CNS Opportunistic Infections: an update

Paola Cinque
Department of Infectious Diseases
San Raffaele Scientific Institute
Milan, Italy

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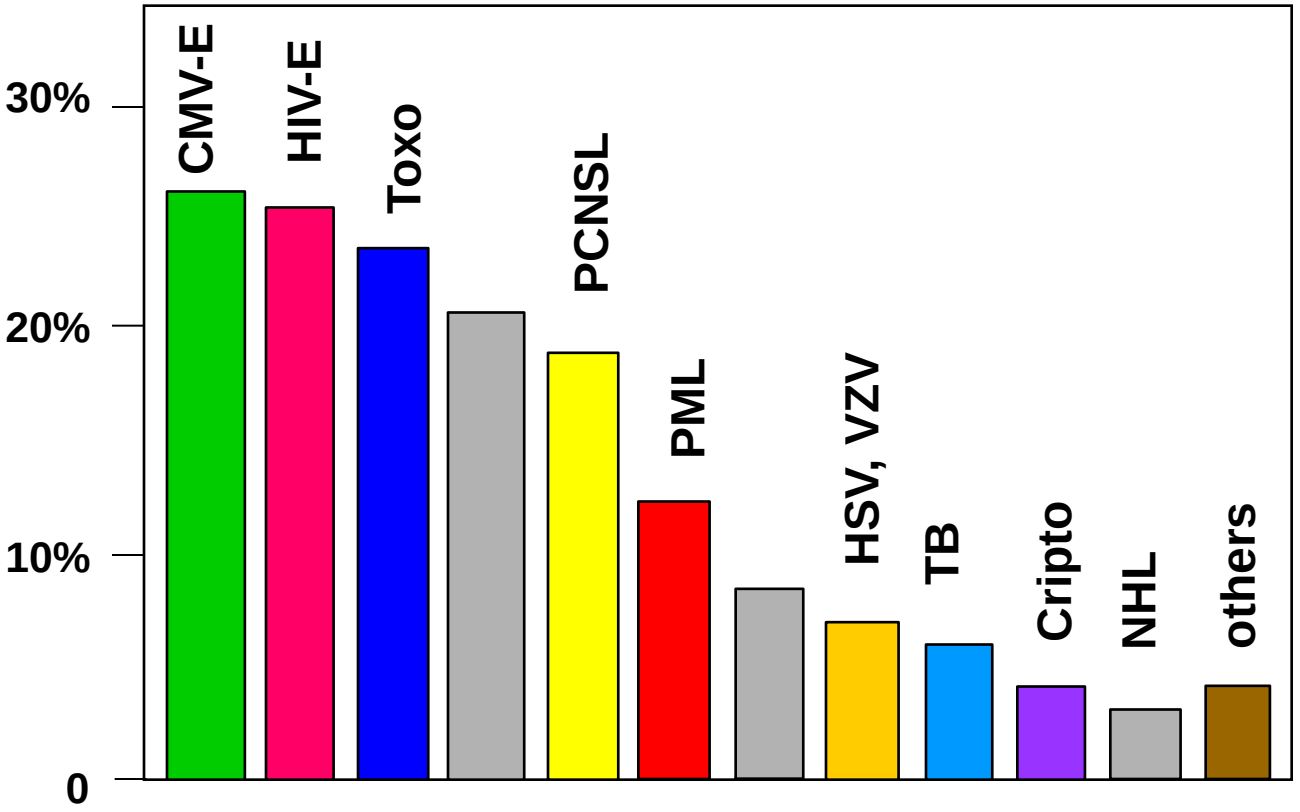
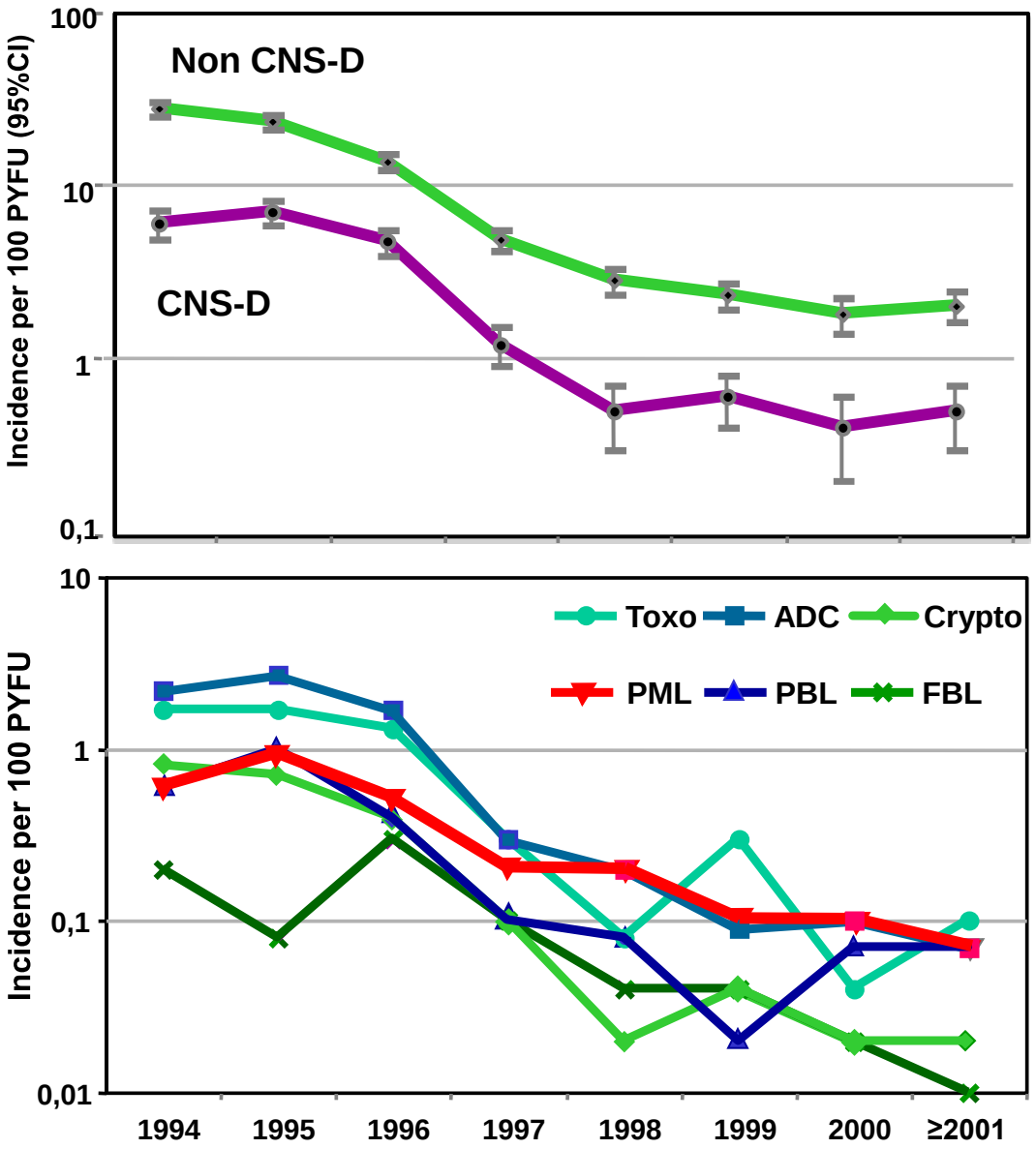
Frequency of HIV-related CNS-D at post-mortem examination

Milano, 1985-1995



Cinque P and Vago L, AIDS 1997

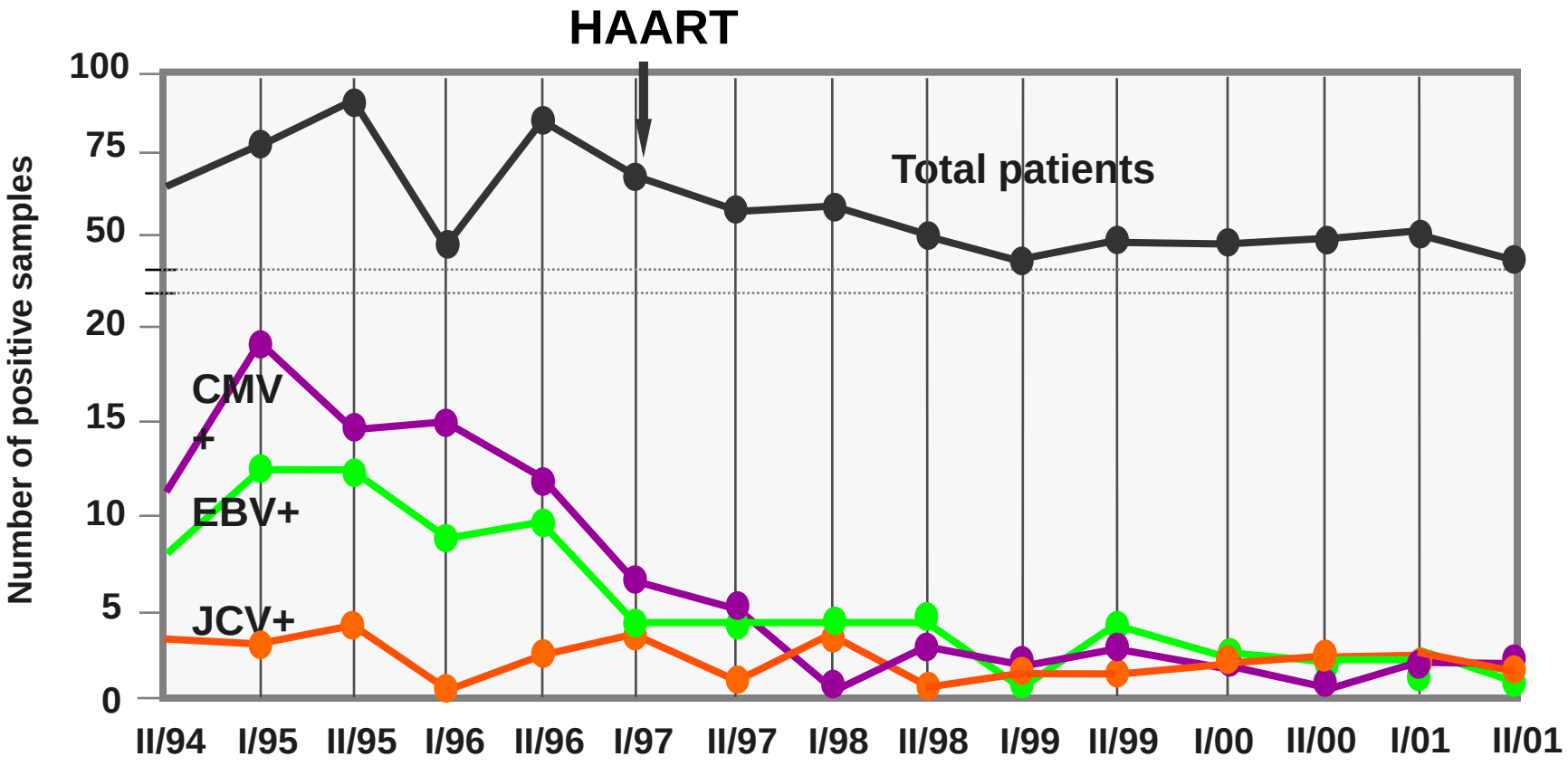
Incidence of CNS-D in the EuroSIDA cohort



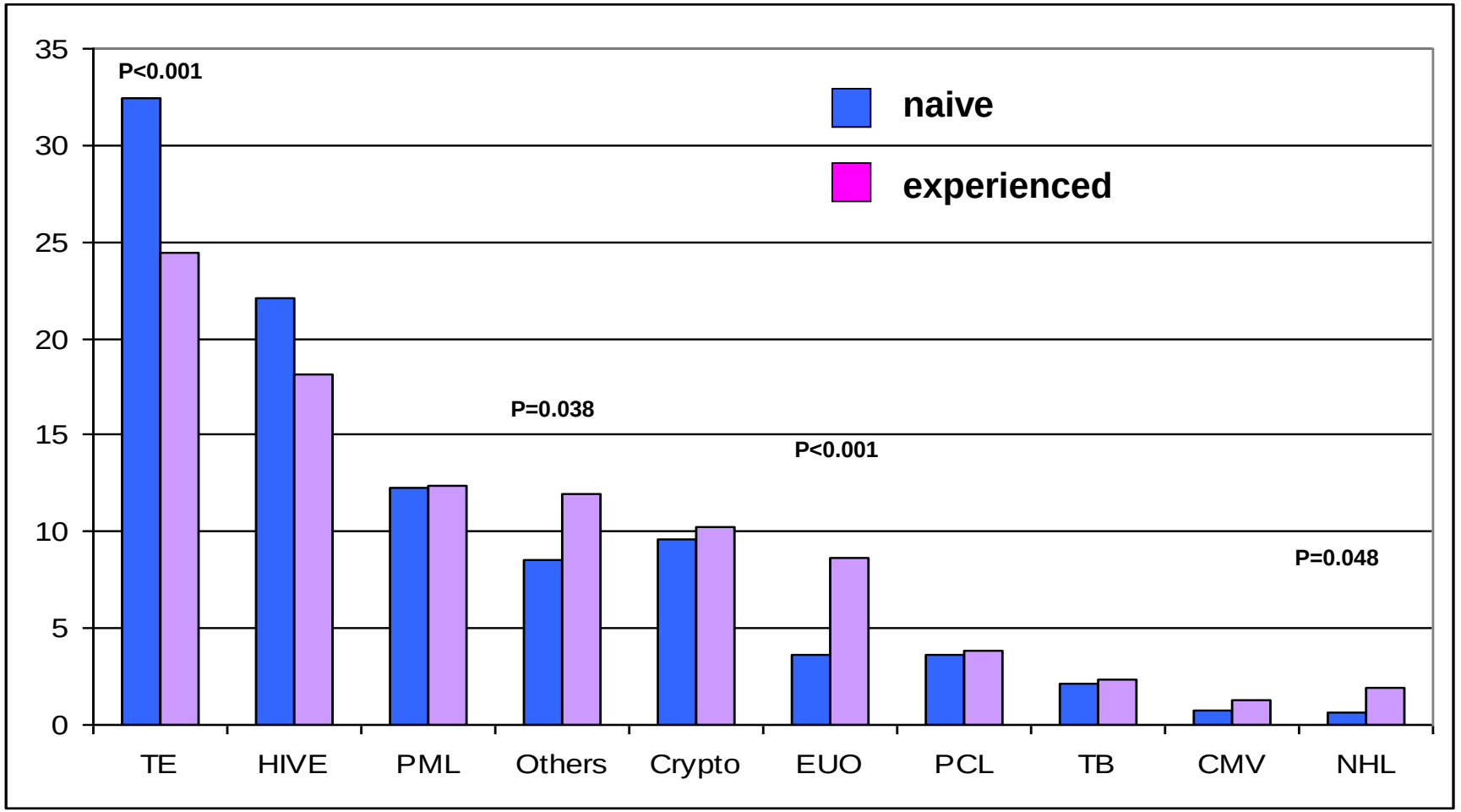
D'Arminio Monforte et al, Ann Neurol 2004

