



Opportunistic infections in the era of cART, still a problem in resource-limited settings

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Are HIV associated cerebral opportunistic infections still a problem in middle and low-income countries?

Even if the global burden of HIV associated neurological opportunistic infection declined in the HAART era, in resource limited settings they can still represent a problem.

Opportunistic infections of the CNS (CNS OIs) determine an increased risk of morbidity and mortality in untreated HIV infected patients or in patients unaware of their HIV status.

Several factors influences the likelihood of a specific aetiology, including CD4 cell count, ethnicity, age, risk group, prophylactic history, geographical location and viral subtype.

Objective

The aim of the study was to evaluate the incidence, demographic and immuno-virological characteristics and outcome in patients with HIV and neurological opportunistic infections and brain tumors in a single HIV center.

Methods

- Retrospective cohort study on HIV infected patients admitted to a specialized department “Casa Doru” at “Victor Babes” Hospital between January 2000 and August 2015.
Patients were followed-up until their death or end of August 2015.
- The most common CNS OIs and brain tumors were evaluated:
 - ✓ Bacterial: Tuberculous meningitis (TBM)
 - ✓ Fungal: Cryptococcal meningitis (CNM)
 - ✓ Parasitic: Cerebral toxoplasmosis (TOXO)
 - ✓ Viral: CMV encephalitis (CMVE)
 - Progressive multifocal leukoencephalopathy (PML)
 - Subacute myoclonic measles encephalitis SMME
 - Primary cerebral lymphoma (PCL)
- Survival was estimated using the Kaplan- Meier method

Diagnostic work-up for patients with HIV infection and presumed CNS OIs

Diagnosis first established using the CDC (1993) criteria was improved

Neuroimaging: brain MRI and CT with contrast enhancement

CSF exam

- Bacterial, fungal and mycobacterial culture
- Microscopy for India ink stain (*C neoformans*) and acid fast bacilli (*M tuberculosis*)
- WBC- count, protein and glucose concentrations
- Cytology and flowcytometry
- PCR for JC, EBV, HSV 1,2, CMV, VZV, *T gondii* and *MTB*
- *Cryptococcal Ag*

Other tests

CD4 cell count

HIV- RNA copies/ml

IgG antibodies to *T gondii*, CMV, HSV, EBV in plasma and CSF

Diagnostic criteria for PML*

Definite (etiological) diagnosis:

CSF - confirmed PML:

- a. Clinical and MRI findings consistent with PML and
- b. Evidence of JCV DNA in CSF

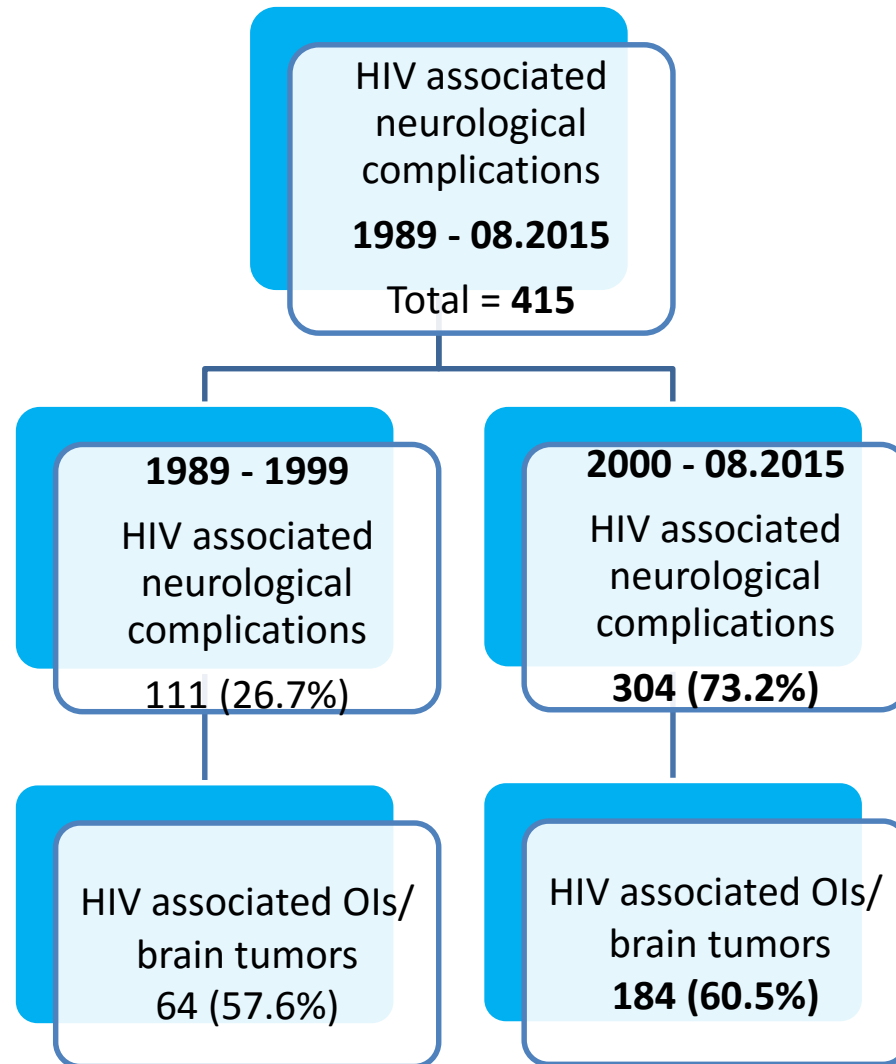
Tissue-confirmed PML:

Evidence of PML neuropathology in brain tissues (biopsy or autopsy) with JCV DNA or protein detected by in situ techniques.

Presumptive (clinical) diagnosis:

- a. Evidence of typical clinical and MRI findings and
- b. Brain biopsy and lumbar puncture either not performed or JCV DNA not detected in CSF

Neurological complications in HIV infected patients admitted to “Casa Doru” between 1989-2015



CNS OIs in HIV infected patients admitted at “Victor Babes” Hospital “Casa Doru” between 2000 and 2015

Type of CNS opportunistic infections	2000 - 08.2015 n (%)	1989 - 1999 n (%)
Cerebral toxoplasmosis	37 (20.1)	9 (14.0)
Tuberculous meningitis/tuberculoma	35 (19.0)	17 (26.5)
Cryptococcal meningitis	31 (16.8)	15 (23.4)
CMV encephalitis	3 (1.6)	-
Progressive multifocal leukoencephalopathy	61 (33.1)	3 (4.68)
Subacute myoclonic measles encephalitis (SMME)	12 (6.5)	20 (31.2)
Primary cerebral lymphoma (PCL)	5 (2.7)	
Total	184	64

	2000 – 08.2015 n (%)	1987 - 1999 n (%)
HIV encephalopathy HIVE	119	47
Subacute sclerosing panencephalitis	1	-

Diagnostic criteria for SMME*

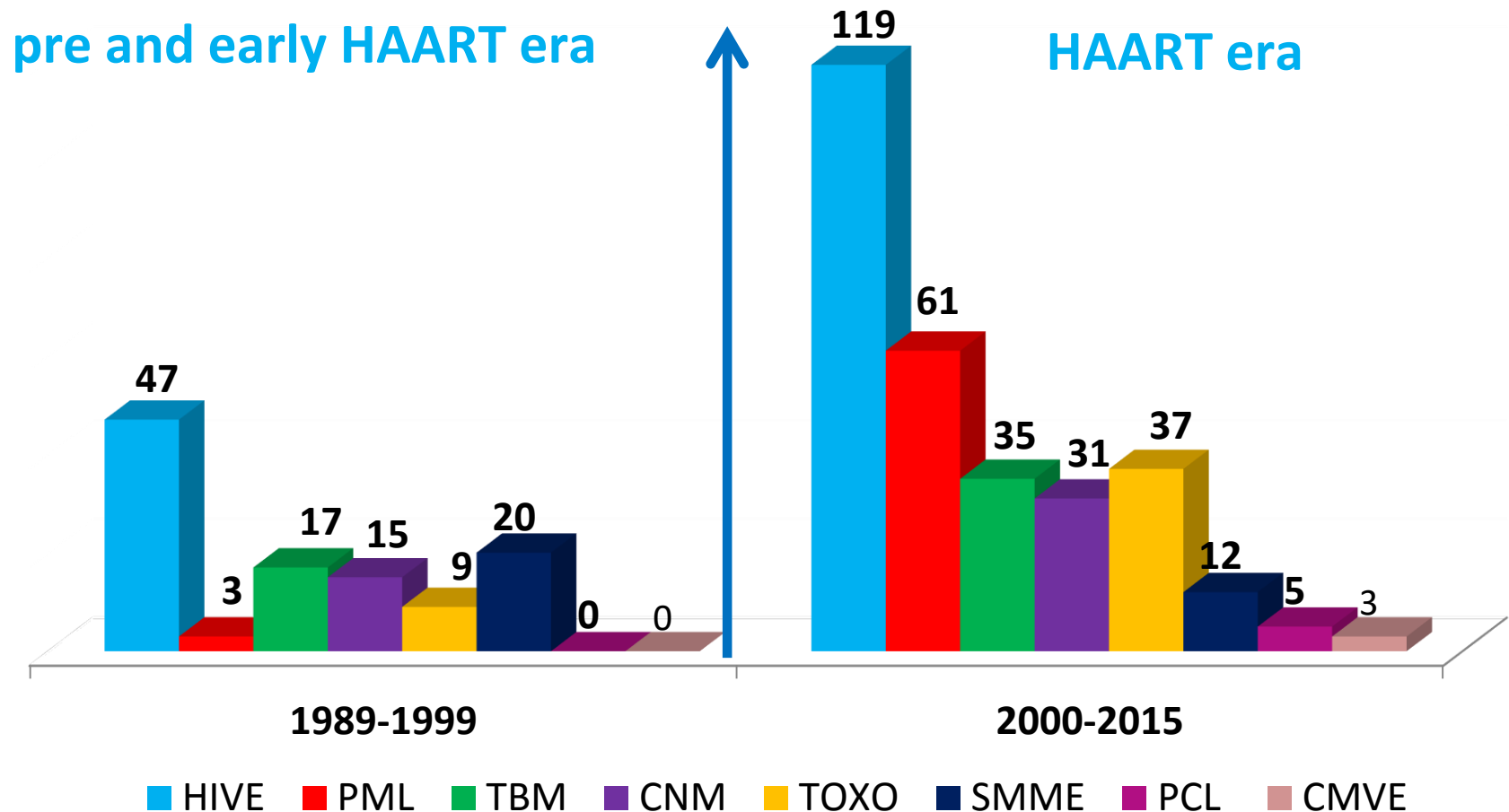
Clinical criteria:

- onset with focal myoclonia - generalized in 2-6 weeks
- local motor deficit with progression to hemi/tetraparesis or plegia
- no changes in mental status
- no fever
- unfavorable outcome

Lab screen

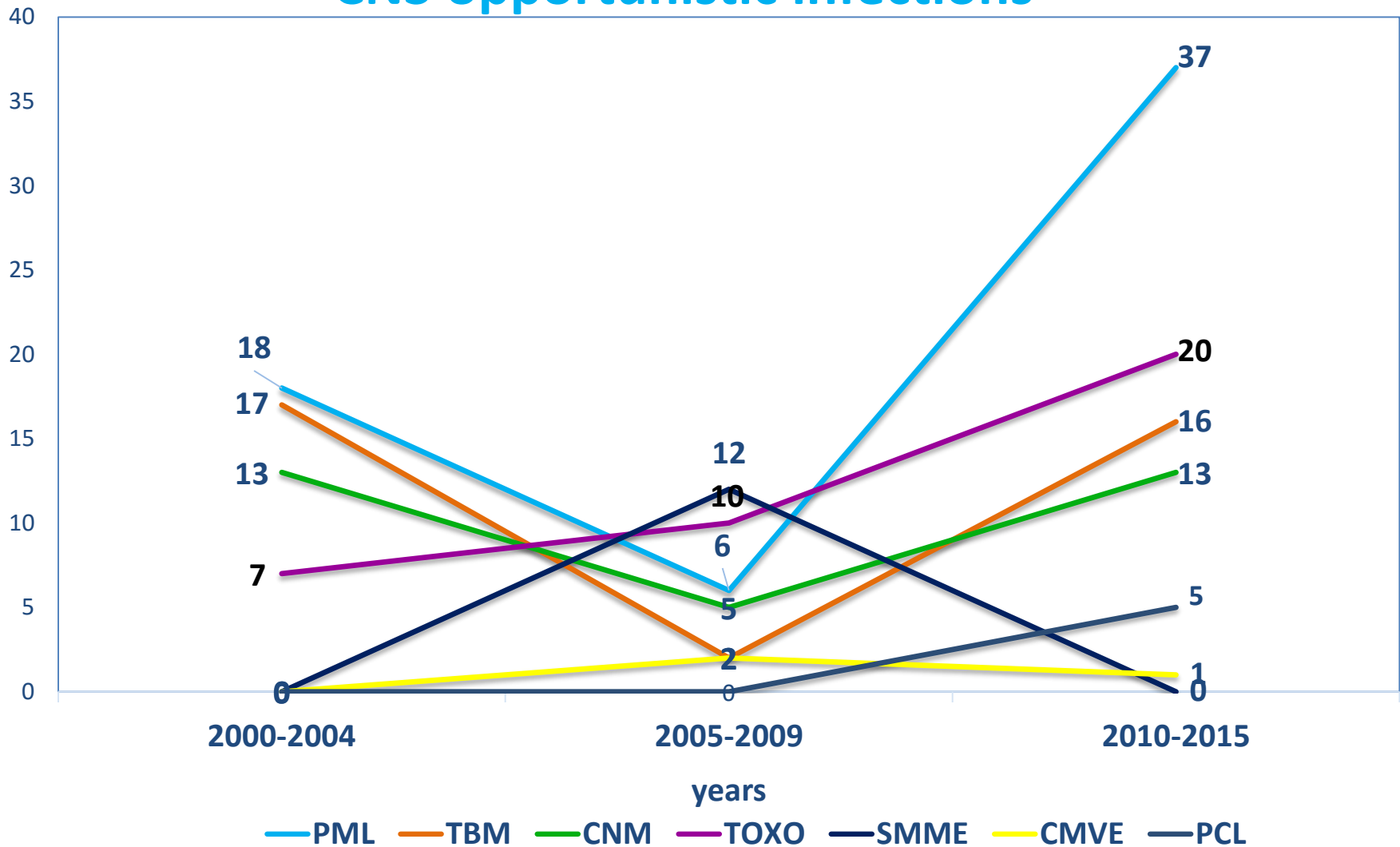
- CD4 cell count $< 200/\text{mm}^3$
- exclusion of other CNS-OIs
- CSF exam - usually normal
- CSF - IgM anti measles virus can be detected

