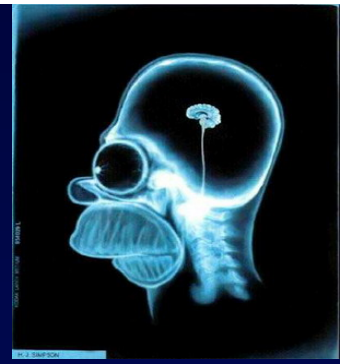
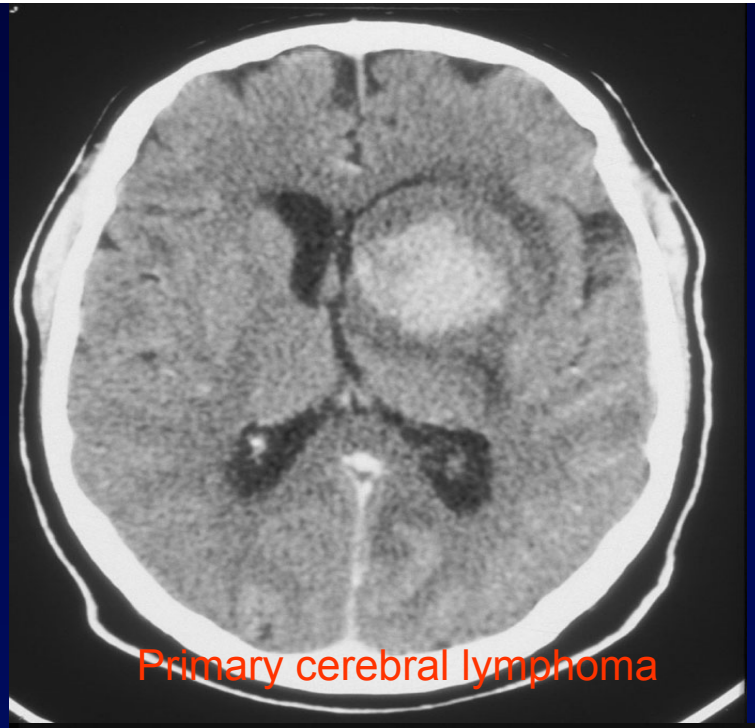
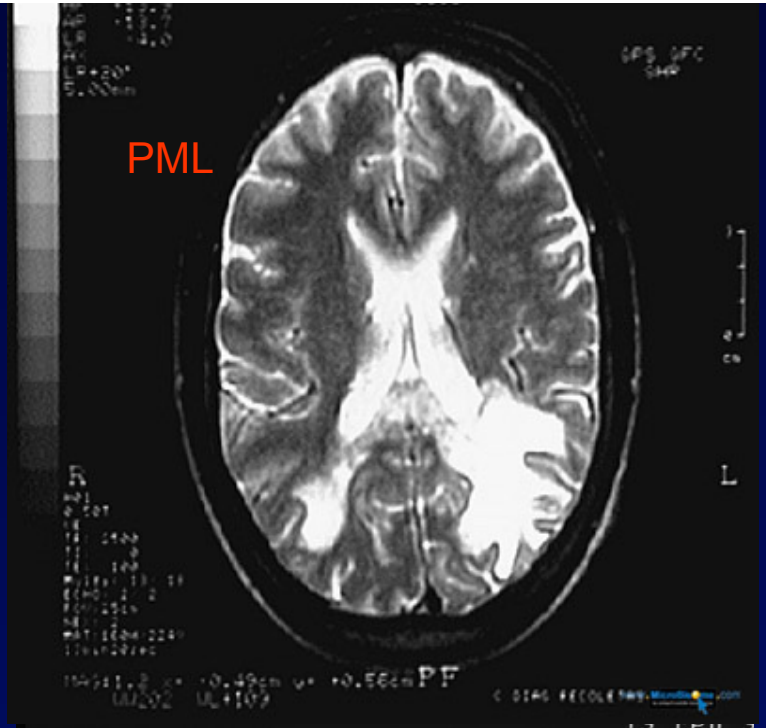


Workshop: Management of neurocognitive disorders in HIV-infected patients

Barcelona, May 2013

Daniel Podzamczer; MD, PhD
HIV/AIDS Program Director
HIV Unit. Infectious Disease Service
Hospital Universitari de Bellvitge
L'Hospitalet, Barcelona, SPAIN


Primary cerebral lymphoma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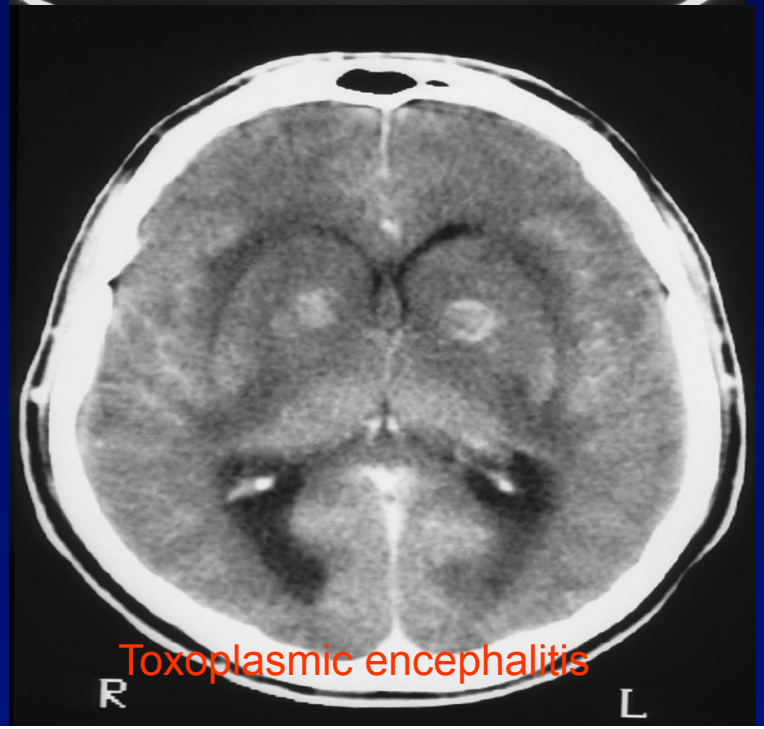
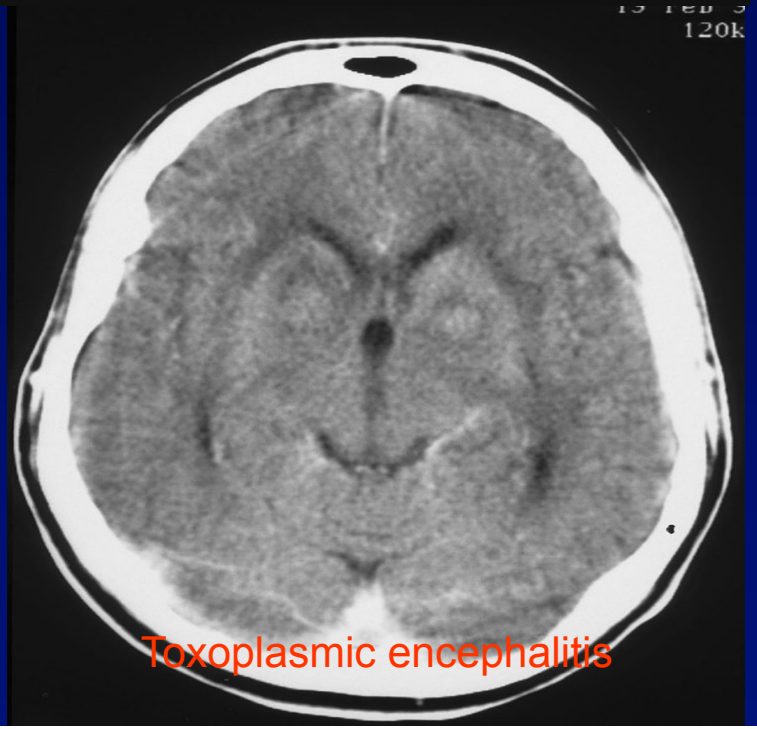
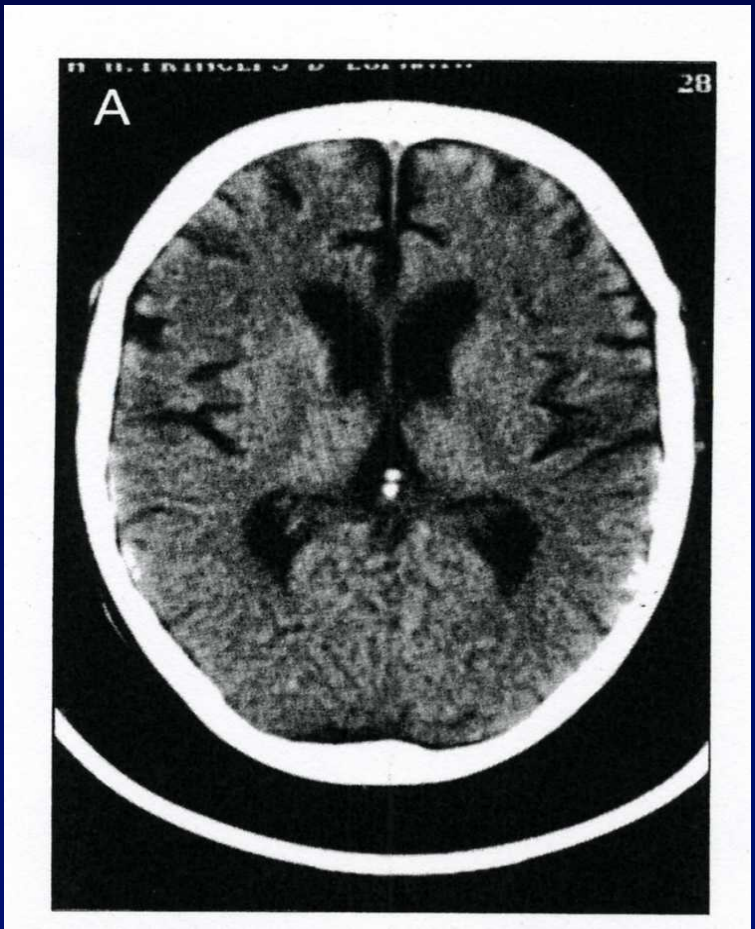

