What is New in CMV Therapy?

Carlos A. Gomez, MD
Associate Professor
Transplant and Oncology ID
University of Nebraska Medical Center (UNMC)
Omaha, NE, USA
carlosgomez@unmc.edu

University of Nebraska Medical Center

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Disclosures

- I have no COI to disclose
- Off-label indications will be discussed

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Talk-outline

- Universal prophylaxis vs. Preemptive therapy in SOT? For whom? when?
- Letermovir for CMV prophylaxis
- Treatment for CMV viremia/Disease: How the new agents (Maribavir, letermovir) are doing?
- Immune monitoring
- CMV vaccine

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Universal Prophylaxis vs Preemptive therapy (PET):

Prophylaxis:
Antiviral given for a **fixed period**
(eg, 3-6 mo)

Preemptive therapy (PET):
Antiviral given if DNAemia surpasses
risk-based **threshold** (eg, 0-1000 IU/mL)
during weekly monitoring

Hybrid: Prophylaxis, then PET

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Universal Prophylaxis vs Preemptive therapy (PET): Guidelines recommendations

Organ	CMV serostatus D+/R-	CMV serostatus R+
Kidney	VGCV, IV GCV, valacyclovir x 6 months *OR* preemptive	VGCV (preferred), GCV, valacyclovir x 3 months *OR* preemptive
Pancreas, kidney/pancreas	VGCV, IV GCV x 3 to 6 months *OR* preemptive	VGCV, IV GCV x 3 months *OR* preemptive
Liver	VGCV, IV GCV x 3 to 6 months *OR* preemptive	VGCV, IV GCV x 3 months *OR* preemptive
Intestine	VGCV, IV GCV x 6 months ± surveillance after	VGCV, IV GCV x 3 months ± surveillance after
Heart	VGCV, IV GCV x 3 to 6 months *OR* preemptive	VGCV, IV GCV x 3 months *OR* preemptive
Lung	VGCV, IV GCV x at least 6 to 12 months Some centers extend beyond 12 months	VGCV, IV GCV x 6 to 12 months

D, donor; R, recipient; SOT, solid organ transplant; VGCV, valganciclovir; GCV, ganciclovir; VGCV preferred over GCV

Kotton CN, et al. *Transplantation*. 2018;102(6):900-931.
Razonable RR, Humar A. *Clin Transplant*. 2019;33(9):e13512.

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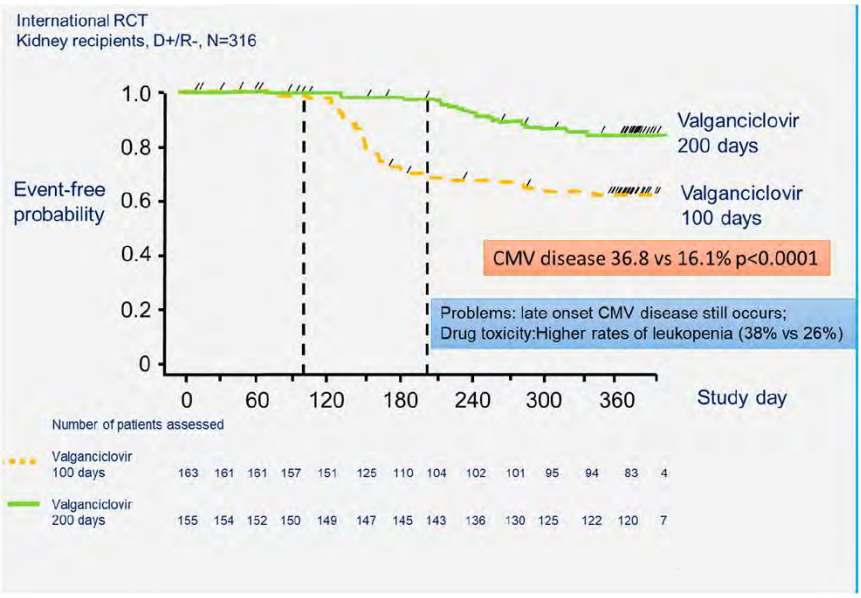
Universal Prophylaxis:

