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Incorporating New Therapies to Hone the Treatment of Resistant or Refractory CMV in the Post-SOT Setting

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Agenda

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Event 1

Evidence-based Management of CMV

By Dr. Kotton

Clinical Games

Event 2

Detecting Resistant or Refractory CMV

By Dr. Pereira

Clinical Games

Event 3

Managing Resistant or Refractory CMV

By Dr. Razonable

Clinical Games

Disclosures

Camille Nelson Kotton, MD, FIDSA, FAST

Camille Nelson Kotton, MD, FIDSA, FAST, has relevant financial relationships with Abbott Laboratories, Biotest, Evrys, Exevir, Hookipa, Merck, Oxford Immunotec, QIAGEN, Roche Diagnostics, Takeda *(Consultant)*.

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Marcus R. Pereira, MD, MPH, FAST, has relevant financial relationships with Takeda *(Consultant)*.

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Raymund R. Razonable, MD, FIDSA, FAST, has relevant financial relationships with Gilead, Regeneron, Roche *(Grant/Research Support)*; Merck *(Other: Data Adjudication Committee).*

All relevant financial relationships listed for these individuals have been mitigated according to RMEI policies.

Evidence-Based Management of CMV in the Post-SOT Setting

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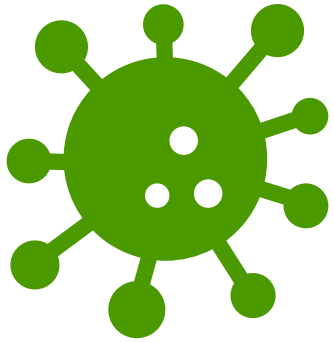
CMV: What is it and Why is it Important?

Cytomegalovirus (CMV)

- Frequently observed opportunistic pathogen in transplant recipients
- Establishes life-long latency after initial infection
- Most transplant patients get prophylactic or preemptive therapy to prevent CMV disease



Consequences in SOT Patients

- Higher risk for complications
- Tissue invasive disease
- Opportunistic co-infections (viral, fungal)
- Higher risk of post-transplant lymphoma
- Higher risk of graft rejection
- Increased mortality

SOT, solid organ transplant

Currently Available CMV Antivirals

Antiviral	Route of Administration	Route of Excretion	Use for CMV in Transplant Patients	
Ganciclovir	Intravenous	Renal	Treatment* and prevention	
Valganciclovir	Oral	Renal	Treatment* and prevention	
Foscarnet	Intravenous	Renal	Treatment*	
Cidofovir	Intravenous	Renal	Treatment*	
Maribavir	Oral	Hepatic	Treatment of post-transplant refractory/resistant CMV infection/ disease	
Letermovir	Oral, intravenous	Hepatic	Prophylaxis in CMV seropositive HCT recipients	

*Not FDA approved for the treatment of CMV infection or disease in transplant patients
HCT, hematopoietic cell transplant

Virus Antiviral Prophylaxis and Treatment Agents

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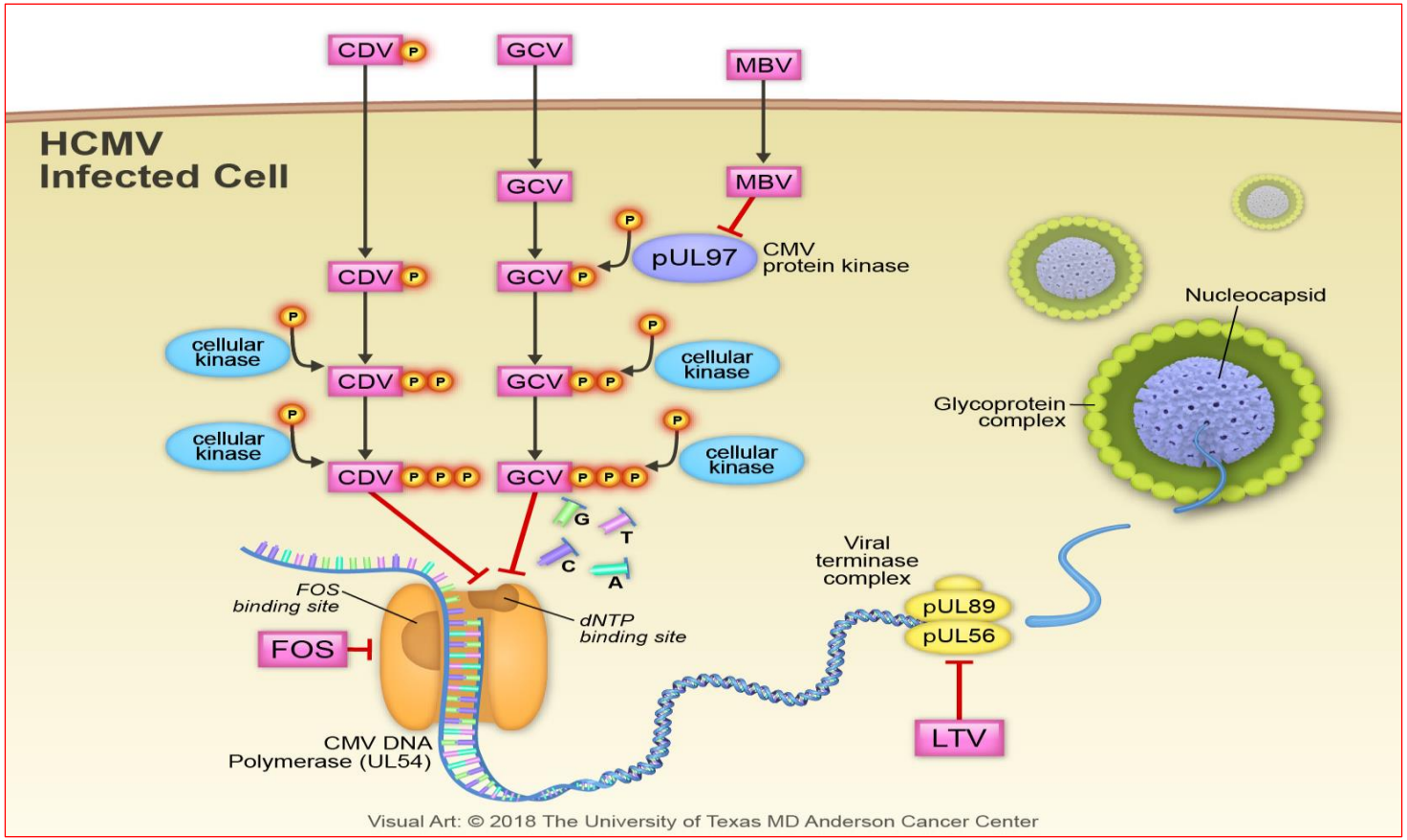
Antiviral Agent	CMV	HHV-6	EBV	HHV-8	HSV	Varicella	BK	Adeno-virus
Commercially Available								
Acyclovir/valacyclovir/famciclovir*	High dose ±				x	x		
Ganciclovir IV/valganciclovir PO	x	x		±	x	x		
Foscarnet**	x	x		±	x	x		
Cidofovir**	x	x		±	x	x	Poor	± IC50
Letermovir (prophylaxis only)	**x**							
Maribavir (resistant/ refractory CMV treatment only)	**x**		*In vitro*					
Novel/Investigational Antiviral Agents (SOT)								
Brincidofovir (not available)	*x*		*x*		*x*	*x*	*x*	*x*
Pritelivir (Phase III)					*x*			