Toxoplasmic encephalitis
R
L


Toxoplasmic encephalitis

HIV encephalitis*



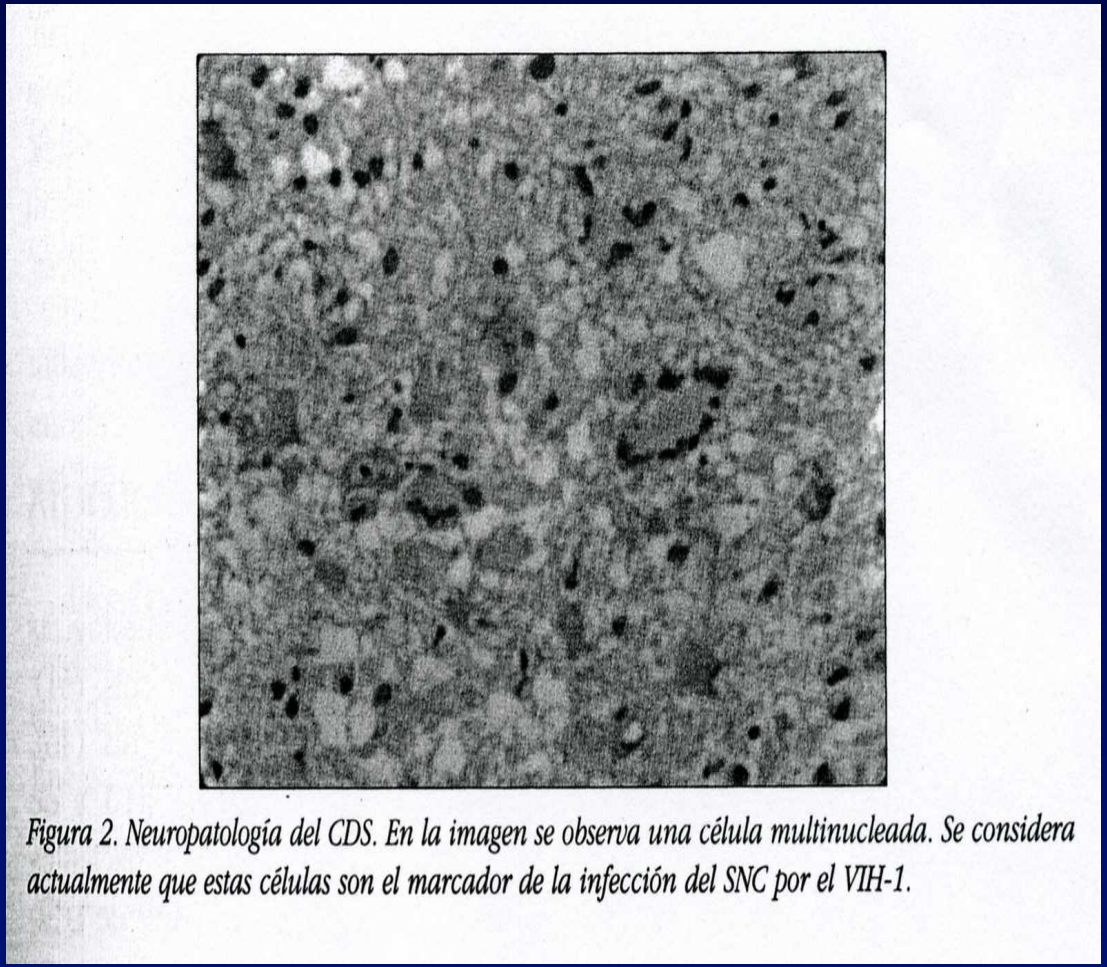
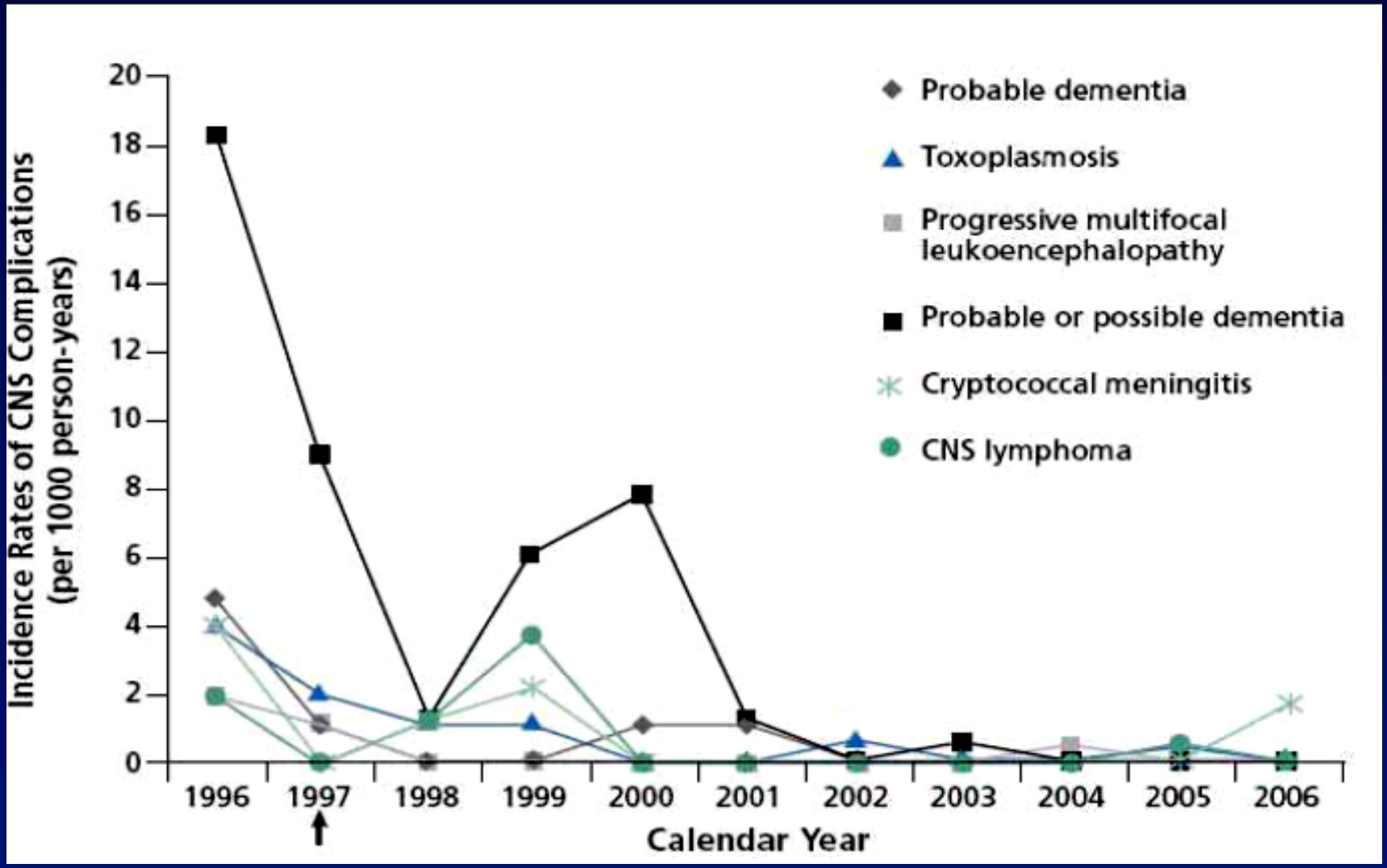


Figura 2. Neuropatología del CDS. En la imagen se observa una célula multinucleada. Se considera actualmente que estas células son el marcador de la infección del SNC por el VIH-1.

* AIDS dementia complex, HAND (**H**IV-**A**ssociated **N**eurocognitive **D**isorders)

Incidence of neurological disorders (1996-2006)

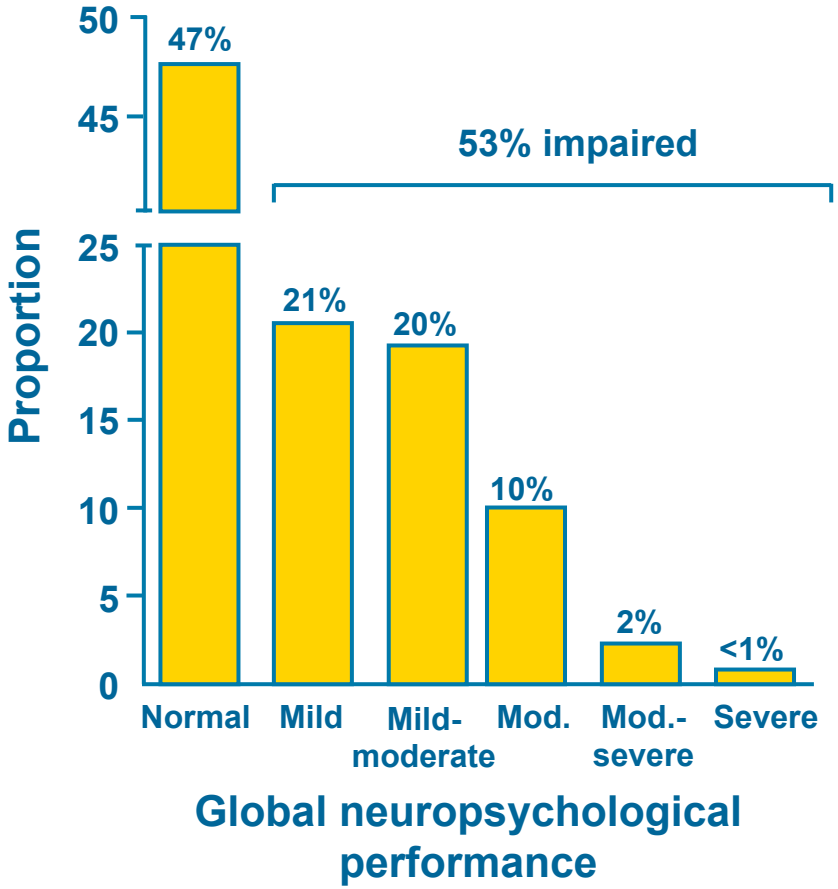


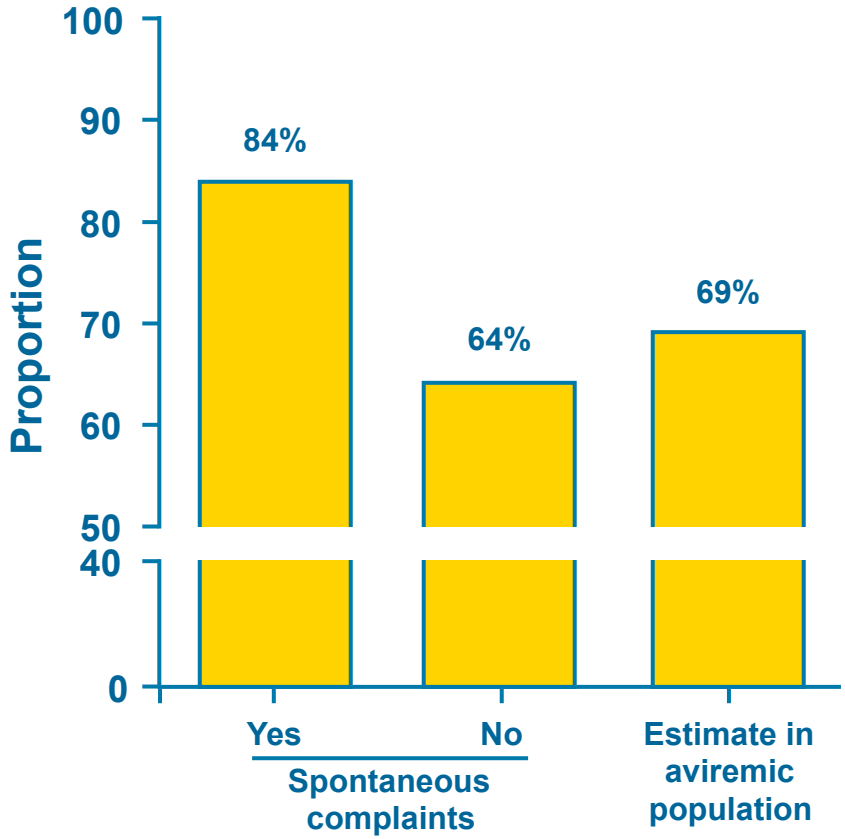
EuroSIDA

D'Arminio Monforte A. Ann Neurol

HAND is common in the US and Europe

More than half of patients are affected





Heaton R et al. CROI 2009. Abstract 154.

Simioni et al. *AIDS* 2010; 24: 1243–1250.

Compartmentalization of HIV in CNS

- Early infection: non-compartmentalized, HIV in CSF and blood identical:

  - derived chiefly from trafficking CD4 cells
  - responds rapidly to ART, in parallel with blood decay
  - Probably not so important CNS drug penetration

- Chronic infection: compartmentalized, the population diverge
  - different cell source: brain macrophagues
  - slower response
  - Importance of drug penetration into CNS

Yilmaz A, et al. J Antimicrob Chemother 2012; 67: 299-311

N Engl J Med. 1988 Dec 15;319(24):1573-8.

Neuropsychological outcome of zidovudine (AZT) treatment of patients with AIDS and AIDS-related complex.

Schmitt FA, Bigley JW, McKinnis R, Logue PE, Evans RW, Drucker JL.

Abstract

Two hundred eighty-one patients with the acquired immunodeficiency syndrome **(AIDS) or advanced AIDS-related complex** were enrolled in a **double-blind, placebo-controlled trial** of the efficacy and safety of orally administered **zidovudine** (azidothymidine or AZT). Significant clinical benefits and adverse experiences have been reported from this trial. Because neuropsychiatric dysfunction is often associated with human immunodeficiency virus (HIV) infection, a brief affective and neuropsychological examination was administered over 16 weeks of the trial to evaluate any changes in neuropsychological function that occurred with drug administration.

