Cryptococcosis of the Central Nervous System: Classical and Immune-Reconstitution Disease

Assist Prof. Somnuek Sungkanuparph
Division of Infectious Diseases
Faculty of Medicine Ramathibodi Hospital
Mahidol University, Bangkok, Thailand
A Global View of HIV Infection

Global: 38.6 [33.4–46.0] million, 2005
Thailand: 0.58 [0.33-0.92] million, 2005
A Global View of Cryptococcosis

- Overall incidence of cryptococcosis is unknown.
- It is higher among patients with AIDS in Africa and Southeast Asia than in the United States and Europe.
- Less frequent in children with AIDS.
- Almost all develop when CD4 cell count < 100 cells/µL.

AIDS-defining illness in Thailand

Cases reported to MOPH 1984 – 1998
(before HAART era in Thailand)

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mycobacterium tuberculosis (Pulmonary or extrapulmonary)</td>
<td>42,182</td>
<td>27.4</td>
</tr>
<tr>
<td>2. <em>P. carinii</em> pneumonia</td>
<td>32,132</td>
<td>19.5</td>
</tr>
<tr>
<td>3. Cryptococcosis</td>
<td>25,815</td>
<td>16.7</td>
</tr>
<tr>
<td>4. Invasive candidiasis</td>
<td>8,131</td>
<td>5.3</td>
</tr>
<tr>
<td>5. Recurrent bacterial pneumonia</td>
<td>5,629</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Source: [http://www.moph.go.th](http://www.moph.go.th)
Cryptococcosis

- The most common life-threatening fungal infection
- Meningoencephalitis is the most frequent manifestation
- Thailand: >90% = cryptococcal meningitis
- Clinical features of cryptococcal meningitis: headache, fever, stiffness of neck, cranial nerve palsies & papilledema
- Cryptococcal Ag titer is useful for diagnosis
- CSF Findings:
  - Open pressure usually high
  - Low glucose, high protein only 25%
  - Cell counts mild pleocytosis ~ 40%
  - India ink positive ~ 75%
  - Cryptococcal Ag positive ~ 99%
Cryptococcosis

- Most deaths occur within the first 2 weeks of therapy and related to increased intracranial pressure.
- Significant decrease in mortality was observed in the trial, in which amphotericin B (0.7 mg/kg/day) + flucytosine was used for the initial 2 weeks followed by 8 weeks of consolidation therapy with fluconazole.

# Primary OI prophylaxis for Persons with HIV Infection

## Table 3. Primary Prophylaxis against Major Infectious Pathogens That Can Cause Complications in the Patient with Newly Diagnosed HIV Infection.*

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>CD4 Count (cells/mm³)</th>
<th>Agent</th>
<th>Major Side Effects</th>
<th>Alternative Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pneumocystis jiroveci</em></td>
<td>&lt;200</td>
<td>Trimethoprim–sulfamethoxazole, 160 mg and 800 mg, once daily</td>
<td>Rash, fever, abnormal liver-enzyme levels, hematologic toxicity, pancreatitis</td>
<td>Dapsone, 100 mg once daily (if G6PD level is normal)</td>
</tr>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>&lt;100</td>
<td>Trimethoprim–sulfamethoxazole, 160 mg and 800 mg, once daily</td>
<td>Rash, fever, abnormal liver-enzyme levels, hematologic toxicity, pancreatitis</td>
<td>Dapsone, 200 mg, plus pyrimethamine, 75 mg, plus leucovorin, 25 mg, once weekly</td>
</tr>
<tr>
<td><em>Mycobacterium avium complex</em></td>
<td>&lt;50</td>
<td>Azithromycin, 1200 mg, once weekly</td>
<td>Gastrointestinal symptoms</td>
<td>Clarithromycin, 500 mg, twice daily</td>
</tr>
<tr>
<td><em>M. tuberculosis</em></td>
<td>Any (tuberculin skin test, positive at induration of ≥5 mm, or history of significant exposure)</td>
<td>Isoniazid, 300 mg, once daily (with pyridoxine, 50 mg, once daily) for 9 months; Active tuberculosis should be ruled out before initiating treatment with isoniazid</td>
<td>Abnormal liver-enzyme levels, peripheral neuropathy</td>
<td>Risks and benefits of alternative prophylactic regimens should be carefully evaluated on an individual basis</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Any, but response to vaccine is better in persons with &gt;200</td>
<td>23-valent pneumococcal polysaccharide vaccine; need for revaccination after 5 years has not been established</td>
<td>Local reaction at site of injection; transient systemic symptoms</td>
<td>—</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>Any</td>
<td>Inactivated influenza vaccine once yearly</td>
<td>Local reaction at site of injection; transient systemic symptoms</td>
<td>Oseltamivir, 75 mg, once daily during outbreak if not protected by vaccination</td>
</tr>
<tr>
<td>Hepatitis A virus</td>
<td>Any</td>
<td>Hepatitis A vaccine</td>
<td>Local reaction at site of injection</td>
<td>Combined hepatitis A and B vaccine now available</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Any</td>
<td>Hepatitis B vaccine</td>
<td>Local reaction at site of injection; transient systemic symptoms</td>
<td>Combined hepatitis A and B vaccine now available</td>
</tr>
</tbody>
</table>

