PML: the old and the new

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Arrow 2015

Bucharest, 5-6 October 2015

PC disclosures (past 12 months)

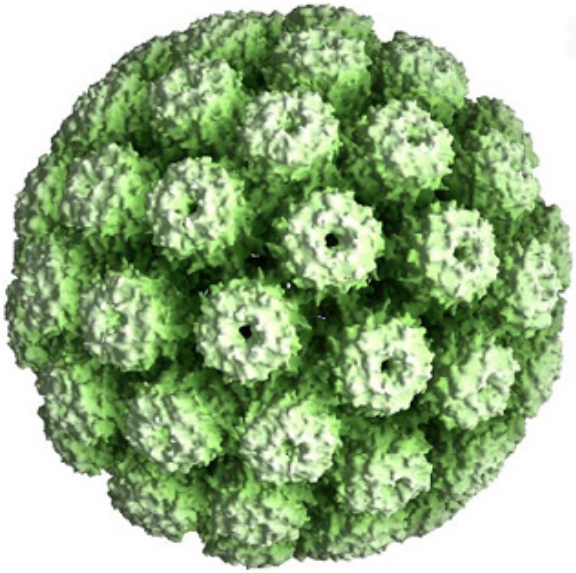
- AbbVie
- Biogen Idec
- Bristol-Myers Squibb
- Gilead
- Inhibikase Ther.
- Janssen Cilag
- Johnson & Johnson
- Merck
- Millenium Pharmaceuticals
- Pfizer
- Viiv Healthcare

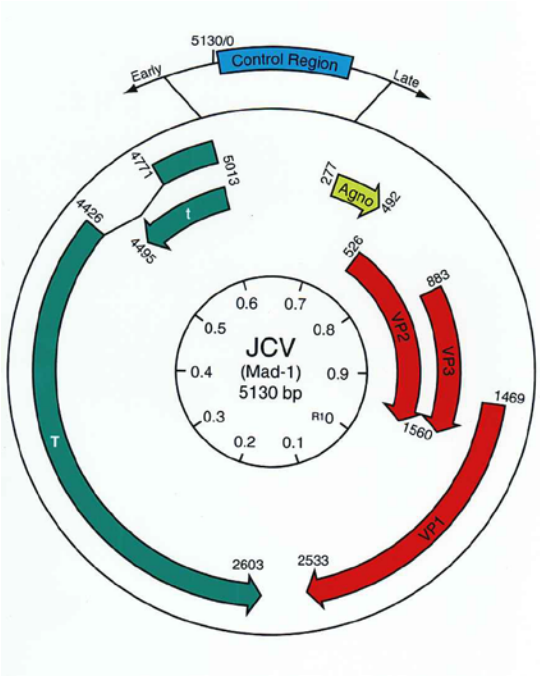
Outline

1. The natural history of JCV infection and PML
2. The clinical relevance of PML in HIV infection
3. Pathogenesis: towards prevention and cure?

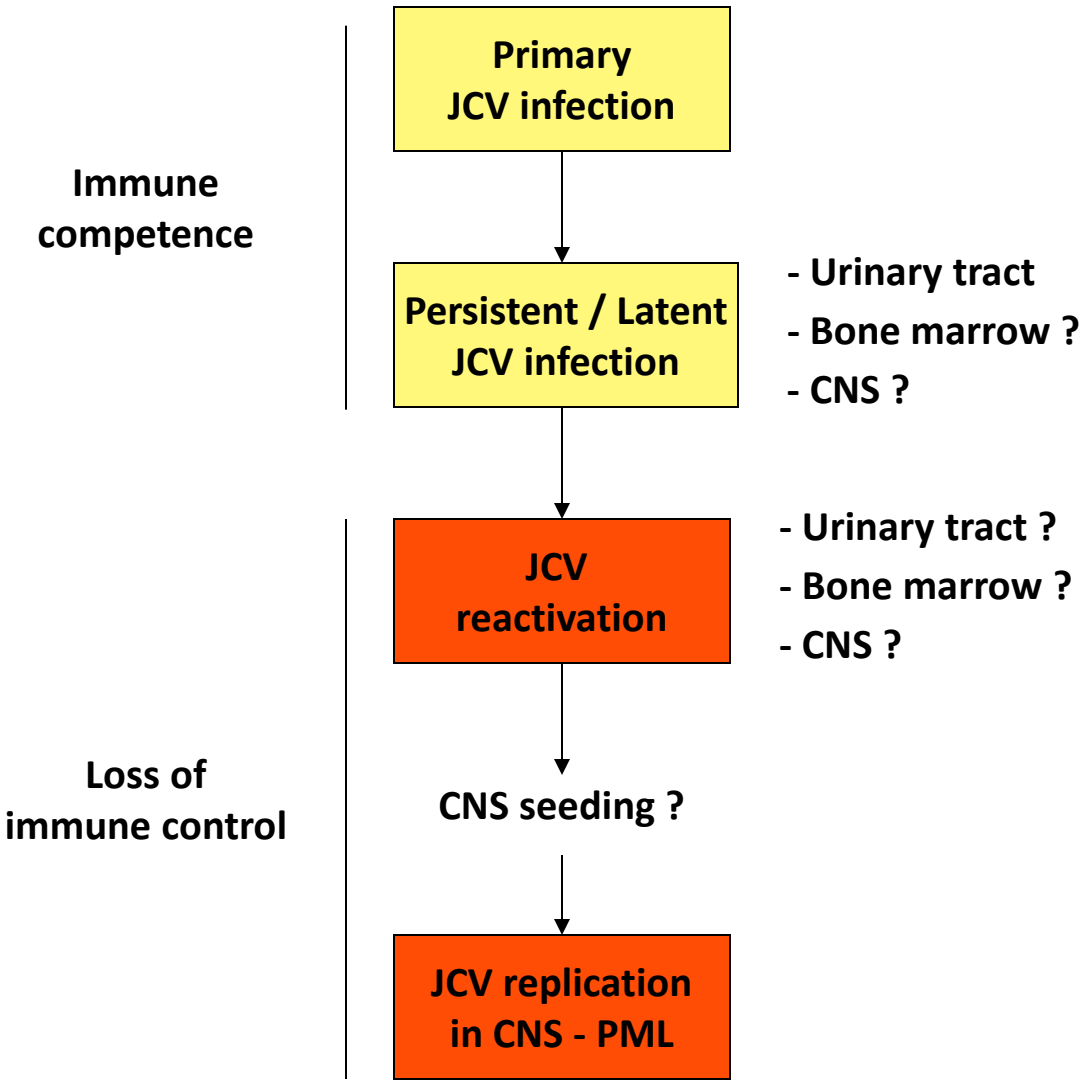
JC virus

- Polyomavirus
- Double-stranded DNA (5130 bp)





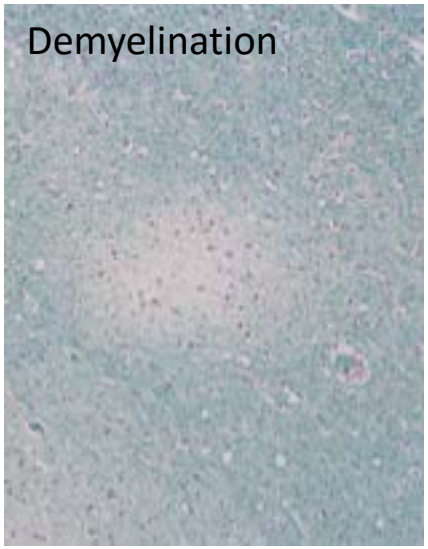
Natural history of JCV infection and PML

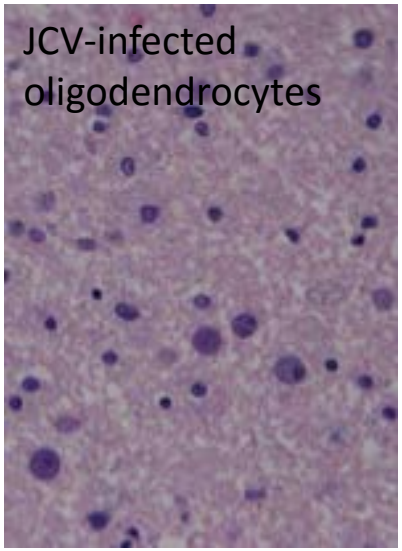


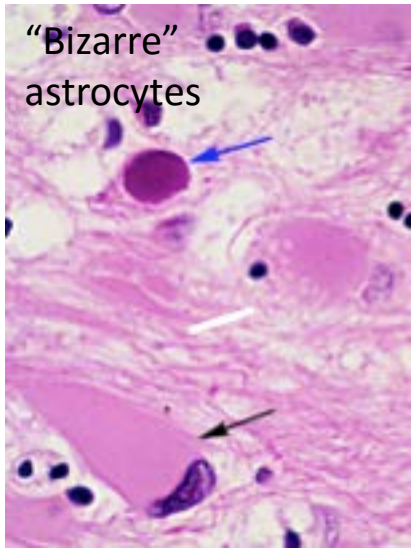
50-80% JCV seroprevalence in healthy adults

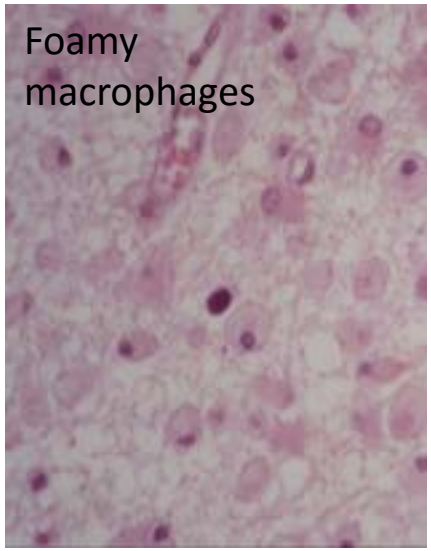
20% JCV DNA excretion in urine in healthy adults