Patients receiving zidovudine, particularly those with AIDS, showed improved cognition as compared with patients receiving placebo. There were no changes in affective symptoms. The zidovudine recipients also had a statistically significant reduction in the intensity of symptomatic distress during the trial that may account in part for the observed cognitive changes. Some improvement in various cognitive measures was also seen in patients with AIDS-related complex. The results of this study suggest HIV-associated cognitive abnormalities may be partially ameliorated after the administration of zidovudine.

HIV and HAND

-Correlation between CSF viral loads and degree of cognitive impairment

-Virologic suppression in the CSF with ART →significant improvement in function

-Pts with ART and VL <400 c/mL can develop cognitive impairment, suggesting:

ONGOING DAMAGE DUE TO IMMUNE ACTIVATION (neopterin, B2-microglobulin, etc) DRIVEN BY CHRONIC LOW-LEVEL INFECTION

Brew, JID 1997; Ellis, Ann Neurol 1997; McArthur, Ann Neurol 1997; Clifford, Neurol 2002

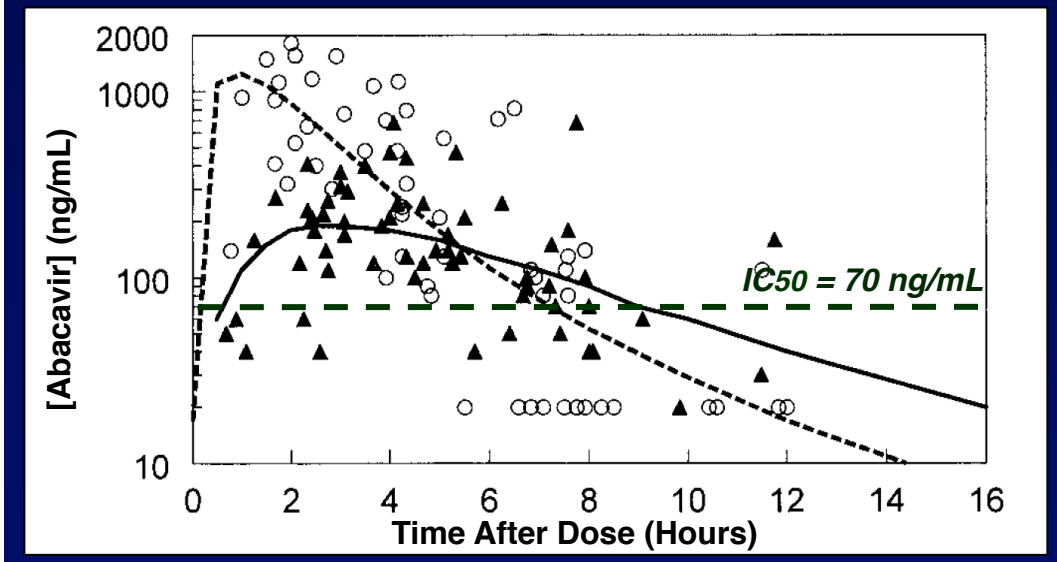
Determinants of Drug Penetration Across the BBB

- Protein Binding
- Molecular Weight
- Lipophilicity
- Ionization
- Molecular pumps

- NRTIs > PIs ~ NNRTIs
- NRTIs > NNRTIs > PIs
- PIs ~ NNRTIs > NRTIs
- Tenofovir
- P-glycoprotein
  Organic anion transporters

Pharmacokinetics in CSF
NRTIs Differ in CSF Penetration

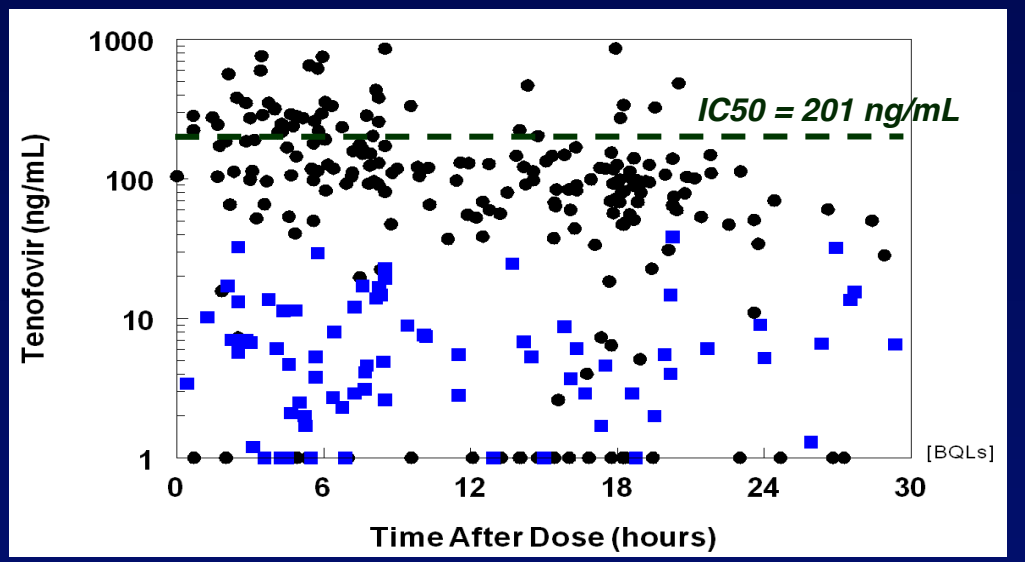
Abacavir



Extent of CSF penetration was 36% of plasma concentrations

Capparelli et al, Antimicrob Agents Chemother 2005, 49: 2504-6

Tenofovir

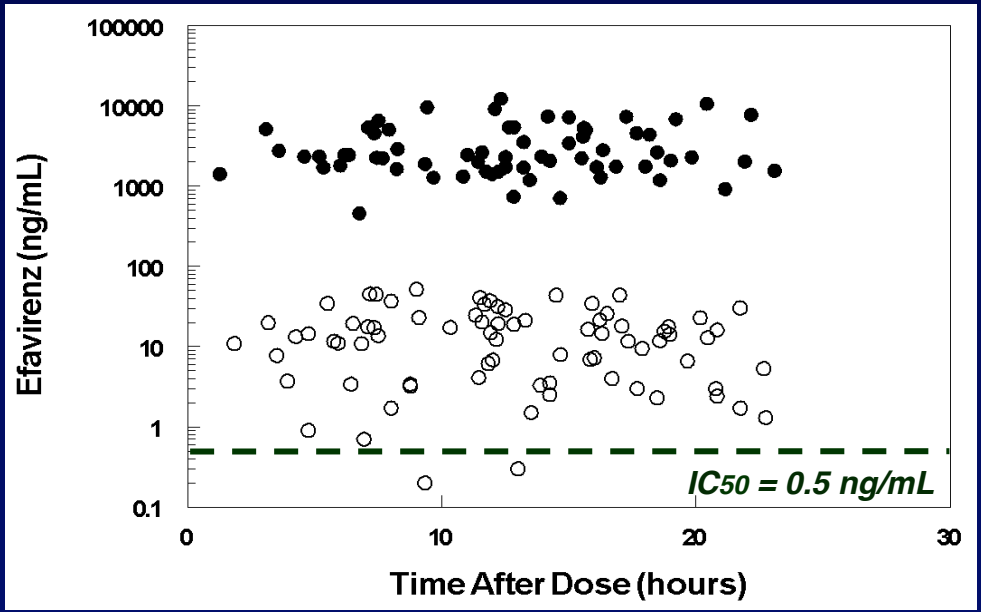


Extent of CSF penetration was 5% of plasma concentrations

Best et al, 15th Conference on Retroviruses and Opportunistic Infections, 2008, Abstract 131

Pharmacokinetics in CSF
NNRTIs Differ in CSF Penetration

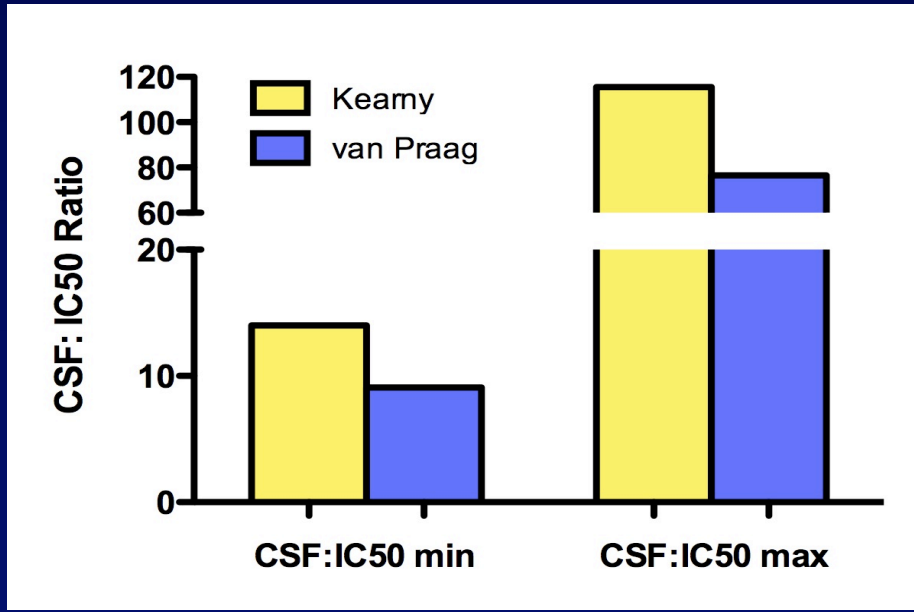
Efavirenz



Extent of CSF penetration was 0.5% of plasma concentrations

Best et al, 16th Conference on Retroviruses and Opportunistic Infections, 2009, Abstract 702

Nevirapine



Extent of CSF penetration was 29-63% of plasma concentrations

van Praag et al, Antimicrobial Agents and Chemotherapy, 2002
Antinori et al, Clinical Infectious Diseases, 2005

