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MEDICAL MYCOLOGY TRAINING NETWORK

Cryptococcal meningitis in HIV/AIDS

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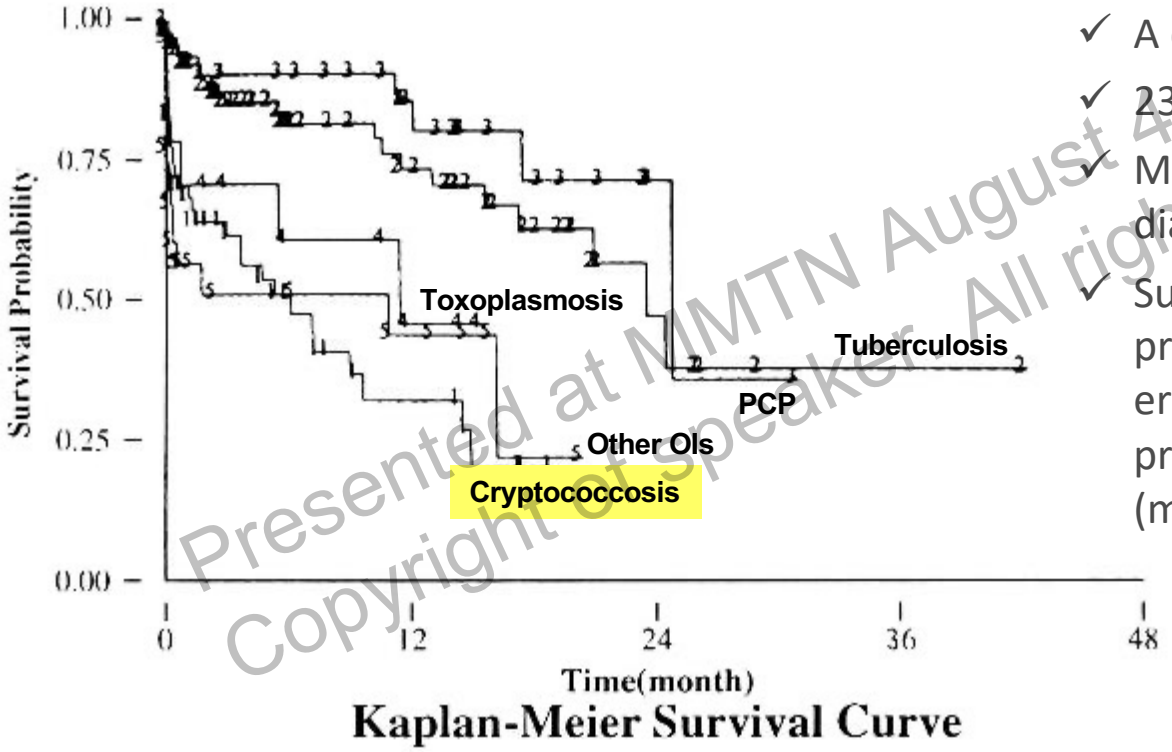
Opportunistic Infections among AIDS Patients in Thailand, 1984-2005 – the Pre-Antiretroviral Therapy (ART) Era

Rank	Opportunistic Infections (OIs)	Number	%
1	Tuberculosis	79,559	29.61
2	*Pneumocystis* pneumonia (PCP)	57,235	21.3
3	Cryptococcosis	43,339	16.14
4	Invasive candidiasis	14,202	5.29
5	Recurrent bacterial pneumonia	10,070	3.75
6	Cerebral toxoplasmosis	8,006	2.98
7	Penicilliosis	6,709	2.5
8	AIDS dementia complex	4,155	1.55
9	*Mycobacterium avium* complex (MAC) infection	2,597	0.97
10	Chronic herpes simplex infection	2,448	0.91

Total = 268,706 AIDS patients reported in 1984-2005. Source: MOPH

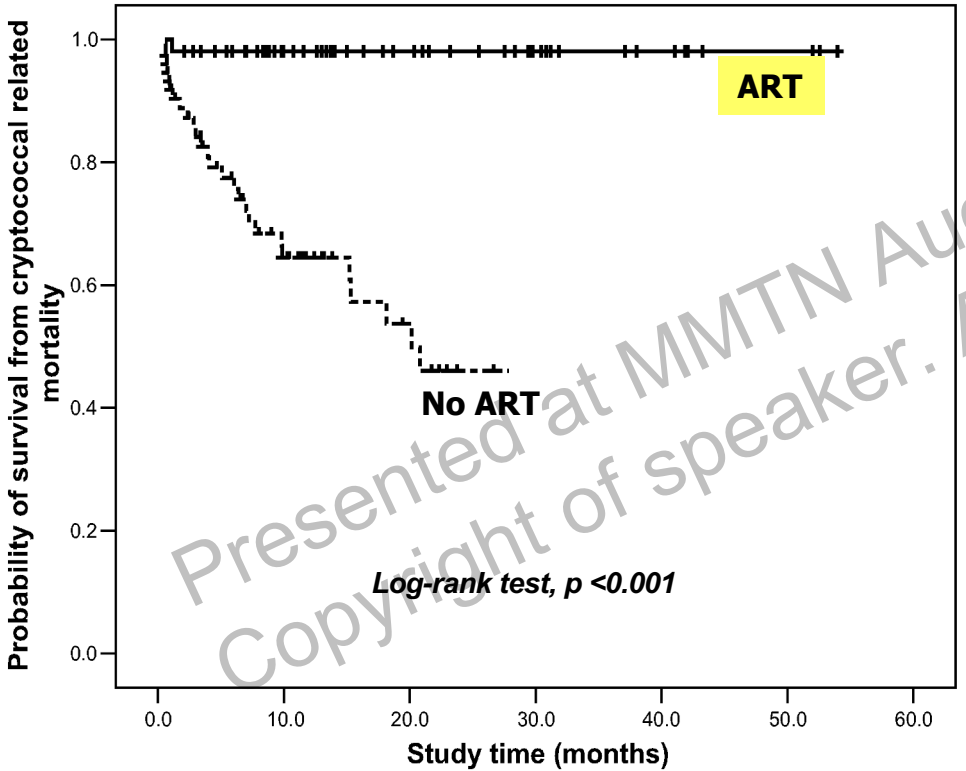
Survival of AIDS Patients by First Presenting Opportunistic Infections in Thailand, 1990-1994



- ✓ A cohort in pre-ART era
- ✓ 235 AIDS patients in Thailand
- ✓ Median survival from AIDS diagnosis was 17.5 months
- ✓ Survival of HIV-infected patients presenting with OIs in the pre-ART era was short, esp. those who presented with cryptococcosis (median survival 6.3 months)

Sathapatayavongs B, et al. J Infect Dis Antimicrob Agents 1999; 16: 69-72.

Impact of ART on the Survival of HIV-infected Patients with Cryptococcosis



- ✓ A retrospective cohort of 149 HIV-infected patients with cryptococcosis, 1997-2005 (median CD4, 22 cells/mm^3)
- ✓ Median time of ART initiation after cryptococcal diagnosis = 2.6 months
- ✓ The 75% survival from cryptococcal-related mortality in no-ART group was 6.4 months whereas >54 months for ART group (p<0.001)
- ✓ In Cox proportional hazards model, ART = the only factor that associated with lower mortality rate (HR 17.6, p<0.001)

Jongwutiwes U, et al. Cur HIV Res 2007; 5: 355-60.

