Practical Management of OIs

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Outline

- Common problems in clinical practice
- Q&A
- Summary

Management of HIV-OIs

- Screening
  - OIs
  - Co-infections: HBV, HCV and syphilis
- Prophylaxis
- Diagnosis
- Treatment
- Antiretroviral regimen
- Monitoring

Question

True or False?

- Routine use of serum cryptococcal Ag screening and antifungal primary prophylaxis are recommended in the ART-naïve patients with CD4<100 cells/mm^3

A. True

B. False

Question

- Serum cryptococcal Ag screening
  - High risk case (CD4 < 100 cells/mm^3) AND
  - High prevalent area i.e. South Africa and Asia
    - >3% of prevalence of cryptococcal antigenemia
    - Cost-effective method
- Antifungal primary prophylaxis
  - Lack of survival benefit
  - No routine recommendation

WHO Guideline 2011 DHHS Guideline 2016

OIs Screening and Prophylaxis

Screening

- CXR (all cases)
- If CD4 <100 cells/mm^3:
  - Serum cryptococcal Ag
  - Indirect ophthalmoscope for CMV

Primary prophylaxis

- Co-trimoxazole
  - CD4 <200 cells/mm^3
  - CD4 <14%
  - Oral candidiasis
  - AIDS defining illness
- Start After ART 2-4 wks
- Other OIs primary prophylaxis: optional

Thai Guideline 2017

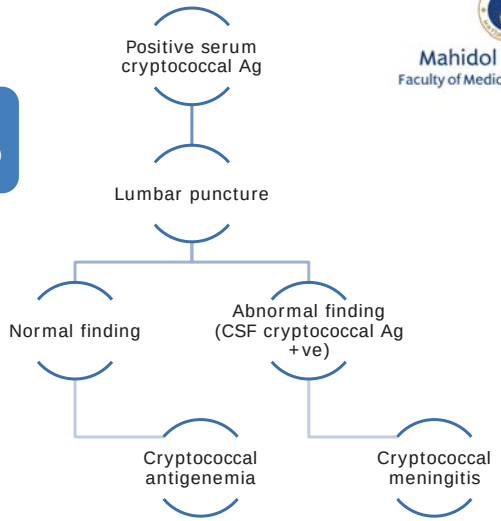
Question

- A 30 YOM with the first diagnosed of HIV
  - Asymptomatic, His CD4 80 cells/mm3
  - CXR –ve, cryptococcal Ag +ve
  - HBs Ag –ve, anti-HCV Ab –ve and VDRL –ve
- Will you perform a lumbar puncture for this case?

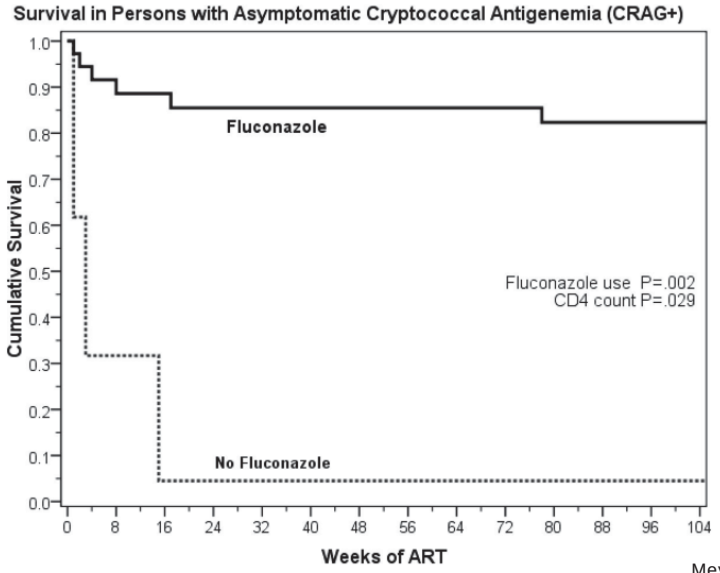
  A. Yes

  B. No

Highly predictive disease
Serum CrAg detection before symptomatic meninigitis develop median 22 d (5-234 d)
Prevent to disease progression



French et al, AIDS 2002 Thai guideline 2017



Meya et al, CID 2010

Cryptococcal Antigenemia

Treatment	Fluconazole 800 mg/d for 2 wks then 400 mg/d for 8 wks (total 10 wks)	ART after 2 wks of antifungal treatment	After 10 wks of treatment; fluconazole 200-400 mg/d until complete 1 y of therapy and CD4 > 100 cells/mm3 for 3 mo