Distribution by years (pre-HAART and HAART era) of HIV associated neurological complications



HIVE - HIV encephalopathy, PML - Progressive multifocal leucoencephalopathy, TBM - Tuberculous meningitis, CNM- Cryptococcal meningitis, TOXO - Cerebral toxoplasmosis, SMME - Subacute myoclonic measles encephalitis, PCL – Primary cerebral lymphoma, CMVE - CMV encephalitis

Distribution by years of HIV associated CNS opportunistic infections



PML - Progressive multifocal leucoencephalopathy, TBM - Tuberculous meningitis, CNM- Cryptococcal meningitis, TOXO - Cerebral toxoplasmosis, SMME - Subacute myoclonic measles encephalitis, CMVE - CMV encephalitis, PCL - Primary cerebral lymphoma

Incidence per person - years of CNS opportunistic infections 2010 - 2015

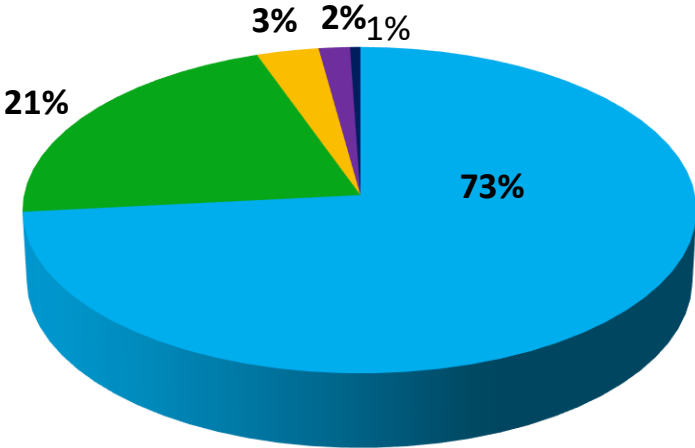
Year	2010	2011	2012	2013	2014	08.2015
No of HIV cases	909	903	962	1098	1434	1189
Incidence n(%)	12 (1.21)	19 (1.66)	11 (1.14)	26 (2.36)	14 (0.97)	11 (0.92)

6497 person-years (PY)

93 diagnosed with CNS OIs (1.43%)

Incidence: **14.3/1000 PY**

Modes of HIV transmission in patients diagnosed with CNS OIs and cerebral tumors (n=184)

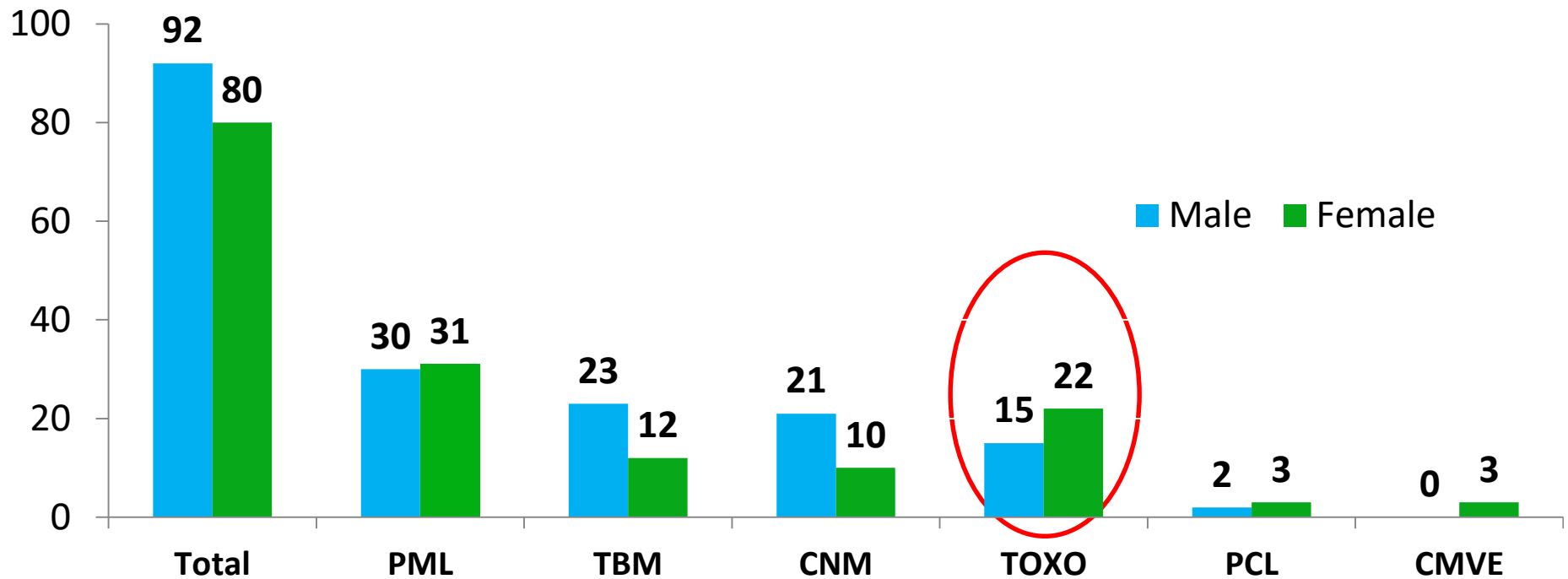


■ Parenteral ■ HSX ■ IDUs
■ MTCT ■ MSM

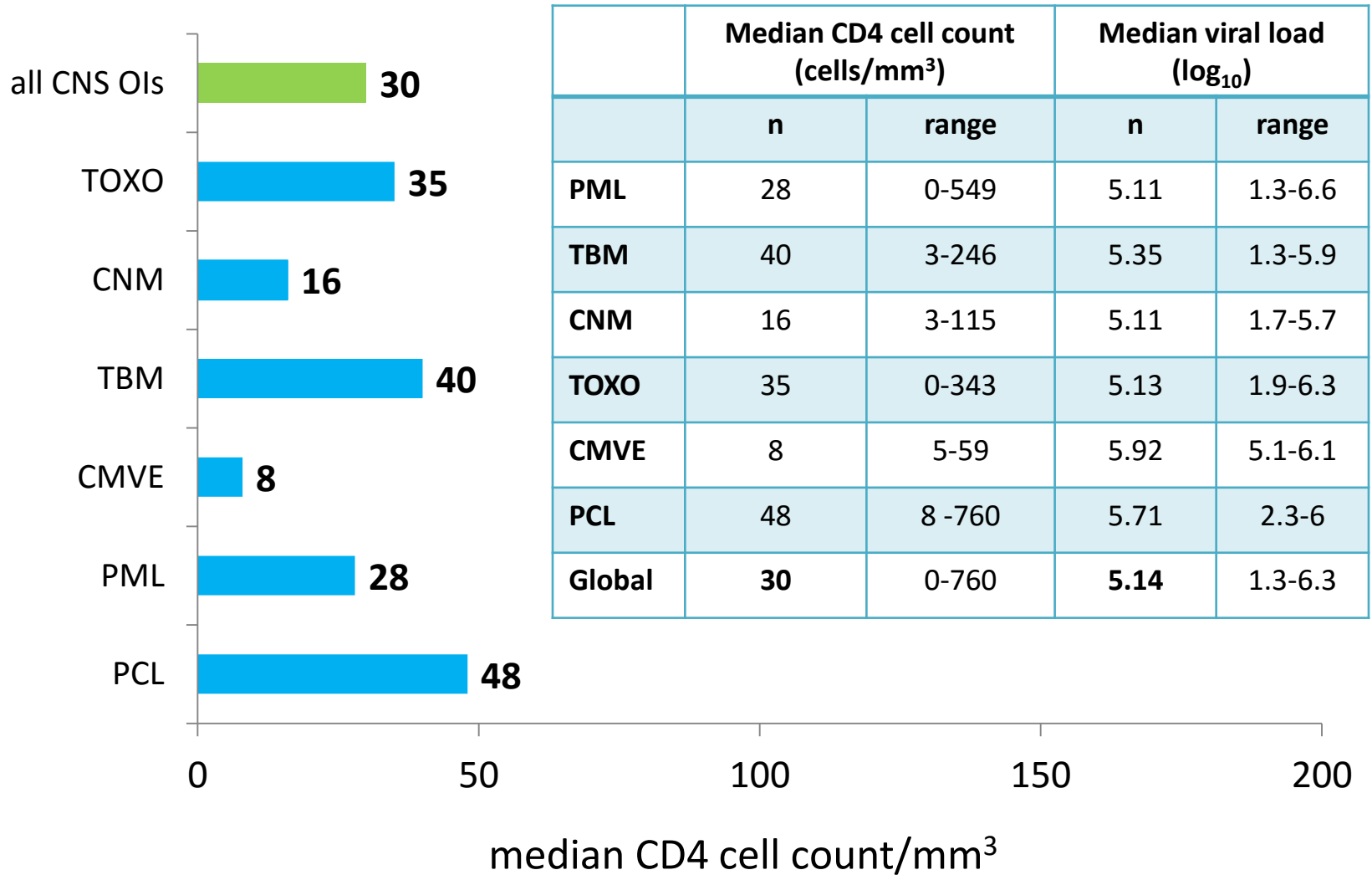
	Parenteral	HSX	IDUs	MTCT	MSM
PML	47	13	0	1	0
TBM	24	6	4	1	0
CNM	24	4	2	1	0
TOXO	25	11	0	0	1
CMVE	2	1	0	0	0
SMME	12	0	0	0	0
PCL	1	4	0	0	0

Median age and gender distribution in HIV infected patients diagnosed with CNS OIs

	Total n=184	PML n=61	TBM n=35	CNM n=31	TOXO n=37	SMME n=12	PCL n=5	CMVE n=3
Median age at dg of OIs years (range)	21 (10-63)	22 (10-60)	19 (10-52)	20 (11-38)	23 (11-67)	17 (16-18)	41 (22-63)	20 (18-33)



Median CD4 cell count and plasma HIV viral load at diagnosis by type of CNS opportunistic infection



CDC classification before the onset of CNS OIs

	Total n=172	PML n=61	TBM n=35	CNM n=31	Toxo n=37	PCL n=5	CMVE n=3
HIV and OIs diagnosed simultaneously n (%)	41 (22.2)	12 (19.6)	7 (20.0)	5 (16.1)	13 (35.1)	3 (60.0)	1 (33.3)

	Total n=132	PML n=49	TBM n=28	CNM n=26	Toxo n=24	PCL n=3	CMVE n=2
CDC category prior to the onset of CNS OIs n(%)							
A	1 (0.7)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
B	74 (56.0)	40 (81.6)	11 (39.2)	6 (23.0)	13 (54.1)	3 (100.0)	1 (50.0)
C	57 (43.1)	8 (16.3)	17 (60.7)	20 (76.9)	11 (45.8)	0 (0.0)	1 (50.0)

Concurrent or consecutive CNS OIs and CNS - IRIS

7 patients (3.8%) diagnosed with multiple OIs

	OI 1	Year	OI 2	Year	OI 3	Year
1	TBM	1999	CNM	1999	-	
2	TBM	2001	CNM	2001	-	
3	TBM	2002	CNM	2003	-	
4	PML	1997	CNM	1998	-	
5	TOXO	2007	CNM	2008	-	
6	TOXO	1999	TBM	2015	-	
7	TOXO	2014	PML	2015	TBM	2015

9 patients (5.2%) diagnosed with CNS - IRIS

1 TBM, 2 CNM, 1 TOXO, 5 PML

Mortality rate and median survival time in HIV infected patients diagnosed with CNS opportunistic infections

	No of patients	Mortality rate n (%)	Median survival time months (range)
PML	61	25 (40.9)	23.0 (0.5-162.6)
Tuberculous meningitis*	35	24 (68.5)	3.0 (0.1-169.6)
Cryptococcal meningitis	31	12 (38.7)	31.3 (0.1-179.6)
Cerebral toxoplasmosis	37	8 (21.6)	46.6 (0.1-181.6)
PCL	5	3 (60.0)	1.75 (0.5-50.1)
CMVE	3	0 (0.0)	87.6 (32.2-115.7)
Total	172	72 (41.8)	17.5 (0.1-181.6)