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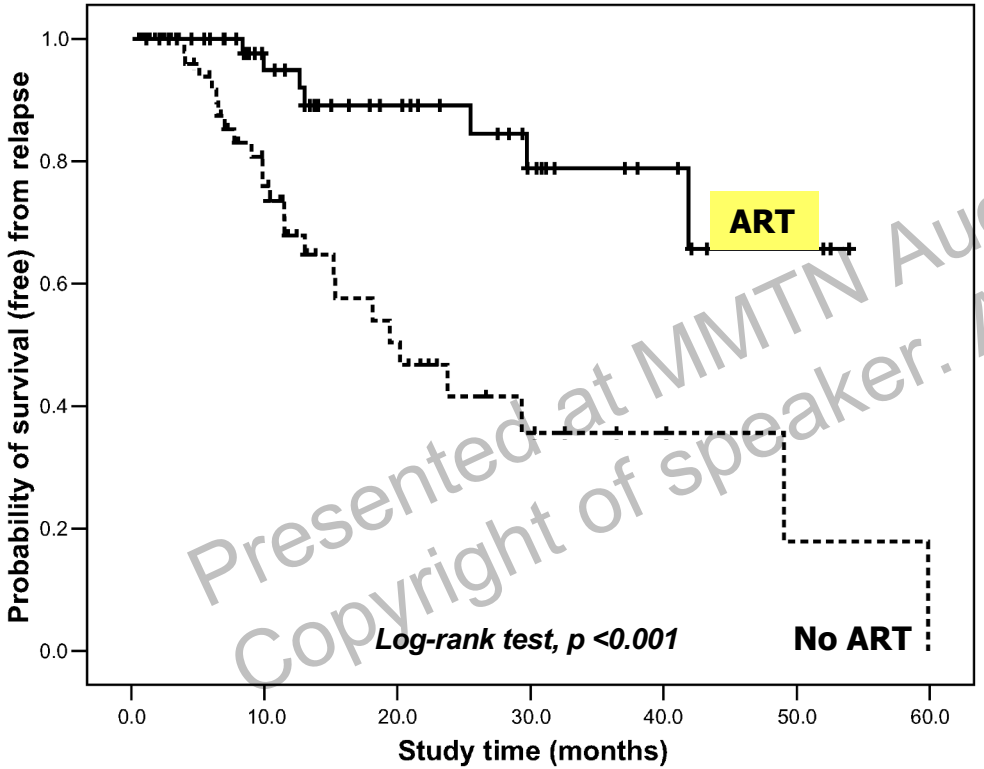
Impact of ART on the Relapse of Cryptococcosis in HIV-infected Patients with Cryptococcosis

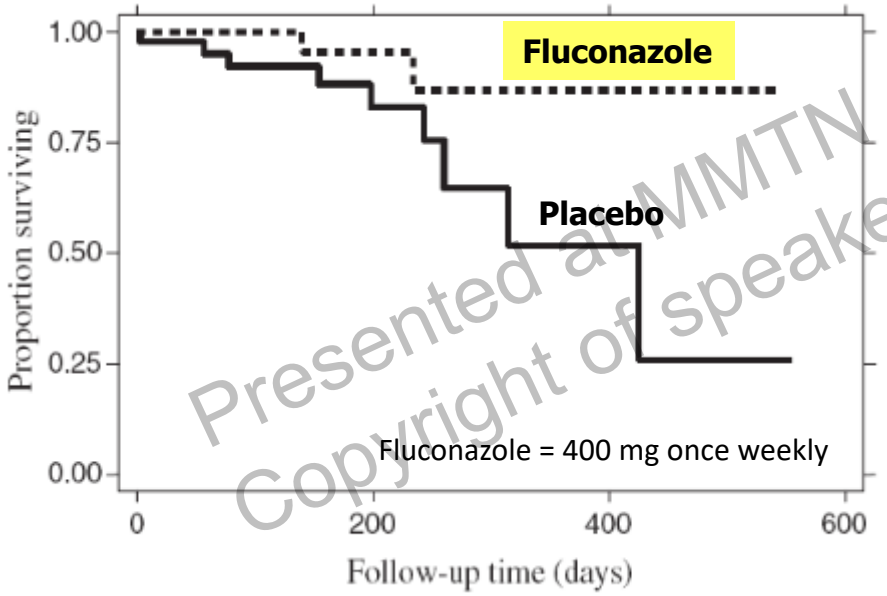


- ✓ The cumulative 75% survival (free) from relapse duration = 10.4 months in no-ART group and = 41.9 months in ART group (p<0.001)
- ✓ In Cox proportional hazards model, ART was the only factor that associated with lower relapse rate (HR = 5.47, p=0.003)

Jongwutiwes U, et al. Cur HIV Res 2007; 5: 355-60.

Primary Prophylaxis for Cryptococcosis in HIV-infected Patients

- *IDSA Guidelines for Cryptococcal Diseases 2010:* primary prophylaxis for cryptococcosis is not recommended in HIV-infected patients in USA and Europe due to the lack of survival benefits



- ✓ A multicenter, randomized, double-blind, placebo-controlled trial in Thailand, 2003-2004
- ✓ 6.8% in fluconazole group and 15.2% in placebo group developed cryptococcosis
- ✓ Number of deaths per 10,000 person-days was 2.7 for fluconazole group and 11.7 for placebo group (rate difference=9; 95%CI: 0.4-17.5; *p*=0.046)
- ✓ Based on survival analysis, patients in placebo group were 4.3 times more likely to die than those in fluconazole group

Chetchotisakd P, et al. HIV Med. 2004; 5: 140-3.

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Primary Prophylaxis for Cryptococcosis in HIV-infected Patients

World Health Organization

Essential Prevention and care Interventions for Adults and Adolescents Living with HIV

In areas where cryptococcal disease is common, antifungal prophylaxis with azoles should be considered for severely immunocompromised people with HIV (WHO clinical stage 4 or CD4 < 100 cells/uL), whether they are on antiretroviral therapy **(C-IV)** or not. **(C-I)**

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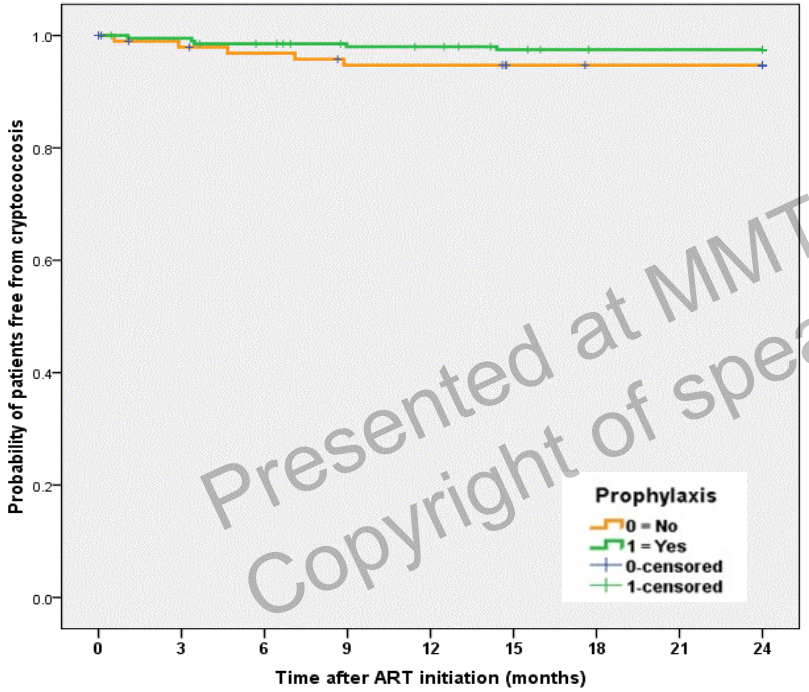
Primary Prophylaxis for Cryptococcosis in HIV-infected Patients Receiving ART

