

# *Toxoplasma Encephalitis*



**David B. Clifford, M.D**

# Support

- Funding: NIH: NINDS, NIAID, NIMH, Fogarty
- Consulting: Biogen, Elan, Genzyme, Genentech, Millennium, Pfizer, Roche, Schering Plough
- Research support: Biogen, Lilly, Pfizer, Neurogesx, Bavarian Nordic, Tibotec

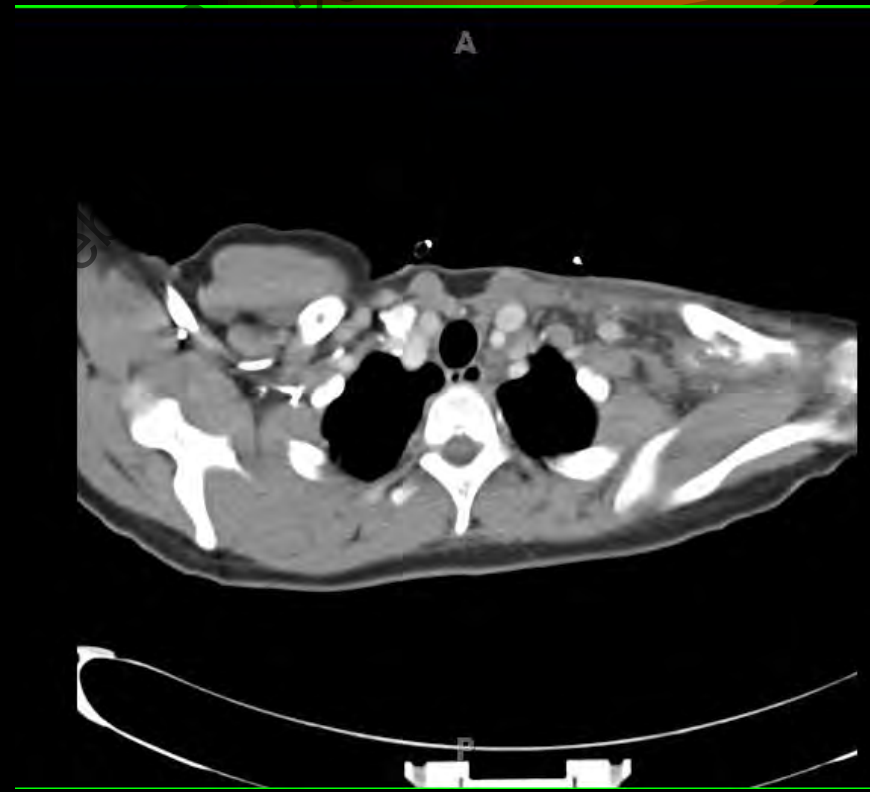


# History

- 34 yo woman from Liberia
- AIDS, off Rx, CD4 <50
- Extrapulmonary tuberculosis in elbow and leg for several years
- Hepatitis B
- Cardiomyopathy
- Positive serum RPR
- Presents with headache 10/09

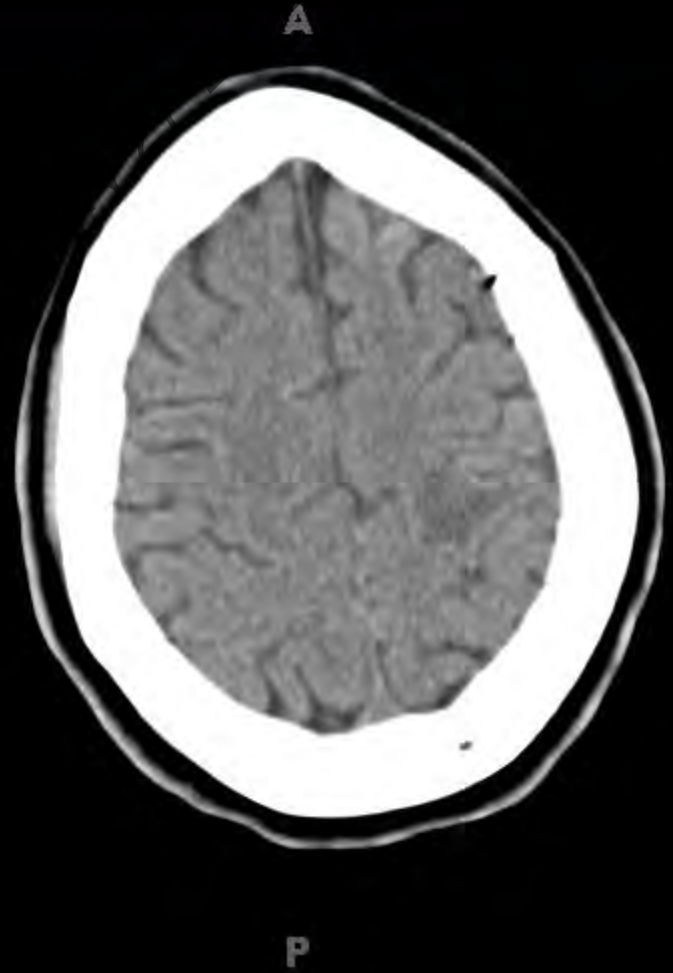
# *Extrapulmonary TBC – 2008*

## *Clavicle*



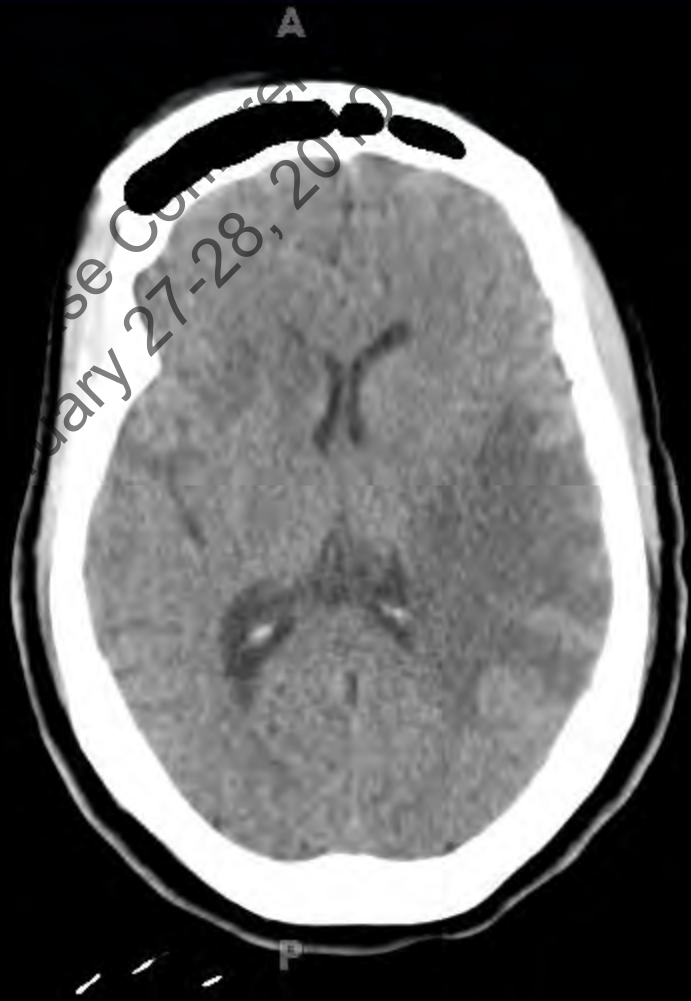
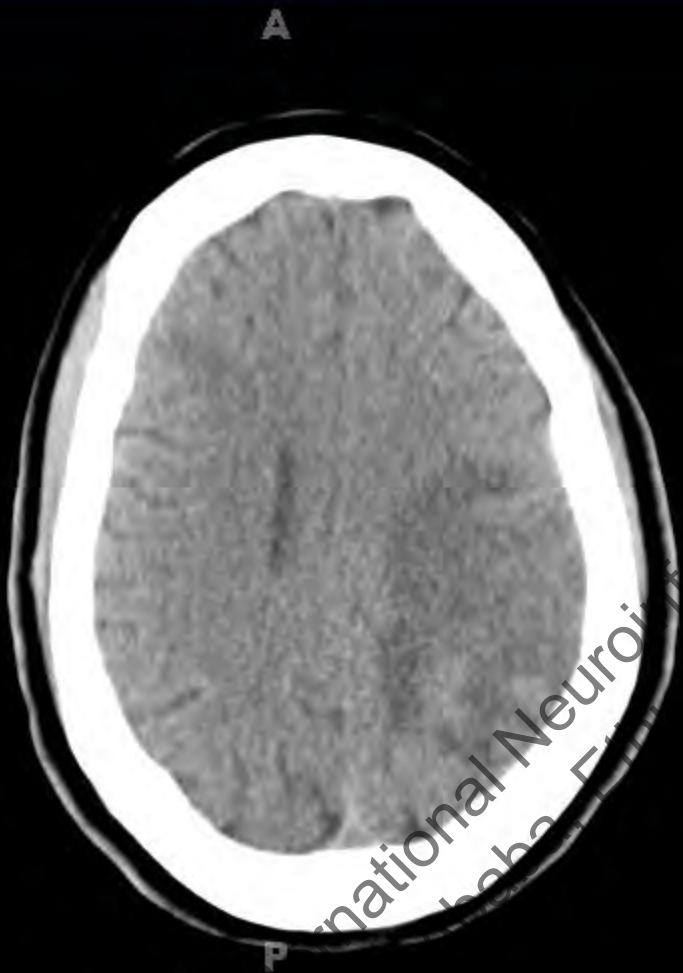
Aspiration of lesion  
yields AFB

# CT Brain – October 2009



## History 2

- Workup non-diagnostic
  - CSF benign
  - CSF PCR negative for EBV, toxo, JC HSV
  - CSF cultures negative
- Neurosurgery unwilling to biopsy brain
- Treated for TBC with four drugs, taken intermittently
- Presents 01/2010 worsening
  - Control right hand poor, decreased feeling in right hand



