

Immunomodulatory effects of CMV disease

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Outline

- The transplant troll
- The “indirect” effects of CMV disease
 - Immunosuppressive effects
 - Proinflammatory effects
- The impact of antiviral prophylaxis

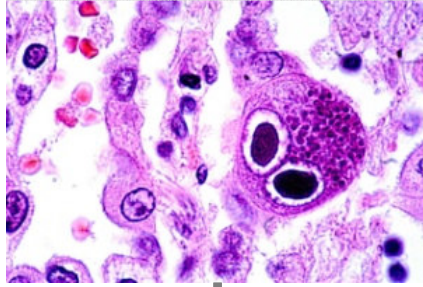
Cytomegalovirus

in organ transplantation

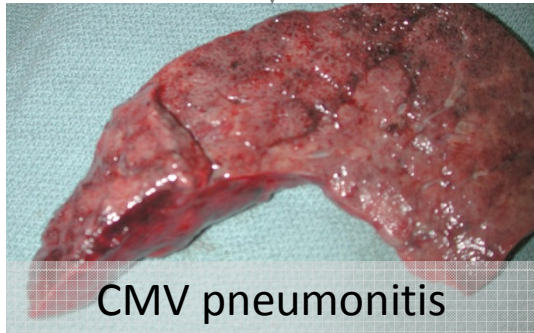
The transplant Troll in the 70's...

- CMV disease was associated with a significantly increased incidence of transplant nephrectomy and death
- 12/60 patients (20%) developed lethal CMV disease
- The only patients to die with serious bacterial, fungal or protozoan infection during the period of this study had concomitant overt CMV disease

CMV infection

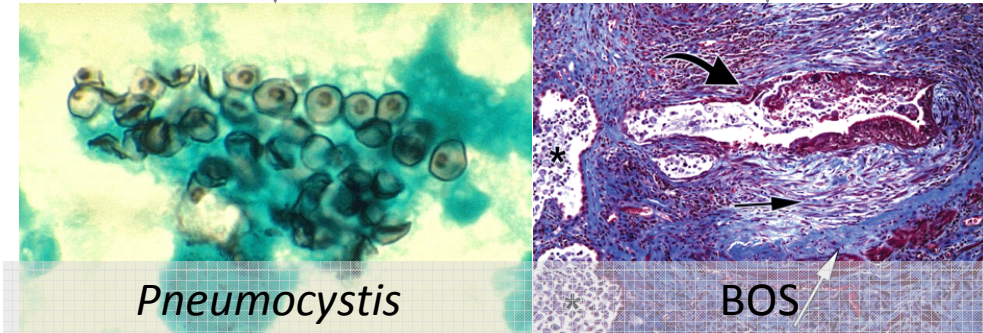


Direct effects



CMV pneumonitis

Immunomodulatory effects



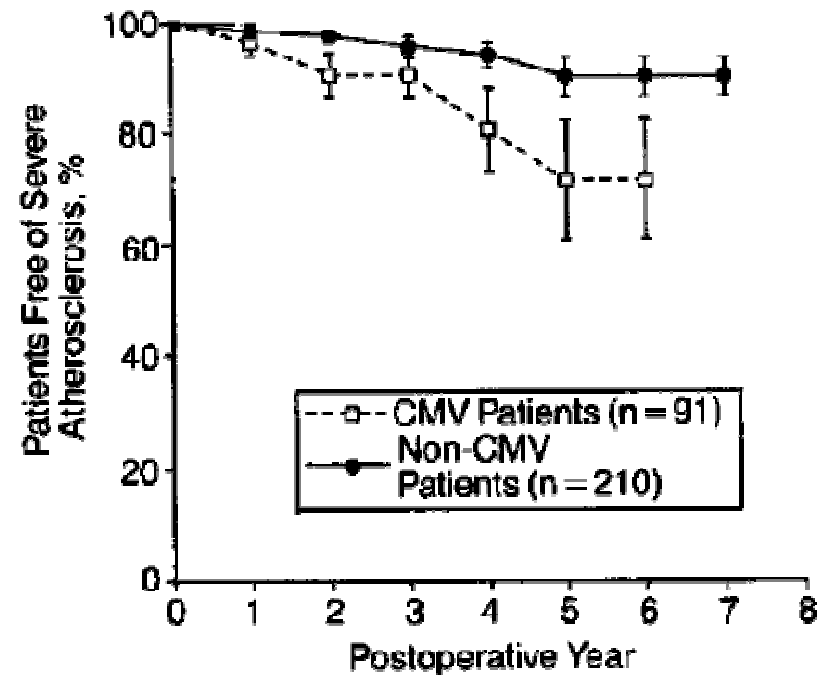
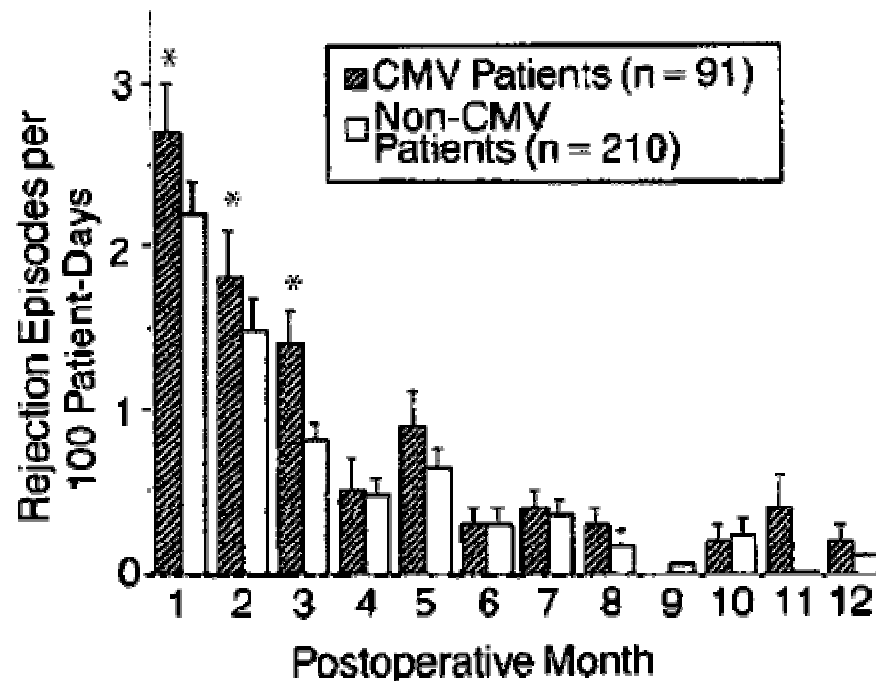
Pneumocystis

BOS

CMV is associated with Bronchiolitis Obliterans Syndrome

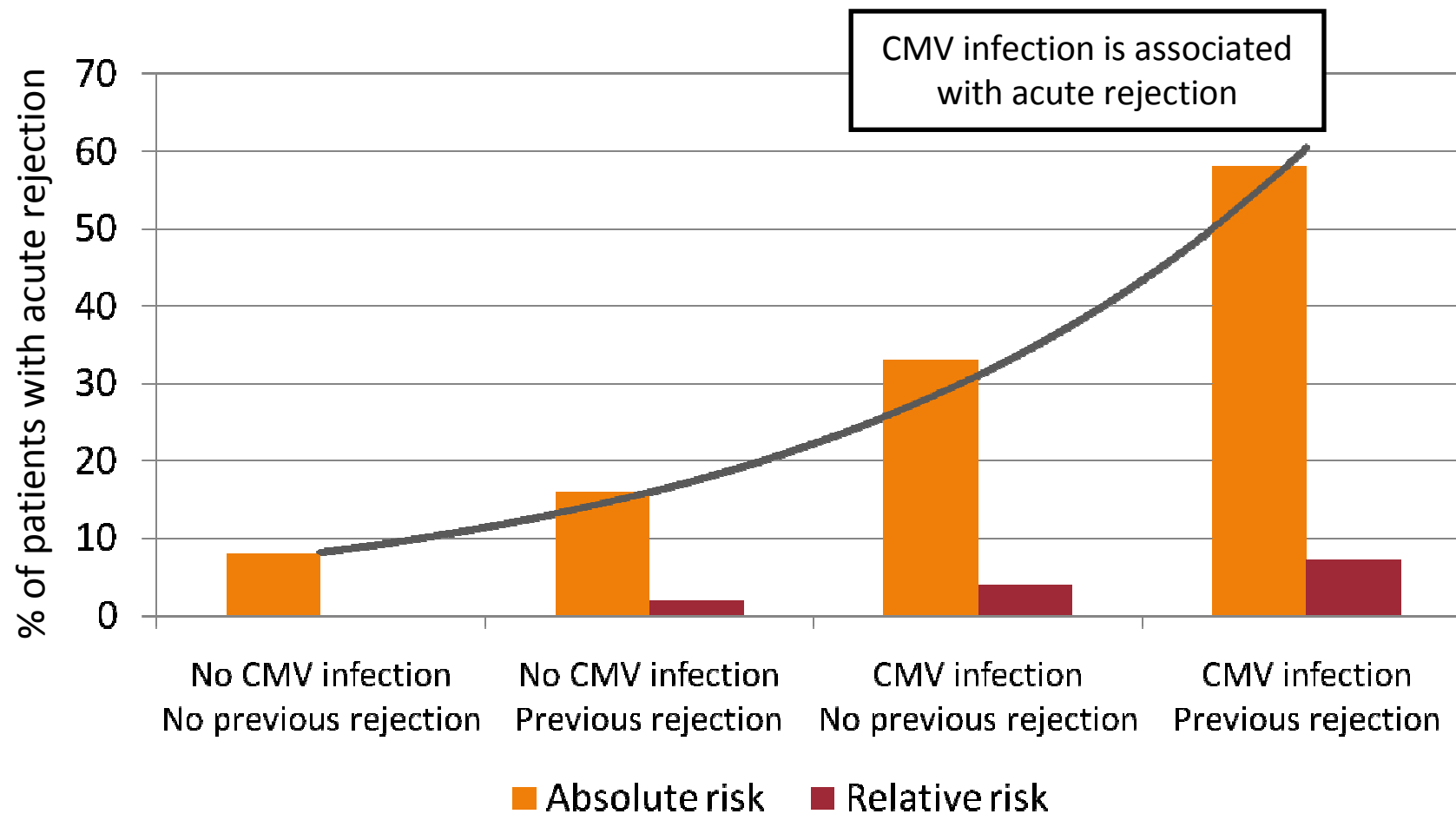
Risk factors for OB	p-value
Airway ischemia	0.004
Late bacterial pneumonia	NS
CMV disease	0.0006
<i>Pneumocystis</i>	NS
Acute rejection 3 times	0.00001
Acute rejection grade III/IV	0.0001

Cytomegalovirus Infection Is Associated With Cardiac Allograft Rejection and Atherosclerosis