- A prospective observational cohort study of 302 patients (201 in fluconazole group/101 in control group)



- ✓ followed up for 2 years after ART initiation
- ✓ 1 patient in each group died (causes of death = sepsis and respiratory failure, not related to cryptococcosis)
- ✓ 5 patients in each group developed cryptococcosis (2.5% vs 5%, *p*=0.311)
- ✓ Kaplan-Meier analysis: no difference of the occurrence of cryptococcosis between 2 groups (log-rank test, *p*=0.221)
- ✓ Primary prophylaxis for cryptococcosis with fluconazole in HIV-infected patients receiving ART, has no survival benefit and may not be necessary

Sungkanuparph S, et al. Clin Infect Dis 2017; 64: 967-70.

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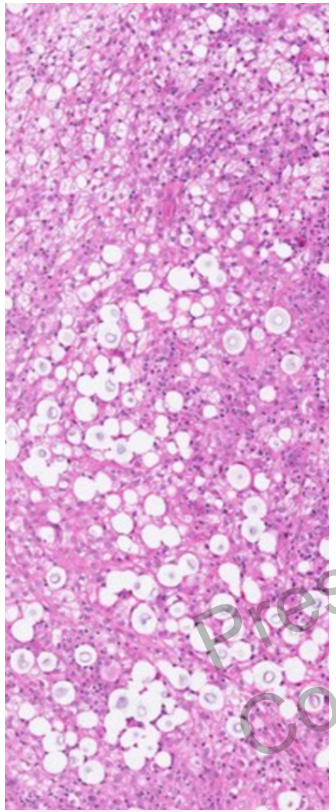
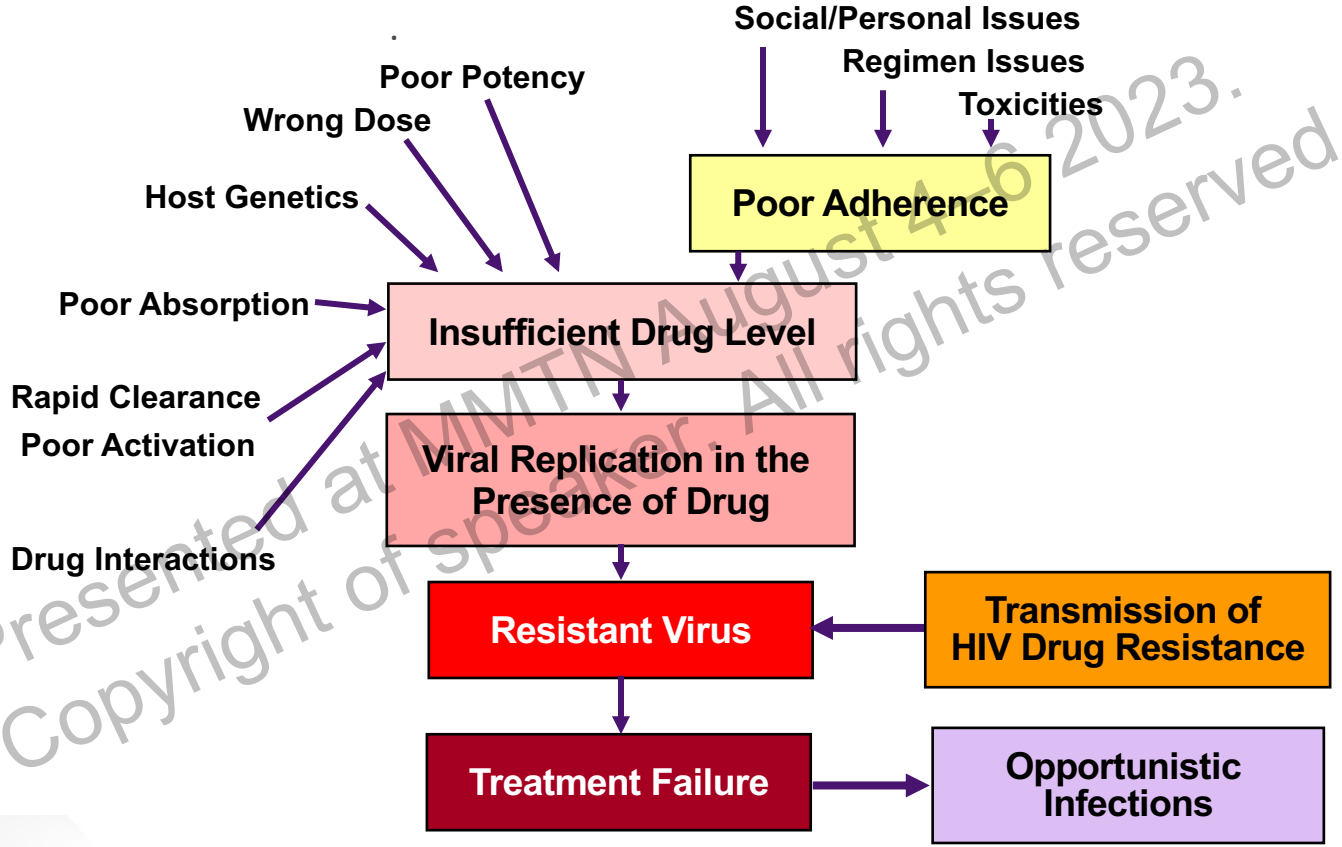
Cryptococcosis in HIV-infected Patients in the ART Era



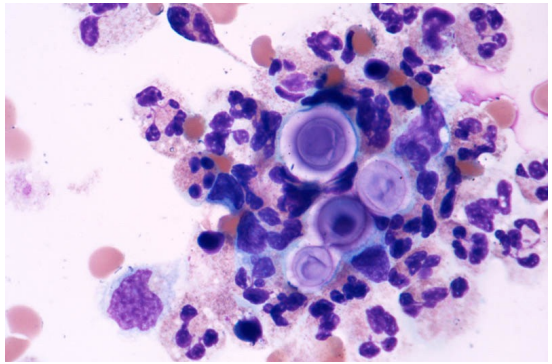
- Scaling up of ART has lowered the incidence of cryptococcosis
- Despite access to advanced medical care and availability of ART
  - ✓ incidence and mortality rate are still high in resource-limited setting
  - ✓ largely consisting of patients with newly diagnosed HIV infection
  - ✓ 3-month mortality rate during management of acute cryptococcal meningitis ~ 20%
  - ✓ without specific antifungal treatment for cryptococcal meningitis, mortality rates of 100% have been reported within 2 weeks after clinical presentation to health care facilities
- It is apparent that insightful management of cryptococcosis is critical to a successful outcome

Perfect JR, et al. Clin Infect Dis 2010; 50: 291-322.