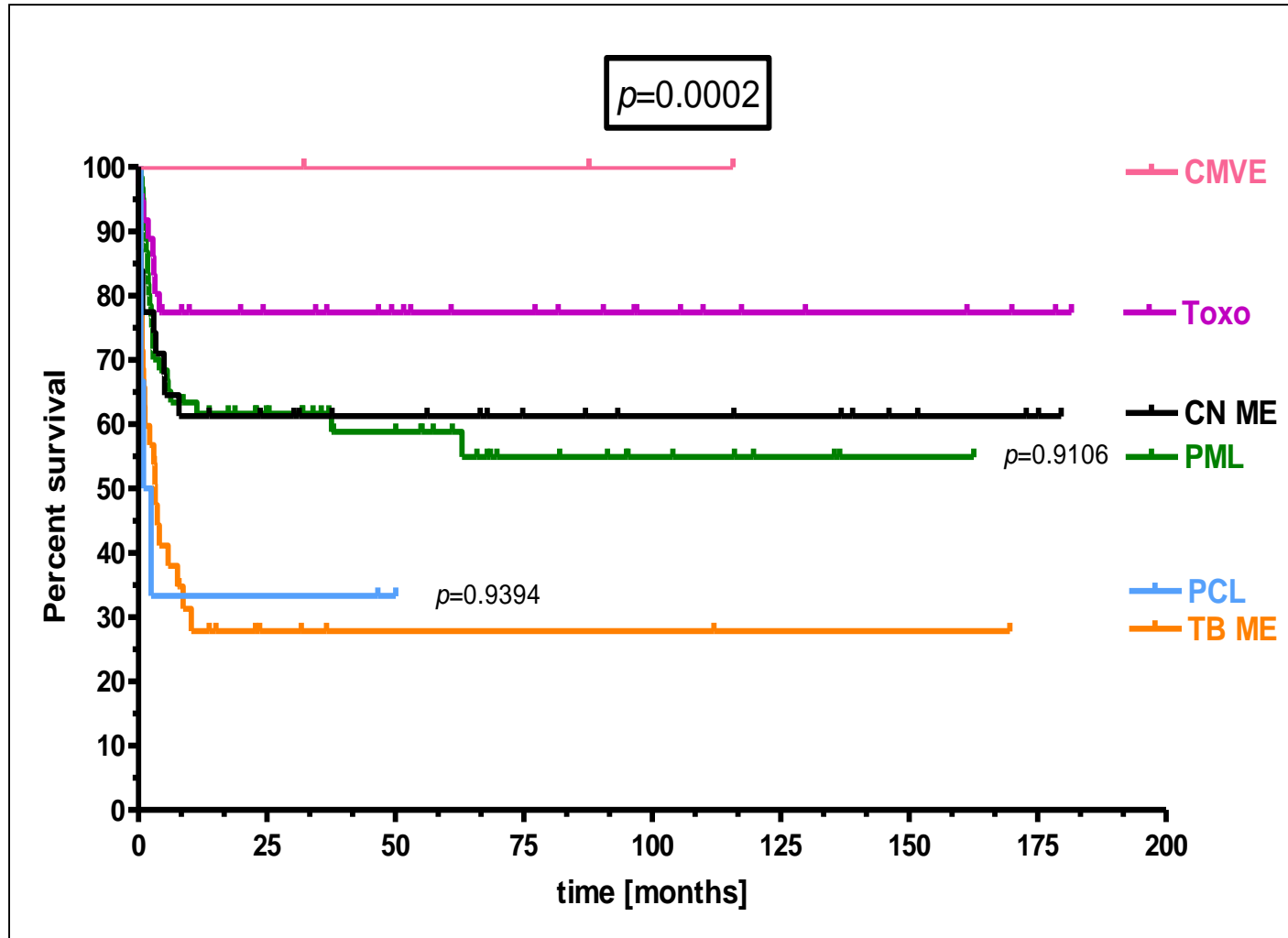
- 14/35 with **resistant TB** (9 MDR and 5 XDR) + 4 with resistance to either INH or RIF

Prior cART and mortality rate in HIV infected patients diagnosed with CNS opportunistic infections

	Mortality rate					
	No prior cART n = 94		Non-adherence to cART n = 69		Adherence to cART n = 2	
	n	%	n	%	n	%
PML	16	17.0	8	11.5	0	0.0
Tuberculous meningitis	15	15.9	8	11.5	-	-
Cryptococcal meningitis	4	4.2	6	8.6	-	-
Cerebral toxoplasmosis	6	6.3	2	2.8	-	-
PCL	3	4.2	1	-	0	0.0
CMVE	0	0.0	0	0.0	-	-
Total	45	47.8	24	34.7	0.0	0.0

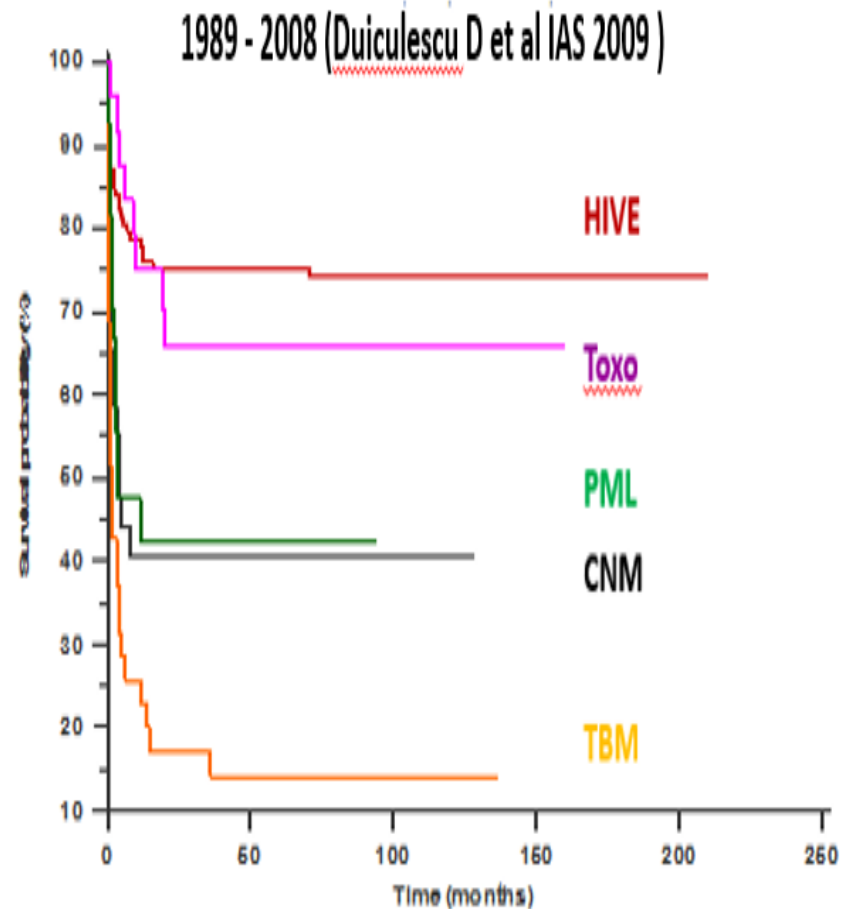
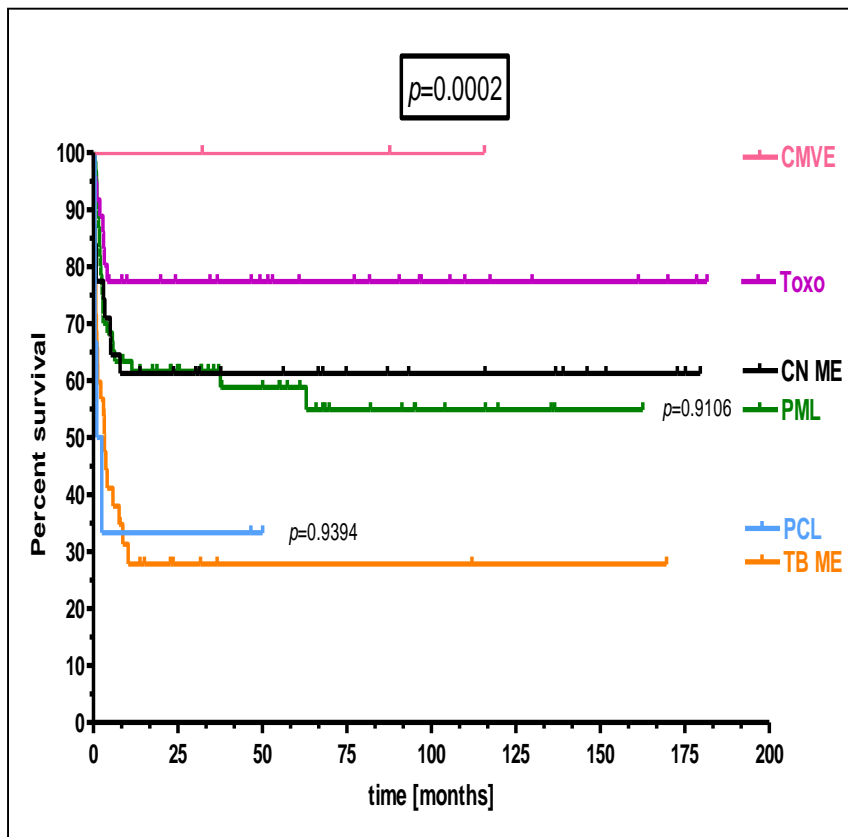
Global survival rate at 3 years after CNS OIs diagnosis 36.4 %
5 years after CNS OIs diagnosis 27.7%

Survival in patients with CNS opportunistic infections diagnosed between 2000-2015



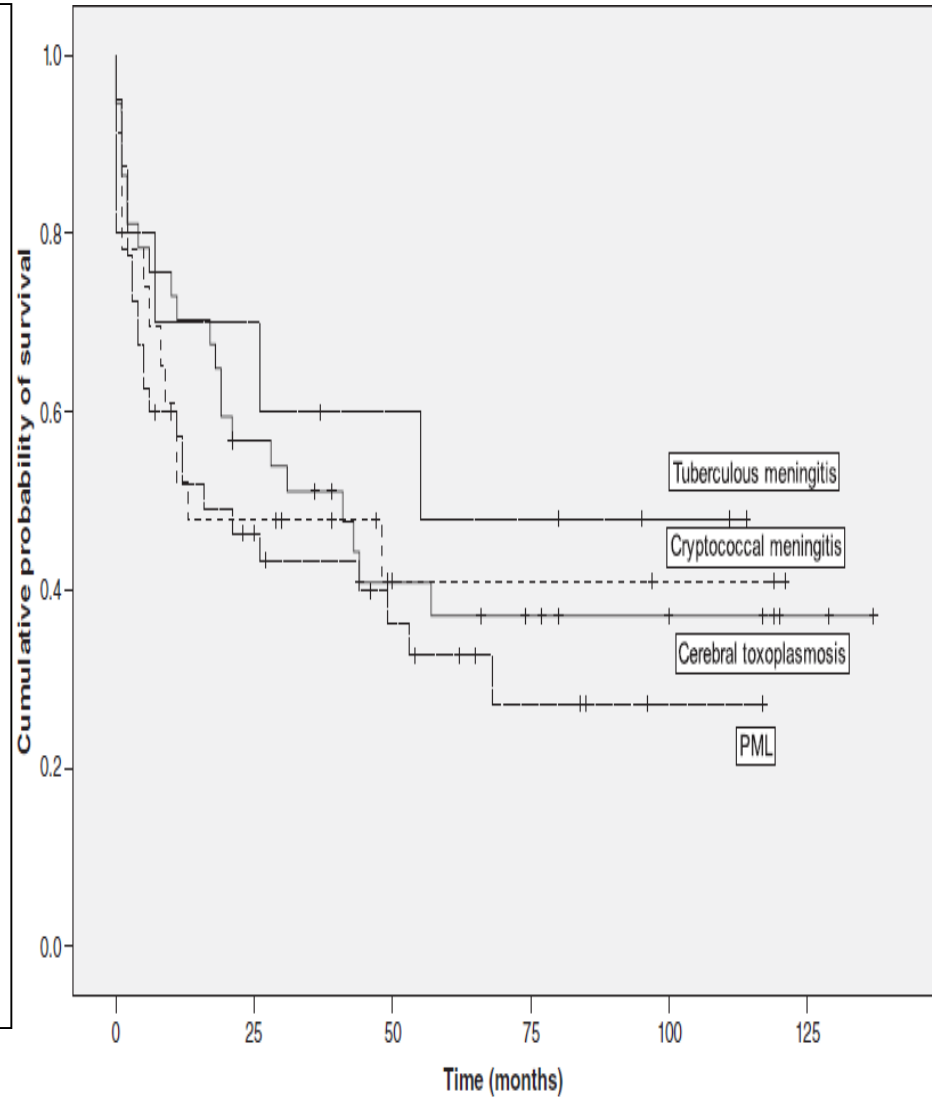
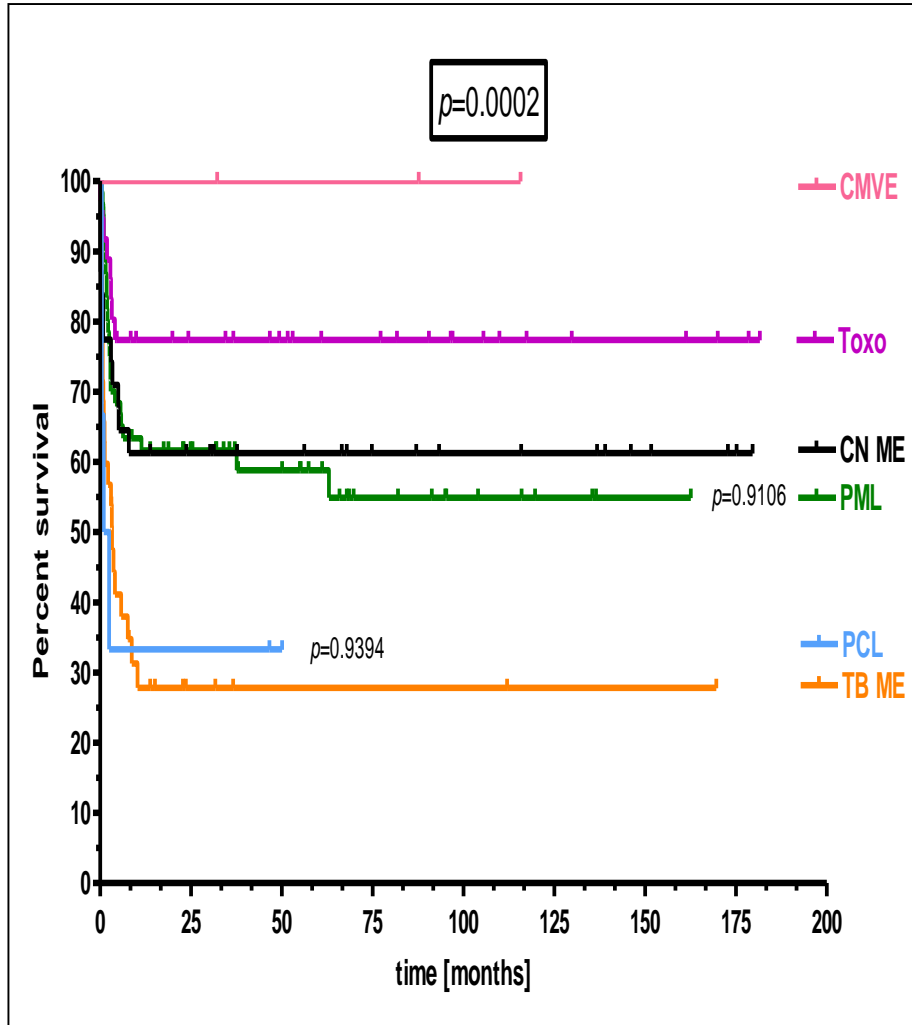
Comparison of Kaplan-Meier curves between different study periods in VBH

