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Cytomégalovirus en transplantation d'organes solides

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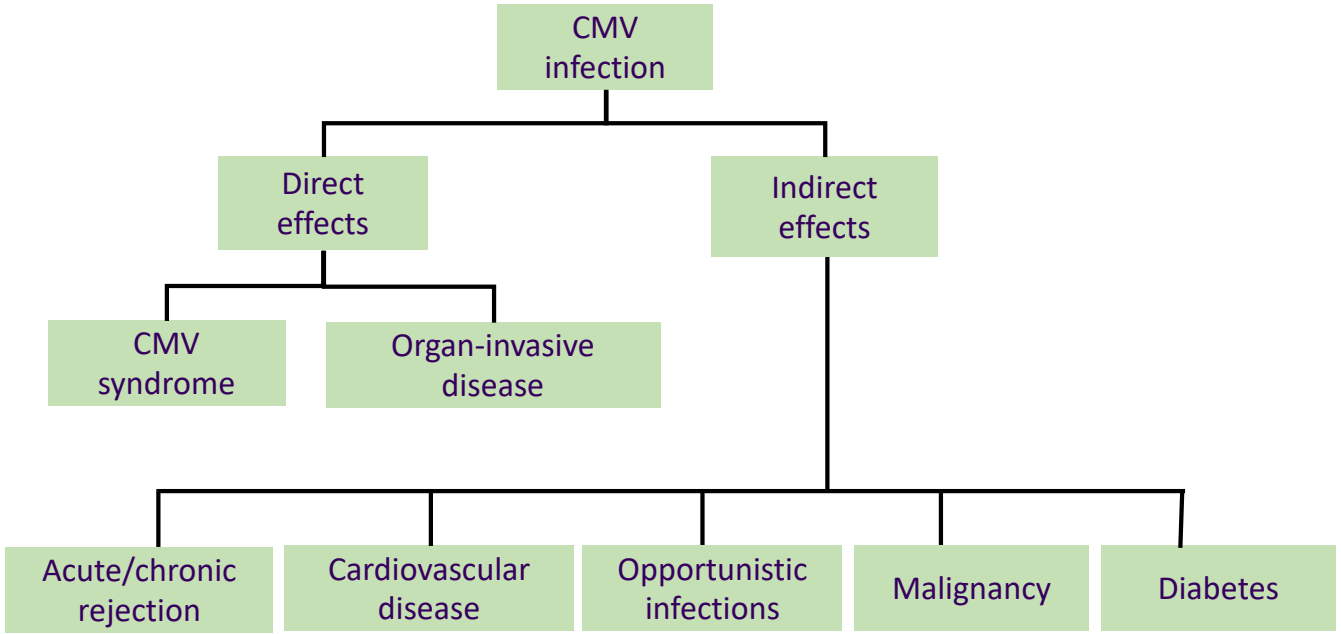
Déclaration d'intérêts

I have received speakers fees and participated to advisory boards for Astellas, AstraZeneca, Biotest, CSL Behring, Chiesi, ExeViR, Hansa, Merck Sharp and Dohme, Glasgow Smith Kline, Novartis Pharma, Sanofi, Sandoz, and Takeda

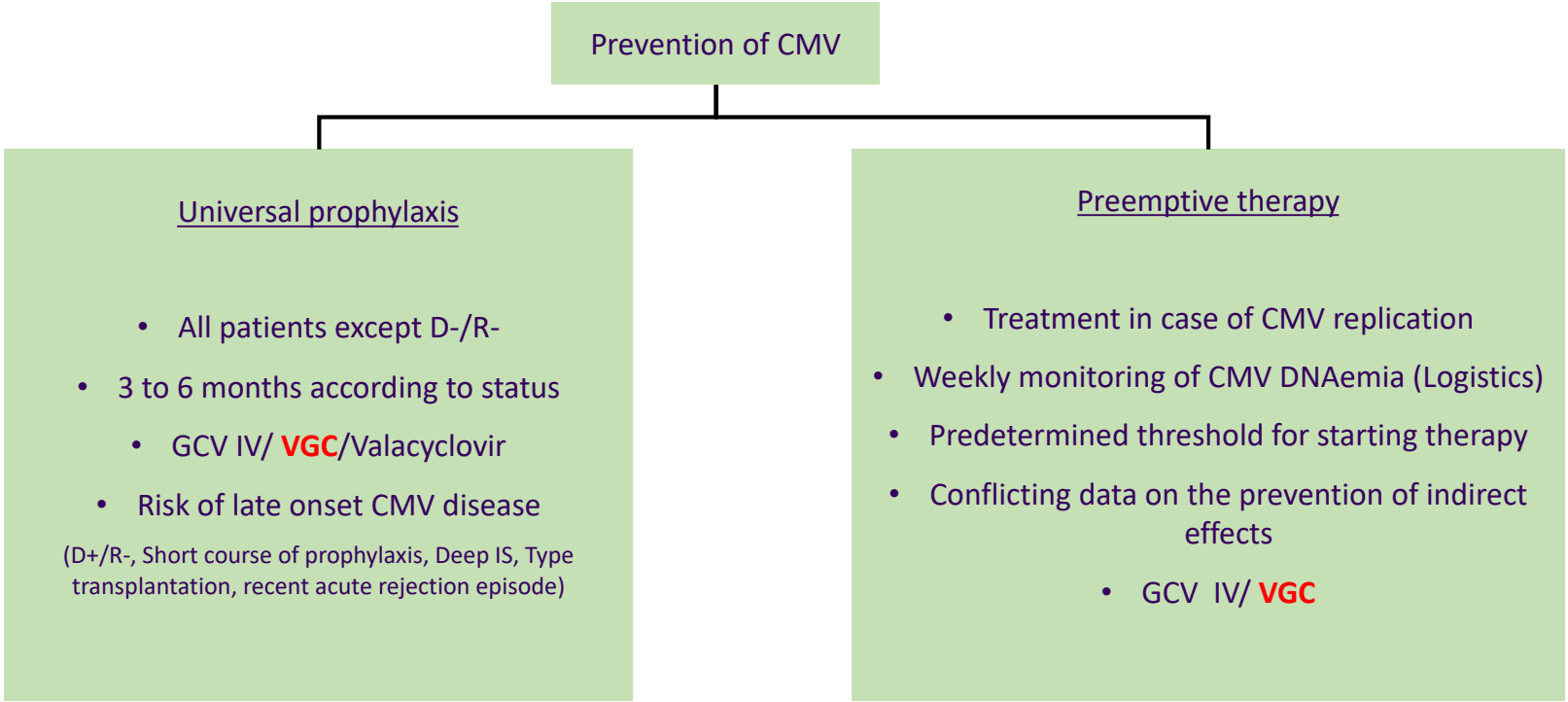
Direct and indirect effects of CMV

- CMV is one of the most common infectious complications after a solid organ transplant (SOT) and is associated with morbidity, graft loss, and mortality



