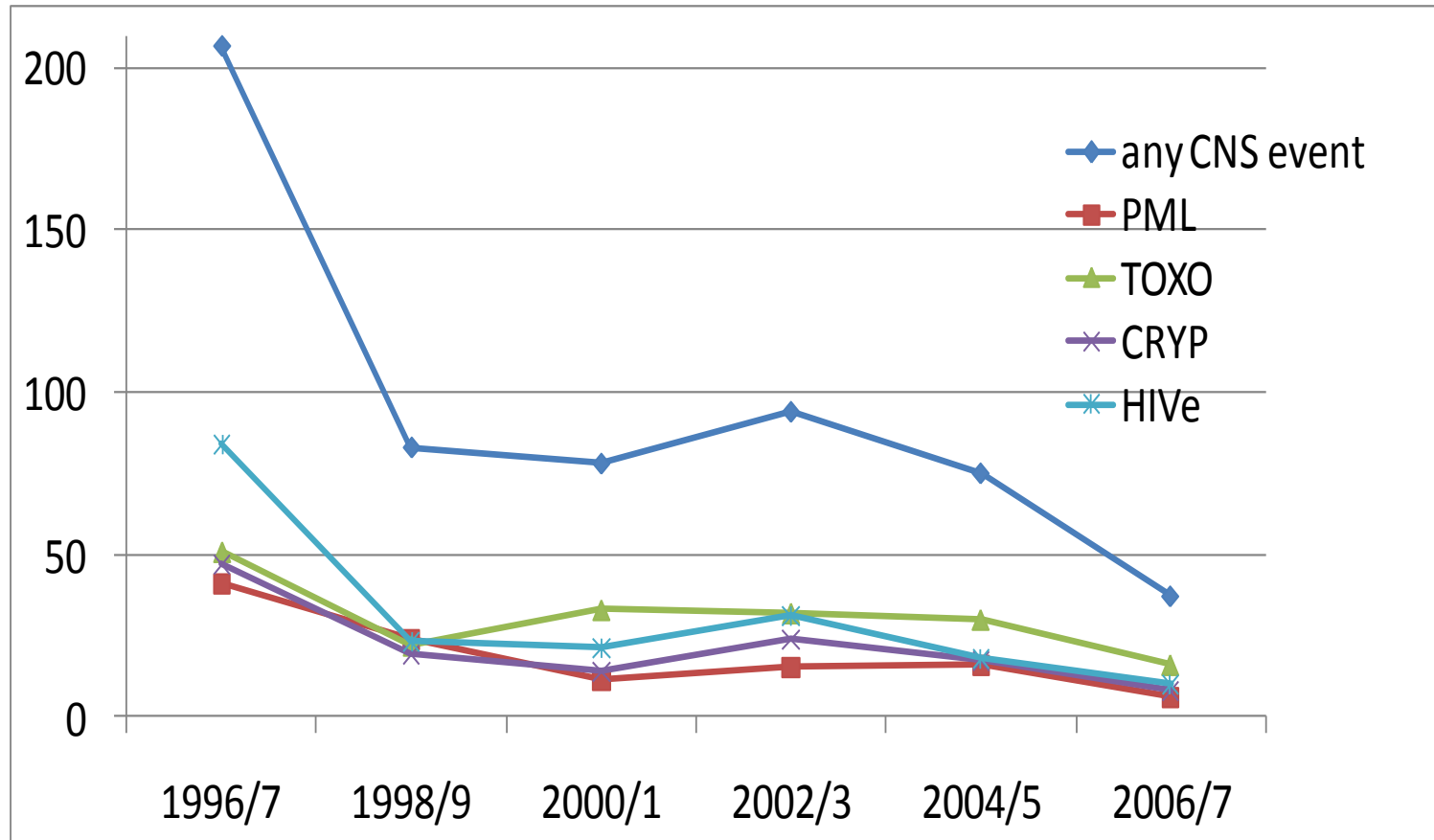


# **HIV and the brain in 2011**

**Dr Alan Winston**

**December 2011**

# Overall CNS disease - UK CHIC 1996 - 2007



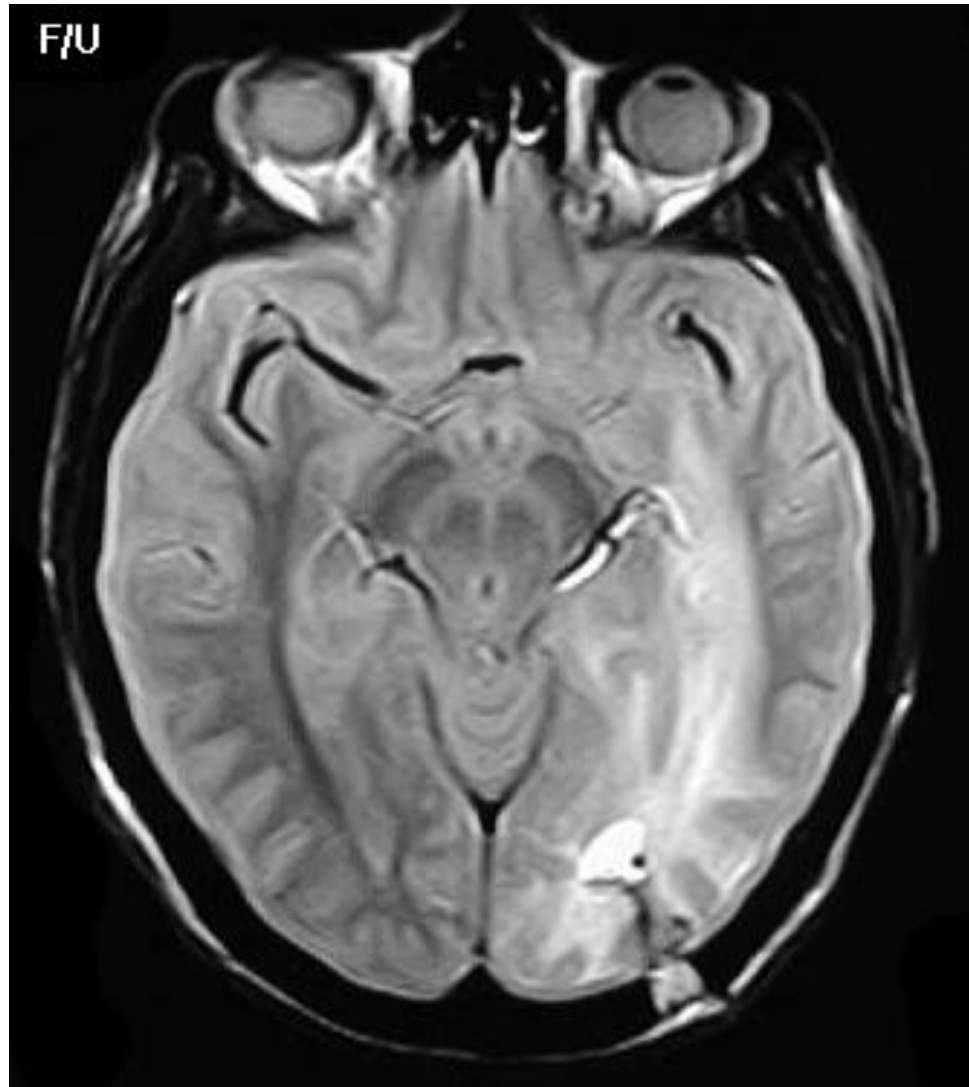
## Neurology of HIV infection

- **PML**
- **HIV associated dementia**
- **Other opportunistic infections**

# Neurology of HIV infection

- **PML**
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# Progressive Multifocal Leucoencephalopathy