Positive CSF PCR findings in HIV-infected patients

San Raffaele Hospital, Milano 1994 - 2001



Prevalence of HIV-related CNS-D
IRINA cohort, Italy, 2000-2005

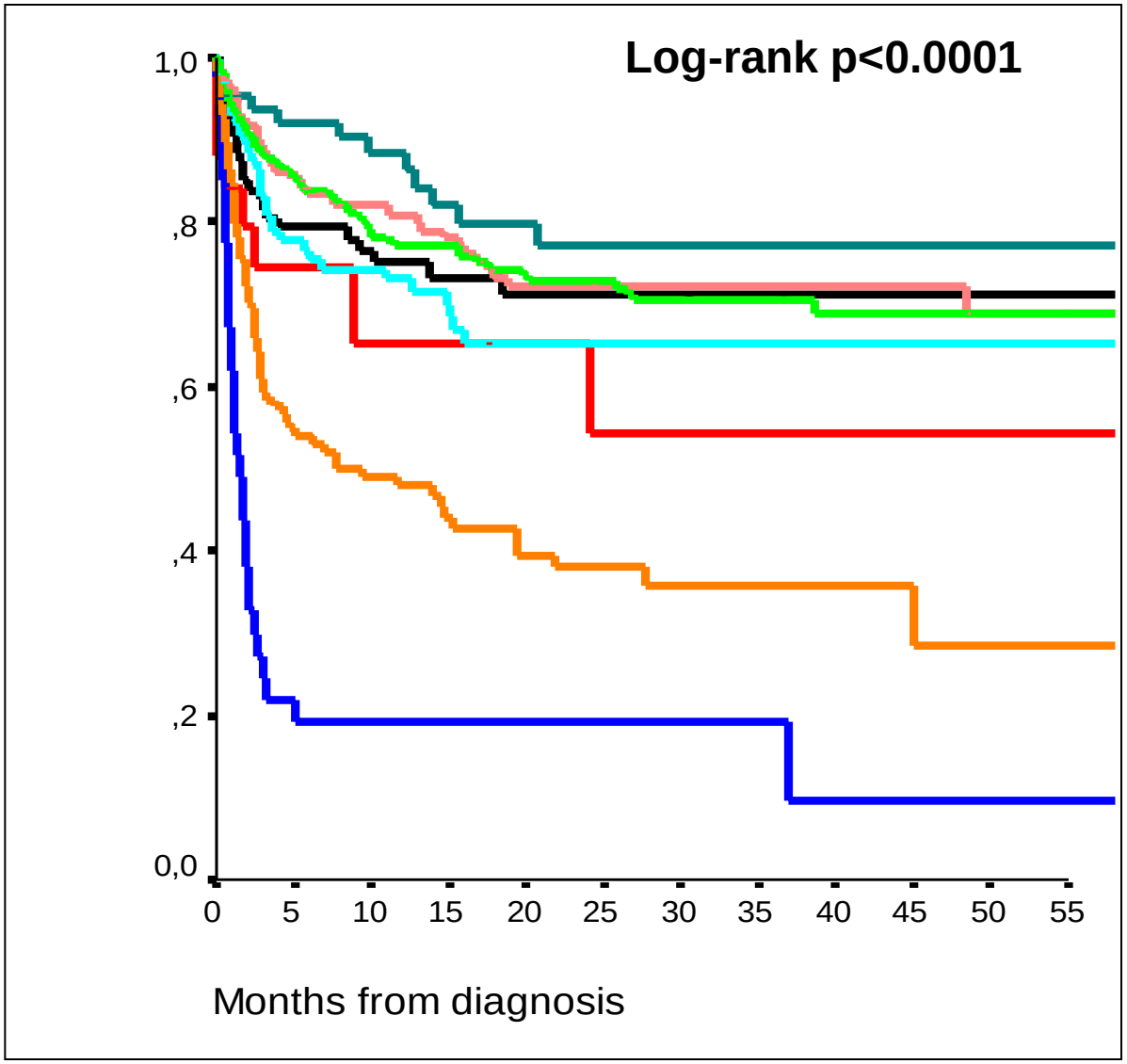


Survival of HIV-related CNS-D

IRINA cohort, 2000-2005

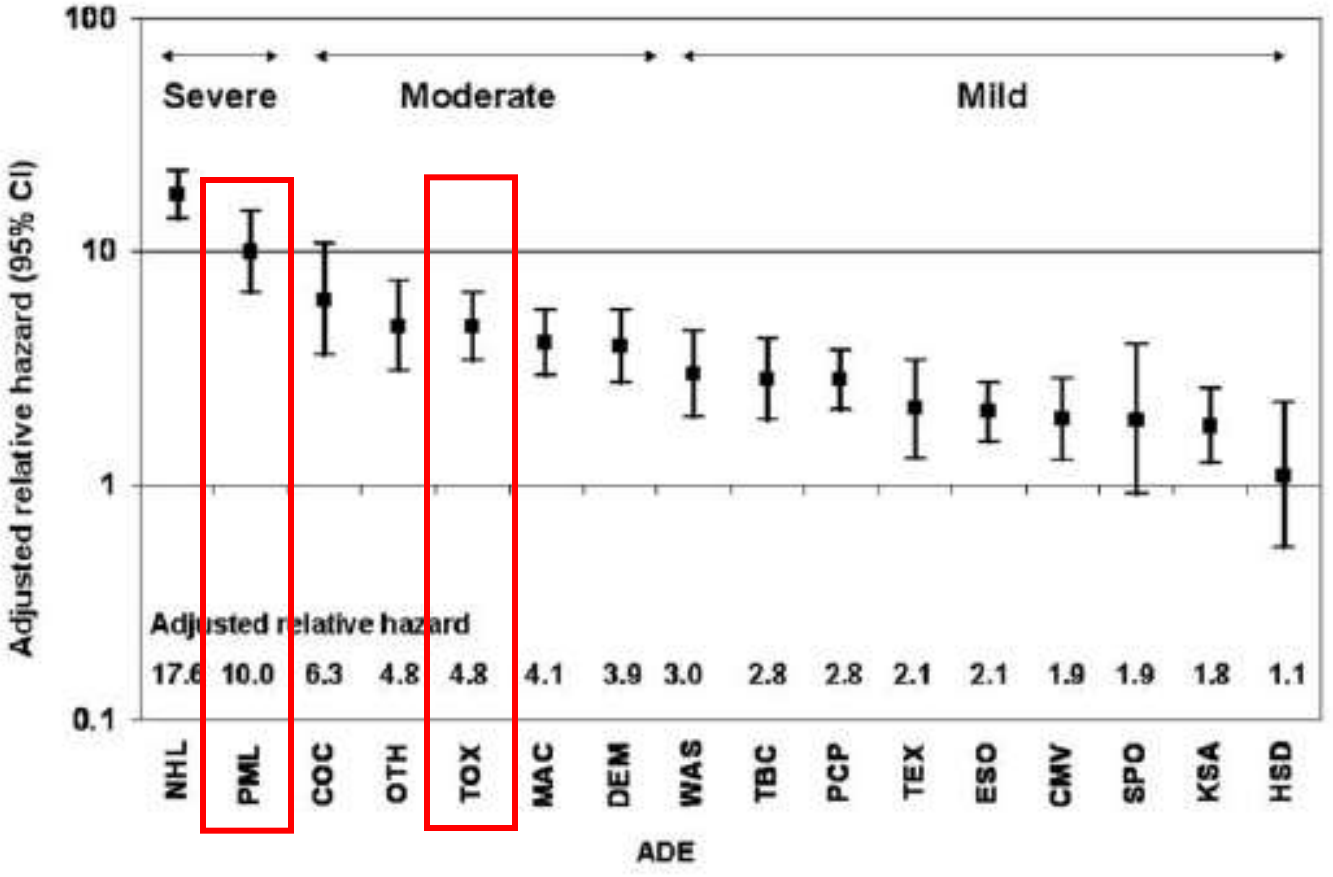
1035 patients

	1-year survival prob.
EUO	86%
HIVE	81%
TE	77%
Other	75%
Crypto	73%
TB	65%
PML	48%
PCL	19%



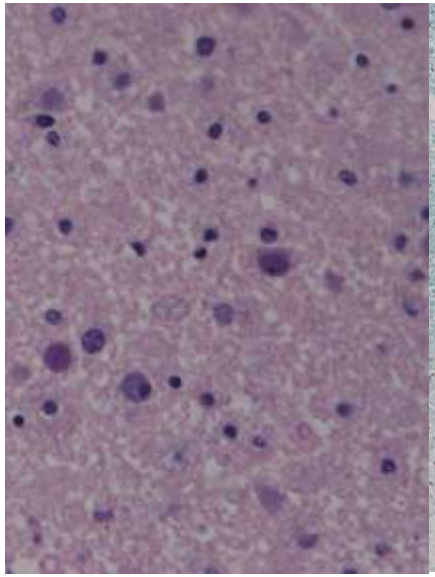
Mortality Hazard Risk of AIDS-associated events (ADE) during cART

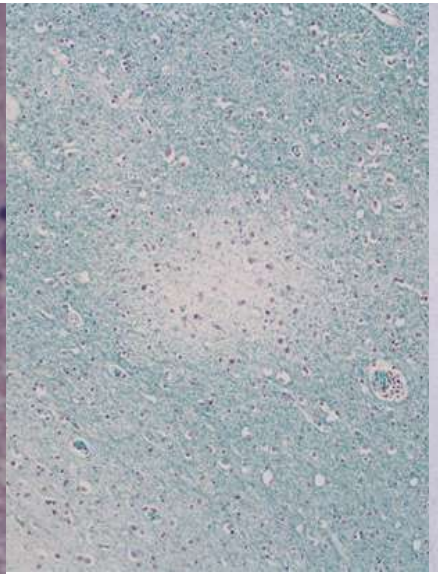
31,620 patients from 15 cohorts
2880 ADE; 377 ADE-related deaths

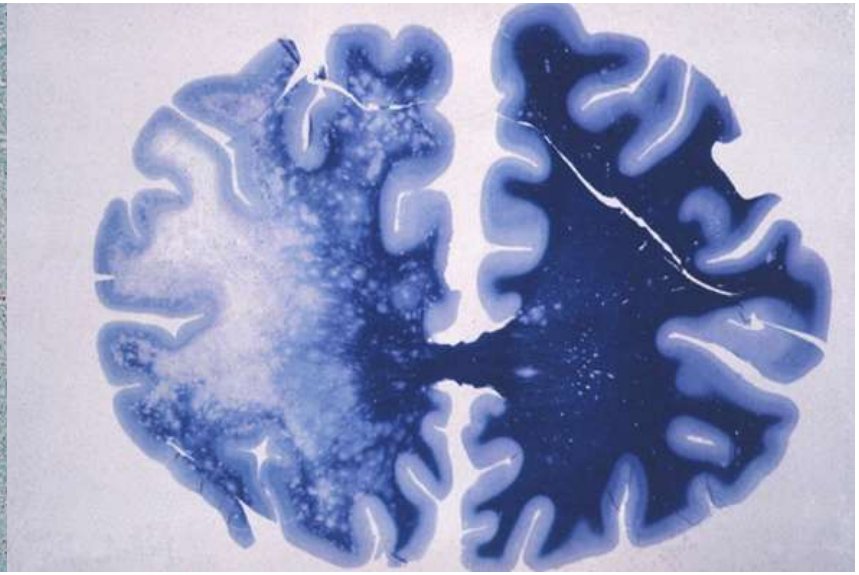


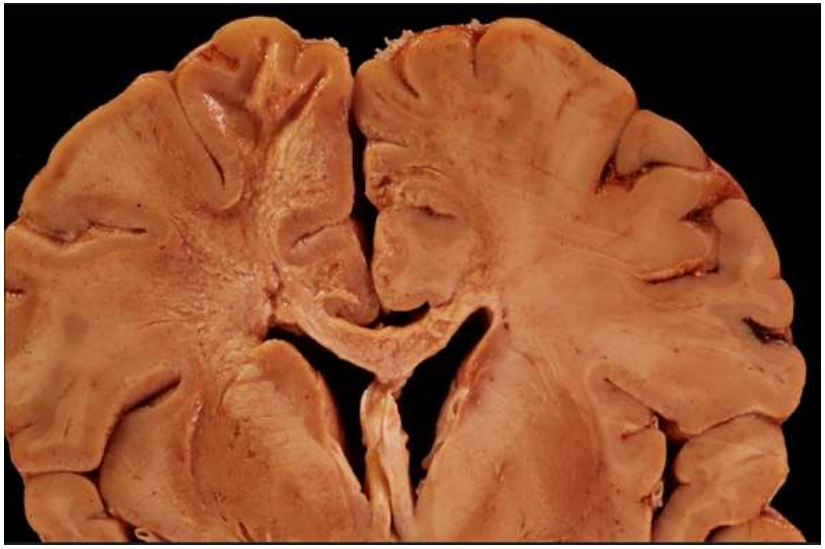
The Antiretroviral Therapy Cohort Collaboration, CID 2009