Kidney Tx D+/R-
100 vs 200 days VGCV



Humar. Am J Transplant. 2010;10:1228

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CAPSIL study

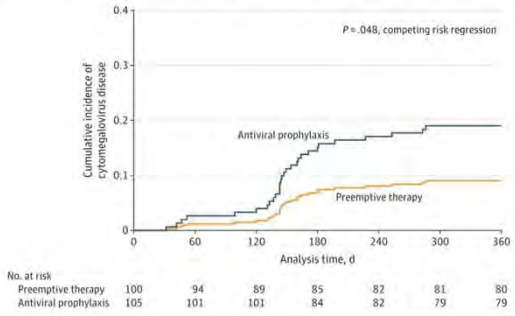
Liver Tx D+/R-
Prophylaxis vs. PET

Original Investigation JAMA. 2020;323:1378.
April 14, 2020

Effect of Preemptive Therapy vs Antiviral Prophylaxis on Cytomegalovirus Disease in Seronegative Liver Transplant Recipients With Seropositive Donors
A Randomized Clinical Trial

Nina Singh, MD[1,2]; Drew J. Winston, MD[3]; Raymund R. Razonable, MD[4]; et al

Figure 2. Cumulative Incidence of Cytomegalovirus (CMV) Disease With Death as a Competing Risk



- 205 CMV D+R- underwent PET or ppx for 100 days post-tx
- Primary outcome: CMV disease by 12 months
- PET: 9/100 (9%) vs Prophy: 20/105 (19%); p=0.04
  - Mainly driven by less delayed onset disease: 6% vs 17% (p=0.01)
  - 14% of PET group never had DNAemia
- Similar rates of rejection, mortality, OIs, graft loss, neutropenia

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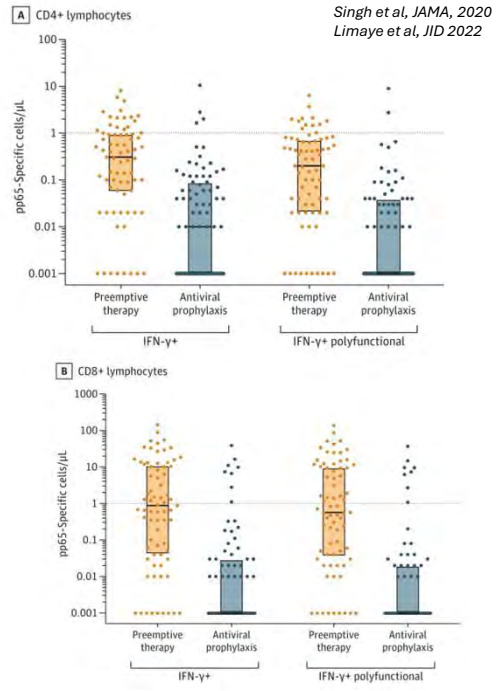
Why was PET better?

- nAb:
  - PET: 42% vs prophy: 26% at 100 days
- Polyfunctional T-cell response:
  - Higher in the PET group at 100 days
- Consistent with other observations of T cell response
  - HSCT: lower rate of T cell response in letermovir grp
- Can we extrapolate to other organs?
  - Only 15% got lymphocyte depletion

- **Viral suppression with antiviral prophylaxis** vs **controlled viral replication in PET** associated with suboptimal CMV-specific immunity, ↑ impairment in CD8+ vs CD4+ T-cell responses

Singh et al, JAMA, 2020
Limaye et al, JID 2022



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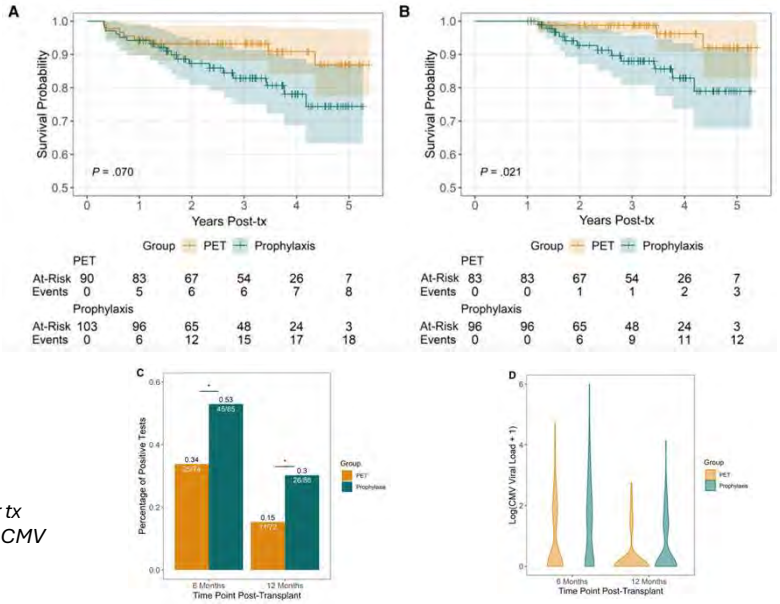
Can the effects of PET go beyond CMV-disease?