PATIENT: ID=5603453  
ZOWAY, HELENA [F]  
DOB: 1975-01-01 [034Y]  
Ref=CLINIC, MEDICINE (SOUTH)

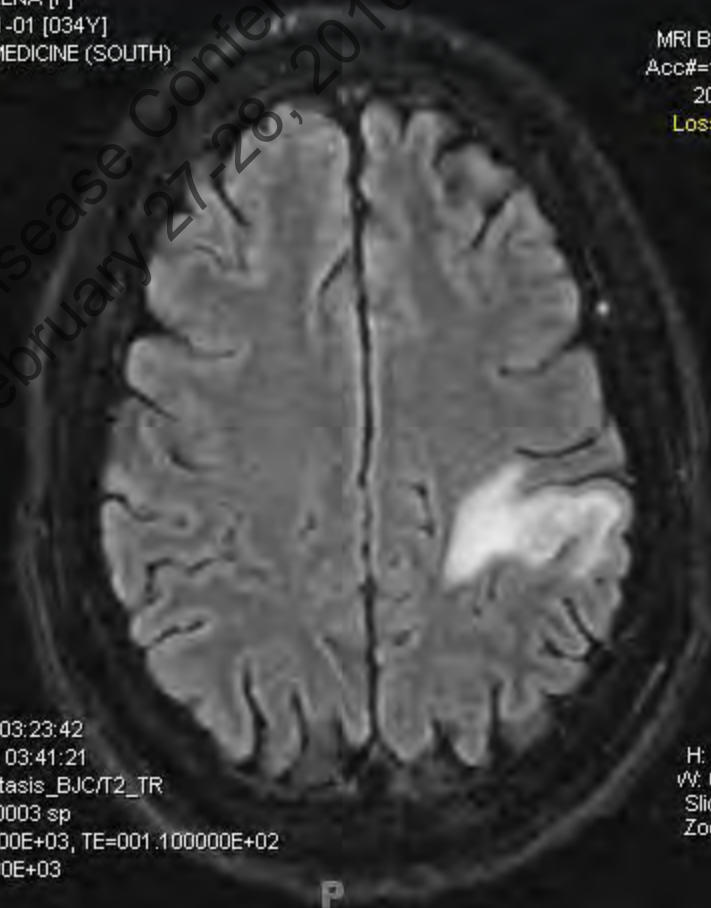


MRI Brain wwo  
Acc#=12749207  
2009-10-23  
Lossy 8:1 ⚠

SERIES: #8  
Study Time = 03:23:42  
Series Time = 03:52:11  
Tumor\_Metastasis\_BJC/T1\_TR  
5.0 thk / 1 sp  
TR=006.720000E+02, TE=001.700000E+01  
IR=  
Contrast=APPLIED

LICE:  
H: 69.30 mm  
W: 1417 L:683  
Slice 8 of 24  
Zoom=198%

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MRI Brain wwo  
Acc#=12749207  
2009-10-23  
Lossy 8:1 ⚠

#6  
Study Time = 03:23:42  
Series Time = 03:41:21  
Metastasis\_BJC/T2\_TR  
5.0 thk / 17 sp  
TR=009.999000E+03, TE=001.100000E+02  
IR=300000E+03  
t=

LICE:  
H: 65.66 mm  
W: 601 L:270  
Slice 6 of 17  
Zoom=198%



# *Lab Eval 2010*

- CSF
  - 15 cells (lyms)
  - Glucose 70 mg/dl, protein 56 mg/dl
  - Toxo PCR positive, EBV negative
- Plasma
  - Neg histoplasma, coccidio
  - RPR 1:4, FTA negative

# HIV-Associated Neurologic Problems



- Secondary neurologic problems
  - Cryptococcal meningitis
  - **Toxoplasmosis**
  - PML
  - Tuberculosis
  - Hepatitis C
  - Primary CNS lymphoma
  - Syphilis
  - Cytomegalovirus encephalitis and radiculomyelitis
  - Complications of therapy

# *Importance of Toxoplasma encephalitis*



- Widespread latent infection
- Common in HIV
- Treatable
- Impact underestimated