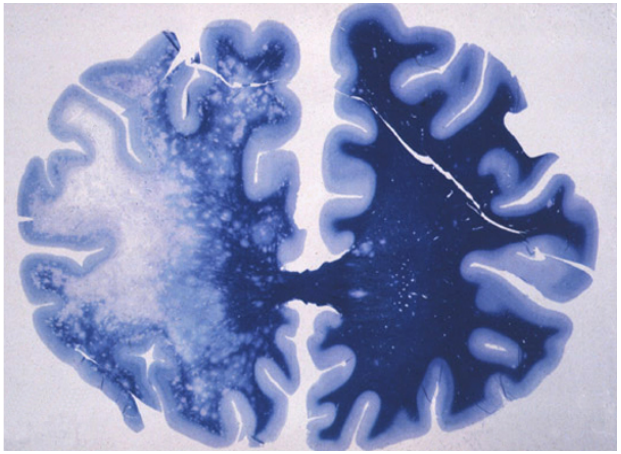
Progressive multifocal leukoencephalopathy (PML)

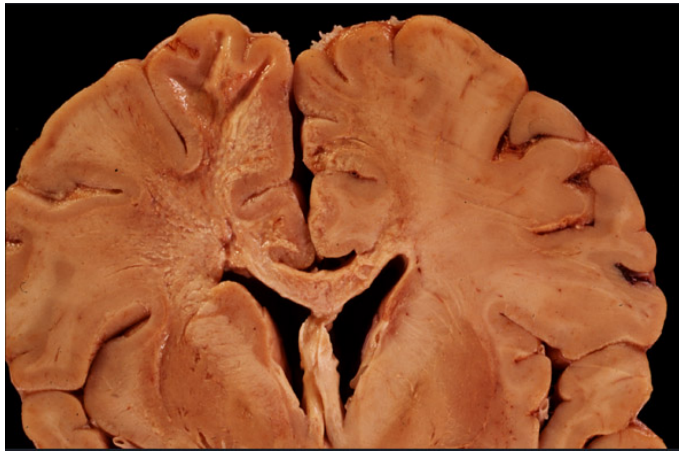


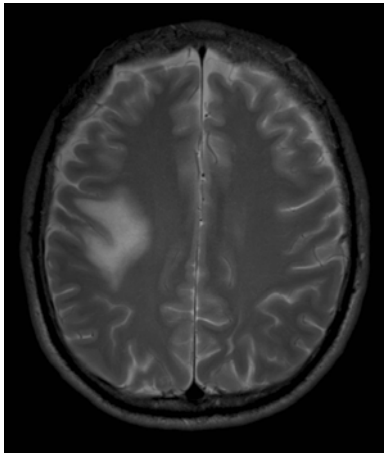




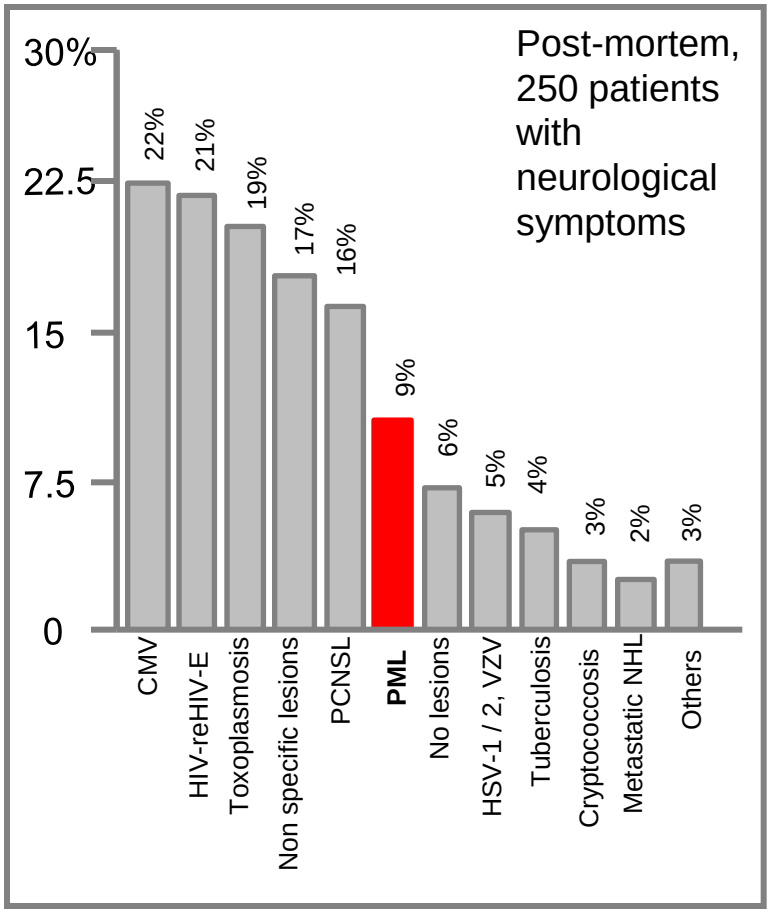






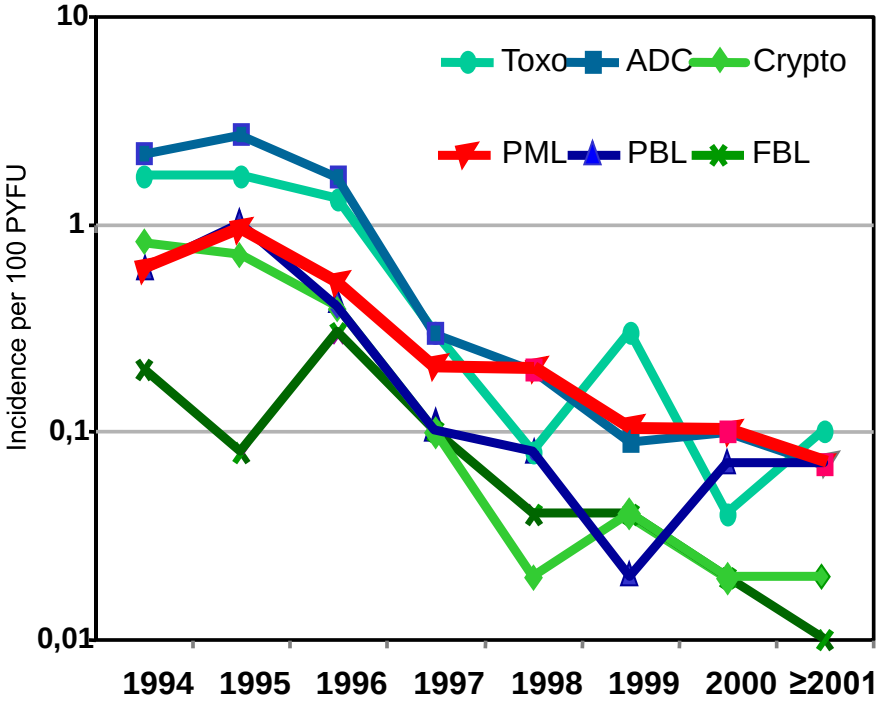


Frequency and incidence of HIV-PML before and after cART



Vago et al., 1995

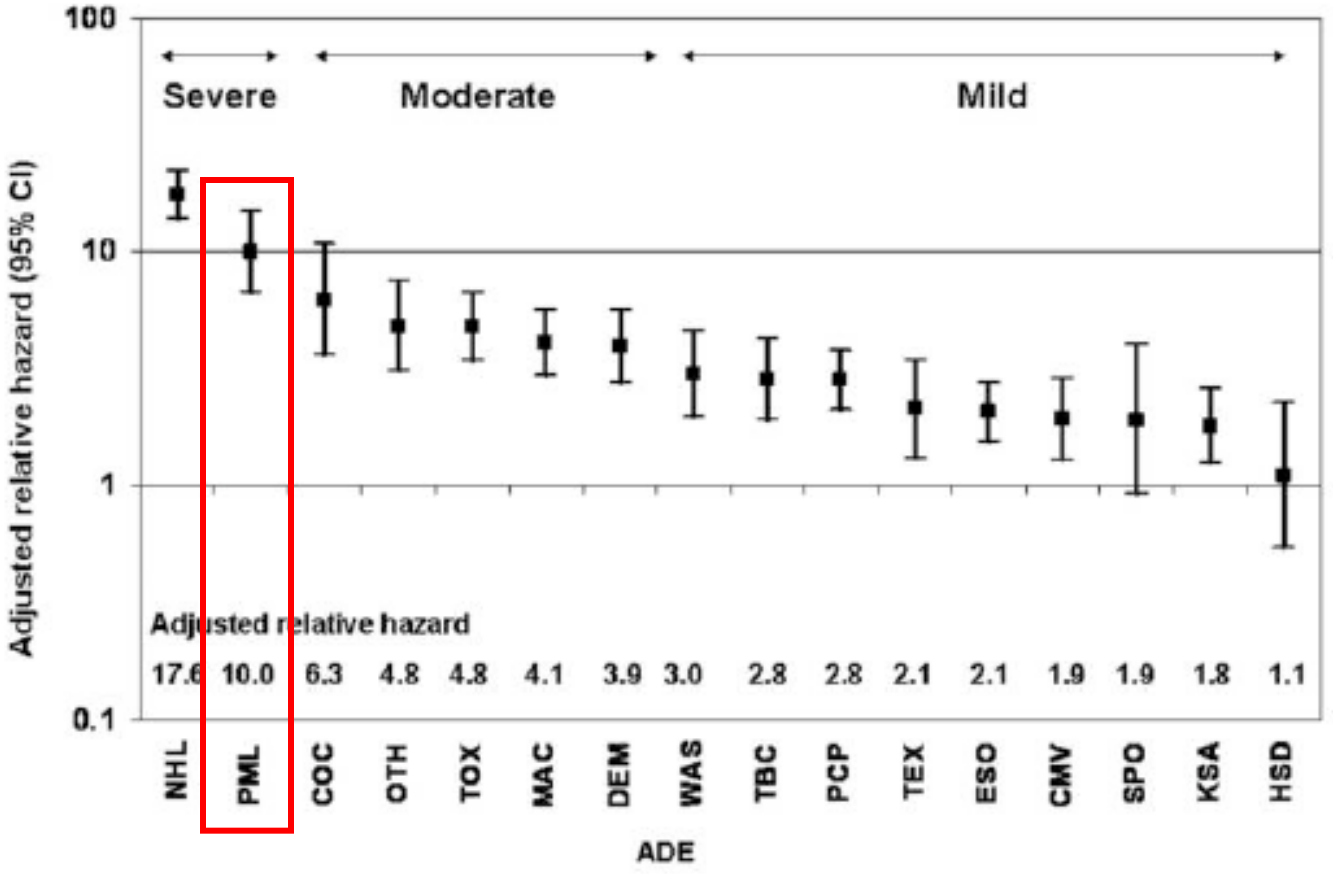
Less marked decrease of incidence than for other CNS OIs