Clinical Infectious Diseases *October, 2023*

BRIEF REPORT

Association of Cytomegalovirus (CMV) DNAemia With Long-Term Mortality in a Randomized Trial of Preemptive Therapy and Antiviral Prophylaxis for Prevention of CMV Disease in High-Risk Donor Seropositive, Recipient Seronegative Liver Transplant Recipients

- CMV DNAemia has been linked to increased inflammation, alloimmune responses, and immune senescence



Post hoc analysis CAPSIL trial

-Improved survival with PET in CMV D+/R- Liver tx

-Quantitive relationship between 6-12-months CMV DNAemia and long-term mortality

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Key Take-home Points

- PET and antiviral prophylaxis are both valid CMV prevention strategies used during high-risk periods
  - The Devil is in the details: Cost, access to timely CMV-DNAemia results and prompt initiation of therapy
    - Immunological benefits of PET, (ie, better control CMV DNAemia)→can improve long-term survival (but need a RCT in D+/R- Kidney transplant)

Table 1
Advantages and disadvantages of universal prophylaxis and preemptive therapy for cytomegalovirus disease prevention in solid organ transplant recipients

	Universal Prophylaxis	Preemptive Therapy
Advantages	• Large body of supporting evidence • Ease of implementation • *Possible* greater impact on indirect effects of CMV	• Reduced drug exposure • Decreased cost, risk of toxicity, and resistance • Lower risk for late-onset CMV
Disadvantages	• Increased antiviral drug exposure • Increased cost, toxicity, and/or resistance • Increased risk for late-onset postprophylaxis CMV disease	• Logistical demands of laboratory monitoring and coordination • Uncertainty about impact on the indirect effects of CMV • CMV viral thresholds for initiating and/or discontinuing therapy are not well-defined • Systematic evaluation in thoracic organ recipients is lacking

Updates in CMV prevention in SOT. ***Infectious Disease Clinics of North America***, in press, Nov 2023

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Agents for Prevention and Treatment of CMV in SOT and HCT

R.R. Razonable / Clinical Microbiology and Infection 29 (2023) 1144–1149

Table 1
Antiviral drugs for prophylaxis and treatment of cytomegalovirus infection and disease

Drug	Target	Route	Indications/clinical uses	Major toxicities	Activity against other herpes viruses	Comments
Cidofovir	UL54 DNA polymerase	IV	Treatment	Nephrotoxicity, myelosuppression, ocular, and alopecia	Yes: HSV, VZV, and HHV6	Alternative for treatment due to high risk of toxicity
Foscarnet	UL54 DNA polymerase	IV	Treatment	Nephrotoxicity, electrolyte loss, and myelosuppression	Yes: HSV, VZV, and HHV6	Alternative for treatment due to high risk of toxicity
Ganciclovir	UL54 DNA polymerase	IV	Treatment and prophylaxis	Myelosuppression, especially leukopenia and neutropenia	Yes: HSV, VZV, and HHV6	First-line treatment of CMV disease, especially if severe and life-threatening
Maribavir	UL97 kinase	Orally or by mouth	Treatment (resistant and refractory CMV)	Dysgeusia and gastrointestinal effects	*In vitro*: EBV (no data *in vivo*)	Poor CNS penetration Consider adding HSV-active drug during high-risk periods May increase levels of immunosuppressants
Letermovir	UL56, UL51, UL89 terminase	IV, orally or by mouth	Prophylaxis	Gastrointestinal effects	None	Consider adding HSV-active drug during high-risk periods Low barrier of resistance May increase levels of immunosuppressants
Valganciclovir	UL54 DNA polymerase	Orally or by mouth	Treatment and prophylaxis	Myelosuppression, especially leukopenia and neutropenia	Yes: HSV, VZV, and HHV6	First-line treatment of asymptomatic and mild-to-moderate CMV disease

The dosages of the antiviral medications should be adjusted on the basis of renal function. Please refer to package insert of each drug for appropriate dosing on the basis of renal function and other considerations.
CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein Barr virus; HHV-6, human herpesvirus-6; HSV, herpes simplex virus; IV, intravenous; VZV, varicella zoster virus.