# *Toxoplasma Encephalitis*

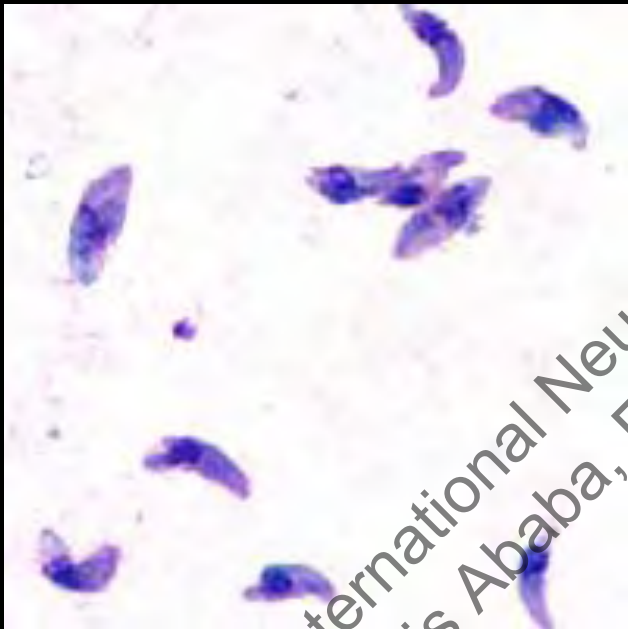




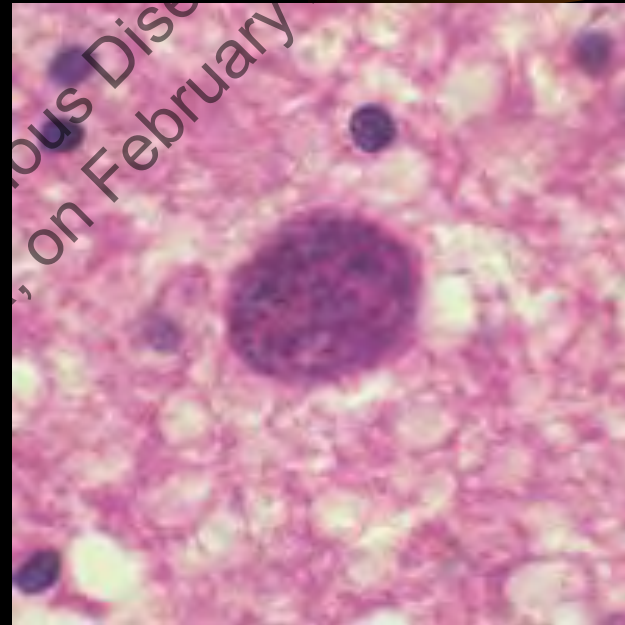
# *Life Cycle of Toxoplasma*

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

# *Toxoplasma gondii*



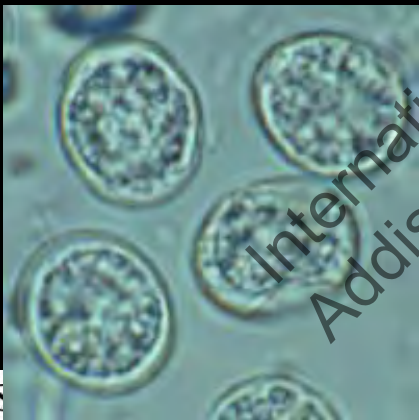
Tachyzoites



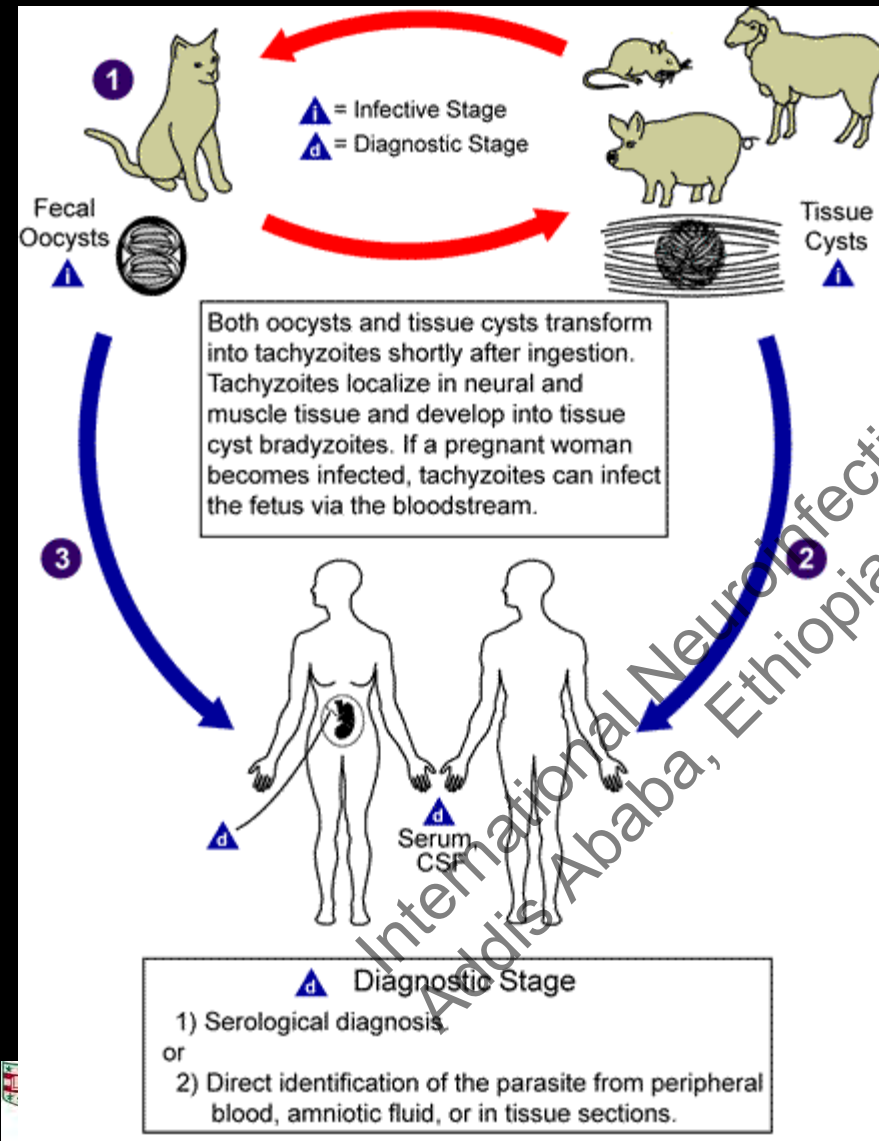
Cyst in brain tissue

# *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

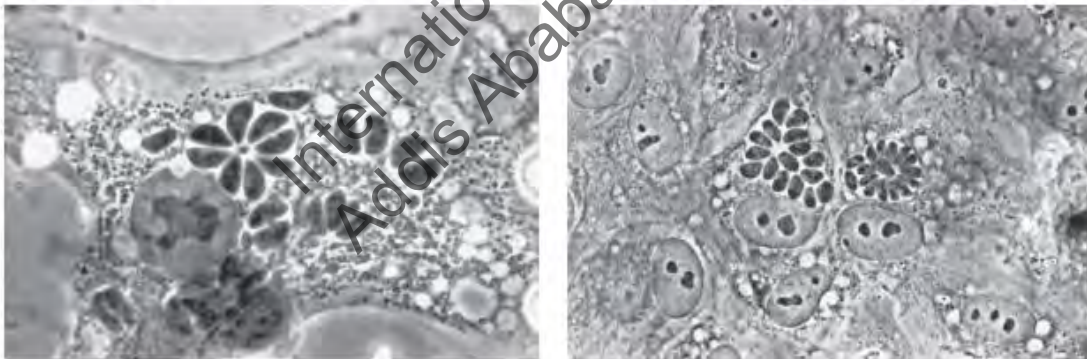


# Toxoplasma

*Semin Hematol* 25:101, 1988.



A



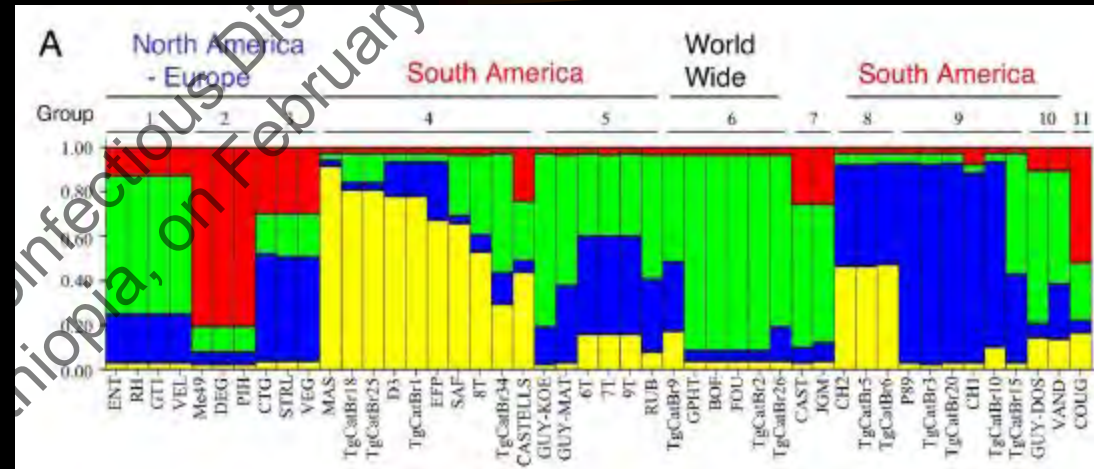
B

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



# *Toxoplasma Strain Differences*

- Toxoplasma virulence associated with strains
- Three strains share 98% genetic identity, yet are markedly different in virulence
- Geographic distribution of strains incompletely described but probably differs

# *Toxoplasma Strains*

- Multiplex PCR assay developed to genotype
- CSF samples from HIV associated human toxoplasma encephalitis cases examined
- A majority had Type I strains in CSF despite this being a rare human pathogen

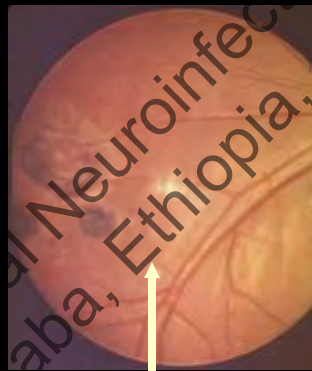
Khan, Su, German, Storch, Clifford and Sibley.  
J. Clin. Microbiol 2005;43:5881.



# Toxoplasma Strains

## Type II

Most commonly cause toxoplasmosis



## Type III

Rarely assoc with dx

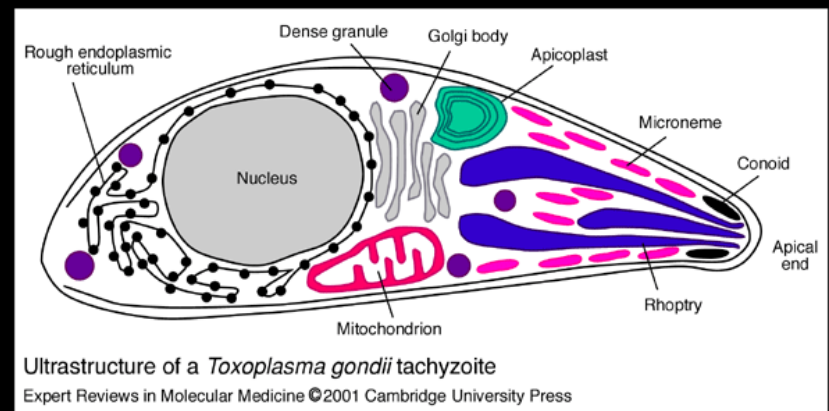


Type I : Rarer but pathologic

# 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

Rhoptry

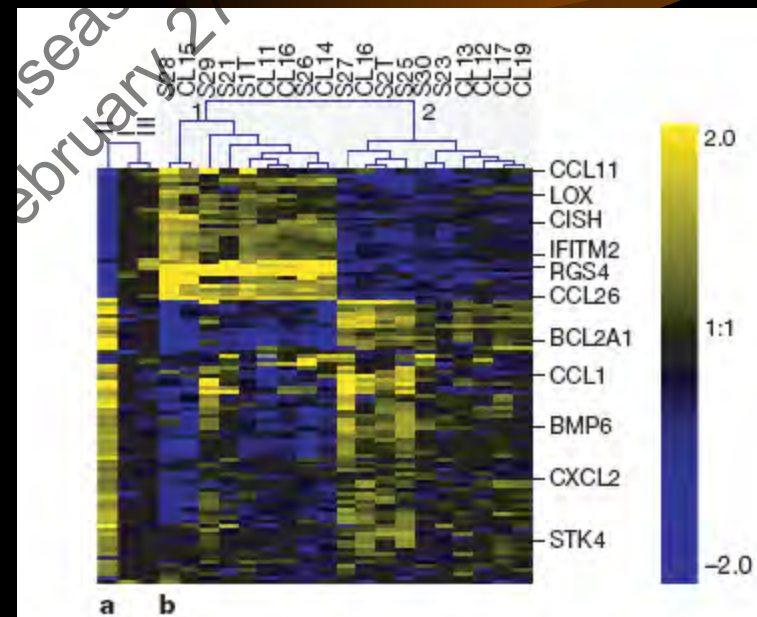


Ultrastructure of a *Toxoplasma gondii* tachyzoite  
Expert Reviews in Molecular Medicine ©2001 Cambridge University Press

# *Toxoplasma* co-opts host gene expression by injection of a polymorphic kinase homologue

J. P. J. Saeij<sup>1\*</sup>, S. Coller<sup>1\*</sup>, J. P. Boyle<sup>1</sup>, M. E. Jerome<sup>2</sup>, M. W. White<sup>2</sup> & J. C. Boothroyd<sup>1</sup>

- Strain specific modulation of host cell transcription, by ROP16
- Injected by rhoptries into host cell
- Ultimately affects signal transducer and activator of transcription (STAT) pathway