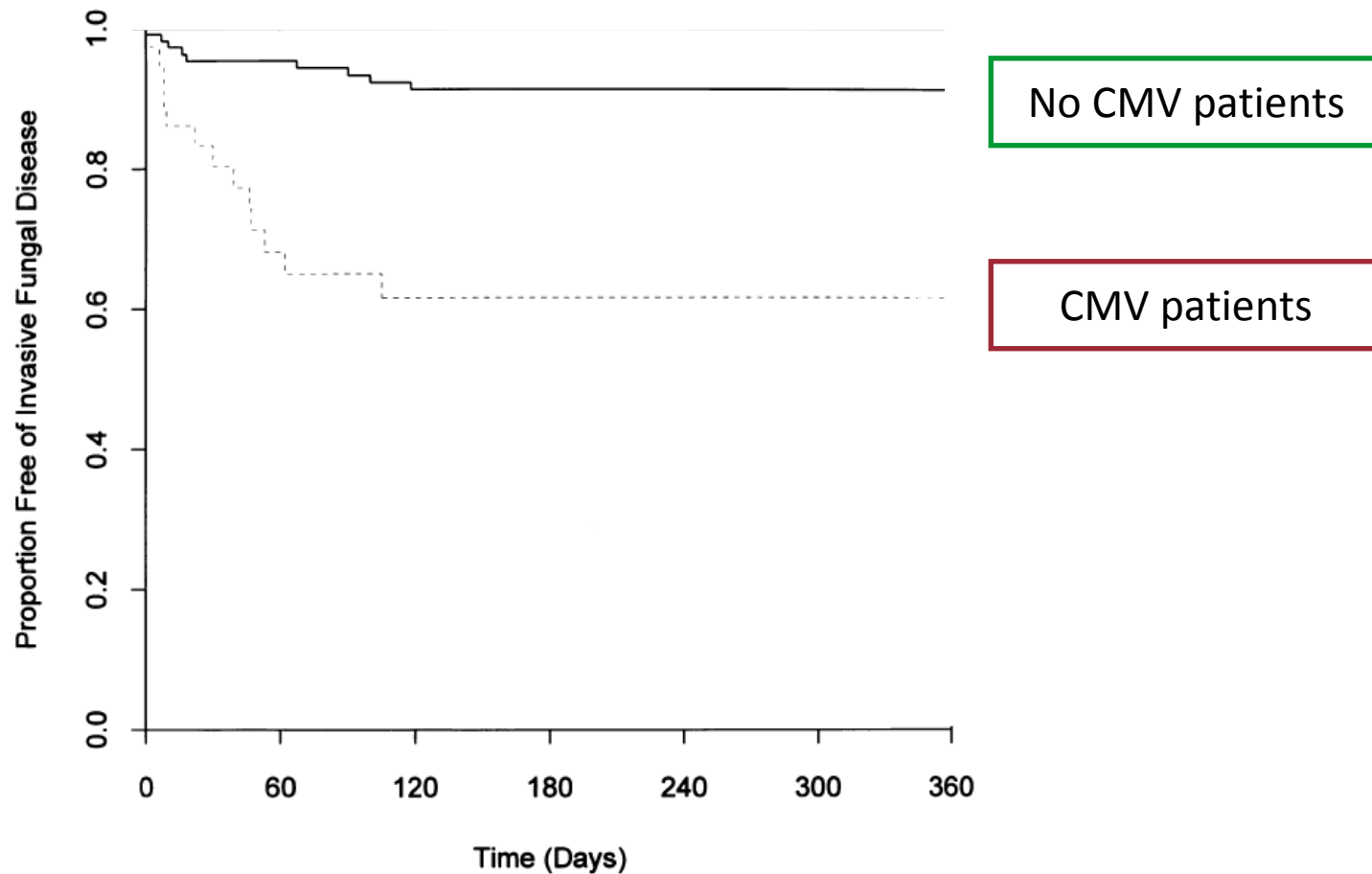


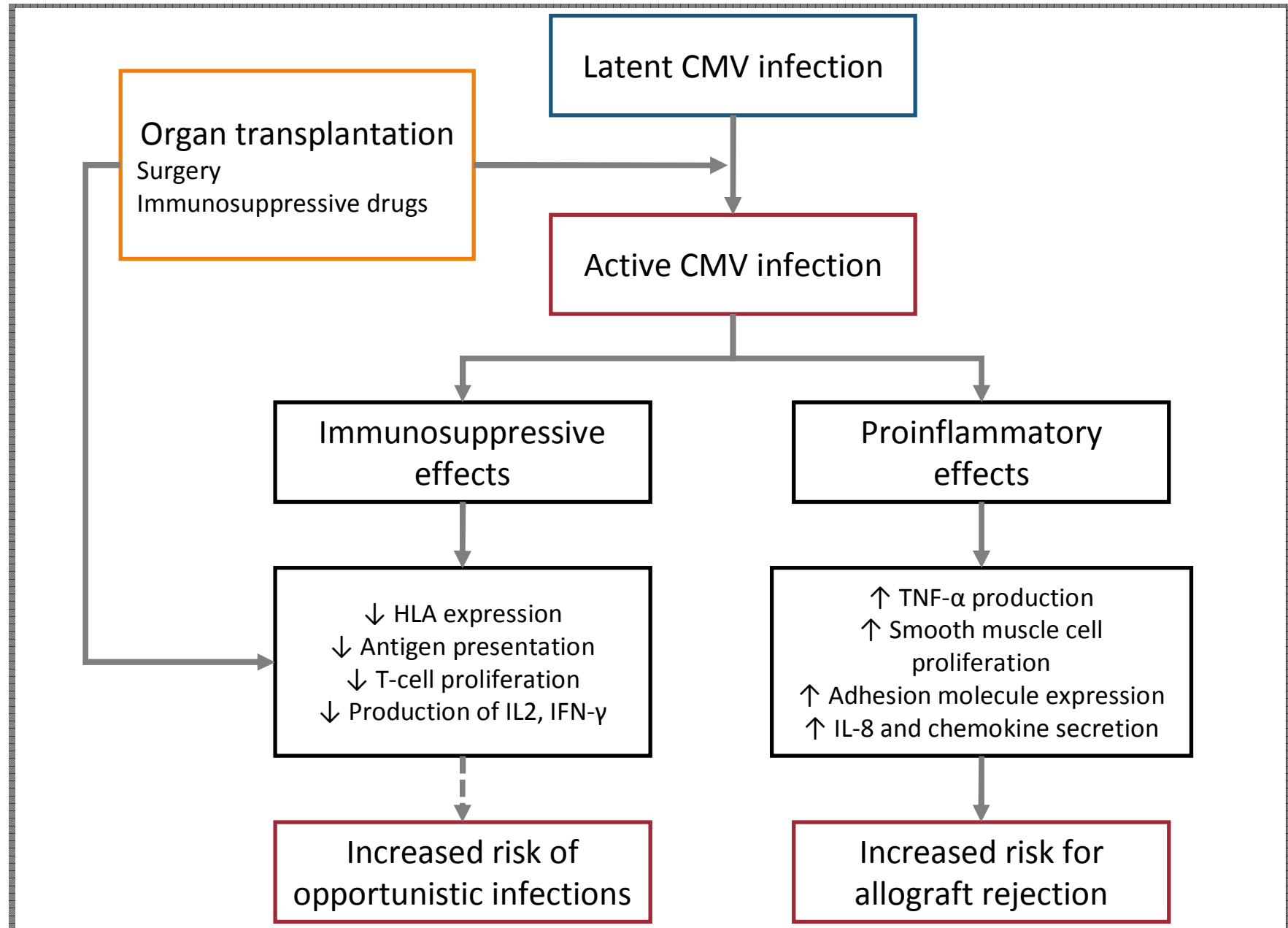
CYTOMEGALOVIRUS INFECTION—AN ETIOLOGICAL FACTOR FOR REJECTION?