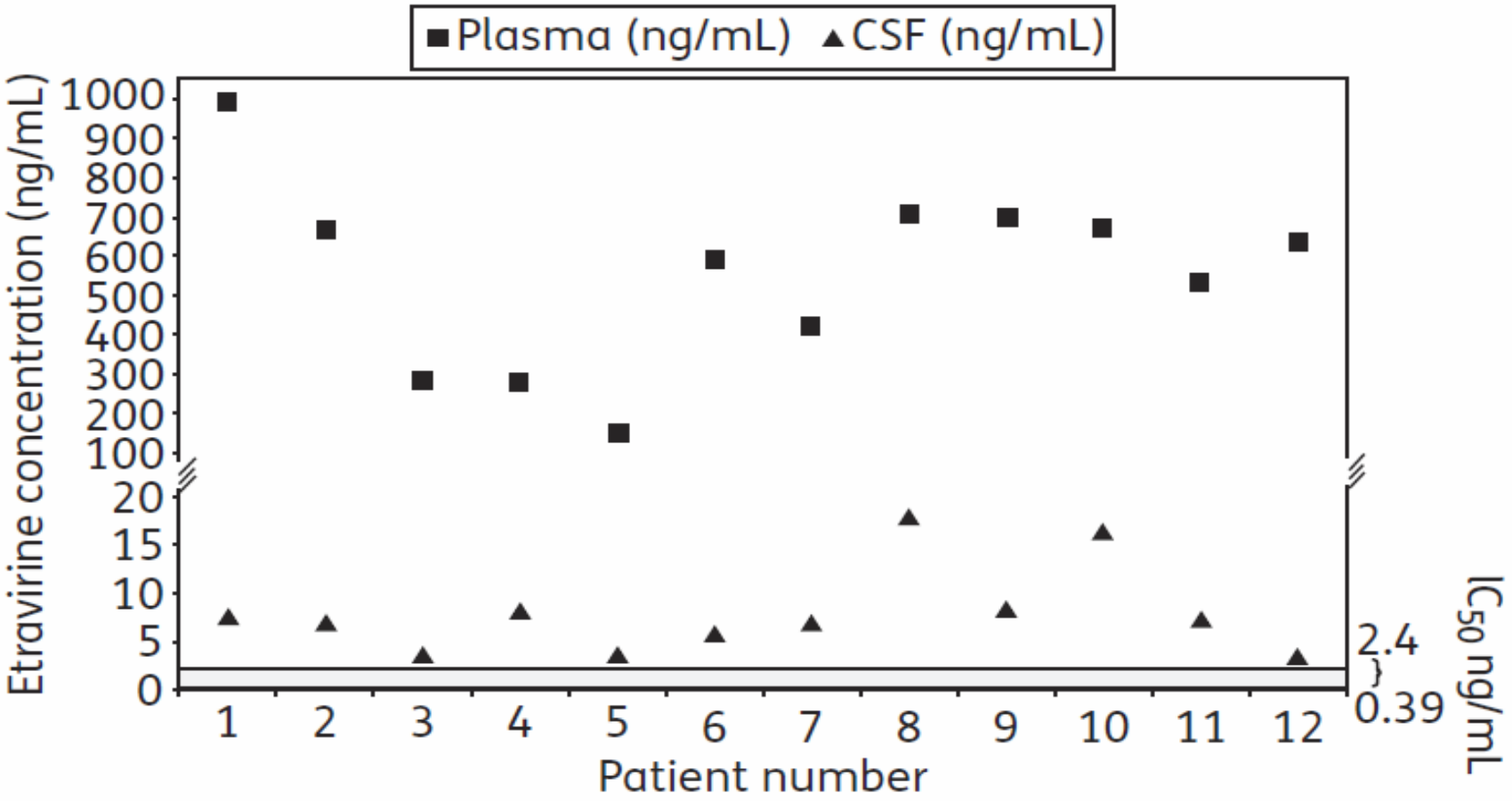
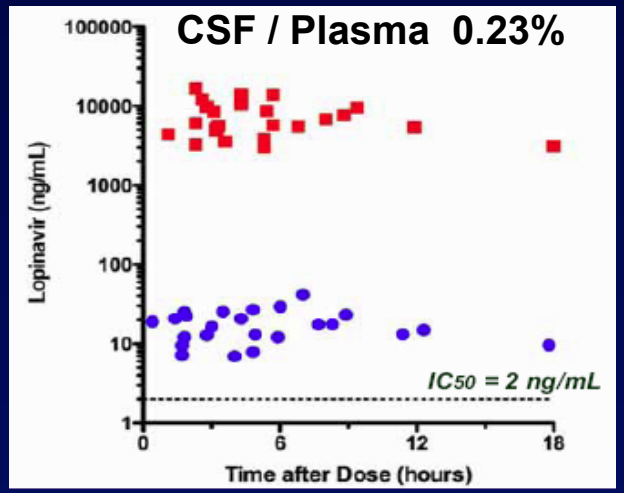


Figure 1. Plasma and CSF concentrations of etravirine.

Tiraboschi JM et al, Etravirine concentrations in CSF in HIV-infected patients. J Antimicrob Chemother. 2012

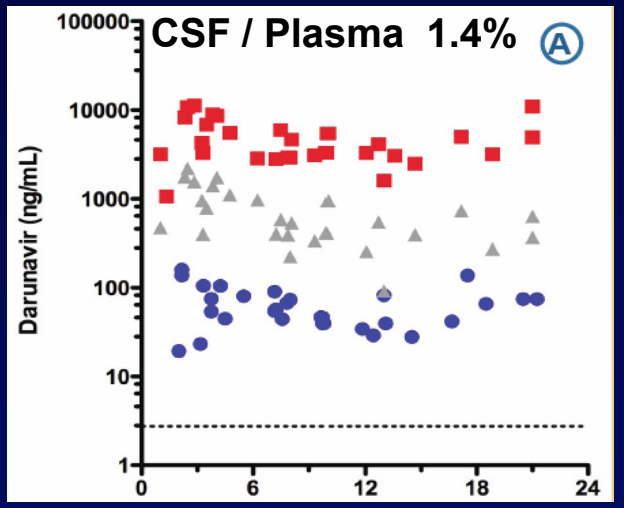
PI/r penetration in CSF

Lopinavir/r



Capparelli EV et al. AIDS 2005;19:949-952

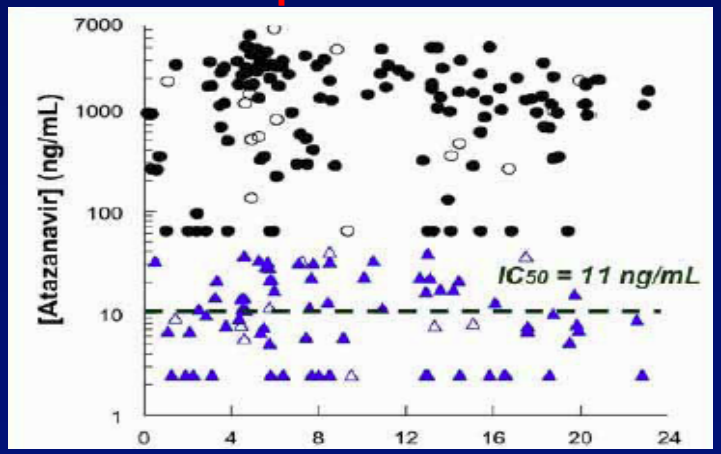
Darunavir/r



Letendre S. 45. ICAAC 2009. San Francisco

Atazanavir/r

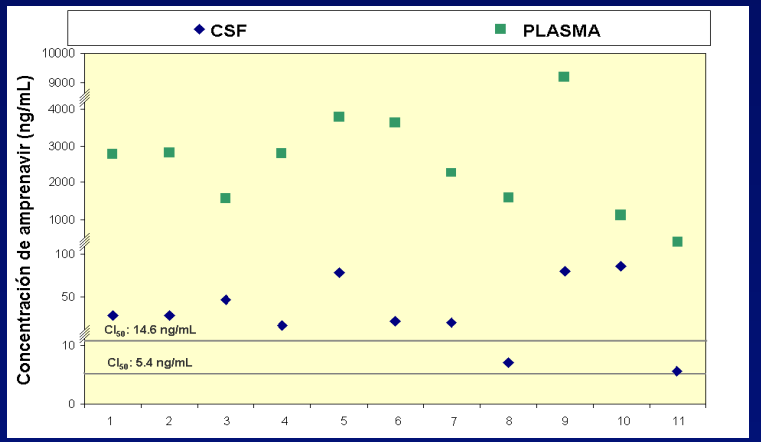
CSF/plasma 1%



Best B. AIDS 2009; 23: 83-7

Fosamprenavir/r

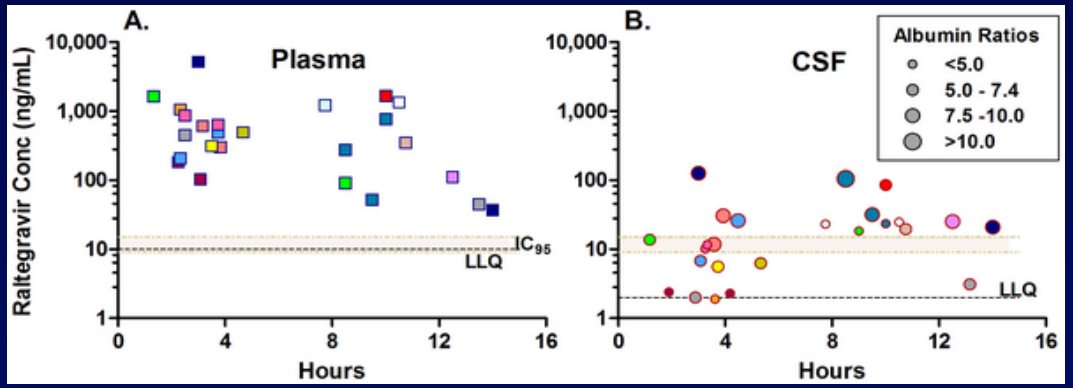
CSF/plasma 1%



Saumoy M, et al. HIV Med 2011; 12: 438-441.

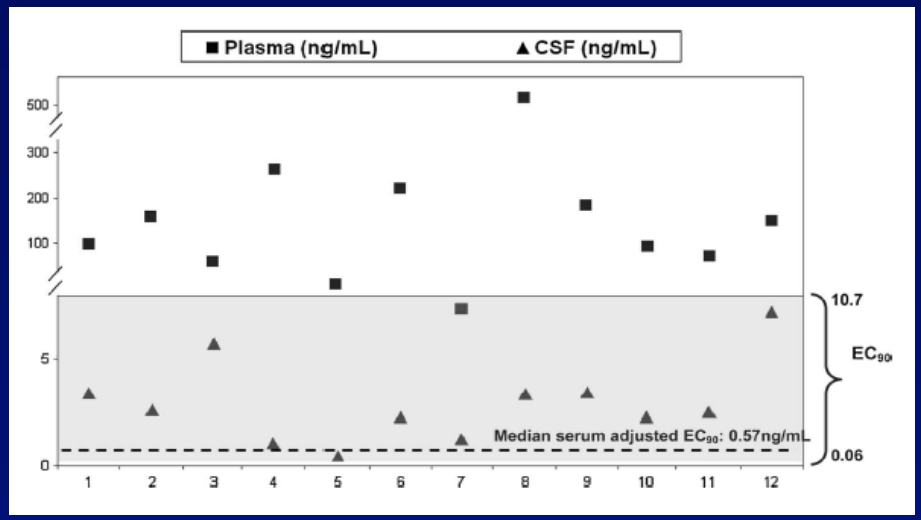
Penetration in CSF of new ARV

Raltegravir



Yilmaz A, et al. PLoS One. 2009 Sep:e6877

Maraviroc



Tiraboschi J, et al. JAIDS 2010; 55: 606-9

CNS Penetration-Effectiveness Ranks 2010

	4	3	2	1
NRTIs	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
NNRTIs	Nevirapine	Delavirdine Efavirenz	Etravirine	
PIs	Indinavir-r	Darunavir-r Fosamprenavir-r Indinavir Lopinavir-r	Atazanavir Atazanavir-r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Entry/Fusion Inhibitors		Maraviroc		Enfuvirtide
Integrase Inhibitors		Raltegravir		

Letendre et al, 17th CROI 2010, Abstract 172

Persistent HIV in CSF despite HAART

-300 pts with CSF VL < 50 copies/mL
  -122 (41%) 2-50 copies/mL
  -Worse CNS penetration score (CHARTER)
  -22% < 2 copies/mL in blood samples
-Worse neuropsychologic testing

CONCLUSIONS

-Substantial proportion of effectively treated HIV pts have low-level HIV in CSF, worse ART penetration and worse NT

-**ONGOING VIRAL-INDUCED INJURY OF THE CNS**

Letendre S, et al. CROI 2009 (abstract 484b)

Neurologic symptoms in pts with discordance between CSF and plasma VL

- Acute/subacute presentation of CNS symptoms (no prior)
  (n=11; 8 moderate/severe; 2 severe headache; 5 cerebellous affect. 1 coma)
- CSF abnormal; MNR suggestive of encephalitis/myelitis
- CSF VL + (880(558-12885 c/mL) despite pVL<50, or CSF VL 1 log > pVL
- CPE score < 2 in 5/11; R mutations in 5 with pVL < 50.

- Treatment and outcome:
  - Change ART to improve CPE score
  - Clinical improvement within 4 weeks
  - CSF normal in 9 and VL < 200 c/mL

Canestri A, et al. CID 2010;50:773-778

Neurologic symptoms in pts with discordance between CSF and plasma VL

- 10 pts, stable HIV (16 yrs); 9/10 2 NA+PI/r. CD4 nadir 35
- Acute/subacute presentation of CNS symptoms (3 prior)
- CSF abnormal; MNR suggestive of encephalitis (7/8)
- CSF VL + (3900(134-9,056 c/mL) despite pVL<50, or CSF VL 1 log > pVL
- CPE score 6.5 (3-13); R mutations in 6/7 pts.

