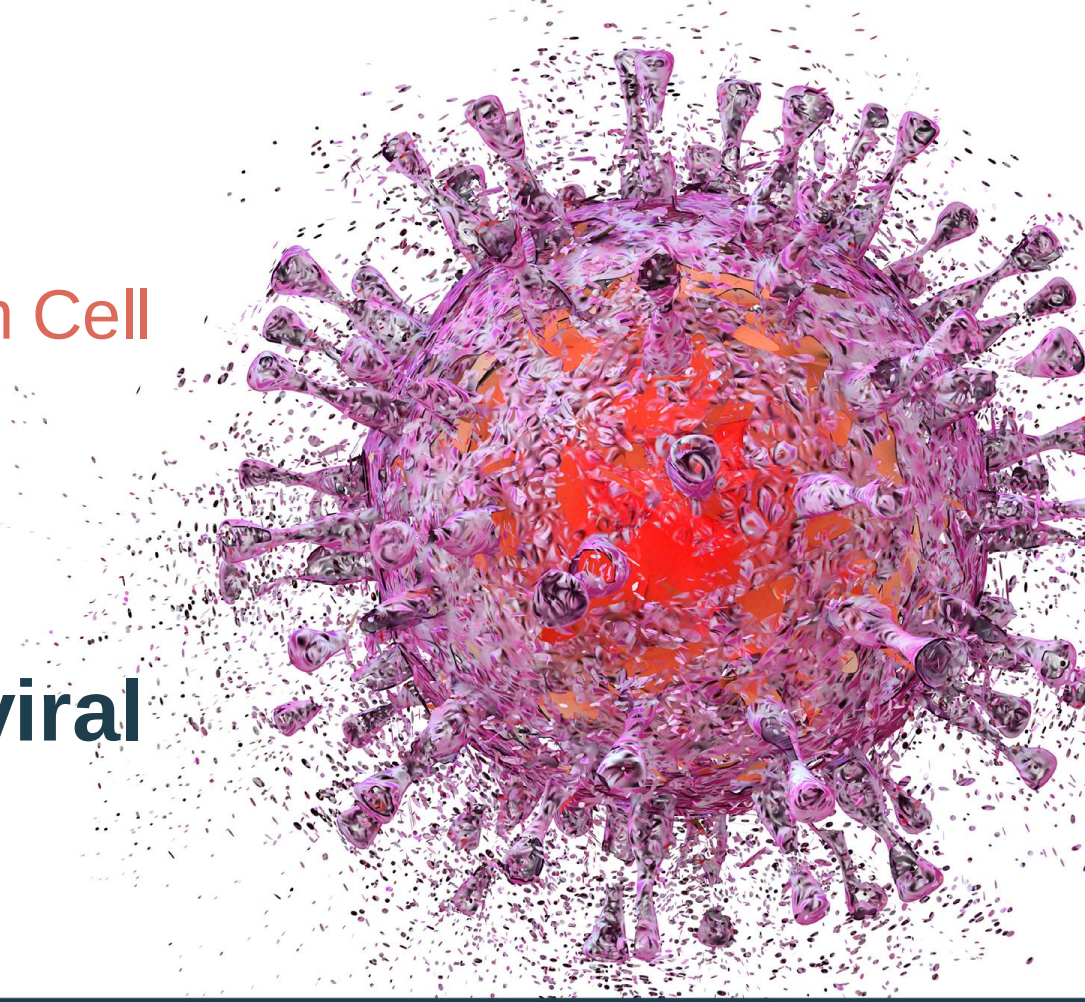
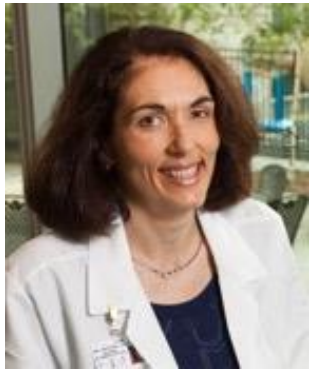
CME OUTFITTERS

Cytomegalovirus in Stem Cell and Kidney Transplant

Overcoming the Limitations of Conventional Antiviral Therapy

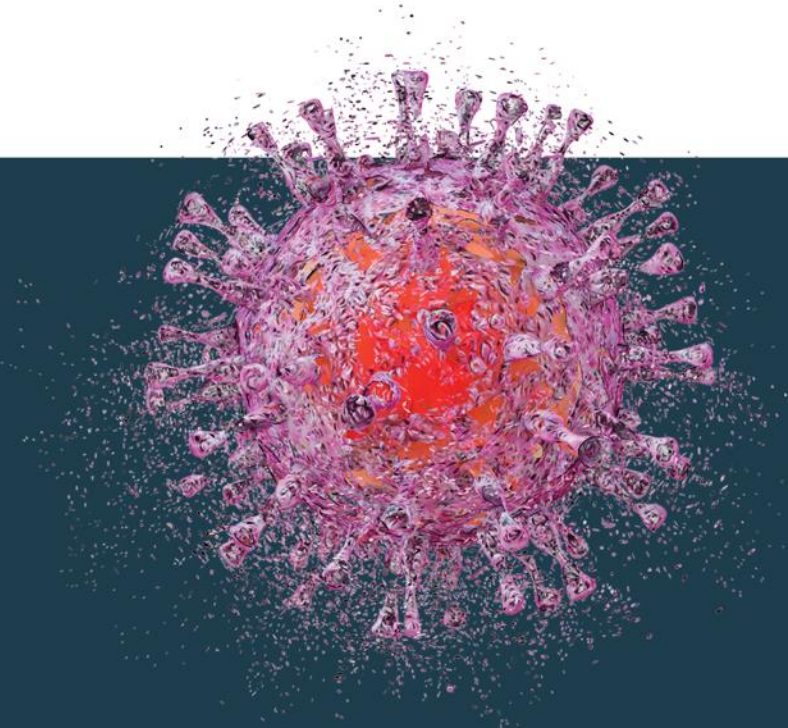


This activity is supported through an independent educational grant from Merck & Co., Inc., Rahway, NJ, USA.



Genovefa Papanicolaou, MD, FIDSA, FASTCT

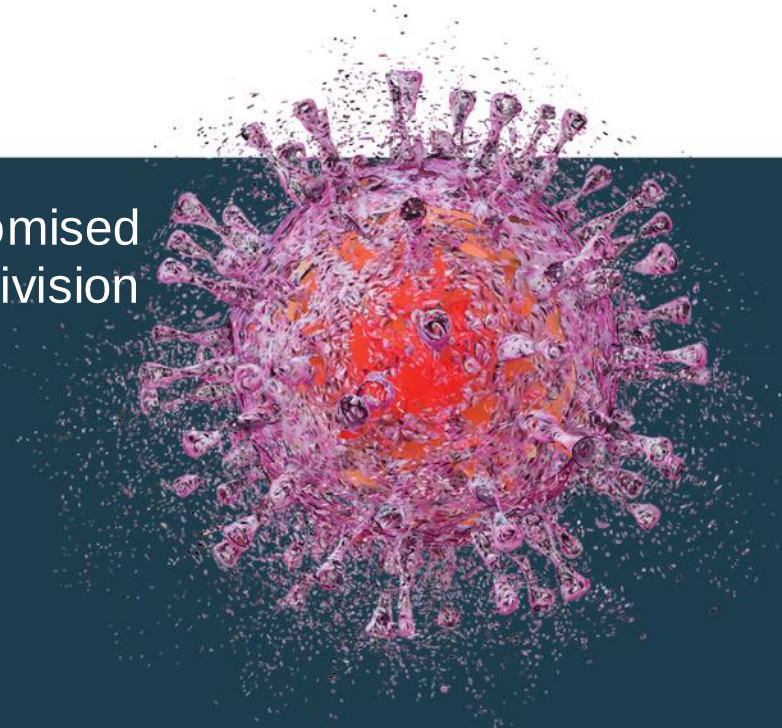
Attending Physician, Infectious Disease Service
Memorial Sloan Kettering Cancer Center
Professor, Weill Cornell Medical College
Cornell University
New York, NY



CME OUTFITTERS

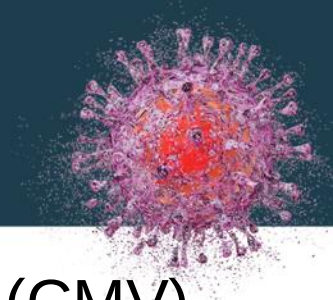
Camille Nelson Kotton, MD, FIDSA, FAST

Clinical Director, Transplant and Immunocompromised Host Infectious Diseases, Infectious Diseases Division
Endowed Chair, MGB Cancer Center
Massachusetts General Hospital
Associate Professor, Harvard Medical School
Boston, MA



CME OUTFITTERS

Learning Objectives



- Identify the burden and impact of cytomegalovirus (CMV) infection in patients receiving renal transplants or hematopoietic stem cell transplants (HSCTs)

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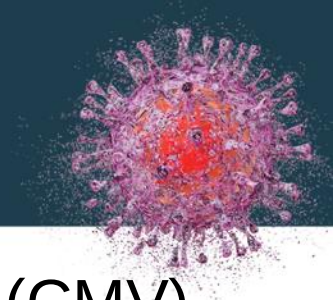

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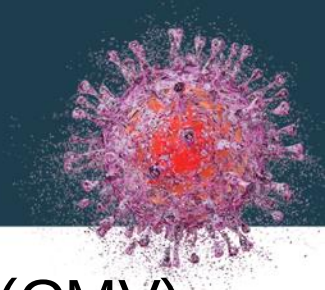

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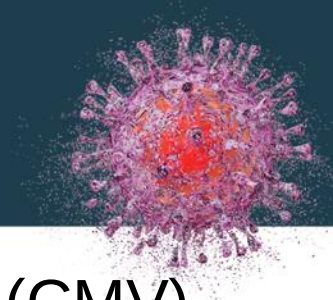

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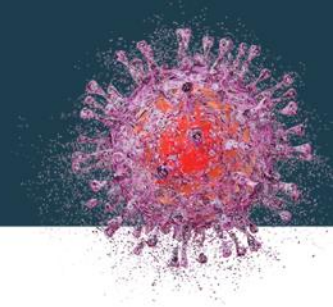
CME OUTFITTERS

Burden and Impact of CMV
Solid Organ Transplantation



- The most common infection after transplantation

Kotton CN, et al. *Am J Transplant*. 2017;17:1439-1446.

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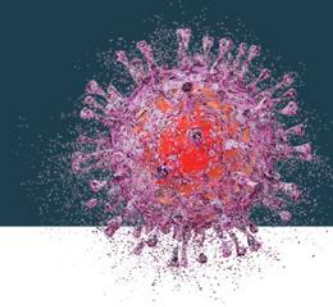

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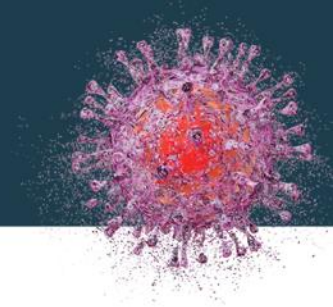

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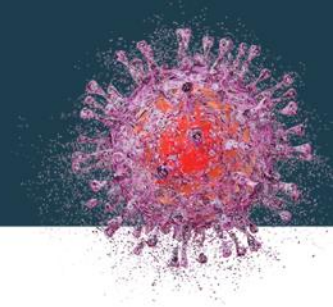

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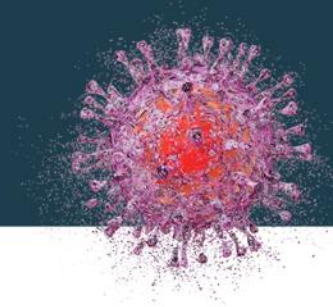

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- Development of highly effective vaccine or other robust immunologic protection has been elusive
- Prevention is key for all transplant recipients
  - Prophylaxis or preemptive therapy (or mTor for CMV R+?)

Kotton CN, et al. *Am J Transplant*. 2017;17:1439-1446.

CMV Serostatus Map: SRTR Data 4/1/15-5/31/19

All kidney transplant recipients (KTR)

>>Deceased donor KTR subgroup

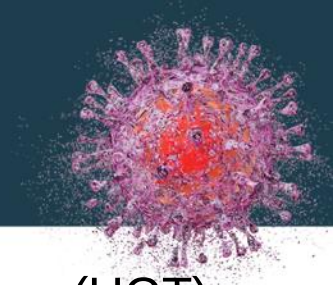
Pancreas recipients
*Data based on n < 20

D+ = CMV seropositive donor; R+ = CMV seropositive recipient; R- = CMV seronegative recipient; SRTR = Scientific Registry of Transplant Recipients.

Jorgenson MR, et al. *Transplant Direct*. 2021;7:e704.

CME OUTFITTERS

Burden and Impact of CMV
Hematopoietic Stem Cell Transplantation



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CME OUTFITTERS

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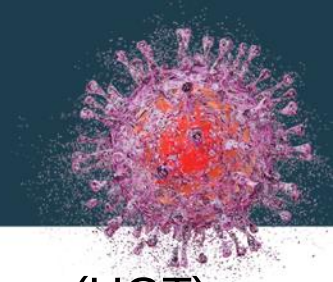

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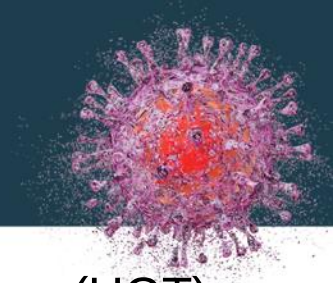

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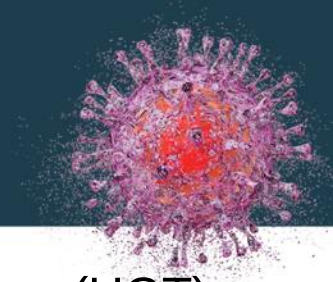

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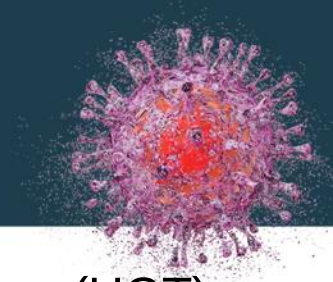

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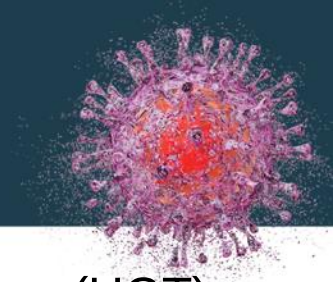

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- Prevention or early therapy are key strategies to minimize morbidity and mortality

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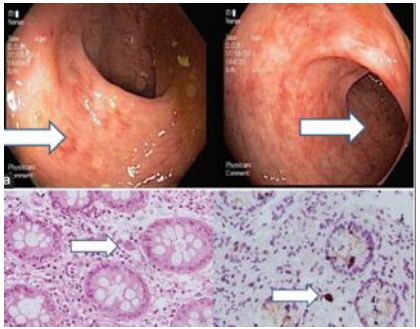
Impact of CMV Infection After HSCT

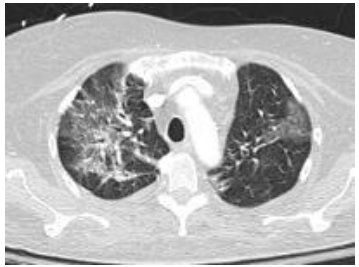
Asymptomatic viremia

CMV disease

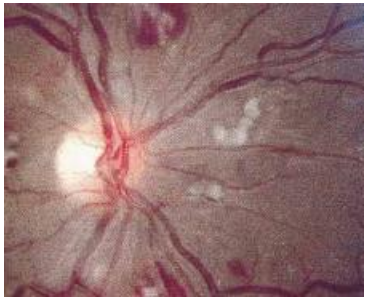
Enterocolitis



Pneumonitis



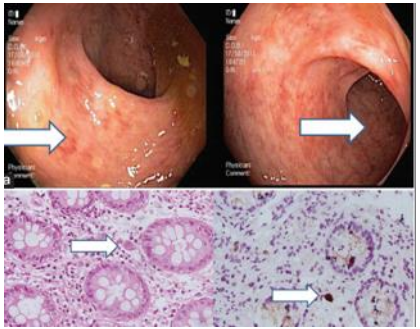
Other
(e.g., retinitis, encephalitis, hepatitis)

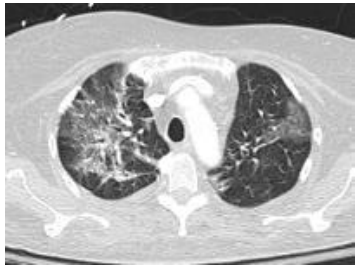


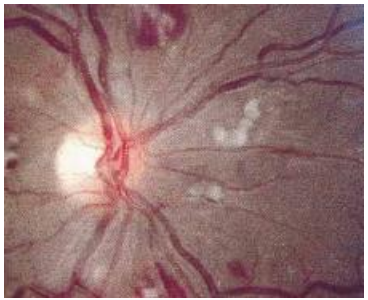
Ranjan P, et al. *J Dig Endosc*. 2015;6:133-138. Ghosh F, et al. *Acta Ophthalmol Scand*. 2002;80:101-104. Horger MS, et al. *AJR Am J Roentgenol*. 2006;187:W636-W643. Teira P, et al. *Blood*. 2016;127:2427-2438.

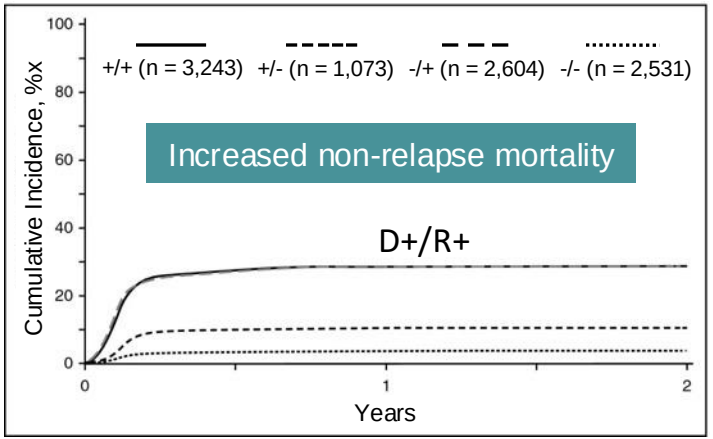
Impact of CMV Infection After HSCT

- Asymptomatic viremia
- CMV disease
  - Enterocolitis
  - Pneumonitis
  - Other (e.g., retinitis, encephalitis, hepatitis)
- Indirect effects









Cumulative incidence curves for CMV reactivation according to D/R serology

Ranjan P, et al. *J Dig Endosc*. 2015;6:133-138. Ghosh F, et al. *Acta Ophthalmol Scand*. 2002;80:101-104. Horger MS, et al. *AJR Am J Roentgenol*. 2006;187:W636-W643. Teira P, et al. *Blood*. 2016;127:2427-2438.

Risk Factors for CMV Disease After Allogeneic HCT

Host	Older age
	Underlying disease of immunodeficiency
Transplant	Allogeneic HSCT
	Myeloablative conditioning
	Unrelated or mismatched donor
	T-cell depletion (*ex vivo* or *in vivo*)
	Cord blood
	Post-transplant cyclophosphamide
	Graft-vs-host disease (GVHD)
	High-dose prednisone (≥ mg/kg/d)
Viral	Seropositivity of recipient (especially if donor seronegative)
	Viremia (especially if high viral burden)
Immune	Lymphopenia or lack of cytotoxic cellular responses

Risk factors can be used to guide management strategy

Beauvais D, et al. *Bone Marrow Transplant*. 2021;56:1305-1315. Hakki M, et al. *Transplant Cell Ther*. 2021;27:707-719.

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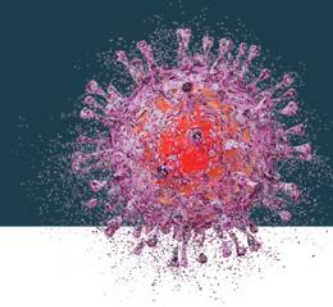
Learning Objectives



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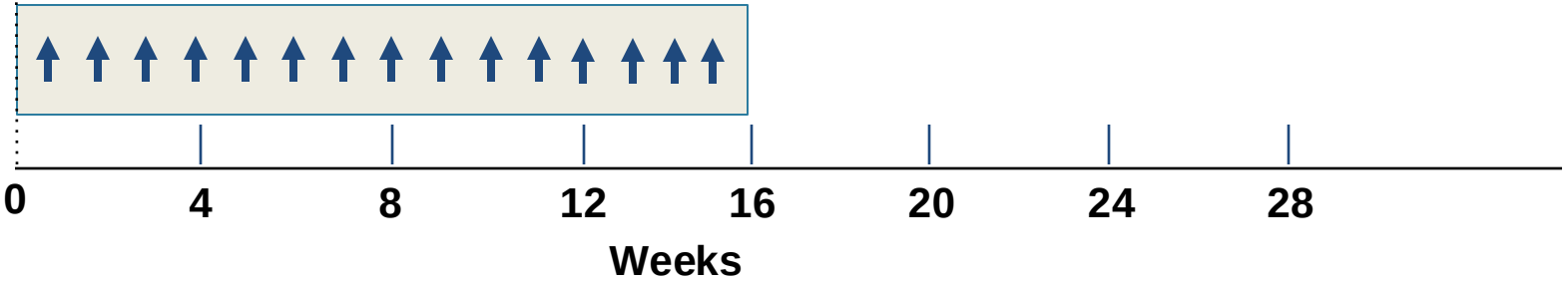
CME OUTFITTERS

CMV Prevention
Prophylaxis vs Preemptive Therapy

Prophylaxis period (typically 3-6 months) after transplantation

Antiviral prophylaxis (valganciclovir or letermovir)

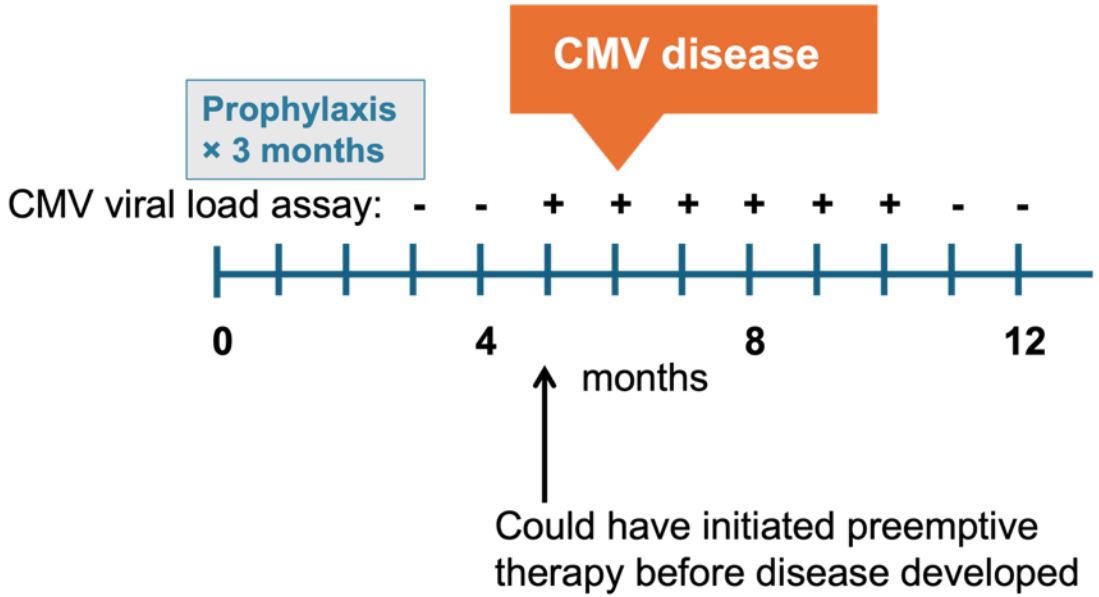
Preemptive monitoring period (once weekly for 12-16 weeks);
If CMV is detected (PCR or pp65 antigenemia), treat until CMV is cleared



PCR = polymerase chain reaction.

