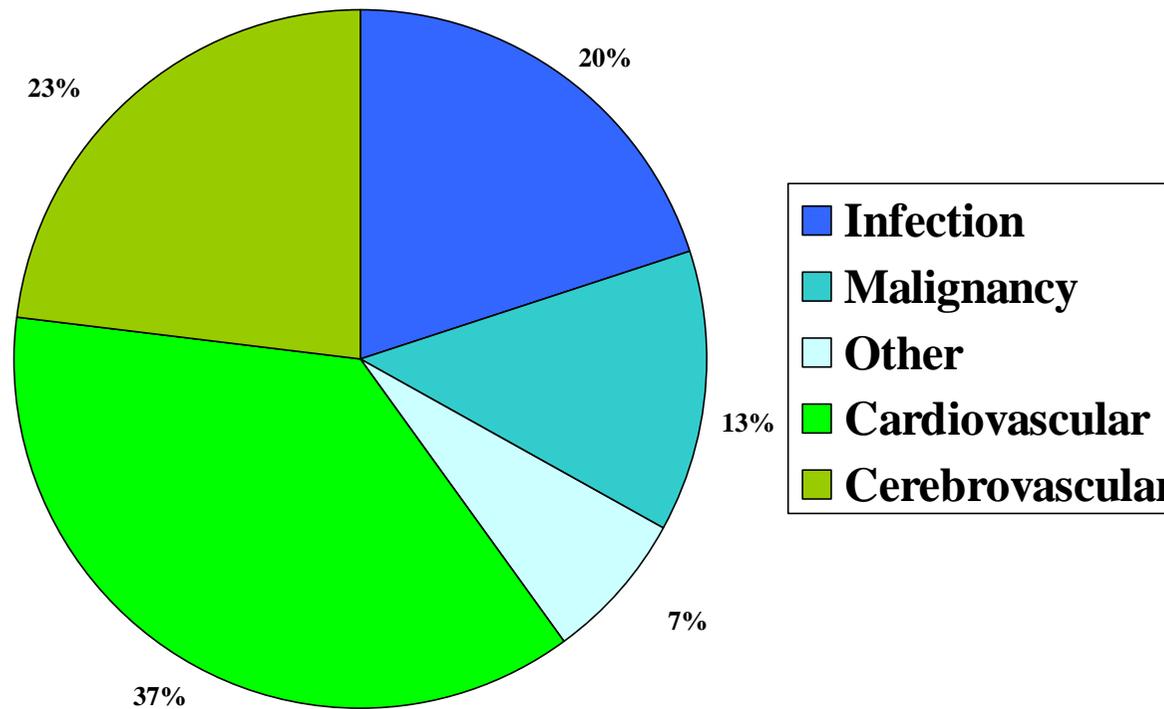


# Infections in renal transplantation



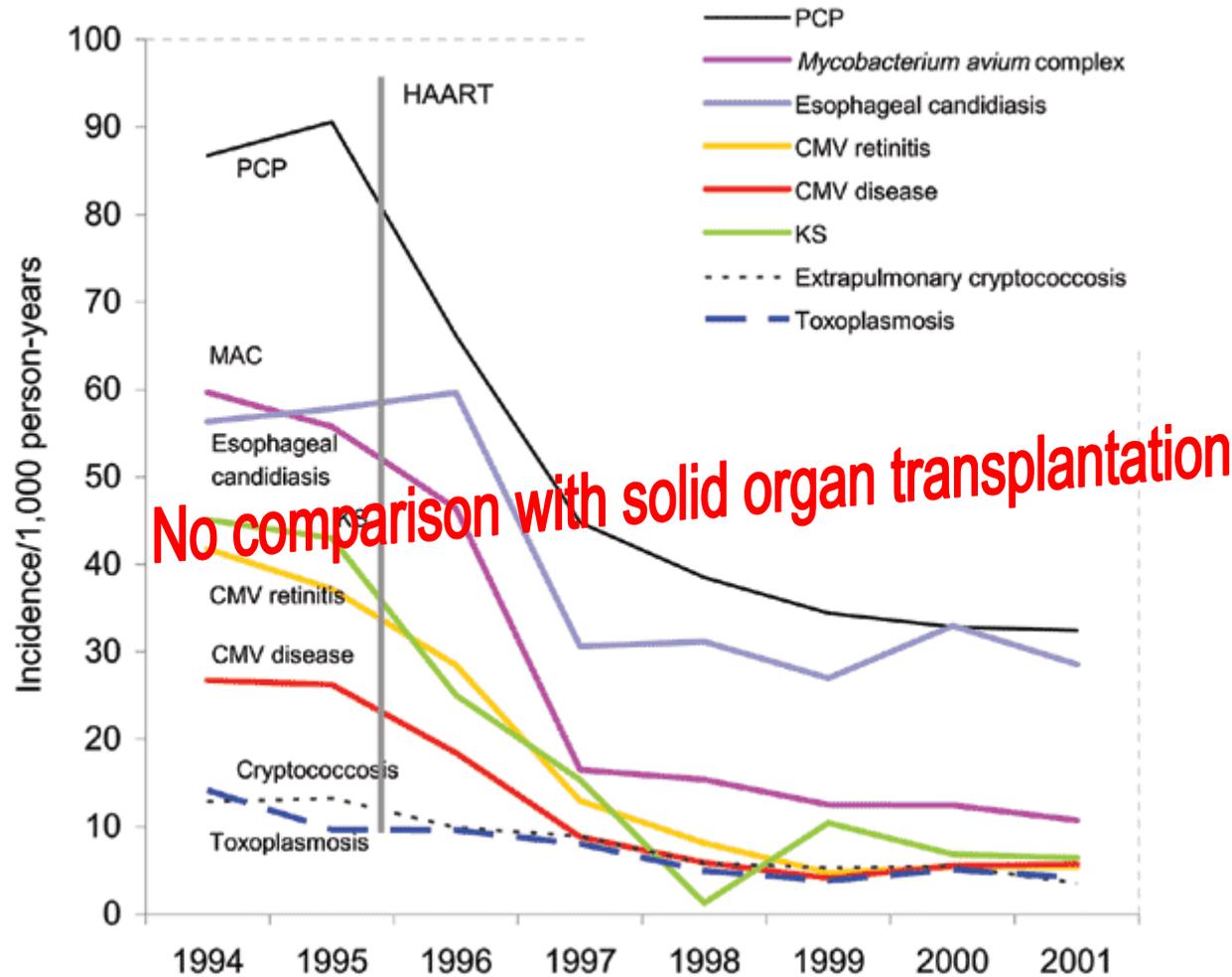
S. Van Laecke,  
University Hospital of Ghent, Belgium

# Mortality following kidney transplantation

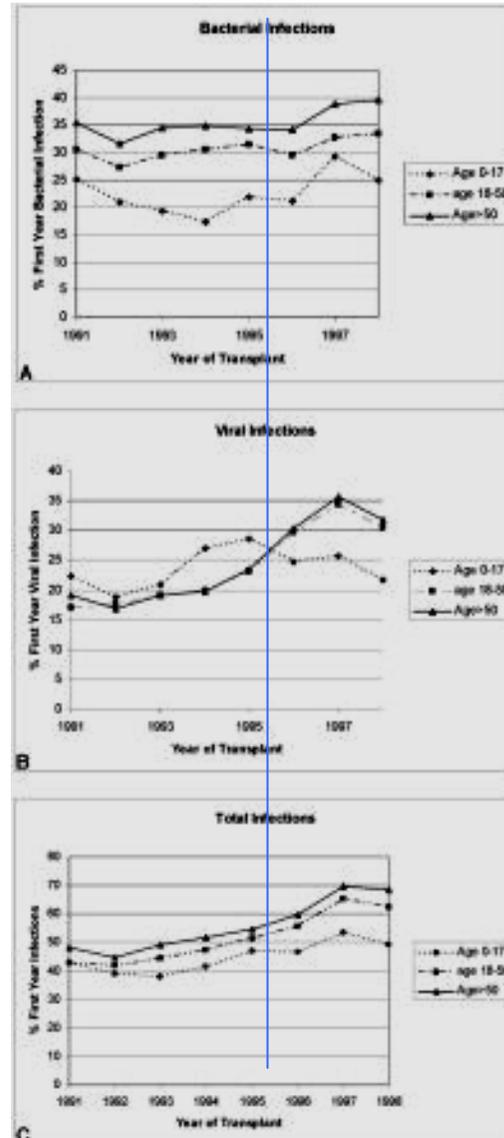


# INFECTION rate IN HIV....

Yearly opportunistic infection rates per 1,000 person-years



# ....Not close to infection rate in kidney transplants in the nineties



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**TABLE 1. FACTORS AFFECTING THE NET STATE OF IMMUNOSUPPRESSION IN TRANSPLANT RECIPIENTS.**

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Immunosuppressive therapy: dose, duration, and temporal sequence

Underlying immune deficiency: autoimmune disease, functional immune deficits

Integrity of the mucocutaneous barrier: catheters, epithelial surfaces

Devitalized tissue, fluid collections

Neutropenia, lymphopenia

Metabolic conditions

Uremia

Malnutrition

Diabetes

Alcoholism with cirrhosis

Infection with immunomodulating viruses

Cytomegalovirus

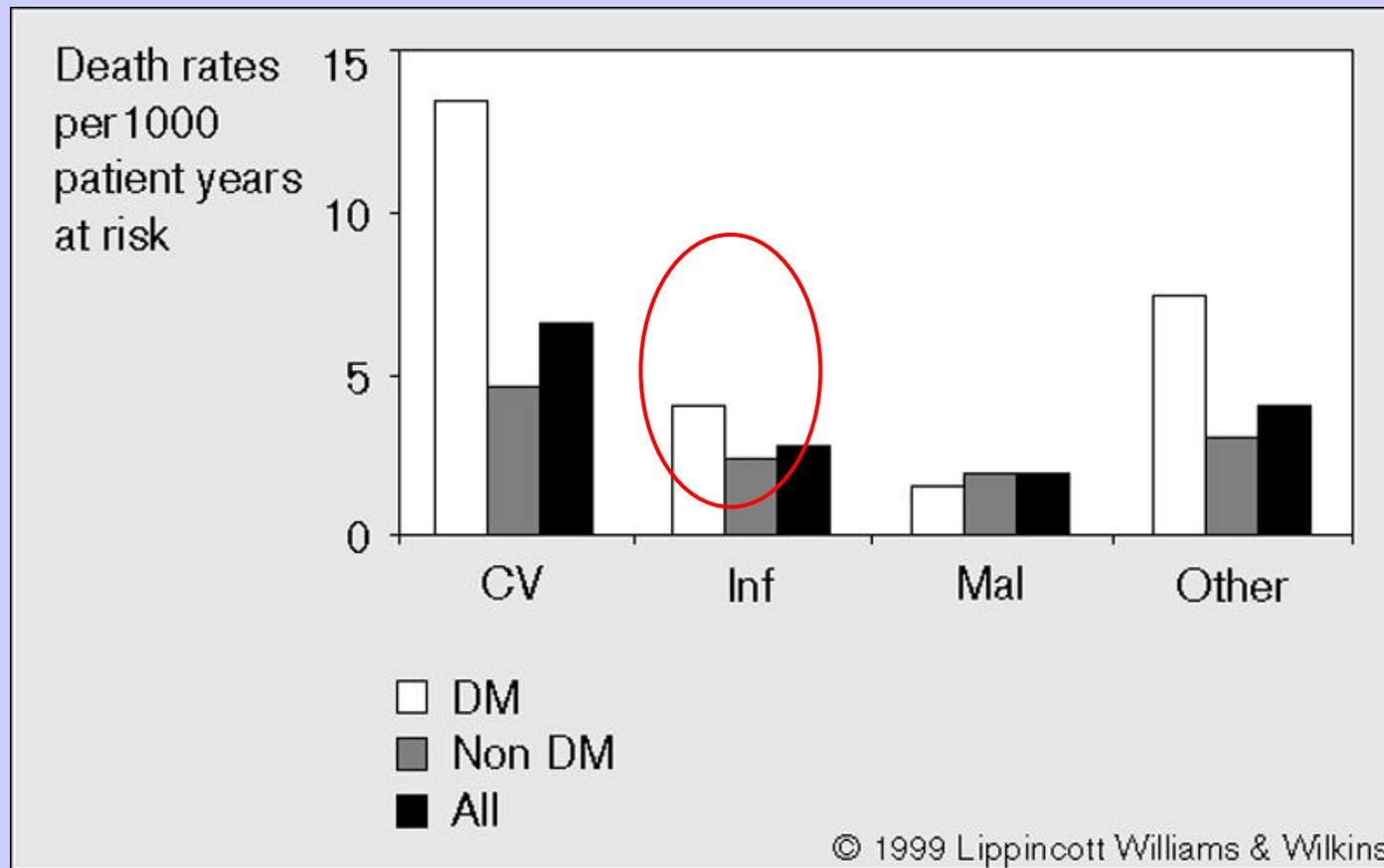
Epstein-Barr virus

Hepatitis B and C viruses

Human immunodeficiency virus

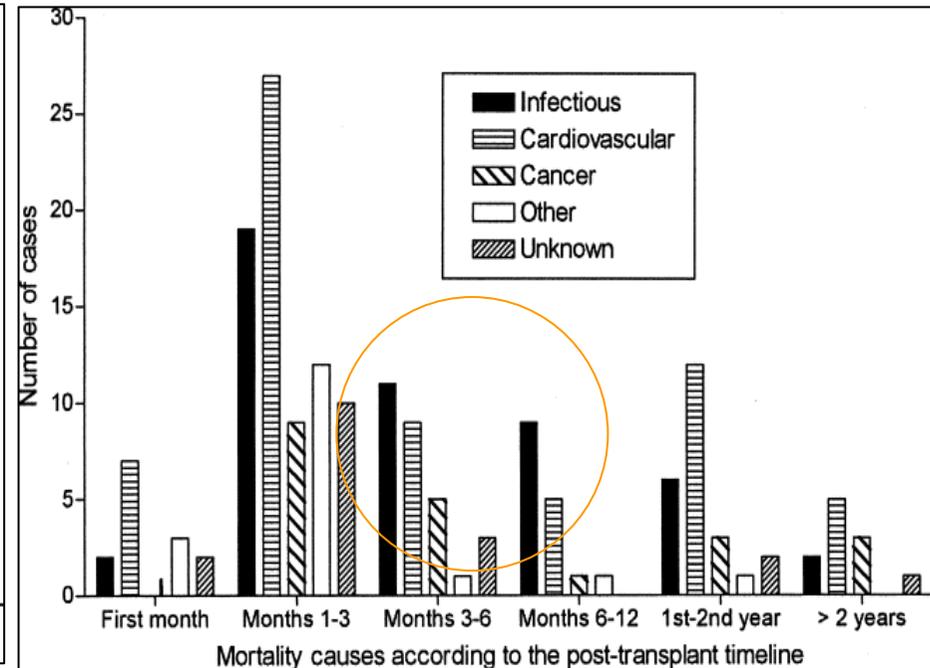
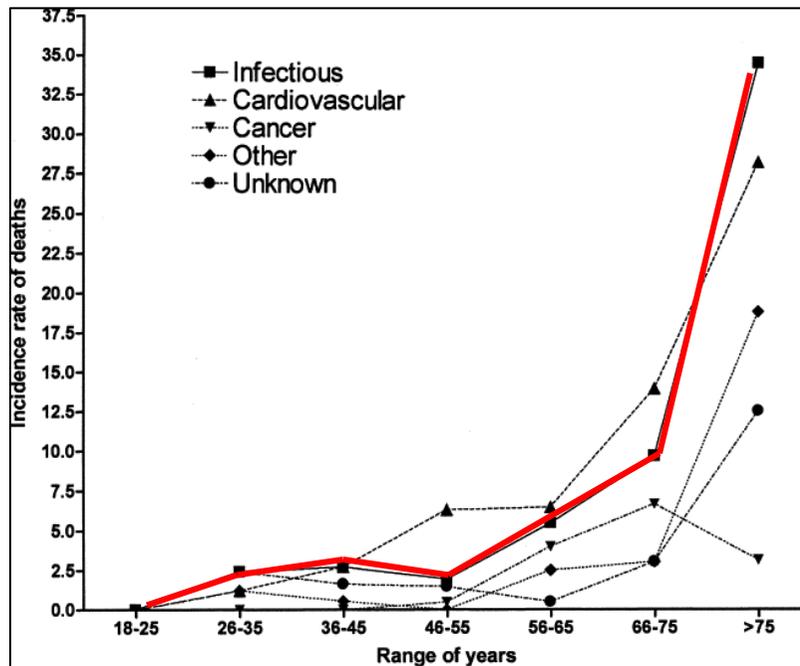
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# Causes of death and death rates in renal transplant patients.

