CMV FOR THE ADVANCED PRACTICE PROVIDER

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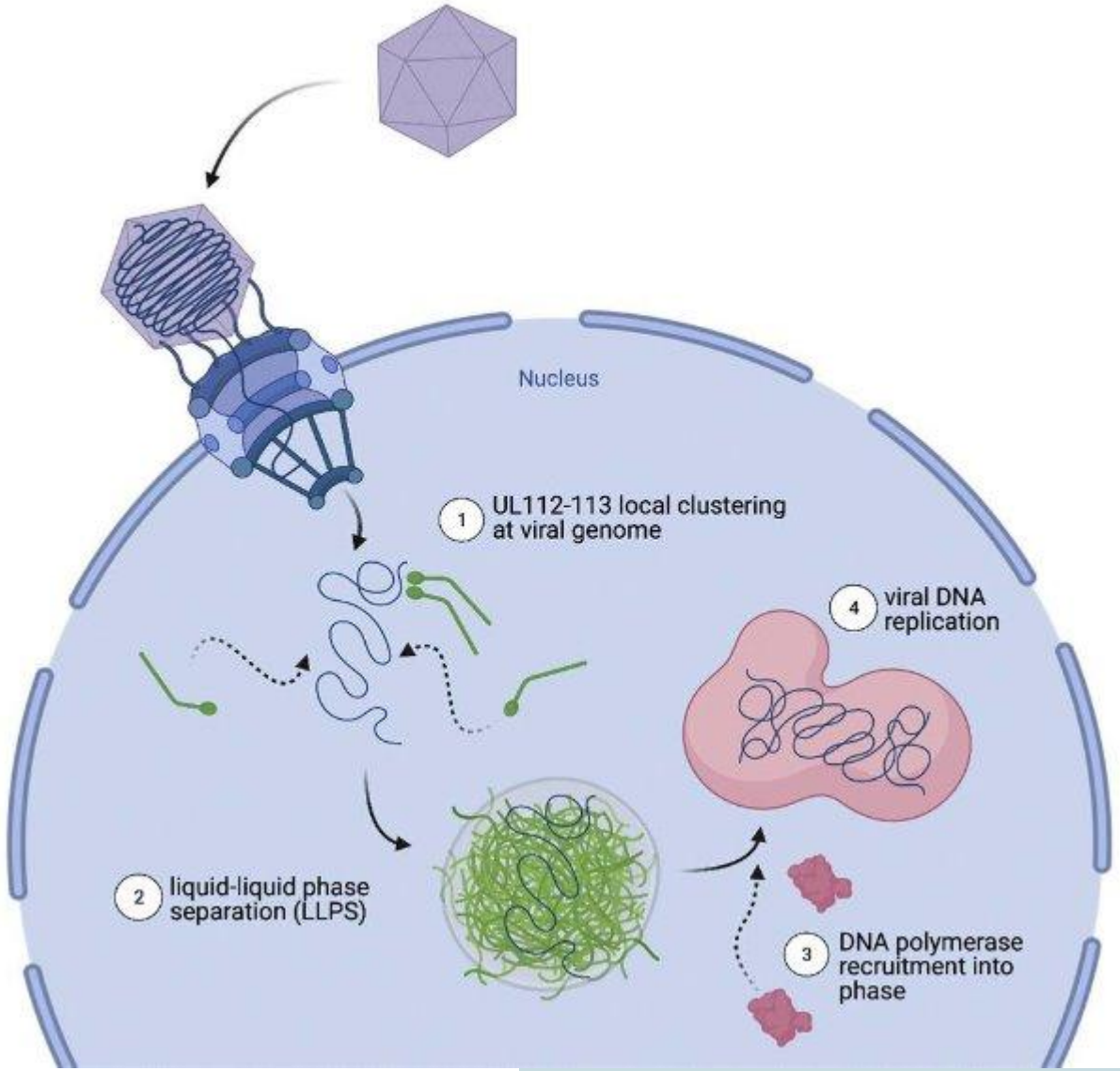
OUTLINE

- CMV REFRESHER
- NEW GUIDELINE HIGHLIGHTS
  - Diagnostics
  - Prevention
  - Immunology
  - Treatment
  - Resistance
- PROPHYLAXIS & TREATMENT OPTIONS
- CLINICAL PEARLS