Survival with CNS-OIs 2000-2015

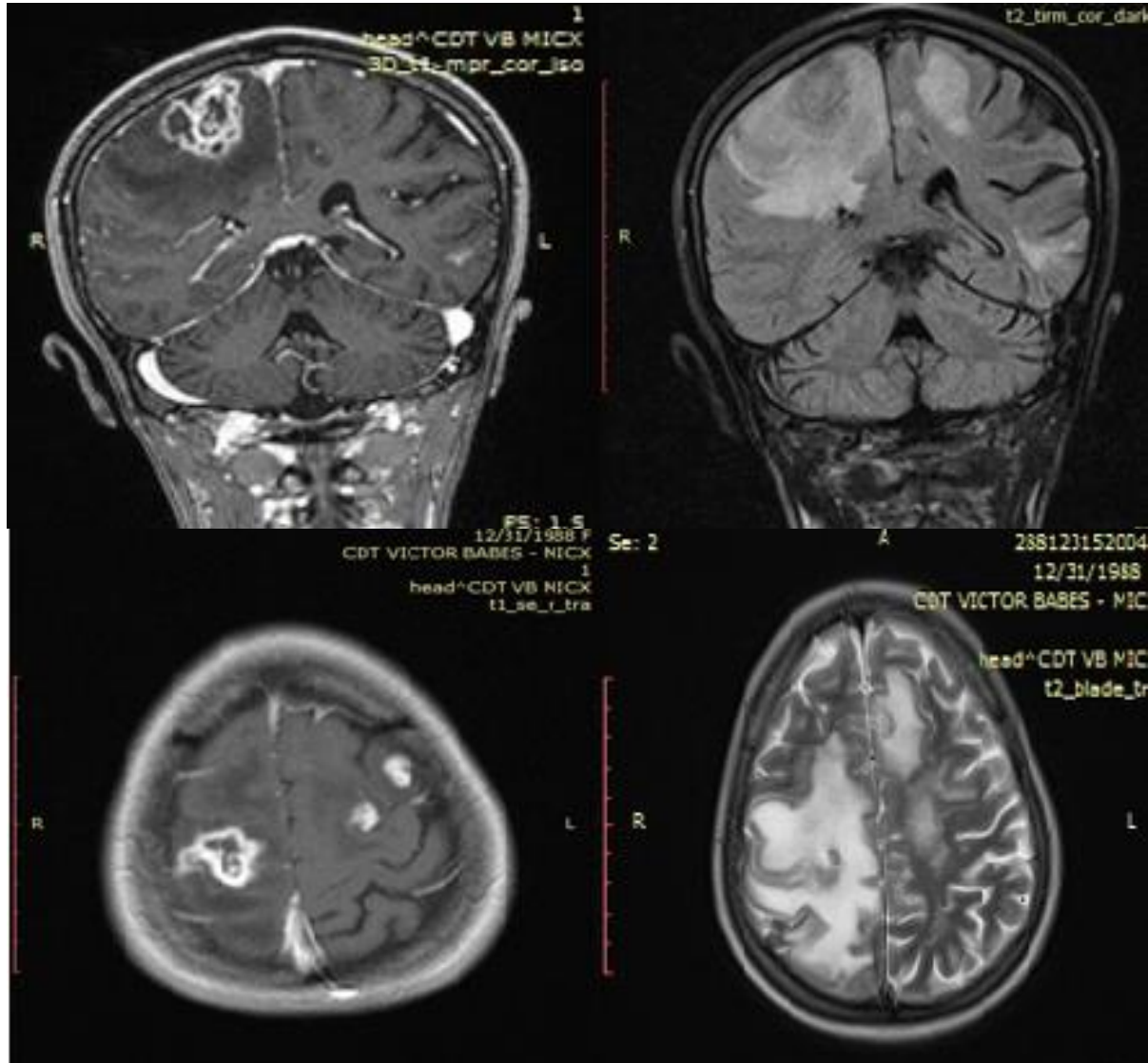


Survival in patients with CNS-OIs in VBH (2000 - 2015)

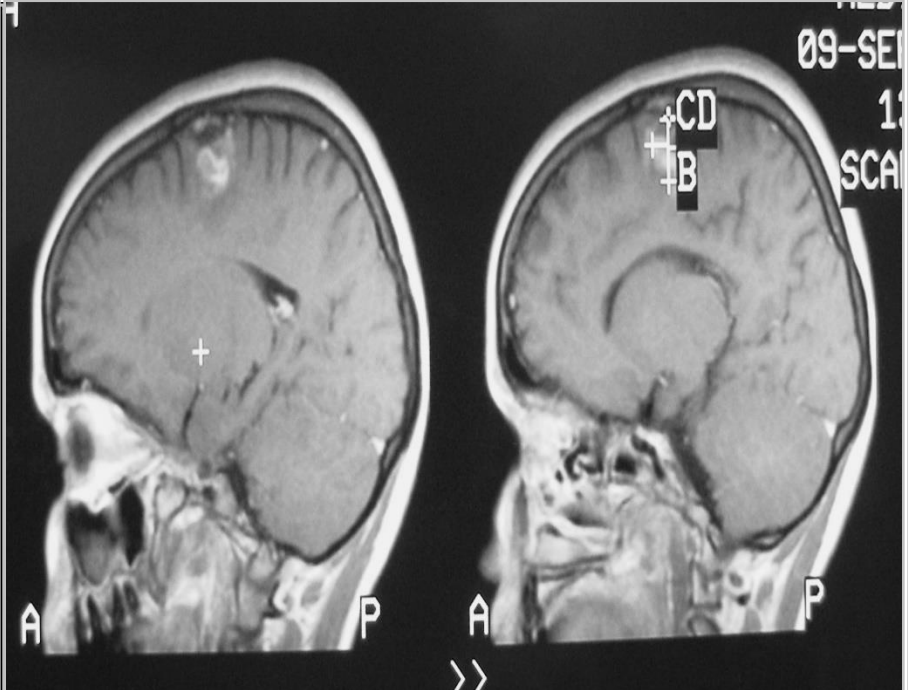
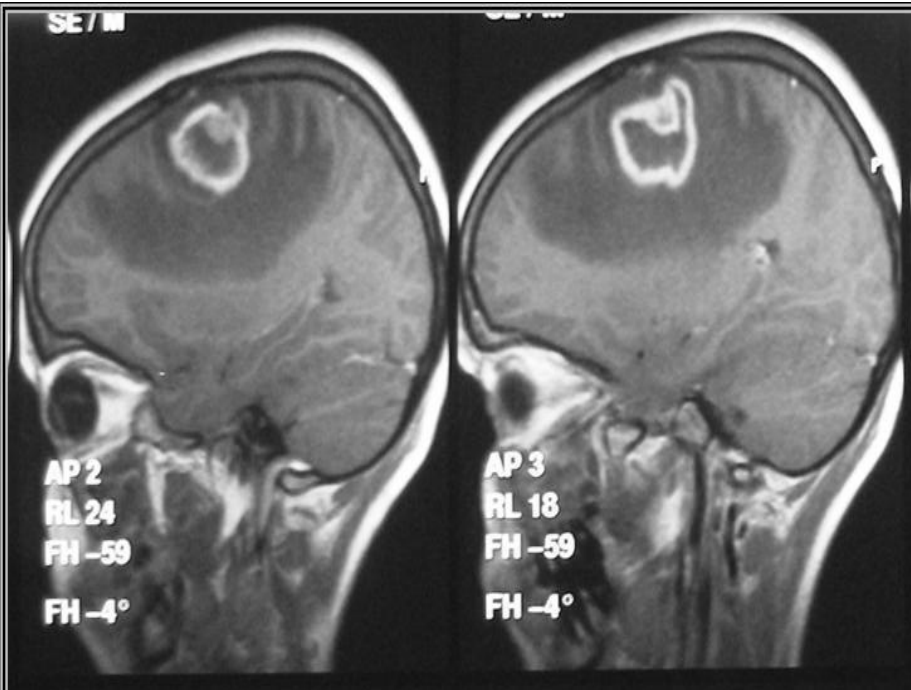
Survival in patients with CNS OIs in a Spanish cohort (2000 - 2010)



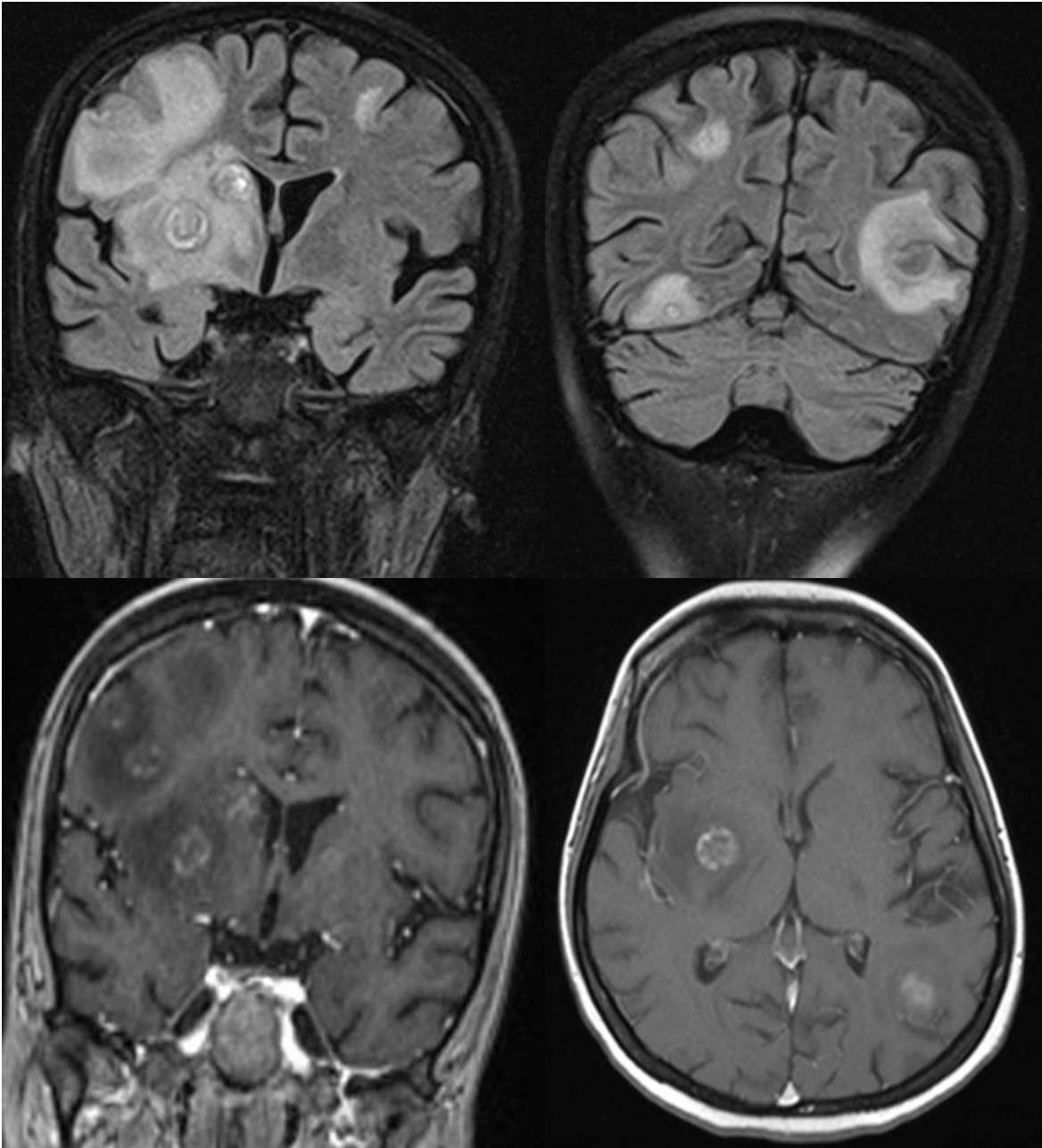
Cerebral toxoplasmosis in a 24 year-old woman who grew up with HIV