*Acyclovir/valacyclovir/famciclovir and letermovir *for prophylaxis only*

**Foscarnet, cidofovir, maribavir not usually used for prophylaxis

Adapted from: Kotton CN. *Curr Opin Organ Transplant*. 2019;24(4):469-475.

Mechanism of Action of Antivirals



CDV, cidofovir; FOS, foscarnet; GCV, ganciclovir; LTV, letermovir; MBV, maribavir

Foolad F, et al. *Expert Rev Clin Pharmacol.* 2018;11(10):931-941.

CMV Prevention Strategies in SOT

	Universal Prophylaxis	Preemptive Therapy
Description	Antivirals for all patients at risk prior to the onset of CMV infection	• Routine monitoring for CMV infection • Treatment upon detection of asymptomatic CMV infection
Early CMV DNAemia/infection	Rare	Common
Late CMV	Common	Rare
Prevention of CMV disease	Yes	Yes
Ease of implementation	Easy	Difficult to coordinate No universal threshold to trigger therapy
Cost	Cost of drug, hospitalization, and disease cost of late CMV	Cost of monitoring
Toxicity	More drug toxicity (myelosuppression)	Less drug toxicity

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

CMV Prevention: Guideline Recommendations

Organ	CMV serostatus D+/R-	CMV serostatus 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 month**s *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

D, donor; R, recipient; 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.

Treatment of CMV in SOT Patients

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Medication*

Oral VGCV	900 mg q12h
IV GCV	5 mg/kg q12h

Consider IV GCV in:

- Life-threatening disease
- Very high viral load
- Patients with questionable GI absorption

Not Recommended for Treatment of CMV Infection/Disease

- Acyclovir, valacyclovir, letermovir

Weekly Monitoring

1. CMV PCR
2. Serum creatinine
3. Complete blood count

- Frequent monitoring of renal function is recommended to guide dose adjustments

Duration

- Until resolution of clinical symptoms
- Virological clearance is below a pre-defined threshold (LLOQ <200 IU/mL) *or* undetectable on 1 or 2 weekly samples
- Minimum of 2 weeks of therapy

*Adjust dose for renal function

VGCV, valganciclovir; GCV, ganciclovir; SOT, solid organ transplant; LLOQ, lower limit of quantification

Kotton CN, et al. *Transplantation.* 2018;120(6):900-931.

Side Effects and Toxicities

Antiviral Agent	Bone Marrow	Kidney	Altered Taste	Nausea
Ganciclovir IV/valganciclovir PO	✓			
Acyclovir at high doses (CMV prophylaxis only)		✓		
Foscarnet		✓		
Cidofovir		✓		
Letermovir (HCT approved, CMV prophylaxis only)				✓
Maribavir (SOT and HCT approved, refractory/resistant CMV treatment)			✓	

HCT, hematopoietic cell transplant; SOT, solid organ transplant

Managing CMV Antiviral Side Effects

Leukopenia

- Reduce or stop MMF and/or stop valganciclovir
- For (val)ganciclovir, do not dose reduce for low WBC, always dose to GFR
  - Increases risk of resistance (especially with infection)
  - Support WBC with growth factors (G-CSF), *or*
    - If prevention: Switch to pre-emptive monitoring with weekly blood checks (± HSV/VZV prophylaxis)
    - If treatment: Switch to foscarnet

Neutropenia

- Reduce/discontinue VGCV
- Reduce/discontinue MPA
- Discontinue cotrimoxazole
- Use of G-CSF

Nephrotoxicity

- Adequate IV hydration
- Avoidance of concomitant nephrotoxic drugs
- Dose adjustment for GFR
- Treatment interruption may be required

MMF, mycophenolate mofetil; WBC, white blood cell; GFR, glomerular filtration rate; G-CSF, granulocyte colony stimulating factor; HSV, herpes simplex virus; VZV, varicella-zoster virus; VGCV, valganciclovir; MPA, mycophenolic acid; IV, intravenous

Kotton CN, et al. *Transplantation.* 2018;120(6):900-931.