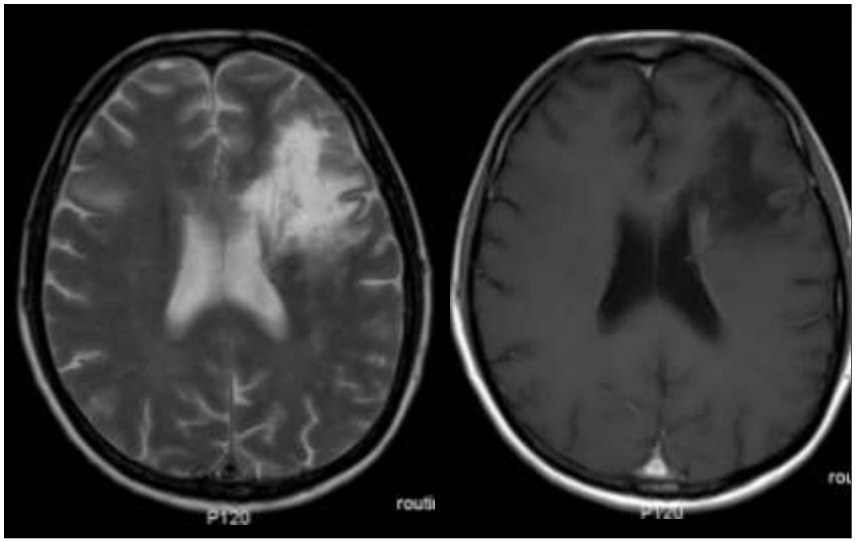
Productive JCV infection of the brain: PML









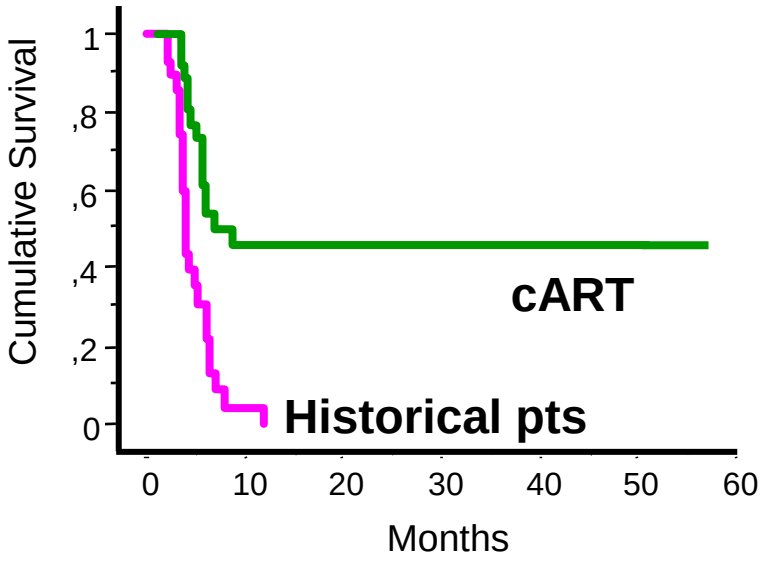


Important progresses in PML

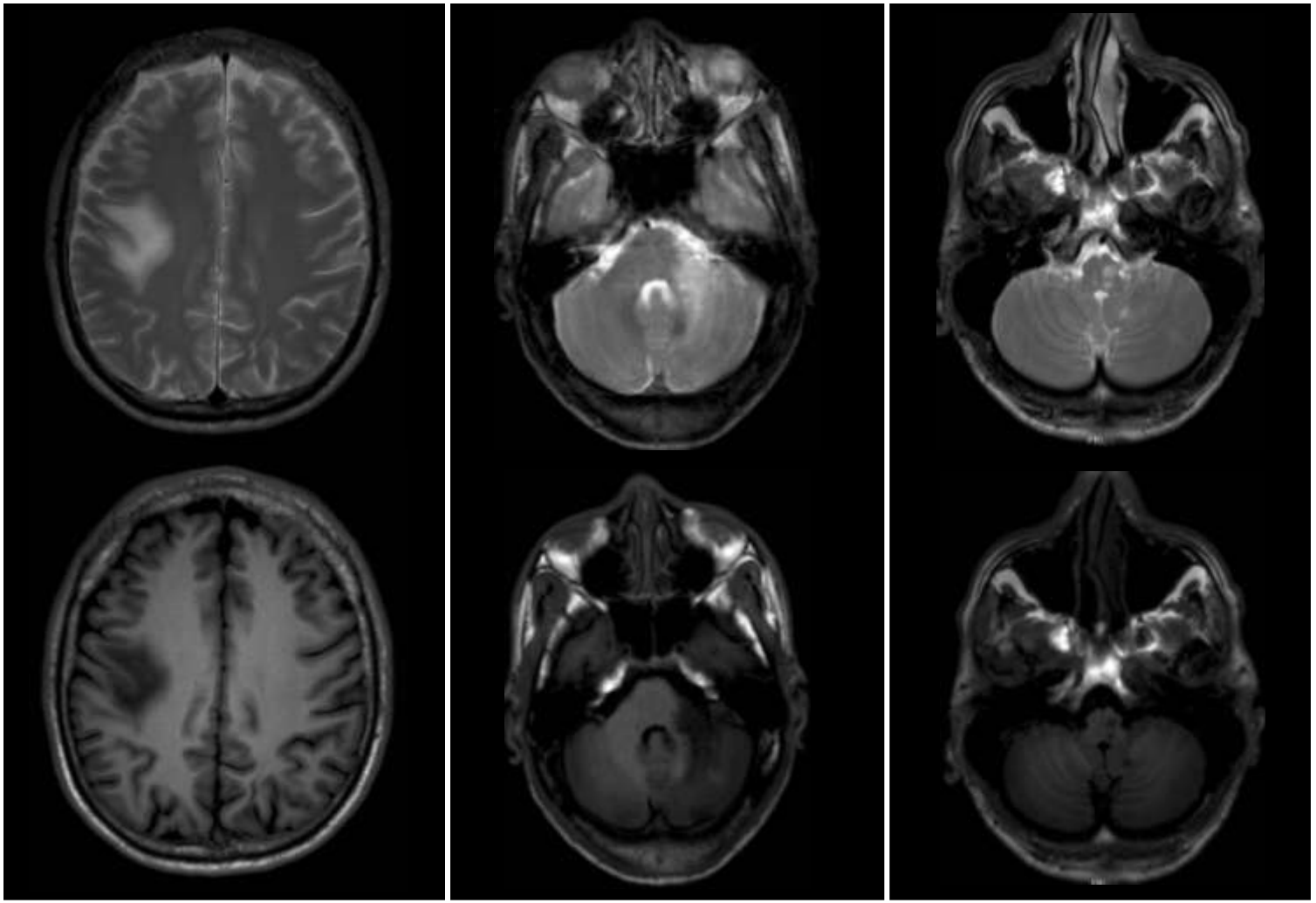
- PML can be (promptly) diagnosed by clinical, neuroimaging and virological assessment

- PML can be monitored by clinical, neuroimaging and virological assessment

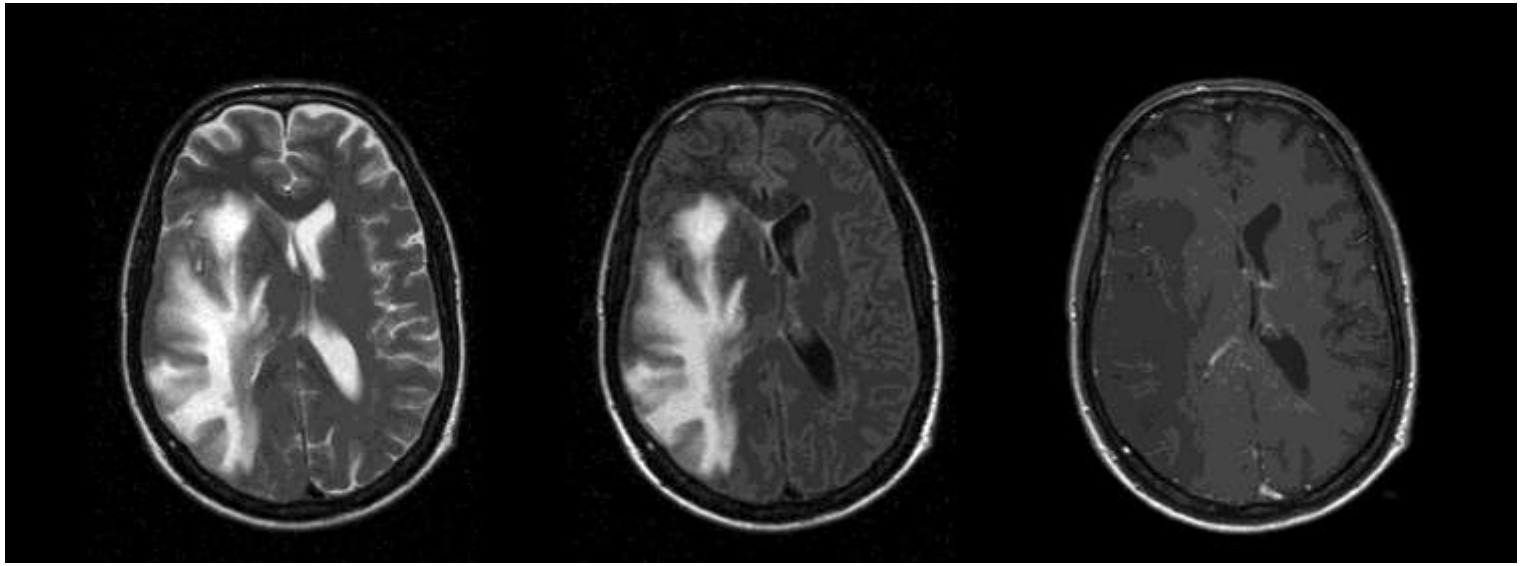
PML can remit following removal immunosuppression, i.e., by initiating cART



PML: MRI presentation



HIV-related PML with atypical MRI presentation and fatal fulminant course



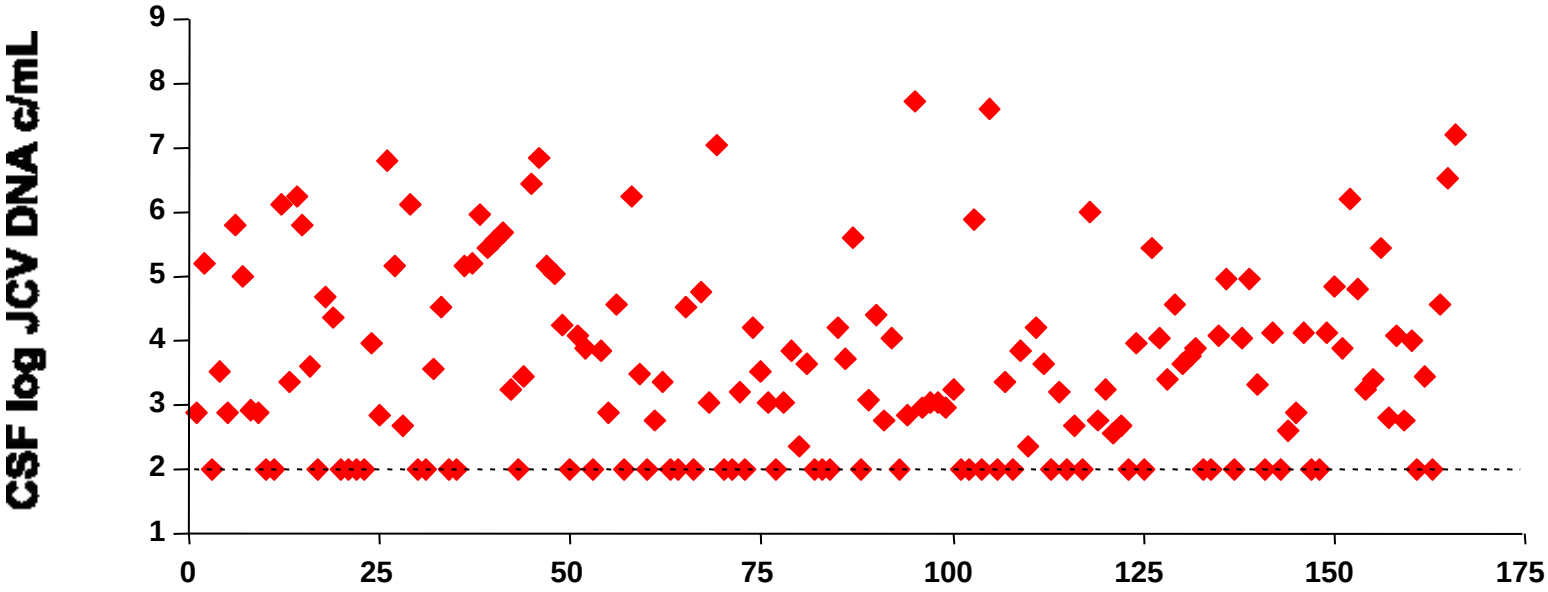
March 2007: - Onset of symtpoms

April 2007: - Diagnosis of HIV infection (CD4 122; VL 182,000 c/mL)
- Diagnosis of PML (CSF JCV-DNA 1,520,000 c/mL,

confirmed by brain biopsy)
- Exitus

JCV DNA detection and quantification in CSF

Diagnostic sensitivity 74%
Diagnostic specificity 99%



Bossolasco et al, Clin Infect Dis 2005

Reduced diagnostic value of JCV-DNA for PML diagnosis in the cART era

	pre-cART	post-cART	p
Sensitivity %	17/19 (89.5%)	23/40 (57.5%)	0.014
Specificity %	82/83 (99%)	141/141 (100%)	ns
NPV %	98	89	0.05
PPV %	95	100	ns