Humar A, Snydman D. *Am J Transplant*. 2009;9 (Suppl 4):S78-S86.

Hybrid Strategy for SOT
CMV Surveillance After Prophylaxis



SOT = solid organ transplantation.

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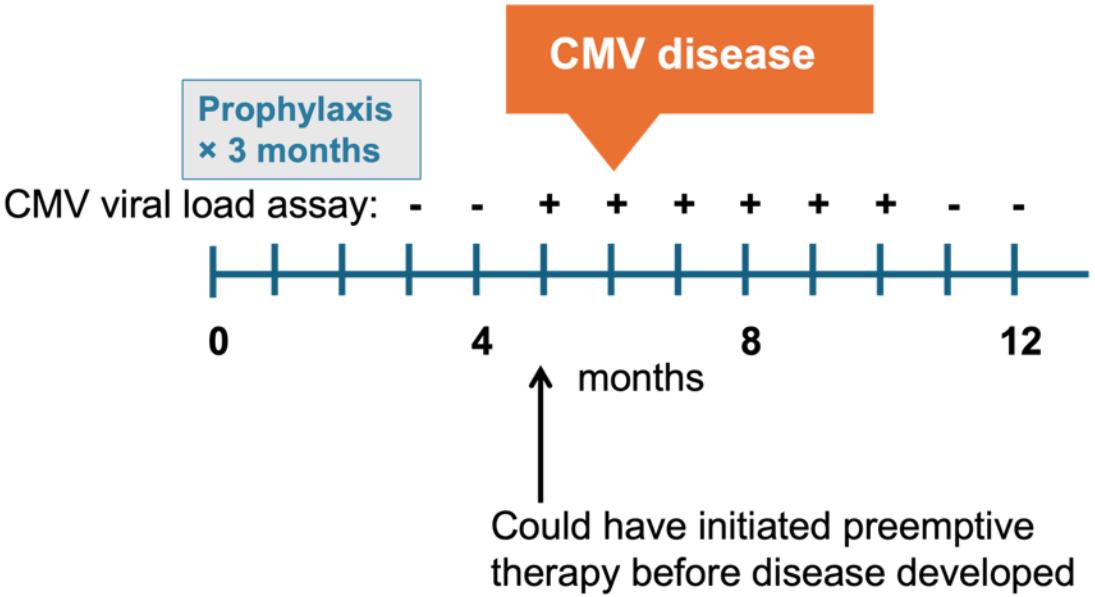

- Weekly monitoring after end of prophylaxis for ~12 weeks

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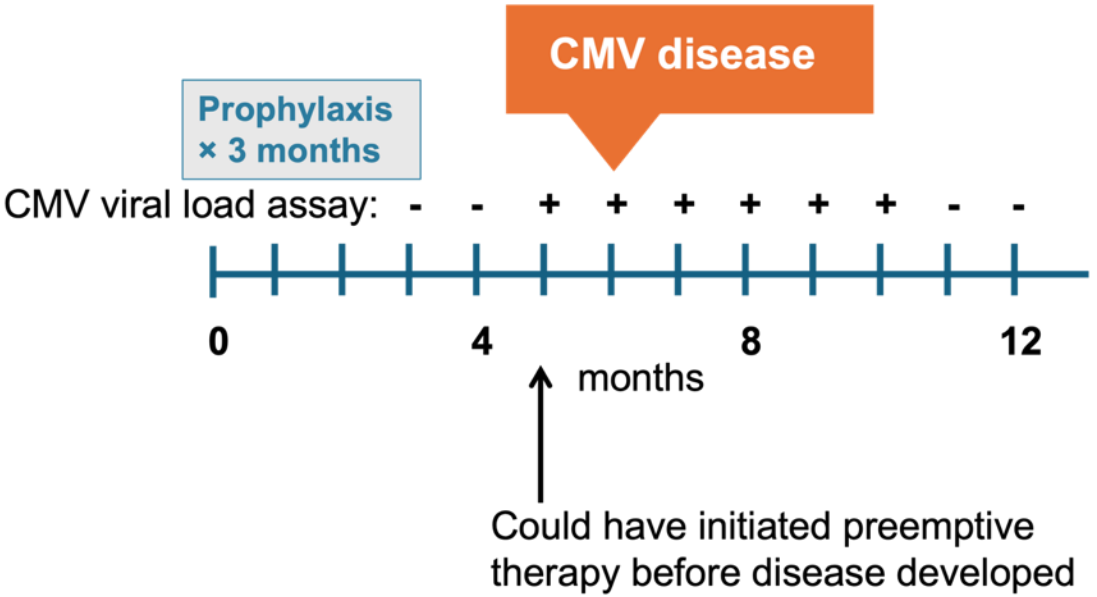

- Weekly monitoring after end of prophylaxis for ~12 weeks
- High risk (D+/R-) may be highest yield population (for late disease)
  - Other high-risk groups (potent immunosuppression)
- Guidelines experts use approach; not strongly evidence-based

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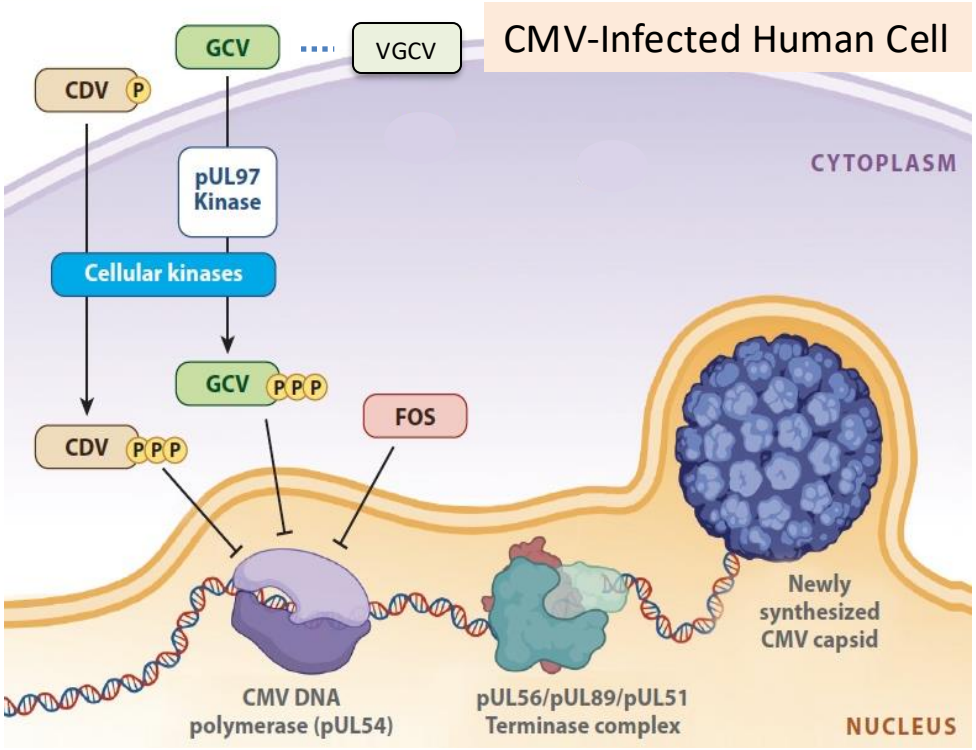
MOAs of Standard Antiviral Therapies



CDV = cidofovir; FOS = foscarnet; GCV = ganciclovir; VGCV = valganciclovir.

Dickter JK, et al. *J Clin Pharm Ther*. 2022;47:699-702. Walti CS, et al. *Transpl Int.* 2023;36:11785.

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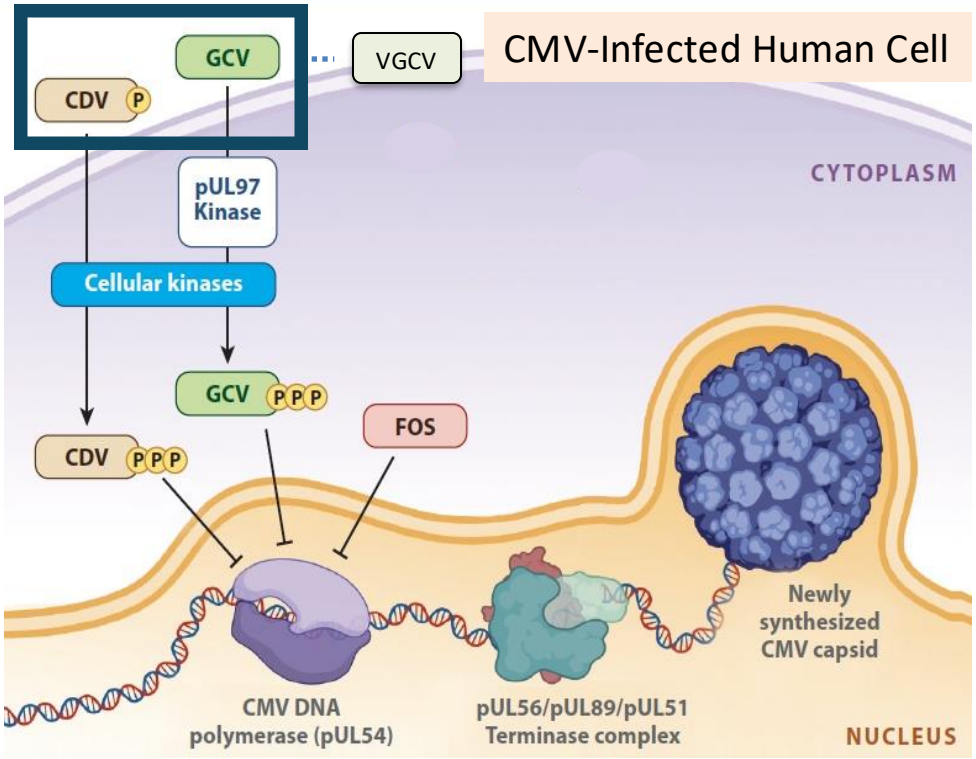

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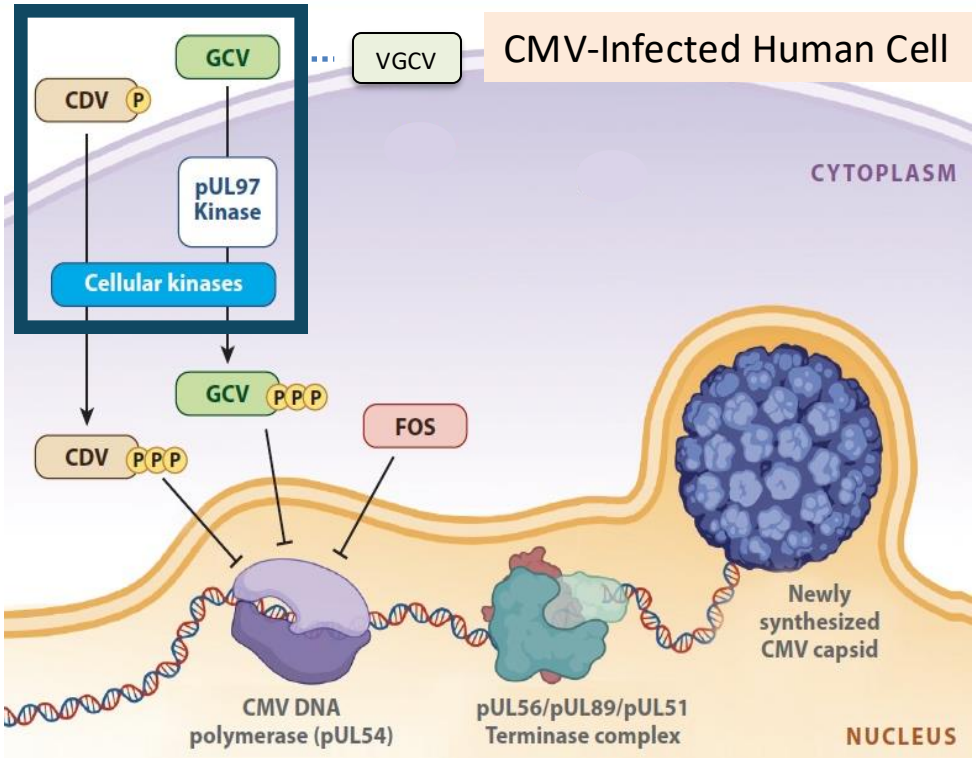

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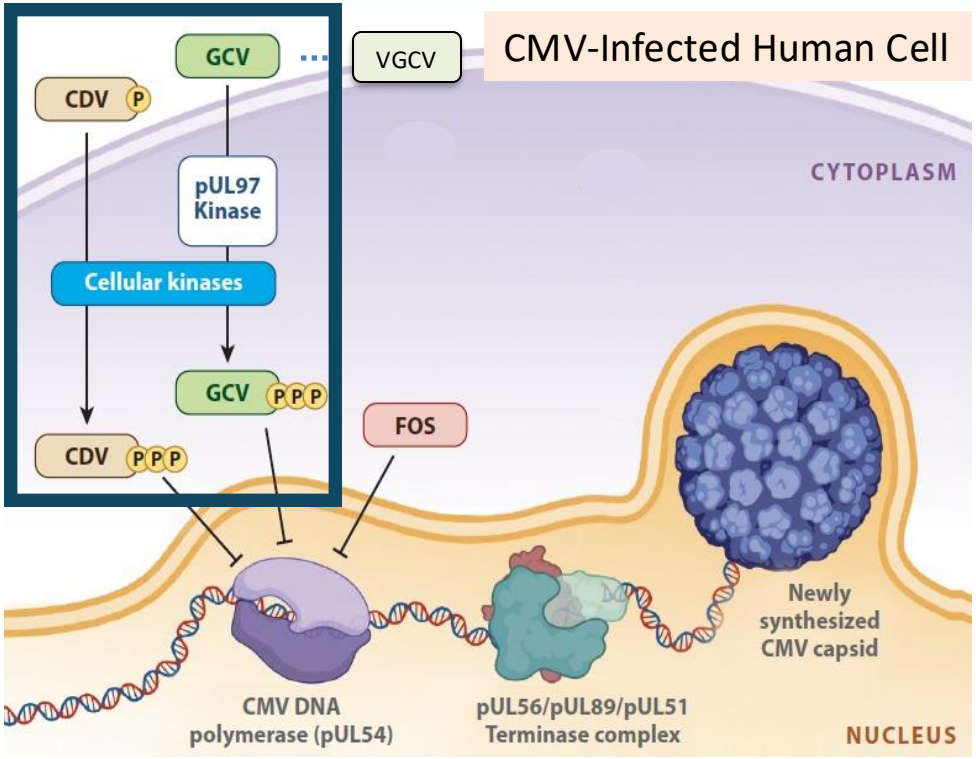

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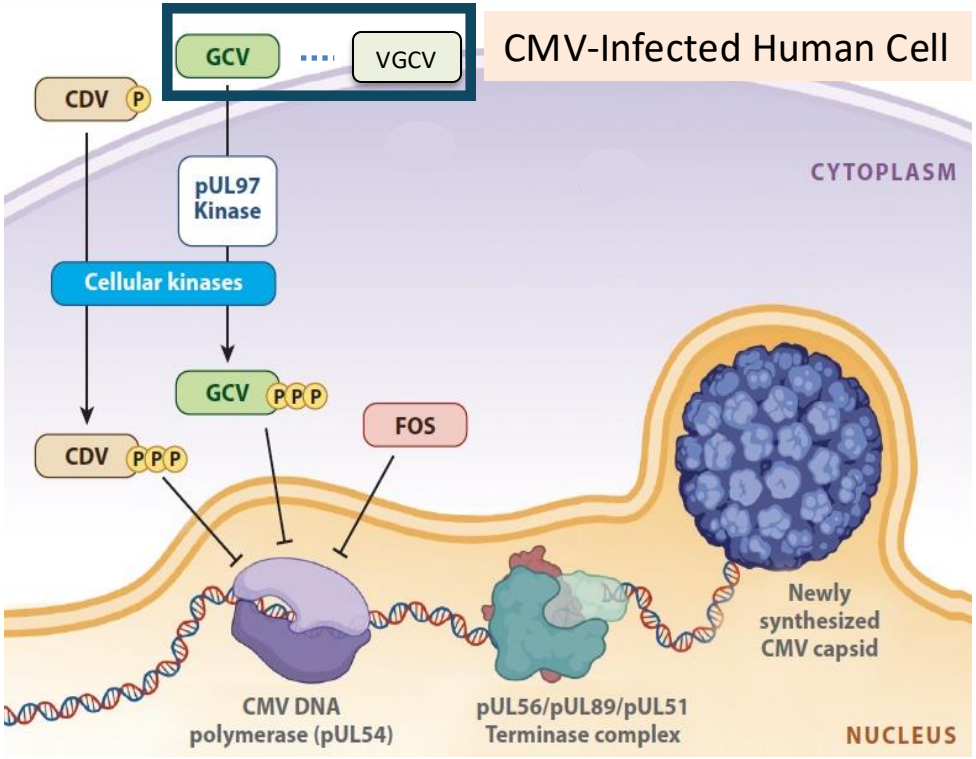

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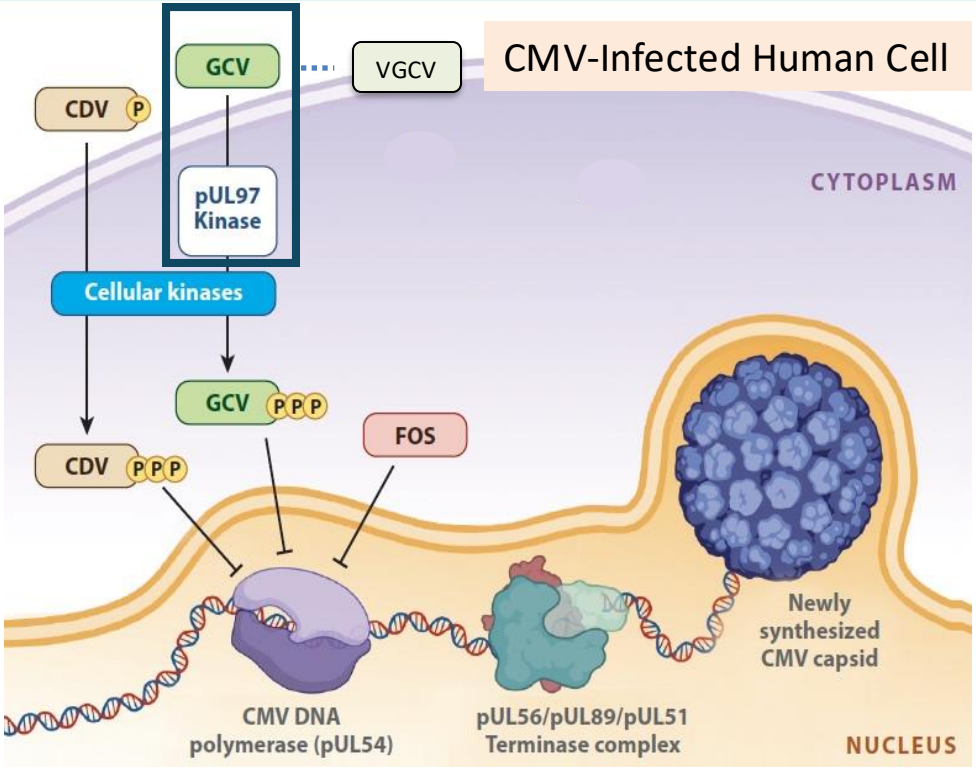

