

# **Discordant CSF and plasma viral loads during cART in a very late presenter patient with HIV-1 associated neurocognitive disorder: what is going on?**

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# Patient information

- 35 y old, male patient from Constanta county
- University education
- MSM – as risk factor (but unconfirmed)
- Past medical history:
  - In 2012 he was diagnosed with anxious-depressive syndrome (he has been receiving psychiatric medication)
  - Measles (2013)
- Current medication:
  - Sertraline
  - Alprazolam

# Signs/symptoms on admission in our hospital (10<sup>th</sup> November 2014)

- **Since 4 months, he has been complaining of:**
  - attention difficulties and memory disturbance
  - walking difficulty that progressively worsened leading to inability to walk
  - weight loss (20 Kg)
  - dysphagia
- **He was admitted in an internal medicine ward in Bucharest**
  - HIV screening: positive (ELISA test)
  - He was referred to our hospital

## Physical exam

- Low-grade fever (37.6°C)
- Oropharyngeal candidiasis
- Molluscum contagiosum
- Advanced onychomycosis
- Hepatomegaly (5 cm bellow costal margin)
- Muscle atrophy
- Tetraparesis (4/5 BRMC) and ataxia
- Increased tendon reflexes without sensory disturbance
- Requires support for maintaining seating position



# Blood and CSF test results

## Blood

- **Anemia: Hb 8.5 g/dl**
- CRP 107 mg/L
- **CD4 6/mmc; CD8 401/mmc;**
- **CD4/CD8: 0.01**
- **HIV-RNA: 1168121 cp/ml**
- VDRL, HBV, HCV, Toxo: neg
- CMV, EBV – pos (IgG);
- **CMV-DNA 455 cp/ml**
- Cryptococcal Ag: neg
- HLA B\*5701: neg