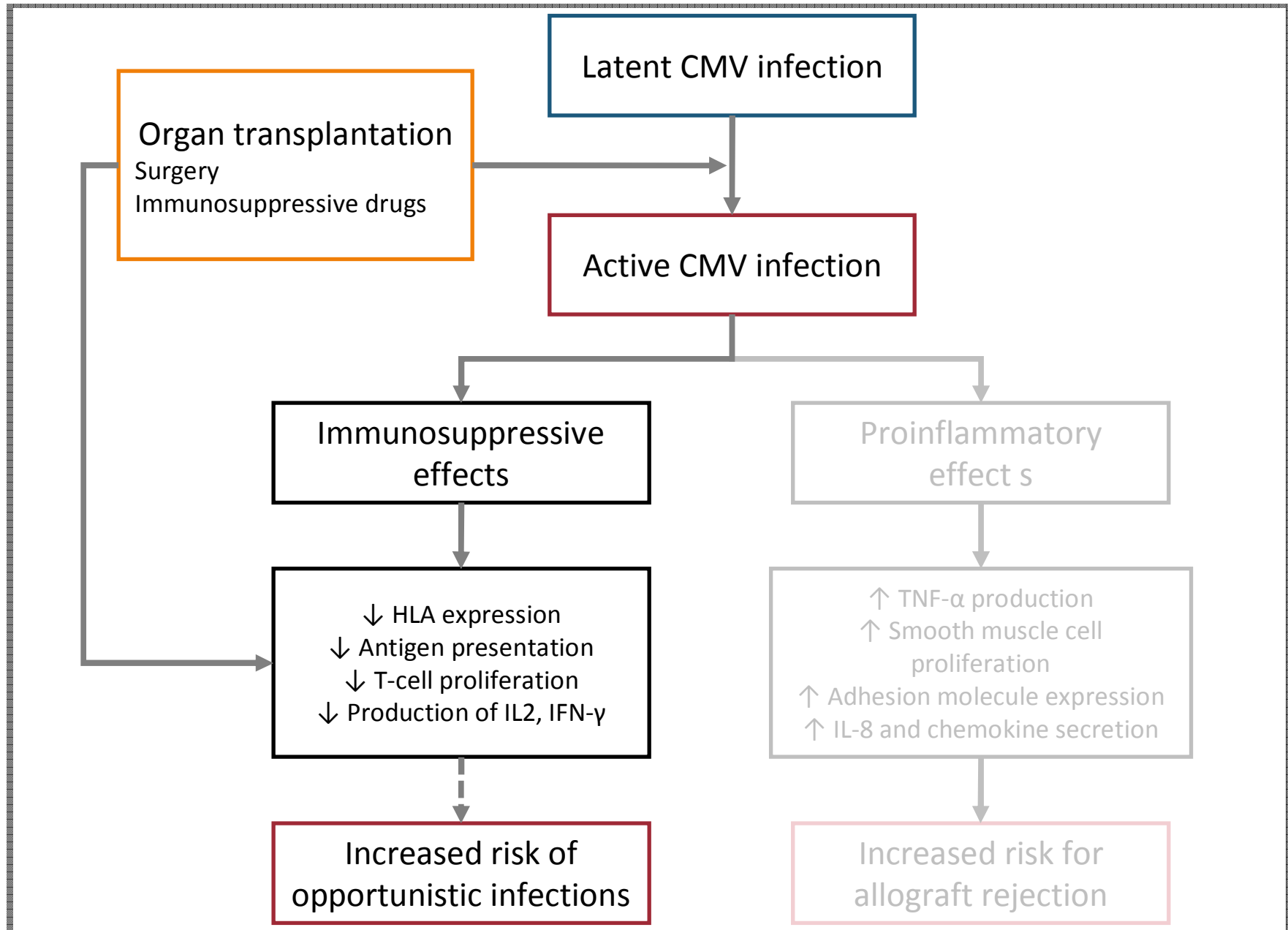
A PROSPECTIVE STUDY IN 242 RENAL TRANSPLANT PATIENTS



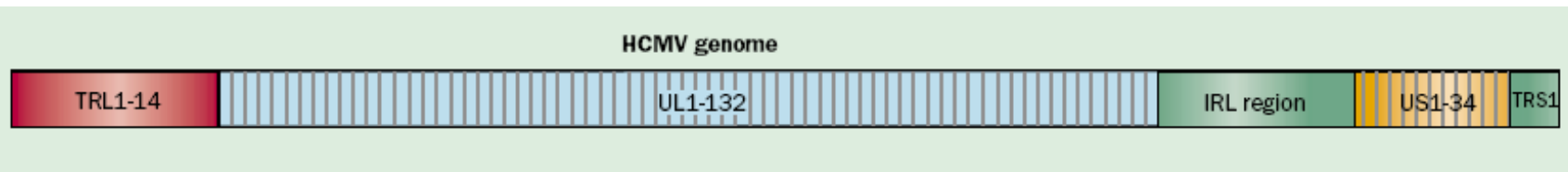
CMV is a risk factor for invasive fungal infection in liver transplant recipients