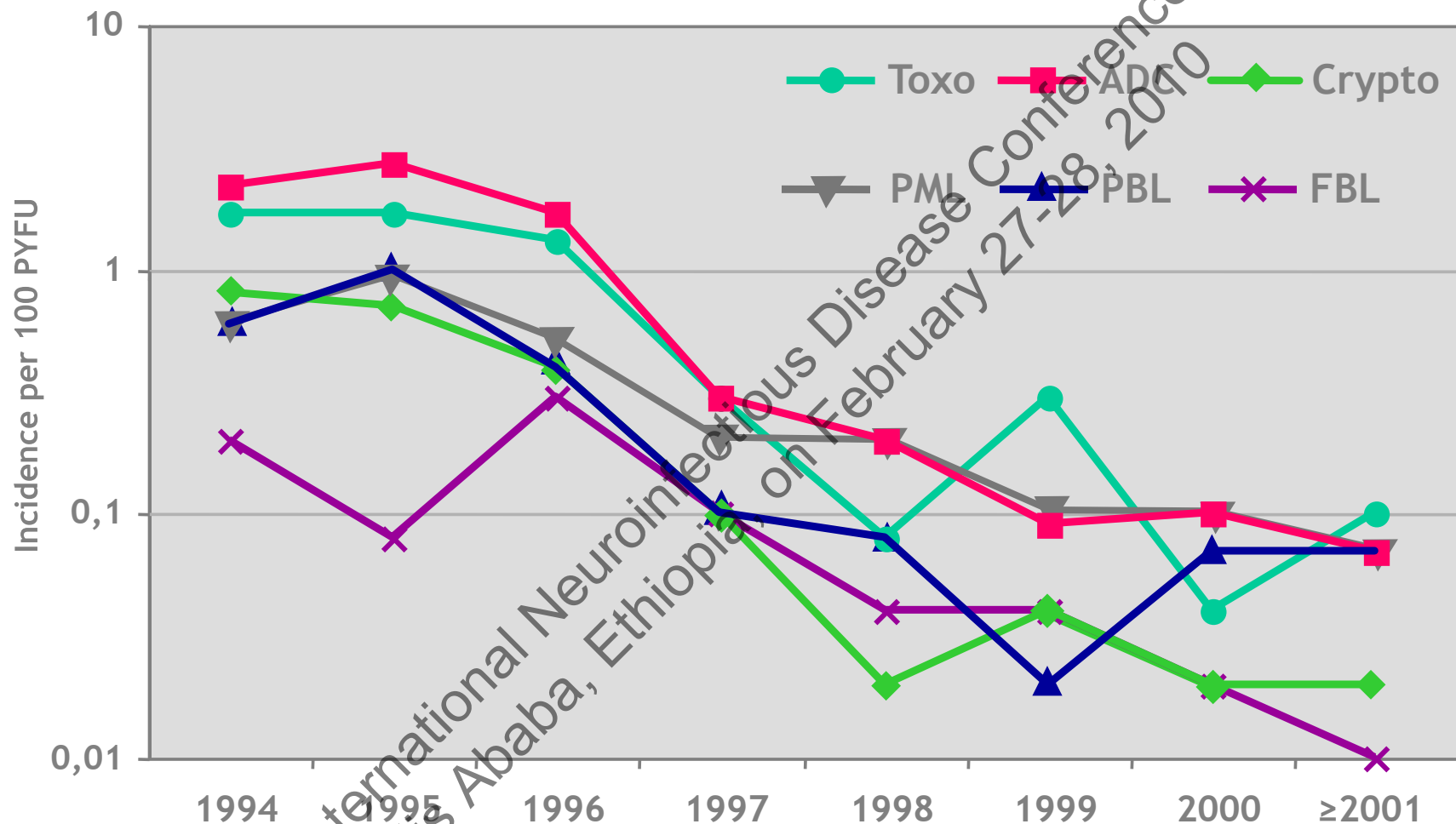
Nature 2007; 445:324

# *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



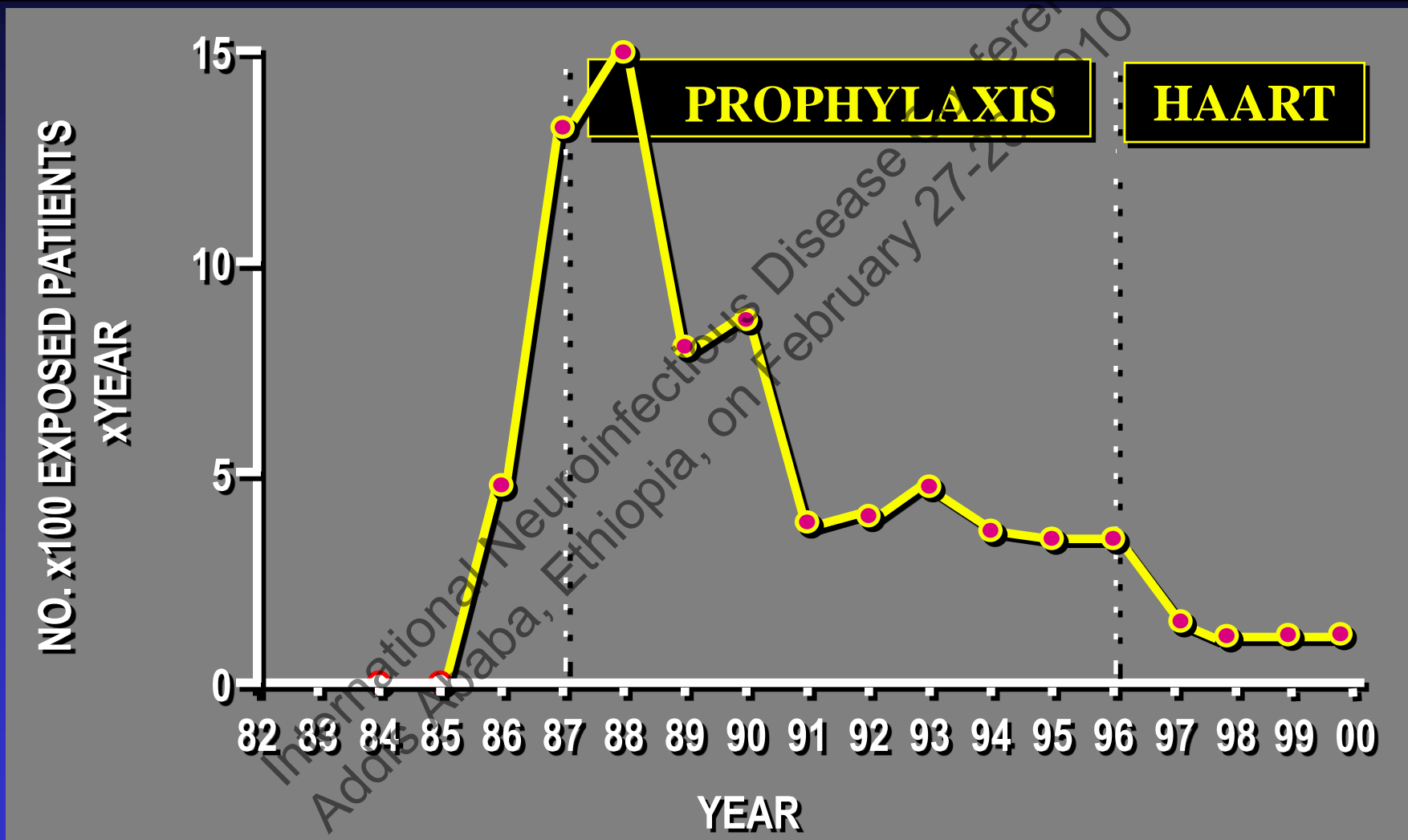
Decline of incidence/year

ADC 45%, 95% CI: 40 - 49%

CNS-OIs 37%, 95% CI: 34 - 41%

$p < 0.01$

# Incidence of CNS toxoplasmosis in AIDS Patients at the Hosp. Clinic (Barcelona, Spain) between 1984 - 2000



**HAART:** Highly Active Antiretroviral Therapy ( $\geq 2$ NRTI plus  $\geq 1$ PI/NNRTI)

# Impact of HAART on cerebral toxoplasmosis incidence

	Before HAART (cases/100 person- years)	During HAART (cases/100 person-years)	$\Delta$
France <sup>1</sup>	3.9	1	↓ 4X
Spain <sup>2</sup>	2.8	0.6	↓ 5X
Brazil <sup>3</sup>	17.5	10	↓ 0.5x

<sup>1</sup>Abgrall *et al.* Clin Infect Dis 2001;33:1747-55

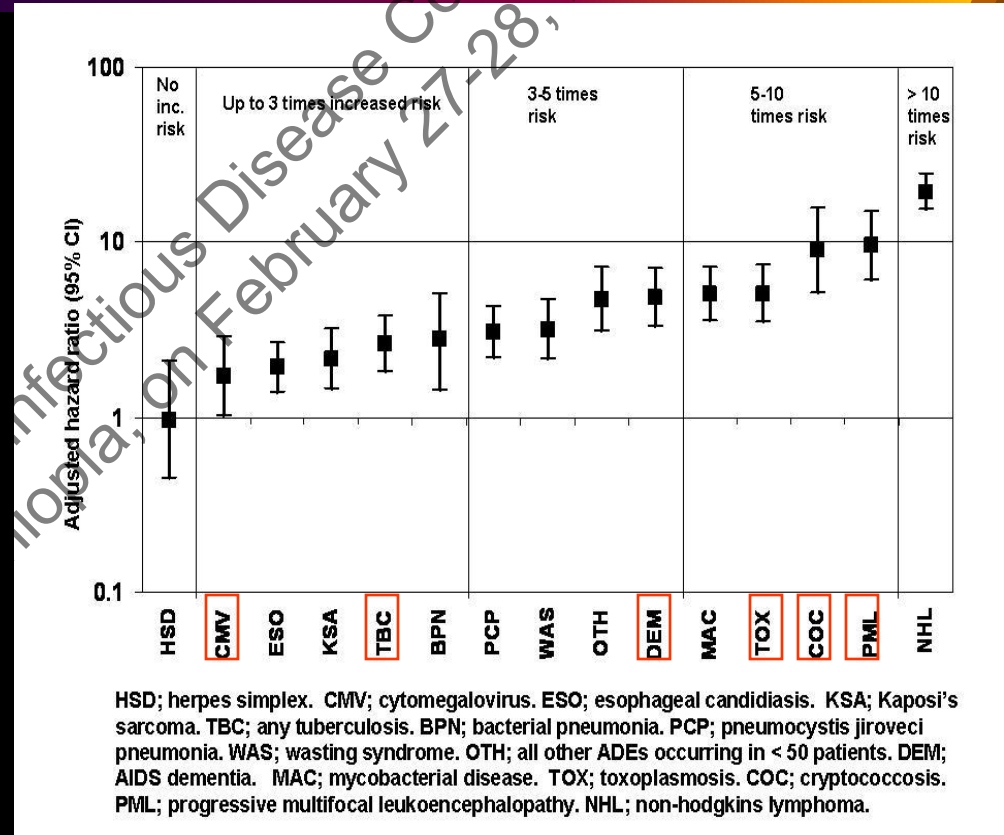
<sup>2</sup>Gaspar *et al.* 14th International AIDS Conference. 2002. Abstract ThPeC7458

