

FATTORI CONDIZIONANTI E PREDITTIVI DELLA SOPRAVVIVENZA DEL RENE TRAPIANTATO

Le infezioni virali intra ed extra renali

Fabrizio Ginevri

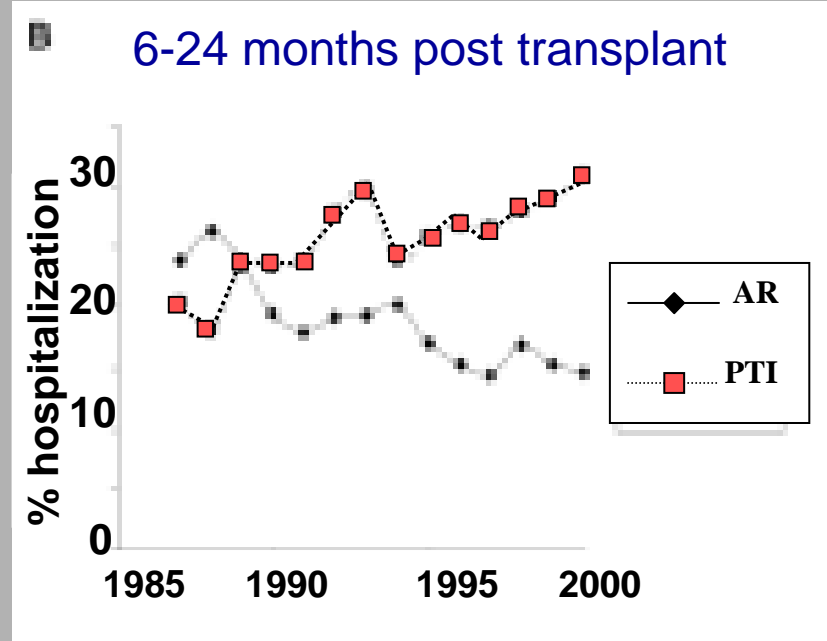
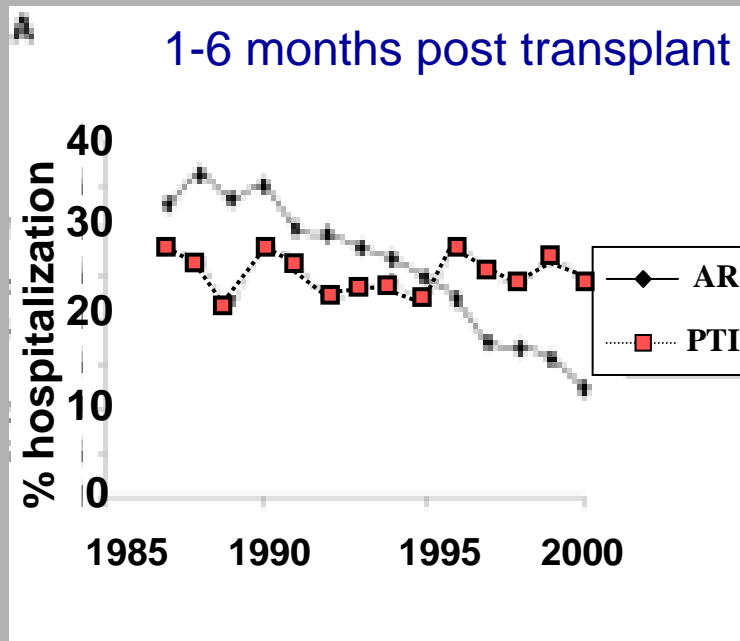
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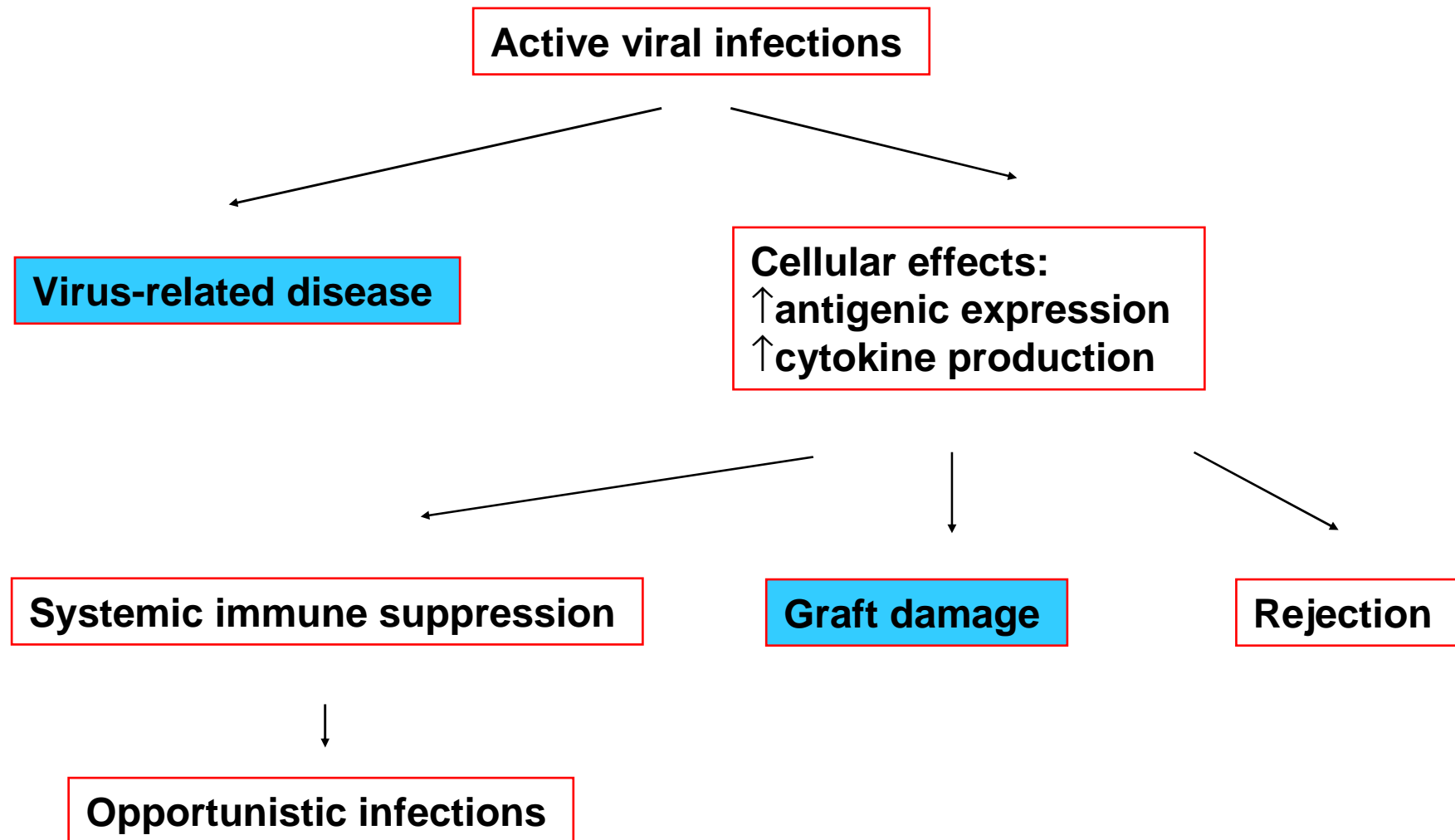
24-26 Ottobre 2012

Hospitalization causes after kidney Tx (1987-2000)