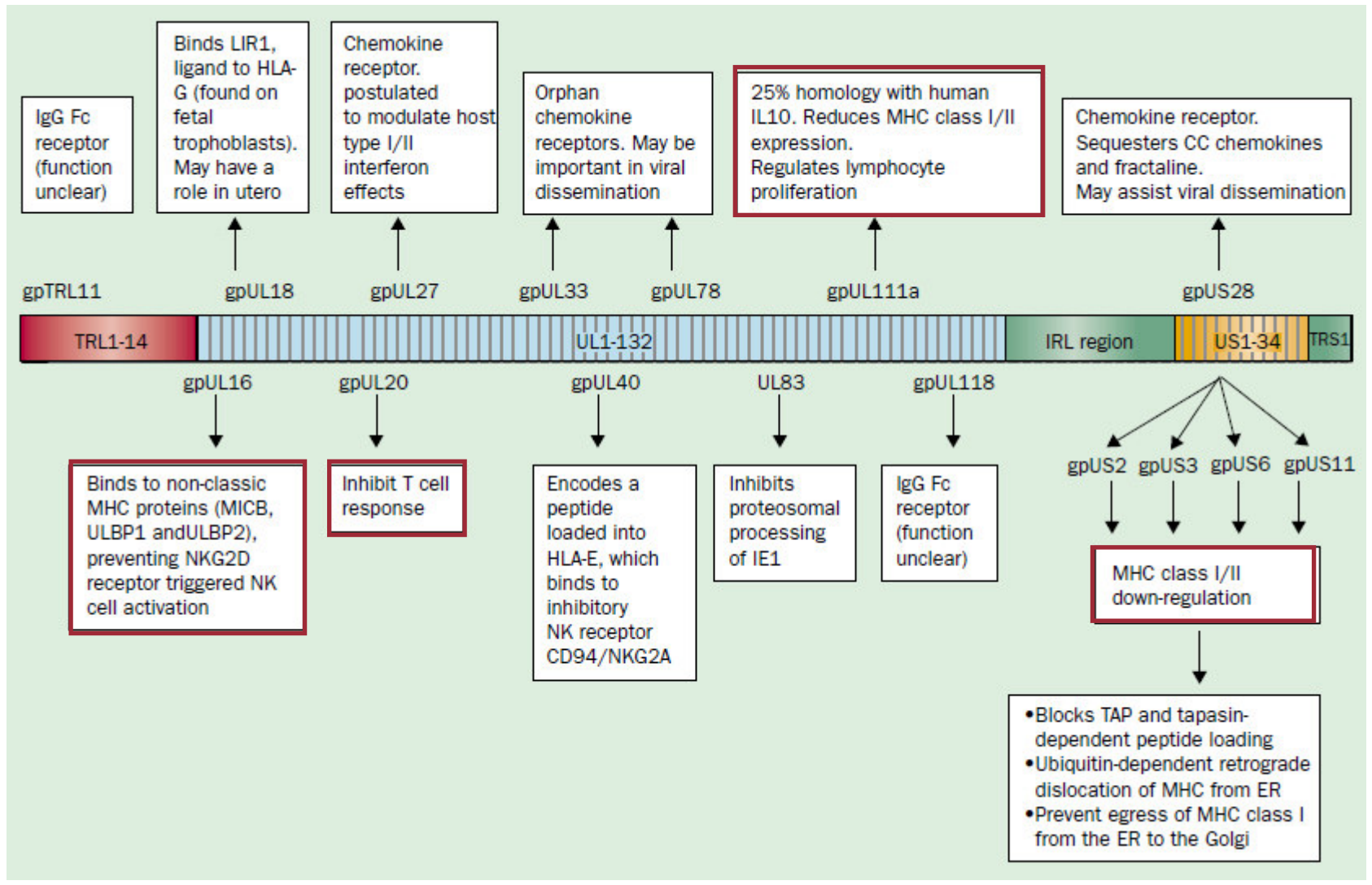
CMV genome structure



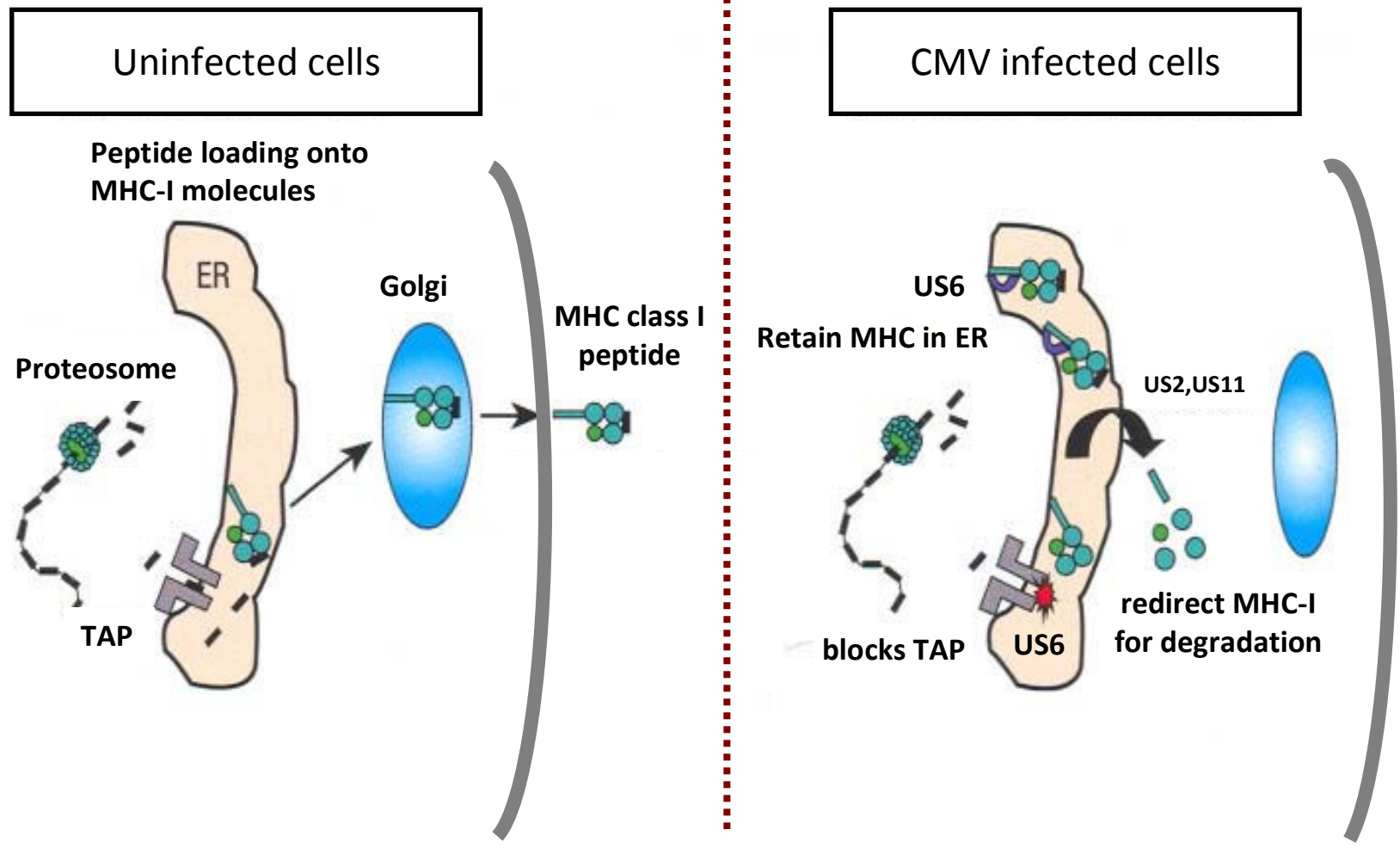
Genetic composition

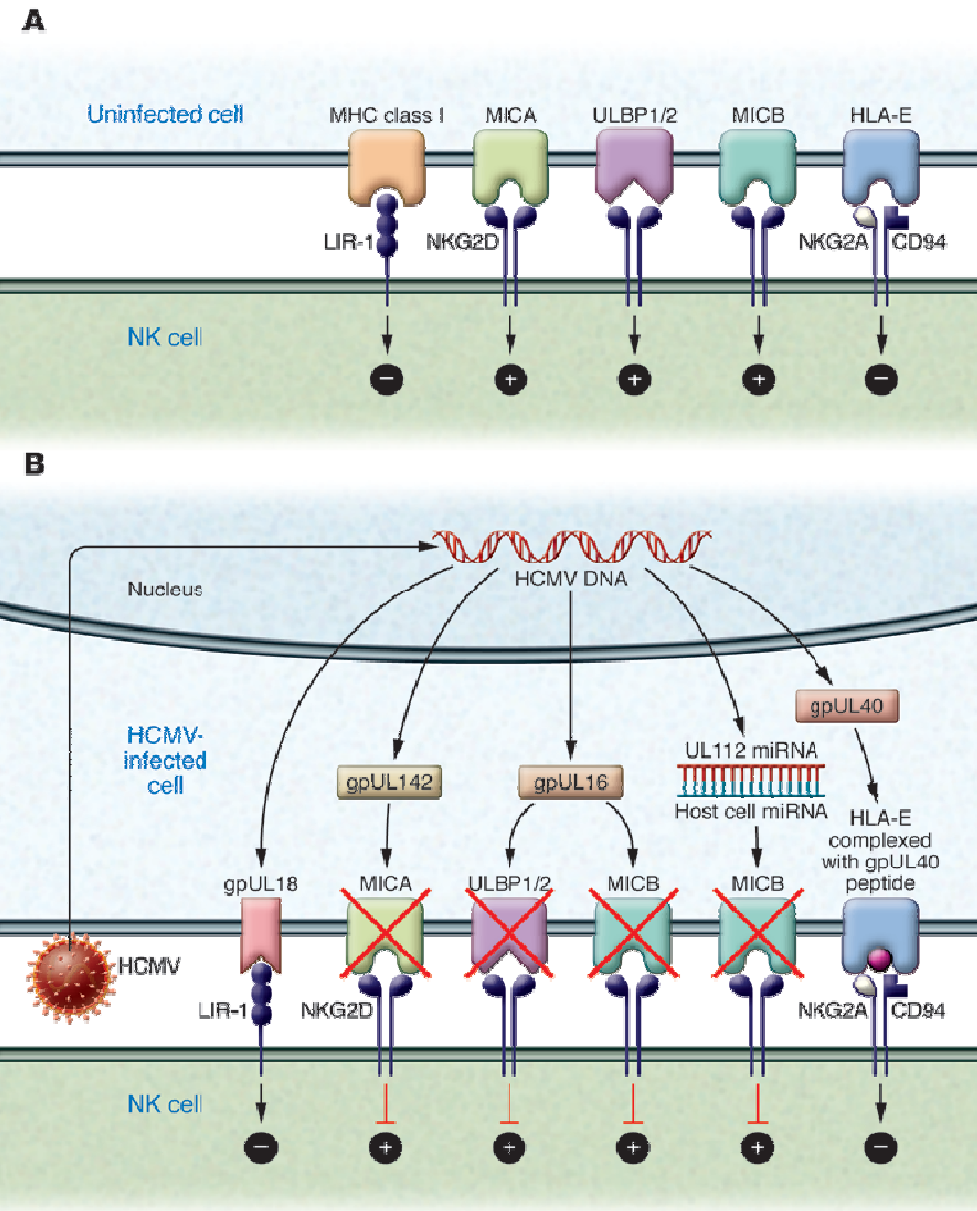
- 2 unique regions of DNA – UL and US and flanking terminal repeat regions (TR) and internal repeat regions (IR)
- Encodes >150 proteins
- Gene expression occurs in a temporal cascade (immediate-early, early, and late)

Many CMV-encoded immune evasion gene products!

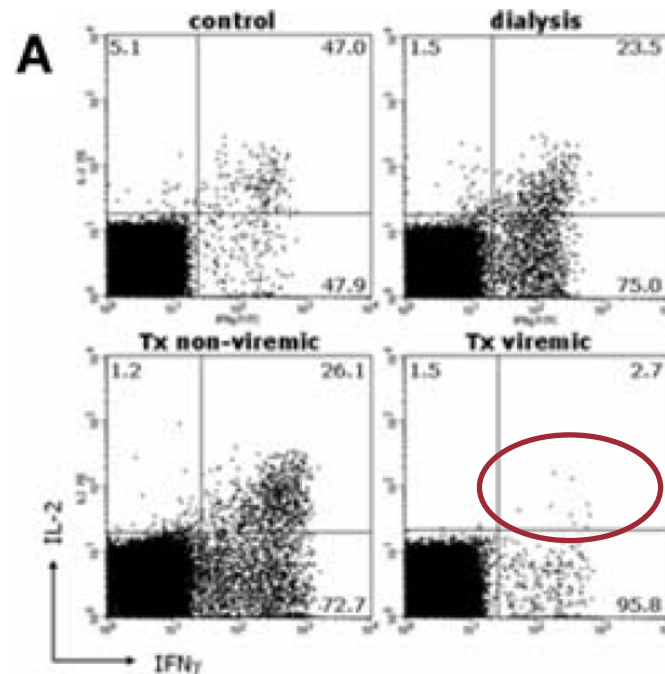


Viral immune evasion strategies





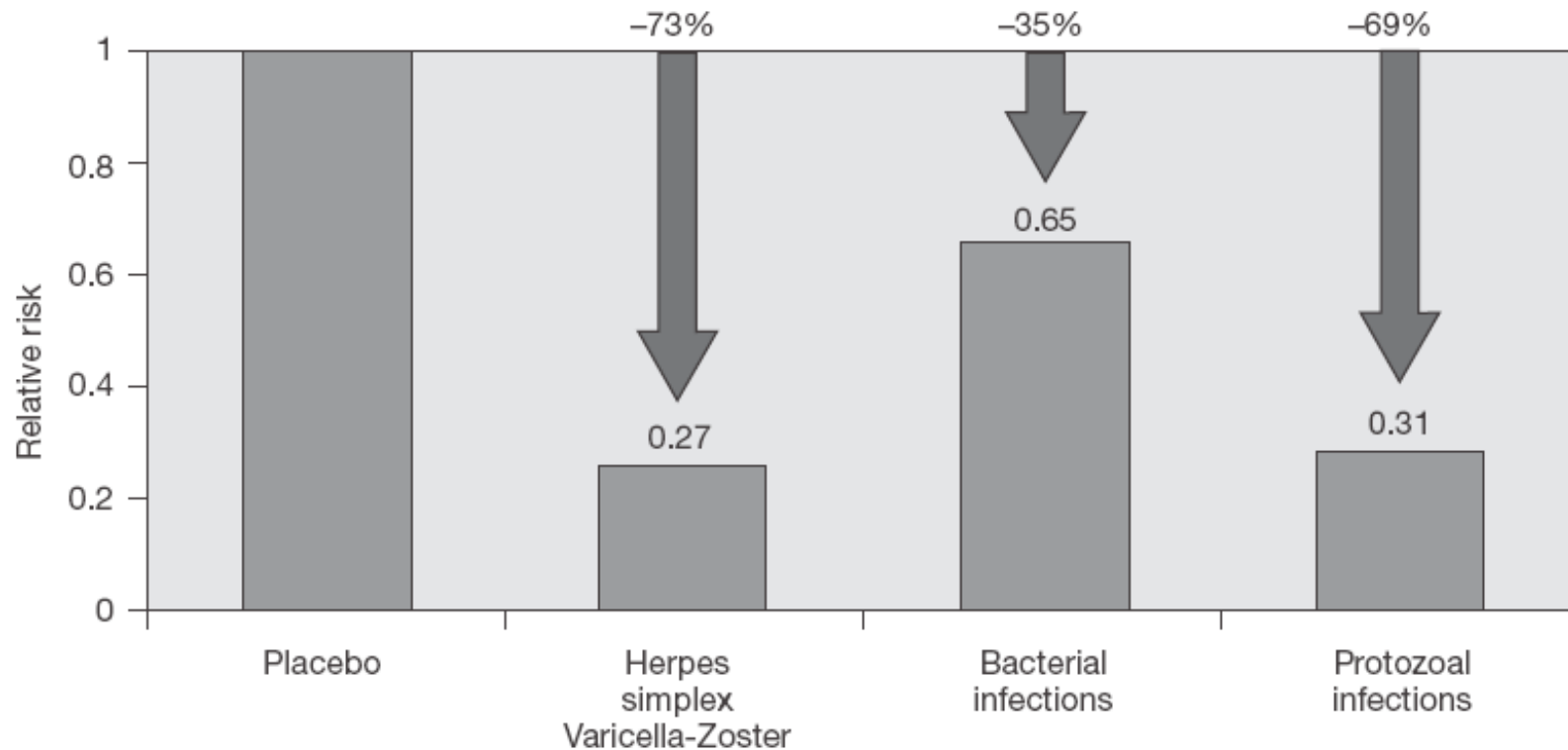
CMV-specific T cells from CMV viremic patients showed a significant loss of IL-2 production