RAISE YOUR HAND IF YOU'VE EVER
FELT PERSONALLY VICTIMIZED BY CMV
imgflip.com

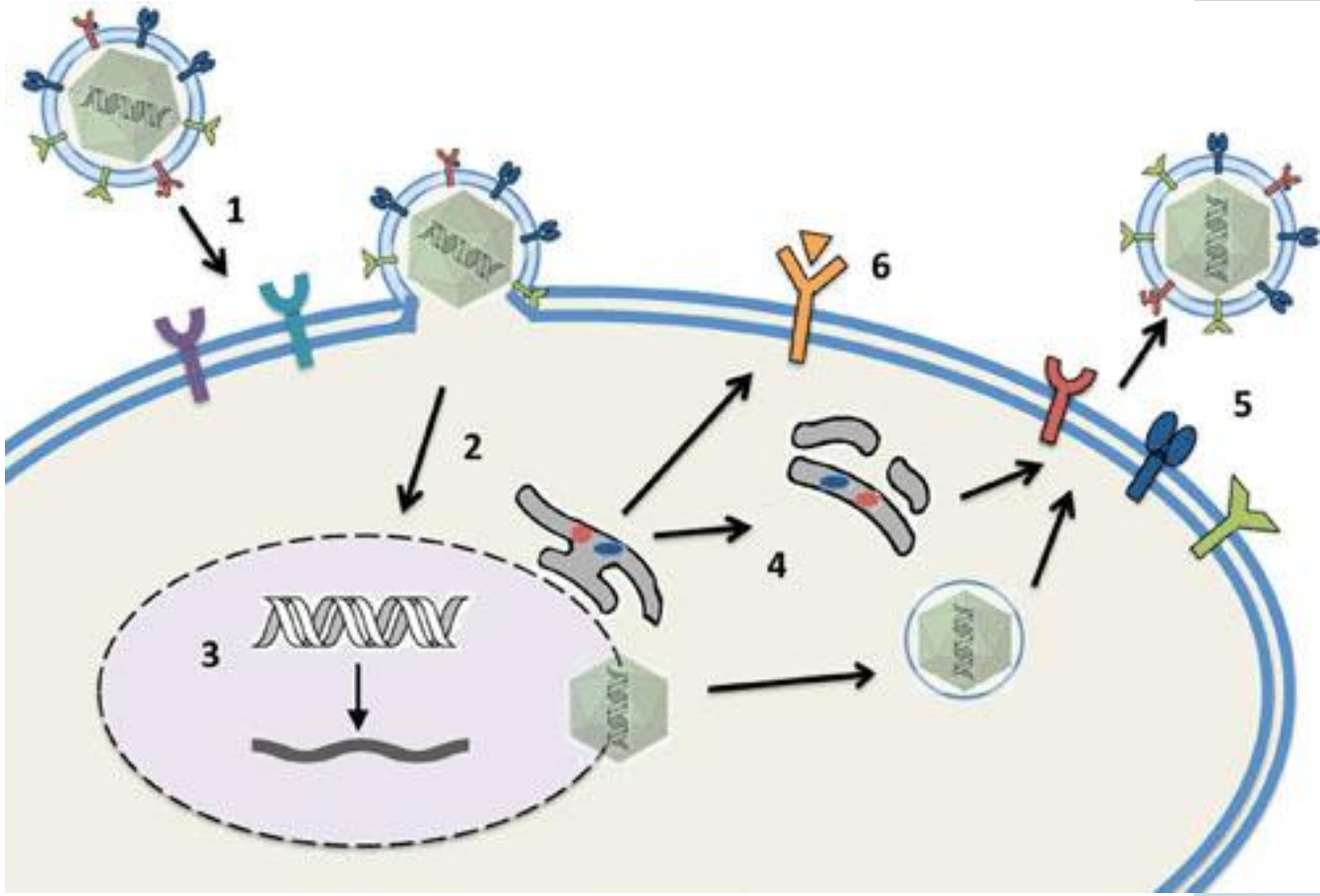
CYTOMEGALOVIRUS

"THE TROLL OF TRANSPLANTATION"

- One of the most common opportunistic infections affecting solid organ transplant (SOT) recipients
- Can lead to serious, life-threatening illness
- Can impact short and long-term graft outcomes

CMV INFECTION

- Beta herpesvirus type 5
  - Related to HSV, EBV, and VZV
- Infects a broad spectrum of cells, allowing it affect multiple organ systems



Special Feature

OPEN

The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation

Camille N. Kotton, MD,[1] Deepali Kumar, MD,[2] Oriol Manuel, MD,[3] Sunwen Chou, MD,[4] Randall T. Hayden, MD,[5] Lara Danziger-Isakov, MD, MPH,[6] Anders Asberg, PhD,[7] Helio Tedesco-Silva, MD,[8] and Atul Humar, MD[2]; on behalf of The Transplantation Society International CMV Consensus Group*

DIAGNOSTICS

- Emphasis on using CMV-QNAT testing calibrated to the World Health Organization (WHO) – approved international standard
  - Results should be reported as log10-transformed data to avoid overinterpreting insignificant changes in CMV DNAemia
  - Changes <0.5 log10 IU/mL (3-fold) may not be clinically significant
  - High sensitivity assays increase rate of detectable but not quantifiable DNAemia and “blips” of singular low results above the lower limit of quantification (LLOQ)

TRENDING CMV QUANTS

- Detectable but not quantifiable DNAemia

		CMV Quant DNA (Quantitative)
Ref. Range & Units		<=0 IU/mL
10/03/25	09:52	<35
09/08/25	09:57	Target Not Detected
08/20/25	07:51	Target Not Detected
06/18/25	09:23	<35
05/28/25	05:12	Target Not Detected

- "Blips" of singular low results above the lower limit of quantification (LLOQ)

		CMV Quant DNA (Quantitative)
Ref. Range & Units		<=0 IU/mL
10/03/25	09:52	<35
09/08/25	09:57	Target Not Detected
08/20/25	07:51	Target Not Detected
06/18/25	09:23	<35
05/28/25	05:12	Target Not Detected
05/05/25	09:29	<35
03/12/25	09:45	36
02/25/25	09:25	68
01/29/25	12:09	<35

TRENDING CMV QUANTS

- Logarithmic vs non-logarithmic change

		CMV Quant DNA (Quantitative)
Ref. Range & Units		<=0 IU/mL
04/22/24	09:38	Target Not Detected
04/16/24	10:19	<35
04/10/24	07:19	<35
04/08/24	09:49	<35
04/04/24	07:29	63
04/01/24	07:09	212
03/26/24	04:55	1,240
03/20/24	11:31	3,250
03/06/24	10:15	2,770
02/29/24	07:12	419
02/14/24	10:42	<35
01/29/24	13:17	Target Not Detected

- Results reported in LOG

		CMV Quant DNA (Log)
Ref. Range & Units		LogIU/mL
09/09/25	09:38	0.0
08/11/25	10:21	1.6
07/03/25	07:24	2.5
06/24/25	11:41	<1.5
06/16/25	08:37	0.0
06/09/25	09:36	0.0
06/03/25	08:33	0.0