Causes of ART Failure



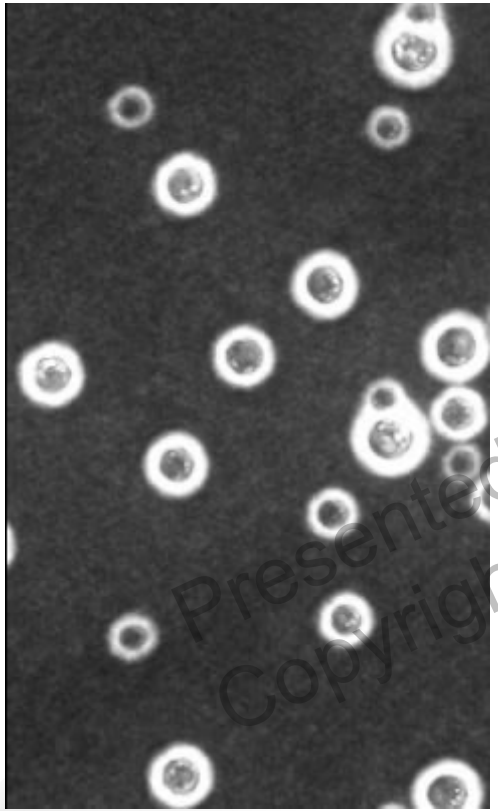
Cryptococcosis in HIV/AIDS



- Initial infection is usually a self-limited pneumonitis
- In AIDS, the most common presentation is subacute meningitis, esp. in patients with CD4 <100 cells/mm^3
- Cryptococcus has a strong affinity for the CNS – this neurotropism is linked to several cryptococcal-specific factors which facilitate the permeability of the blood-brain barrier

- *Cryptococcus neoformans,* an encapsulated yeast found throughout the world
- The genus *Cryptococcus* contains >50 species, but only *C. neoformans* and *C. gattii* are considered principal pathogens in humans
- These 2 species have 5 serotypes based on antigenic specificity of the capsular polysaccharide; these include serotypes A, D, and AD (*C. neoformans*) and serotypes B and C (*C. gattii*)
- Worldwide, *C. neoformans* serotype A causes most cryptococcosis in HIV/AIDS

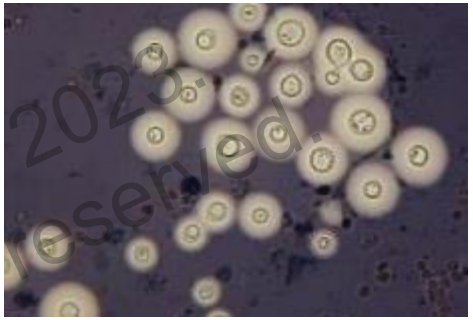
Cryptococcal Meningitis in HIV/AIDS



- **Meningitis and meningoencephalitis** are most common manifestations of cryptococcosis in HIV/AIDS, usually subacute or chronic in nature
- Common symptoms:
  - ✓ headache, confusion, lethargy, coma
  - ✓ nausea and vomiting (with increased ICP)
  - ✓ fever and stiff neck (with an aggressive inflammatory response; less common)
  - ✓ blurred vision, photophobia, and diplopia
  - ✓ hearing defects
  - ✓ seizures
  - ✓ coma

Cryptococcal Meningitis in HIV/AIDS

- Diagnosis can be made by
  - ✓ visualizing the yeast in CSF, using India ink, or
  - ✓ detecting cryptococcal Ag in CSF (latex agglutination test)
  - ✓ If LP is contraindicated, presumptive diagnosis can be made with a serum antigen test

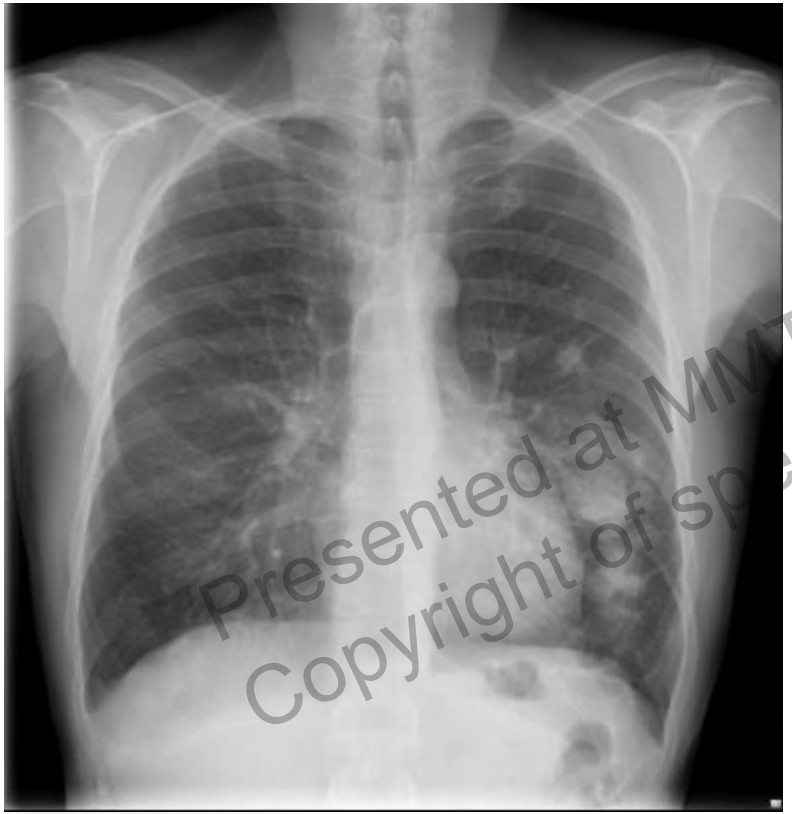


- AIDS patients may not have CSF cellular pleocytosis, abnormal protein, or low CSF glucose

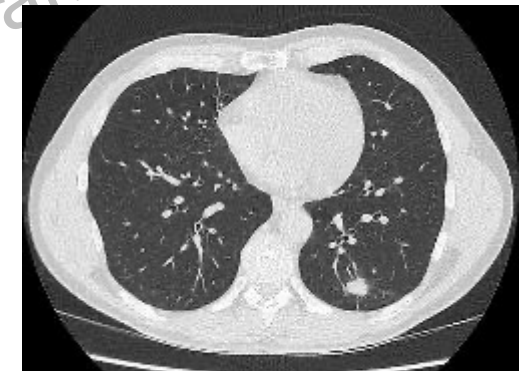
CSF Profile of Cryptococcal Meningitis
- Normal in 20%
- WBC: 0-100 (>50% mononuclear cells)
- Protein: 30-150 mg/dl
- Glucose: 50-70 mg/dl
- India ink positive: 60-80%
- Cryptococcal Ag nearly 100% sensitivity and specificity
- Culture positive: 95-100%

CSF Profile of Tuberculous Meningitis
- Normal in <1%
- WBC: 10-1000 (80% mononuclear cells)
- Protein: 50-1000 mg/dl
- Glucose: <40 mg/dl
- AFB positive: 40-80%
- Culture positive for TB: 60-90%
- PCR for TB positive: 75-95%

