Neurologic Complications of HIV

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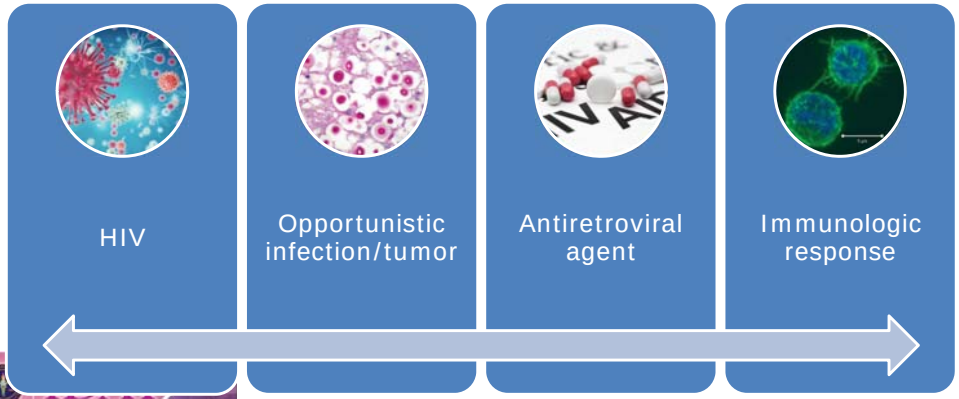
Outline

- Clinical problems
- Q&A
- Summary

Neurologic Complications of HIV



Question

- Which of the following is the **MOST** prevalent HIV-related neurologic condition?
  - A. HIV-related aseptic meningitis
  - B. HIV-related AIDP
  - C. HIV distal sensory polyneuropathy
  - D. HIV-associated dementia

Question

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- Which of the following is the **MOST** likely condition that required ART for its treatment?
  - A. HIV-related aseptic meningitis
  - B. HIV-related AIDP
  - C. HIV distal sensory polyneuropathy
  - D. HIV-associated dementia
  - E. All of the above

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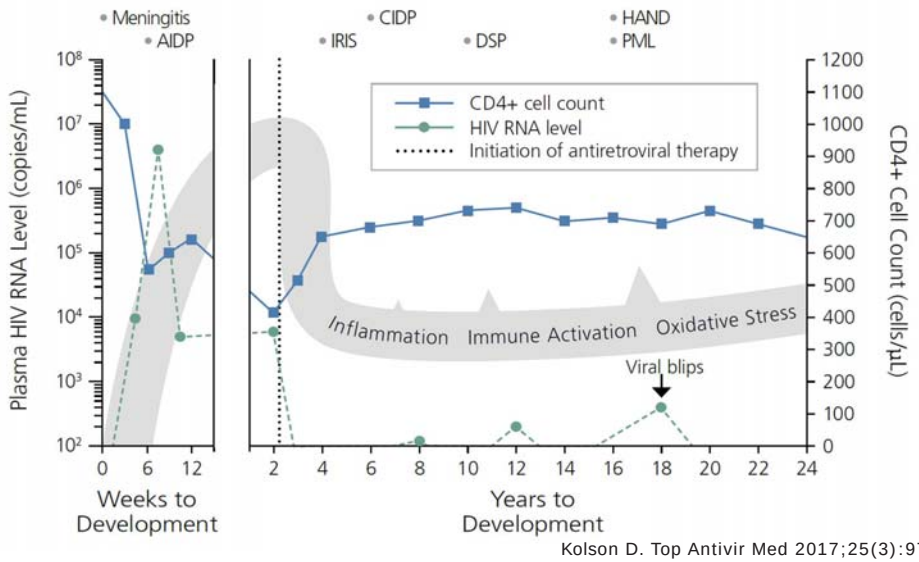