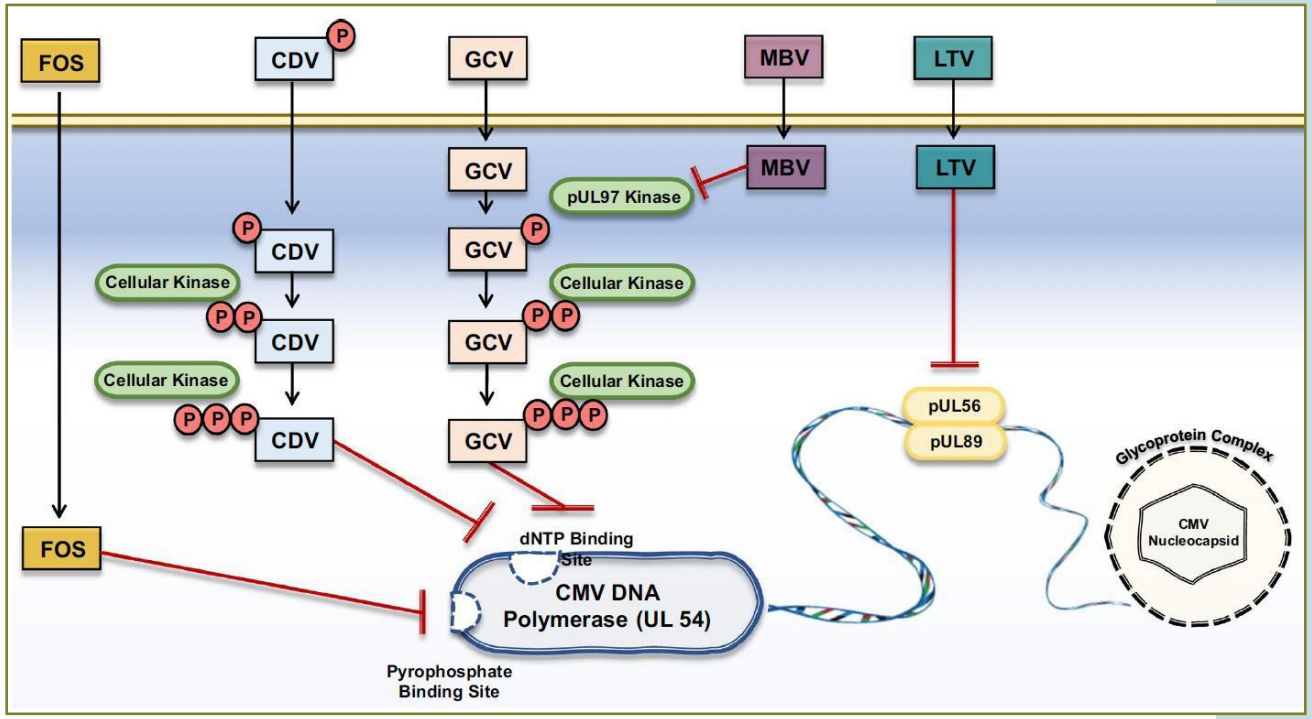
		CMV Quant DNA (Quantitative)
Ref. Range & Units		<=0
09/09/25	09:38	Target Not Detected
08/11/25	10:21	37 ▲
07/03/25	07:24	299 ▲
06/24/25	11:41	<35 ▲
06/16/25	08:37	Target Not Detected
06/09/25	09:36	Target Not Detected
06/03/25	08:33	Target Not Detected

PREVENTION

- Letermovir now FDA approved for prophylaxis in kidney transplant
- More data comparing prophylaxis and preemptive strategies
- Better understanding of mTOR inhibitor use for the reduction of CMV risk

LETERMOVIR

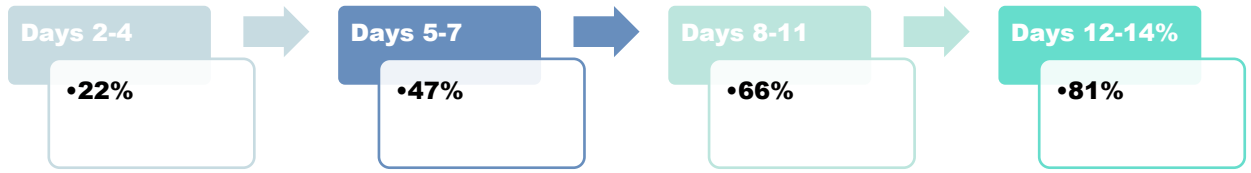
- Inhibits DNA processing and packaging by inhibiting the CMV DNA terminase complex (pUL51, pUL56, pUL89)
- Dose: 480mg daily PO
  - Reduce to 240mg when used with cyclosporine
- Interactions: CYP3A4
- SE: GI



LETERMOVIR AND TACROLIMUS

- 35 stem-cell transplant recipients
- Concentration to dose ratio measured for 14 days post-initiation

Evaluation of the Pharmacokinetic Interaction Between Letermovir and Tacrolimus in Allogeneic Hematopoietic Cell Transplantation Recipients



LETERMOVIR AND TACROLIMUS

- 5 phase I trials conducted on 73 healthy female participants
- Co-administration with tacrolimus resulted in 2.4-fold increase in AUC, 1.6-fold increase in max plasma concentration

Drug Interactions

Pharmacokinetic Drug-Drug Interactions Between Letermovir and the Immunosuppressants Cyclosporine, Tacrolimus, Sirolimus, and Mycophenolate Mofetil

McCrea JB, Macha S, Adedoyin A, et al. Pharmacokinetic Drug-Drug Interactions Between Letermovir and the Immunosuppressants Cyclosporine, Tacrolimus, Sirolimus, and Mycophenolate Mofetil. *J Clin Pharmacol*. 2019;59(10):1331-1339. doi:10.1002/jcph.1423

CMV PREVENTION STRATEGIES

	Valganciclovir	Letermovir	Pre-emptive
Early CMV	Rare	Rare	Common
Efficacy	Good	Good	Good
Late CMV	Common	Common	Rare
Resistance	Uncommon	Rare	Uncommon (with weekly testing)
Ease of implementation	Relatively easy	Relatively easy	More difficult
Prevention of other viruses	Prevents HSV, VZV	None	None
Costs	$$ - drug	$$$ - drug	$ - $$ -monitoring
Safety	Myelosuppression	Drug interactions	Less drug toxicity