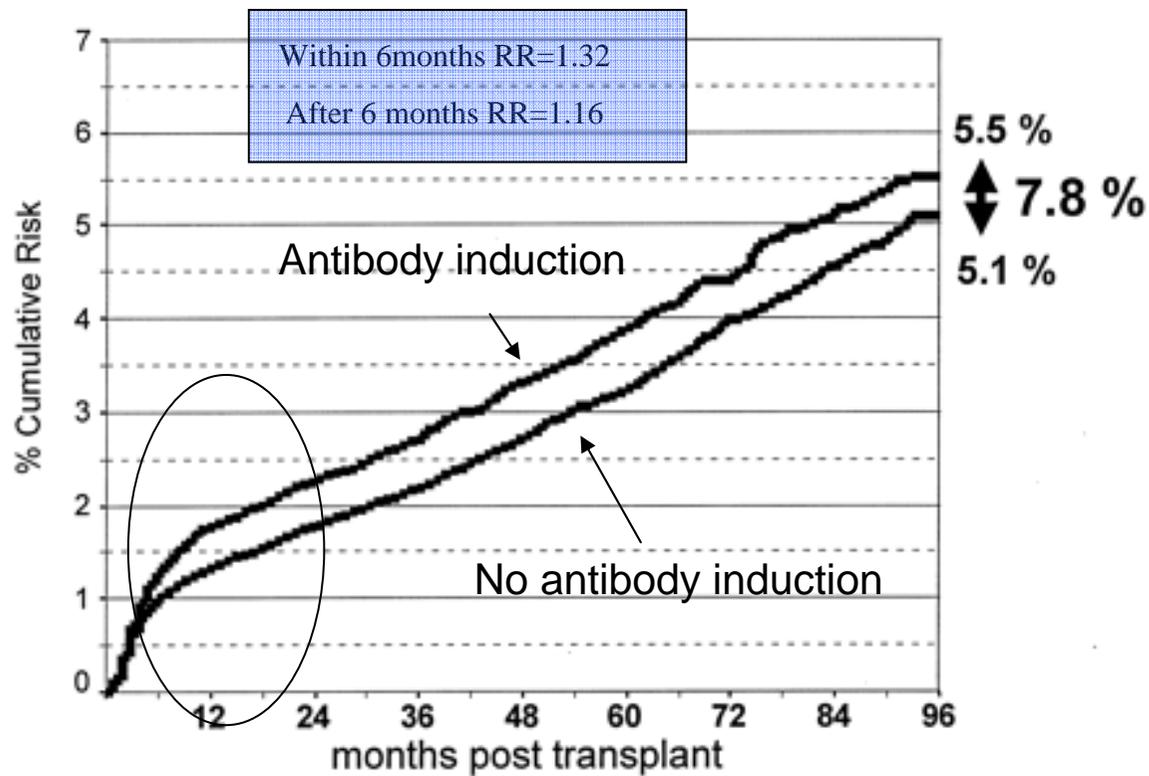


United States Renal Data System. USRDS 1998 Annual Data Report

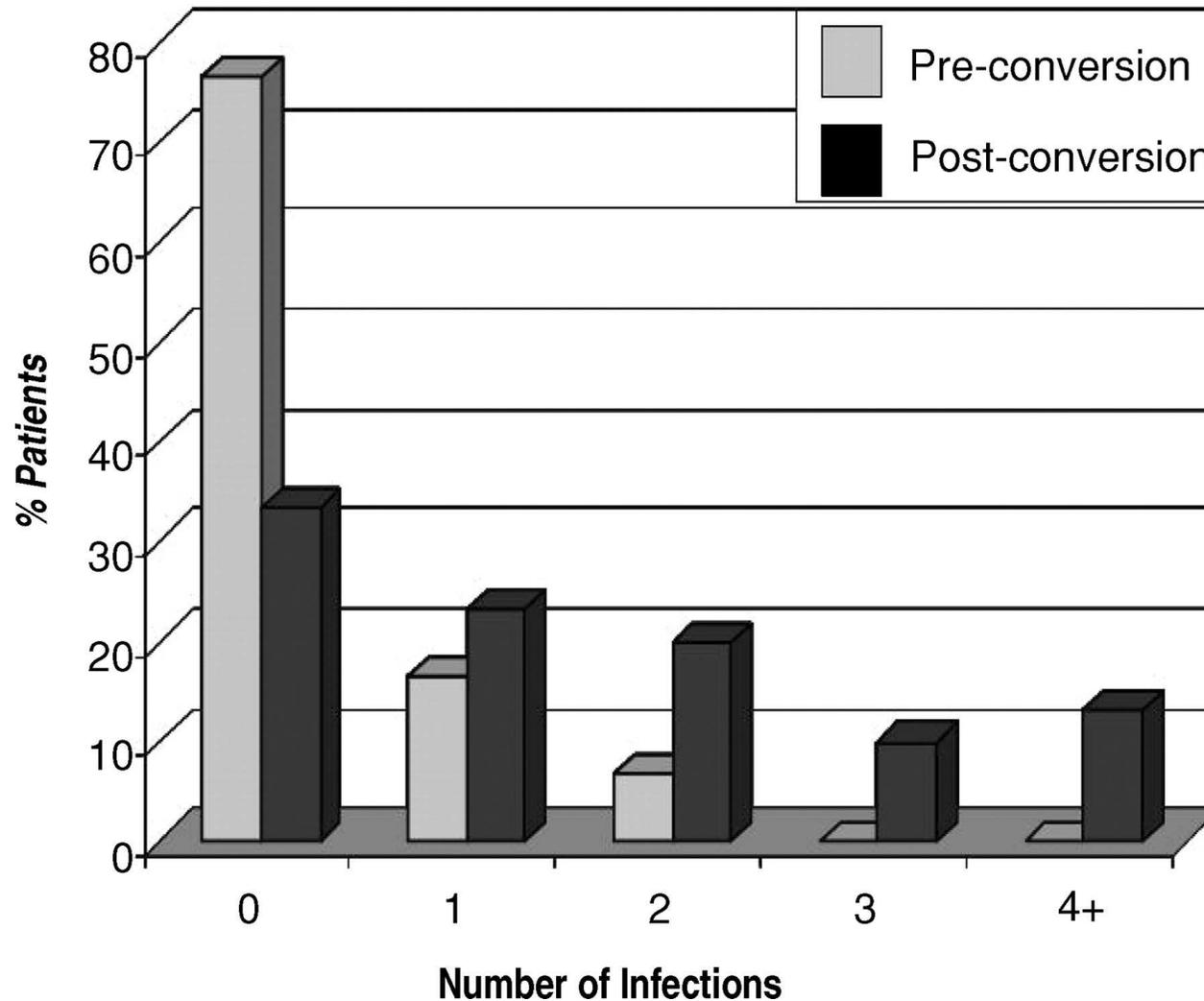
# Infection-Related Mortality in a Large Cohort of Renal Transplant Recipients



# Cumulative Risk for Infection-related Death Post Transplant: Antibody Induction



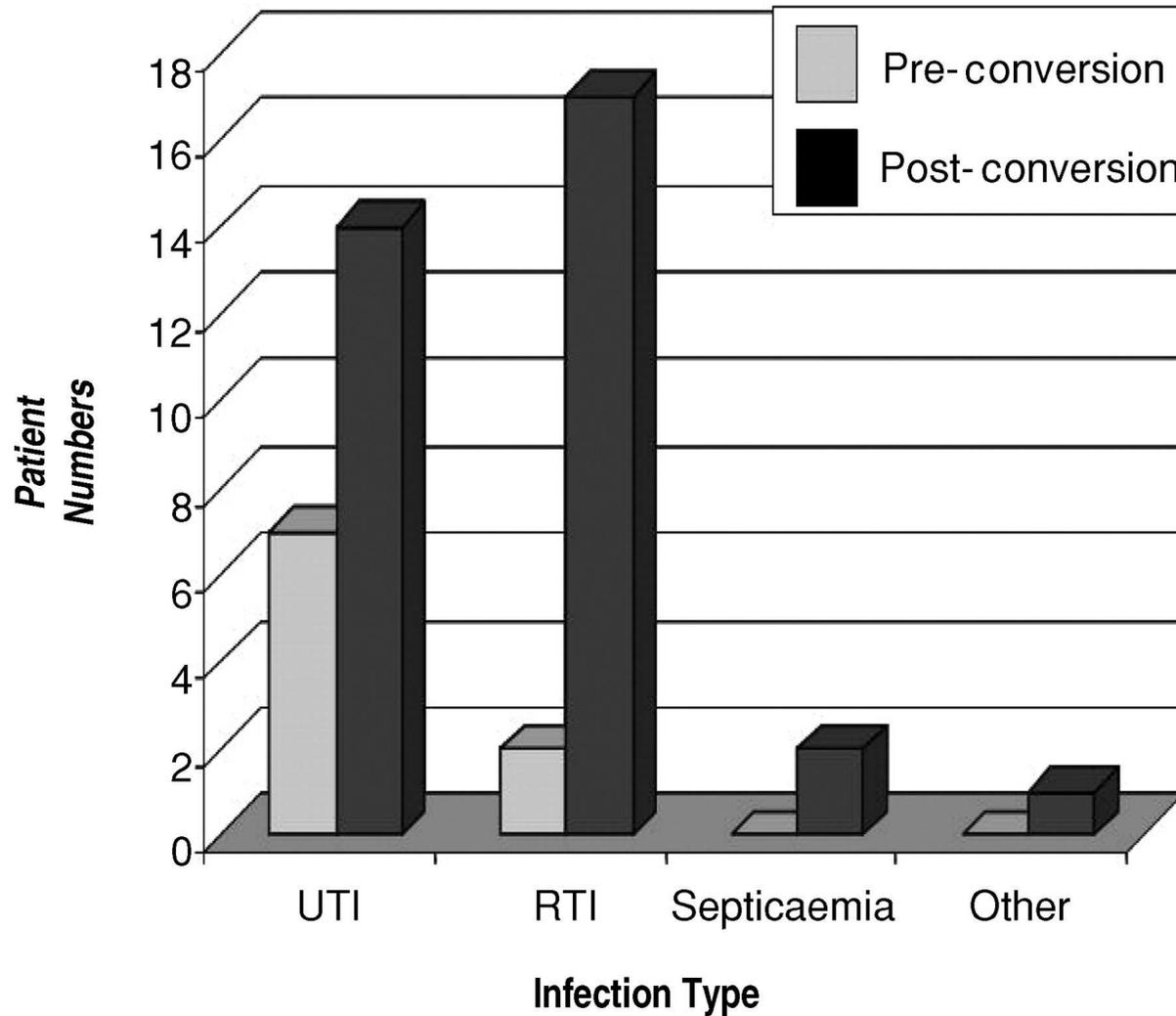
# Increased incidence of infections following the late introduction of MMF in renal transplant recipients.



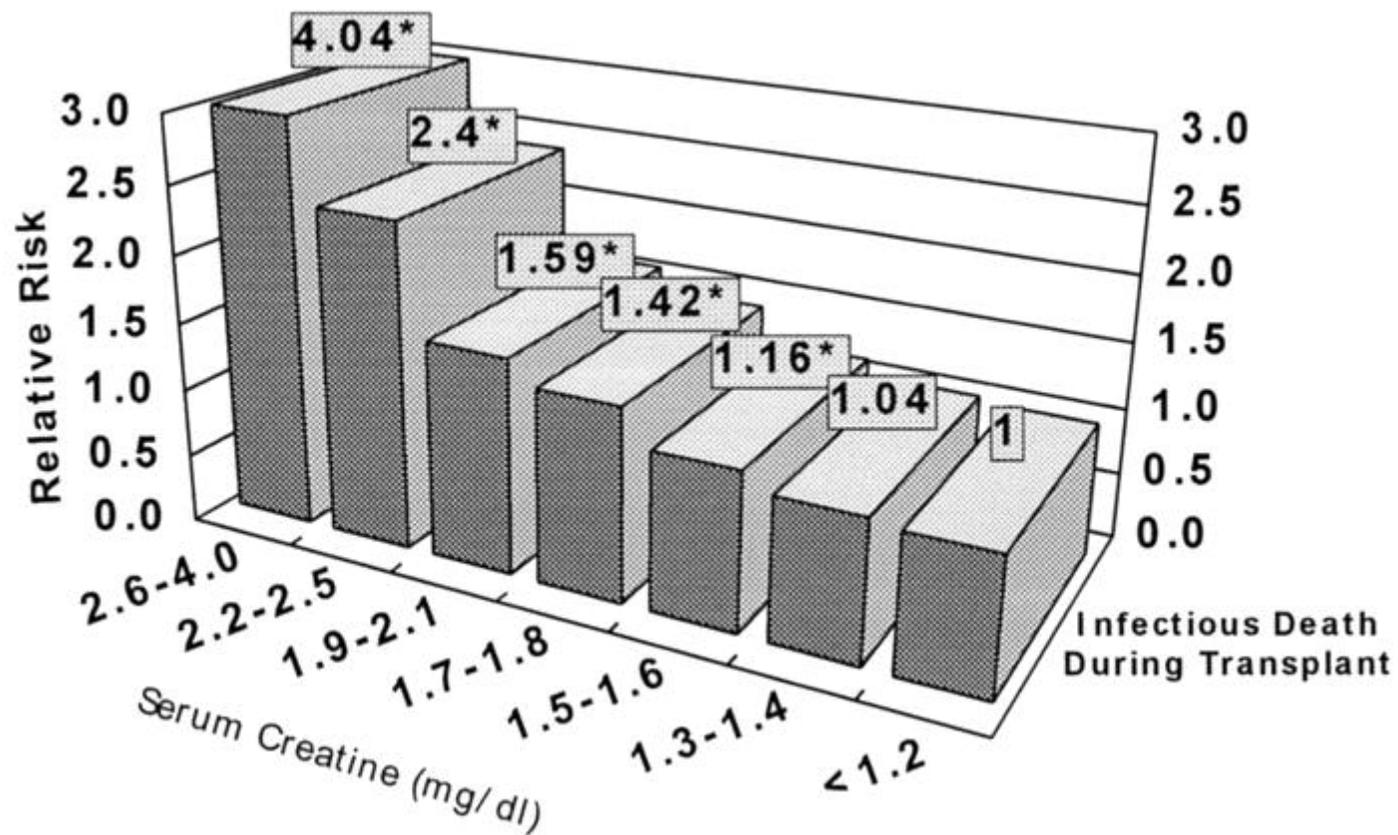
Havesakul, R. et al. Nephrol. Dial. Transplant. 2008

# Sites of infections (by patient numbers) pre-conversion and post-conversion to MMF

CAVEAT MPA-exposure



# Risk of Infectious Death Post Transplant: Impact of Allograft Function



# Infection risk according to the Symphony Study

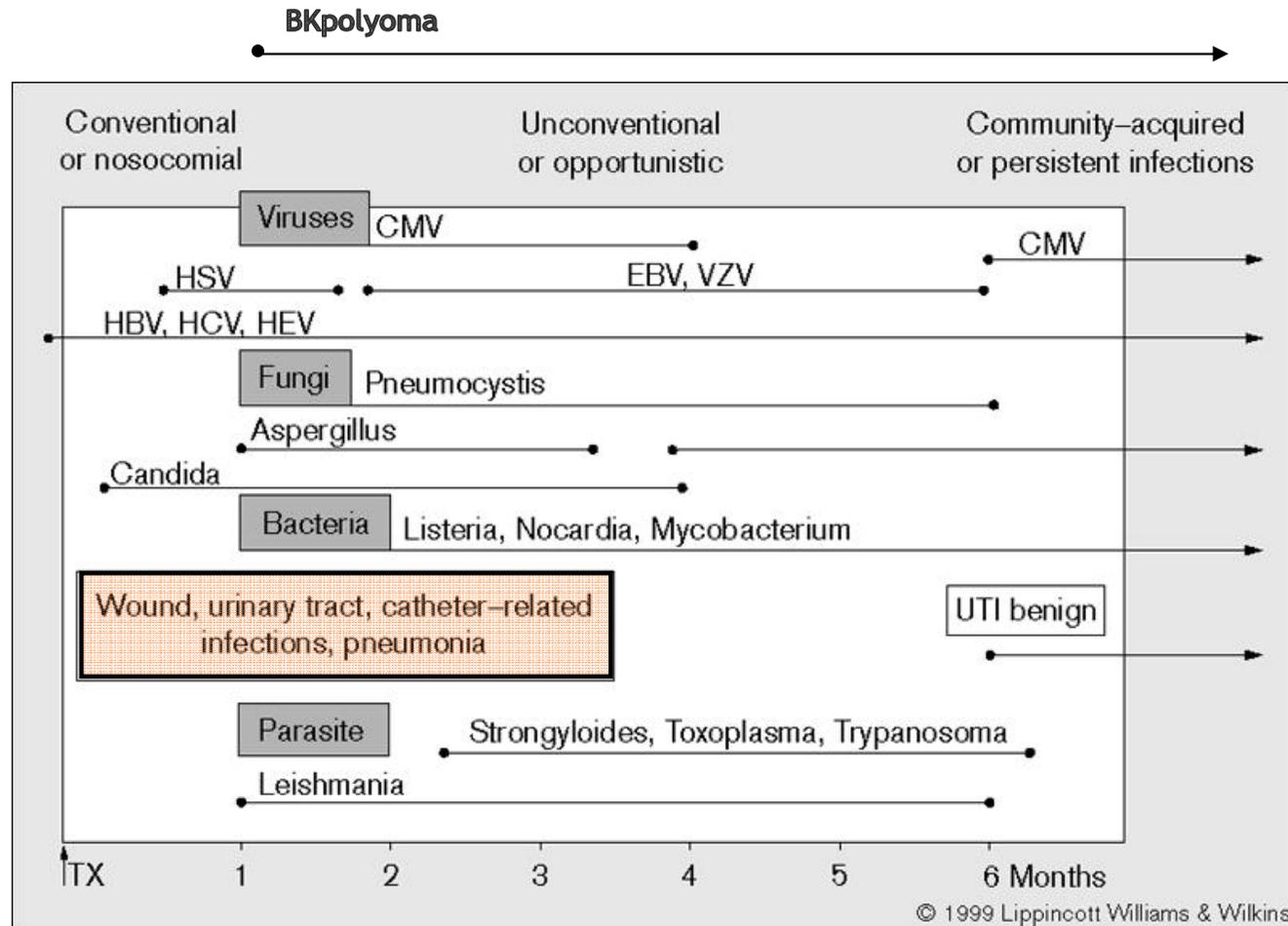
Opportunistic infection p=0.03

CMV-infection p=0.003

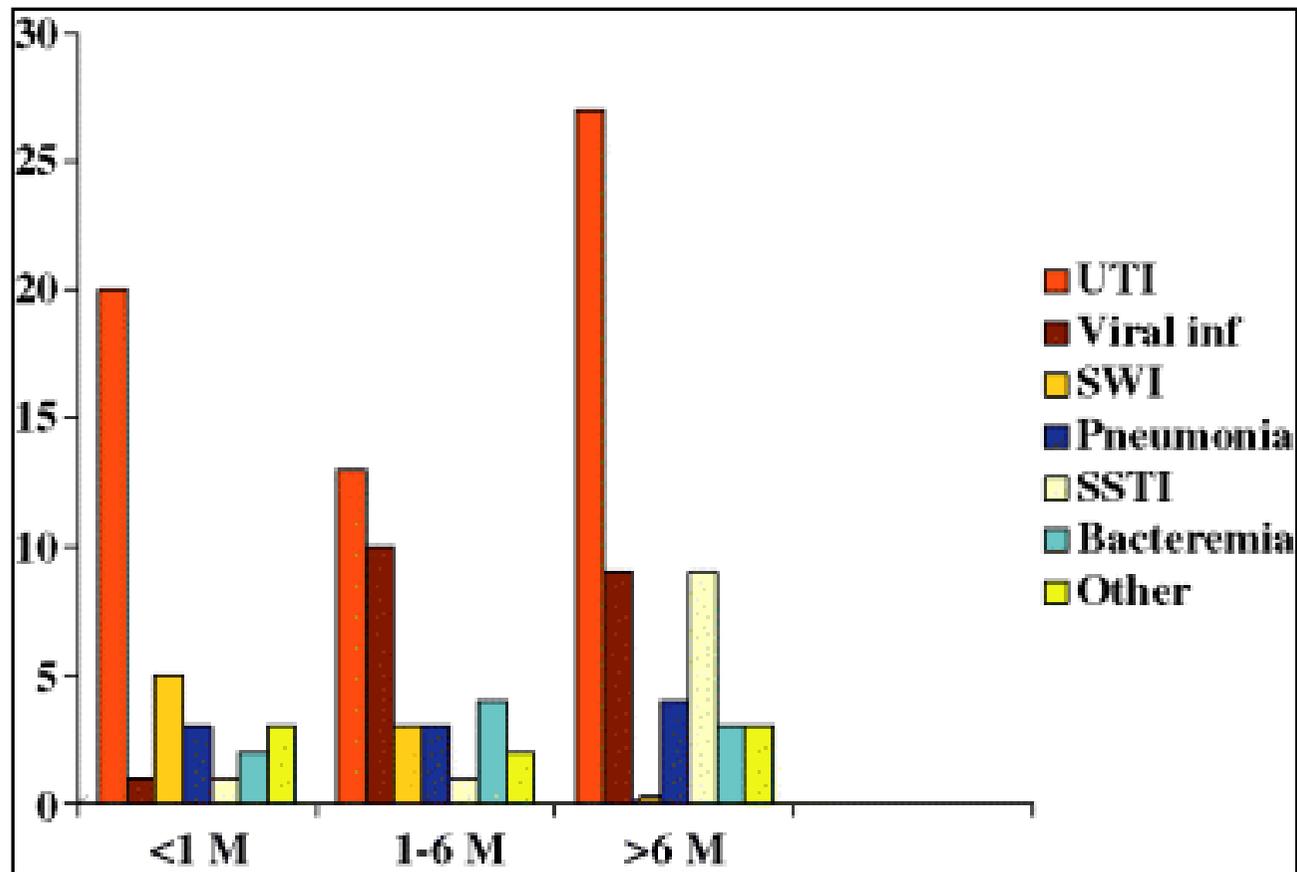
**Table 3. Adverse Events and Serious Adverse Events.\***