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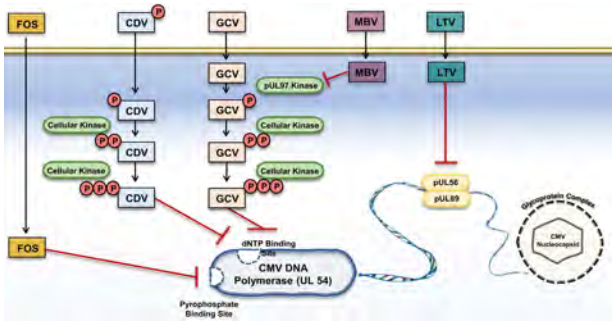
Letermovir

- Novel mechanism of action
  - Inhibits viral terminase complex (DNA cleavage and packaging)
- No activity against herpesviruses other than CMV
- Toxicity: comparable to placebo in trials, drug interactions (vori)
- Clinical use: Approved for CMV prophylaxis in HCT
  - Low barrier to resistance
- Mechanism of resistance
  - UL56, UL89



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Letermovir: A new option for CMV Prophylaxis

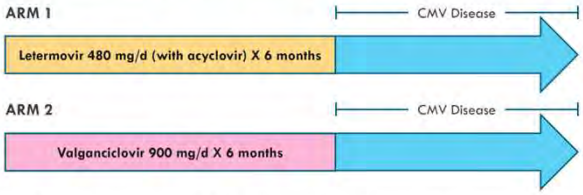
JAMA | Original Investigation

Letermovir vs Valganciclovir for Prophylaxis of Cytomegalovirus in High-Risk Kidney Transplant Recipients
A Randomized Clinical Trial

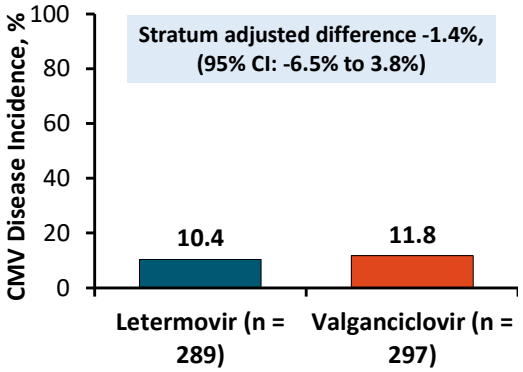
Ajit P. Limaye, MD; Klemens Budde, MD; Atul Humar, MD, MSc; Flavio Vincenti, MD; Dirk R. J. Kuypers, MD, PhD; Robert P. Carroll, BM, BCh, DM; Nicole Stauffer, BS; Yoshihiko Murata, MD, PhD; Julie M. Strizki, PhD; Valerie L. Teal, MS; Christopher L. Gilbert, BS; Barbara A. Haber, MD

- 589 D+/R- kidney recipients

Patients randomized 1:1 within 7 days post-kidney transplant to Arm 1 or 2



Endpoint: CMV disease through week 52, adjudicated by independent committee



Stratum adjusted difference -1.4%, (95% CI: -6.5% to 3.8%)

- **Letermovir** non-inferior to **valganciclovir** in preventing CMV disease through Wk 52

Limaye. JAMA. 2023;330:33.

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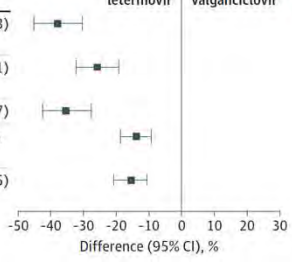
Letermovir vs VGCV: (D+/R-) Kidney Transplant

Figure 3. Leukopenia or Neutropenia Events and Time to Onset Through Week 28 in the Safety Population

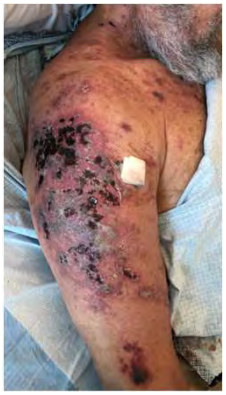
A Adverse events (AEs)

Events	No./total No. (%) Letermovir (n = 292)[a]	Valganciclovir (n = 297)	Difference (95% CI), %
≥1 leukopenia or neutropenia event[b]	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)



Letermovir noninferior to valganciclovir for CMV prevention with improved safety profile

DO NOT forget:
Val/Acyclovir for HSV/VZV prophylaxis: when using Letermovir



Limaye. JAMA. 2023;330:33.

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R/R CMV Infection or Disease:

- Refractory*
  - Increasing or persistent viral load after at least 2 weeks of adequate antiviral therapy
- Resistant
  - Viral genetic alteration that decreased susceptibility to one or more drugs

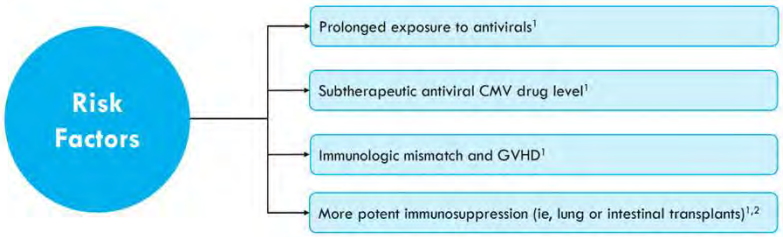
*Not all patients with refractory CMV have resistant virus

Incidence of Resistance

- 0% to 3% after 100 to 200 days of GCV or VGCV prophylaxis in D+/R− kidney recipients
- 1.7% to 14.5% in HCT patients

Incidence Higher After GCV Therapy

- 5% to 12% among all SOT recipients
- Up to 18% among lung recipients
- Up to 31% among intestinal/multivisceral recipients



CMV, cytomegalovirus; R/R, refractory/resistant

Chemaly RF, et al. *Clin Infect Dis*. 2019;68(8):1420-1426.