# Progressive Multifocal Leucoencephalopathy

## JC virus

- Reactivation John Cunningham virus (JCV)
- human polyomavirus

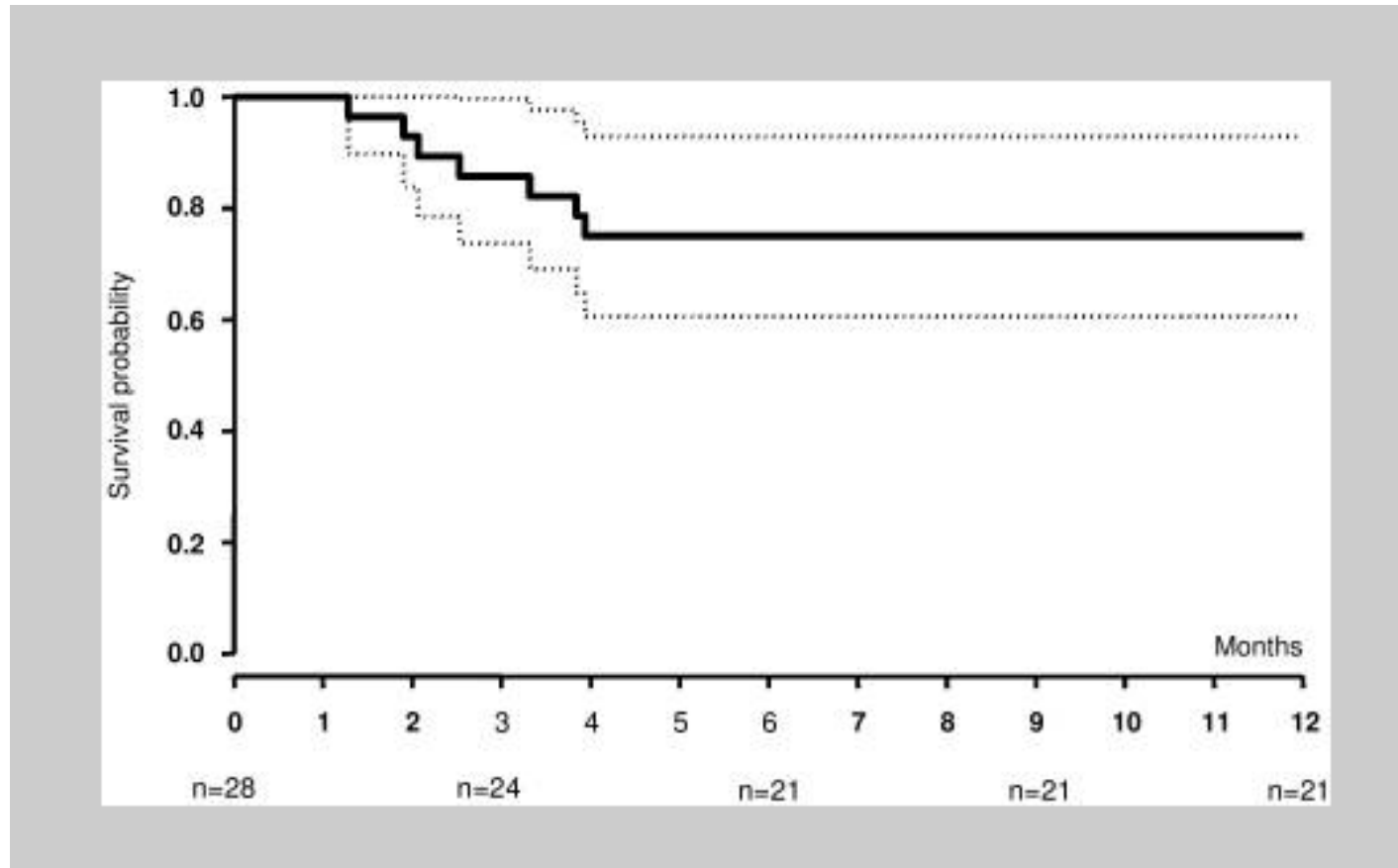
## Causes

- HIV disease and other immunocompromised states
- Low CD4 + counts
- Drug induced
  - efalizumab, rituximab infliximab
  - chemotherapy
  - steroid

## Survival

- Remains poor in post-HAART era (<50% alive at 5 years)

## Survival PML



# Neurology of HIV infection

- PML
- **HIV associated dementia**
- Other opportunistic infections



# HIV associated dementia

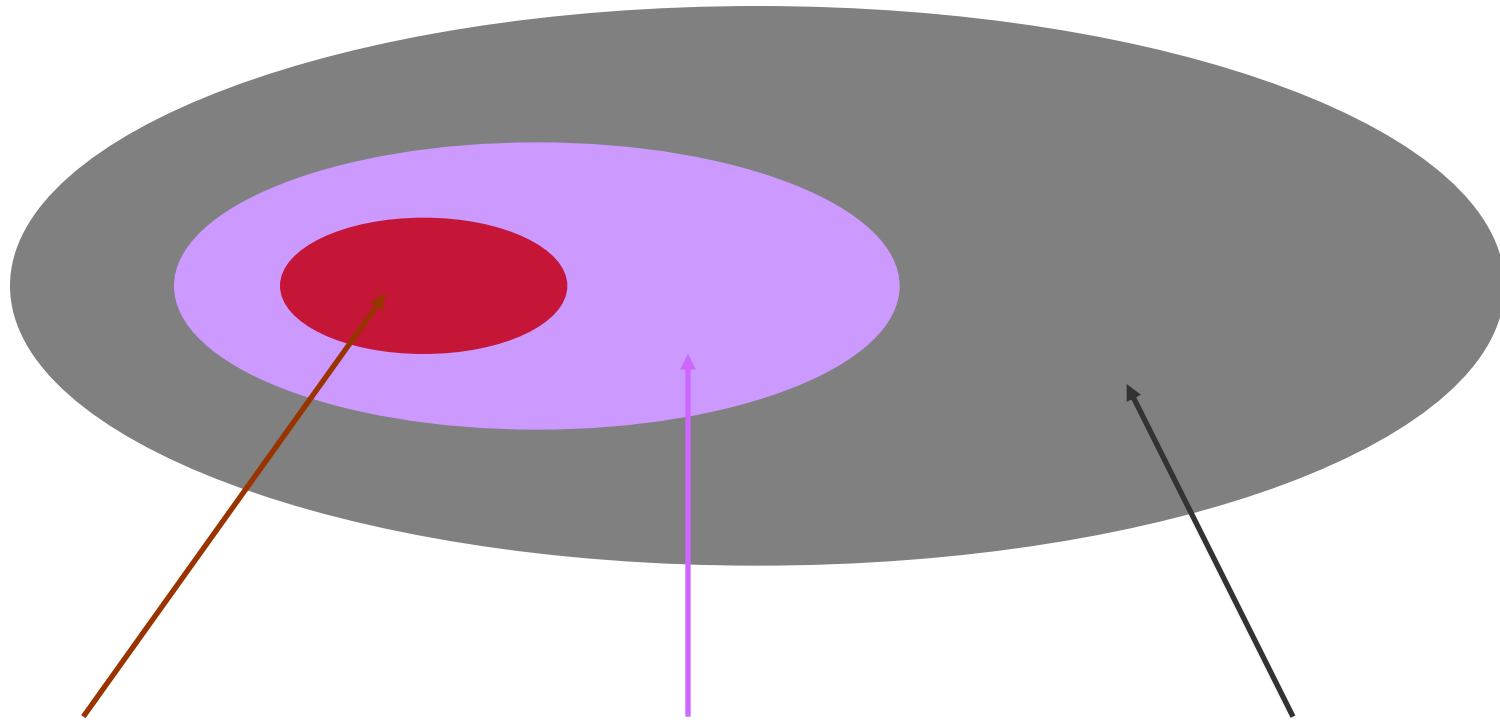
Described 1986

- AIDS dementia complex
- Associated low CD4 count other OI
- Sub cortical dementia
  - » involving the deep gray (ie, basal ganglia, thalamus)

	Cortical	Sub-cortical
<b>Type of dementia</b>	Alzheimers, fronto-temporal dementia	HIV-dementia, Parkinsons, Huntingtons
<b>Main area(s) of damage</b>	Cerebral cortex	Basal ganglia, thalamus
<b>Language problems / aphasia</b>	Common, early	No
<b>Memory problems</b>	Common, early	Rare
<b>Personality / frontal changes</b>	No	Common (typically emotional / irritable / personality change )
<b>Executive / higher function decisions</b>	Yes	Yes
<b>Attention / motivation problems</b>	No	Common, early