Marzocchetti A. J Clin Microbiol 2005

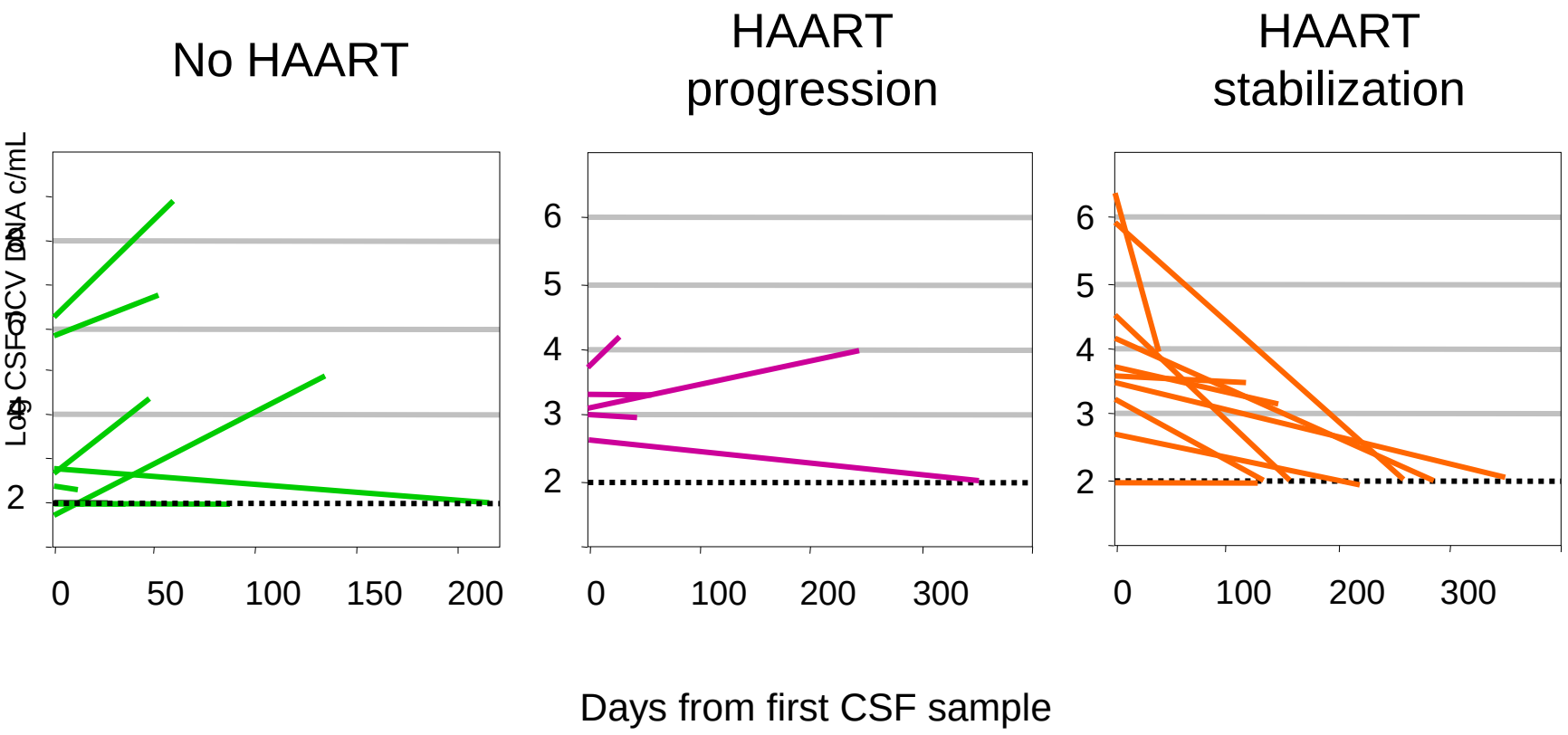
Diagnostic criteria for PML

In the presence of progressive uni or multifocal neurological disease and typical MRI lesions:

- Histology-confirmed PML: brain biopsy (or post-mortem examination) showing typical pathologic features with JCV confirmed either by IHC or ISH
- Laboratory-confirmed PML: demonstration of JCV DNA in CSF by nucleic acid amplification methods
- Possible PML: absence of both histological confirmation and JCV demonstration in CSF

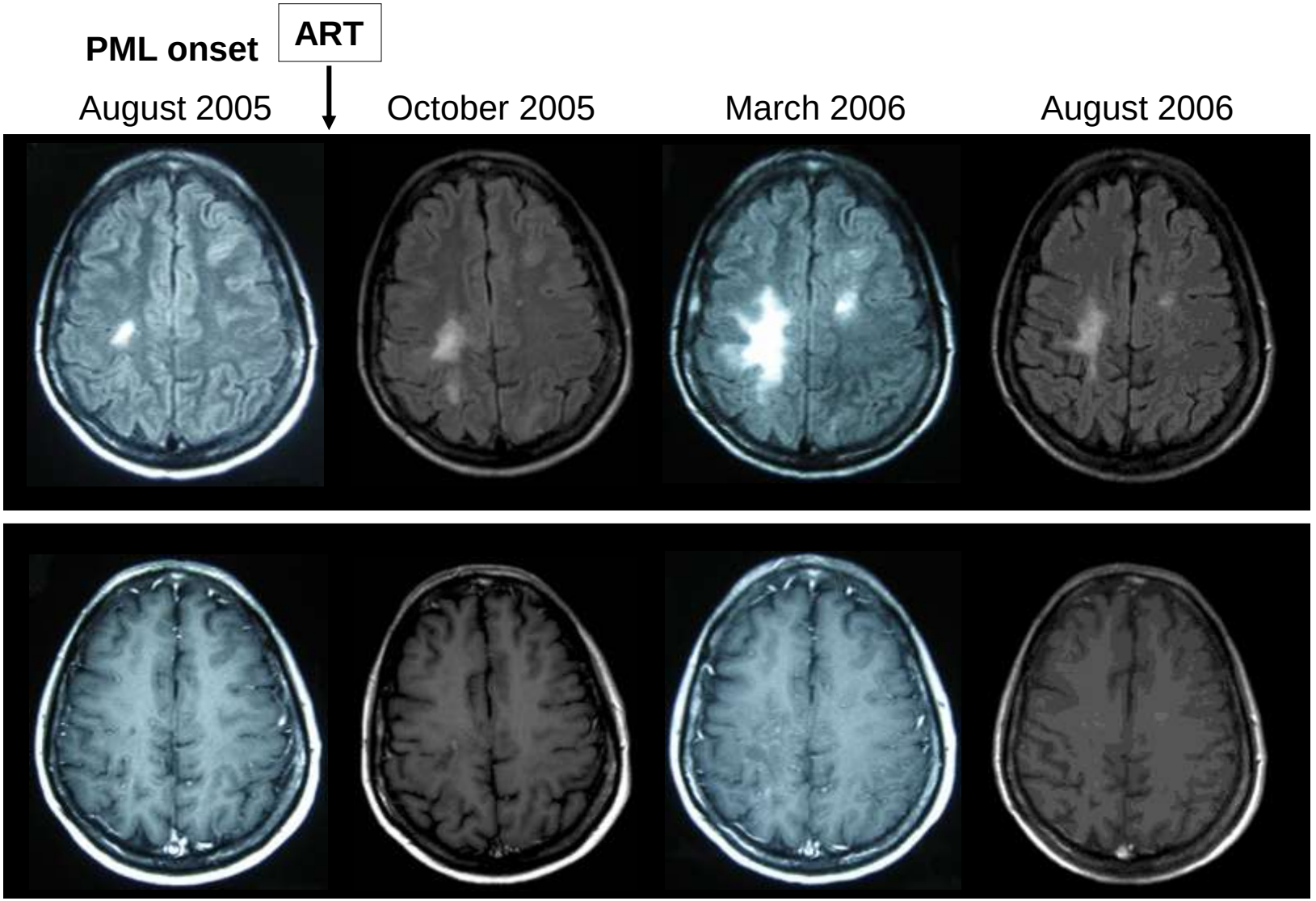
Cinque, Koralnik and Clifford, JNV 2002
Portegies, EJN 2004
CDC, NIH, HMA-IDSA guidelines for HIV-OIs, 2009

JCV-DNA level in CSF
as a marker for monitoring PML activity



Bossolasco et al., CID 2005

JCV-DNA level in CSF in a case with favorable outcome



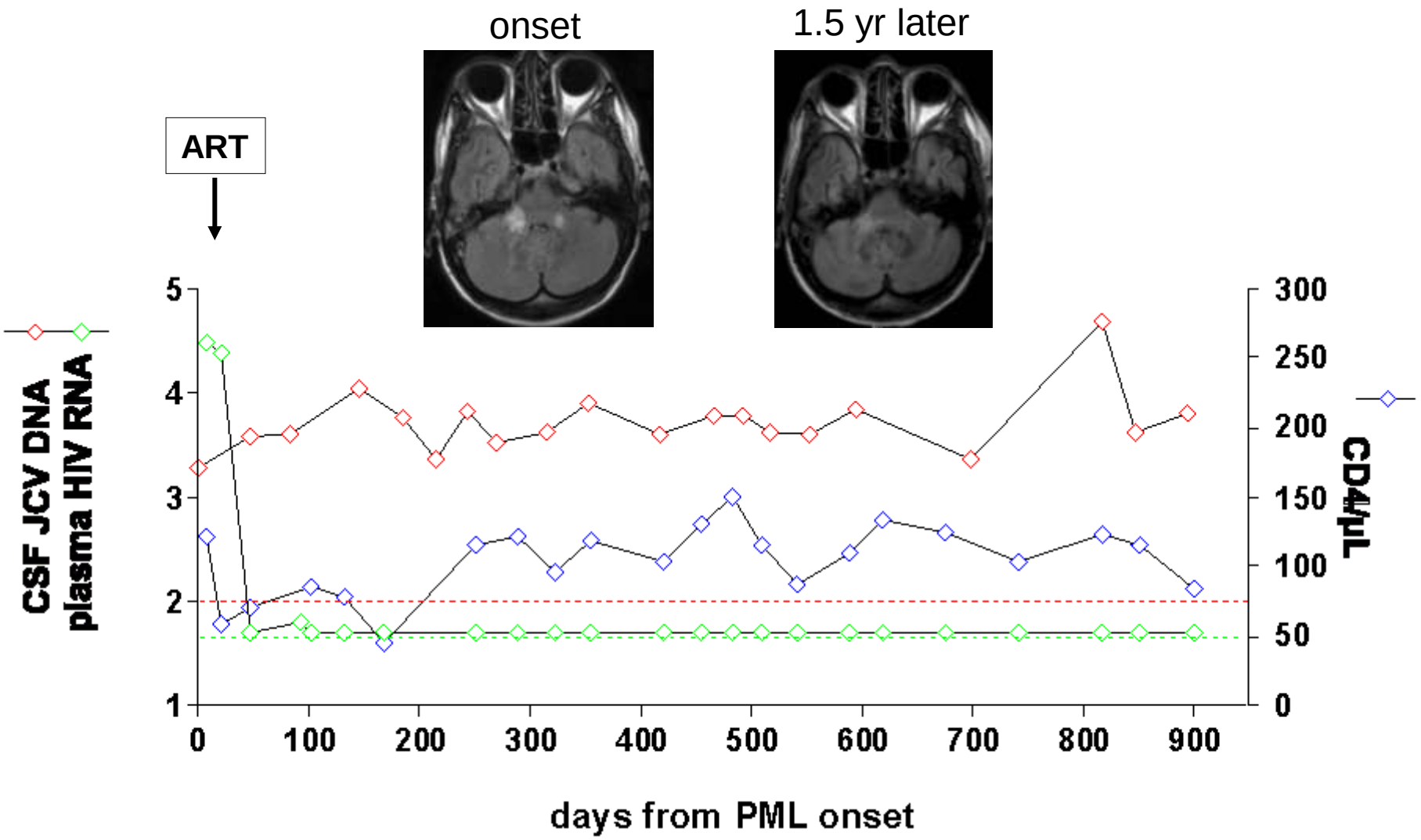
JCV-DNA 10,792 c/mL
CD4 495 (11%);
VL 262,000 c/mL

JCV-DNA 335 c/mL
CD4 619 (33%)
VL 4198 c/mL

JCV-DNA <100 c/mL
CD4 804 (44%)
VL <50 c/mL

JCV-DNA nd
CD4 1252 (45%)
VL <50 c/mL

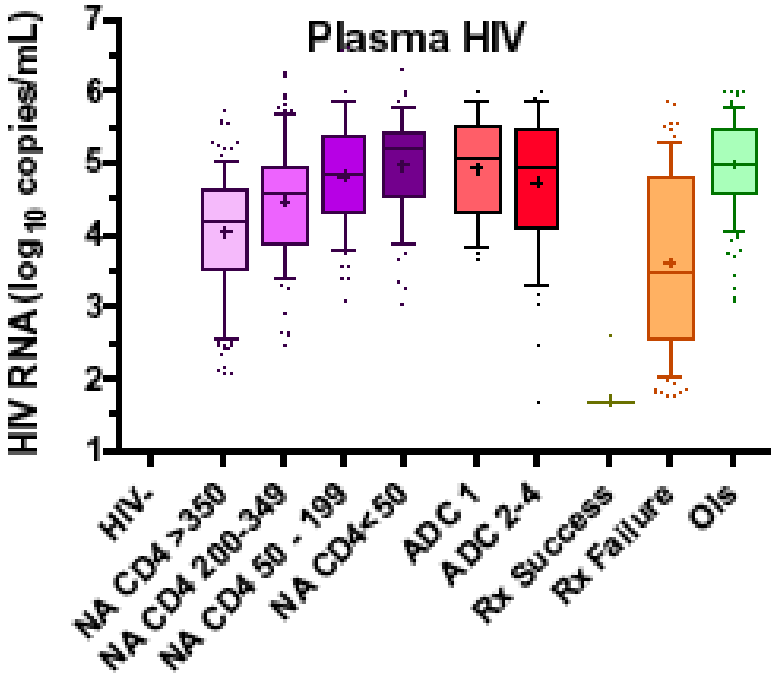
JCV-DNA level in CSF in a PML case progressing over 2.5 years

