

In memoriam Mark Wainberg  
21 April 1945- 11 April 2017



# **CULPRIT OR FACILITATOR HIV in the CNS**

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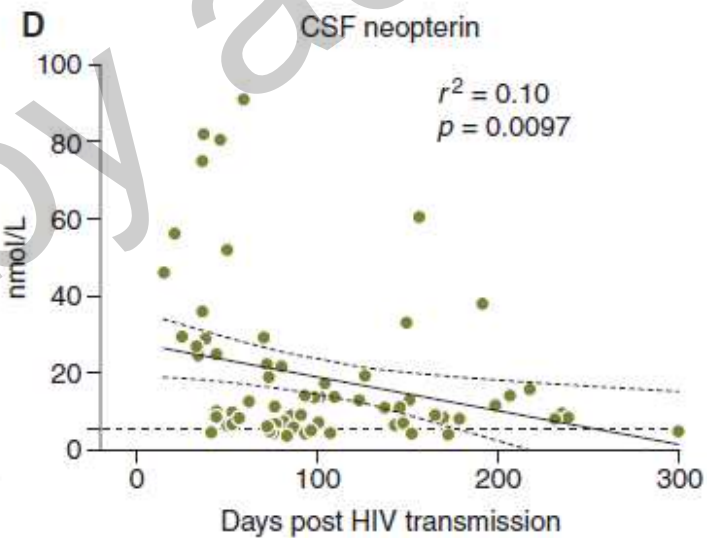
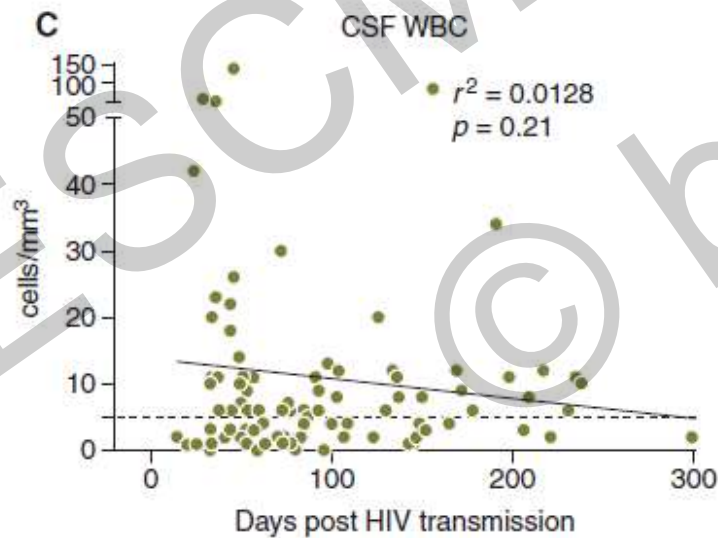
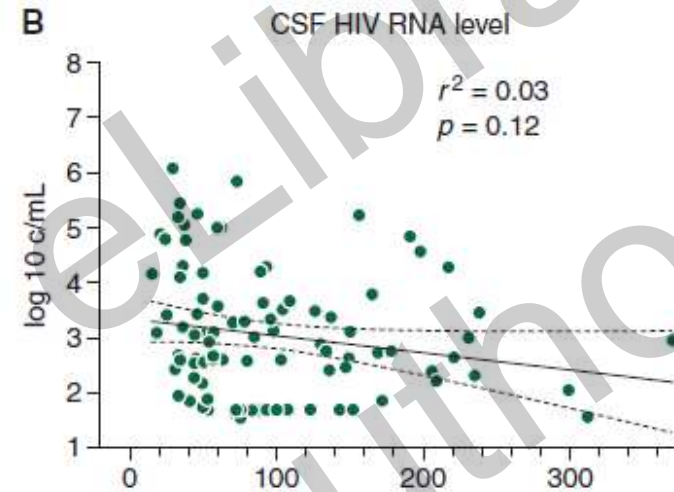
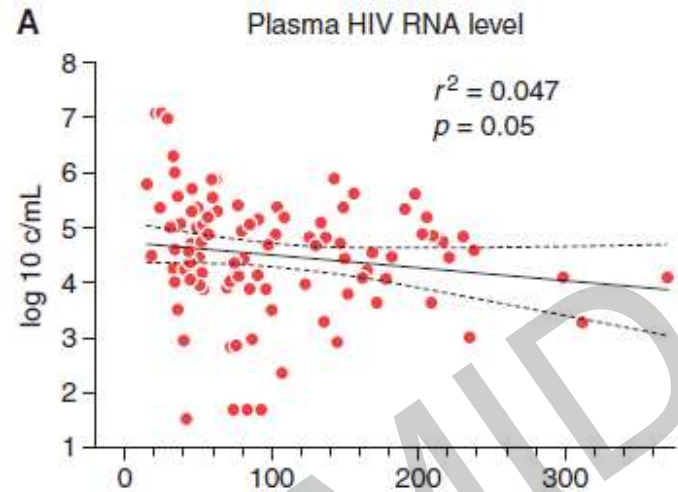
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# HIV in the brain