Event	Standard-Dose Cyclosporine (N=384)	Low-Dose Cyclosporine (N=408)	Low-Dose Tacrolimus (N=403)	Low-Dose Sirolimus (N=380)
	<i>percent</i>			
<b>Adverse event</b>				
Blood or lymphatic	33.3	33.6	36.2	36.1
Anemia	18.5	17.4	17.1	25.0
Leukopenia	10.2	10.1	13.4	10.3
Gastrointestinal	33.3	32.6	41.4	34.7
Abdominal pain	3.9	4.2	5.2	2.6
Constipation	6.5	5.2	6.7	6.1
Diarrhea	15.6	13.0	25.3	19.5
Vomiting	4.7	3.9	5.5	2.6
General or site of drug administration	23.2	22.6	22.1	27.4
Peripheral edema	12.0	12.5	11.2	13.2
Pyrexia	4.4	5.6	5.0	9.0
Opportunistic infection†	26.0	22.8	19.9	20.3
Candida	7.6	4.7	3.0	5.0
Cytomegalovirus	14.3	11.0	9.7	6.1
Herpes simplex virus	5.5	3.7	4.5	6.1
Other infection or infestation	54.2	50.5	52.4	52.6
Nasopharyngitis	5.7	7.8	7.9	4.0
Pneumonia	4.7	1.2	3.2	5.0
Urinary tract infection	28.4	23.8	23.6	23.2

# The Classic Timeline

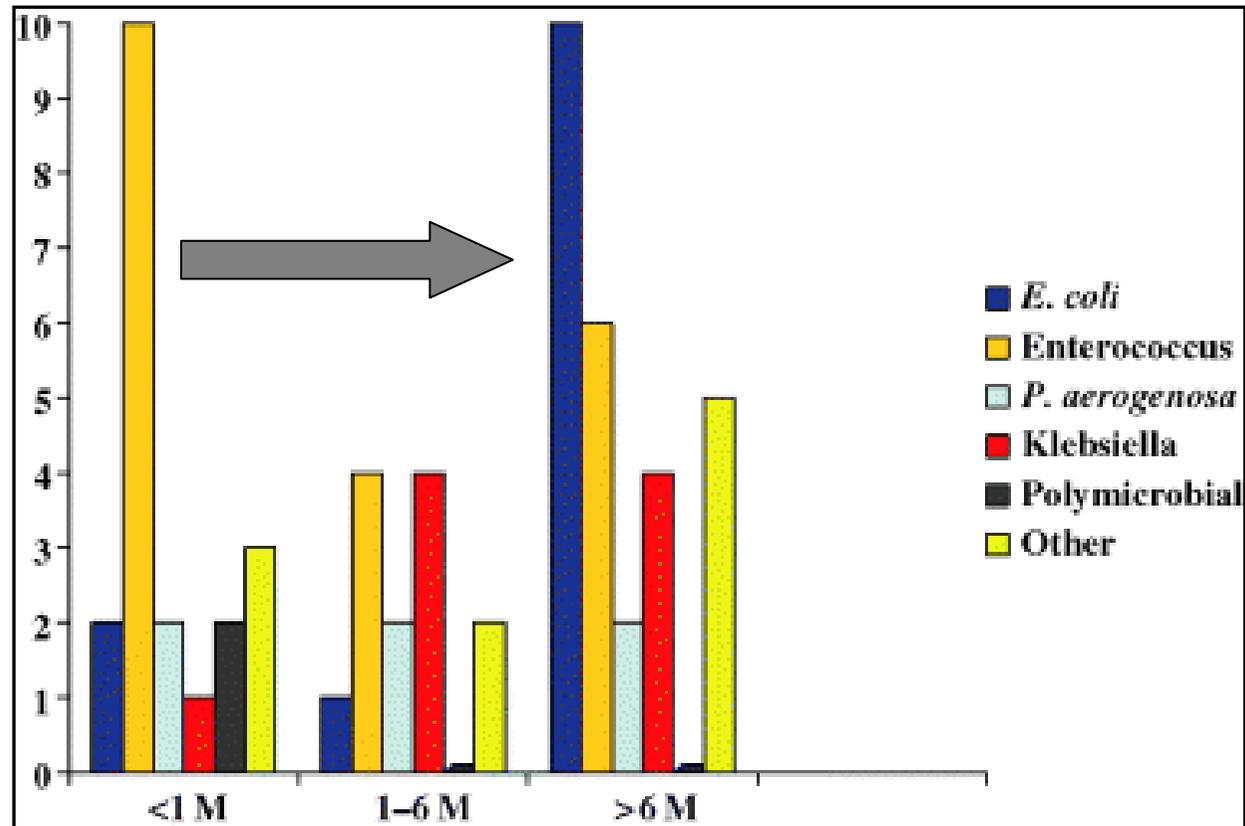


# Time Course and Frequency of Infections after Transplantation



Alengraden et al. Clin Transplant 2006

# Time Course of Urinary Tract Infections by the Causative Uropathogen



Alengraden et al. Clin Transplant 2006

# Risk factors for patients at risk of urinary tract infections after renal transplantation

---

Long period of haemodialysis before transplantation

Female sex

Indwelling catheterization

Urinary tract infection before kidney transplantation

Vesicoureteral reflux

Polycystic kidney disease with a history of recurrent UTI without  
birephrectomy before grafting

Diabetes mellitus

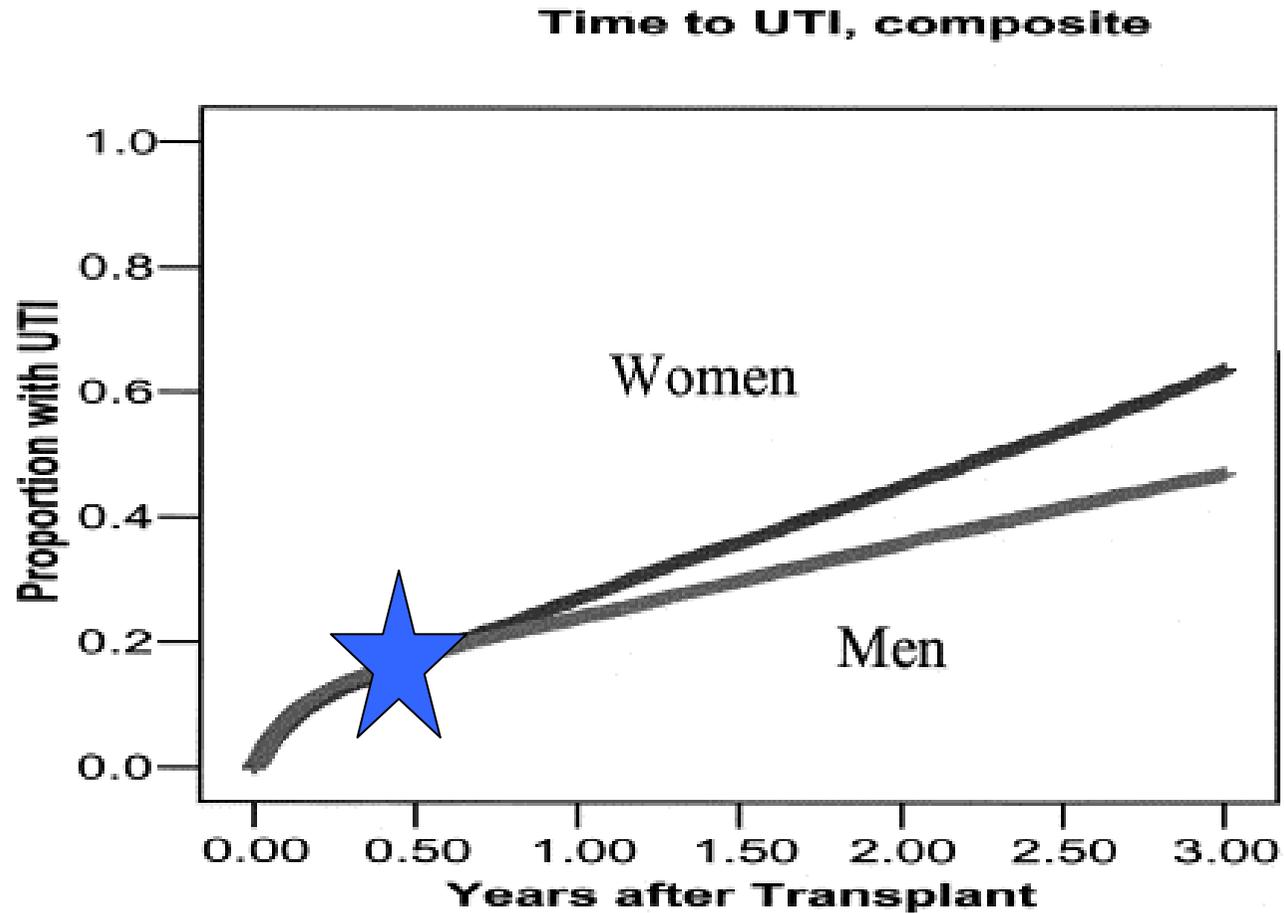
Chronic viral infections

Increased urinary aluminium excretion

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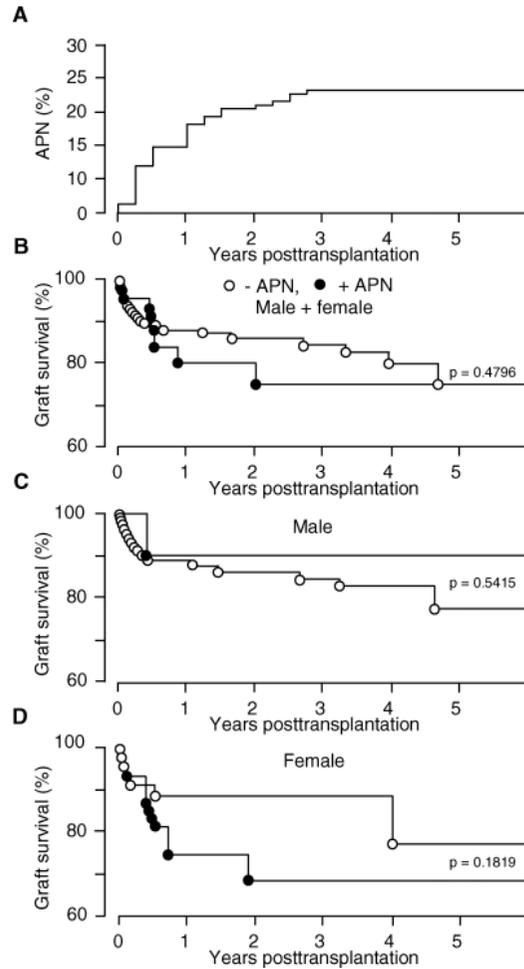
UTI, urinary tract infection.

# Time to first UTI according to sex in US Renal Transplant patients (1996-2000)

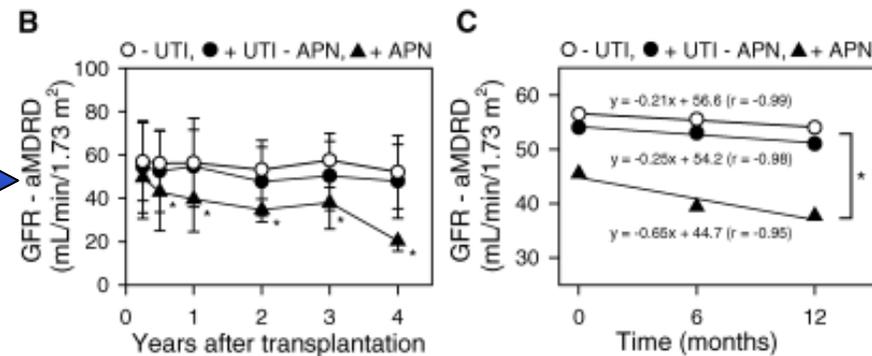
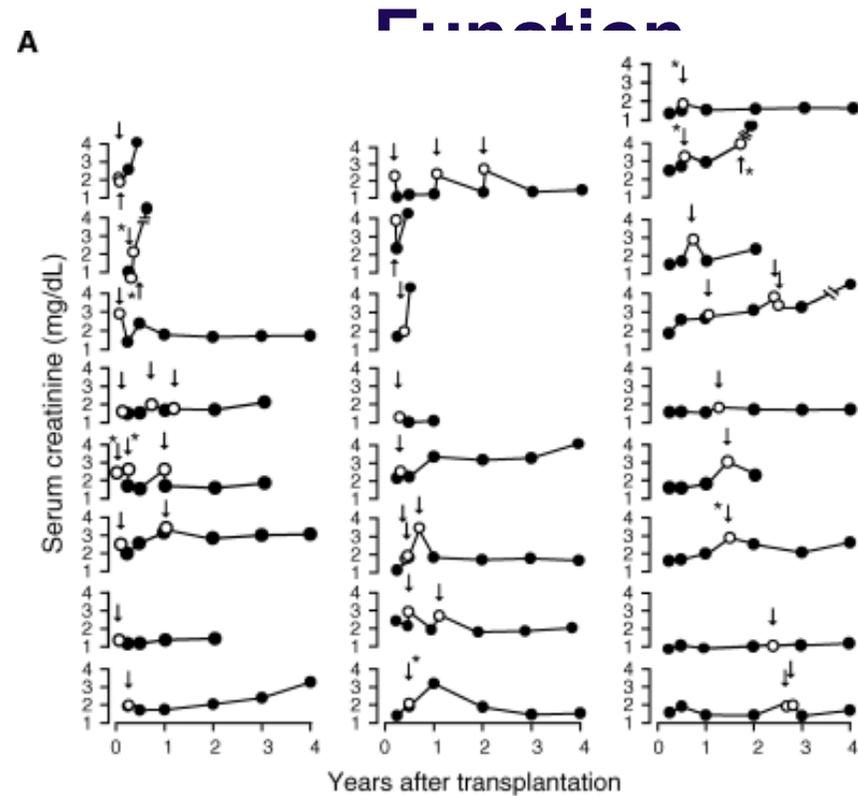


