NERVOUS SYSTEM COMPLICATIONS OF HIV

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Disclosure

I HAVE NOTHING TO DISCLOSE

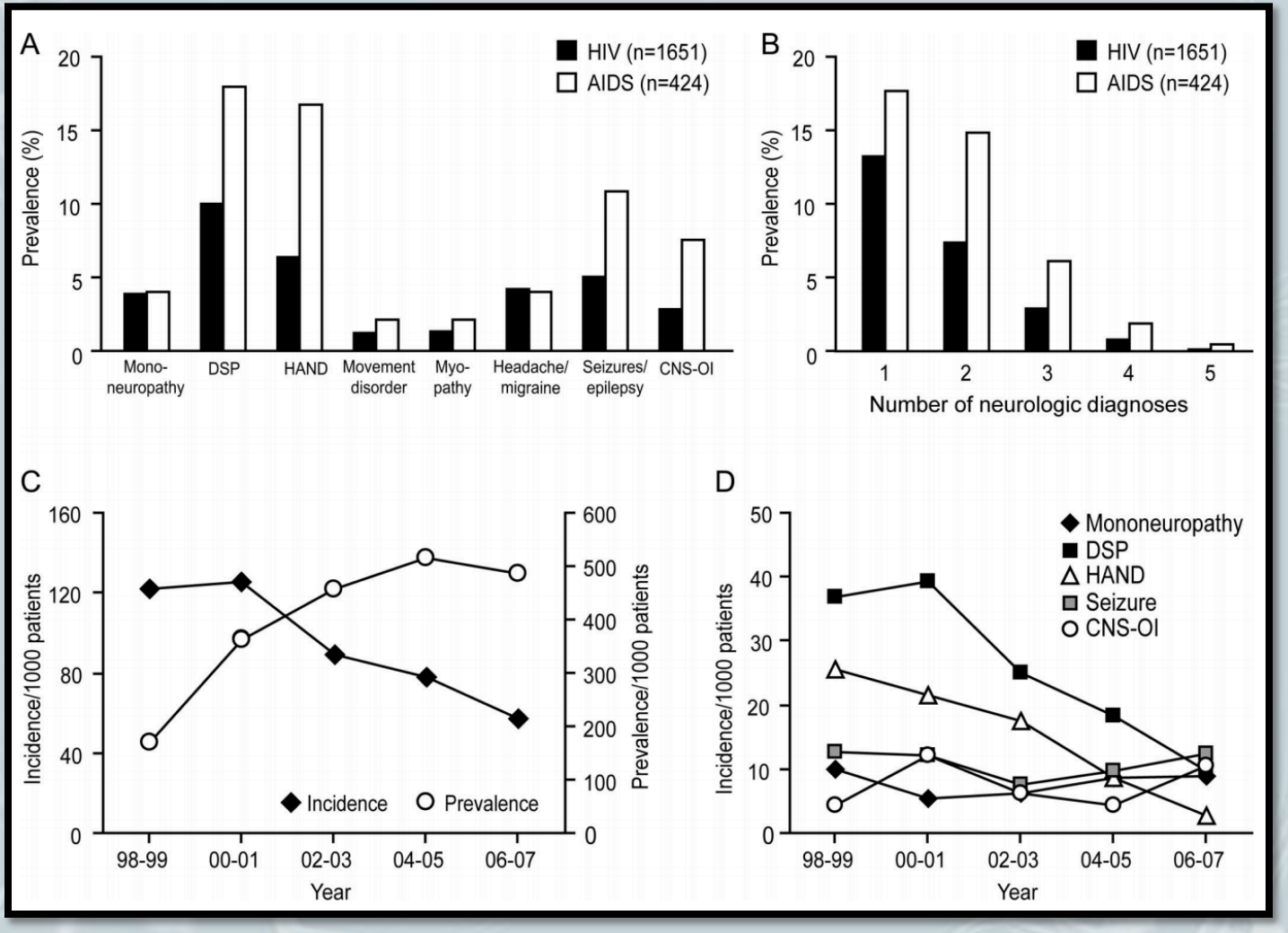
Outline

- Neurological Manifestations of HIV
- CNS Opportunistic Infections
- Clinical Scenarios
- HIV & Cognitive Impairment
- Peripheral & Toxic Neuropathy

Neurological manifestations of HIV/AIDS

Primary HIV neurologic disease (HIV is necessary and sufficient to cause the illness)	Secondary or opportunistic neurologic disease	Treatment-related neurologic disease
HIV dementia HIV vacuolar myelopathy HIV neuropathy Autoimmune	PML Toxoplasmosis TB meningitis Cryptococcus meningitis	IRIS NRTI-induced neuropathy

HIV Neurological Disease Prevalence



Vivithanaporn et al. Neurology 2010

Common CNS Opportunistic Infections Incidence

	Common CNS opportunistic infections
Asian and Pacific regions[3]	Cryptococcal meningitis, cerebral toxoplasmosis, tuberculous meningitis, Japanese encephalitis B
Sub-Saharan Africa[4]	Tuberculous meningitis, cryptococcal meningitis, cytomegalovirus, malaria
Europe and North America[2]	PML, toxoplasmic encephalitis, cryptococcal meningitis
South America[5]	Cerebral toxoplasmosis, tuberculous meningitis, cryptococcal meningitis; Chagas disease is reported in southern US states and South America[6]

PML=progressive multifocal leukoencephalopathy.