Cerebral toxoplasmosis in a 15 year-old girl



Brain MRI - in a 25 year-old woman with cerebral toxoplasmosis



Brain MRI in a 8 year-old child with multiple cerebral toxoplasma abscesses



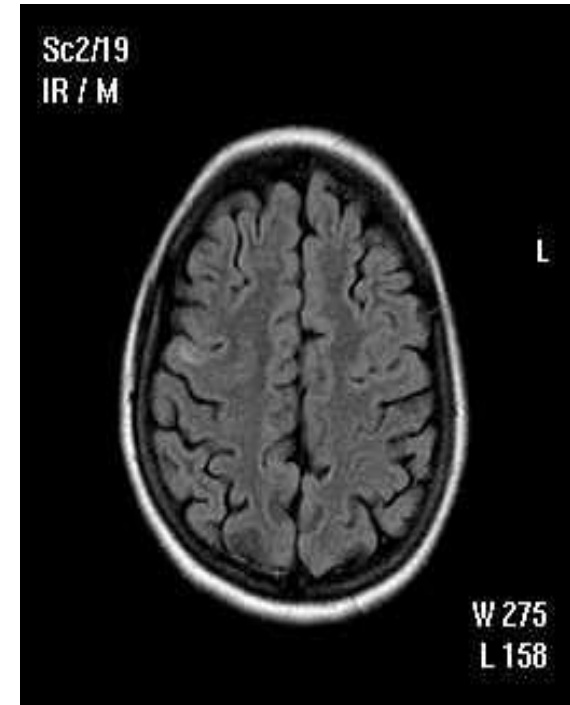
Unique toxoplasma abscess in a 17 year-old girl



unique temporal lesion

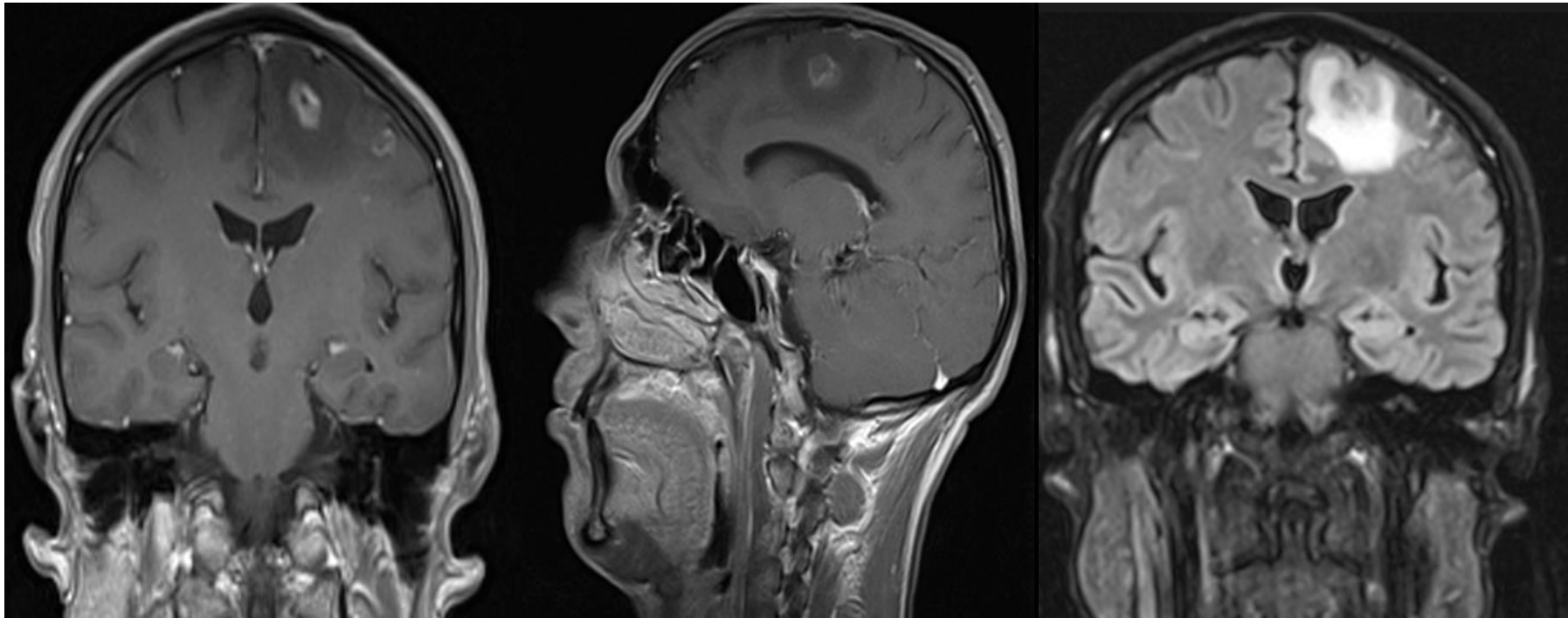


after 1 month of anti toxo treatment

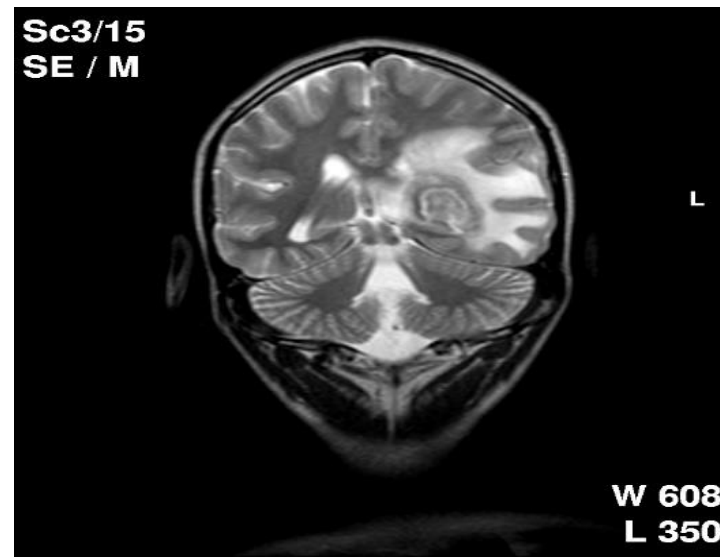
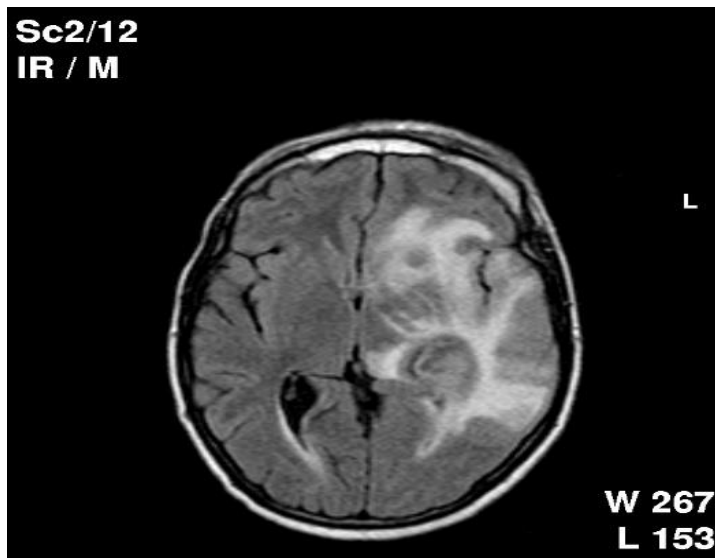
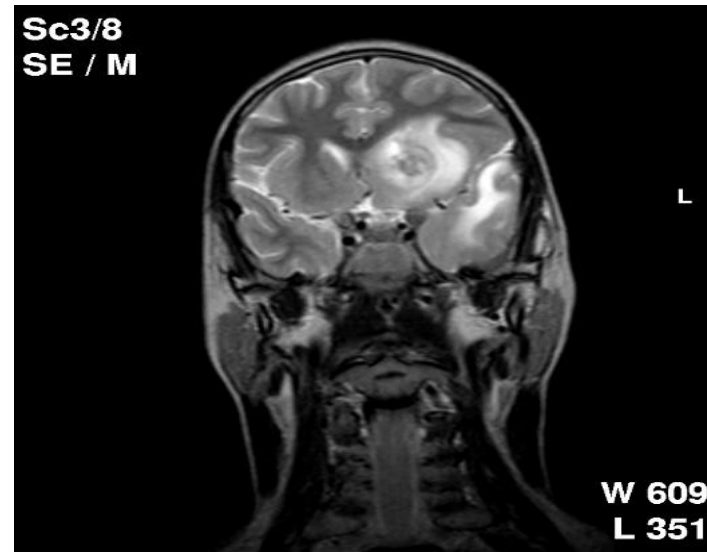
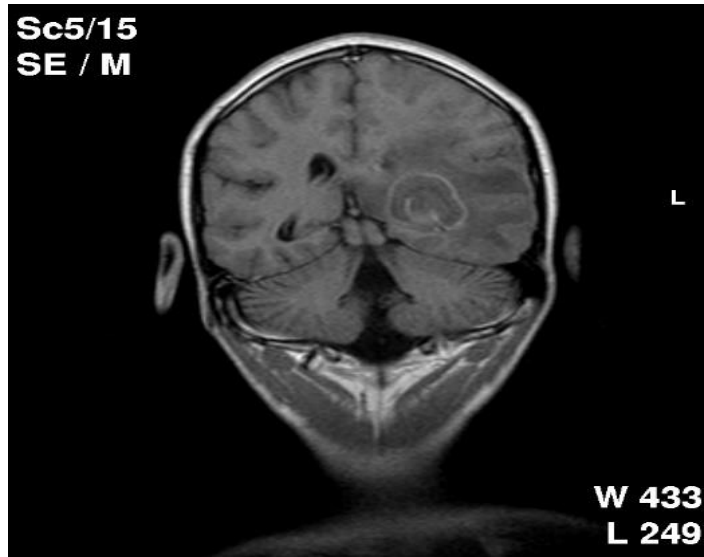


after 3 months of antitoxo treatment

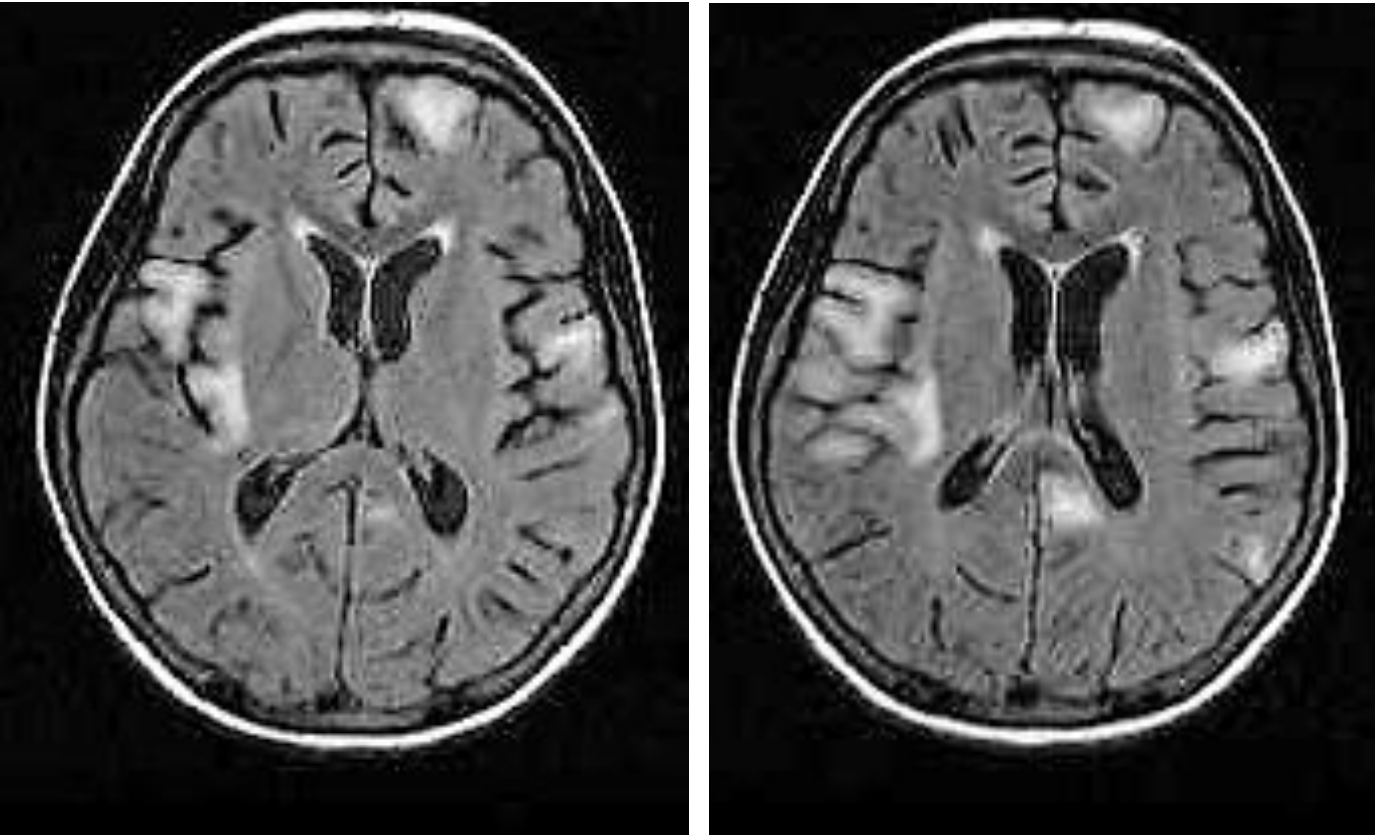
Recurrent cerebral toxoplasmosis in a 43 year-old man



Cerebral toxoplasmosis in a 18 year-old boy diagnosed simultaneously with HIV infection