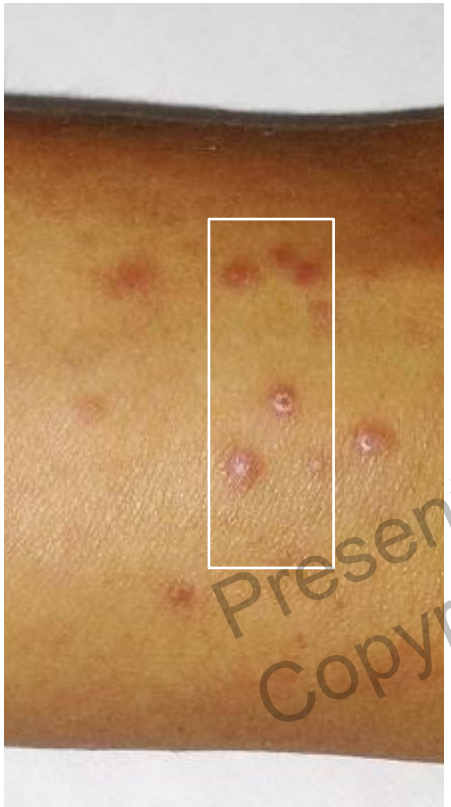
Other Forms of Cryptococcosis in HIV/AIDS

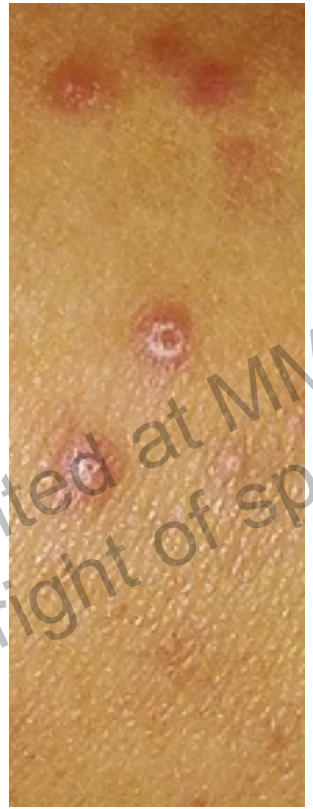


- **Pulmonary cryptococcosis**
- Common symptoms:
  - ✓ fever, cough, dyspnea
  - ✓ headache, weight loss
  - ✓ pleuritic pain, hemoptysis
  - ✓ rales or pleural rub
  - ✓ acute respiratory distress syndrome (ARDS)

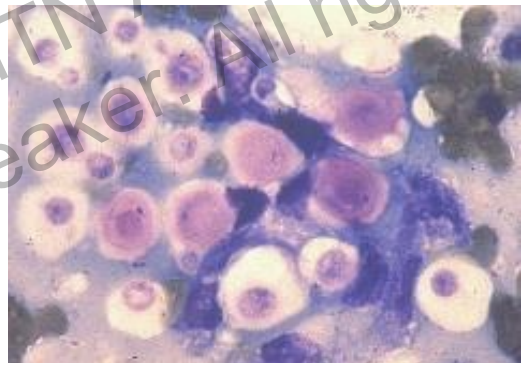


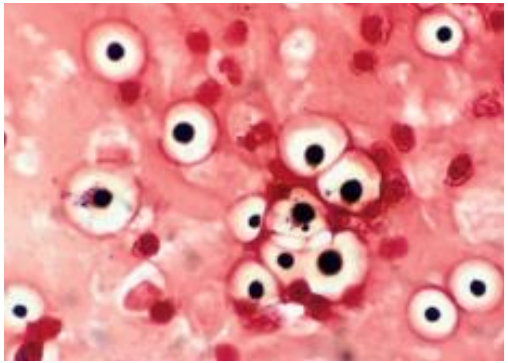
Other Forms of Cryptococcosis in HIV/AIDS





- **Disseminated cryptococcosis**
- Most commonly involved organs:
  - ✓ Skin (umbilicated papules)
  - ✓ Prostate (prostatitis)
  - ✓ Bone marrow (cytopenia)





- Less common: eye, liver, peritoneum, kidney, muscle, bone, adrenal gland

Fungicidal Activity of Antifungals for Cryptococcosis

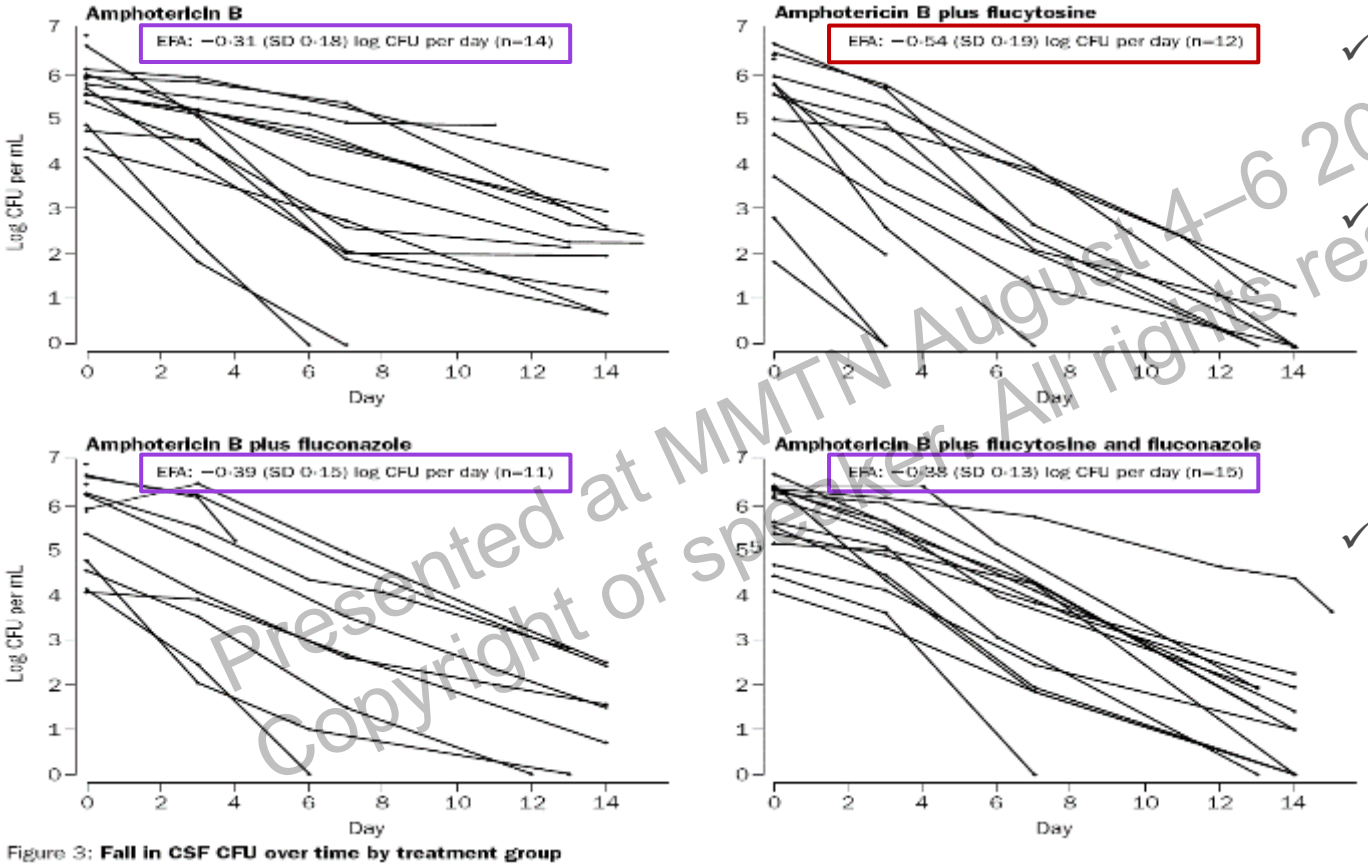


Figure 3: **Fall in CSF CFU over time by treatment group**

Brouwer AE, et al. Lancet 2004; 363: 1764-7.