EuroSida - D'Arminio Monforte et al., Ann. Neurology 2004

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

Diagnostic criteria for PML

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

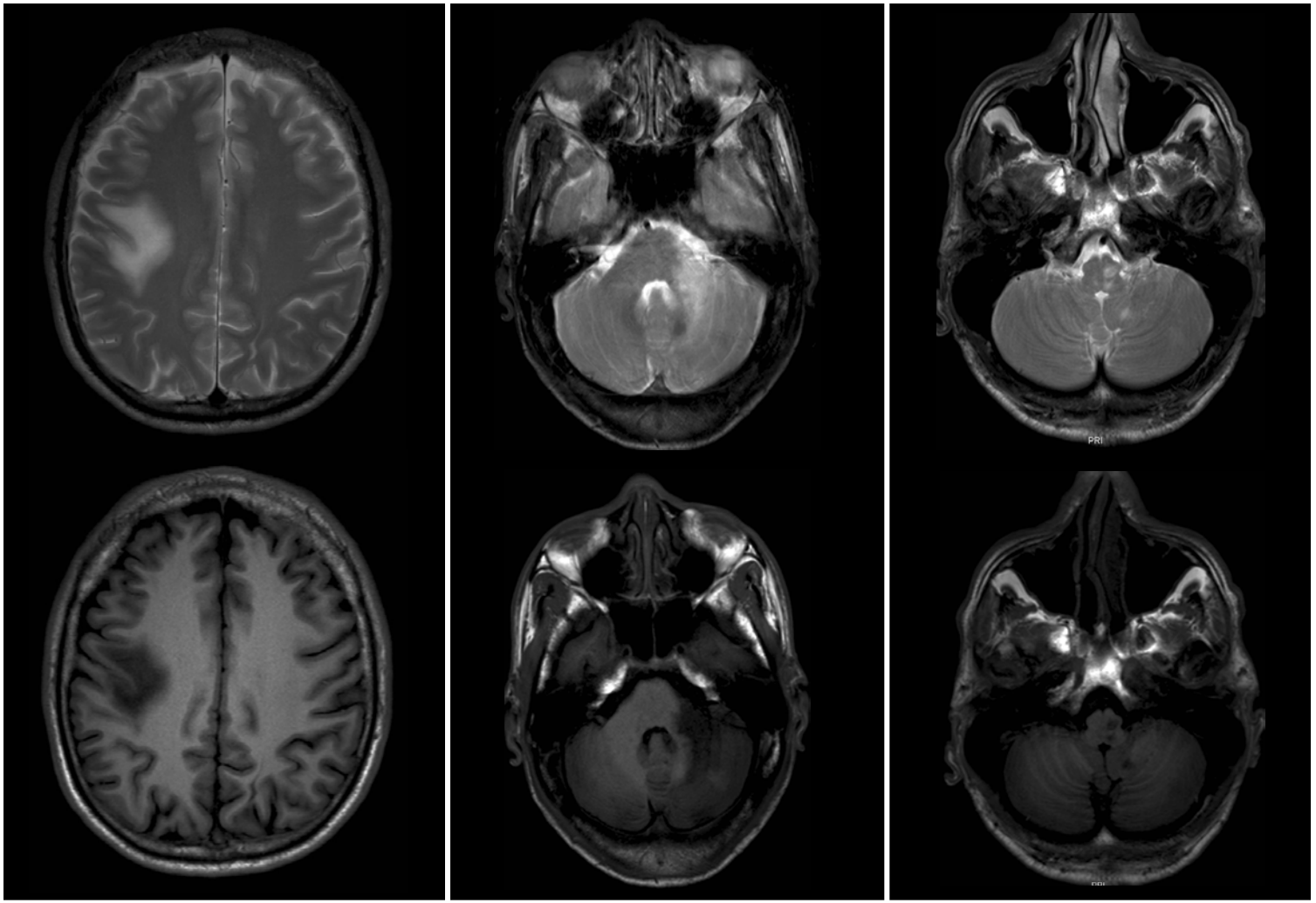
- Histology-confirmed PML: brain biopsy (or post-mortem examination) showing typical pathologic features with JCV confirmed either by IHC or ISH
- Laboratory-confirmed PML: demonstration of JCV DNA in CSF by nucleic acid amplification methods
- Possible PML: absence of both histological confirmation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

Cinque, Koralnik and Clifford, JNV 2002
Portegies et al (HIV-PML), EJN 2004
CDC, NIH, HMA-IDSA Guidelines for HIV-OIs, 2009
Mentzner et al (Moabs-PML), JNNP 2012
AAN Neuroinfectious Disease Section, Neurology 2013

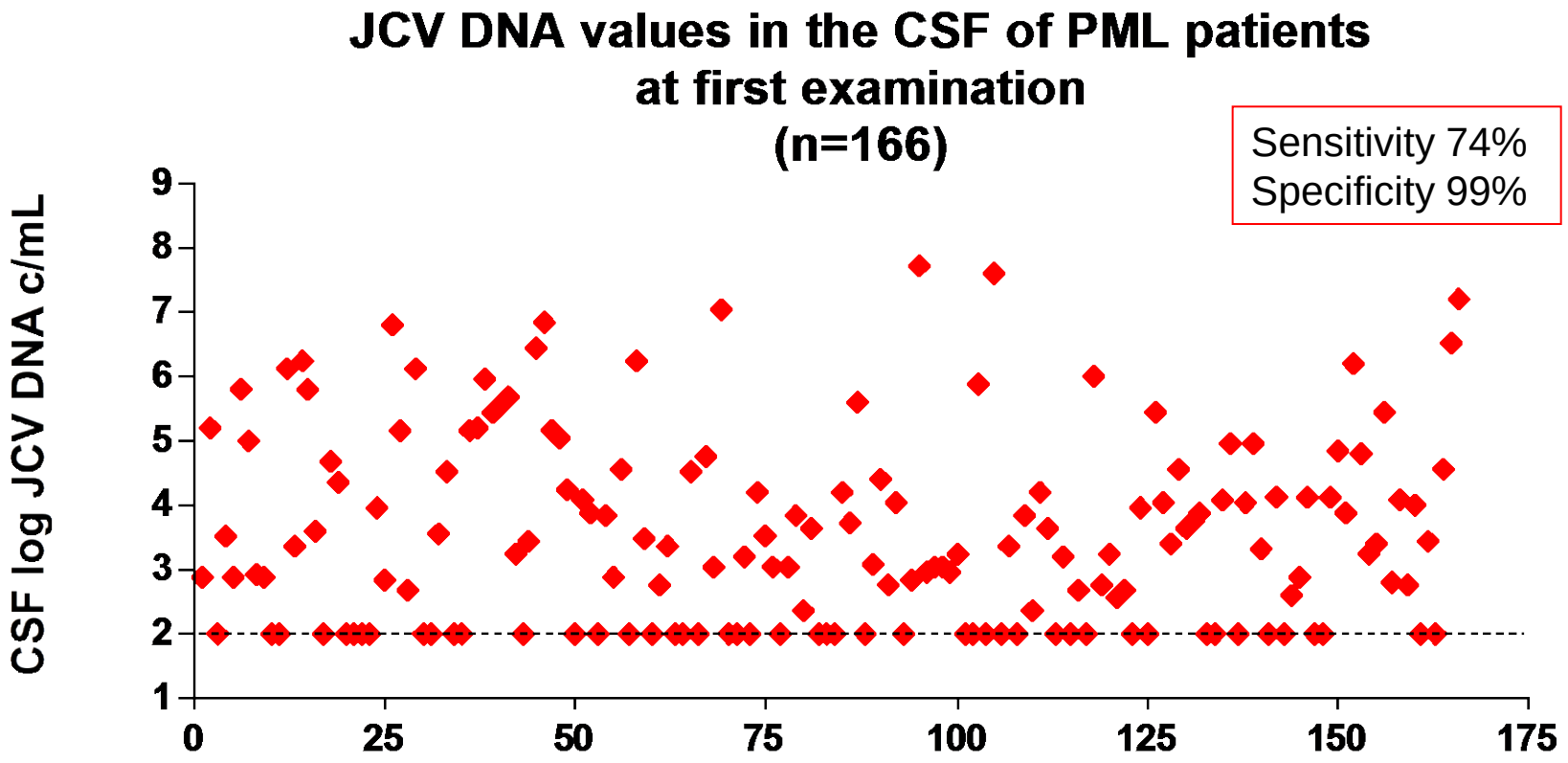
“Typical” clinical manifestations of PML

- Focal neurological deficits that vary with lesion localization - Neuropsychiatric symptoms
- Insidious presentation, progressive worsening
- Seizure in 15-20% of cases
- Fever and headache usually absent (except for inflammatory forms)

PML: MRI presentation



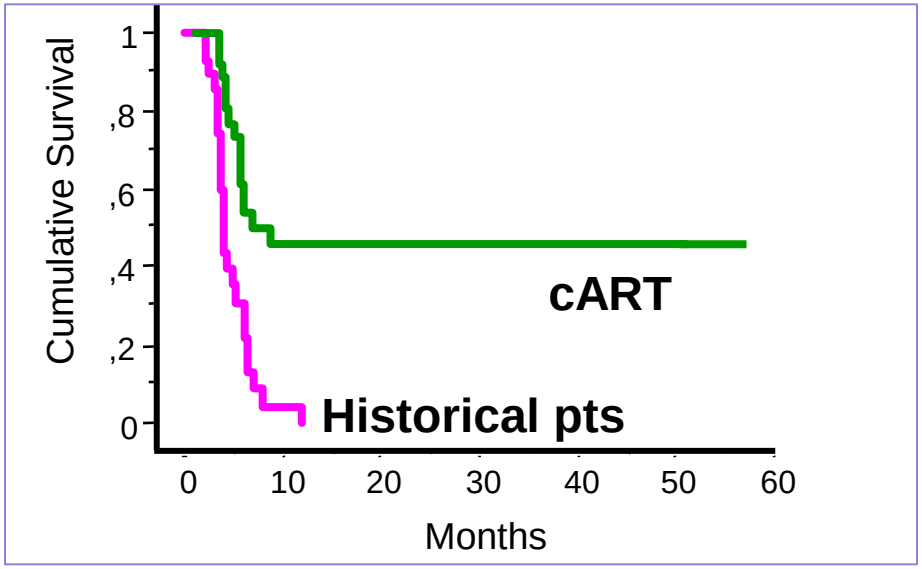
Quantitative CSF PCR for detection of JCV DNA