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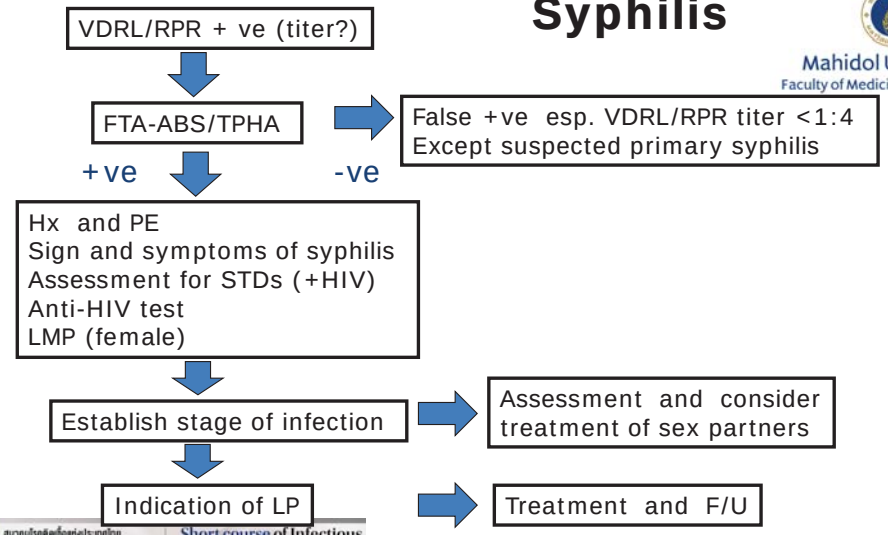
Question

- A 30 YOM with the first diagnosed of HIV
  - Asymptomatic, His CD4 350 cells/mm^3
  - CXR –ve
  - HBs Ag –ve and anti-HCV Ab –ve
  - VDRL 1:16 and TPHA +ve
- Will you perform a lumbar puncture for this case?

  A. Yes

  B. No

Syphilis



STD Guideline 2015

Syphilis: Lumbar puncture

- Neurologic, ophthalmic, or otic signs and symptoms
- Active tertiary syphilis
- Treatment failure
  - Sustained ≥ 4-fold increase of titer (> 2 wks)
  - High titer (≥1:32) fails to decline ≥ 4-fold within 12–24 mo of therapy
  - Signs or symptoms develop

Syphilis in HIV

- Atypical presentation
  - Severe or neurological involvement
- Modified serologic response
  - False negative and false positive test
- Treatment failure
  - More frequent F/U (q 3 mo during the first year after treatment)
- LP is not routinely indicated in all HIV cases

Question

- Which of the following is **NOT** diagnostic method of active tuberculosis?
  - A. AFB
  - B. Interferon Gamma Releasing Assay
  - C. GeneXpert MTB/RIF
  - D. Lipoarabinomannan (LAM)

Diagnosis of TB in HIV

Tests	Sensitivity	Specificity	Remarks
Active TB			
AFB	low	low	
CXR	✓	low	
Culture	✓	✓	✓DST
GeneXpert	✓	✓	✓DST, RIF
LAM	low	✓	CD4<100, urine
Latent TB			
TST	medium	✓	
IGRA	medium	✓	

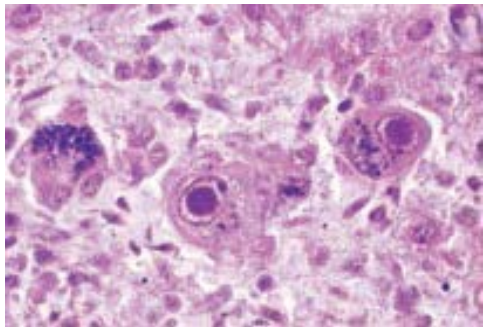
Question

- Which of the following is the most likely diagnosis of CMV disease?
  - A. CMV viremia ~ 50,000 copies/mL
  - B. Positive serum CMV Ab
  - C. Positive CMV culture in BAL
  - D. Positive CMV PCR in CSF

Diagnosis of CMV in HIV

Samples	Tests	Remarks
Blood	CMV Ag, PCR, and culture CMV Ab	No recommendation for diagnosis of CMV end-organ disease
CSF	PCR	Highly suggestive CMV disease
Aqueous or vitreous fluid	PCR	Highly suggestive CMV disease (CMV retinitis is clinical diagnosis)
Respiratory sample	Cytology Histopathology	Presence of characteristic intranuclear and intracytoplasmic inclusions
GI sample	Histopathology	Presence of characteristic intranuclear and intracytoplasmic inclusions
Positive CMV culture is insufficient to establish the diagnosis of CMV disease*		