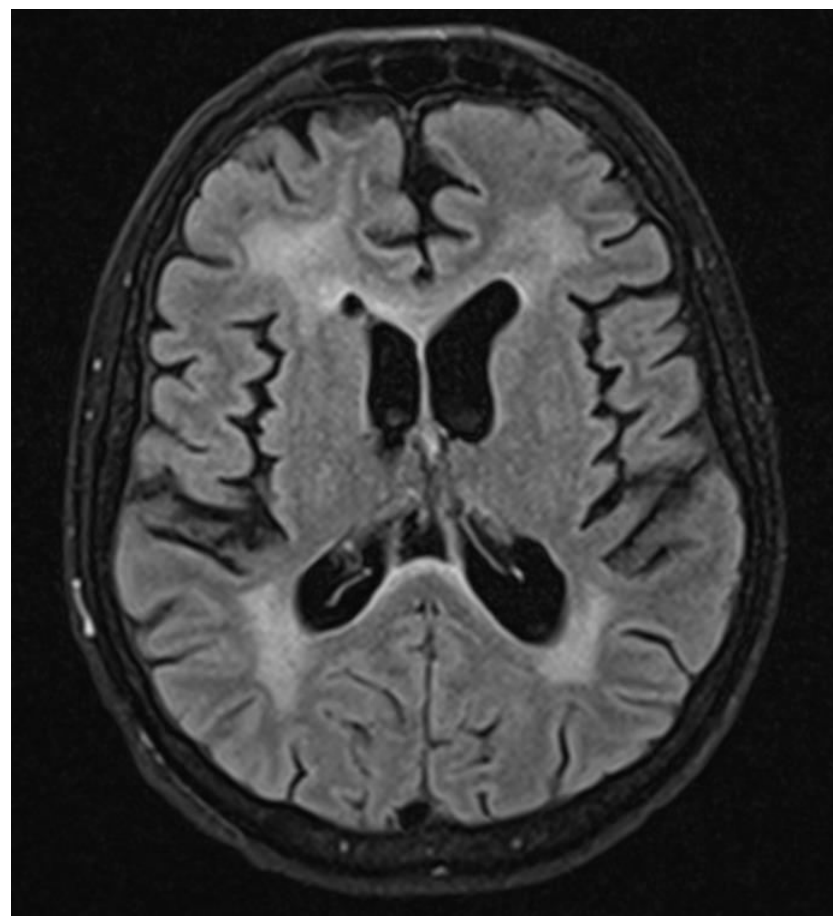
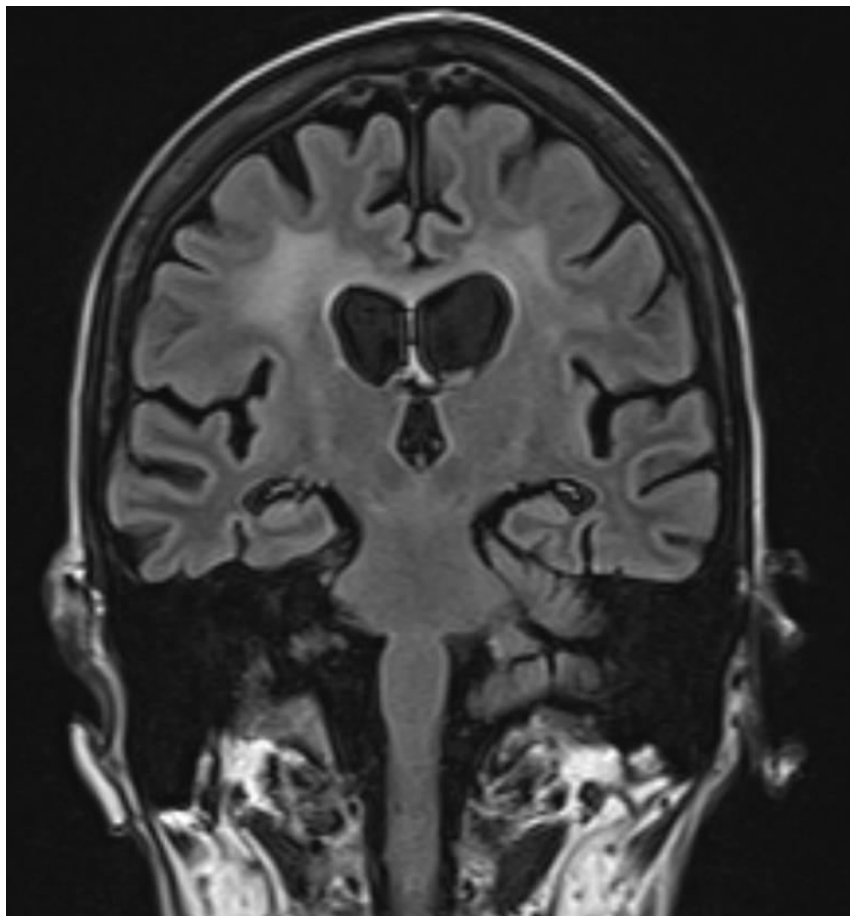
## CSF

- Clear CSF
- **Pandy +/-**
- No leucocytes
- **Proteinorahia: 107 mg/dl**
- Normo-glicorahia: 45 mg/dl
- China ink stain: neg
- Cryptococcal Ag: neg
- **JCV-DNA: undetectable**
- **MTB-DNA: undetectable**
- **HIV-RNA: 317898 cp/ml**

## Neurocognitive assessment & other tests

- **HIV dementia scale: 2 points**
  - neurocognitive impairment (motor, psycho-motor and memory domains)
- **Montreal Cognitive Assessment (MOCA): 25 points**
  - slightly neurocognitive impairment (temporal-spatial orientation difficulties, memory and language disturbance)
- **Electromyography (EMG)**
  - sensory and motor axonal polyneuropathy of the legs