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# HIV enters the CNS within the first weeks after initial systemic infection



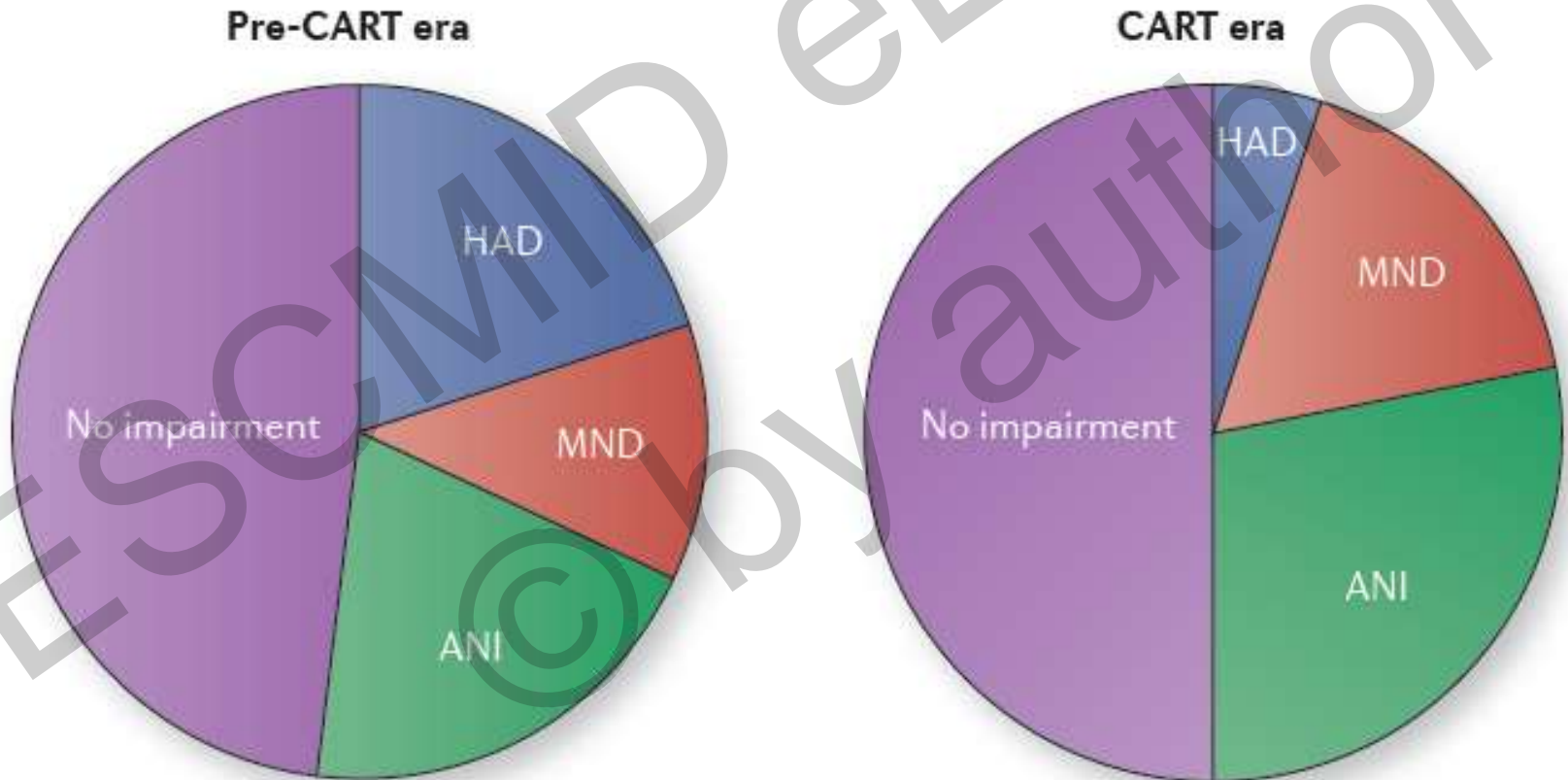
# Clinical impact

## HAND (HIV associated neurocognitive disorder)

Condition	Cognitive performance	Functional status	No delirium	No other confounding condition
<b>Asymptomatic</b> neurocognitive impairment (ANI)	Acquired impairment in $\geq 2$ cognitive domains ( $>1$ SD)	Normal	✓	✓
<b>Mild</b> neurocognitive Disorder (MND)	Acquired impairment in $\geq 2$ cognitive domains ( $>1$ SD)	Interference with daily function	✓	✓
<b>HIV-associated dementia</b> (HAD)	Acquired impairment in $\geq 2$ cognitive domains, with severe impairment ( $>2$ SD)	Marked impact on daily function	✓	✓