<sup>3</sup>Guimarães. Cad Saúde Pública 2000;16(Suppl 1):21-36

# Mortality of AIDS Defining Complications

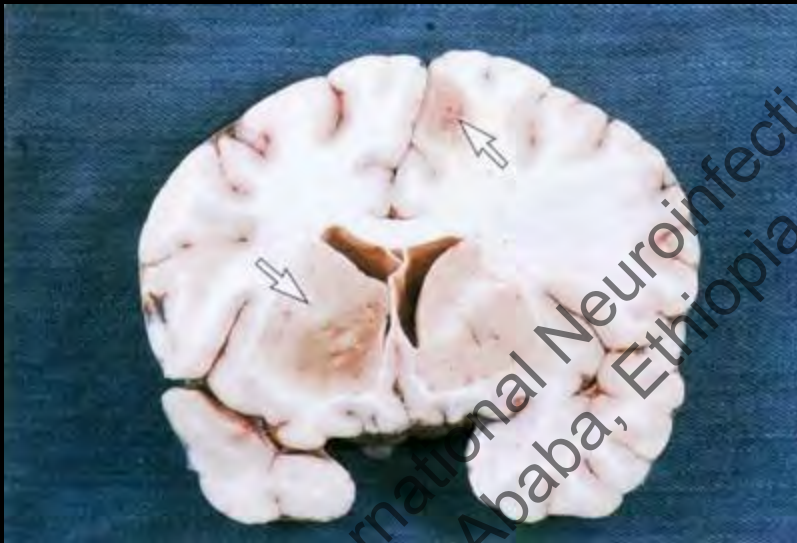
CROI 2007,  
Abstract 80,  
Mocroft et al

Data derived from  
15 HIV cohort  
studies including  
>30K subjects





# *Signs/Sx of Toxoplasmosis*



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

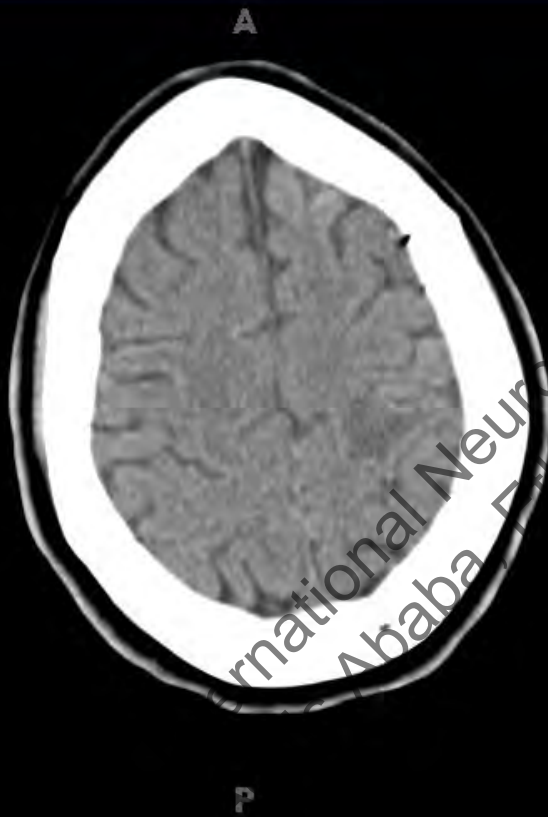
# *Toxoplasmosis – ocular lesions*



# *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 N, Protein – mild elevations, Cells modest, PCR for toxo DNA
- Clinical response
- Biopsy