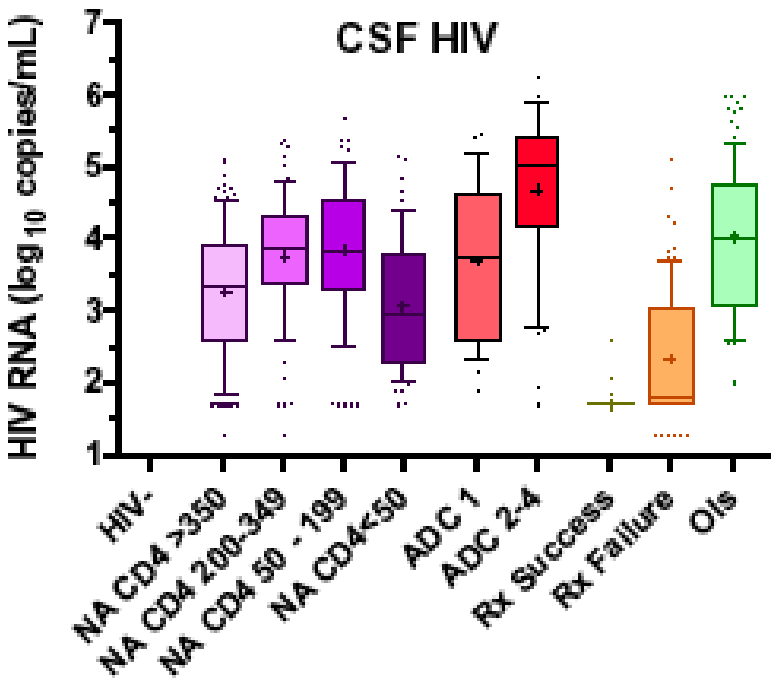


Some important, unanswered questions

- Why and how a benign infection will progress into a fatal CNS disease?
- Why will some treated HIV-infected patients develop PML? Why only half of treated patients will respond to cART?
- When will we have a specific treatment for JCV infection and PML?

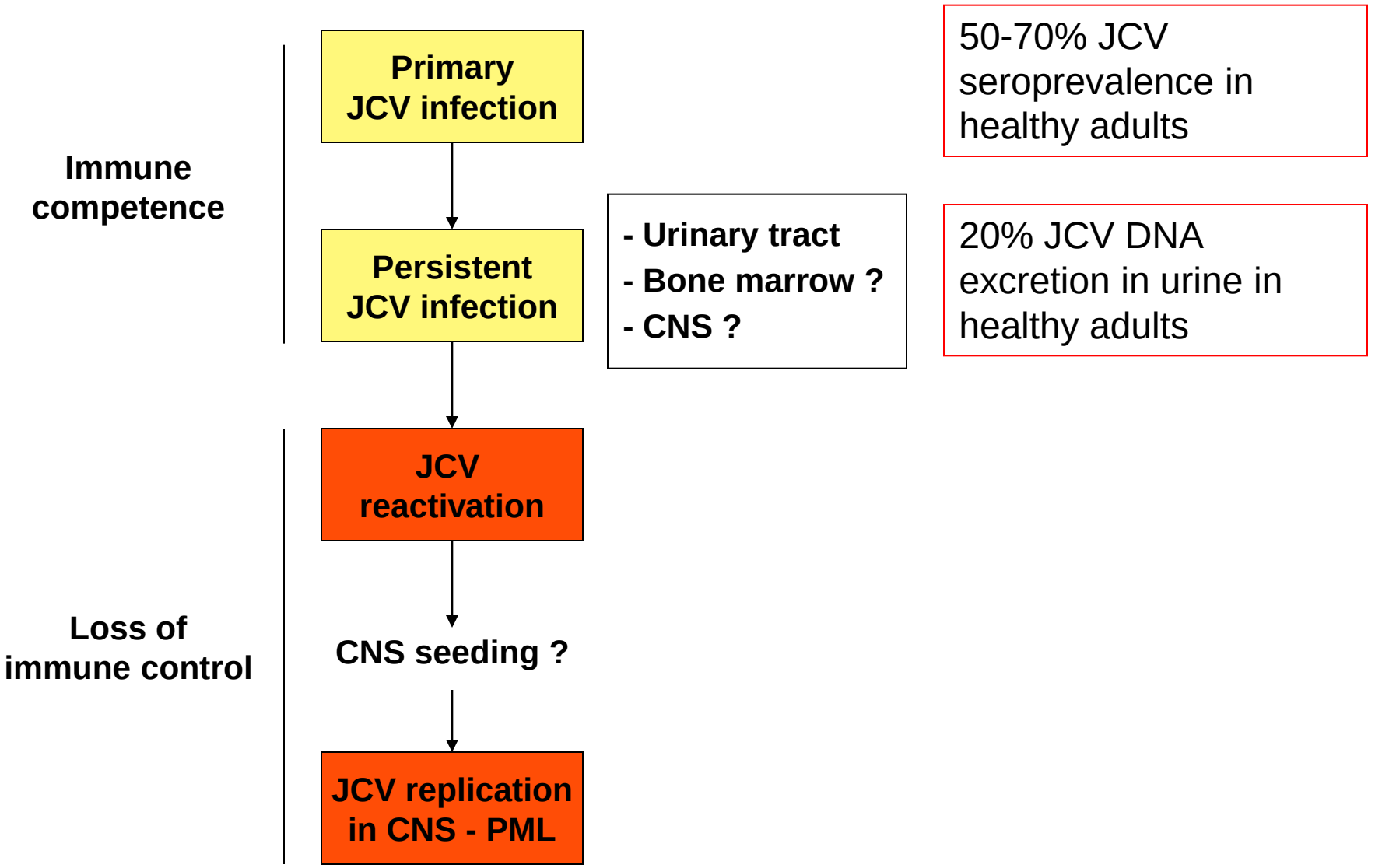
CNS-OIs and CNS HIV replication



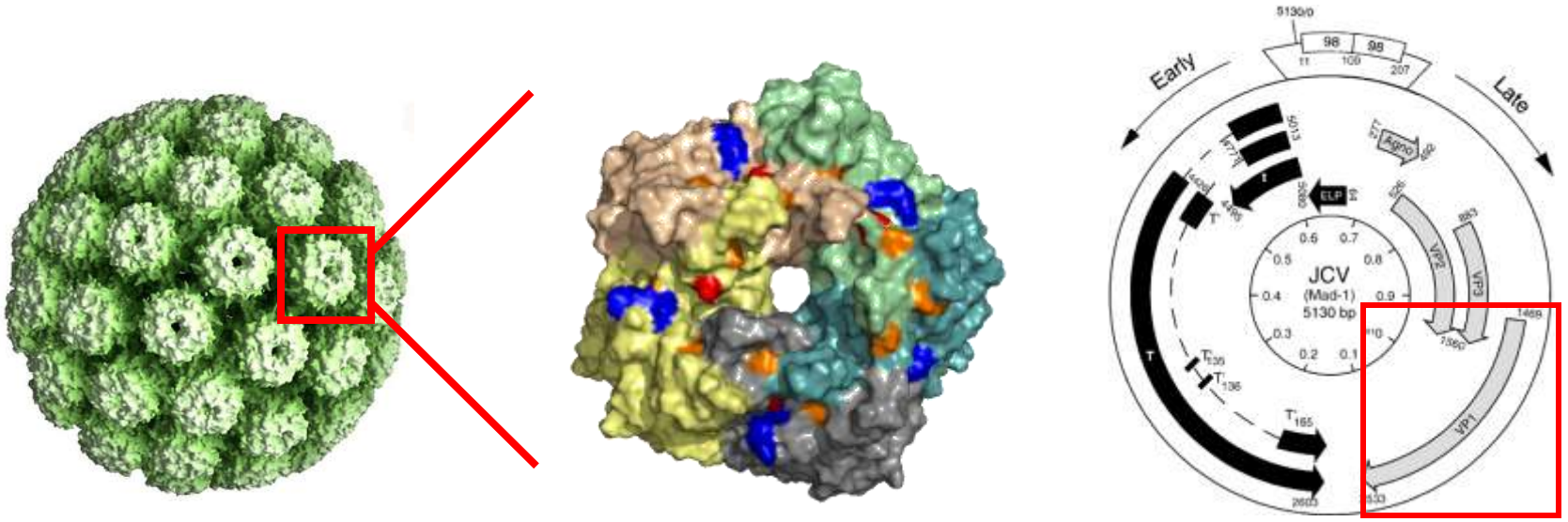


Hagberg L. et al., AIDS Res Ther 2010

Natural history of JCV infection and PML

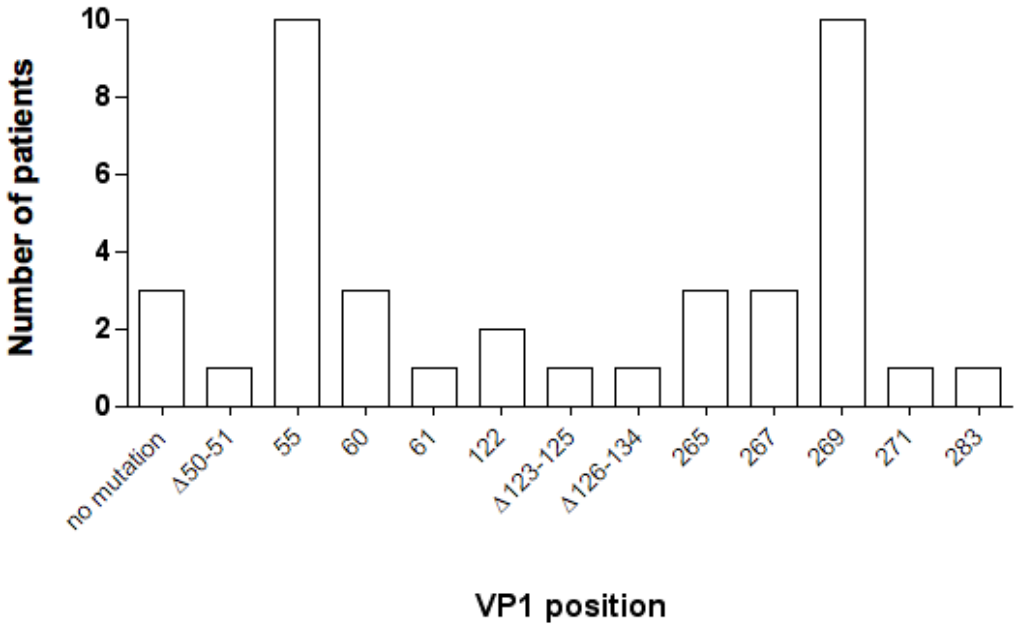


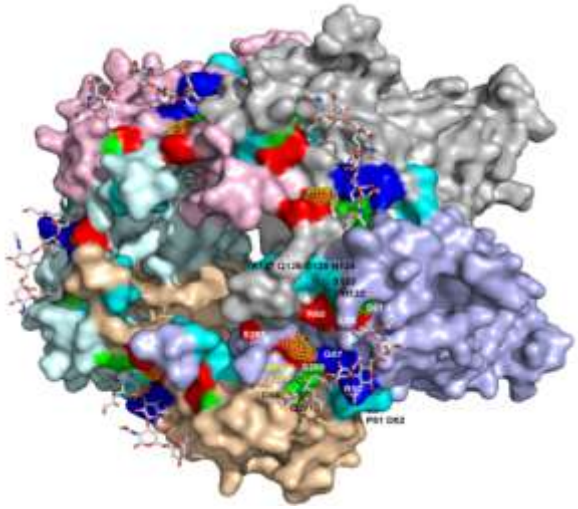
JCV capside viral protein-1 (VP-1)



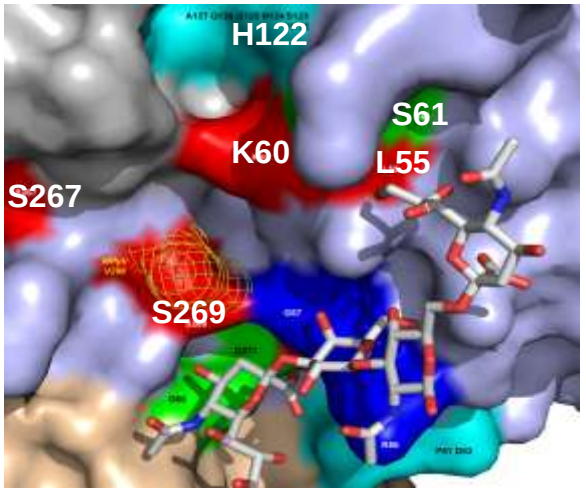
- Critical for virus entry in the host cell - interaction with sialic acid on cell receptor
- Main target for both B-cell and T-cell immune response

PML-specific JCV VP-1 mutations in CSF





L55, K60, S267, S269, S61, P51, H122



37/40 patients had one of 12 different PML-specific mutations or deletions in CSF