Abbott KC et al. AJKD 2004

# Acute Pyelonephritis Represents a Risk Factor Impairing Long-Term Kidney Graft Function

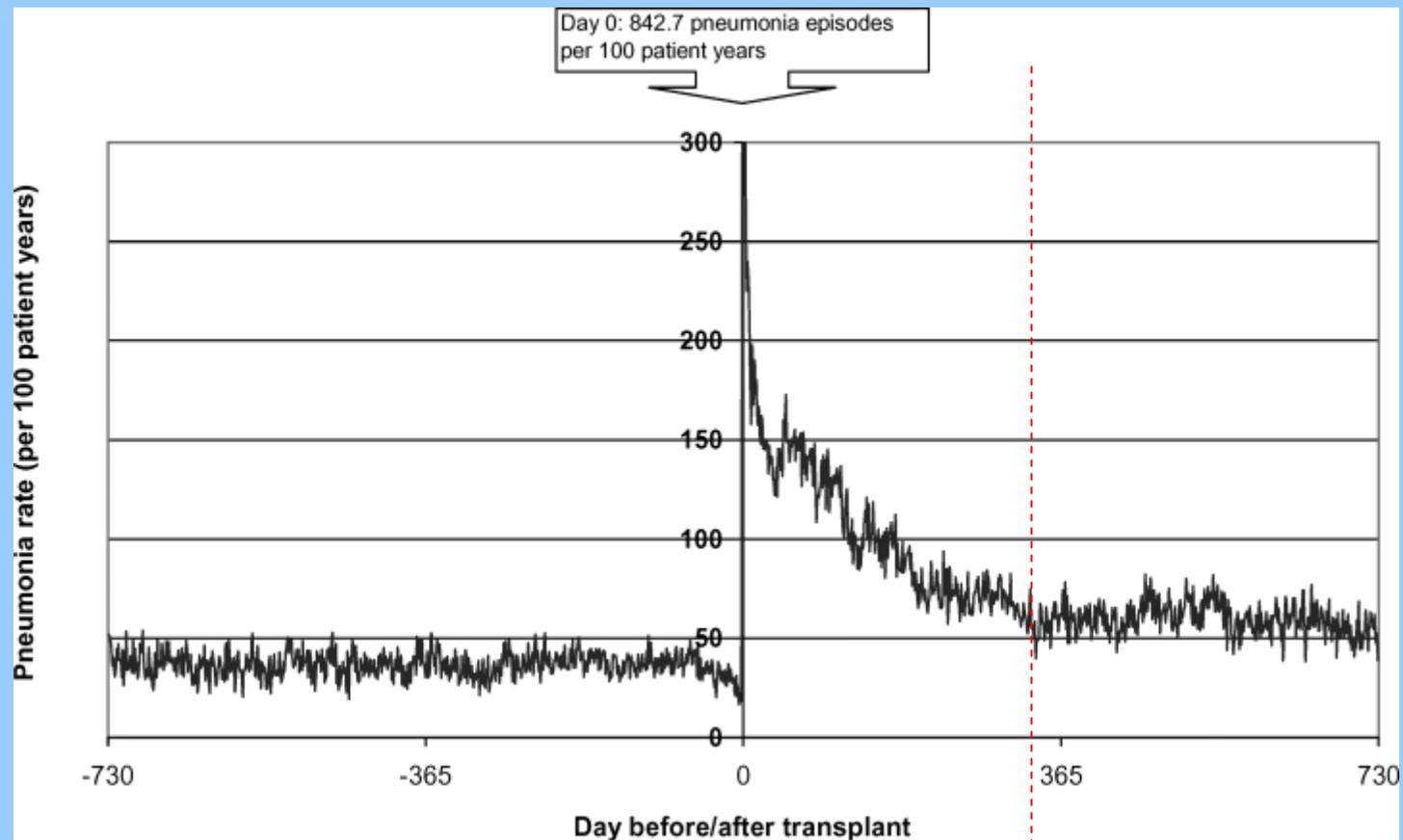


# Acute Pyelonephritis Represents a Risk Factor Impairing Long-Term Kidney Graft Function



Pelle et al. AJT 2007

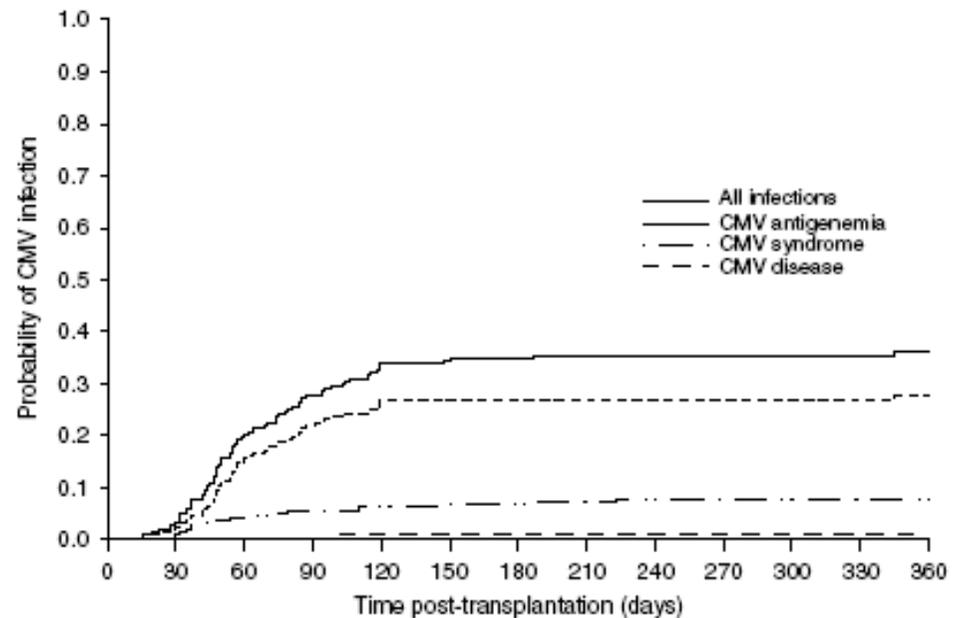
# The Incidence of Pneumonia Before and After Renal Transplantation



Kutinova et al. AJT 2006

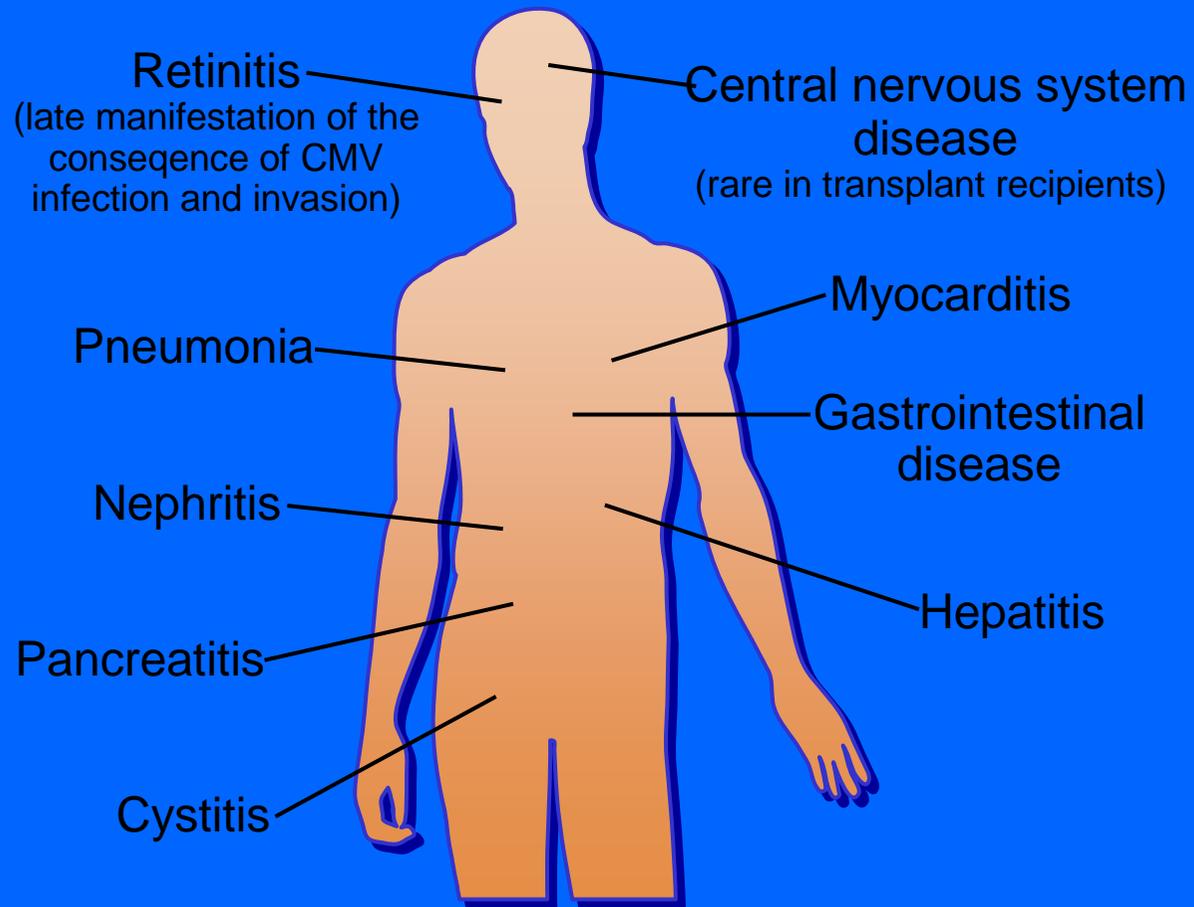
# Cytomegalovirus

- **CMV infection:** isolation of CMV or detection of viral proteins or nucleic acids in any body fluid or tissue specimen
- **CMV disease:** the presence of signs and/or symptoms of tissue injury combined with virus isolation and/or histopathologic or immunochemical evidence of CMV in tissue samples



Dmitrienko et al. KI 2007

# CMV End-Organ Disease



# CMV pneumonia



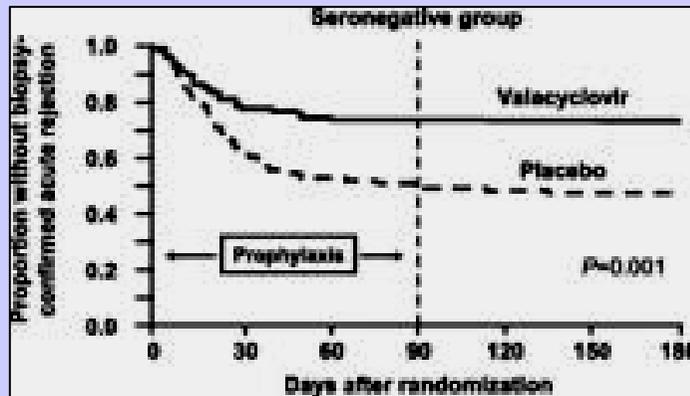
Lung: frequently lethal

- all patterns (*interstitial, alveolar, symmetrically, lower lobes > unilaterally, localised*)
- Gradual, over days, **association with PCP**
- When rapid evolution (12-24 h) to respiratory insufficiency: coinfection (bacterial, fungal)

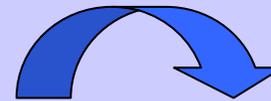
Courtesy of Ajit Limaye, MD.

# CMV: clinical effects

- *Direct*: tissue-damage
- *Indirect*: immunomodulation
  - higher ‘net state of immunosuppression’
  - role in acute rejection (controversial)
  - role in chronic allograft injury
  - more PTLD



Lowance et al. NEJM 1999



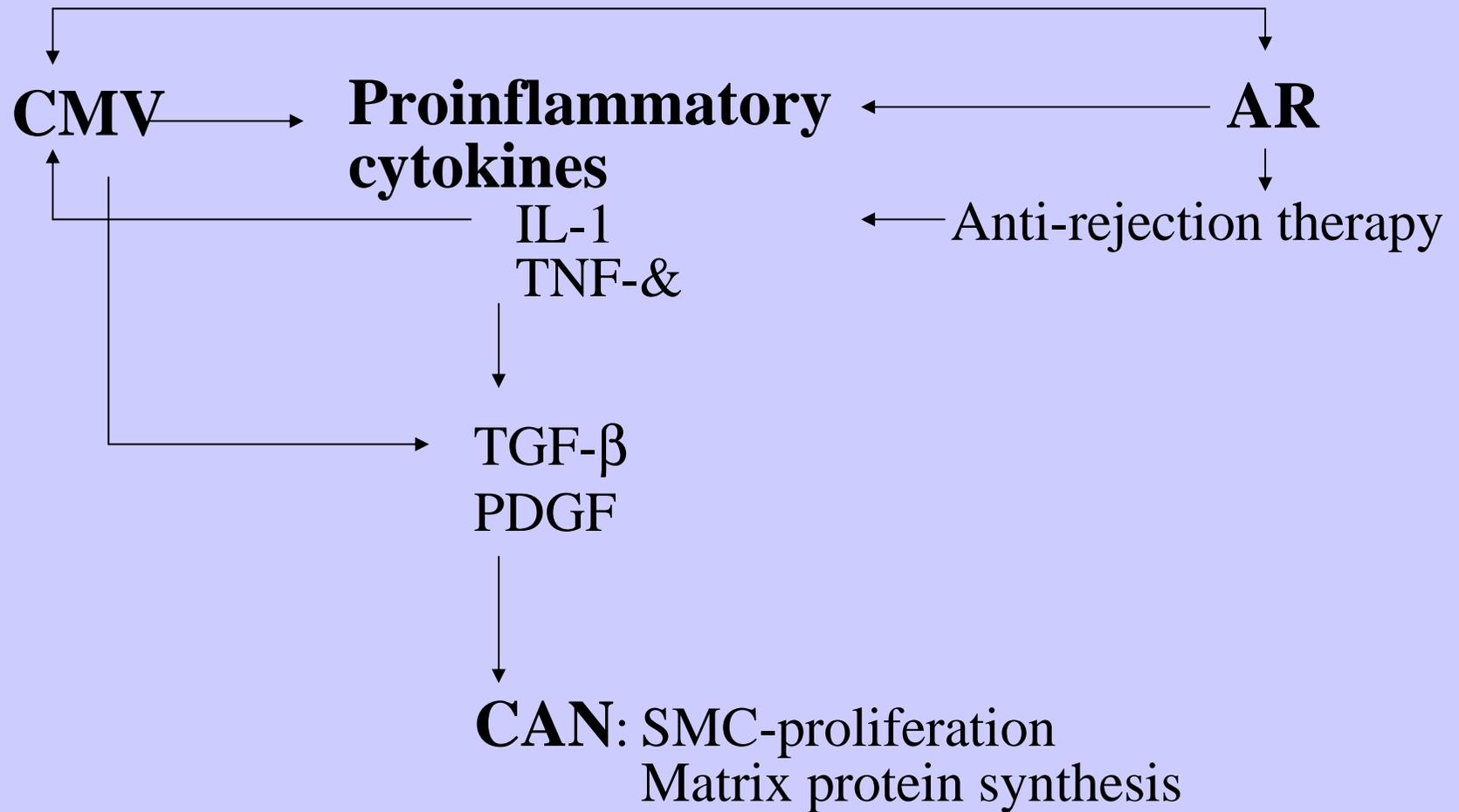
**Sagedal, AJT 2002:** CMV disease as predictor for acute tubulo-interstitial rejection (RR 3.1)  
**Lowance, NEJM 1999:** prophylaxis with valacyclovir : acute allograft rejection in D+/R- : minus 50 %.

## Mechanisms

- Upregulation of MHC II antigens on allograft
- Enhancing adhesion molecules (eg. ICAM-1) on endothelium
- Release of large array of cytokines

