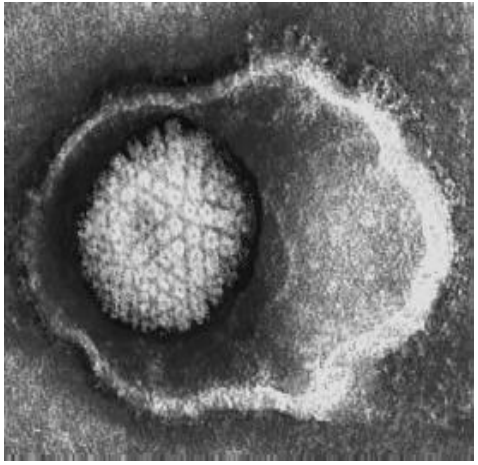
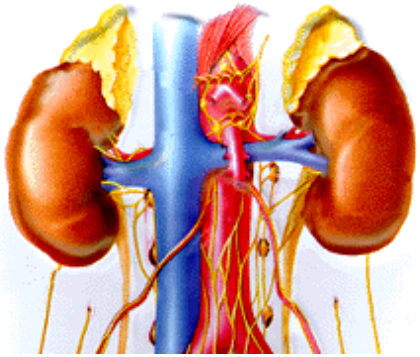
2017 CST-Astellas Canadian Transplant Fellows Symposium

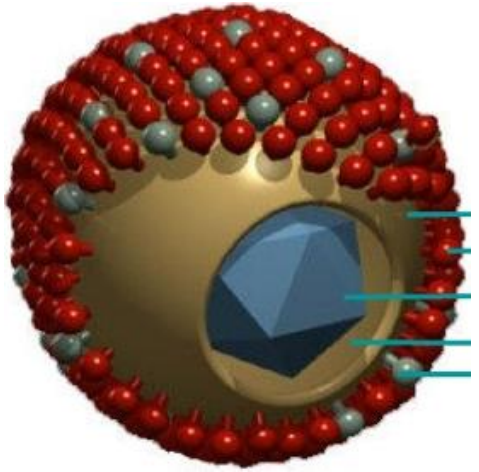
Optimizing use of organs from Increased Risk Donors

Atual Humar, MD

Atul Humar is a Professor in the Department of Medicine, University of Toronto. Dr. Humar received his medical degree from the University of Ottawa. He completed his residency and did further training in Transplant Infectious Diseases in Toronto and Boston. Dr. Humar's research interests are in virology with a focus on the pathogenesis of herpesvirus infections post-transplant. He is involved in both basic and clinical research assessing immunologic and virologic determinants of infection. Dr. Humar is the Director of Multi Organ Transplant Program at the University Health Network and the University of Toronto Transplant Institute. He is also active in the Canadian Society of Transplantation as a President and has been very active in both the AST and TTS. Dr. Humar operates a joint research lab with his wife, Dr. Deepali Kumar, who is also a faculty member at the University of Toronto.







What's New in CMV in Solid Organ Transplantation

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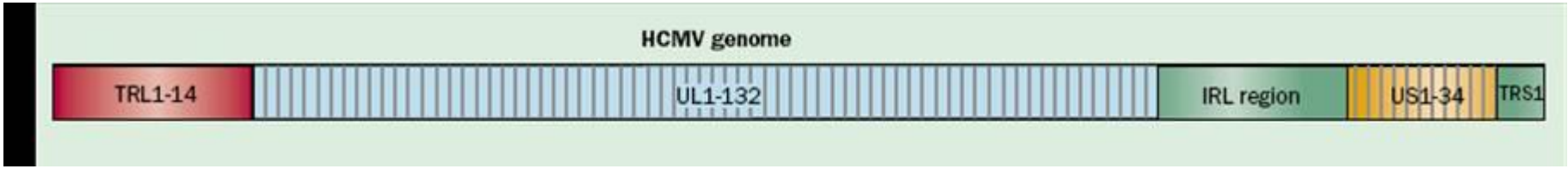
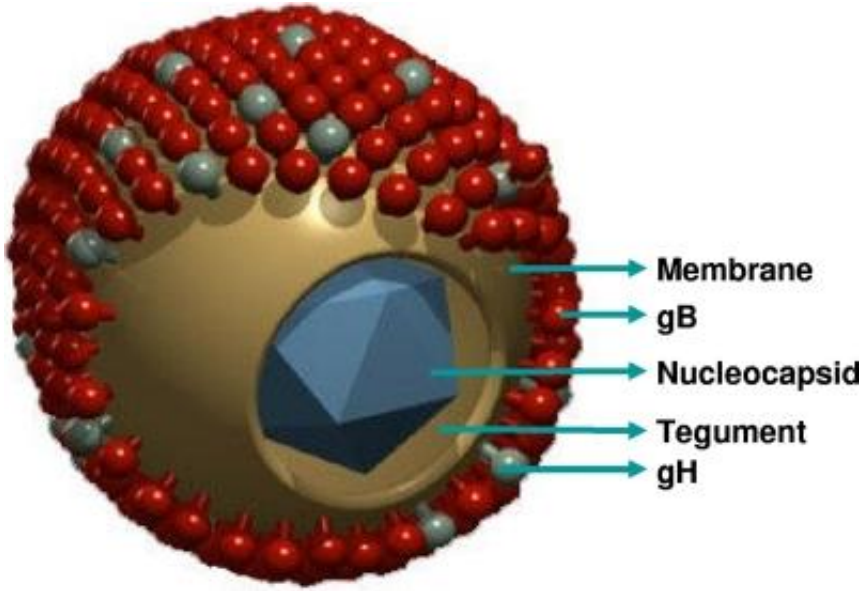
Disclosure

- Research Grant – Roche, Qiagen, Astellas
- Consultant – Qiagen, Astellas, Chimerix
- Honoraria – Astellas, Merck

CMV is the most common viral infection in SOT



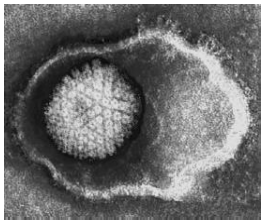
- DNA herpesvirus with >160 genes
- Establishes lifelong latency in different cell types (T-cells, monocytes, macrophages, epithelial cells)
- ~60-70% of population is infected and incidence increases with age



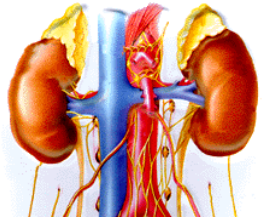
Crough, Clin Micro Rev 2009, Gandhi MK, Lancet ID 2004

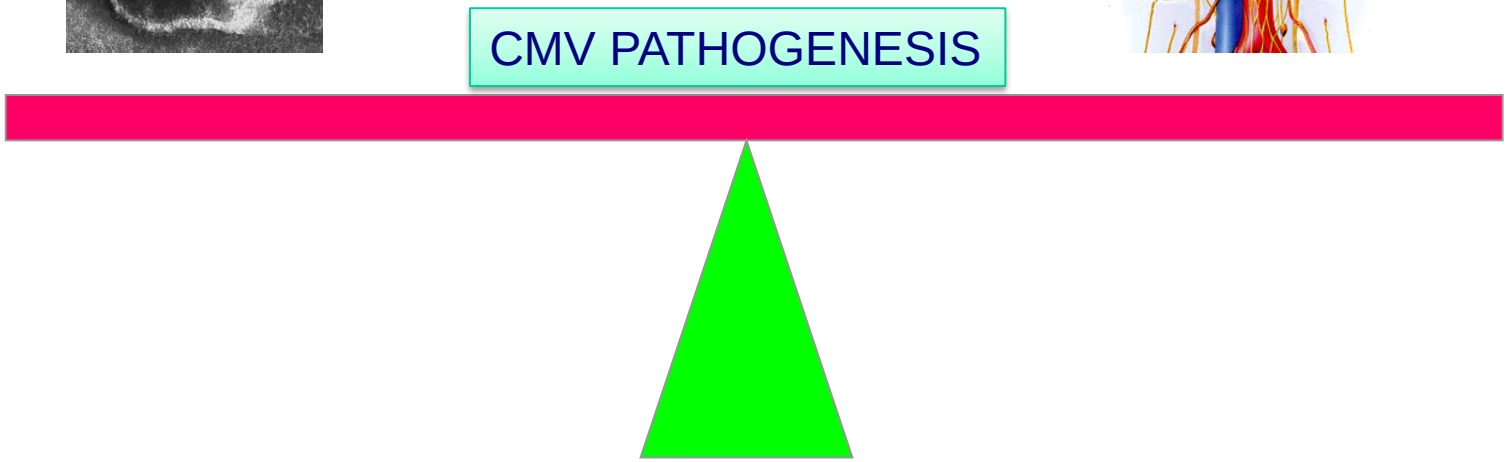
What leads to CMV replication post-transplant

- **Viral factors**
  - Replication dynamics
  - Immune evasion
  - Viral heterogeneity
  - Viral co-infections



- **Host factors**
  - CD4+, CD8+ T-cell
  - NK cell, B-cell
  - Exogenous immunosuppression
  - D/R serostatus