# Brain MRI with contrast (nov. 2014)



# Antiretroviral therapy and Co-med

**2 weeks after admission (Clarithromycin, Cotrimoxazol, Fluconazole)**

**I. AZT/3TC + DRV/r 1200 mg (7 days)**

**Severe anemia**

**II. ABC/3TC + DRV/r 1200 mg (1 month)**

**Severe sepsis with MODS**

**III. ABC/3TC + RAL 800mg (1 month)**

**Intra-abdominal lymph node unmasking TB IRIS (H/R/P/E - 7/7; steroids)**

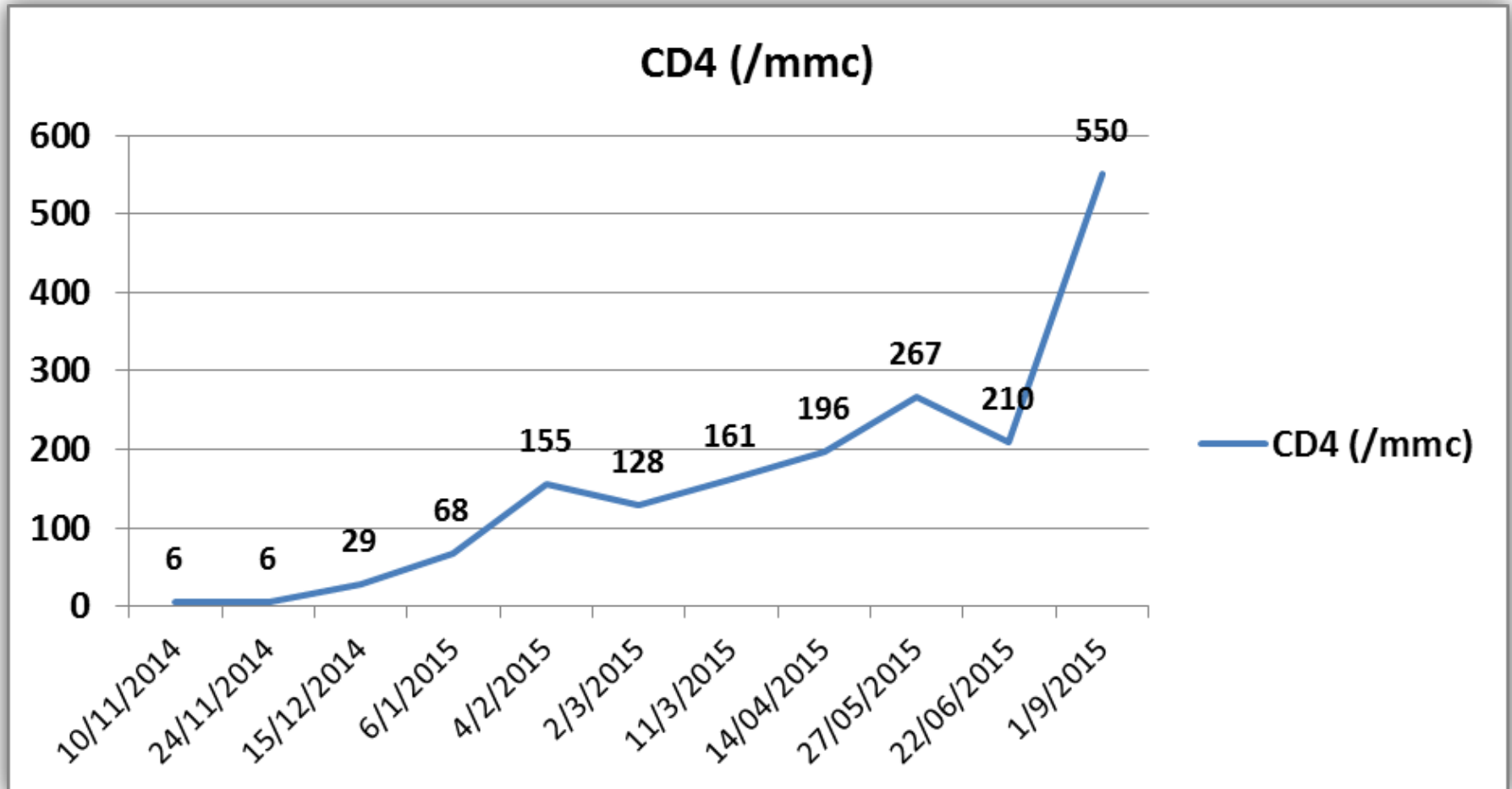
**IV. ABC/3TC + RAL 1600 mg (3 months)**