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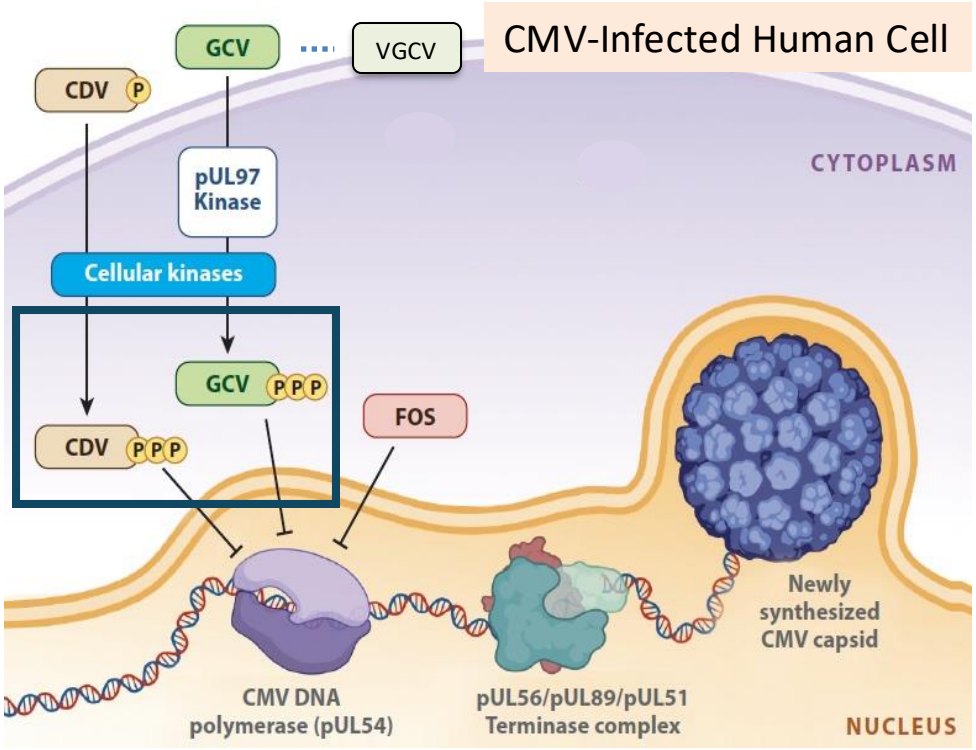

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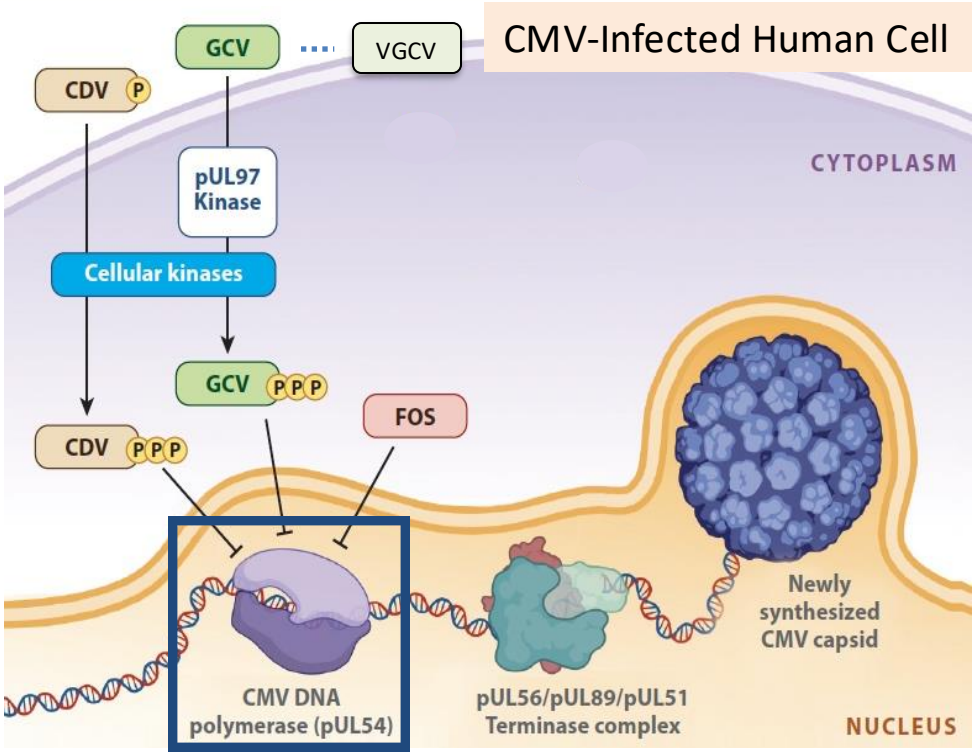

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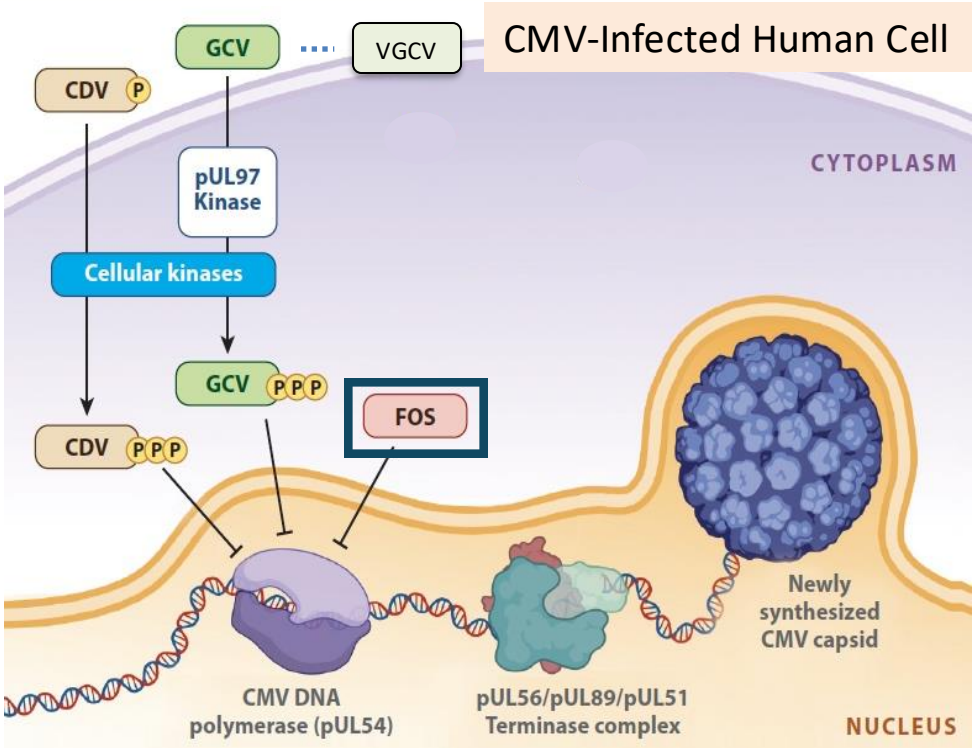

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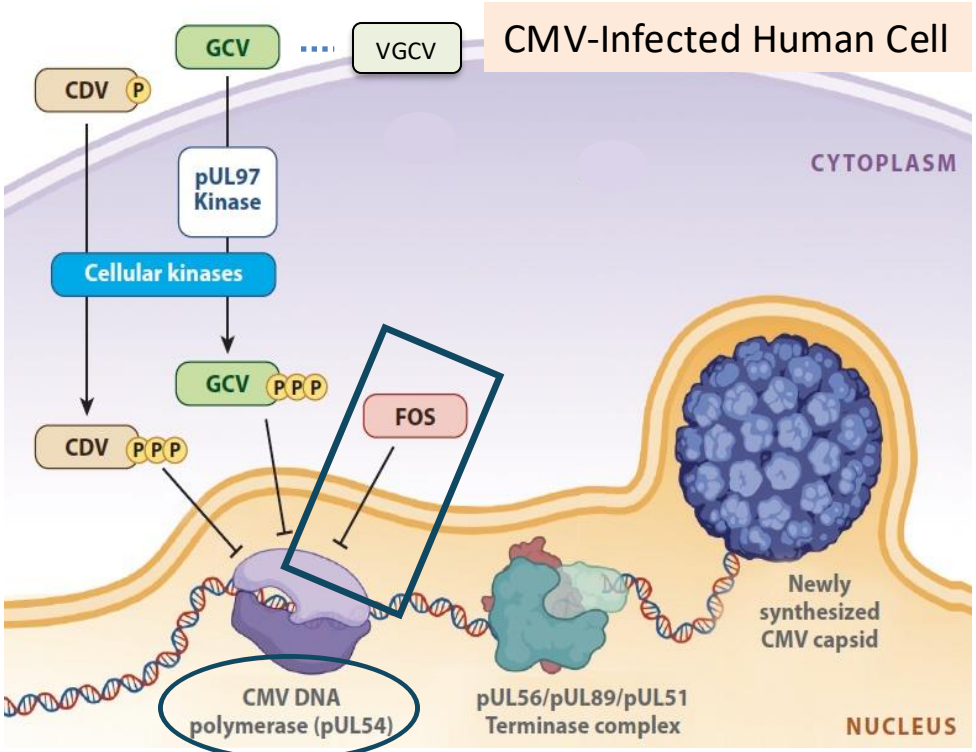

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Standard CMV Agents

Agent	Formulation	Adverse Event (AE)	Notes
Ganciclovir	IV (oral formulation not used in practice due to poor bioavailability)	• Boxed warning: hematologic toxicity, infertility, fetal toxicity • Nephrotoxicity, diarrhea	• Administer over a minimum of 1 hour • May support neutrophils with growth factor
Valganciclovir	Oral, tablet, solution	• Boxed warning: hematologic toxicity, infertility, fetal toxicity • Nephrotoxicity, diarrhea, headache	• Administer with meals • Do not crush or break tablet • Hazardous agent (NIOSH)
Foscarnet	IV	• Boxed warning: seizures, nephrotoxicity • Headache, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, nausea, diarrhea, vomiting, anemia, granulocytopenia	• IV normal saline or dextrose 5% recommended prior to and during infusion; avoid nephrotoxins • Infusion rate should not exceed 1 mg/kg/min
Cidofovir	IV (topical and intravesicular formulations not used for systemic CMV)	• Boxed warning: nephrotoxicity, neutropenia, carcinogenic and teratogenic • Infusion reactions, headache, nausea	• Hydrate with 1 L normal saline over 1-2 hours prior to cidofovir; repeat following infusion • Hazardous agent (NIOSH)

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Barlow A. *US Pharm.* 2021;46:HS2-HS9.

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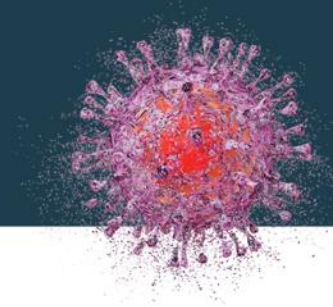
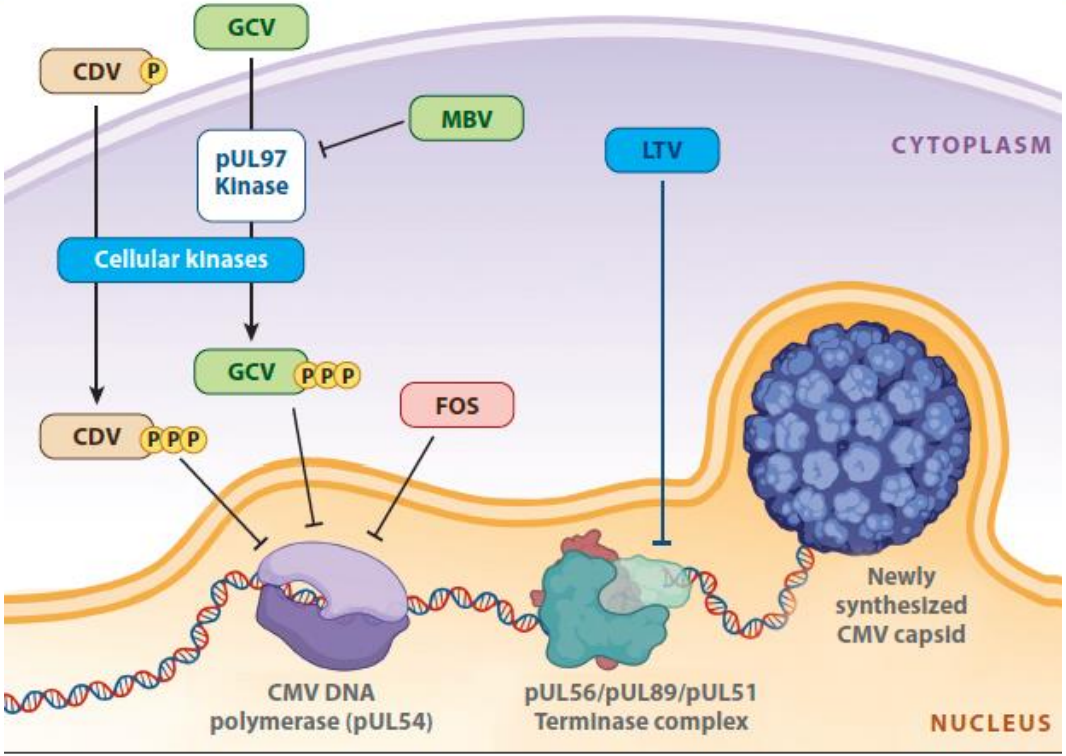
Learning Objectives



- Identify the burden and impact of CMV infection in patients receiving renal transplants or HSCTs
- Review the benefits and limitations of standard antiviral therapies for the prevention and treatment of CMV
- Incorporate novel antivirals for CMV prophylaxis and treatment into clinical practice

CME OUTFITTERS

MOAs of Novel Antiviral Therapies



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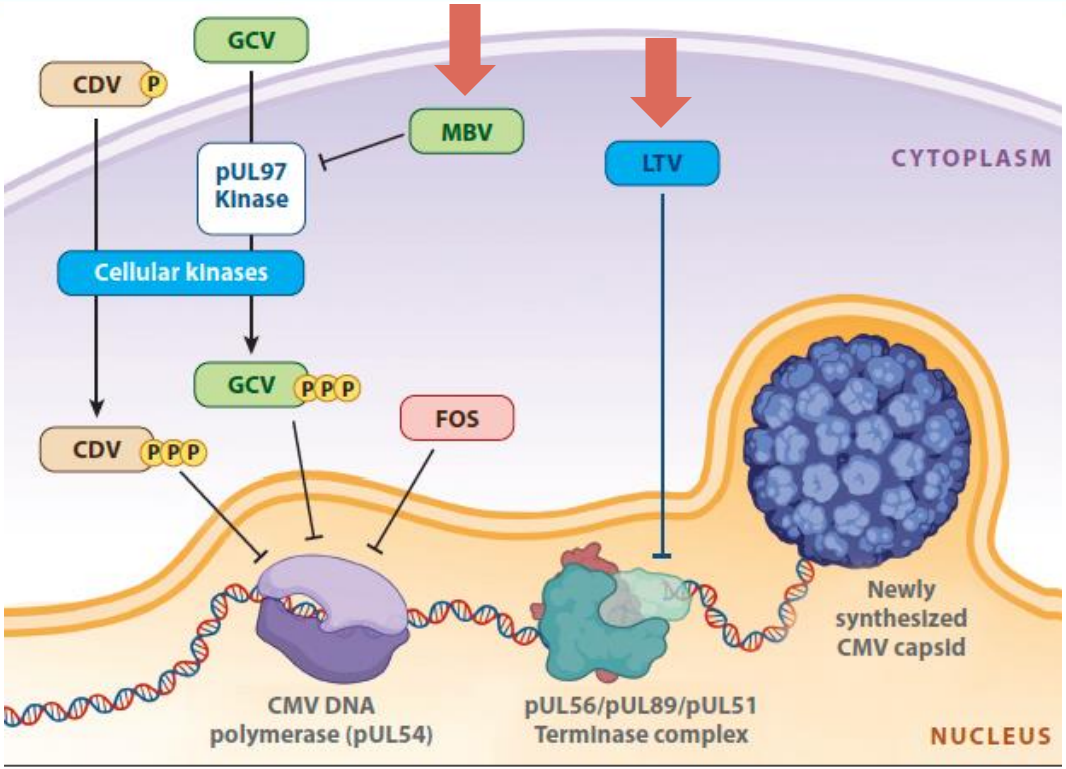

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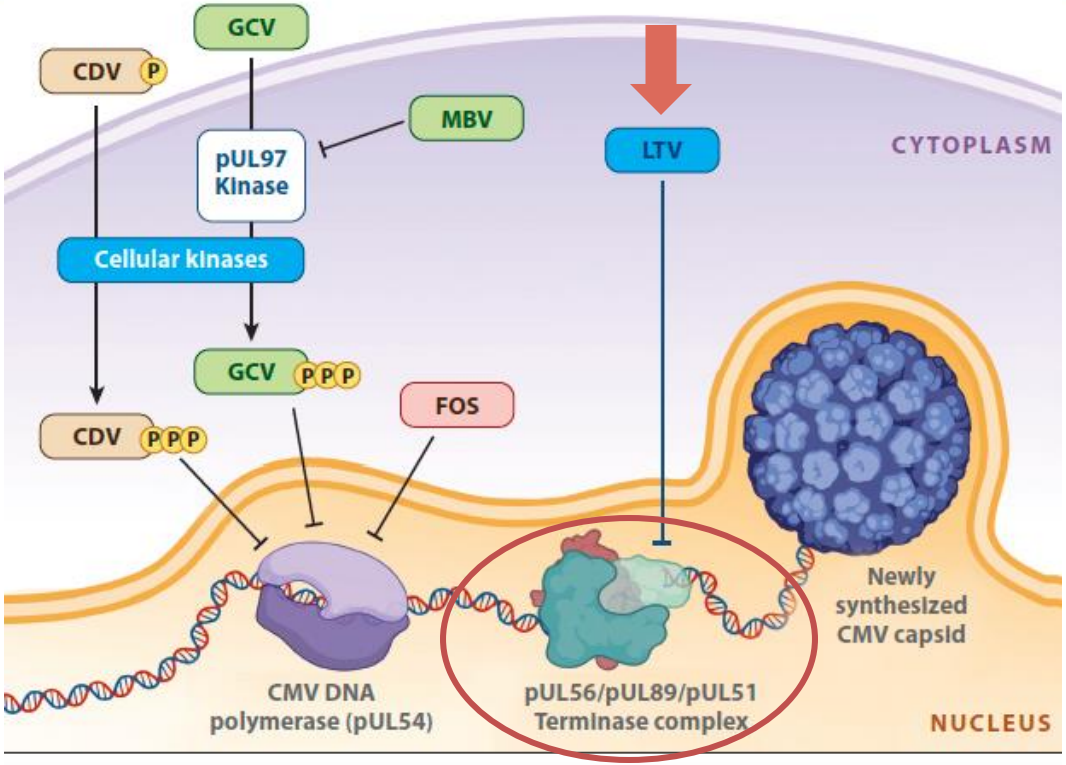

Letermovir (LTV)

- Exerts its action at a unique site of the CMV DNA synthesis pathway, beyond the DNA polymerase complex
- Virus-specific, which may be why it lacks some of the toxicities associated with other CMV antivirals

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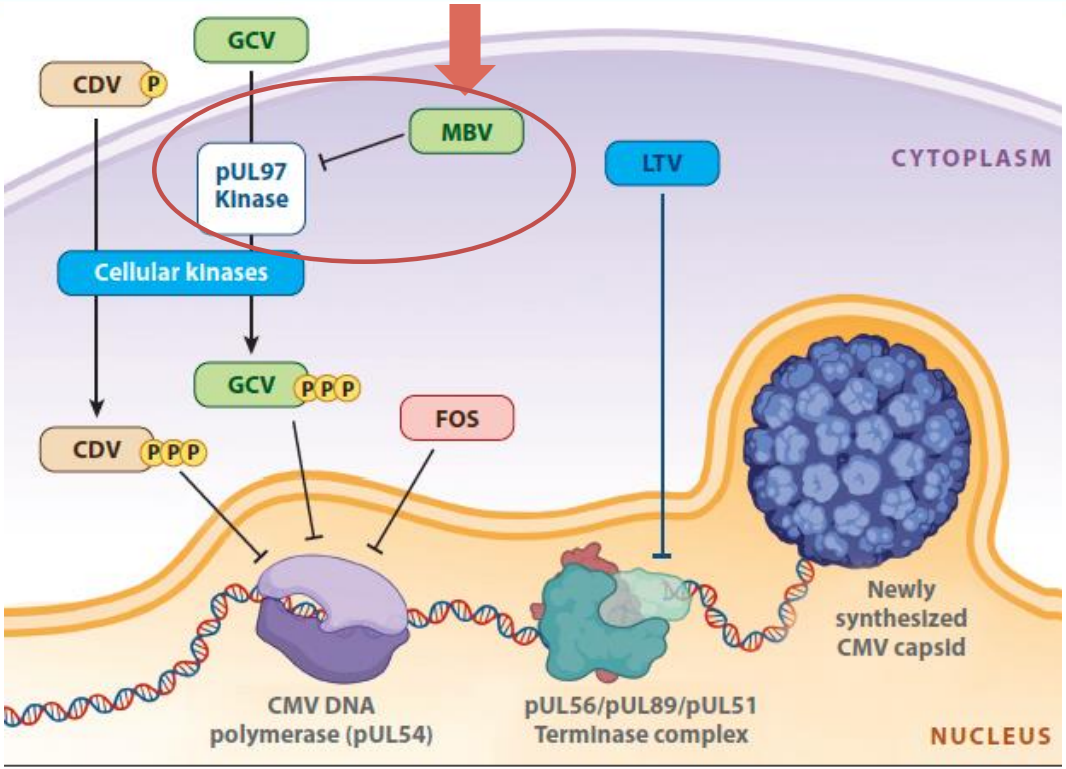

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Maribavir (MBV)

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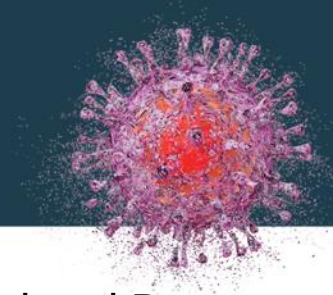

----------RECENT MAJOR CHANGES----------

Indications and Usage, CMV Prophylaxis in Kidney Transplant Recipients (1.2)	06/2023
Dosage and Administration, Recommended Dosage for Adult Patients (2.2)	06/2023

----------INDICATIONS AND USAGE----------

PREVYMIS is a CMV DNA terminase complex inhibitor indicated for:

- Prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). (1.1)
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---------- DOSAGE AND ADMINISTRATION ----------

- HSCT: 480 mg administered once daily orally or as an intravenous (IV) infusion over 1 hour through 100 days post-transplant. (2.1, 2.2)
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  - 2017: R+ HSCT recipients
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Letermovir [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209939orig1s000,209940orig1s000lbl.pdf.