Kolson D. Top Antivir Med 2017;25(3):97-101

HIV-related Neurologic Disorders

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Conditions	Stage	Prevalence	Characteristics	Treatment
Aseptic meningitis	early	1-2%	Occur 10-20 d after infection	Self-limited (2-4 wks)
AIDP (GBS-like)	early	1%	Occur 3-4 wks after infection Cellular CSF!!	IVIG, PE
CIDP	late	<1%	Occur >1 y of infection Chronic, relapse	IVIG, PE, steroid
DSP	late	30-50%	Axonal neuropathy (painful) (Sensory >>>motor)	AEDs, capsaicin
HAND	late	20-70%	Cognitive impairment (ANI, MND, HAD)	ART
Myelopathy	Any	rare	Vacuolar myopathy (painless, T level)	ART?
Myopathy	Any	rare	Polymyositis	Corticosteroid?

Carroll A, et al. F1000Res 2017;6:312 Kolson D. Top Antivir Med 2017;25(3):97-101

HIV-associated Neurocognitive Disorder (HAND)

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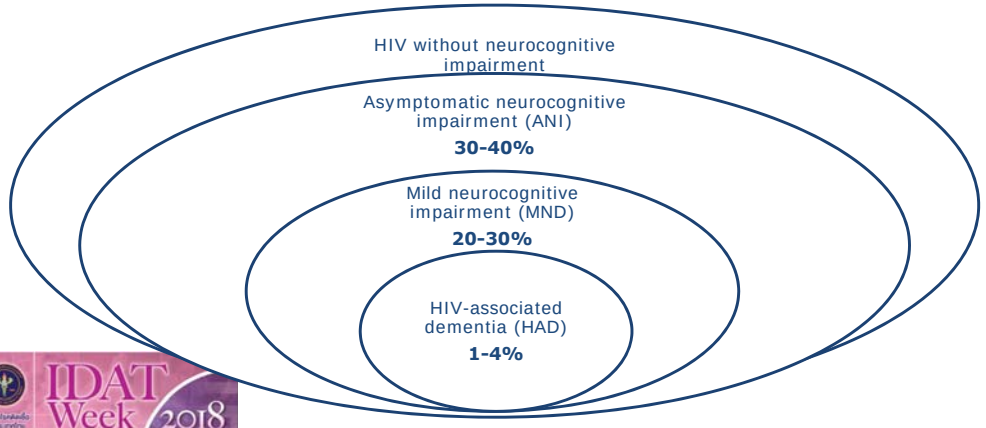

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Heaton RK, et al. Neurology 2010;75(23):2087-96 Kolson D. Top Antivir Med 2017;25(3):97-101

HIV-associated Neurocognitive Disorder (HAND)

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	No pre-existing cause	No delirium	Acquired impairment in ≥2 cognitive functions	Interfere with daily functioning
ANI	√	√	√	No
MND	√	√	√	Mild
HAD	√	√	Marked	Marked

- Neuropsychological test
- Brain MRI: cortical atrophy, diffuse abnormal signals
- CSF study
- W/U other causes: depression, delirium, OIs/tumor

Heaton RK, et al. Neurology 2010;75(23):2087-96

HAND and ART

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- ART shows clinical benefit in HAD
  - ↓incidence of HAD, ↑survival
- No clinical benefit of ART in ANI and MND
- Early ART in HAND is controversial
- ART regimen consideration
  - Standard effective ART is recommended
  - High CNS penetration effectiveness (CPE) drugs is not routinely recommended
  - Avoidance of EFV in HAD