Viral infections after kidney transplantation:

clinical effects



Viral infections after KTx

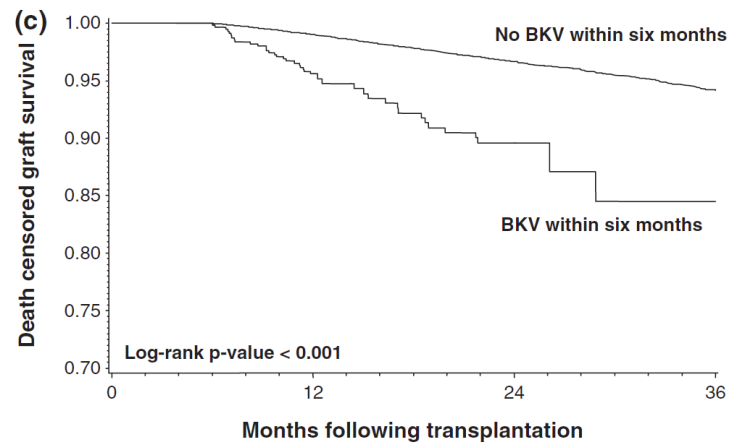
- Herpesviruses:
 - EBV
 - CMV
 - HHV8
 - HHV6-7
 - VZV
- Polyomaviruses
 - BKV
 - JCV
- Hepatitis viruses
 - HBV
 - HCV
- HIV, HTLV
- Adenovirus
- Parvovirus B19
- RSV
- Bocavirus
- Rotavirus
- West-Nile virus
- LCMV
- Coronavirus
- Parainfluenzavirus
- Mumps/Measles

Direct and indirect effects of virus replication

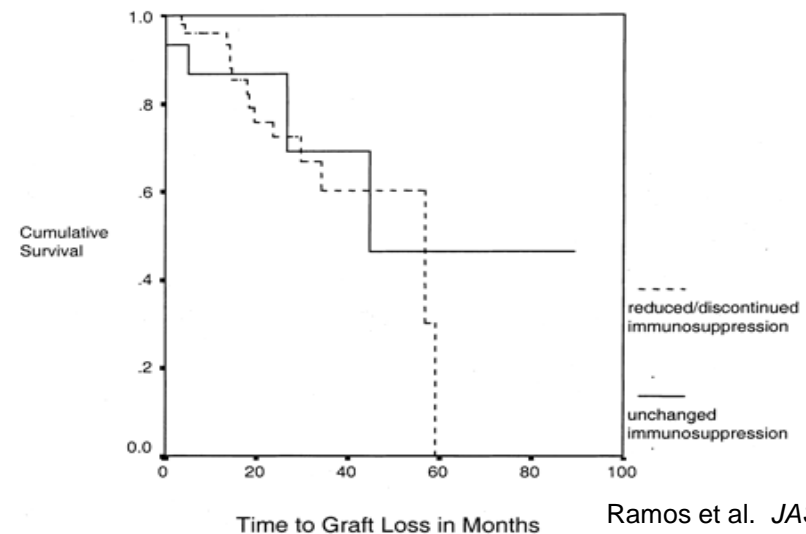
Table 1 Direct and indirect effects of virus replication in solid-organ transplant recipients					
	Adenovirus	Polyomavirus BK and JC	Cytomegalovirus	Human Herpesvirus-6 and -7	Parvovirus B19
Direct	Nephritis Cystitis Hepatitis	PyVAN Cystitis Ureter stenosis PML	Colitis Hepatitis Pneumonitis Nephritis Retinitis	Encephalitis Hepatitis Pneumonitis Colitis?	Anemia Enteritis Nephritis Collapsing glomerulopathy
Indirect	Bronchiolitis obliterans	Acute rejection?	Graft rejection Coinfection Allograft nephropathy Cardiac allograft vasculopathy Vanishing bile duct syndrome Bronchiolitis obliterans Posttransplant lymphoproliferative disorder Chorioretinitis uveitis	Graft rejection Coinfection Allograft nephropathy?	Glomerulonephritis Chronic allograft nephropathy Acute rejection?

BKV infection after KTx: PyVAN

- **Incidence rate 5% after kidney transplantation** (range 1-10%)
 - ✓ Graft loss in ~50% (range 10% - 90%)
- **No effective antiviral drug**
- **Treatment by reducing immunosuppression:**
 - ✓ 35-50% of PyVAN treated with any protocol → marked graft dysfunction, with possible progression to graft loss;