* G6PD denotes glucose-6-phosphate dehydrogenase. Data are from the CDC²⁴ and the U.S. Public Health Service.²⁵

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Cryptococcosis: Primary prophylaxis

- Fluconazole 100 mg daily
- Fluconazole 200 mg daily
- Fluconazole 200 mg 3 times weekly.
- Fluconazole 400 mg weekly

- Significantly decrease incidence of cryptococcosis but not mortality rate.

Cryptococcosis: Primary prophylaxis

- Thailand: a randomized, double-blind, placebo-controlled study of 90 patients with CD4 counts <100 cells/µL
- Received fluconazole 400 mg weekly or placebo

2.7 vs. 11.7 death/10,000 p-days [rate difference = 9; 95% CI: 0.4-17.5; p = .046].

Cryptococcosis: Primary prophylaxis


- Experts’ opinion: use of primary prophylaxis are suggested in resource-poor settings where
  - the incidence of cryptococcosis is significantly higher
  - there is limited access to ART
  - and generic fluconazole or donated fluconazole is available

- concern?
Antifungal Susceptibilities of *Cryptococcus Neoformans* Cerebrospinal Fluid Isolates and Clinical Outcomes of Cryptococcal Meningitis in HIV-Infected Patients with/without Fluconazole Prophylaxis

A: no primary prophylaxis (n=80)
B: prior primary prophylaxis (n=18)

Median time of FLU prophylaxis was 217 (42-537) days in group B.

- Median (range) MIC of FLU:
  - A: 8.0 (0.5-32) µg/ml
  - B: 6.0 (0.5-32) µg/ml
  
  (p = 0.926).

- Complete recovery after 10-week treatment
  - A: 65%  - B: 50%  (p=0.364)

Cryptococcosis: Treatment

- Amphotericin B 0.7 mg/kg IV + flucytosine 100 mg/kg PO daily for 2 weeks,
- then fluconazole 400 mg PO daily for 8 weeks,
- then fluconazole 200 mg PO daily for secondary prophylaxis.

- There was no significant difference in clinical outcomes between amphotericin B + flucytosine and amphotericin B alone.
- A trend toward better mycologic cure in the amphotericin B plus flucytosine arm (60% vs 51%, NS)

Amphotericin B plus flucytosine had significantly higher early fungicidal activity than other 3 groups (p<0·05).