# Assessment of Neurocognitive Impairment

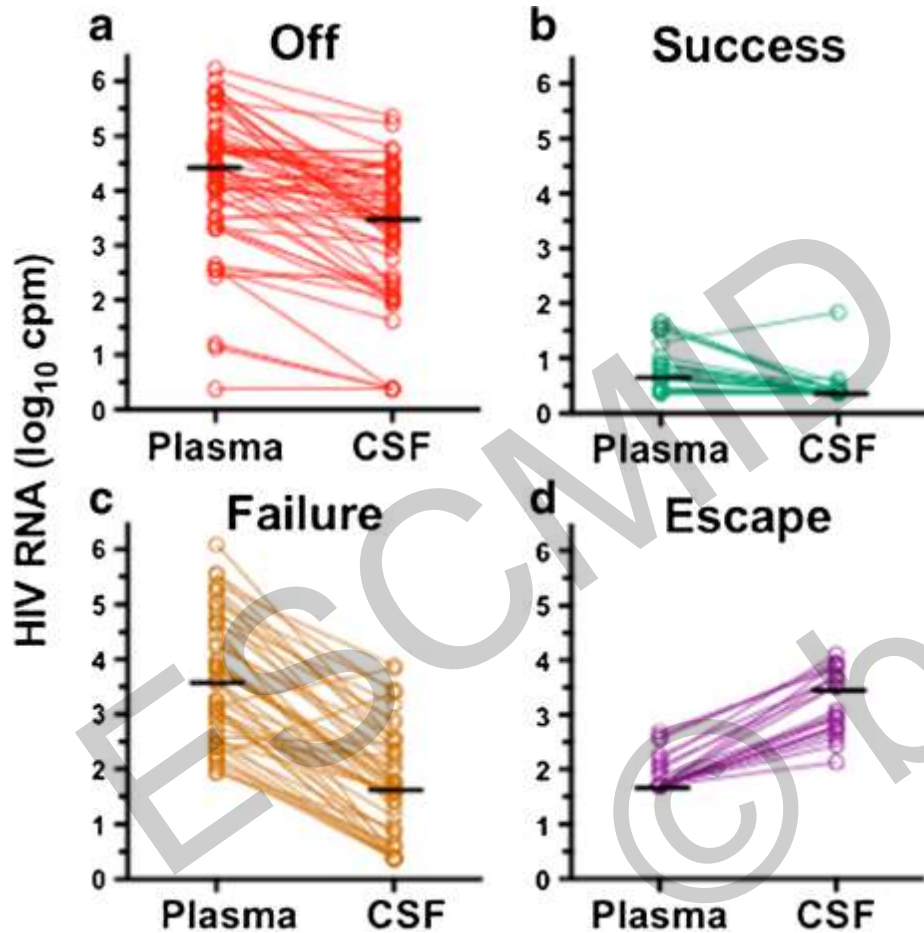
More-effective therapies have reduced the severity of HIV-associated neurocognitive disorders



**HIV in the brain in patients on  
antiretroviral therapy**

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# CSF HIV escape in the CNS in patients on stable cART



CSF viral escape can occur in 5–10% of cART recipients and is associated with immune activation<sup>1</sup>