PREVENTION STRATEGY BY ORGAN AND SEROSTATUS

Organ	Serostatus	Risk Level	Recommendation
All	D-/R-	Low	Monitor for symptoms, consider HSV prophylaxis
Kidney	D+/R-	High	6 months of prophylaxis OR preemptive therapy
	R+	Intermediate	3 months of valganciclovir OR preemptive therapy
Liver	D+/R-	High	3–6 months of valganciclovir OR preemptive therapy
	R+	Intermediate	3 months of valganciclovir OR preemptive therapy
Heart	D+/R-	High	3–6 months of valganciclovir
	R+	Intermediate	3 months of valganciclovir OR preemptive therapy
Lung	D+/R-	High	12 months of valganciclovir
	R+	Intermediate	6-12 months of valganciclovir

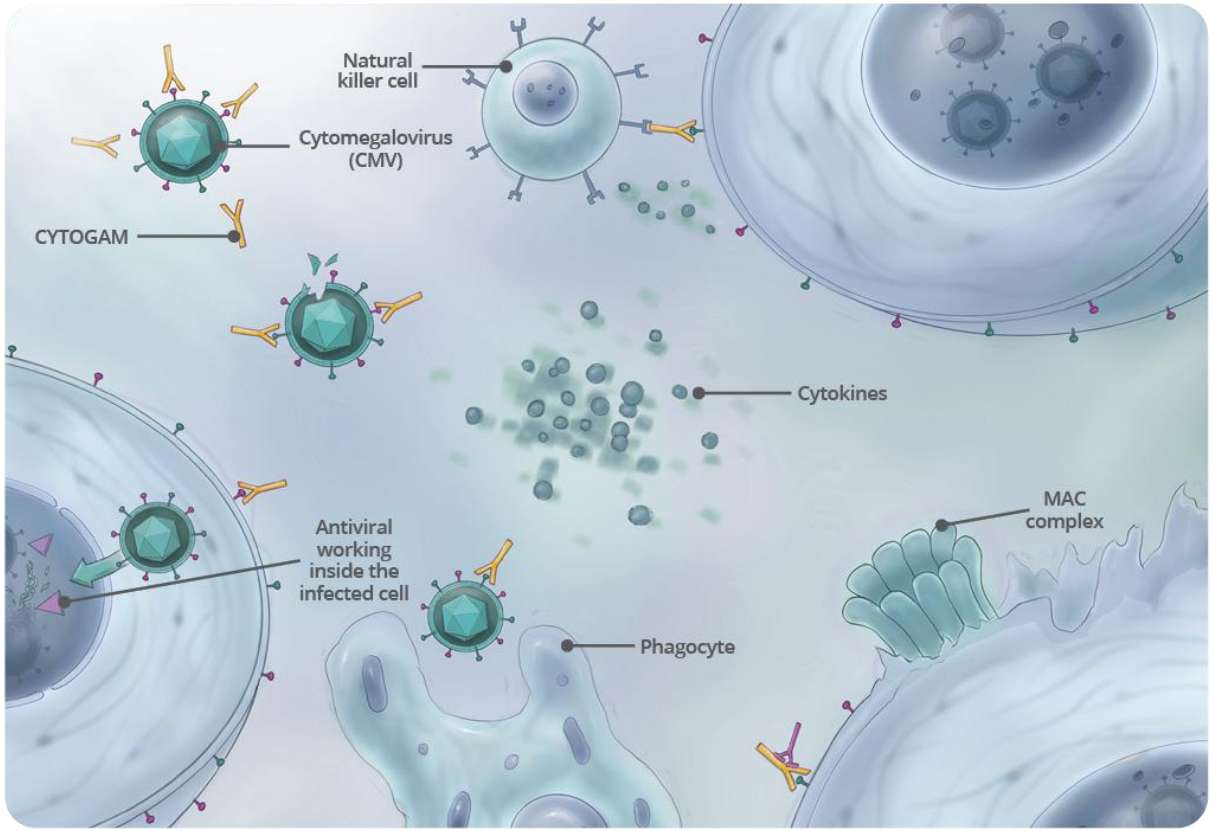
MTOR INHIBITORS AND CMV

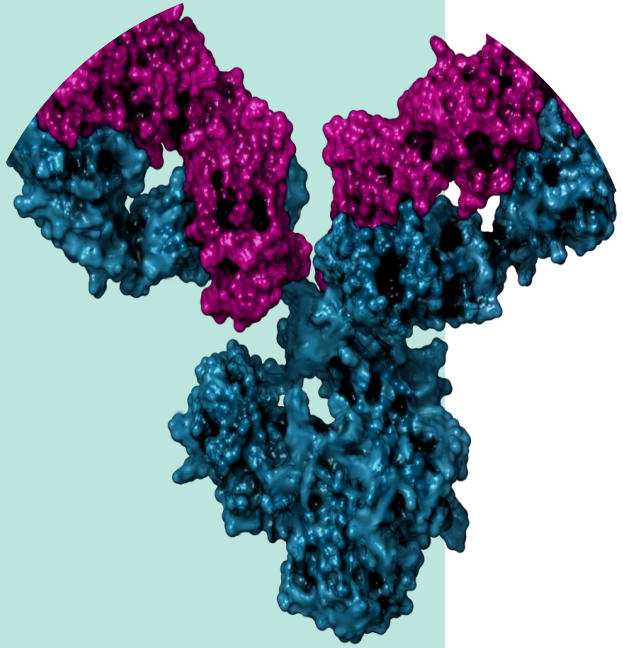
- 10 systematic reviews / meta-analyses showing lower incidence of CMV in heart or kidney recipients on mTOR inhibitors
- Antiviral effect of mTOR has been linked to improvement in T-cell functionality and inhibition of some CMV replication pathways
- Most evidence is from de novo mTOR with reduced CNI goal in kidney transplant recipients
- Benefit largely limited to CMV IgG+ recipients and those on lower doses of CNI

- RECOMMENDATION:
  - In R+ kidney transplant patients after first episode of CMV, consider switching antiproliferative agent to mTOR inhibitor to reduce the rate of recurrence

CMV IMMUNOGLOBULIN FOR PROPHYLAXIS

- Higher CMV antibody titer than IVIG
- May be useful in combination with antivirals in higher risk lung or small bowel transplant
- Should not be used a sole agent