- Treatment and outcome:

  Change ART to improve CPE score

  Clinical improvement in 8/9

  CSF VL undetect in 4/9 in 70 (11-189d)

Peluso MJ, et. AIDS 2012;26:000-000

Failure of LPV/r monotherapy: impact on CNS

- Randomized open study: LVP/r vs. triple ART (n=60)
- No prior VF to any ARV. Viral suppression 50 (9-63) m.
- 6/42 vs. 0/31 VF after 12 (6-24) weeks
- VL in CSF 4.2 vs. 3.4 in blood (+ ↑WBC)
- 4/6 CNS symptoms: headache, dizziness, visual disturbances, deficit in concentration, ataxic gait
- No resistance mutations
- In 45 pts: 8/25 LPV/r vs. 0/15 triple (p=0.01) detect VL in CSF
- Higher VL in CSF than in blood

- ***Elevated VL in CSF undetected for long time in pts with IP/r monotherapy?***

Gutmann C, et al. AIDS 2010; 24: 2347-54

Recent Findings Supporting Penetration are Consistent but Not Uniformly

	Cysique	Tozzi	Ellis	Marra
Study	UCSD CIT	NIID	ALLRT	ACTG 736
Sample Size	37	185	2,636	26
Prospective	Yes	Yes	Yes	Yes
Controlled	No	No	No	No
Number of NP Tests	6	15	3	4
CPE: CSF VL	**Lower VL**	No CSF	No CSF	**Lower VL**
CPE: NP Tests	**Better**	**Better**	**Better**	***Less Improvement***
Used Norms for NP Change	**Yes**	No	No	No

Cysique et al, Neurology 2009, 73(5):342-8; Tozzi et al, J Acquir Immune Defic Syndr 2009;52:56–63; Ellis et al, Annual Meeting American Neurological Association 2009; Marra et al, AIDS 2009, 23(11):1359-66

CNS controversies

- Discontinuing cART is associated with an improvement in neuropsychological tests (CNS toxicity of ARV drugs?)

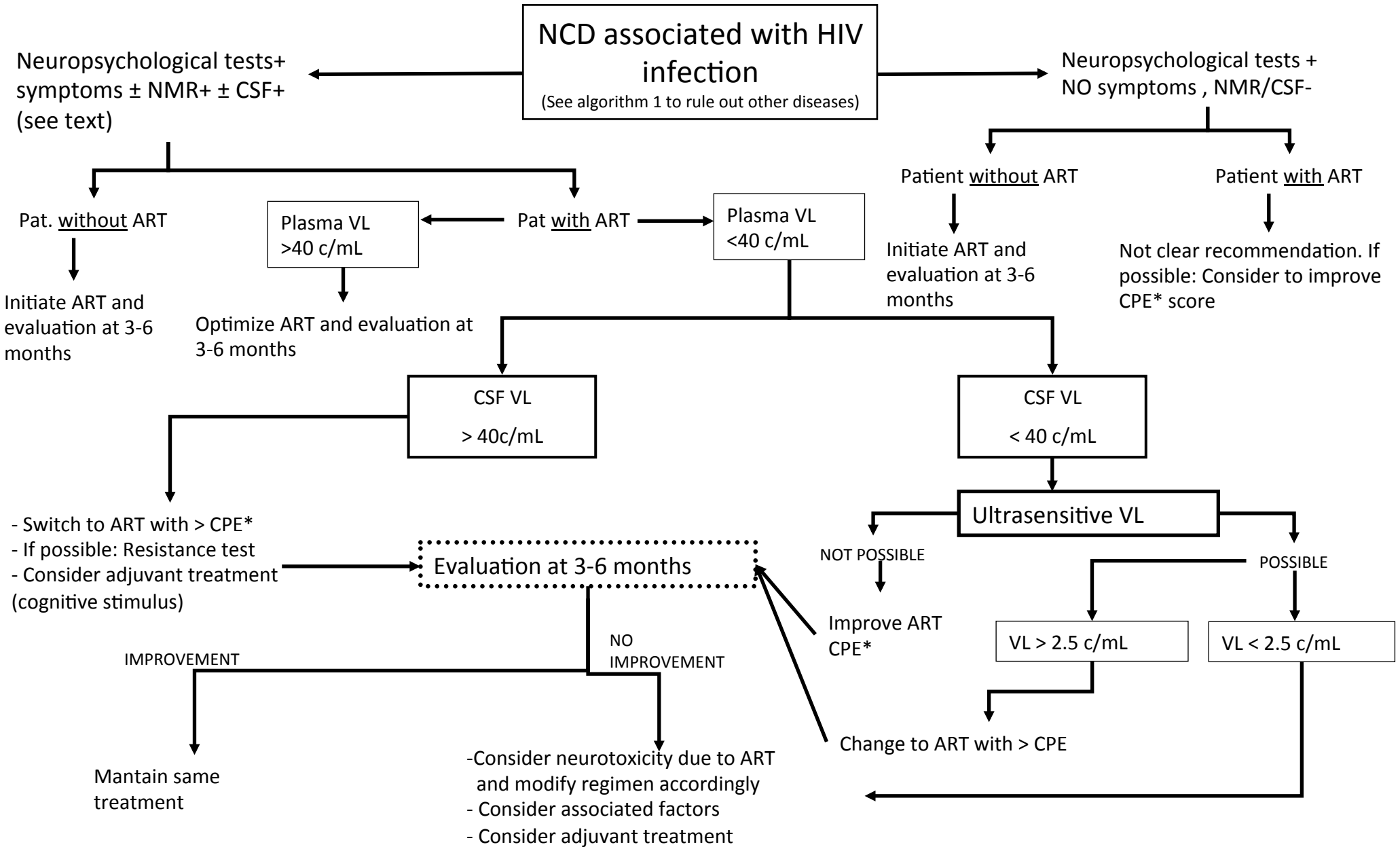
  Robertson KR, et al. Neurology 2010; 74: 1260-6

- ART intensification (with LPV/r or MVC) did not reduce residual CSF VL or intrathecal immunoactivation

  Yilmaz A, et al. JAIDS 2010 (in press)

Consensus document between GeSIDA and the Secretariat of the National AIDS Plan (PNS) on the clinical management of neurocognitive disorders associated with HIV infection

ALGORITHM 2. Treatment and follow up of neurocognitive disorders in HIV-1 infected patients



* CPE score: Antiretroviral CNS Penetratrion-Effectiveness score (Letendre 2010)

CLINICAL CASES

Clinical case #1

46-year-old transgender male, with no pathologic history, admitted to hospital in March 2010 due to instability

Signs and symptoms:

Generalized muscle weakness, gait instability and frequent falls in the last month.

Recent memory loss, more noticeable in the last few days, and slow movements.

Physical examination:

Conscious, normal cranial nerves. Generalized reduced muscle strength, more pronounced in legs, with preserved sensitivity and reflexes.

Mild symmetrical dysmetria in upper limbs, no nystagmus or adiadochokinesia. No dysarthria.

Ataxic gait

Lab. findings: Urea 6.3mmol/L, creatinine 68umol/L, sodium 141mmol/L, potassium 3.7mmol/L, pH 7.38 bicarbonate 27mmol/L, Hb 125g/L, Ht 37.1%, MCV 89 fL, platelets 141,000/mm3, white-cell count 5500/mm3 (neutrophils 3600/mm3, lymphocytes 1500/mm3). ESR: 21mm/h, PCR 44. Normal liver enzymes. Proteinogram: polyclonal hypergammaglobulinemia.

Serologies: Toxoplasma IgG, syphilis, HCV, HBsAg, and HBc Ac negative. IgG CMV positive. Cryptococcal antigen in blood negative.

HIV (ELISA): POSITIVE

HIV-1 RNA: 86,060 copies/mL (4.9 log) CD4: 90 cells/uL

Brain and spine MRI: No spinal cord abnormalities. Bilateral, symmetrical hyperintense areas affecting periventricular white matter, corona radiata, and centrum semiovale. Possible small calcified meningioma

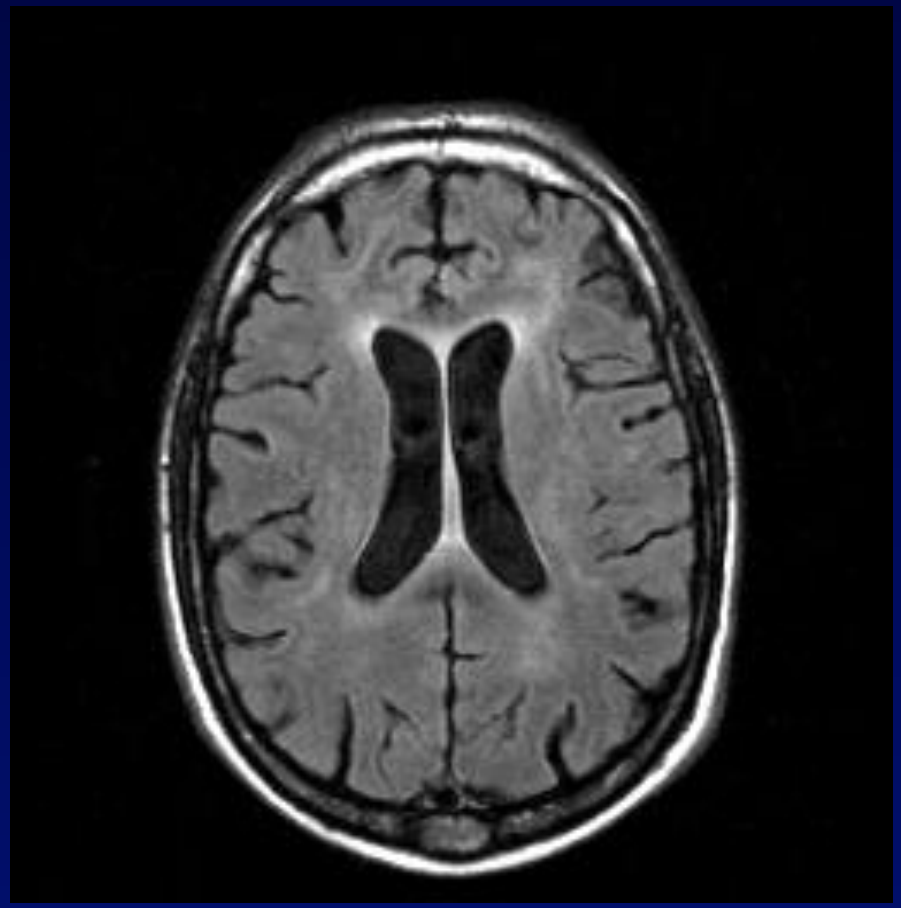
EMG: rules out muscle and peripheral nerve disturbance.

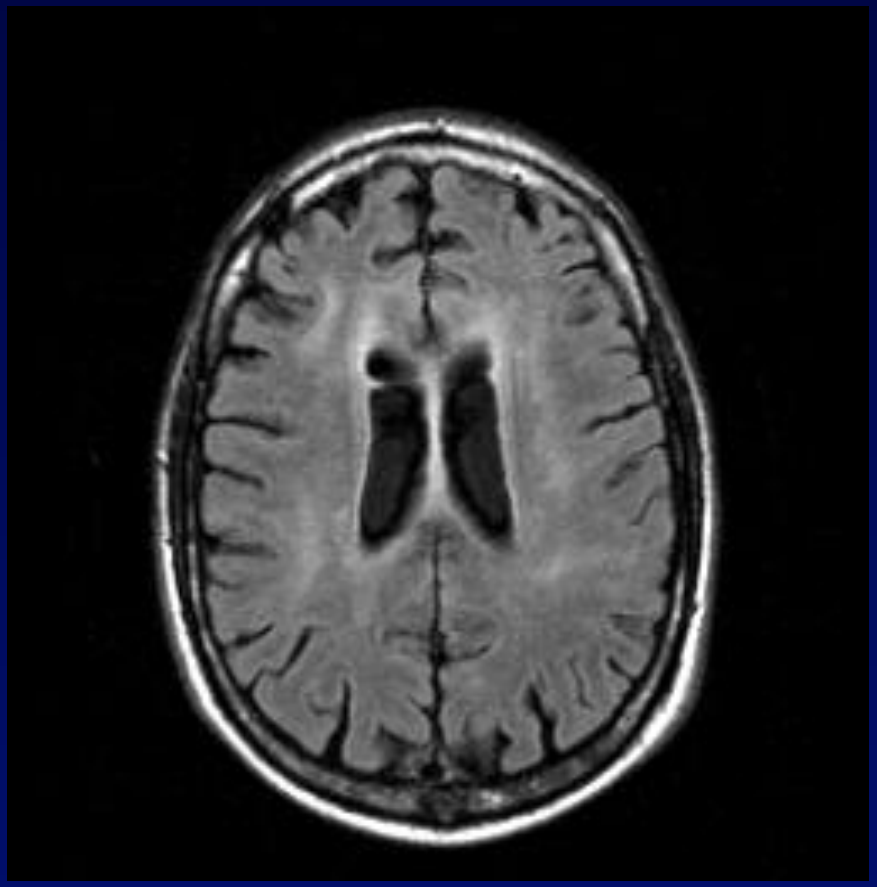
LP: 6 cells, proteins 0.5 mg/dL, glucose 2.4mmol/L. PCR for JC virus and CMV negative. ZN staining and mycobacterial culture: negative.