Tan et al. Lancet Neurol 2012

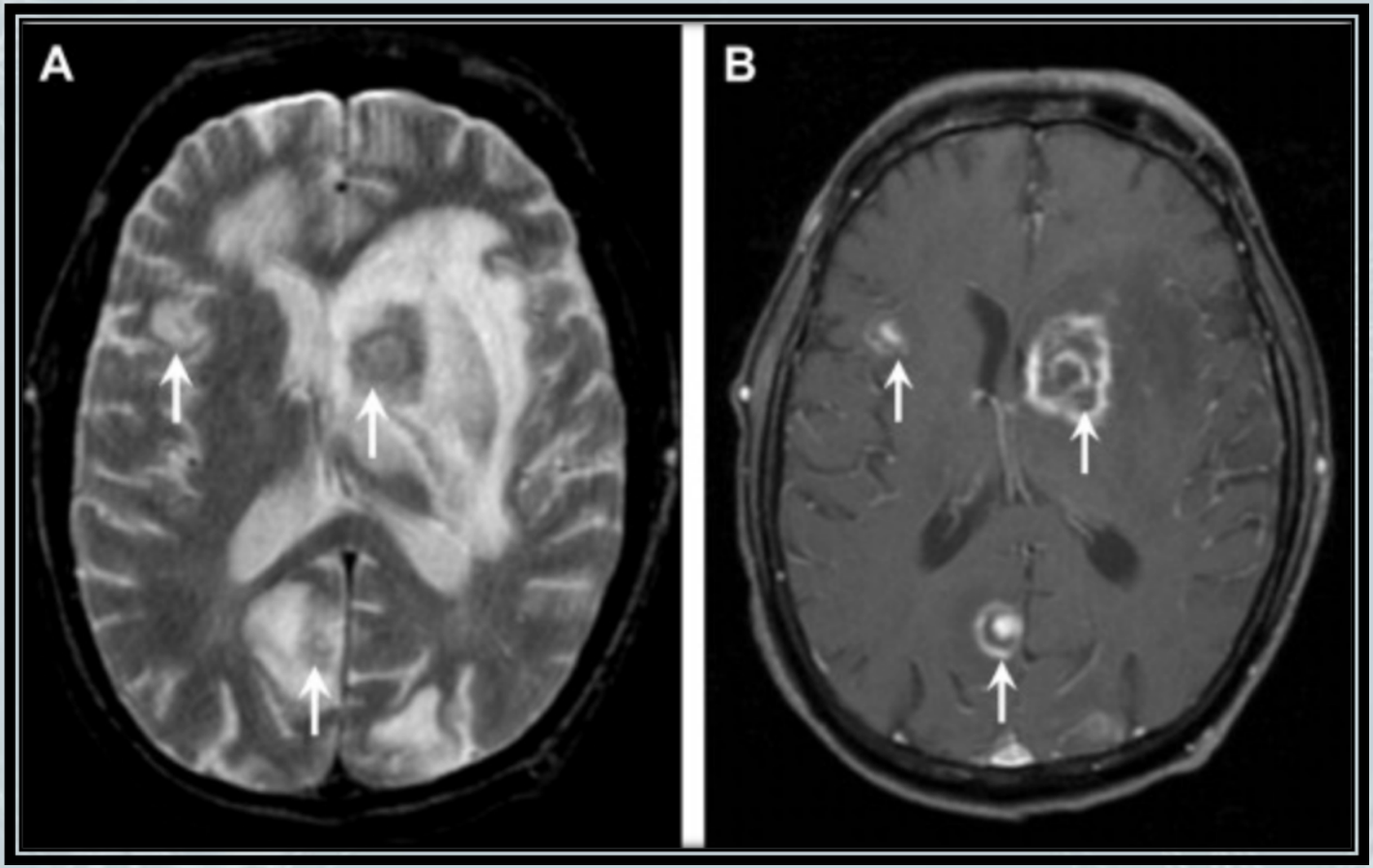
Clinical Case

- A 37 years old man with new diagnosis of HIV (CD4 90, viral load 35K)
- Presented with 1-month worsening of right sided weakness
- No fever, headache or neck stiffness
- Unable to work due to weakness

Physical Examination

- Thin, chronically-ill appearing man
- Appropriately interactive, language fluent
- Moderately spastic right sided weakness involving arm and leg
- Reflexes +3 at Biceps, Triceps, Knee
- Upgoing toe on right

MRI Brain



Focal Lesions Vs. Diffuse Disease in HIV

Focal Lesions	Diffuse Disease
Toxoplamosis	PML
CNS lymphoma	Cryptococcal meningitis
Tuberculoma	TB meningitis
Cryptococcoma	Acute HIV
Pyogenic abscess	CMV encephalitis
	Neurosyphilis
	HIV Dementia

Investigations

- Blood: RPR, CrAg, Toxo IgM antibody negative
- CSF: WBC 14, RBC 27, glucose 47, protein 55, VDRL, CrAg negative
- Micro: Blood cultures negative, CSF: Cultures negative

Toxoplasmosis

- Most common focal lesion in HIV patients in West
- Clinical presentation is variable
- Treat empirically and monitor for improvement
- Toxoplasmosis in HIV is reactivation of prior infection, e.g. IgM not helpful
- Serum IgG is positive in around 95% of patients
- Toxoplasma CSF PCR 35% sensitive, 100 % specific

Initiation of ART in Toxoplasmosis

- When do we initiate the treatment?