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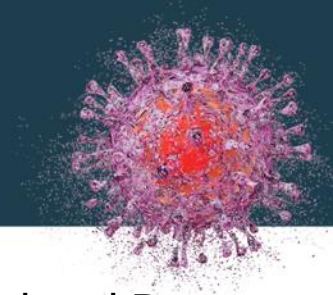

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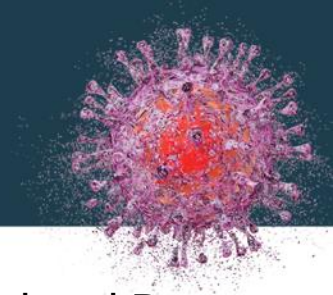

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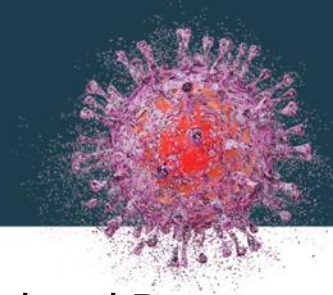

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A significant drug interaction was noted with tacrolimus, leading to a recommendation to reduce the dose by 40%-50% upon initiation of letermovir —Winstead RJ, et al

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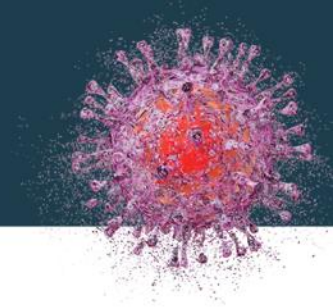

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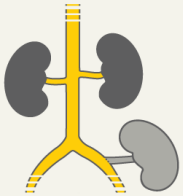
Letermovir [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209939orig1s000,209940orig1s000lbl.pdf.

LTV vs VGCV for Prophylaxis of CMV in High-Risk Kidney Transplant Recipients: Trial Design

POPULATION



422 Men
167 Women

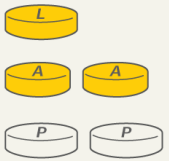
Adult CMV-seronegative kidney transplant recipients receiving an organ from a CMV-seropositive donor

Mean age: 50 years

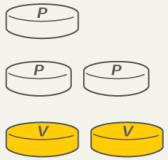
LOCATIONS

94
Hospitals worldwide

INTERVENTION



601 Patients randomized
586 Patients analyzed



301
Letermovir
480 mg of letermovir orally daily, 400 mg of acyclovir twice daily, and a valganciclovir placebo

300
Valganciclovir
900 mg of valganciclovir orally daily with letermovir and acyclovir placebos

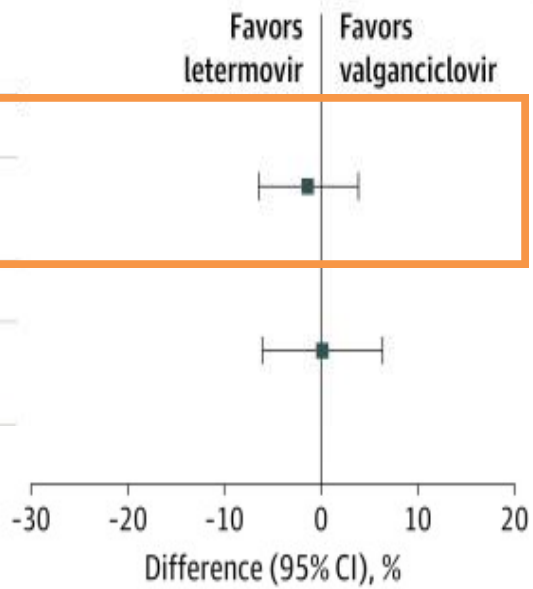
PRIMARY OUTCOME

CMV disease through 52 weeks after transplant

Limaye AP, et al. *JAMA*. 2023;330(1):33-42.

LTV vs VGCV for Prophylaxis of CMV in High-Risk Kidney Transplant Recipients: Outcomes

	No./total No. (%)		Difference (95% CI), %
	Letermovir	Valganciclovir	
Primary outcome			
CMV disease	30/289 (10.4)	35/297 (11.8)	-1.4 (-6.5 to 3.8) (noninferior)
Sensitivity analysis			
Investigator-reported CMV disease	50/289 (17.3)	51/297 (17.2)	0.1 (-6.1 to 6.3)



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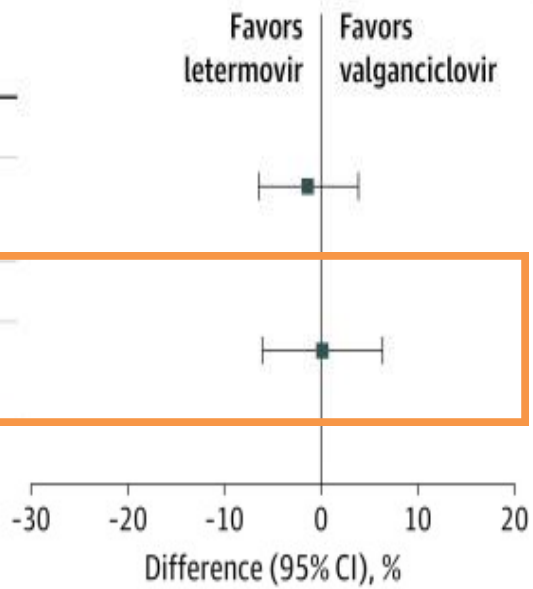
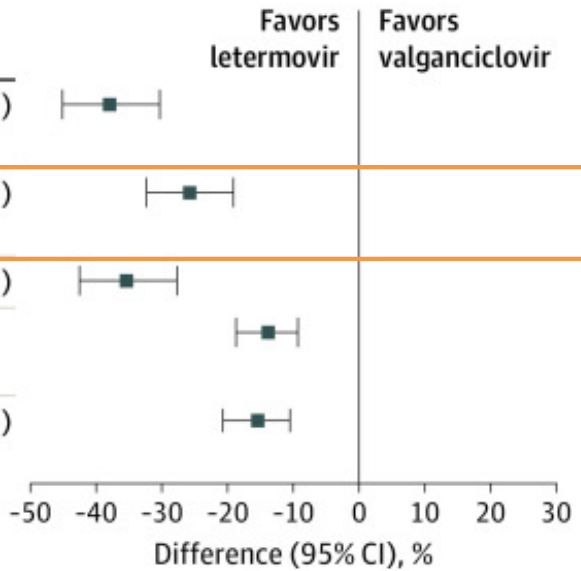


Limaye AP, et al. *JAMA*. 2023;330(1):33-42.

LTV vs VGCV for Prophylaxis of CMV in High-Risk Kidney Transplant Recipient: AEs

Events	No./total No. (%) Letermovir (n = 292)	Valganciclovir (n = 297)	Difference (95% CI), %
≥1 leukopenia or neutropenia event	76 (26.0)	190 (64.0)	-37.9 (-45.1 to -30.3)
Leukopenia reported as an AE	33 (11.3)	110 (37.0)	-25.7 (-32.3 to -19.1)
WBC count <3500 cells/μL	66 (22.6)	172 (57.9)	-35.3 (-42.5 to -27.7)
Neutropenia reported as an AE	8 (2.7)	49 (16.5)	-13.8 (-18.7 to -9.3)
ANC <1000 cells/μL	12 (4.1)	58 (19.5)	-15.4 (-20.7 to -10.5)



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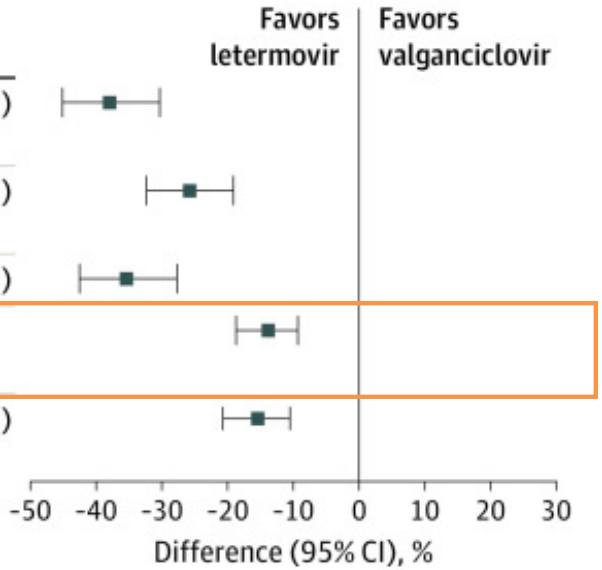

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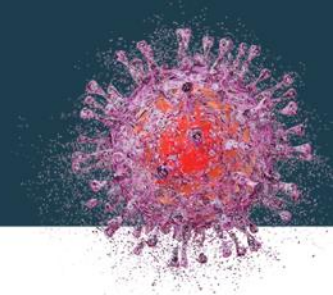
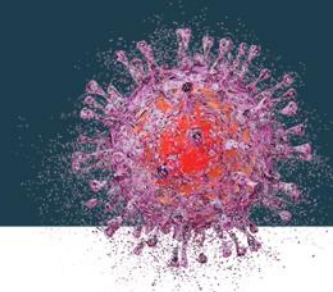
LTV vs VGCV for Prophylaxis of CMV in High-Risk Kidney Transplant Recipient:[1] AEs



- Quantifiable CMV DNAemia detected in 2.1% on LTV vs 8.8% on VGCV by week 28

1. Limaye AP, et al. *JAMA*. 2023;330(1):33-42 2. Humar A, et al. *Am J Transplant*. 2010;10:1228-1237..

LTV vs VGCV for Prophylaxis of CMV in High-Risk Kidney Transplant Recipient:[1] AEs



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  - Of participants evaluated for suspected CMV disease or CMV DNAemia, 0% (0/52) with LTV and 12.1% (8/66) with VGCV had resistance-associated substitutions

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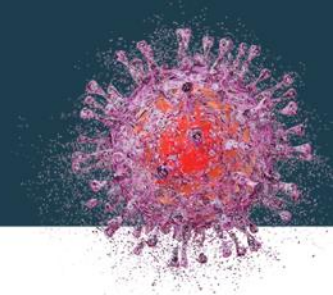

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AEs Through Week 28	LTV (n = 292)	VGCV (n=297)	Difference (95% CI), %
Discontinued due to AEs	12 (4.1)	40 (13.5)	-9.4 (-14.1 to -4.9)
Discontinued due to drug-related AEs	8 (2.7)	26 (8.8)	-6.0 (-10.1 to -2.4)

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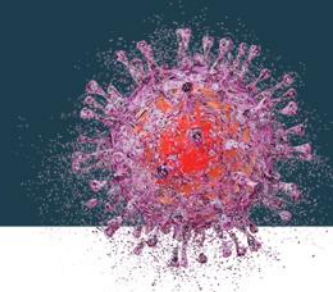

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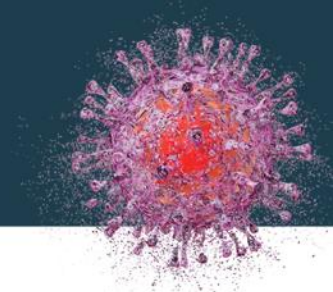

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- **VGCV dosing adjusted to renal function (details not available) could explain neutropenia and breakthrough infections**
- IMPACT trial:[2] Compared 100 vs 200 days of VGCV prophylaxis reported neutropenia rate of 3% after 100 days and 5% after 200 days (19% leukopenia), 15% at some point in trial

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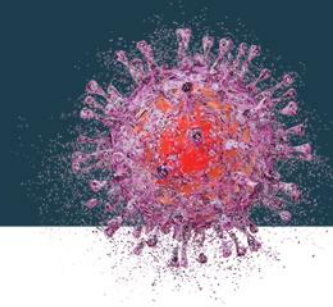
Letermovir for Use in Non-Kidney Organ Transplant Recipients



- Primarily single center studies

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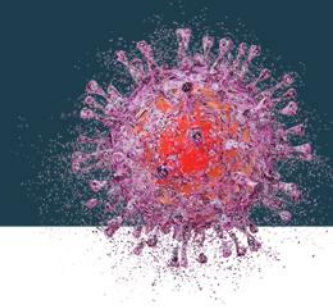

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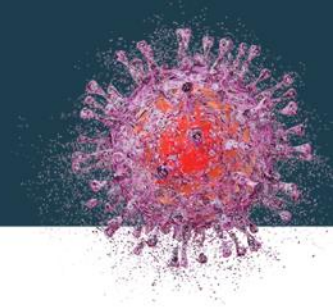

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- Prevents CMV but not other human herpes viruses; may wish to include an additional agent to prevent disseminated zoster (e.g., acyclovir, valacyclovir, famciclovir)

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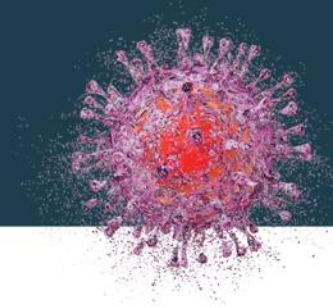

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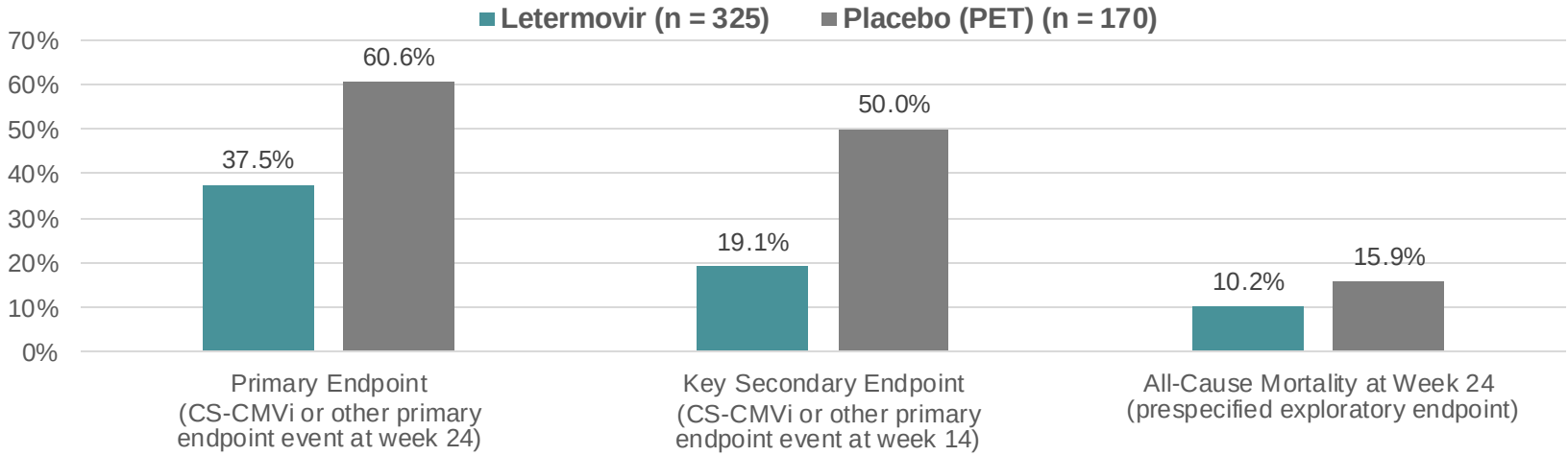
- Prevents CMV but not other human herpes viruses; may wish to include an additional agent to prevent disseminated zoster (e.g., acyclovir, valacyclovir, famciclovir)
- Given significant drug interaction with tacrolimus, reduce the dose by 40%-50% upon initiation of letermovir[1]

1. Winstead RJ, et al. *Transpl Infect Dis*. 2021;23:e13570.

Protocol 001: Phase III Study of LTV Prophylaxis for CMV in R+ HSCT

- Randomized, placebo controlled, double-blind, multi-center superiority study of adult CMV R+ HSCT
- 67 centers, 20 countries
- Randomized 2:1 to LTV or placebo, PO or IV, through week 14 (day 100) after transplantation



- **Primary endpoint:** proportion of patients with CS-CMV infection through week 24 after transplantation among patients without detectable CMV DNA at randomization (primary efficacy population); patients who discontinued the trial for any reason before week 24 (day 168) after transplantation or who had missing data at week 24 were imputed as having a primary endpoint event
- **Key secondary endpoint:** proportion of patients with CS-CMV infection through week 14 after transplantation
- **Prespecified exploratory endpoint:** all-cause mortality

CS-CMVi = clinically significant CMV infection (CS-CMVi = CMV disease or CMV viremia leading to preemptive treatment).

Marty FM, et al. *N Engl J Med*. 2017;377:2433-2444.

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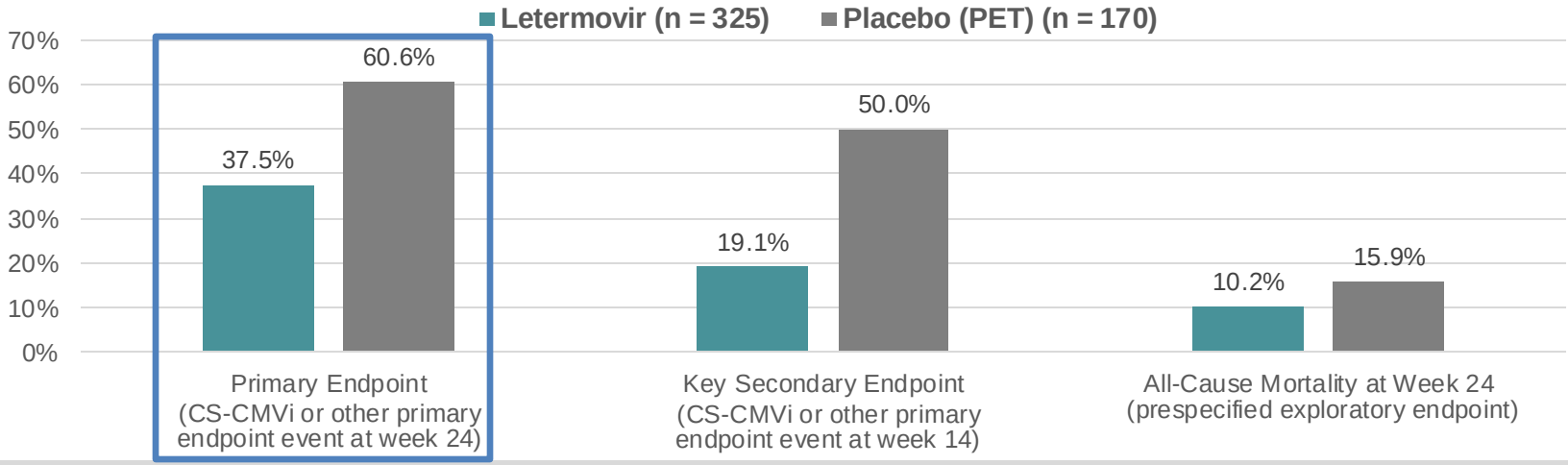

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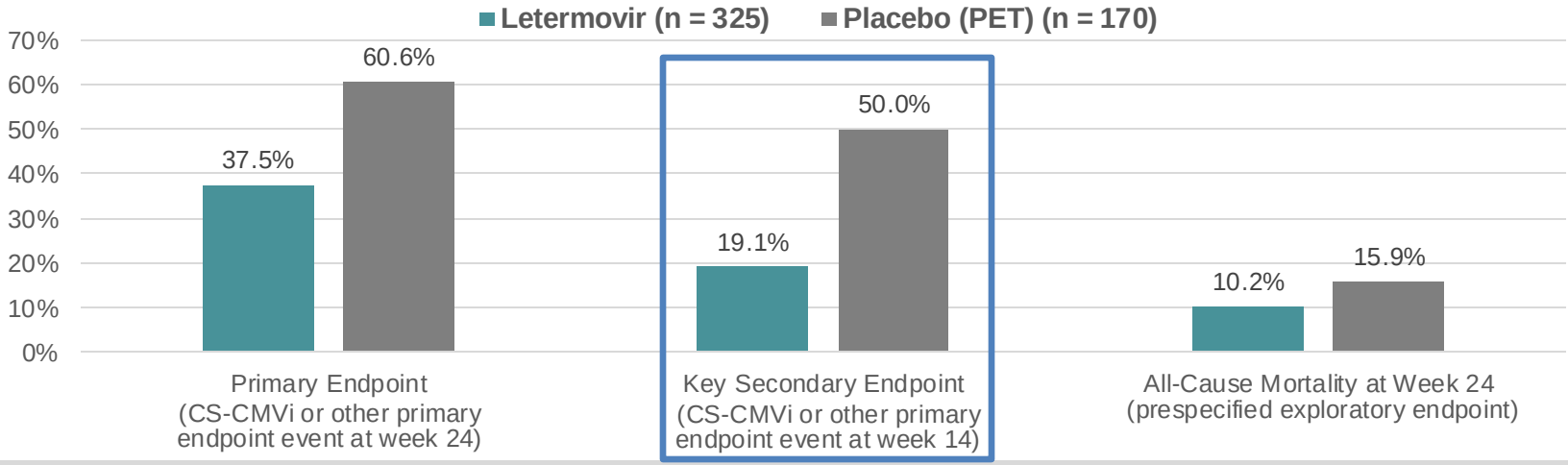

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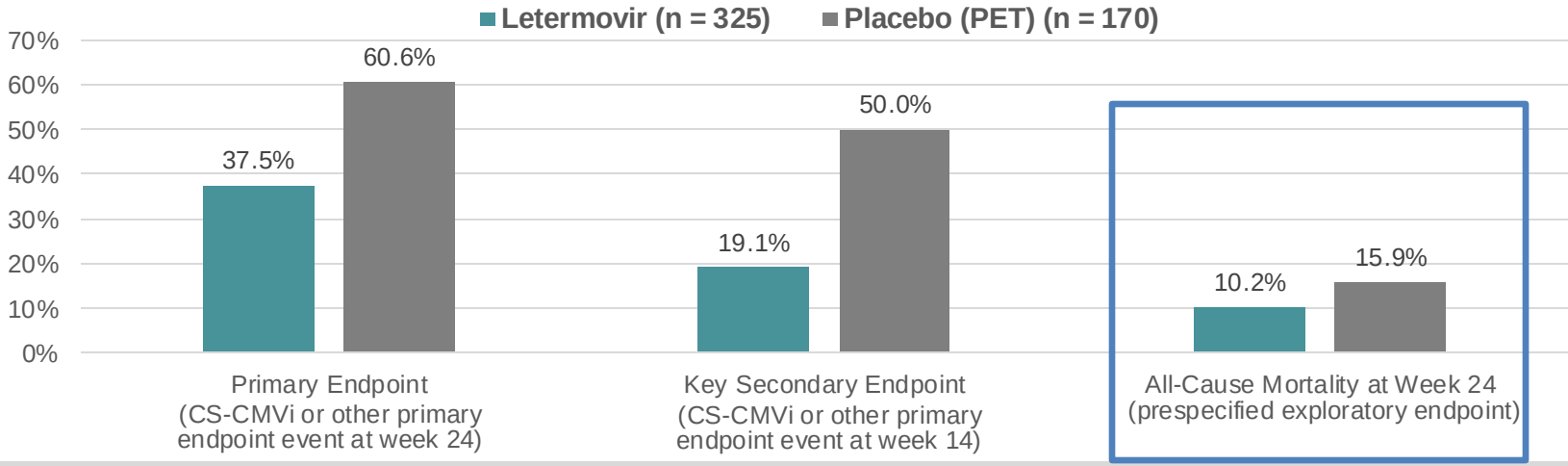

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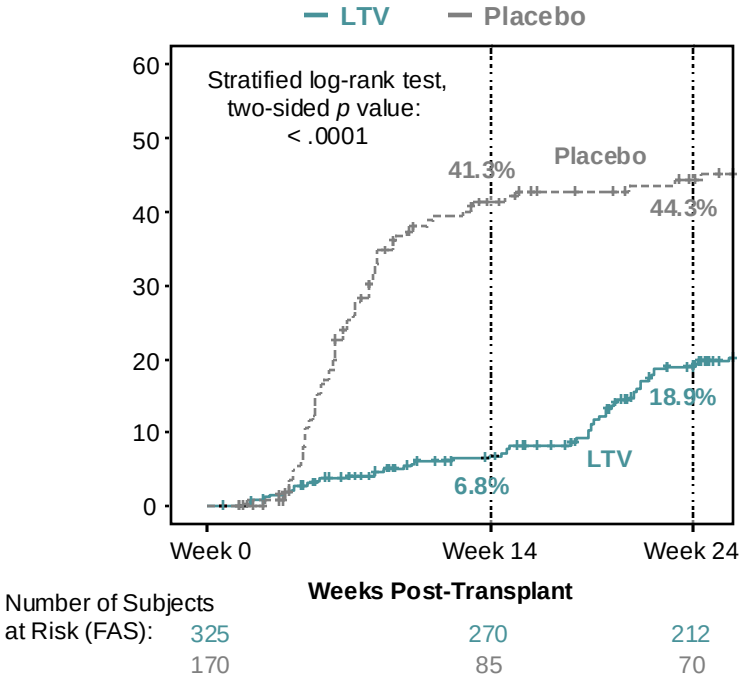
P001: Time to CS-CMVi Through Week 24 Post-transplant



Rationale for Protocol 40

- LTV was superior to placebo in preventing CS-CMV infection (CS-CMVi) through week 24 (~200 days) post-transplant when administered until week 14 (~100 days) post-transplant in Protocol 001
- There was an increased incidence of CS-CMVi after treatment ended between weeks 14 and 24 post-transplant

Russo D, et al. *Lancet Haematol*. 2024;11:e127-e135. Marty FM, et al. *N Engl J Med*. 2017;377:2433-2444.

