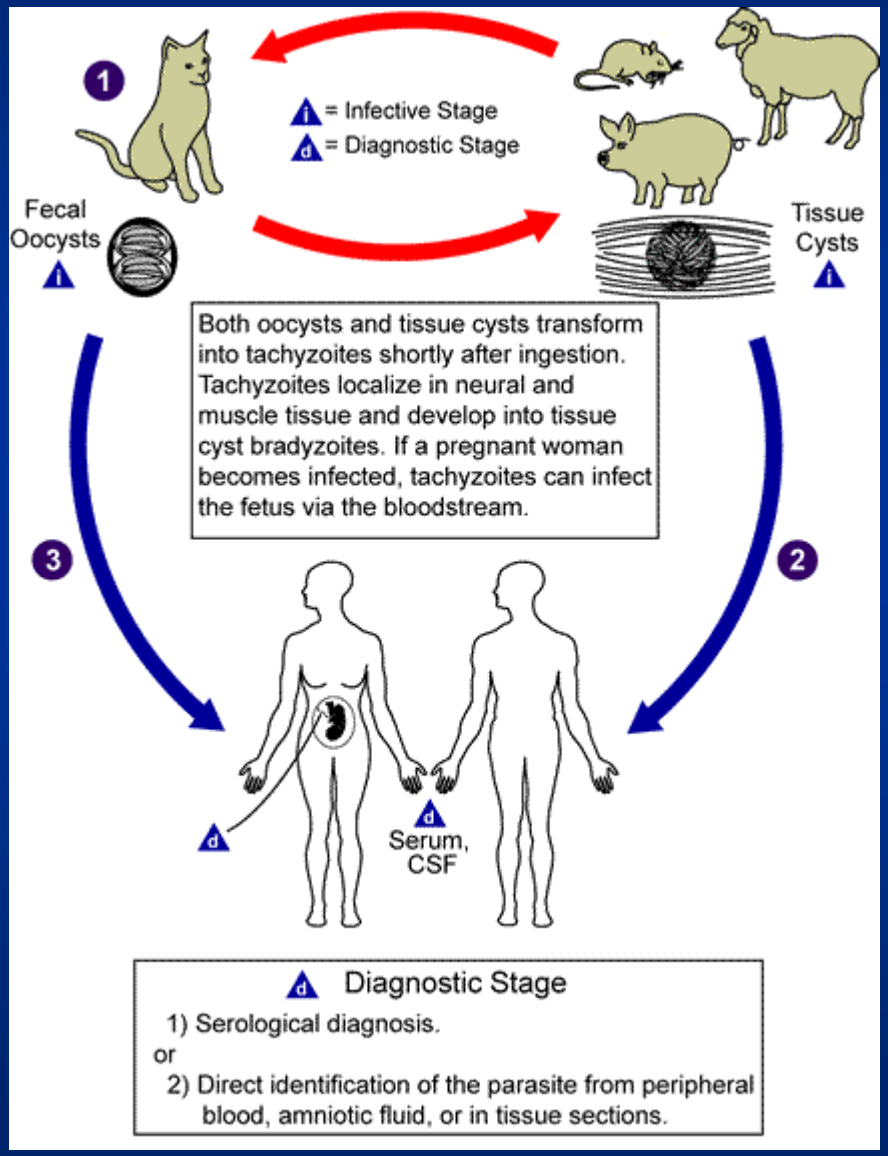
- Survives in the environment for several months
- Resistant to disinfectants, freezing, and drying
- Killed by heating to 70°C for 10 minutes
- Sporulation 1-5 days







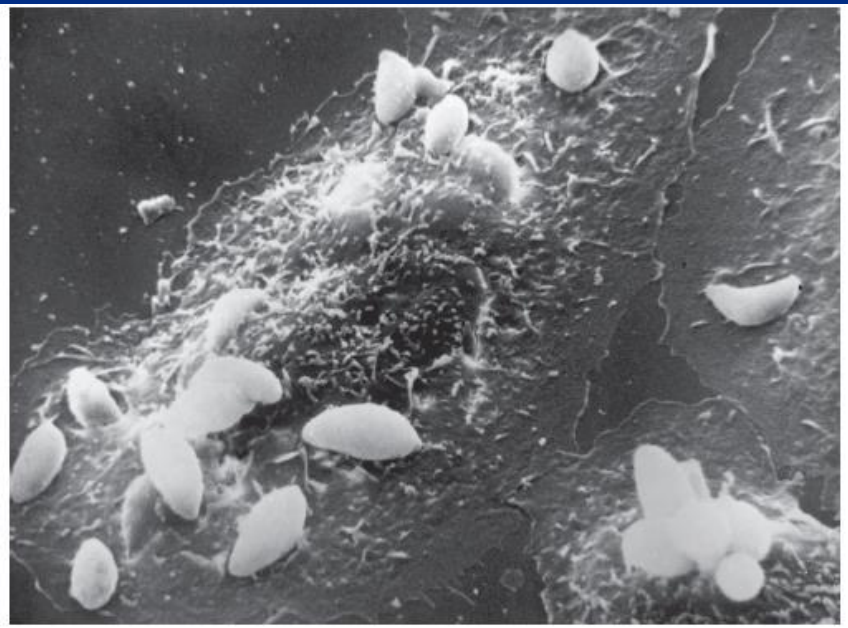
Toxoplasma gondii – life cycle



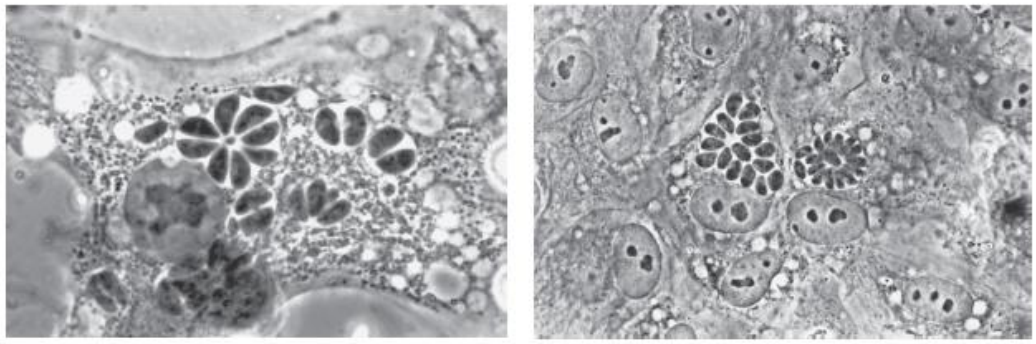
- Presence of cats in environment is necessary
  - Oocyst excretion in 1% of cats in various areas
  - No *T. gondii* infection in areas without cats

Toxoplasma

Semin Hematol 25:101, 1988.



A



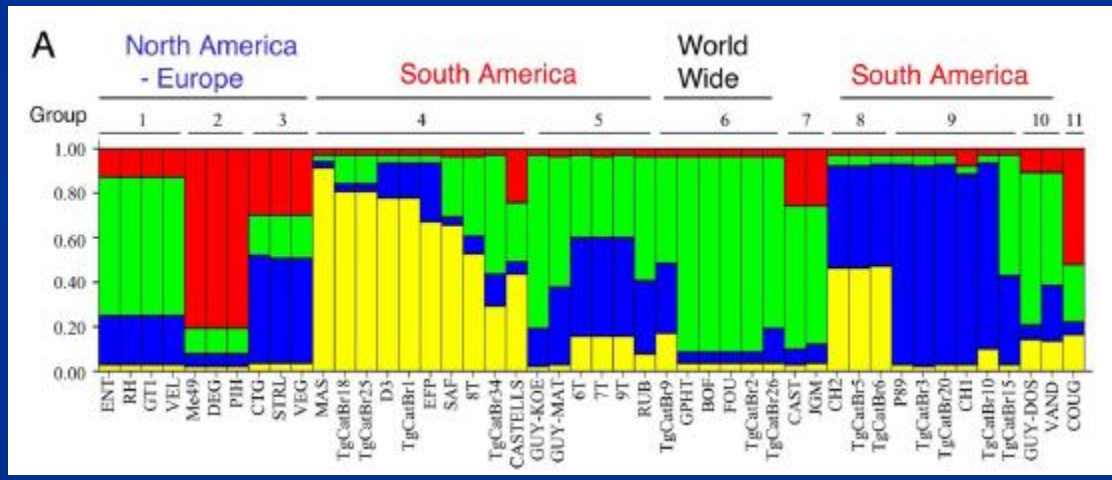
B

Tachyzoites in cultured cell

Replication over 20 hr from single tachyzoite to 8-16 tachyzoites per vacuole

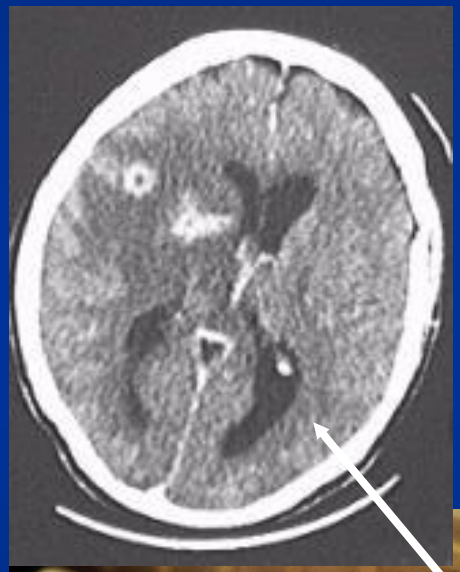
Epidemiology

- Wide geographic variability dependent at least on age, dietary habits, climate and proximity of cats
- Genetic variation may in part explain regional differences



PNAS | September 11, 2007 | vol. 104 | no. 37 | 14873

Toxoplasma Strains



Type II
Most commonly cause toxoplasmosis

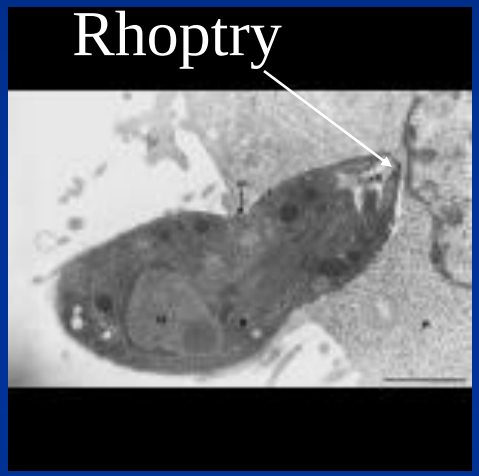
Type III
Rarely assoc with dx

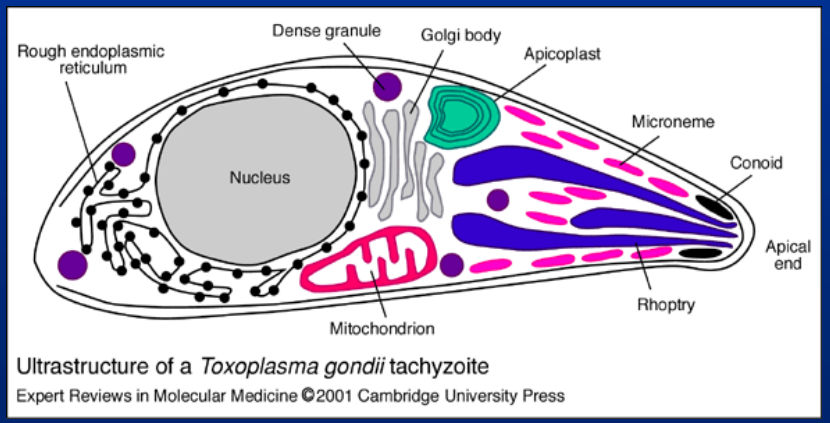
Type I : Rarer but pathologic

Khan, Su, German, Storch, Clifford and Sibley.
J. Clin. Microbiol 2005;43:5881.

Biological Basis for Virulence

- Genetic mapping of virulence locates gene on parasite chromosome VIIa
- Strain specificity
- ROP18, serine-threonine kinase secreted into host cell on invasion



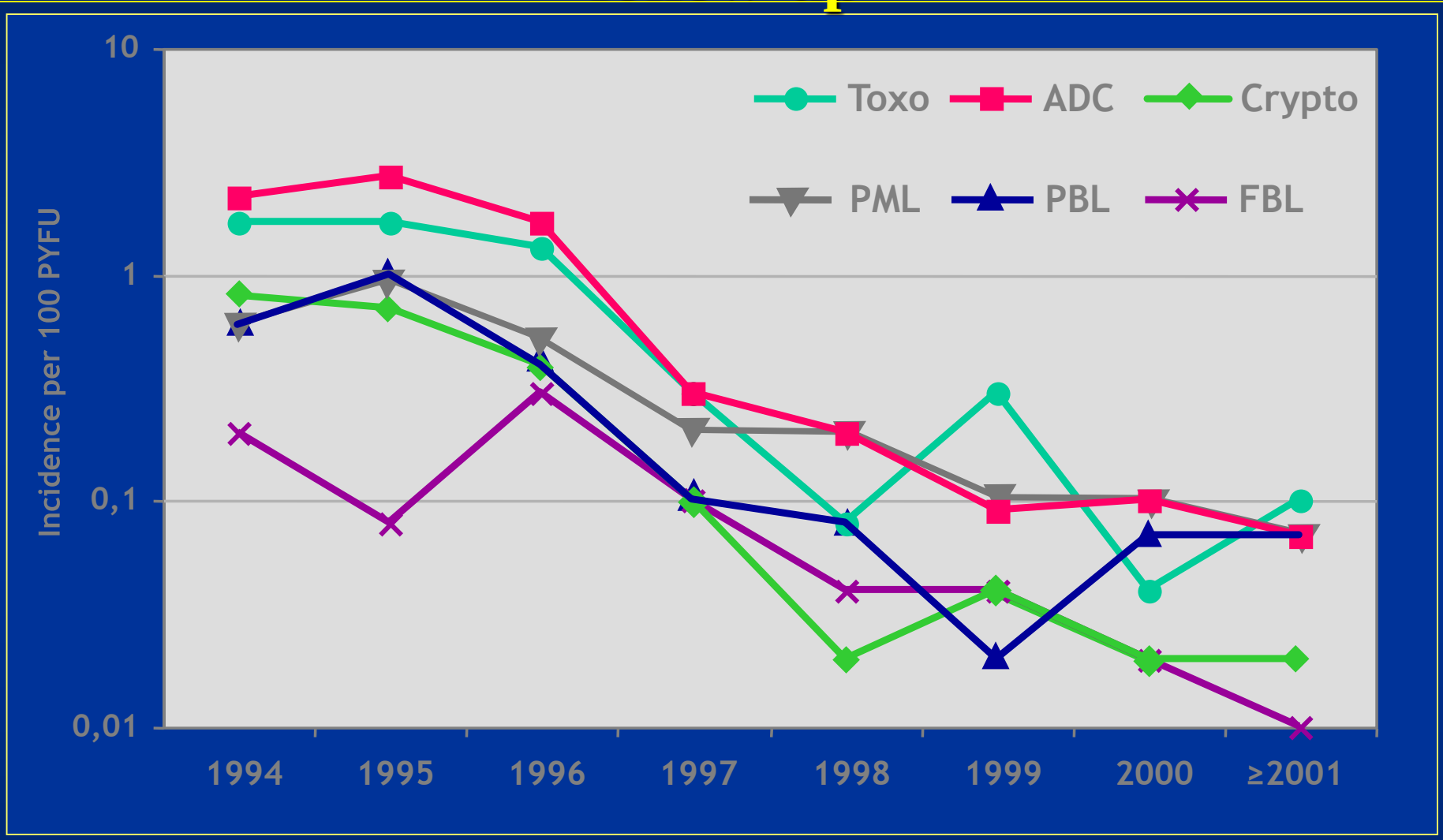


Ultrastructure of a *Toxoplasma gondii* tachyzoite

Toxo and HIV

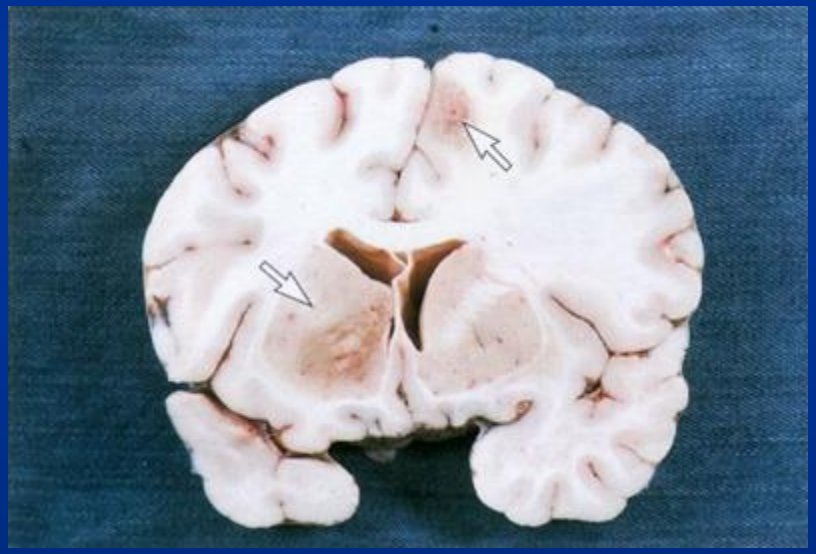
- Dramatic unmasking of this latent infection
- Common cause for encephalitis, generally with CD4 <100 cells
- Reflects the critical part cell mediated immunity plays in life cycle
- Treatable complication with potential for good long term recovery