A. Immediately

B. After two weeks with close observation

C. Wait for 4-6 weeks before initiating ART given the risk of IRIS

D. Preferable to wait until the lesions resolve radiologically

IRIS

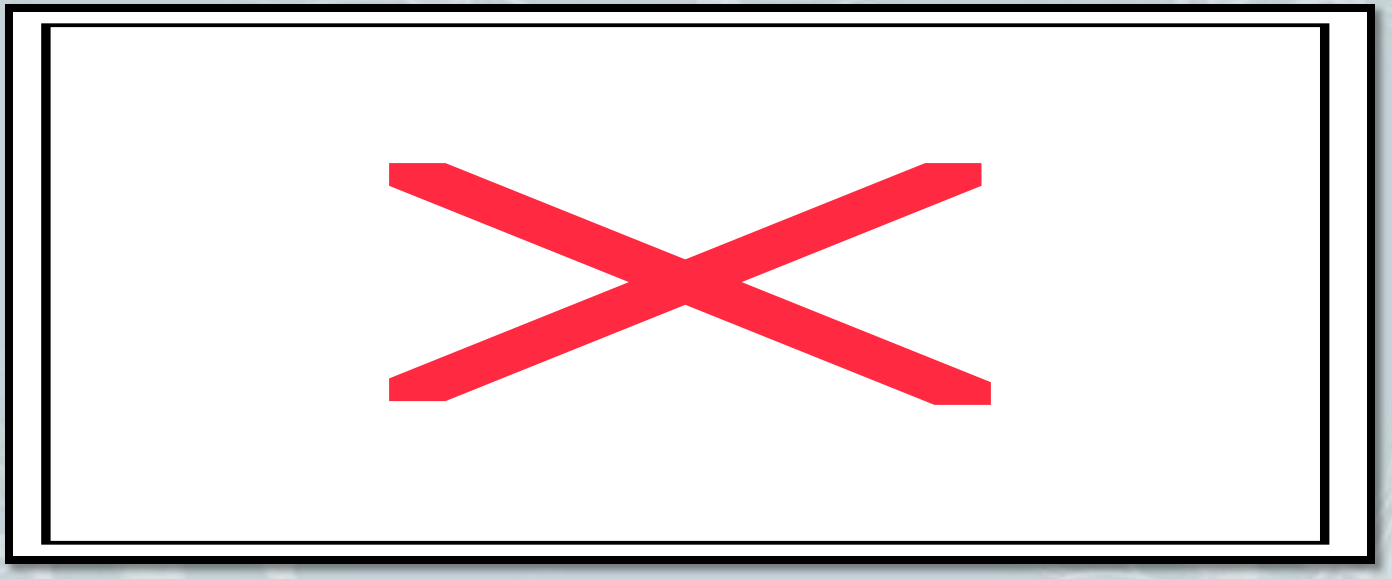
- **Immune Reconstitution Inflammatory Syndrome**
- Paradoxical clinical worsening, in 4-8 weeks after starting HAART
  - Worsening of a known infection
  - Unmasking of subclinical infection
- Neuroimaging: contrast enhancing lesions
- Steroids may be needed for ↑ICP, although therapeutic benefit controversial
- Most patients survive

Clinical Case

- A 42 years old man with HIV diagnosed in 2001 not on any treatment
- Severe headache and altered mental status
- CD4 29, viral load 150K
- LP with opening pressure of 28 cm H2O, CSF WBC 16, RBC 0, Protein 60, Glucose 27
- Serum CrAg 1:4096, CSF CrAg > 1:1024
- Started on Amphotericin & Flucytosine
- Ongoing headache with double vision
- Right CN VI palsy

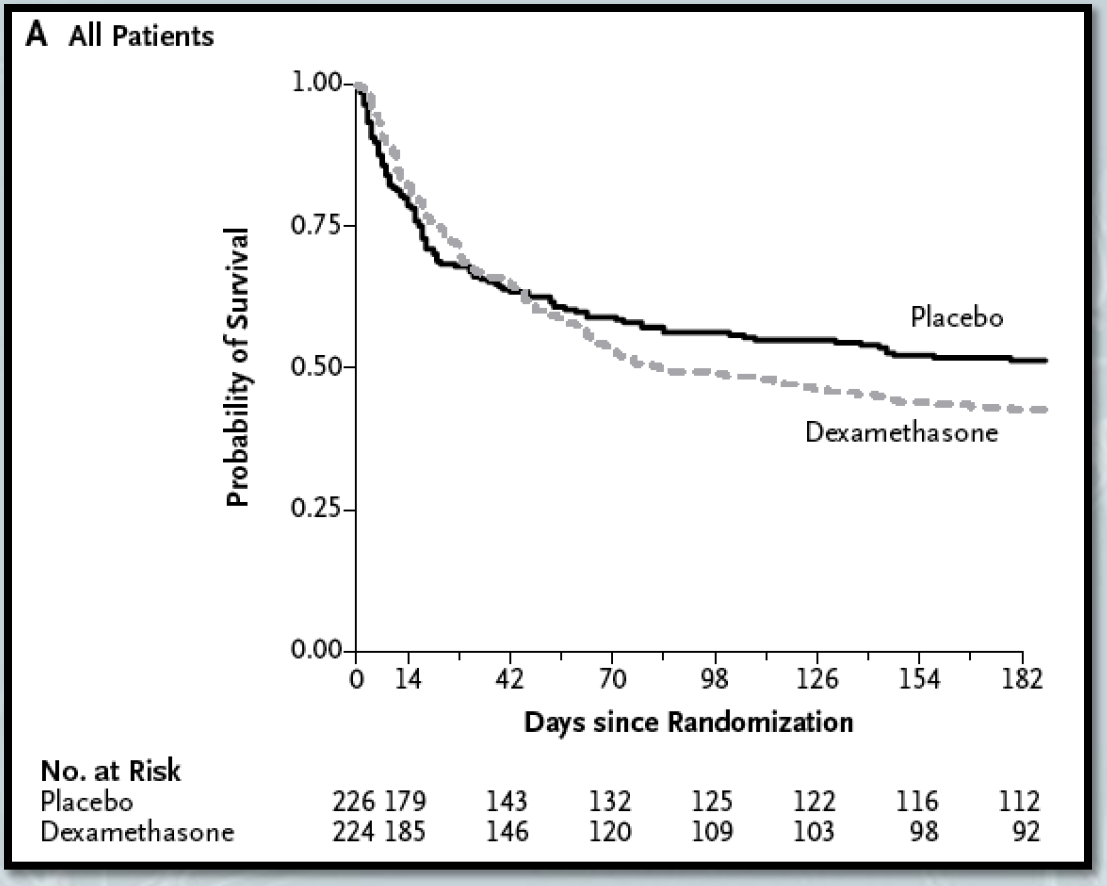
CM and Intracranial Pressure

- Raised ICP is a common complication (75% > 20 and 25% > 35 mm H2O
- Larger capsule size is associated with worse ICP and less inflammation