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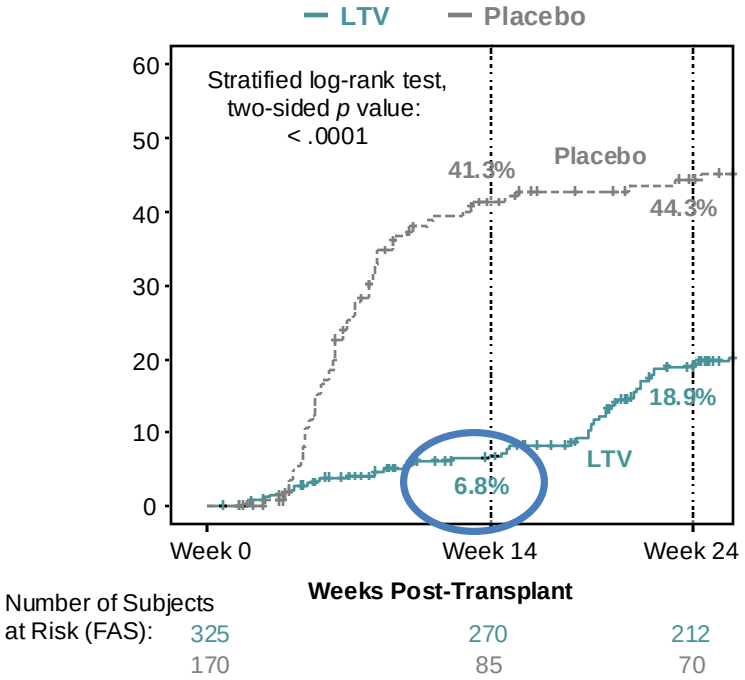

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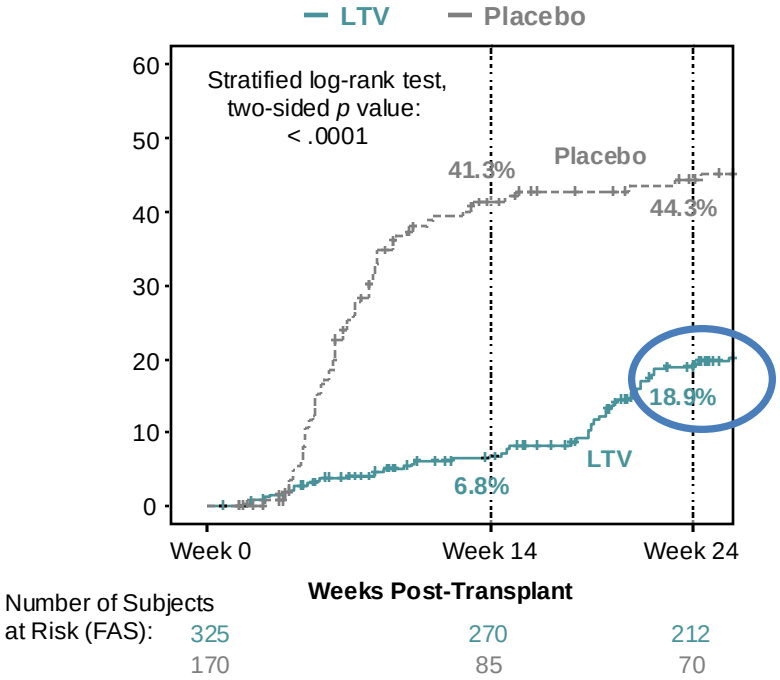

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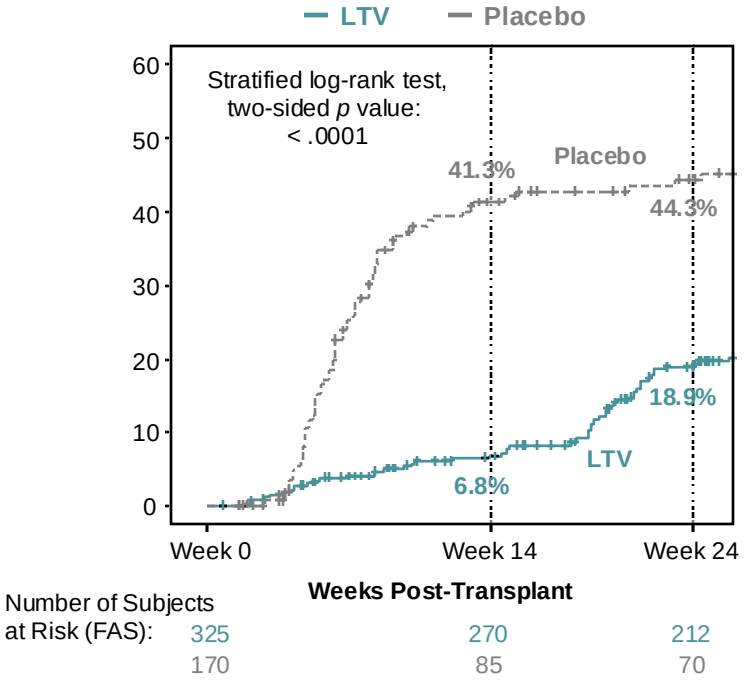

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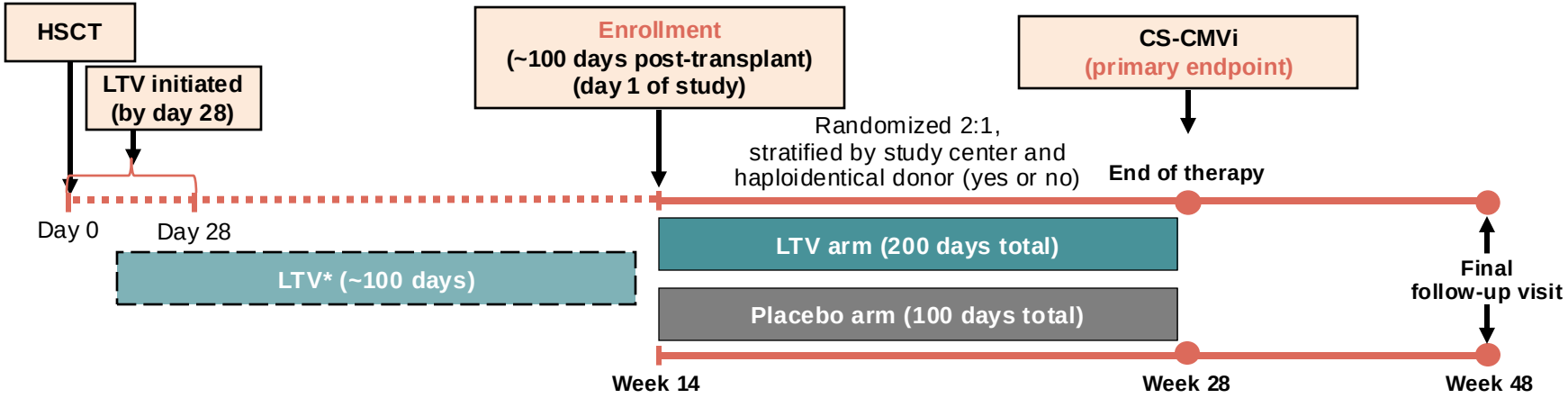
- There was an increased incidence of CS-CMVi after treatment ended between weeks 14 and 24 post-transplant
- Post-hoc analyses indicated that GVHD after randomization, concomitant steroid use, and baseline high-risk stratum (as defined in Protocol 001) were associated with developing CS-CMVi following completion of 100 days of LTV

Russo D, et al. *Lancet Haematol*. 2024;11:e127-e135. Marty FM, et al. *N Engl J Med*. 2017;377:2433-2444.

Phase III Study of Extended Duration LTV in High-Risk HSCT

R+ HSCT at Risk of CMVi and/or Disease Beyond Day 100

- Randomized, placebo-controlled, double-blinded, superiority trial of adult CMV R+ HSCT
- 32 participating sites, 6 countries (France, Germany, Italy, Japan, UK, USA); June 21, 2019, and March 16, 2022
- 220 R+ HSCT patients randomized; 181 completed treatment (efficacy population); 218 received ≥ 1 dose (safety population)



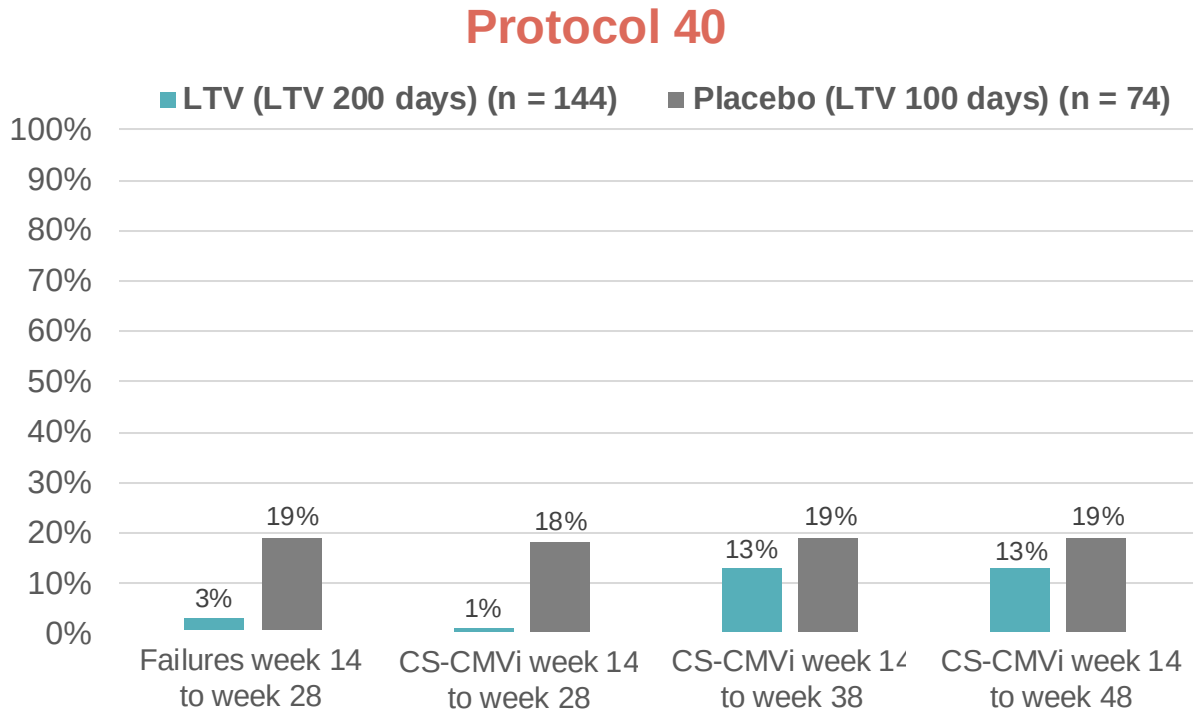
- **Primary endpoint:** proportion with CS-CMVi from randomization (week 14) to end of prophylaxis at week 28
- **Secondary endpoints included:** proportion with CS-CMVi from randomization to week 38 and to week 48; time to onset of CS-CMVi; proportion with PET; proportion with all-cause mortality
- **Safety and tolerability:** AEs and discontinuations due to AEs

PET = pre-emptive therapy.

Russo D, et al. *Lancet Haematol*. 2024;11:e127-e135.

Phase III Study of Extended Duration LTV in High-Risk HSCT

R+ HSCT at Risk of CMVi and/or Disease Beyond Day 100



For the primary endpoint, an observed failure approach was used to handle missing data values, in which failure was defined as all participants who developed CS-CMVi or discontinued prematurely from the study with CMV viremia; the categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed

Russo D, et al. *Lancet Haematol*. 2024;11:e127-e135.

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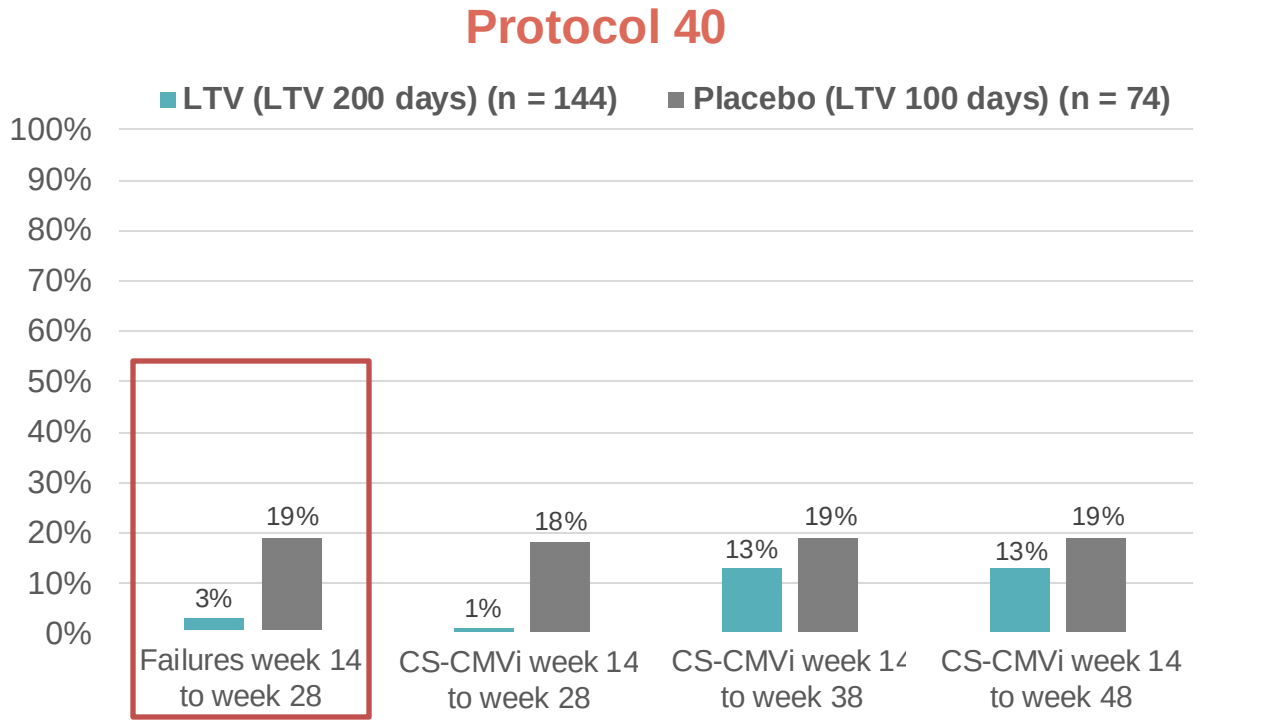

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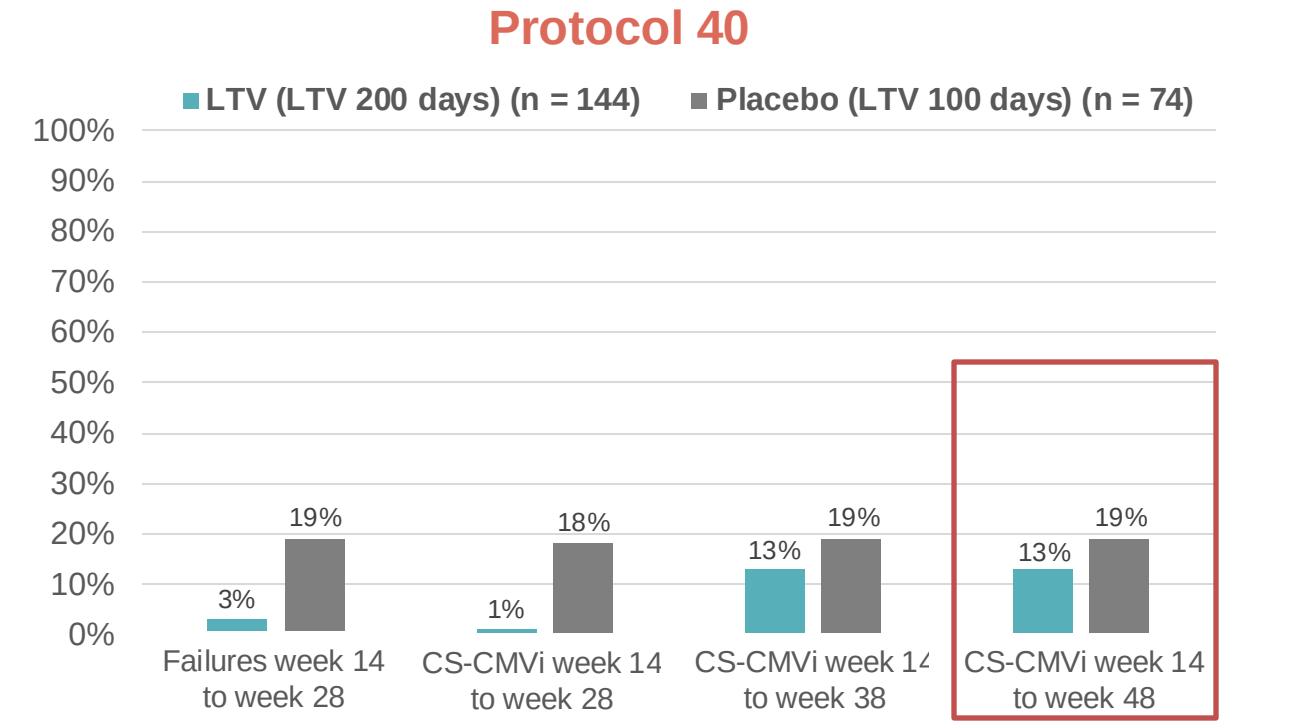

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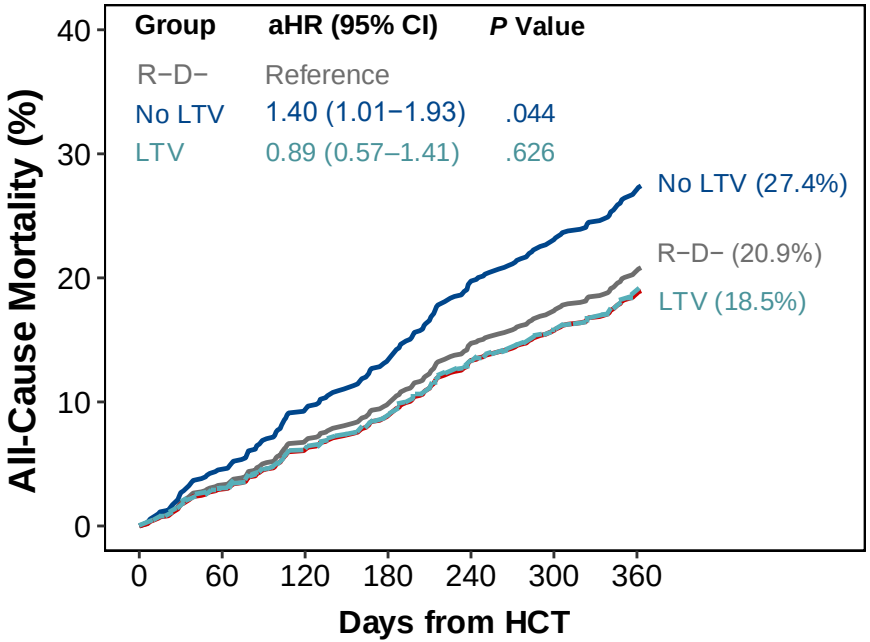
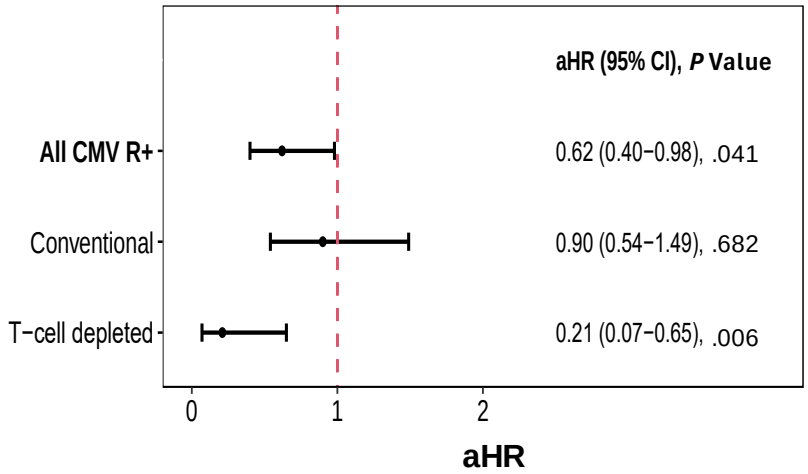
Extended Duration LTV in High-Risk Patients Was Associated with Less All-Cause Mortality at 1 Year

Adjusted Mortality Curves; Cox Models



All-Cause Mortality, Multivariate Model



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Su Y, et al. *Clin Infect Dis*. 2022;75:795-804.

