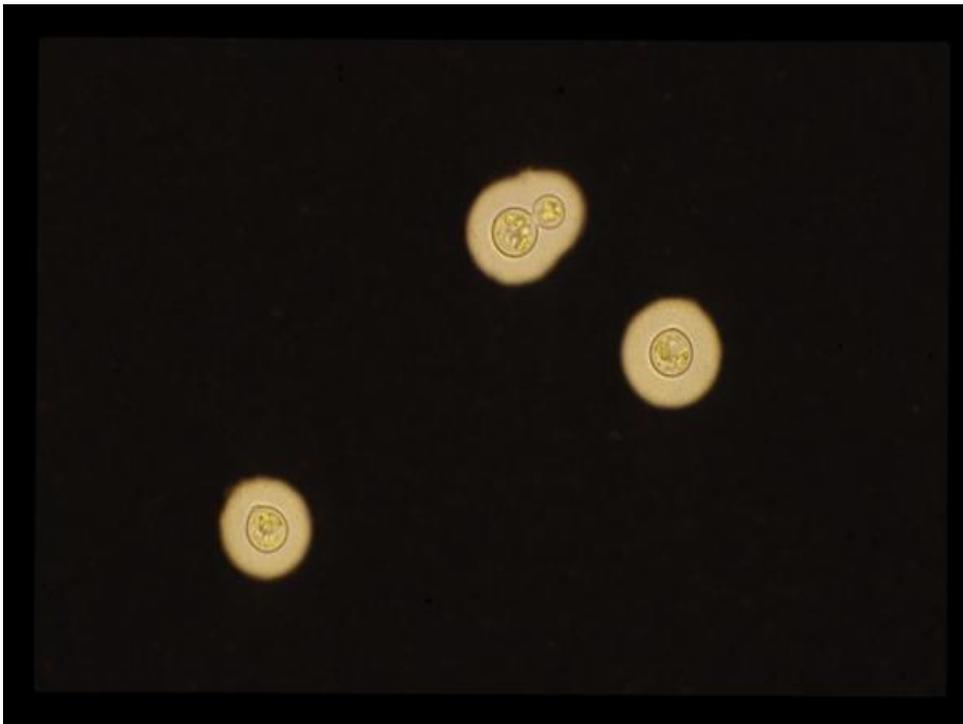


# Cryptococcal Treatment Guidelines : Experience, Evidence and Controversies

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## Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Disease Society of America

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Clinical Infectious Diseases 2010; 50:291-322

## Abstract

Cryptococcosis is a global invasive mycosis associated with significant morbidity and mortality. These guidelines for its management have been built on the previous Infectious Diseases Society of America guidelines from 2000 and include new sections. There is a discussion of the management of cryptococcal meningoencephalitis in 3 risk groups: (1) human immunodeficiency virus (HIV)-infected individuals, (2) organ transplant recipients, and (3) non-HIV-infected and nontransplant hosts. There are specific recommendations for other unique risk populations, such as children, pregnant women, persons in resource-limited environments, and those with *Cryptococcus gattii* infection. Recommendations for management also include other sites of infection, including strategies for pulmonary cryptococcosis. Emphasis has been placed on potential complications in management of cryptococcal infection, including increased intracranial pressure, immune reconstitution inflammatory syndrome (IRIS), drug resistance, and cryptococcomas. Three key management principles have been articulated: (1) induction therapy for meningoencephalitis using fungicidal regimens, such as a polyene and flucytosine, followed by suppressive regimens using fluconazole; (2) importance of early recognition and treatment of increased intracranial pressure and/or IRIS; and (3) the use of lipid formulations of amphotericin B regimens in patients with renal impairment. Cryptococcosis remains a challenging management issue, with little new drug development or recent definitive studies. **However, if the diagnosis is made early, if clinicians adhere to the basic principles of these guidelines, and if the underlying disease is controlled, then cryptococcosis can be managed successfully in the vast majority of patients.**