Challenges of CMV Treatment in SOT Patients

Current CMV treatment options remain limited by:

- Significant toxicities: Renal, bone marrow, ocular
- Need to dose medications as per renal function, which can be hard to accurately assess
- Cost and complexity
  - Close laboratory monitoring
  - For some: Intravenous requirement, need for hospitalization
- Potential for development of CMV resistant/refractory disease with prolonged use

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Detecting Resistant or Refractory CMV: Key Tactics and Considerations

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Refractory and Resistant CMV

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Refractory CMV Infection

CMV viremia that increases after at least 2 weeks 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 weeks of appropriately dosed antiviral therapy

Antiviral Drug Resistance

Viral genetic alteration that decreases susceptibility to one or more antiviral drugs

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

Incidence of Antiviral Drug Resistance in SOT Patients

Incidence of Resistance

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

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

Associated with Poor Outcomes

- Higher rates of hospitalization, increased length of stay, higher costs
- Increased adverse events from alternative therapies
- Increased rejection and allograft loss
- Increased mortality

Severity

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

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

Kotton CN, et al. *Transplantation.* 2018;120(6):900-931.

Understanding Refractory Disease

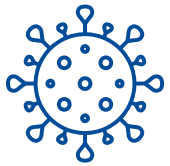
Development of Refractory Disease

- Can develop to all available therapies
- Usually occurs after prolonged anti-viral treatment + higher immunosuppression
- Not all patients with refractory CMV have drug-resistant virus documented by genotypic testing

Risk Factors for CMV Resistance

Reduced CMV-specific Host Immunity

- CMV serostatus D+/R-
- Potent immunosuppressive therapy
- Lung transplant recipients



Antiviral Therapies

- Prolonged exposure to antiviral therapy
  - Median 5 months for GCV
- Prolonged DNAemia (>21 days) while on antiviral therapy

Subtherapeutic Drug Concentrations

- Decreased oral absorption
- Inappropriately reduced dose (to avoid bone marrow suppression)

D, donor; R, recipient; GCV, ganciclovir

Kotton CN, et al. *Transplantation*. 2018;102(6):900-931.
Boivin G, et al. *J Clin Virol*. 2012;53(3):208-213.

When to Suspect Antiviral Resistance

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Antiviral resistance may be present if:

- Rising viral load (VL) on antivirals after initial viral suppression
- Failure of VL to decrease by at least 1 $\log_{10}$ after antiviral induction therapy

Resistance most common when:

- Prolonged exposure to antivirals (>6 weeks)
- Persistent viremia
- Antiviral dosage adjusted due to toxicity or reduced creatinine clearance

Immunosuppressive therapy should be decreased, if feasible

Chemaly RF, et al. *Clin Infect Dis*. 2019;68(8):1420-1426.
Kotton CN, et al. *Transplantation*. 2018;102(6):900-931.

Monitoring for Resistance

When to Test

- Antiviral drug resistance should be suspected and tested for when there is persistent or recurrent CMV DNAemia or disease during prolonged antiviral therapy
- For GCV, at least 6 or more weeks
  - Including longer than 2 weeks of ongoing full and appropriately dosed therapy

How to Test

- Genotypic assays for viral drug resistance mutations in UL97 and UL54 genes
  - 7 most common (“canonical”) UL97 mutations – 80% cases
  - Several UL54 mutations

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

Testing for Resistance

Genotypic Assays

- Performed on viral sequences amplified from blood (whole blood, plasma, or leukocytes), fluids (urine, cerebrospinal, lung, eye) or tissue specimens
- Results are more reliable if the CMV copy number in the specimen is at least 1000 IU/mL.
- Quality control concerns:
  - False positives due to mixed populations from low viral-load specimens
  - False negatives due to insensitivity in detecting mutant subpopulations comprising less than 20% to 30% of the total

Genotypic assays to detect UL97 mutation should be performed among patients suspected to have resistance to ganciclovir

Genotypic assays to detect UL54 mutations should be performed among patients suspected to have resistance to ganciclovir, foscarnet, and cidofovir

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

Mutations Associated With Resistance

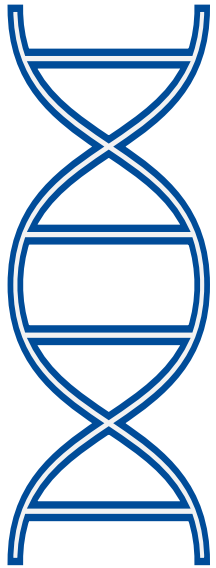
Genotypic resistance testing detects mutations in UL97, UL56, and UL54 genes

UL97

- Mutations common conferring resistance to ganciclovir

UL97: Specific mutations (T409M, H411Y)

- Confer resistance to maribavir



UL54

- Mutations may confer resistance to foscarnet, ganciclovir, or cidofovir

UL56

- Mutations may confer resistance to letermovir only. No cross resistance with ganciclovir, foscarnet, or cidofovir

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

GCV Resistance Levels

GCV resistance levels are determined by the fold change in EC50 (drug concentration that reduces viral growth by 50%)