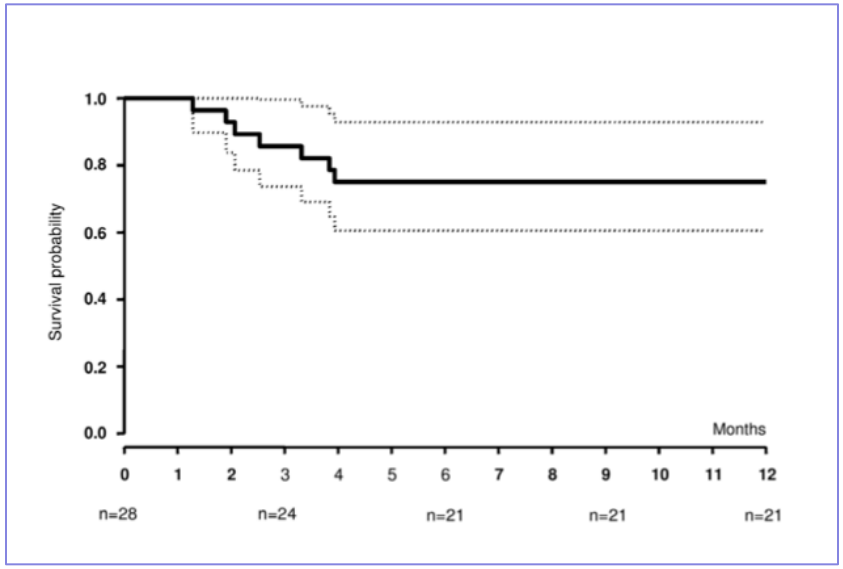
Current treatment options for HIV-related PML

- Reduction of immunosuppression
  - cART
  - (Interleukin-7?)
- JCV-targeted treatments

Patient survival in HIV-associated PML among cART-treated patients



Bossolasco et al. CID 2005



Gasnault J et al., PLOS One 2011

JCV-targeted treatments in PML: a story of disappointed needs

• 5HT2a inhibitors **	*Entry inhibitor*
• Topotecan *	*Topoisomerase inhibitor*
• Cytarabine **	*Polimerase inhibitor*
• Cidofovir *	*Polimerase inhibitor*
• CMX-001 *	*Polimerase inhibitor*
• Mefloquine *	

* Non-recommended **(AII)**
** Use not justified in routine **(BIII)**
(CDC, NIH, HMA-IDSA guidelines for HIV-OIs, 2009)

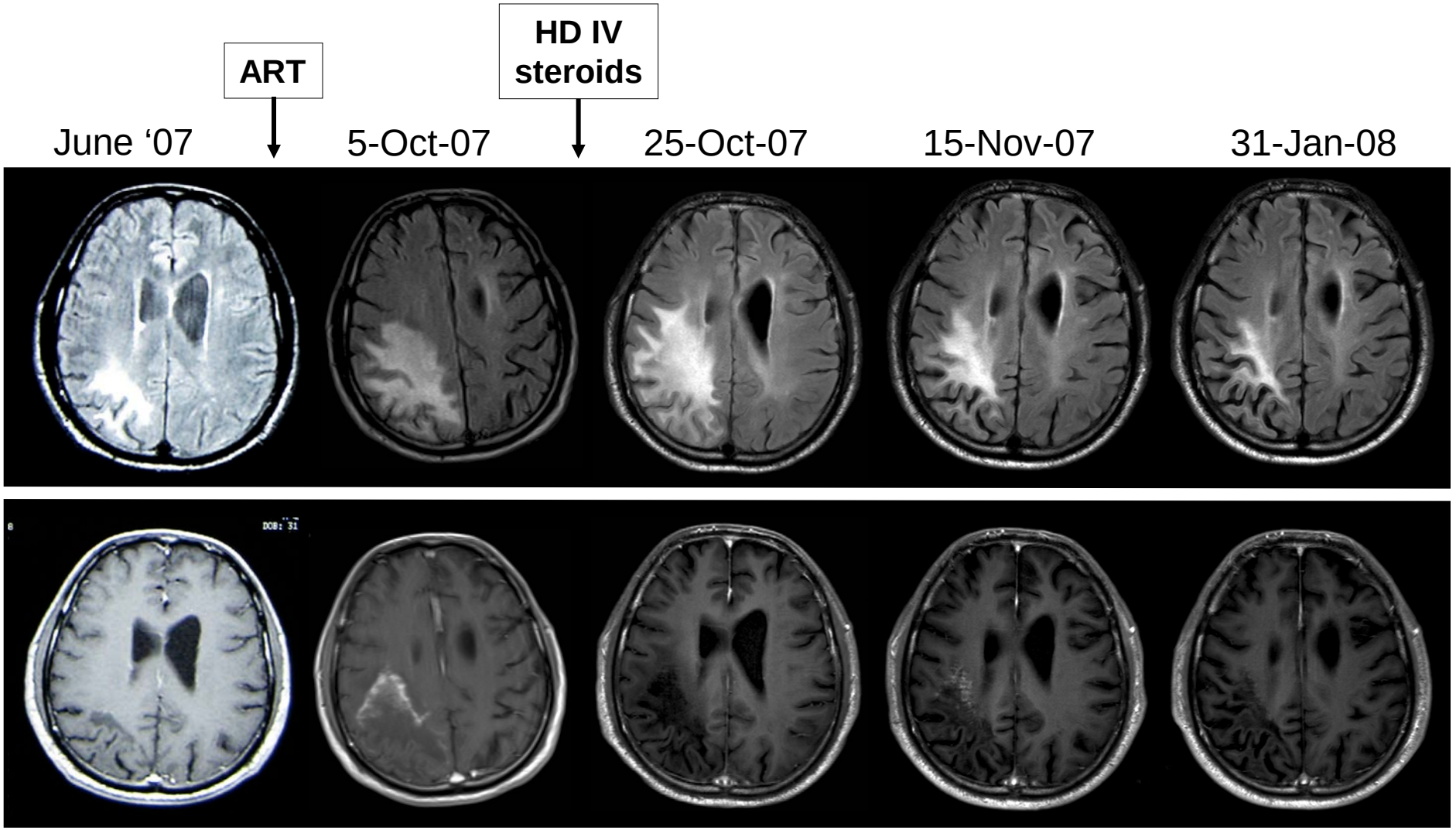
* Controlled trials showed no efficacy compared to SOC

Immune Reconstitution Inflammatory Syndrome (IRIS)-PML

- Definition: “Worsening of neurologic deficits during the immune reconstitution, with inflammatory changes on neuroimaging”