Underwood J, et al. Curr HIV/AIDS Rep 2016;13(5):235-40

Management of HAND

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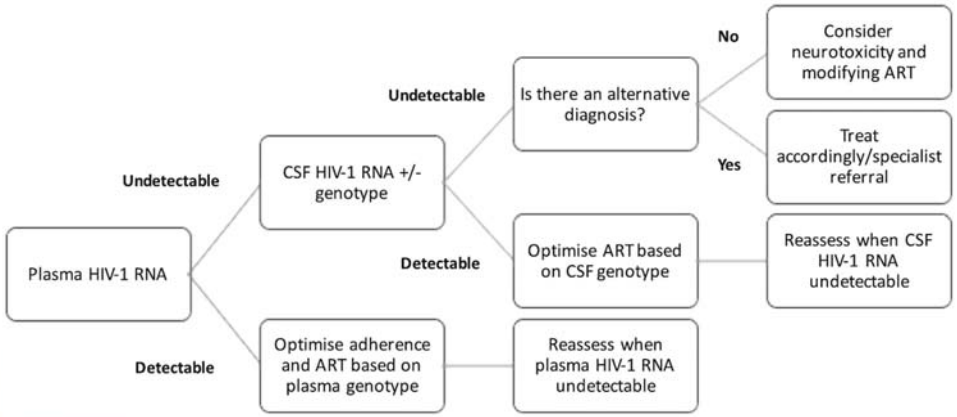

Underwood J, et al. Curr HIV/AIDS Rep 2016;13(5):235-40

CNS-OIs/Tumor

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- Common problem in Thailand with high M&M
- Atypical manifestations
- Multiple CNS OIs can be found
- Approach
  - Clinical presentations
  - Stage of HIV/ CD4 status
  - Imaging
  - Lumbar puncture

CNS-OIs/Tumor

Space occupying lesions	Meningitis
Toxoplasmosis	**Cryptococcal meningitis**
TB	**TB**
Cryptococcoma	**Syphilis**
PML	**Bacteria**
PCNSL	***S. pneumoniae***
	L. monocytogenes
	Virus (+HIV seroconversion)

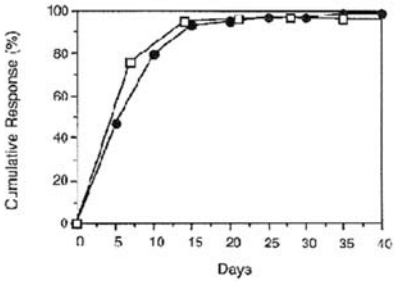
BHIVA Guideline 2011

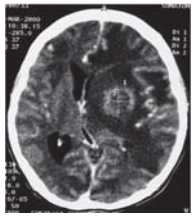
Cerebral Toxoplasmosis vs. PCNSL

	Toxoplasmosis	PCNSL
Size	<4 cm	>4 cm
Numbers	Multiple	Solitary or few
Distribution	Basal gg., grey-white interface	Periventricular
Hemorrhage	+	+/-
Edema	+++	+
Enhancement	Ring, thin wall	Irregular, thick wall
Leptomeningeal or ependymal enhancement	No	Yes
CT	Hypodense/isodense	Hyperdense
SPECT/PET	Normal/low metabolism	Increased metabolism

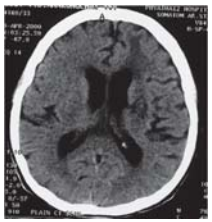
Provenzale JM, Radiol Clin North Am 1997;35(5):1127-66 BHIVA Guideline 2011

Cerebral Toxoplasmosis





Before Rx



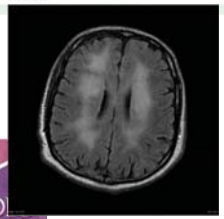
After Rx

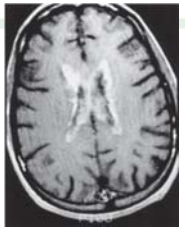
- Response ≈90% at 14 d with anti-toxoplasma agents
- ↓ size or ↓number
- ≠ edema or enhancement

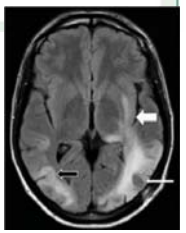
Porter SB, et al. N Engl J Med 1992;327(23):1643-8

HAD vs. CMV vs. PML

	HIV-D	Cytomegalovirus encephalitis	Progressive multifocal leucoencephalopathy
Features	Memory disturbances, mental slowing, gait disturbances	Delirium, seizures, brainstem signs	Focal neurological signs
Course	Several months	Days to weeks	Weeks to months
MRI	Diffuse atrophy, symmetrical deep white-matter diffuse hyperintensities	Normal or periventriculitis	Scattered, asymmetrical subcortical white-matter lesions
CSF	Non-diagnostic: immune activation less marked in patients treated with HAART	PCR+ for cytomegalovirus 90%	PCR+ for JC/BK virus 60%