CSF HIV-1 RNA: 511,914 (5.7 log)

Diagnosis: HIV encephalopathy

ART initiated with DRV/r/TDF/FTC *(CPE 7).*





Bilateral, symmetrical hyperintense areas affecting
periventricular white matter, corona radiata, and centrum semiovale

March 2010

Follow up:

At a scheduled visit one month later, symptoms had improved, mainly in gait, but memory dysfunction persisted.

At the same time, marked reduction in plasma HIV-1 RNA reaching undetectable levels (<40 copies/mL), but detectable HIV-1 RNA in CSF (233 copies/mL).

To improve CNS penetration, ART was changed to DRV/r/ABC/3TC (May 2010). *(CPE 8).*

Three months later, the patient's condition worsened. Neurologic symptoms included incoherent speech and delirium.

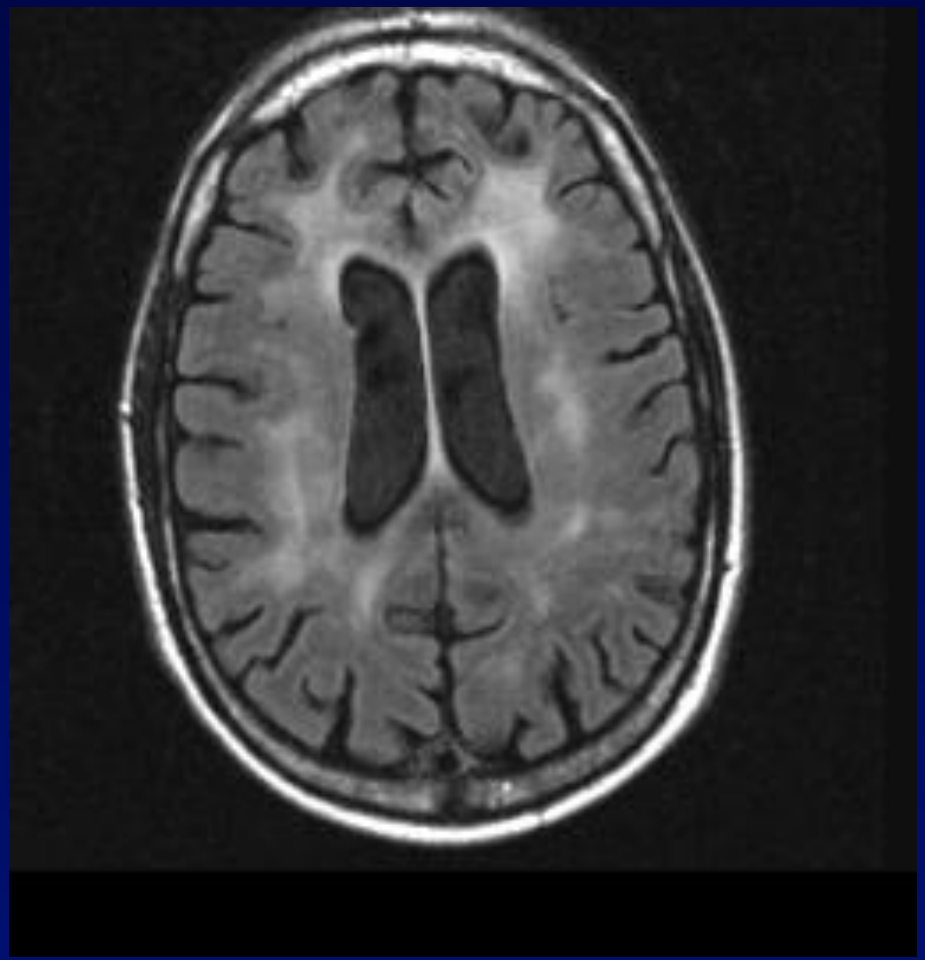
Focal neurologic alterations or gait disturbances were not observed.

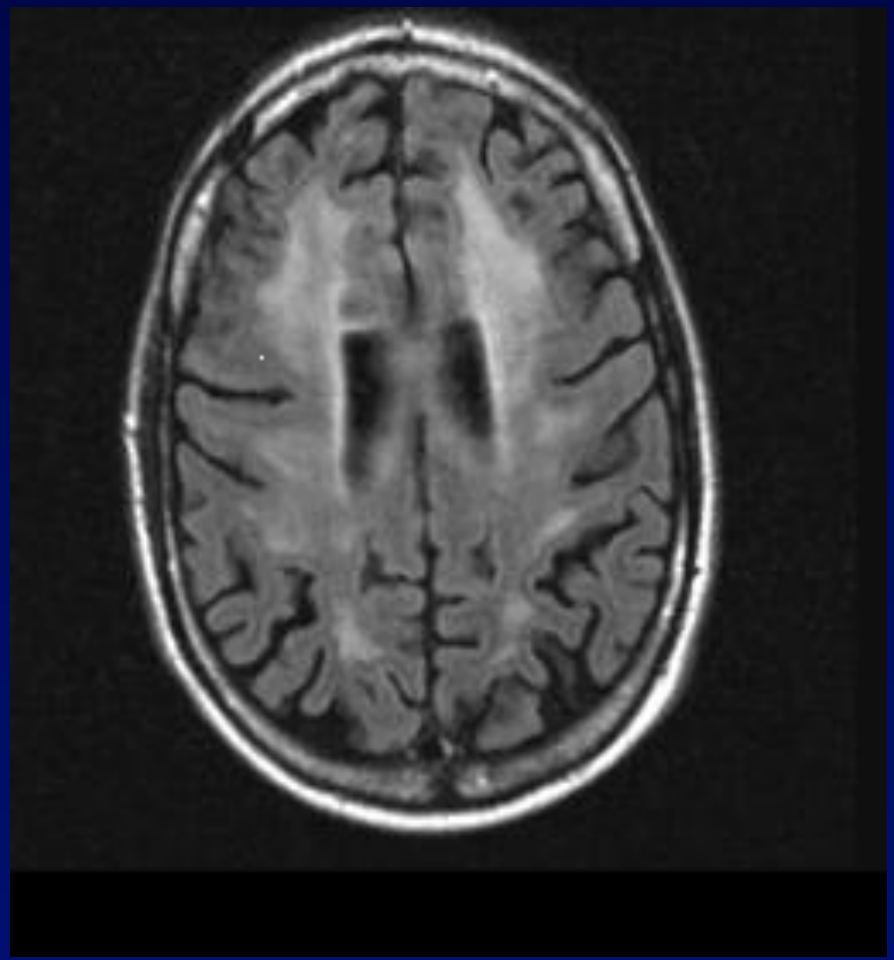
Plasma HIV-1 RNA <40 copies/mL, CD4 204 (12%)

LP: CSF HIV-1 RNA <40 c/mL.

New brain MRI (Oct 2010): worsening of periventricular leukoencephalopathy.

Diagnosis: IRS associated with HIV encephalopathy





October 2010

HIGH LIGHT
CME

Immune reconstitution inflammatory syndrome in the CNS of HIV-infected patients

A. Venkataramana, MBBS; C.A. Pardo, MD; J.C. McArthur, MBBS, MPH; D.A. Kerr, MD, PhD; D.N. Irani, MD, PhD; J.W. Griffin, MD; P. Burger, MD; D.S. Reich, MD, PhD; P.A. Calabresi, MD; and A. Nath, MD

Neurology; 2006: 67; 383-88

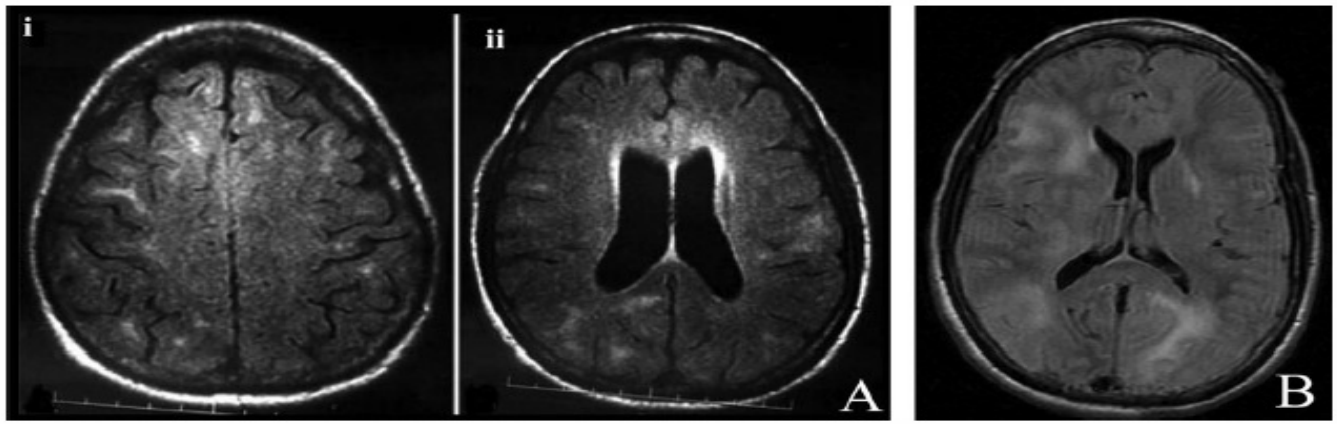


Figure 3. Case 3. (A) FLAIR images show extensive, patchy high signal intensity lesions in the white matter and involve the periventricular regions and the uncinate fibers. (B) MRI scan 3 months later shows progression of the white matter changes with confluence of the lesions.

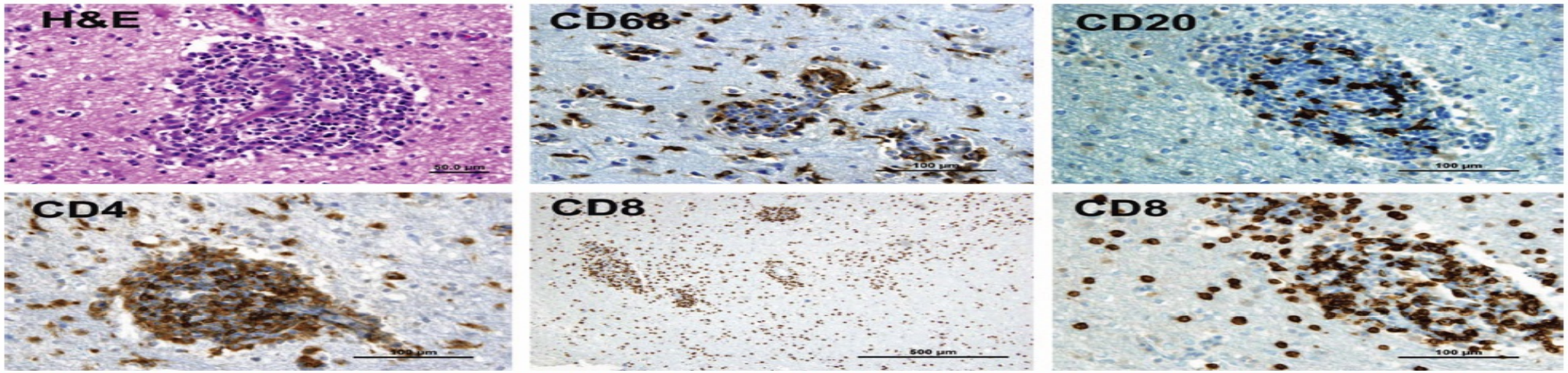


Figure 4. Characterization of inflammatory infiltrate in a patient with HIV dementia and immune reconstitution inflammatory syndrome. Case 3 brain biopsy: Histologic and immunocytochemical studies demonstrated the presence of marked perivascular and parenchymal infiltration by T cells and microglia. Perivascular cuffing in the cerebral cortex (H-E) were comprised of monocytes (CD68), B lymphocytes (CD20), CD4, and CD8 T lymphocytes. In addition to the perivascular infiltration, there was a marked infiltration by CD8 into the cerebral cortex and brain parenchyma.