Robertson et al. J Infect Dis 2014

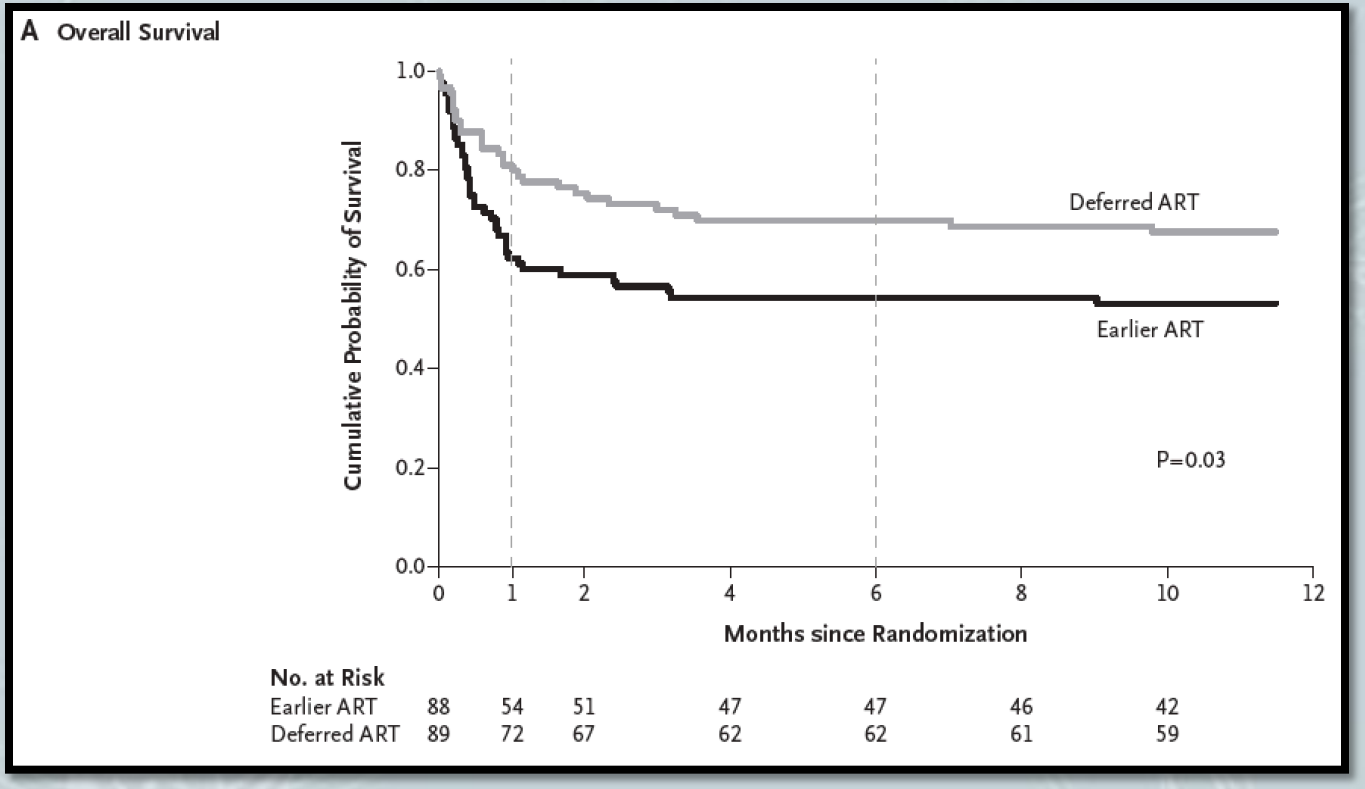
Adjunctive Dexamethasone Therapy for CM in HIV



Trial stopped for safety reasons. At 10 weeks, mortality was 47% in dexa. vs 41% in placebo. Disability was 25% vs 13%.