Prevention of CMV infection/disease

- CMV prophylaxis decreases the risk of CMV infection and disease



Kotton et al., Transplantation 2018

Comparison of both strategies

	Prophylaxis	Preemptive therapy
Early CMV DNAemia / infection	Rare	Common
Prevention of CMV disease	Good efficacy	Good efficacy
Late CMV (infection / disease)	Common	Rare
Resistance	Uncommon	Uncommon (with weekly testing)
Ease of implementation	Relatively easy	More difficult
Prevention of other herpes viruses	Prevents HSV, VZV	Does not prevent
Other opportunistic infections	May prevent	Unknown
Costs	Drug costs	Monitoring costs
Safety	Drug side effects	Less drug toxicity
Prevention of rejection	May prevent	Unknown
Graft survival	May improve	May improve

Kotton et al., Transplantation 2018

CMV Prevention Guideline Recommendations

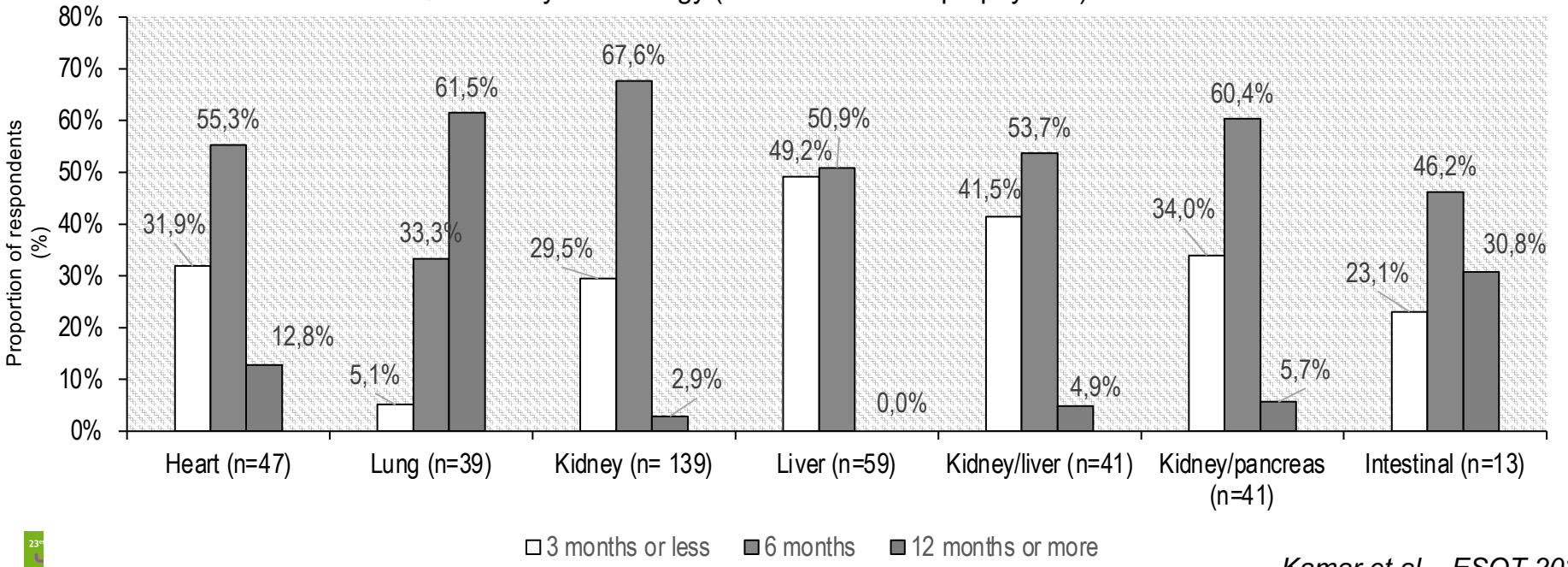
Organ	D+R-	R+
Kidney	VGCV, IV GCV, valacyclovir x 6 months OR pre-emptive	VGCV (preferred), GCV, valacyclovir x 3 months OR pre-emptive
Pancreas, kidney/pancreas	**VGCV, IV GCV** x 3 to 6 months OR pre-emptive	**VGCV, IV GCV** x 3 months OR pre-emptive
Liver	VGCV, IV GCV x 3 to 6 months OR pre-emptive	VGCV, IV GCV x 3 months OR pre-emptive
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 pre-emptive	**VGCV, IV GCV** x 3 months OR pre-emptive
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

Kotton et al., Transplantation 2018

Real world CMV management (ESOT survey: 224 transplant centres)

D+/R-

- 90% of centres reported using prophylaxis
- 95% of centres reported using valganciclovir / 5% used valacylcovir
- 8% added CMV Ig IV
- 12% Hybrid strategy (Surveillance after prophylaxis)