Incidence of individual CNS-Diseases during follow-up



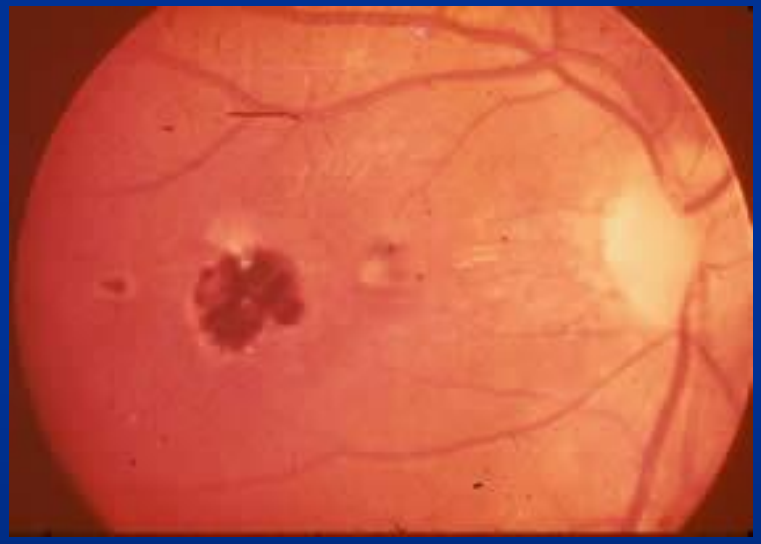
Decline of incidence/year	ADC	45%, 95% CI: 40 - 49%	p < 0.01
	CNS-OIs	37%, 95% CI: 34 - 41%	

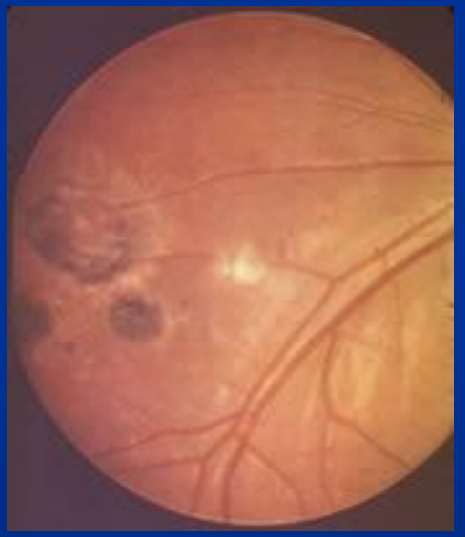
Signs/Sx of Toxoplasmosis



- Headache
- Fever
- Confusion
- Hemiparesis, other focal signs
- Posterior fossa syndrome
- Seizures
- ICP elevation

Toxoplasmosis – ocular lesions





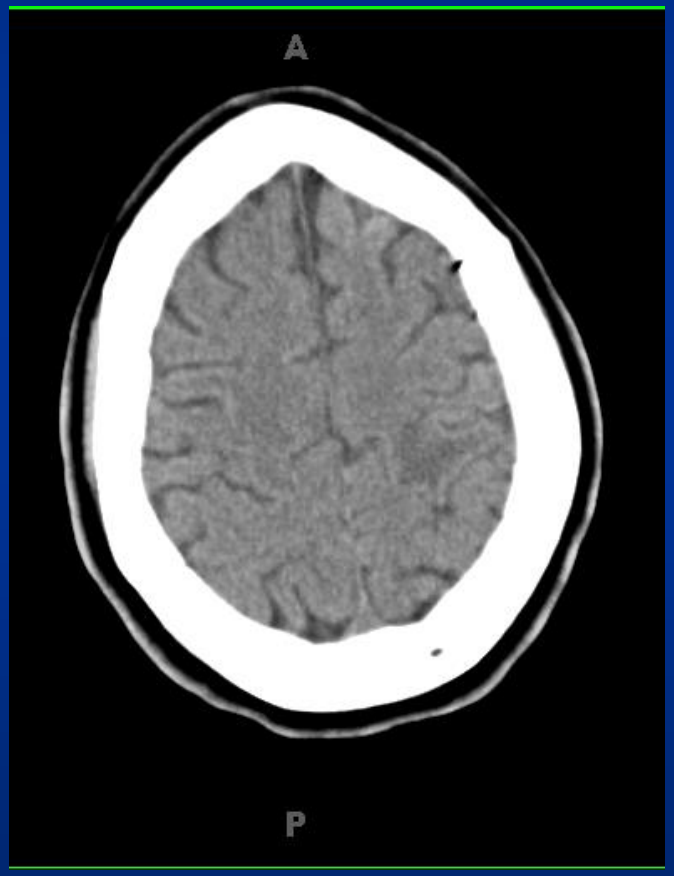
Diagnosis overview

- Context: HIV, Low CD4, subacute brain dx
- Toxo IgG positive (reactivation dx)
- Imaging: Generally multifocal, mass producing lesions (CT may show solitary that on MR is multifocal)
- CSF: Glu, Protein – mild elevations, Cells modest, PCR for toxo DNA
- Clinical response
- Biopsy

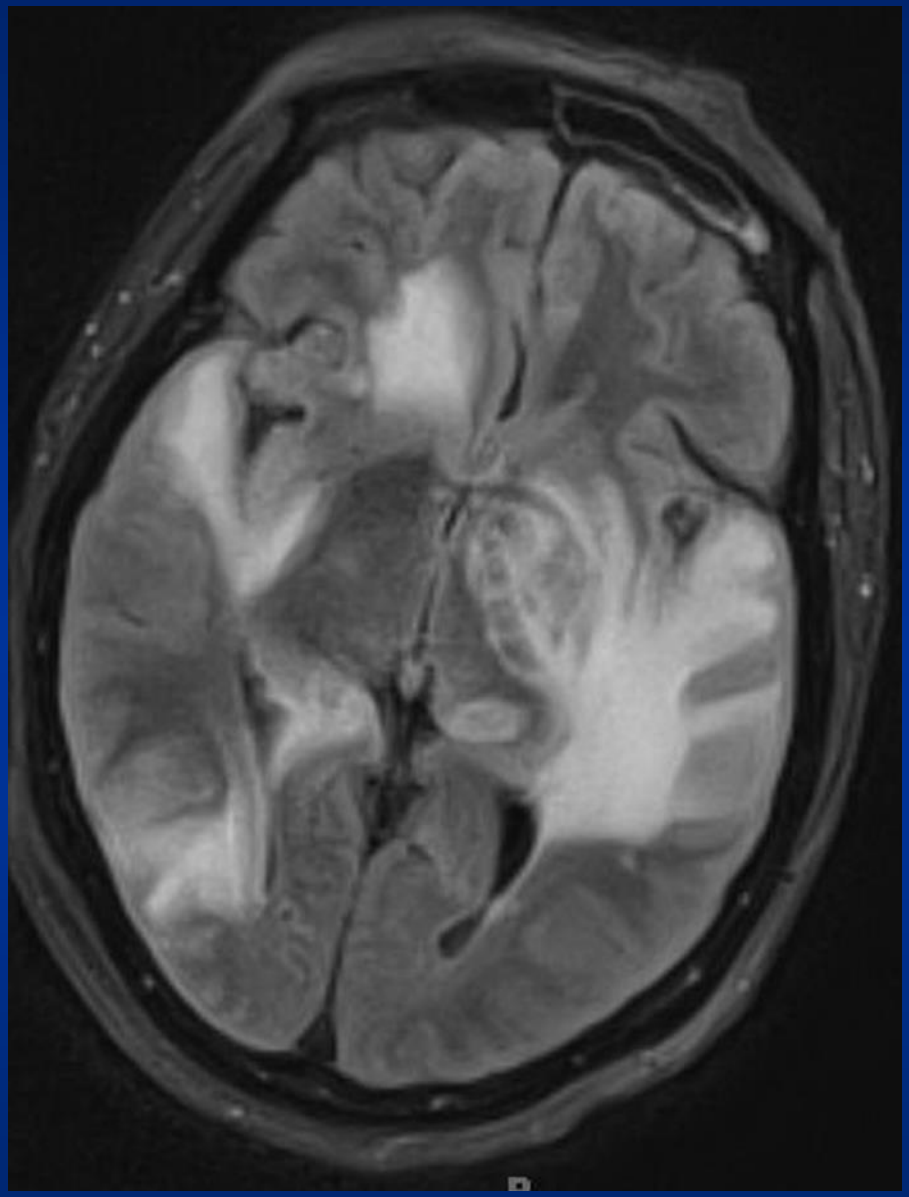
Differential of Multifocal Brain Dx in HIV

- CNS lymphoma
- PML
- Tuberculosis
- Fungal (Cryptococcus)
- Chagas disease
- Pyogenic brain abscess (esp drug abuse associated)

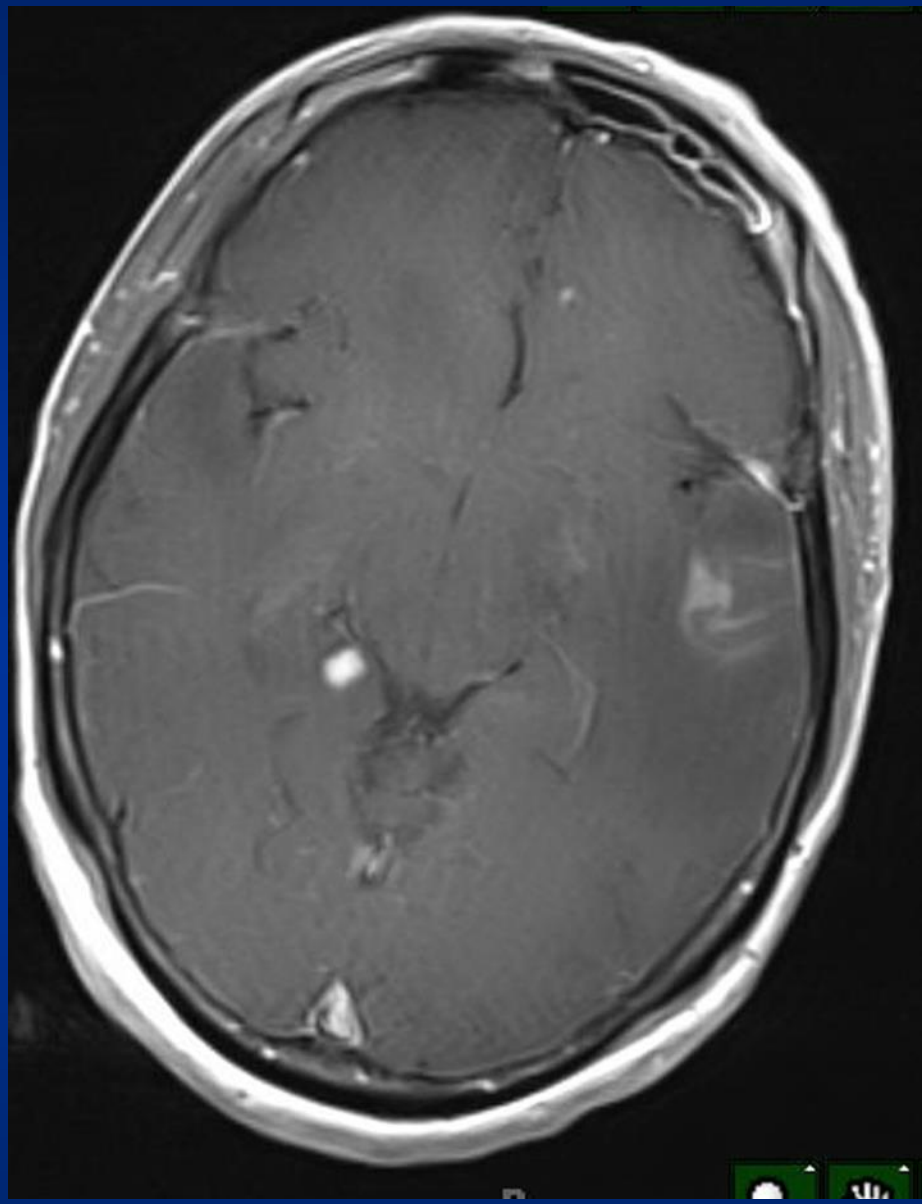
Brain CT Scan



- Generally abnormal with TE
- Contrast enhancement, often in ring pattern common
- Edema often seen