Gorelik L. et al, JID, in press

Intra-Patient Appearance of PML-Specific VP1 Mutations

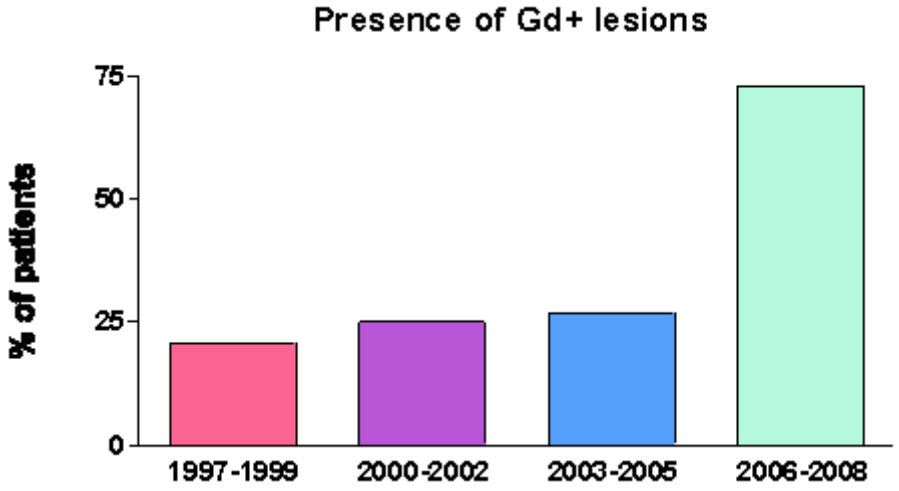
Pt Lab ID	SAMPLE	mutation	mt clone #	total clone#	type
5067	CSF	122R	25	25	1A
5067	PLASMA	122R	26	26	1A
5067	URINE	0	na	11	1A
5166	CSF	269F	11	11	1Av75R
5166	PLASMA	269F	13	16	1Av75R
5166	URINE	0	na	26	1Av75R
5174	CSF	269F	27	27	1B
5174	PLASMA	269F	37	38	1B
5174	URINE	0	na	13	1B

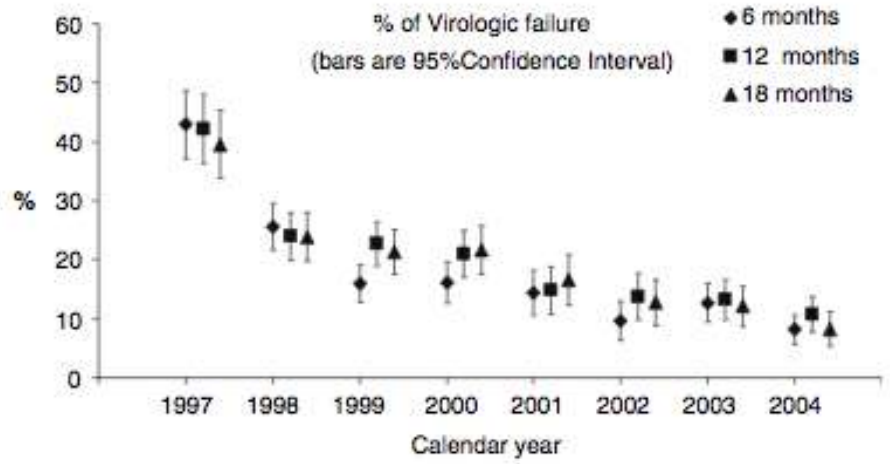
Gorelik L. et al, JID, in press

PML onset or progression despite succesful cART: why?

- cART immunereconstitution insufficient or too slow?
- cART immunereconstitution exaggerated or too fast?
- Other mechanisms?

Increased frequency of Gd-enhancing MRI PML lesions paralleles increased ART potency

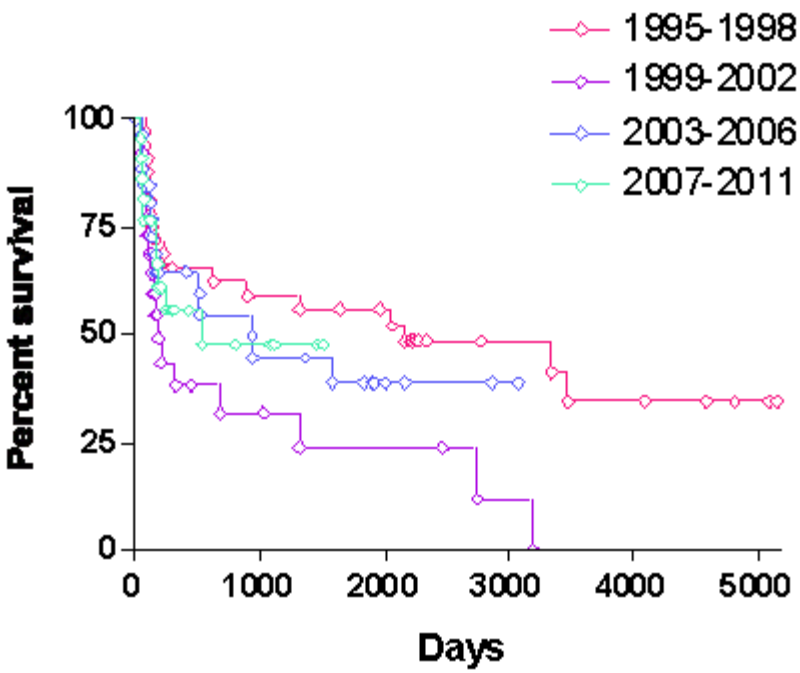


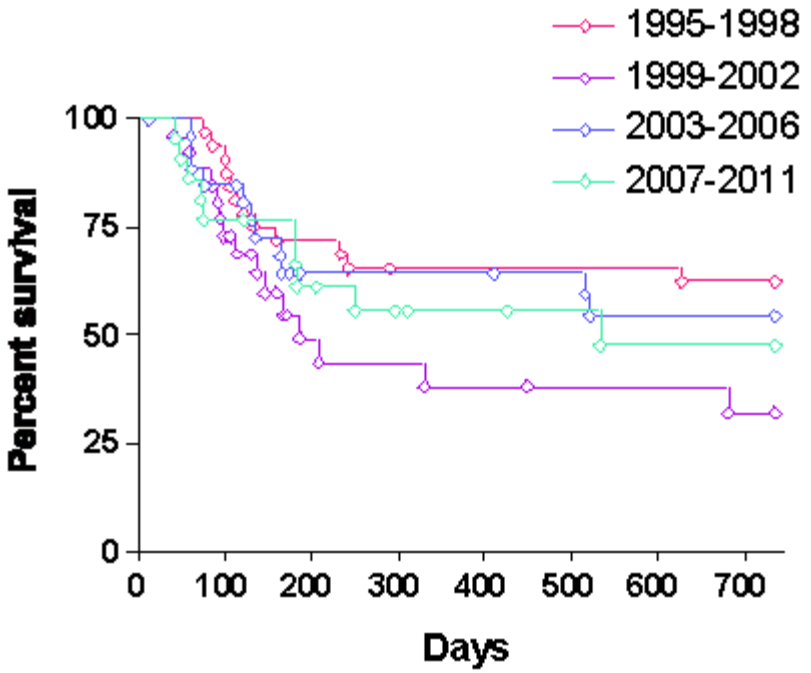


Sighinolfi et al. 2008

PML survival in the cART period

San Raffaele Hospital, Milano 1995-2001 (n=108)

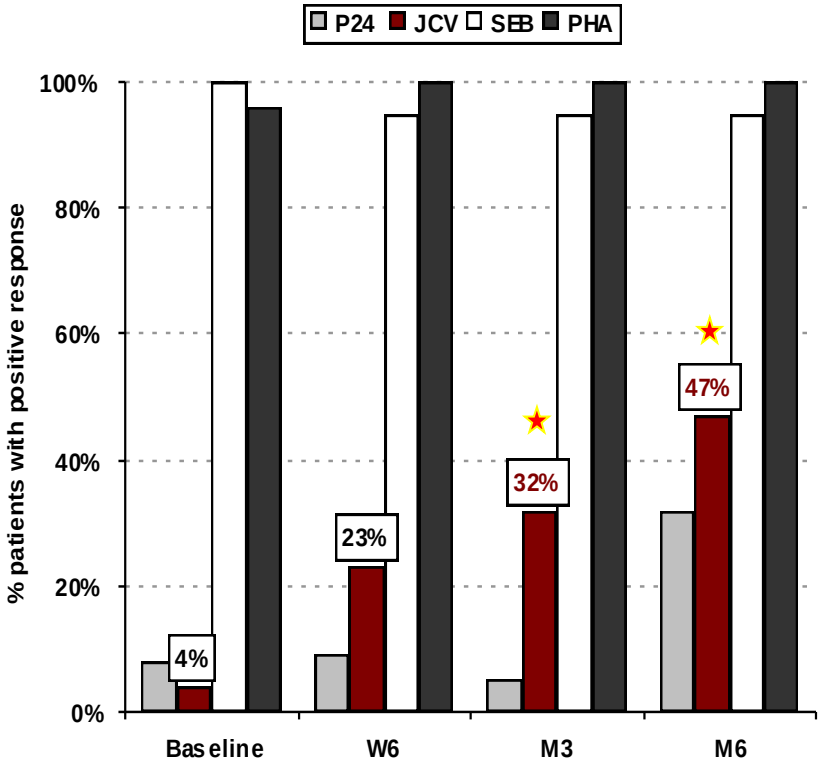




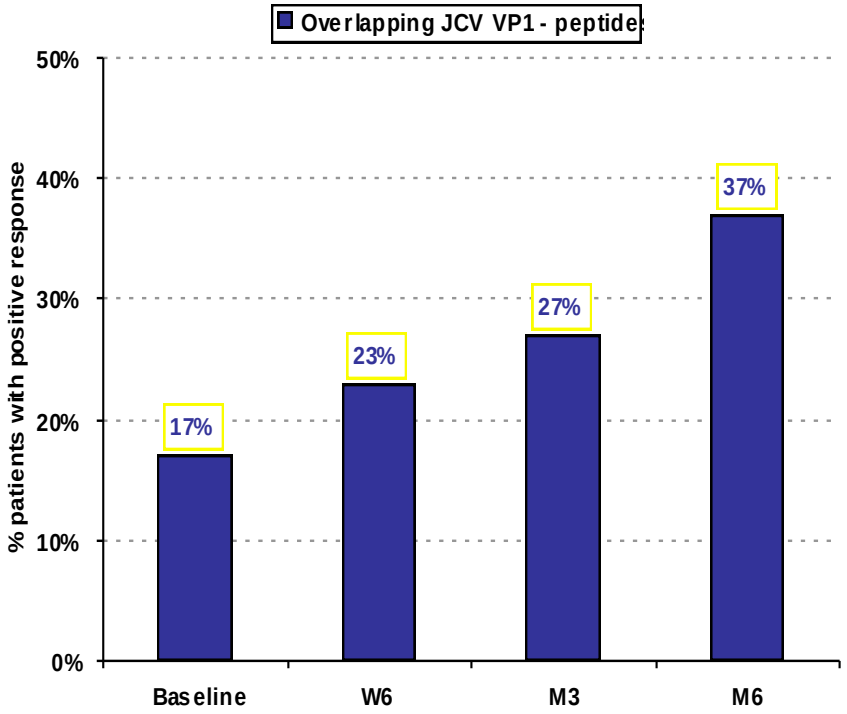
Unpublished data

JCV-specific T-cell responses in cART-treated patients with PML

Anti-JCV CD4 T cell proliferative assay



IFN-gamma CD8 T cell ELISPOT

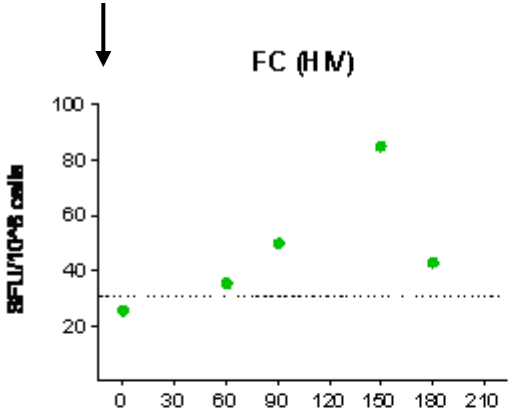


Gasnault J et al., CROI2007, Poster 379

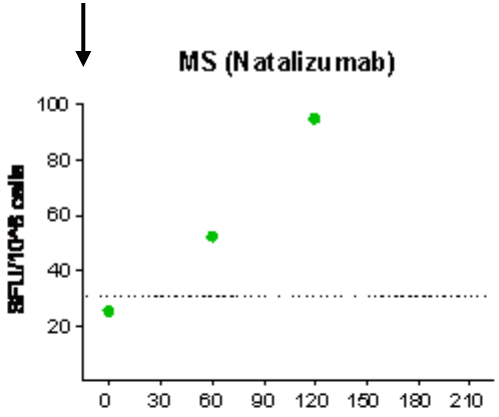
Longitudinal assessment of T-cell responses against JCV VP1-p261 in patients with active PML