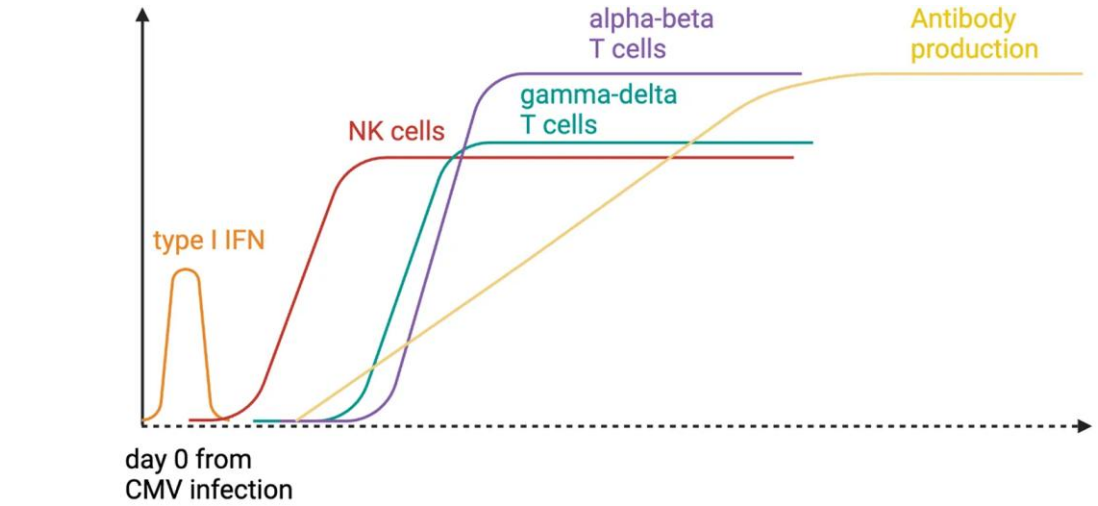


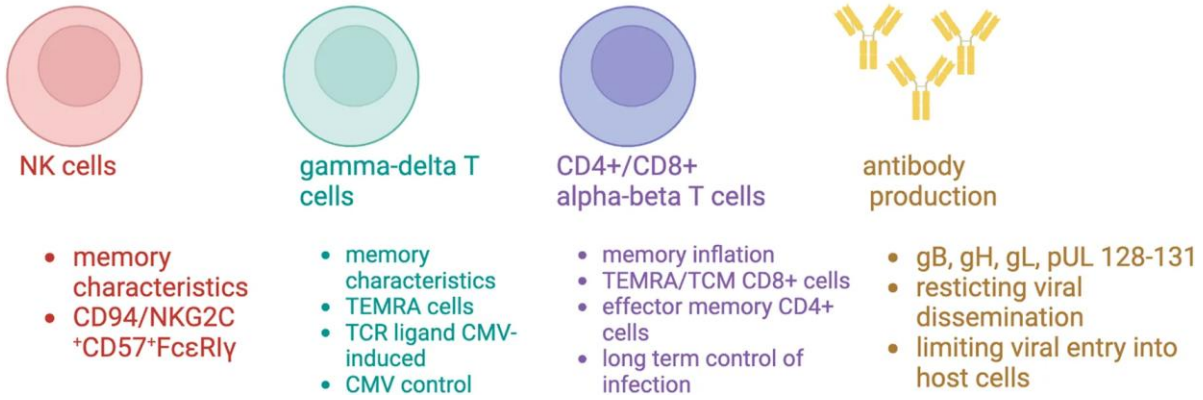


IMMUNOLOGY

- New CMV-cell mediated immunity (CMI) recommendations in CMV R+ kidney transplant recipients to help personalize prophylaxis

CMV CELL-MEDIATED IMMUNITY ASSAYS





- Five main cell types have been studied during CMV infection
- Adaptive immunity
  - CD4+ T cells
  - CD8+ T cells
  - B cells / antibodies
- Innate immunity
  - Natural Killer (NK) cells
  - Gamma-delta T cells

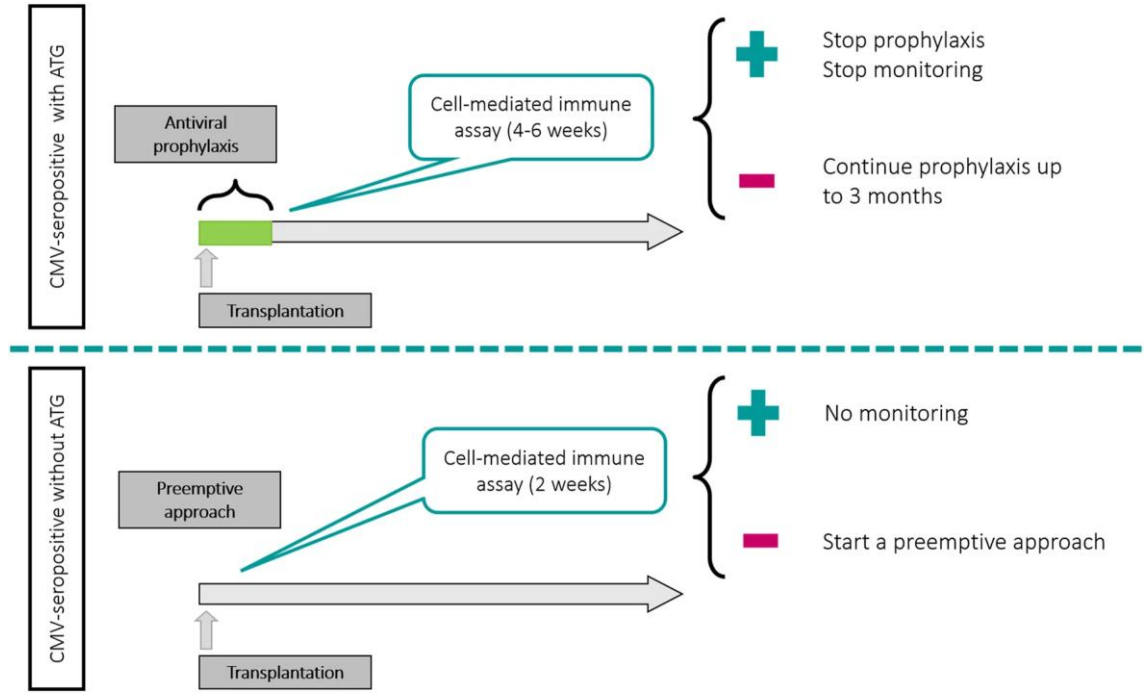
CMV CELL-MEDIATED IMMUNITY ASSAYS

- Potential uses of CMV-CMI assays in CMV+ patients
- Guideline recommendation:

  If available, recommend a CMV-cell mediated immunity (CMI) test in R^+ kidney transplant recipients with or without lymphocyte-depleting antibodies and discontinuing antiviral prophylaxis if positive

  Precise time point cannot be recommended

  - Consider a single time point at 1 month post-transplant or once per month during prophylaxis.