# CMV AND CAN

## POSSIBLE MECHANISMS



# CMV

Replication

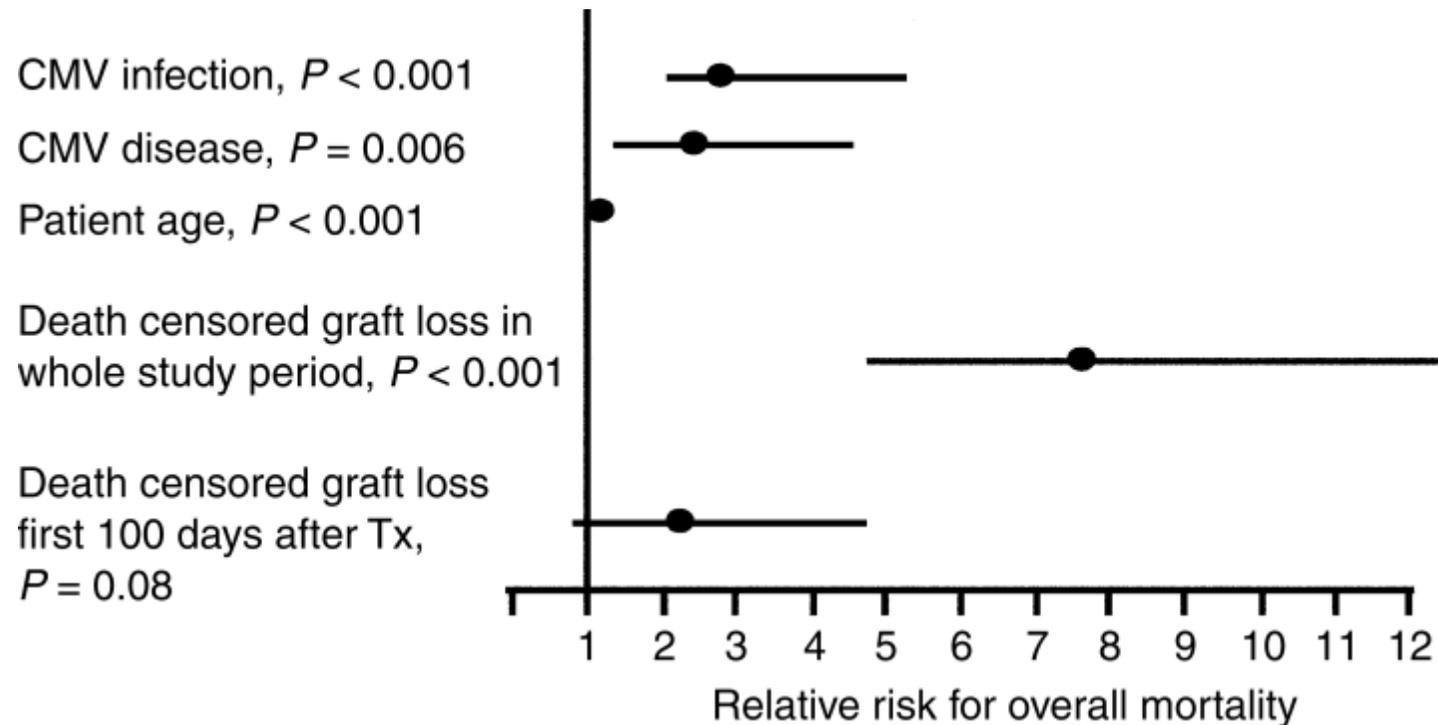


Amplification / Dissemination



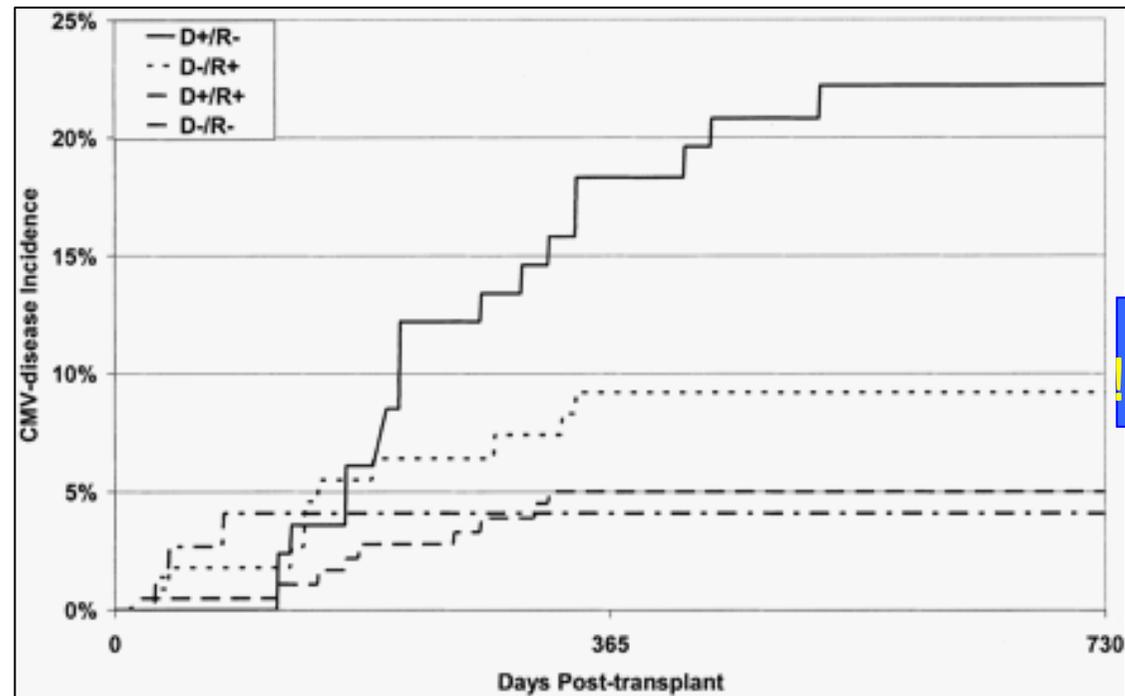
MHC Restricted, CMV specific T cells

# Risk factors for Mortality >100 days Post Transplantation



# Incidence of CMV Disease by D/R - status

Oral ganciclovir (1000mg TID) for 3m in D-R+ and 6m in D+/R+ and D+/R-

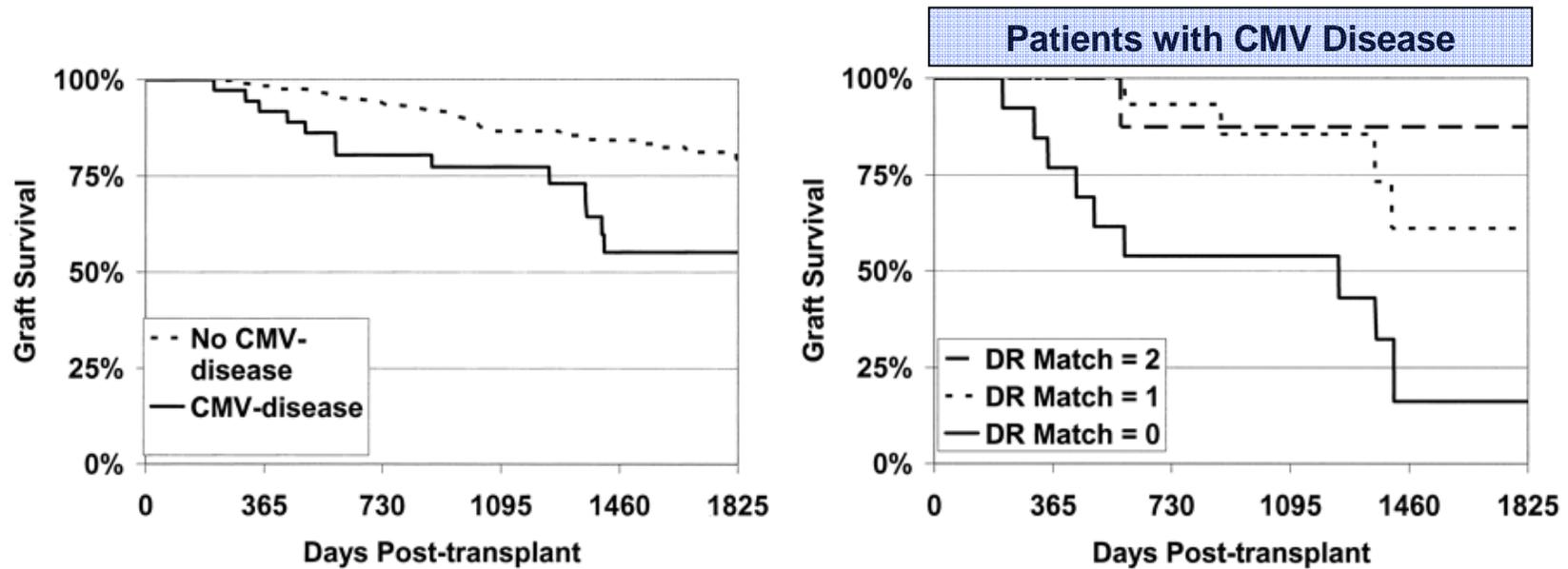


! zero HLA-DR matches

Schnitzler et al. JASN 2003;14:780.

# Five-year Graft Survival in Patients with CMV Disease and a Functioning Graft at 6 Months

Oral ganciclovir (1000mg TID) for 3m in D-R+ and 6m in D+/R+ and D+/R-



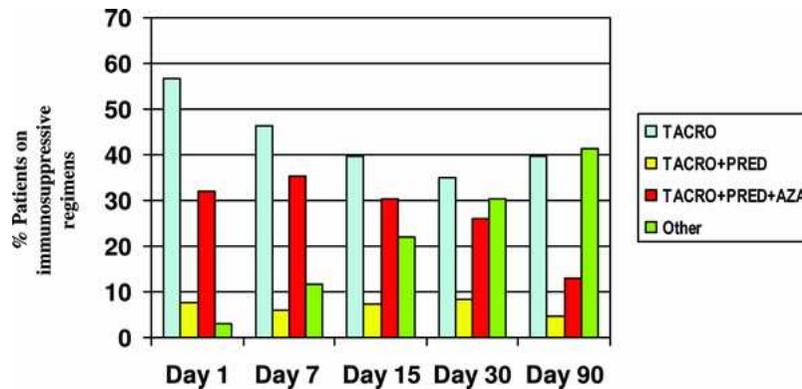
Schnitzler et al. JASN 2003;14:780.

# Effects of Different Immunosuppressive Drugs on CMV

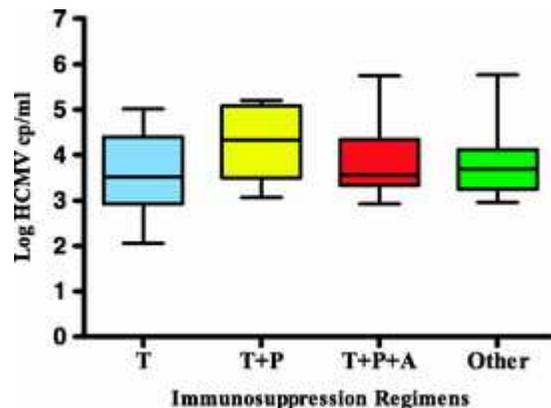
<b>Drug</b>	<b>Activation From Latency</b>	<b>Amplification of Replicating Virus</b>
ATG, OKT3	4+	1-2+
Azathioprine	1+	1-2+
Mycophenolate mofetil	1+	1-2+
Cyclosporine	0	4+
Tacrolimus	0	4+
Prednisone	0	2-3+
Sirolimus	0	3+

# CMV and immunosuppressive treatment

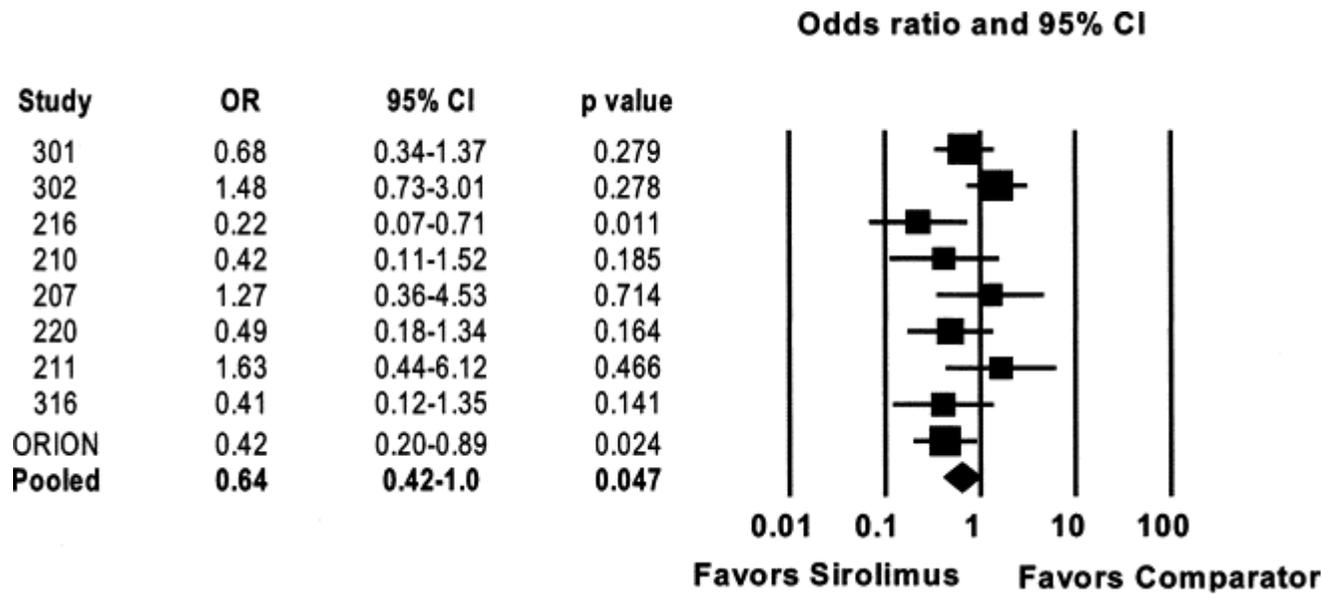
Differential effects of **prednisolone** and **azathioprine** on the development of human cytomegalovirus replication post liver transplantation.



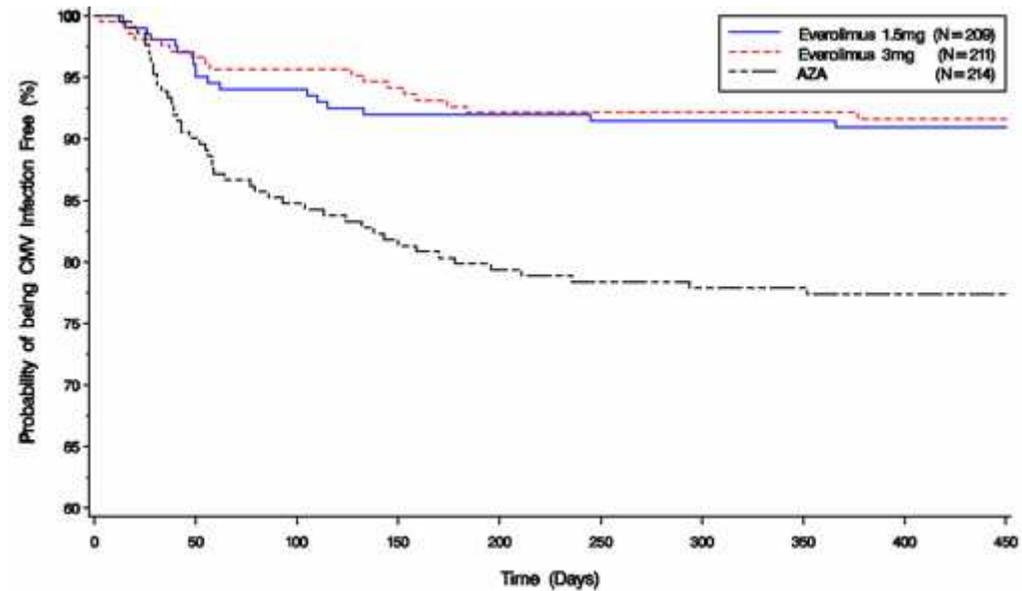
BASELINE IMMUNOSUPPRESSION	RR	95%CI	P value
TACRO	1	-	-
TACRO+PRED	4.34	2.03-9.26	0.0001
TACRO+PRED+AZA	1.61	0.96-2.72	0.07
OTHER	2.98	1.6-5.55	0.0006



# Reduced risk of cytomegalovirus infection in solid organ transplant recipients treated with **sirolimus**: a pooled analysis of clinical trials.



# A lower incidence of CMV infection in *de novo* heart transplant recipients randomized to everolimus



Logrank p values: 0.0002 (1.5 mg Everolimus vs. AZA) and <0.0001 (3 mg Everolimus vs. AZA).

Hill et al. Transplantation 2007

## CMV: Antiviral strategies: prophylaxis, pre-emptive treatment and therapy

### Rate of CMV Disease Despite Antiviral Prophylaxis (D+/R-)

	Renal Transplants	
	Placebo	Valacyclovir
<b>Prophylaxis (3 mo)</b>	45%	3%
<b>Postprophylaxis (6 mo)</b>	45%	16%

Lowance D, et al, for the International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group.  
*N Engl J Med.* 1999;340:1462-1470.

Meta-Analysis: The Efficacy of Strategies To Prevent Organ Disease by Cytomegalovirus in Solid Organ Transplant Recipients

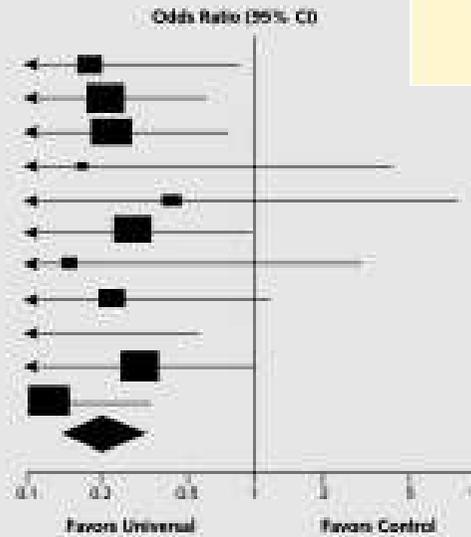
Andre C. Kall, MD; Josh LeVitsky, MD; Elizabeth Lyden, MS; Julie Stoner, PhD; and Allison G. Fretfeld, MD



CMV Organ Disease—Universal Prophylaxis Trials

Study, Year (Reference)	Odds Ratio	95% CI		Patients with CMV Organ Disease/ Total Patients, n/n	
		Lower Limit	Upper Limit	Universal Prophylaxis Group	Control Group
Balfour et al., 1989 (59)	0.18	0.04	0.89	2/53	9/51
Merigan et al., 1992 (62)	0.22	0.08	0.62	5/76	18/72
Sallba et al., 1993 (36)	0.23	0.07	0.76	4/60	14/60
Rostaing et al., 1994 (60)	0.17	0.01	3.78	0/19	2/18
Wetzmayr et al., 1996 (33)	0.43	0.02	7.63	1/22	1/10
Postell-Noble et al., 1996 (37)	0.29	0.09	0.95	6/24	14/26
Brennan et al., 1997 (61)	0.15	0.01	3.10	0/19	3/23
Gavaldà et al., 1997 (34)	0.50	0.13	1.89	4/37	7/36
Gate et al., 1997 (63)	0.07	0.01	0.56	1/159	13/154
Barkholt et al., 1999 (35)	0.31	0.10	0.97	7/28	14/27
Lowance et al., 1999 (14)	0.12	0.04	0.34	4/206	21/210
Overall effect	0.20	0.13	0.31	34/794	126/788

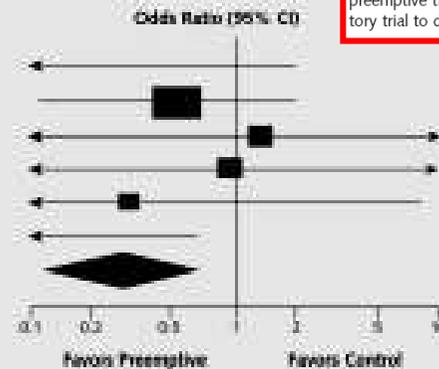
Prophylactic trials



CMV Organ Disease—Preemptive Trials

Study, Year (Reference)	Odds Ratio	95% CI		Patients with CMV Organ Disease/ Total Patients, n/n	
		Lower Limit	Upper Limit	Preemptive Group	Control Group
Coelli et al., 1995 (65)	0.10	0.00	2.04	0/22	3/18
Hilberd et al., 1995 (64)	0.55	0.12	2.60	3/54	4/49
Brennan et al., 1997 (66)	1.43	0.08	24.81	1/15	1/21
Rayes et al., 2001 (66)	1.00	0.06	16.76	1/30	1/30
Faya et al., 2002 (67)	0.21	0.01	7.99	0/35	1/34
Sagedal et al., 2003 (68)	0.04	0.00	0.76	0/42	0/38
Overall effect	0.28	0.11	0.69	5/208	18/190

Preemptive trials



Cautions

Most trials were small and were not blinded.

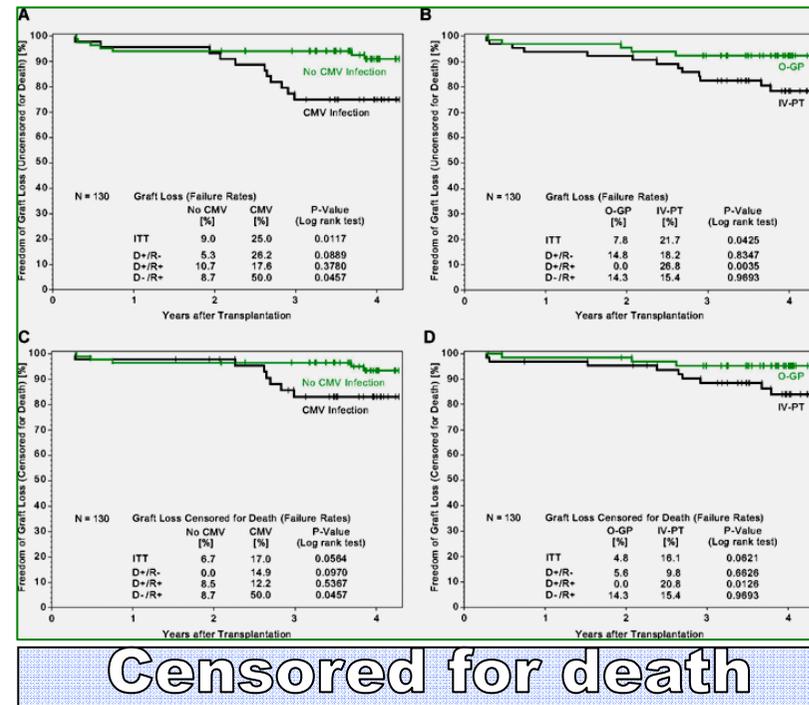
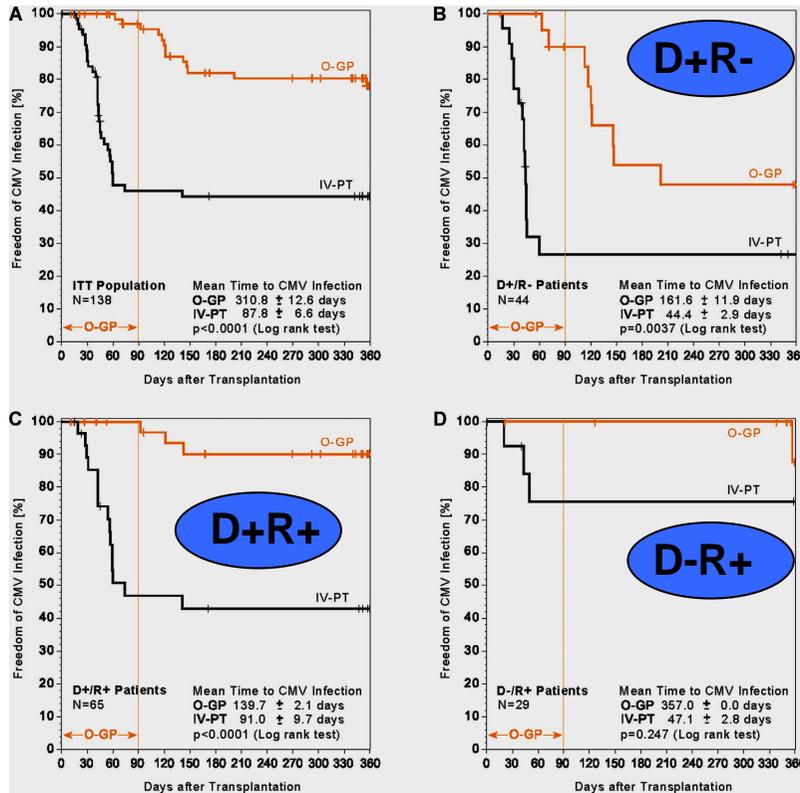
Implications

Although the authors prefer universal prophylaxis over preemptive treatment, they recommend a large confirmatory trial to directly compare the 2 strategies.