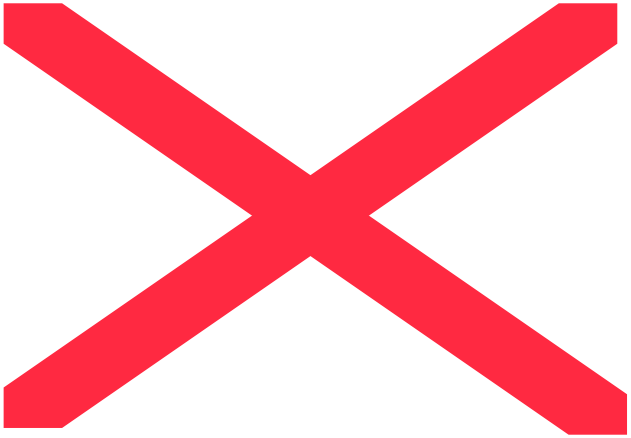
Beardsley et al. NEJM 2016

Cryptococcal Optimal ART Timing (COAT) Trial



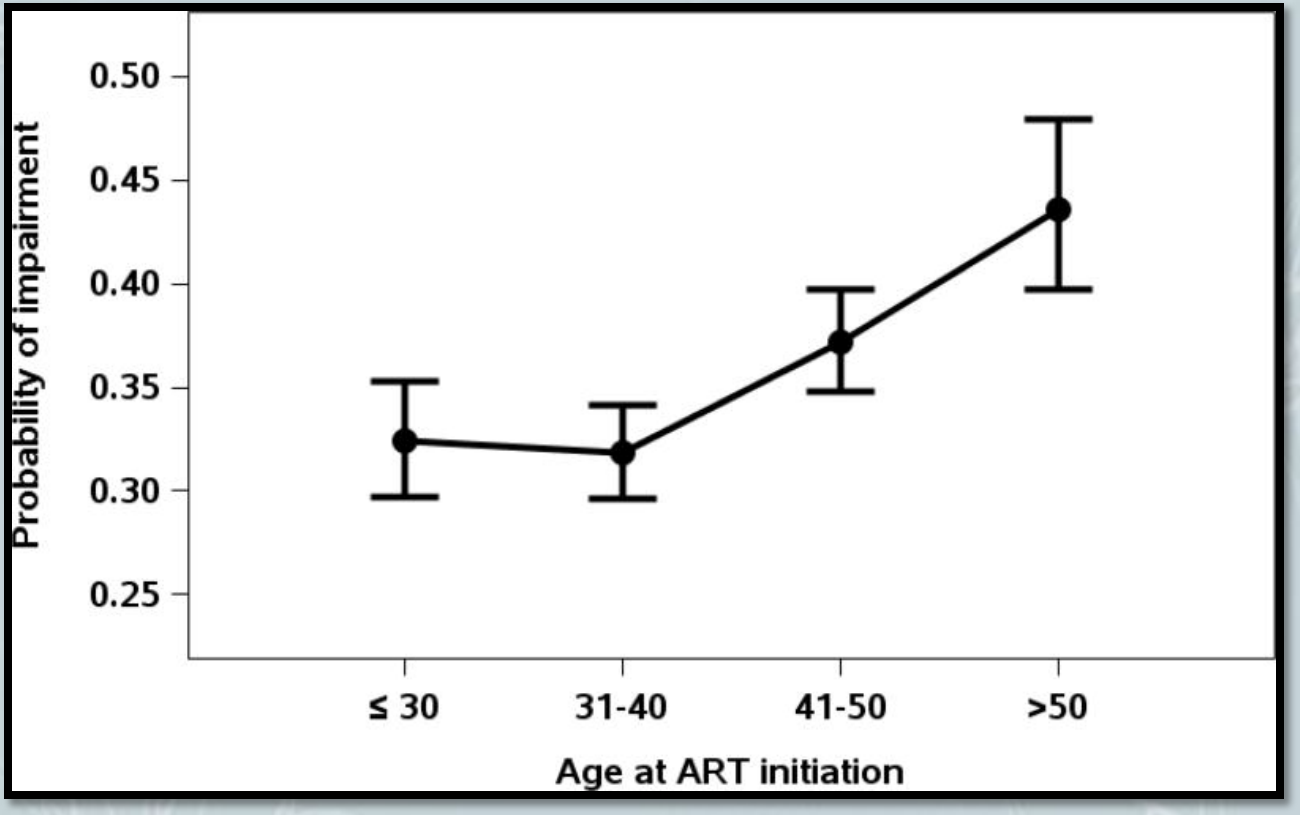
Boulware et al. NEJM 2014

Mechanisms of HIV-related CNS Injury



Sutherland et al. Neurol Clin 2018

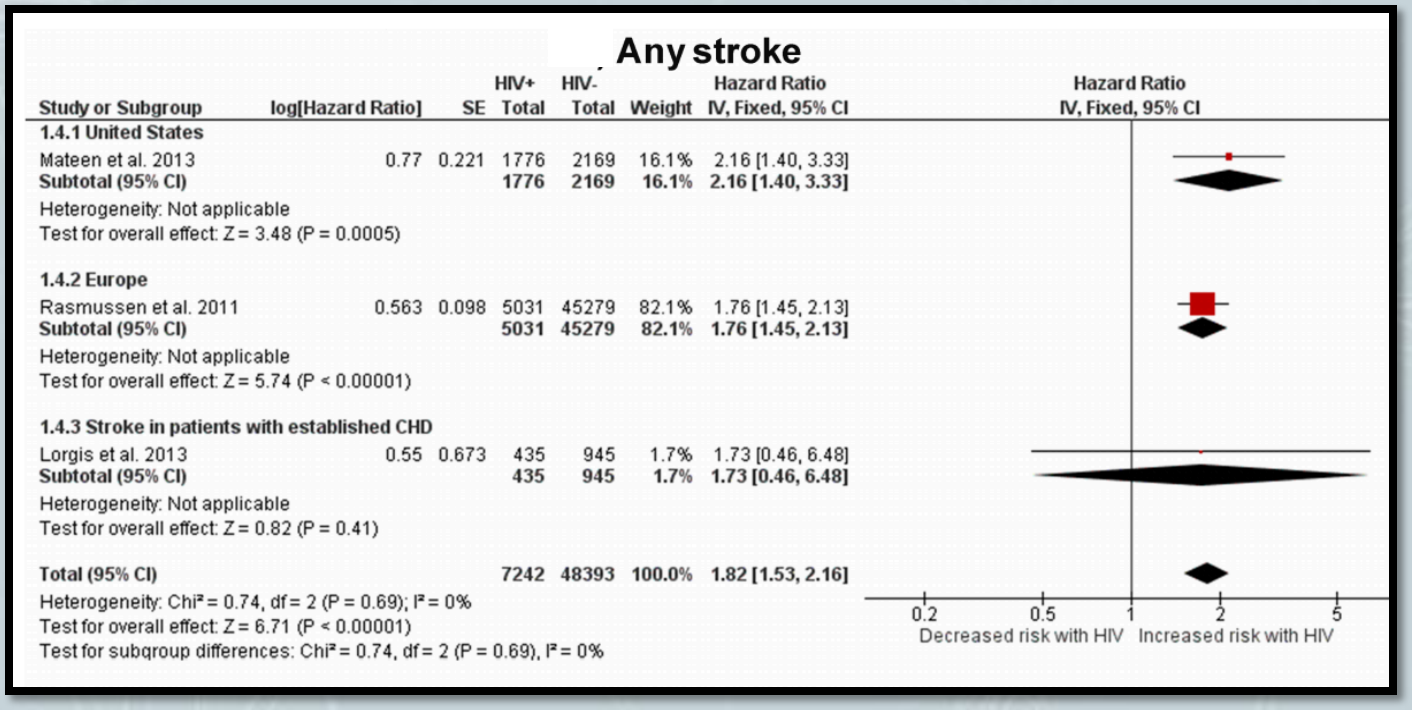
Age & HIV+ Cognitive Impairment



Cognitive impairment at follow-up among the HIV+ increased by 20% for each decade of advancing age