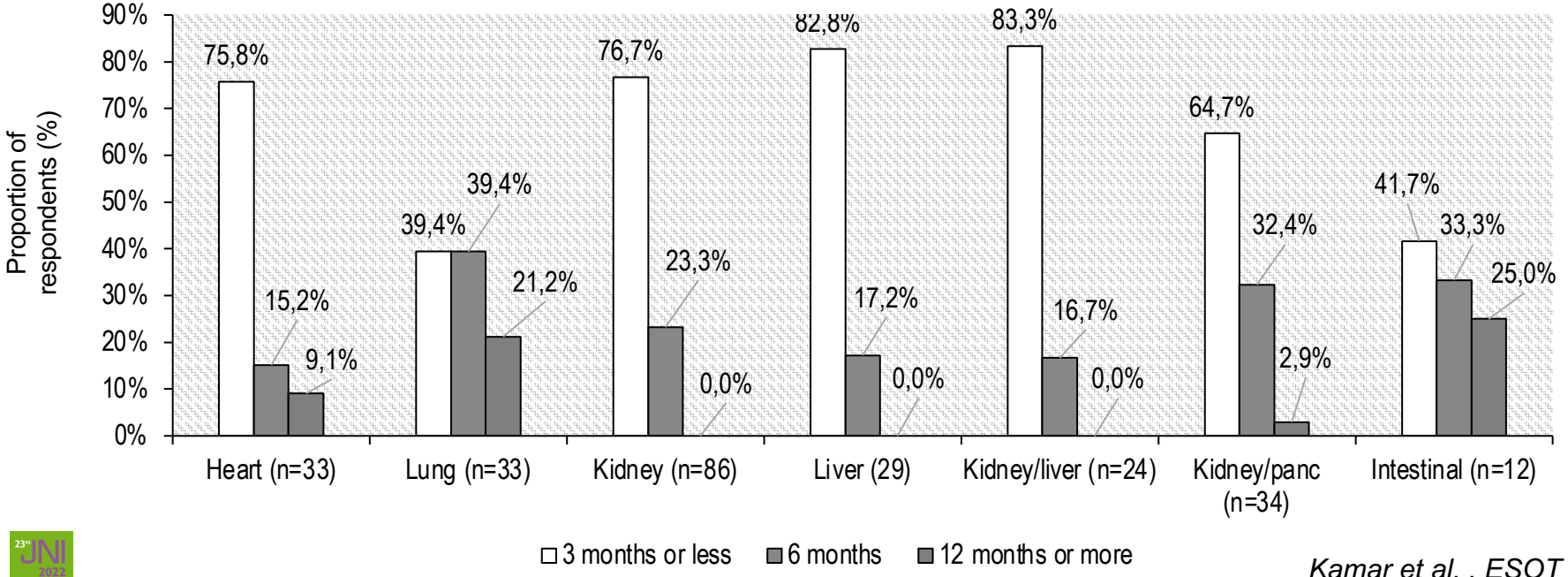
Kamar et al. , ESOT 2021

Real world CMV management (ESOT survey: 224 transplant centres)

R+

- 47% of centres reported using prophylaxis
- 48% of centres reported using premptive therapy (Liver +++)
- 18% no prevention in D+/R+
- 26% no prevention in D-/R+

Duration of prophylaxis



Kamar et al. , ESOT 2021

International Guidelines Treatment of CMV in SOT pts

- Drug: Oral VGCV 900 mg PO q12h or IV GCV 5 mg/kg q12h , adjusted for renal function
  - IV GCV: Life-threatening disease, very high viral load, questionable GI absorption
  - Acyclovir, valacyclovir, letermovir not recommended

- Monitoring: Weekly CMV PCR, serum creatinine, and complete blood count

- Duration:
  - Until resolution of clinical symptoms
  - Virological clearance below a pre-defined threshold or undetectable on 1 or 2 weekly samples
  - Minimum of 2 weeks of therapy

Kotton et al., Transplantation 2018

First Unmet need: Myelotoxicity of GCV/VGC

Antiviral Agent	Bone Marrow	Kidney	Altered Taste	Drug Interactions
Ganciclovir IV/valganciclovir PO	✓			
Acyclovir at high doses (prophylaxis only)		✓		
Foscarnet		✓		
Cidofovir		✓		
Letermovir (**HSCT approved**, prophylaxis only)				✓
Maribavir			✓	

	VGC 200 days (n=156)	VGC 100 days (n=164)
Leukopenia	38%	26%
Neutropenia	15%	15%
Anemia	15%	18%

Humar et al., AJT 2010

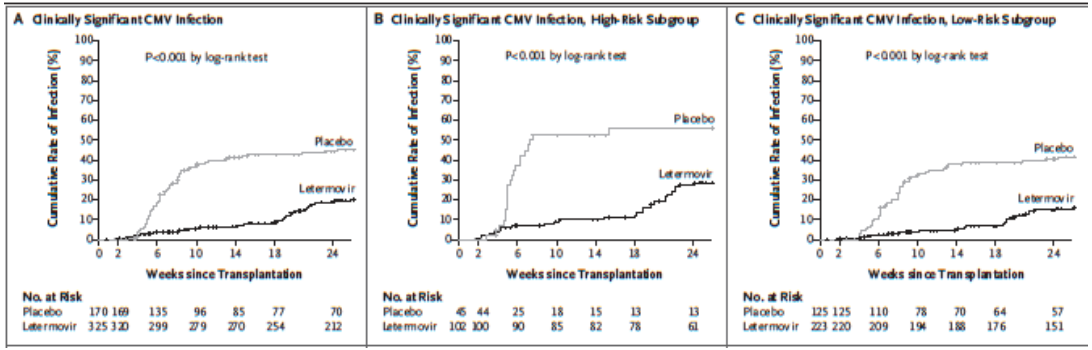
Real life setting: The ESOT survey

« Myelotoxicity was reported by 64% of centers»

Kamar et al., ESOT 2021

Letermovir for prophylaxis in SOT patients ?

- Letermovir:
  - Selective terminase inhibitor, inhibits formation and release of virions particles
  - Approved for prophylaxis in HCT (fewer clinically significant CMV events versus placebo)
  - No myelo or nephrotoxicity
  - Not recommended for therapy due to lack of efficacy data and emergence of resistance
  - Ongoing trial of letermovir versus valganciclovir to prevent CMV in kidney transplant recipients



Marty et al., NEJM 2017

Complicated CMV

Refractory

Recurrent

Resistant

Table 2. Summary of the Definitions of Refractory Cytomegalovirus Infection and Disease and Antiviral Drug Resistance for Use in Clinical Trials

Term	Definition
Refractory CMV infection	CMV viremia that increases[a] after at least 2 wk of appropriately dosed antiviral therapy
Probable refractory CMV infection	Persistent viral load[b] after at least 2 wk of appropriately dosed antiviral therapy
Refractory CMV end-organ disease	Worsening in signs and symptoms or progression into end-organ disease after at least 2 wk of appropriately dosed antiviral therapy
Probable refractory CMV end-organ disease	Lack of improvement in signs and symptoms after at least 2 wk of appropriately dosed antiviral drugs
Antiviral drug resistance	Viral genetic alteration that decreases susceptibility to one or more antiviral drugs[c]

Chemaly et al., Clin Infect Dis 2019

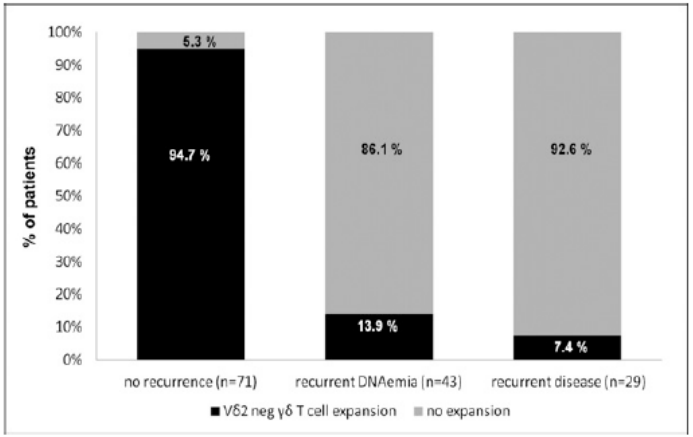
Risk factors for recurrent CMV

- **Recurrent CMV DNAemia: 30%**
- **Recurrent CMV disease: 15%**

- **Risk factors:**

- Immunosuppression: induction therapy, polyclonal antibodies, acute rejection, belatacept
- High viral load at diagnosis
- Failure to eradicate DNAemia at day 21 posttreatment
- Lack CMV immunity
- D+/R-
- Lymphopenia