## Duke Data have Important glimpses (14 years 1996-2009) of cryptococcal Management 204 pts. \*

- Not receiving IDSA Guidelines recommended initial induction regimen had a higher relative risk of persistent infection (RR 1.9 95% CI 0.9-4.3)
- Not receiving the IDSA Guidelines recommended dose of initial induction therapy had a higher relative risk of attributable mortality (RR 2.3 ,95% CI 1.0-5.0)
- > 7 days of flucytosine exposure was associated with lower rate of attributable mortality (RR 0.2, 95% CI 0.1-0.5) (only 37% of combo therapy received at least 14 days of flucytosine)
- 1/3 of patients changed their initial induction therapy with average of approximately a week longer induction therapy
- Mortality 16% in HIV and transplants patients and 31% in non-HIV, non-transplant patients

\* Bratton EW et al. Antimicrob. Agents Chemother 57: 2485-95, 2013

## Feedback concerns for 2010 IDSA Guidelines that I have received

- Why do non-HIV, non transplant patients have longer induction period for cryptococcal meningitis than other groups 2 vs 4 wks?
- Why are corticosteroids not considered for increased intracranial pressure?
- Why are there not recommendation for non-HIV, non-transplant patients in resource-limited environment?
- Why isn't lipid formulation of amphotericin B primary recommendation for induction therapy of cryptococcal meningitis and amphotericin B deoxycholate as alternative?

## Organization of the Guidelines

- I. Treatment of Cryptococcal Meningoencephalitis
  - A. HIV
  - B. Organ transplant recipients
  - C. Non-HIV, non transplant
  
- II. Management of complications
  - A. Persistence and relapse
  - B. Immune Reconstitution Inflammatory Syndrome (IRIS)
  - C. Elevated intracranial pressure
  - D. Mass lesions (Cryptococcomas)

## Organization of Guidelines (continued)

- III. Non-meningeal Cryptococcosis
  - A. Pulmonary: 1) Immunosuppressed  
2) Non-immunosuppressed
  - B. Extrapulmonary
  
- IV. Cryptococcosis in special situations
  - A. Pregnancy
  - B. Children
  - C. Resource-Limited environment
  - D. *Cryptococcus gattii*

What is the treatment of cryptococcal meningoencephalitis in HIV-infected individuals?  
(Induction/consolidation)

- **Amphotericin B 0.7mg/kg/d-1.0mg/kg/d IV plus flucytosine 100mg/kg/d po for 2 wks then fluconazole 400mg/d po for minimum of 8 weeks (with renal concerns: substitute Liposomal 3-4mg/kg/d or ABLC 5mg/kg/d)**

**Alternative Regimens**

- Amphotericin B 0.7-1.0/kg/d IV or liposomal AmB 3-4 or ABLC 5mg/kg/d for 4-6 wks then fluconazole 400mg/d po minimum 8 wks

**Alternative Regimens**

- Amphotericin B 0.7mg/kg/d IV plus fluconazole 800mg/d po x 2wks then fluconazole 800mg/d po for minimum 8wks
- fluconazole 400 – 800mg/d po plus flucytosine 100 – 150mg/kg/d po for 6 wks
- fluconazole  $\geq 800$ -2000mg/d po for 10 -12 weeks  
**( fluconazole 1200mg/d favored)**
- itraconazole 400mg/d po for 10 – 12 weeks.

## What is the treatment of cryptococcal meningoencephalitis in HIV-infected individuals? (maintenance or suppressive therapy)

- fluconazole 200mg/d po
- Itraconazole 200mg/d po (drug level monitoring)
- Amphotericin B 1mg/kg/wk IV (less effective;azole intolerant)
- **START HAART 2 – 10 weeks after beginning of antifungal treatment**
- Length: May consider discontinuing suppressive therapy on HAART with CD4 cell count  $> 100/\mu\text{l}$  and undetectable HIV RNA level sustained for  $\geq 3$  months (minimum of 12 months)
- **Asymptomatic antigenemia**  
**fluconazole 200-400mg/d until immune reconstitution**
- Primary prophylaxis not recommended

## What is the appropriate management of CNS and non-CNS cryptococcosis in transplant recipients?

- **CNS disease: Liposomal AmB 3-4mg/kg/d or ABLC 5mg/kg/d plus flucytosine 100mg/kg/d for 2 wks** then fluconazole 400 – 800 mg/d for 8 wks and finally fluconazole 200mg/d po for 6 - 12 months. If induction therapy does not include flucytosine consider polyene for 3 – 4 weeks.
- Mild – to – moderate non CNS disease: fluconazole 400mg/d for 6 – 12 months
- Severe non – CNS disease: treat same as CNS disease