- ✓64 patients with a first episode of HIV-associated cryptococcal meningitis
- ✓Randomized to initial Rx: ampho B (0.7 mg/kg/day); ampho B + flucytosine (100 mg/kg/day); ampho B + fluconazole (400 mg/day) ; or triple therapy
- ✓Amphotericin B plus flucytosine had significantly higher early fungicidal activity (EFA) than other 3 groups ($p<0.05$)

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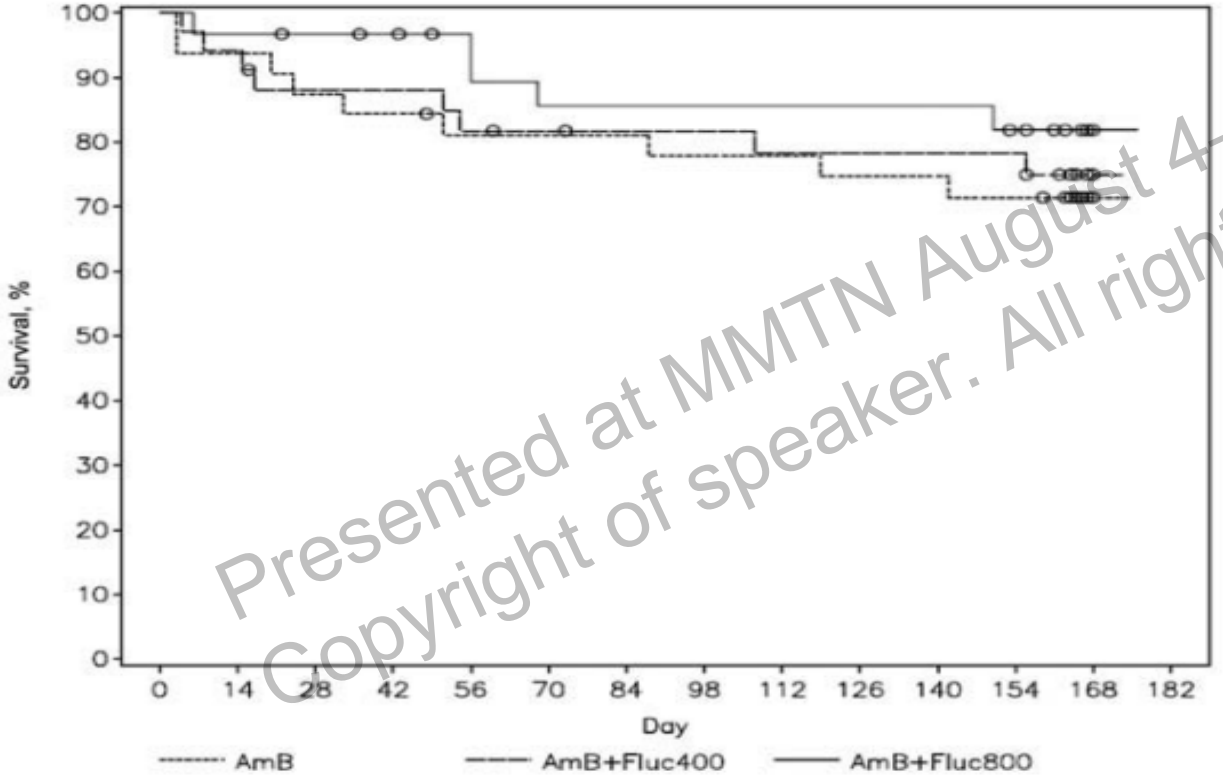
A Phase II RCT of Amphotericin B Alone or Combined with Fluconazole for Cryptococcal Meningitis



- ✓ Of 143 patients, no differences in treatment-related toxicities among 3 arms
- ✓ Survival (%) at day 14:
  - AmB: 41%
  - AmB + Flu400: 27%
  - AmB + Flu800: 54%
- ✓ There was a trend towards improved early survival among subjects in AmB + Flu800 compared to AmB arm

Pappas PG, et al. Clin Infect Dis 2009; 48: 1775-83.

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Antifungal Therapy for Cryptococcal Meningitis

- Treatment consists of three phases:
  - Induction therapy
  - Consolidation therapy
  - Maintenance therapy (secondary prophylaxis)

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

Developed by the National Institutes of Health, the Centers for Disease Control and Prevention, and the HIV Medicine Association of the Infectious Diseases Society of America Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV—A Working Group of the NIH Office of AIDS Research Advisory Council (OARAC)

Cryptococcosis

Updated: July 01, 2021
Reviewed: January 11, 2023

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cryptococcosis

Antifungal Therapy for Cryptococcal Meningitis

- Induction therapy (duration of therapy: 2 weeks):
  - ✓ Preferred regimens
    - Liposomal amphotericin B (Li-AmB) 3-4 mg/kg IV once daily + flucytosine (AI), or
    - Amphotericin B deoxycholate (AmB) 0.7-1.0 mg/kg IV once daily + flucytosine (AI) — if cost is an issue and the risk of renal dysfunction is low
  - ✓ Alternative regimens
    - AmB 0.7-1.0 mg/kg IV once daily plus fluconazole 800-1,200 mg once daily (BI); or
    - Li-AmB 3-4 mg/kg IV once daily alone (BI); or
    - AmB 0.7-1.0 mg/kg IV once daily alone (BI); or

Note:

- Dosage of flucytosine = 25 mg/kg PO four times a day
- Flucytosine dose should be adjusted in renal impairment

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cryptococcosis

Antifungal Therapy for Cryptococcal Meningitis

- Induction therapy (duration of therapy: 2 weeks):
  - ✓ Alternative regimens *(continued)*
    - Amphotericin B lipid complex 5 mg/kg IV once daily + flucytosine (BII); or
    - Li-AmB 3-4 mg/kg IV once daily + fluconazole 800-1,200 mg once daily (BIII); or
    - Fluconazole 1,200 mg once daily + flucytosine (BII); or
    - Fluconazole 800 mg once daily + flucytosine (BIII); or
    - Li-AmB 3-4 mg/kg IV once daily + flucytosine for 1 week followed by fluconazole 1,200 mg once daily (BIII); or
    - Fluconazole 1,200 mg once daily alone (CI)

    Note:

    - If not improved clinically or remain clinically unstable, continue induction therapy until the CSF culture is confirmed to be negative (BIII)

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cryptococcosis

Antifungal Therapy for Cryptococcal Meningitis

- Consolidation therapy (duration of therapy: ≥8 weeks):
  - ✓ Preferred regimens
    - Fluconazole 800 mg PO once daily (AI)
    - For clinically stable patients with negative CSF cultures, dose can be reduced to 400 mg PO once daily (AII)
    - If CSF remains positive (but clinically stable) after 2 weeks of induction therapy, increase fluconazole dose to 1,200 mg and perform LP 2 weeks later (BIII); duration of consolidation therapy should be 8 weeks from the time of negative CSF culture (AI)
- Maintenance therapy (duration of therapy: ≥1 year):
  - ✓ Preferred regimen
    - Fluconazole 200 mg PO once daily for ≥1 year from initiation of antifungal therapy (AI)