CME OUTFITTERS

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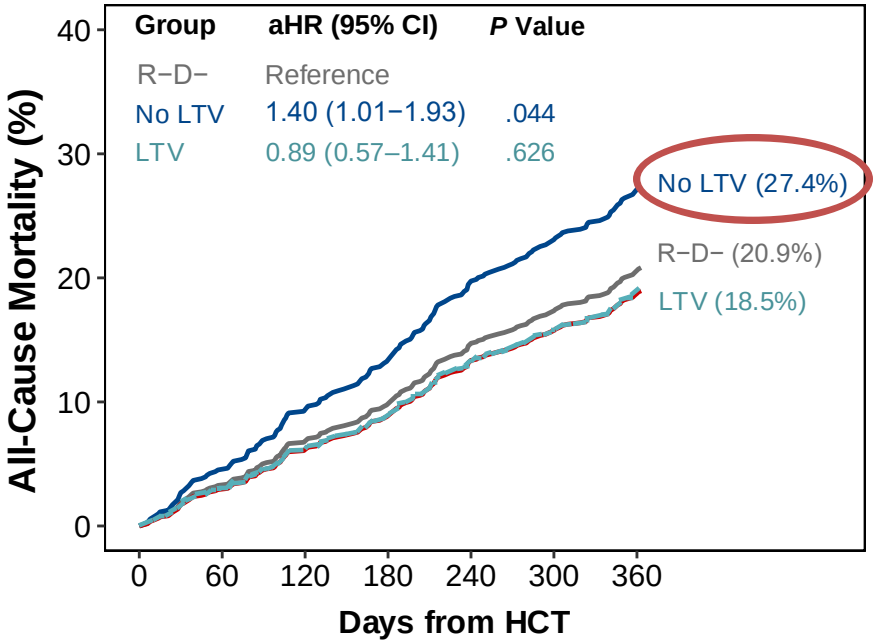

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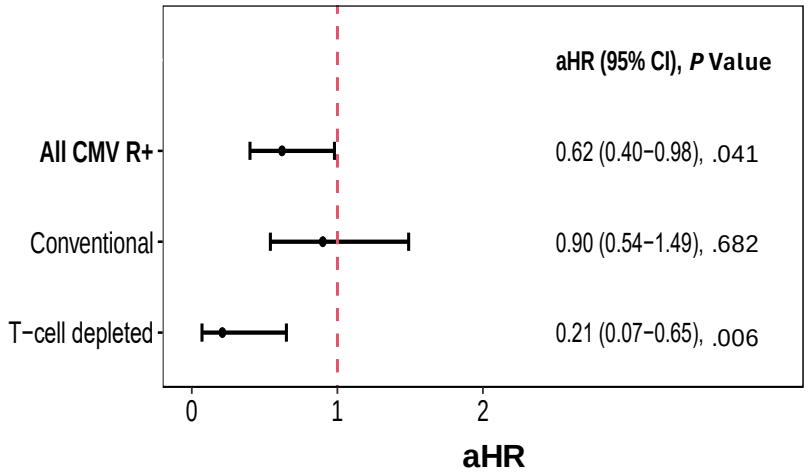

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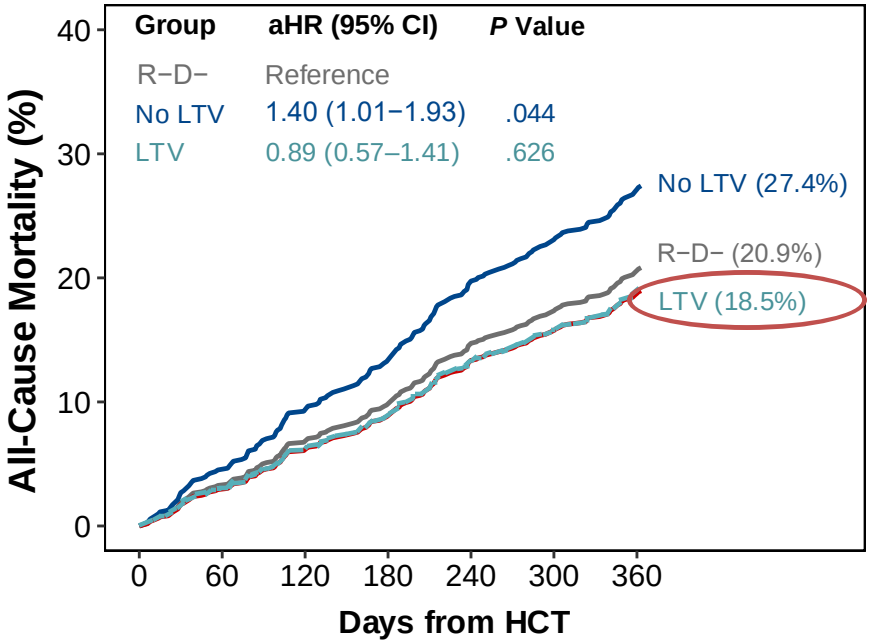

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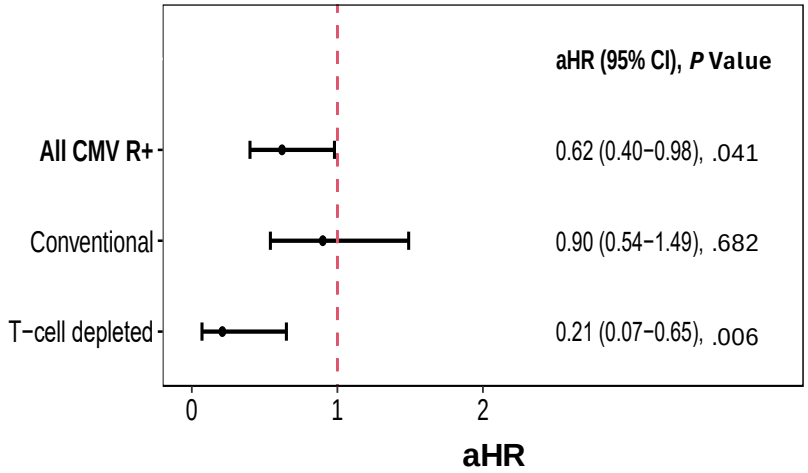

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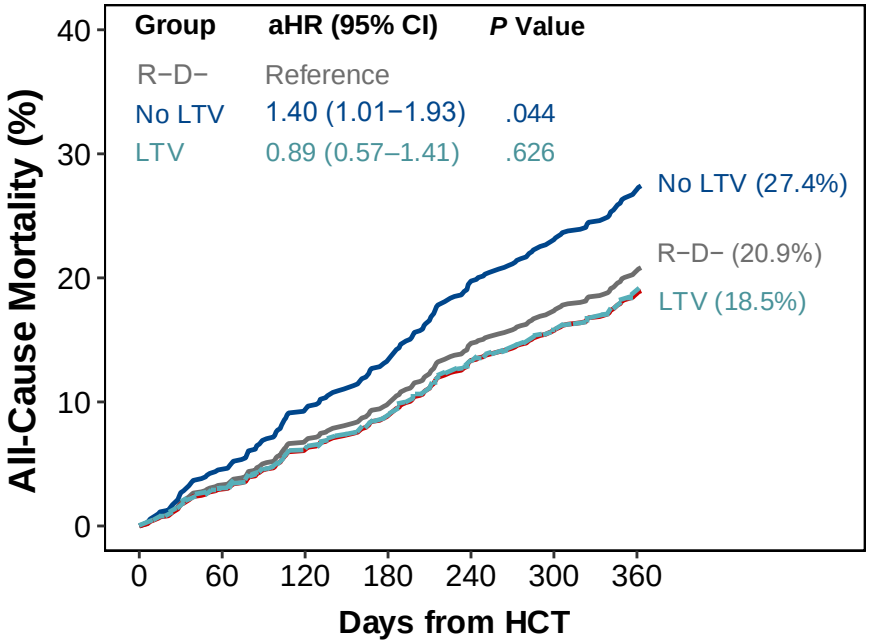

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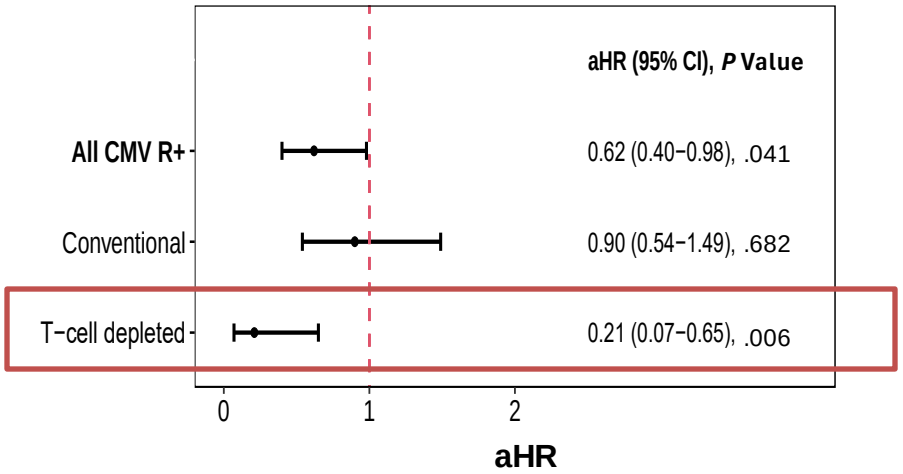


40% reduction in the entire cohort
80% reduction in T-cell–depleted HCT

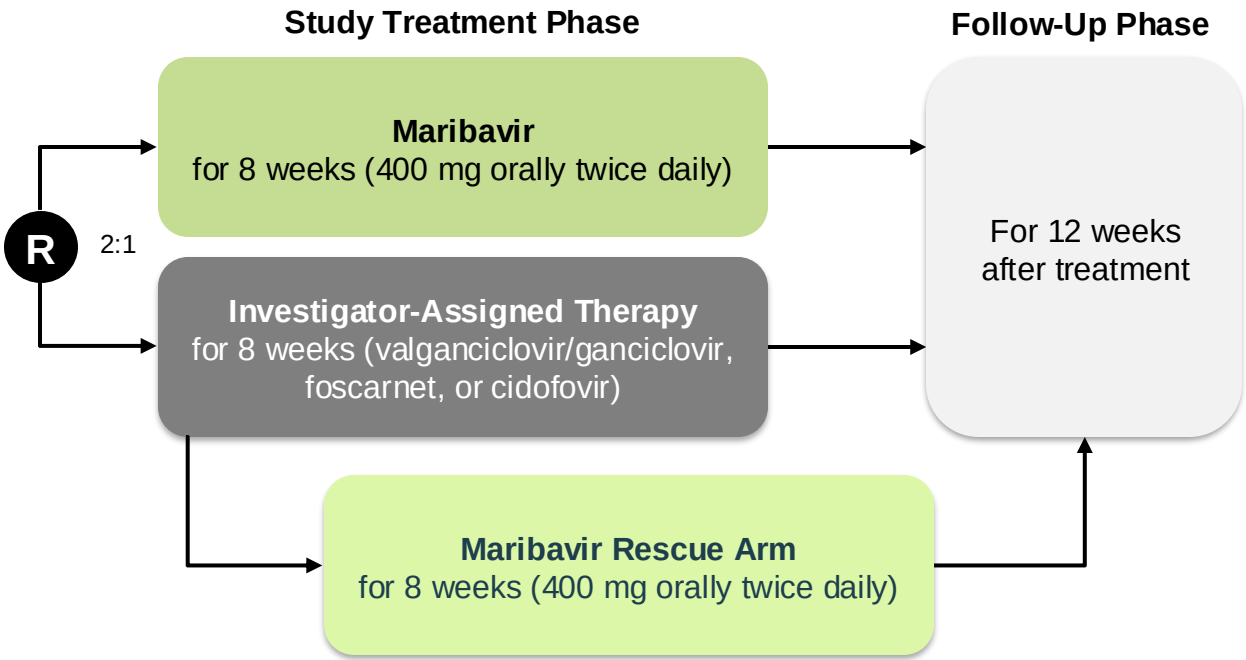
aHR = adjusted hazard ratio; CI = confidence interval.

Su Y, et al. *Clin Infect Dis*. 2022;75:795-804.

CME OUTFITTERS

Maribavir

Phase III SOLSTICE Trial (Patients with Treatment-Refractory CMV)



Stratified by **transplant type** (SOT or HCT) and **screening plasma CMV DNA level** (high: ≥91,000 IU/mL; intermediate: ≥9,100 and <91,000 IU/mL; low ≥910 and <9,100 IU/mL)

Avery RK, et al. *Clin Infect Dis.* 2022;75:690-701.

Maribavir

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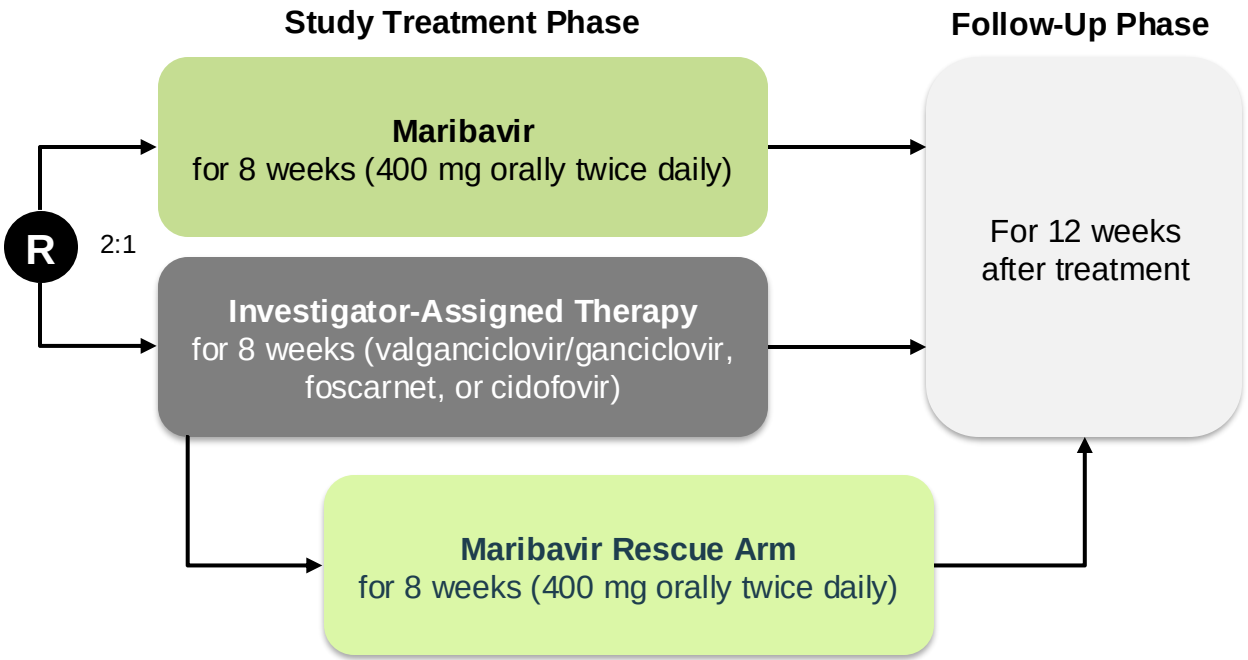

- **Primary endpoint:** confirmed CMV viremia clearance at the end of week 8 (regardless of premature treatment discontinuation)
- **Key secondary endpoint:** composite of confirmed CMV viremia clearance and symptom control at the end of study-assigned treatment

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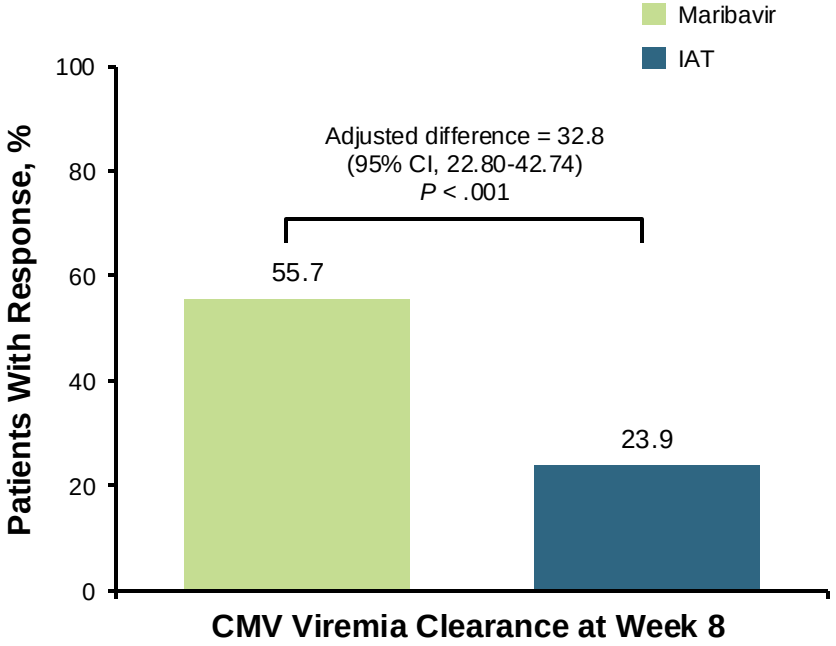
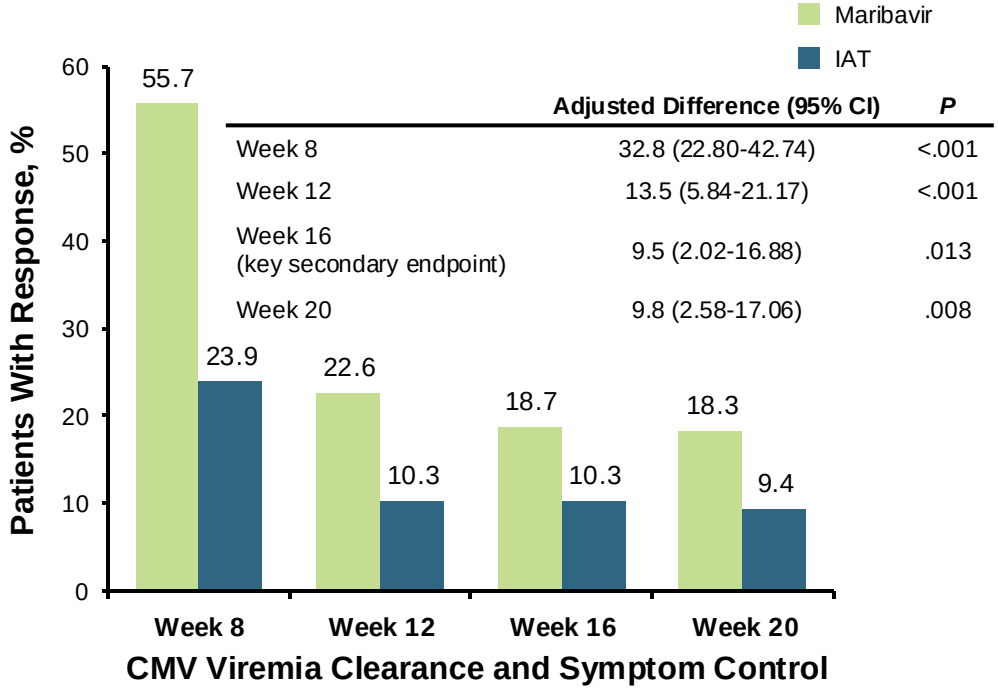
Maribavir

Superior to IAT for CMV Viremia Clearance Plus Symptom Control





	Adjusted Difference (95% CI)	*P*
Week 8	32.8 (22.80-42.74)	<.001
Week 12	13.5 (5.84-21.17)	<.001
Week 16 (key secondary endpoint)	9.5 (2.02-16.88)	.013
Week 20	9.8 (2.58-17.06)	.008

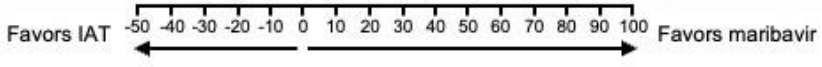
Led to FDA approval for treatment of adults and pediatric* patients with post-transplant CMVi/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet

IAT = autologous islet cell transplantation.
*Age ≥12 and weight ≥35 kg.
Avery RK, et al. *Clin Infect Dis.* 2022;75:690-701.