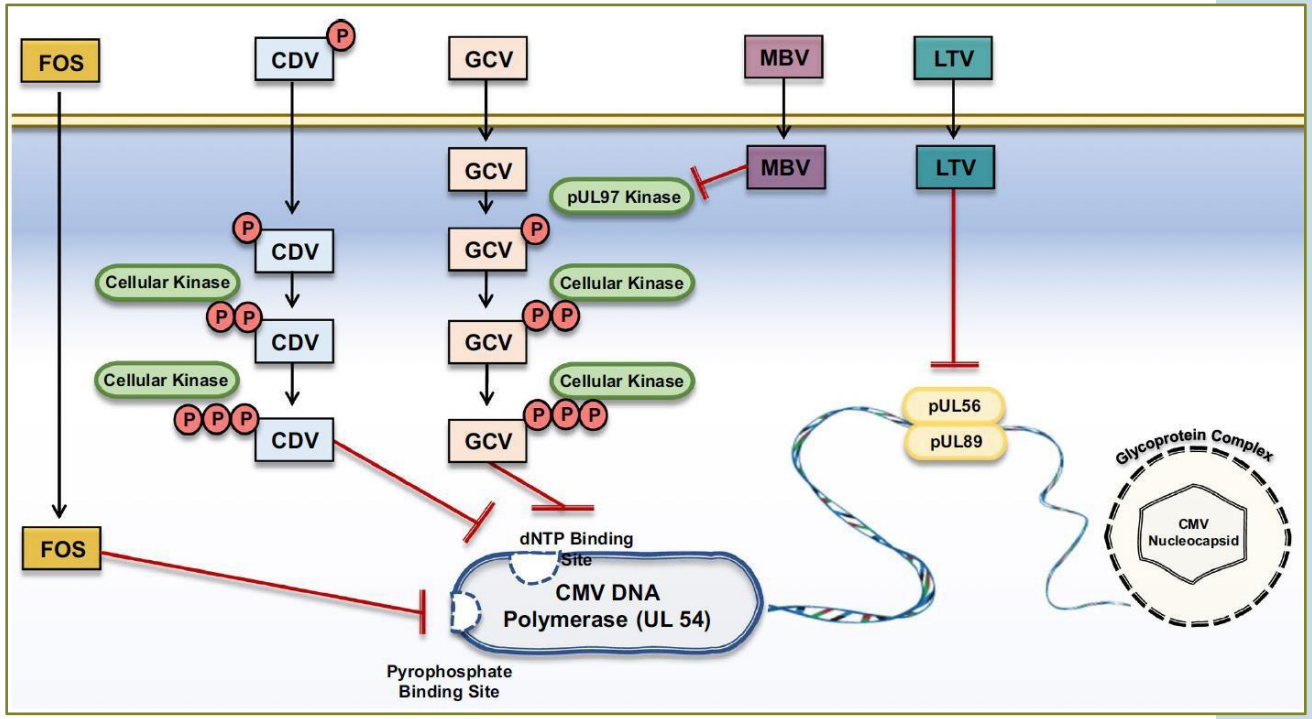


TREATMENT

- Valganciclovir and ganciclovir remain primary treatment options
- Viral load threshold for discontinuation remains challenging with highly sensitive assays

GANCICLOVIR & VALGANCICLOVIR

- Inhibit viral DNA polymerase UL54
  - Metabolized by UL97 kinase to *ganciclovir monophosphate*
  - Phosphorylated 2 more times by cellular kinases to *ganciclovir triphosphate*
- SE: myelosuppression



VALGANCICLOVIR VS GANCICLOVIR

- Preferred when feasible due to oral formulation
  - Reduces or prevents hospital stays
  - Minimize vascular access complications associated with IV therapy
- Dose: 900mg BID PO
  - Must be renally dose adjusted

- Preferred as initial treatment in life-threatening or sight-threatening CMV disease
- Preferred in severe gastrointestinal CMV disease
  - Concern for adequate bioavailability of PO valganciclovir
- Dose: 5 mg/kg q12h IV
  - Must be renally dose adjusted