## What are specific issues in management of cryptococcosis in solid organ transplant recipients?

- In absence of any evidence for extra pulmonary or disseminated cryptococcosis, pulmonary disease in serum positive or negative cryptococcal antigen patient, management is same.
- Length of fluconazole maintenance (at least 6 months, preferably 12 months)
- **Immunosuppressive management: sequential or step wise reduction with consideration of lowering corticosteroid dose first**
- Amphotericin B deoxycholate use (must weigh risk of renal dysfunction)

## What is the treatment for CNS cryptococcosis in non-HIV, non transplant individual?

- **Amphotericin B  $\geq 0.7-1.0\text{mg/kg/d}$  IV plus flucytosine  $100\text{mg/kg/d}$  for  $\geq 4$  wks\***
- If Amphotericin B intolerant, liposomal amphotericin B  $3-4\text{mg/kg/d}$  or ABLC  $5\text{mg/kg/d}$  plus flucytosine; if flucytosine not given or interrupted, consider lengthening polyene therapy x 2 wks
- Consolidation with fluconazole  $400\text{mg/d}$  for minimum of 8wks
- After induction/consolidation therapy, fluconazole  $200\text{mg/day}$  for 6 – 12 months.

\*2 wk induction for patient with low risk of therapeutic failure (early diagnosis by history, no uncontrolled underlying condition or severe immunocompromised state and an excellent clinical response to initial 2 wk combination course)

How do you manage a patient who has persistent infection or relapses with meningoen­cephalitis or at another site?

### Persistence

- **Definition of persistence: positive cultures at  $\geq 4$  wks of appropriate antifungal therapy**
- Re-institute induction phase of primary therapy for longer course (4 – 10 wks).
- Consider increasing dose if initial induction  $\leq 0.7\text{mg/kg/d}$  AmB or lipid product of AmB  $\leq 4\text{mg/kg/d}$
- If patient is polyene intolerant, consider fluconazole 800mg/d plus Flucytosine 100mg/kg/d
- If patient is Flucytosine intolerant, consider Amphotericin B 0.7mg/kg/d IV plus fluconazole 800mg/d

### Persistence (continued)

- Intrathecal or Intraventricular amphotericin B should be used only as last resort because of complications.
- All cryptococcal isolates should be stored for 1 year, persistent or relapse isolate should be checked for MIC changes with original;  $\geq 3$  titer differences suggest drug resistance or if no original isolate, perform MIC of relapse isolate (resistance  $\geq 16\text{mcg/ml}$  fluconazole;  $\geq 64\text{mcg/ml}$  Flucytosine).
- Changing or increasing dose of azole alone is unlikely to be successful
- **Consider with standard induction therapy, recombinant interferon gamma (100mcg sq. 3 x wk for 12wks)**

How do you manage a patient who has persistent infection or relapses with meningoencephalitis or at another site?

### Relapse

- **Restart induction phase therapy (see Persistence)**
- Check susceptibility of relapse isolate (see Persistence)
- After induction therapy and in vitro testing (azole susceptible) consider salvage therapy fluconazole 800mg/d, Voriconazole 200-400 mg po bid or Posaconazole 200mg po qid or 400mg po bid for 10 – 12 weeks

What is the Management of Immune Reconstitution Inflammatory Syndrome?

- **Recognition essential**
- No need to change or restart antifungal therapy
- No definitive treatment recommendation for minor manifestations since will resolve spontaneously in days to weeks
- Major complications such as CNS inflammation and intracranial pressure; consider corticosteroids (0.5 - 1.0mg/kg/d of prednisone equivalent) and possibly dexamethasone at higher doses for severe CNS signs and symptoms (length and dose empiric and requires careful following of patient) consider at least 4-6 wks
- Nonsteroidal anti-inflammatories and thalidomide have been used but too little experience to make a solid recommendation.

What is the optimum management of elevated cerebrospinal fluid pressure in patients with cryptococcal meningoencephalitis?