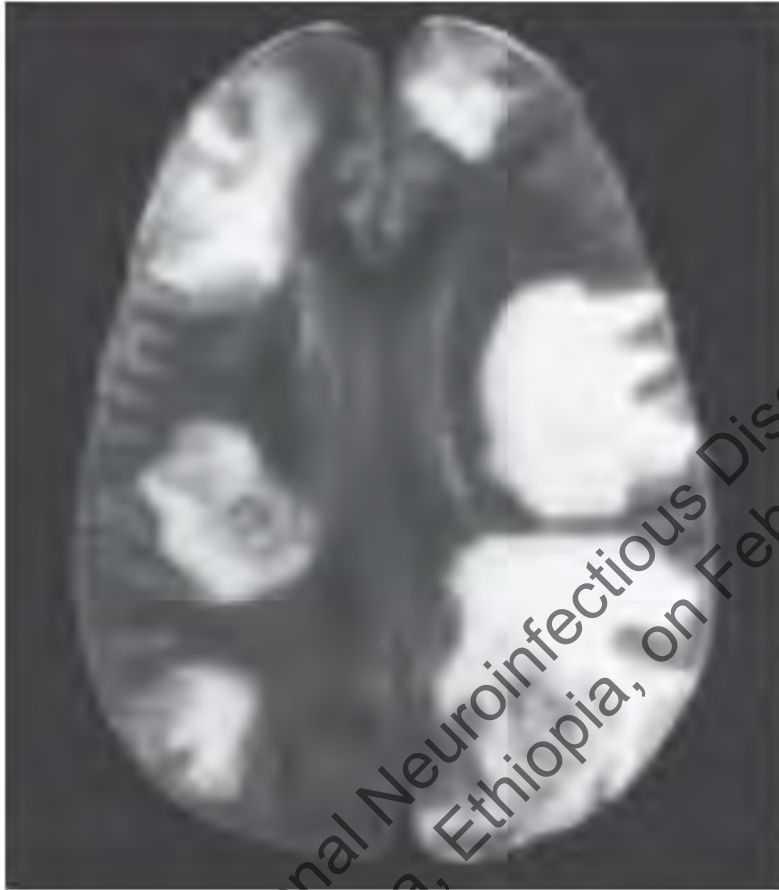
# Brain CT Scan



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

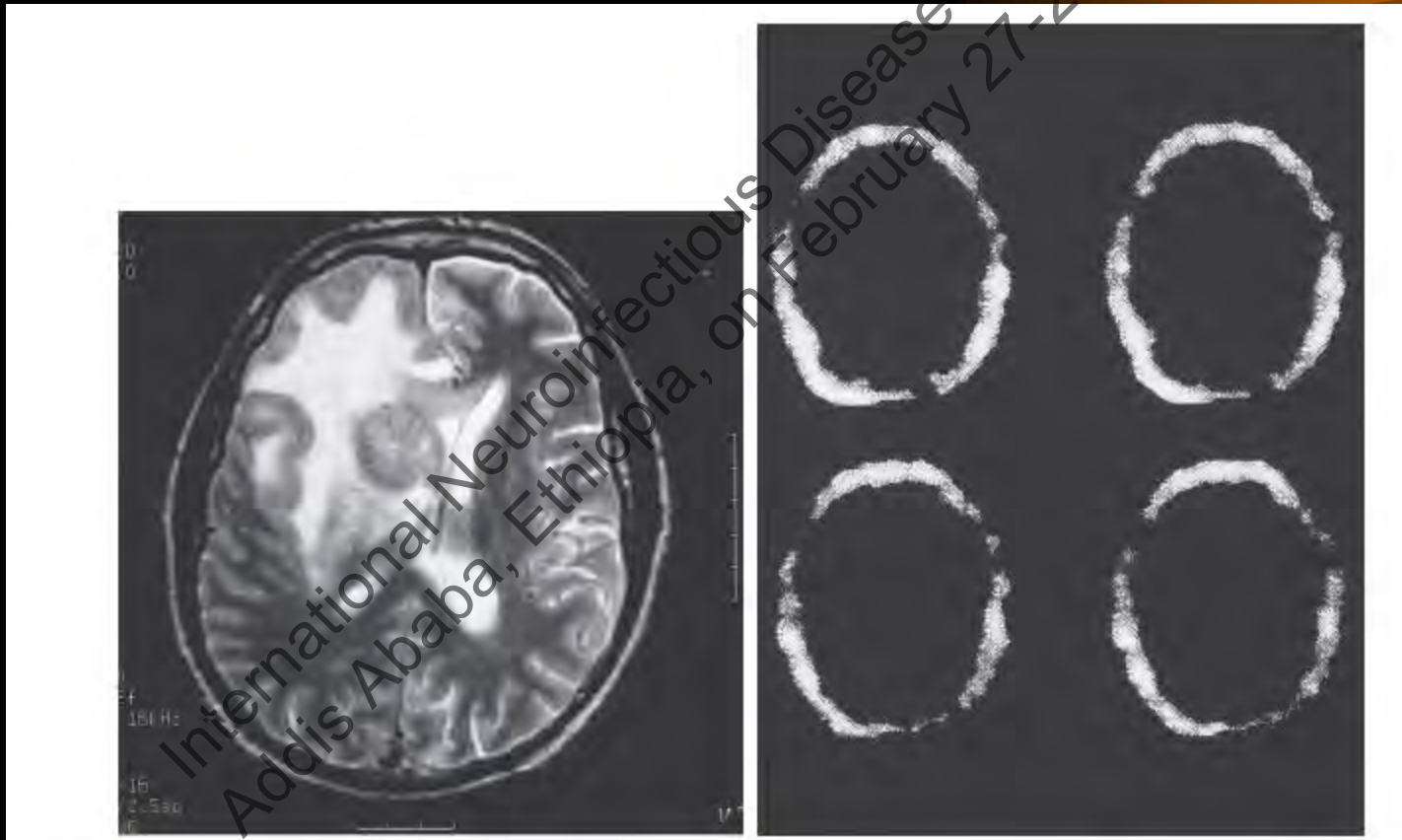


# Brain MRI

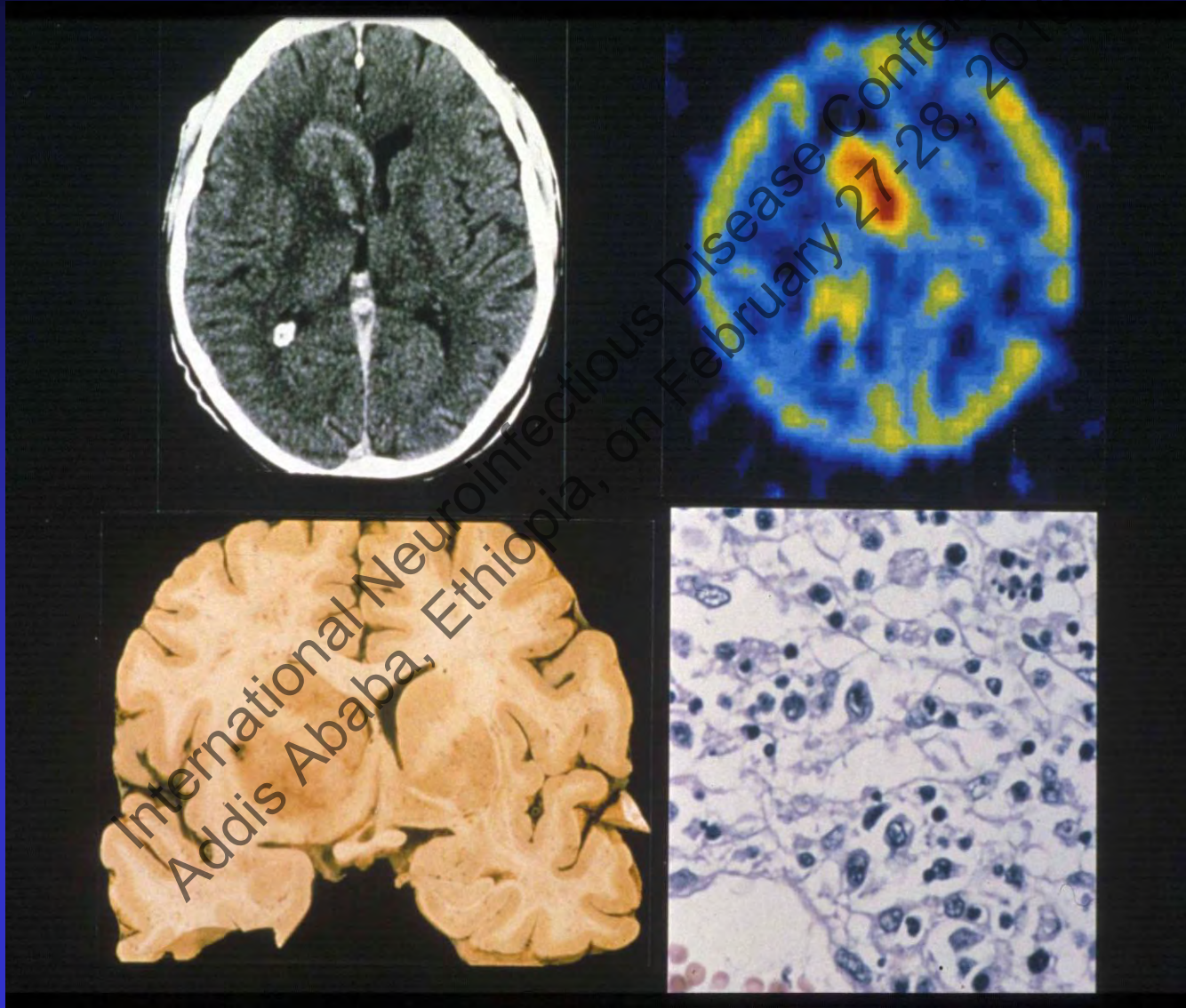


**Figure 37-3** ■ Magnetic resonance image (MRI) showing multifocal brain lesions with pronounced edema in an AIDS patient with toxoplasmosis. Courtesy of Dr Henry Masur, National Institutes of Health.

# *Differentiation of Toxo and Lymphoma*



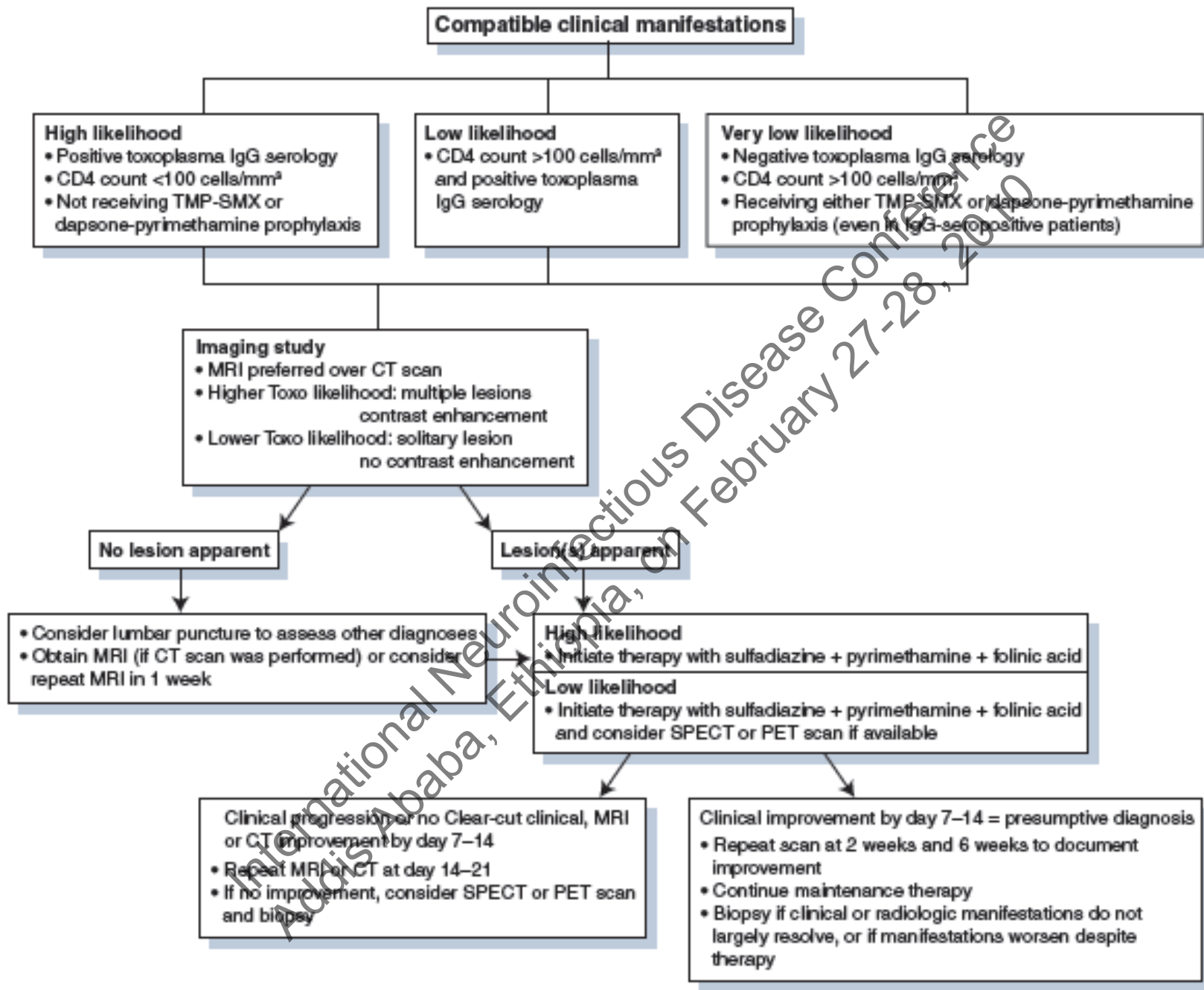
# Primary CNS Lymphoma in an AIDS Patient



# CSF Diagnostics

- Routines
  - Protein – slight elevations
  - Glucose – normal
  - Cells – variable, rarely many, lymphocytes
- Toxoplasma PCR
  - Specificity superb
  - Sensitivity modest
- EBV PCR helps greatly with differential with primary CNS lymphoma

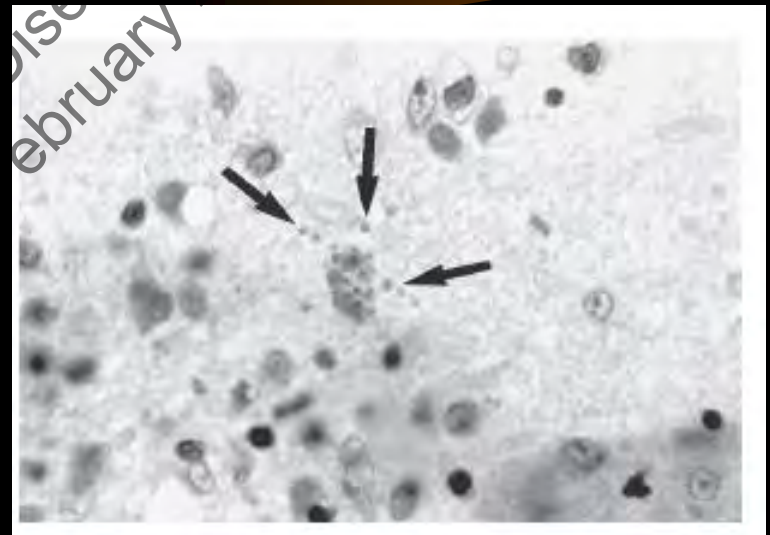




**Figure 37-6** ■ Algorithm indicating an approach to the diagnosis and initial management of suspected toxoplasmosis.

# Brain Biopsy

- Needle aspirations
- Reasonable safety
- Good sensitivity overall
- Rare due to success of therapeutic trials



Cyst breakdown and  
Released tachyzoites

# Yield of brain biopsy in patients with AIDS who have focal neurological disease

Skiest DJ. Clin Infect Dis. 2002; 34:103-15

Reference	No. of subjects	Percentage of patients with				Definitive diagnosis	Major morbidity, % <sup>a</sup>	Mortality, % <sup>b</sup>
		Lymphoma	PML	Toxoplasmosis	Other			
[3]	50	28	28	26	18	96	8	0
[15]	251	33	30	15	16	94	3.2	2.8
[120]	26	42	15	23	12	96	4	4
[121]	13	31	23	38	15	85	8	0
[122]	25	36	44	8	12	80	4	0
[123]	23	39	22	30	4	88	0	8.7
[124]	20	15	35	25	15	70	5	0
[125]	12	50	25	0	17	92	8.3	0
[126]	26	46	23	15	8	92	11.5	0
[127]	25	40	8	40	4	92	0	0
[128]	58	51	17	6	14	86	3.7	3.1

**NOTE.** PML, progressive multifocal leukoencephalopathy.

<sup>a</sup> Defined as hemorrhage or permanent neurological deficits; does not include death.