# HIV associated dementia (classification)

Neurology 2007;69;1789-1799



## *HAD*

- *Marked interference with daily life*

## *Symptomatic NCI*

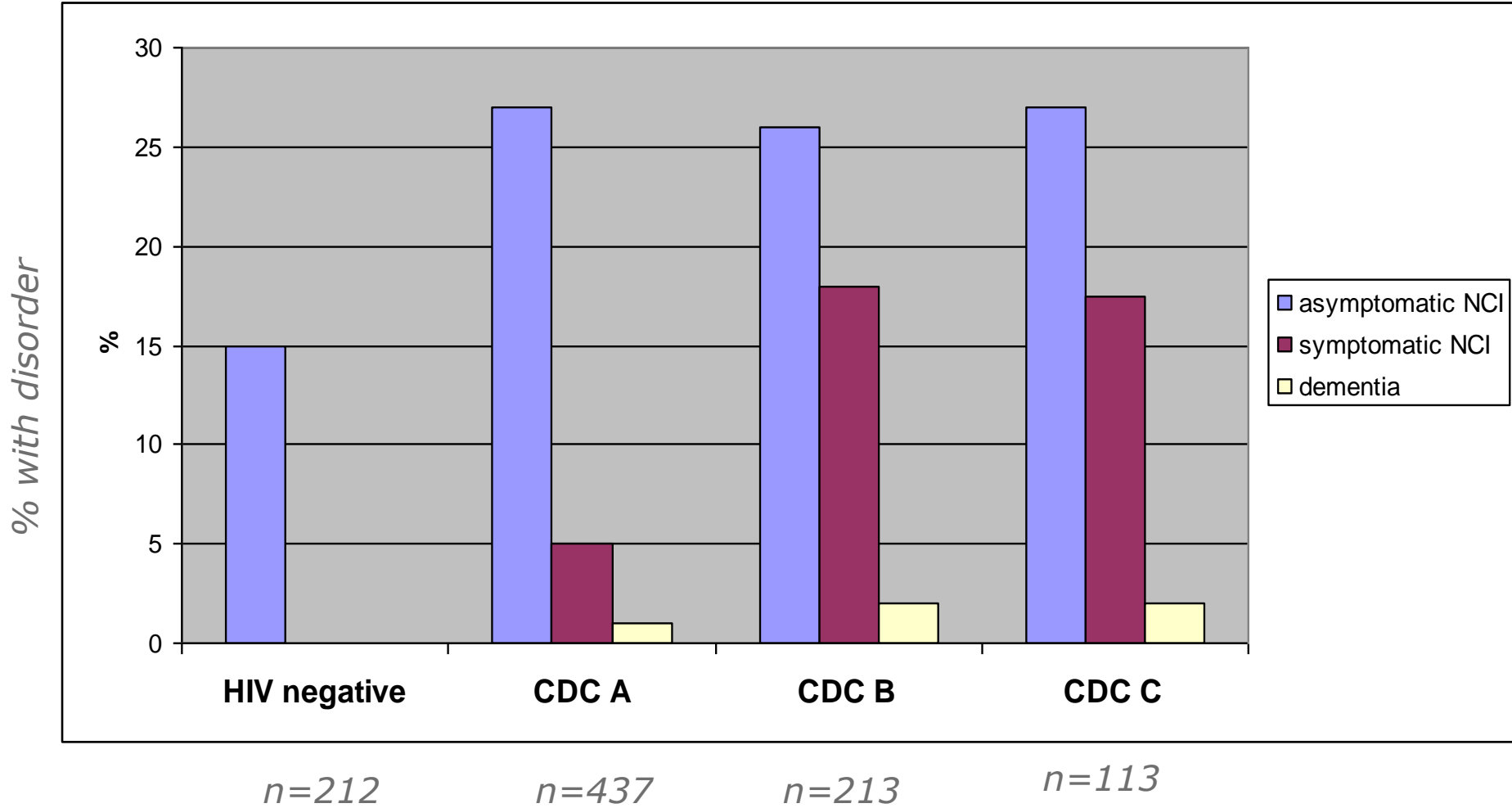
- *impairment >1 SD in 2 or more domains \**
- *does interfere with daily life*

## *Asymptomatic NCI*

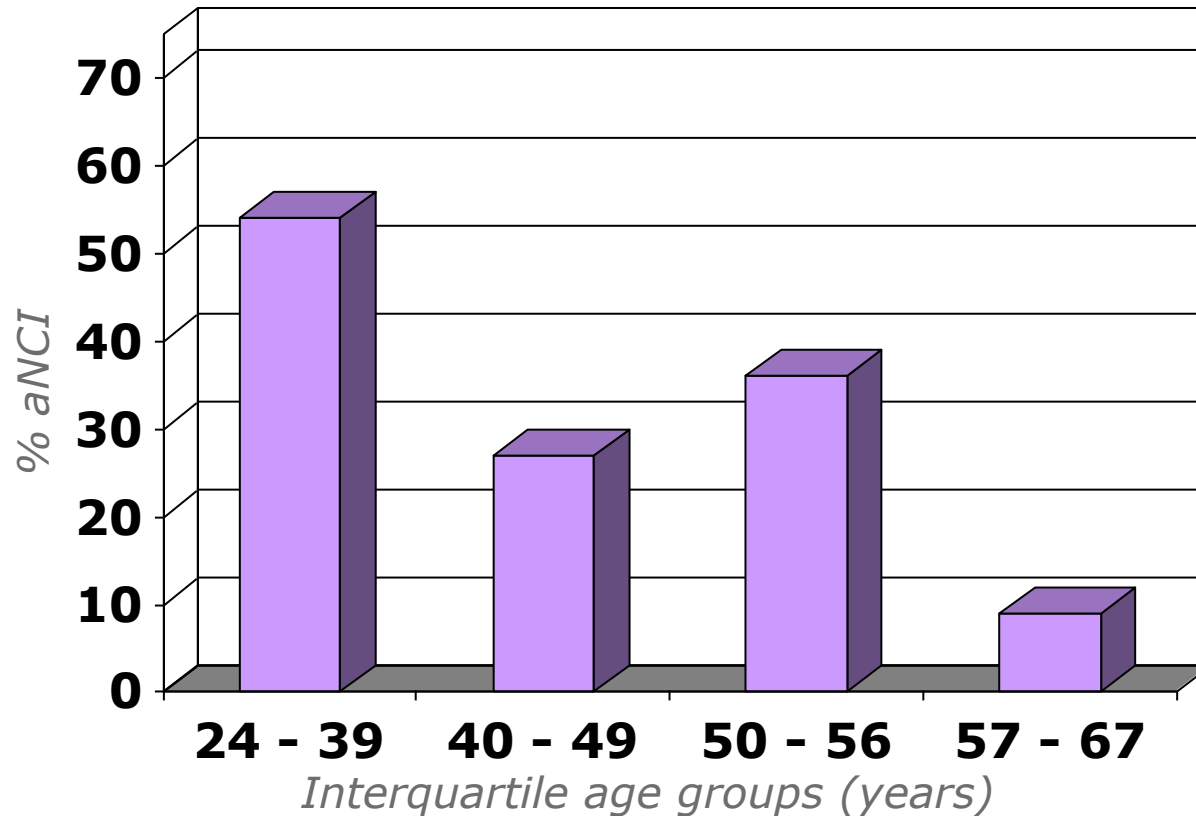
- *impairment >1 SD in 2 or more domains \**
- *does not interfere with daily life*