CME OUTFITTERS

Improved CMV Clearance with Maribavir Across Subgroups

Characteristic	Maribavir, n/N (%)	IAT, n/N (%)	Adjusted Difference in Proportion of Responders (95% CI)
Age group, y			
18-44	28/55 (50.9)	8/32 (25.0)	26.4 (6.06-46.74)
45-64	71/126 (56.3)	19/69 (27.5)	29.9 (16.18-43.64)
≥65	32/54 (59.3)	1/16 (6.3)	53.9 (36.81-71.08)
Sex			
Male	87/148 (58.8)	15/65 (23.1)	35.7 (22.76-48.58)
Female	44/87 (50.6)	13/52 (25.0)	27.4 (11.35-43.46)
Region			
North America	72/134 (53.7)	19/71 (26.8)	26.9 (13.75-40.11)
Europe	56/97 (57.7)	8/39 (20.5)	42.0 (26.90-57.05)
Asia	3/4 (75.0)	1/7 (14.3)	56.1 (-25.30 to 100.00)
Transplant type			
SOT	79/142 (55.6)	18/69 (26.1)	30.5 (17.31-43.61)
HCT	52/93 (55.9)	10/48 (20.8)	36.1 (20.92-51.37)
IAT			
Valganciclovir/ganciclovir	NA	15/56 (26.8)	31.7 (18.63-44.78)
Foscarnet	NA	9/47 (19.1)	36.4 (23.37-49.40)
>1 IAT	NA	4/7 (57.1)	-3.2 (-40.31 to 33.96)
Baseline CMV viral load			
Low	95/153 (62.1)	21/85 (24.7)	37.4 (25.41-49.37)
Intermediate/high	36/82 (43.9)	7/32 (21.9)	21.8 (3.93-39.67)
Presence of IAT resistance mutation			
Yes	76/121 (62.8)	14/69 (20.3)	44.1 (31.33-56.94)
No	42/96 (43.8)	11/34 (32.4)	12.6 (-6.24 to 31.43)
Antilymphocyte globulin use			
Yes	53/100 (53.0)	12/49 (24.5)	29.9 (14.30-45.46)
No	78/135 (57.8)	16/68 (23.5)	35.0 (21.94-48.01)
Symptomatic CMV Infection by EAC			
Yes	10/21 (47.6)	1/8 (12.5)	30.6 (-7.46 to 68.57)
No	121/214 (56.5)	27/109 (24.8)	32.5 (22.05-43.01)



Avery RK, et al. *Clin Infect Dis*. 2022;75:690-701.

Maribavir Safety Summary: What Are the Events of Interest?

TEAEs Occurring in ≥10% of Patients in Either Treatment Group or for Individual Investigator-Assigned Therapy (Safety Population)

System Organ Class Preferred Term	Maribavir (n = 234)	IAT (n = 116)	IAT Type		
			Ganciclovir/ Valganciclovir (n = 56)	Foscarnet (n = 47)	Cidofovir (n = 6)
Any TEAE	**228 (97.4)**	**106 (91.4)**	**51 (91.1)**	**43 (91.5)**	**5 (83.3)**
Dysgeusia	87 (37.2)	4 (3.4)	2 (3.6)	0	1 (16.7)
Nausea	50 (21.4)	25 (21.6)	8 (14.3)	14 (29.8)	1 (16.7)
Diarrhea	44 (18.8)	24 (20.7)	13 (23.2)	9 (19.1)	1 (16.7)
Vomiting	33 (14.1)	19 (16.4)	7 (12.5)	8 (17.0)	2 (33.3)
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Pyrexia	24 (10.3)	17 (14.7)	6 (10.7)	9 (19.1)	2 (33.3)
Neutropenia	22 (9.4)	26 (22.4)	19 (33.9)	7 (14.9)	0
Acute kidney injury	20 (8.5)	11 (9.5)	1 (1.8)	10 (21.3)	0

TEAE = treatment-emergent AE.

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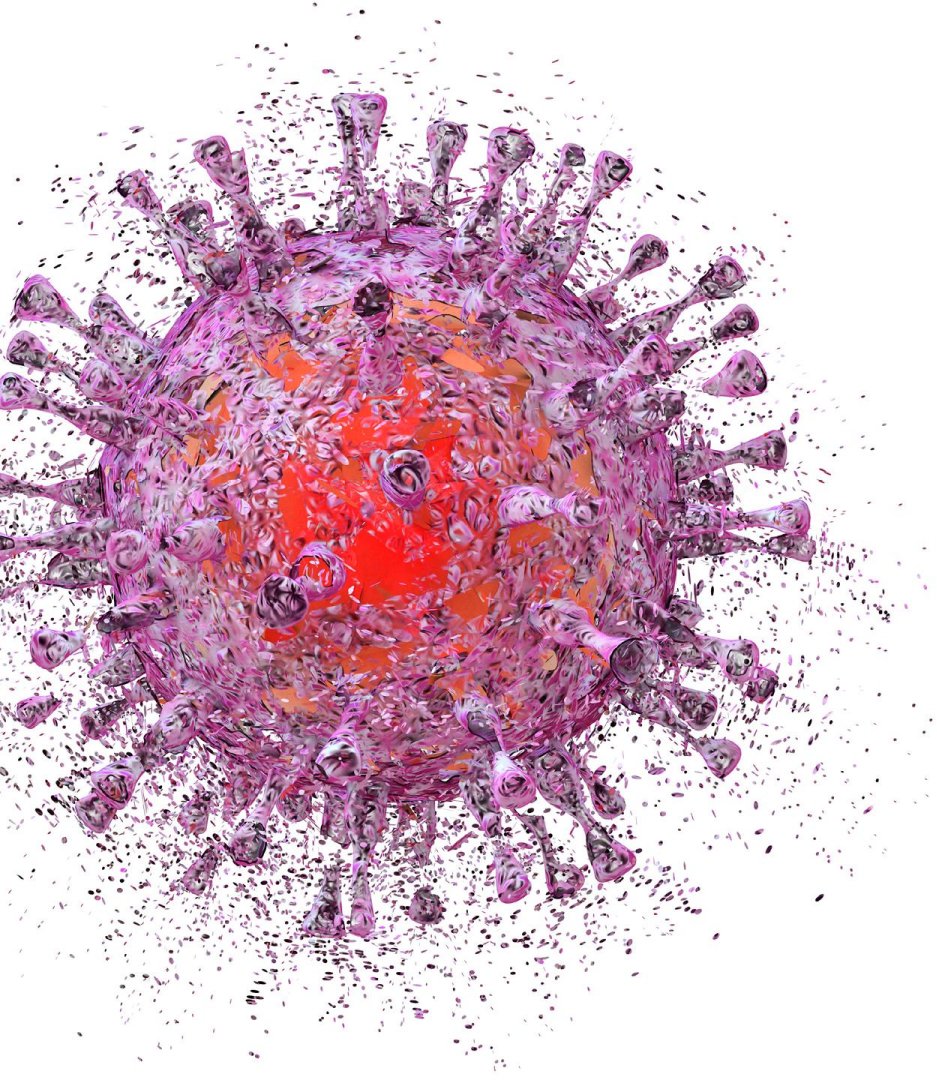
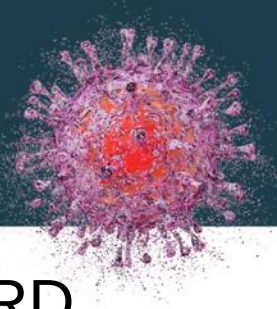


CMV Case Studies

- **SOT**
- HSCT

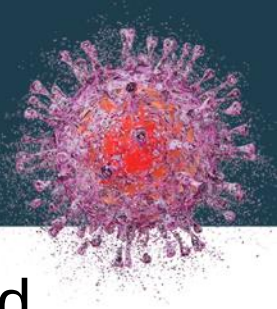
CMV Case Study in Solid Organ Transplant



- 72-year-old man with history of T2D, HTN, gout, ESRD
- Underwent deceased donor kidney transplant
  - CMV D+/R-
  - Induction immunosuppression: anti-thymocyte globulin
  - Maintenance immunosuppression: tacrolimus and mycophenolate
- Prophylaxis
  - Valganciclovir x 6 months
  - Trimethoprim/sulfamethoxazole x 12 months

ESRD = end-stage renal disease; HTN = hypertension; T2D = type 2 diabetes.

CMV Case Study in Solid Organ Transplant *(continued)*



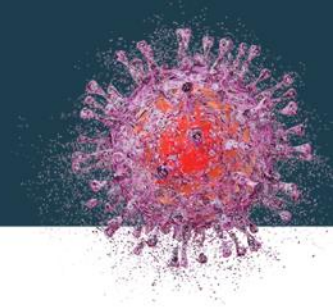
- 16 months after transplant presented with fatigue and chills
  - Afebrile
  - Exam unremarkable
  - WBC 1.6 cells/µL (16% atypical lymphocytes), previously 3.7 cells/µL
  - Platelets 90,000 cells/µL, previously 350,000 cells/µL
- CMV plasma PCR 25,340 IU/mL

ESRD = end-stage renal disease; HTN = hypertension; T2D = type 2 diabetes; WBC = white blood cell.

CMV Case Study in Solid Organ Transplant *(continued)*

- Initiated valganciclovir treatment dose 900 mg PO b.i.d.
- Week 2
  - Symptoms improved
  - CMV PCR 7,000 IU/mL
- Week 4
  - CMV PCR 5,000 IU/ml
- Week 6
  - CMV PCR 18,000 IU/mL

Definitions



- Treatment-refractory CMV
  - Plasma viral load not decreasing by at least 1 $\log_{10}$ after ≥2 weeks of appropriately dosed antiviral therapy
  - Worsening signs and symptoms or progression into end-organ disease after at least 2 weeks of appropriately dosed antiviral therapy

Chemaly RF, et al. *Clin Infect Dis*. 2019;68:1420-1426.

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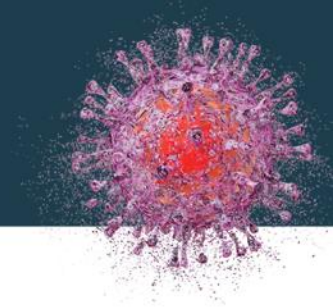

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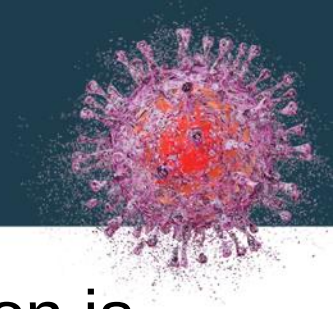
  - Worsening signs and symptoms or progression into end-organ disease after at least 2 weeks of appropriately dosed antiviral therapy
- Drug-resistant CMV
  - A viral genetic alteration that decreases susceptibility to one or more antiviral drugs

Chemaly RF, et al. *Clin Infect Dis*. 2019;68:1420-1426.

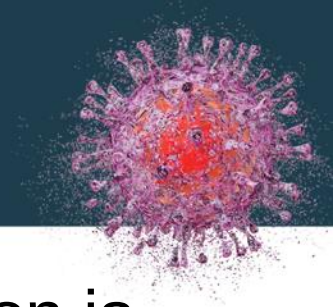
Impact of Drug-Resistant CMV



- Frequency of CMV resistance in SOT population is variable
  - 0%-3% after 100-200 days of GCV or VGCV prophylaxis in D+/R− kidney recipients

Boivin G, et al. *J Clin Virol*. 2012;53:208-213. Kotton CN, et al. *Transplantation*. 2018;102:900-931. Chemaly RF, et al. *Clin Infect Dis.* 2019;68:1420-1426.

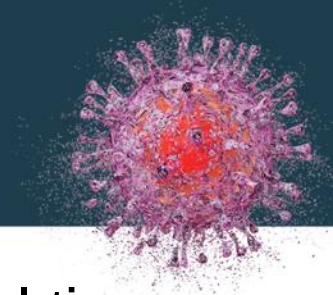
Impact of Drug-Resistant CMV



- Frequency of CMV resistance in SOT population is variable
  - 0%-3% after 100-200 days of GCV or VGCV prophylaxis in D+/R− kidney recipients
  - Incidence higher after GCV therapy
    - 5%-12% among all SOT recipients
    - Up to 18% among lung recipients
    - Up to 31% among intestinal/multivisceral recipients

Boivin G, et al. *J Clin Virol*. 2012;53:208-213. Kotton CN, et al. *Transplantation*. 2018;102:900-931. Chemaly RF, et al. *Clin Infect Dis*. 2019;68:1420-1426.

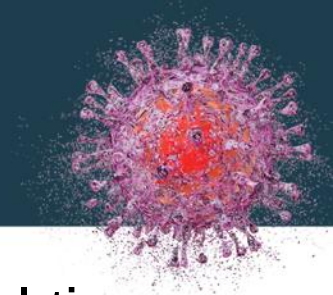
Impact of Drug-Resistant CMV *(continued)*



- Ranges from asymptomatic infection to severe/fatal tissue invasive disease

Boivin G, et al. *J Clin Virol*. 2012;53:208-213. Kotton CN, et al. *Transplantation*. 2018;102:900-931. Chemaly RF, et al. *Clin Infect Dis.* 2019;68:1420-1426.

Impact of Drug-Resistant CMV *(continued)*



- Ranges from asymptomatic infection to severe/fatal tissue invasive disease
- Associated with poor outcomes
  - Increased AEs from alternative therapies
  - Increased rejection and allograft loss
  - Increased mortality

Boivin G, et al. *J Clin Virol*. 2012;53:208-213. Kotton CN, et al. *Transplantation*. 2018;102:900-931. Chemaly RF, et al. *Clin Infect Dis.* 2019;68:1420-1426.

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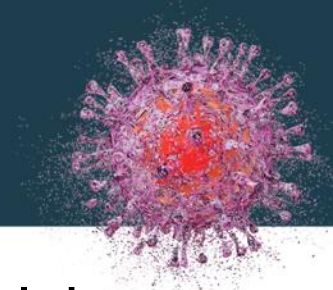
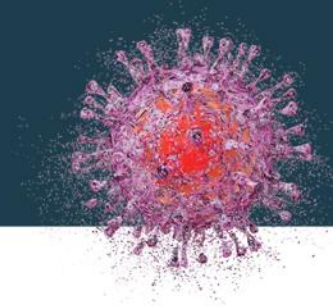


- Ranges from asymptomatic infection to severe/fatal tissue invasive disease
- Associated with poor outcomes
  - Increased AEs from alternative therapies
  - Increased rejection and allograft loss
  - Increased mortality
- Higher rates of hospitalization, increased length of stay, higher costs

Boivin G, et al. *J Clin Virol*. 2012;53:208-213. Kotton CN, et al. *Transplantation*. 2018;102:900-931. Chemaly RF, et al. *Clin Infect Dis.* 2019;68:1420-1426.

Risk Factors for CMV Resistance



- Reduced CMV-specific host immunity
  - CMV D+/R-
  - Potent immunosuppressive therapy
  - Lung transplant recipients

Kotton CN, et al. *Transplantation*. 2018;102:900-931. Razonable RR and Humar A. *Clin Transplant*. 2019;33:e13512. Chemaly RF, et al. *Clin Infect Dis.* 2019;68:1420-1426.

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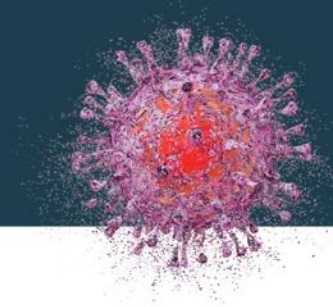
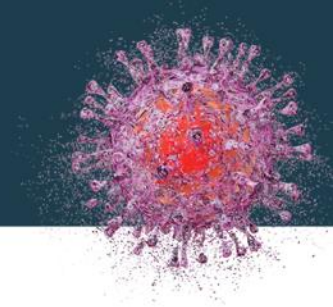


- Reduced CMV-specific host immunity
  - CMV D+/R-
  - Potent immunosuppressive therapy
  - Lung transplant recipients
- Prolonged exposure to antiviral therapy
  - At least 6 weeks for ganciclovir

Kotton CN, et al. *Transplantation*. 2018;102:900-931. Razonable RR and Humar A. *Clin Transplant*. 2019;33:e13512. Chemaly RF, et al. *Clin Infect Dis.* 2019;68:1420-1426.

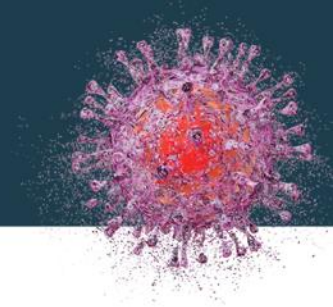
Risk Factors for CMV Resistance *(continued)*



- Prolonged DNAemia (>21 days) while on antiviral therapy

Kotton CN, et al. *Transplantation*. 2018;102:900-931. Razonable RR and Humar A. *Clin Transplant*. 2019;33:e13512. Chemaly RF, et al. *Clin Infect Dis.* 2019;68:1420-1426.

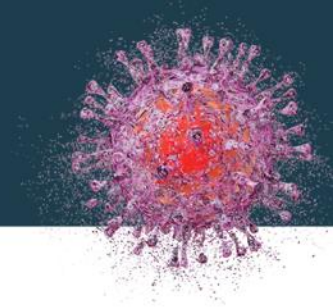
Risk Factors for CMV Resistance *(continued)*



- Prolonged DNAemia (>21 days) while on antiviral therapy
- Subtherapeutic drug concentrations
  - Decreased oral absorption
  - Inappropriately reduced dose (to avoid bone marrow suppression)

Kotton CN, et al. *Transplantation*. 2018;102:900-931. Razonable RR and Humar A. *Clin Transplant*. 2019;33:e13512. Chemaly RF, et al. *Clin Infect Dis.* 2019;68:1420-1426.

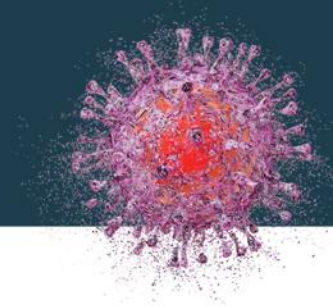
Drug-Resistant CMV



- When to test
  - Antiviral drug resistance should be suspected and tested for when there is refractory CMVi despite at least 2 continuous weeks of appropriately dosed antiviral therapy

Kotton CN, et al. *Transplantation*. 2018;102:900-931.

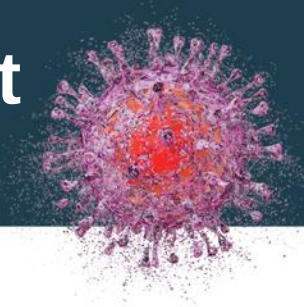
Drug-Resistant CMV



- When to test
  - Antiviral drug resistance should be suspected and tested for when there is refractory CMVi despite at least 2 continuous weeks of appropriately dosed antiviral therapy
- How to test
  - Genotypic assays for viral drug resistance mutations in *UL97*, *UL54*, and *UL56* genes

Kotton CN, et al. *Transplantation*. 2018;102:900-931.

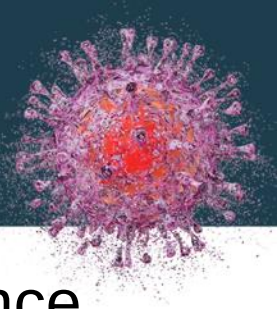
CMV Case Study in Solid Organ Transplant *(continued)*



- Resistance testing

Ganciclovir UL54 Gene Target	None Detected	[None Detected]	Final
Ganciclovir UL97 Gene Target	Resistant at Site H520Q	[None Detected]	Final
Foscarnet UL54 Gene Target	None Detected	[None Detected]	Final
Cidofovir UL54 Gene Target	None Detected	[None Detected]	Final
Letermovir UL56	None Detected	[None Detected]	Final

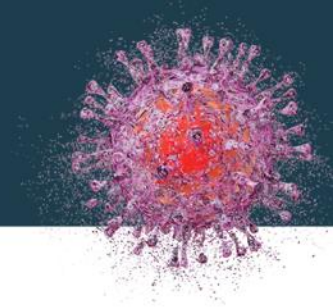
CMV Case Study in Solid Organ Transplant *(continued)*



- Kidney transplant team asking for therapeutic guidance
- eGFR 38 mL/min/1.73m
- WBC 1,700 cells/µL
- Patient expressing priority in preserving renal allograft

eGFR = estimated glomerular filtration rate.

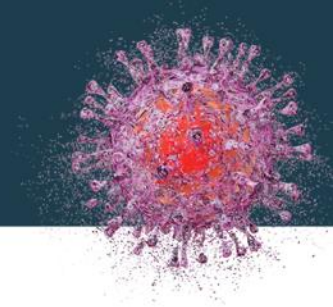
Treatment of Drug-Resistant or Refractory CMV



- No controlled trial data define a best practice
  - Algorithms are based on expert opinion

Kotton CN, et al. *Transplantation*. 2018;102:900-931. Razonable RR and Humar A. *Clin Transplant*. 2019;33:e13512.

Treatment of Drug-Resistant or Refractory CMV



- No controlled trial data define a best practice
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- First step: reduce immunosuppressive therapy to lowest feasible amount

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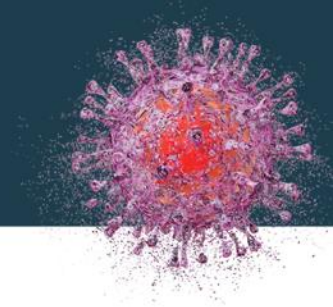
Treatment of Drug-Resistant or Refractory CMV

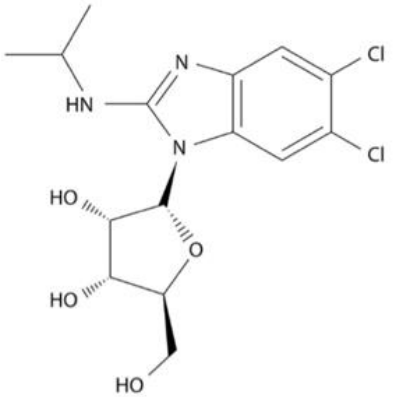


- No controlled trial data define a best practice
  - Algorithms are based on expert opinion
- First step: reduce immunosuppressive therapy to lowest feasible amount
- Available therapies
  - High-dose ganciclovir
  - Maribavir
  - Foscarnet
  - Cidofovir

Kotton CN, et al. *Transplantation*. 2018;102:900-931. Razonable RR and Humar A. *Clin Transplant*. 2019;33:e13512.