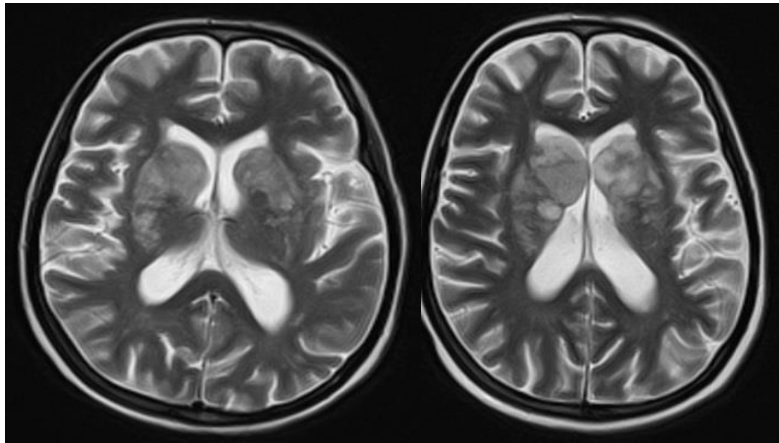


Focal type CMV encephalitis in a 20 year-old girl

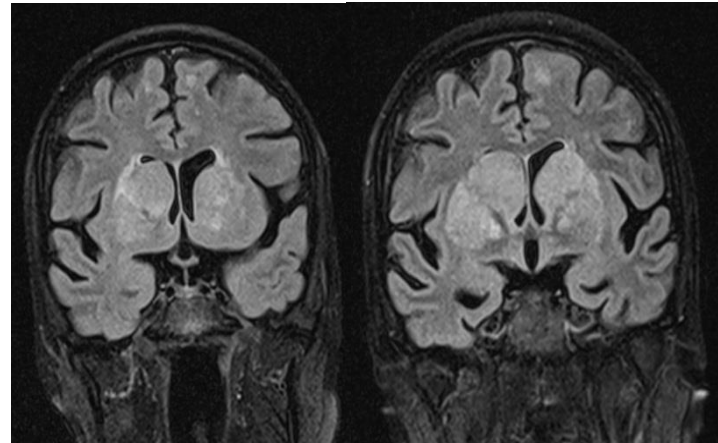


Gelatinous pseudocysts of cryptococcosis in a 24 year-old girl

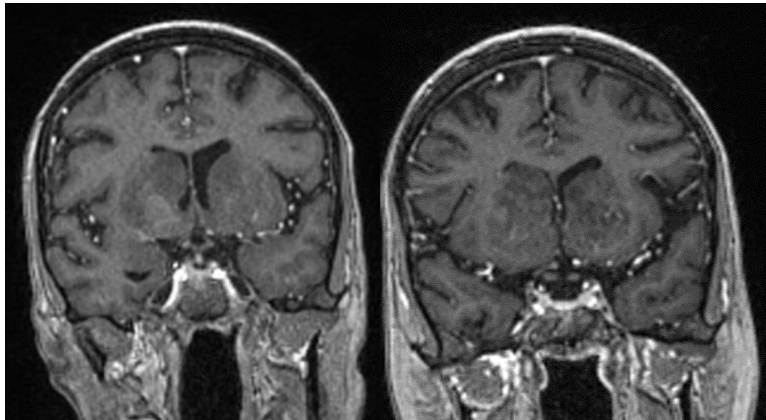
T2 sagittal



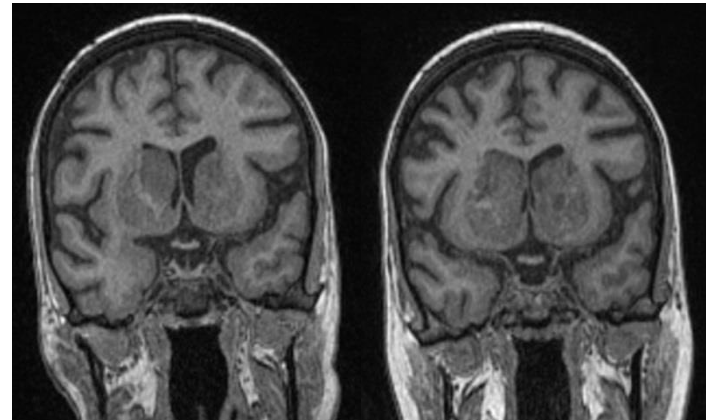
FLAIR coronal



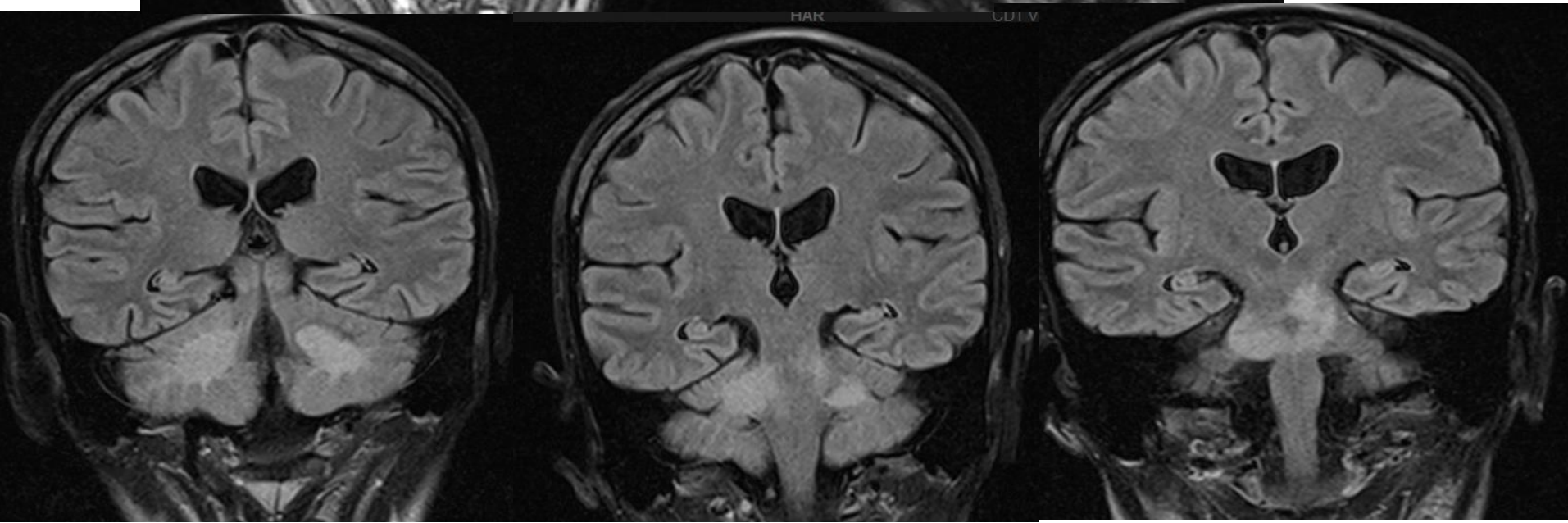
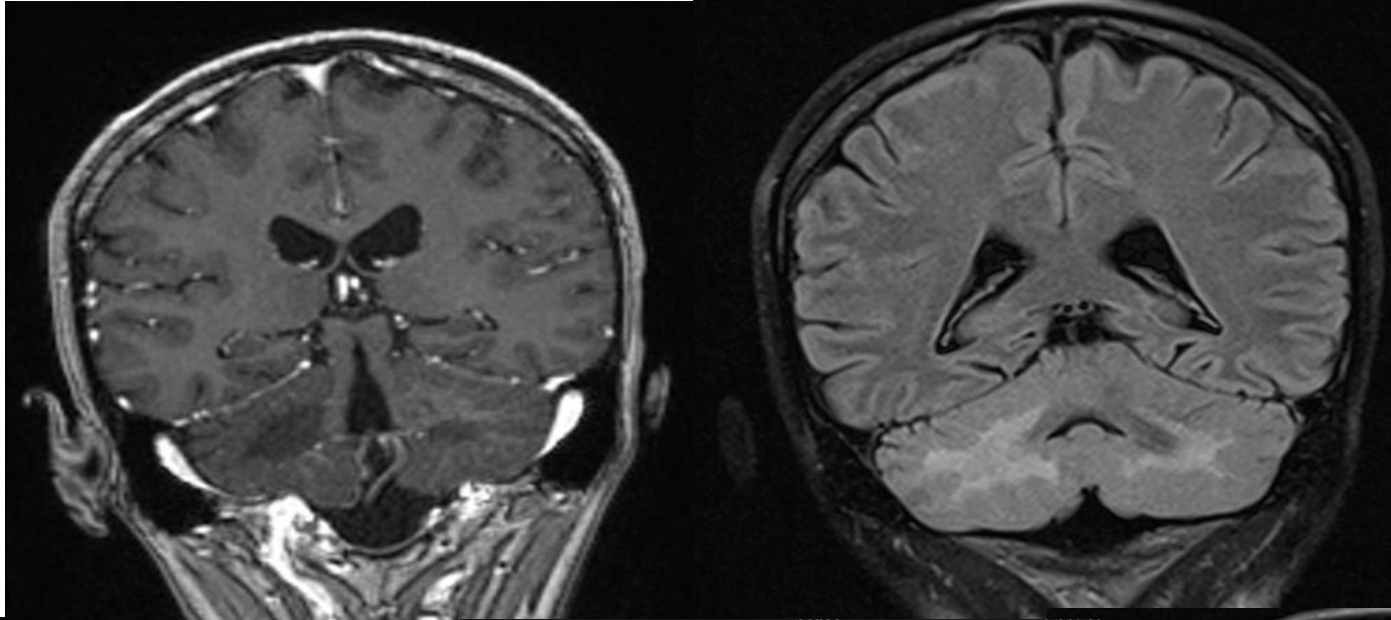
T1 contrast



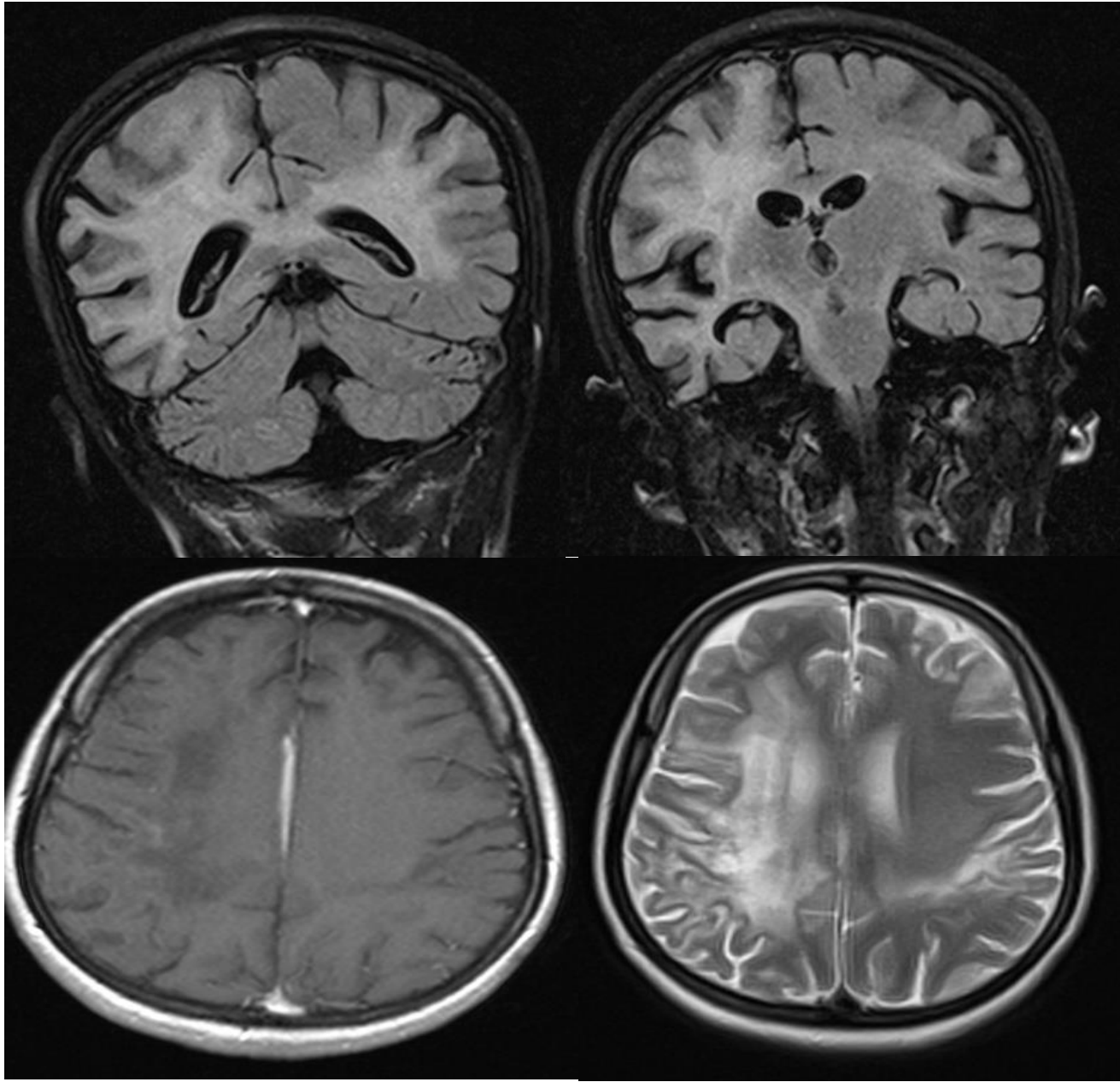
T1 coronal



Bilateral cerebellar and brain stem lesions in a 37-year-old woman with PML and non-Hodgkin lymphoma