**Anti-TB drugs (H/E – 7/7) + CSF virological failure ?**

**V. ABC/3TC + ETR 400 mg + DRV/r 1200 mg + RAL 800 mg (current ART)**



# Immune response during cART

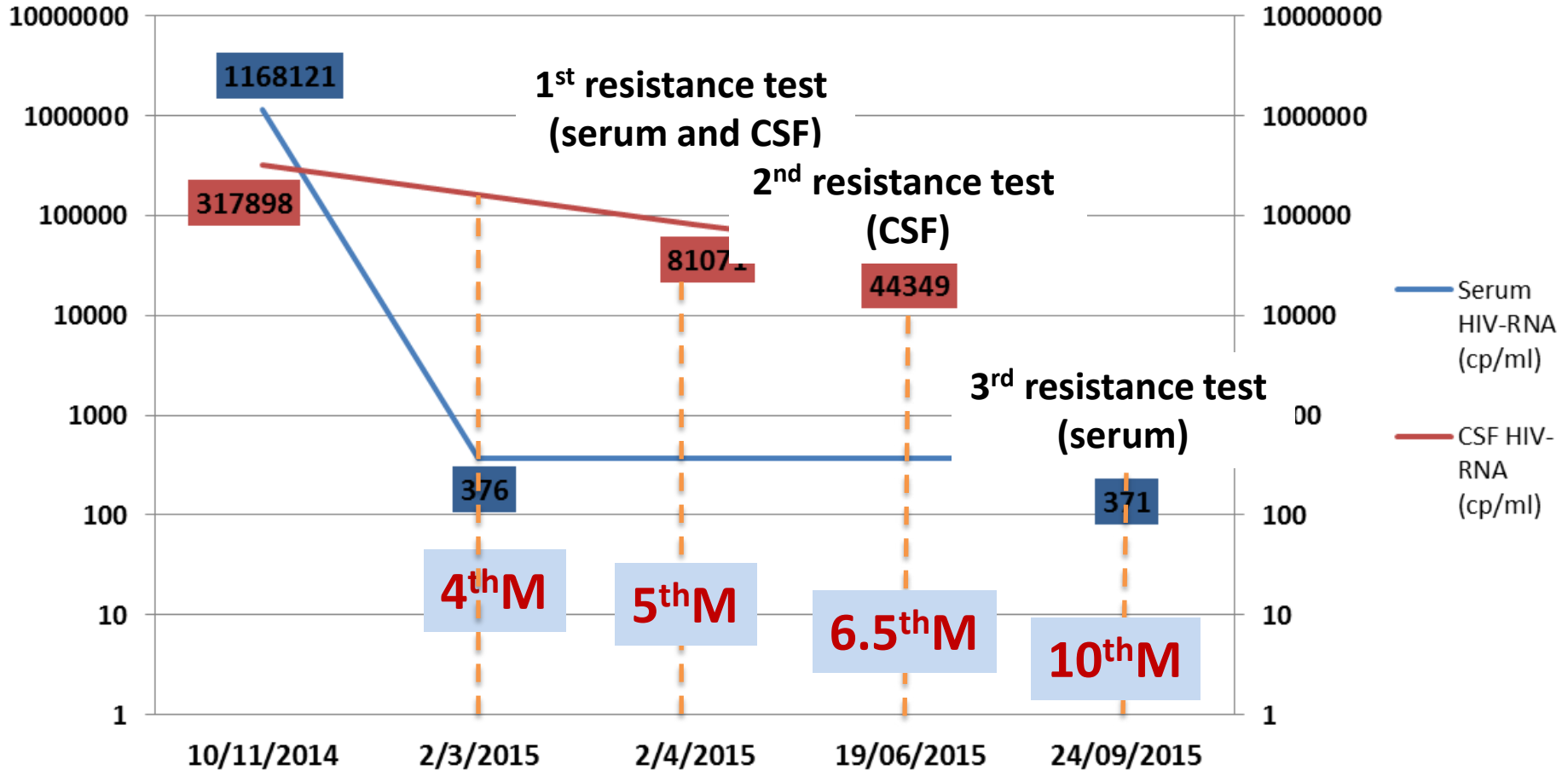


## Clinical evolution:

- Neurocognitive impairment recovery
- Intra-abdominal lymph node regression under anti-TB drugs