Serologic Risk Profile for CMV

Risk Category	Donor (D) / Recipient (R) Serologic Status (+/-)
High	D+/R-
Intermediate*	D+/R+, D-/R+
Low	D-/R-

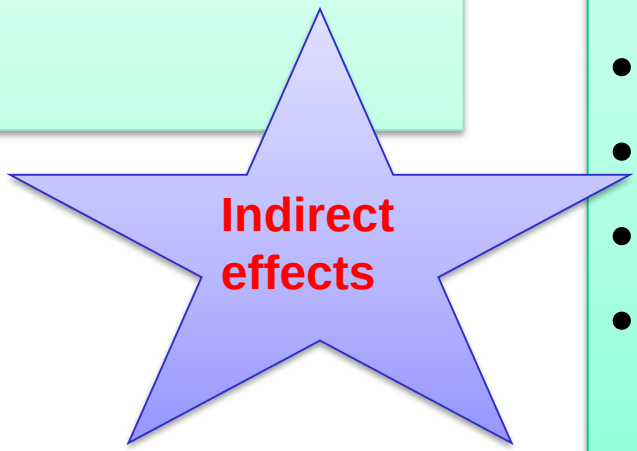
* D+/R+ generally at higher risk than D-/R+

Humar et al., AJT 2009; Fishman et al., Clin Transplant 2007

Effects of CMV Infection post-transplant

CMV Viral Syndrome

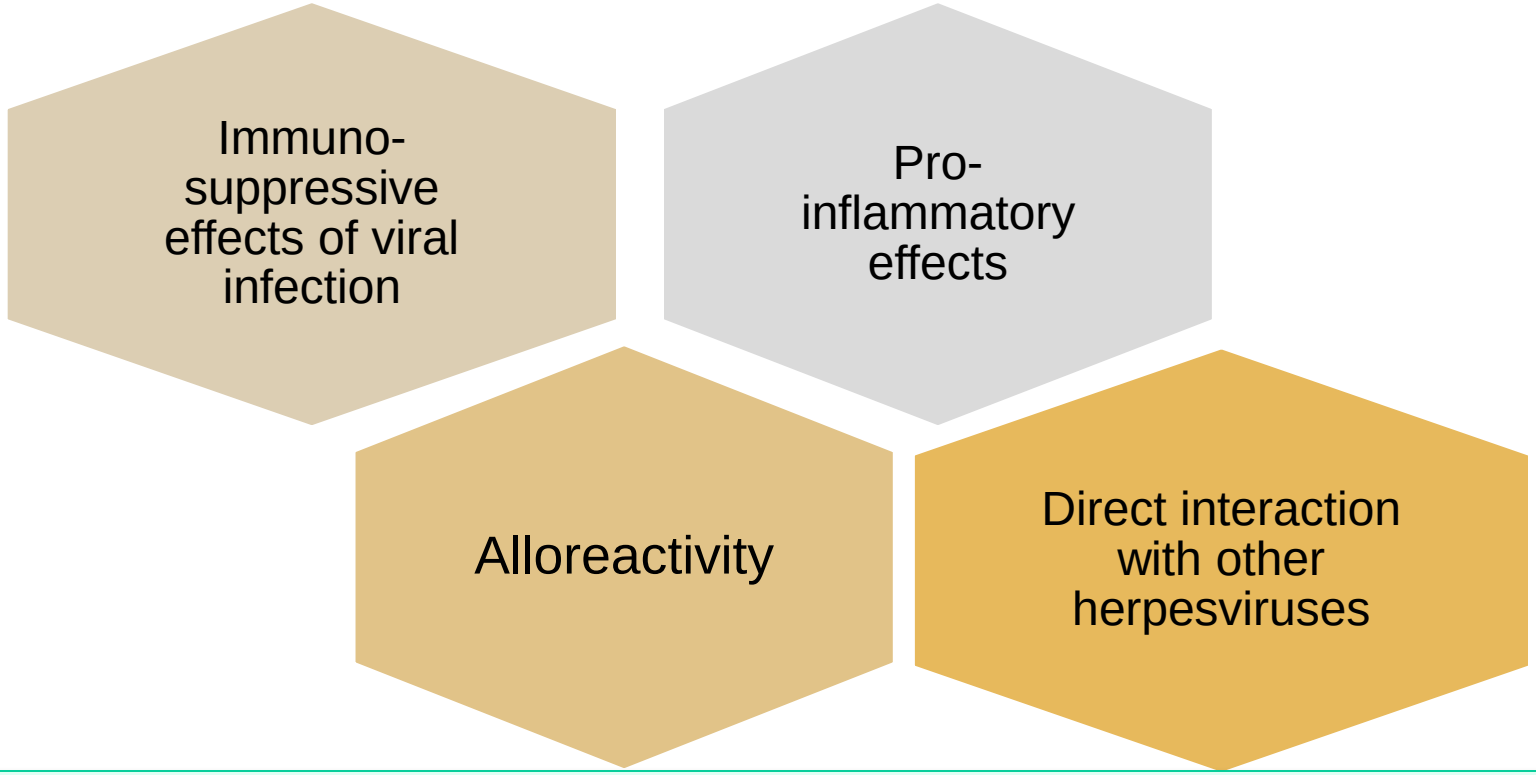
- Fever, malaise, myalgias
- Leukopenia, thrombocytopenia, and other laboratory abnormalities



Tissue Invasive Disease

- Hepatitis
- Pneumonitis
- Colitis
- Carditis
- Nephritis
- Pancreatitis
- Retinitis

Indirect Effects of CMV



Graft rejection; graft dysfunction

Opportunistic infections: Bacterial, fungal superinfection

Decreased graft and patient survival

Herpesvirus interactions: EBV/PTLD

CASE

- **55 y.o. woman deceased donor kidney transplant CMV D+/R-**
- **ATG induction, is on Tac/Pred/MPA**
- **For CMV prevention you would use:**

QUESTION 1

- **For CMV prevention you would use (adjusted for renal function)**
  - **a) Valganciclovir 900mg/d x 3 months**
  - **b) Valganciclovir 900mg/d x 6 months**
  - **c) Preemptive strategy (VL monitoring)**
  - **d) 3 months prophylaxis followed by pre-emptive strategy**

QUESTION 1B

- **The patient is placed on Valganciclovir. At 2.5 months post-transplant the patient develops low WBC of 1.7 with ANC of 0.9. TMP/SMX is held. You would**
  - **a) Hold Valganciclovir**
  - **b) Hold MPA**
  - **c) Hold both a) and b)**
  - **d) Not hold anything but give GCSF**