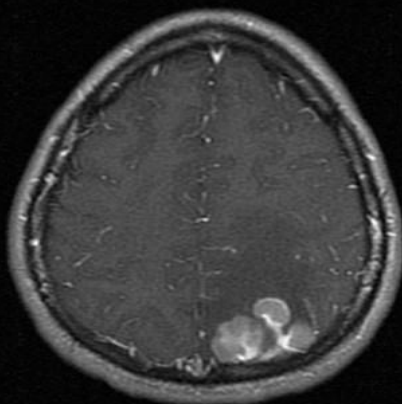


PML in a 18 year-old girl non-adherent to cART

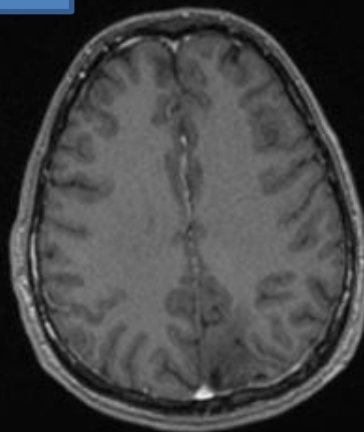


Brain MRI in a 22 year-old woman with primary cerebral lymphoma before and after DeAngelis protocol (T1 sequence)

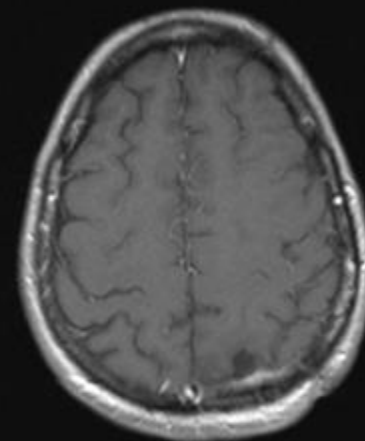
07.2011



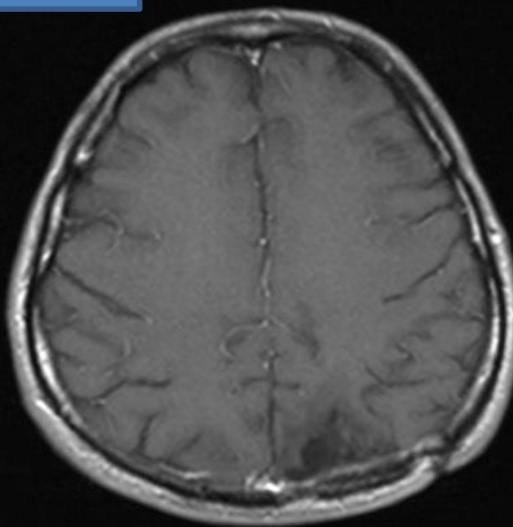
02.2012



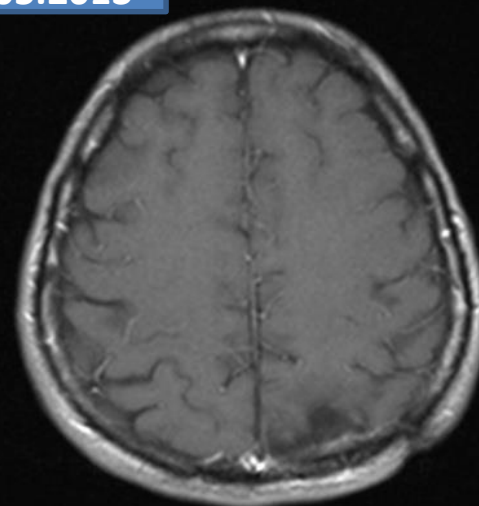
04.2012 after RxT



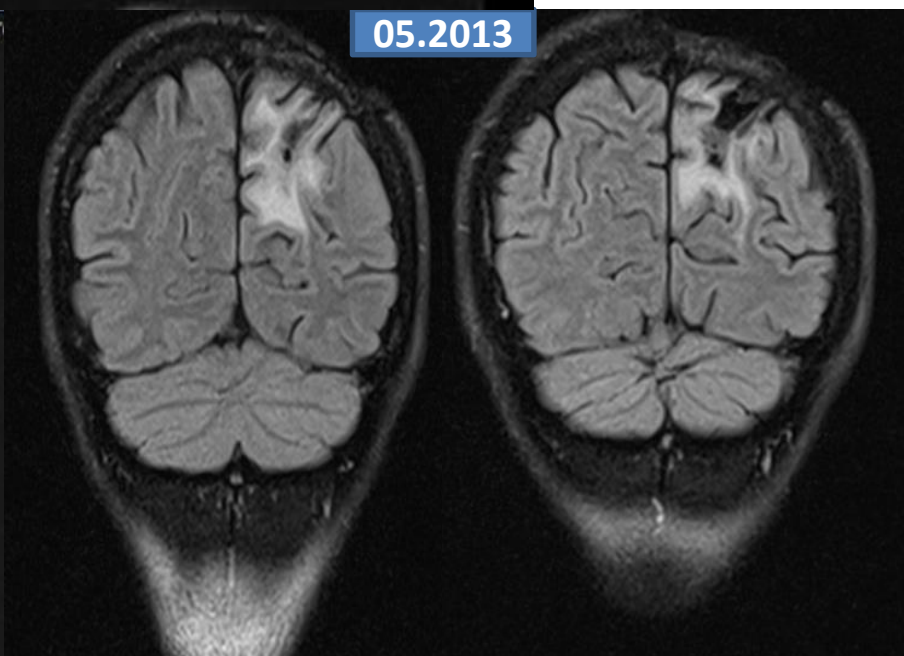
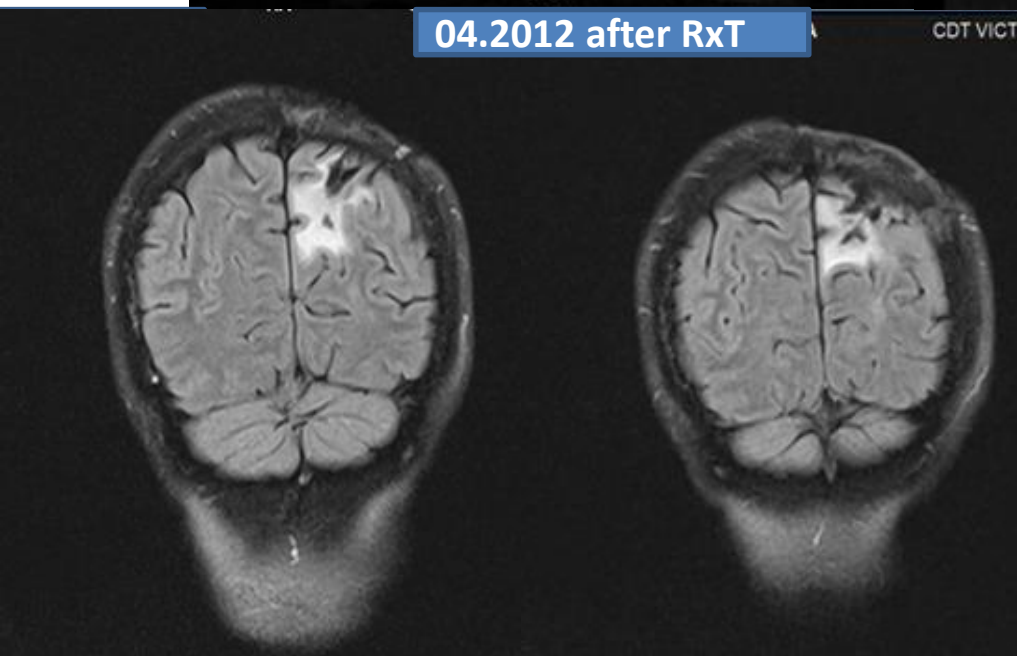
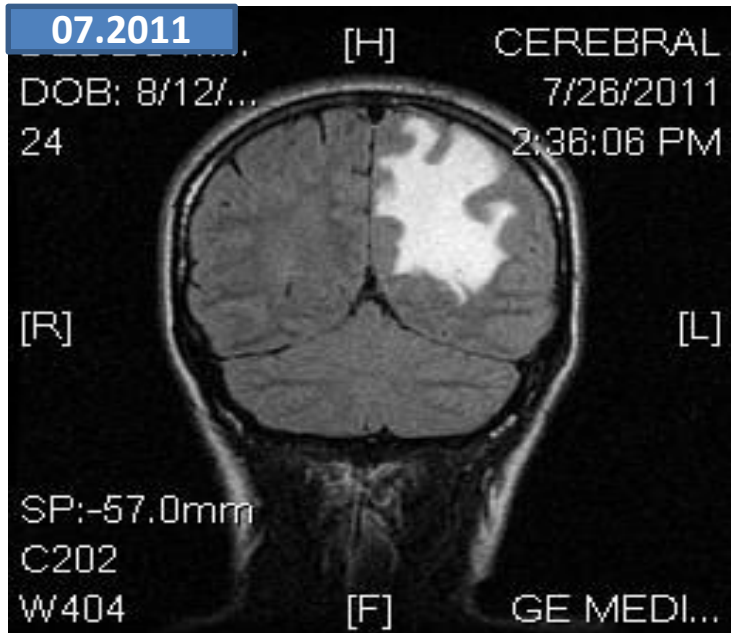
05.2013



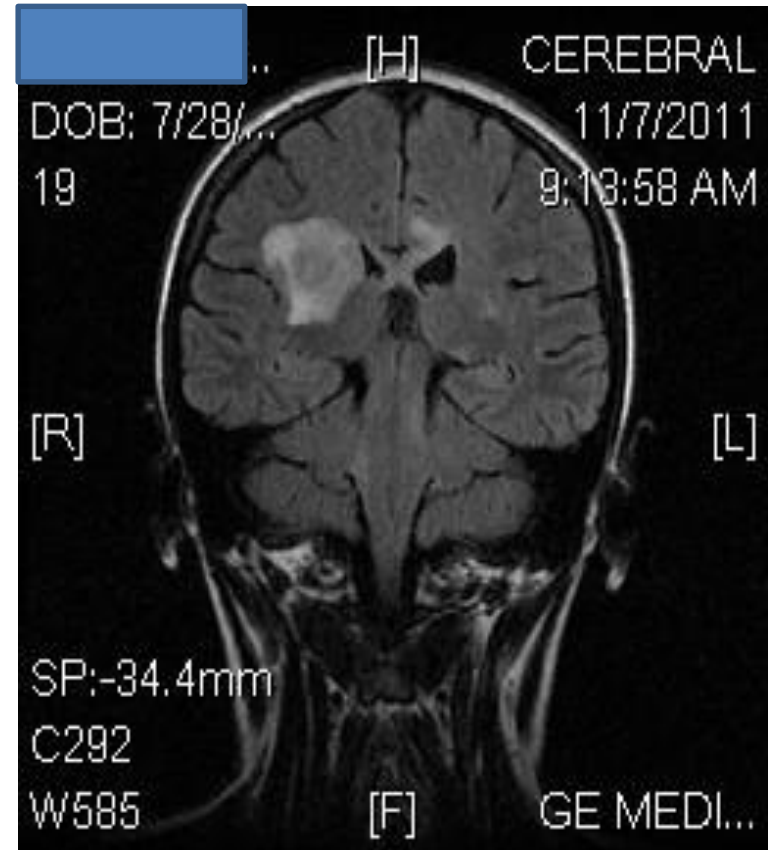
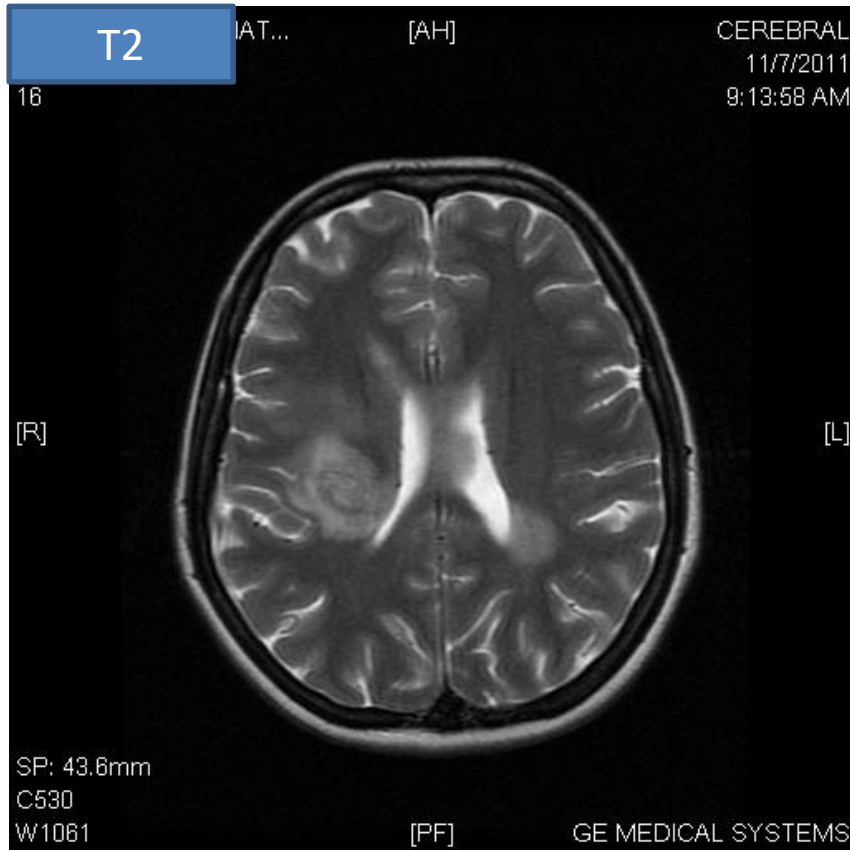
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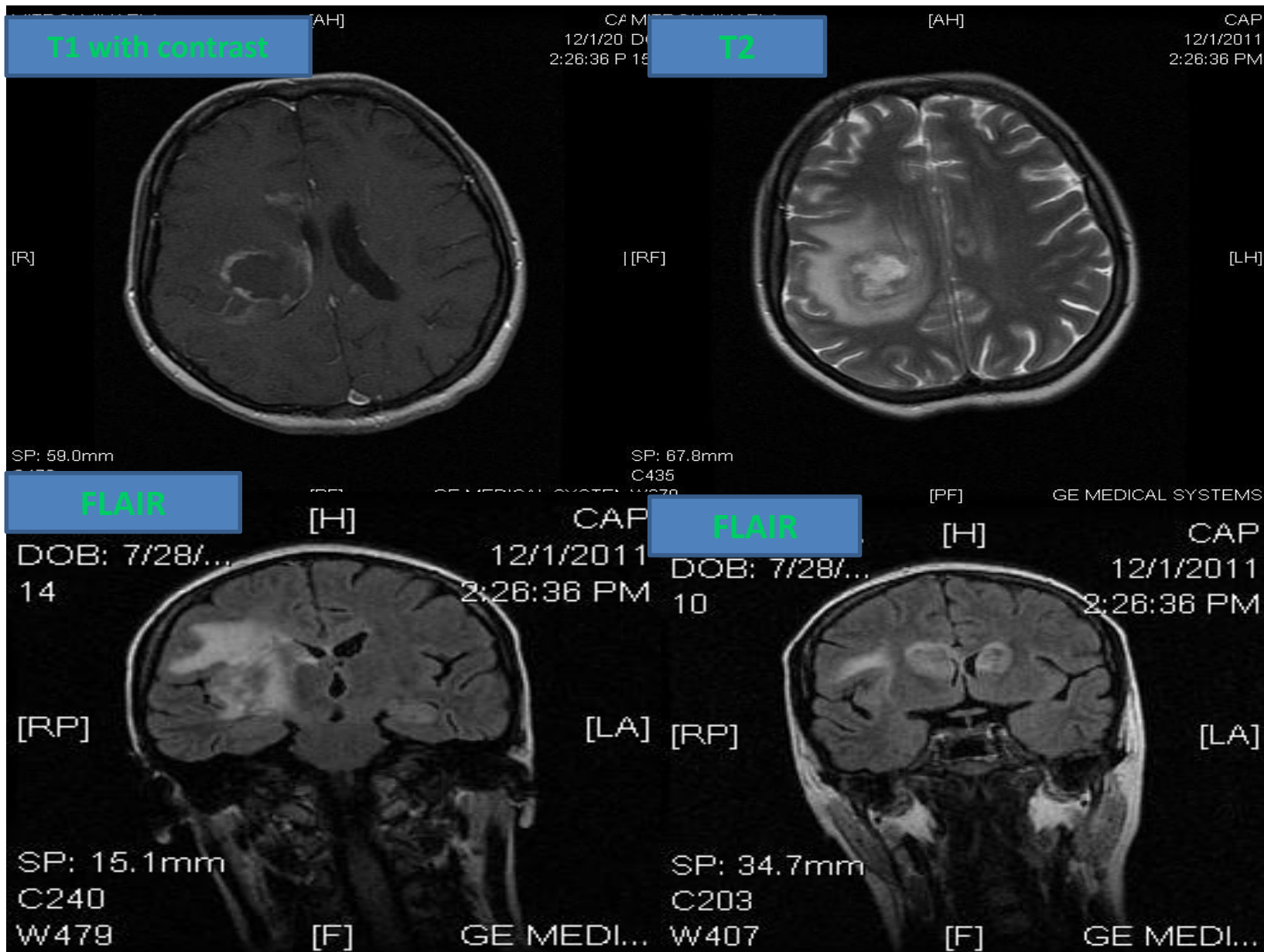
Brain MRI (FLAIR) before and after DeAngelis protocol