Low Grade

2-fold to 5-fold

Moderate Grade

5-fold to 15-fold

- A level that may result from a single UL97 mutation

High Grade

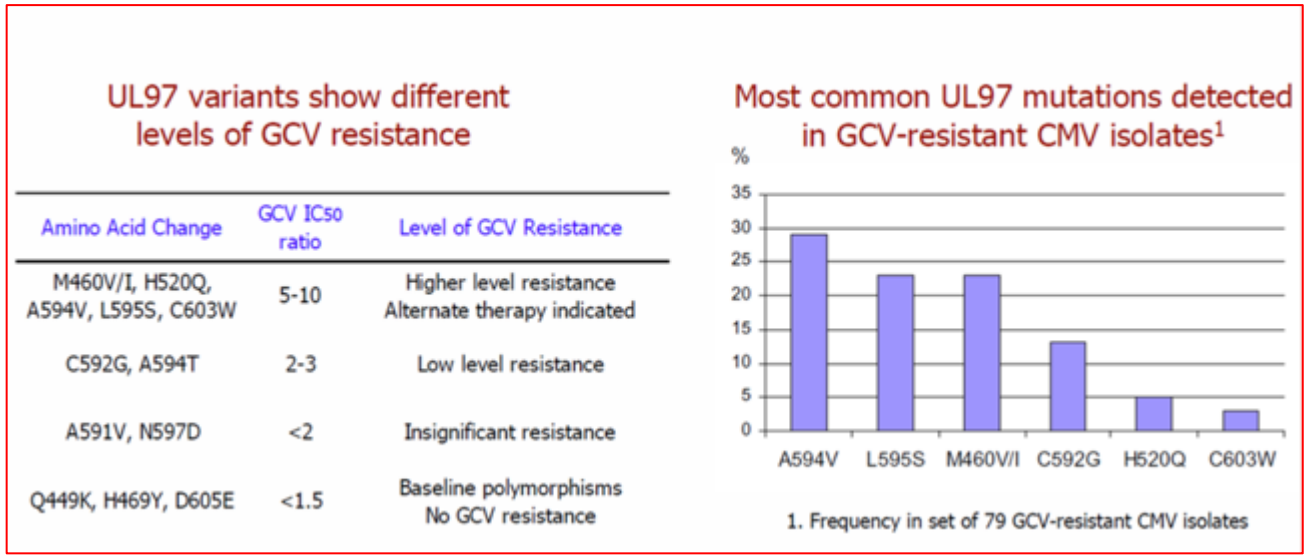
Greater than 15-fold

- Suggests the combined effect of UL97 and UL54 mutations

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

How Do You Confirm Resistant CMV

- Genotypic resistance testing involves sequencing of relevant portions of the CMV genome and is the preferred method
- Phenotypic resistance testing involves culturing the virus in the presence of different drug concentrations and is more labor intensive



UL97 variants show different levels of GCV resistance

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

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

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

Courtesy S. Chou

Lurain NS, Chou S. *Clin Microbiol Rev.* 2010;23(4):689-712.
Chou S. *Curr Opin Infect Dis.* 2015;28(4):293-299.

Interpreting Resistance Test Results

	Value	Range
Ganciclovir UL54 Gene Target	**None Detected**	None Detected
Ganciclovir UL97 Gene Target	**Resistant at Site A594V (A)**	None Detected
Foscarnet UL54 Gene Target	**None Detected**	None Detected
Cidofovir UL54 Gene Target	**None Detected**	None Detected
Letermovir UL56 Gene Target	**None Detected**	None Detected

Comments:

If a mutation has been detected in a Gene Target, the mutation site is indicated. A result of "None Detected" indicates that no mutations were detected for that gene target. A two fold impact of the mutation in the IC50 value must be indicated to assign a result of resistance. A complete list of mutations that have been reported in the literature

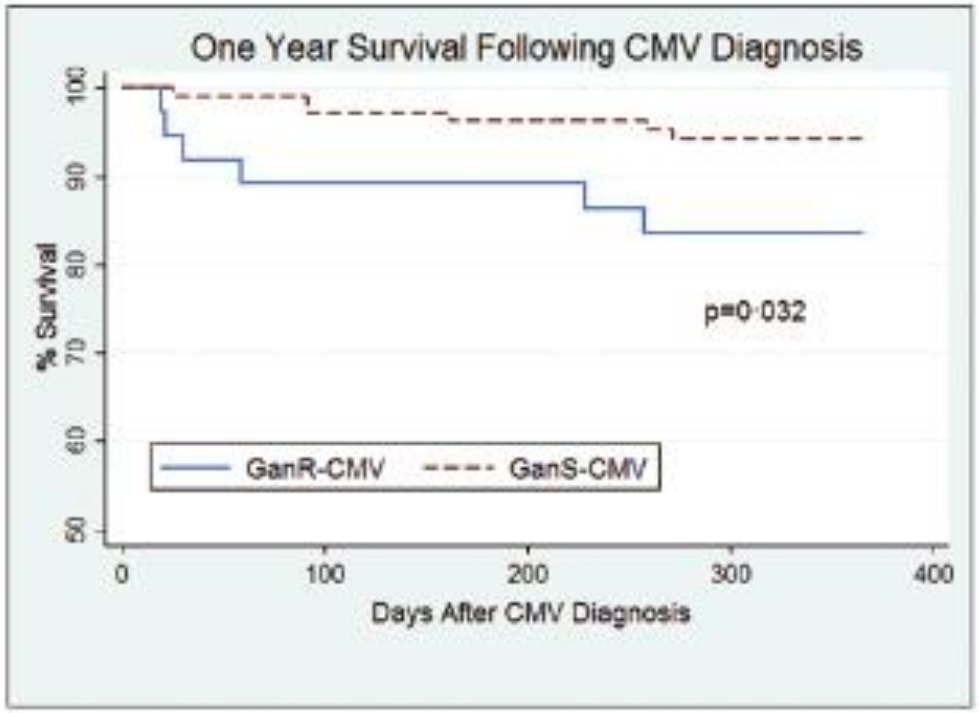
This test was developed and its performance characteristics determined by . It has not been cleared or approved by the U.S. Food and Drug Administration. Results should be used in conjunction with clinical findings, and should not form the sole basis for a diagnosis or treatment decision. Mutations may develop and confer resistance that have not yet been reported in the literature.