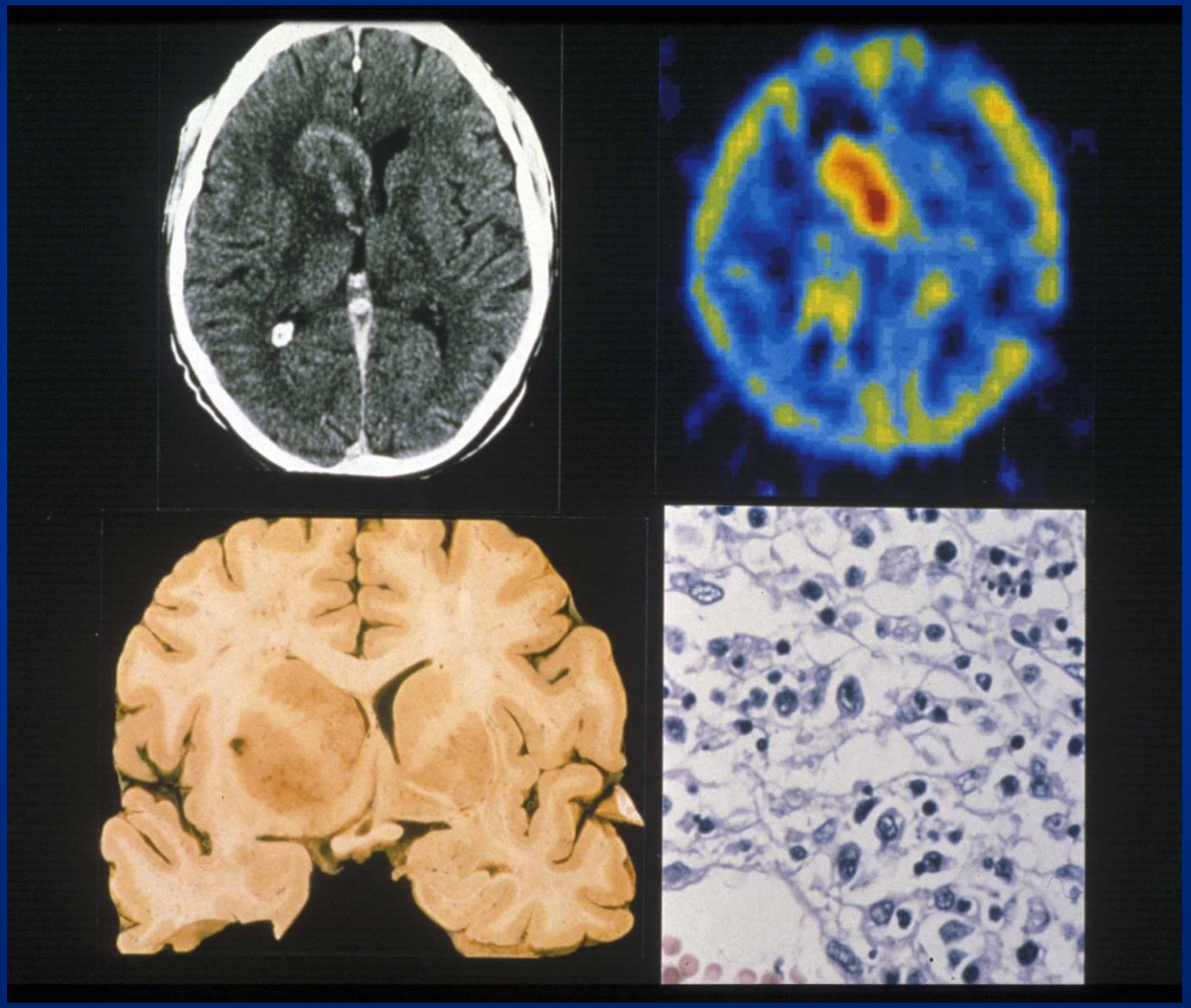


FLAIR



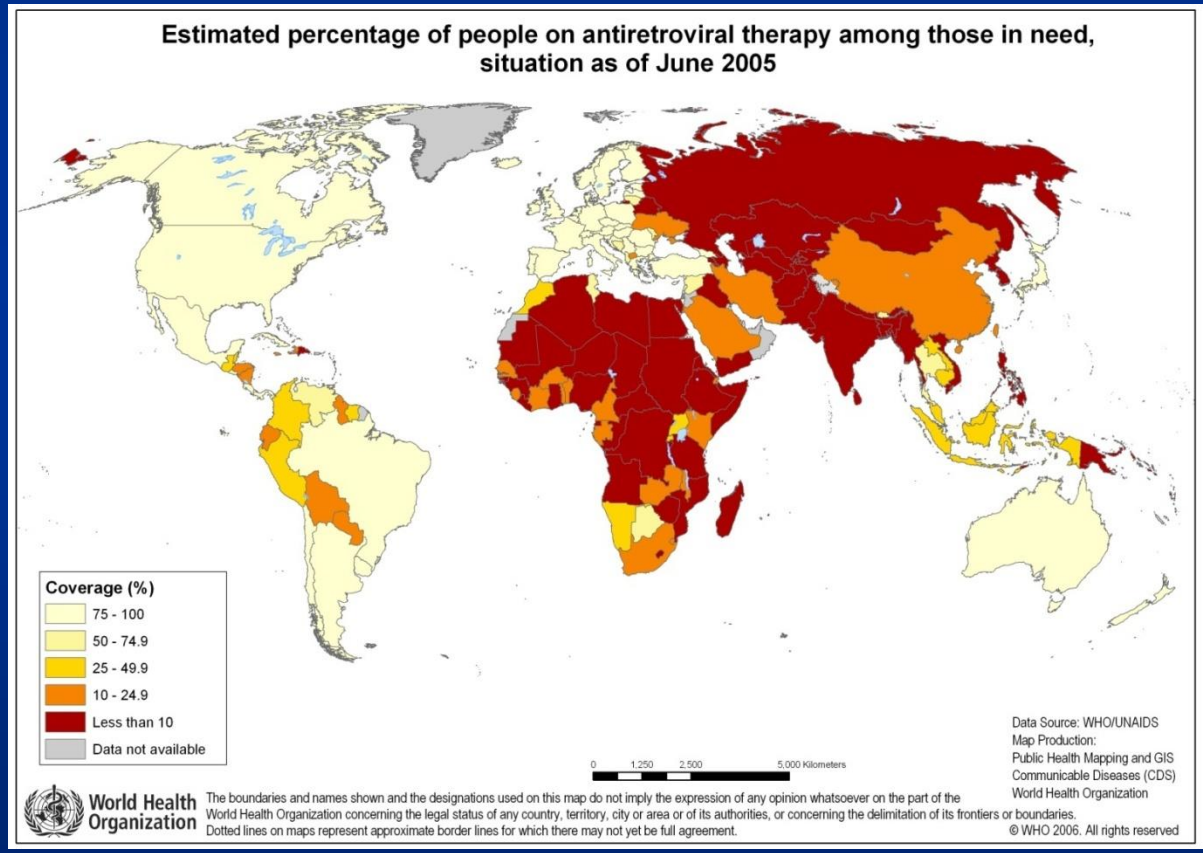
T1 + Gd

PET SCANS HYPERMETABOLIC for PCNS Lymphoma but not Toxoplasma Encephalitis



Therapy for Toxoplasma encephalitis

- Initiation of HAART at appropriate time
- Primary prevention
  - If CD4 < 200 use primary prophylaxis
  - Same as for P. jerevicii



Primary Prophylaxis

Primary Prophylaxis to Prevent First Episode of AIDS-Related Toxoplasmosis

Table 37-5

Oral Drug[a]	Suggested Regimens
Preferred Treatment	
TMP-SMX[b]	1 DS tablet qd Alternatives: 1 SS tablet qd, 1 DS tablet q12h tiw, or 1 DS tablet tiw
Pyrimethamine–dapsone	50 mg q wk/50 mg qd Alternatives: 25 mg + 100 mg qd biw, or 75 mg + 200 mg q wk
Other Treatments	
Pyrimethamine–sulfadoxine (Fansidar)	25 mg/500 mg (1 tablet) biw or 3 tablets once q 2 wk
Atovaquone	1500 mg qd
Atovaquone–pyrimethamine	1500 mg qd/25 mg qd

biw, twice weekly; q wk, once weekly; q 2 wk, every 2 weeks; tiw, three times per week.

[a]Folinic acid (10–25 mg/day) should be given with any pyrimethamine-containing regimen.

TE Therapy

- Sulfadiazine/Pyrimethamine/Folinic Acid
  - Pyrimethamine 200 mg po loading dose, then 75 mg PO qd
  - Sulfadiazine 1.5 grams q 6 h
  - Folinic acid 5-10 mg qd PO
- Problems
  - Sulfa allergies
  - Crystalluria
  - Oral Pill burden
  - Cost

TE Therapy

- Alternative for sulfadiazine: Clindamycin 150-300 mg q6h IV/PO
  - Allergies
  - GI toxicity

Co-trimoxizole as therapy

- Anecdotal experience and case reports
- Pilot study: Torre et al (Italian Collaborative Study Group), Antimicrob Agents and Chemoth 1998; 1346-9.
- Randomized pilot study
- Suggests trimethoprim – sulfamethoxazole (T-S) may be reasonable alternative to P-S, but lacked power to demonstrate noninferiority

Efficacy

TABLE 2. Clinical response at the end of acute therapy for TE[a]

Treatment response	No. (%) of patients	
	P-S (n = 35)	TMP-SMX (n = 37)
Complete	23 (65.7)	23 (62.1)
Partial	7 (20.0)	8 (21.6)
No change or progression	5 (14.2)	6 (16.2)

[a] Data are not statistically significant.

Torre et al, AAC 1998:1346.

Radiologic Response

TABLE 3. Radiologic response at the end of acute therapy for TE

Treatment response	No. (%) of patients	
	P-S (n = 33)	TMP-SMX (n = 37)
Complete	13 (39.3)	23 (62.1)
Partial	10 (30.3)	4 (10.8)
No change or progression	10 (30.3)	10 (27.0)

[a] P = 0.0478.

Torre et al, AAC 1998:1346.

Adverse Effects Profile

TABLE 4. Adverse reactions in AIDS patients with TE during the acute and the maintenance therapy

Adverse reaction	No. (%) of patients		
	TMP-SMX (n = 40)	P-S (n = 37)	P value
Any of at least one adverse reaction	5 (12.5)	8 (21.6)	0.36
Fever	0	1	0.48
Skin rash	0	6	0.0098
Diarrhea	1	0	1.00
Gastric disturbances	0	2	0.22
Vomiting	0	1	0.48
Toxic effect on liver	1	1	1.00
Toxic effect on kidneys	0	1	0.48
Leukopenia	1	0	1.00
Neutropenia	1	1	1.00
Thrombocytopenia	0	1	0.48
Pancytopenia	1	0	1.00
Total	5 (12.5)	14 (37.8)	0.00162

Torre et al, AAC 1998:1346

Alternate drugs

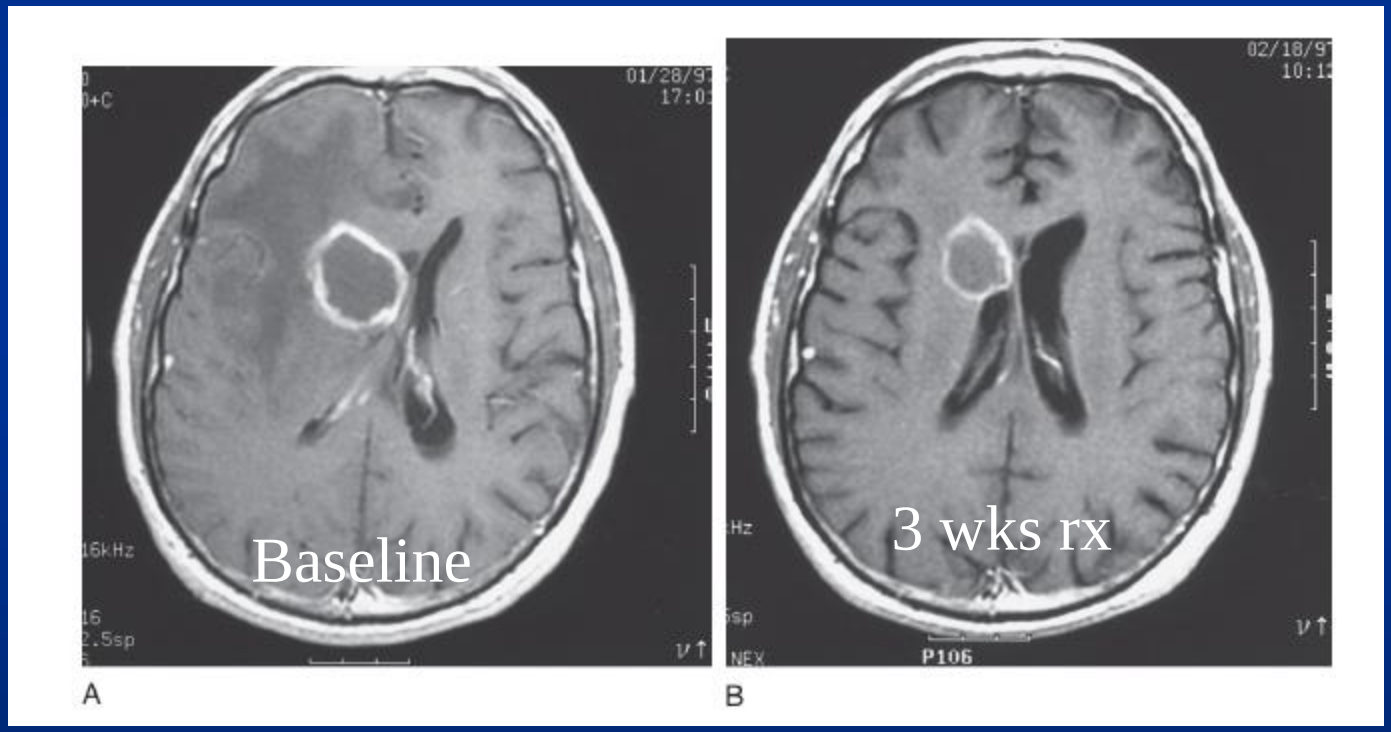
- Atovaquone
- Fansidar (sulfadoxine/pyrimethamine)
- Macrolides (azithromycin)
- Dapsone
- Other sulfa drugs
- Minocycline/doxycline

Response to therapy

- Prompt clinical response often seen in first 5 -10 days
- Radiological response seen in first 21 days
- Often diagnosis is confirmed by appropriate clinical response

Response to therapy

Corticosteroids complicate interpretation of clinical response



Miro, Murray, Katlama, AIDS Therapy

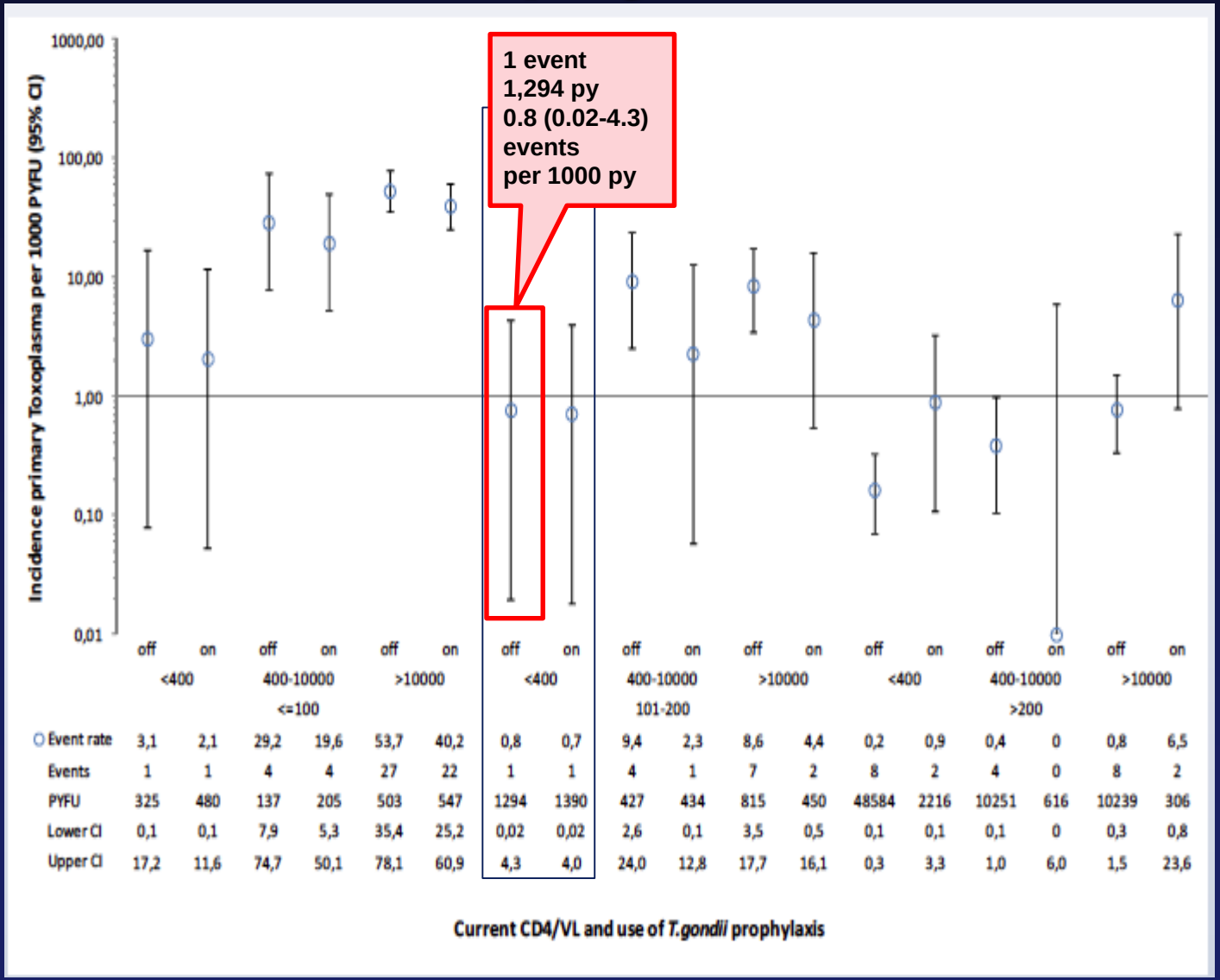
Toxoplasma: Stopping Primary Prophylaxis

- COHERE database (11,015 pts. toxo. seropositive, 10 cohorts)
- Incidence rate, events/1,000 patient-years; Poisson generalized additive model

	Total	Stopping Prophylaxis
Number of patients	11,015	1,484
Male sex	73%	72%
Age (median, IQR)	37 (32-46)	41 (36-50)
Prior AIDS	1,600 (15%)	484 (33%)
VL <400	2,326	960
On cART	3,584 (33%)	1,484 (100%)
CD4	353 (190-533)	257 (188-340)
Total Follow-up time (years)	79,220	
Number of events	99	

Jose Miro for the OI working group of COHERE in EuroCoord,
CROI, 2016

Toxoplasma: Stopping Primary Prophylaxis



Jose Miro for the OI working group of COHERE in EuroCoord, CROI, 2016

Maintenance Therapy

- Required when CD4 <200
- Generally half acute treatment dose
- Less aggressive rx may be satisfactory
- Can be discontinued after >6 months with CD4 > 200 cells

Maintenance Regimens (Secondary Prophylaxis) for AIDS-Related Toxoplasmosis

Table 37-2

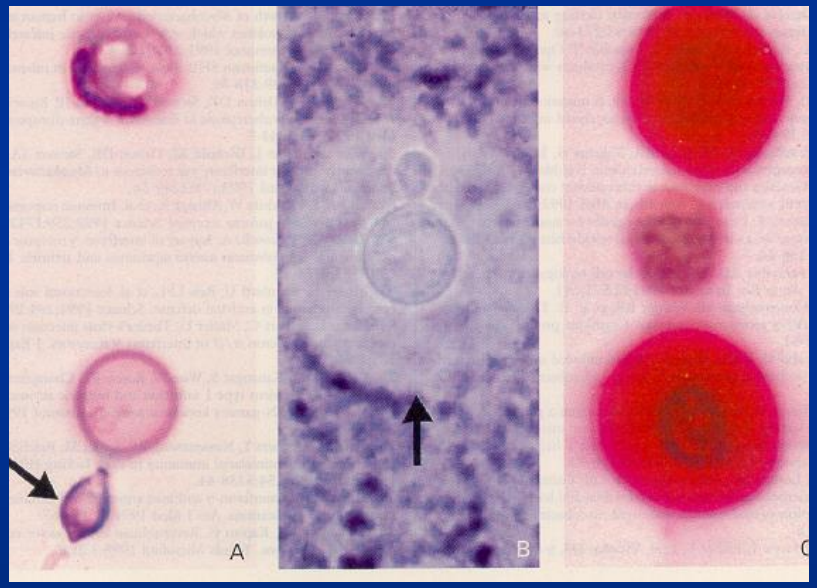
Oral Drug	Suggested Regimens
Preferred Combinations[a]	
Daily treatment	
Pyrimethamine plus	25–75 mg qd
Sulfadiazine or	500–1000 mg q6h or 1 g q12h
Clindamycin	600 mg q8h
Intermittent treatment	
Pyrimethamine plus	50 mg thrice weekly
Sulfadiazine	1 g q12h thrice weekly
Other Regimens[a]	
Atovaquone alone	750 mg q6h
Pyrimethamine alone or plus	50 mg qd or 25 mg qd
Atovaquone or	750 mg q6h
Clarithromycin or	1000 mg qd
Dapsone or	100 mg twice weekly
Azithromycin	600–1800 mg qd
Pyrimethamine-sulfadoxine (Fansidar®)	25 mg/500 mg (1 tablet) twice weekly

[a]Folinic acid (10–25 mg/day) should be used with all pyrimethamine-containing regimens.