Kotton CN, et al. *Transplantation*. 2018;102(6):900-931.
Yong MK, et al. *Transplant Cell Ther*. 2021;27(12):957-967.

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4 Principles for Treatment of R/R CMV in 2024

1. Reduce Immunosuppression to lowest feasible amount (antimetabolite,MMF)
2. Therapies options:
   - Maribavir
   - Letermovir?
   - Foscarnet
   - High-dose IV GCV
   - Cidofovir
3. Investigational agents
   - Brincidofovir?
4. Adjunctive therapies
   - CMV IgG or IVIG
   - mTOR inhibitors as part of IS regimen
   - Leflunomide and artesunate
   - Adoptive T-cell therapy

Kotton CN, et al. *Transplantation*. 2018;102(6):900-931.

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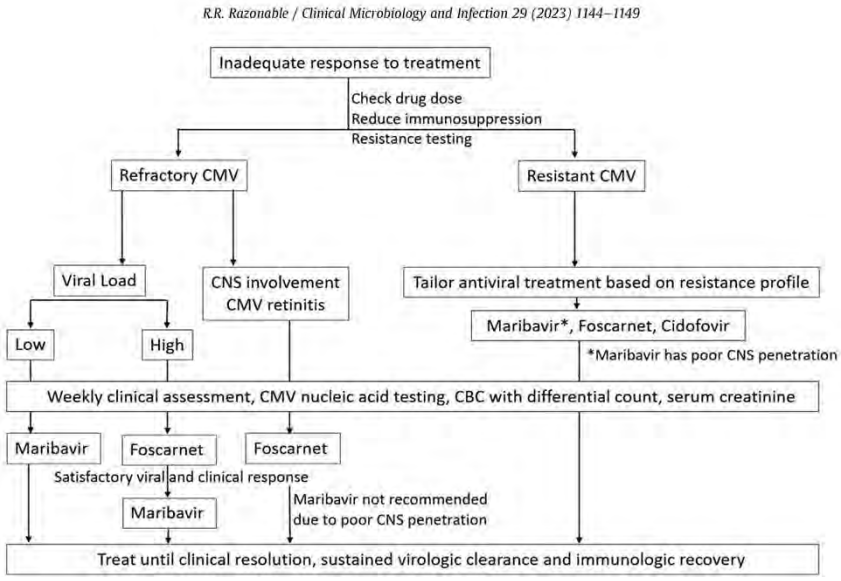
Management of R/R CMV Disease



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Letermovir for Refractory/Resistant CMV

- Limited clinical studies in R/R CMV disease –off-label indication
- Multicenter study 47 SOT and HCT[1]
  - VL (<1000 IU/mL): 35/37 clear, 5% failure rate
  - VL (>1000 IU/mL): 6/10 clear, 40% failure rate

28-Lung transplant patients with R/R CMV[2]

- 14 patients with VL >10,000 IU/mL
- 82% response with VL decline >1 log
- 3 patient developed LTMV resistance (UL56, C325y)

- Uncertainty about adequate dosing and low barrier to resistance[3]
- More studies needed before can be recommended first line for treatment[4]

1. Linder KA, et al. *Transpl Infect Dis*. 2021;23(4):e13687.
2. Veit T, et al. *Am J Transplant*. 2021;21(10):3449-3455.
3. Hakki M. *Curr Hematol Malig Rep*. 2020;15(2):90-102.
4. Shigle TL, et al. *Ther Adv Hematol*. 2020;11:2040620720937150.