Outcomes of Ganciclovir Resistance

Patient Outcomes

Outcome	Cases (n = 37)	Controls (n = 109)	*P* Value
Morbidity measures			
Days to clearance of viremia, median (IQR)	113 (50–394)	53 (32–149)	.006
≥20% decrease in eGFR by 3 mo after CMV diagnosis	15 (41.7)	21 (19.4)	.008
Well days[a] in the 3 mo after CMV diagnosis, mean (SE)	72.7 (4.8)	81.0 (1.7)	.039
Rejection within 1 y following CMV diagnosis			
All organs	15 (40.5)	38 (34.9)	.54
Kidney	4 (66.7)	2 (10.5)	.005
Mortality			
3 mo	4 (10.8)	1 (0.92)	.004[b]
12 mo	6 (16.2)	6 (5.5)	.032

Kaplan-Meier Survival Curve



Comparison of outcomes in patients with GCV resistance versus GCV sensitivity

Fisher C, et al. *Clin Infect Dis*. 2017;65(1):57-63.

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Managing Drug-Resistant or Treatment-Refractory CMV in the Post-SOT Population

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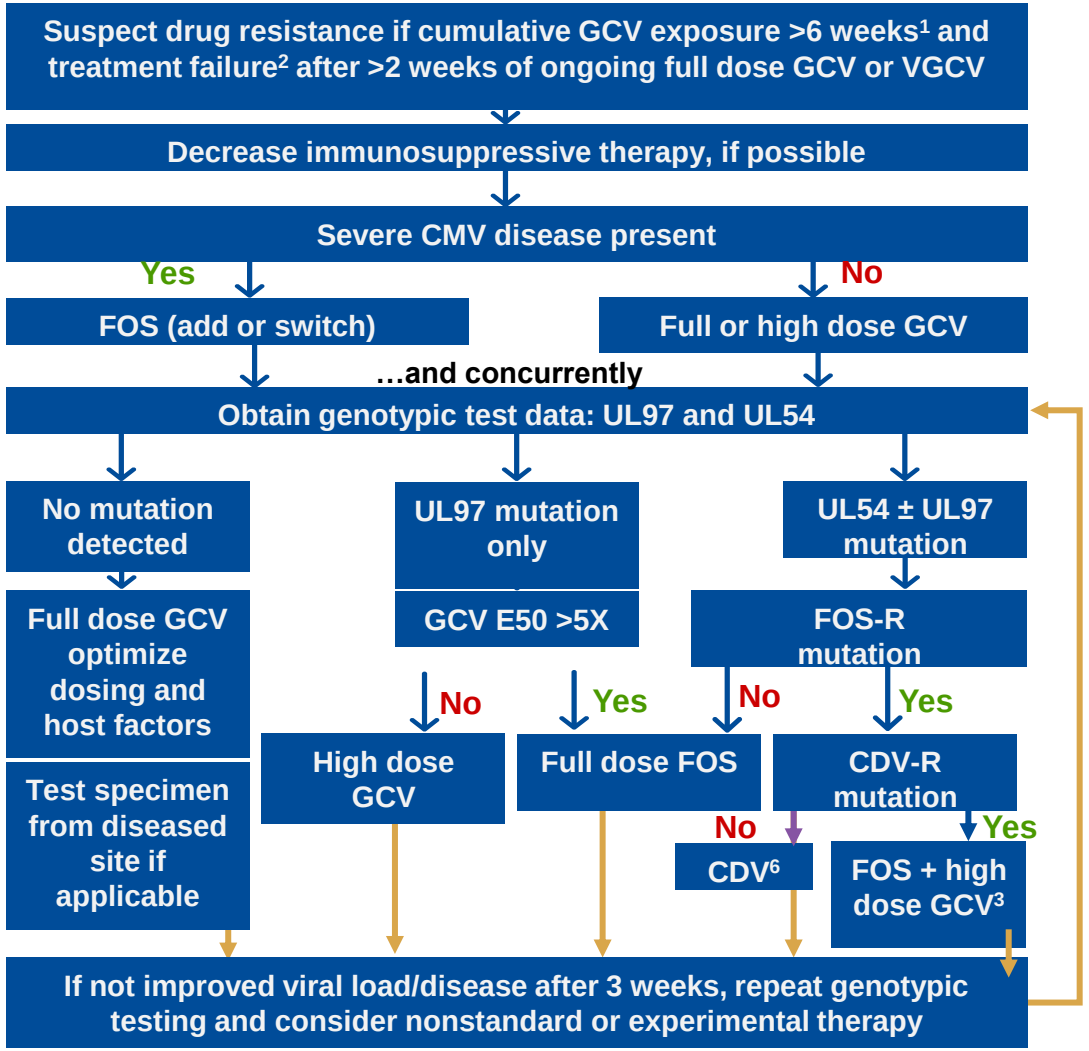
Resistant CMV Management Guidelines