- Relevance: May benefit from steroids

Paradoxical worsening of PML following cART: IRIS-PML



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

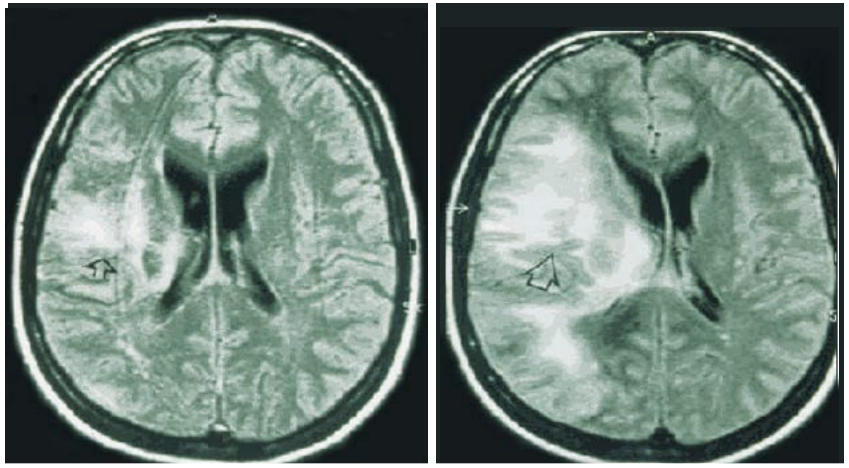
JCV-DNA 455 c/mL
CD4 79
VL <50 c/mL

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

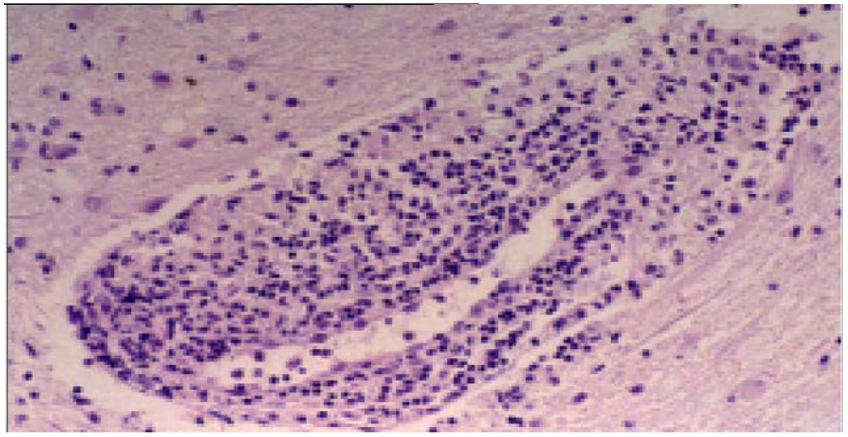
JCV DNA n.d.
CD4 31 (3.8%);
VL <50 c/mL

IRIS-PML:
Immune Reconstitution Inflammatory Syndrome

PML onset

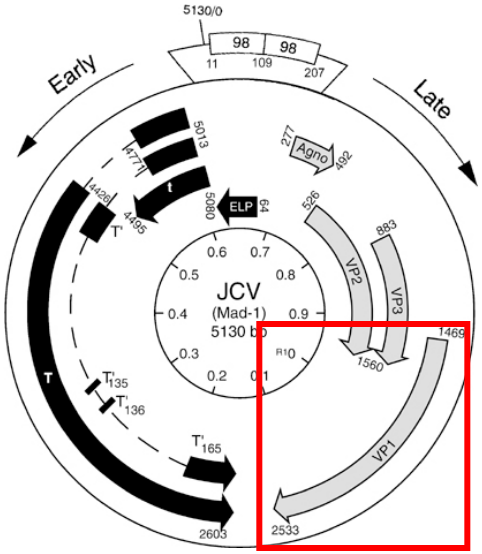


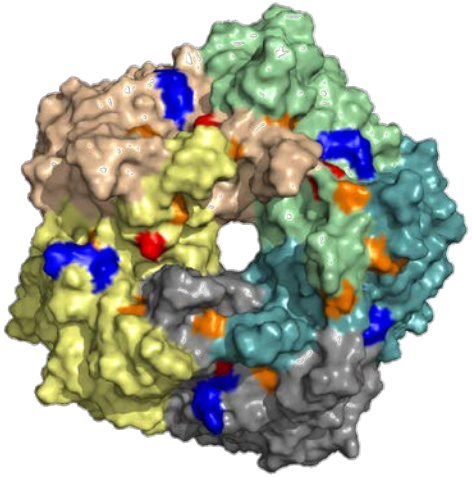
After 12 weeks
of cART

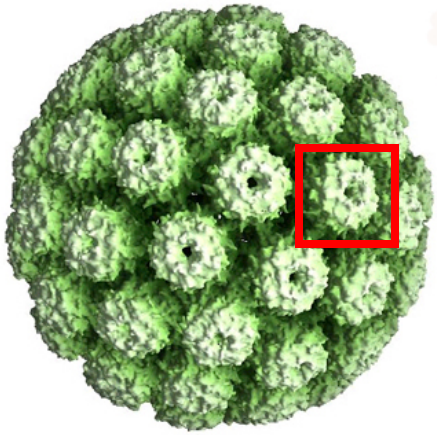


Courtesy of
Pilar Miralles, Madrid, Spain

JCV capsid viral protein-1 (VP-1)

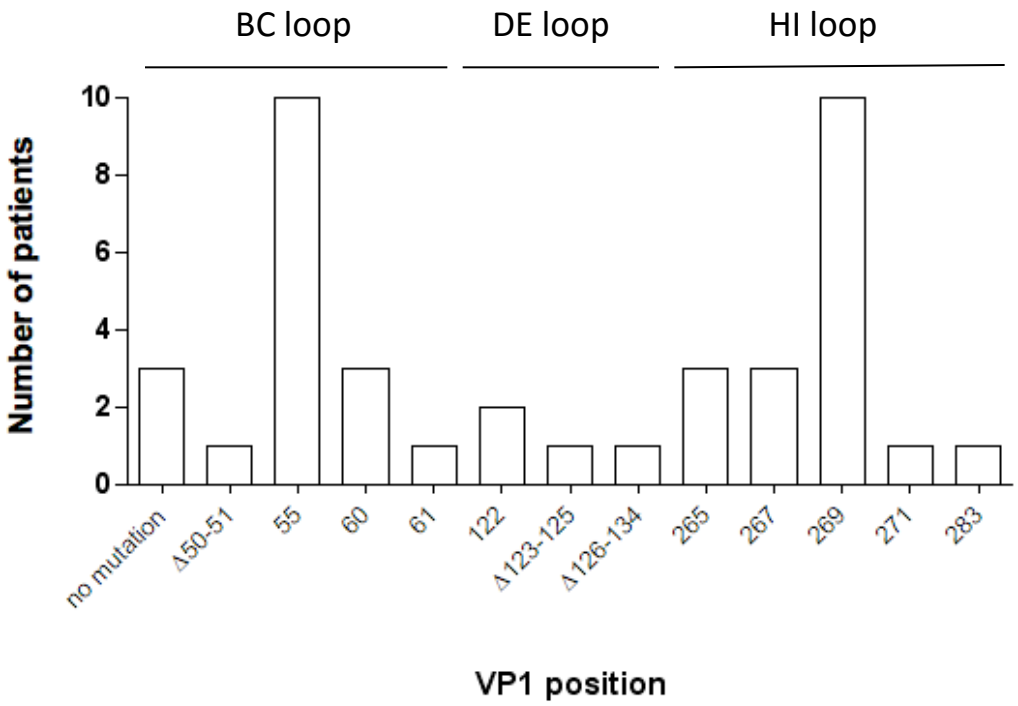


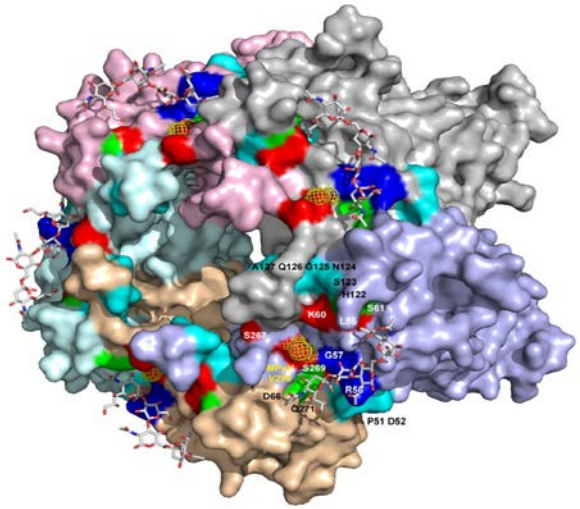




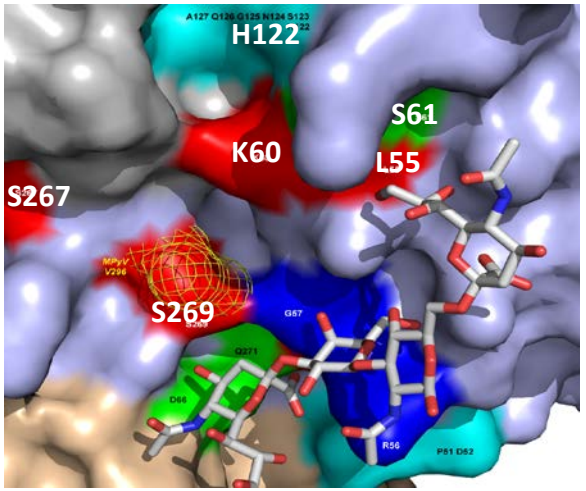
- Critical for virus entry in the host cell - interaction with sialic acid on cell receptor
- Main target for both B-cell and T-cell immune response

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

→ Involving aa in the VP1 sialic acid cell-receptor binding pocket

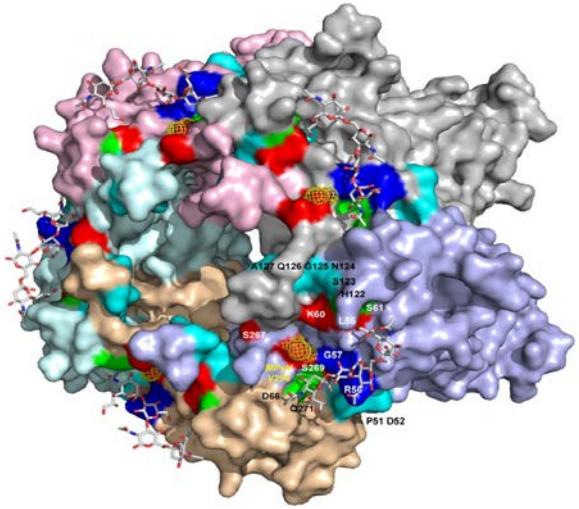
Gorelik L. et al, JID 2011

PML-Specific VP1 mutations develop within patient from existing WT virus

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 2011

PML-specific mutations



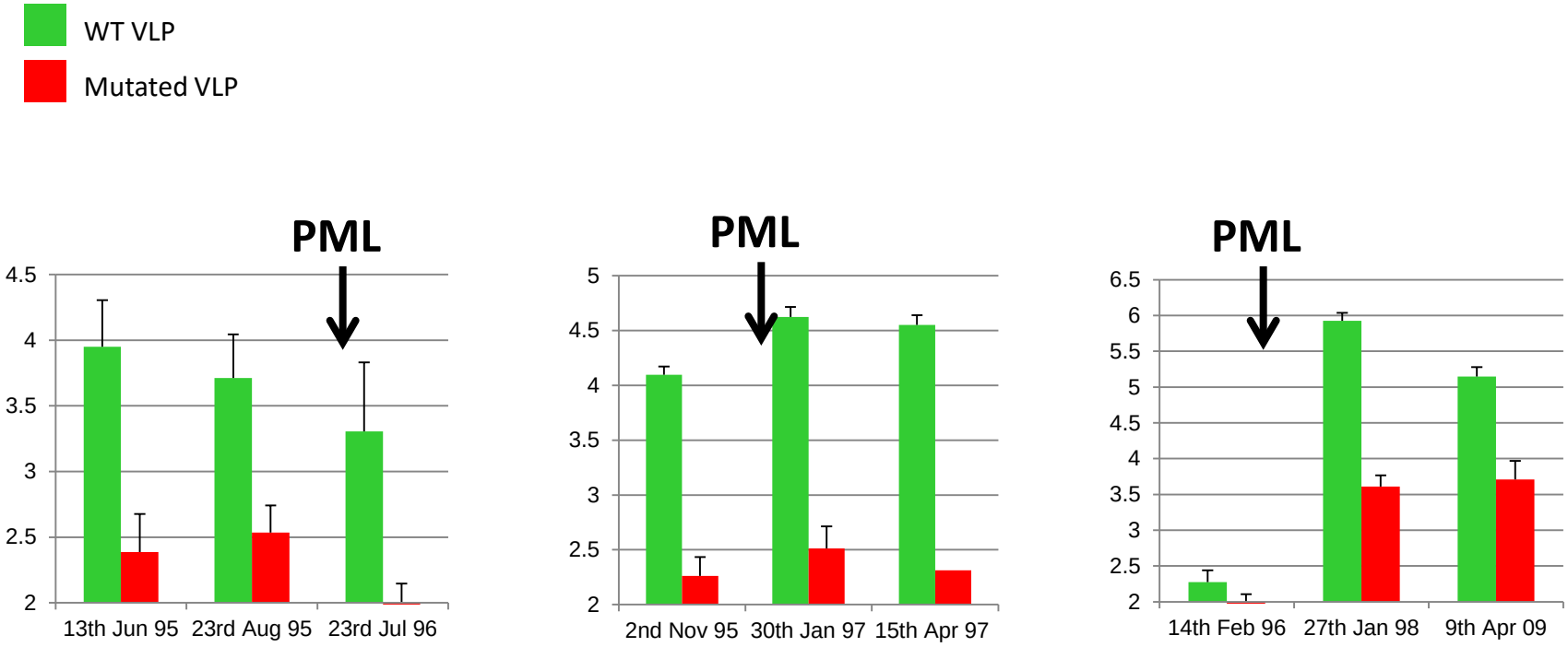
- May affect binding with sialic acid molecules
- Will they affect immune responses ?