# CMV and prophylaxis

## Improvement in Long-Term Renal Graft Survival due to CMV Prophylaxis with Oral Ganciclovir

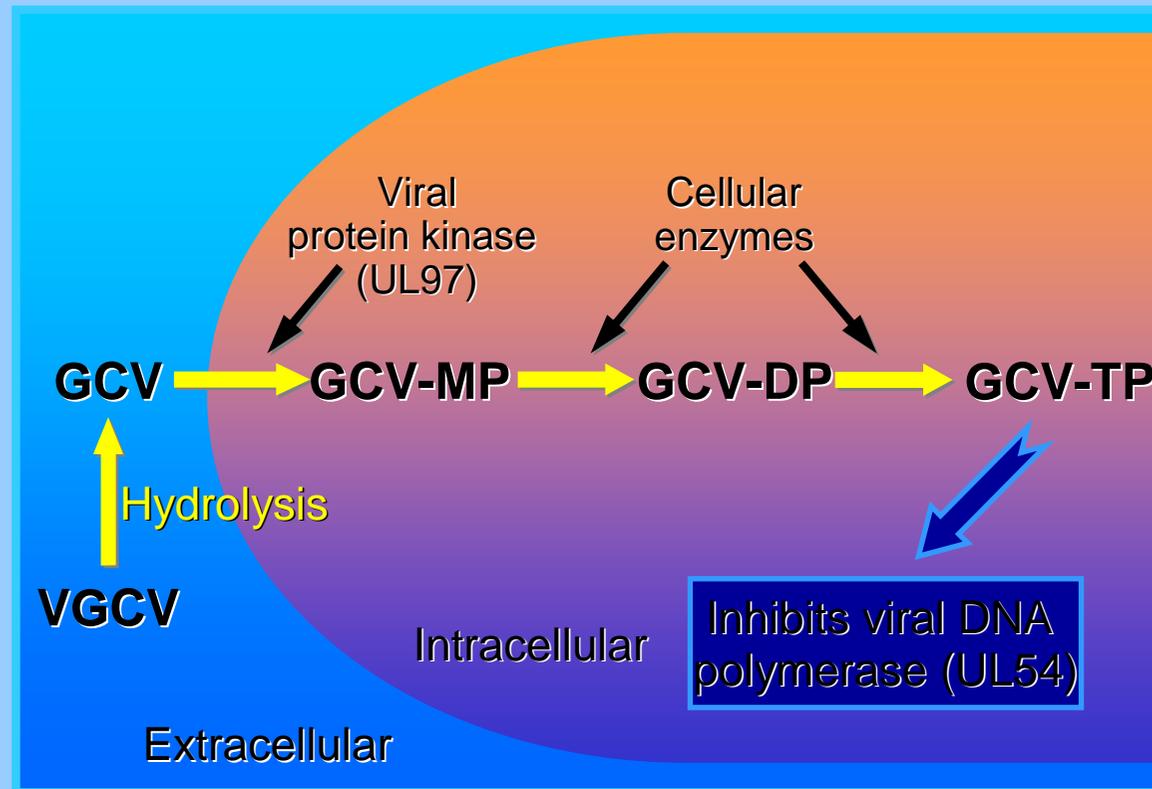
Freedom of CMV infection



Freedom of graft loss

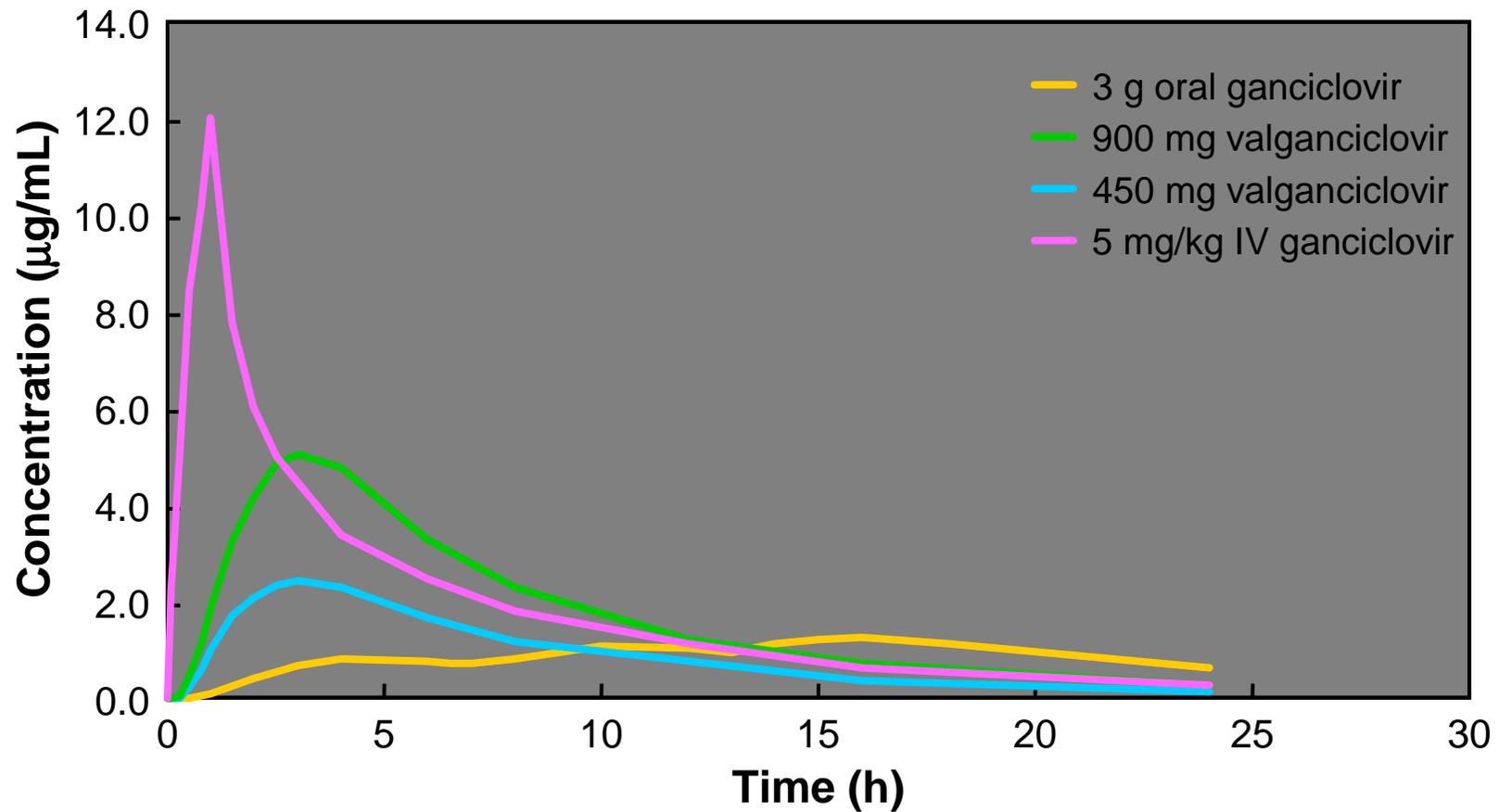
Censored for death

# Valganciclovir Mechanism of Action



VGCV = valganciclovir; GCV = ganciclovir; GCV-MP = ganciclovir monophosphate; GCV-DP = ganciclovir diphosphate; GCV-TP = ganciclovir triphosphate.  
Courtesy of Mark D. Pescovitz, MD.

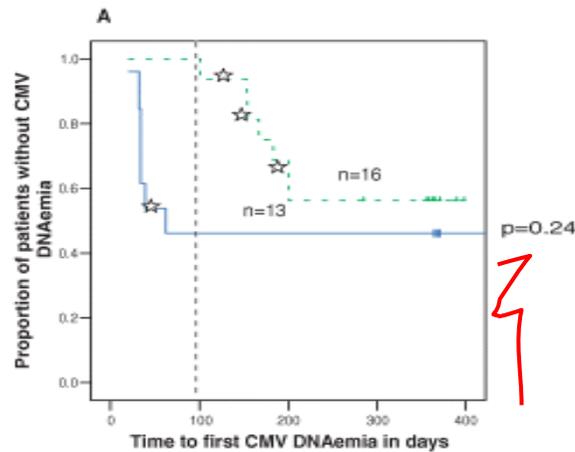
# Valganciclovir Oral Absorption Study



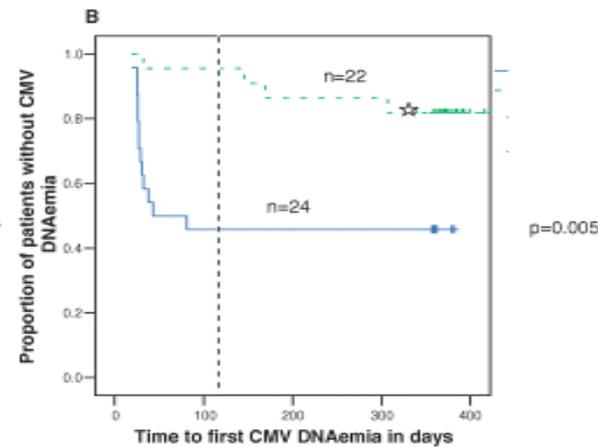
# CMV: prophylaxis versus pre-emptive treatment

## Time to occurrence of CMV DNAemia.

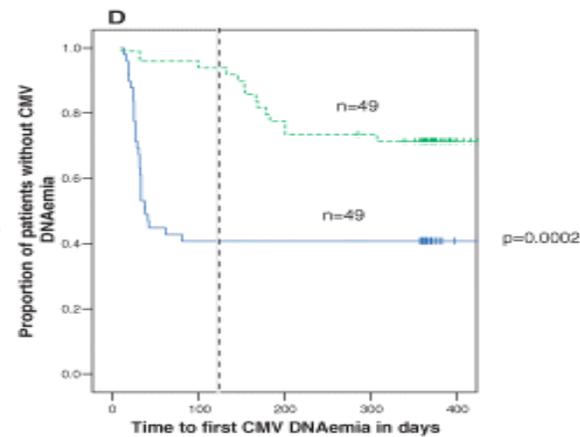
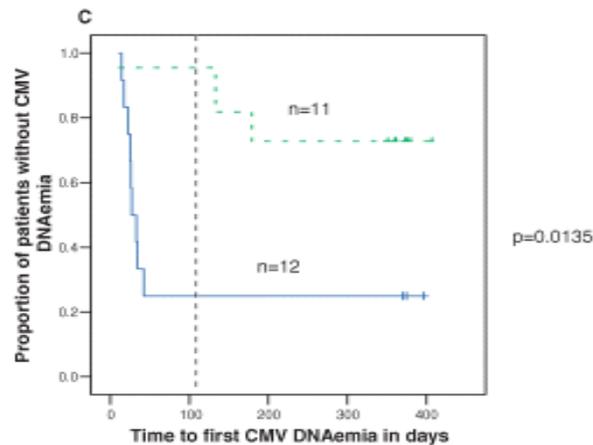
D+R-