DHHS Guideline 2016



Owl's eye

Diagnosis of Other OIs

OIs	Remarks
PCP	Induced sputum: sens. 55-78% spec. 100% BAL: sens. 90-98% spec. 100% 1,3 BDG: sens. 93% spec. 75% PCR: increased sensitivity
Cryptococcosis	Cryptococcal Ag (LFA): sens. 99% (CSF) > 95% (blood) > 70% (urine) Culture- gold standard
Toxoplasmosis	Toxoplasma IgG +ve > 90% PCR: sens. 50-80% spec. 100% Histopathology- gold standard

Question

- A 30 YOF HIV with suspected severe PCP has no response to a combination of co-trimoxazole and corticosteroid for 3 days
- What should you do next?
  - A. Bronchoscopy with BAL
  - B. Switching to another regimen
  - C. Continue the previous regimen

Question

- Response of PCP: >4-8 days after treatment
  - Patients often worsen within the first 3-5 days
- Treatment failure: Clinical RS & ABG
  - Concomitant infections
    - Bronchoscopy with BAL
  - Drug toxicity
    - Switching to another regimen
  - Lack of drug efficacy (10%)
    - No correlation with DHPS mutation

DHHS Guideline 2016

Salvage Treatment of PCP

Salvage treatment of PCP

- No consensus guideline for co-trimoxazole non-responsive PCP

Meta-analyses

- Clindamycin and primaquine: First choice (superior efficacy)
- Pentamidine: comparable efficacy and more frequent toxicity

Case reports

- Caspofungin plus other agents i.e. co-trimoxazole (data from non-HIV cases)

ECIL Guideline 2016 DHHS Guideline 2016

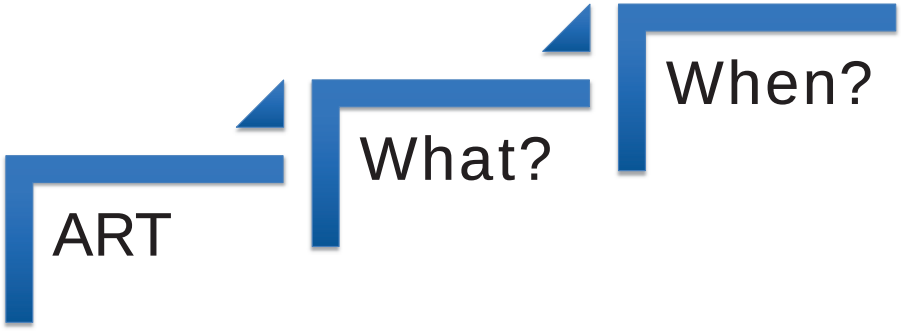
Question

- A 30 YOF HIV with disseminated TB and history of ART failure (AZT/3TC/NVP)
- She receives anti-TB (IRZE) for 2 wks
- Her CD4 17 cells/mm^3
- What is your ART choice?
  - A. Start TDF/3TC + LPV/r ASAP
  - B. Start TDF/3TC + EFV ASAP
  - C. Start TDF/3TC + RAL ASAP

Question

- A 30 YOF HIV with cryptococcal meningitis
- She receives amphotericin B and fluconazole for 2 wks with clinically improved and F/U CSF culture is negative
- Her CD4 50 cells/mm^3
- When will you initiate ART in this case?
  - A. After 2 wks of antifungal agents
  - B. After 5 wks of antifungal agents
  - C. After 10 wks of antifungal agents

ART for HIV-OIs



Short course of Infectious Diseases of the Year 2017

What to Start ART

Patient / Regimen characteristics	Clinical Settings	Considerations
Presence of co-infections	HBV	TDF or TAF + FTC or 3TC
	HCV	Avoid AZT, ddI, d4T (depend on HCV treatment)
	TB	If rifampicin is used: (decreased PIs level 90%) - EFV (600 mg/d) - NVP (200 mg bid, no lead-in) - RAL (400-800 mg bid; use RAL TDM) - DTG (50 mg bid; no INSTI resistance) - MVC 200 mg bid (Avoid uses: PIs, cobi, ETR, RPV and TAF) If PIs-based is selected: - Rifabutin or FQs