McArthur JC, et al. Lancet Neurol 2005;4(9):543-55 Vieira DR, et al. Dement Neuropsychol 2016;10(2):165-7

CSF Findings in Common HIV-related CNS Conditions

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CSF	Opening pressure	Protein	Cell count	Microscopy	Culture
Cryptococcal meningitis	Very high	Slightly elevated or normal	Slightly elevated or normal	+ India ink stain	+
TB meningitis*	High or normal	Slightly elevated to very high	Elevated (lymphocytes predominate)	+/- - -	+/-
Toxoplasmal encephalitis	Normal	Normal or slightly elevated	Normal	-	-
HIV/PML/CMV*	Normal	Slightly elevated or normal	Slightly elevated or normal	-	-
Lymphoma	Normal	Normal	Normal	-	-

* PMN predominate in CSF: CMV radiculitis or early TB meningitis

DHHS Guideline 2017

Question

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Which of the following statements regarding HIV and PML is **TRUE**?

A. PML lesions on MRI are always non-enhancing
B. The most sensitive and specific test for PML is CSF JCV PCR
C. Seizure is a common presentation of PML
D. ART has been shown to improve PML survival in HIV

PML in HIV

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- Focal demyelinating lesions (oligodendrocyte!!)
  - Occipital, frontal, parietal, cerebellar, deep white matter> spinal cord > optic nerve
- Insidious & steady progression (JCV reactivation)
  - Headache, fever – uncommon (other OIs?)
  - Seizure: 10-20%
- MRI: white matter lesions and no mass effect
- CSF PCR JCV DNA: +ve 70-90% (no ART), 60% (ART)
- Without ART: mean survival only 3-6 mo

DHHS Guideline 2017

Treatment of PML in HIV

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- ART should be started immediately
  - Prognosis: >50% no disease progression (survival 2.5 y)
  - High CPE ART?
    - No established effectiveness
    - Systemic effect > CNS effect
  - Others (cytarabine, cidofovir, etc): no recommendation
    - 5HT2a receptor blocker i.e. mirtazapine (block JCV)
- PML-IRIS
  - Lesions: edema, mass effect, enhancement
  - May require the corticosteroid treatment

DHHS Guideline 2017

Question

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Which of the following statements is **FALSE**?

A. Suggestive MRI finding of CMV encephalitis is periventricular enhancement
B. CSF CMV PCR is the gold standard for identifying CNS CMV infection
C. CMV encephalitis in HIV can be treated with ganciclovir, foscarnet, or cidofovir
D. ART should be delayed until 2-4 wks of anti-CMV treatment

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CMV Infection of the CNS

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Diseases	Characteristics
Dementia	o Lethargy, confusion, fever o CSF finding: Lymphocytic pleocytosis and low-to-normal glucose & normal-to-elevated protein levels
Ventriculoencephalitis	o More acute course o Focal neurologic signs, CN palsy, nystagmus o Rapid progression to death o MRI/CT: periventricular enhancement
Polyradiculomyelitis	o Progressive lower extremity weakness (~GBS), pain, spasticity, areflexia, urinary retention & hyporethesia o CSF finding: PMN pleocytosis and low glucose level
Polyneuropathy	o Non-specific, similar to other causes