- Current algorithms are based on expert opinion due to limited data
- Maribavir is the only FDA approved treatment for post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with GCV, VGCV, CDV, or FOS



GCV, ganciclovir; FOS, foscarnet; CDV, cidofovir; VGCV, valganciclovir

1. Resistance rare before 6 weeks
2. Symptomatic disease or viral load not improving
3. Case reports of GCV EC50 5x-10x successfully treated with high-dose GCV

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

Treatment of Drug-Resistant/ Refractory CMV

- First step is to reduce immunosuppressive therapy to the lowest feasible amount
- Therapies
  - Maribavir
  - High-dose ganciclovir
  - Foscarnet
  - Cidofovir
- Adjunctive therapies
- Investigational therapies
- Off-label therapies

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

High-dose Ganciclovir

Appropriate Candidates

Best for those with:

- Low-level resistance UL97 gene mutations (C592G)
- Low-level DNAemia
- Asymptomatic or mildly symptomatic disease

Regimen

Dose escalation from 7.5 to 10 mg/kg every 12 hours in normal renal function

Adverse Events

Neutropenia reported in approximately 50% of patients

Limitations

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
- Narrow applicability

SOT, solid organ transplant

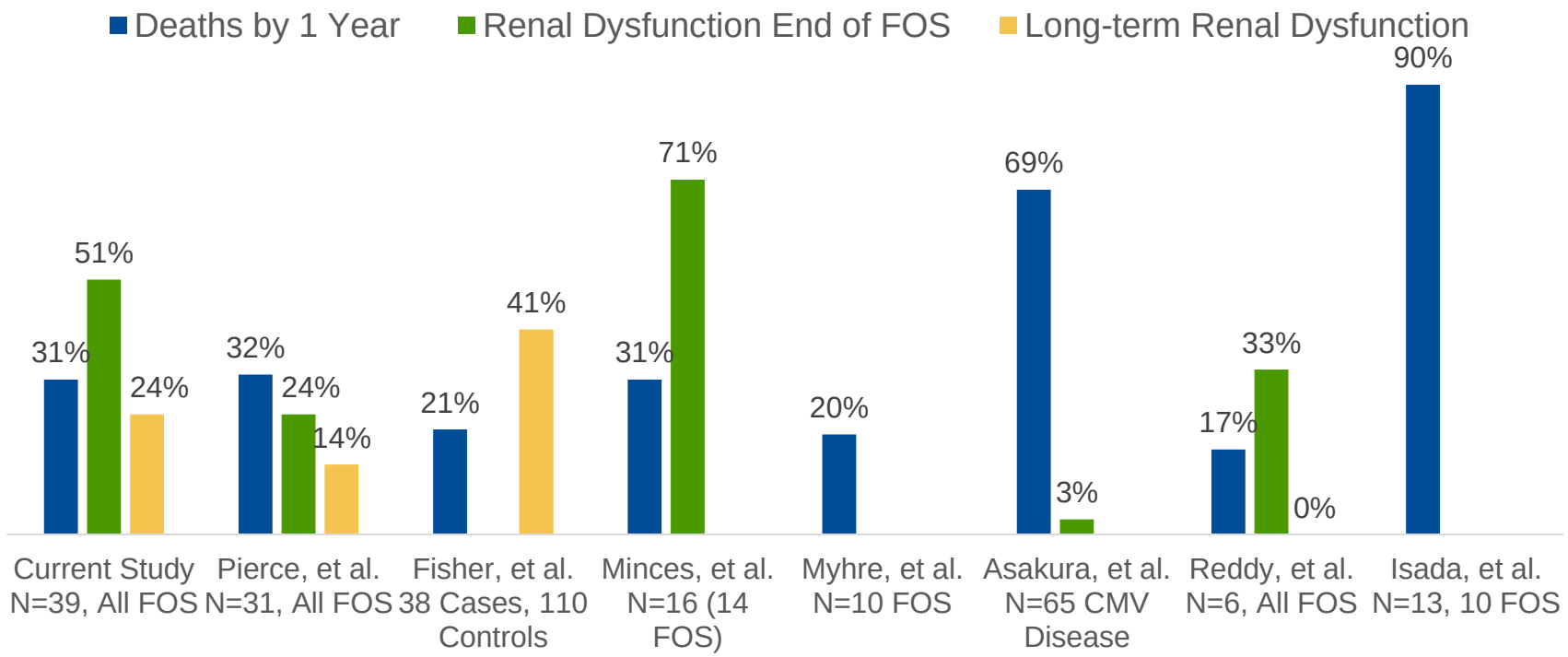
Kotton CN, et al. *Transplantation*. 2018;102(6):900-931.

Foscarnet

Studies Published After the Year 2000, Reporting Outcomes of 6 or More Transplant Recipients Treated with Foscarnet for Established CMV Infection

Overall

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



Limitations:
Metabolic and renal toxicity

Avery RK, et al. Transplantation. 2016;100(10):e74-80.

Cidofovir

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%)	

Steinke SAM, et al. *Transpl Infect Dis.* 2021;23(3):e13521.

Cidofovir

Treatment outcomes for transplant recipients treated with CDV for resistant/refractory CMV

	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)

Limitations:
Nephrotoxicity

Steinke SAM, et al. *Transpl Infect Dis.* 2021;23(3):e13521.