Expansion of gamma delta T-cells



Natori et al., Transplantation 2017
Garnier, Clin Infect Dis 2018

Kaminski et al., JASN 2016

Risk factors for resistant CMV

Risk factors for resistant CMV
Prolonged antiviral drug exposure
D+/R-
Heavy immunosuppression (Polyclonal antibodies, belatacept)
Inadequate antiviral drug delivery
Anti-CMV drug modifications due to modification in kidney function or toxicity

Kotton et al., Transplantation 2013

Incidence of resistant CMV

- SOT: 5 to 12%
- Lung transplantation: up to 18%
- Kidney transplantation: 0 to 3% in D+/R- given VGC prophylaxis

Kotton et al., Transplantation 2018

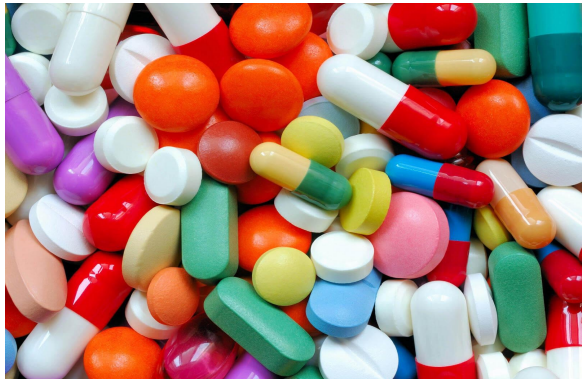
ESOT Survey: Rate of ganciclovir resistance:

- <1%: (164 centers, 74.2%)
- 1–5%: (52 centers, 23.5%) a rate of 1–5%
- 6–10% : (5 centers, 2.2%)

Kamar et al., ESOT 2021

Management of complicated CMV

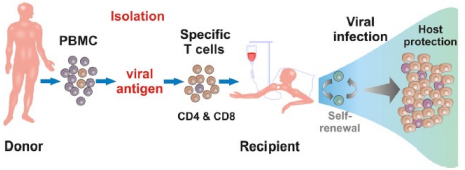
Anti-viral drugs



Improving anti-CMV immune response

Reducing immunosuppression

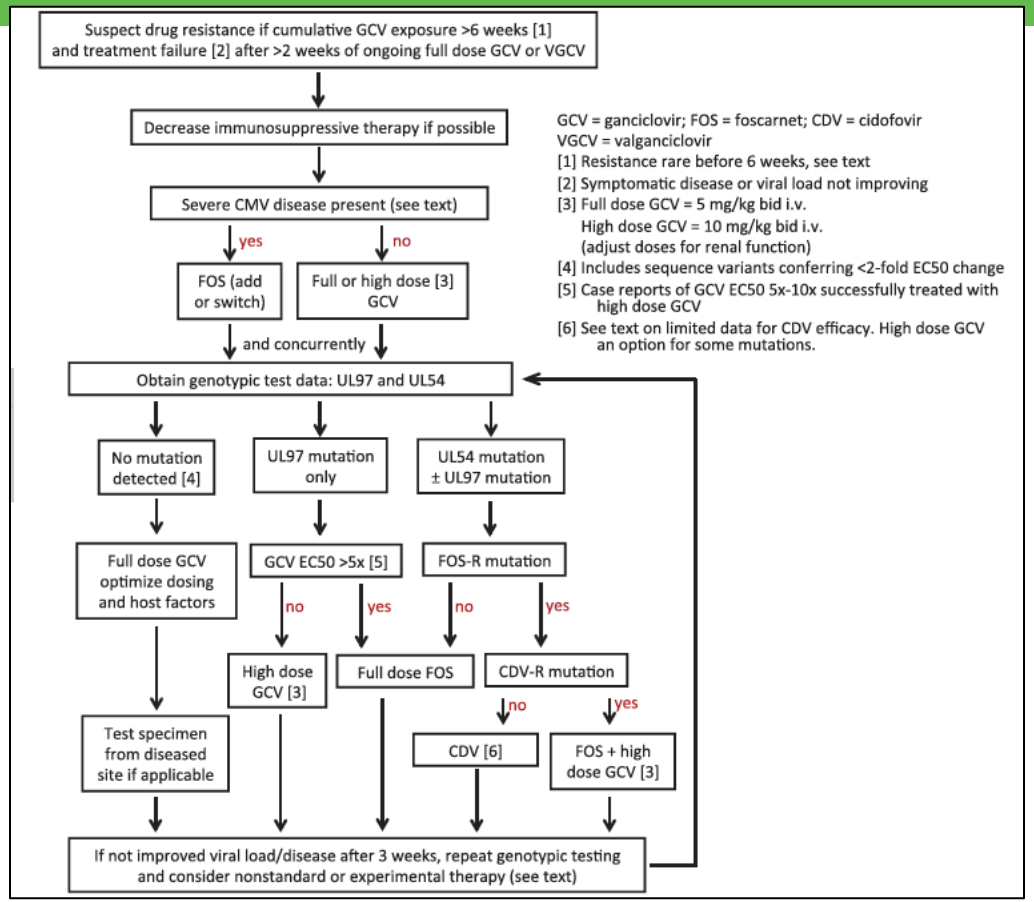
Autologous adoptive specific T-cell Immunotheray: CD4, CD8, γδ T-cells