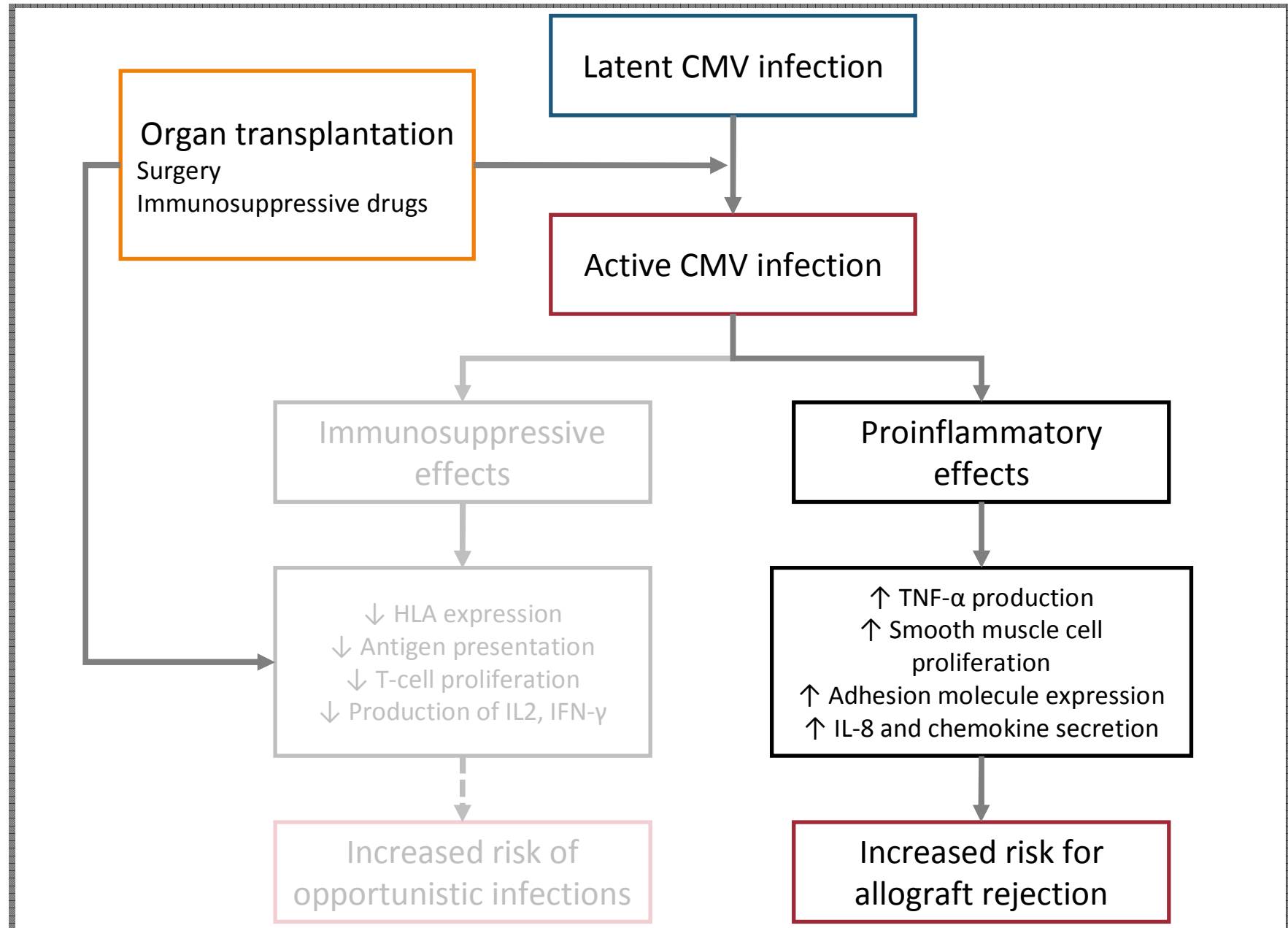


IL-2

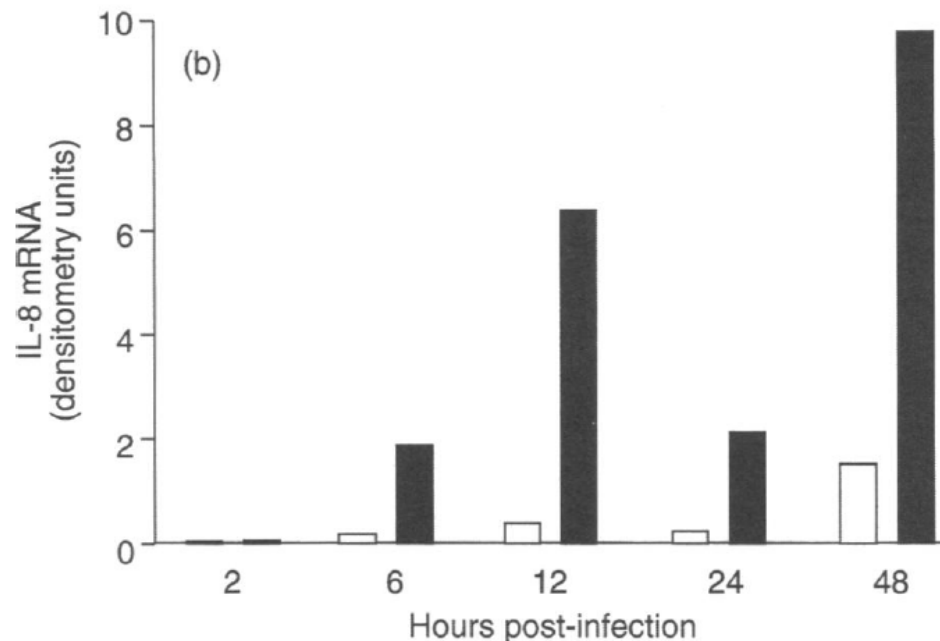
Stimulates the growth, differentiation and survival of antigen-selected cytotoxic T cells
Necessary for the development of T cell immunologic memory

Anti CMV prophylaxis is associated with less opportunistic and other infections





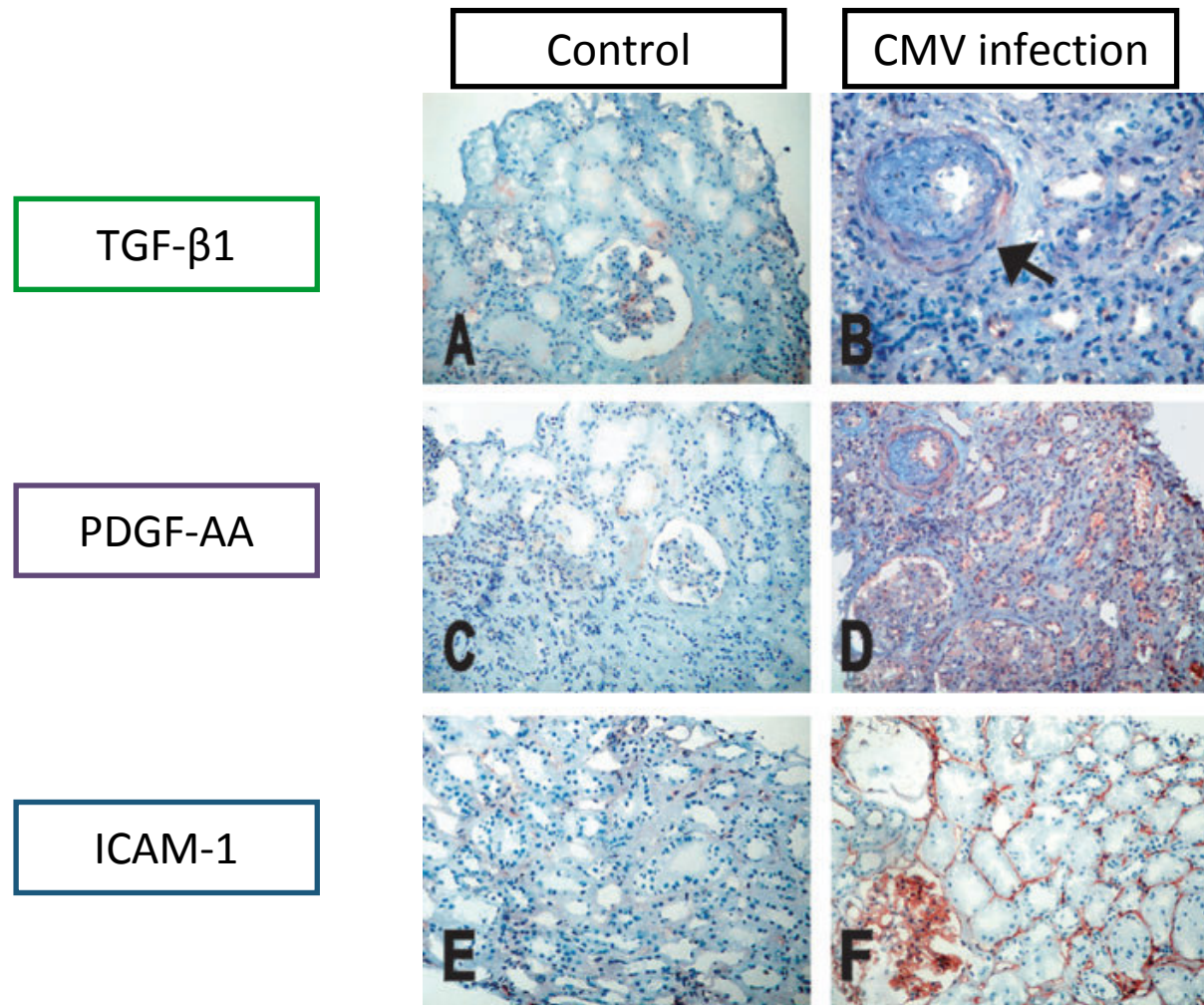
CMV infection up-regulates interleukin-8 gene expression in fibroblasts



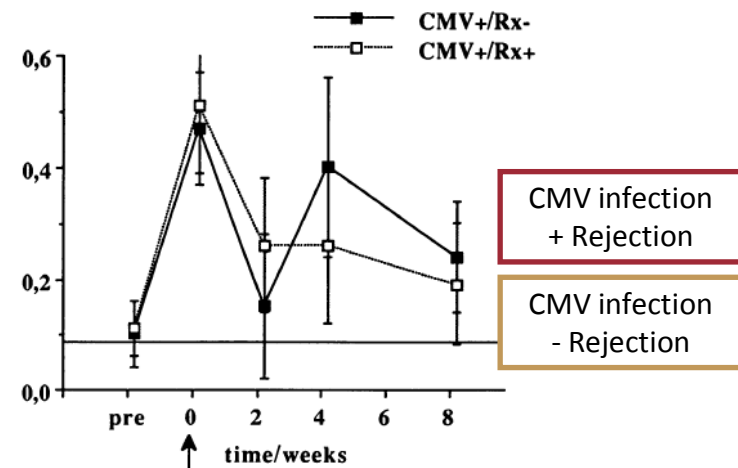
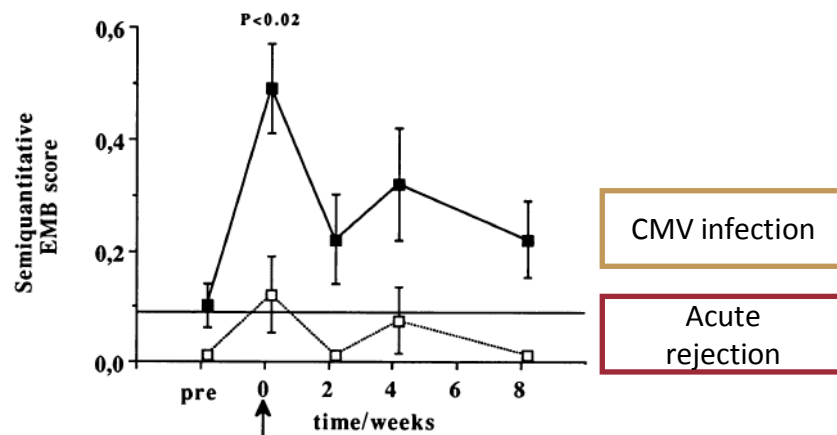
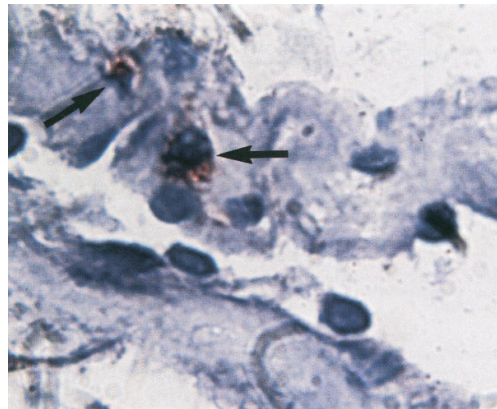
IL-8

Major mediators of the inflammatory response
Induction of chemotaxis in neutrophils
Plays a role in the pathogenesis of bronchiolitis

Persistent CMV infection is associated with increased expression of growth factors



CMV infection is associated with endothelial inflammation in HTx recipients



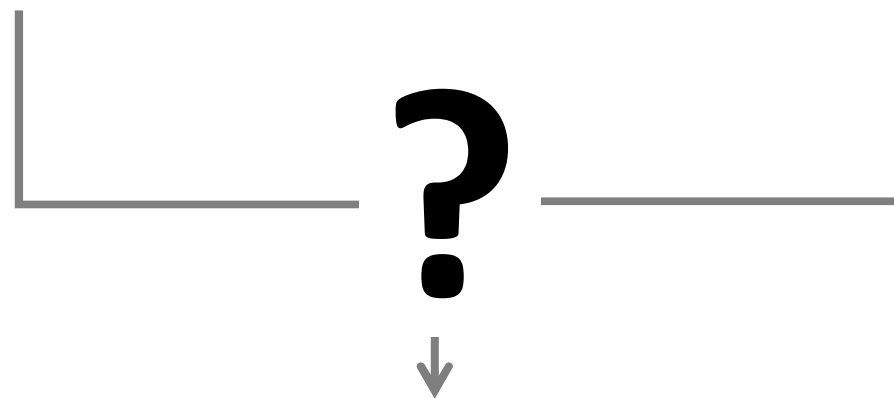
Possible role of MBL deficiency in CMV diases and post transplant diabetes