In 2011 ART discontinued for 6-7 months, increasing plasma VL (60,000-200,000 c/mL). Re-started end 2011. pHIV-1 RNA <40 in May and July 2012, and CSF HIV-1 RNA <40 in July 2012. Marked MRI improvement

However, worsening of superior functions. Consultation in Psychiatry Service, diagnosis: HIV dementia

His family took him to a psychiatric clinic in Girona.

Discussion

Dementia due to another cause? (several ruled out: syphilis, thyroid, vitamin deficiency…, other?)

HIV dementia with bad evolution despite ART? (poor adherence, low but detectable HIV-1 RNA with inflammation?)

Worsening after immune reconstitution with brain damage unresponsive to ART?

Should steroids have been given? Should “neuro-ART” have been intensified? (+ MVC, ETR…)

Clinical case #2

32-year-old male

HIV-1 infection diagnosed in 1997 (prison).

B3 (oral candidiasis and herpes zoster)

Other background:

- Smoker (20 cig/d) Former moderate alcohol drinker
- Active drug user
- HCV chronic hepatitis, no treatment or liver decompensation
- Tricuspid valve endocarditis by *S. aureus* in 2007
- Negative tuberculin test (repeated)

History of ART/Admissions

1997: bitherapy with AZT/3TC for several months

2000-2008: started different ART while in prison

- NVP, 3TC and ddI: 2003-2004 reaching undetectable VL
- SQV/r, ABC, 3TC; LPV/r, TDF, FTC (CD4 93; VL 462,812)

April-09: Admitted due to idiopathic esophageal ulcers (CD4 88 (10%) and VL 732,518 c/mL)

- DRV/r, etravirine and raltegravir.
- After 10 days, presented moderate skin rash: ART stopped
- Genotypic resistance test: NO mutations

Oct-09: Admitted due to respiratory infection by *H. influenzae* and *P. aeruginosa*

- VL 1,042,259 c/mL and CD4 84/uL (12%)
- ART started: TDF/FTC/ATZr *(CPE 6).*

March-10: Lumbar herpes zoster; VL 623 copies/mL

New admission, April 2010

Generalized myoclonia (2-3 months) and consciousness alteration (last few days). Alprazolam use in previous weeks.

Physical examination: C and O, generalized myoclonia, no meningeal signs, T 37.3ºC

CSF: Proteins 2.7 g/L, glucose 1.8 mmol/L, cells 146 (lymphocytes 94%).

Blood: plasma VL: 833 copies/mL, RT: M184V.
CD4 224 (14%)

What is your diagnosis??

TB meningitis?

Empirical treatment for TB, mycotic disease, and steroids were initiated

Worsening of consciousness level up to coma.

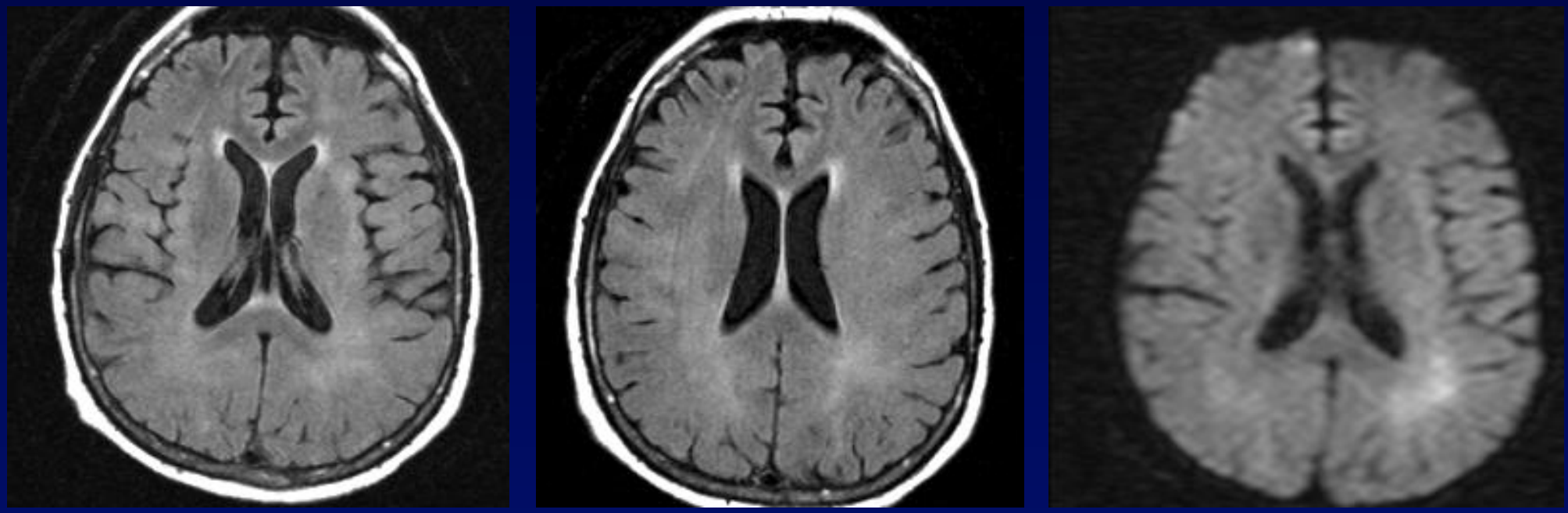
Admitted to the ICU with mechanical ventilation.

And now, what????

CSF: HIV-1 RNA 12,097 copies/mL. RT: M184V

MRI: Next slide

EEG:: Non-specific left temporal irritative activity and diffuse neuronal dysfunction.



Brain MRI: Hyperintense periventricular areas in corona radiata and centrum semiovale on DP, T2-W, and FLAIR sequences, suggestive of ***HIV-associated encephalopathy.***

Diagnosis: **HIV encephalitis**

DRV/r/ABC/RAL/MVC was initiated *(CPE 12).*

Microbiologic findings: Bacterial, fungal, mycobacterial cultures: negative. PCR for *Mycobacterium tuberculosis*, JC virus, CMV, toxoplasma, HSV and VHZ: negative

TB and antimycotic treatment, as well as steroids, were discontinued.

Follow-up

Progressive clinical improvement with restoration of consciousness level and disappearance of myoclonia

July-10: OK, VL 53 copies/mL

Clinical case #3

44-year-old woman, past IVDU, past smoker (up to 1993)

No current alcohol consumption, no allergies

Pathologic history

HIV infection diagnosed in 1992

CD4 nadir 58 (12%) Feb-96, highest VL 22,700 c/m

OI: *P. jiroveci* pneumonia in 1996

ART started in 1996

- d4T+3TC+RTV, d4T+3TC+NFV: between 1996 and 2000, VL always detectable (between 880-6096 c/mL)
- d4T, 3TC, LPV/r in 2000, since then, **undetectable VL**
- TDF+3TC+LPV/r, TDF/FTC+ LPV/r
- LPV/r monotherapy since 30/8/2011
- At BL CD4 1104 48%, VL<40; March 2012: 810 45%, CV<40

-

Other pathologic background

- Chronic HCV hepatitis, genotype 1a
- Liver fibrosis F1-2 (Fibroscan 7.6 kPa)
- Pneumococcal pneumonia
- Lymphocytic meningoencephalitis of uncertain cause in Jan-06
- Depression for many years, currently stable. Treated with citalopram

Treatment

LPV/r 400/100 mg bid

- Good adherence
- No adverse effects

Citalopram 10 mg/d

Current disease

Clonic movements associated with paresthesia in left upper and lower limbs for 5 days; initially self-limited, with no language or consciousness disturbances. Generalized seizures, followed by paralysis of left limbs. Admitted to hospital.

Physical examination

General status well. Conscious and orientated. General examination: OK

Neurologic examination: left brachiocrural paresis 4+/5. Remainder: normal

Initial follow-up

Fever: 37.7º-38ºC

Persistent clonic movements in left limbs: With a diagnosis of partial status epilepticus, therapy with levetiracetam (Keppra)1500 mg bid was initiated. As symptoms were not controlled, therapy was intensified: levetiracetam (Keppra) 1500 mg bid + oxcarbazepine 600 mg tid, achieving remission.

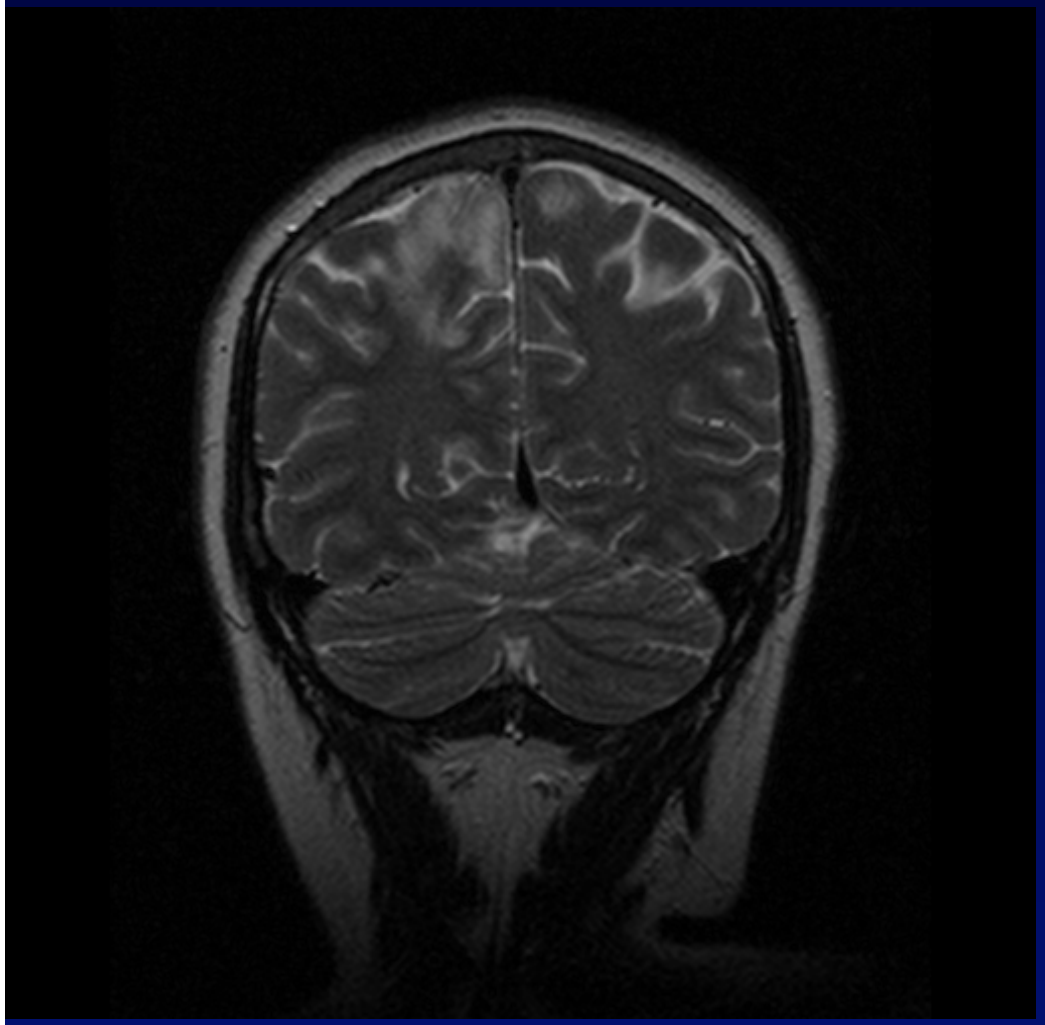
Left BC paresis: initially 4+/5. Progression in first week in hospital: LUL 2/5, LLL 1/5. No sensory symptoms. Left perioral paresthesia.