CMV immunoglobulins

Recommendation for treating resistant CMV

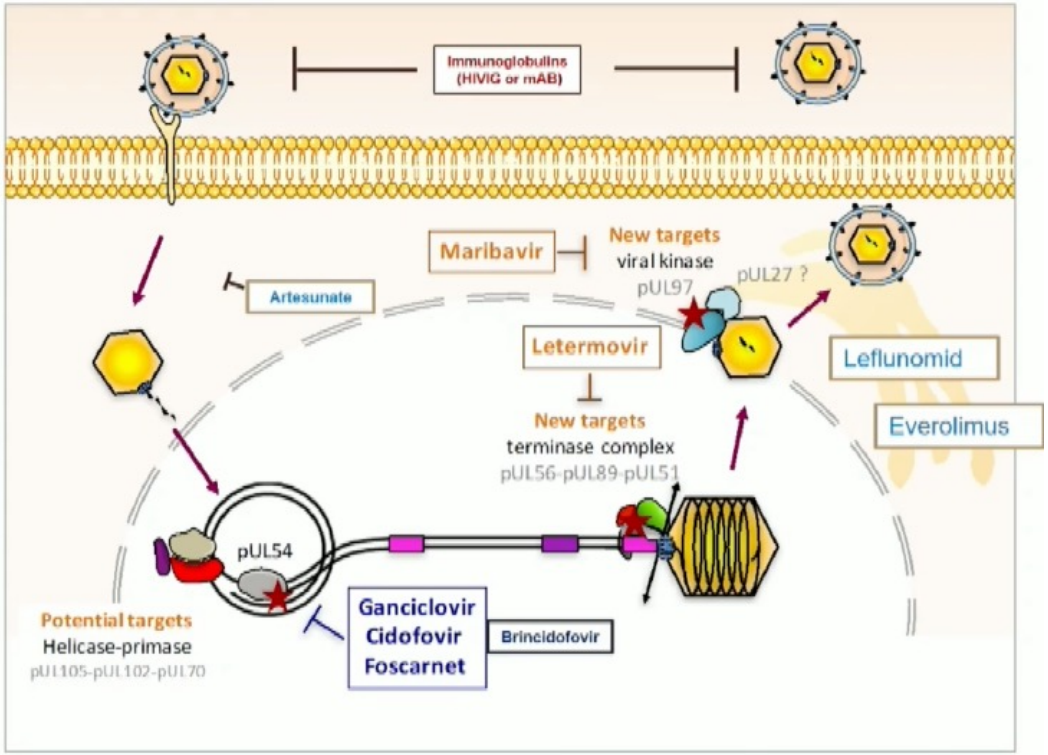
Genotyping



Kotton et al., Transplantation 2018

CMV resistance

CMV Gene	Role	Associated Drug Resistance
UL97	Kinase	Ganciclovir, valganciclovir, maribavir
UL54	Polymerase	Ganciclovir, valganciclovir, cidofovir, foscarnet, brincidofovir
UL27	Cell cycle regulation	Maribavir (low level)
UL51/UL56/UL89	Cleavage and packaging	Letermovir



High-dose Ganciclovir

- **Dose escalation from 7.5 to 10 mg/kg every 12 hours in normal renal function**
- **Data in SOT limited to few case series**
  - Successful outcomes in 6 patients with low-level DNAemia
  - 21% clearance rate in 14 patients with genotypic resistance and high-level DNAemia
- **Neutropenia reported in approximately 50% of patients**
- **Narrow applicability**
  - Low-level resistance UL97 gene mutations (C592G)
  - Low-level DNAemia
  - Asymptomatic or mildly symptomatic disease

Outcomes in Transplant Recipients Treated With Foscarnet for Ganciclovir-Resistant or Refractory Cytomegalovirus Infection

Robin K. Avery, MD,[1] Ravit Arav-Boger, MD,[2] Kieren A. Marr, MD,[1] Edward Kraus, MD,[3] Shmuel Shoham, MD,[1] Laura Lees, PharmD,[4] Brandon Trollinger, PharmD,[4] Pali Shah, MD,[5] Rich Ambinder, MD,[6] Dionysios Neofytos, MD,[1] Darin Ostrander, PhD,[1] Michael Forman, BS,[7] and Alexandra Valsamakis, MD, PhD[7]

TABLE 1.

Demographic and clinical characteristics and outcomes of SOT and HCT recipients treated with foscarnet for resistant/refractory CMV

	SOT (n = 22)[a]	HCT (n = 17)[b]
GCV-resistant[d]	13/22 (59%)	2/17 (12%)
Median peak viral load,[e] IU/mL	241500 (765-45500000)	16100 (617-469000)
Median days posttransplant when FOS started	194 (93-542)	73 (29-521)
Tissue-invasive CMV	7/22 (32%)	4/17 (24%)
Virologic failure on FOS	6/22 (27%)	7/17 (41%)
Mortality within 1 y[d]	2/22 (9%)	10/17 (59%)
>20% Decrease in eGFR by end of FOS	12/22 (55%)	8/17 (47%)

Overall

- Virologic clearance: 66%
- CMV relapse: 31%
- Renal dysfunction: 51%
- 1 year mortality: 31%

TABLE 4.

Studies published after the year 2000, reporting outcomes of 6 or more transplant recipients treated with foscarnet for established CMV infection

Study	Year/center	Patients	Total, n	Deaths by 1 y	Renal dysfunction end of FOS	Renal dysfunction long term
Current study	2015 Johns Hopkins	FOS-treated R/R SOT + HCT	39 (all FOS)	12/39 (31%)	20/39 (51%)	7/25 (24%) at 6 mo
Pierce et al[21]	2015 Northwestern	FOS-treated R/R SOT	31 (all FOS)	10/31 (32%)	5/21 (24%)	3/21 (14%)
Fisher et al[20]	2014 University of Washington	GCV-R SOT	38 cases, 110 controls	8/38 (21%)	NR	15/37 (41%) at 3 mo
Minces et al[19]	2014 University of Pittsburgh	GCV-R lung transplant	16 (14 FOS)	5/16 (31%)	10/14 (71%)	NR
Myhre et al[17]	2011 Oslo University	GCV-R kidney transplant	27 (10 FOS)	2/10 (20%)	NR	NR
Asakura et al[16]	2010 Nagoya University	FOS-treated HCT	65 CMV disease (all FOS)	45/65 (69%)	3%[a]	NR
Reddy et al[15]	2007 Duke University	GCV-R lung transplant	6 (all FOS)	1/6 (17%)	2/6 (33%)	0/6 (0%)
Isada et al[2]	2002 Cleveland Clinic	GCV-R SOT	13 (10 FOS)	9/10 (90%)	NR	NR[b]

Avery et al., Transplantation 2016

Outcomes of transplant recipients treated with cidofovir for resistant or refractory cytomegalovirus infection

Seema A. Mehta Steinke[1,6] | Mona Alfares[1] | Alexandra Valsamakis[2,7] | Shmuel Shoham[1] | Ravit Arav-Boger[3,8] | Laura Lees[4] | Darin Ostrander[1] | Michael S. Forman[2] | Audra Shedeck[5] | Richard F. Ambinder[5] | Richard John Jones[5] | Robin K. Avery[1]

TABLE 1 Summary statistics of transplant recipients treated with CDV for resistant/refractory CMV