D+R+



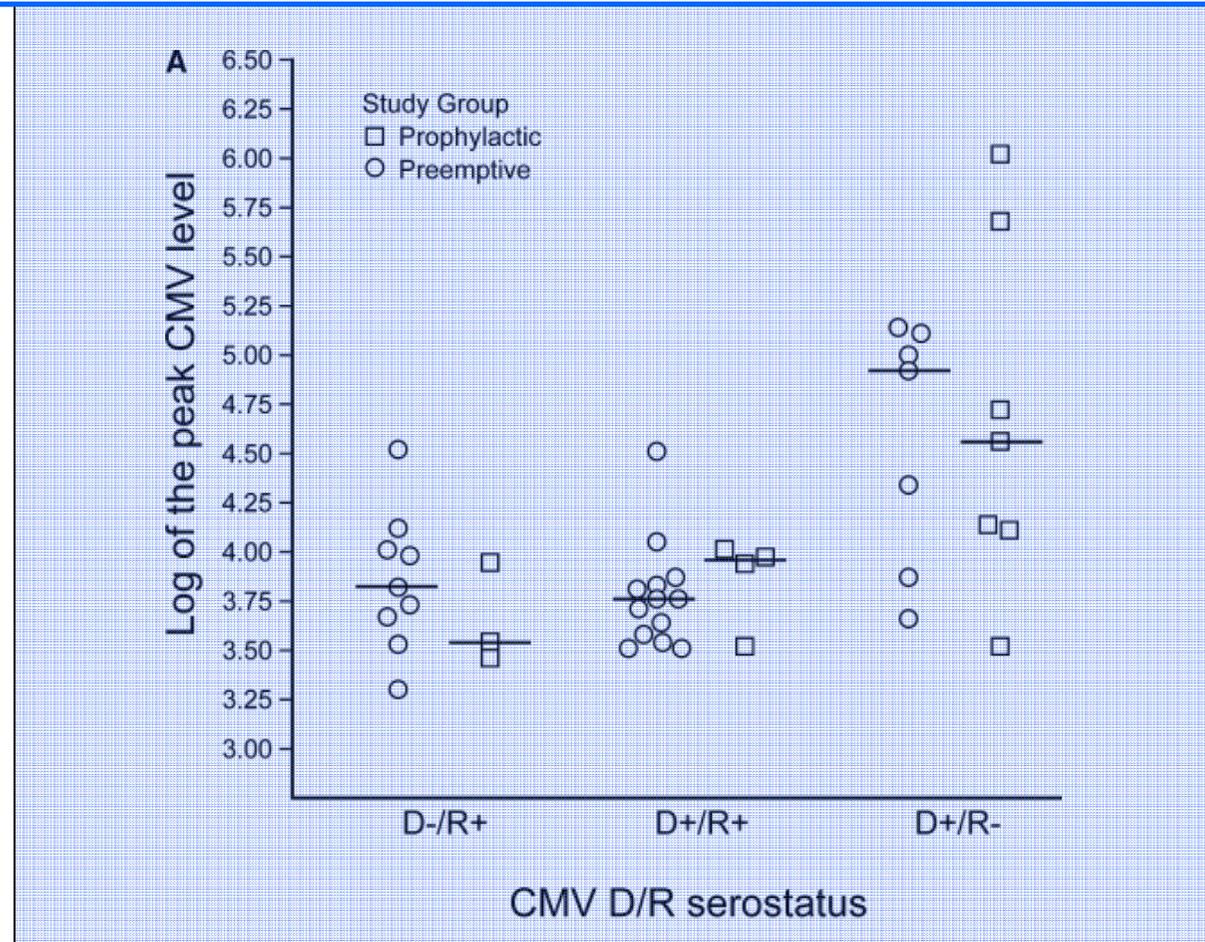
D-R+



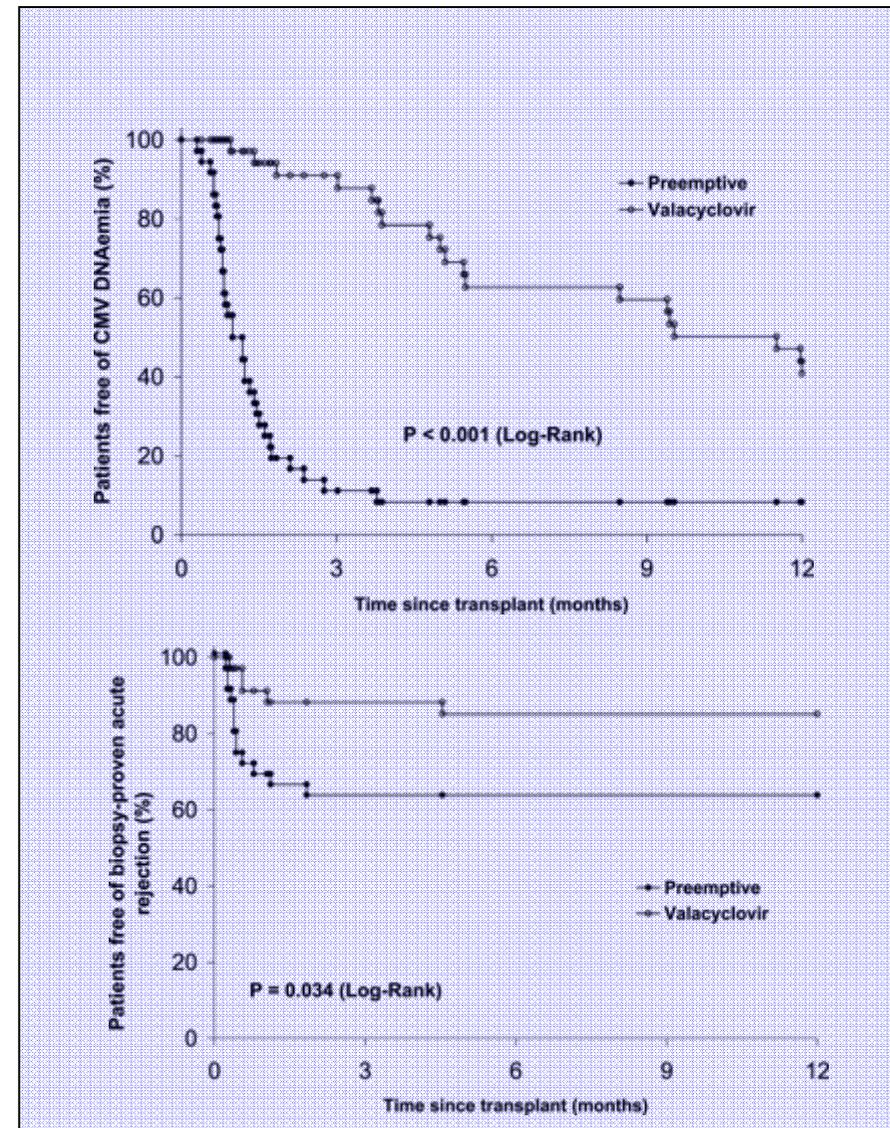
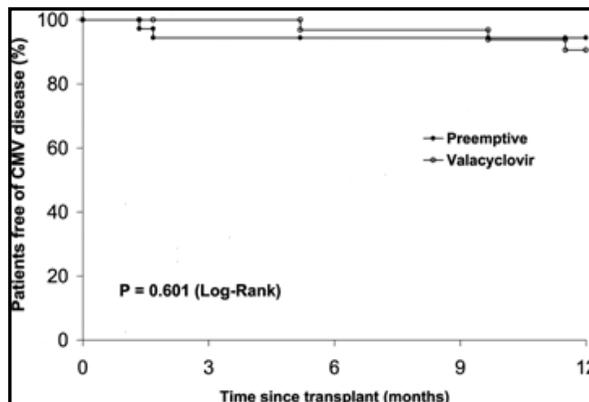
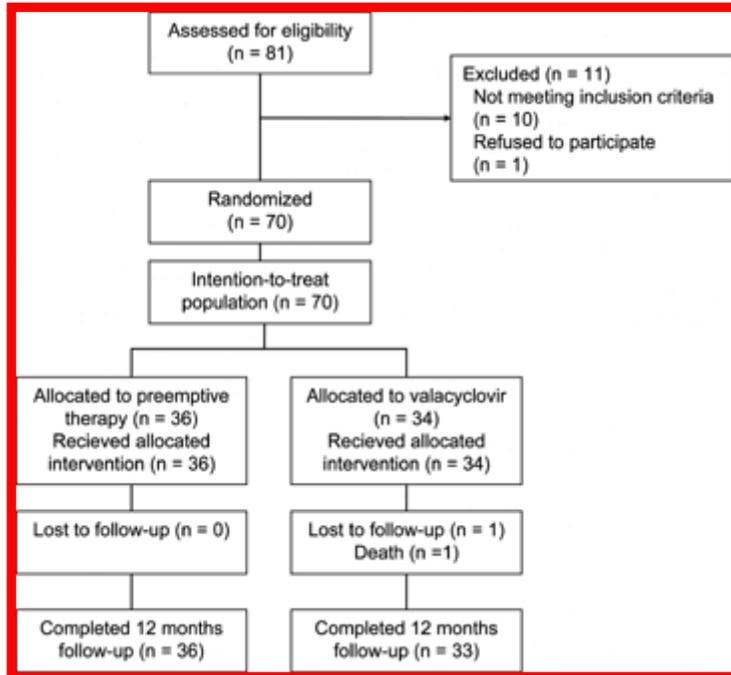
Study Group: — Preemptive  
- - - Prophylactic

# CMV: prophylaxis versus pre-emptive treatment

**D+/R- Have higher CMV levels which are highest in the Preemptive group**



# Valacyclovir prophylaxis versus preemptive valganciclovir therapy to prevent CMV disease



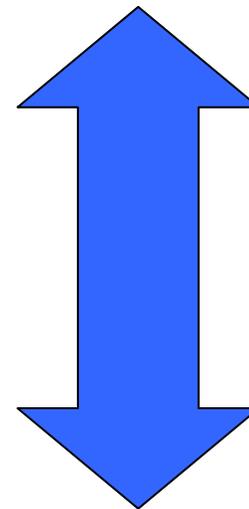
# CMV: prophylaxis versus pre-emptive treatment: pro/con

- PRO:

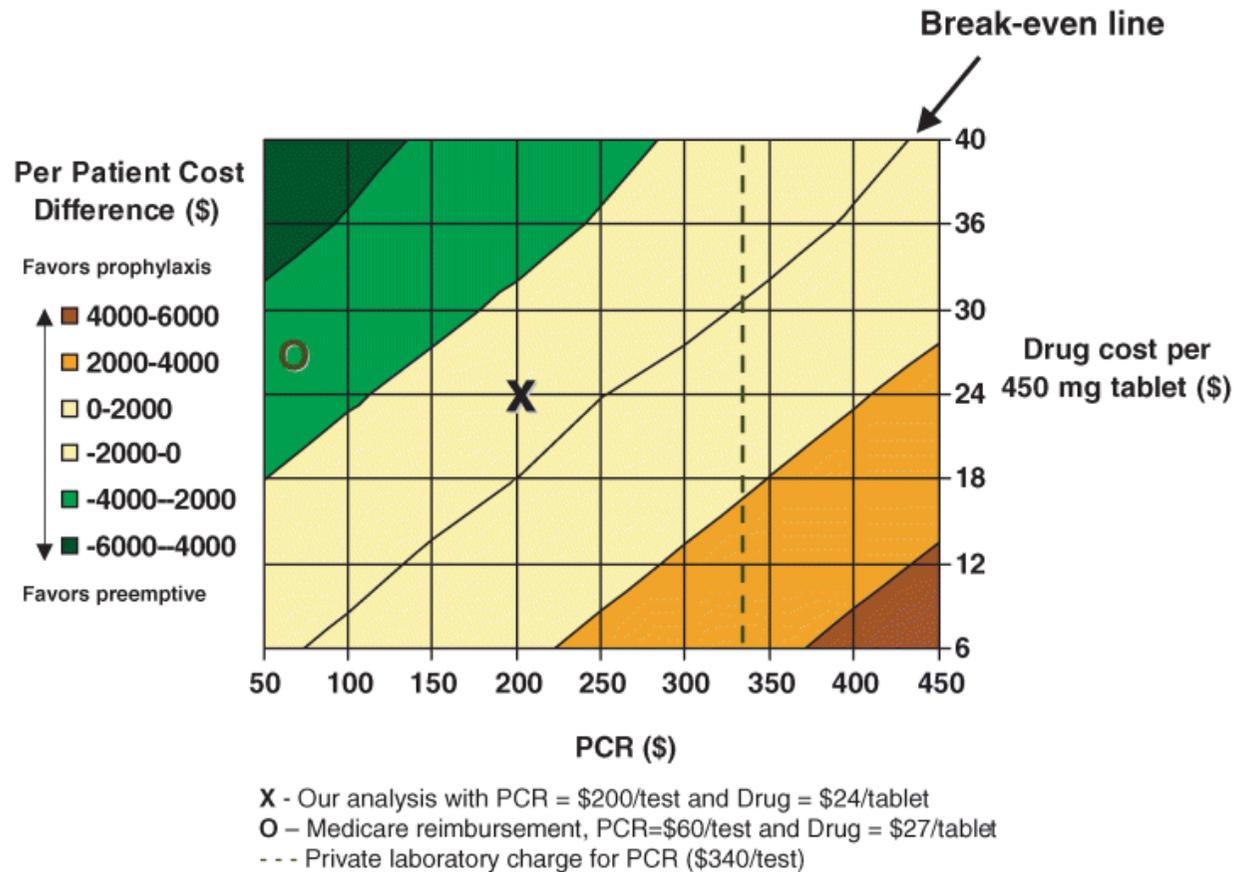
- prevention end-organ disease
- reduction of acute rejection
- reduction of opportunistic infections
- improved survival

- CON:

- cost
- potential resistance
- delayed CMV-specific T-cell responses
- late onset CMV disease

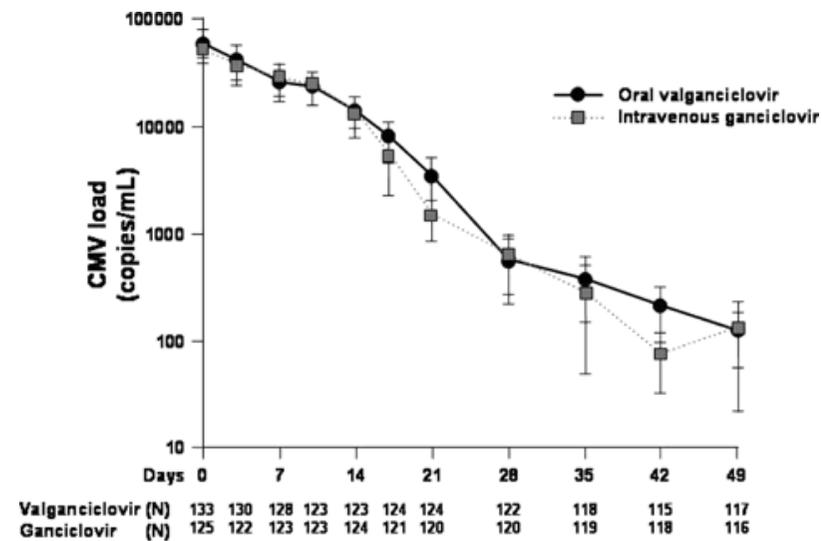
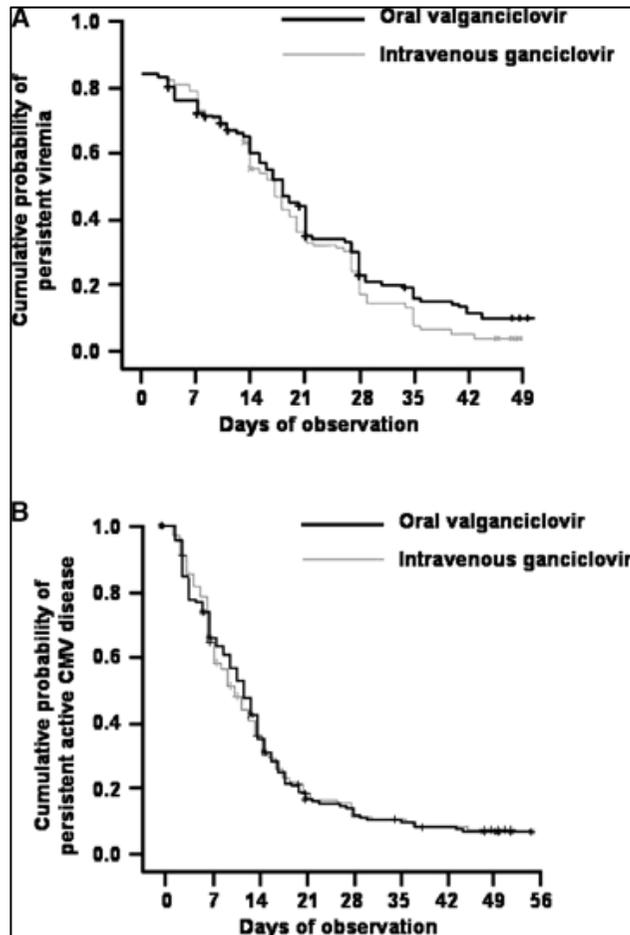


# Cost-efficiency of prophylactic versus preemptive valganciclovir



# CMV: therapeutic approach

## VICTOR-trial

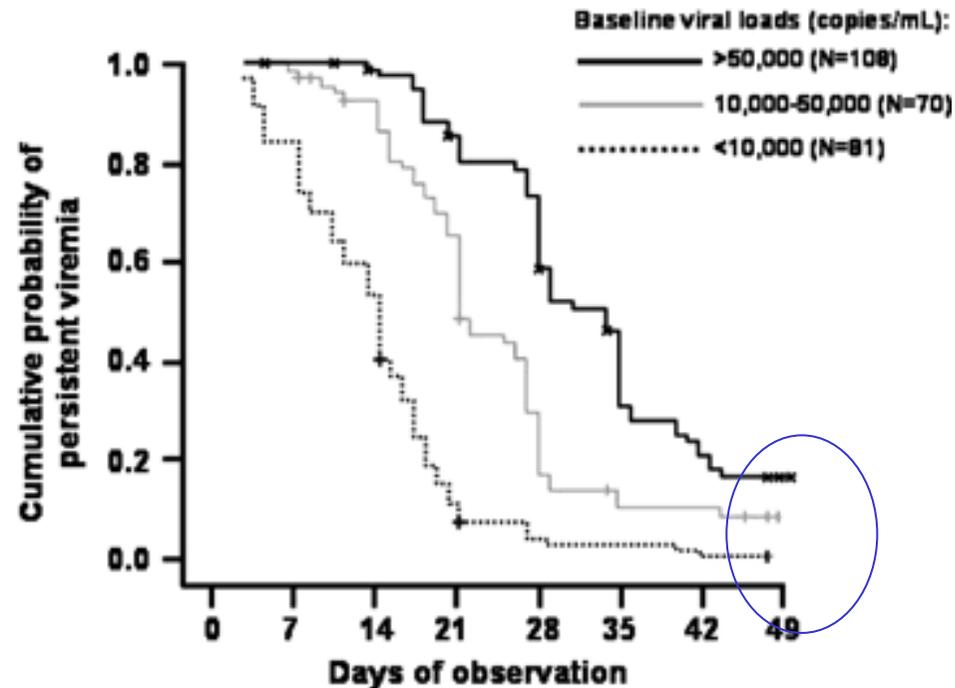


Reduction in CMV viral load with time in patients treated with oral valganciclovir or i.v. ganciclovir. There was no difference in viral load reduction rate between the treatment groups

(cutoff level of 600 copies/mL plasma).

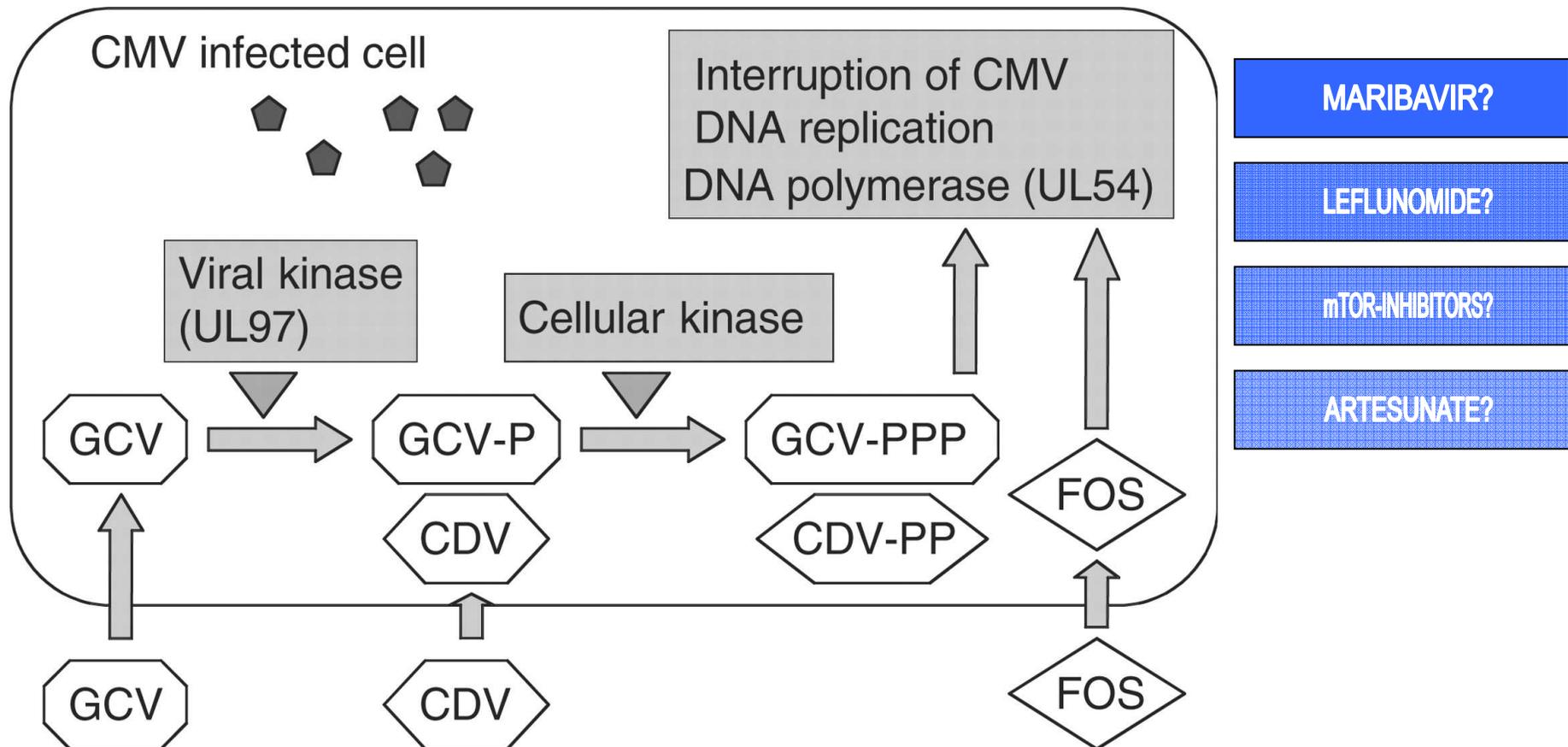
# CMV: therapeutic approach

## VICTOR-trial

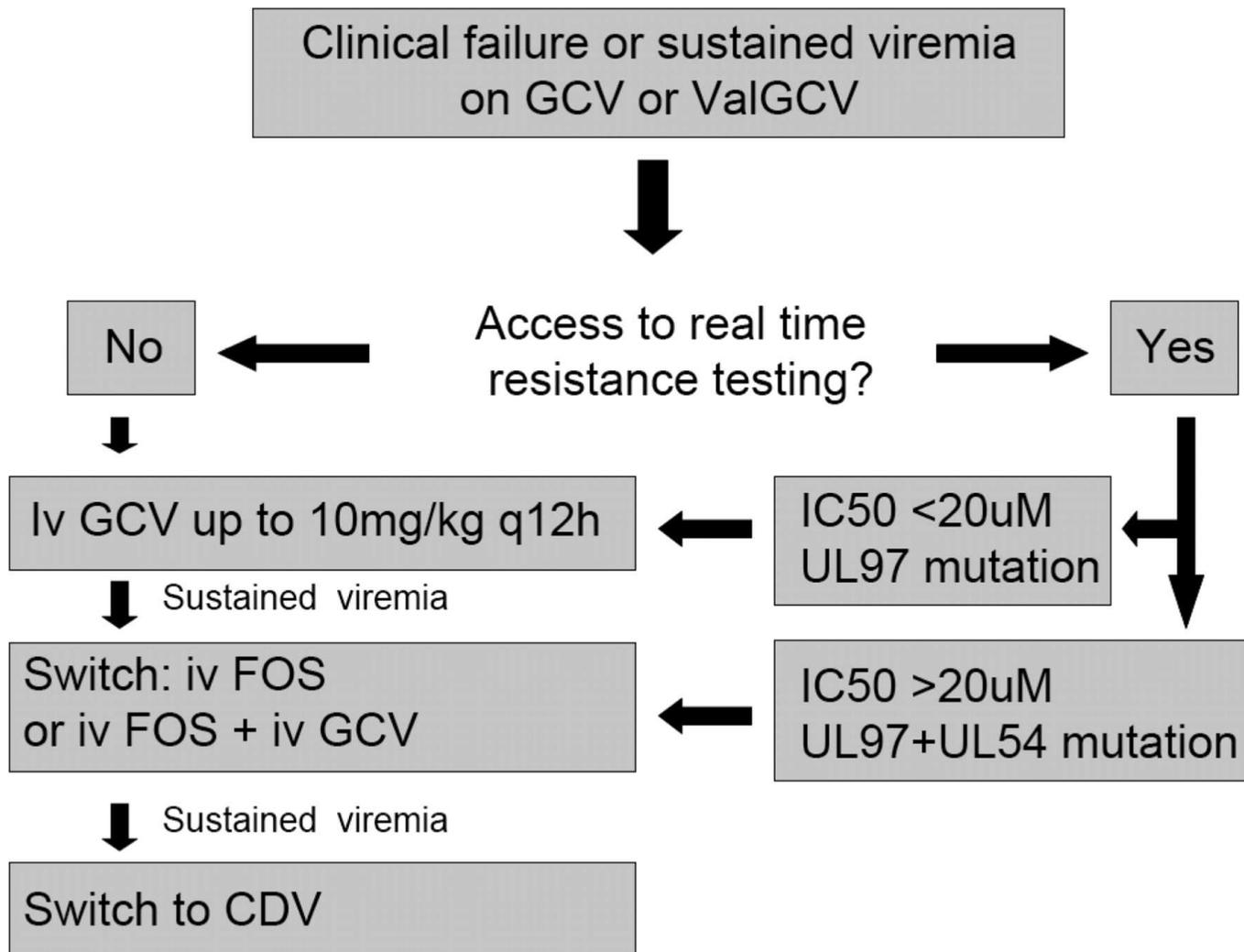


Kaplan–Meier curves showing the influence of three different baseline viral load levels on efficacy of treatment (viral eradication with cutoff level of 600 copies/mL plasma; per-protocol population) ( $p < 0.001$ , log-rank test).