Drew WL, Lalezari JP. Cytomegalovirus and HIV 2006

ART for HIV-OIs

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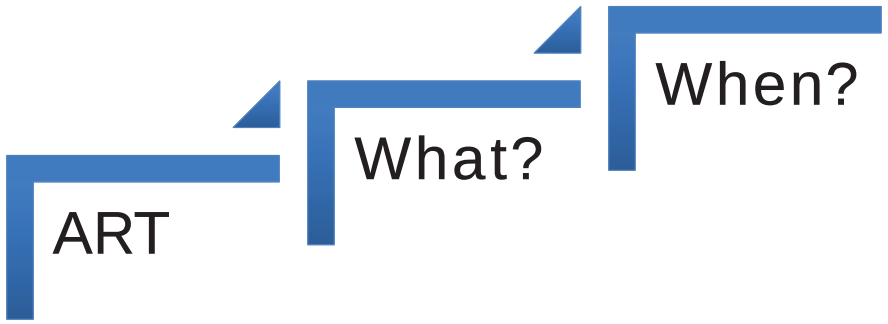

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What to Start ART in CNS OIs

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Patient/ Regimen characteristics	Clinical Settings	Considerations
Presence of OIs	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) (Avoid uses: PIs, cobi, ETR, RPV and TAF) If PIs-based is selected: - Rifabutin or FQs
	Others	Use standard effective ART

DHHS Guideline 2017 EACS 2017 Thai guideline 2017

When to Start ART in CNS OIs

Active OIs	Time to start ART
Tuberculous meningitis*	≥2 wks
Cryptococcal meningitis**	≥5 wks
Toxoplasmosis	2-3 wks
CMV***/PML/PCNSL	As soon as possible

*CNS TB: Start ART after 2 wks of TB treatment (early ART: increased co-toxicity, severe IRIS, no survival benefit)

**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)

***CMV replication is controlled within 1-2 wks after anti-CMV treatment; early ART (<2 wks) is recommended (Rate of CMV IRIS 0.04/person-year)

Thai Guideline 2014 DHHS Guideline 2017 Thai guideline 2017

Question

- Which of the following is **CORRECT** about ART-related neurologic complications?
  - A. AZT: myopathy
  - B. d4T: peripheral neuropathy
  - C. TPV: intracerebral hemorrhage
  - D. RTV: circumoral paresthesia
  - E. All of the above

ART-related Neurologic Complications

ART	Clinical findings	Comments
NRTIs	o Peripheral neuropathy o d4T, ddI (10-30%) >> others (mitochondrial toxicity)	o Distal symmetrical sensory (painful) neuropathy o Dose-dependent toxicity o Occur within 3-6 mo (LE>UE) o ≈HIV DSP (≠ high lactate level)
AZT	o Myopathy o 10-20% (mitochondrial toxicity)	o Proximal myopathy o Dose-dependent toxicity o Occur within 6-12 mo (thigh, calf) o ≈HIV myopathy o Pathology: ragged red fibers

Abers MS, et al. CNS Drugs 2014;28(2):131-45 DHHS Guideline 2017

ART-related Neurologic Complications

ART	Clinical findings	Comments
EFV	o CNS toxicity o 50% due to EFV o Uncommon in other NNRTIs (unknown mechanism)	o Acute effect: occur within 2-4 wks i.e. dizziness, anxiety, insomnia, agitation, nightmare (usually resolve within 6-8 wks) o Chronic effect: headache, loss of attention, mood disturbance o Others: forgetfulness, hallucination, depression o Discontinuation rate 2-8%

Abers MS, et al. CNS Drugs 2014;28(2):131-45 DHHS Guideline 2017

ART-related Neurologic Complications

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ART	Clinical findings	Comments
PIs	o Sensory neuropathy o Full dose RTV (600-1200 mg/d) o 10-25% >> others (unknown mechanism)	o RTV: circumoral paresthesia > dysgeusia > peripheral neuropathy o Dose-dependent toxicity o Occur within 4 wks o Reversible if dose reduction o Other PIs: dysgeusia o TPV: intracerebral hemorrhage
RAL	o Myopathy o 5-20% (unknown mechanism)	o Idiopathic myopathy (mild, self-limited) > proximal myopathy o Rhabdomyolysis (rare)

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Abers MS, et al. CNS Drugs 2014;28(2):131-45 DHHS Guideline 2017