\* The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills

# Prevalence of HIV NCI



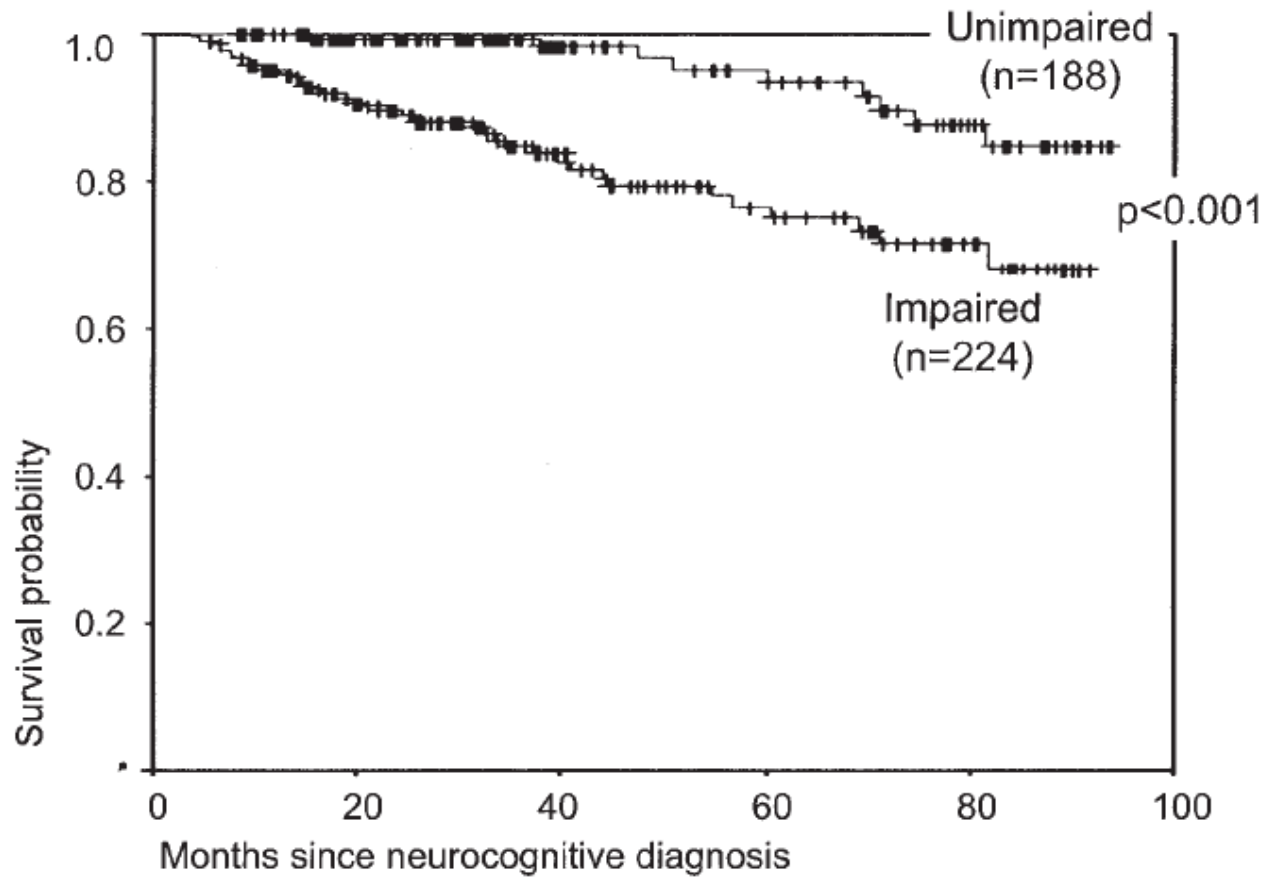
## St. Mary's cohort – asymptomatic NCI



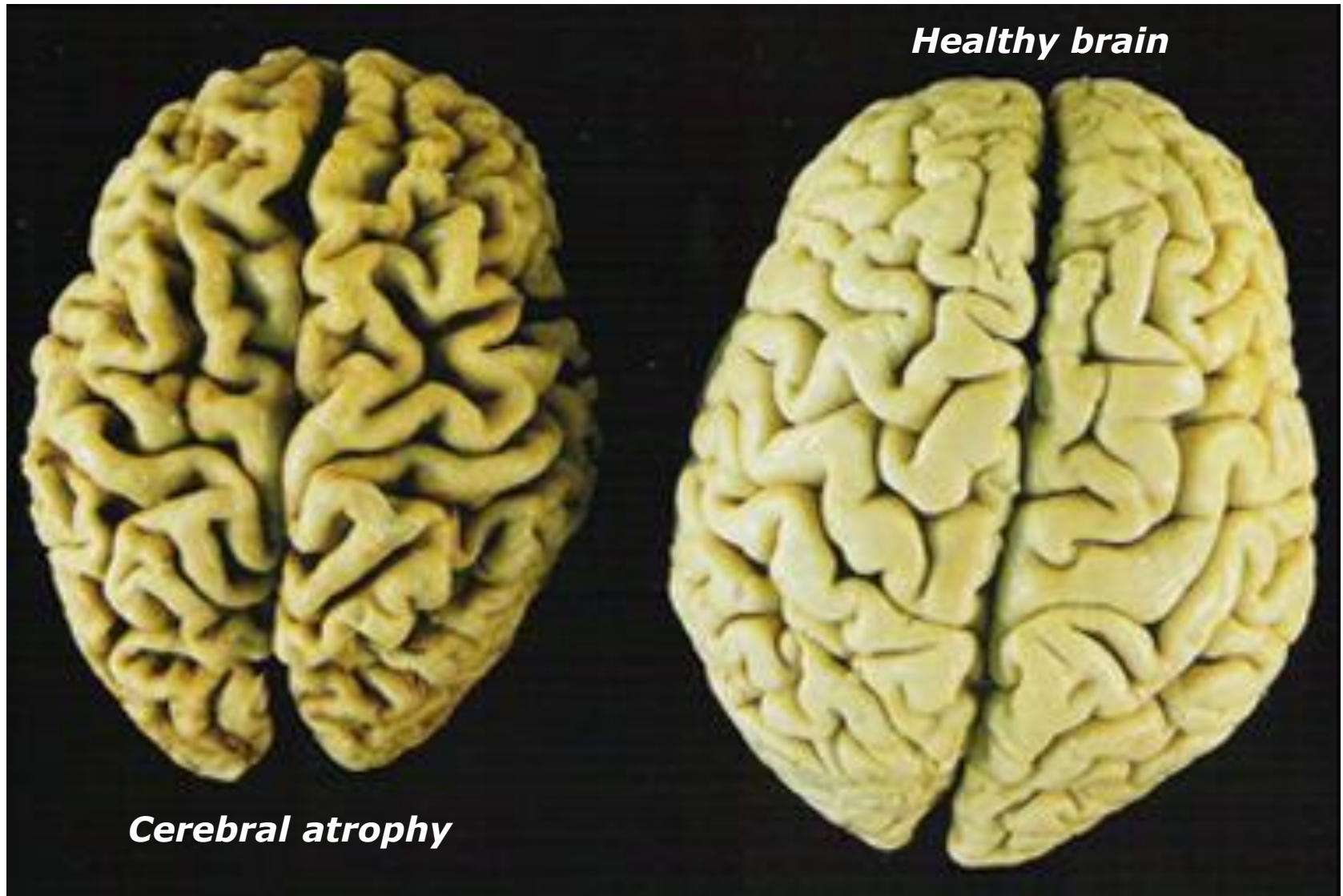
*aNCI observed in 14/45 (31%) subjects.*

*Significantly associated with younger age ( $p=0.03$ )*

# Outcome neurocognitive impairment



## Diseased brain



## Risk factors HIV associated dementia

### Pre-HAART

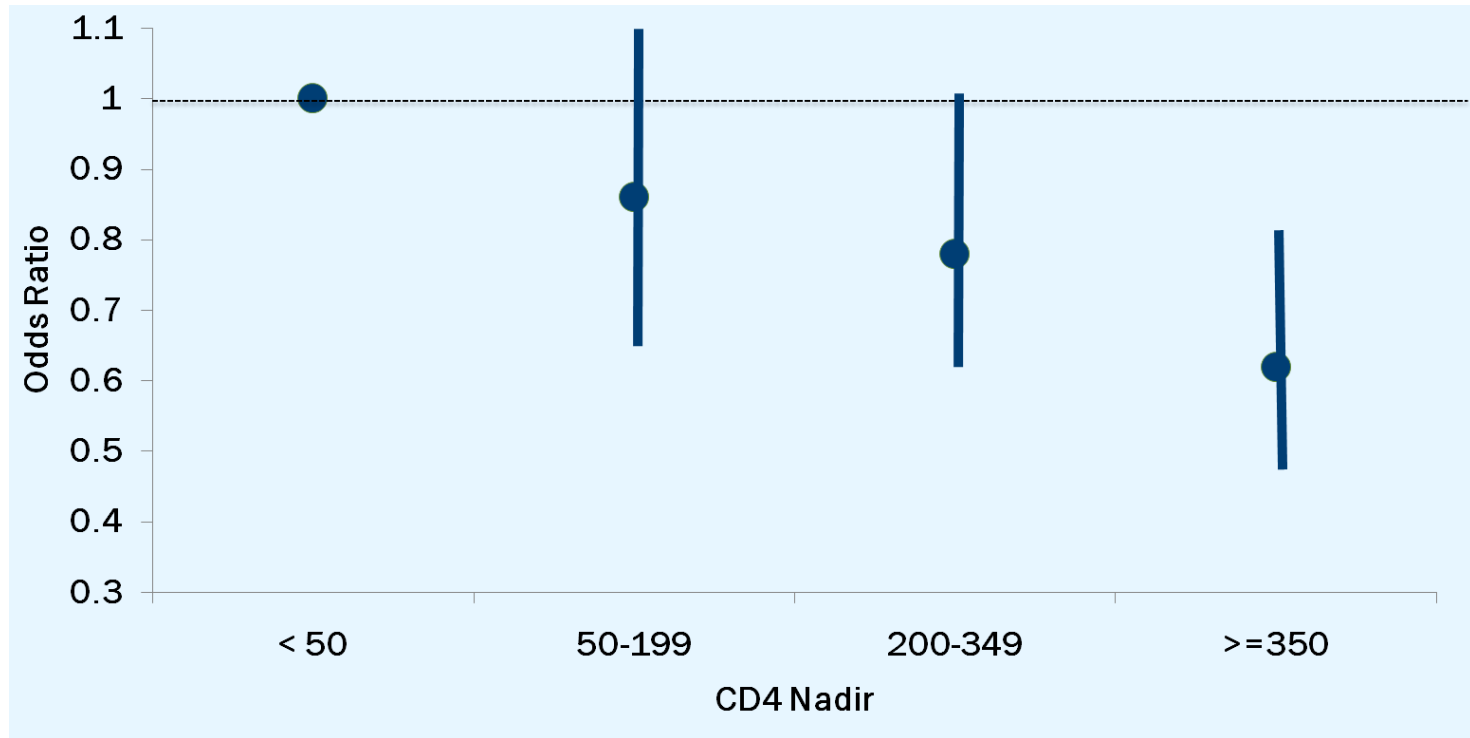
- CD4 count

### Post HAART era

- Nadir CD4 count
- HCV
- CSF parameters including HIV RNA
- Plasma HIV RNA
- Antiretroviral regimens
- Co-morbidities