Summary

- Toxoplasma encephalitis is a frequent treatable complication
- Optimal therapy can give excellent clinical results
- Further attention to early diagnosis and cost effective therapy may still be needed
- Should be studied in Africa
- Updated treatment info available at http://aidsinfo.nih.gov/guidelines

Cryptococcal Meningitis

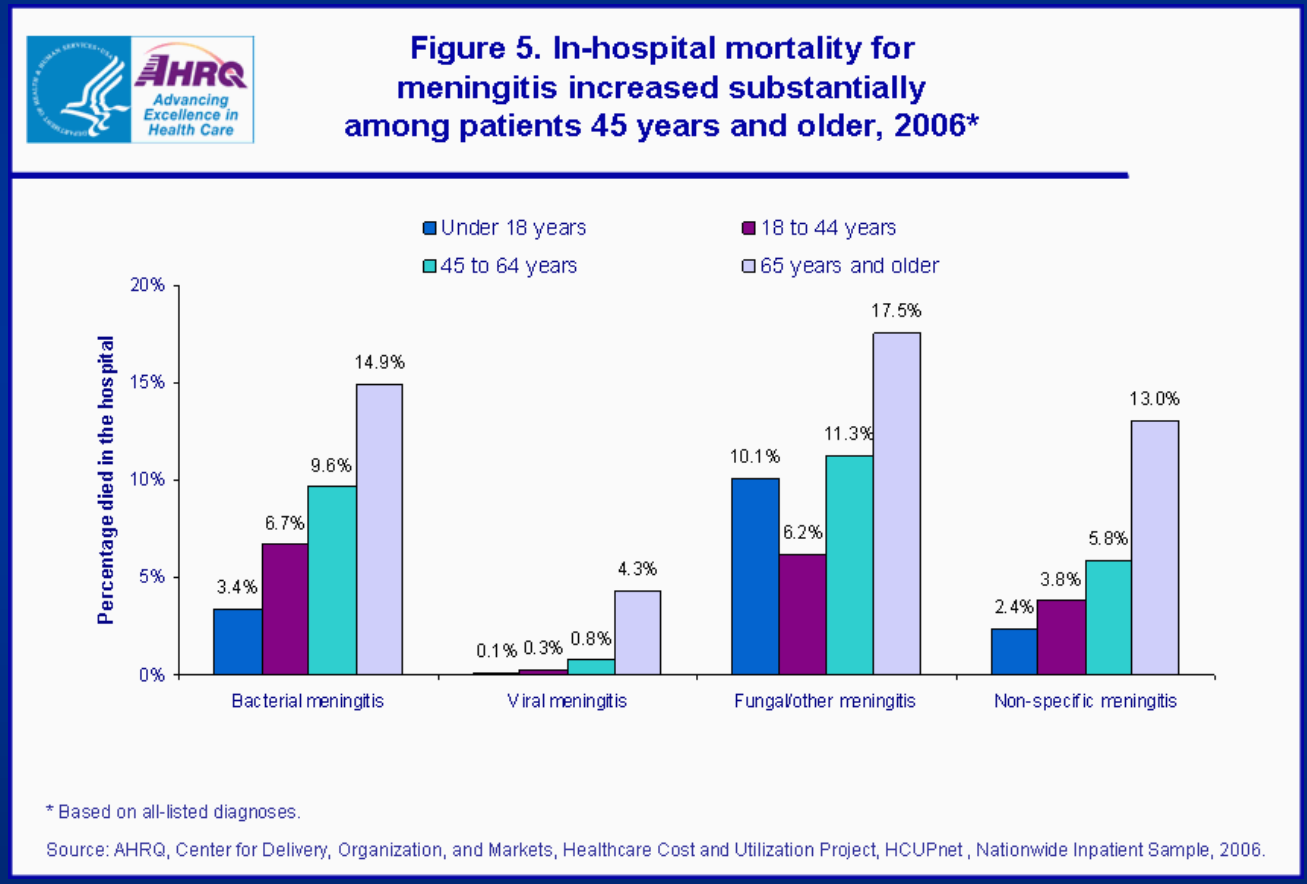


- Most common CNS complication of AIDS
- Accounts for a third of AIDS deaths some areas of developing world
- Treatment can be effective

Objectives

- Fundamentals of Cryptococcal meningitis
  - Diagnosis and management
- Importance of IRIS in cryptococcal disease
- Pre-symptomatic detection and treatment of cryptococcus
- Intro to Cryptococcus gattii

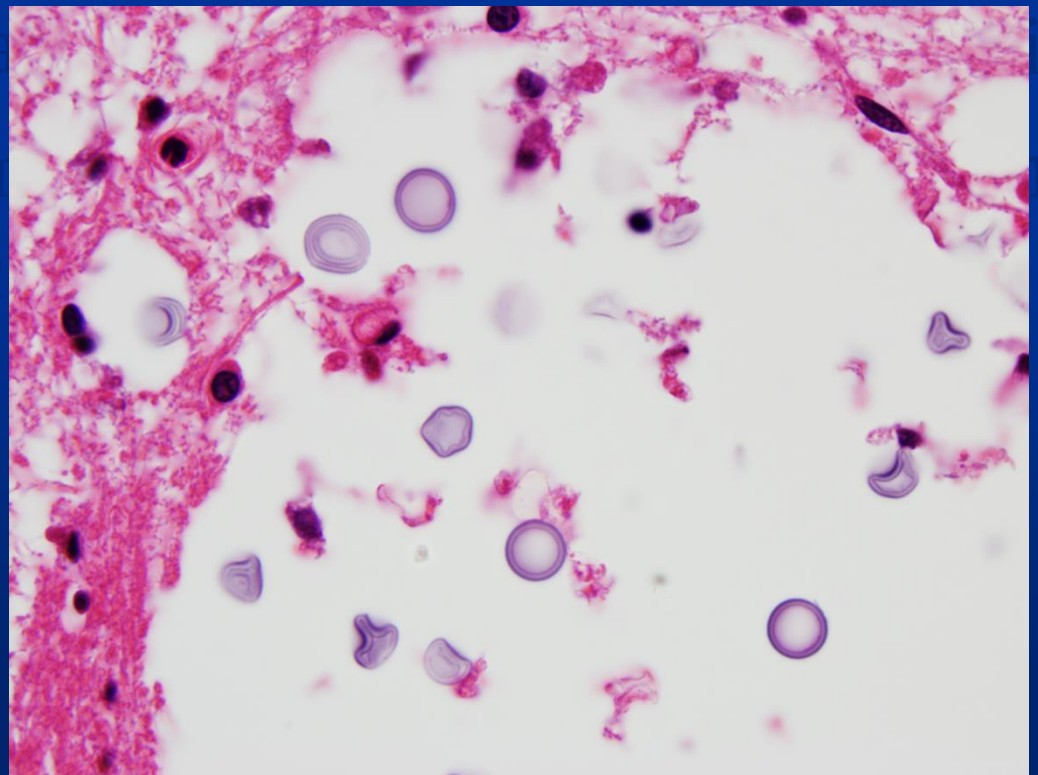
Higher mortality with fungal meningitis than with other forms



600,000 Deaths a Year Due to Crypto Meningitis

Objectives

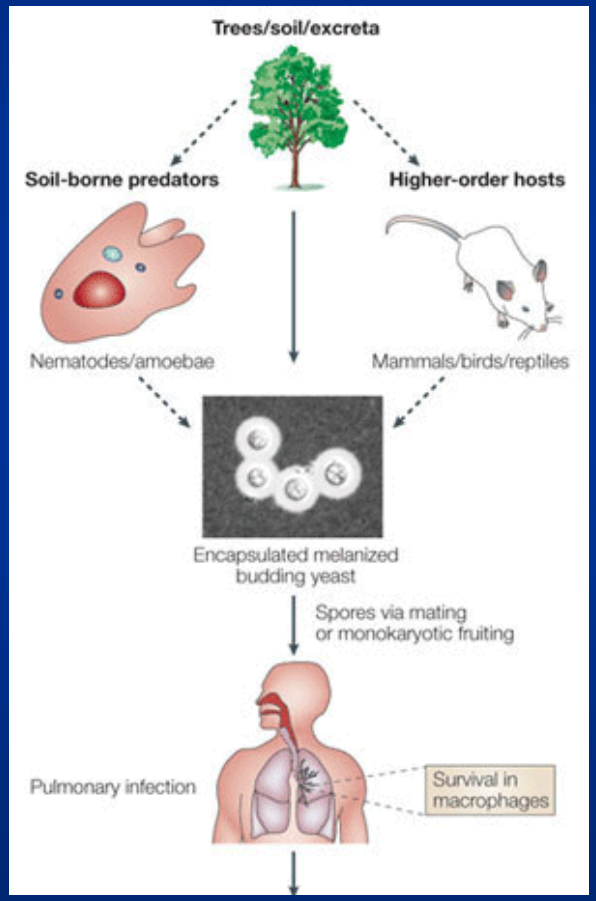
- Fundamentals of Cryptococcal meningitis
  - Diagnosis and management
- Importa sease
- Pre-syn ent of cryptoc
- Intro to

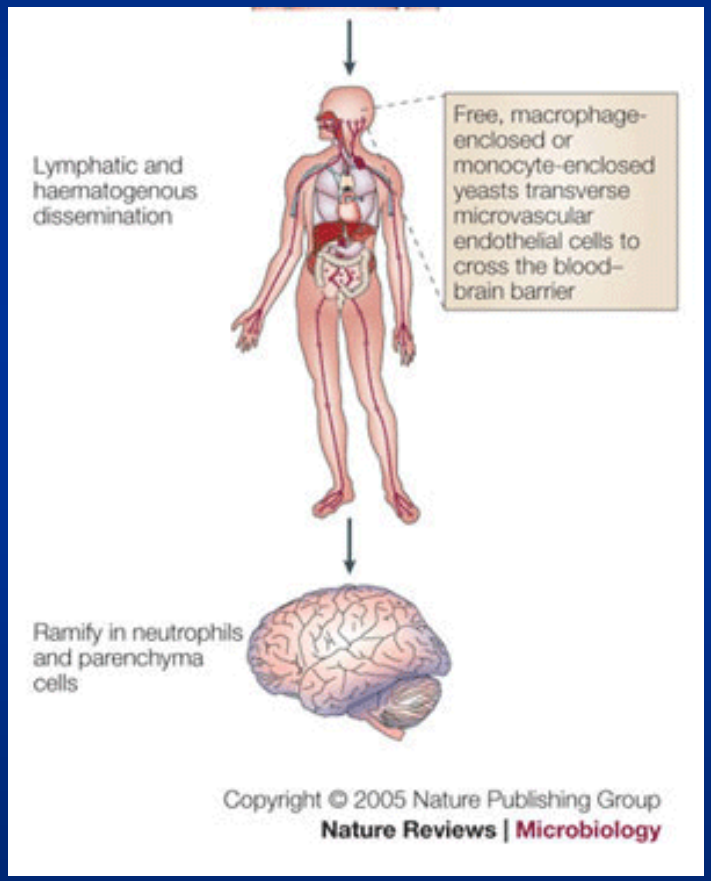


Cryptococcus Meningitis
Associated disorders

- Normal People (~<1:100,000)
- AIDS (1.9-11% of all AIDS patients)
- Corticosteroid therapy
- Leukemia and lymphoma
- Diabetes mellitus, cirrhosis, renal disease
- Sarcoidosis, SLE
- Idiopathic CD4 lymphopenia

Cryptococcus neoformans
Pathogenesis





Cryptococcus neoformans
Properties enabling CNS invasion

- Receptor on CNS cells for yeast ligand
- Ability to grow at 37^{o} C
- Melanin production by yeast (antioxidant)
- Production of capsule (protective)
- Resistance against *C. neoformans* chiefly CMI: corticosteroid therapy and HIV

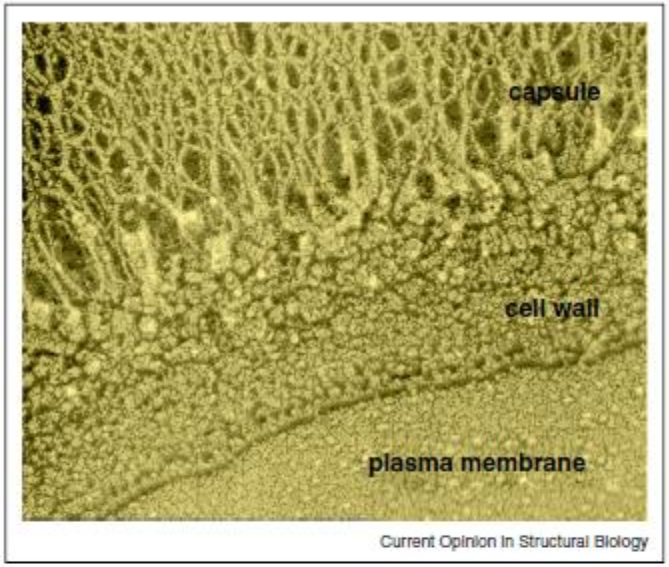
Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Structural Biology
ELSEVIER

Emerging themes in cryptococcal capsule synthesis

Pardeep Kumar*, Meng Yang*, Brian C Haynes, Michael L Skowyra and Tamara L Doering

Current Opinion in Structural Biology 2011, 21:597–602

- Capsule key factor in virulence of Crypto
- Composed of polysaccarides with carefully regulated synthetic pathways
- Changes between strains, and by growth conditions



Cryptococcal surface structures. This quick-freeze deep-etch electron micrograph of the edge of a cryptococcal cell (J. Heuser and T.L. Doering, unpublished) shows a segment of the cell wall separating a region of the plasma membrane from the radiating capsule fibers. The capsule extends upwards from the cell body and only the inner portion of the structure is visible; the entire capsule would extend significantly beyond the region shown.