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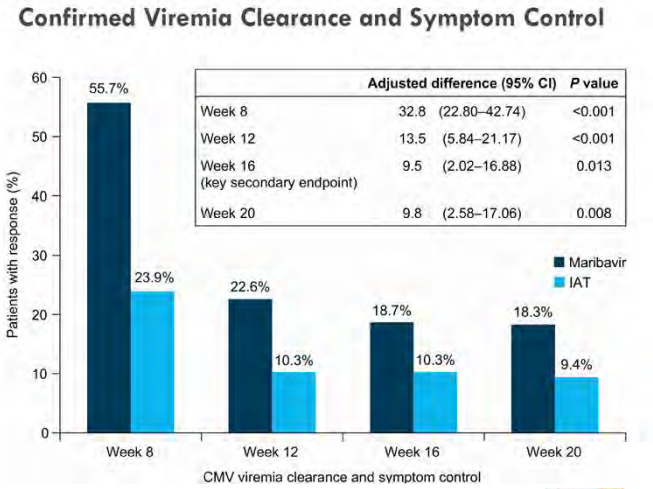
SOLSTICE: Marabivir vs Investigator Assigned Therapy (IAT) for R/R CMV Infections

- Randomized, open-label phase III study in HSCT and SOT recipients with refractory CMV infections (± resistance); treated x 8 wk
- **Primary endpoint: maribavir** superior to **IAT** for CMV clearance at end of Wk 8
- **Safety endpoints: maribavir** associated with **lower rates of AKI vs FOS** (8.5% vs 21.3%) and **neutropenia vs GCV/VGCV** (9.4% vs 33.9%



Avery. Clin Infect Dis. 2022;75:690.

Slide credit: clinicaloptions.com

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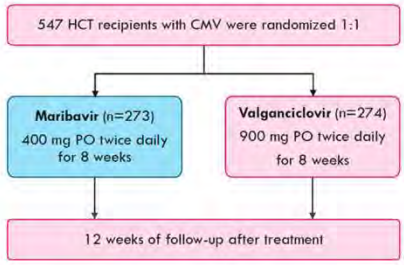
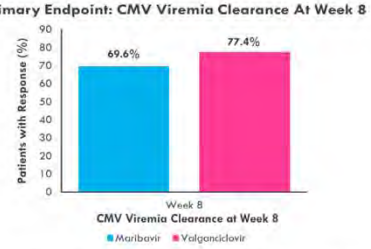
Phase 3 AURORA Trial results:

Clinical Infectious Diseases
MAJOR ARTICLE

Treatment for First Cytomegalovirus Infection Post–Hematopoietic Cell Transplant in the AURORA Trial: A Multicenter, Double-Blind, Randomized, Phase 3 Trial Comparing Maribavir With Valganciclovir

Genovefa A. Papanicolaou,[1] Robin K. Avery,[2] Catherine Cordonnier,[3] Rafael F. Duarte,[4] Shariq Haider,[5] Johan Maertens,[6] Karl S. Peggs,[7] Carlos Solano,[8] Jo-Anne H. Young,[9] Martha Fournier,[10,©] Rose Ann Murray,[10] Jingyang Wu,[10] and Drew J. Winston[11]; for the AURORA Trial Investigators[a]





- Maribavir demonstrated clinically meaningful efficacy in confirmed CMV viremia clearance
- It did not meet its primary endpoint of non-inferiority vs valganciclovir based on a prespecified non-inferiority margin of 7% (maribavir 69.6% vs valganciclovir 77.4%; adjusted difference, -7.7%; 95% CI: -14.98, -0.36)

CID published online, 30 November, 2023

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Phase 3 AURORA Trial results:

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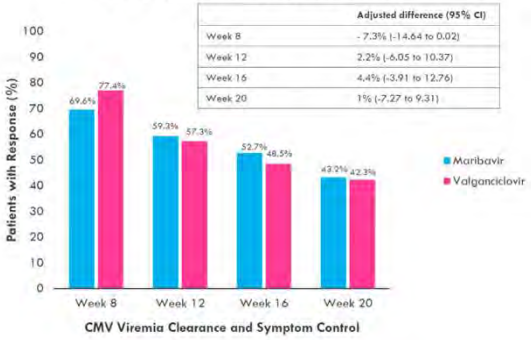
- At week 16, *a key secondary endpoint*, a higher proportion of patients treated with maribavir maintained viremia clearance and symptom control.
- A sustained maintenance effect was observed with maribavir during post-treatment evaluations at week 12 and week 20.
- Reaffirmed maribavir's favorable safety profile compared to valganciclovir.
  - Treatment-emergent neutropenia was 21.2% for maribavir vs 63.5% for valganciclovir.
  - Rate of premature discontinuation of therapy due to neutropenia was 4% for maribavir vs 17.5% for valganciclovir.

Secondary Endpoint: Confirmed Viremia Clearance and Symptom Control

	Adjusted difference (95% CI)
Week 8	-7.3% (-14.64 to 0.02)
Week 12	2.2% (-6.05 to 10.37)
Week 16	4.4% (-3.91 to 12.76)
Week 20	1% (-7.27 to 9.31)



CMV Viremia Clearance and Symptom Control

CID published online, 30 November, 2023

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Maribavir for Refractory/Resistant CMV: Caution!