# Nadir CD4

## Odds Ratios for Cognitive Impairment According to CD4 Nadir Strata (All Subjects)



Neurology  
sub-study



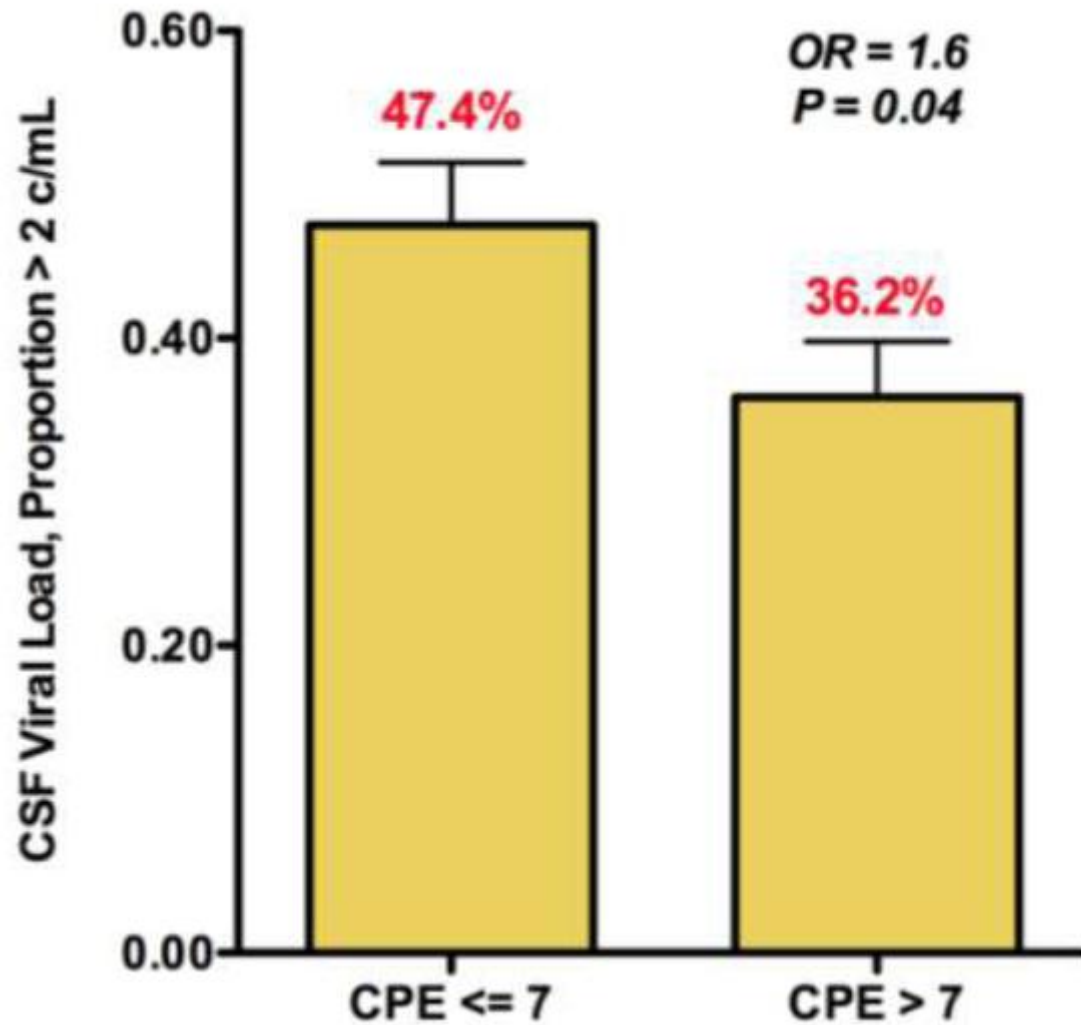


## CHARTER score

	Increasing CNS Penetration →		
	0	0.5	1
nRTIs	Didanosine Tenofovir Zalcitabine*	Emtricitabine Lamivudine Stavudine	Abacavir Zidovudine
NNRTIs		Efavirenz	Delavirdine Nevirapine
PIs	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r	Amprenavir* Atazanavir Fosamprenavir Indinavir	Amprenavir*/r Atazanavir/r Fosamprenavir/r Indinavir/r Lopinavir/r
Other	Enfuvirtide		

CHARTER indicates Central Nervous System HIV Antiretroviral Effects Research; CNS, central nervous system; nRTI, nucleoside analogue reverse transcriptase inhibitor; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; r, ritonavir. Asterisk indicates no longer on the market. Adapted from Letendre et al, CROI, 2006.

# CSF HIV RNA



# IHDS – International HIV dementia scale

## Consists of 3 parts

### 1. Memory recall of 4 words



(dog, hat, bean, red)