TREATMENT DURATION

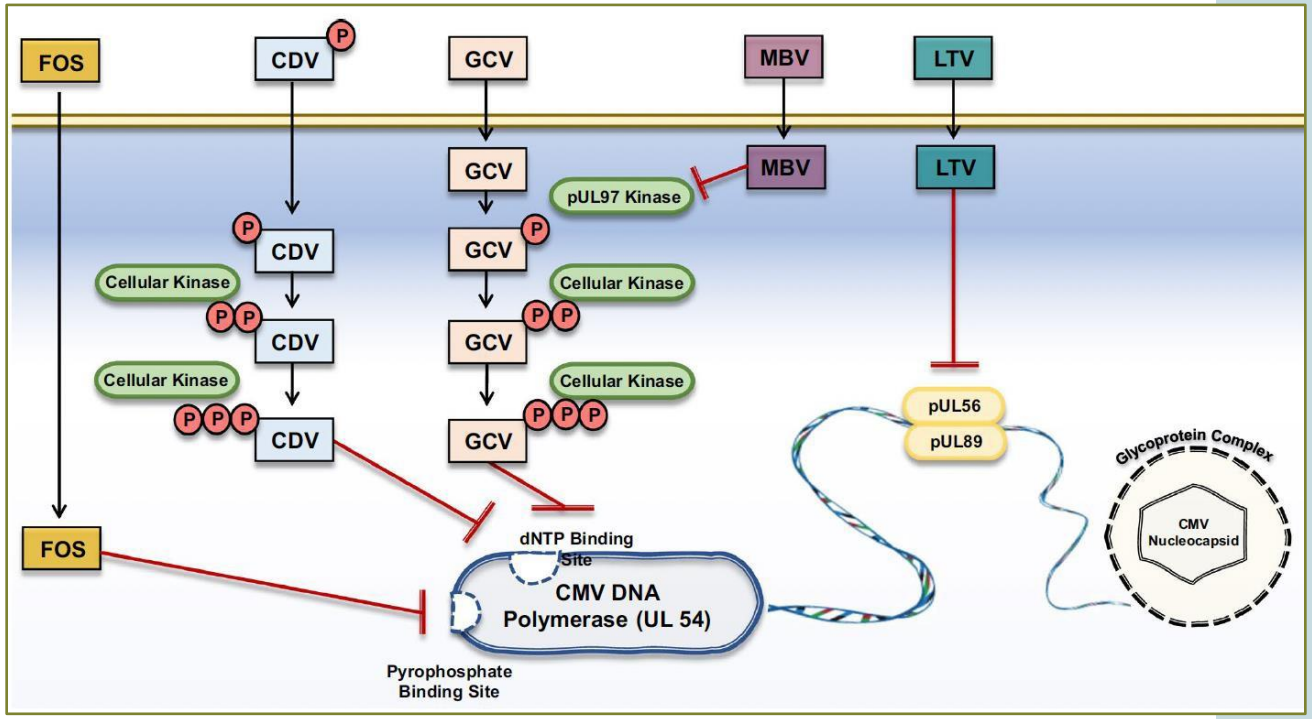
- CMV viral load should be monitored weekly to guide duration of therapy
- Failure to eradicate plasma DNAemia is a major predictor of recurrence
- **Treatment doses of valganciclovir or ganciclovir are recommended until CMV DNAemia has decreased below an institutional, laboratory-specific, threshold**
- With modern highly sensitive assays, a completely undetectable viral load may not always be achievable
  - below LLOQ on a single highly sensitive (LLOQ <200 IU/mL) assay or 2 consecutive weekly samples on a less sensitive assay may be an appropriate target

RESISTANCE

- Maribavir is now recommended as a principal alternative in cases of resistance
- Foscarnet still recommended in severe resistant cases with high viral loads

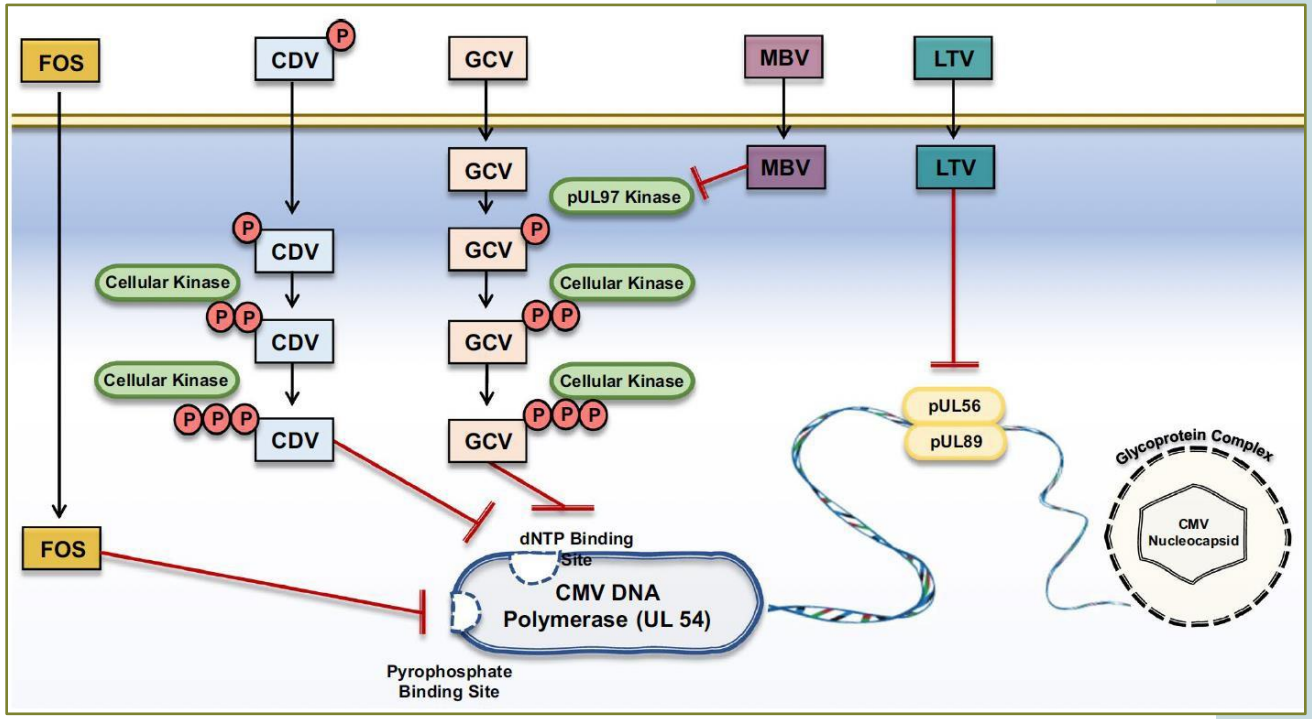
MARIBAVIR

- Inhibits pUL97 kinase, inhibiting phosphorylation of cellular proteins
- Dose: 400mg BID PO
- Interactions: CYP3A4, valganciclovir/ganciclovir
- SE: taste disturbance (46%), GI
- Special access program