Received: 7 October 2022 | Revised: 14 December 2022 | Accepted: 2 February 2023
DOI: 10.1111/ctr.14929

LETTER TO THE EDITOR

Clinical TRANSPLANTATION WILEY

Real world experience with Maribavir for the treatment of cytomegalovirus in solid organ transplant recipients

Open Forum Infectious Diseases
CORRESPONDENCE

Maribavir for Cytomegalovirus Treatment in the Real World—Not a Silver Bullet

Received: 5 February 2024 | Revised: 8 February 2024 | Accepted: 12 February 2024
DOI: 10.1111/iid.14259

CLINICAL CORRESPONDENCE

Development of cytomegalovirus resistant to maribavir: real world, real problem?

TABLE 1 Comparison of patients who experienced CMV breakthrough versus those who did not

	No breakthrough ($n = 9$)	Breakthrough ($n = 4$)
Transplant type		
Kidney	7 (77.8)	2 (50)
Lung	2 (22.2)	2 (50)
CMV D+/R-	7 (77.8)	4 (100)
AR treatment within preceding 6 months of first CMV detection	0 (0)	1 (25)
Median time from transplant to first CMV detection, days (IQR)	153 (78–285)	222 (149–268)
Median peak CMV viral load prior to maribavir initiation, IU/ml (IQR)	28,300 (13,700–105,000)	121,350 (4,956–716,500)
Documented CMV resistance at maribavir initiation	Yes: 5 Indeterminate: 2 No: 2	Yes: 2 Indeterminate: 1 No: 1
Median CMV viral load at maribavir initiation, IU/ml (IQR)	5,714 (200–13,700)	1,556 (106–8,486)
Median duration of maribavir exposure, days (IQR)	146 (67–217)	76 (66–94)

Note: *n* (%) unless otherwise specified.
Abbreviations: AR, acute rejection; IQR, interquartile range.

and resistance.

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Maribavir for Refractory/Resistant CMV: Caution!

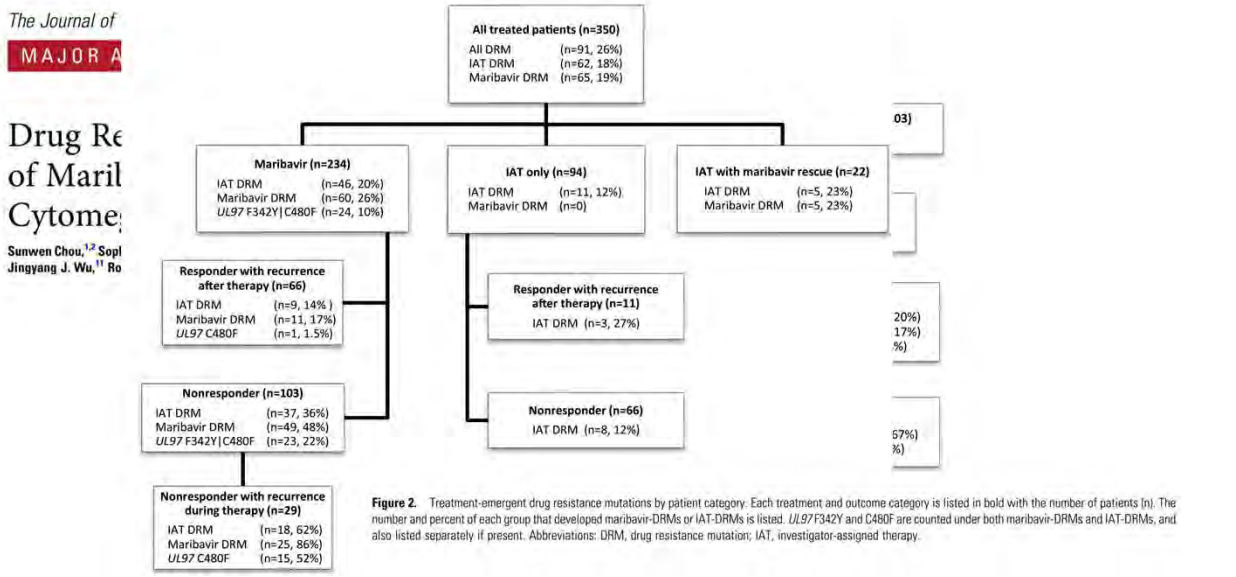

Figure 2. Treatment-emergent drug resistance mutations by patient category. Each treatment and outcome category is listed in bold with the number of patients (n). The number and percent of each group that developed maribavir-DRMs or IAT-DRMs is listed. *UL97* F342Y and C480F are counted under both maribavir-DRMs and IAT-DRMs, and also listed separately if present. Abbreviations: DRM, drug resistance mutation; IAT, investigator-assigned therapy.