Coban et al. AIDS 2017

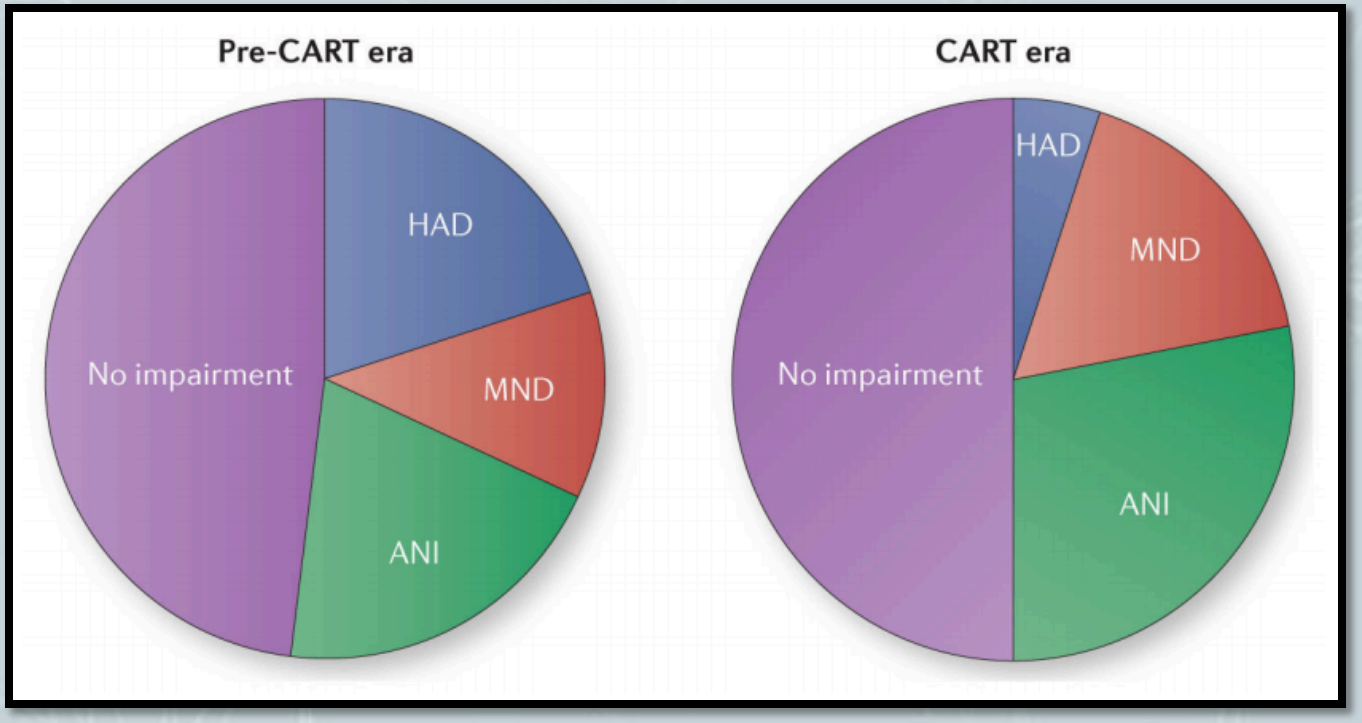
HIV & Stroke



Gutierrez et al. PLoS One 2017

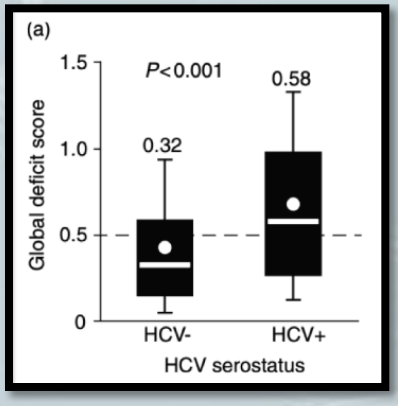
Range of HIV Neurocognitive Disorders

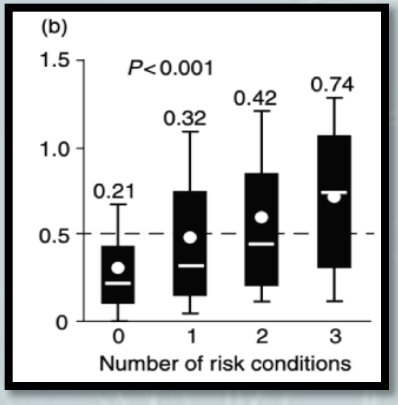
HAND in Pre & Post CART

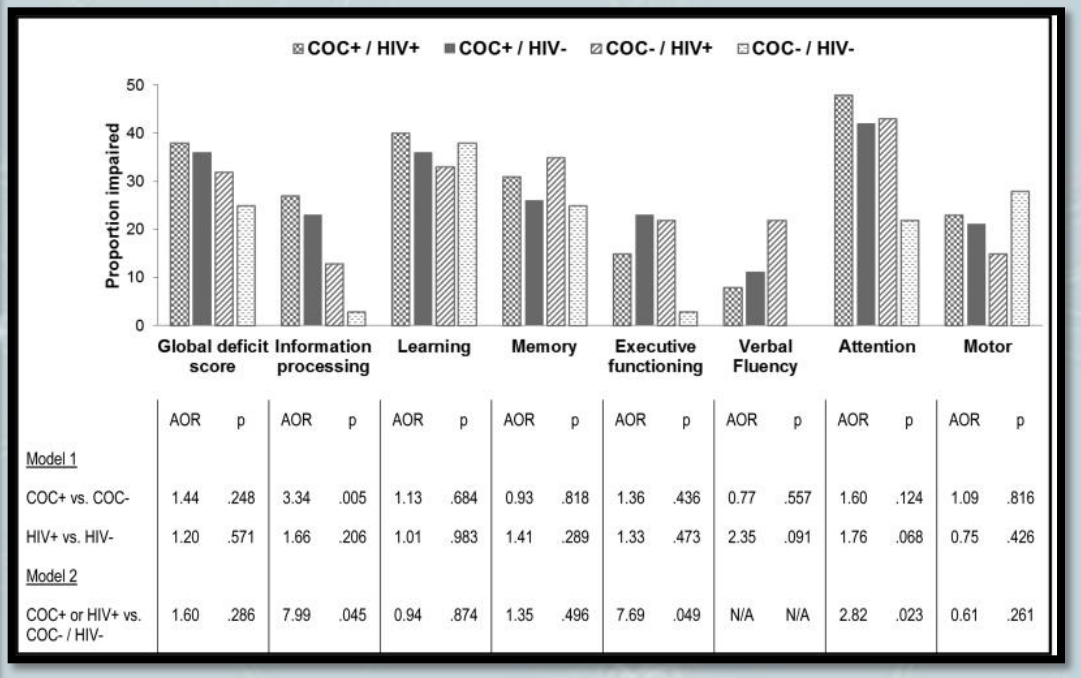


Saylor et al. Continuum 2018

HIV, HCV & Psychostimulants



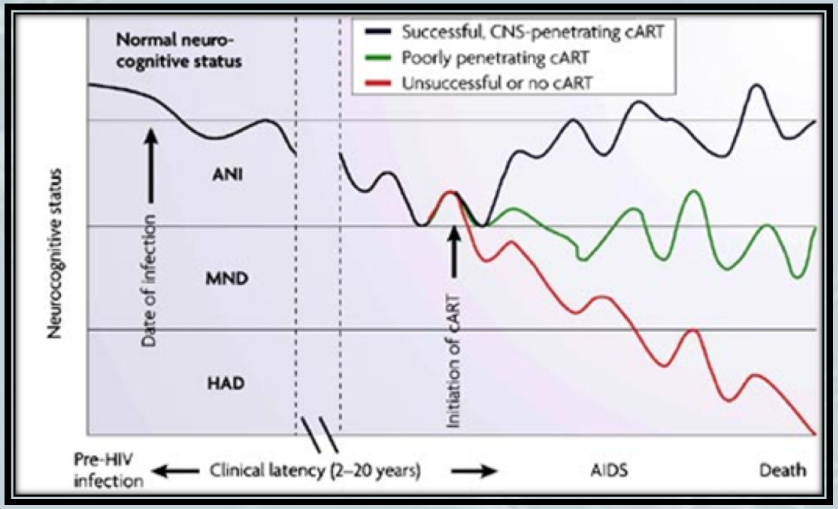




	AOR	p	AOR	p	AOR	p	AOR	p	AOR	p	AOR	p	AOR	p
Model 1														
COC+ vs. COC-	1.44	.248	3.34	.005	1.13	.684	0.93	.818	1.36	.436	0.77	.557	1.60	.124	1.09	.816
HIV+ vs. HIV-	1.20	.571	1.66	.206	1.01	.983	1.41	.289	1.33	.473	2.35	.091	1.76	.068	0.75	.426