Remission

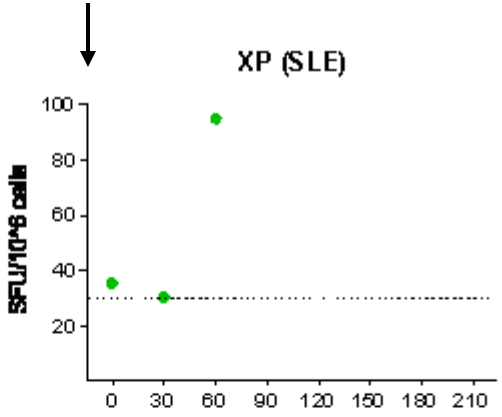
cART



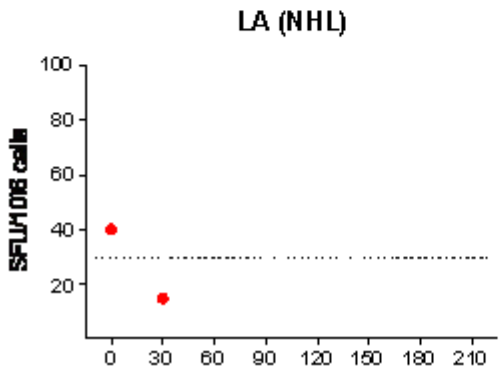
Plex



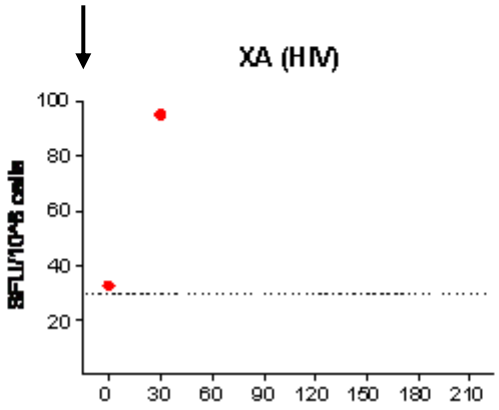
Stop IS



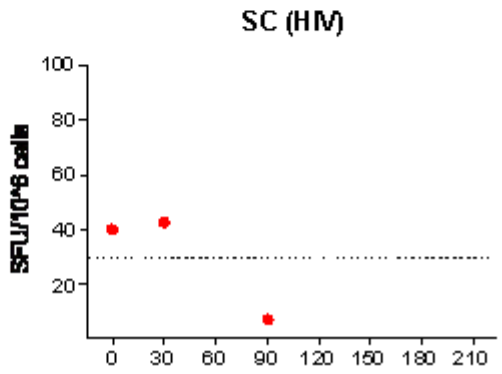
Progression



cART



cART ongoing

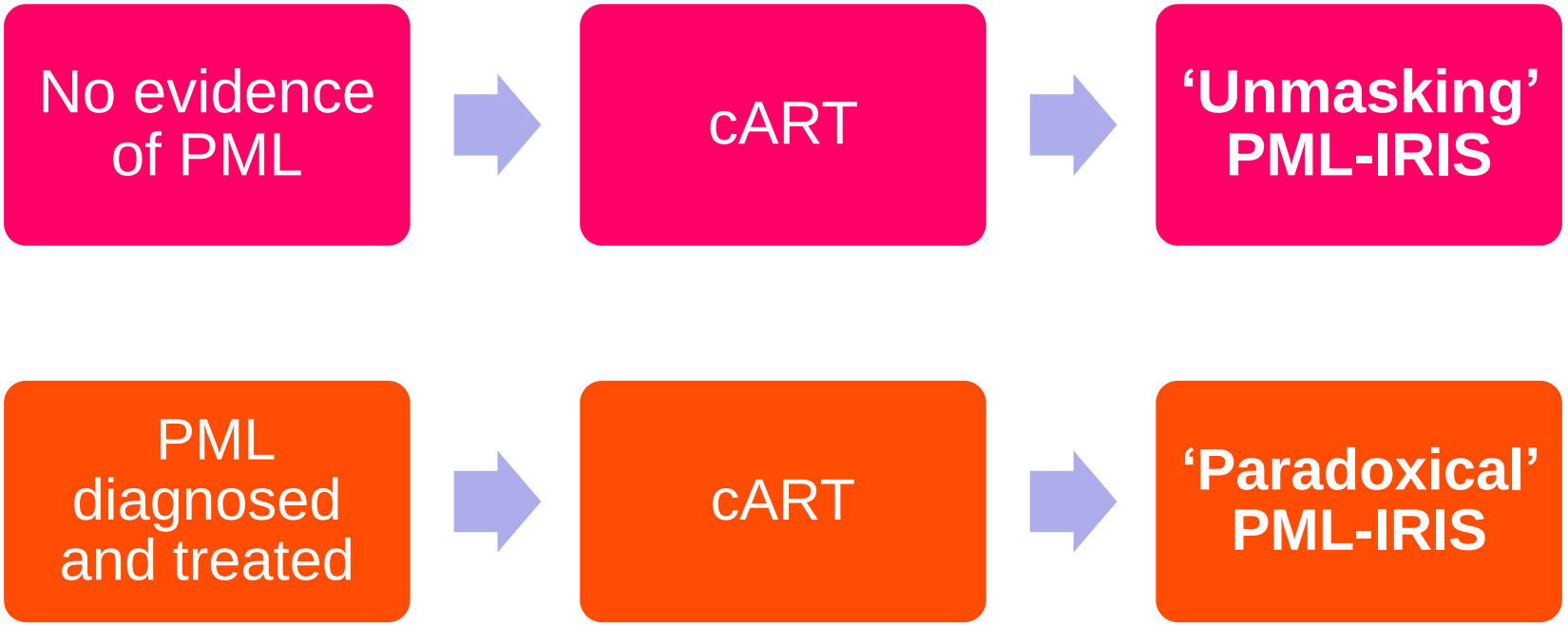


Days from 1st sampling

PML onset or progression despite succesful cART: why?

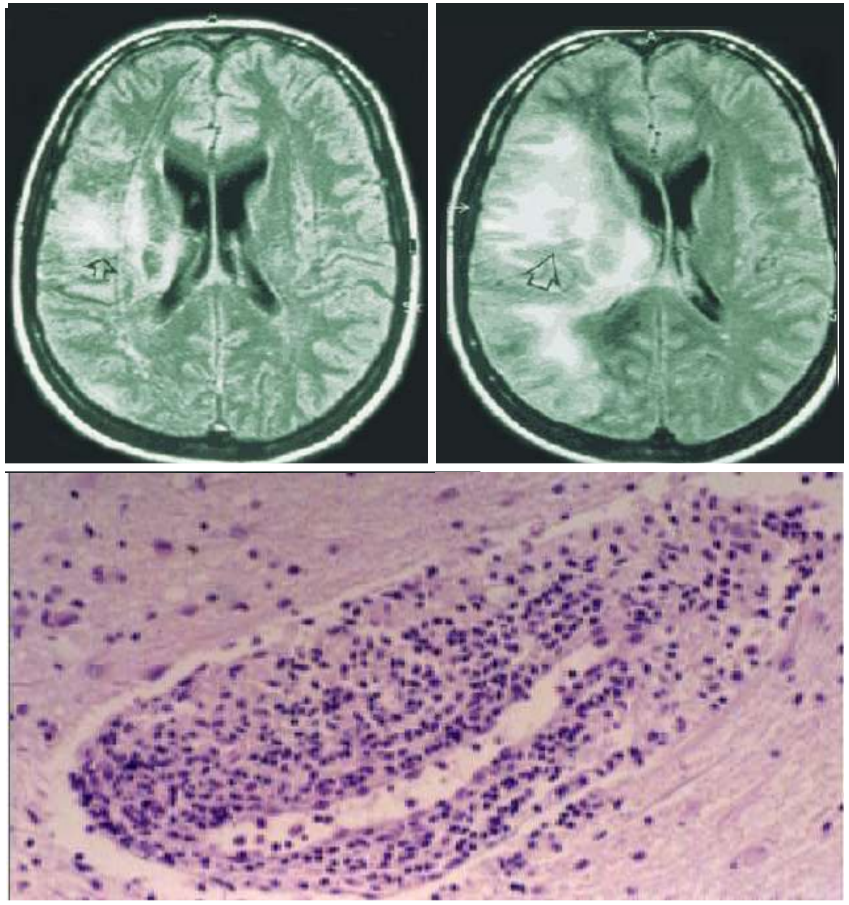
- cART immunereconstitution insufficient or too slow?
- cART immunereconstitution exaggerated or too fast?
- Other mechanisms?

PML, cART and immunoreconstitution



Paradoxical worsening of PML following cART

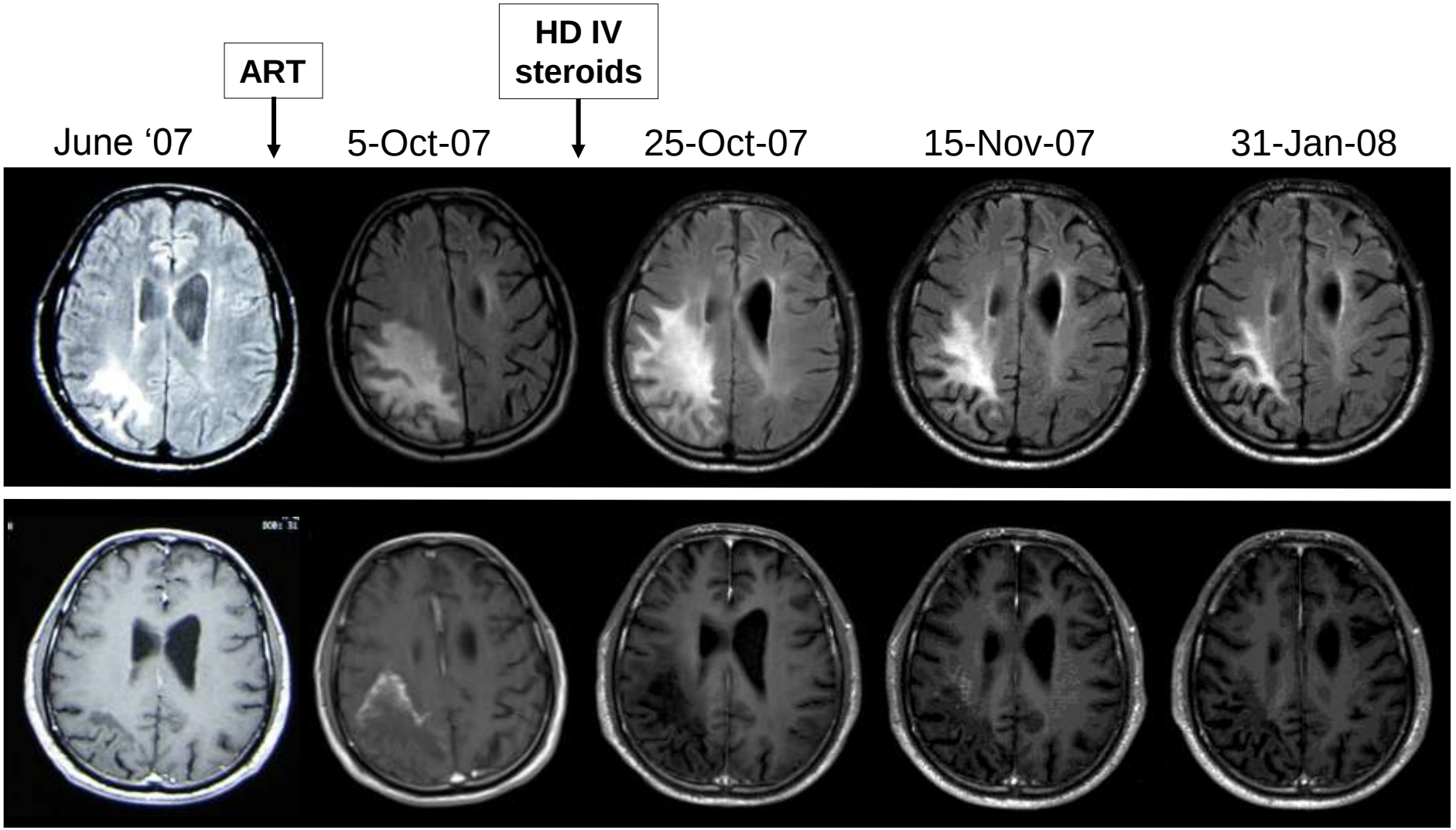
PML onset



After 12 weeks of cART

Courtesy of
Pilar Miralles, Madrid, Spain

Paradoxical worsening of PML following cART and response to corticosteroids



JCV-DNA 2320 c/mL
CD4 9
VL 2930 c/mL

JCV-DNA 455 c/mL
CD4 79
VL <50 c/mL

JCV-DNA <100 c/mL
CD4 37
VL <50 c/mL

JCV DNA n.d.
CD4 31 (3.8%);
VL <50 c/mL

PML onset or progression despite succesful cART: why?

- cART immunereconstitution insufficient or too slow?
- cART immunereconstitution exaggerated or too fast?
- Other mechanisms?