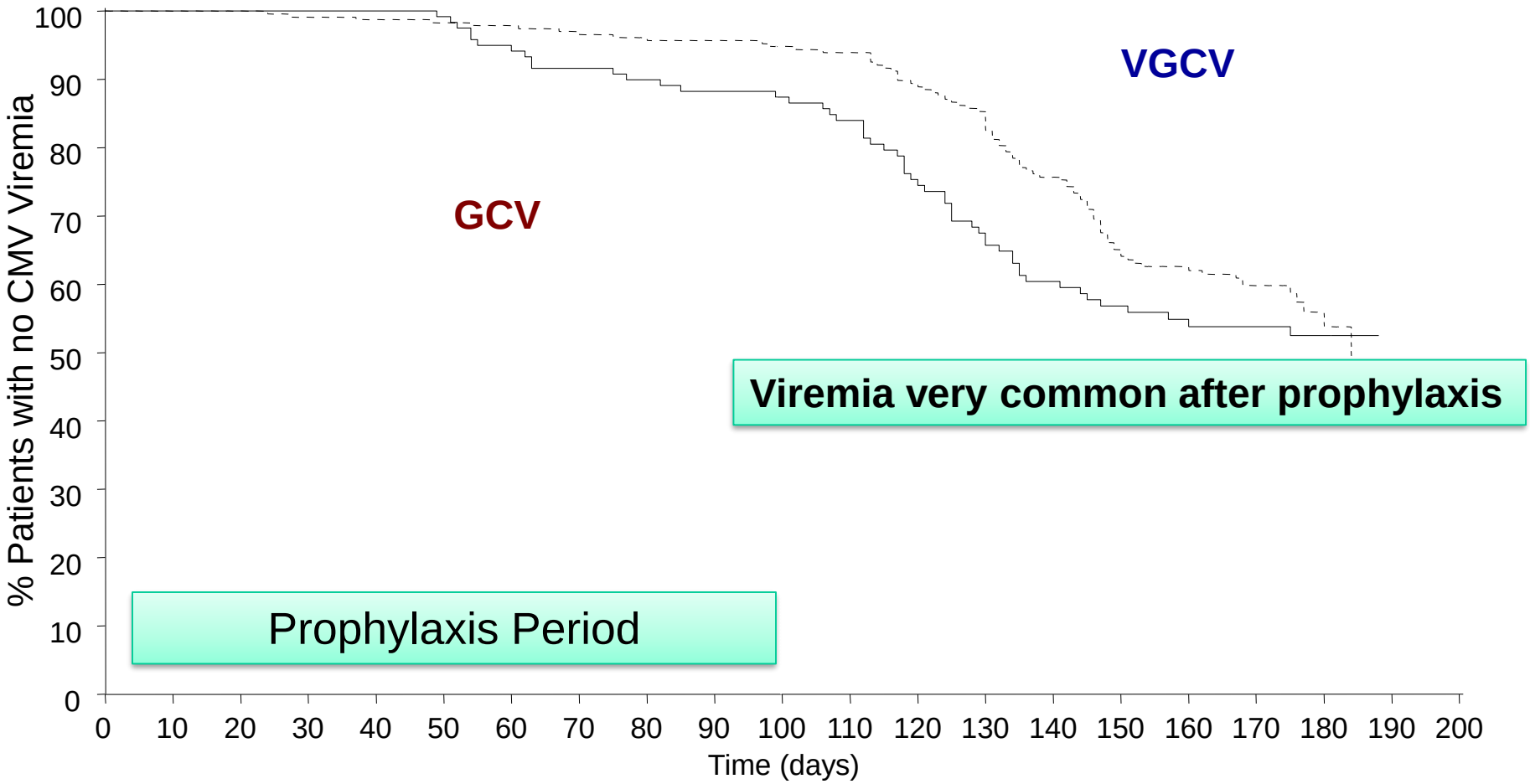
CMV PREVENTION: Universal Prophylaxis

- Antiviral therapy from the time of transplant to all patients or a subgroup of patients (3-6 months of antiviral prophylaxis in all D+/R- transplant patients)

- Prophylaxis very successful in multiple clinical trials for CMV prevention

RCT of oral GCV vs. VGCV

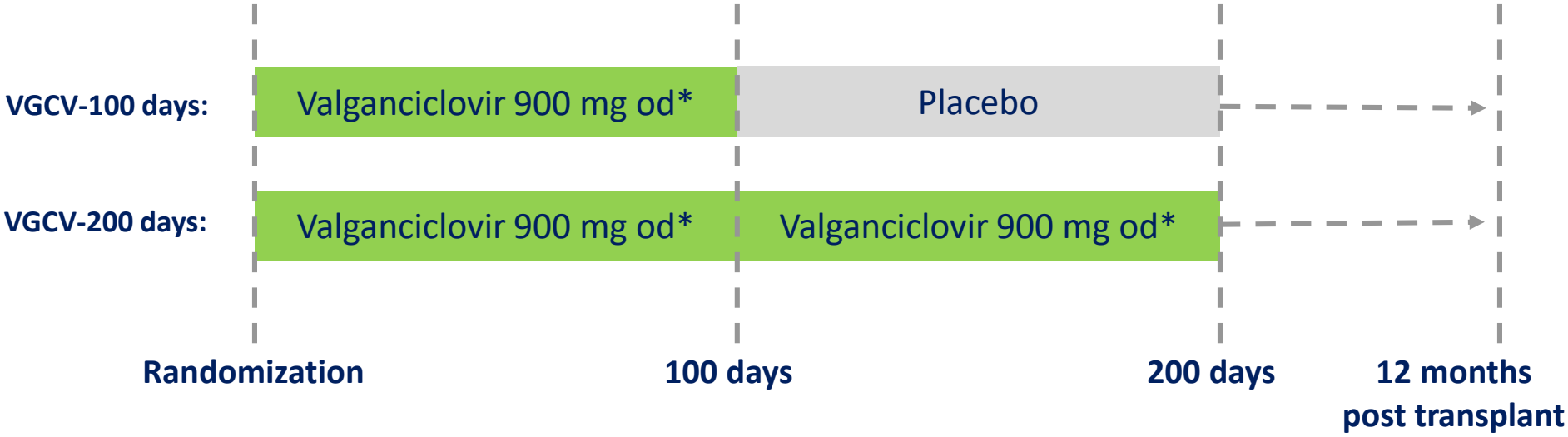
n=364 D+/R- kidney,liver,heart



Paya, et al AJT 2004

Impact Trial: RCT of 100d vs 200d VGCV

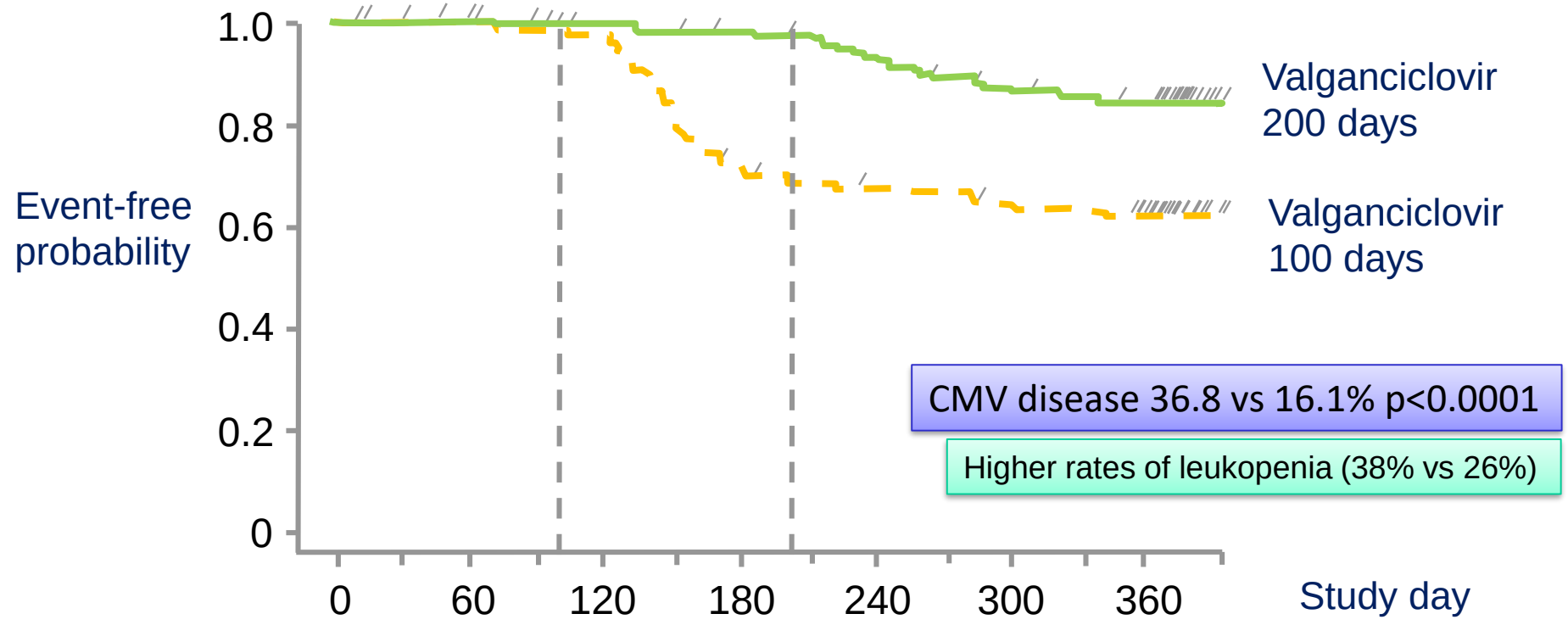
International RCT
Kidney recipients, D+/R-, N=316