Maribavir Phase 3 SOLSTICE Trial: Study Design

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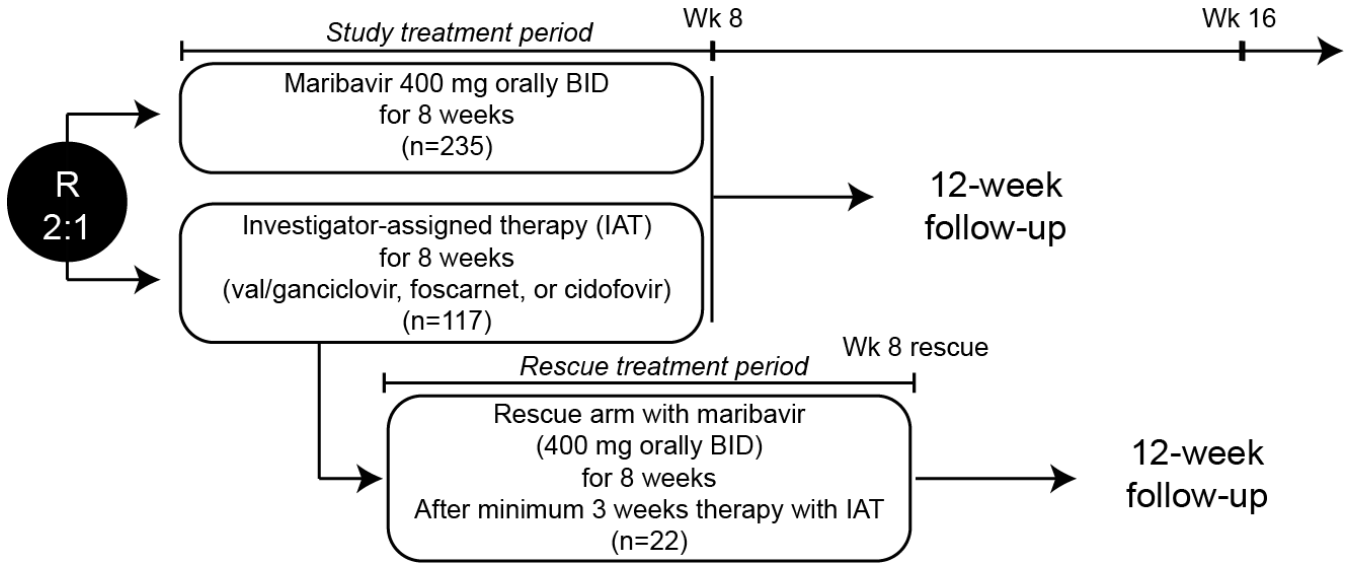
Key Study Inclusion Criteria

- 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)



End Points

Primary	Key Secondary	Other Secondary
Confirmed CMV viremia clearance (plasma CMV DNA <LLOQ in 2 consecutive tests ≥5 days apart at central laboratory) at end of Week 8	Composite of CMV viremia clearance and symptom control at end of Week 8 and maintained through Week 16	Assess the efficacy (including symptom control) and safety of maribavir as rescue treatment

SOT, solid organ transplant; HCT, hematopoietic cell transplant; BID, twice daily; LLOQ, lower limit of quantification

Avery RK, et al. *Clin Infect Dis.* 2022;75(4):690-671.