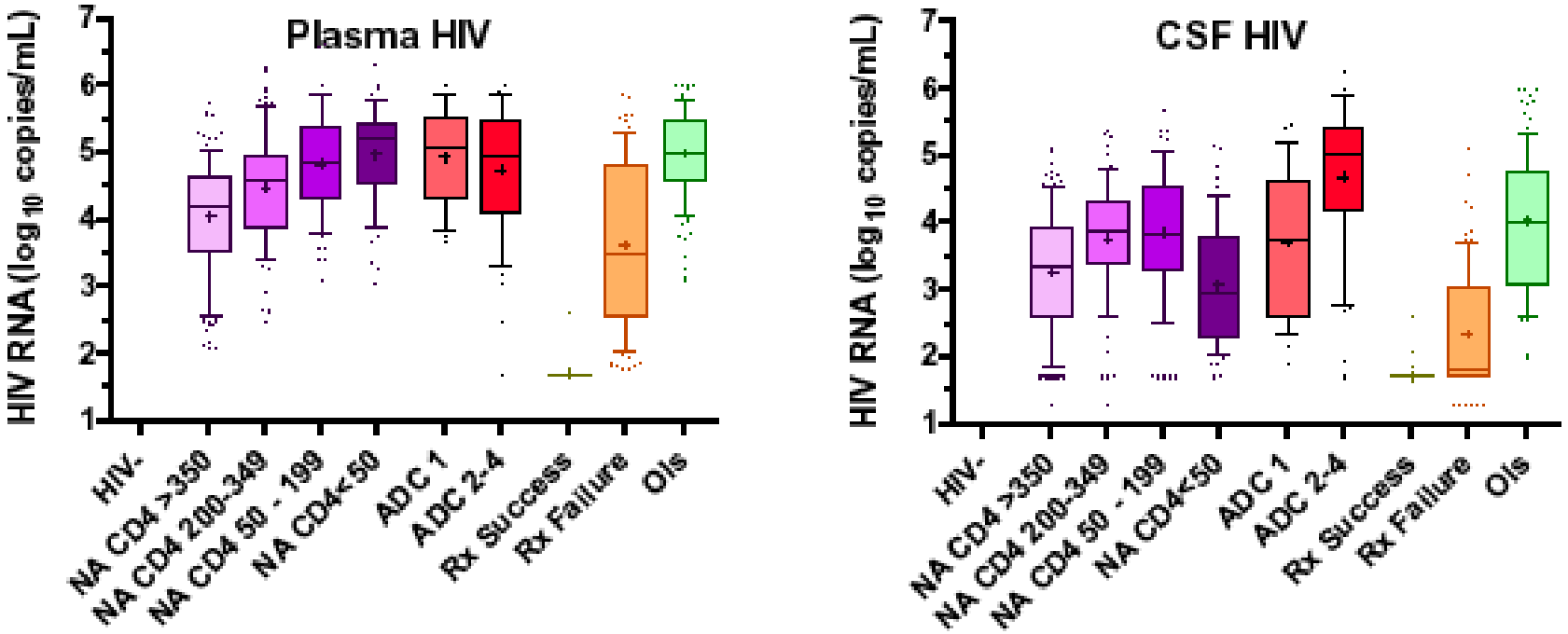
PML-specific treatments

- Non-recommended*
  - Cytarabine (**AII**)
  - Cidofovir (**AII**)
  - IFNα (**BIII**)
  - Topotecan (**BIII**)
- Use not justified in routine*
  - 5HT2a Inhibitors (**BIII**)

CDC, NIH, HMA-IDSA guidelines for HIV-OIs, 2009

- Clinical trial on Mefloquine: terminated
- CMX-001 ??? (*Patel A, JAC 2010*)
- Immune-based interventions
  - Adoptive JCV-specific T-cell transfer ??? (*Balduzzi A, BMT 2010*)
  - IL-7 ??? (*Patel A, JAC 2010*)

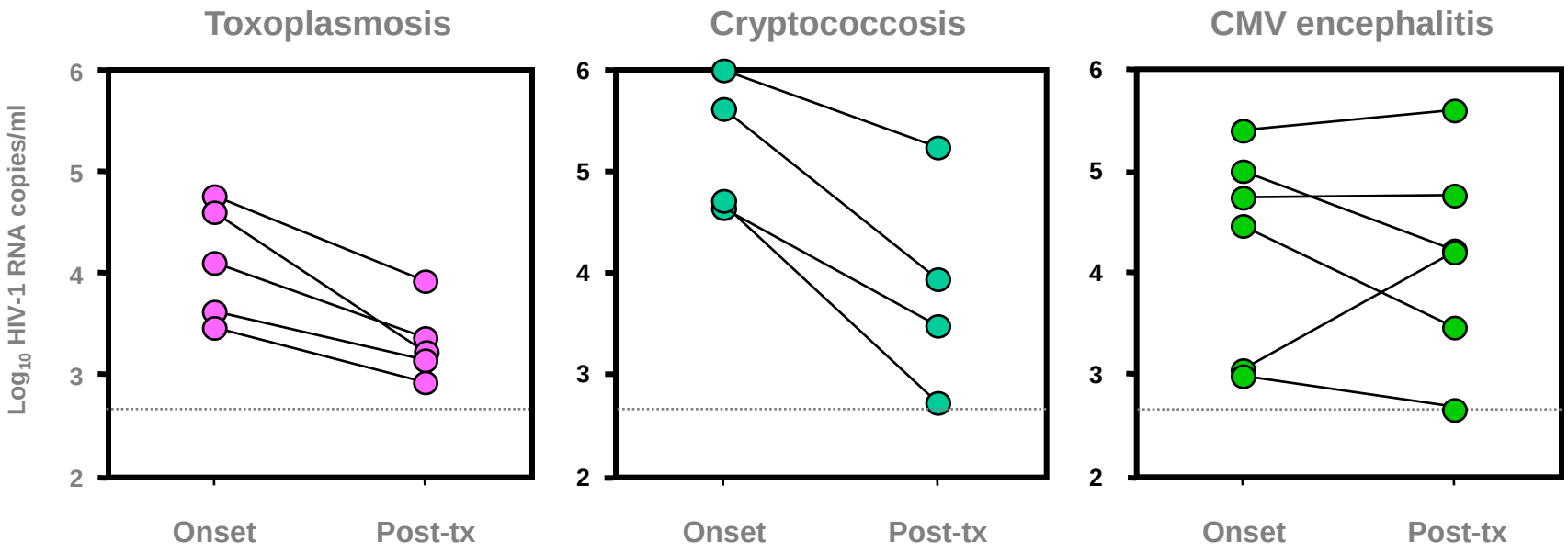
High CSF HIV RNA level in CNS-OIs



Hagberg L. et al., AIDS Res Ther 2010

Changes of CSF HIV RNA level in patients with CNS-Ois

No cART, CNS OI treatment only



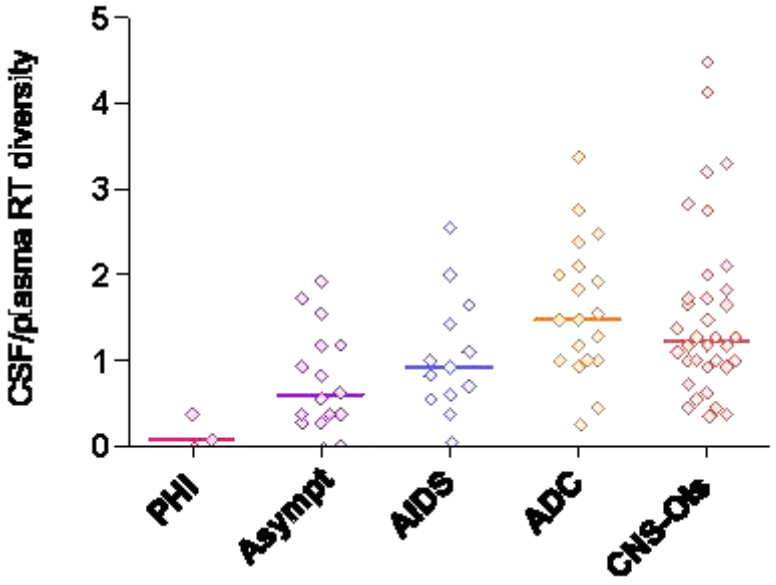
CNS-OIs and CNS HIV replication

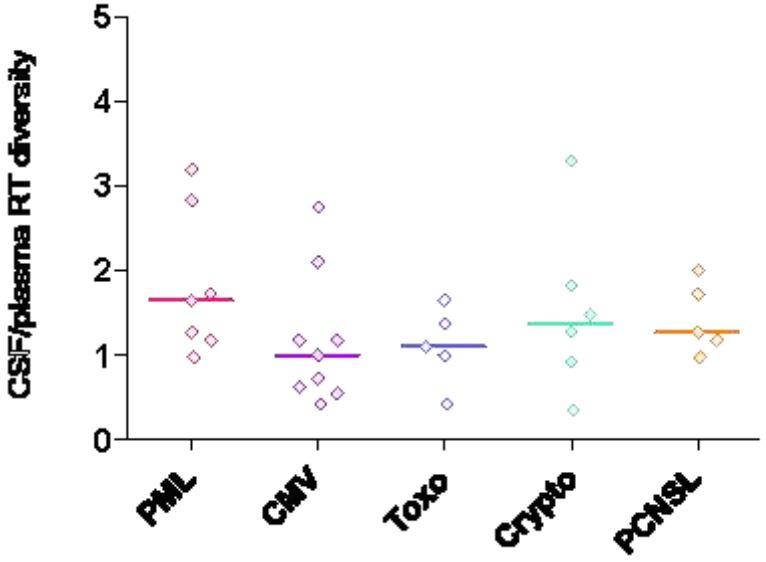
- May CNS-OIs favor HIV replication?
  - High CSF level due to brain barriers dysruption?
  - Other mechanisms?

- May HIV replication favor onset or progression of CNS-OI?

Origin of high CSF HIV RNA level in CNS-Ois (peripheral vs. intrathecal)

% diversity between CSF and plasma RT sequences





- CSF HIV infection seems to be compartmentalized in a significant number of CNS-OI cases

Lower rate of death in treated patients with CPE score >1.5

9932 pts with first neurological AIDS-defining event
FHDH-ANRS CO4

	1992-1995[b]	1996-1998[b]	1999-2004[b]
HIV-related encephalopathy	0.64 (0.47-0.86)	0.45 (0.35-0.58)	1.11 (0.58-2.11)
Progressive multifocal leukoencephalopathy	0.79 (0.55-1.12)	0.45 (0.31-0.65)	1.30 (0.61-2.39)

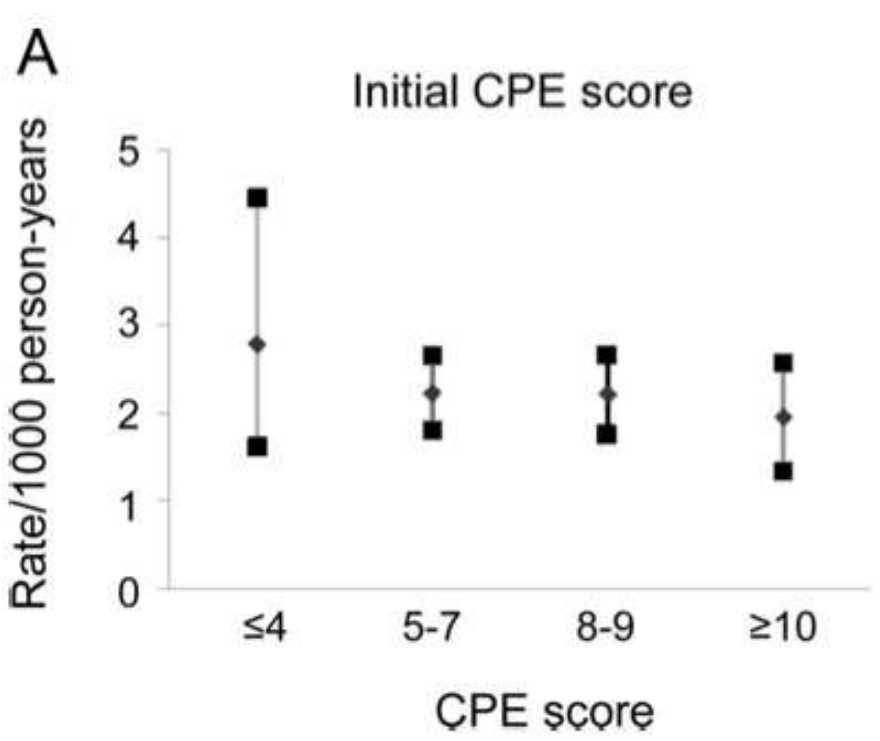
	1992-2004
Cerebral toxoplasmosis	0.68 (0.56-0.84)
Cryptococcal meningitis	0.50 (0.34-0.74)

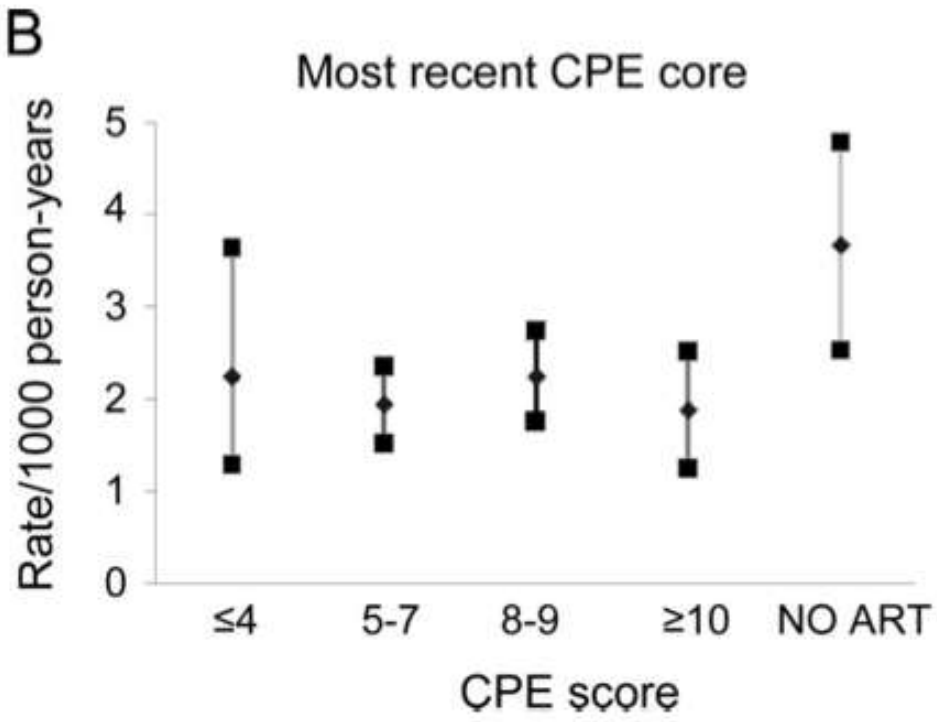
But loss of association if model adjusted for plasma VL

Lenoy et al, Neurology 2011

Non significantly higher incidence of CNS-D in patients with higher CPE score

251/22356 patients who started ART (1996-2008)
UK CollaborativeHIV Cohort (CHIC) Study





Lenoy et al, Neurology 2011

CNS-OIs and HIV replication

- High CSF HIV RNA levels in CNS-OIs
- Possible synergistic effect of HIV and opportunistic agents on the CNS
- Whether treatment of HIV CNS infection is beneficial for care or prevention of CNS OIs is unknown

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