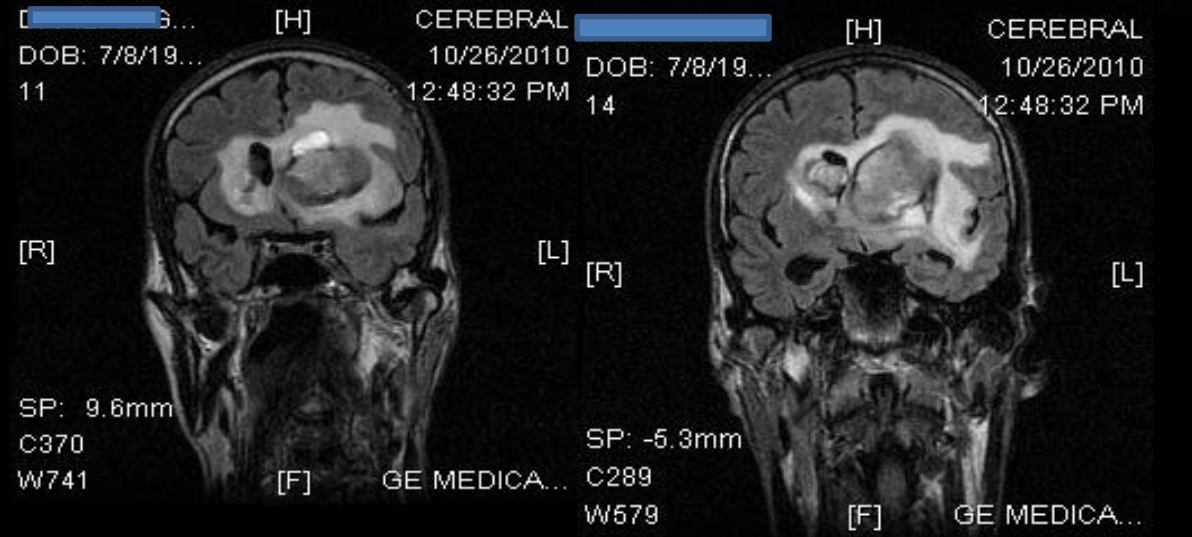
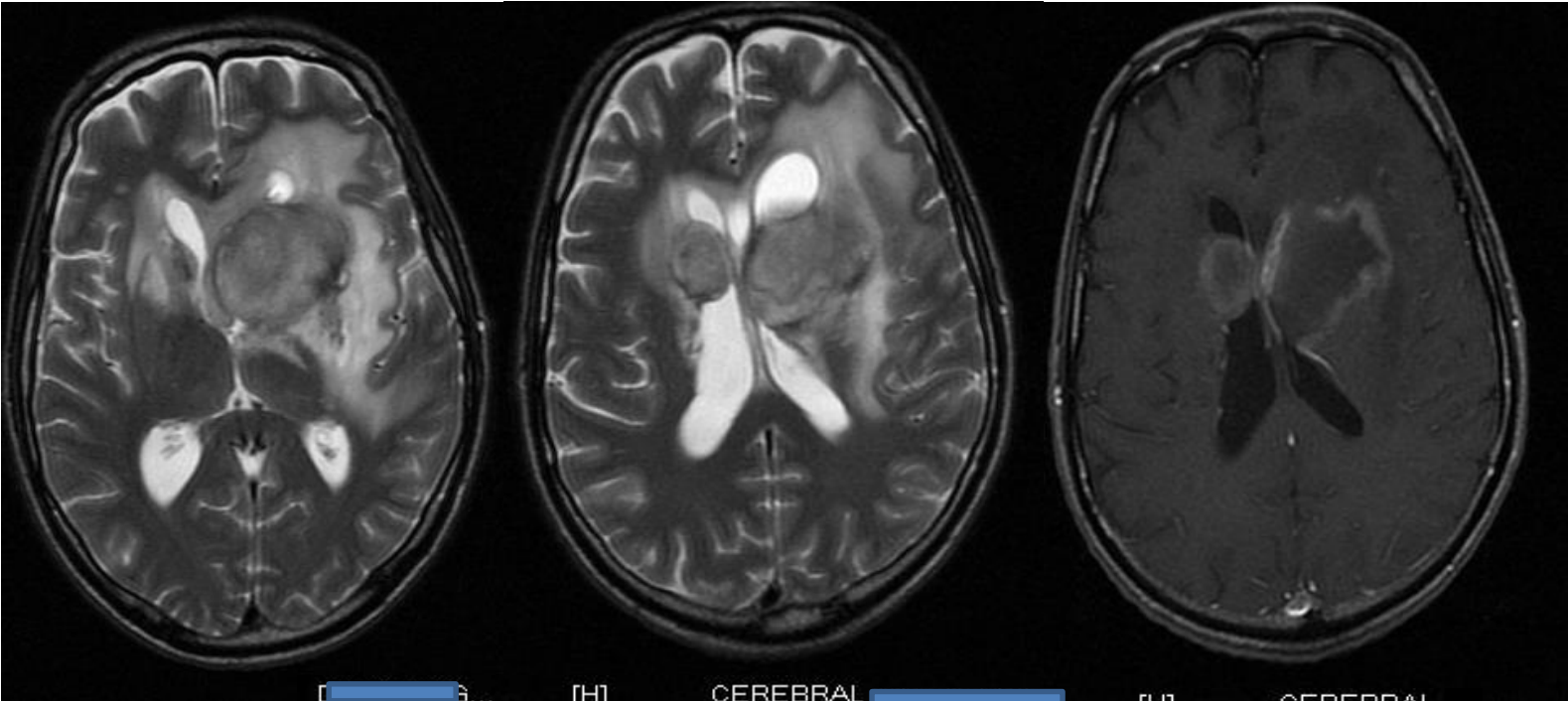
Brain MRI in 25 year-old woman with multifocal cerebral lymphoma



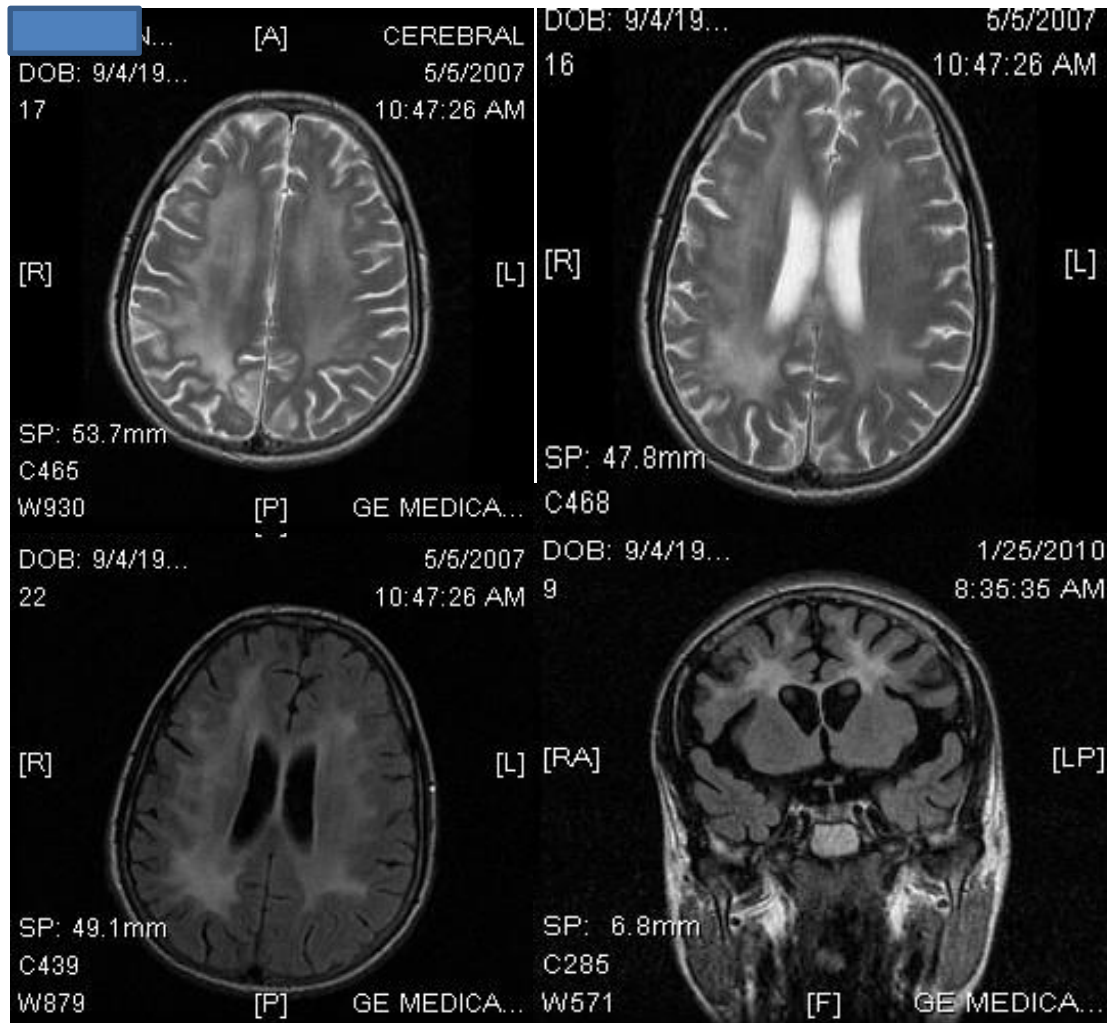
Brain MRI in 25 year-old woman with multifocal cerebral lymphoma



Brain tumor in a 39 year-old man



Brain MRI in a 19 year-old boy diagnosed with HIV infection and PESS



Discussions 1

- The incidence of CNS OIs in the cART era was relatively high due to:
 - ✓ non-adherence caused by “therapeutic fatigue” in the group of young adults infected parenterally in their first years of life (young by age but old by infection!)
 - ✓ late diagnosis of HIV and/or CNS OIs (lesions in silent brain areas)
 - ✓ the increase in the number of Neuro HIV cases referred to our hospital (recognized as a reference center)
- The survival rate was higher than in early cART period

Discussions 2

- Challenges:
- ✓ **Diagnostic:** CNS OIs with atypical clinical presentation and brain imaging
CNS - IRIS
- ✓ **Treatment:** multiple CNS OIs (concurrent or consecutive)
preferred regimens for some CNS OIs (Toxoplasmosis, Cryptococcosis) are not available
- The overall prognosis in CNS OIs was poor, especially in patients with late diagnosis and/or lack of adherence to cART
- Neurotropic potential for HIV clade F (?)

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Gratiela Tardei

Manuela Nica

to our brave nurses



to all our patients from “Casa Doru”