Question

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- A 30 YOM HIV CD4 30 cells/mm^3 with tuberculous meningitis is treated with IRZE and TDF/FTC/EFV
- 2 wks after ART, he develops high fever and headache
- What is your differential diagnosis?
  - A. Poor compliance
  - B. Resistant organisms
  - C. IRIS
  - D. Other OIs
  - E. All of above

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IRIS Pathogenesis

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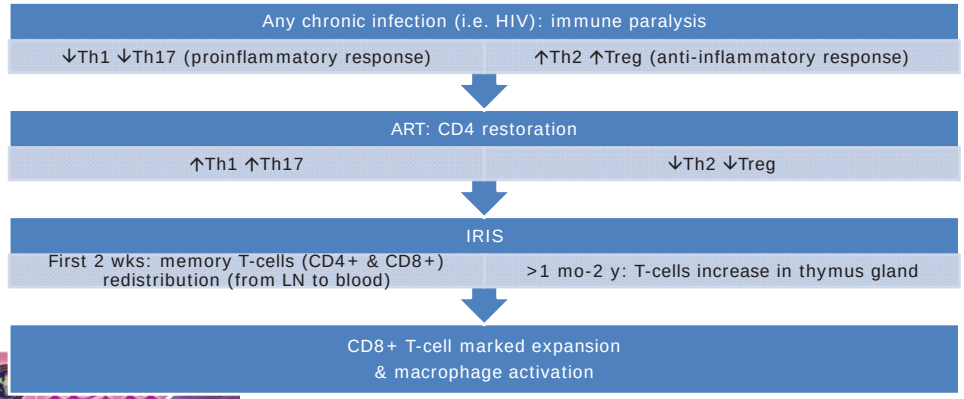

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Sun HY, et al. Curr Opin Infect Dis 2009 ;22(4):394-402

Immune Reconstitution Inflammatory Syndrome (IRIS)

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- Common CNS-IRIS:
  - TB CNS-IRIS
  - Cryptococcal meningitis (CM)-IRIS
  - PML-IRIS
- Uncommon CNS-IRIS:
  - Toxoplasmosis encephalitis-IRIS
  - CMV CNS-IRIS
  - CD8+ T-cell encephalitis (no organism found)

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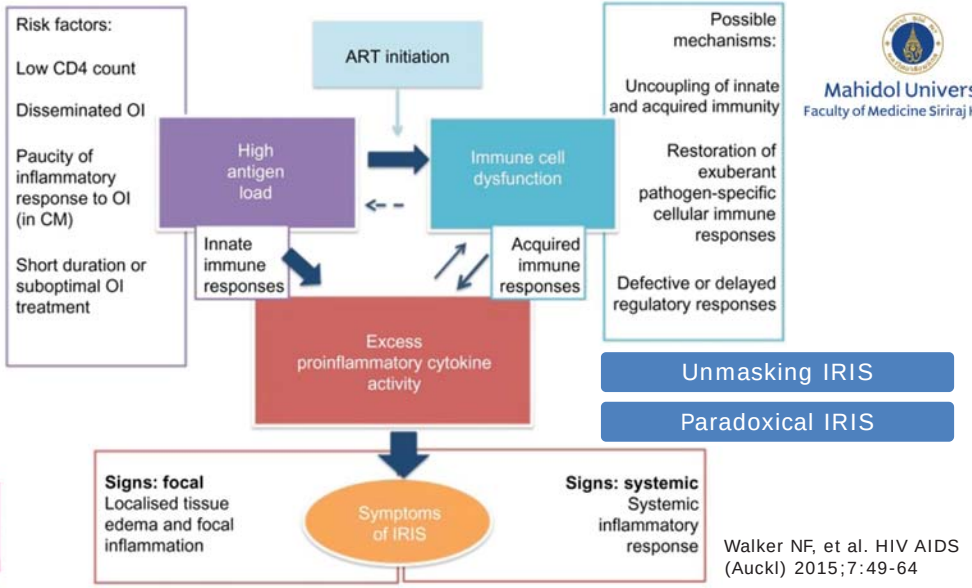
Walker NF, et al. HIV AIDS (Auckl) 2015;7:49-64 DHHS Guideline 2017