*** dose adjusted for renal function**

Humar A, et al. *Am J Transplant.* 2010

Impact Trial



Number of patients assessed

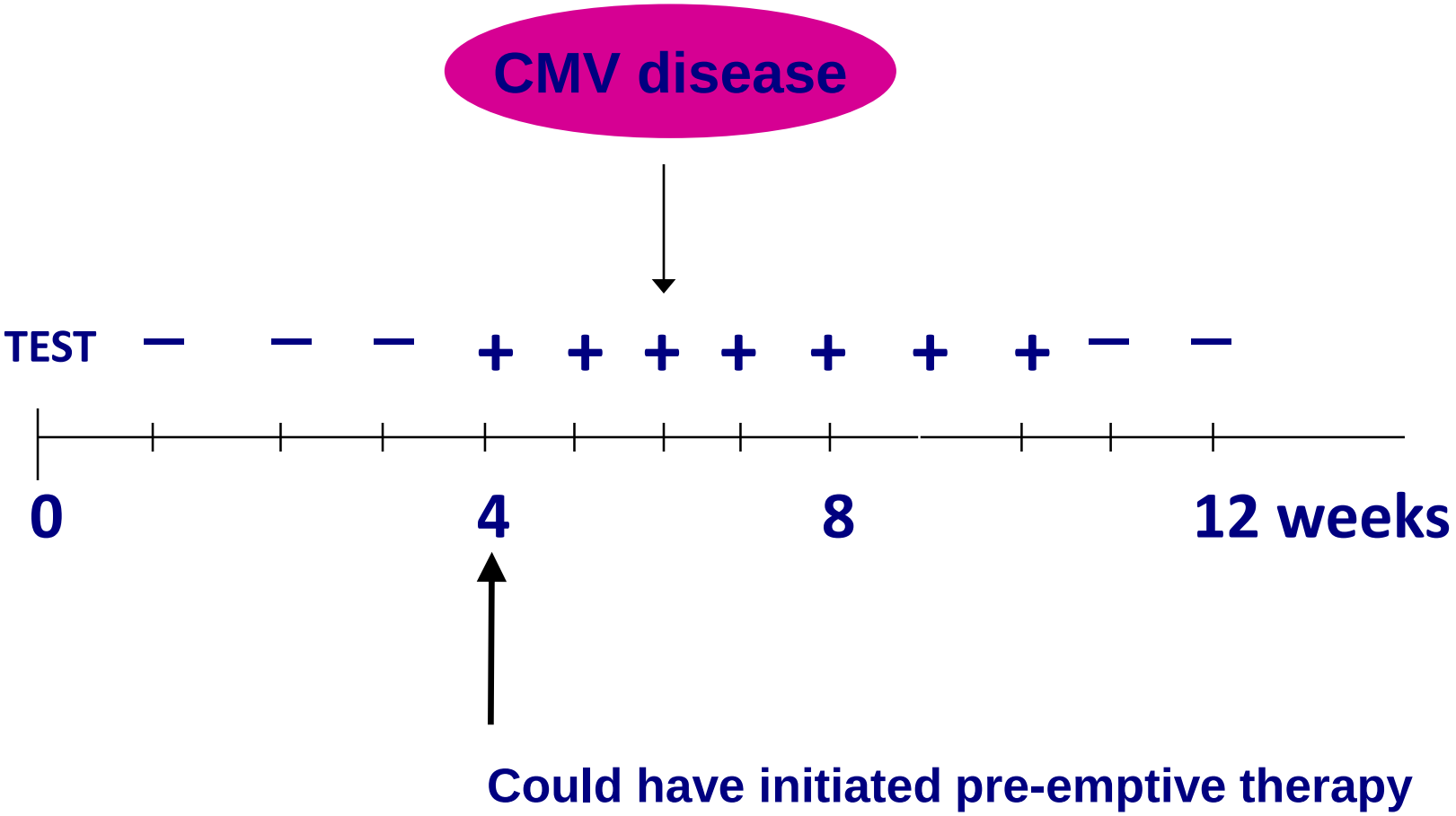
Valganciclovir 100 days	163	161	161	157	151	125	110	104	102	101	95	94	83	4
Valganciclovir 200 days	155	154	152	150	149	147	145	143	136	130	125	122	120	7

Humar A, et al. *Am J Transplant.* 2010

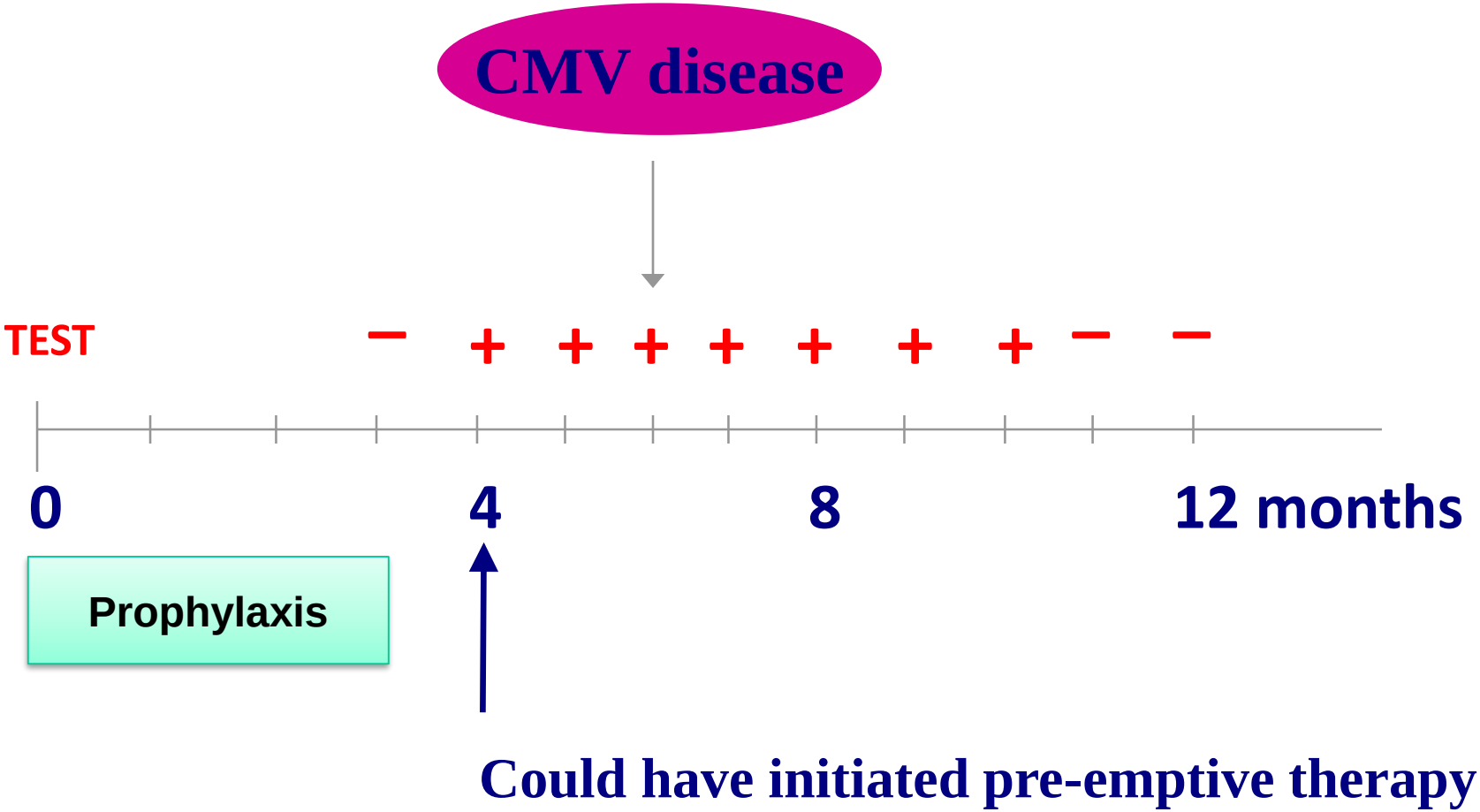
The Problem with Prophylaxis

1. **Drug toxicity**
2. **After discontinuation of prophylaxis – viremia and disease often develops**
    - **“Late onset CMV disease”**
        - **May present with atypical symptoms (no fever – malaise, fatigue); diagnosis can be missed**

CMV PREVENTION: Pre-emptive Therapy



Combination strategy: Surveillance after Prophylaxis



The Problem with Pre-emptive therapy

- Weekly monitoring (needs patient compliance and physician review)
- Short viral doubling time in some patients
- Thresholds for treatment not established (likely different for D+/R- vs. R+)
- Effect of low level replication on graft not fully defined

Prophylaxis vs pre-emptive therapy

	Prophylaxis	Pre-emptive
Evidence of efficacy	+++	++
Indirect effects/mortality	++	+
Other viruses	+ for some	-
Ease	++	+/-
Late onset disease	++	-
Resistance	Low	Low

Guidelines for CMV Prevention

Organ	CMV serostatus	Prophylaxis or Pre-emptive	Duration
Kidney, Liver, Pancreas, Heart	D+/R-	Val(ganciclovir) x 3-6 months is preferred Pre-emptive strategy can be used	6 months for kidney 3 months for others
Kidney, Liver, Pancreas, Heart	R+	Val(ganciclovir) x 3 months (especially if ATG) OR Pre-emptive strategy	3 months
Lung or Heart-Lung	D+/R-	Universal prophylaxis recommended with valganciclovir	6-12 months
Lung or Heart-Lung	R+	Universal prophylaxis recommended with valganciclovir	3-12 months