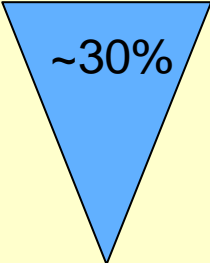
Schold et al. *Transpl Int* 2009



Ramos et al. *JASN* 2002

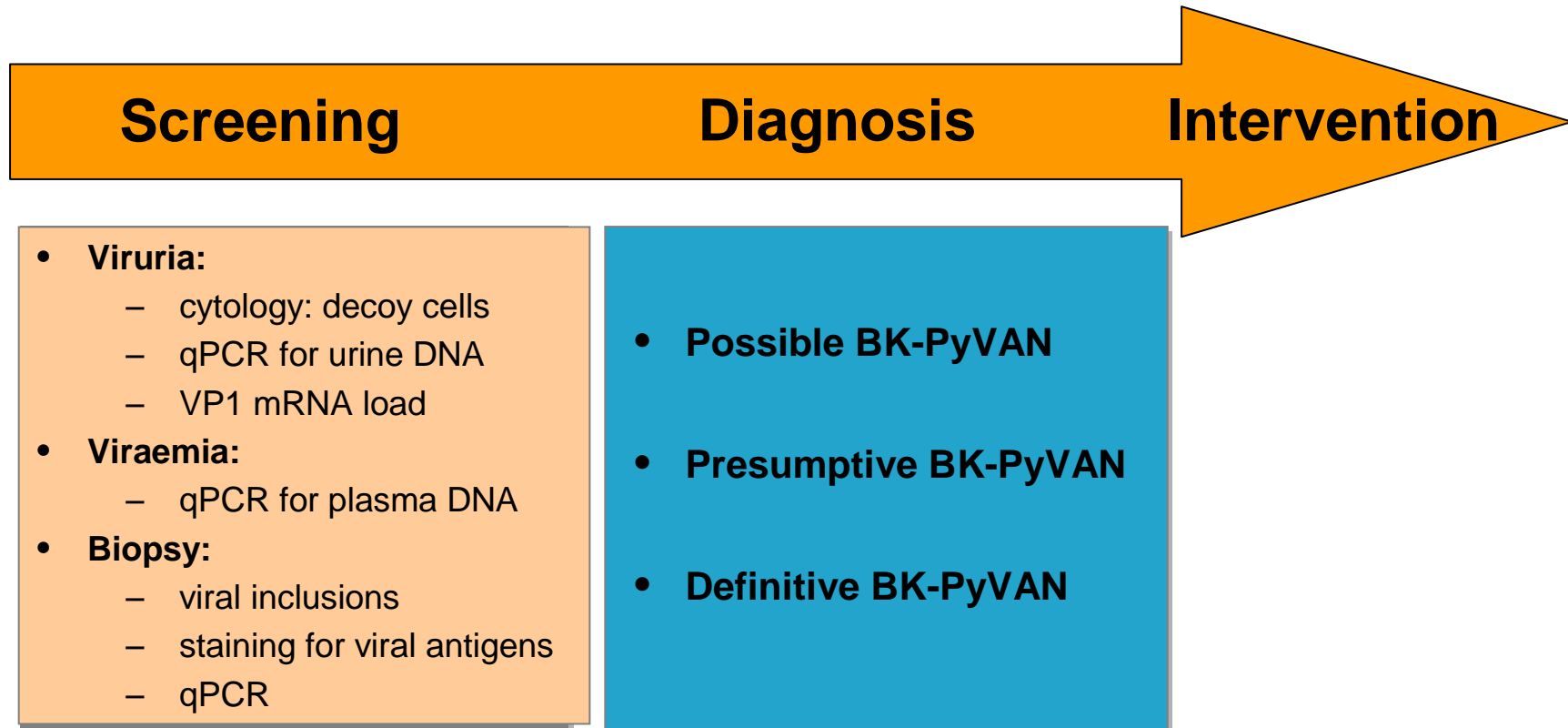
BKV infection after KTx: PyVAN

- **Extent and pathology of PyVAN correlate with graft loss**


Graft function	Risk of false negative on biopsy	BK-PyVAN pathology / stage	Risk of graft loss
Mostly baseline	 ~30%	A	<15%
Mostly impaired		B	50%
Significantly impaired / progressive failure		C	>80%

Drachenberg CB *et al. Am J Transplant* 2004
Hirsch HH *et al. Am J Transplant* 2009;9(Suppl 4)

BKV screening : available options



BKV screening : intervention indicators

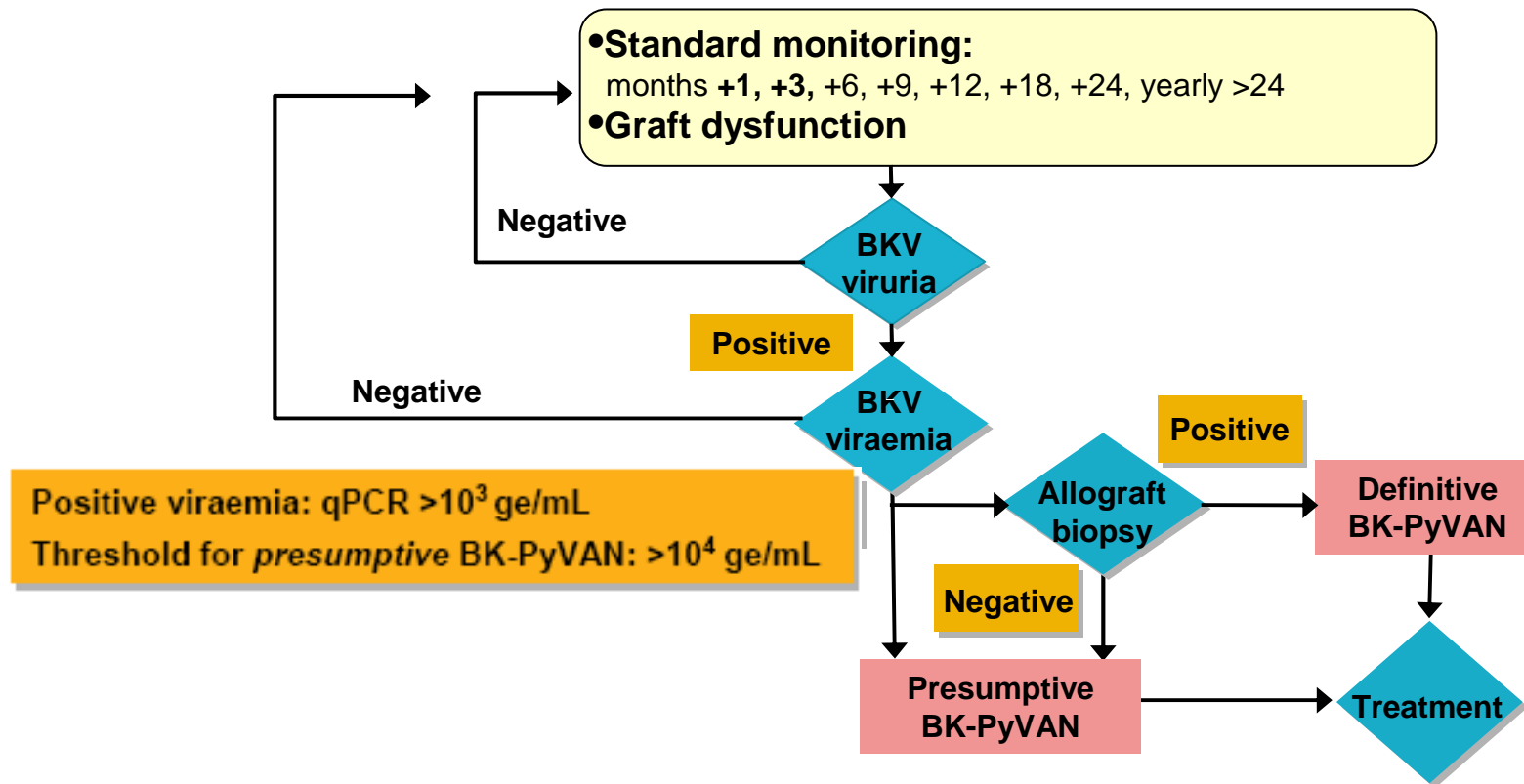
	Possible BK-PyVAN	Presumptive BK-PyVAN	Definitive BK-PyVAN
Indicator	Viruria	Viruria + viraemia	Viruria, viraemia + BK-PyVAN
Screening test	+	+	+
Adjunct test	–	+	+
Biopsy	–	–	+
			
Intervention	No	Consider	Yes

Hirsch HH *et al. Transplantation* 2005;79:1277–86;

Ramos E *et al. Transplantation* 2009;87:621–30;

Ginevri F, Hirsch HH. Chapter 26 in *Evidence-Based Nephrology* (Molony DA, Craig JC) 2008

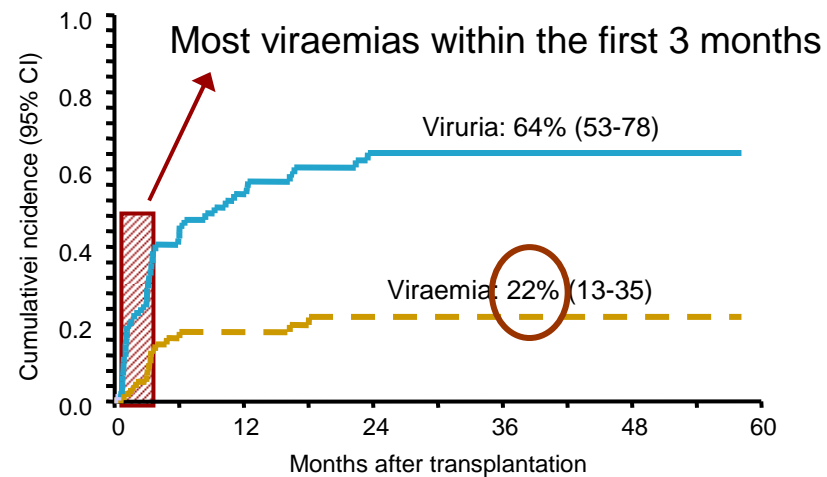
Italian pediatric clinical experience: prospective screening and treatment of presumptive PyVAN



- **Further screening in case of positive viraemia**
 - Augment frequency of screening to assess sustained replication
 - 2–4 week screening until viral clearance
- **Screening after therapeutic intervention**
 - To assess response to treatment
 - 2–4 week screening until viral clearance