Association Between Mannose-Binding Lectin Deficiency and Cytomegalovirus Infection After Kidney Transplantation

Oriol Manuel,¹ Manuel Pascual,² Marten Trendelenburg,³ and Pascal R. Meylan^{4,5}

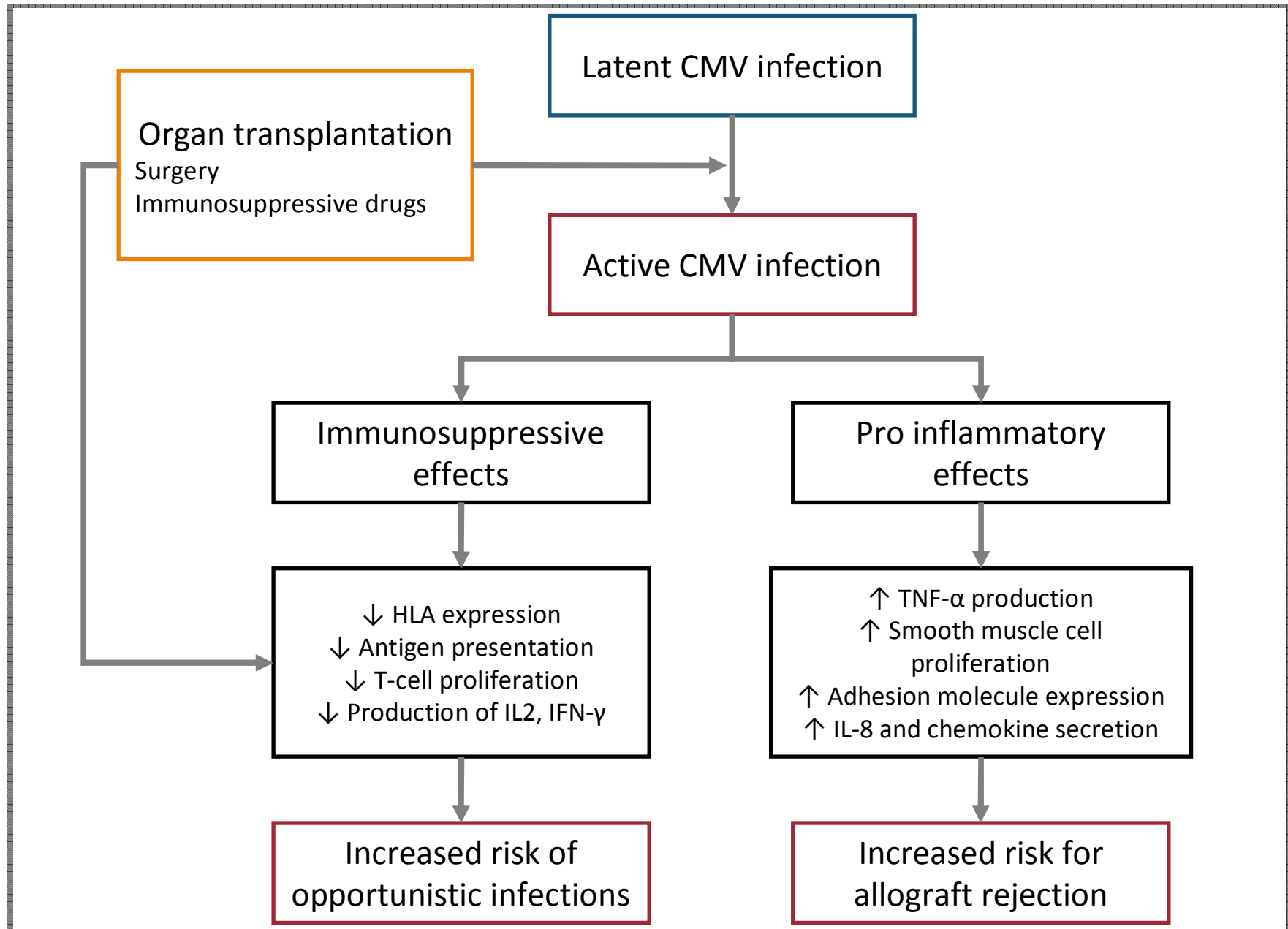
Low Serum Mannose-Binding Lectin as a Risk Factor for New Onset Diabetes Mellitus After Renal Transplantation

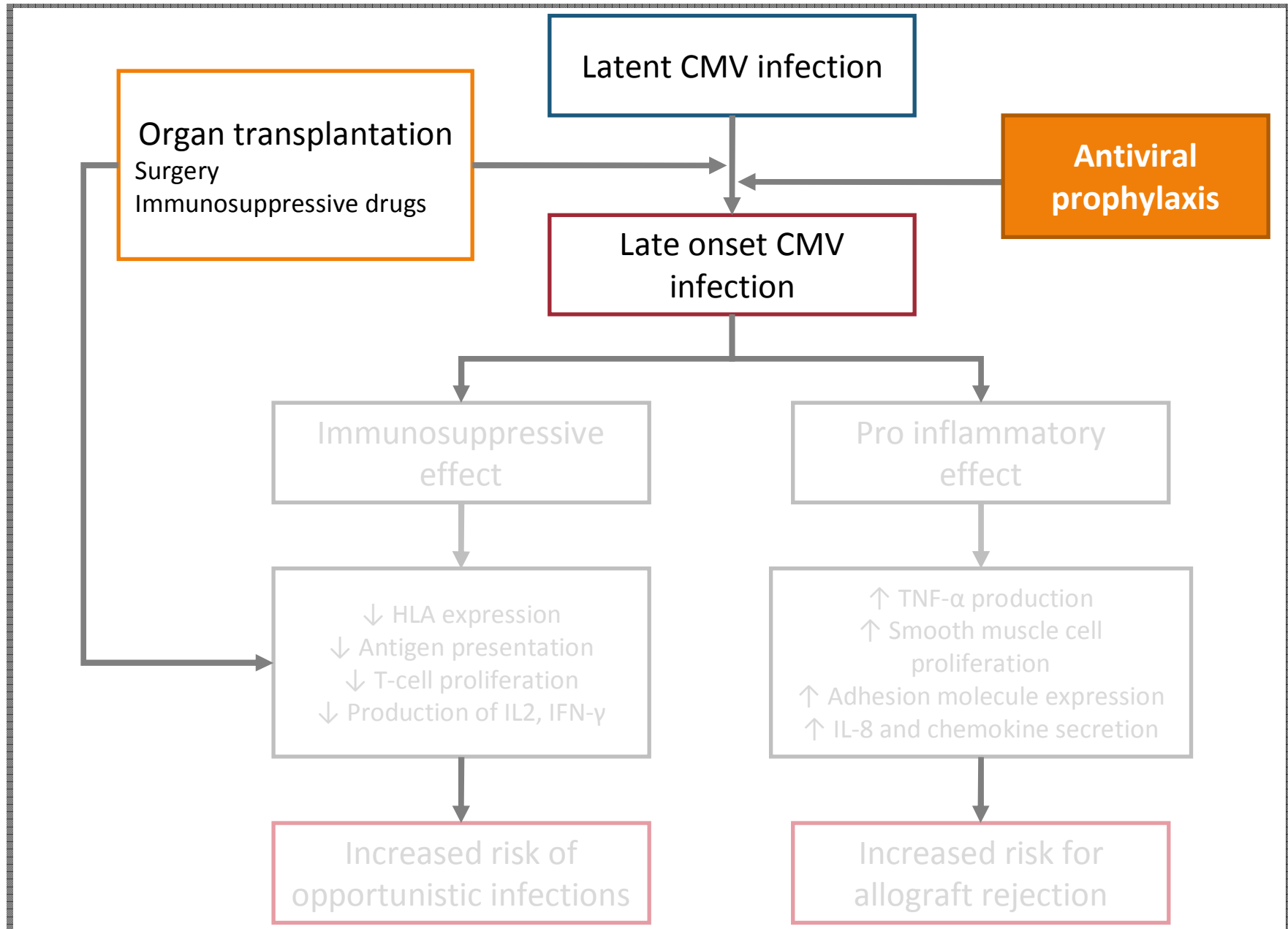
Meritzell Ibernou,¹ Francesc Moreso,² José M. Moreno,³ Oriol Bestard,² Josep M. Cruzado,² Josep M. Grinyó,² Wifredo Ricart,³ José M. Fernández-Real,³ and Daniel Sorón^{2,4}