AST Guidelines 2013, International Guidelines 2013

CASE

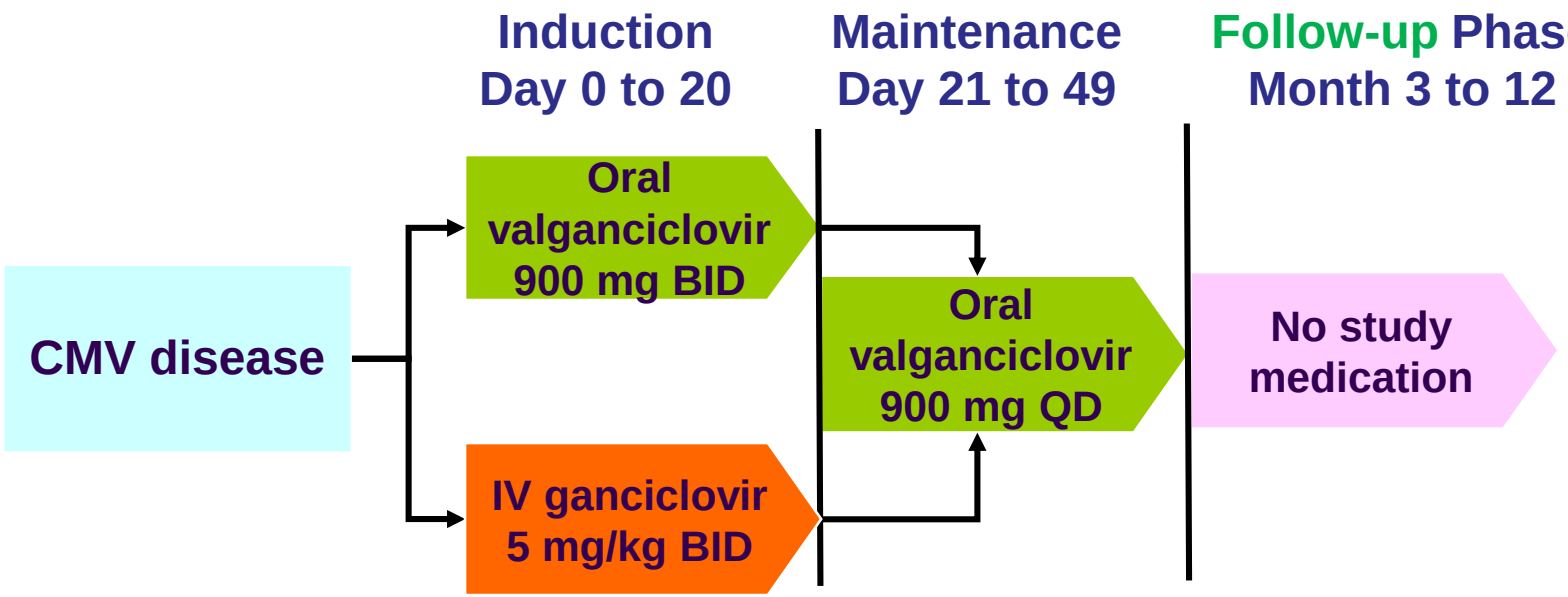
- **The patient received valganciclovir prophylaxis x 6 months**
- **Currently on Tac/MPA 540bid/Pred 5mg**
- **At month 9 develops increased fatigue and malaise, mild diarrhea. T37.6; WBC 2.4; Cr 132; AST 64; ALT 4**

QUESTION 2

- **The CMV VL is 20,000 IU/ml; you would**

  a) **Valganciclovir alone**
  b) **Valganciclovir plus reduce IS**
  c) **IV ganciclovir to start with**
  d) **IV ganciclovir plus reduce IS**

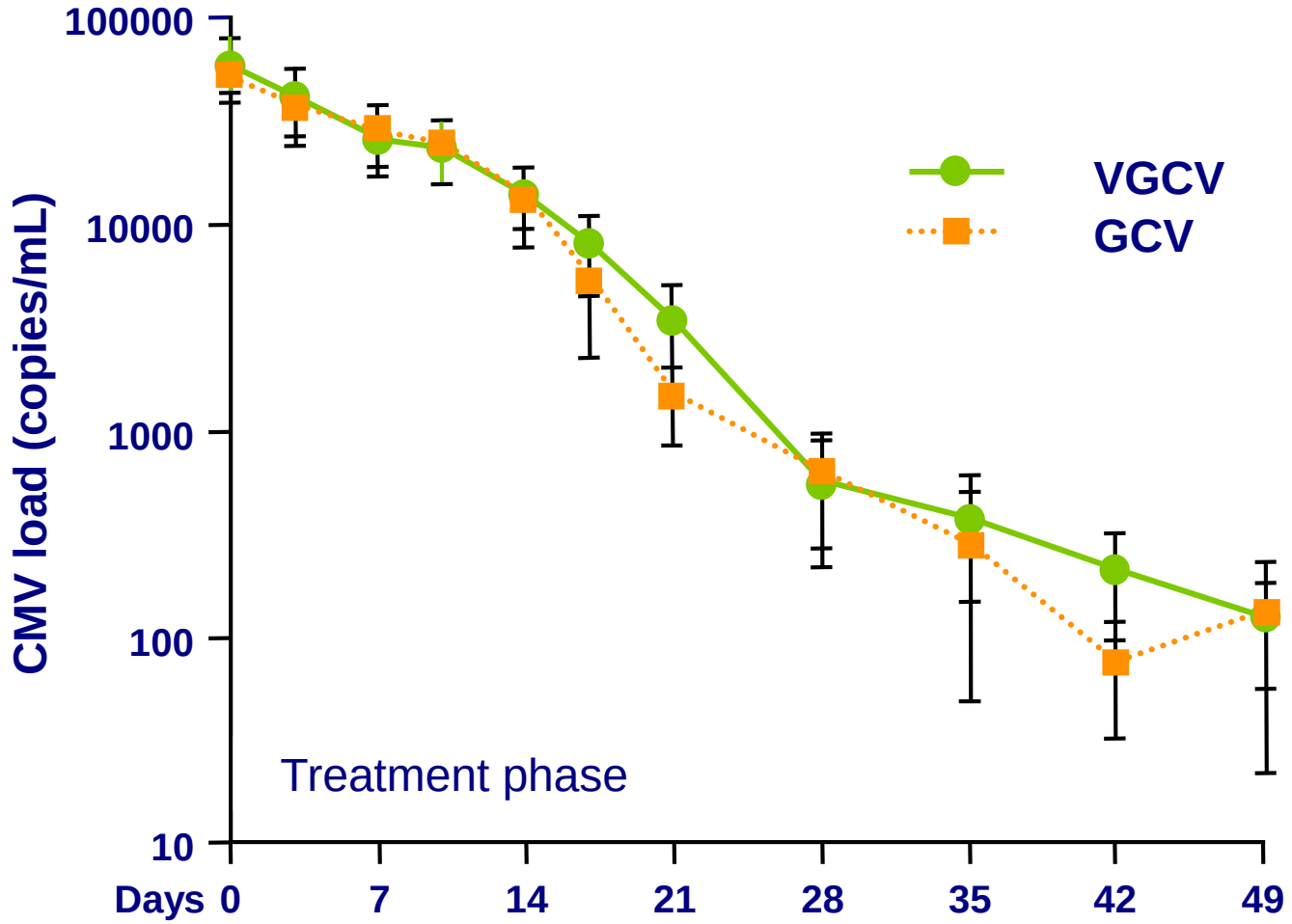
CMV Disease: Treatment



- Multicenter non-inferiority study
- 42 centers: 25 in Europe, 9 in Latin America, 4 in India, 2 in Canada, 2 in Australia and New Zealand

Anders*, Humar* (co-first author); AJT 2007

Cytomegalovirus Clearance Kinetics



Valganciclovir (N)	133	130	128	123	123	124	124		122		118		115		117
IV Ganciclovir (N)	125	122	123	123	124	121	120		120		119		118		116

Asberg A et al. *Am J Transplant*. 2007;7:2106-2113.

Treatment Recommendations

- **Start oral VGCV in most cases**
  - **Choose IV for severe disease or concern about absorption or very heavily IS**
- **Monitor viral load weekly; monitor CBC, Cr**
- **Treat until negative [generally]**
- **Post-treatment**
  - **Monitoring [clinical vs. virologic]**
  - **Secondary prophylaxis 1-3 months**

QUESTION 3

- 2 weeks after valganciclovir treatment the VL is now 25,000 IU/ml
- Patient feels about the same
- What do you do?

CMV Antiviral Resistance

Suspect when increasing or high-level CMV viremia or progressive clinical disease is observed during prolonged antiviral therapy.

Risk factors for drug resistance are:

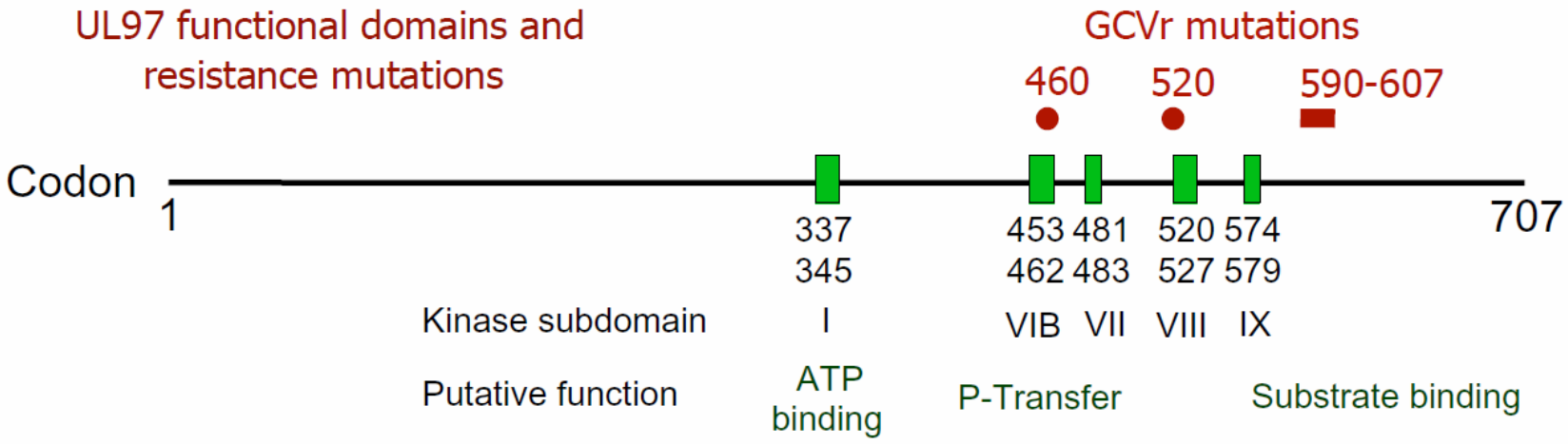
- **Prolonged low-dose oral prophylaxis**
- **Increased immunosuppression**
- **CMV D+/R-**
- **Lung transplantation**

Resistance risk:

- **Boivin (2004) reported ~ 1%-2% risk with 3 months prophylaxis.**
- **May be higher in sub-populations, Limaye et al and Li et al reporting rates of 5% to 10% in D+/R- lung transplant recipients.**

Cotton CN, et al. *Transplantation*. 2010;89. Humar A, et al. *Am J Transplant*. 2009;9(suppl 4):S78-S86. Boivin G, et al. *J Infect Dis*. 2004;189:1615-1618. Limaye AP, et al. *Lancet*. 2000;356:645-649.