- Identify at diagnosis and radiographic scan with focal neurological signs.
- **If CSF pressure  $\geq$  25cm of water with symptoms of intracranial pressure, relieve by CSF drainage (Lumbar puncture-reduce 50% if extremely high or to normal  $\leq$  20cm of water)**
- Persistent elevation  $\geq$  25cm and symptoms, repeat lumbar puncture daily until pressure and symptoms stabilize  $>$  2 days and consider percutaneous lumbar drains or ventriculostomy for those requiring repeated ( $\geq$  3) lumbar punctures.

What is the optimum management of elevated cerebrospinal fluid pressure in patients with cryptococcal meningoencephalitis?

- Acetazolamide and corticosteroids have no role in AIDS patients without IRIS
- Management of HIV-negative patient with acute elevated intracranial pressure with much less data for recommendation
- **Ventriculoperitoneal shunts are more permanent** solutions to acute and chronically elevated intracranial pressure. These should be placed only when patient is receiving or has received appropriate antifungal therapy.

## How are cerebral cryptococcomas managed?

- Induction therapy with Amphotericin B  $\geq 0.7$ - 1.0mg/kg/d IV or 3-6 mg/kg/d of liposomal amphotericin B or 5mg/kg/d ABLC plus flucytosine 100mg/kg/d **for at least 6 wks**
- Maintenance therapy with fluconazole 400mg/d for 6-18 months
- Adjunctive therapies:
  - 1) **Corticosteroids for mass effect, surrounding edema, IRIS**
  - 2) Surgery: Large ( $\geq 3$ cm lesion), accessible lesion with mass effect consider open or stereotactic guided debulking/removal; also enlarging lesions not explained by IRIS for further tissue diagnosis

## How do you treat pulmonary cryptococcosis in the immunosuppressed host?

- Pneumonia associated with CNS or documented dissemination and/or ARDS treated like CNS disease
- ARDS in the context of IRIS may require corticosteroids
- **In immunosuppressed patients with pulmonary cryptococcosis there is need to rule out disseminated disease; all require treatment**
- Mild-to-moderate symptoms, absence of diffuse infiltrates, no severe immunosuppression, and negative work-up for dissemination, fluconazole 400 mg/d for 6 -12 months.
- In HIV-infected patients on HAART with CD4 count  $> 100$  cells/ml and cryptococcal antigen  $\leq 1:512$  and/or not increasing, could consider to discontinue maintenance fluconazole after 1 year of treatment

## What is the treatment of pulmonary cryptococcosis in the non-immunosuppressed patient?

- Mild to moderate symptoms, fluconazole 400mg/d po 6 – 12 months
- Severe disease (treat similar to CNS disease)
- If fluconazole contradicted, itraconazole 200-400 mg po daily; voriconazole 200 mg po bid, posaconazole 400mg po bid are acceptable alternatives
- Role of surgery for diagnosis and persistent radiographic abnormalities and symptoms not responding to antifungals
- **In patients with pulmonary cryptococcosis should consider lumbar puncture to rule out CNS involvement (exception: normal host with asymptomatic nodule(s)/infiltrates, no CNS symptoms, and low or absent serum CRAG.)**

## What is treatment of non-meningeal, non-pulmonary cryptococcosis?

- **Cryptococemia or dissemination (at least two non-contiguous sites involved) treat as CNS disease**
- If CNS disease ruled out, no fungemia and single site, consider fluconazole 400mg/d 6 – 12 months

## What is the appropriate treatment for cryptococcosis during pregnancy?

- **Disseminated and CNS disease, Amphotericin B with or without flucytosine; lipid AmB may be substituted.**
- Start fluconazole after delivery or late in pregnancy
- Limited and stable pulmonary cryptococcosis – close follow-up and fluconazole after delivery
- Watch for IRIS in postpartum period

## What is the appropriate treatment for children with cryptococcosis?

- CNS and disseminated disease, **Amphotericin B 1mg/kg/d** plus flucytosine 100mg/kg/d x 2 weeks followed by **fluconazole 10 – 12 mg/kg/d** x 8 weeks; (polyene – intolerant pt); liposomal AmB 5mg/kg/d. Maintenance therapy: fluconazole (6mg/kg/d)
- Discontinuance of maintenance therapy in children with HAART poorly studied and must be individualized
- Cryptococcal pneumonia. fluconazole 6mg/kg/d for 6 – 12 months