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Current Opinion in Structural Biology

Emerging themes in cryptococcal capsule synthesis

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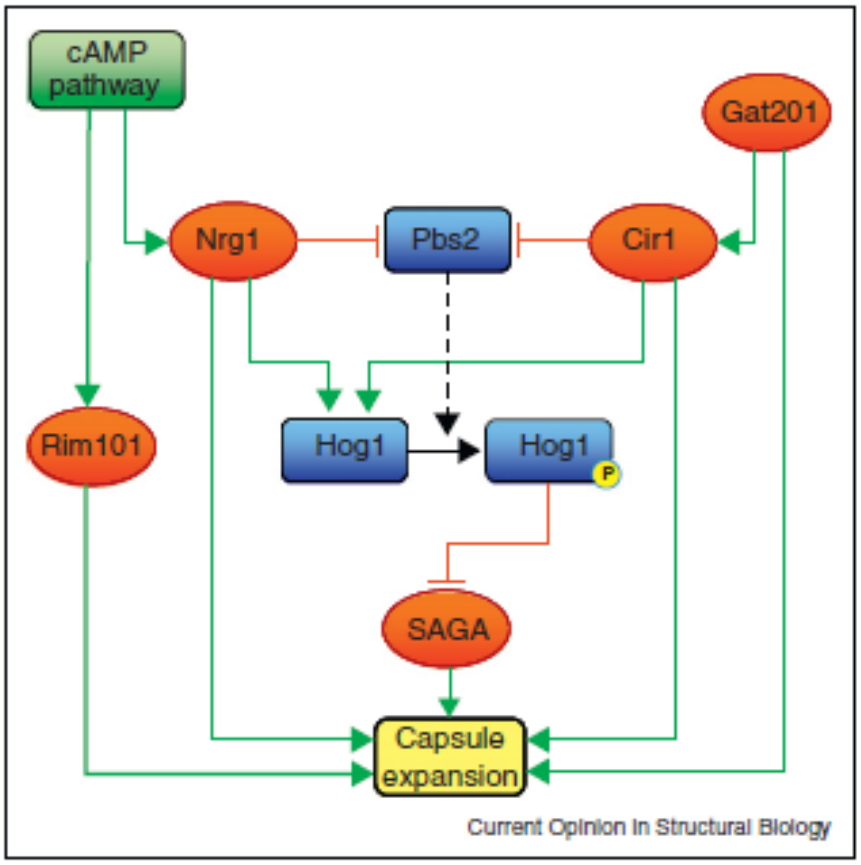
Figure 4



Capsule is regulated by a complex network, as exemplified by this subset of regulatory interactions involving transcription factors that influence capsule size (red ovals; see text). Several of the interactions shown are mediated by Hog1, a MAP kinase involved in stress response and virulence factor synthesis in *C. neoformans*, which is phosphorylated by the MAPK kinase Pbs2 [39]. SAGA is a multiprotein complex that regulates transcription [48]; deletion of genes encoding two of its component proteins, Gcn5 and Ada2, yields hypocapsular cryptococci ([45] and our unpublished work, respectively). The diagram is based on our analysis of gene expression profiles generated by microarray [41,42,43•,46•] or RNA sequencing (our unpublished data on strains deleted for *NRG1*, *CIR1*, and *ADA2*). Green lines, stimulation of transcription; red lines, inhibition of transcription; solid black arrow, phosphorylation; P, phosphate; dashed arrow, reaction catalyzed by Pbs2.

Cryptococcal meningitis

Signs and symptoms (Sabetta and Andriole 1985)

• Headache	87%
• Fever	60%
• Nausea and vomiting	53%
• Altered mental status	52%
• Meningeal signs	50%
• Visual disturbances	33%
• Cranial nerve palsies	32%

Cryptococcal meningitis

Signs and symptoms (Sabetta and Andriole 1985)

- Papilledema 28%
- Ataxia 26%
- Seizures 15%
- Aphasia 10%
- No signs or symptoms 10%

Cryptococcal meningitis
CSF findings

- ↑ WBC (<800 cells;lymph) 97%
- ↑protein (<600 mg/dl) 90%
- ↑opening pressure 64%
- ↓glucose (15-35 mg/dl) 55%

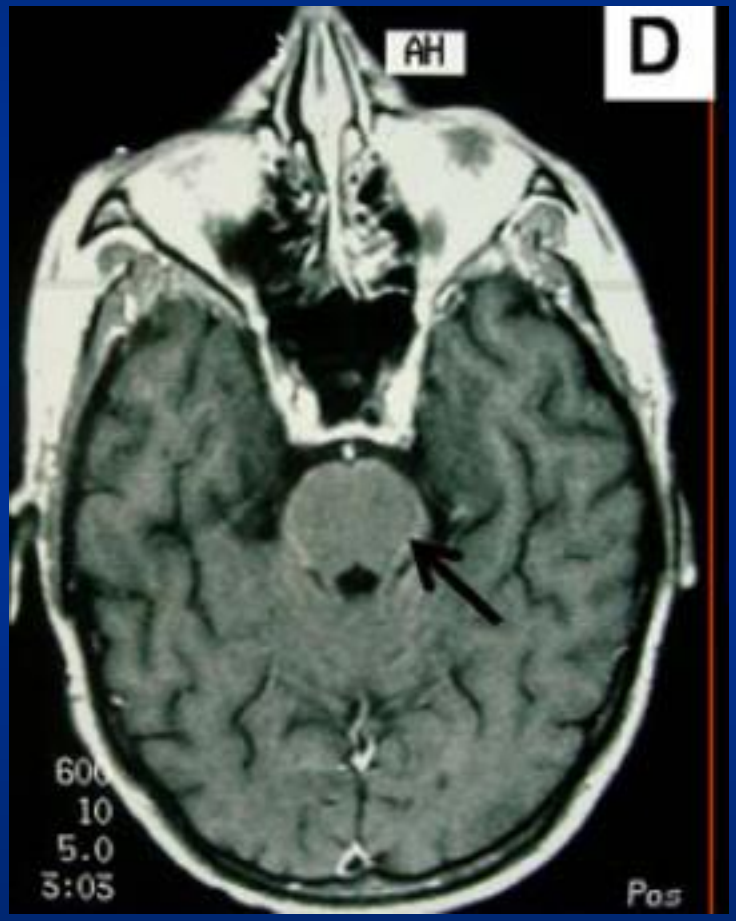
Cryptococcal Meningitis: CSF

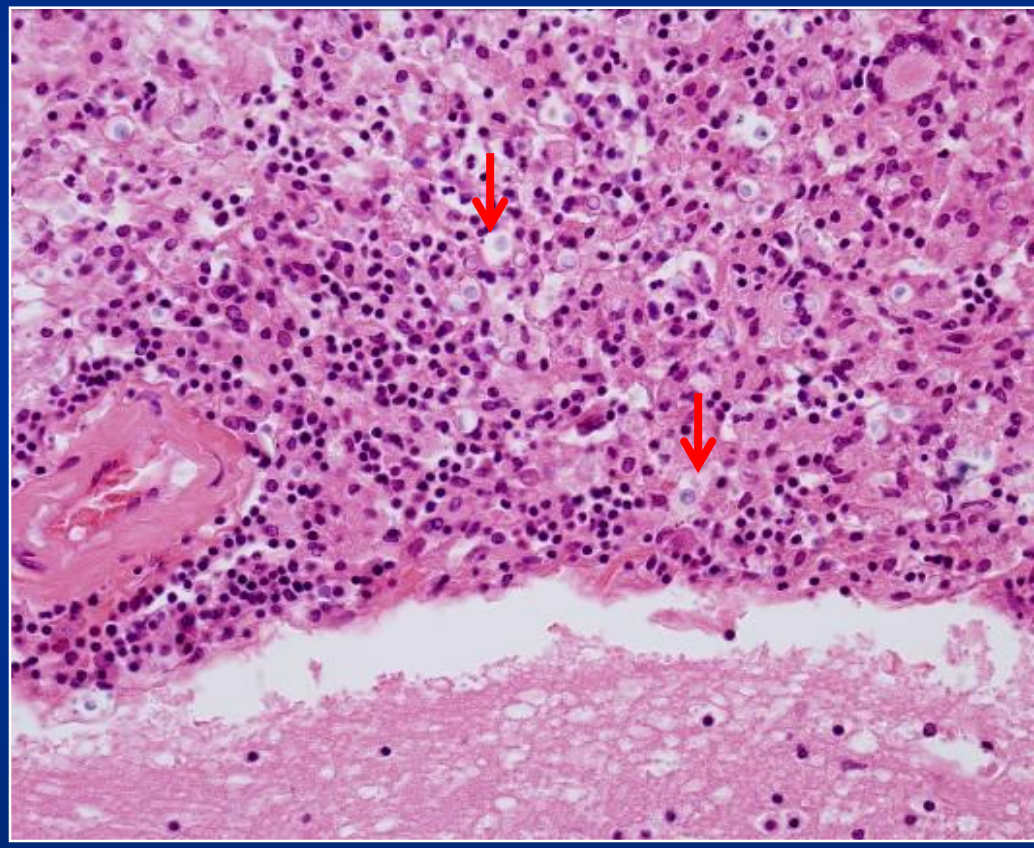
- Culture is gold standard – sensitive and specific, but too slow
- Direct visualization (India ink) – requires expertise, and not sufficiently sensitive or specific, but quick
- Antigen testing
  - Latex agglutination (LA) – Manual, slow, used for titers
  - Enzyme Immunoassay (EIA) –automated
  - **Lateral flow assay (LFA) – quick, inexpensive**

Causes of Hypoglycorrhachia

- acute bact meningitis
- TB meningitis
- syphilitic meningitis
- mening. cysticercosis
- trichinosis
- fungal meningitis
- viral mening.(mumps)
- amebic meningitis
- SAH
- CA meningitis
- drug-induced(NSAID)
- chemical (IT inject)
- rheumatoid mening.
- lupus cerebritis/sp.cd
- hypoglycemia

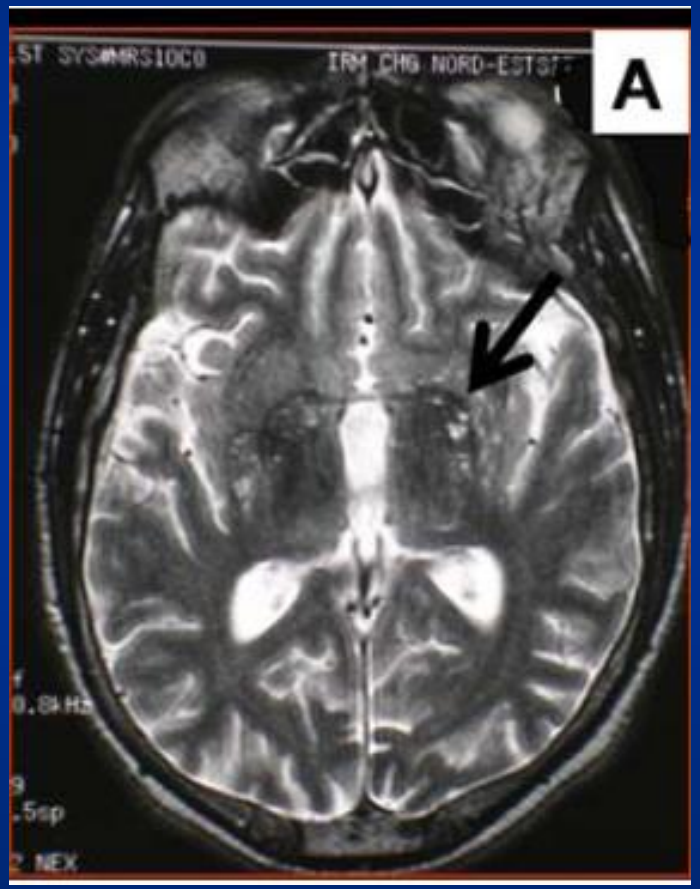
Basilar Meningitis

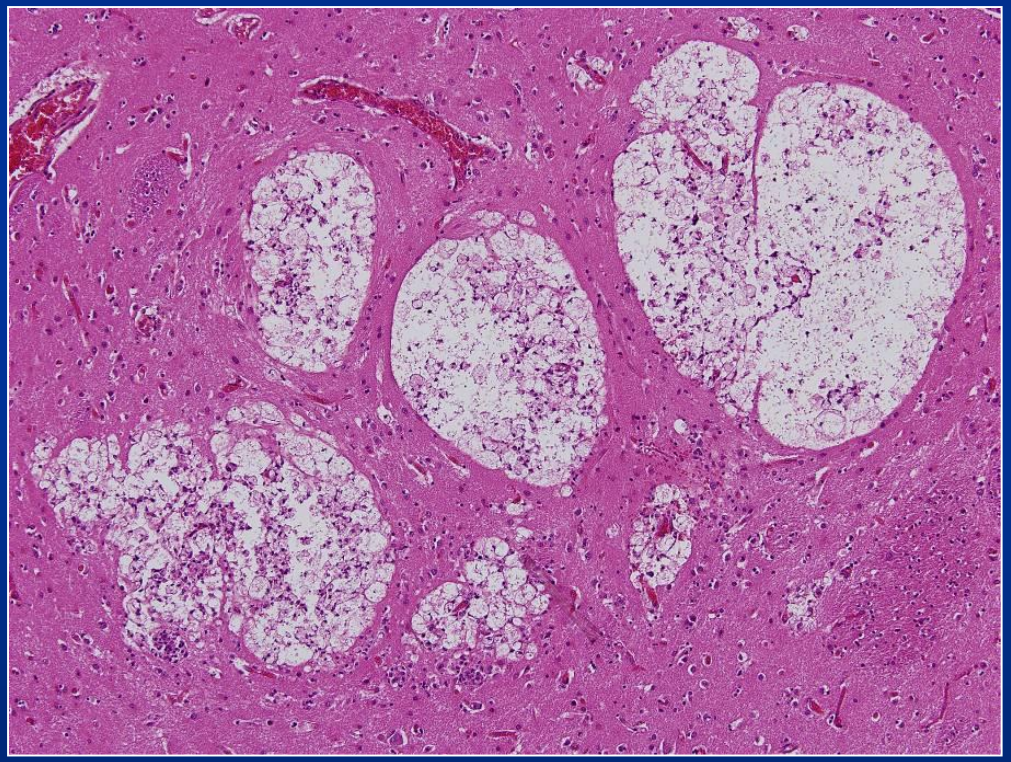




Path: R Schmitt, MD, PhD

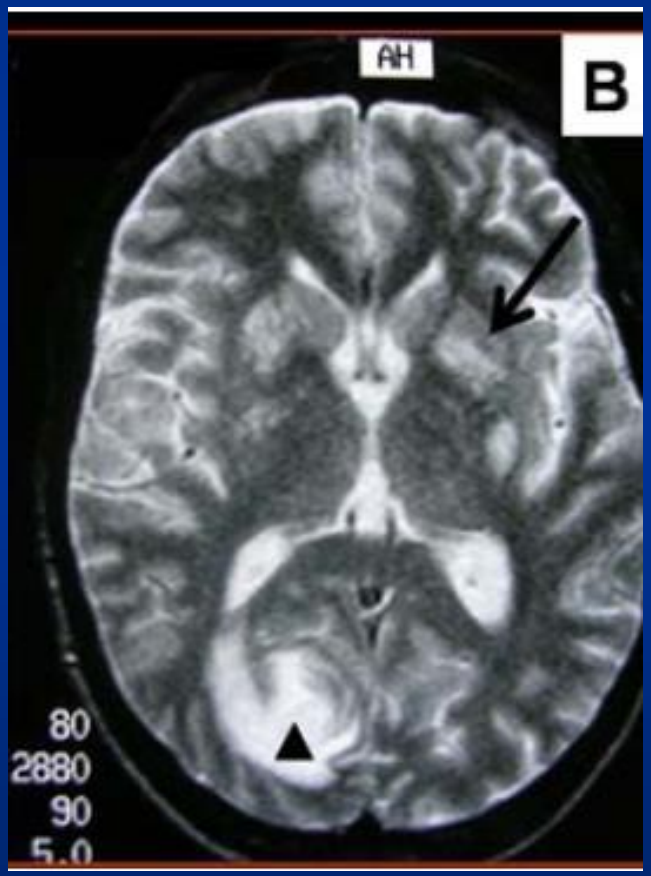
Dilated Virchow Robin Spaces

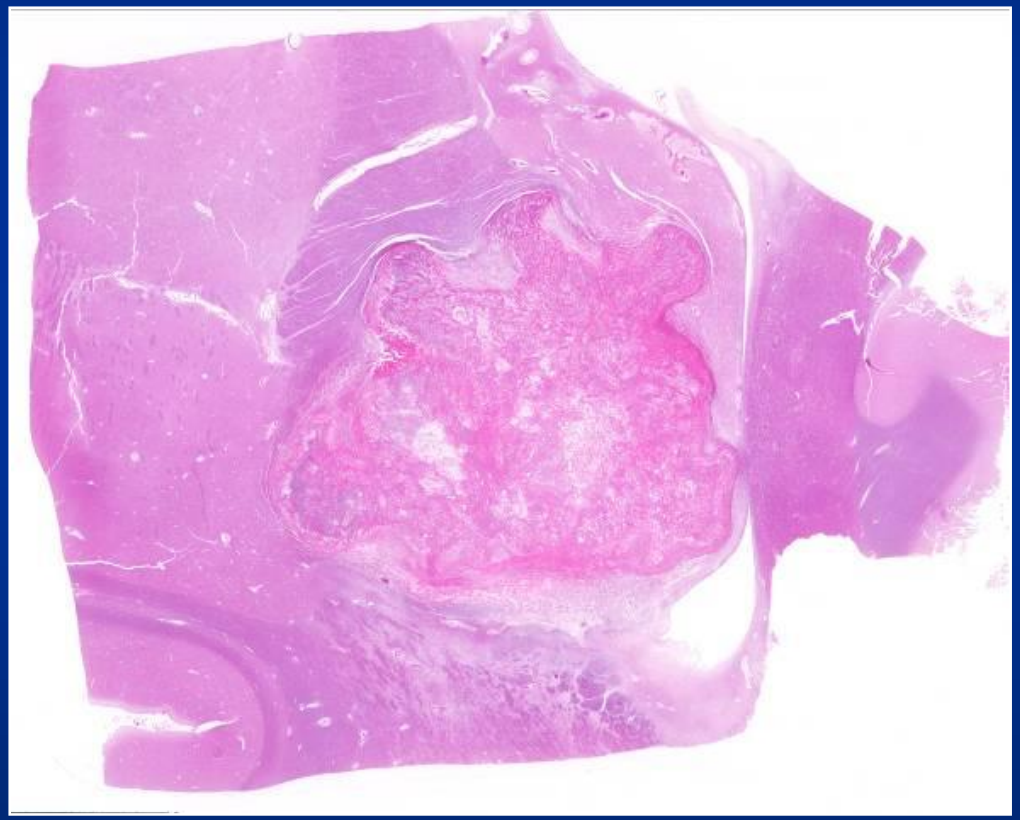




Path: R Schmitt, MD, PhD

Mass Lesion in Crypto





Path: R Schmitt, MD, PhD

Treatment

- Antifungal pharmacotherapy
  - Phases: Induction, consolidation, maintainence
- Intracranial pressure management
- Immune reconstitution