# HIV-RNA kinetics in serum and CSF during cART

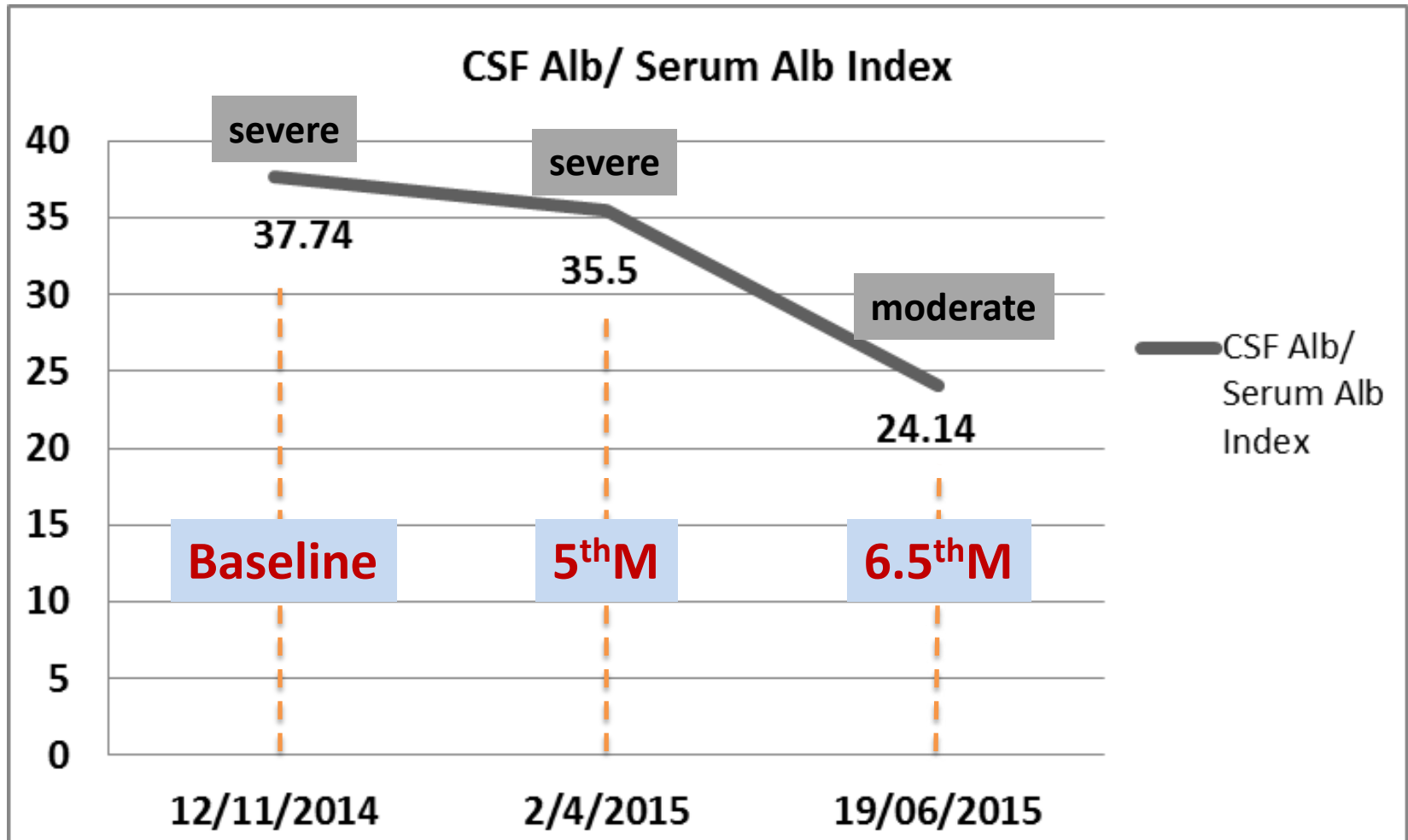
HIV-RNA (cp/ml) kinetics in serum and CSF