*Amphotericin B*

- EFA: $-0.31$ (SD 0.18) log CFU per day (n=14)

*Amphotericin B plus flucytosine*

- EFA: $-0.54$ (SD 0.19) log CFU per day (n=12)

*Amphotericin B plus fluconazole*

- EFA: $-0.39$ (SD 0.15) log CFU per day (n=11)

*Amphotericin B plus flucytosine and fluconazole*

- EFA: $-0.38$ (SD 0.13) log CFU per day (n=15)

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

Cryptococcosis: Treatment

Other options:

- Amphotericin B 0.7 mg/kg IV + flucytosine 100 mg/kg PO daily for 6-10 weeks
- Fluconazole 400-2000 mg PO daily for 10-12 weeks
- Fluconazole 400-800 mg PO daily + flucytosine 100 mg/kg daily for 10 weeks
- Itraconazole 400 mg PO daily for 10-12 weeks
- Lipid-formulation amphotericin B 3-6 mg/kg IV daily for 6-10 weeks
- Amphotericin B 1 mg/kg IV 1-3 times weekly

- Combination therapy??
- A large-scale randomized control trial (NIH, MSG) in Thailand and USA has just closed.
Cryptococcosis: secondary prophylaxis

- a prospective, multicenter, randomized study on discontinuing secondary prophylaxis
- in 60 HIV-infected subjects who were treated successfully for acute cryptococcal meningitis and received ART.
- Subjects were randomized to continue or discontinue secondary prophylaxis when the CD4 count had increased to >100 cells/µL and HIV RNA level had been undetectable for 3 months.
- At a median of 48 weeks after randomization, there were no episodes of cryptococcal meningitis in either group.

Cryptococcosis: secondary prophylaxis

- The USPHS/IDSA guidelines recommend discontinuation of secondary prophylaxis if patients...
  - successfully complete a course of initial therapy for cryptococcosis
  - remain asymptomatic with respect to signs and symptoms of their cryptococcosis
  - and have a sustained increase (>6 months) in their CD4 counts to >100-200 cells/μL on ART.
- Prophylaxis should be restarted if the CD4 count declines to <100-200 cells/μL.

Recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 2004.
ART in Cryptococcocosis

• Efavirenz-based regimen as treatment of advanced AIDS with cryptococcal meningitis.

• 60 patients with cryptococcal meningitis after 10-week treatment and 2 months of secondary prophylaxis.

First-line ART in Thailand

**GPOvir S 30**
- d4T (30)
- 3TC (150)
- NVP (200)

*<60 kg>*
- 1 tab q 12 hr

**GPOvir S 40**
- d4T (40)
- 3TC (150)
- NVP (200)

*≥60 kg*
- 1 tab q 12 hr

**GPOvir Z 250**
- AZT (250)
- 3TC (150)
- NVP (200)

*1 tab q 12 hr*

30-35 USD/month
ART in Cryptococcosis

Safety and tolerability of nevirapine-based ART in patients receiving fluconazole for cryptococcal prophylaxis: 686 cases

Table 2: Frequency of adverse events among the three groups.

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Not receiving fluconazole (n = 225)</th>
<th>Receiving fluconazole</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>400 mg/week (n = 392)</td>
<td>200 mg/day (n = 69)</td>
</tr>
<tr>
<td>Clinical hepatitis</td>
<td>2/225 (0.9%)</td>
<td>4/392 (1.0%)</td>
<td>0/69 (0%)</td>
</tr>
<tr>
<td>Elevated AST &gt; 3 times from baseline</td>
<td>3/104 (2.9%)</td>
<td>5/188 (2.7%)</td>
<td>3/36 (8.3%)</td>
</tr>
<tr>
<td>Elevated ALT &gt; 3 times from baseline</td>
<td>6/71 (8.5%)</td>
<td>7/95 (7.4%)</td>
<td>2/22 (9.1%)</td>
</tr>
</tbody>
</table>

Table 5: Tolerability of NVP-based HAART among the three groups.