Cryptococcal meningitis Antifungals for Immunosuppressed

- Induction (2 weeks – or until CSF sterile)
  - Amphotericin B deoxycholate 0.7-1.0 mg/kg/d IV
  - +/- flucytosine 100 mg/kg/d PO in 4 doses
  - Liposomal AmB has less renal toxicity and may be used if pre-existing renal dx, not more effective
  - Developing world: fluconazole 1200 mg/d (or higher) often used
  - AmB + fluconazole 800 mg/d superior to AmB alone or with lower dose fluconazole
  - Voriconazole or posaconazole are alternatives if fluconazole resistance develops

A5225: High Dose Fluconazole to Treat Crypto Meningitis

- Standard rx uses amphotericin B
  - IV med that is somewhat toxic (renal)
- Protocol meant to explore oral alternative
- Fluconazole active, but at doses used previously not as good as ampho B
- Protocol compares standard rx with increasing doses of fluconazole
- Very challenging, but impressive progress being made

CM Treatment(s)

Curr HIV/AIDS Rep (2012) 9:267–277

Table 2 Regimens for antifungal pharmacotherapy for cryptococcal meningitis in different scenarios (authors' preferences)

Scenario	Proposed induction (should prolong if CSF sterility not achieved)	Consolidation	Maintenance
Optimal resources	AmB or L-AmB×14 d + 5FC×14 d	Fluconazole 400 mg/d×8 wk	Fluconazole 200 mg/d
5FC unavailable/intolerant	AmB or L-AmB×14 d + fluconazole 1,200 mg/d×14 d Or AmB or L-AmB×4–6 wk[a]	Fluconazole 800 mg/d×8 wk	Fluconazole 200 mg/d
Limited AmB available, (limited monitoring and resources available)	AmB×7 days + fluconazole 1,200 mg/d×14 d (if available add 5FC×14 d)	Fluconazole 800 mg/d×8 wk	Fluconazole 200 mg/d
AmB unavailable	Fluconazole 1,200 mg/d×14 d (if available add 5FC×14 d)	Fluconazole 800 mg/d×8 wk	Fluconazole 200 mg/d

AmB dose: 0.7–1 mg/kg/d; L-AmB dose: 5 mg/kg/d; 5FC dose: 25 mg/kg every 6 h

[a] Included in Infectious Diseases Society of America guidelines but not favored by authors of this review.

5FC flucytosine; *AmB* amphotericin B; *CSF* cerebrospinal fluid; *L-AmB* liposomal amphotericin B

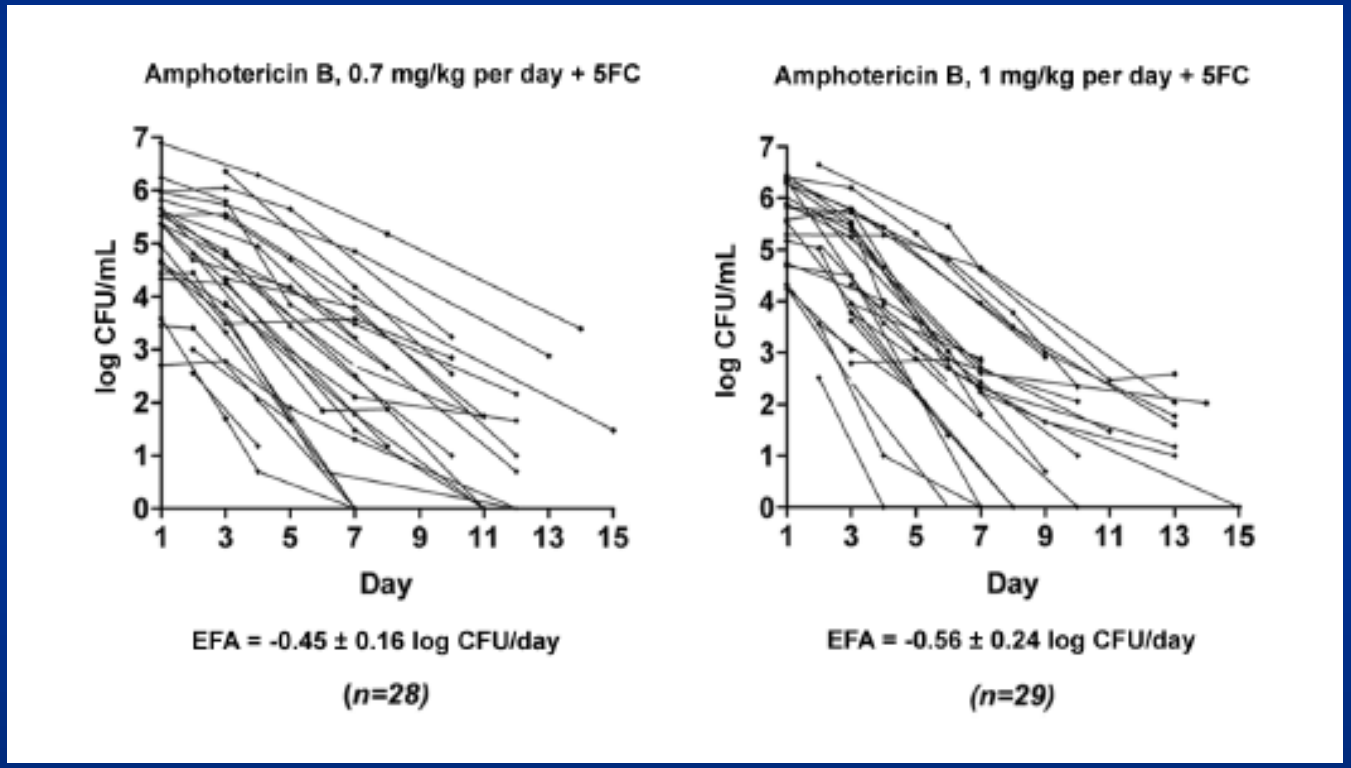
Dose of AmB

- Trial comparing 0.7 mg/kg to 1.0 mg/kg AmB with 5FC
- Higher dose more rapidly fungicidal
- Renal toxicity and anemia were reversible
- Outcomes similar, limited by small size of study (64 pts)

Bicanic, et al

Clinical Infectious Diseases 2008;47:123–30

Clearing Fungus – Quantitative Cultures



Bicanic, et al

Clinical Infectious Diseases 2008;47:123–30

Antifungals

- Consolidation (8 weeks)
  - fluconazole 400 to 800 mg/d or
  - Itraconazole, voriconazole, posaconazole alternatives
- Maintenance
  - fluconazole 200 mg/d
  - In AIDS x 12 mo and with CD4 >200, VL controlled
  - In apparent immunocompetent x 12 mo

Cryptococcus neoformans

Side effects of treatment

- **Amphotericin**
  - fever, chills, H/A, N&V, phlebitis, cardiotoxicity, nephrotoxicity, hypomagnesemia, hypokalemia, hepatotoxicity, cytopenias
- **5-Flucytosine**
  - cytopenias, nephrotoxicity, hepatoxicity, confusion, H/A, hallucinations
- **Fluconazole**
  - nausea and vomiting, headache, skin rash, abd pain, diarrhea, hepatotoxicity, seizures

Prognosis – Importance of Fungal Load

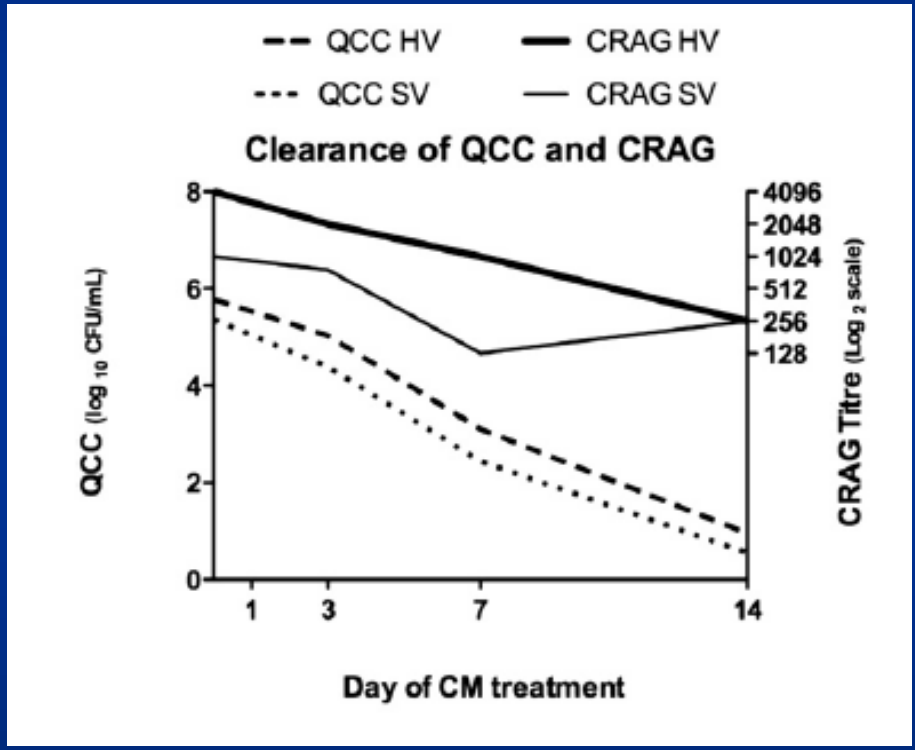
- Elevated CSF pressure common
- CSF outflow through arachnoid villa thought to be blocked by fungus or capsule
- Communicating hydrocephalus leads to headache, vomiting, visual/hearing loss, CN palsy depressed consciousness
- LP may reverse these transiently

Management of Raised ICP

- Serious complication associated with increased mortality
- Daily LP recommended if >250 cm CSF
- Drain up to 30 cc, decreasing pressure to at least 200 cm
- Lumbar drain, shunting rarely justified
- Mannitol, corticosteroids, acetazolamide probably not effective and should not be used

Drainage of CSF to Control ICP

- >100 cc tapped over 2 wks = high volume
- <25 cc tapped over 2 wks = standard
- Therapy same
- Immune status comparable
- QCC = quantitative crypto cultures
- Drop in capsule antigen by two wks of rx forms rationale for delay in HIV Rx start



Ishan Wijewardana
Journal of Infection (2011) 63, 484–486

Objectives

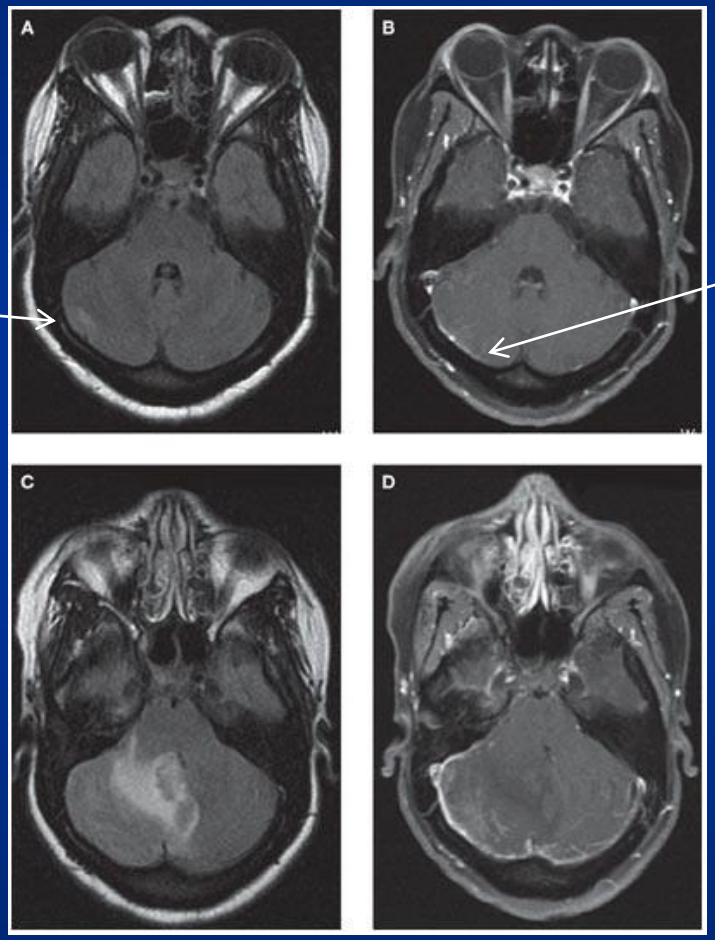
- Fundamentals of Cryptococcal meningitis
  - Diagnosis and management
- Importance of IRIS in cryptococcal disease
- Pre-symptomatic detection and treatment of cryptococcus
- Intro to Cryptococcus gattii

What is IRIS?