## What are the treatment issues specifically for *Cryptococcus gattii* infections?

- **CNS and disseminated disease, treatment same as *C. neoformans***
- More focus on cryptococcomas/hydrocephalus than *C. neoformans* but principles same
- Pulmonary cryptococcosis (same as *C. neoformans*), Single small cryptococcoma fluconazole 400mg/d; very large and multiple cryptococcomas consider combination therapy for 4 – 6 weeks followed by fluconazole for 6 -18 mos. depending on surgery.
- Surgery: compression of vital structures, failure to reduce in size after 4 wks of therapy or failure to thrive

## What are the treatment issues for cryptococcosis in a resource limited health environment?

- CNS and/or disseminated disease where flucytosine is not available, **Amphotericin B 1mg/kg/d** x 2 wks; then fluconazole 800mg/d x 8 weeks and finally 200 – 400mg/d in maintenance
- CNS and/or disseminated disease where polyene not available, **fluconazole  $\geq 800\text{mg/d} - 2000\text{mg/d}$**  for 10wks or until CSF culture negative, then maintenance fluconazole 200 – 400mg/d
- CNS and/or disseminated disease when polyene not available but flucytosine is, fluconazole 400-800mg/d plus flucytosine 100mg/kg/d for 2-10 weeks followed by maintenance therapy with fluconazole 200 – 400mg/d
- With use of primary fluconazole therapy for induction, direct drug resistance for isolate may be issue and comparative MIC testing is advised.

## History around quantitation of microbe burden and clinical management decisions

- Bacterial counts in Urine<sup>†</sup>
- HIV viral loads  
(HCV and CMV)
- CSF yeast counts (cryptococcal meningitis)  
measurement of Effective Fungicidal Activity  
(EFA) and fungal burden

<sup>†</sup> (MacDonald et al N. Engl. J. Med. 256: 915-22, 1957)

## Quantitative Yeast Counts in CSF

Studies	References
Rabbit cryptococcal meningitis (Amphotericin B the best and combination better)	Perfect et al Am.J. Path. 1980 and JID, 1982
<b>Human Studies:</b>	
(a) AmB+ flucytosine (b) Antigen titers and yeast counts (c) Gamma interferon and yeast counts (d) Fluconazole doses (e) Outcome and yeast counts (f) Combination Flucytosine/Fluconazole; Combination high dose AmB/Flucytosine	(Brouwer Lancet et al , 2004) (Brouwer et al, JID 2005) (Siddigui J. immunol. et al, 2005) (Longley et al, CID 2008) (Bicanic et al, CID 2009) (Nussbaum JC et al, 2010)(Bicanic, CID 2008) (Day et al NEJM, 2013) (Jarvis et al CID, 2014)
Why do a 2 wk LP after start of therapy?	

## Questions (Yes or No)

- (1) Should we elevate Lipid Formulations of Amphotericin B over Amphotericin B in resource-available environments?
- (2) In non-HIV and non-transplant patients should we encourage prolonged induction time (4 wks vs 2 wks) ?
- (3) With Lateral Flow Assay, should we aggressively re-write an integrative strategy for antigen detection and treatment in resource-limited environments?
- (4) Are the broad recommendations of 2-10 wks for starting HAART after beginning cryptococcal induction in need of revision?
- (5) Should corticosteroid therapy in cryptococcosis be readdressed?
- (6) Should in vitro susceptibility testing be encouraged on all isolates?

## Questions (yes or no)

- (7) Should we consider EFA measurements?
- (8) Have we done enough with increased intracranial pressure recommendations?
- (9) Is *C. neoformans* and *C. gattii* treated the same?
- (10) In resource-limited settings without flucytosine, should the combo of amphotericin B plus fluconazole be elevated to primary therapy?
- (11) Should we recommend timing of follow- up LP's?
- (12) Should we elevate gamma interferon status from alternative to primary?

## Final Question

Do the IDSA Guidelines need a revision in the next 1-2 years or are they good for another 5 years?