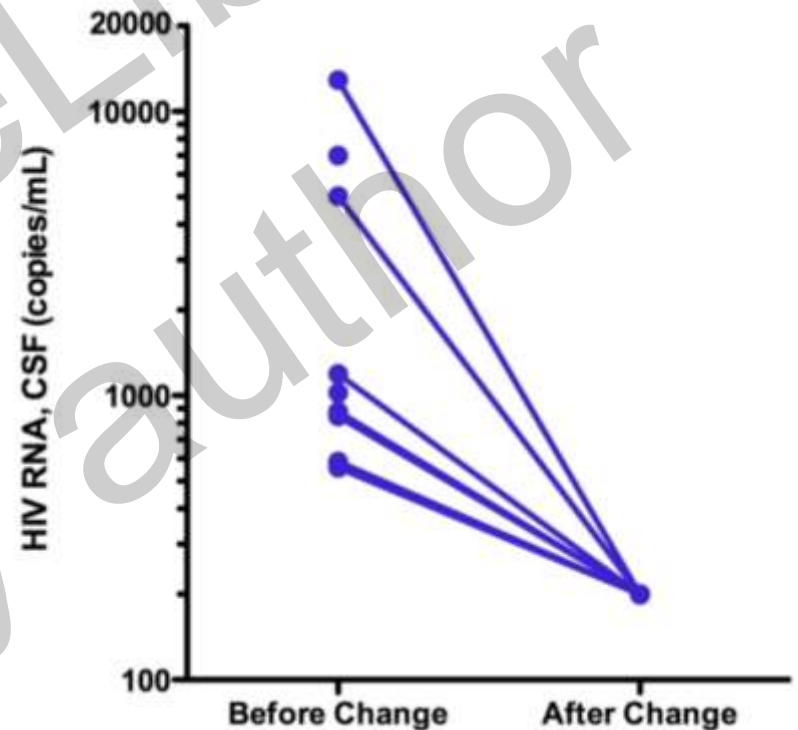


# Classification of CSF viral escape

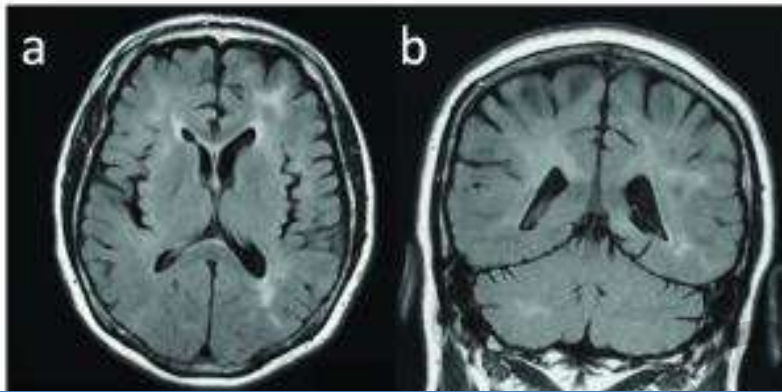
	Biology CSF	Neurological presentation	Plasma HIV RNA	HIV RNA CSF	WBC
<b>Asymptomatic CSF escape</b>	Equivalent to plasma blips?	Stable or asymptomatic incidental finding in cohort or other study	<50	50–200*	Normal
<b>Neuro-symptomatic CSF escape</b>	Virological failure in CNS compartment	New or progressive CNS symptoms and signs	<50 or 50–500	>50 or >×2 plasma	Usually elevated
<b>Secondary CSF escape</b>	CNS viral replication related to another infection with inflammation	Reflects provoking infection	<50 or 50–500	>50 or >plasma	Elevated, as by provoking infection

# Symptomatic CSF Viral Escape and Emergence of Drug Resistance in CSF

- 11 patients with neurological symptoms while on active cART in plasma
  - HIV RNA median in CSF : 880 c/mL
  - Median cART duration : 13 months
- **7 of 8 patients had resistance mutations in CSF**
  - cART was modified based on resistance and on penetrability rank
- **All patients improved concomitant with reduction of HIV RNA in CSF**