<sup>b</sup> Biopsy-related mortality (death related to biopsy complication within 30 days of biopsy).

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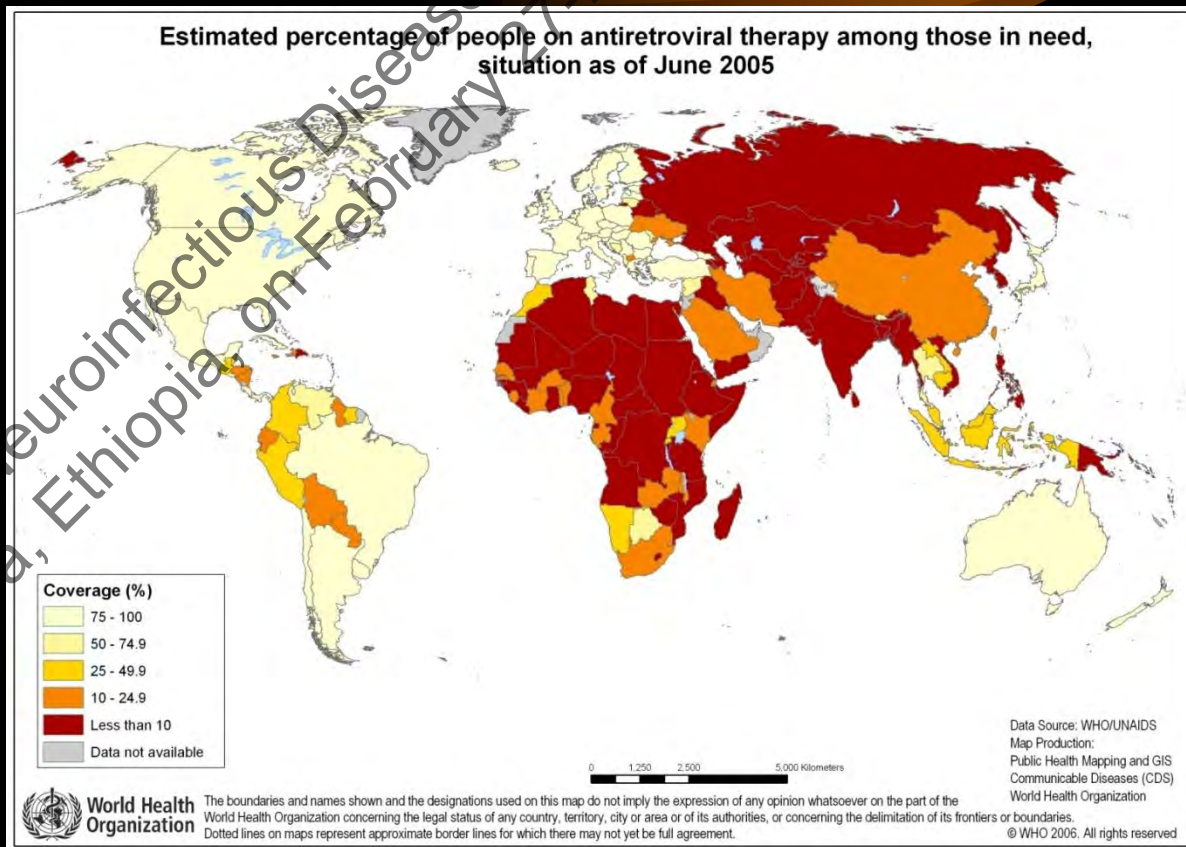
<sup>a</sup> Defined as hemorrhage or permanent neurological deficits; does not include death.

<sup>b</sup> Biopsy-related mortality (death related to biopsy complication within 30 days of biopsy).



# 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 <sup>a</sup>	Suggested Regimens
<b>Preferred Treatment</b>	
TMP-SMX <sup>b</sup>	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
<b>Other Treatments</b>	
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.

<sup>a</sup>Folic 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

## *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 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<sup>a</sup>

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)

<sup>a</sup> 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.T. (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)

<sup>a</sup>  $P = 0.0478$ .

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		P value
	TMP-SMX (n = 40)	P-S (n = 37)	
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

# *Alternate drugs*

- Atovaquone
- Fansidar
- Macrolides (azithromycin)
- Dapsone
- Other sulfa drugs
- Minocycline/doxycycline

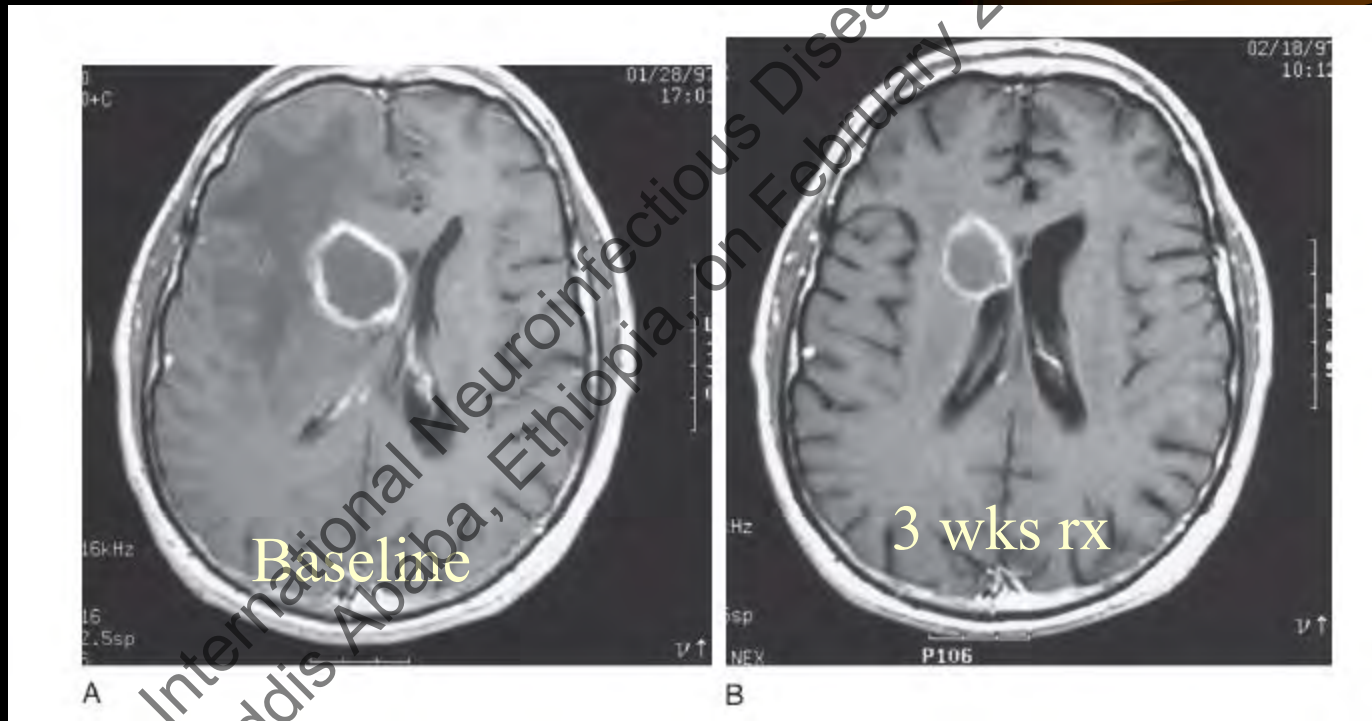
# *Response to therapy*

- 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

# *Immune Reconstitution Inflammatory Syndrome (IRIS)*

- Seen in HIV with successful HIV therapy
- Increases when pathogen present, immunity poor at start of HAART, rapid improvement
- Develops weeks to months following initiation of HAART
- Can be life threatening
- IRIS from Toxo is generally not a severe problem

# A5164

## Early Antiretroviral Therapy Reduces AIDS Progression/ Death in Individuals with Acute Opportunistic Infections: A Multicenter Randomized Strategy Trial

Andrew R. Zolopa<sup>1\*</sup>, Janet Andersen<sup>2</sup>, Lauren Komarow<sup>8</sup>, Ian Sanne<sup>5</sup>, Alejandro Sanchez<sup>4</sup>, Evelyn Hogg<sup>7</sup>, Carol Suckow<sup>6</sup>, William Powderly<sup>3</sup> for the ACTG A5164 study team

1 Stanford University AIDS Clinical Trials Unit, Stanford University, Stanford, California, United States of America, 2 Statistical and Data Analysis Center, Harvard School of Public Health, Boston, Massachusetts, United States of America, 3 University College Dublin, Belfield, Ireland, 4 University of Southern California, Los Angeles, California, United States of America, 5 Wits Health Consortium, Helen Joseph Hospital, Johannesburg, South Africa, 6 Frontier Science & Technology Research Foundation, Amherst, New York, United States of America, 7 Social & Scientific Systems, Inc., Silver Spring, Maryland, United States of America, 8 Statistical and Data Analysis Center, Harvard School of Public Health, Boston, Massachusetts, United States of America



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May 2009 | Volume 4 | Issue 5 | e5575