Italian pediatric clinical experience: prospective screening and treatment of presumptive PyVAN

- 62 pediatric KTx recipients referred between 01/02 and 08/05:
 - BKV infection monitoring
 - BKV immunity monitoring



Treatment of *presumptive* PyVAN: IS reduction

	Brennan et al (n=200)	Ginevri et al (n=62)	Saad et al (n=24)
Patients with viraemia			
Number (%)	23 (11.5)	13 (20.9)	24 (100)
Type	Adult	Paediatric	Adult
Intervention	Step 1: Discontinue AZA or MMF Step 2. Reduce CNi	Step 1: Reduce CNi Step 2: Reduce or discontinue MMF	Reduce CNi and MMF
Outcome at 1 year			
Clearance of viraemia	95% (22/23) patients	100%	100%
Mean (range) time to clearance	54 days (7–213)	2 months (1–8)	5.8 months (1–9.5)
BK-PyVAN incidence	No losses	No losses	1 BKV-related loss
Acute rejection, n (%)	1 (4.3)	0	3 (13%)

Brennan DC *et al.* *Am J Transplant* 2005;5:582–94;
 Ginevri F *et al.* *Am J Transplant* 2007;7:2727–35;
 Saad ER *et al.* *Transplantation* 2008;85:850–54

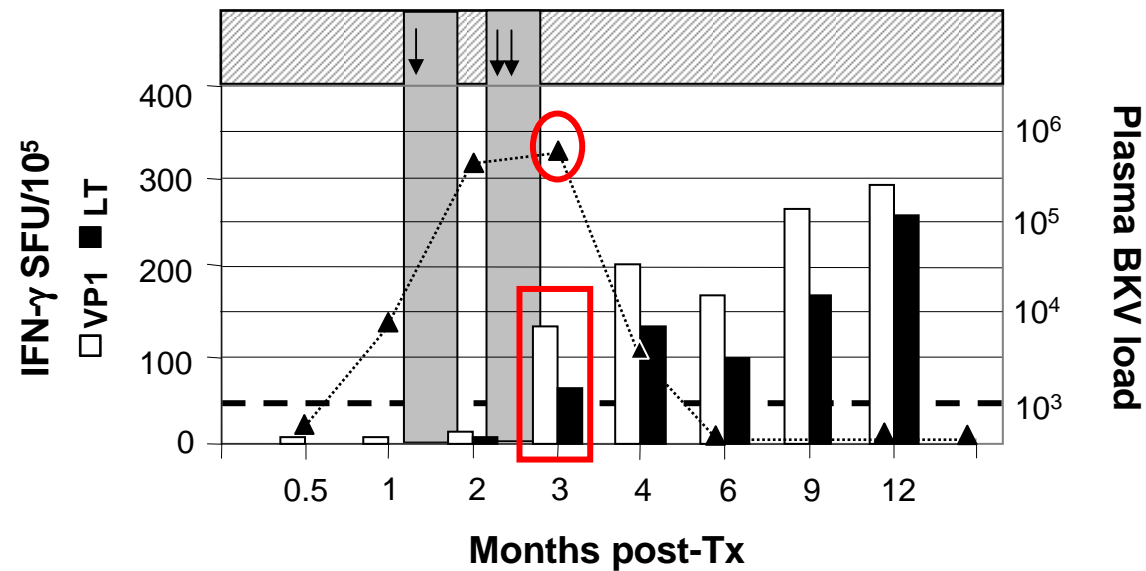
Italian pediatric clinical experience:

short term outcome

- Historical cohort: 100 patients evaluated retrospectively
 - 5/100 found viremic, 3 patient presented with concomitant BK-PyVAN
 - median sCr at onset 168 mmol/L
 - At follow-up:
 - 1 graft loss
 - the other 4 patients cleared viremia after therapeutic reduction: median sCr at f-up 141 mmol/L
- Screened cohort: 62 patients
 - No patient developed BK-PyVAN
 - 13/62 patients developed viremia
 - median sCr at onset 106 mmol/L
 - At follow-up, all patients cleared viremia
 - 7 patients cleared after protocol reduction of IS, 6 after therapeutic reduction
 - no episode of rejection observed
 - median sCr at f-up 80 mmol/L

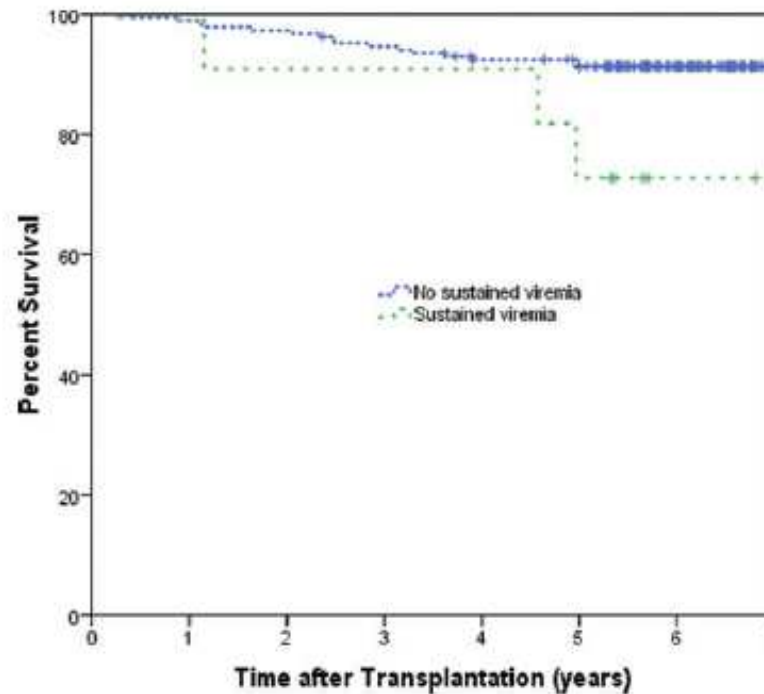
Monitoring of specific immunity in patients with BK viremia

Modulation of IS reduction according to cellular immunity analysis



Preemptive IS reduction: long term outcome in the US cohort

- Patient survival
 - worse overall patient survival in recipients who experienced sustained BK viremia (72% vs 91% in patients without sustained viremia)
 - graft survival at 5 yrs in the BKV sustained viremia group 73% vs 83% in pts without viremia