Scored out of 4

1 point for every word remembered

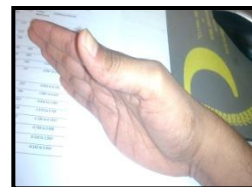
### 2. Tapping fingers



Scored out of 4

No. of finger tapping complete in 5 secs recorded

### 3. Performing sequence with wrist (non dominant hand) Scored out of 4

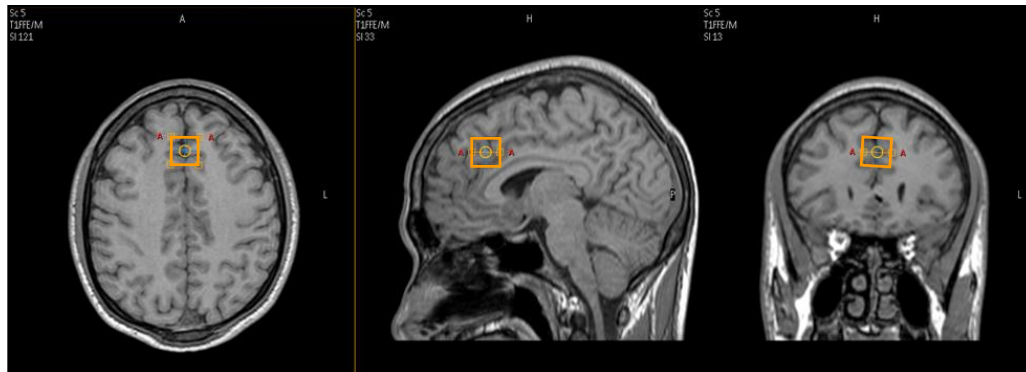


No. of times sequence complete in 10 secs recorded

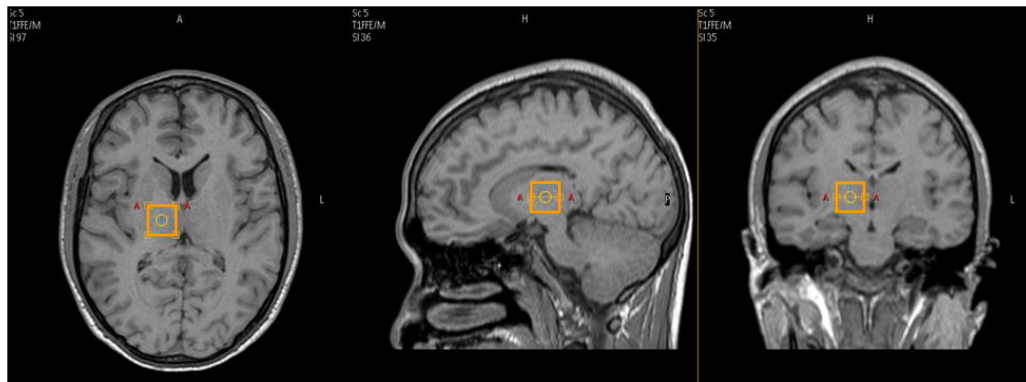
# magnetic resonance spectroscopy



frontal white matter



frontal grey matter

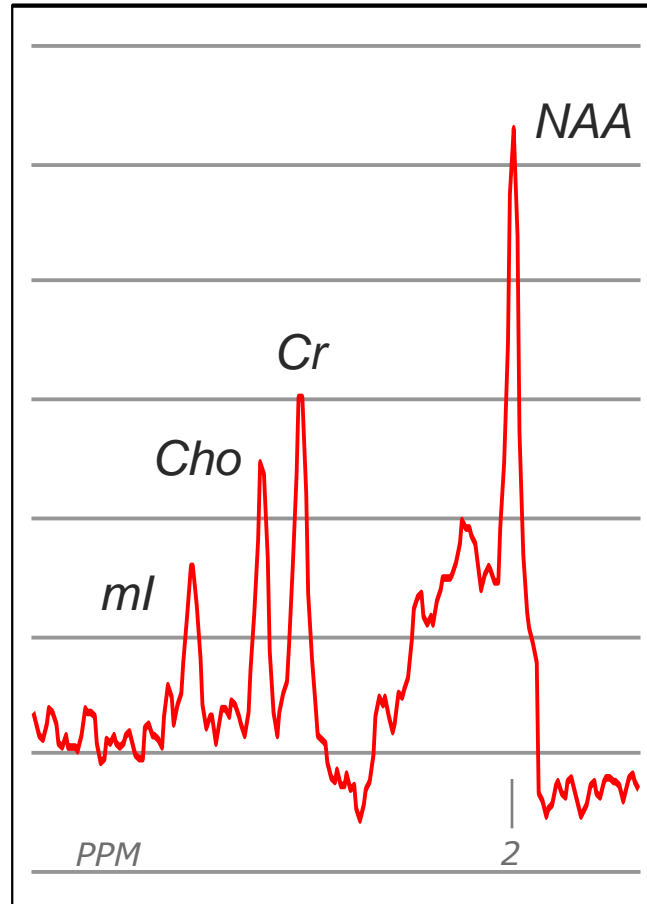


right basal ganglia

## magnetic resonance spectroscopy



## Proton magnetic resonance spectroscopy



*volunteer*

*NAA (n-acetyl-aspartate)*

- Neuronal marker

*Cr (creatine)*

- Metabolism marker

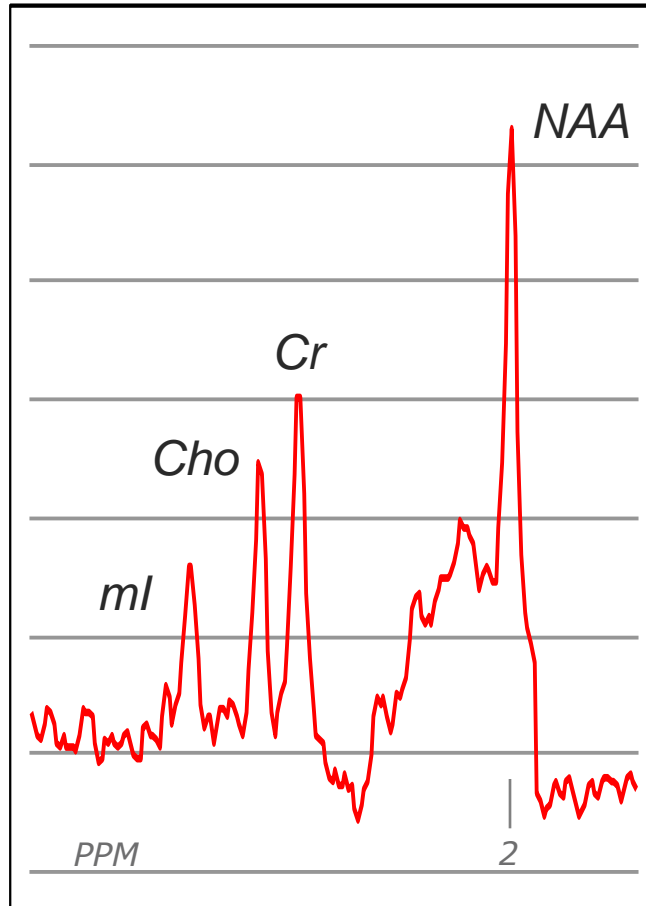
*Cho (choline)*

- Inflammatory marker

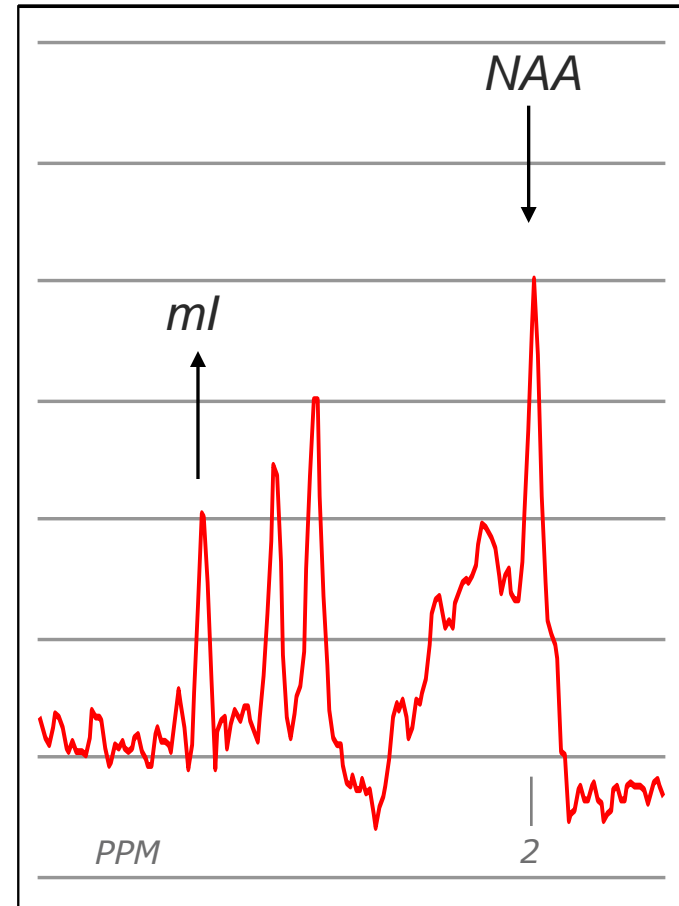
*ml (myo-Inositols)*

- Inflammatory marker

# Proton magnetic resonance spectroscopy

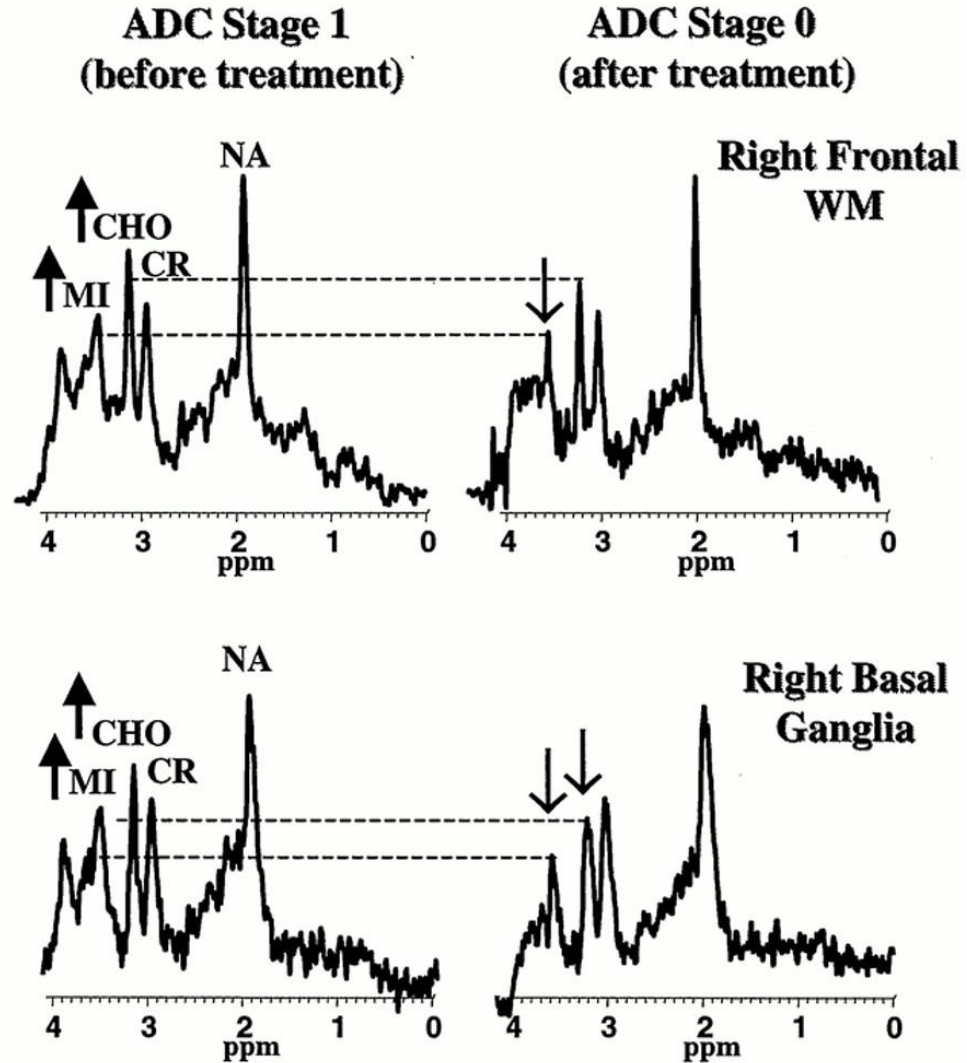
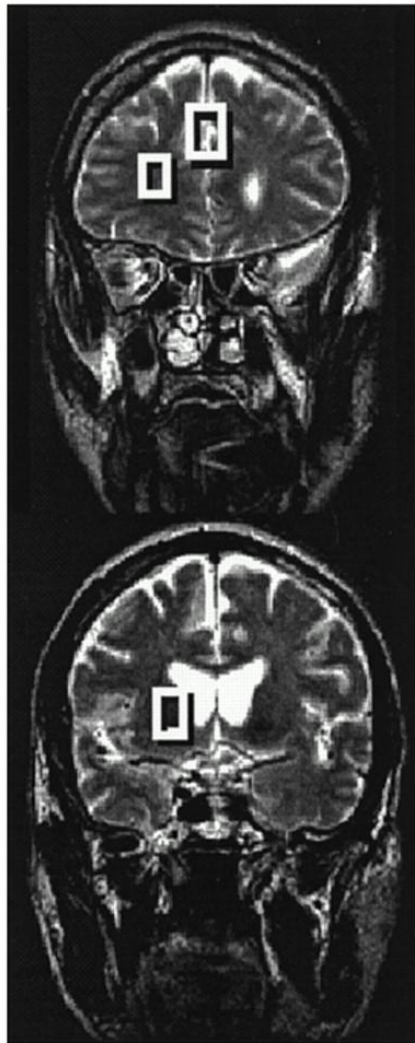


*volunteer*



*HIV-1 subject naive therapy*

# MR Spectroscopy and ART





## Neurology of HIV infection

- PML
- HIV associated dementia
- **Other opportunistic infections**

# Cryptococcal meningitis

- likely inhaled → blood → CSF
- remains a common OI in patients unaware of HIV serostatus
- sub-acute syndrome [median 30 days symptoms → diagnosis]
  
- non-specific
  - fever
  - headache
  - malaise
  - confusion
  
- ± extra-neural disease coexisting
  - pneumonia
  - cryptococcaemia

# Cryptococcal meningitis

## *Diagnosis of cryptococcal meningitis in an HIV infected patient*

### *serum*

- antigen detection (+) in >99%
- cryptococcal latex agglutination (CrAg)