DHHS Guideline 2016 EACS 2016 Thai guideline 2017

When to Start ART

Active OIs	CD4 count (cells/mm^3)		
	< 50	≥ 50	
		Severe**	Non-severe
Tuberculosis*	≤2 wks (up to 4 wks)	≤2 wks (up to 4 wks)	2-8 wks
Cryptococcal meningitis***	4-6 wks		
PCP/MAC/others	2-4 wks		
CMV/PML/cryptoporidiosis	As soon as possible		

*CNS TB: Start ART after 2 wks of TB treatment (early ART: increased co-toxicity (G3&4), severe IRIS, no survival benefit; HR 1.12 95% CI 0.81-1.55, p =0.52)

**Severe TB: disseminated TB, low BW, low albumin, anemia

***Cryptococcal meningitis: Early ART (< 2 wks) vs. Late ART (5 wks): 6 mo MR 45% vs. 30% (p=0.03). (Delay ART if increased ICP or CSF WBC < 5 cells/mm^3)

Thai Guideline 2014 DHHS Guideline 2016 Thai guideline 2017

Question

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- A 30 YOF HIV with CMV retinitis and colitis
- She receives IV ganciclovir for 3 wks and ART(TDF/FTC/EFV) for 2 wks with clinical response
- Her initial CD4 17 cells/mm^3
- What is your next management?
  - A. Stop anti-CMV treatment, continue ART
  - B. Continue anti-CMV treatment and ART

Treatment of CMV in HIV

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Diseases*		Induction phase	Maintenance phase	Stop anti-CMV treatment
CMV retinitis	Central (impend-ing sight loss)	Intravitreal ganciclovir **PLUS** systemic agents (oral or IV) for 14-21 d	Continue anti-CMV treatment at least 3-6 mo	- Complete duration of treatment **AND** - Inactive lesions **AND** - CD4>100 cells/mm^3 for 3-6 mo in response to ART - If CD4<100 cells/mm^3 reinstitute maintenance therapy
	Peripheral	Oral valganciclovir or IV ganciclovir for 14-21 d		
CMV diseases	GI, RS, CNS	IV ganciclovir for 21-42 d	None	Resolved signs and symptoms

* CMV replication is controlled within 1-2 wks after anti-CMV treatment; early ART (< 2wks) is recommended

DHHS Guideline 2016

Question

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- A 30 YOF HIV with initial CD4 17 cells/mm3
- He never has any episodes of OIs
- She receives ART(TDF/FTC/EFV) for 2 years with PCP primary prophylaxis
- Her current CD4 150 cells/mm^3
- What is your next management?
  - A. Continue PCP primary prophylaxis
  - B. Stop PCP primary prophylaxis

Stop OIs prophylaxis

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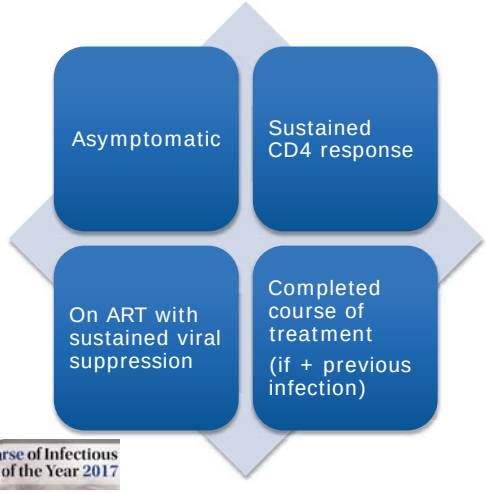


OIs prophylaxis

OIs	Criteria for Initiating Primary Prophylaxis	Criteria for Discontinuing Primary Prophylaxis	Criteria for Restarting Primary Prophylaxis	Criteria for Initiating Secondary Prophylaxis	Criteria for Discontinuing Secondary Prophylaxis	Criteria for Restarting Secondary Prophylaxis
PCP	CD4 < 200	CD4 > 200 for 3 mo	CD4 < 200	Prior PCP	CD4 > 200 for 3 mo	CD4 < 200
Toxoplasmosis	CD4 < 100	CD4 > 200 for 3 mo	CD4 < 100–200	Prior TE	CD4 > 200 for 6 mo and completed therapy and asymptomatic	CD4 < 200
MAC	CD4 < 50	CD4 > 100 for 3 mo	CD < 50–100	Documented disseminated disease	CD4 > 100 for 6 mo and completed 12 mo of MAC treatment and asymptomatic	CD4 < 100
Cryptococcosis	CD4 < 100	CD4 > 100 for 3 mo	CD4 < 100	Documented disease	CD4 > 100 for 3 mo and completed 12 mo of therapy and asymptomatic	CD4 < 100-200
CMV	None	N/A	N/A	Documented end-organ disease	CD4 > 100 for 3-6 mo and completed therapy and no evidence of active disease	CD4 < 100