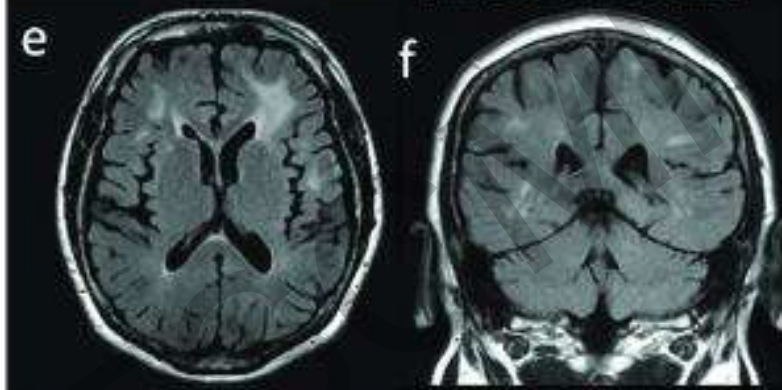


# In patients with CSF HIV escape diffuse leukoencephalopathy persists after clinical improvement



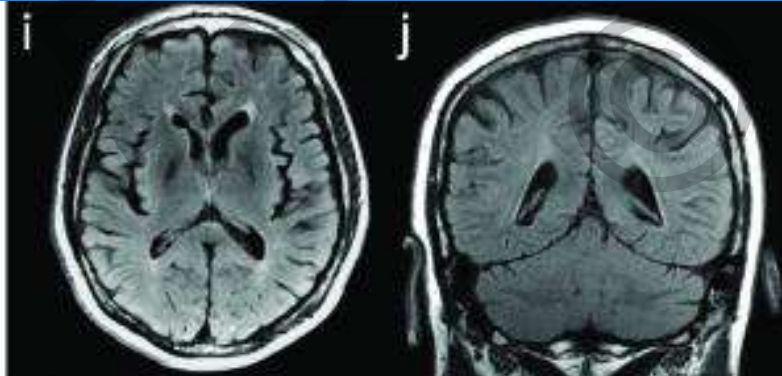
## At time of viral escape

- diffuse T2 prolongation



## Follow-up at 111 days

- persistence of diffuse leukoencephalopathy



## Follow-up at 567 days ,

- significant interval decrease in T2-prolongation

# Hypothesis for HIV associated neurological damage in the era of cART

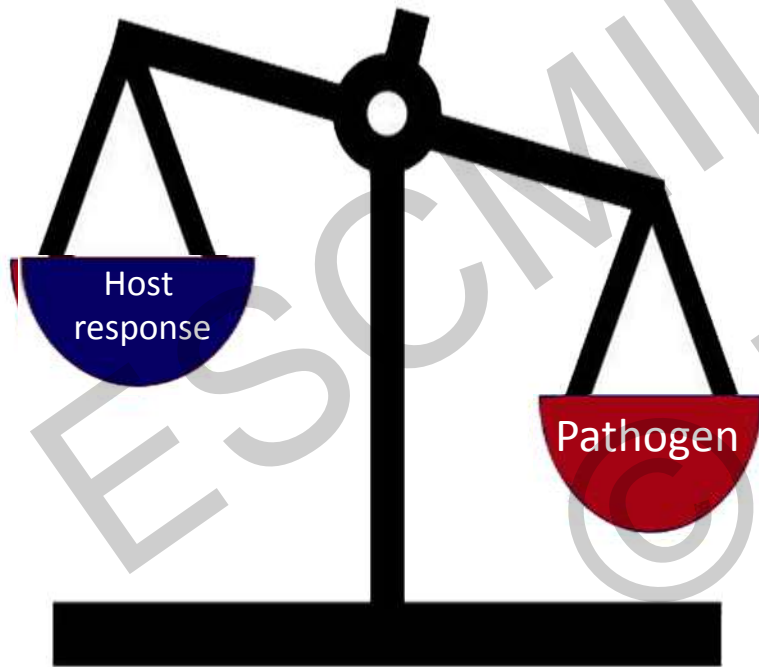
- possible ongoing low-grade viral replication and inflammation within the CNS
- cumulative exposure to antiretroviral and other medications/toxicity
- chronic systemic inflammation leading to accelerated vascular disease
- effects of comorbidities and neurodegeneration that occur with ageing

**HIV is not lonely in the brain**

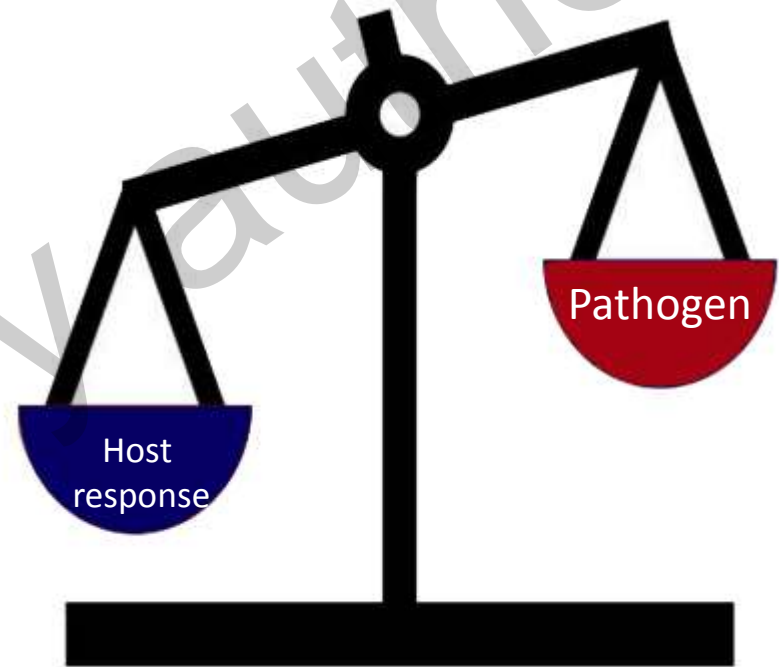
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# Interaction between microbial virulence factors and host immune responses

Advanced HIV infection



In treated HIV infection  
Immune reconstitution inflammatory syndrome (IRIS)