	BMT/Oncology (N = 6)		SOT (N = 10)	
Male	2 (33.3%)		5 (50%)	
Female	4 (66.7%)		5 (50%)	
Median age at transplant (y)	23 (IQR 20.8-31)		60 (IQR 43.3-60.5)	
Type of Transplant	DC MA HI NMA HI	1 (16.7%) 1 (16.7%) 4 (66.7%)	Kidney Heart Lung Liver	6 (60%) 2 (20%) 1 (10%) 1 (10%)
Donor and recipient CMV IgG serostatus	D+/R− D−/R+ D+/R+ D−/R− D?/R?	2 (33.3%) 1 (16.7%) 1 (16.7%) 1 (16.7%) 1 (16.7%)	D+/R− D−/R+ D+/R+ D−/R− D?/R?	6 (60%) 0 3 (30%) 0 1 (10%)
Median time to CMV DNAemia from transplant (d)	37 (IQR 30.8-133.3)		168 (IQR 112.2-253.5)	
Median peak CMV viral load, IU/mL[a]	116 850 (IQR 16,143.8-2 582 500)		72 959 (IQR 8694.3-759 750)	
Tissue-invasive CMV disease[b]	3 (50%)		4 (40%)	

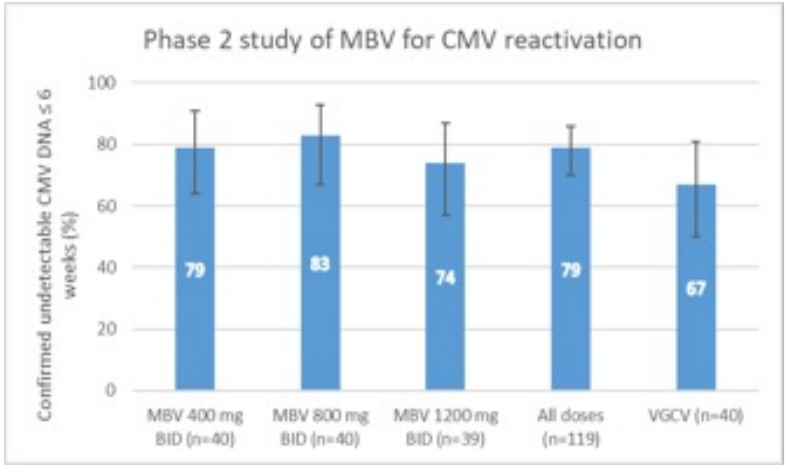
TABLE 3 Treatment of CMV, and outcomes of treatment

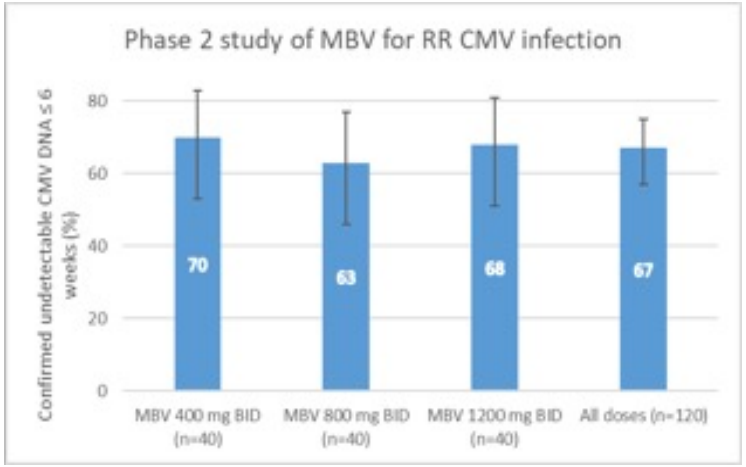
	BMT/Oncology (N = 6)	SOT (N = 10)	Total (N = 16)
Treated with GCV/VGCV before CDV	6 (100%)	10 (100%)	16 (100%)
Treated with FOS before CDV	5 (83.3%)	4 (40%)	9 (56.3%)
Median time to CDV after first CMV+ (d)	90 (IQR 43-230.75)	112 (IQR 21-154)	112 (IQR 38-152)
Median duration CDV received (d)	30 (IQR 15.25-68.25)	16 (IQR 8-35.5)	21.5 (IQR 8.3-47.3)
Median number of CDV doses received	3 (IQR 2-10)	2 (IQR 1-4)	3 (IQR 1-4)
CDV dosing schedule weekly × 2 doses then every 2 wk[a]	1	3	4
CDV dosing schedule weekly[a]	5	7	12
CMV Immune globulin received	5 (83.3%)	3 (30%)	8 (50%)
GCV/VGCV given after CDV therapy	2 (33.3%)	3 (30%)	5 (31.3%)
Uveitis	1 (16.7%)	3 (30%)	4 (25%)
Nephrotoxicity[b]	3 (50%)	3 (30%)	6 (37.5%)
Recovery of renal function[c]	0	1 (10%)	1 (6.3%)
Failure to clear CMV DNAemia[d]	4 (66.7%)	4 (40%)	8 (50%)
Death[e]	4 (66.7%)	4 (40%)	8 (50%)
Median time to death (days) for patients who died (4 BMT, 4 SOT)	667.5 (range, 13-2606)	28.5 (range 21-53)	33.5 (IQR 22-988)

Mehta Steinke et al, TID 2021

Emerging anti-CMV therapy

- Maribavir
  - Inhibits CMV DNA replication, encapsidation, and nuclear egress of viral capsids via inhibition of the UL97 protein kinase
  - CMV viremia clearance within 6 weeks of treatment in HCT and SOT:





Maertens et al., NEJM 2019

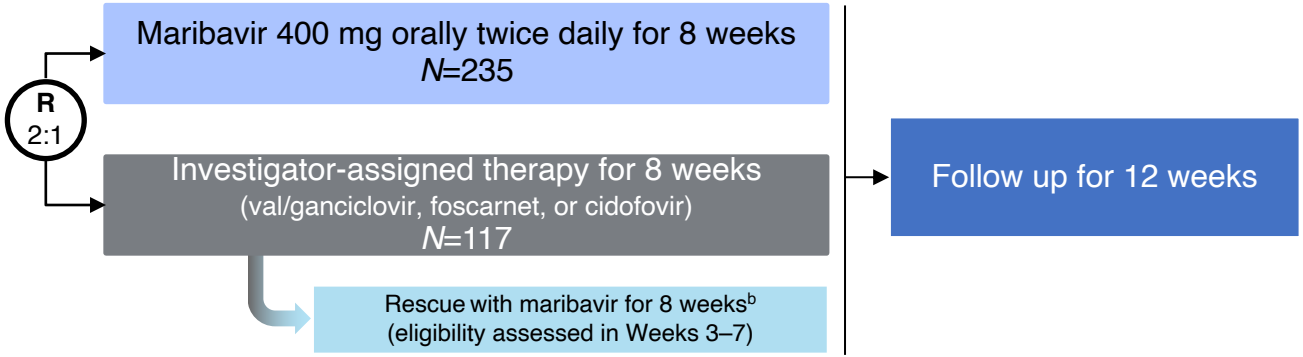
Maribavir
Phase 3, randomized, open-label, multicenter study