Walker NF, et al. HIV AIDS (Auckl) 2015;7:49-64

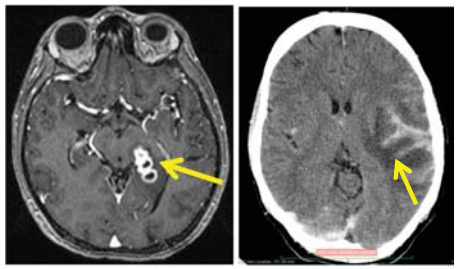
CNS-IRIS

	TB CNS-IRIS	CM-IRIS	PML-IRIS
Incidence	16%	20%	17%
Risk factors	o ↑PMN in CSF o CSF C/S +ve	o No WBC in CSF o H/C +ve o High CrAg titer	o Rapidly increased CD4 o Large lesion
Time after ART	<3 mo (median 2 wks)	<12 mo (median 4-10 wks)	<26 mo (median 4-6 wks)
Clinical features	New/worsening S&S, IICP	New/worsening S&S, IICP	New/worsening S&S, seizure
Investigations	o C/S –ve o CT/MRI↓ ✓ Enhancing/abscess	o C/S –ve o CT/MRI↓ ✓ Enhancing	o Biopsy (CD8↑) o CT/MRI↓ ✓ Enhancing
Treatment	Corticosteroids*	Corticosteroids?	Corticosteroids?
Mortality	13-30%	20-36%	22-32% (up to 50%)

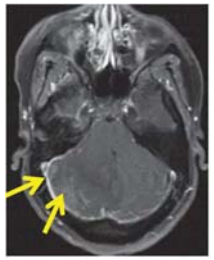
*Prednisolone 1.5 mg/kg for 14 d then 0.75 mg/kg for 14 d; tapering dose by clinical response (3-4 mo)

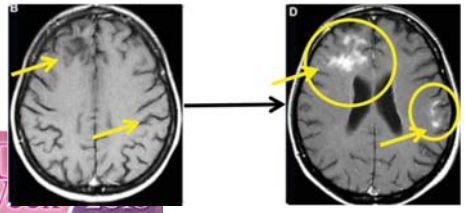
Walker NF, et al. HIV AIDS (Auckl) 2015;7:49-64

TB CNS-IRIS



CM-IRIS





PML-IRIS

Bahr N, et al. Curr Infect Dis Rep 2013 ;15(6):583-93

Neurologic Complication of HIV

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SiID 2018
Siriraj Infectious Disease Conference 2018
อัตราค่าลงทะเบียน
บุคคลภายในและภายนอกคณะฯ
ก่อน/ถึงวันที่ 31 มี.ค.61
ตั้งแต่วันที่ 1 เม.ย.61
อบรมระยะสั้น 26-27 พ.ค.61
2,500
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อบรมเชิงปฏิบัติ 28 พ.ค.61
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อบรมทั้ง 3 วัน
4,000
5,000
Siriraj Infectious Disease Conference 2018
26-28 May 2018
มหาวิทยาลัยมหิดล
SiID 2018
Siriraj Infectious Disease Conference 2018
การอบรมระยะสั้น
Management of Infectious Diseases : From Theory to Reality
26-27 พฤษภาคม 2561
8.00-17.00น.
การอบรมเชิงปฏิบัติ
การใช้ยาต้านจุลชีพอย่างสมเหตุผล : จากมาตรฐาน Rational Drug Use Hospital (RDU), Hospital Accreditation (HA) และ Joint Commission International (JCI) สู่การปฏิบัติ (Antimicrobial Stewardship Program: From RDU, HA, JCI Standards to Implementation)
28 พฤษภาคม 2561
8.00-17.00น.
ณ ห้องประชุมวิกาจ วิรานุวัตติ์
ตึกอัษฎางค์ ชั้น 4 ร.พ. ศิริราช กรุงเทพฯ