- Immune reconstitution inflammatory syndrome
- Successful HIV therapy associated with worsening symptom/sign
- Driven by exuberant inflammatory response

Cryptococcal neoformans
Radiographic findings – IRIS in AIDS

Small cerebellar lesion



Meningeal enhancement

2 weeks after the initiation of HAART

Riedel DJ *et al.* (2006) *Nat Clin Pract Neurol* **2:** 557

Crypto IRIS

- More likely in setting of:
  - Advanced HIV
  - Advanced crypto
  - Early concurrent treatment
- Onset variable but 2-6 wk after HIV Rx start is typical
- Variable compliance with HIV meds can contribute to late IRIS with residual antigen present in brain

OPEN ACCESS Freely available online

PLoS MEDICINE

Clinical Features and Serum Biomarkers in HIV Immune Reconstitution Inflammatory Syndrome after Cryptococcal Meningitis: A Prospective Cohort Study

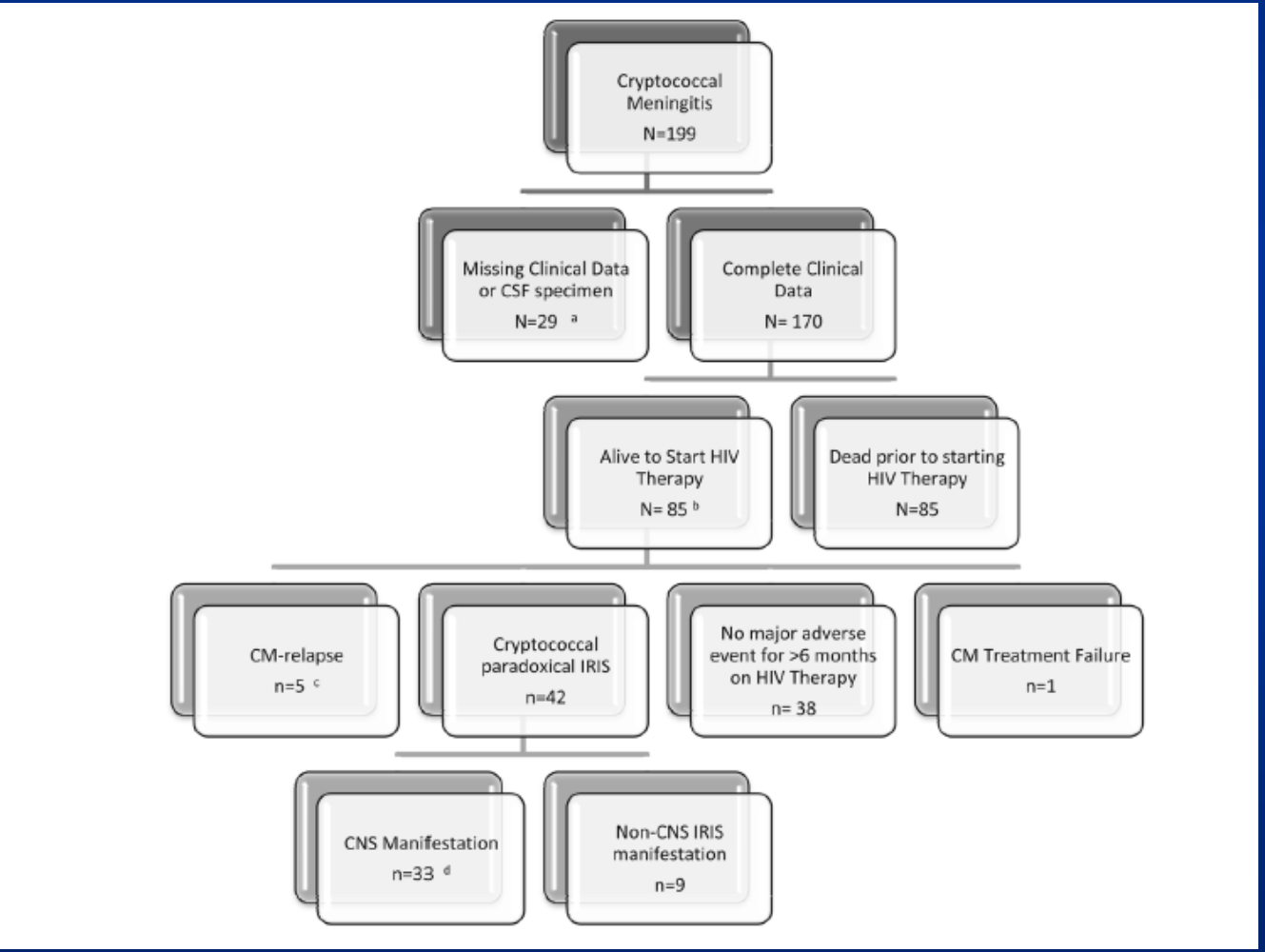
David R. Boulware[1,2*], David B. Meya[1,3], Tracy L. Bergemann[4], Darin L. Wiesner[2], Joshua Rhein[1,2], Abdu Musubire[3], Sarah J. Lee[1], Andrew Kambugu[1,3], Edward N. Janoff[5], Paul R. Bohjanen[1,2,6]

December 2010 | Volume 7 | Issue 12 | e1000384

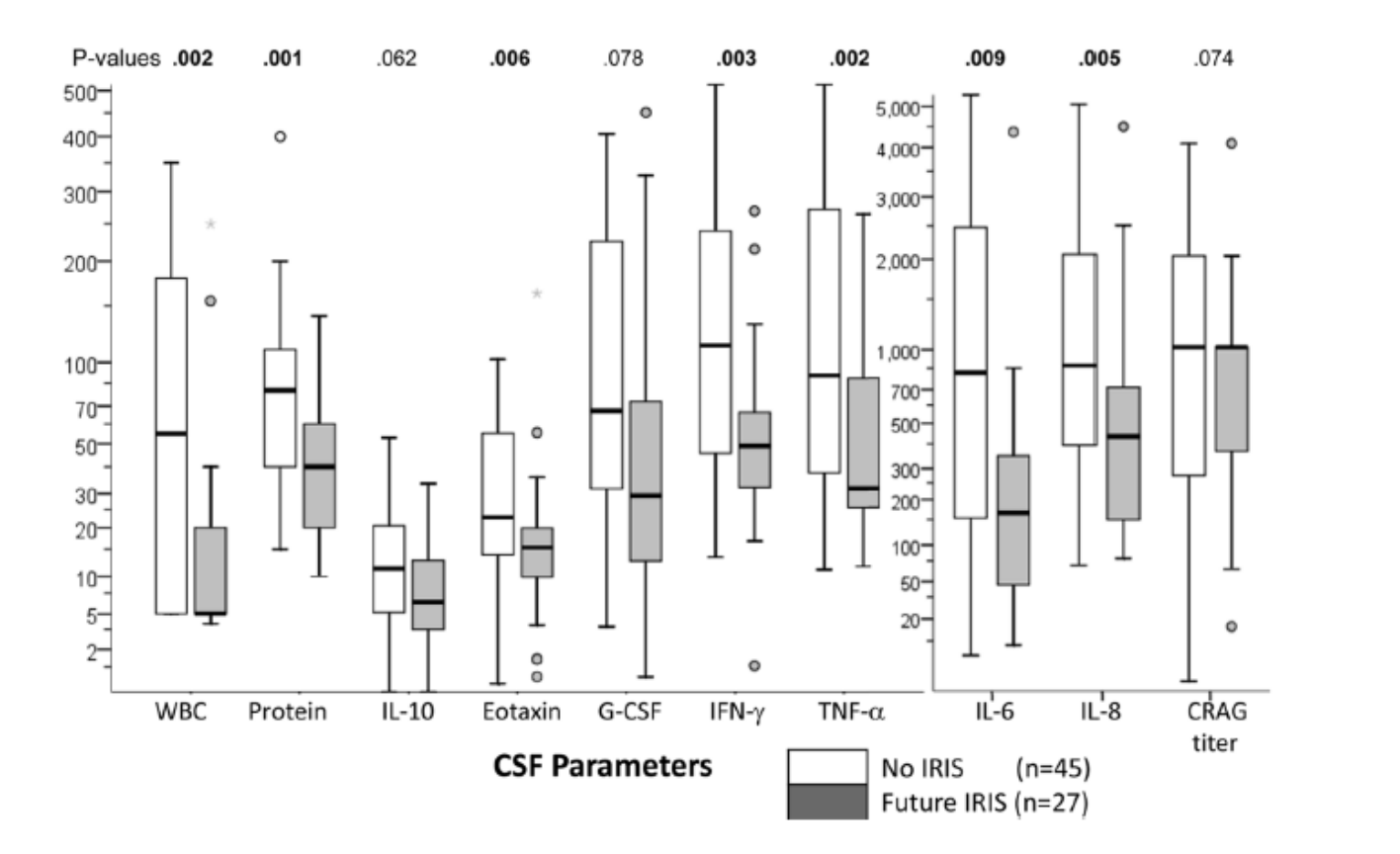
- ART-naïve pts with AIDS and recent CM
- Rx: Amphotericin B x 14 doses, then fluconazole 400 mg/d, ART ~ 1 mo after CM rx start
- IRIS by INSHI definition

Mulago Hospital, Uganda

Importance of IRIS in Crypto



Poor CSF Inflammatory Response at Baseline Predicts Future IRIS



IRIS Associated with Poorer Survival

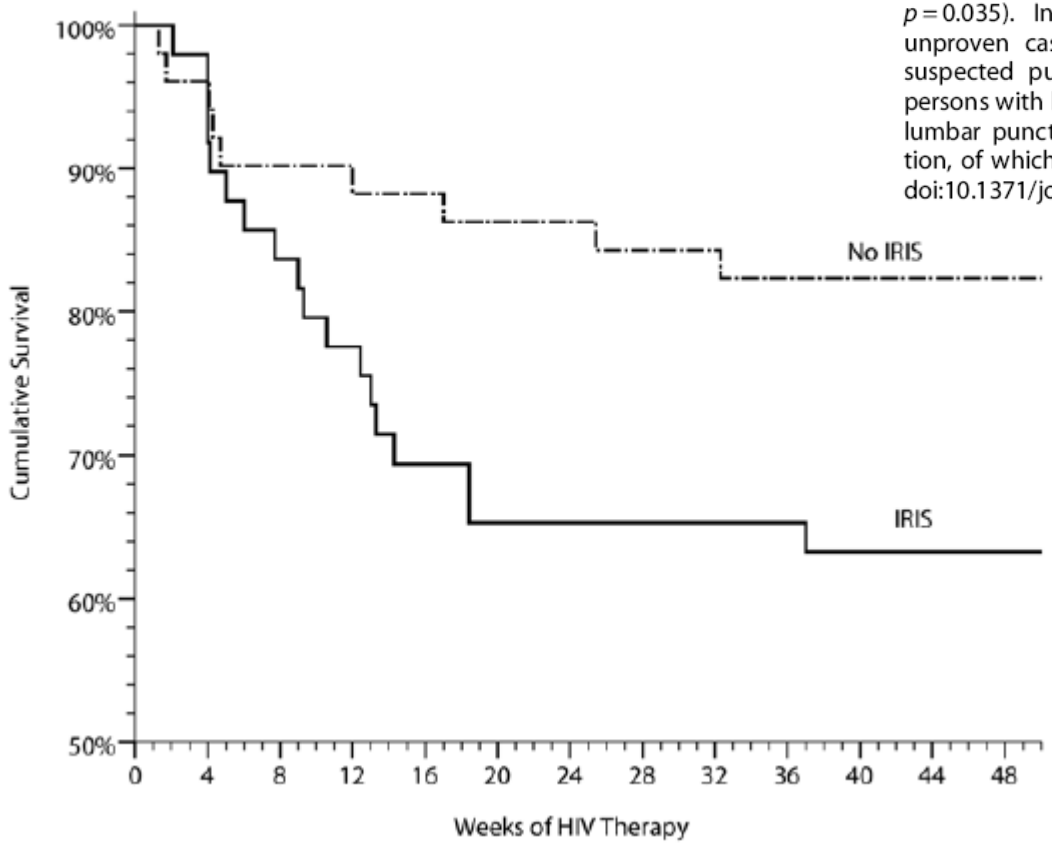


Figure 2. Cumulative survival in persons with prior cryptococcal meningitis newly initiating HIV therapy in Uganda is stratified by the occurrence of cryptococcal IRIS. IRIS was associated with increased mortality (HR = 2.4, 95% CI 1.1–5.3, $p = 0.035$). Included with the controls are three suspected, but unproven cases of CM-IRIS, three unknown causes of death (two suspected pulmonary emboli). Two deaths have been excluded of persons with known virologic suppression with clinical IRIS who refused lumbar punctures to exclude alternative etiologies of their deterioration, of which one of these deaths was attributed to suicide.
doi:10.1371/journal.pmed.1000384.g002

IRIS in Cryptococcus

- Occurs in <50% of crypto cases
- More likely in severe cases, unmasking crypto with HIV therapy
- Management
  - Continue HIV med
  - Manage pressure with taps
  - R/o TB, recurrent crypto (while on crypto rx)
  - Corticosteroids are indicated if severe

COATS Study

Cryptococcal Optimal ART Timing

- Randomize patients to start early (7-11 days) or late (~5 weeks) after start of cryptococcal therapy
- Standard crypto therapy with AmB + fluconazole 800 mg induction
- 26 week followup, survival endpoint
- Stopped by DSMB with ~176 patients randomized due to higher mortality in early HIV rx group (42.5% vs 27.6%)

http://www.niaid.nih.gov/news/QA/Pages/COATqa.aspx

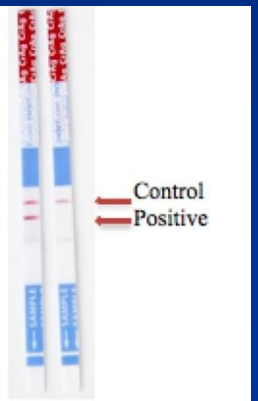
Pre-symptomatic Therapy

- 21st century trend in neurology
- Early deaths in therapy a major problem throughout the world
- Should advanced HIV patients with crypto be tested and treated before starting HIV therapy?

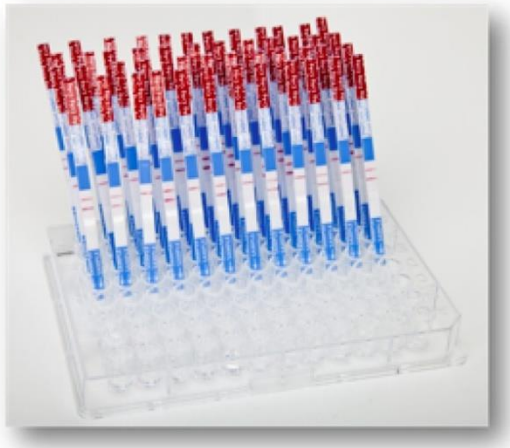
Cryptococcal Meningitis: CSF Lateral Flow Assay

- High sensitivity and specificity
- Allows titers (but may give higher numbers than LA)
- Doesn't require expensive equipment
- Can be done quickly

High Thoroughput Example in 96-well plate



LFA strips produce a definitive result for presence of CRAG within 5-15 minutes.

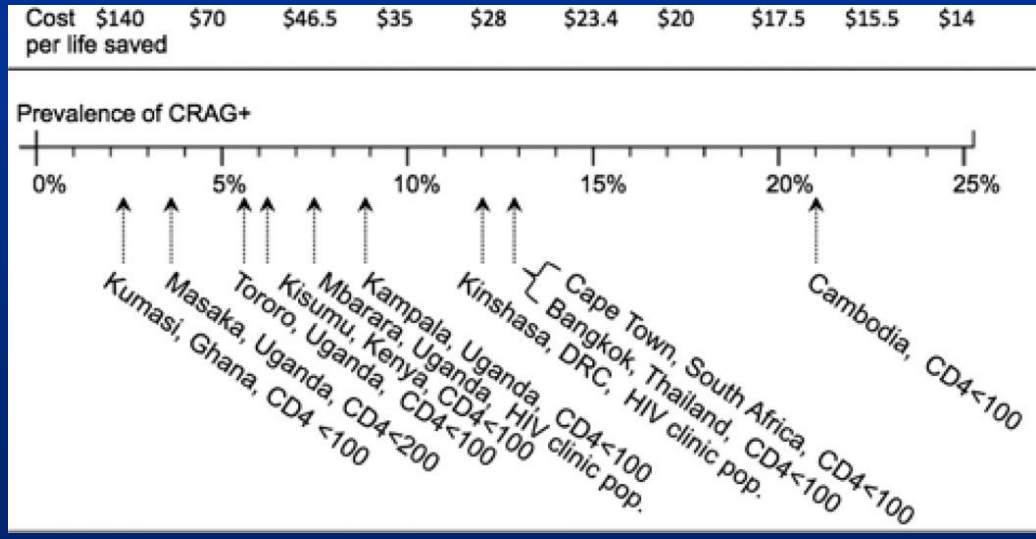


M. J. Binnicker, D. J. Jespersen, J. E. Bestrom and L. O. Rollins
Clin. Vaccine Immunol. 2012, 19(12):1988. DOI: 10.1128/CVI.00446-12.

Cryptococcal Meningitis: CSF Lateral Flow Assay

- Antigen present 20-100 days before symptomatic meningitis develops
- Low cost, convenient, site of service test could allow pre-symptomatic diagnosis
- Cost effective in high risk patients (eg CD4<100)

Cost to save one life is between $20 and $140 in sub-Saharan Africa



Rajasingham et al, JAIDS 2012

Objectives

- Fundamentals of Cryptococcal meningitis – Diagnosis and management
- Importance of IRIS in cryptococcal disease
- Pre-symptomatic detection and treatment of cryptococcus
- Introduction to Cryptococcus gattii

Emergence of C. *gattii*

- Geographically in tropics and subtropics, but now expanding
- More successful pathogen in immunocompetent hosts, more cryptococomas in brain and lungs
- Differentiate from *C neoformans* with canavanine glycine bromothymol blue (DGB) agar
- Evidence emerging of differing innate immune response stimulation dependent on species (involving TLR9 in particular)

C. gattii Environmental Hosts Vary

Koala host C Gattii in Australia

Dophins

10^5 fungi / gm soil in drip line of tree!!