Key inclusion criteria

- SOT/HCT recipients
- CMV infection (plasma CMV DNA ≥910 IU/mL)
- Refractory to most recent therapy (failure to achieve >1 $\log_{10}$ decrease in CMV DNA after ≥14 days)

Stratification factors

- Transplant type (HCT vs SOT)
- Screening CMV DNA level (low vs intermediate vs high)[a]



Endpoints

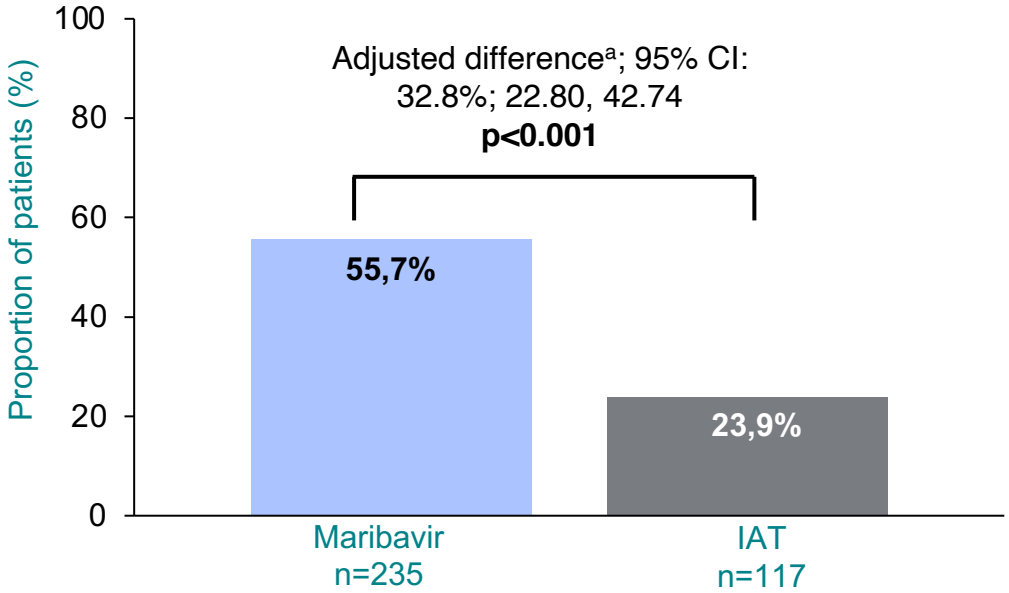
Primary
Confirmed CMV clearance (plasma CMV DNA <LLOQ[c] in 2 consecutive tests ≥5 days apart at central laboratory) at end of Week 8

Key secondary
CMV clearance and symptom control at end of Week 8 and maintained through Week 16

[a]CMV DNA levels in plasma (high: ≥91,000 IU/mL; intermediate: ≥9,100 and <91,000 IU/mL; low: <9,100 and ≥910 IU/mL). [b]Rescue arm data not presented. [c]LLOQ was defined as <137 IU/mL when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test at a central specialty laboratory.
CMV, cytomegalovirus; HCT, hematopoietic cell transplant; LLOQ, lower limit of quantification; R, randomization; SOT, solid organ transplant.

Avery et al., Clin Infect Dis 2021

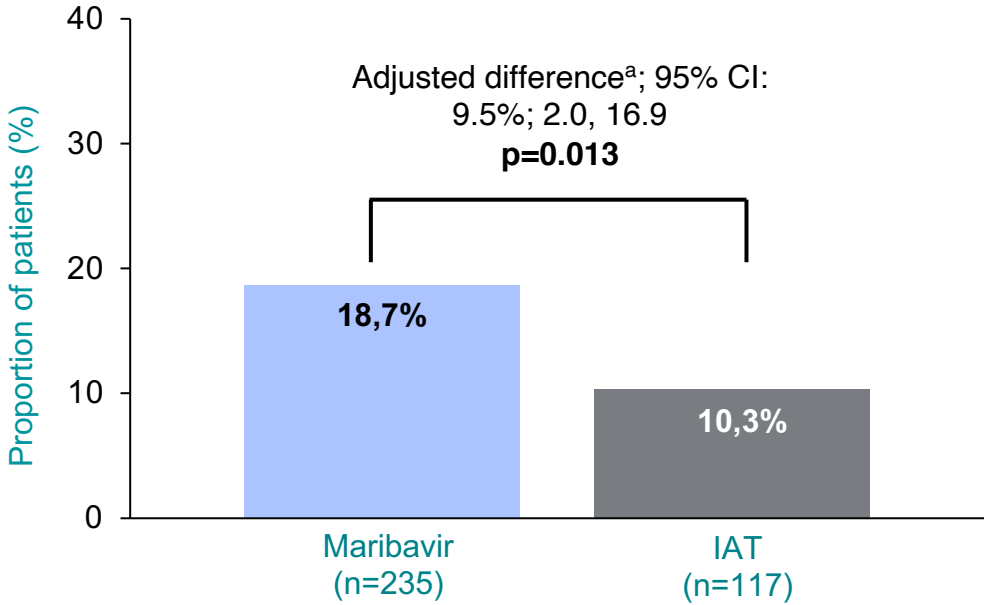
Primary endpoint: Significantly more patients achieved CMV viremia clearance at the end of Week 8 with maribavir versus IAT



[a]Between-group difference among all randomized patients, adjusted for baseline CMV viral load (low, <9,100 IU/mL; intermediate/high, ≥9,100 IU/mL [plasma]; central laboratory COBAS CAP/CTM assay), and SOT/ HCT was compared with Cochran–Mantel–Haenszel tests (p≤0.05 significant).
CMV, cytomegalovirus; HCT, hematopoietic cell transplant; IAT, investigator-assigned therapy; SOT, solid organ transplant.

Avery et al., Clin Infect Dis 2021

Key secondary endpoint: Significantly more patients achieved CMV viremia clearance and symptom control at end of Week 8, and maintained through Week 16, with maribavir versus IAT



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CMV, cytomegalovirus; HCT, hematopoietic cell transplant; IAT, investigator-assigned therapy; SOT, solid organ transplant.