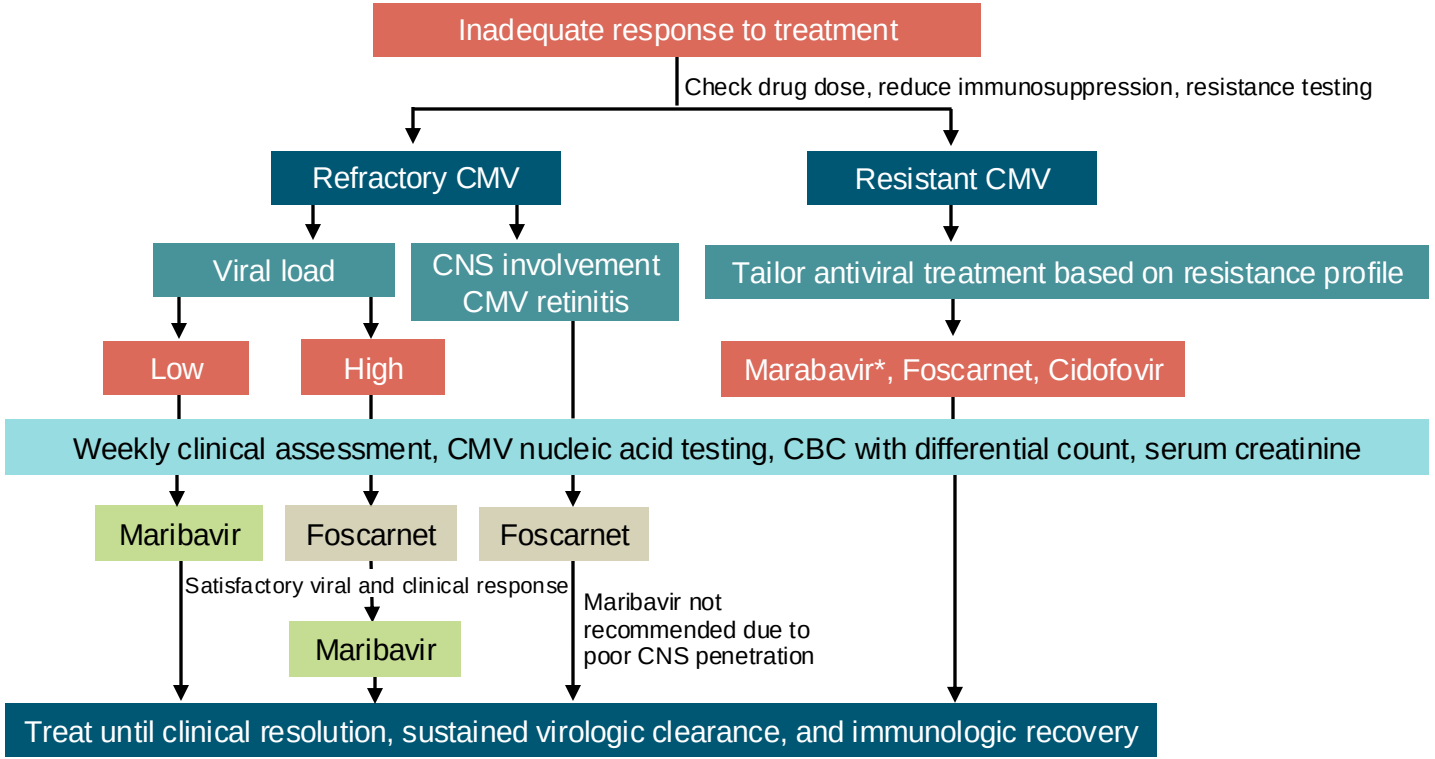
Maribavir

- Competitively inhibits protein kinase activity of UL97, resulting in inhibition of the phosphorylation of proteins
- Nontoxic
  - No renal or bone marrow toxicity
  - Taste disturbance



Halpern-Cohen V, Blumberg EA. *Antimicrob Agents Chemother*. 2022;66(9):e02405-02421.

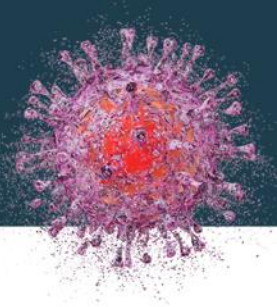
Suggested Algorithm for the Treatment of Refractory and Resistant CMV Disease



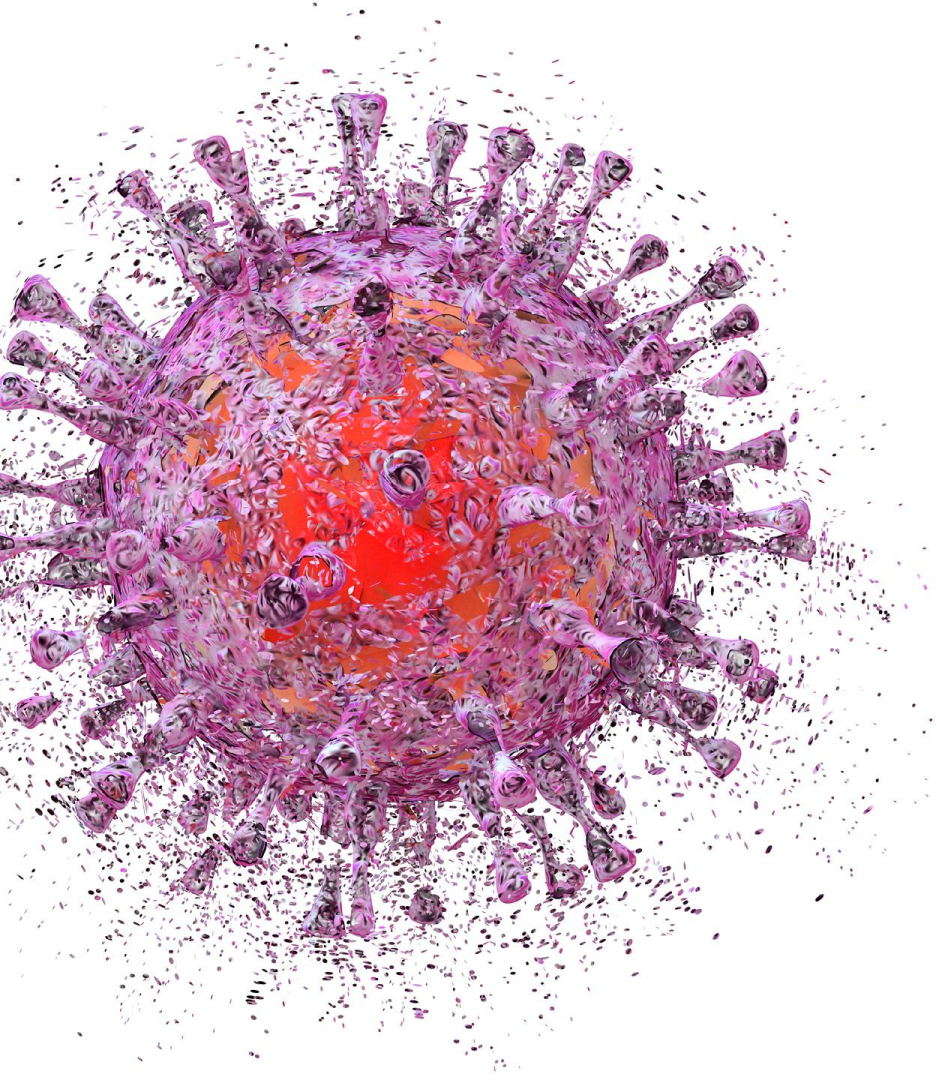
*Maribavir has poor central nervous system penetration.
CBC = complete blood count.
Razonable RR. *Clin Microbiol Infect.* 2023;29:1144-1149.

CME OUTFITTERS

CMV Case Study in Solid Organ Transplant *(Conclusion)*



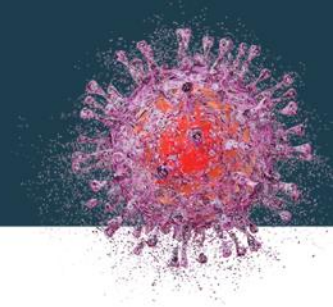
- Initiated on maribavir 400 mg PO twice daily
- CMV PCR steadily declined
- WBC and eGFR remained unchanged
- PCR <35 IU/mL by week 7 of maribavir treatment
- Switched to letermovir prophylaxis
  - Stopped after 3 months without further CMV infection



CMV Case Studies

- SOT
- **HSCT**

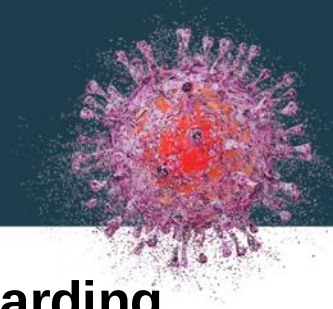
CMV Case Study in HSCT



Clinical Scenario

- 62-year-old male with AML in CR1 received an unrelated donor 7/8 HLA-mismatched graft after reduced intensity conditioning
- Patient was CMV seropositive, donor was CMV seronegative
- Post-transplant cyclophosphamide given for GVHD prophylaxis

CMV Case Study in HSCT



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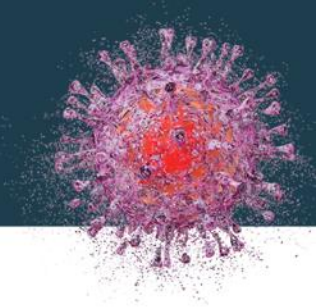
- Post-transplant cyclophosphamide given for GVHD prophylaxis

Points to Consider Regarding CMV Management

- Patient has multiple high-risk features
- Recipient CMV seropositive
- Donor CMV seronegative
- Mismatched donor
- Post-transplant cyclophosphamide

CMV Case Study in HSCT *(continued)*



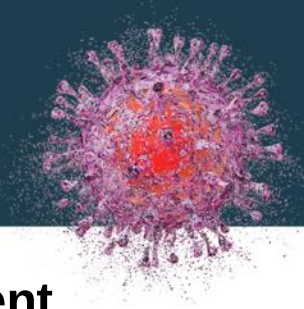
CMV Management Options

- Letermovir prophylaxis or PCR-guided preemptive use of ganciclovir or valganciclovir

*Nonsignificant lower mortality noted in patients on letermovir, more pronounced in high-risk versus low-risk patients. ASTCT = American Society for Transplantation and Cellular Therapy. Marty FM, et al. *N Eng J Med*. 2017;377:2433-2444. Hakki M, et al. *Transplant Cell Ther*. 2021;27:707-719. Sourisseau M, et al. *Blood Adv*. 2023;7:856-865.

CME OUTFITTERS

CMV Case Study in HSCT *(continued)*



CMV Management Options

- Letermovir prophylaxis or PCR-guided preemptive use of ganciclovir or valganciclovir

Points to Consider on Management

- Both strategies have been shown to be effective in reducing CMV serious disease
- Letermovir prophylaxis reduces clinically significant CMVi in both high- and low-risk patients at risk 24, but no survival advantage at week 48*
- ASTCT guidelines endorse letermovir prophylaxis in high-risk patients, with acknowledgement of either strategy in low-risk patients

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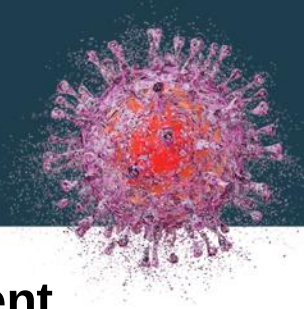
CME OUTFITTERS

CMV Case Study in HSCT *(continued)*



CMV Management Options

- Letermovir prophylaxis or PCR-guided preemptive use of ganciclovir or valganciclovir

Strategy Chosen

- Letermovir prophylaxis

Points to Consider on Management

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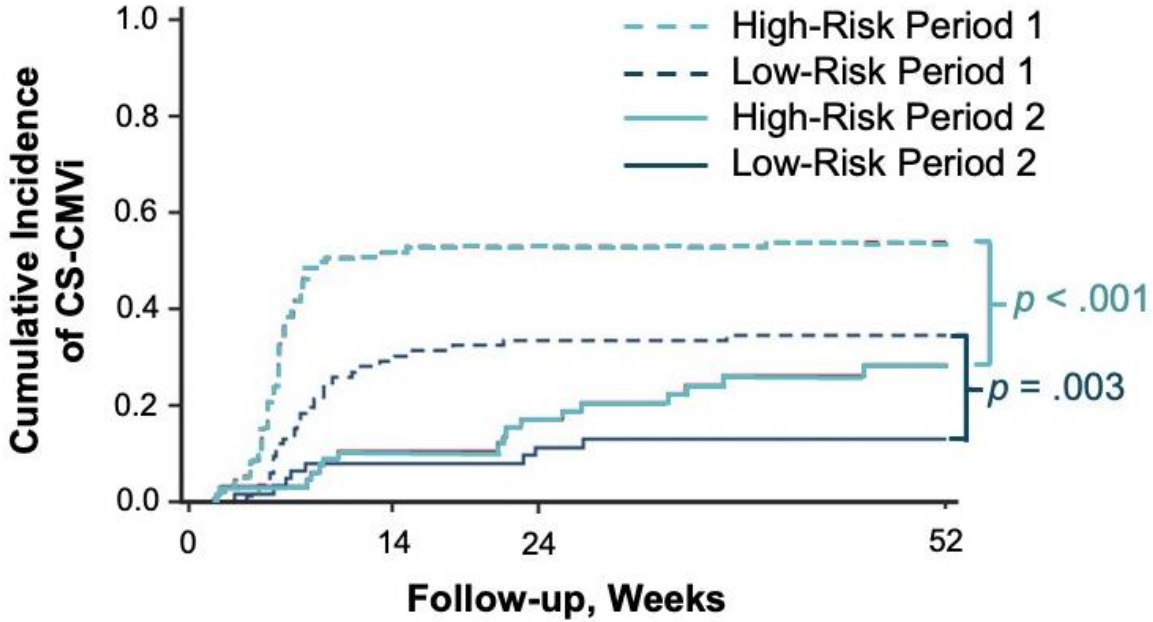
CME OUTFITTERS

Risk-Based Letermovir Prophylaxis Strategy in CMV-Positive Allogeneic HCT Recipients

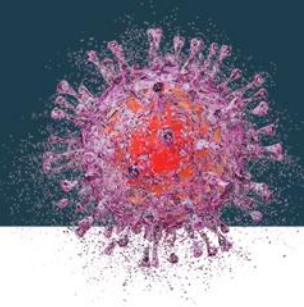


Note: Letermovir prophylaxis was used in all high-risk patients in period 2 but only in patients administered high-dose prednisone in low-risk patients.

Sourisseau M, et al. *Blood Adv*. 2023;7:856-865.

CME OUTFITTERS

CMV Case Study in HSCT *(continued)*



Clinical Course Continued:

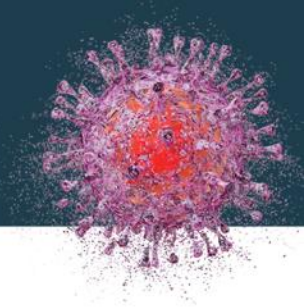
- Engraftment occurred on day 18
- Letermovir begun on day 21
- Weekly CMV PCR testing begun on day 18
- On day 44, PCR was positive (630 copies/mL)

What was Done

- Letermovir was continued
- Repeat PCR was negative

Cassaniti I, et al. *Am J Transplant*. 2021;21:1622-1628. Robin C, et al. *Biol Blood Marrow Transplant*. 2020;26:978. Girmenia C, et al. *Clin Transplant*. 2019;33:e13666. Hakki M, et al. *Transplant Cell Ther*. 2021;27:707-719.

CMV Case Study in HSCT *(continued)*



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What was Done

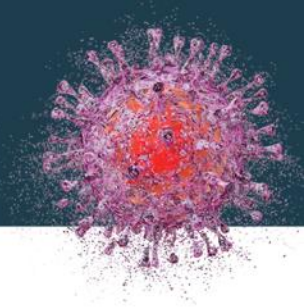
- Letermovir was continued
- Repeat PCR was negative

Points to Consider

- DNA positivity can be seen in some patients on letermovir prophylaxis
  - Typically, low level (<10,000 copies/mL)
  - Often transient
  - May reflect abortive infection
  - May not require change in course unless high level, repeatedly positive and rising
- ASTCT guidelines recommend PCR monitoring during letermovir prophylaxis

Cassaniti I, et al. *Am J Transplant*. 2021;21:1622-1628. Robin C, et al. *Biol Blood Marrow Transplant*. 2020;26:978. Girmenia C, et al. *Clin Transplant*. 2019;33:e13666. Hakki M, et al. *Transplant Cell Ther*. 2021;27:707-719.

CMV Case Study in HSCT *(continued)*



Clinical Course Continued:

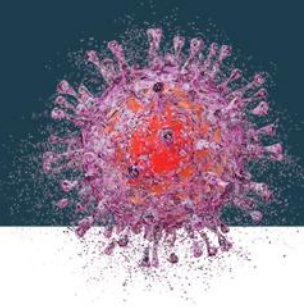
- Acute GVHD, grade 2, developed on day 66
- Prednisone was given 2 mg/kg/d and tapered after 1 week
- Letermovir prophylaxis was stopped on day 100 after HCT
- PCR was positive 6,000 copies/mL on day 140

What was Done

- Valganciclovir was initiated and once viremia resolved stopped with resumption of PCR monitoring

Marty FM, et al. *N Eng J Med*. 2017;377:2433-2444. Liu LW, et al. *Transplant Cell Ther*. 2022;28:510.e1-510.e9.
Hakki M, et al. *Transplant Cell Ther*. 2021;27:707-719.

CMV Case Study in HSCT *(continued)*



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What was Done

- Valganciclovir was initiated and once viremia resolved stopped with resumption of PCR monitoring

Points to Consider

- Clinically significant CMV infection can occur after completion of prophylaxis in about 20% of high-risk patients
- ASTCT recommends continuation of PCR monitoring through 6 months, with preemptive therapy if positive
- The optimal duration and frequency of PCR monitoring late after HCT has not been adequately studied

Marty FM, et al. *N Eng J Med*. 2017;377:2433-2444. Liu LW, et al. *Transplant Cell Ther*. 2022;28:510.e1-510.e9.
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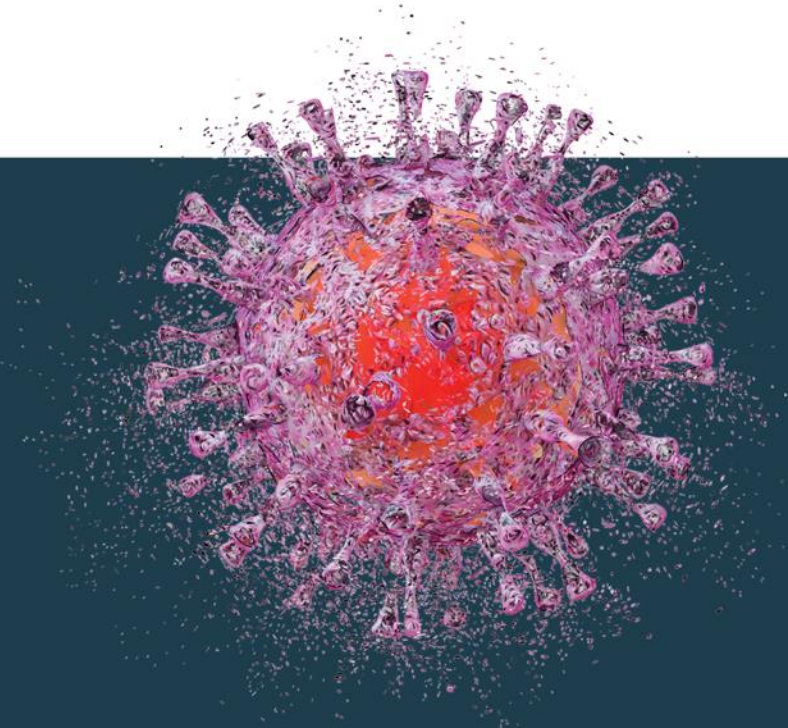
Cytomegalovirus in Stem Cell and Kidney Transplant

Overcoming the Limitations of Conventional Antiviral Therapy

Concluding Remarks



CME OUTFITTERS

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Be vigilant for CMV infection/disease in both SOT and HSCT

CME OUTFITTERS

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- Implement strategies to prevent/treat CMV infection in transplantation patients that include the appropriate use of standard and novel antivirals

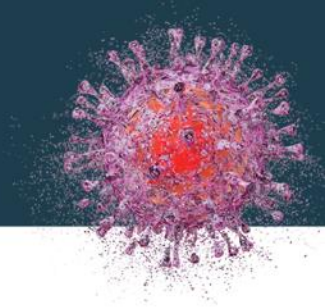
SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Be vigilant for CMV infection/disease in both SOT and HSCT
- Implement strategies to prevent/treat CMV infection in transplantation patients that include the appropriate use of standard and novel antivirals
- Apply relevant CMV clinical guidelines and best practices to optimize the quality of care and outcomes for patients receiving SOT or HSCT

CME OUTFITTERS

To Receive Credit

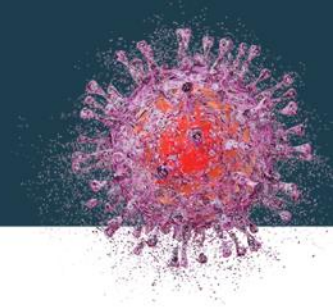


- To receive CME/CE credit for this activity, participants must complete the post-test and evaluation online
- Participants will be able to download and print their certificate immediately upon completion

CME OUTFITTERS

Claim ABIM MOC Credit

3 Steps to Complete



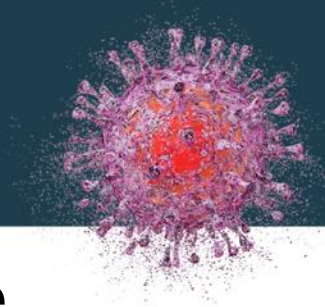
1. Complete the post-test and evaluation at the conclusion of the activity
2. Enter your **ABIM ID number** and **DOB** (MM/DD) on the evaluation, so credit can be submitted to ABIM

ABIM CME MOC ACCREDITED

CME OUTFITTERS

CME for MIPS Improvement Activity

How to Claim This Activity as a CME for MIPS Improvement Activity



- Complete the post-test and activity evaluation at the conclusion of the activity
- Over the next 3 months, actively work to incorporate improvements from this presentation into your clinical practice
- In approximately 3 months, complete the follow-up survey from CME Outfitters

CME for MIPS
IMPROVEMENT ACTIVITY

CME Outfitters will send you confirmation of your participation to submit to CMS attesting to your completion of a CME for MIPS Improvement Activity.

CME OUTFITTERS