Cytomegalovirus infection and new-onset post-transplant diabetes mellitus

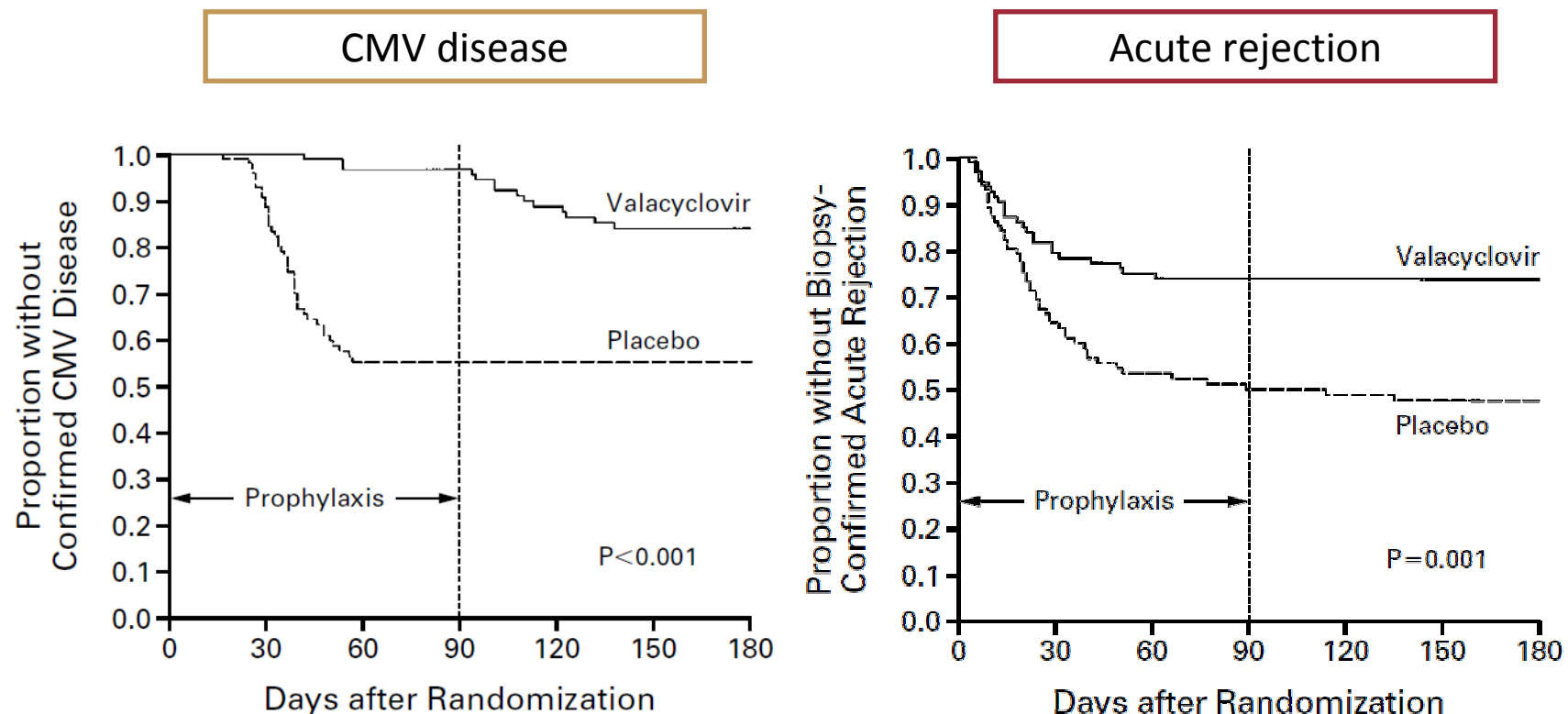
Leung Ki E-L, Venetz J-P, Meylan P, Lamoth F, Ruiz J, Pascual M.
Cytomegalovirus infection and new-onset post-transplant diabetes mellitus.
Clin Transplant 2008; 22: 245–249. © 2008 Blackwell Munksgaard



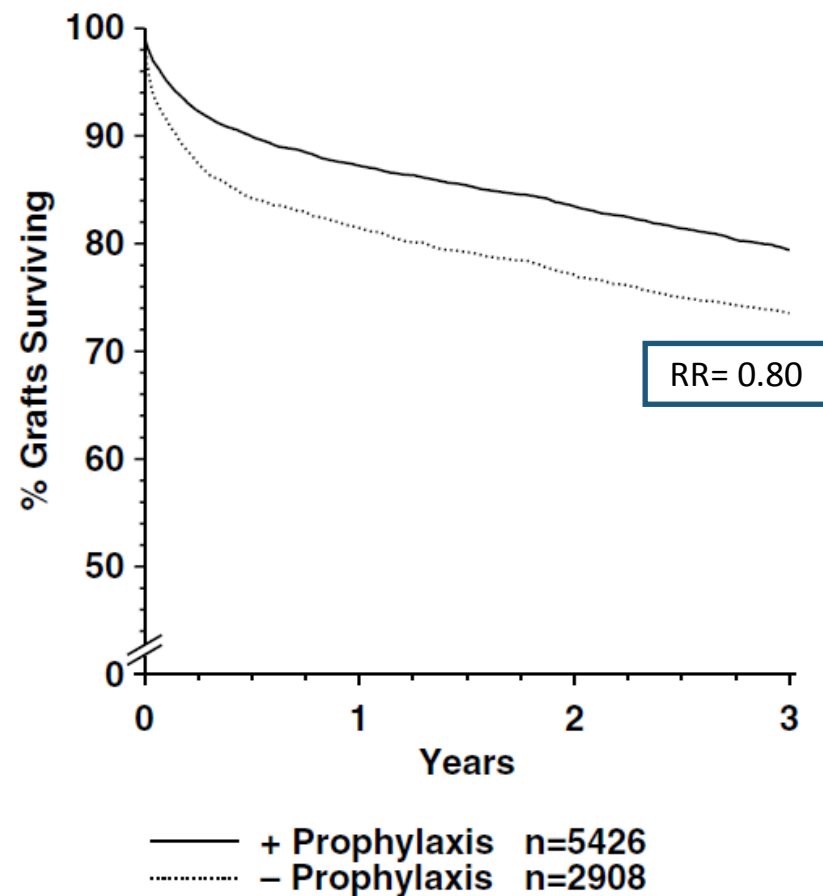


	1980s	1990s	2000s
Diagnostic	↑ x4 Ig	Viral culture / Antigenemia	Antigenemia / PCR
Prevention	None	iv GCV, po GCV, Preemptive	po VGC, Preemptive
Treatment	None / ivGCV	ivGCV	ivGCV / VGC
Acute rejection rates	50%	20-50%	10-20%
Immunosupresion	AZA +/- Cyclo	Cyclo/tacro + AZA/MMF	CNI + MMF, mTORs, etc

Antiviral prophylaxis reduces the rate of acute rejection

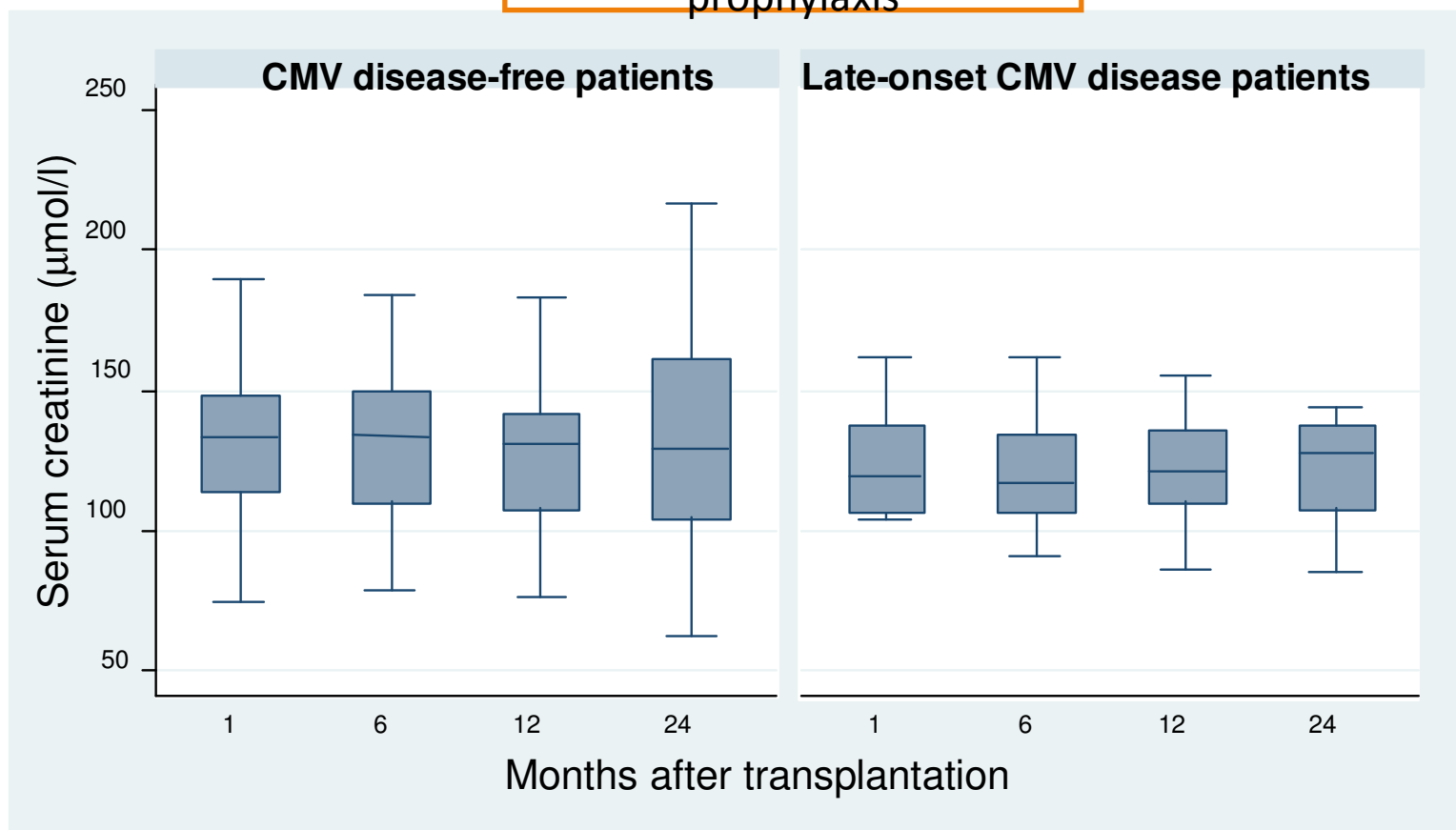


Antiviral prophylaxis reduces graft loss in D+/R- patients (Collaborative Transplant Study)

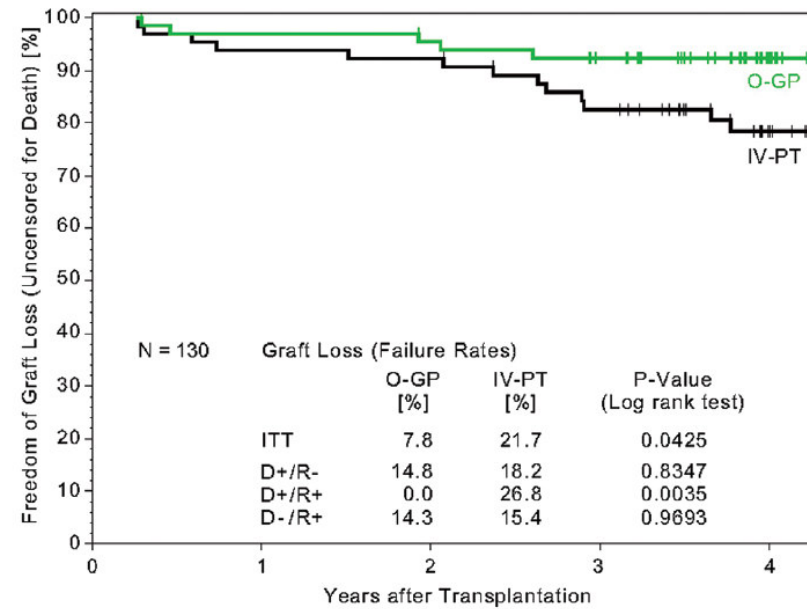
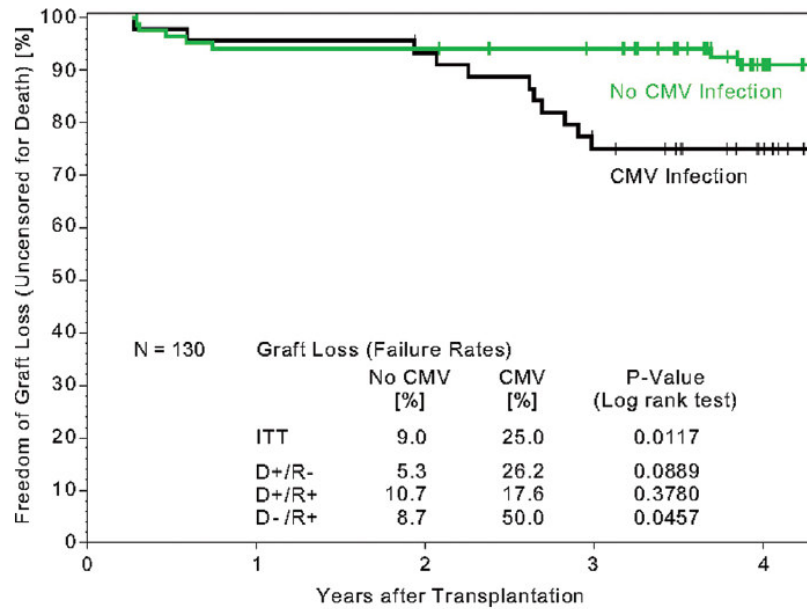