Model 2														
COC+ or HIV+ vs. COC- / HIV-	1.60	.286	7.99	.045	0.94	.874	1.35	.496	7.69	.049	N/A	N/A	2.82	.023	0.61	.261

Letendre et al. AIDS 2005
Meade et al. Drug Alcohol Depend 2015

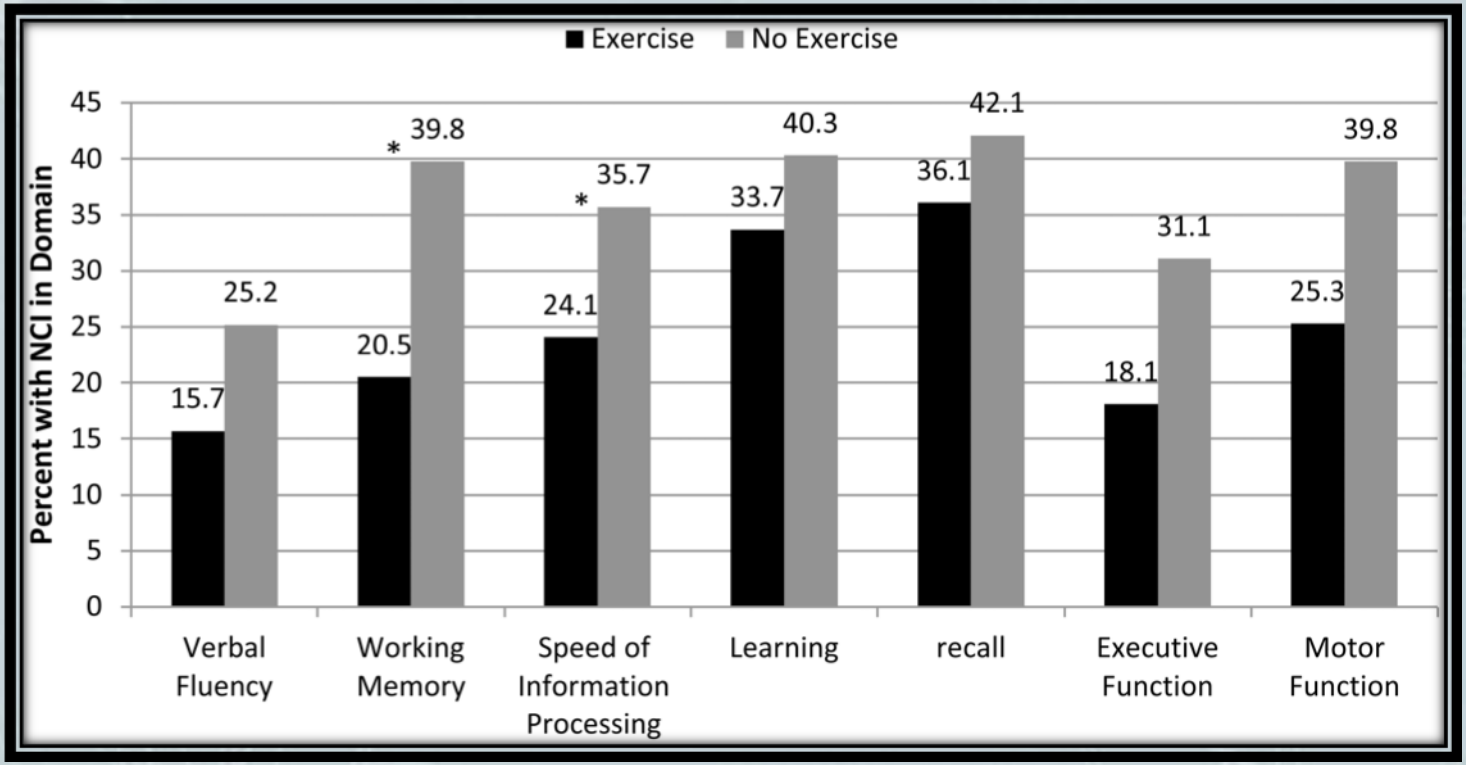
Treatment -
CNS Penetration-Effectiveness Score



	1	0.5	0
NRTIs	Abacavir Emtricitabine Zidovudine	Lamivudine Stavudine	Didanosine Tenofovir Zalcitabine
NNRTIs	Delavirdine Nevirapine	Efavirenz	
PIs	Indinavir Indinavir-r Lopinavir-r	Amprenavir-r Atazanavir Atazanavir-r Darunavir-r	Amprenavir Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Fusion Inhibitors			Enfuvirtide