## IDSA Guidelines and Conflict of Interests for Members and Chairs

### Prohibited

- 1) Royalties licensing fees patents on products under consideration
- 2) Serving a officer, board of directors, or employee of a commercial product under consideration
- 3) Honoraria, gifts or payments from a relevant health-care-related entity such as speaker bureaus and only unrestricted grant to a CME approved entity
- 4) Any activity not sponsored by research arm of company will not be allowed

## IDSA Guidelines and Conflict of Interests for Members and Chairs

### Relationships allowed

1. Advisory/consultancies when research-related will be considered research activity
2. Serve as an investigator on a company-supported research study (but chair will need a co-chair)
3. Presentations at national or international meetings ( non-promotional); no direct payment to individual and must be through third-party organization (CME, IDSA, ATS etc. (exception Chair)

## WHO Guidelines MARCH, 2018

- Initiate ART after start of treatment-4-6 weeks
- Pre-emptive CRAG; CRAG + should be given fluconazole 800mg/day 2 wks then consolidation, and maintenance
- No CRAG, fluconazole prophylaxis for those with CD4 count < 100/ul
- Induction Amphotericin B (0.7mg/kg/d) flucytosine (100mg/kg/d) for 1 wk followed by 1200mg of fluconazole/day

## NIH/CDC Cryptococcal Guidelines (AIDS info) June, 2017

- CrAg (pre-emptive testing) is recommended by some experts for CD4 count < 100/ul and positive antigen should prompt CSF evaluation
- No prophylaxis
- An amphotericin B formulation given with flucytosine is recommended
- Prudent to delay ART from 2-10 wks

## Up-to-Date Guidelines 2018 (over 100,000 hits per year)

*“For non pregnant adults, we suggest that induction therapy consist of a lipid formulation of amphotericin B plus flucytosine”*

## International Antiretroviral Society-USA Panel

For patients with cryptococcal meningitis in high-resourced setting with access to optimal antifungal therapy, frequent monitoring and aggressive management of intracranial pressure, ART should begin within two weeks of diagnosis\*

\*IDSA Guidelines  
Ingle et al abst. 837,2015

## Do Resource-limited studies inform Guidelines?

### Five Pivotal Studies

Fungicidal response- Day et al N. Engl. J. Med. 368: 1291-1302,2013

Steroid impact- Day et al N Engl. J. Med. 374: 542-554, 2006

ART timing – Boulware et al N. Engl. J. Med. 370-2487-98, 2014

ACTA – Molloy et al N. Engl. J. Med. 378: 1004-1017, 2018

Immune Modulation – Jarvis et al AIDS 26:1105-13,2012

## Where have all the crypto studies gone in USA?

[van der Horst CM](#), [Saag MS](#), [Cloud GA](#), [Hamill RJ](#), [Graybill JR](#), [Sobel JD](#), [Johnson PC](#), [Tuazon CU](#), [Kerkering T](#), [Moskovitz BL](#), [Powderly WG](#), [Dismukes WE](#). Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. N Engl J Med. 1997 Jul 3;337(1):15-21

[Hamill RJ](#), [Sobel JD](#), [El-Sadr W](#), [Johnson PC](#), [Graybill JR](#), [Javalay K](#), [Barker DE](#).

Comparison of 2 doses of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis: a randomized, double-blind clinical trial of efficacy and safety.

Clin Infect Dis. 2010 Jul 15;51(2):225-32. doi: 10.1086/653606.

[Pappas PG](#)<sup>1</sup>, [Bustamante B](#), [Ticona E](#), [Hamill RJ](#), [Johnson PC](#), [Reboli A](#), [Aberg J](#), [Hasbun R](#), [Hsu HH](#). Recombinant interferon- gamma 1b as adjunctive therapy for AIDS-related acute cryptococcal meningitis. J Infect Dis. 2004 Jun 15;189(12):2185-91. Epub 2004 May 24

## Summary Cryptococcal Guidelines

- They are working and probably robust
- **For Resource-Available countries**
  - (1) Need to be committed to flucytosine and completion of combination induction – maybe more use of lipid amphotericin B formulations
  - (2) Fungicidal regimen is essential: may be it is time to use CSF quantitative yeast counts in clinical practice
- **For Resource-Limited countries**
  - (1) Lateral Flow Assay could make major impact on management by identifying antigen positivity
  - (2) Needs to be commitment to amphotericin B ± flucytosine or fluconazole
- **For Both.....**IRIS and ICP are troublesome and deadly.....management is empiric and evolving

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