JCV-specific immunity in PML

- T-cell immunity
  - CD8+ responses
  - CD4+ responses

- B-cell immunity
  - VP1-IgG
  - **Neutralizing antibodies**

PML patients have blind spots to mutated JCV months-years before PML



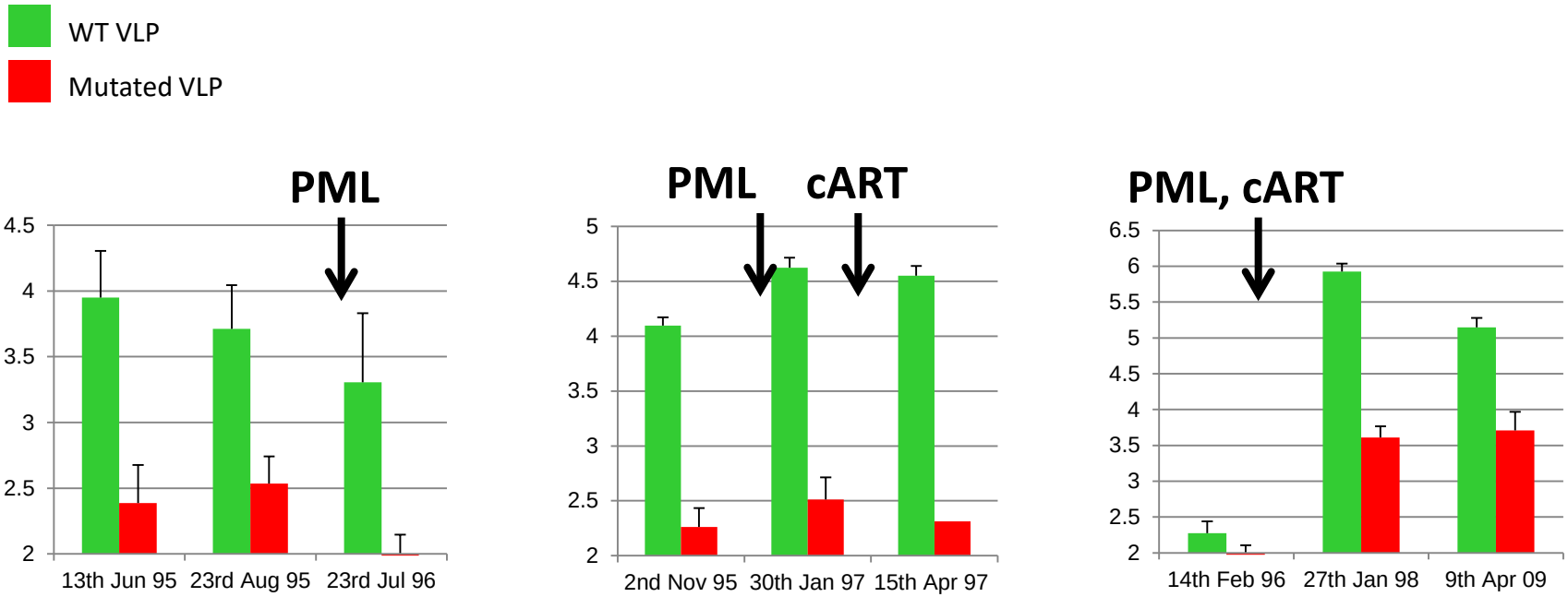
Pt. 5029 **(S269F)**

Pt. 5031 **(S269F)**

Pt. 5053 **(L55F)**

Ray U. et al., Science Transl Med 2015

PML patients who survive cover blind spots to mutated JCV



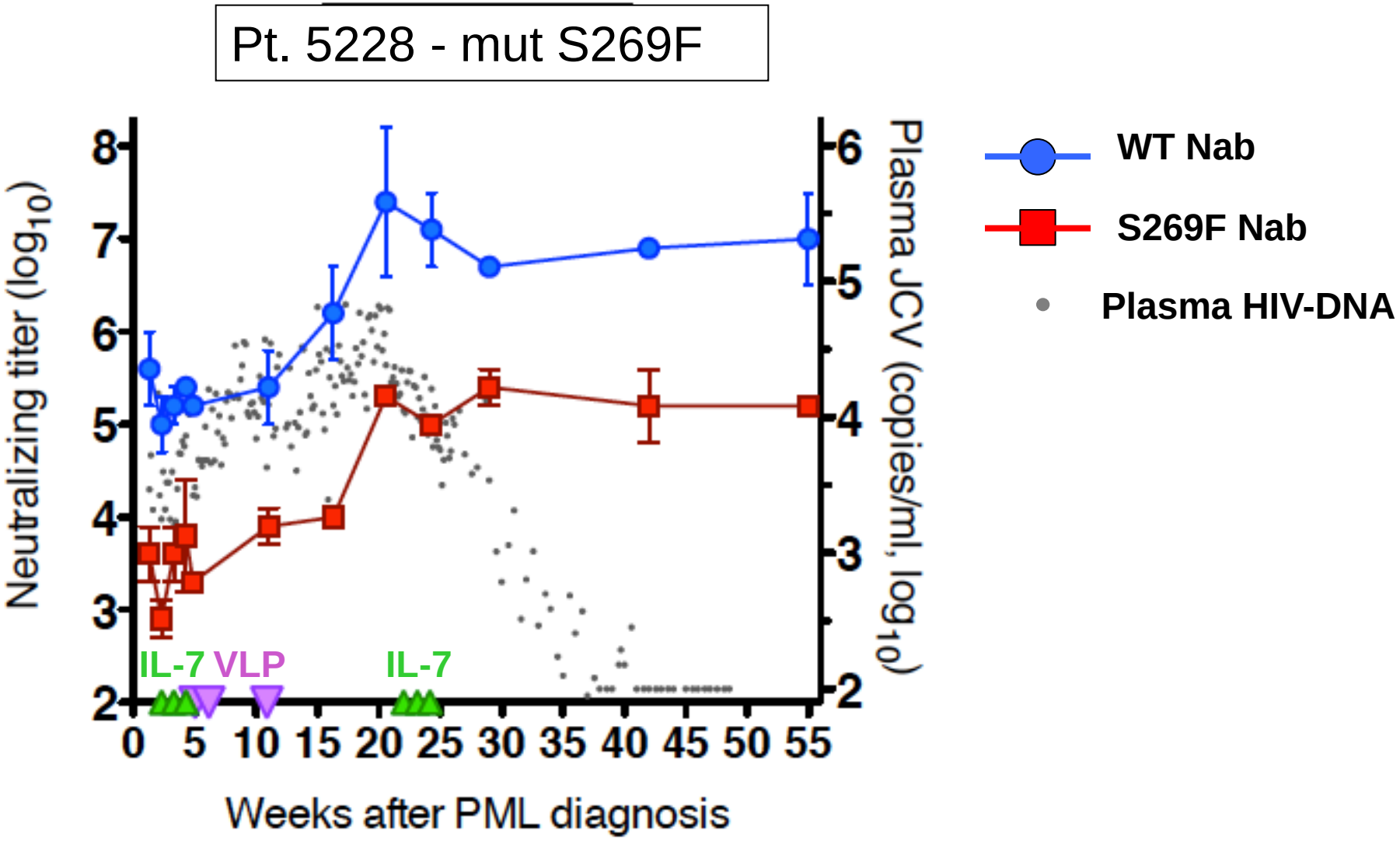
Pt. 5029 (S269F)
No cART
PML progression

Pt. 5031 (S269F)
cART
PML progression

Pt. 5053 (L55F)
cART
PML remission

Ray U. et al., Science Transl Med 2015

Neutralizing ab against WT and mutated VLPs following IL-7 and JCV-VLP administration in a PML patient with ICL



Conclusions

- Relatively infrequent, but still lethal
- Improvements in diagnosis
- Selection of VP1 mutant key for development of PML
- Strategies to enhance JCV-specific immune responses might help treat and prevent PML

Acknowledgements

PML patients and families

San Raffaele Scientific Institute, Milano

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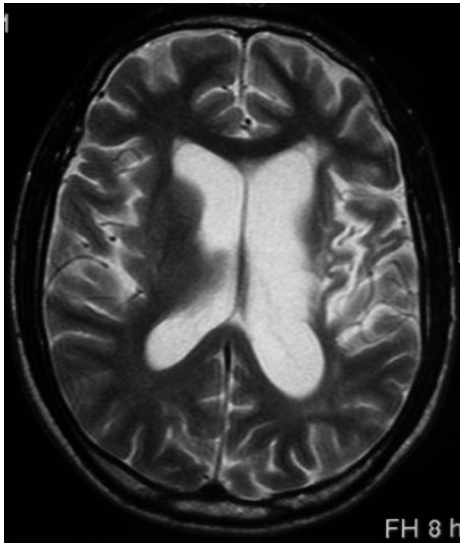
Beyond response to “reduction of immunesuppression”

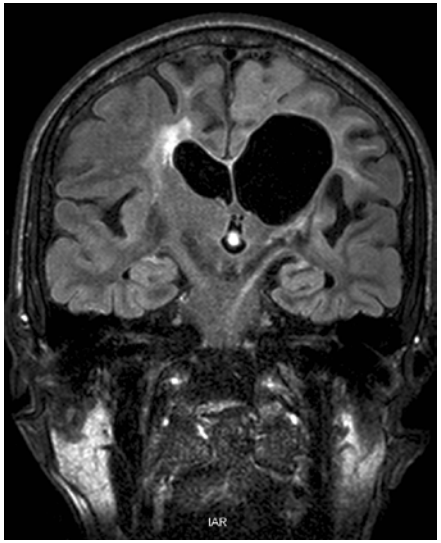
- Bad survival
- IRIS (Immune Reconstitution Inflammatory Syndrome)

Clinical outcome of PML survivors

24 pts assessed by MRDS (Modified Rankin Disability Scale)

MRDS=1	n=8 (33%)
MRDS=2	n=6 (25%)
MRDS=3	n=5 (21%)
MRDS=4	n=5 (21%)