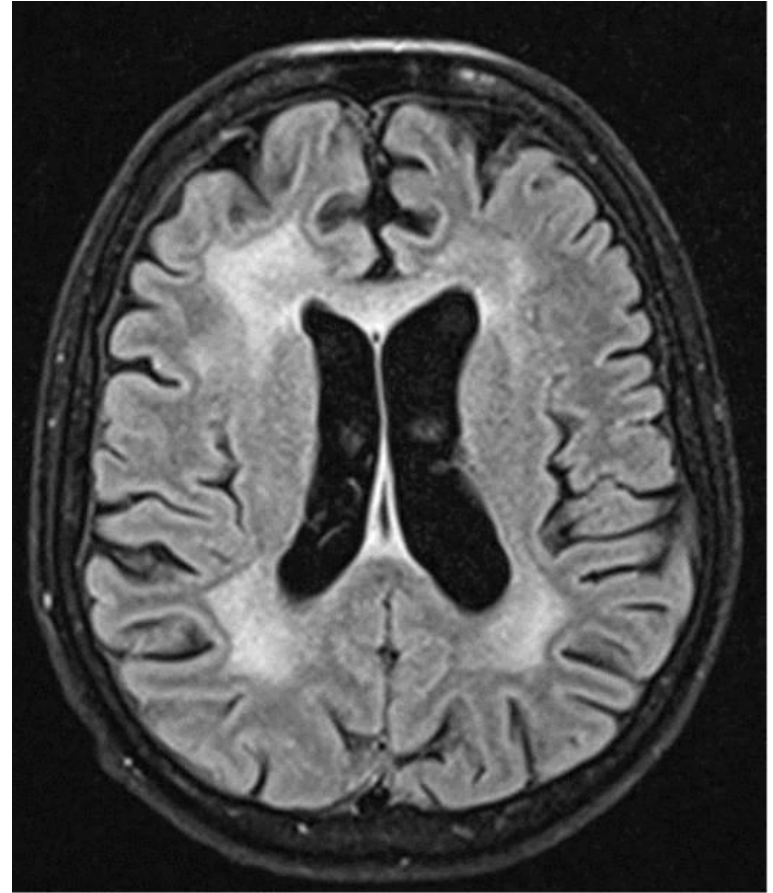
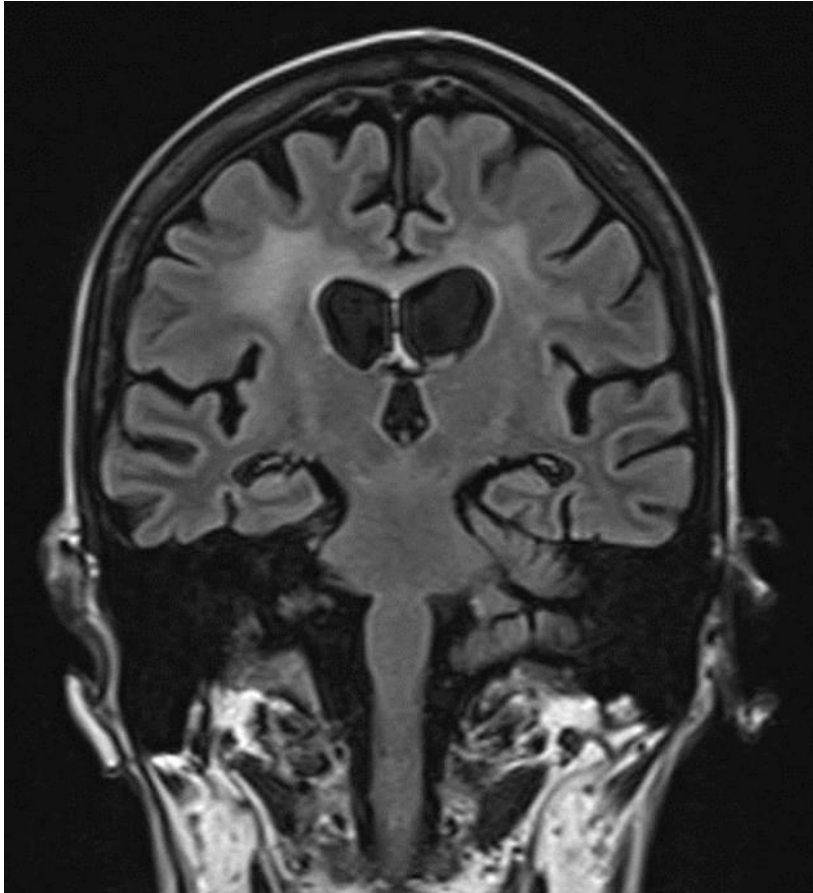
- I. AZT/3TC + DRV/r 1200 mg (7 days)
- II. ABC/3TC + DRV/r 1200 mg (1 month)
- III. ABC/3TC + RAL 800 mg (1 month)
- IV. ABC/3TC + RAL 1600 mg (3 months)