Maribavir Resistance in a Phase 3 Trial **The Journal of Infectious Diseases®** **2024;229:413–21**

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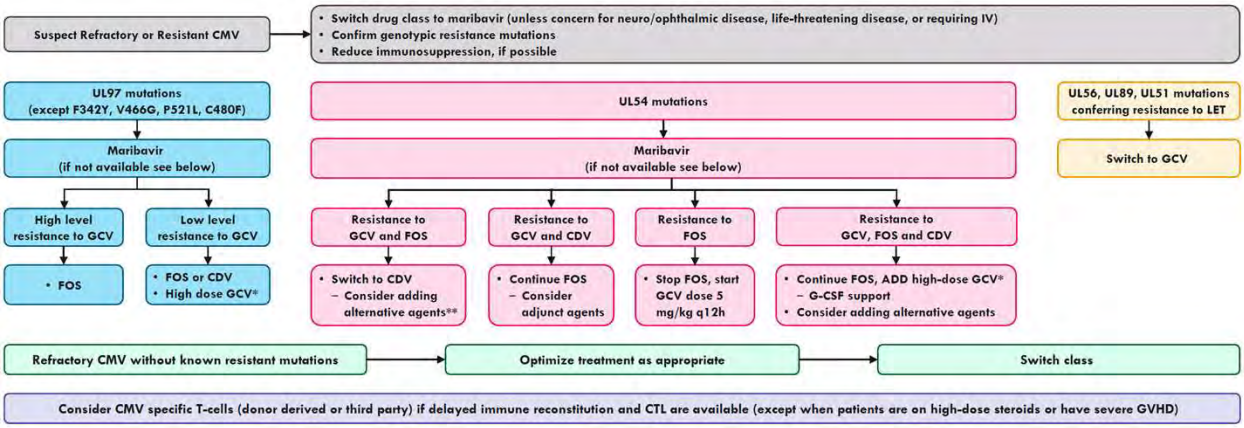
Management of R/R CMV Disease: Summary



*High-dose GCV - 7.5 mg to 10 mg/kg q12h (use when no other option ie; patient cannot tolerate foscarnet)
** leflunomide or artesunate
GCV, ganciclovir; FOS, foscarnet, CDV, cidofovir; LET, letermovir; CTL, CMV specific T-cells; GVHD, graft-vs-host disease
Modified from: Yong MK, et al. *Transpl Cell Ther.* 2021 Dec;27(12):957-967.

CARE TEAM FORUM

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Key Take-home Points in R/R CMV

- Recurrent CMV: 19-30% SOT
  - D+/R-
  - Lung transplants
- Resistance <5%
  - Prolonged drug exposure
  - Inadequate antiviral delivery/dosing
- Maribavir (blocks UL97 protein kinase): newest agent for R/R CMV
  - More CMV clearance than "best-available therapy" (56% vs 23%); but still high rate of rebound viremia after 8-weeks
  - Treatment-emergent UL97 mutations occur frequently:
    - 48% non-responders
    - 86% non-responder with recurrence while on therapy
    - 17% responders with recurrence after on therapy
- Letermovir
  - Concern for low-barrier resistance
  - Role in R/R likely highly individualized for those with VL and lacking alternatives
  - Further studies needed

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Unmet needs in CMV and Transplantation

Burden	CMV remains a common problem posttransplant despite decades of treatment and diagnostic advances
Guidelines	Good guidelines are available but unable to personalize the best prophylactic and treatment course for individual patients
Antiviral management	Late CMV remains a major concern in high-risk patients at the end of prophylaxis
	Few RCTs have compared prophylaxis with pre-emptive therapy
	In allo-HCT, not all patients are eligible for standard CMV prophylaxis and appropriate management is still to be established in these patients
	Resistant/refractory CMV infection remains an issue for a small subset of patients
	Current prophylactic and therapeutic agents have issues of toxicity and cost, although letermovir as prophylaxis in kidney transplant recipients may be associated with less toxicity
Immune modulation	An "ideal" CMI assay is required before immune monitoring becomes part of routine clinical practice in all laboratories and a clinical tool for individualized decision making
	How to use CMVIG or CMV-specific T cells in clinical practice is still to be established
Vaccination	Lack of effective CMV vaccines remain a major deficit in the field

Slaying the "Troll of Transplantation"—new frontiers in cytomegalovirus management: A report from the CMV International Symposium, Barcelona May 2023

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