MRDS=1 no significant disability despite persistent symptoms

MRDS=2 slight disability, living independently

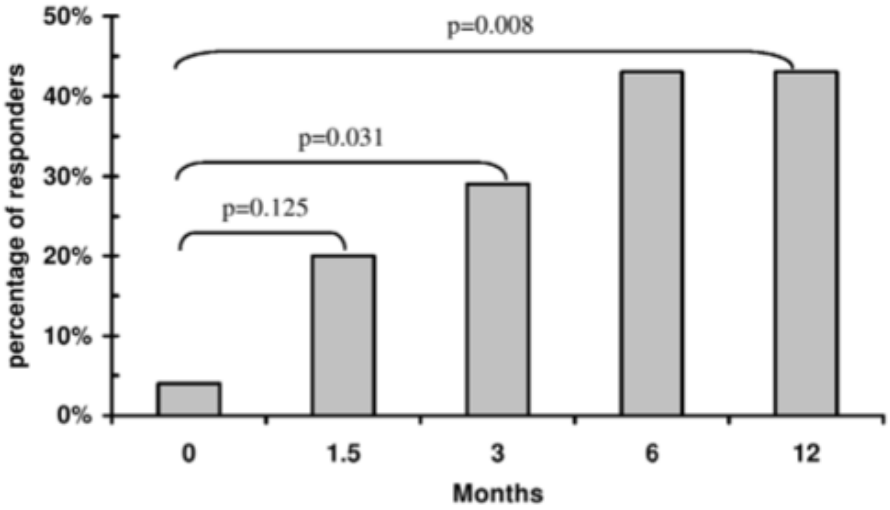
MRDS=3 moderately disabled, requiring help during daily living activities

MRDS=4 severe disability, requiring constant help or institutionalisation

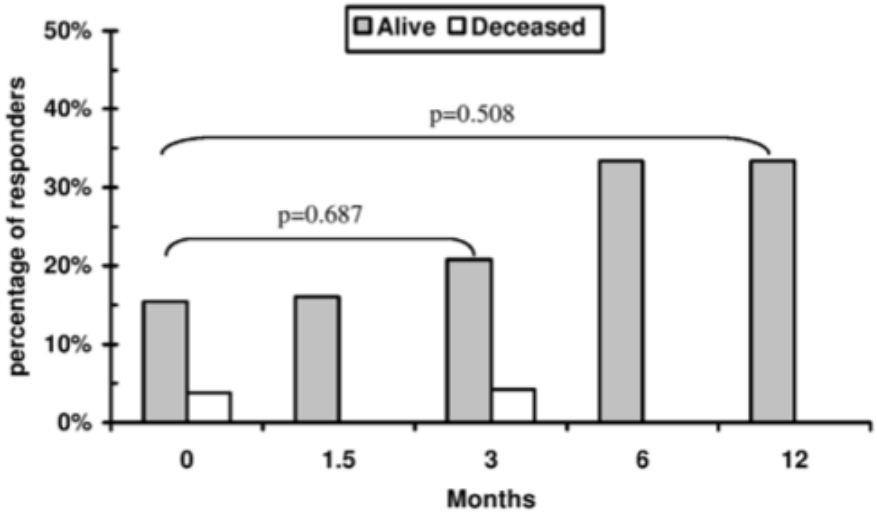
Lima MA et al., JNNP 2010

JCV-specific T-cell responses are low in patients with HIV-PML, but increase with cART

Anti-JCV CD4 T cell proliferative responses



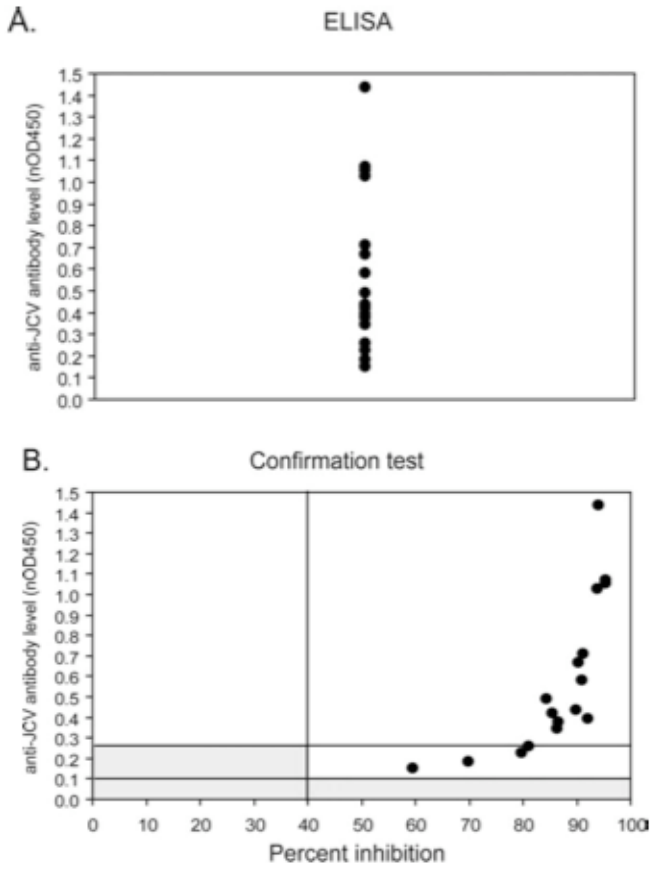
Anti-JCV CD8 T cell responses



Gasnault J et al., PLOS One 2011

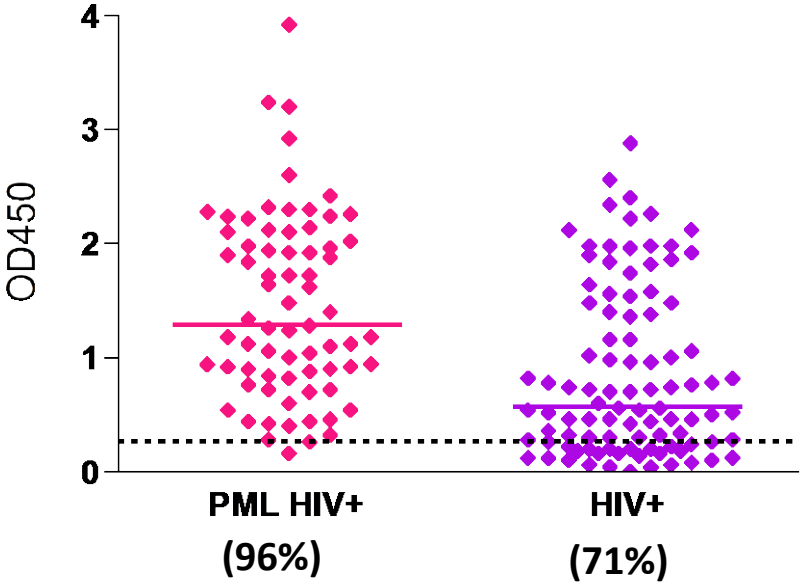
Anti-JCV VP1 IgG are not protective in PML patients