- V. ABC/3TC + ETR 400 mg + DRV/r 1200 mg + RAL 800 mg (current ART)

# The permeability of BBB during cART (assessed by CSF Alb: Serum Alb Index)



## Brain MRI evolution (apr. 2015)



**What is going on ?**

Suboptimal adherence ?

- **Maybe NOT...**

Drug-drug interactions ?

[www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)

- **NO significant DDI**

## CNS/CSF ineffective drug concentration?

- CNS Penetration-Effectiveness (CPE) score:
  - AZT/3TC + DRV/r 1200 mg (7 days): 9 p
  - ABC/3TC + DRV/r 1200 mg (1 month): 8 p
  - ABC/3TC + RAL 800 mg (1 month): 8 p
  - ABC/3TC + RAL 1600 mg (3 months): 8 p
  - **ABC/3TC + ETR 400 mg + DRV/r 1200 mg + RAL 800 mg: 13 p**

## Resistance issue?

- ✓ **Subtype F-1 virus**
- ✓ **1<sup>st</sup> resistance test (5 months of ART)**
  - ❑ Serum (failed to amplify)
  - ❑ CSF (HIV-RNA 81072 cp/ml): no major RAM in the RT and PR genes (no IN sequencing)
- ✓ **2<sup>nd</sup> resistance test (6.5 months of ART)**
  - ❑ CSF (HIV-RNA 44349 cp/ml): no major RAM in the RT, PR and IN genes
- ✓ **3<sup>rd</sup> resistance test (10 months of ART)**
  - ❑ Serum (HIV-RNA 371 cp/ml): in progress





## 2<sup>nd</sup> resistance test (6.5 months of ART)

- **PR:**
  - PI Major Resistance Mutations: None
  - PI Minor Resistance Mutations: M46N, I47DY, G48R, I50N
  - Other Mutations: E35D, M36I, R41K, R57K, L63T, E65D, K70R, I72T, L89M
- **RT:**
  - NRTI Resistance Mutations: None
  - NNRTI Resistance Mutations: V106I
  - Other Mutations: V35IM, T39S, G45EG, S48T, V60I, D123E, I135T, S162F, Q174K, D177E, I178L, V179I, I195IL, T200A, Q207D, R211K, V245Q, E248N, A272P, L283IL, T286A, E291D, V292I, I293V, P294PS, E297K, A304E, K311R, D320DN, D324DE, L325IL
- **IN:**
  - Major Resistance Mutations: None
  - Accessory Mutations: None
  - Other Mutations: S17N, A21S, P30S, I60V, L101I, T112I, S119T, T124S, T125A, K136Q, V201I, L234V, D256E, S283G, D286N

# HIVdb: Genotypic Resistance Interpretation Algorithm

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
V106I	-	-	-	-	-	-	-	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
<b>Total:</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>

PR	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
M46N	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
I47DY	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
G48R	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
I50N	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
<b>Total:</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>

IN	DTG	EVG	RAL
<b>Total:</b>	<b>0</b>	<b>0</b>	<b>0</b>

# Discussions (Q&A)

- ✓ On-going replication of HIV in serum and CNS/CSF under ART, with either wild type virus or resistance virus (minority population with unfit viral strains?)
- ✓ How can we explain the discordant evolution of HIV-RNA in serum and CSF during effective CNS penetration ART regimen?
- ✓ Should we be concerned about the risk of developing drug resistance in CNS/CSF (compartmentalization phenomenon/ potential for reseeding of systemic compartment) ?
- ✓ What about the risk of progression of HAND ?
- ✓ What should we do next, taking into account the good clinical and immunological response despite virological failure in serum and CSF as well ?