Eucalyptus

Table 1
Descriptions of the four *C. gattii* molecular types.

Molecular type	Clinical features	Environmental features	Distribution
VGI	Most common molecular type in humans and animals and highly clonal	Commonly associated with *Eucalyptus* trees, particularly in Australia [17,58]	Global with high distribution in Australia
VGII	Responsible for Pacific Northwest outbreak, clonal in outbreak region but diverse globally, highly virulent genotypes (VGIIa, VGIIc) identified	Associated with native tree species, with common isolation from Douglas-fir and Alder trees in British Columbia [59]	Global, also the cause of the first outbreak in a temperate climate on Vancouver Island
VGIII	Frequently associated with infection of HIV/AIDS patients	Isolates are highly fertile, and have been found in *Corymbia ficifolia* (Red Flowering Gum, Colombia) [124] and *Eucalyptus* (California) [22]	Global, high levels observed in Southern California, Mexico, and South America
VGIV	Frequently associated with infection of HIV/AIDS patients	Largely unknown, but one positive isolate from an Almond tree [43,125,126]	Rare, reported in Africa, India, and South America

C gatti

- Australian experience affirms majority in non-immunosuppressed hosts
- Disease presentation and course typical
- Worse prognosis if immunosuppressed

Table 1. Characteristics of Patients With *Cryptococcus gattii*[a] Infection, 2000–2007

Patient Characteristic	No. (%)
Male	51 (59)
Female	35 (41)
Age	
15–30	14
31–49	40
50–64	17
65–80	15 (17)
Ethnicity[b]	
Caucasian	50 (58)
Australian Aborigine	23 (27)
Asian	7 (8)
Pacific Islander	4 (5)
Underlying conditions	
None	62 (72)
Leukemia[c]	4 (5)
Solid organ cancer	3 (3)
Kidney transplantation	3 (3)
Collagen vascular disorders	2 (2)
Idiopathic CD4 lymphopaenia	6[d]
Corticosteroid/ immunosuppressive therapy	12 (14)
Diabetes mellitus	5 (6)
Pregnancy	3[e]

Chen, et al

Clinical Infectious Diseases 2012;55(6):789–98

C gatti

- Australian experience affirms majority in non-immunosuppressed hosts
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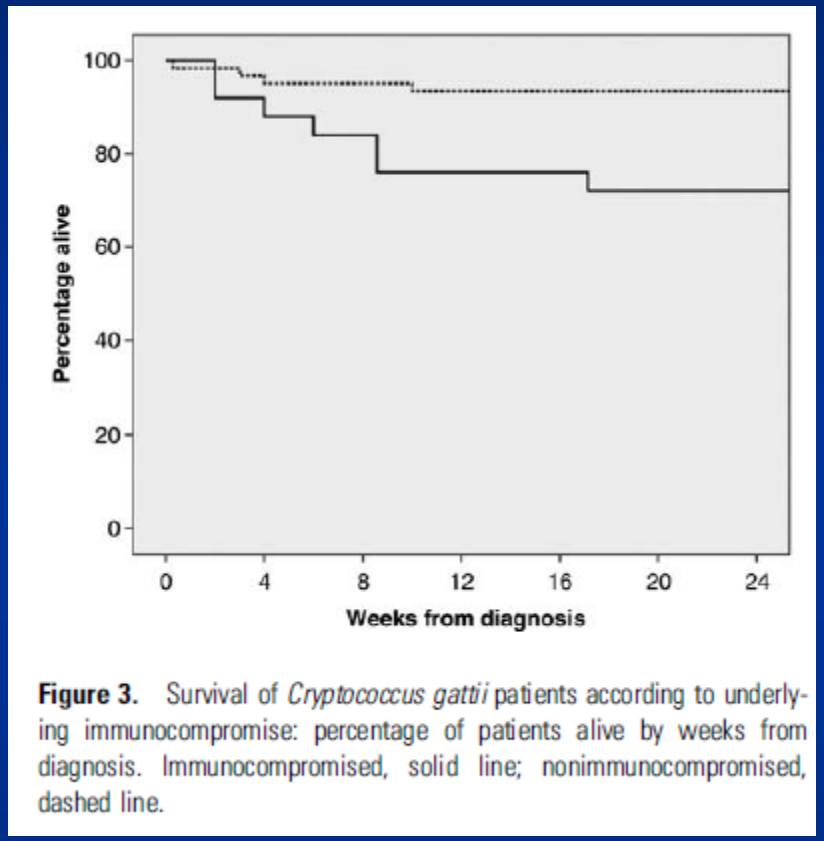


Figure 3. Survival of *Cryptococcus gattii* patients according to underlying immunocompromise: percentage of patients alive by weeks from diagnosis. Immunocompromised, solid line; nonimmunocompromised, dashed line.

Chen, et al

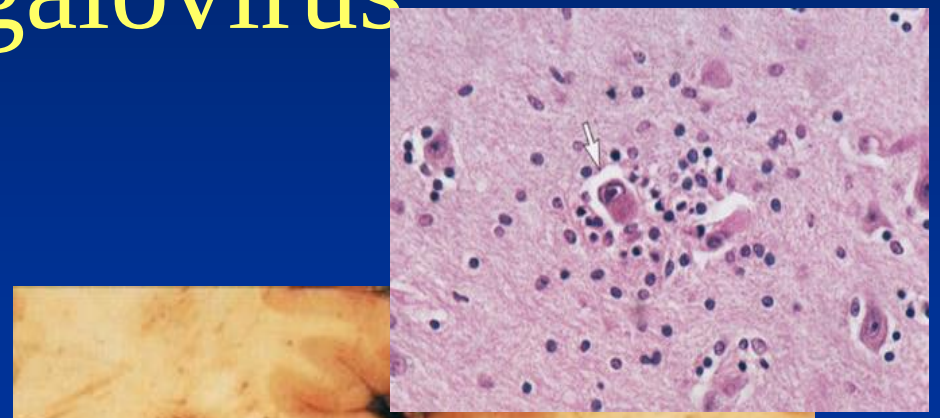
Clinical Infectious Diseases 2012;55(6):789–98

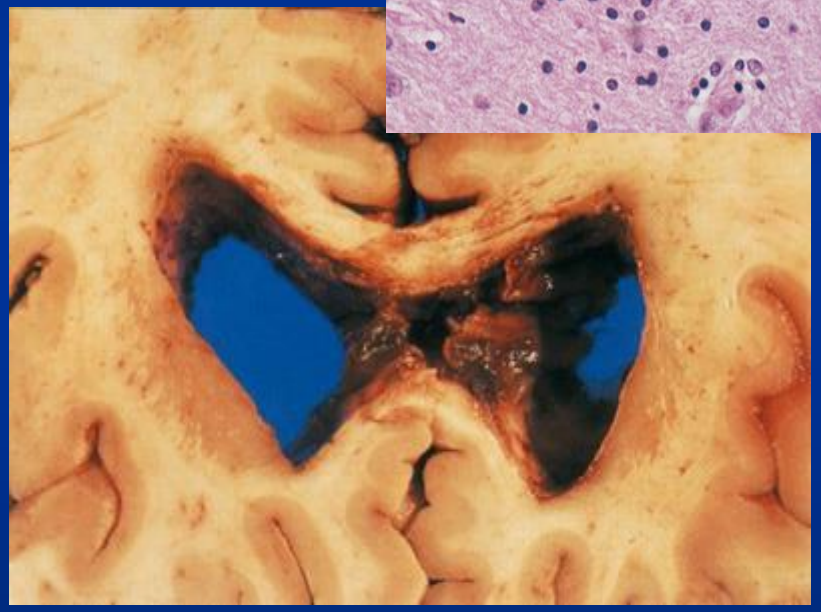
Conclusion

- Cryptococcal meningitis remains a major lethal complication particularly in HIV
- Optimal management by skilled clinicians can improve outcomes
- Even with optimal care, this disease is too often fatal
- Better therapy is urgently needed

Cytomegalovirus

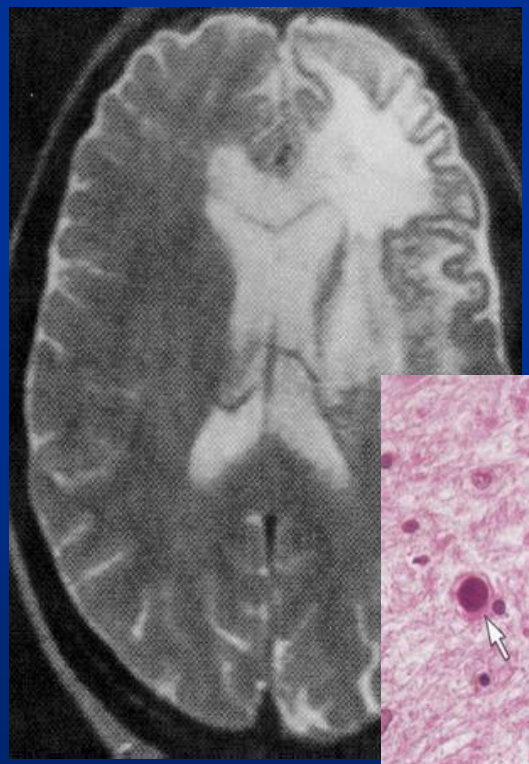
- Herpes virus, re-activation to cause aggressive disease
  - Encephalitis
  - Radiculomyelitis
  - Neuritis
- Dx: PCR testing
- Rx: ganciclovir, foscarnet, cidofovir

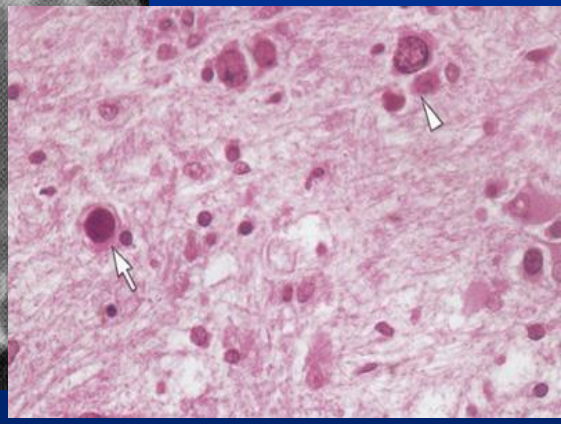




Progressive Multifocal Leukoencephalopathy

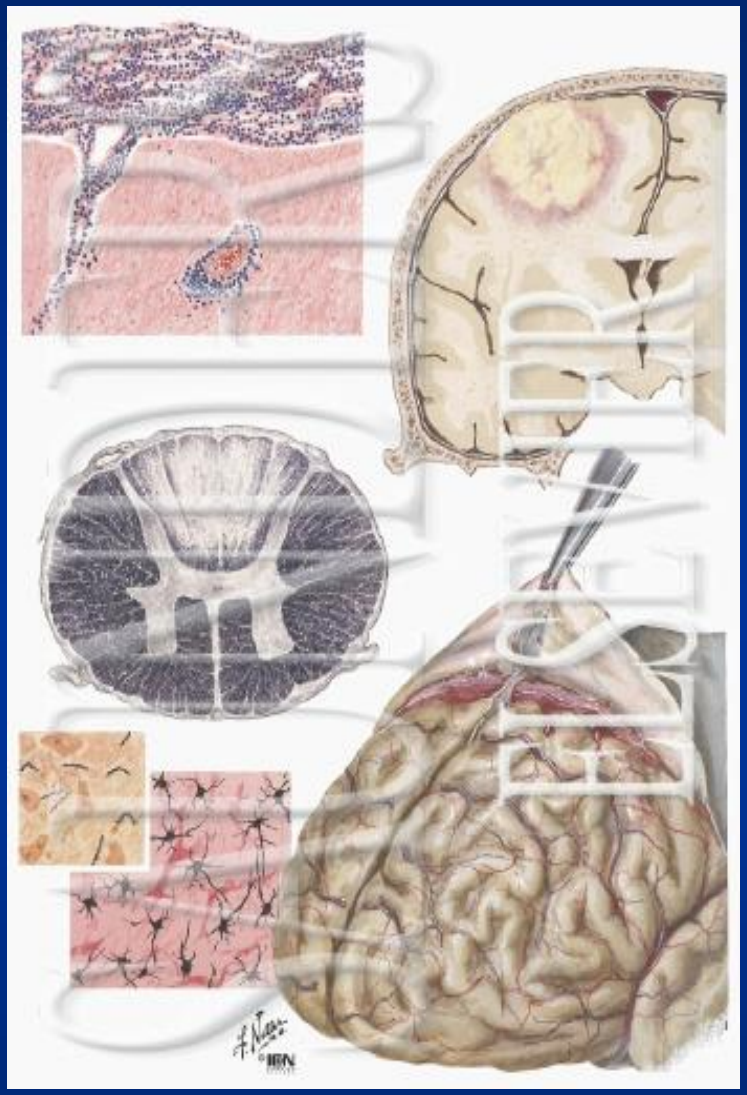
- Acquired demyelinating CNS disease
- JC virus is etiologic agent
- DNA virus
- Virus exposure is almost universal in population
- Disease exclusively in immunocompromised
- Characterized by progressive focal deficits





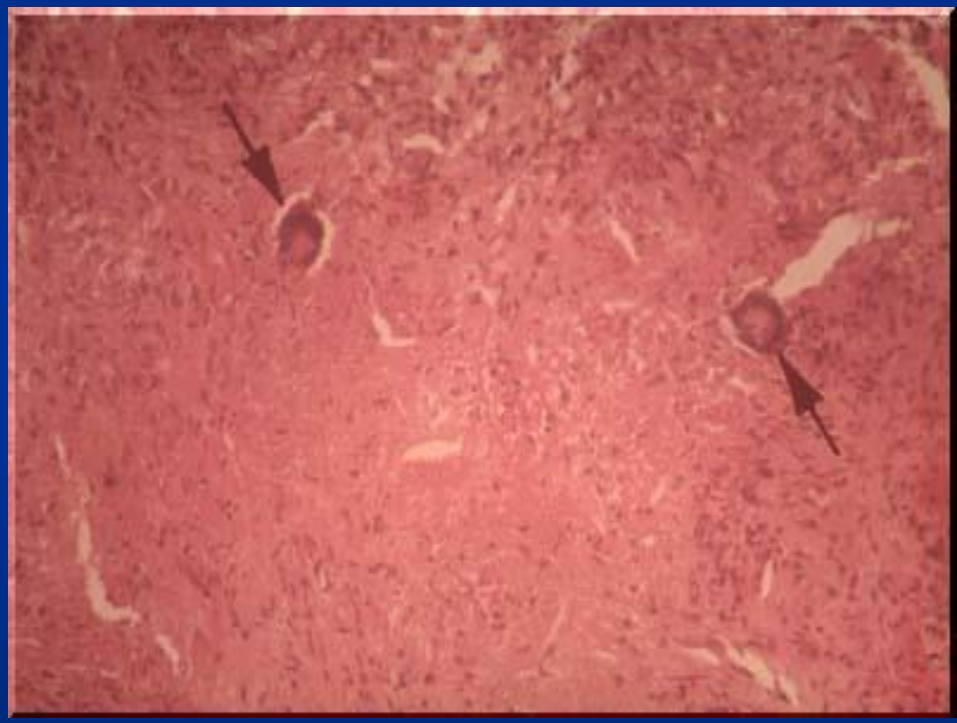
Neurosyphilis

- Treponeman pallidum often invades CNS
- Untreated, late neurologic manifestations include:
  - Meningovascular syphilis
  - Meningitis
  - Gumma
  - Tabes dorsalis
- Earlier, more frequent neurosyphilis occurs in immunosuppressed including HIV
- CSF evaluation is required to diagnose



Tuberculosis and HIV

- Worldwide most serious opportunistic infection
- CNS affected by TBC abscess or meningitis
- Aggressive rx required to treat using 4 anti-TBC drugs
- Interaction with anti-retrovirals problematic



Thanks!

- AAN
- Course Organizers
- CHARTER investigators
- NARC investigators
- ACTG investigators
- Washington U – STL
  - Turner Overton
  - **Beau Ances**
  - Mary Gould
  - Mengesha Teshome
- Patients and families