Maribavir Phase 3 SOLSTICE Trial: Primary and Secondary Endpoint Results

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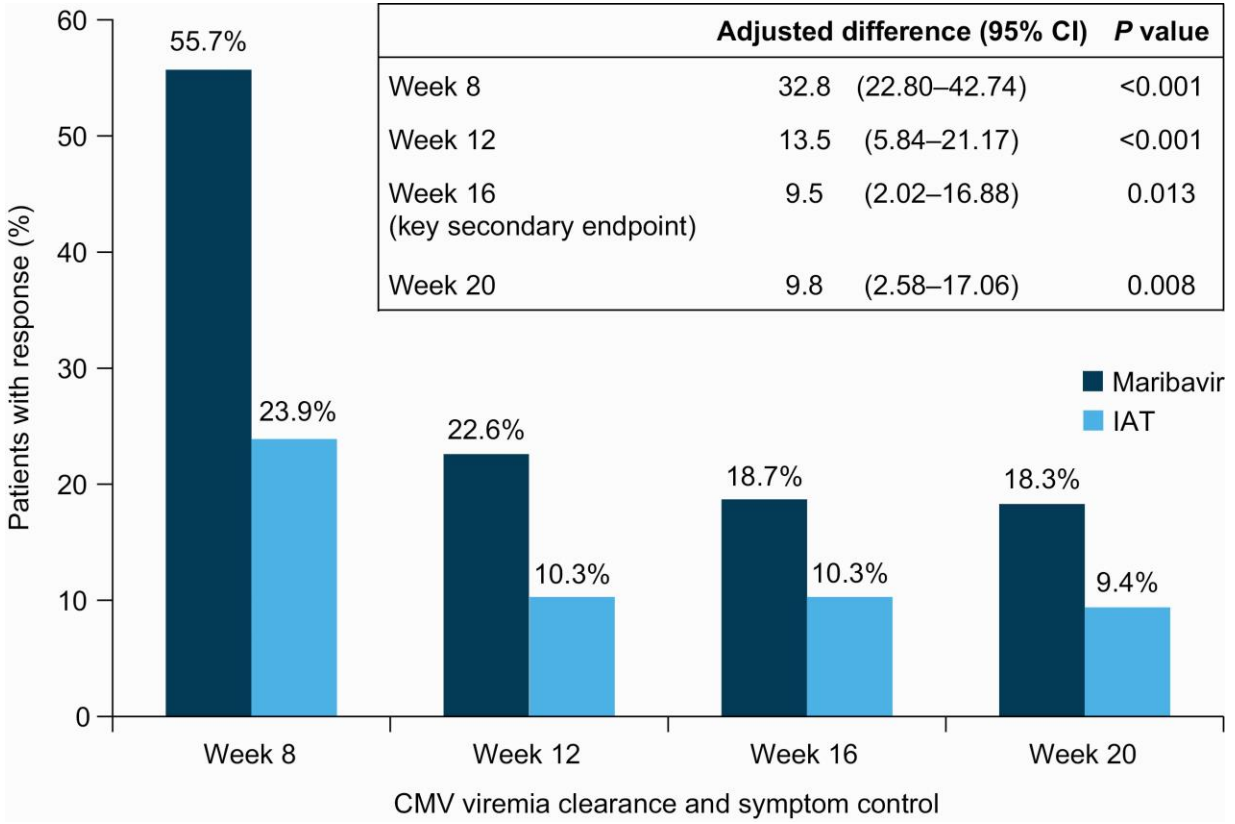
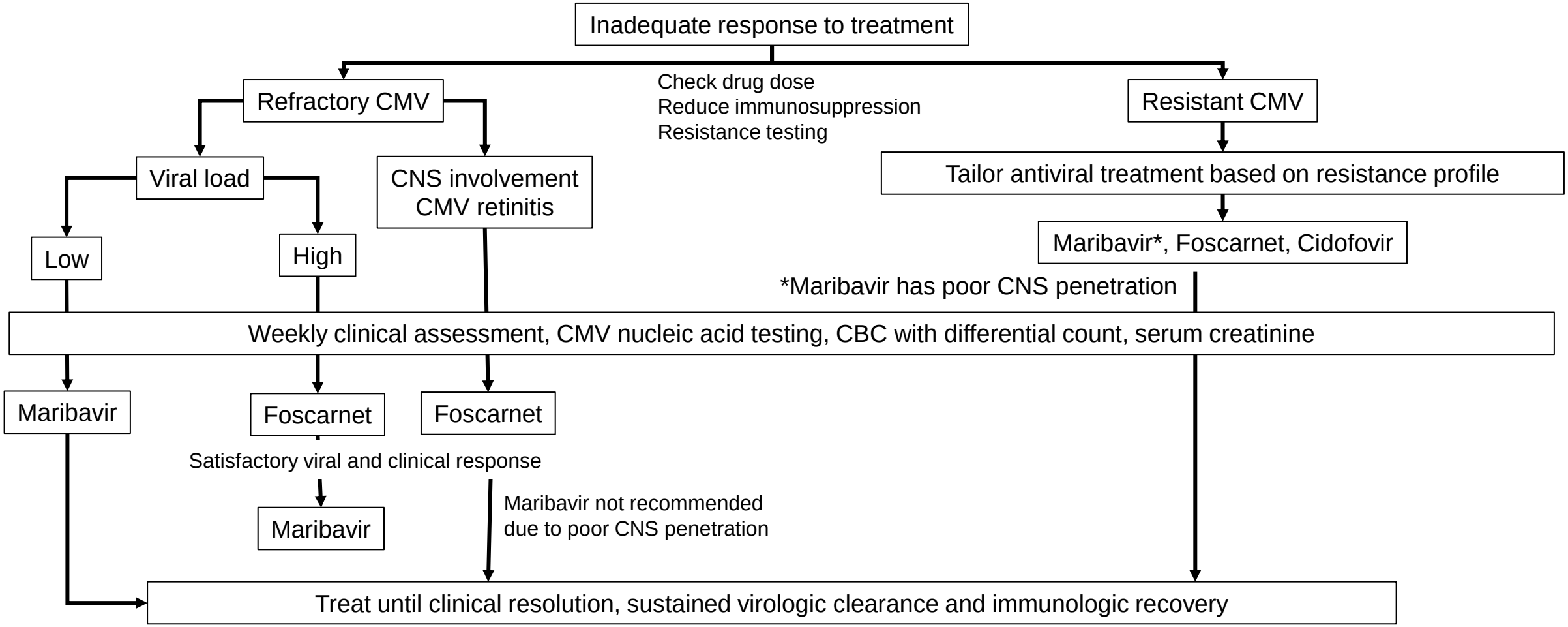
Confirmed Viremia Clearance and Symptom Control

	Adjusted difference (95% CI)		*P* value
Week 8	32.8	(22.80–42.74)	<0.001
Week 12	13.5	(5.84–21.17)	<0.001
Week 16 (key secondary endpoint)	9.5	(2.02–16.88)	0.013
Week 20	9.8	(2.58–17.06)	0.008



Avery RK, et al. *Clin Infect Dis.* 2022;75(4):690-671.

Algorithm for the Management of Refractory or Resistant CMV in SOT



Razonable RR. *Clin Microbiol Infect.* Published online March 23, 2023. Available at: https://doi.org/10.1016/j.cmi.2023.03.020.

Adjunctive, Investigational, and Off-label Therapies

- **CMV-Ig or IVIG**
  - Adjunctive use in severe disease
  - Supply and cost limitations
- **Adoptive T-cell Therapy**
  - High rates of response
  - Low toxicity
  - Logistical and cost limitations
  - Phase 1 studies in SOT recipients ongoing (NCT03950414, NCT03665675)
- **mTOR Inhibitors as Part of Immunosuppressive Regimen**
  - Reduces risk of CMV infection
  - Tolerability an issue
- **Leflunomide and Artesunate**
  - Mixed outcomes in very limited data
  - Caution advised

Haidar G, et al. *J Infect Dis.* 2020;221(Suppl 1):S23-S31.
Kotton CN, et al. *Transplantation.* 2018;102(6):900-931.