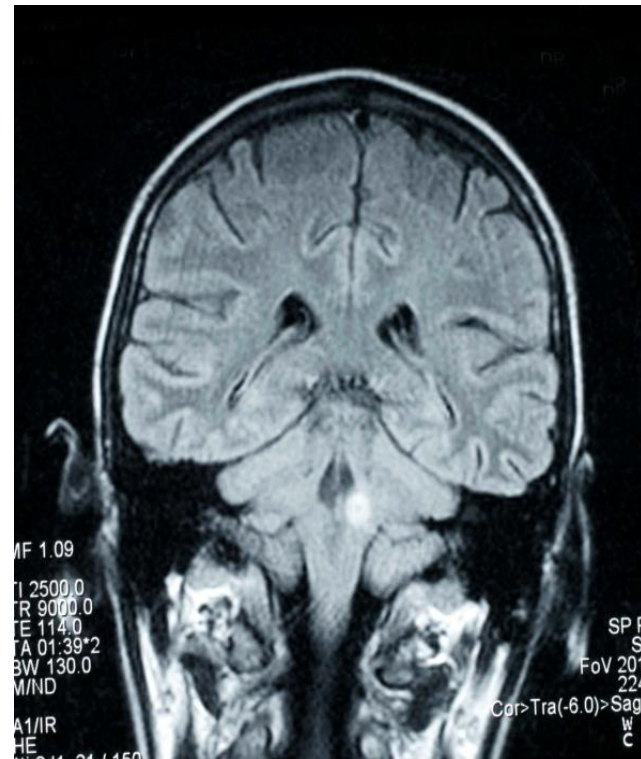
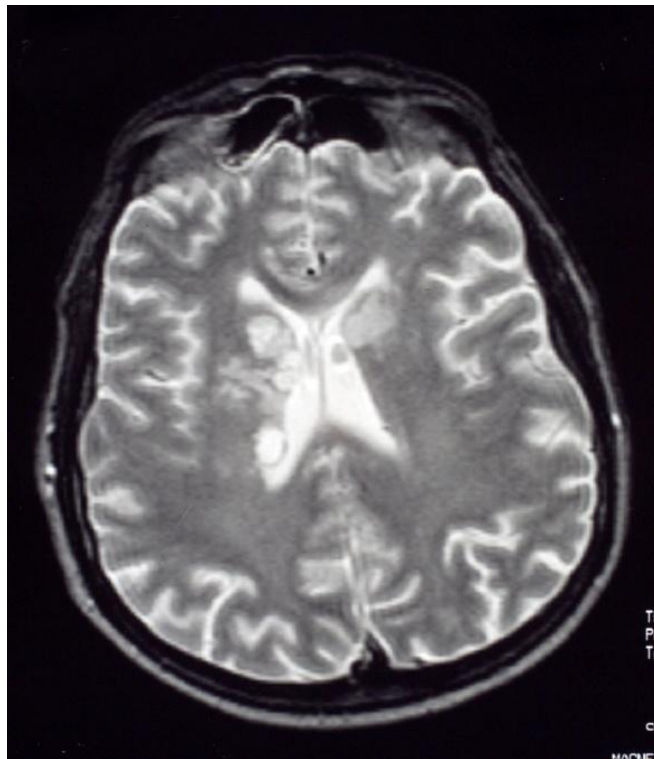
### *CSF*

- cell count/protein = normal in ~60%
- opening pressure raised in ~60%
- culture organism

# Cryptococcal meningitis

CT/MR imaging =

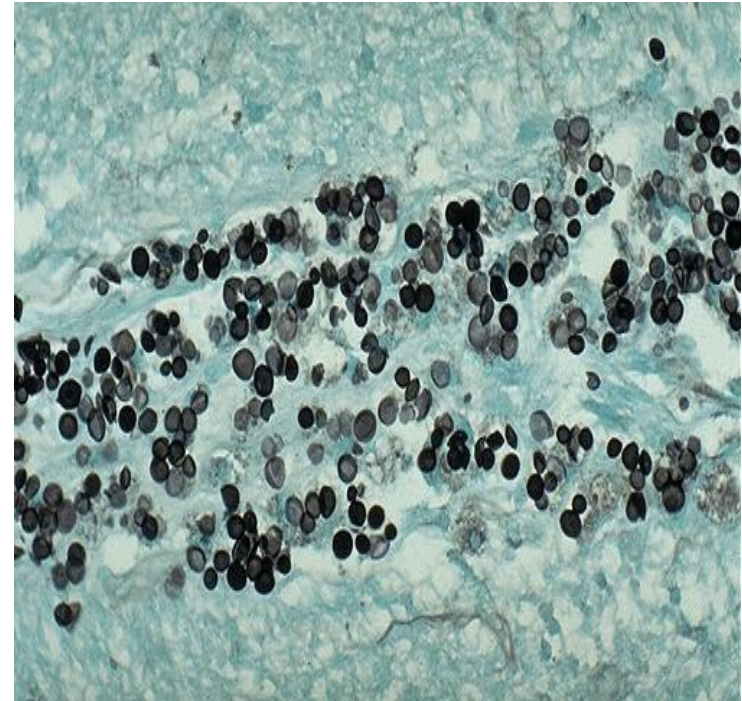
- usually normal
- no meningeal enhancement
- cryptococcomas



# Cryptococcal meningitis

*Explanation for raised  
pressure*

- organisms/fungal polysaccharide antigen
- mechanically interfere with CSF re-absorption in arachnoid villi



# Cryptococcal meningitis

## *Prognostic factors*

### Abnormal mental state

- Lethargy, obtundation, coma

### Visual abnormalities

- blurred vision
- papilloedema

### *CSF*

- High opening pressure (>25 cm water)
- Markers of high organism load, (+) india ink
- CrAg > 1:1024
- Poor inflammatory response, <20 WBC/mm<sup>3</sup>

### *Extra-neural disease*

- pneumonia

## Cryptococcal meningitis

### *Antifungal therapy plus HAART*

*Treatment:*

- **amphotericin B 0.7-1.0 mg/kg/d**
- **+ / - flucytosine 100 mg/kg/d for 2 weeks**

*Then, either*

- **a) continue with above, for further 4-8 weeks, or**
- **b) fluconazole 4-600 mg/d for  $\geq 10$  weeks**

**NB : lipid formulations of amphotericin B 3 – 6 mg/kg/d for 6-10 weeks  
[AmBisome 4mg/kg/d]**

# Repeating the lumbar puncture

## Initial CSF OP =

- *normal/patient stable:*  
repeat LP at 2 weeks: stain, culture, CrAg
- *> 25 cm water*  
repeat LP DAILY until OP <20 cm water & patient stable  
drain 'dry' vs drain >10-15mL of CSF  
once controlled OP may defer LP for several days

*Failure to control OP by repeat LP*

Lumbar drain

Ventriculo-peritoneal shunt

**No evidence for benefit from**

- glucocorticoids
- acetazolamide



## **Nomenclature:**

- Immune reconstitution inflammatory syndrome (IRIS)
- Immune reconstitution syndrome (IRS)
- Immune reconstitution inflammatory disease (IRD)
- Paradoxical reactions
- 'HAART attacks'

# IRIS

## Two types:

### 1 Unmasking IRIS

- OI appears for the first time in a patient who, prior to commencing HAART, did not manifest that OI.
- Sub-clinical or unrecognised infections surface because of the emergence of pathogen-specific immune responses

### 2 Paradoxical IRIS

- An individual with a previously diagnosed OI or malignancy experiences a clinical deterioration while on effective HAART.
- Most commonly described in association with mycobacterial disease and cryptococcal disease.

## ACTG A5164: Immediate vs.. deferred ART in setting of OI

Immediate Rx ,  $\leq 14$ d after OI treatment  
(n=141)

Deferred Rx ,  $\geq 28$ d after OI treatment  
(n=141)

### Randomised phase IV strategy trial

- 85% male, 37% Black, 36% Hispanic, 23% White.
- Median CD4 ct =28, VL 5.07 log, ART 90% PI
- 63% PCP, 13% CM, 10% pneumonia, 5% Toxo, 2% MAC, 2% CMV, ex TB
- End-points 48 wk death/AIDS progression, no progression VL>50 cpm, VL<50 cpm

# ACTG A5164

	Immediate	Deferred	
Time to Rx	12d	45d	
Death/AIDS progression	20 (14.2%)	34 (24.1%)	
VL >50	54 (38.3%)	44 (31.2%)	p=0.035
VL<50	67 (47.5%)	63 (44.3%)	
ART changes	45	32	
Confirmed IRIS	8 (5.7%)	12(8.5%)	
Time to CD4 >50	4wk	8.1wk	
Time to CD4>100	4.3wk	12.1wk	

## **CNS mass lesions**

---

### ***Infections***

- **Toxoplasmosis**
- ***M. Tuberculosis***

### ***Malignancy***

- ***Primary cerebral lymphoma***
- ***CNS involvement with systemic lymphoma***
- ***Glioma***
- ***Breast Ca***