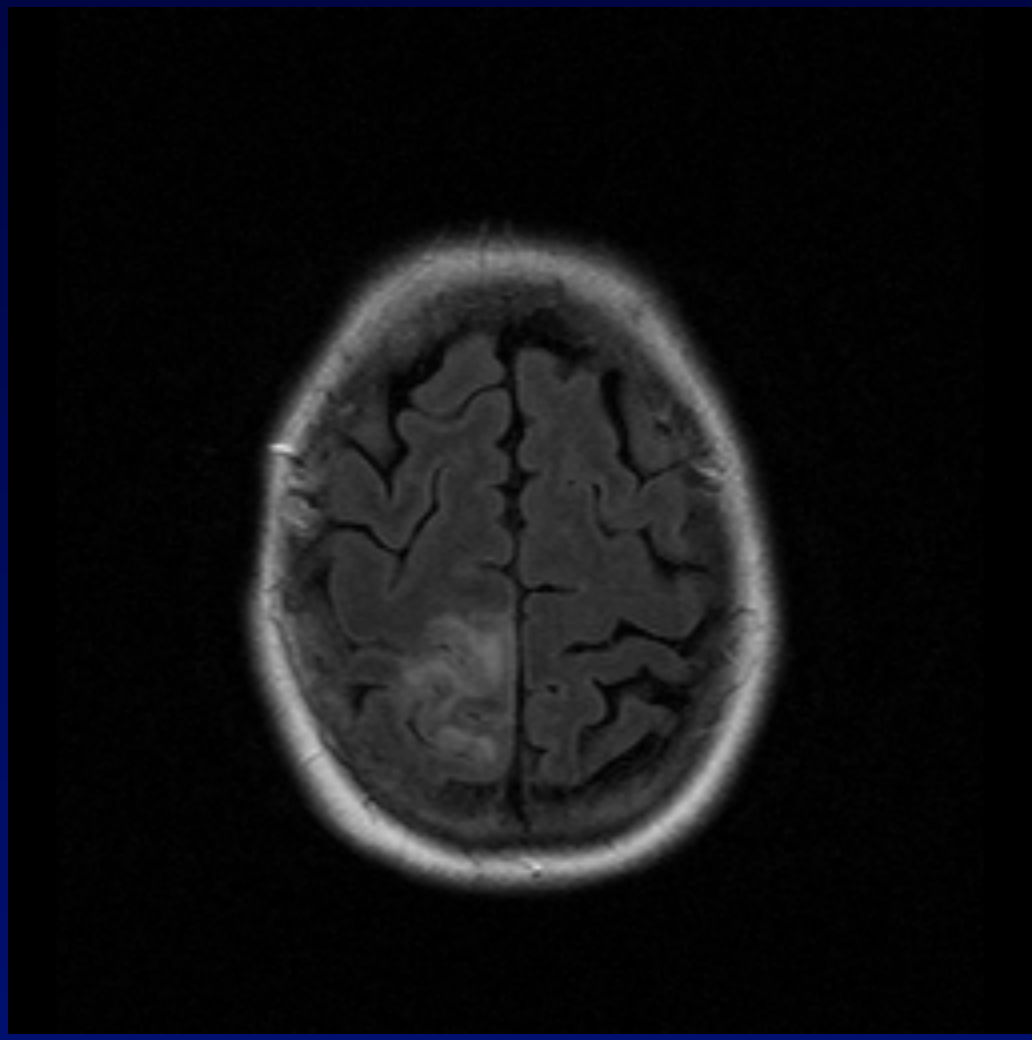
Tests:

Lab. findings:
Hb 122 g/L, Leukocytes 3,700/mm3 (N 1800, L 1200), platelets 286,000/mm3
Biochemistry normal. LDH normal. TSH and T4 normal. Vit B12 and folic acid normal
Polyclonal hypergammaglobulinemia
CD4 576 (48%), CD4/CD 8 2.6; HIV VL 216 copies/mL

Cranial CT (emergency study): No abnormalities
EEG: No significant alterations

CSF*: leukocytes 130/mm3, 99% lymphocytes; proteins 0.71 g/L (0.15-0.45), glucose: normal (*LP at 3rd day of admission, after presenting fever)





Extense area of confluent signal change, mainly affecting subcortical white matter of right parietal region, with no mass effect

Tests (II)

Microbiological findings: Blood cultures: negative

CSF:

Bacterial culture: negative
Cryptococcal antigen: negative
PCR *Toxoplasma gondii:* negative
PCR HSV: negative
PCR CMV: negative
PCR EBV: 1304 copies/mL
PCR JC virus: negative
PCR *Mycobacterium tuberculosis* complex: negative
HIV-1 RNA: 24,016 copies/mL

Cytology: Benign inflammation

Flow cytometry: NOT suggestive of neoplastic disease

Diagnosis: HIV encephalitis

Tests (III)

Genotype resistance testing in CSF:

Reverse transcriptase: T69N, V108I, M184V

Protease: V32I, L33F, I54V, L63P, A71V, V82A, L90M

Follow-up:

5/5/2012 Admitted to hospital

7/5/2012 EEG normal, but due to persistent clonic movements, antiepileptic therapy was intensified

8/5/2012 Based on fever and CSF data, empirical treatment with acyclovir and ampicillin iv started

12/5/2012 After known VL data in CSF (>plasma), ART was changed to ABC/3TC/ETR/DRV/r *(CPE 10)*.
Skin rash appeared, treatment changed again to ABC/3TC/RAL/DRV/r *(CPE 11)*.
Due to the absence of data suggestive of other infections, acyclovir and ampicillin were discontinued.

Progressive clinical improvement: fever disappeared and strength restored in left limbs

23/5/2012 CSF: leuk 13, prot 0.36 (N), glucose N; HIV-1 RNA <40 c/mL
18/6/2012 CD4 870 (58%), HIV-1 RNA (plasma) <40 copies/mL

Follow-up (II):

October 2012

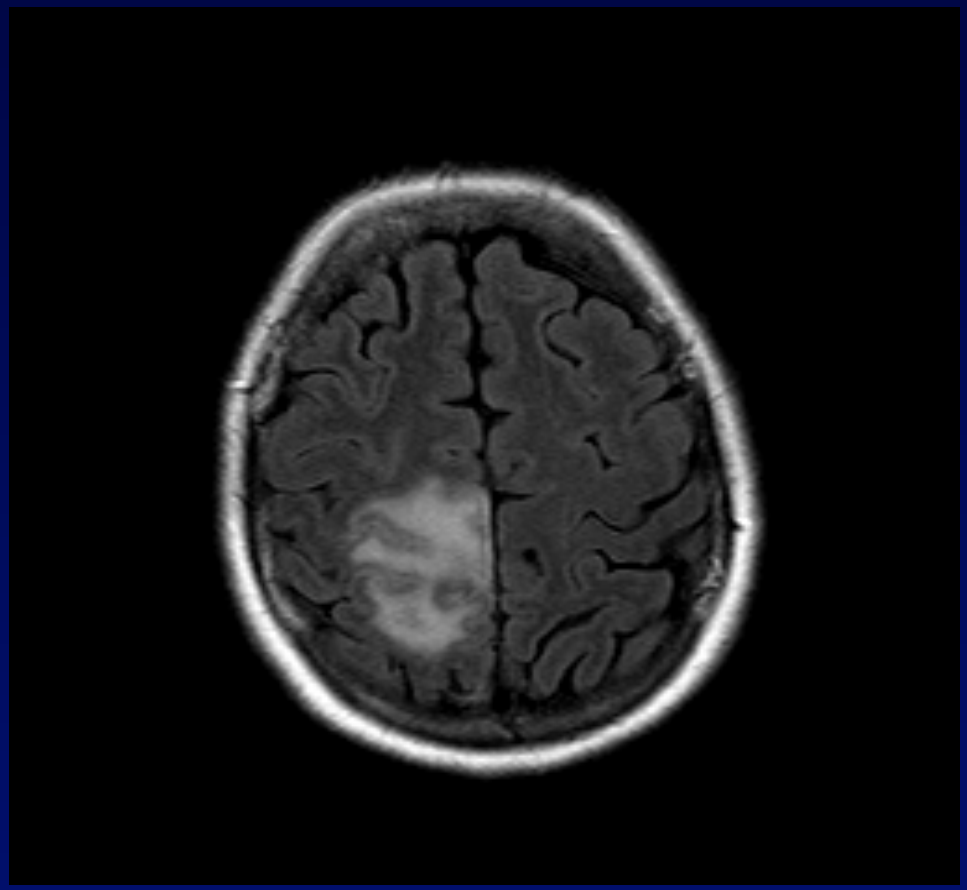
Clinical symptoms: Improvement of strength in left upper (5-/5) and lower (5-/5) limbs. No seizures

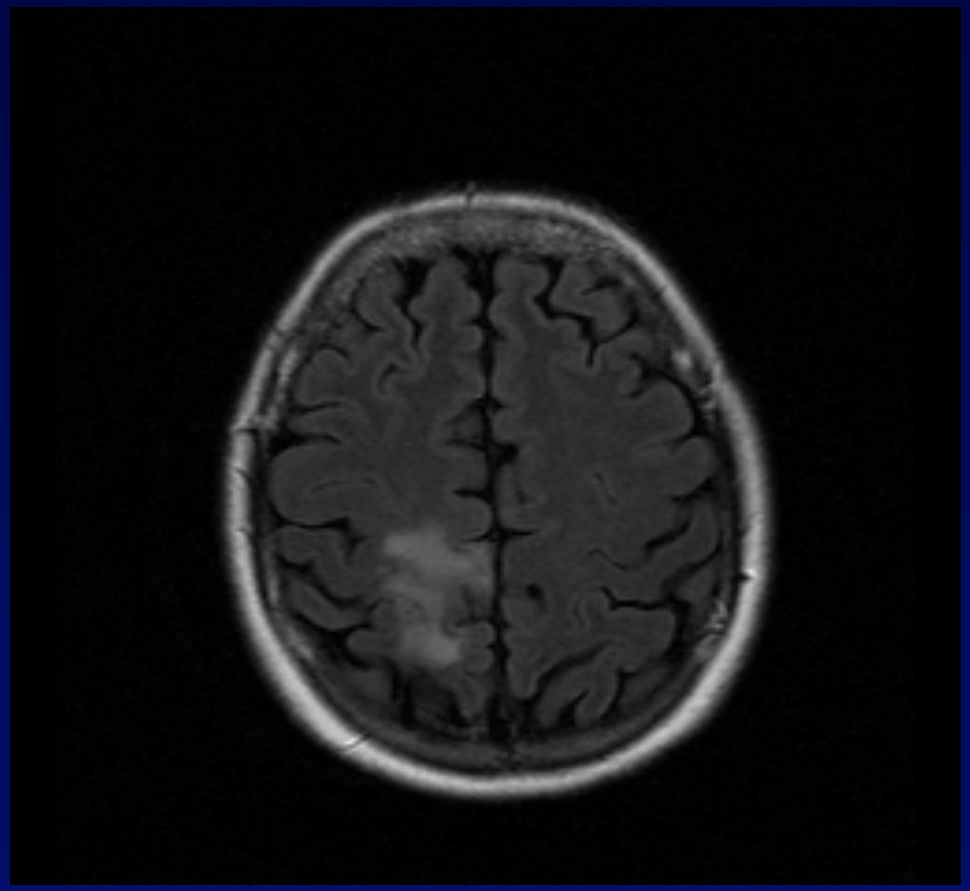
CD4 918 (54%), HIV-1 RNA (plasma) <40 copies/mL

CSF: leukocytes 0, proteins 0.33 (normal), glucose normal. HIV-1 RNA <40 copias/mL

MRI: Decreased size of right frontoparietal lesion, with less mass effect and contrast enhancement

Decrease in lesion size





FLAIR May

FLAIR August

Thanks, folks!!