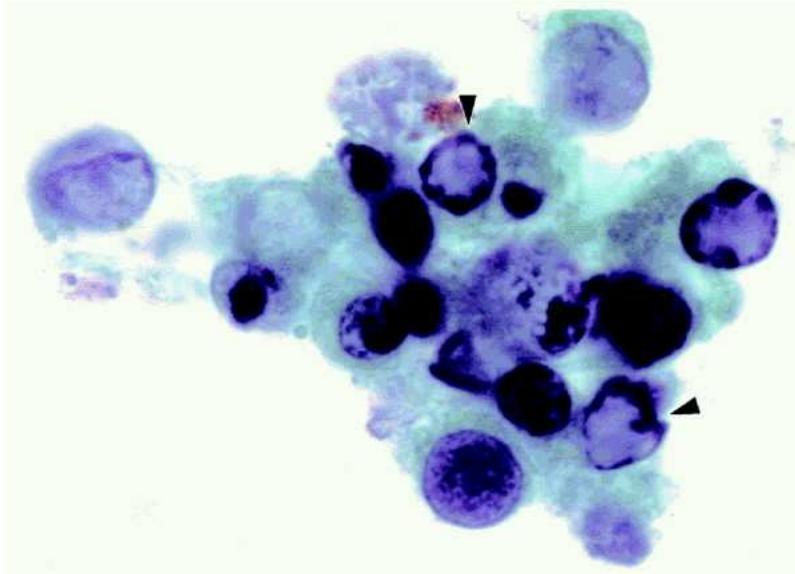
# CMV: Mechanisms of UL97 and UL54 associated Ganciclovir resistance



# CMV: resistance

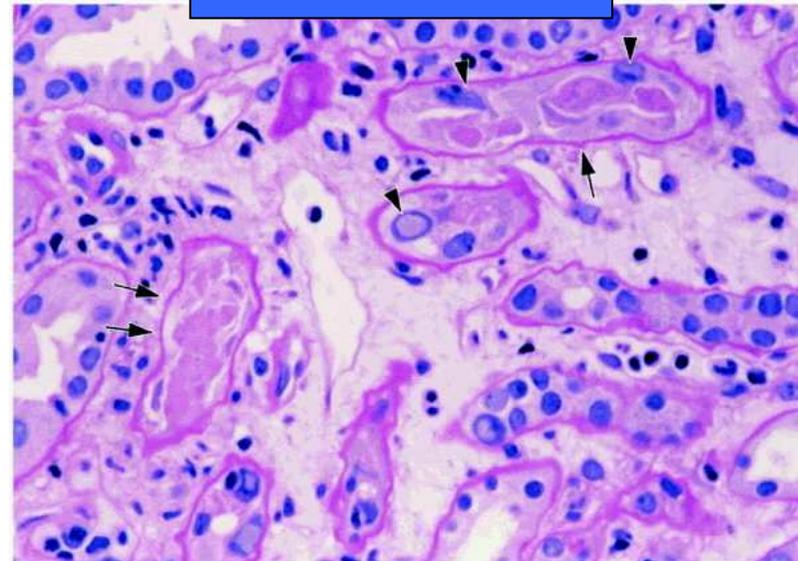


# BK polyoma



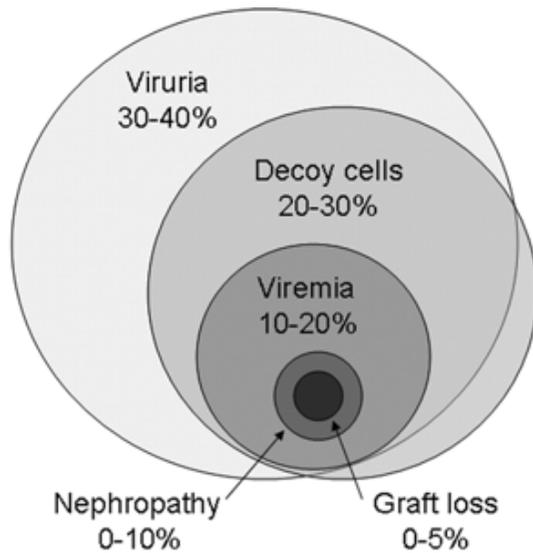
Bonvoisin C et al. Transplantation 2008

CAVEAT focal presentation



The nephropathy is characterized by typical intranuclear viral inclusion bodies in tubular epithelial cells (arrowheads). Tubules show severe virally induced epithelial cell necrosis and denudation of basement membranes (arrows).

# Type and prevalence of BK virus (BKV) infections in kidney transplant recipients.



\*Rare cases of nephropathy without viremia or viremia without viruria may occur

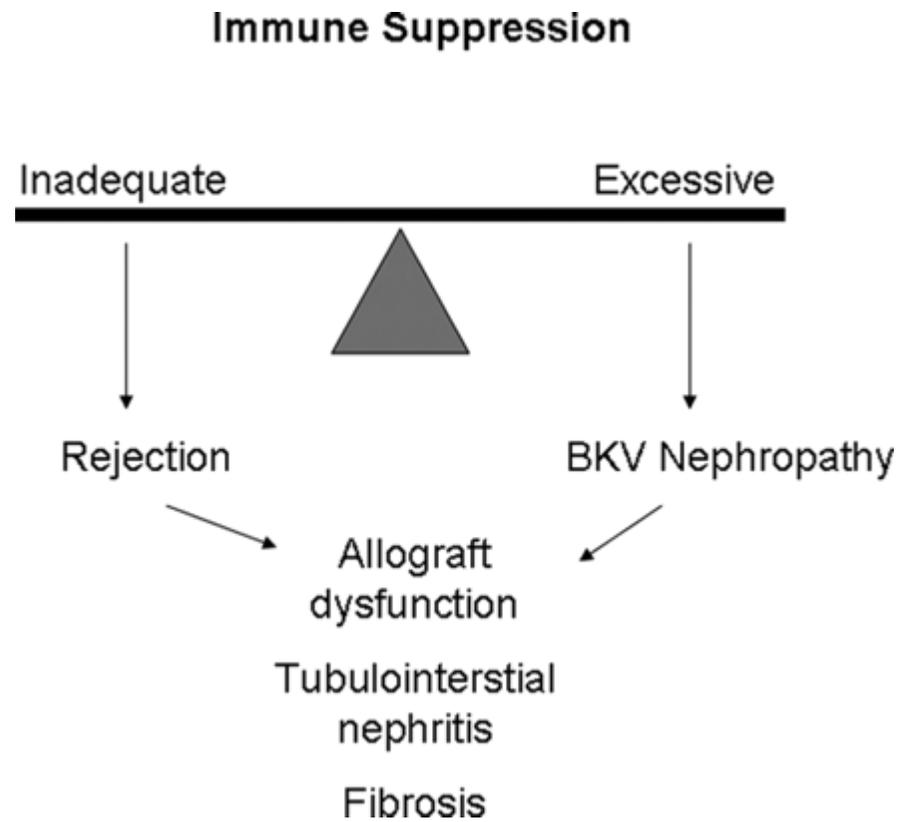
Histologic Pattern	Biopsy Findings	Outcome (ESRD) <sup>a</sup>	Differential
A	Intranuclear viral inclusions Minimal inflammation tubular cell necrosis fibrosis	13%	Normal Coexisting diagnosis
B	Intranuclear viral inclusions	55%	Interstitial nephritis
<b>B1</b>	Moderate to severe interstitial inflammation		
<b>B2</b>	Tubular cell necrosis		
<b>B3</b>	Minimal tubular atrophy and fibrosis		Acute tubular necrosis Acute rejection
C	Intranuclear viral inclusions Moderate to severe tubular atrophy and fibrosis	100%	Chronic allograft nephropathy

# BKVN

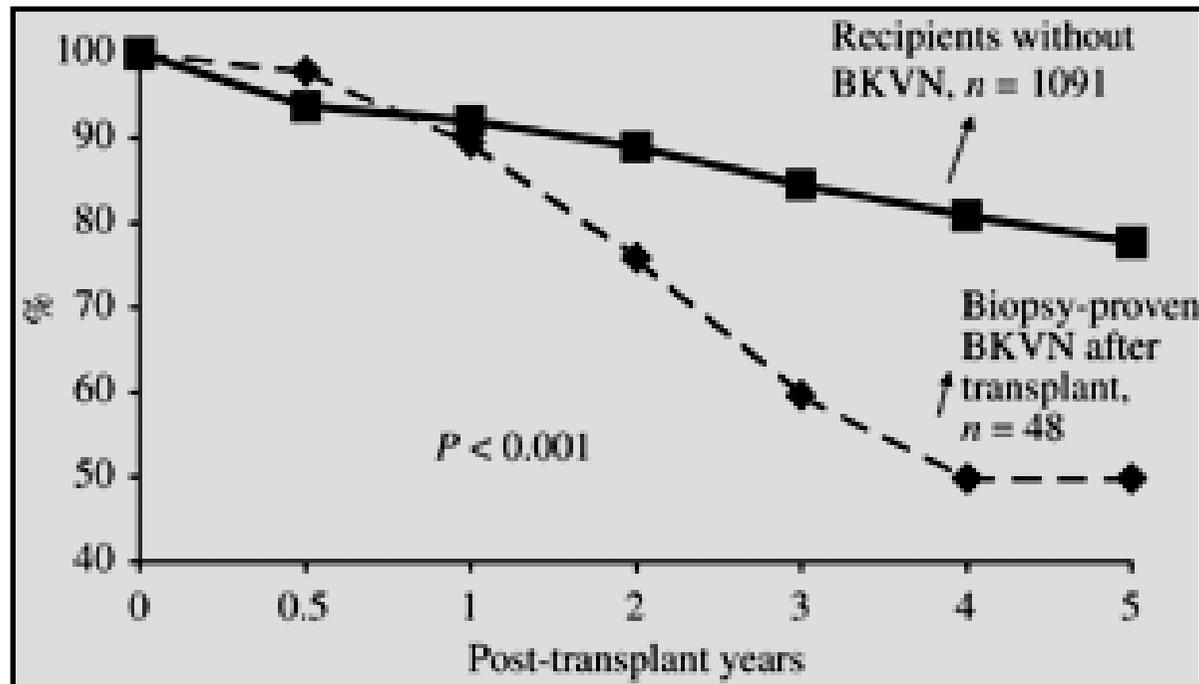
## risk factors

- Immunosuppressive therapy ?
  - Dose reduction can be beneficial
  - TRL, MMF, ATG, corticoid pulses implicated
- Rejection ?
  - Many cases of preceding/coïncidence with acute rejection
    - Augmentation of IS ?
    - BK promoted by rejection?
    - Upregulation of MHC Ag by viral replication?
- Number of HLA mismatches?
- Age
- Gender
- Diabetes mellitus
- Serostatus donor
- HLA C7 allele

# Immunosuppression and BKVN



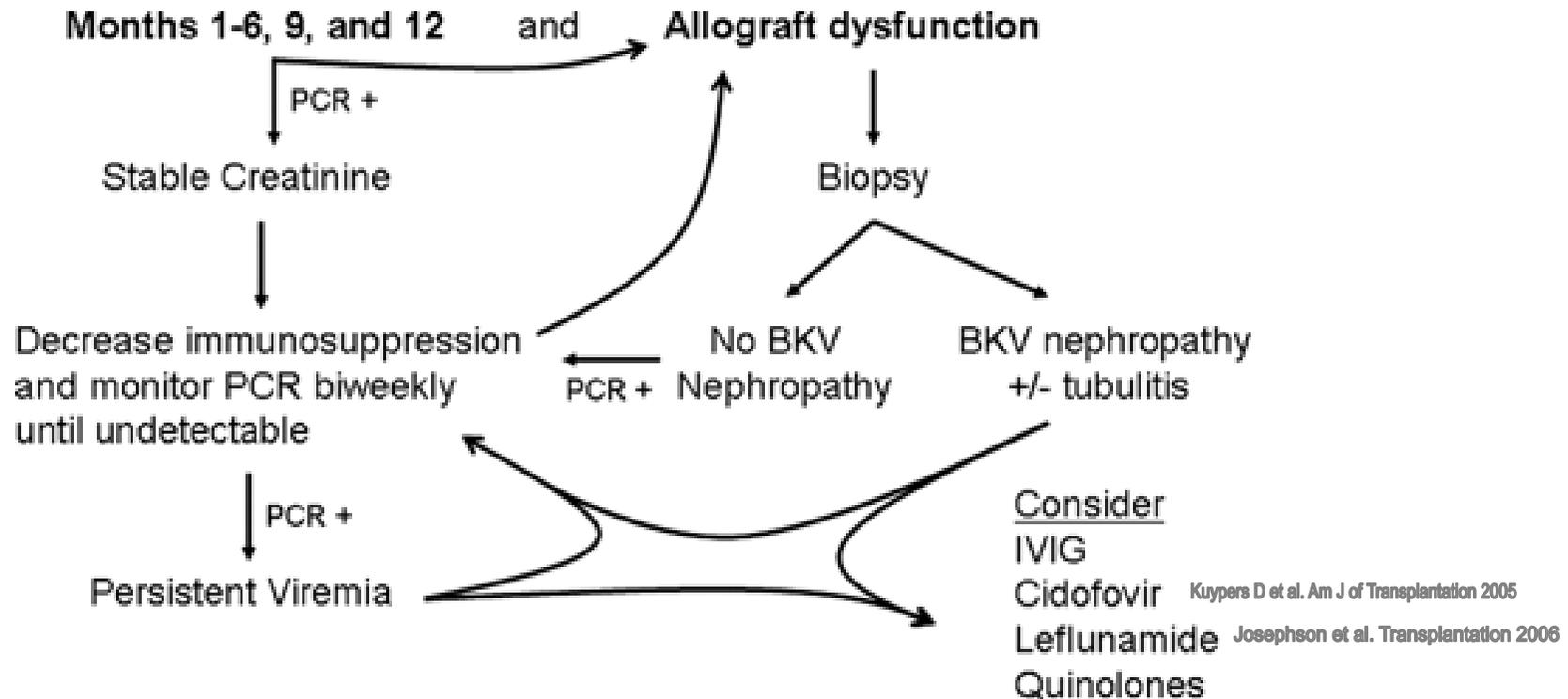
## Lower actuarial graft survival rates in patients with BK polyoma nephropathy.



results from the Medical College of Wisconsin 1996–  
2004

Hariharan S et al. KI 2006

# Screening protocol based on plasma BKV DNA PCR.



# Summary of outcomes in small series of treatment of PVAN since 2002

Parameter	Cidofovir	Leflunomide	Fluoroquinolones	IVIg
Period	2002–08	2003–08	2004–07	2003–07
No. of reports	27	18	2	5
No. of patients per report	1–26	1–30	4–10	1–11
Total no. of patients	184 <sup>a,b</sup>	189 <sup>a,c</sup>	14	29 <sup>b,c</sup>
Percentage of eventually cleared viraemia	82/168 (49%)	72/148 (49%)	0/10 (0%)	15/29 (52%)
Percentage of graft loss	42/184 (23%)	32/189 (17%)	0/14 (0%)	2/29 (7%)

All patients also had concomitant immunosuppression dose reduction.

<sup>a</sup>Three reports included a total of 25 patients on combined cidofovir and leflunomide.

<sup>b</sup>One report included one patient on combined cidofovir and IVIg.

<sup>c</sup>Two reports included 16 patients on combined leflunomide and IVIg.

# CONCLUSION

- Many studies about infections in SOT single-center, retrospective, prone to bias
- Unfortunately no trend in decrease of (bacterial/fungal) infections
- CMV: still remaining questions about
  - resistance
  - the optimal duration of both prevention and treatment
  - genotyping and the place of newer drugs in treatment and prevention
  - prophylaxis versus pre-emptive treatment: no multicenter well-designed RCT
- BK polyoma: still controversial issues such as treatment, retransplantation and screening protocols.
- Poor ability to measure alloimmune activation and net state of immunosuppression