No differences in creatinine clearance in patients with and without CMV disease

3 months of VGC prophylaxis

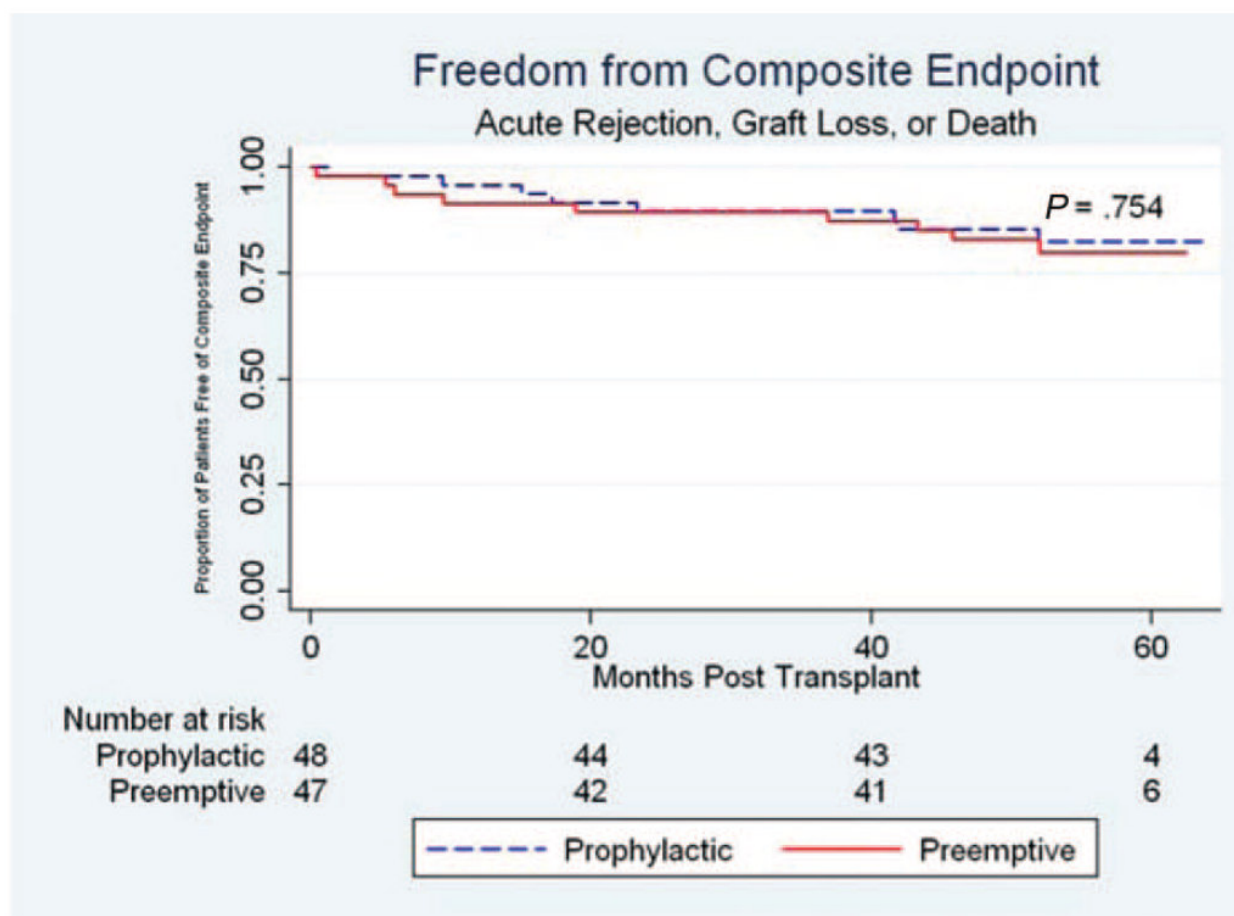


CMV prophylaxis reduces graft loss compared to a preemptive approach

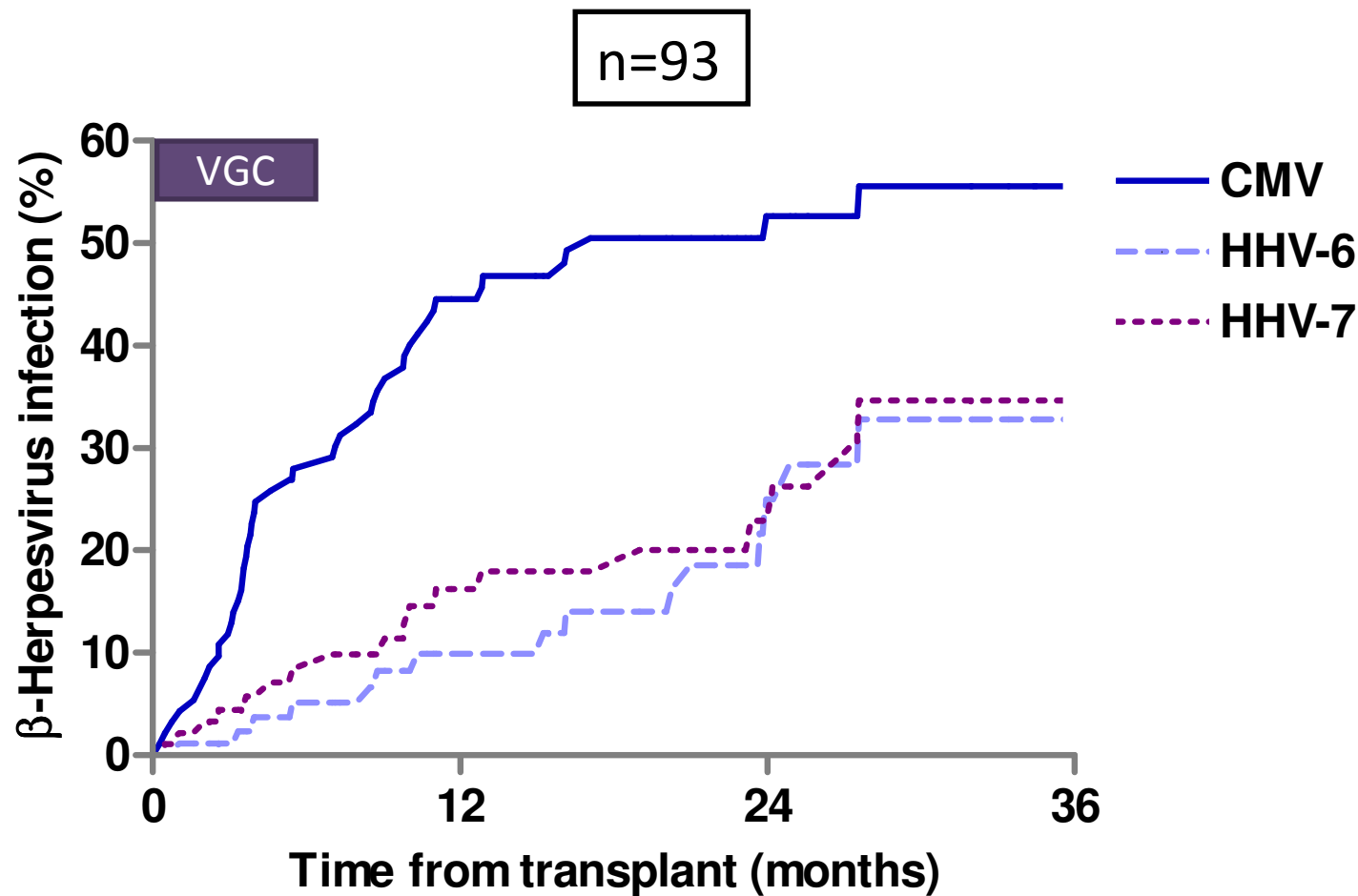


Impact of Prophylactic Versus Preemptive Valganciclovir on Long-Term Renal Allograft Outcomes

Michael L. Spinner,¹ Georges Saab,¹ Ed Casabar,² Lyndsey J. Bowman,² Gregory A. Storch,^{1,3} and Daniel C. Brennan^{1,4}



β -herpesvirus detection in BAL is common after lung transplantation



CMV is not a risk factor for BOS and acute rejection

Risk factors	BOS		Acute rejection	
	HR	P-value	HR	P-value
CMV detection in BAL	1.04	0.89	0.81	0.30
HHV-6 detection in BAL	1.13	0.69	1.15	0.70
HHV-7 detection in BAL	1.31	0.15	0.90	0.57
Bacterial pneumonia	9.89	<0.001*	2.57	0.009*
Invasive fungal infection	10.39	0.002*	4.31	0.15
Acute rejection	10.08	<0.001*		
Induction therapy	1.55	0.37	0.65	0.21
Multivariate analysis	HR	P-value		
Invasive fungal infection	1.97	0.42		
Acute rejection	8.72	<0.001*		

Conclusions

- The indirect effects of CMV in transplant recipients are due to survival mechanisms of the virus:
 - Immunosuppressive effects: to avoid recognition by the immune system
 - Proinflammatory effects: to replicate and disseminate
- The causal relationship between CMV infection and rejection is difficult to determine due to multiple confounders:
 - Differences in preventive strategies and diagnostic tools of CMV
 - Differences in immunosuppression and rejection rates over time
 - Concept of bidirectional relationship
- The stronger clinical evidence of the immunomodulatory effects of CMV is the reduction of other infections and acute rejection with the introduction of universal antiviral prophylaxis (3-6 months)

1980

Universal preventive strategies
Improvement of immunosuppressive
regimens

2010



A scenic landscape featuring a large body of water in the background, a small town with a church spire in the middle ground, and terraced vineyards in the foreground. The sky is filled with dramatic, dark clouds, and the sun is low on the horizon, creating a shimmering reflection on the water. The overall color palette is dominated by blues, greens, and yellows.

Moltes gràcies
per la seva atenció

Acknowledgments:

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