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cryptococcosis

Antifungal Therapy for Cryptococcal Meningitis

- Stopping maintenance therapy: if all the following criteria are fulfilled (BII)
  - ✓ At least 1 year from initiation of antifungal therapy, and
  - ✓ Patient remains asymptomatic from cryptococcal infection, and
  - ✓ CD4 count ≥100 cells/mm^3 and suppressed HIV RNA in response to effective ART
- Restarting maintenance therapy:
  - ✓ If CD4 count declines to ≤100 cells/mm^3 (AIII)
- Treating asymptomatic patients with isolated cryptococcal antigenemia:
  - ✓ Serum LFA titer ≥1:640 – same treatment as for CNS disease (BIII)
  - ✓ Serum LFA Titer ≤1:320 – fluconazole 400-800 mg daily for 10 weeks followed by fluconazole 200 mg daily for a total of 6 months (BIII)

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cryptococcosis

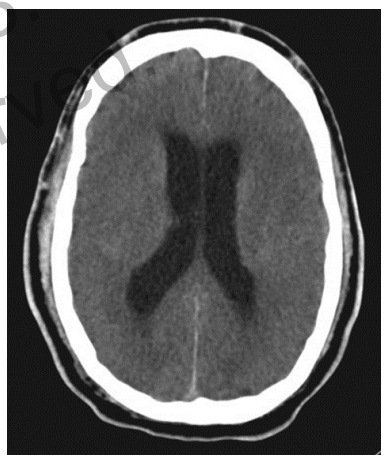
Antifungal Therapy for Cryptococcal Meningitis

- Other considerations:
  - ✓ Addition of flucytosine to an amphotericin B-based regimen is associated with more rapid sterilization of CSF, decreased risk for subsequent relapse, and improved survival
  - ✓ If flucytosine levels cannot be measured (TDM not available), at least twice weekly CBC may be used to monitor for cytopenia
  - ✓ In the setting of severe AmB-induced toxicity, at least 1 week of AmB is needed (BIII)
  - ✓ Corticosteroids should not be used routinely during induction therapy unless used for management of IRIS (AI)
  - ✓ Corticosteroids and mannitol are ineffective in reducing ICP and are not recommended (AIII)

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cryptococcosis

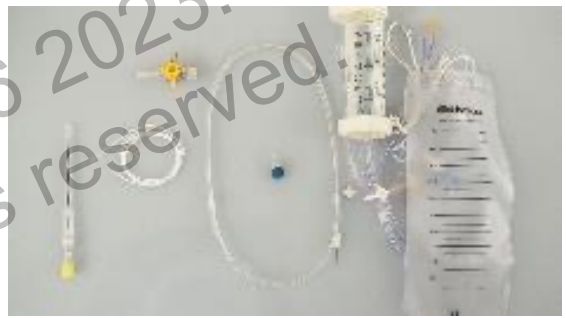
Managements for Cryptococcal Meningitis

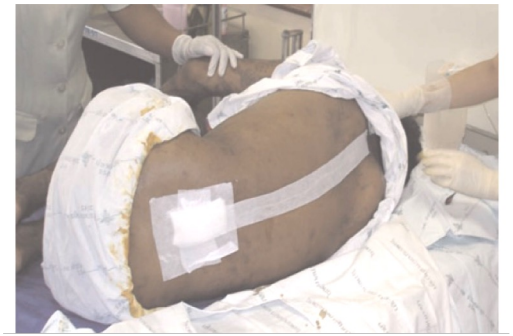
- Immediate treatment is essential to prevent loss of brain function and mortality
- Even with optimal treatment, the mortality rate is still 15%
- Control of CSF pressure is critical to the patient's survival
- Failure to control CSF pressure may result in blindness, permanent neurologic deficits, or death
- CSF can be removed by repeated (daily) spinal taps, or a spinal fluid drainage until pressures are controlled
- An initial opening pressure of 25 cmH_2O or greater must be reduced and kept around 20 cmH_2O throughout therapy
- In rare cases, control of elevated CSF pressures may require a ventriculoperitoneal shunt
- Acetazolamide or corticosteroids should also be avoided for cryptococcal meningitis
- Mannitol has no proven value in reducing pressure in cryptococcal meningitis



Temporary External Lumbar Drainage for Cryptococcal Meningitis in HIV-infected Patients

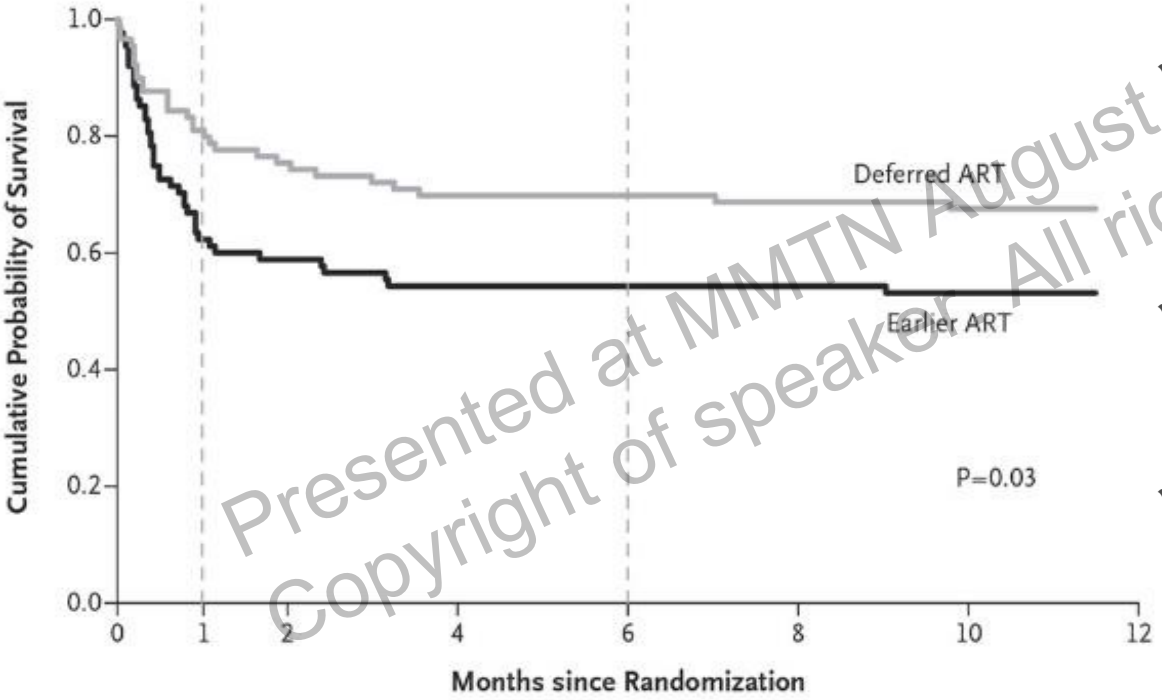
- A retrospective cohort study
- Temporary external lumbar drains were placed to reduce intractable elevated ICP
- 54 of 601 patients with cryptococcal meningitis underwent lumbar drainage
- Median duration 7 days / total 473 device-days observation
- No patient died or brain herniation
- Incidence of secondary bacterial infection = 6.3/1000 device-days
- 4.9% of catheters became secondarily infected with nosocomial bacteria – all drains were removed and appropriate antibiotics were given





Manosuthi W, et al. Int J STD AIDS 2008; 19: 268-71.