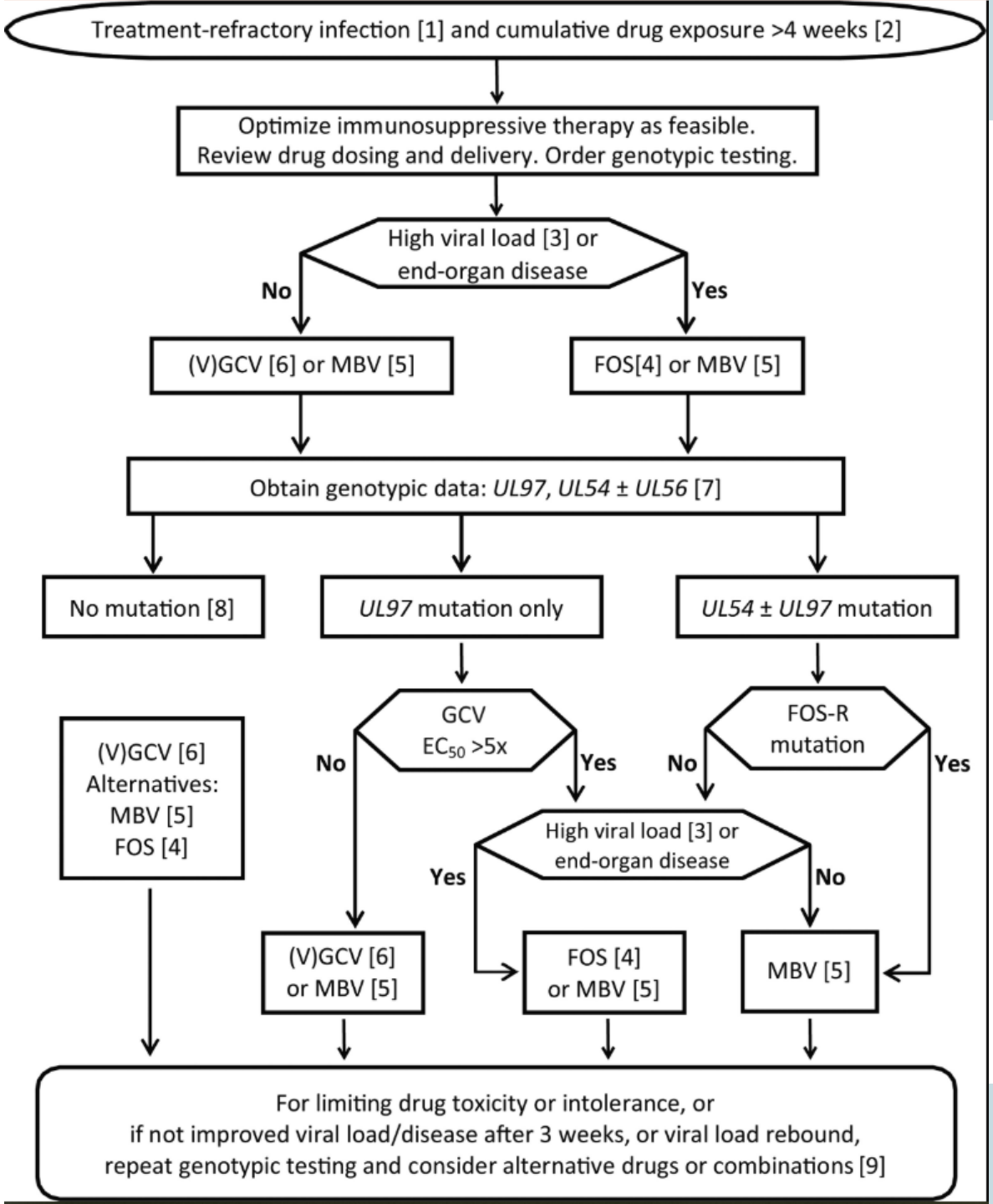


FOSCARNET

- Inhibits pyrophosphate binding site on polymerase UL54
- Dose: 180 mg/kg/day IV
  - Requires renal dose adjustment
  - Based on CrCl per weight (mL/min/kg)
- SE: nephrotoxicity, anemia, electrolyte wasting
  - (K, Ca, Mg, Phos)



MANAGEMENT OF RESISTANT CMV

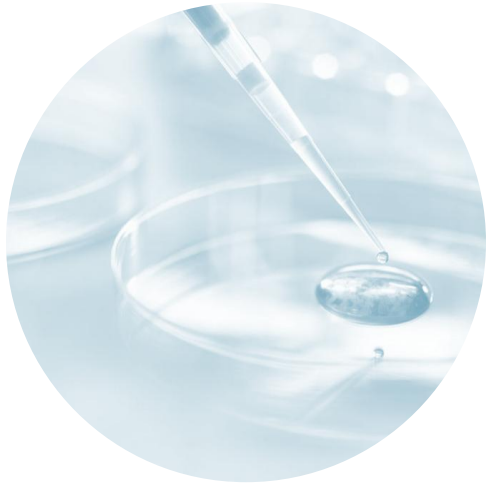


CMV PROPHYLAXIS & TREATMENT OPTIONS

ANTIVIRAL AGENT SUMMARY

Agent	Dose	Drug interactions	Adverse Effects	Place in therapy
Letermovir	480mg daily PO Reduce to 240mg when used with cyclosporine	CYP3A4 Monitor tacrolimus levels	GI	Prophylaxis only
CMV immunoglobulin	150mg/kg IV initially, changes depending on organ and time from transplant	none	Infusion reactions	Prophylaxis in certain cases
Valganciclovir	900mg BID PO (treatment) 900mg daily PO (prophylaxis) Adjust for renal function	No relevant	Myelosuppression	Treatment, prophylaxis
Ganciclovir	5 mg/kg q12h Adjust for renal function	No relevant	Myelosuppression	Treatment of severe disease
Maribavir	400mg BID PO	CYP3A4 Monitor tacrolimus levels	Taste disturbances GI	Treatment of resistant or refractory disease
Foscarnet	180 mg/kg/day IV Adjust for renal function	No relevant	Nephrotoxicity Anemia Electrolyte disturbances	Treatment of severe resistant disease

Q & A



THANK YOU

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