# Management of paradoxical IRIS –practical points

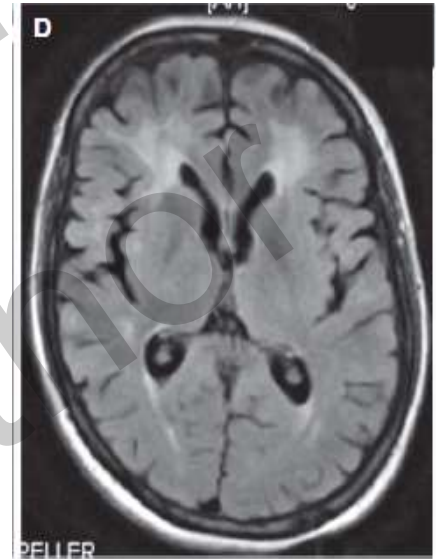
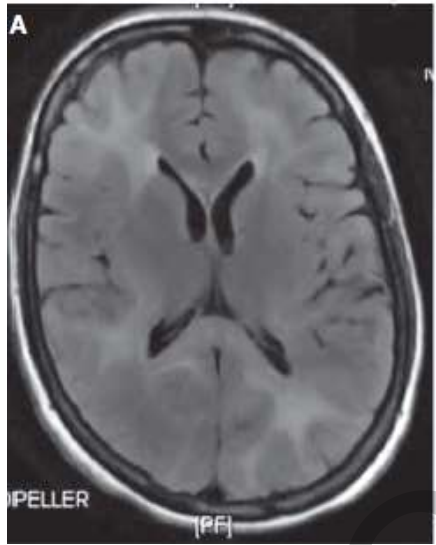
- Paradoxical IRIS is an exclusion criteria
- Ensure CSF pathogen load is reduced before cART initiation
  - Prolonged induction therapy
  - Higher dose initial consolidating therapy
- Delay ART initiation if CNS IRIS is a threat (e.g. C. neoformans meningitis, TB meningitis)
- Systemic corticosteroids for severe forms of IRIS inflammation, in the absence of contraindications
- Stop cART- under exceptional circumstances

# The unusual suspects

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# EBV encephalitis in the setting of HAND – diagnosis challenge



12 mths follow-up

NCI -gradually worsening  
ART: DDI+3TC+ATV/r  
CD4=833 lf/mmc  
HIV RNA plasma=700c/ml

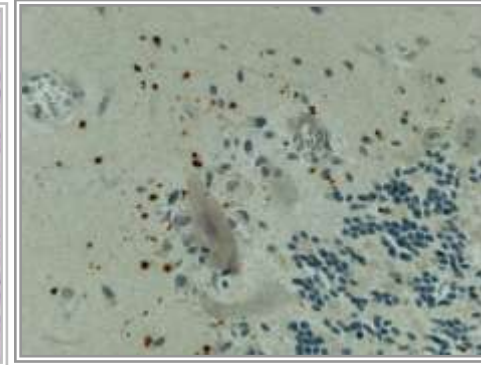
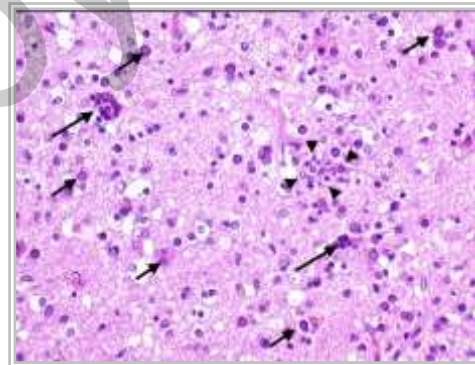
Severe NCI + ataxia, +  
lower limb weakness  
HIV RNA CSF= 7000 c/ml  
CSF 24 cells, Prot=1.12g%

**Positive EBV DNA in CSF  
and brain biopsy**

Recovery after new cART:  
3TC+RAL+ETV+DRV/r  
&  
6 mths: Valgancyclovir

# Subacute measles encephalitis

- occurred as a cluster during 2 consecutive measles epidemics in Romania in parenterally HIV infected children and adolescents with severe immune suppression (1997-1998 and 2006-2007)<sup>1</sup>
- myoclonus as characteristic symptom → motor deficit rapid extension → eventually cognitive decline → coma (after median 19 days) → exitus<sup>1</sup>
- **immunocytochemistry confirmation of measles in the brain**<sup>1</sup>
- strikingly low HIV RNA levels in CSF compared to plasma ( $2.31 \pm 0.23$  vs.  $4.22 \pm 1.31$ ) possibly due to inhibitory effect of measles virus on HIV<sup>2</sup>