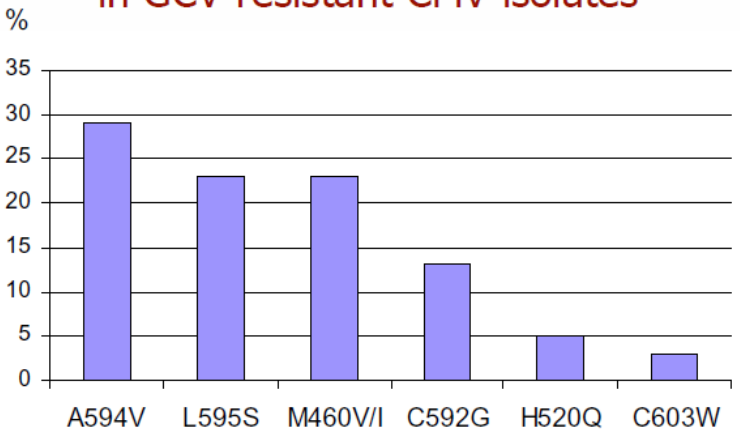
UL97 functional domains and resistance mutations



UL97 variants show different levels of GCV resistance

Amino Acid Change	GCV IC_{50} ratio	Level of GCV Resistance
M460V/I, H520Q, A594V, L595S, C603W	5-10	Higher level resistance Alternate therapy indicated
C592G, A594T	2-3	Low level resistance
A591V, N597D	<2	Insignificant resistance
Q449K, H469Y, D605E	<1.5	Baseline polymorphisms No GCV resistance

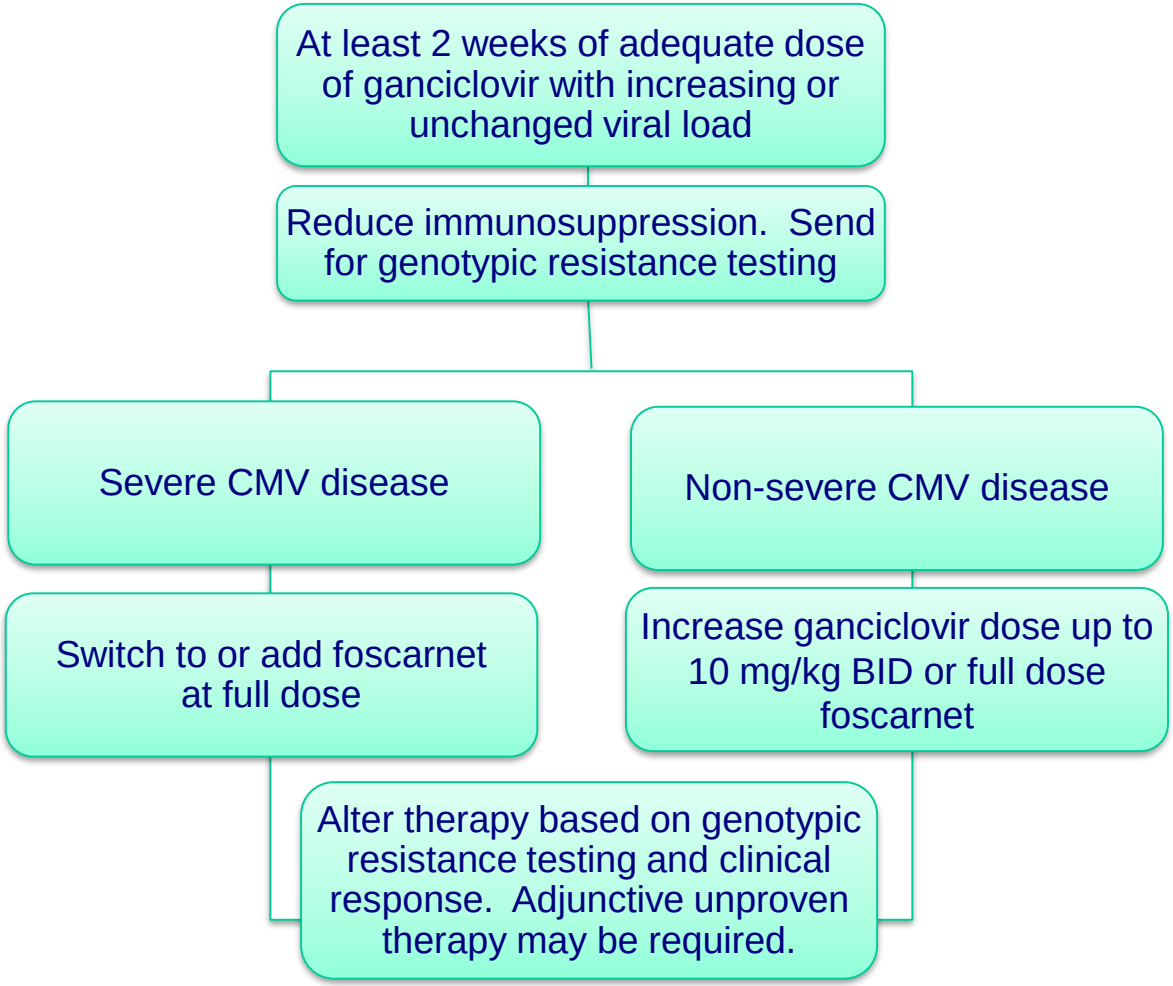
Most common UL97 mutations detected in GCV-resistant CMV isolates[1]



1. Frequency in set of 79 GCV-resistant CMV isolates

Kotton et al. Transplantation 2013

CMV Resistance: Proposed Treatment Algorithm



Razonable and Humar; AST Guidelines. Am J Transplant 2013

NEW Developments

- **New Antivirals**
  - **Maribavir (Shire), Letermovir (Merck), Brincidofovir (Chimerix)**
- **Cell mediated immunity assays**
- **CMV vaccines**

NEW Antiviral Options

Drug	Mechanism	Side effect	Trials
Maribavir po (Shire)	UL97 protein kinase inhibitor	Taste disturbance	Phase III for refractory / resistant CMV in SOT and HSCT
Letermovir po(Merck)	CMV viral terminase inhibitor	no significant adverse effects noted – but no coverage for HSV/VZV	Phase II SOT study
Brincidofovir po(Chimerix)	DNA polymerase inhibitor	GI side effects	CMV trials on hold Adenovirus
leflunomide, artesunate, mTOR inhibitors don't appear to be potent antivirals and controlled trials for treatment have not been done			