### ***Presentation***

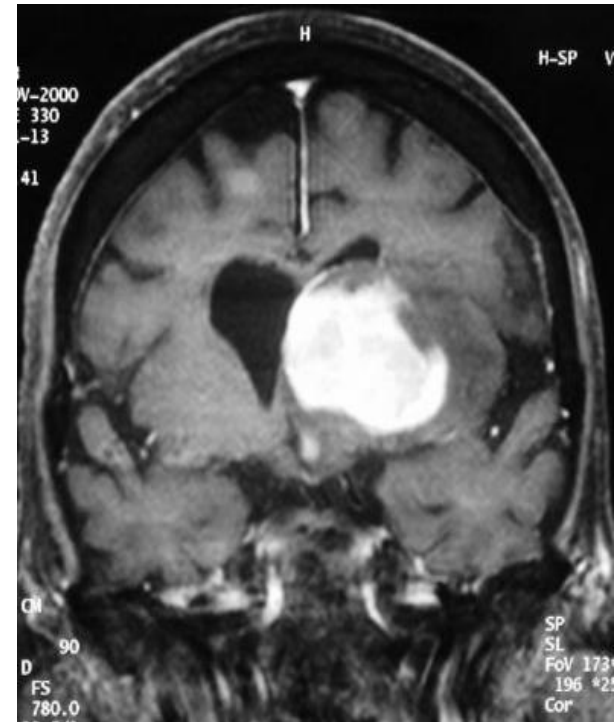
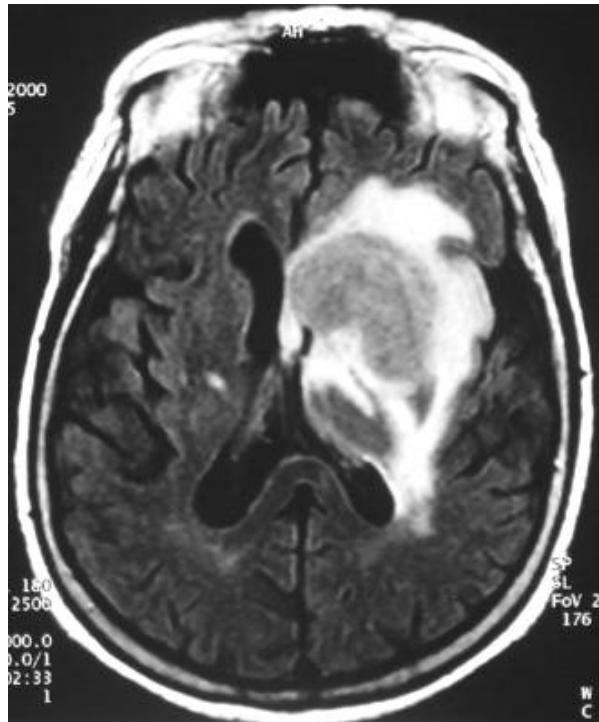
- **Headache**
- **Seizures**
- **Focal neurology**
- **Co-incident - MRI for another reason**

# CNS mass lesions

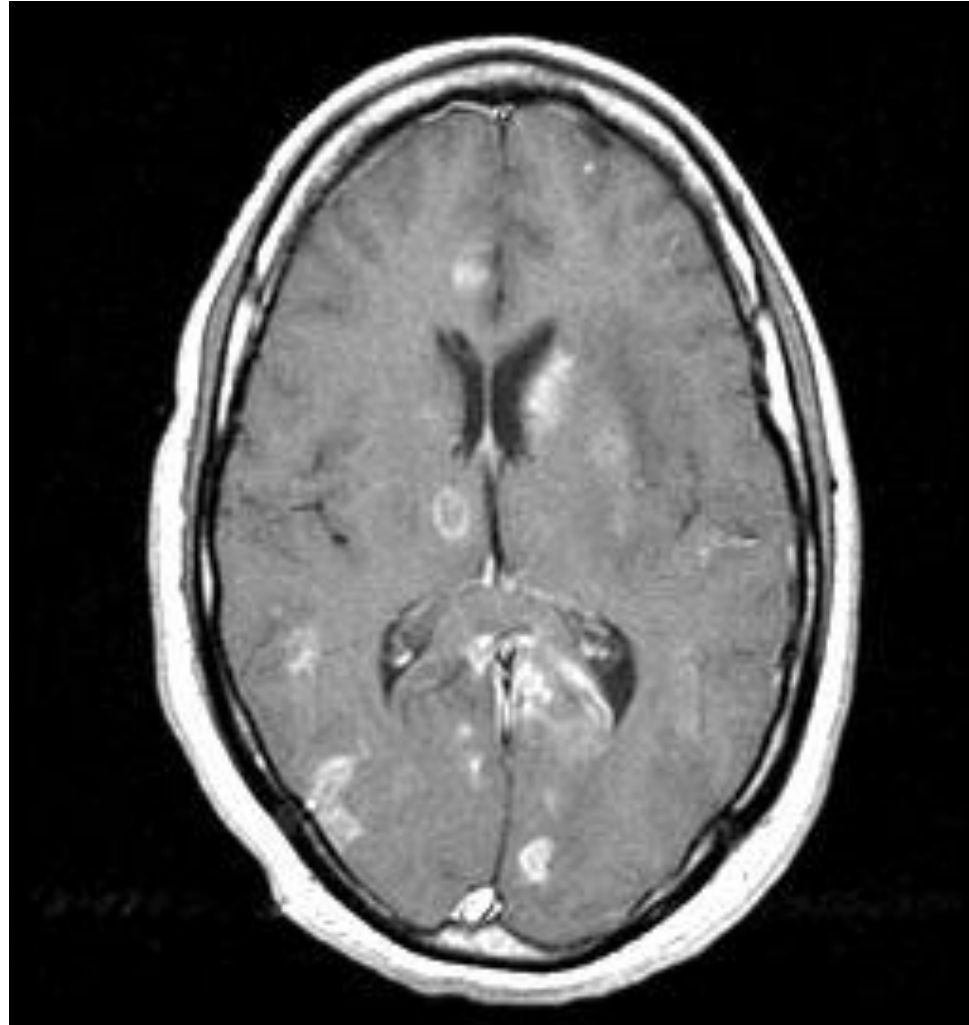
## Neuroimaging

- MRI is better than CT
- MRI appearances are not pathognemonic!
- Single lesion +/- abutting ventricle = '*more likely*' to be lymphoma
- Multiple lesions '*more likely*' to be Toxo

# MRI CNS mass lesions 1

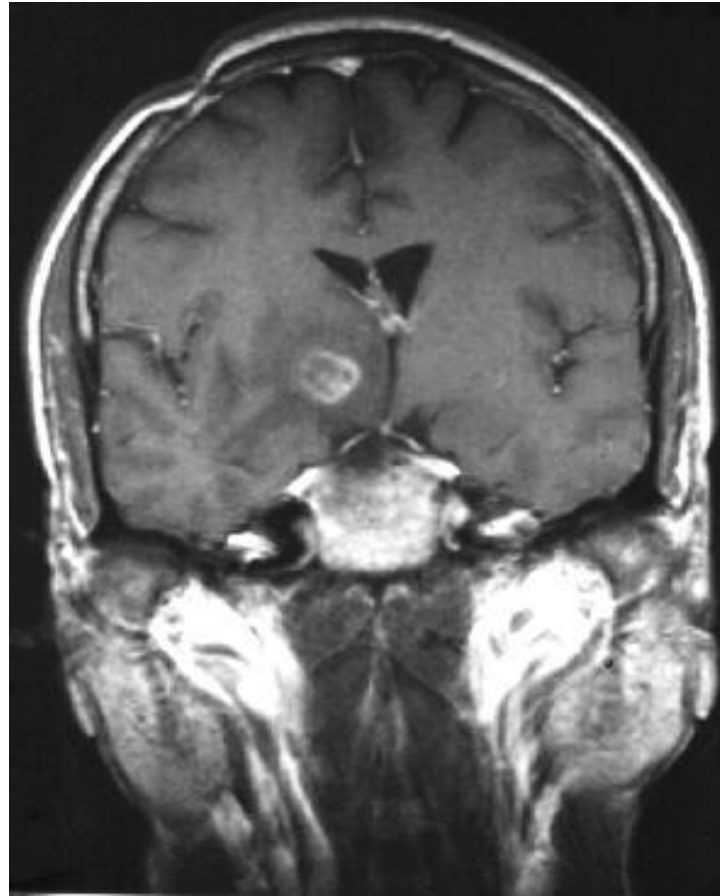


## MRI CNS mass lesions 2





## MRI CNS mass lesions 3



## CNS mass lesions

Empirical therapy for Toxoplasmosis

- **sulphadiazine / pyrimethamine**
  - **clindamycin / pyrimethamine**
  - **atovaquone / pyrimethamine**
- 
- Defervescence of fever/“toxicity” takes 7-10 days
  - Improvement in neurology takes longer
  - Neuroimaging takes 3-6 weeks to improve
  - Cannot rely on positive response to empirical therapy if also give corticosteroids  
[Neurogenic oedema will improve regardless of aetiology = false sense of security ]

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