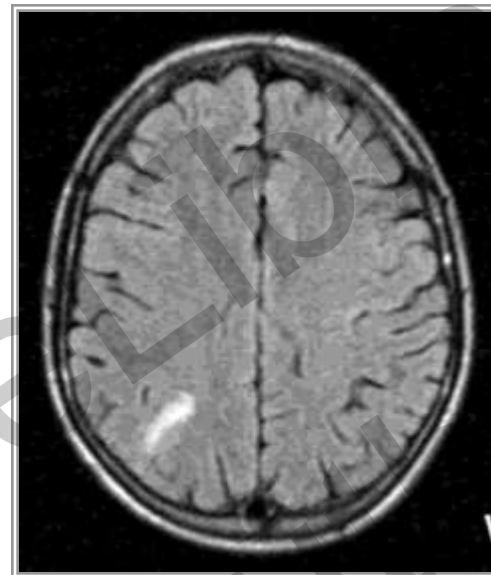


<sup>1</sup>Duiculescu D, et.al, J Neurovirol 13/suppl 1/2007, p77

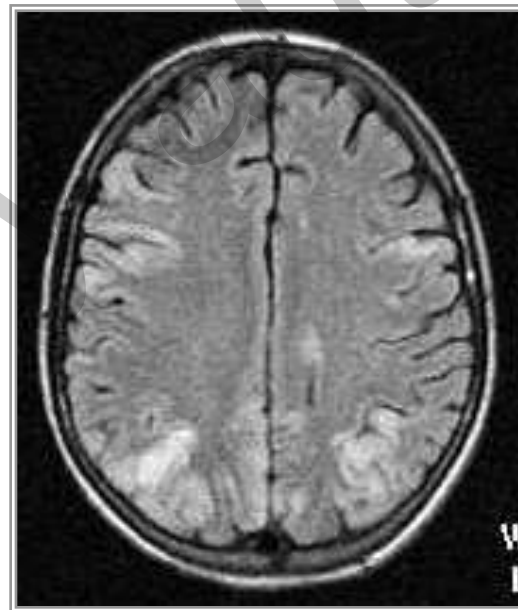
<sup>2</sup>Ene L, et. al, J Neurovirol 13/suppl 1/2007, p78

# MRI aspects in a 17 year old adolescent with myoclonic measles encephalitis

At onset of myoclonic jerks  
125 days after uncharacteristic measles episode

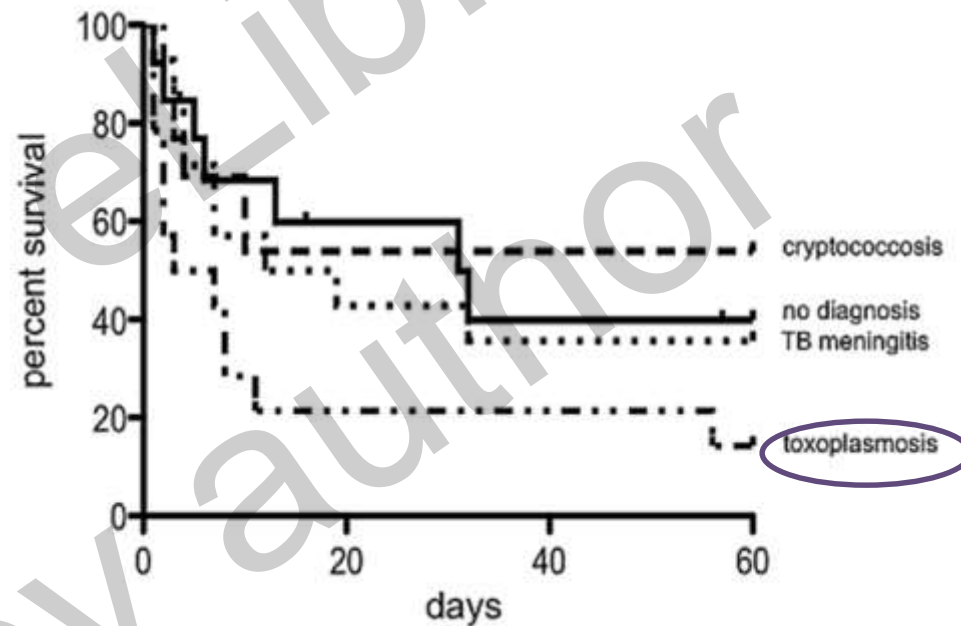


20 days later  
coma



# Toxoplasma gondii - another pathogen to consider in subacute HIV-associated meningitis

- CSF *T. gondii* DNA, performed retrospectively, was positive in 32.8%
- Highest mortality in DNA *T. gondii* + group (untreated)



**Toxoplasmosis should be included in the differential diagnosis of HIV-infected patients with subacute meningitis and empiric treatment for toxoplasmosis should be considered**