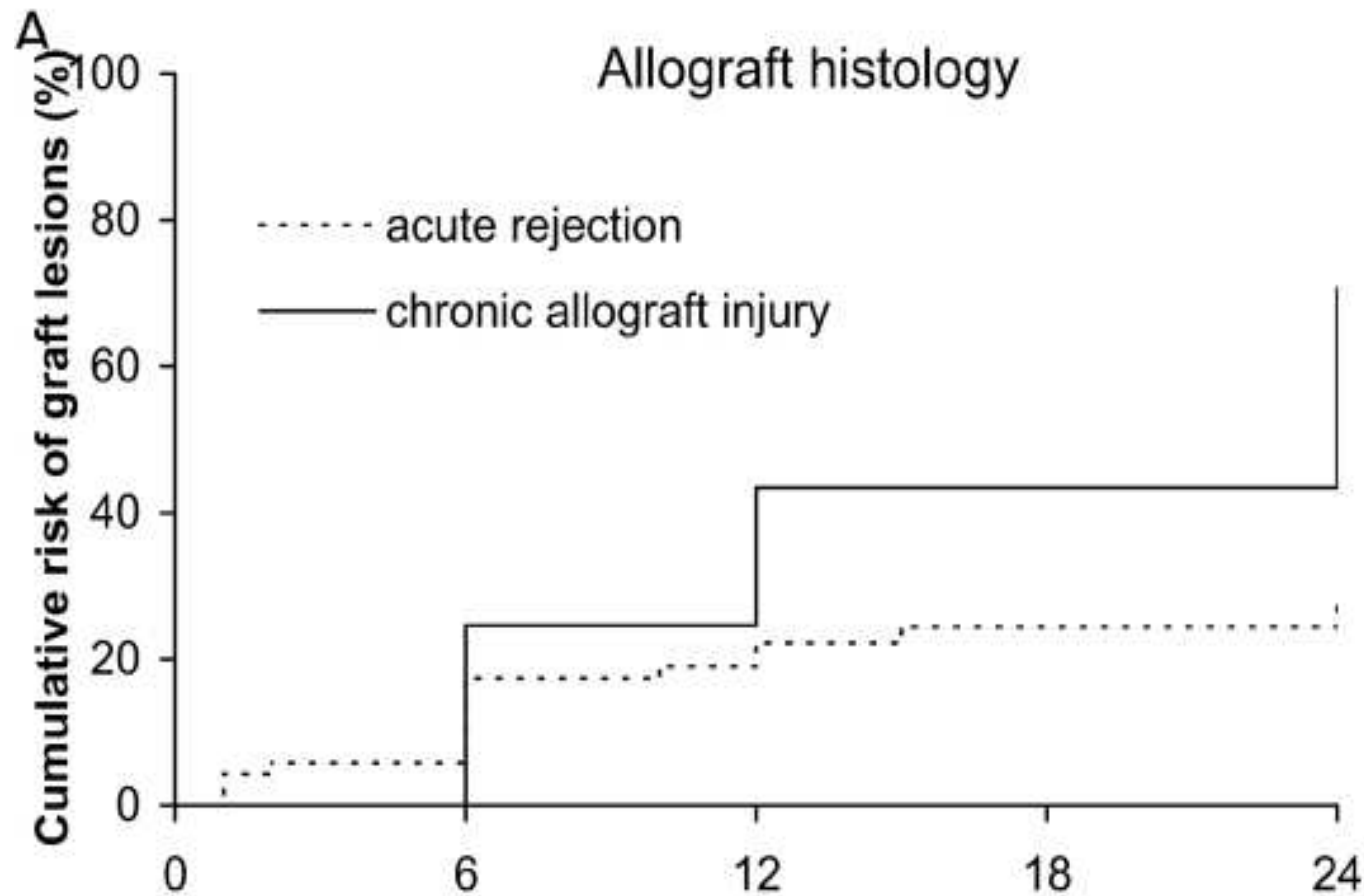


Hardinger *et al.* Am J Transpl 2010

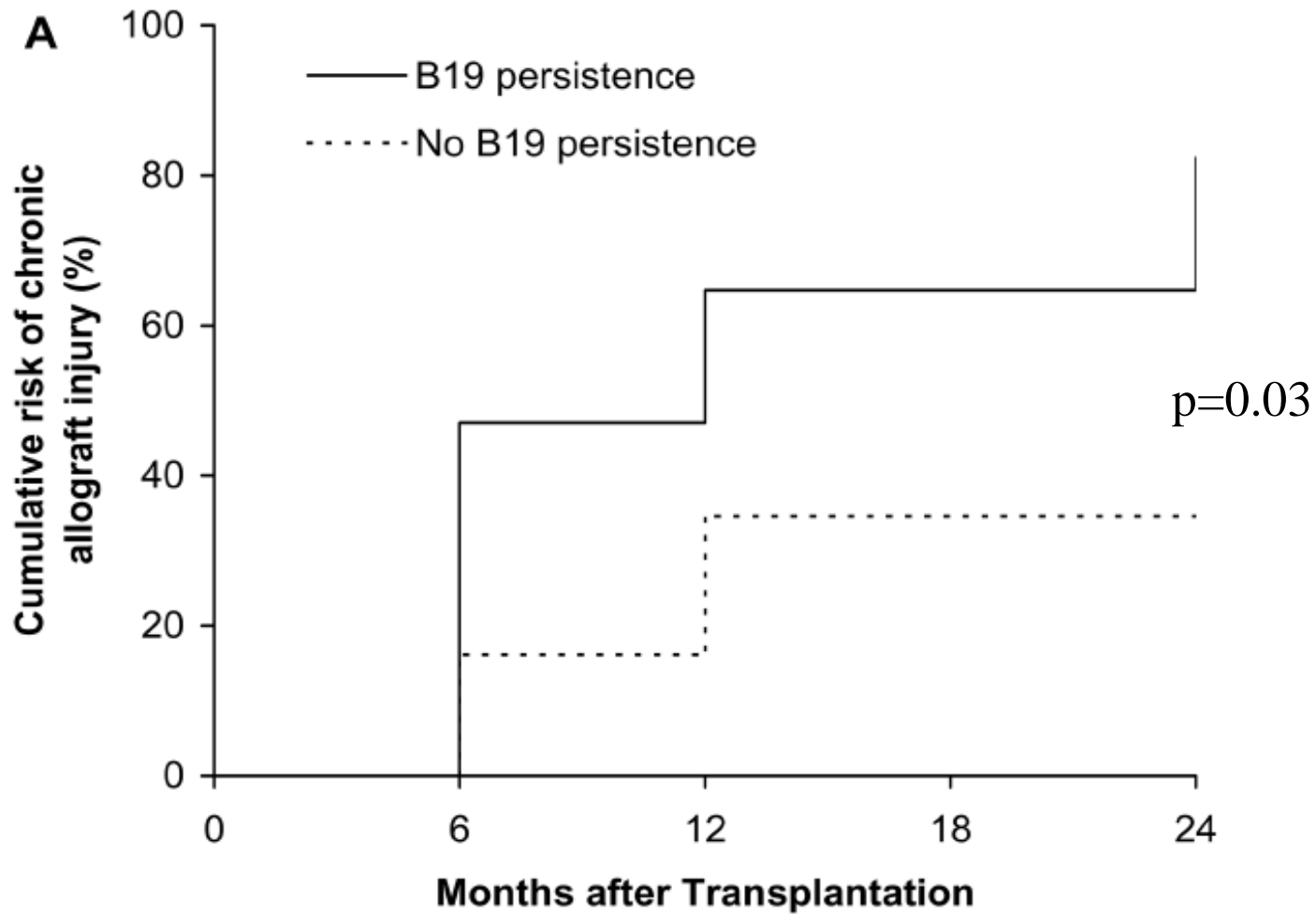
Intrarenal viral infections

Finding	Baseline (n = 57)	Follow-up		
		6 months (n = 69)	12 months (n = 64)	24 months (n = 45)
Viral genome detection in allograft				
Any virus	46	65	69	73
Coinfection	19	26	21	27
HCMV	0	3	0	0
EBV	0	11	12	20
HHV-6	25	25	22	23
HHV-7	2	5	3	5
HHV-8	0	2	2	2
HSV-1	0	0	0	0
HSV-2	0	0	0	0
VZV	0	0	0	0
BKV	5	17	24	20
JCV	0	2	2	2
B19	35	31	33	32