Timing of ART Initiation after Diagnosis of Cryptococcal Meningitis



- ✓ 177 HIV-infected patients with cryptococcal meningitis and had not previously received ART in Uganda/South Africa
- ✓ Randomly assigned to either earlier ART (1-2 wks after Dx) or deferred ART (5 wks after Dx)
- ✓ 26-week mortality 45% vs 30%; HR for death 1.73; P=0.03

Boulware DR, et al. N Engl J Med 2014; 370: 2487-98.

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Drug-drug Interaction between Antifungal and Antiretroviral Drugs

Drugs	EFV	NVP	RPV	ATV	DRV	LPV	RTV	Cobi	ETG	DTG	RAL
Amphotericin B	◆	◆	◆	◆	◆	◆	◆	◆	■	◆	◆
Fluconazole	◆	■	■	◆	◆	◆	◆	△	△	◆	◆
Itraconazole	■	●	■	■	■	■	■	■	■	◆	◆

●	These drugs should not be coadministered
■	Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration
△	Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required
◆	No clinically significant interaction expected
✦	There are no clear data, actual or theoretical, to indicate whether an interaction will occur

- PIs, NNRTIs are substrates of CYP3A4
- PIs are typically inhibitors of CYP3A4
- NNRTIs are inducers of CYP3A4
- Azoles are all substrates of CYP3A4
- Azoles are typically inhibitors of CYP3A4 + CYP2C19, 2C9, 1A2

www.hiv-druginteractions.org

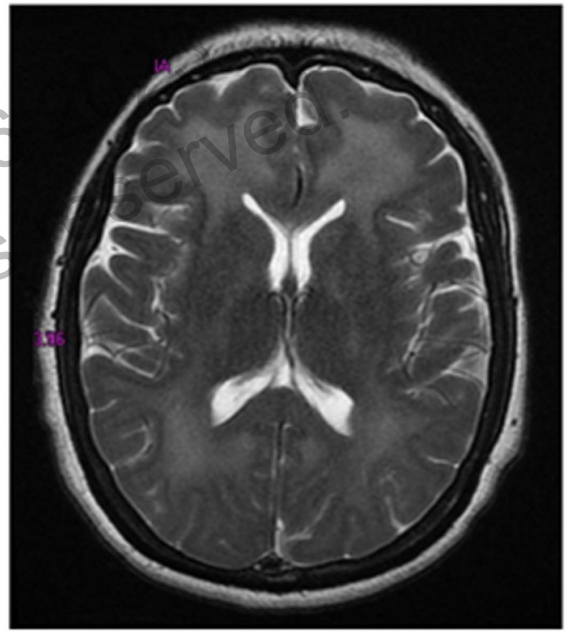
Immune Reconstitution Inflammatory Syndrome (IRIS)

- A serious problem complicating the treatment of AIDS
- A group of syndromes characterized by paradoxical clinical worsening that usually occurs within the first 4-8 weeks after starting ART
- The reconstituted immune system generates an inflammatory response, resulting in either a worsening of a known, underlying infection, or the unmasking of a subclinical, indolent infection
- Neuroimaging features include development of, or increase in, contrast enhancement, and unusual patterns of contrast enhancement
- Intracranial pressure may rise, requiring the use of corticosteroids
- Risk factors: starting ART in active or subclinical OI with CD4 <50 cells/mm^3 and a rapid decline in HIV viral load

Skiest DJ, et al. J Infect 2005; 51: e289-97.
Shelburne SA, et al. Clin Infect Dis 2005; 40: 1049-52.
Lortholary O, et al. AIDS 2005; 19: 1043-9.

Cryptococcal IRIS

- Up to 30% of patients with cryptococcal meningitis develop IRIS after initiation of ART
- Closed monitoring few months after initiation of ART
- Need to exclude active OI prior to diagnosis of IRIS
- Management: continue ART and antifungal therapy
- If severe IRIS symptoms, consider short course of corticosteroids (prednisone 0.5-1.0 mg/kg/day or dexamethasone)
- To prevent IRIS: delaying initiation of ART until 6 weeks of treatment for cryptococcal meningitis



Skiest DJ, et al. J Infect 2005; 51: e289-97.
Shelburne SA, et al. Clin Infect Dis 2005; 40: 1049-52.
Lortholary O, et al. AIDS 2005; 19: 1043-9.

Cryptococcal IRIS after ART in AIDS Patients with Cryptococcal Meningitis: A Multicenter RCT

- ✓ A total of 101 patients and 13 patients with IRIS were identified
- ✓ Overall incidence of cryptococcal IRIS: 47 cases per 100 person-years
- ✓ Median interval from ART initiation to diagnosis of IRIS was 63 days (range, 12–129 days)
- ✓ In the multivariable model, only serum Cryptococcal antigen titer at baseline was associated with cryptococcal IRIS (OR 1.37; 95%CI, 1.08-1.74; p <0.05).

Characteristics	At first diagnosis of cryptococcal meningitis	At first CSF culture negative for *Cryptococcus*	At the time of cryptococcal IRIS diagnosis
Opening pressure, median (10^{th}-90^{th} percentiles), mmH_2O	270 (130-520)	200 (100-330)	460 (225-600)
Cryptococcal Ag titer, median (10^{th}-90^{th} percentiles)	1:1024 (1:16 – 1:10000)	-	1:128 (1:4 – 1:256)

Sungkanuparph S, et al. Clin Infect Dis 2009; 49: 931-4.

MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

Successful Management of Cryptococcal Meningitis in HIV-infected Patients

- ✓ Early diagnosis, especially when the patient's symptoms and signs are subtle
- ✓ Administer appropriate antifungal therapy
- ✓ Prevent and manage antifungal drug toxicity
- ✓ Control the elevated intracranial pressure
- ✓ Restoration of host immunity with effective ART
  - Start ART at the right time
  - Start optimal ART regimen
- ✓ Anticipate and manage immune reconstitution inflammatory syndrome (IRIS)
  - Continue ART and antifungal therapy
  - Consider short course of corticosteroids in severe cases

Srichatrapimuk S and Sungkanuparph S. AIDS Res Ther 2016; 13: 42.

General Concept of Integrated Care for Cryptococcosis in HIV-infected Patients

- Successful model of integration of care for both HIV and cryptococcosis mainly use a single facility and a single health care provider delivering care for both diseases
  - ✓ Providing optimal timing for initiation of ART
  - ✓ Holistic evaluation of the patients
  - ✓ Practical management when patients encounter adverse drug effects
  - ✓ More feasible to set up, maintain, and train the healthcare providers in resource-limited settings
  - ✓ No losing patients to follow-up during the referral process between cryptococcosis and HIV clinics
  - ✓ Less travel costs and time spent in clinics
  - ✓ Interventions for improving adherence and social support can better reinforce

Srichatrapimuk S and Sungkanuparph S. AIDS Res Ther 2016; 13: 42.

“Only the unknown frightens men.
But once a man has faced the unknown,
that terror becomes the known.”

Antoine de Saint-Exupery
‘The Little Prince’