Maribavir: Treatment of CMV Viremia in SOT and HSCT patients

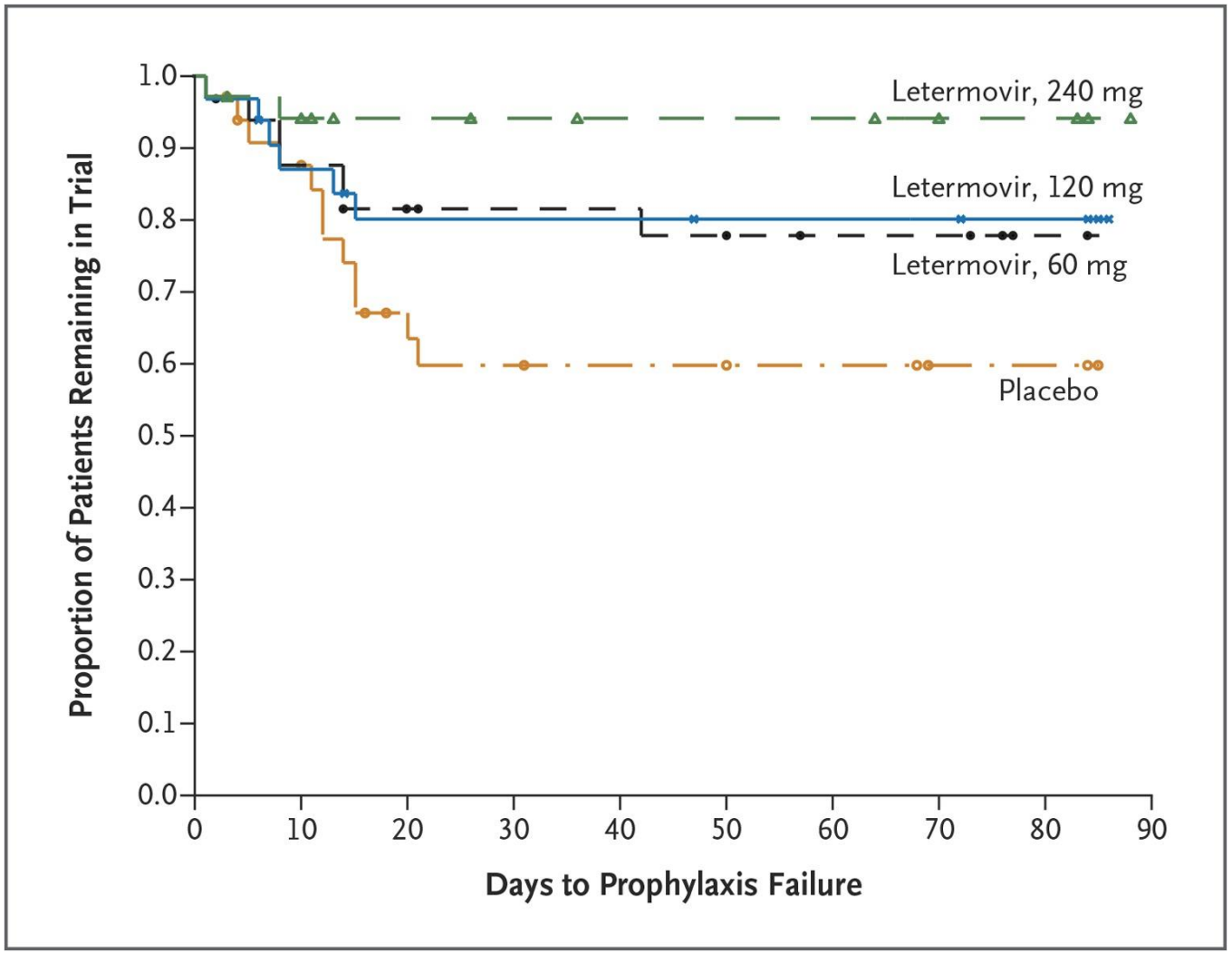
Responders (treatment effect estimate), n(%); 95% CI	All Maribavir Doses, n=120	Valganciclovir N=40
Week 3	72/117 (62%); [52, 70]	22/39 (56%); 40, 72
	OR 1.42; 95% CI 0.62, 3.24; p=0.41	
Week 6	92/117 (79%); 70, 86	26/39 (67%); 50,81
	OR 2.12; 95% CI 0.62, 4.96; P=0.08	

Maribavir 203 abstract Dr. Faouzi Saliba; New Orleans, 2016

Letermovir

- po (once daily)
- CMV viral terminase enzyme inhibitor (ie inhibits cleavage and packaging of DNA into capsids)
- Does not cover other herpesviruses (HSV, VZV)
- No significant adverse events noted in studies

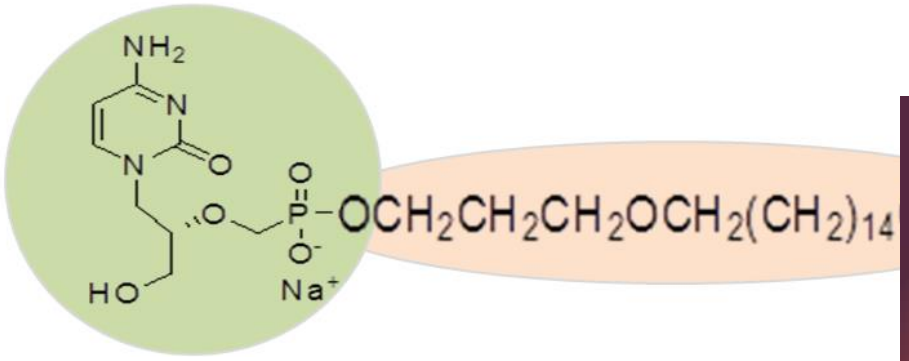
Kaplan–Meier Plot of the Time to Failure of Prophylaxis against Cytomegalovirus Infection during the 12-Week Treatment Period (Modified Intention-to-Treat Population).

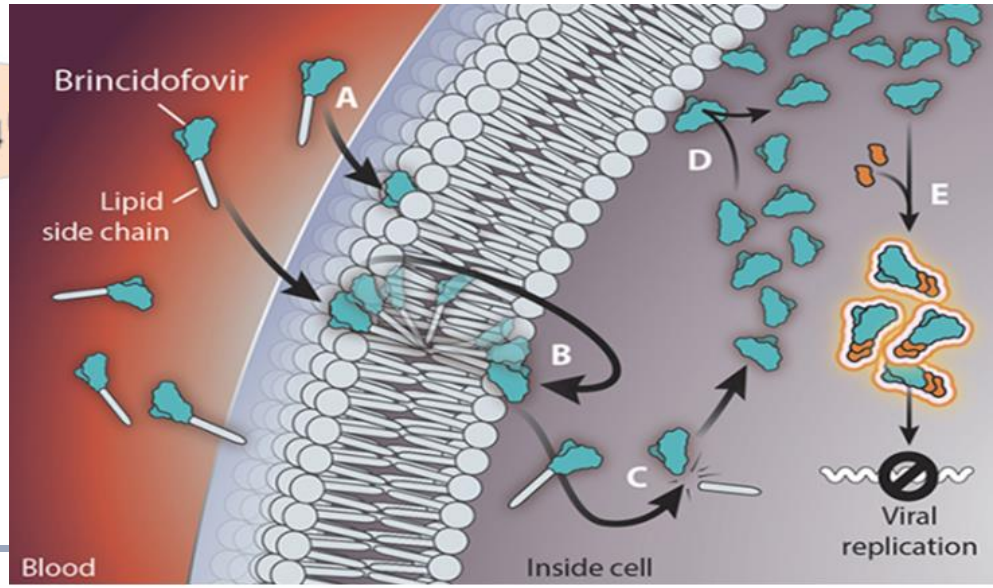


Chemaly RF et al. N Engl J Med 2014;370:1781-1789

Brincidofovir (BCV, CMX001)

- **CMX001 is a lipid conjugated cidofovir (po drug given twice weekly)**
- **After po dose absorbed in SI, penetrates target cells before being cleaved to free the antiviral, cidofovir**
- **Aim – increase potency, decrease toxicity and allow for oral formulation**