Impact of viral infections on KTx

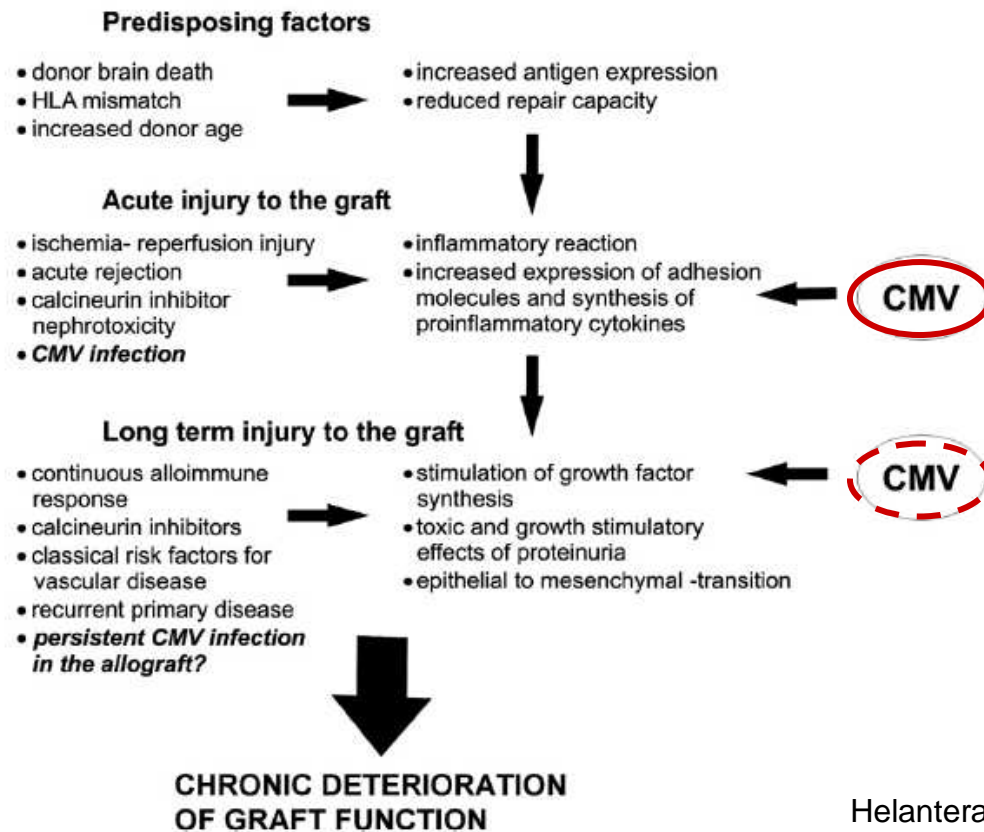


Impact of parvovirus B19 on KTx



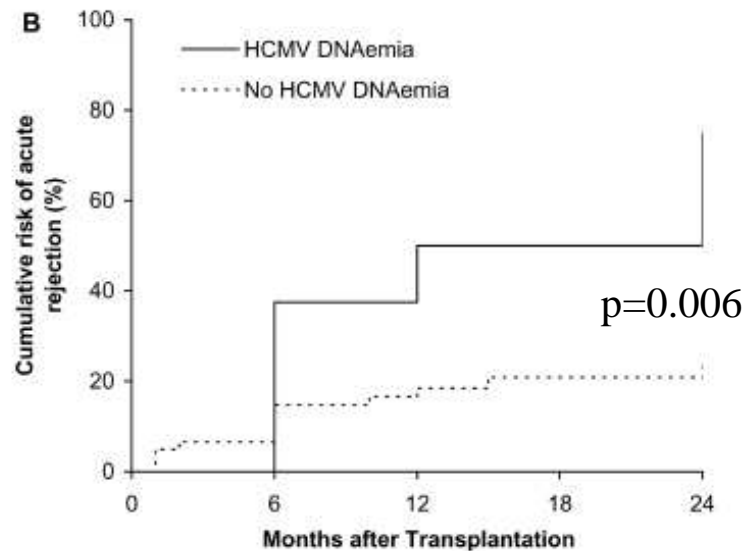
Viral infections after KTx: CMV

- **CMV infection:** the most common viral infection after SOT
 - CMV-disease: tissue-invasive (GI, lung) plus indirect effects (graft dysfunction)
 - Antiviral drugs: available and effective

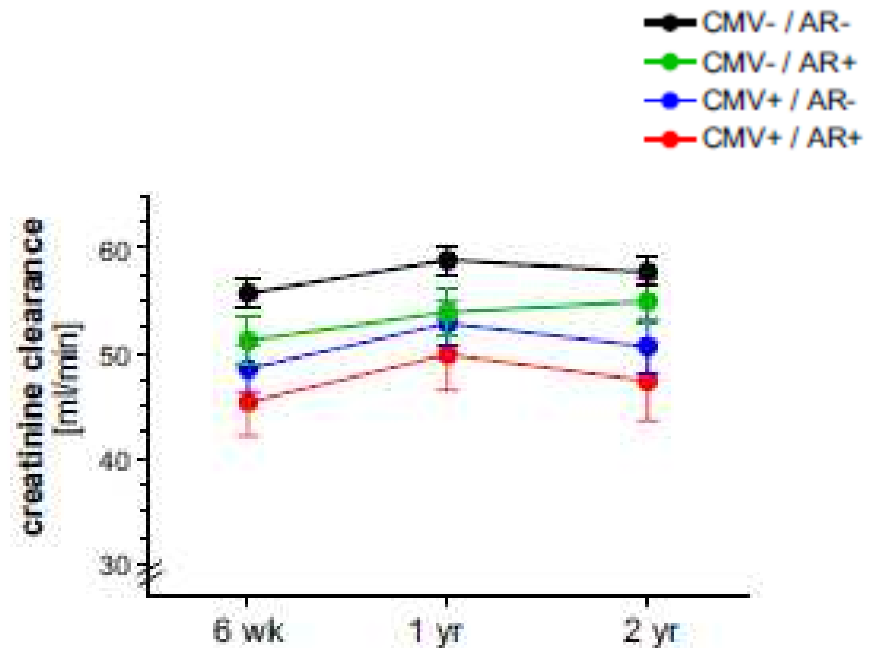


Impact of CMV infection on KTx:

acute rejection



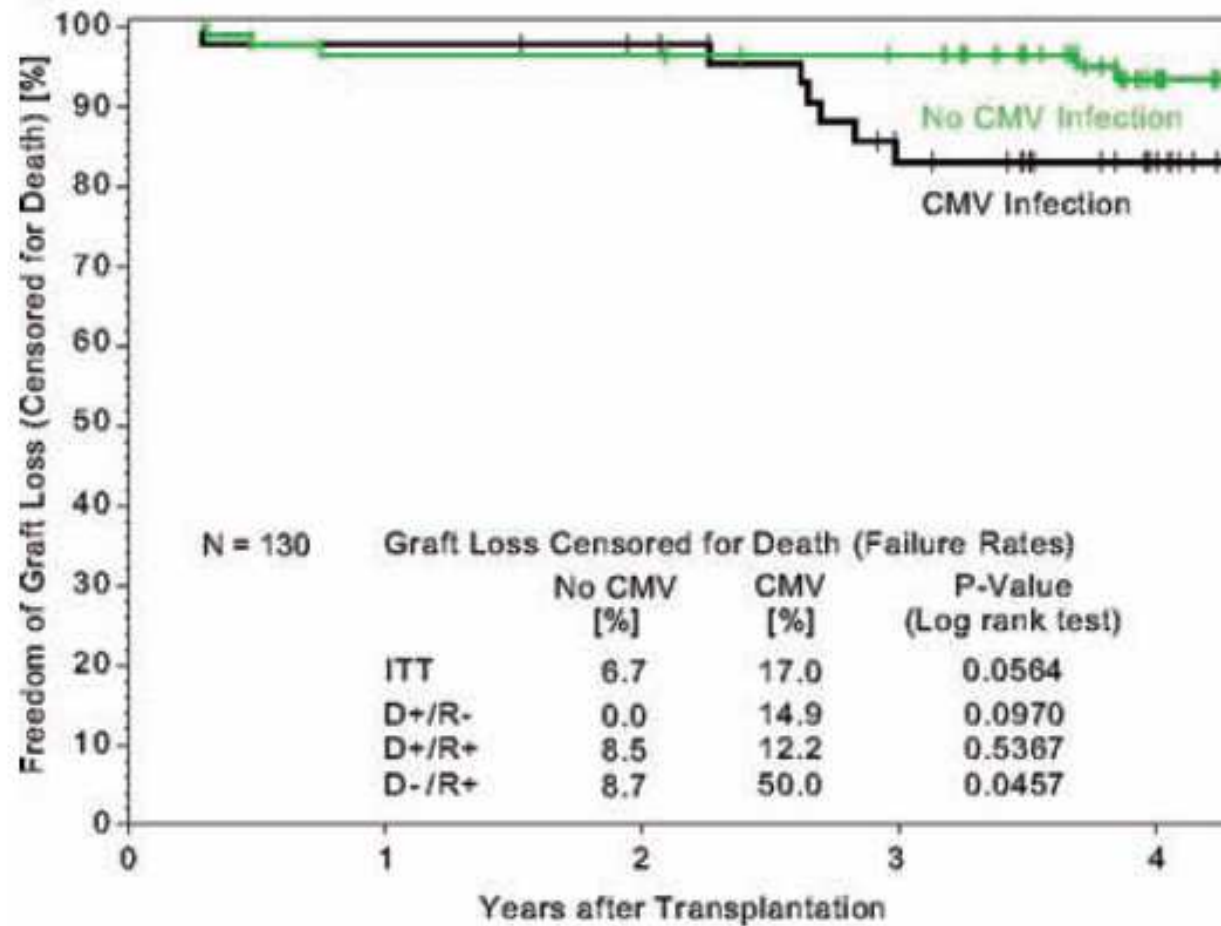
Barzon *et al.* J Infect Dis 2009



Erdbruegger *et al.* Nephrol Dial Transplant 2012

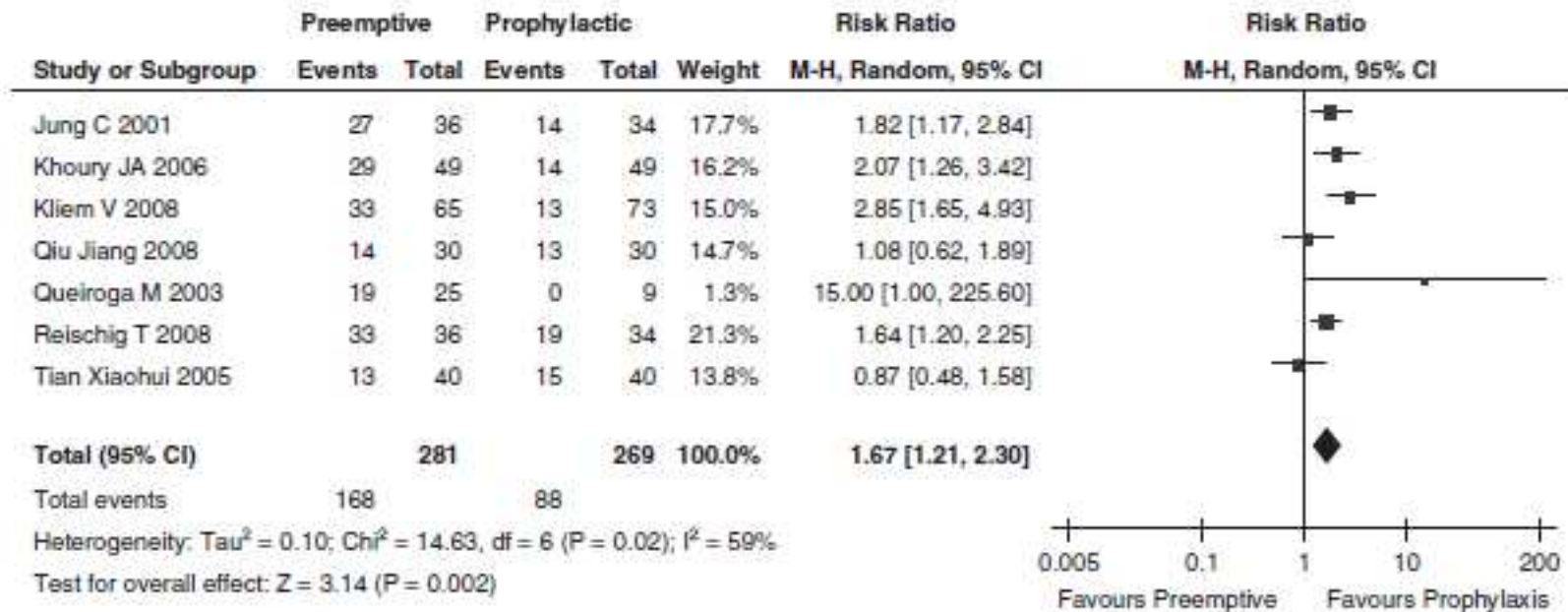
Impact of CMV infection on KTx:

long term outcome



Treatment choice for CMV infection after KTx:

preemptive therapy vs prophylaxis

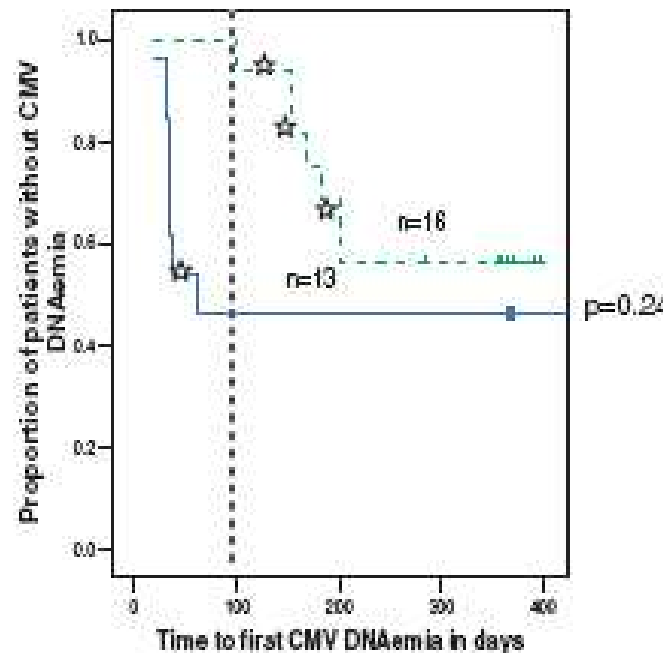


Treatment choice for CMV infection after KTx:

CMV disease after prophylaxis discontinuation

D+/R- patients are, in the majority of cases, managed with a prophylactic therapeutic strategy, due to the risk profile