100% seroprevalence in natalizumab-PML

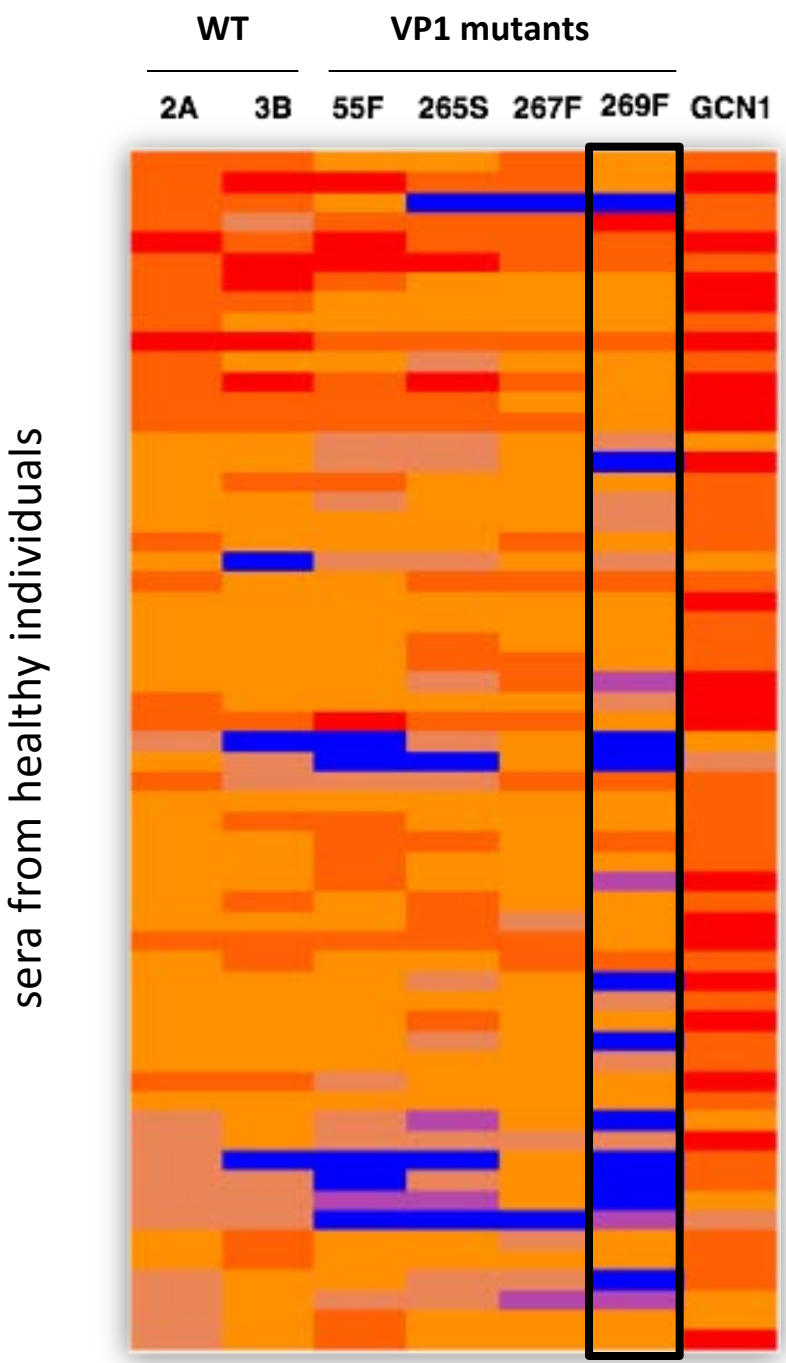


Gorelik et al., Ann Neurol 2010

Almost 100% seroprevalence in HIV-PML



Bossolasco S et al., 2010



Neutralizing Ab responses in healthy donors against WT and mutated VLPs

Neutralizing titer (log_{10} EC_{50}) on SFT cells

1.7-2.0	2.0-2.3	2.3-3.0
3.0-4.0	4.0-5.0	5.0-7.0

→ Healthy adults neutralize WT JCV

→ But some fail to neutralize some VP1-mutant JCV: **"blind-spots"**

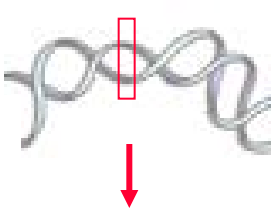
Ray U. et al., unpublished

Underlying immune dysfunction in PML

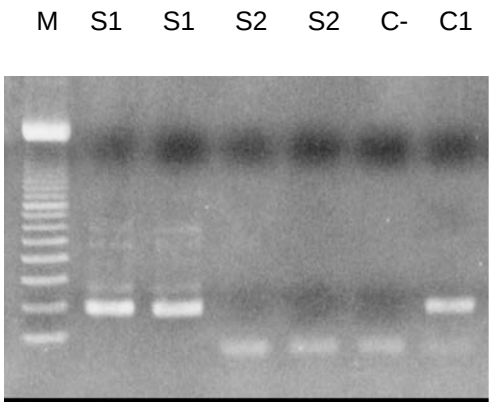
- **HIV infection**
- Treatment with natalizumab, rituximab, efalizumab and other immunomodulant drugs
- Idiopathic CD4 lymphopenia (ICL) and other primary or acquired immunodeficiencies
- Hematologic malignancies
- Transplantation - Immunosuppressive treatments
- Autoimmune diseases - Immunosuppressive treatments

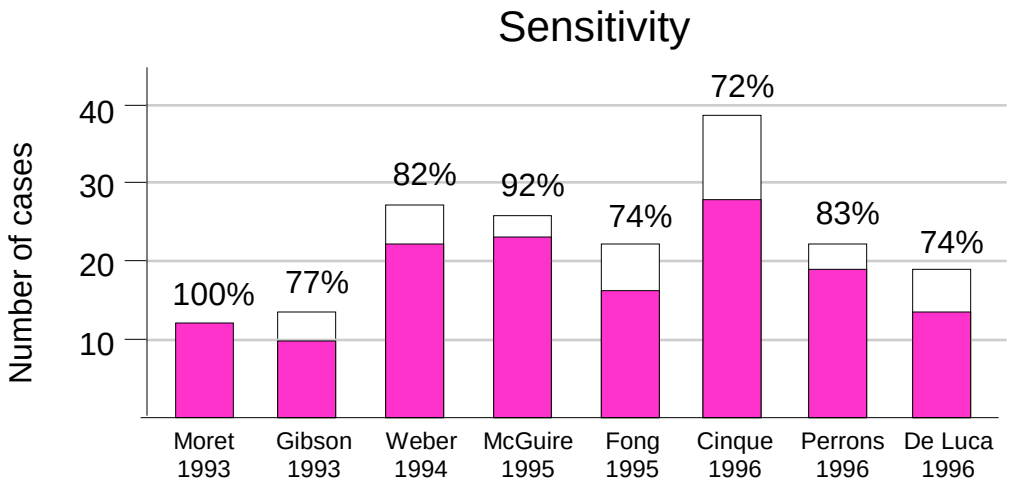
CSF PCR for detection of JCV DNA

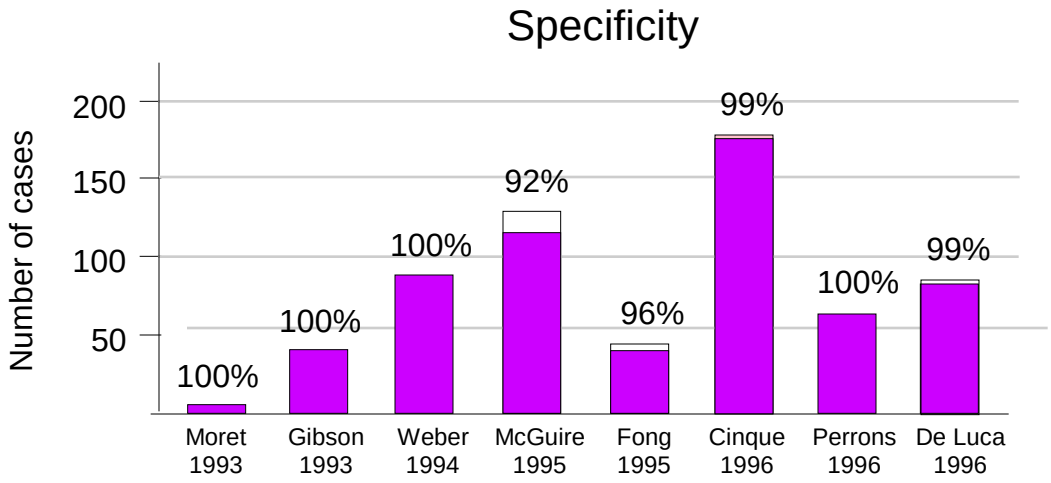
1990:
Qualitative PCR



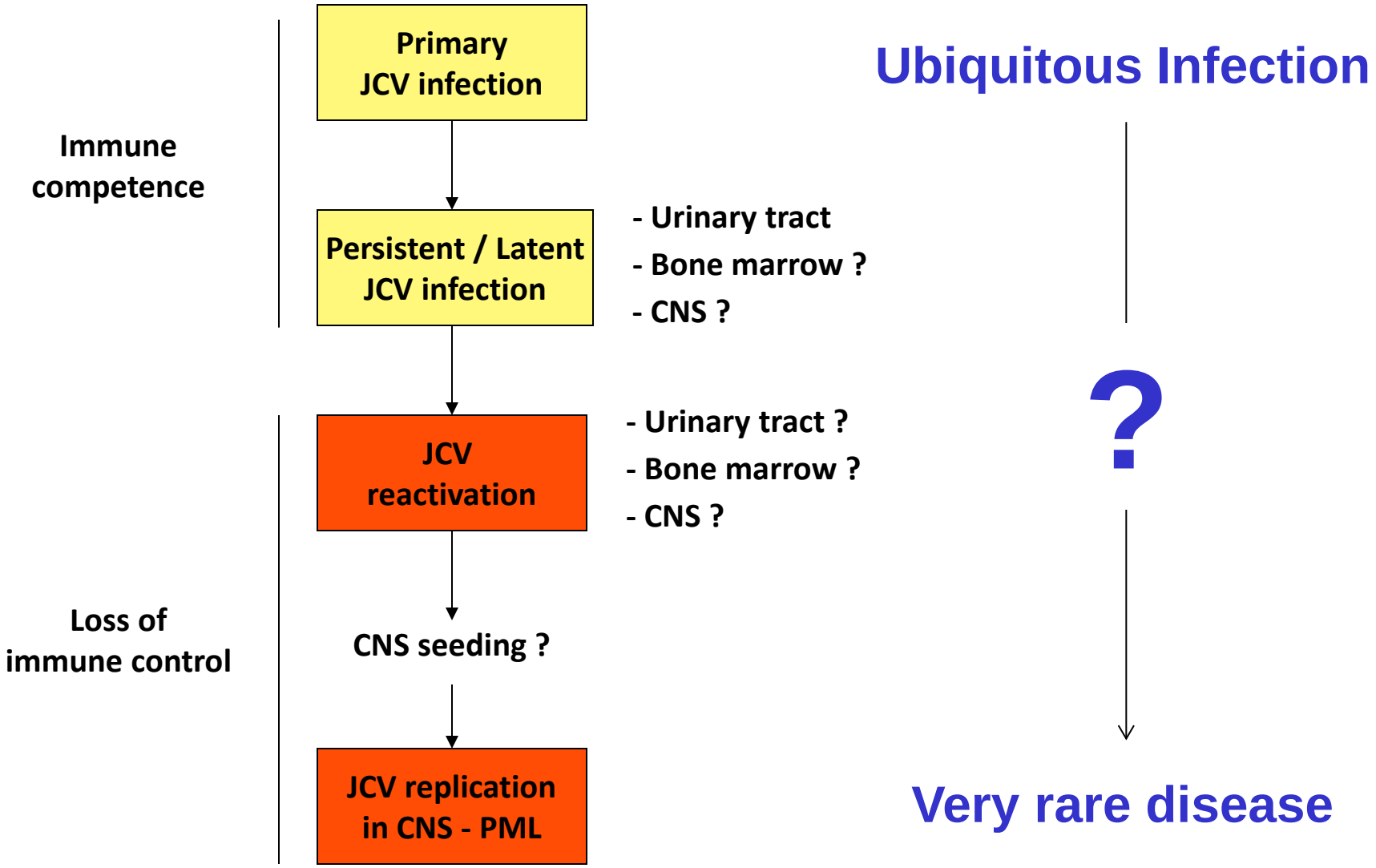
DNA amplification







Natural history of JCV infection and PML



JCV VP1 genotypes

TYPE	cons. Cubitt	1A	1B	2A1	2A2	2B/D2	2E	3A/B	4	6	7A	7B1	7B2	8A/B
12	D	D	D	D	D	D	D	D	D	D	D	D	D	H
37	I	I	I	I	I	I	I	I	I	I	I	I	V	I
74	N	N	S	N	N	N	N	N	N	N	N	N	N	N
75	K	R	K	K	K	K	K	K	K	K	K	K	K	K
113	I	I	I	L	L	I	L	I	I	I	L	L	I	I
117	T	S	S	A	T	T	T	T	T	T	T	T	T	T
128	T	T	A	A	T	A	T	T	T	T	T	T	T	T
134	G	G	G	G	G	G	G	A	A	G	G	G	G	G
158	V	L	V	V	V	V	V	V	V	V	V	V	V	V
164	K	K	K	T	K	K	K	T	T	T	K	K	K	T
321	V	V	V	V	V	V	I	I	V	V	I	V	I	V
332	E	E	E	E	E	E	E	Q	E	E	E	E	E	E
345	R	K	R	R	R	R	R	R	R	R	R	R	R	R

- Polymorphic region
- JCV VP1 genotyping mainly used for epidemiological purposes and studies on human migration
- No association between genotypes and PML