<table>
<thead>
<tr>
<th>Tolerability outcomes</th>
<th>Not receiving fluconazole (n = 225)</th>
<th>Receiving fluconazole</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>400 mg/week (n = 392)</td>
<td>200 mg/day (n = 69)</td>
</tr>
<tr>
<td>On NVP-based HAART at six months</td>
<td>174 (77.3%)</td>
<td>309 (78.8%)</td>
<td>58 (84.1%)</td>
</tr>
<tr>
<td>Reasons of discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>26 (11.5%)</td>
<td>29 (7.4%)</td>
<td>3 (4.3%)</td>
</tr>
<tr>
<td>Skin rashes</td>
<td>25/26 (96.2%)</td>
<td>26/29 (89.7%)</td>
<td>3 of 3 (100.0%)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>1/26 (2.8%)</td>
<td>3/29 (10.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.4%)</td>
<td>8 (2.0%)</td>
<td>-</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>20 (8.9%)</td>
<td>39 (9.9%)</td>
<td>7 (10.1%)</td>
</tr>
<tr>
<td>Refer</td>
<td>4 (1.8%)</td>
<td>7 (1.8%)</td>
<td>1 (1.4%)</td>
</tr>
</tbody>
</table>

ART in Cryptococcosis

Plasma nevirapine levels, adverse events and efficacy of antiretroviral therapy among HIV-infected patients concurrently receiving nevirapine-based antiretroviral therapy and fluconazole

Impact of ART on Cryptococcosis: Relapse


HR = 5.47, P = 0.003
Impact of ART on Cryptococcosis: Mortality

HR = 17.6, P <0.001

Immune Reconstitution Inflammatory Syndrome (IRIS) after ART in Patients with Cryptococcal Meningitis

- 60 patients (50 men) with a mean age of 33.1 ± 6.0 years
- Baseline median CD4 cell count was 9 cells/µl
- Baseline median HIV-RNA level was 5.18 log copies/ml.
- % patients with HIV-RNA <400 copies/ml at 48 weeks = 87.8%
- Median CD4 cell counts at 48 weeks = 168 cells/µl
- During the 48-week period after the initiation of HAART, 14 of 60 patients (23.3%) had 20 episodes of OIs:
  - Tuberculosis (8 episodes),
  - MAC infection (3 episodes),
  - Cryptococcal meningitis (3 episodes), one died
  - Herpes zoster (3 episodes),
  - Toxoplasmosis (2 episodes), one died
  - Herpes genitalis (1 episode).
- OIs occurred at a median (range) duration of 16 (4–32) weeks.

Immune Reconstitution Inflammatory Syndrome (IRIS) after ART in Children

- A study in Thailand
- IRIS incidence of 19% (29 cases) among 153 symptomatic HIV-infected children receiving ART
- 3 of 29 (10%) cases were cryptococcal IRIS.
- IRIS events occurred at a median of 4 weeks (range: 2-31 weeks) after initiation of ART.

IRIS of Cryptococcosis

- IRIS of cryptococcosis was initially reported with unusual manifestations associated with immune recovery on ART.
- A report described 25 cases of IRIS.
  - 14 cases of lymphadenitis
  - 10 CNS complications (meningitis in 6 and mass lesions in 4)
  - 1 pulmonary cavitary lesion.
- Median CD4 at time of initial cryptococcosis = 25 cells/µL.
- Median CD4 at time of cryptococcal IRIS = 197 cells/µL
- Median times to development of IRIS
  - after cryptococcal diagnosis was 11 (7 wk – 3 yr)
  - after initiation of ART were 7 months (<2 wk - 22 m)

IRIS of Cryptococcosis

• retrospective review of 84 patients with HIV-associated cryptococcal disease
• authors addressed the difficulty in differentiating IRIS from relapsed disease
• proposed criteria:
  – clinically responded to anticryptococcal treatment
  – after ART was initiated, the original symptoms returned or new inflammatory symptoms developed
  – all culture results were negative
  – CSF CrAg, if still present, had to show at least a 4-fold decrease from initial cryptococcosis.
• 59 of 84 patients initiated ART
• 18 of 59 (30.5%) developed IRIS as defined above
• after a median time of 30 days (range: 3-330 days) on ART

IRIS of Cryptococcosis

• Patients who developed IRIS were more likely to be
  – antiretroviral naïve
  – have a higher CSF CrAg
  – have a higher baseline HIV viral load
  – have initiated ART within 30 days after cryptococcal diagnosis.