DHHS Guideline 2016 Thai Guideline 2017

PCP Prophylaxis: Current Evidences

Discontinuation of PCP prophylaxis if CD4 < 200 cells/mm^3

- Discontinuation of primary PCP prophylaxis
  - CD4 count >100 cells/mm^3
  - On ART with suppressed HIV viral load
- Discontinuation of secondary PCP prophylaxis
  - No consensus recommendation from the current evidences

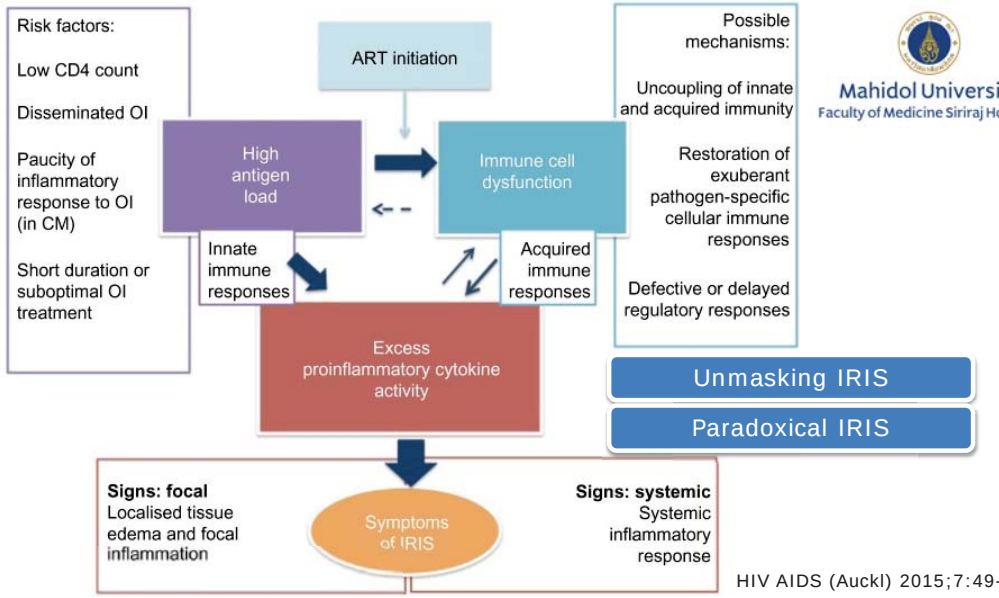
Thai guideline 2017

- Discontinuation of primary PCP prophylaxis
  - CD4 100-200 cells/mm^3 and sustained viral suppression > 1 y

COHERE. CID 2010;51:611-9 Ann Pharmacother 2015; 49:1343-8 Thai Guideline 2017

Question

- A 30 YOF HIV CD4 33 cells/mm^3 with pulmonary TB is treated with IRZE, At first there is a good response
- 2 wks after starting treatment he's getting fever, cervical lymphadenopathy and dyspnea
- What is your differential diagnosis?
  - A. Poor compliance
  - B. Resistant organisms
  - C. IRIS
  - D. Other OIs
  - E. All of above



HIV AIDS (Auckl) 2015;7:49-64

Common IRIS

	TB-IRIS	Cryptococcal-IRIS
Incidence	2-54%	13-45%
Key risk factors	Shorter interval between anti-TB and ART Disseminated TB Low CD4 count prior to ART	High fungal burden (fungemia, high CrAg titer) Lack of CNS inflammation prior to ART
Onset	<3 mo (median 14 days)	<12 mo (median 4-9 wks)
DDx	Drug-resistant TB Drug toxicity Another OI Poor adherence to therapy	Relapse cryptococcal meningitis Fluconazole resistance Another OI Poor adherence to therapy
Investigations	Culture and DST Molecular tests for DR	Culture and DST CrAg titers are not helpful
Treatment	Moderate-severe cases: Prednisolone 1.5 mg/kg for 14 d then 0.75 mg/kg for 14 d (RCT data)	Optimize antifungal treatment Management of increased ICP Steroid of severe or refractory (no support evidence)

HIV AIDS (Auckl) 2015;7:49-64

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