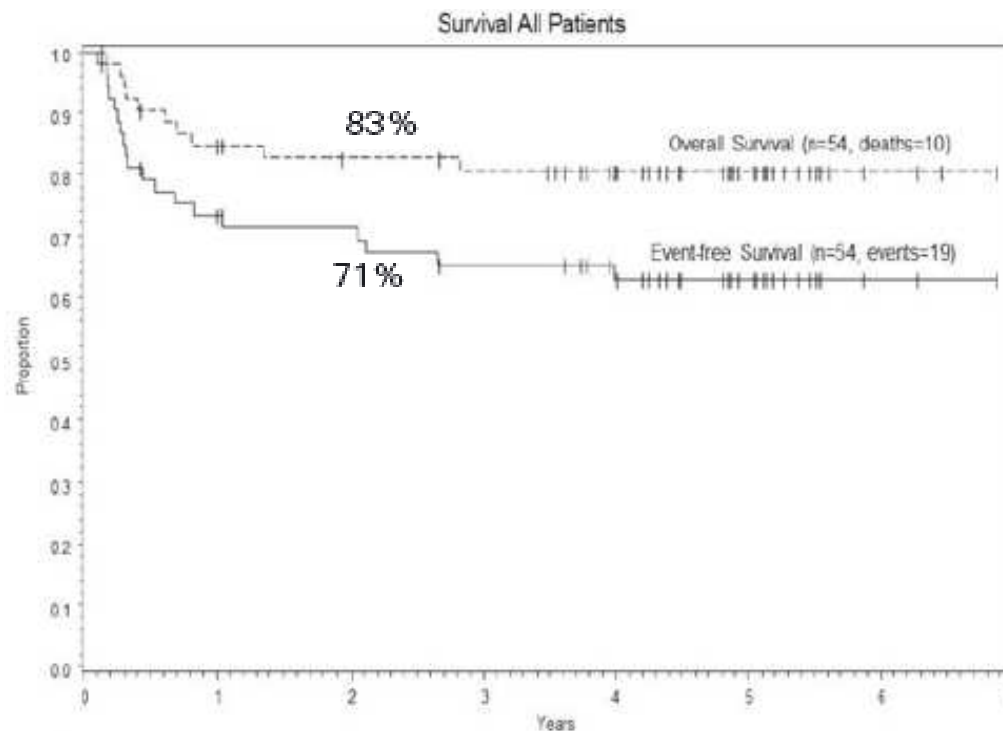
High incidence of late onset CMV disease in D+/R- KTx recipients, after discontinuation of antiviral prophylaxis



Khoury *et al.* Am J Transplant 2006
Paya *et al.* Transplantation 2004

Viral infections after KTx: EBV

- **EBV-related disease: PTLD**
 - incidence rate of 1-3% after kidney transplantation
 - severe condition: reduced survival of host and graft



Events: 19

PTLD progression 8

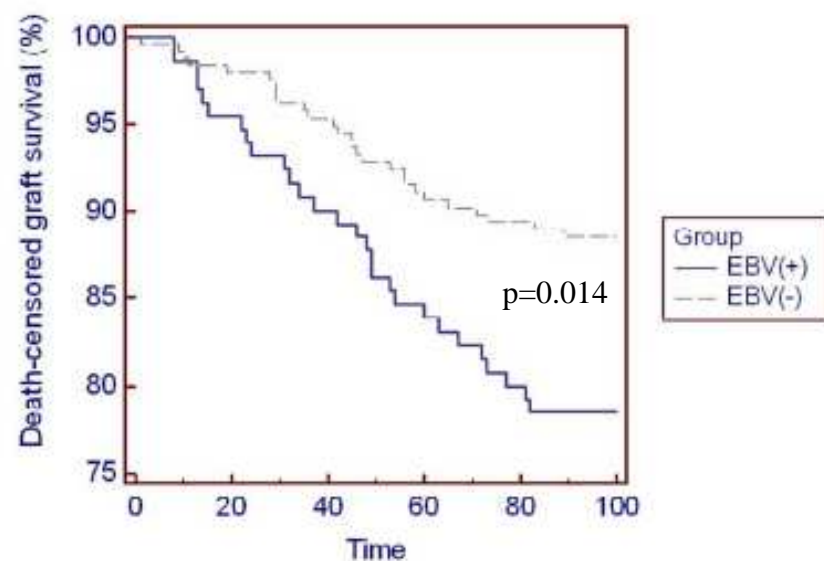
Relapse after CR 3

Graft loss 5

Infections 3

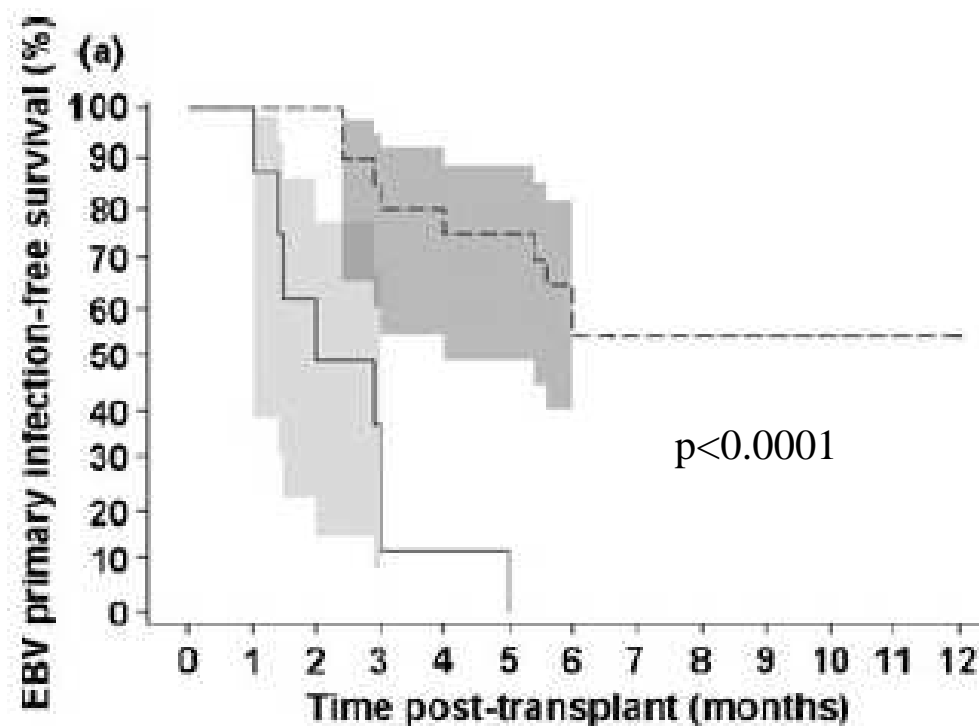
Viral infections after KTx: EBV

- **Effect of EBV on long term outcome: ?** Limited evidence to date



Viral infections after KTx: EBV

(Val-)Ganciclovir reduces EBV primary infection



Viral infections after KTx: conclusions

- Viral infections have emerged as important modifiers of graft function and survival after transplant.
- While the role of CMV, BKV and ADV in acute and chronic injury is clearly recognized, other suspects such as EBV, HHV-6 and PVB19 require further studies.
- Antiviral prophylaxis and screening and intervention algorithms have been found valuable for CMV and BKV
 - similar approaches are largely lacking for EBV, ADV, HHV-6, and PVB19, as the significance of viral DNA detection and pathology is less well understood
- Future studies are needed to address these open issues.