Avery et al., Clin Infect Dis 2021

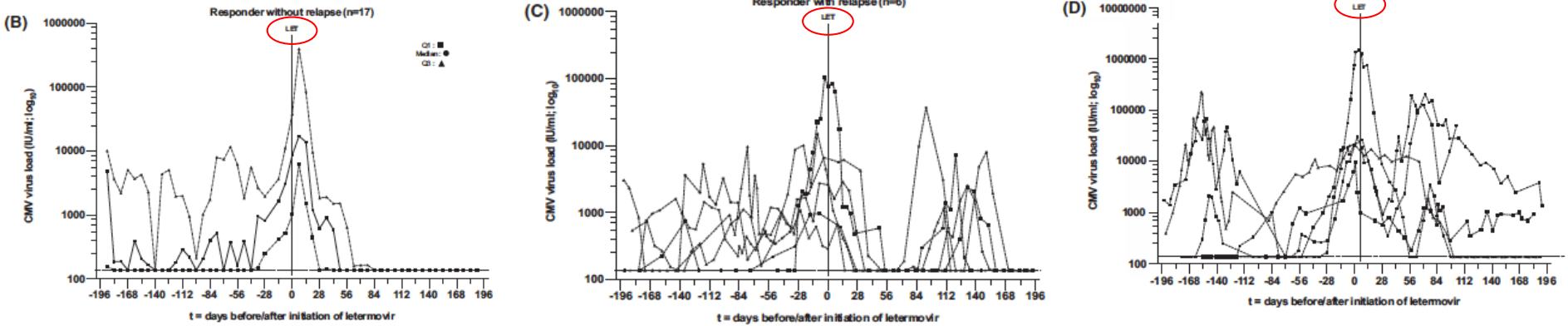
Adverse events: Maribavir vs. IAT

Preferred term, n (%) of patients	Maribavir (n=234)	IAT (n=116)	By drug (IAT arm)[b]		
			Val/ganciclovir (n=56)	Foscarnet (n=47)	Cidofovir (n=6)
Dysgeusia	**87 (37.2)**	**4 (3.4)**	**2 (3.6)**	**0**	**1 (16.7)**
CMV viremia[c]	24 (10.3)	6 (5.2)	4 (7.1)	1 (2.1)	0
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**

Avery et al., Clin Infect Dis 2021

Letermovir for refractory CMV infection in lung transplant patients

- All patients were previously treated with GCV and CMV Ig
- 15 (53.6%) had a CMV disease
- 12 (42%) had GCV resistant (UL97 or UL54)

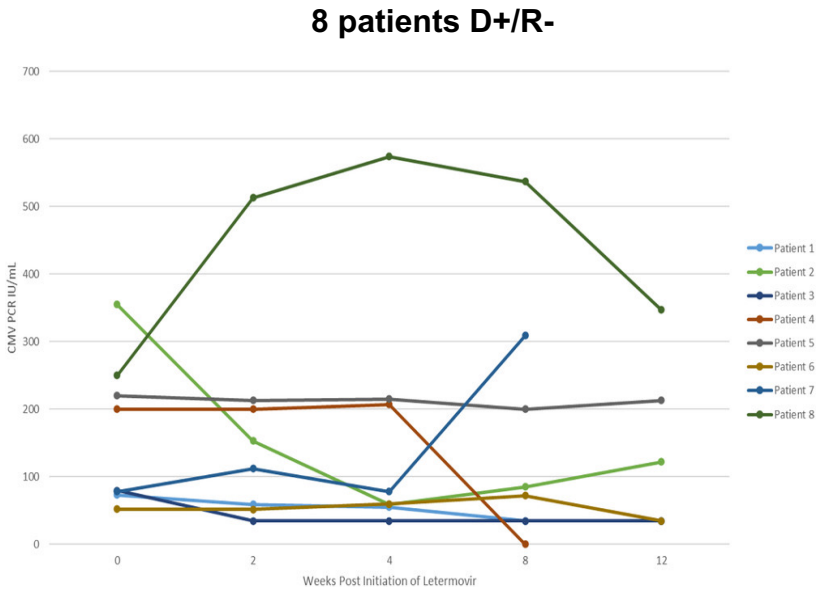


A rapid response was observed in 23 patients (82.1%)

Veit et al., AJT 2021

The addition of adjunctive letermovir to valganciclovir for refractory cytomegalovirus viremia in kidney transplant recipients

- **Letermovir was introduced 223 +/- 105 days after treatment of CMV**
- **VGC 900 mg/d**

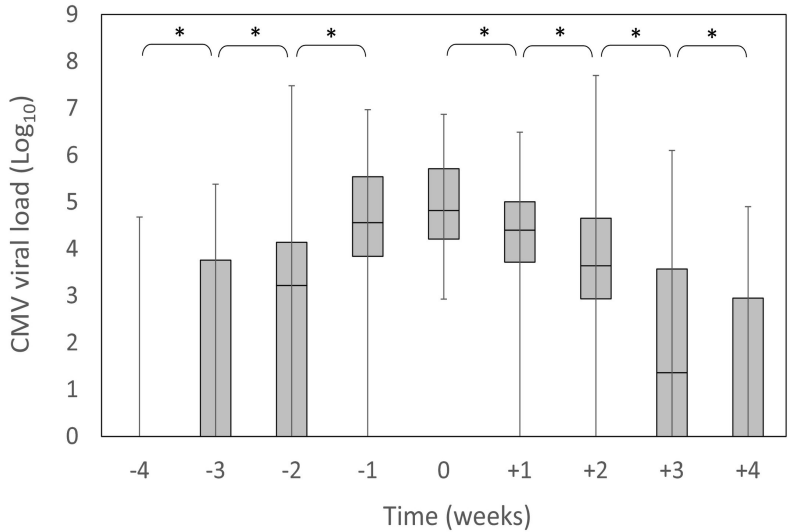


The use of adjunctive letermovir did not result in viral clearance

Jorgenson et al., TID 2021

CMV Ig rescue therapy in cardiothoracic transplantation

- **35 cardiothoracic transplant patients (L, H or H+L)**
- **8 had detected mutations**
- **Anti-CMV Ig (Biotest, 2 to 3 mL/kg): 13 (1 to 25 doses)**
- **Add to GCV/VGC + Leflunomide in patients with detected resistance**



After 4 weeks, CMV DNA was reduced in all patients (range: 10%-100% reduction), and was undetectable in 73% (24/33) cases

Santhanakrishnan et al., Clin Transplant 2019
Santhanakrishnan et al., Transplant Infect Dis 2021

Conclusion

- Unmet needs:
  - Myelotoxicity of available anti-CMV therapies
  - Improvement in the management of complicated CMV (Recurrence, Refractory and Resistant)

- Maribavir has been shown to be efficient for treating refractory and resistant CMV. However, a proportion of patient remains viremic or relapses after therapy

- Anti-CMV Ig seems also to be efficient for treating complicated CMV

- Further studies are required for determining the best option for treating complicated CMV


Thank you for your attention