**Latent pathogens  
still suspects for neurocognitive  
impairment (NCI)**

# Neurocognitive impairment in HIV-infected individuals with previous syphilis

HIV individuals with prior syphilis had

- a greater number of impaired neuropsychological test domains

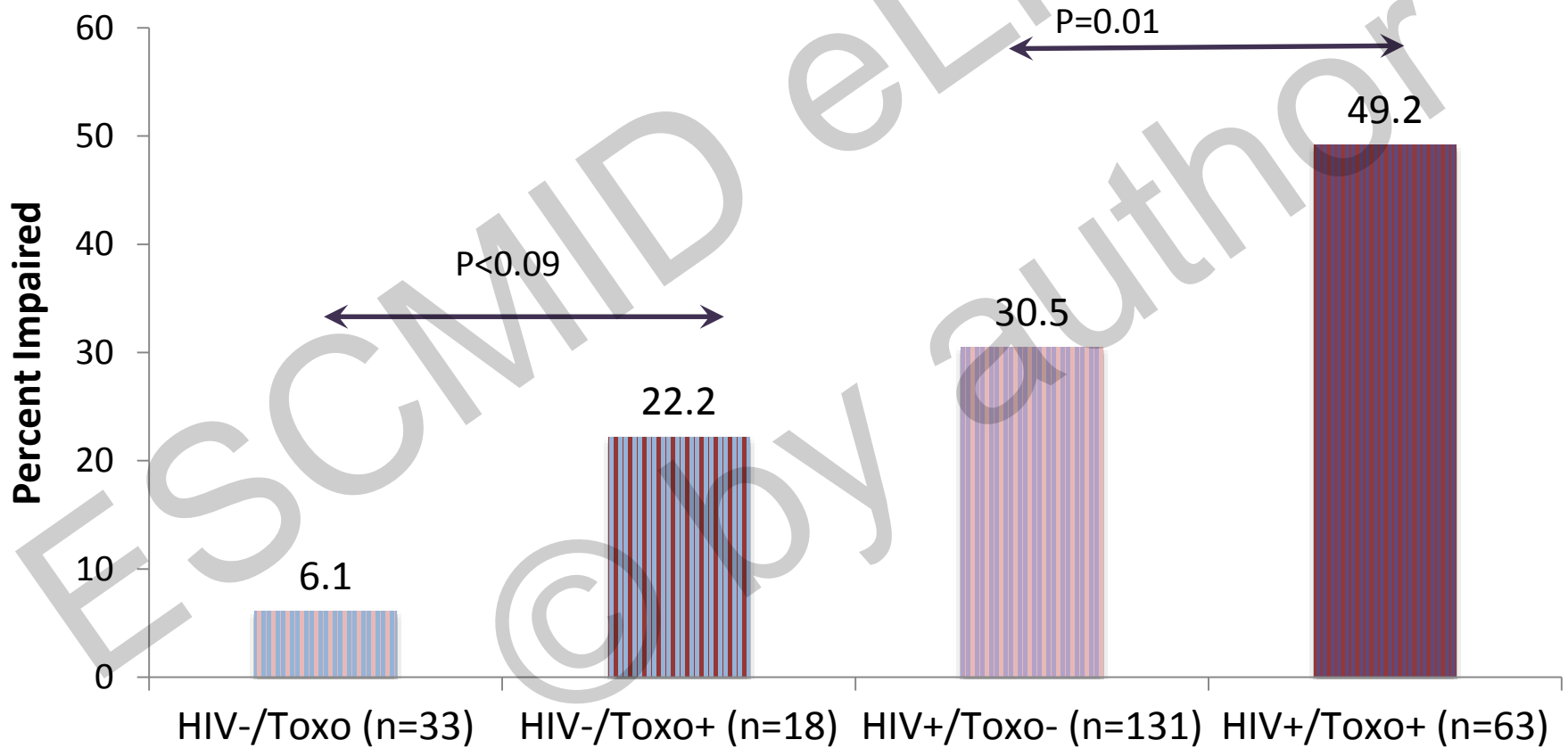
(1.90 [1.77] versus 1.25 [1.52],  $P = 0.03$ ),

- a higher global deficit score

(0.47 [0.46] versus 0.31 [0.33],  $P = 0.03$ ),

These effects of prior syphilis remained after controlling for education and premorbid intelligence

# Latent Toxoplasma infection may result in increased cognitive difficulties in co-infected individuals



## Latent CMV infection and NCI

- Levels of CMV lysate antibody correlated with neurocognitive performance ( $p = .045$ )
- Associations between levels of CMV antibodies, cardiovascular risk, and neurocognitive health in HIV+ patients stable on ART **are moderated by age-associated increases in response to CMV**



## Conclusion

- HIV enters the brain early and may determine local inflammation, and viral persistence
- Neurocognitive impairment can be associated with HIV directly or through other uncontrolled/latent infections
- The approach of CNS infections in the setting of chronic HIV-infection has to address the balance between pathogen and host immune responses
- **Think holistically : HIV can be both the culprit and the facilitator for brain damage**

Thank you for attention



Dr. Victor Babes