• At the time of IRIS, these patients had
  – higher CSF opening pressures
  – increased CSF whole blood counts
  – higher glucose levels

When compared with acute cryptococcal meningitis.

• no statistical difference in mortality between those who had IRIS compared with those who did not (18 m follow-up)

IRIS of Cryptococcosis

- a retrospective chart review of 120 patients with cryptococcal disease who initiated combination ART
- 10 patients (11%) developed IRIS within a median of 8 months (range: 2-37 months) after initiating ART
- 3 of 10 patients with IRIS died.
- Risk of developing IRIS
  - Having previously undiagnosed HIV
  - CD4 count <7 cells/µL
  - starting ART within 2 months of cryptococcosis diagnosis

IRIS of Cryptococcosis: Implication

- Avoid prescribing ART within the first 2-3 months following the diagnosis of cryptococcosis.
- Closed monitoring few months after initiation of ART.
- However, there is no prospective data to support specific recommendations.
- Studies evaluating the timing of when to start ART in the setting of acute opportunistic infections are on-going.
**IRIS of Cryptococcosis: Long-term follow up**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, number (%)</td>
<td>31 (60)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>34.4 (6.9)</td>
</tr>
<tr>
<td>Median (range) CD4 cell count, cells/mm³</td>
<td>26 (1-93)</td>
</tr>
<tr>
<td>Median (range) time of ART initiation after diagnosis of cryptococcal meningitis, months</td>
<td>2.6 (0.8-2.6)</td>
</tr>
<tr>
<td>ART regimen, number (%)</td>
<td></td>
</tr>
<tr>
<td>NNRTI-based regimen</td>
<td>50 (96)</td>
</tr>
<tr>
<td>PI-based regimen</td>
<td>2 (4)</td>
</tr>
<tr>
<td>At 6 months of ART</td>
<td></td>
</tr>
<tr>
<td>Median (range) CD4 cell count, cells/mm³</td>
<td>121 (59-203)</td>
</tr>
<tr>
<td>Achieve HIV RNA &lt;50 copies/mL, number (%)</td>
<td>46 (88)</td>
</tr>
<tr>
<td>At 12 months of ART</td>
<td></td>
</tr>
<tr>
<td>Median (range) CD4 cell count, cells/mm³</td>
<td>237 (87-302)</td>
</tr>
<tr>
<td>Achieve HIV RNA &lt;50 copies/mL, number (%)</td>
<td>41 (79)</td>
</tr>
</tbody>
</table>

IRIS of Cryptococcosis: Long-term follow up

- 52 patients with cryptococcal meningitis received ART.
- median (range) follow-up period of 15.7 (7.9-54.0) m.
- 10 patients (19%) developed cryptococcal IRIS at a timing of 3.0-27.3 months after initiation of ART.
- median time to develop this syndrome was 9.9 (95% CI, 3.9-17.9) m.
- cumulative 25% and 75% occurrence of cryptococcal IRIS were at 8.6 and 21.0 m.

IRIS of Cryptococcosis: Long-term follow up

• From Cox proportional hazard model including
  - baseline CD4
  - baseline HIV RNA
  - fungemia at baseline
  - cryptococcal antigen titer
  - type of ART regimen
  - initiation of ART within 2 months of cryptococcosis,
  - CD4 and HIV RNA change at 6 and 12 months after ART

• there were no factors to predict the occurrence or timing of cryptococcal IRIS.

Summary

• Cryptococcosis is still common in developing countries
• Primary prophylaxis should be considered
• EFV-based and NVP-based ART are safe in patients with cryptococcosis and receiving fluconazole
• IRIS is common and can occur at a wide period of time
• Closed monitoring after initiation ART
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