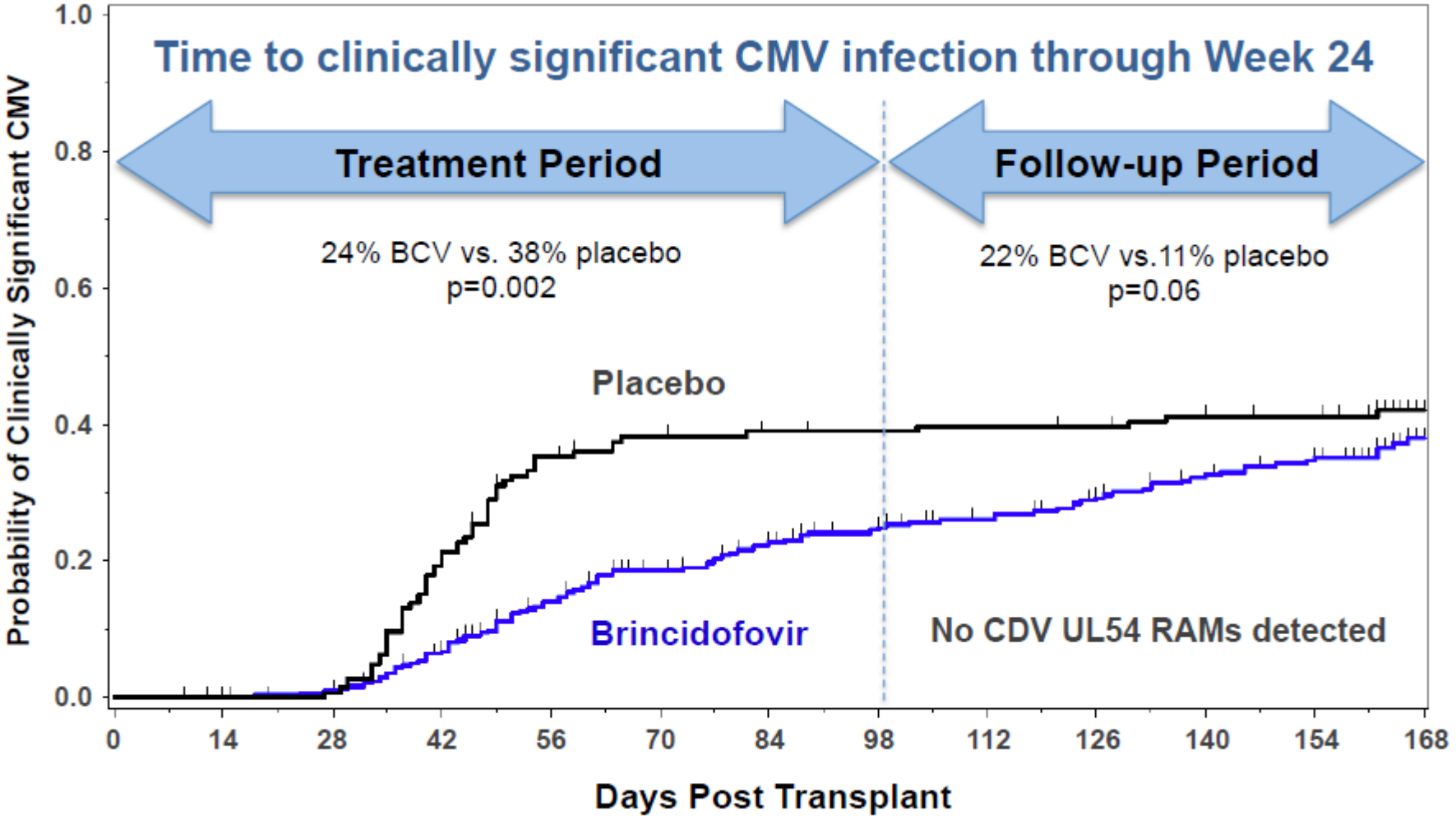


Brincidofovir: *In Vitro* Antiviral Activity Against All 5 Families of dsDNA viruses Pathogenic to Humans

Viral Family	dsDNA Virus	Brincidofovir	Cidofovir	Ganciclovir*	Foscarnet	Acyclovir	Maribavir	Letermovir
Herpes	Cytomegalovirus (CMV, HHV-5)	0.001	0.4	3.8	50-800	>200	0.31	0.005
	Epstein-Barr Virus (EBV, HHV-4)	0.03	65.6	0.9	<500	6.2	0.63	>10
	Human Herpesvirus 6 (HHV-6A)	0.003	2.7	5.8	16	10	Inactive	>10
	Human Herpesvirus 8 (HHV-8)	0.02	2.6	8.9	177	>100	Inactive	—
	Herpes Simplex Virus 1 (HSV-1)	0.01	3.0	0.7	92-95	3.8	Inactive	>10
	Herpes Simplex Virus 2 (HSV-2)	0.02	6.5	2.5	91-96	4.4	Inactive	>10
	Varicella Zoster Virus (VZV, HHV-3)	0.0004	0.5	1.3	39.8	3.6	Inactive	>10
Adenovirus	Adenovirus (AdV-B7)	0.02	1.3	4.5-33	Inactive	>100	—	>10
Polyoma	BK Virus (BKV)	0.13	115	>200	Inactive	>200	—	—
	JC Virus (JCV)	0.045	>0.1	—	Inactive	—	—	—
Papilloma	Human Papillomavirus 11 (HPV-11)	17	716	Inactive	—	Inactive	—	—
Pox	Variola	0.1	27	—	—	—	—	—
	Vaccinia	0.8	46	>392	Inactive	>144	—	—

Potency expressed as EC_{50} = concentration in µM required to reduce viral replication by 50% *in vitro;* "—" indicates no data.
Data are compiled from multiple sources and include multiple materials and methodologies.
*Valganciclovir is rapidly converted to ganciclovir *in vivo*. Therefore, ganciclovir is the relevant compound for cell activity studies.

Brincidofovir prophylaxis in HSCT: Phase 3 trial results

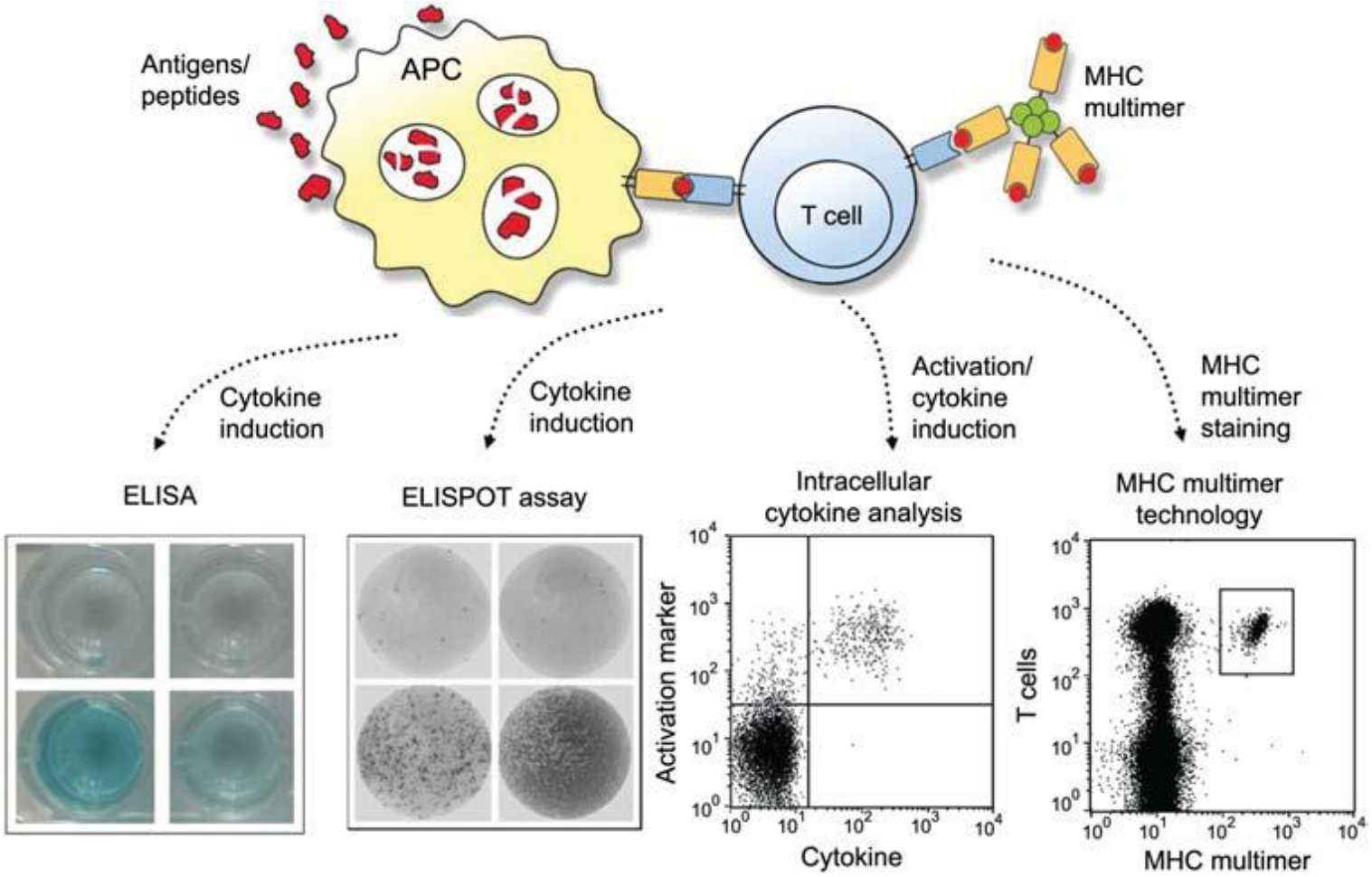


Abstract Presentation BMT Tandem Meeting, Feb 2016

NEW Developments

- **New Antivirals**
  - **Maribavir (Shire), Letermovir (Merck), Brincidofovir (Chimerix)**
- **Cell mediated immunity assays**
- **CMV vaccines**

Specific CMI Assays: Characterizing CMV-specific T cells



Assays based on measurement of IFN-γ production by cells stimulated with CMV peptides, whole proteins or CMV whole virus

Sester M, *J Lab Med.* 2008.

How can T-cell immunity be used in clinic?

CMV D+/R-

Time Post-Transplant

Antiviral prophylaxis

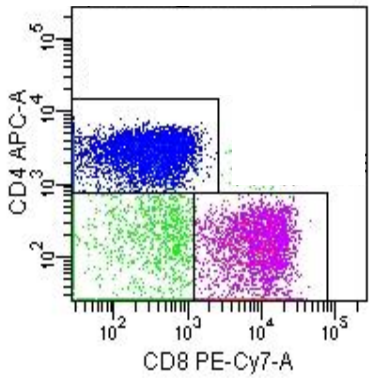
Monitor CMI

D/C Prophylaxis

+

Prolong Prophylaxis or Monitor more closely

-



Updated International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation

Camille N. Kotton,[1,8] Deepali Kumar,[2] Angela M. Caliendo,[3] Anders Åsberg,[4] Sunwen Chou,[5] Lara Danziger-Isakov,[6] and Atul Humar,[7] on behalf of The Transplantation Society International CMV Consensus Group

Transplantation 2013
(update in progress)

Cytomegalovirus in Solid Organ Transplantation

R. R. Razonable[a,*], A. Humar[b] and the AST Infectious Diseases Community of Practice

AJT 2013 (update in progress)

Gracias / Thank you!

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