# ACTG A5164: Final 48-Week Results

Outcome	Total	Early	Deferred	p-value
<b>No Endpoint Information</b>	36 (12.8%)	18 (12.8%)	18 (12.8%)	
<b>Primary Endpoint</b>				
AIDS Progression/Death	54 (19.1%)	20 (14.2%)	34 (24.1%)	
Plasma Viral Load >50 copies: no progression*	98 (34.8%)	54 (38.3%)	44 (31.2%)	
Plasma Viral Load ≤50 copies: no progression	130 (46.1%)	67 (47.5%)	63 (44.7%)	0.215 <sup>b</sup>
<b>Secondary Endpoints</b>				
AIDS Progression/Death	54 (19.1%)	20 (14.2%)	34 (24.1%)	0.035 <sup>b</sup>
HIV VL % ≤50 copies at 48 wks (ITT analysis)	143 (51%)	71 (50%)	72 (51%)	0.48 <sup>c</sup>
CD4 count at 24 weeks (median change from baseline) (OR)	+116 (+71–160)	+118 (+75–186)	+104 (+66–171)	0.22 <sup>c</sup>
CD4 count at 48 weeks (median change from baseline) (OR)	+167 (+106–260)	+187 (+95–268)	+187 (+124–271)	0.50 <sup>c</sup>
<b>Safety Outcomes</b>				
Had at least one ART Switch or interruptions	104 (39%)	59 (42%)	45 (35%)	0.26 <sup>d</sup>
IRIS Confirmed	20 (7.1%)	8 (5.7%)	12 (8.5%)	0.49 <sup>d</sup>
Laboratory Adverse Events Grades 2–4	192 (68%)	90 (64%)	102 (72%)	0.16 <sup>d</sup>
Clinical Adverse Events Grades 2–4	130 (46%)	61 (43%)	69 (50%)	0.40 <sup>d</sup>
Subjects with Hospitalization	106 (38%)	55 (39%)	51 (36%)	0.71 <sup>d</sup>
Median Hospital Days (among hospitalizations)	5 (2–10)	5 (2–10)	6 (2–10)	0.79 <sup>e</sup>

\*Includes subjects with missing outcomes.

<sup>b</sup>Stratified Wilcoxon Rank Sum test.

<sup>c</sup>Stratified exact test.

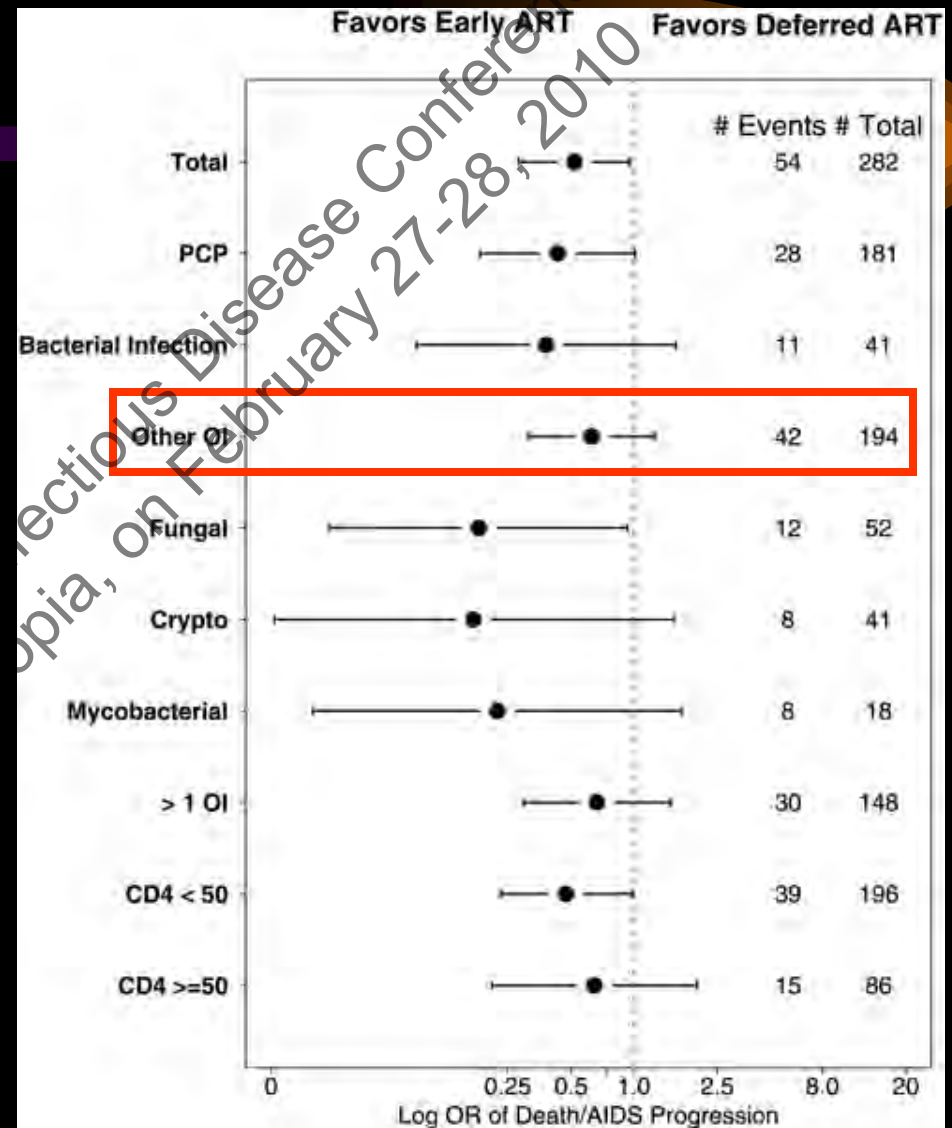
<sup>d</sup>Wilcoxon Rank Sum.

<sup>e</sup>Fisher's Exact Test.

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# AIDS Progression/Death by Entry Diagnoses.





# Conclusions

- Early treatment reduced likelihood of progression to AIDS or death
- Significant decrease in the “Window of Vulnerability”
  - Time with CD4 count  $<50$  or  $<100$
- No difference in virologic outcomes at 1 year (~50% complete suppression at 1 year)
- IRIS was uncommon (only 8%)
  - Traditionally 15-45% for persons with this level of CD4 counts at time of HAART initiation

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

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

# Discontinuation of Prophylaxis

**Discontinuation of Primary Anti-Toxoplasma Prophylaxis in T. Gondii Co-Infected Patients who had a CD4 + T Lymphocyte >200 Cells/mm<sup>3</sup> During More than 3 Months Due to Effective HAART**

**Table 37-6**

Study	No.	Mean Follow Up (Months)	Patient-Years	Incidence/100 Patient-Years (95% CI)
HOPS <sup>180</sup>	146	18.2	402	0
Paris <sup>160</sup>	34	16.0		0
Swiss cohort-1 <sup>179</sup>	121	11.7	109	0 (0-2.73)
Swiss cohort-2 <sup>182</sup>	199	10.8	272	0 (0-1.10)
Eighth European Cohorts <sup>181</sup>	65	13.0	374	0
CIOP <sup>183</sup>				
Stop	115	7.2	72	0 (0-7.3)
Continue	128	6.0	72	0 (0-7.3)
GESIDA <sup>164</sup>				
Stop	196	24.9	400	0 (0-0.80)
Continue	185	24.9	379	0 (0-0.86)

# 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
- Questions/Discussion

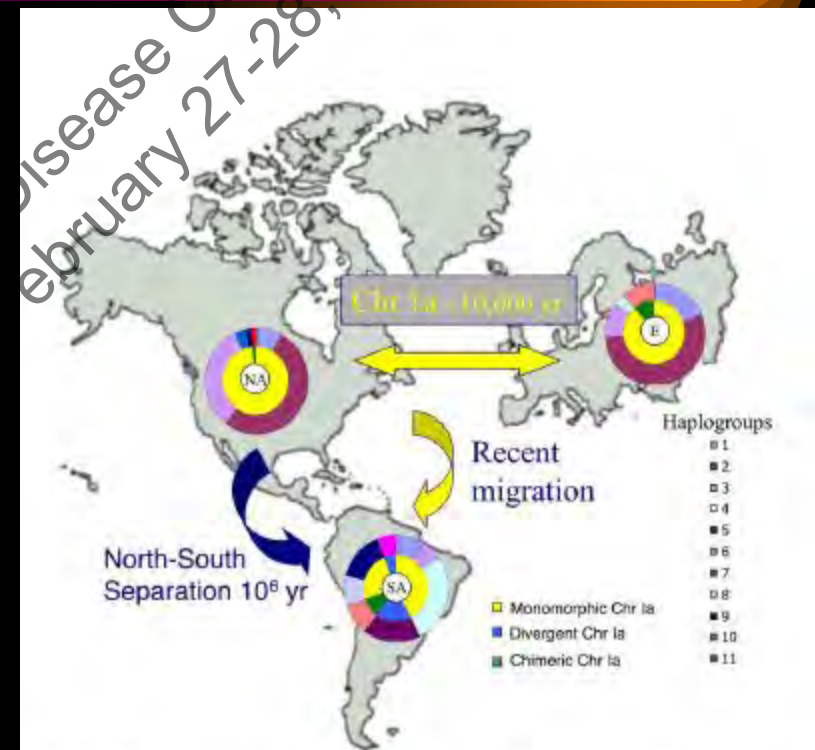


Fig. 4. Proposed model for the dissemination of *T. gondii* strains in E, NA, and SA. The spread from NA to SA is estimated at  $10^6$  yr (curved blue arrow). Emergence of Mono-Chr1a occurred  $\sim 10,000$  yr ago (horizontal yellow arrow) and spread between NA and E. More recently, Mono-Chr1a penetrated into SA (curved yellow arrow). The outer color wheels show the prevalence of haplogroups in current populations; the inner color wheel depicts Chr1a. Strains used include those studied here plus previously isolated strains (2, 12, 19, 27).

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