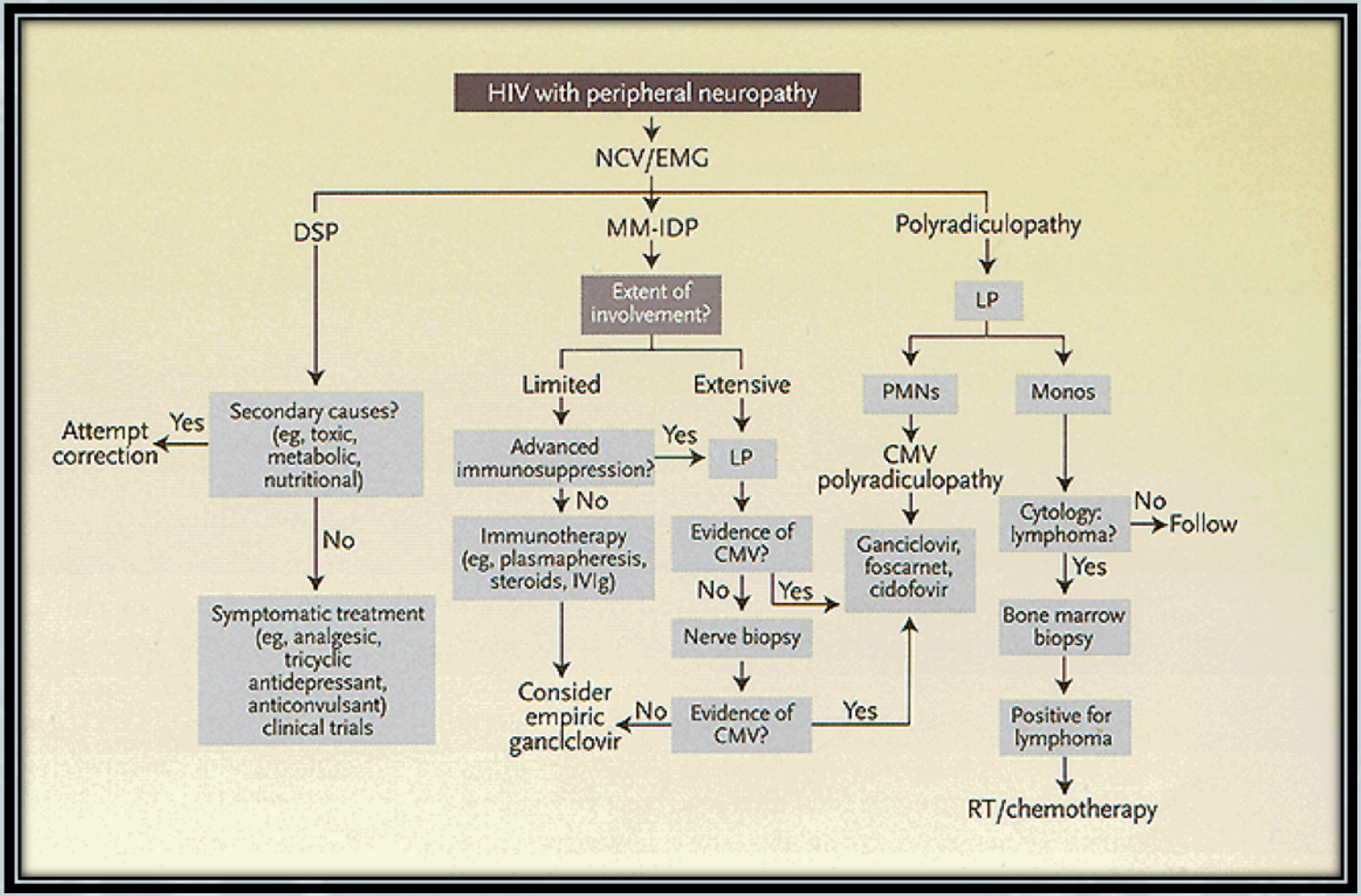
Ellis et al. Nature Reviews Neuroscience 2007
Letendre et al. Arch Neurol 2008

Exercise & Neurocognitive Impairment in HIV+



Dufour et al. J Neurovirol 2013

Peripheral Neuropathy in HIV

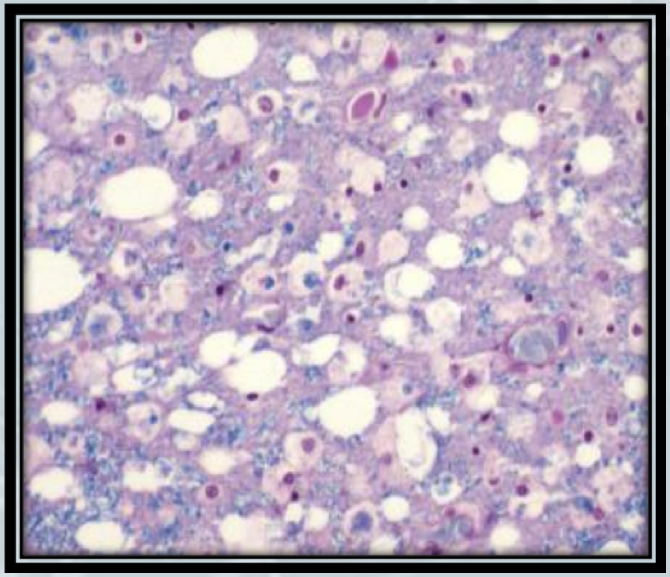


ART Toxic Neuropathy

- Mostly related to exposure to specific dideoxynucleosides (stavudine, didanosine)
- Prominent mitochondrial abnormalities, inhibit gamma DNA polymerase
- NRTIs not associated with toxic neuropathy: zidovudine, lamivudine, abacavir, tenofovir
- Risk factors include lower CD4 count, body mass index <18, age <35 years, genetic factors

Vacuolar Myelopathy

- "Holes" in spinal cord seen in advanced cases
- Clinical Features – onset over weeks-months
  - Painless spastic paraparesis, sensory ataxia, neurogenic bladder, paresthesia
  - Affects the thoracic cord & cervical cord



Key Message

- HIV causes neurological impairment either directly or by promoting opportunistic infections
- Significant improvement has occurred since the HAART introduction
- HAART can lead to CNS and PNS neuropathy
- HAND remains a significant problem
- Presence of other factors increase the burden on cognition

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Thank You